Christian Reichardt

Solvents and Solvent Effects in Organic Chemistry

Solvents and Solvent Effects in Organic Chemistry, Third Edition. Christian Reichardt

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Solvents and Solvent Effects in Organic Chemistry

Third, Updated and Enlarged Edition

WILEY-VCH

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To Maria
and in memory of my parents

Preface to the Third Edition

Meeting the demand for the second edition of this book, which is – despite a reprint in 1990 – no longer available, and considering the progress that has been made during the last decade in the study of solvent effects in experimental and theoretical organic chemistry, this improved third edition is presented to the interested reader.

Following the same layout as in the second edition, all topics retained have been brought up to date, with smaller and larger changes and additions on nearly every page. Two Sections (4.4.7 and 5.5.13) are completely new, dealing with solvent effects on host/guest complexation equilibria and reactions in biphasic solvent systems and neoteric solvents, respectively. More than 900 new references have been added, giving preference to review articles, and many older ones have been deleted. New references either replace older ones or are added to the end of the respective reference list of each chapter. The references cover the literature up to the end of 2001.

From the vast number of published papers dealing with solvent effects in all areas of organic chemistry, only some illustrative examples from the didactic and systematic point of view could be selected. This book is not a monograph covering *all* relevant literature in this field of research. The author, responsible for this subjective selection, apologizes in advance to all chemists whose valuable work on solvent effects is not mentioned in this book. However, using the reviews cited, the reader will find easy access to the full range of papers published in a certain field of research on solvent effects.

Great progress has been made during the last decade in theoretical treatments of solvent effects by various quantum-chemical methods and computational strategies. When indicated, relevant references are given to the respective solution reactions or absorptions. However, a critical evaluation of all the theoretical models and methods used to calculate the differential solvation of educts, activated complexes, products, ground and excited states, is outside the expertise of the present author. Thus, a book on all kinds of theoretical calculations of solvent influences on chemical reactions and physical absorptions has still to be written by someone else.

Consistent use of the nomenclature,[a] symbols,[b] terms,[c] and SI units[d] recommended by the IUPAC commissions has also been made in this third edition.

For comments and valuable suggestions I have to thank many colleagues, in particular Prof. E. M. Kosower, Tel Aviv/Israel, Prof. R. G. Makitra, Lviv/Ukraine, Prof. N. O. Mchedlov-Petrossyan, Kharkiv/Ukraine, and Prof. K. Möckel, Mühlhausen/Germany. For their assistance in drawing formulae, preparing the indices, and providing me with difficult to obtain literature, I thank Mr. G. Schäfer (technician), Mrs. S. Schellenberg (secretary), and Mrs. B. Becht-Schröder (librarian), all at the Department

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[a] G. J. Leigh, H. A. Favre, and W. V. Metanomski: *Principles of Chemical Nomenclature – A Guide to IUPAC Recommendations*, Blackwell Science Publications, London, 1998.

[b] I. Mills, T. Cvitas, K. Homann, N. Kallay, and K. Kuchitsu: *Quantities, Units and Symbols in Physical Chemistry*, 2nd ed., Blackwell Science Publications, London, 1993.

[c] P. Müller: *Glossary of Terms used in Physical Organic Chemistry – IUPAC Recommendations 1994*, Pure Appl. Chem. *66*, 1077 (1994).

[d] G. H. Aylward and T. J. V. Tristan: *SI Chemical Data*, 4th ed., Wiley, Chichester, 1999; *Datensammlung Chemie in SI-Einheiten*, 3rd ed., Wiley-VCH, Weinheim/Germany, 1999.

of Chemistry, Philipps University, Marburg/Germany. Special thanks are due to the staff of Wiley-VCH Verlag GmbH, Weinheim/Germany, particularly to Dr. Elke Westermann, for their fine work in turning the manuscript into the final book. Lastly, my biggest debt is to my wife Maria, not only for her assistance in the preparation of the manuscript, but also for her constant encouragement and support during the writing of this book.

Marburg (Lahn), Spring 2002 Christian Reichardt

Preface to the Second Edition

The response to the first English edition of this book, published in 1979, has been both gratifying and encouraging. Its mixed character, lying between that of a monograph and a textbook, has obviously made it attractive to both the industrial and academic chemist as well as the advanced student of chemistry.

During the last eight years the study of solvent effects on both chemical reactions and absorption spectra has made much progress, and numerous interesting and fascinating examples have been described in the literature. In particular, the study of ionic reactions in the gas phase – now possible due to new experimental techniques – has allowed direct comparisons between gas-phase and solution reactions. This has led to a greater understanding of solution reactions. Consequently, Chapters 4 and 5 have been enlarged to include a description of ionic gas-phase reactions compared to their solution counterparts.

The number of well-studied solvent-dependent processes, *i.e.* reactions and absorptions in solution, has increased greatly since 1979. Only a representative selection of the more instructive, recently studied examples could be included in this second edition.

The search for empirical parameters of solvent polarity and their applications in multiparameter equations has recently been intensified, thus making it necessary to rewrite large parts of Chapter 7.

Special attention has been given to the chemical and physical properties of organic solvents commonly used in daily laboratory work. Therefore, all Appendix Tables have been improved; some have been completely replaced by new ones. A new well-referenced table on solvent-drying has been added (Table A-3). Chapter 3 has been enlarged, in particular by the inclusion of solvent classifications using multivariate statistical methods (Section 3.5). All these amendments justify the change in the title of the book to *Solvents and Solvent Effects in Organic Chemistry*.

The references have been up-dated to cover literature appearing up to the first part of 1987. New references were added to the end of the respective reference list of each chapter from the first edition.

Consistent use of the nomenclature, symbols, terms, and SI units recommended by the IUPAC commissions has also been made in the second edition.*)

I am very indebted to many colleagues for corrections, comments, and valuable suggestions. Especially helpful suggestions came from Professors H.-D. Försterling, Marburg, J. Shorter, Hull/England, and R. I. Zalewski, Poznań/Poland, to whom I am very grateful. For critical reading of the whole manuscript and the improvement of my English I again thank Dr. Edeline Wentrup-Byrne, now living in Brisbane/Australia. Dr. P.-V. Rinze, Marburg, and his son Lars helped me with the author index. Finally, I would like to thank my wife Maria for her sympathetic assistance during the preparation of this edition and for her help with the indices.

Marburg (Lahn), Spring 1988 Christian Reichardt

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* *Cf.* Pure Appl. Chem. *51*, 1 (1979); ibid. *53*, 753 (1981); ibid. *55*, 1281 (1983); ibid. *57*, 105 (1985).

Preface to the First Edition

The organic chemist usually works with compounds which possess labile covalent bonds and are relatively involatile, thereby often rendering the gas-phase unsuitable as a reaction medium. Of the thousands of reactions known to occur in solution only few have been studied in the gas-phase, even though a description of reaction mechanisms is much simpler for the gas-phase. The frequent necessity of carrying out reactions in the presence of a more or less inert solvent results in two main obstacles: The reaction depends on a larger number of parameters than in the gas-phase. Consequently, the experimental results can often be only qualitatively interpreted because the state of aggregation in the liquid phase has so far been insufficiently studied. On the other hand, the fact that the interaction forces in solution are much stronger and more varied than in the gas-phase, permits to affect the properties and reactivities of the solute in manifold modes.

Thus, whenever a chemist wishes to carry out a chemical reaction he not only has to take into consideration the right reaction partners, the proper reaction vessels, and the appropriate reaction temperature. One of the most important features for the success of the planned reaction is the selection of a suitable solvent. Since solvent effects on chemical reactivity have been known for more than a century, most chemists are now familiar with the fact that solvents may have a strong influence on reaction rates and equilibria. Today, there are about three hundred common solvents available, nothing to say of the infinite number of solvent mixtures. Hence the chemist needs, in addition to his intuition, some general rules and guiding-principles for this often difficult choice.

The present book is based on an earlier paperback "Lösungsmitteleffekte in der organischen Chemie" [1], which, though following the same layout, has been completely rewritten, greatly expanded, and brought up to date. The book is directed both toward the industrial and academic chemist and particularly the advanced student of chemistry, who on the one hand needs objective criteria for the proper choice of solvent but on the other hand wishes to draw conclusions about reaction mechanisms from the observed solvent effects.

A knowledge of the physico-chemical principles of solvent effects is required for proper bench-work. Therefore, a description of the intermolecular interactions between dissolved molecules and solvent is presented first, followed by a classification of solvents derived therefrom. Then follows a detailed description of the influence of solvents on chemical equilibria, reaction rates, and spectral properties of solutes. Finally, empirical parameters of solvent polarity are given, and in an appendix guidelines to the everyday choice of solvents are given in a series of Tables and Figures.

The number of solvent systems and their associated solvent effects examined is so enormous that a complete description of all aspects would fill several volumes. For example, in Chemical Abstracts, volume 85 (1976), approximately eleven articles per week were quoted in which the words "Solvent effects on ..." appeared in the title. In the present book only a few important and relatively well-defined areas of general importance have been selected. The book has been written from the point of view of practical use for the organic chemist rather than from a completely theoretical one.

In the selection of the literature more recent reviews were taken into account mainly. Original papers were cited in particular from the didactic point of view rather than priority, importance or completeness. This book, therefore, does not only have the character of a monograph but also to some extent that of a textbook. In order to help the reader in his use of the literature cited, complete titles of the review articles quoted are given. The literature up until December 1977 has been considered together with a few papers from 1978. The use of symbols follows the recommendations of the Symbols Committee of the Royal Society, London, 1971 [2].

I am very grateful to Professor Karl Dimroth, Marburg, who first stimulated my interest in solvent effects in organic chemistry. I am indebted to Professors W. H. Pirkle, Urbana/Illinois, D. Seebach, Zürich/Switzerland, J. Shorter, Hull/England, and numerous other colleagues for helpful advice and information. Thanks are also due to the authors and publishers of copyrighted materials reproduced with their permission (cf. Figure and Table credits on page 495). For the careful translation and improvement of the English manuscript I thank Dr. Edeline Wentrup-Byrne, Marburg. Without the assistance and patience of my wife Maria, this book would not have been written.

Marburg (Lahn), Summer 1978 Christian Reichardt

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[1] C. Reichardt: *Lösungsmitteleffekte in der organischen Chemie*. 2nd edition. Verlag Chemie, Weinheim 1973;
Effets de solvant en chimie organique (translation of the first-mentioned title into French, by I. Tkatchenko), Flammarion, Paris 1971;
Rastvoriteli v organicheskoi khimii (translation of the first-mentioned title into Russian, by E. R. Zakhsa), Izdatel'stvo Khimiya, Leningrad 1973.

[2] *Quantities, Units, and Symbols*, issued by The Symbols Committee of the Royal Society, London, in 1971.

Contents

List of Abbreviations

Abbreviations and Recommended Values of Some Fundamental Constants and Numbers[a,b]

N_A	Avogadro constant	$6.0221 \cdot 10^{23}$ mol^{-1}
c_0	speed of light in vacuum	$2.9979 \cdot 10^{8}$ m $\cdot$ s^{-1}
ε_0	absolute permittivity of vacuum [$= 1/(\mu_0 \cdot c_0{}^2)$; μ_0 = permeability of vacuum]	$8.8542 \cdot 10^{-12}$ C^2 $\cdot$ J^{-1} $\cdot$ m^{-1}
e	elementary charge	$1.6022 \cdot 10^{-19}$ C
h	Planck constant	$6.6261 \cdot 10^{-34}$ J $\cdot$ s
R	gas constant	8.3145 J $\cdot$ K^{-1} $\cdot$ mol^{-1} (or 0.08206 L $\cdot$ atm $\cdot$ K^{-1} $\cdot$ mol^{-1})
k_B	Boltzmann constant ($= R/N_A$)	$1.3807 \cdot 10^{-23}$ J $\cdot$ K^{-1}
V_m	standard molar volume of an ideal gas (at $t = 0$ °C and $p = 100$ kPa)	22.711 L $\cdot$ mol^{-1}
T_0	zero of the Celsius scale	273.15 K
π	ratio of the circumference to the diameter of a circle	3.1416
e	exponential number and base of natural logarithms (ln)	2.7183
ln 10	natural logarithm of ten (ln x = ln 10 $\cdot$ lg x; lg = decadic logarithm)	2.303

Abbreviations and Symbols for Units[a,b]

bar	bar ($= 10^5$ Pa $= 10^5$ N $\cdot$ m^{-2})	pressure
cg/g	centigram/gram	weight percent
cL/L, cl/l	centilitre/litre	volume percent
cmol/mol	centimol/mol	mole percent
cm	centimetre (10^{-2} m)	length
cm^3	cubic centimetre (millilitre mL; 10^{-6} m^3)	volume
C	coulomb	electric charge

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[a] I. Mills, T. Cvitaš, K. Homann, N. Kallay, and K. Kuchitsu: *Quantities, Units and Symbols in Physical Chemistry*. 2nd ed., Blackwell Scientific Publications, London, 1993.

[b] G. H. Aylward and T. J. V. Tristan: *SI Chemical Data*. 4th ed., Wiley, Chichester, 1999; *Datensammlung Chemie in SI-Einheiten*. 3rd ed., Wiley-VCH, Weinheim/Germany, 1999.

°C	degrees centigrade (Celsius)	temperature
dm^3	cubic decimetre (litre L; 10^{-3} m^3)	volume
J	joule	energy
kJ	kilojoule (10^3 J)	energy
K	kelvin	temperature
L, l	litre (1 dm^3; 10^{-3} m^3)	volume
m	metre	length
min	minute	time
mol	mole	amount of substance
MPa	megapascal (10^6 Pa)	pressure
mT	millitesla (10^{-3} T)	magnetic flux density (magnetic field)
nm	nanometre (10^{-9} m)	length
Pa	pascal ($1\ \mathrm{N} \cdot \mathrm{m}^{-2} = 10^{-5}$ bar)	pressure
percent (%)	part per hundred (10^{-2})	dimensionless fraction
ppm	part per million (10^{-6})	dimensionless fraction
s	second	time

Abbreviations and Symbols for Properties[c)]

a_i	activity of solute i	
$a(^1\mathrm{H})$	ESR hyperfine coupling constant (coupling with ^{1}H)	mT ($= 10^{-3}$ T)
A_j	the solvent's anion-solvating tendency or 'acity' (Swain)	
AN	solvent acceptor number, based on ^{31}P NMR chemical shift of Et_3PO (Gutmann and Meyer)	
α	electric polarizability of a molecule, polarizability volume	$\mathrm{C}^2 \cdot \mathrm{m}^2 \cdot \mathrm{J}^{-1}$ or $4\pi\varepsilon_0 \cdot \mathrm{cm}^3$
α	empirical parameter of solvent hydrogen-bond donor acidity (Taft and Kamlet)	
B	empirical parameter of solvent Lewis basicity (Palm and Koppel)	
B_MeOD	IR based empirical parameter of solvent Lewis basicity (Palm and Koppel)	

[c)] P. Müller: *Glossary of Terms used in Physical Organic Chemistry – IUPAC Recommendations 1994*. Pure Appl. Chem. *66*, 1077 (1994).

B_{PhOH}	IR based empirical parameter of solvent Lewis basicity (Koppel and Paju; Makitra)	
B_{j}	the solvent's cation-solvating tendency or 'basity' (Swain)	
β	empirical parameter of solvent hydrogen-bond acceptor basicity (Taft and Kamlet)	
c	cohesive pressure (cohesive energy density) of a solvent	MPa (= 10^6 Pa)
$c_{\mathrm{i}}, c(\mathrm{i})$	molar concentration of solute i	$\mathrm{mol \cdot L^{-1}}$
$C_{\mathrm{A}}, C_{\mathrm{B}}$	Lewis acidity and Lewis basicity parameter (Drago)	
cmc	critical micelle concentration	$\mathrm{mol \cdot L^{-1}}$
D_{HA}	molar bond-dissociation energy of the bond between H and A	$\mathrm{kJ \cdot mol^{-1}}$
D_{π}	empirical parameter of solvent Lewis basicity, based on a 1,3-dipolar cycloaddition reaction (Nagai *et al.*)	
DN	solvent donor number (Gutmann) $[= -\Delta H(\mathrm{D{-}SbCl_5})]$	$\mathrm{kcal \cdot mol^{-1}}$
DN^{N}	normalized solvent donor number (Marcus)	
$\delta, \delta_{\mathrm{H}}$	Hildebrand's solubility parameter	$\mathrm{MPa^{1/2}}$
δ	chemical shift of NMR signals	ppm
δ	solvent polarizability correction term (Taft and Kamlet)	
E	energy, molar energy	$\mathrm{kJ \cdot mol^{-1}}$
E	electric field strength	$\mathrm{V \cdot m^{-1}}$
E	enol constant (K. H. Meyer)	
E	empirical parameter of solvent Lewis acidity (Palm and Koppel)	
$E_{\mathrm{A}}, E_{\mathrm{a}}$	Arrhenius activation energy	$\mathrm{kJ \cdot mol^{-1}}$
$E_{\mathrm{A}}, E_{\mathrm{B}}$	Lewis acidity and Lewis basicity parameter (Drago)	
EA	electron affinity	$\mathrm{kJ \cdot mol^{-1}}$
$E_{\mathrm{B}}^{\mathrm{N}}$	empirical solvent Lewis basicity parameter, based on the $n \rightarrow \pi^*$ absorption of an aminyloxide radical (Mukerjee; Wrona)	
E_{K}	empirical solvent polarity parameter, based on the $d \rightarrow \pi^*$ absorption of a molybdenum complex (Walther)	$\mathrm{kcal \cdot mol^{-1}}$

E^{*}_{MLCT}	empirical solvent polarity parameter, based on the $d \rightarrow \pi^{*}$ absorption of a tungsten complex (Lees)	
E_{T}	molar electronic *t*ransition *e*nergy, molar electronic excitation energy	$\mathrm{kJ \cdot mol^{-1}}$ or $\mathrm{kcal \cdot mol^{-1}}$
$E_{\mathrm{T}}(30)$	empirical solvent polarity parameter, based on the intramolecular CT absorption of a pyridinium-*N*-phenolate betaine dye (Dimroth and Reichardt)	$\mathrm{kcal \cdot mol^{-1}}$
$E_{\mathrm{T}}^{\mathrm{N}}$	normalized $E_{\mathrm{T}}(30)$ solvent polarity parameter (Reichardt)	
$E_{\mathrm{T}}^{\mathrm{SO}}$	empirical solvent polarity parameter, based on the $n \rightarrow \pi^{*}$ absorption of an *S*-oxide (Walter)	$\mathrm{kcal \cdot mol^{-1}}$
EPA	electron-pair acceptor	
EPD	electron-pair donor	
ε_{r}	relative permittivity ($=\varepsilon/\varepsilon_0$) ("dielectric constant")	
$\mathit{\Phi}$	empirical solvent polarity parameter, based on the $n \rightarrow \pi^{*}$ absorption of ketones (Dubois)	
G	IR based empirical solvent polarity parameter (Schleyer and Allerhand)	
ΔG°	standard molar Gibbs energy change	$\mathrm{kJ \cdot mol^{-1}}$
$\Delta G^{\neq}$	standard molar Gibbs energy of activation	$\mathrm{kJ \cdot mol^{-1}}$
$\Delta G^{\circ}_{\mathrm{solv}}$	standard molar Gibbs energy of solvation	$\mathrm{kJ \cdot mol^{-1}}$
$\Delta G^{\circ}_{\mathrm{hydr}}$	standard molar Gibbs energy of hydration	$\mathrm{kJ \cdot mol^{-1}}$
$\Delta G^{\circ}_{\mathrm{t}}(\mathrm{X, O \rightarrow S})$, $\Delta G^{\circ}_{\mathrm{t}}(\mathrm{X, W \rightarrow S})$	standard molar Gibbs energy of transfer of solute X from a reference solvent (O) or water (W) to another solvent (S)	$\mathrm{kJ \cdot mol^{-1}}$
γ_{i}	activity coefficient of solute i	
ΔH°	standard molar enthalpy change	$\mathrm{kJ \cdot mol^{-1}}$
$\Delta H^{\neq}$	standard molar enthalpy of activation	$\mathrm{kJ \cdot mol^{-1}}$
ΔH_{v}	molar enthalpy (heat) of vapourization	$\mathrm{kJ \cdot mol^{-1}}$
H_0	acidity function (Hammett)	
HBA	hydrogen-bond acceptor	

HBD	hydrogen-bond donor	
HOMO	highest occupied molecular orbital	
E_i, I, IP	ionization energy	$kJ \cdot mol^{-1}$
I	gas-chromatographic retention index (Kováts)	
J	NMR spin-spin coupling constant	Hz
k	rate constant for monomolecular ($n = 1$) and bimolecular ($n = 2$) reactions	$(L \cdot mol^{-1})^{n-1} \cdot s^{-1}$
k_0	rate constant in a reference solvent or in the gas phase for monomolecular ($n = 1$) and bimolecular reactions ($n = 2$)	$(L \cdot mol^{-1})^{n-1} \cdot s^{-1}$
k_0	in Hammett equations the rate constant of unsubstituted substrates	$(L \cdot mol^{-1})^{n-1} \cdot s^{-1}$ with $n = 1$ or 2
K, K_c	equilibrium constant (concentration basis; v = stoichiometric number)	$(mol \cdot L^{-1})^{\Sigma v}$
K_a, K_b	acid and base ionization constants	$(mol \cdot L^{-1})^{\Sigma v}$
K_{auto}	autoionization ion product, autoprotolysis constant	$mol^2 \cdot L^{-2}$
$K_{Assoc}, K_{Dissoc}, K_{ion}, K_T$	equilibrium constants of association, dissociation, ionization, resp. tautomerization reactions	$(mol \cdot L^{-1})^{\Sigma v}$
$K_{o/w}$	1-octanol/water partition constant (Hansch and Leo)	
KB	kauri-butanol number	
L	desmotropic constant (K. H. Meyer)	
LUMO	lowest unoccupied molecular orbital	
λ	wavelength	nm ($= 10^{-9}$ m)
m	mass of a particle	g
M_r	relative molecular mass of a substance ("molecular weight")	
M	miscibility number (Godfrey)	
MH	microscopic hydrophobicity parameter of substituents (Menger)	
μ	empirical solvent softness parameter (Marcus)	
μ	permanent electric dipole moment of a molecule	$C \cdot m$ (or D)
μ_{ind}	induced electric dipole moment of a molecule	$C \cdot m$ (or D)

μ_i°	standard chemical potential of solute i	$\mathrm{kJ \cdot mol^{-1}}$
μ_i^∞	standard chemical potential of solute i at infinite dilution	$\mathrm{kJ \cdot mol^{-1}}$
n, n_D	refractive index (at sodium D line) $(= c_0/c)$	
N	empirical parameter of solvent nucleophilicity (Winstein and Grunwald)	
N_+	nucleophilicity parameter for (nucleophile + solvent)-systems (Ritchie)	
ν	frequency	Hz, $\mathrm{s^{-1}}$
ν°	frequency in the gas phase or in an inert reference solvent	Hz, $\mathrm{s^{-1}}$
$\tilde{\nu}$	wavenumber $(= 1/\lambda)$	$\mathrm{cm^{-1}}$
Ω	empirical solvent polarity parameter, based on a Diels-Alder reaction (Berson)	
p	pressure	Pa $(= 1\mathrm{N \cdot m^{-2}})$, bar $(= 10^5$ Pa)
P	measure of solvent polarizability (Palm and Koppel)	
P	empirical solvent polarity parameter, based on ^{19}F NMR measurements (Taft)	
PA	proton affinity	$\mathrm{kJ \cdot mol^{-1}}$
Py	empirical solvent polarity parameter, based on the $\pi^* \rightarrow \pi$ emission of pyrene (Winnik)	
$P_\mathrm{o/w}$	1-octanol/water partition coefficient (Hansch and Leo)	
pH	$-\lg[\mathrm{H_3O^+}]$, $-\lg c(\mathrm{H_3O^+})$ (abbreviation of *p*otentia *h*ydrogenii or *p*uissance d'*h*ydrogène (Sörensen 1909)	
pK	$-\lg K$	
π	internal pressure of a solvent	MPa $(= 10^6$ Pa)
π^*	empirical solvent dipolarity/polarizability parameter, based on the $\pi \rightarrow \pi^*$ absorption of substituted aromatics (Taft and Kamlet)	

π^*_{azo}	empirical solvent dipolarity/polarizability parameter, based on the $\pi \to \pi^*$ absorption of azo merocyanine dyes (Buncel)	
π_{x}	hydrophobicity parameter of substituent X in H_5C_6-X (Hansch)	
r	radius of sphere representing an ion or a cavity	cm (= 10^{-2} m)
r	distance between centres of two ions or molecules	cm (= 10^{-2} m)
ρ	density (mass divided by volume)	$g \cdot cm^{-3}$
ρ, ρ_{A}	Hammett reaction resp. absorption constants	
S	generalized for solvent	
S	empirical solvent polarity parameter, based on the Z-values (Brownstein)	
$\mathscr{S}$	lg k_2 for the Menschutkin reaction of tri-*n*-propylamine with iodomethane (Drougard and Decroocq)	
ΔS°	standard molar entropy change	$J \cdot K^{-1} \cdot mol^{-1}$
$\Delta S^{\neq}$	standard molar entropy of activation	$J \cdot K^{-1} \cdot mol^{-1}$
S_{p}	solvophobic power of a solvent (Abraham)	
SA	empirical parameter of solvent hydrogen-bond donor acidity (Catalán)	
SB	empirical parameter of solvent hydrogen-bond acceptor basicity (Catalán)	
SPP	empirical parameter of solvent dipolarity/polarizability, based on the $\pi \to \pi^*$ absorption of substituted 7-nitrofluorenes (Catalán)	
σ	Hammett substituent constant	
σ	NMR screening constant	
t	Celsius temperature	°C
T	thermodynamic temperature	K
t_{mp}	melting point	°C
t_{bp}	boiling point	°C
U	internal energy	kJ
ΔU_{v}	molar energy of vapourization	$kJ \cdot mol^{-1}$

V_m, $V_{m,i}$	molar volume (of i)	$cm^3 \cdot mol^{-1}$
$\Delta V^{\neq}$	molar volume of activation	$cm^3 \cdot mol^{-1}$
$x_i, x(i)$	mole fraction of i ($x_i = n_i / \sum n$)	
X	empirical solvent polarity parameter, based on an S_E2 reaction (Gielen and Nasielski)	
χ_R, χ_B	empirical solvent polarity parameters, based on the $\pi \rightarrow \pi^*$ absorption of merocyanine dyes (Brooker)	$kcal \cdot mol^{-1}$
${}^{O}y_X^S$, ${}^{W}y_X^S$	solvent-transfer activity coefficient of a solute X from a reference solvent (O) or water (W) to another solvent (S)	
Y	empirical parameter of solvent ionizing power, based on *t*-butyl chloride solvolysis (Winstein and Grunwald)	
Y_{OTs}	empirical parameter of solvent ionizing power, based on 2-adamantyl tosylate solvolysis (Schleyer and Bentley)	
Y	measure of solvent polarization (Palm and Koppel)	
z_i	charge number of an ion i	positive for cations, negative for anions
Z	empirical solvent polarity parameter, based on the intermolecular CT absorption of a substituted pyridinium iodide (Kosower)	$kcal \cdot mol^{-1}$

> "*Agite, Auditores ornatissimi, transeamus alacres ad aliud negotii! quum enim sic satis excusserimus ea quatuor Instrumenta artis, et naturae, quae modo relinquimus, videamus quintum genus horum, quod ipsi Chemiae fere proprium censetur, cui certe Chemistae principem locum prae omnibus assignant, in quo se jactant, serioque triumphant, cui artis suae, prae aliis omnibus effectus mirificos adscribunt. Atque illud quidem Menstruum vocaverunt.*"*⁾
>
> Hermannus Boerhaave (1668–1738)
> *De menstruis dictis in chemia*, in:
> *Elementa Chemiae* (1733) [1, 2].

1 Introduction

The development of our knowledge of solutions reflects to some extent the development of chemistry itself [3]. Of all known substances, water was the first to be considered as a solvent. As far back as the time of the Greek philosophers there was speculation about the nature of solution and dissolution. The Greek alchemists considered all chemically active liquids under the name "Divine water". In this context the word "water" was used to designate everything liquid or dissolved.

The alchemist's search for a universal solvent, the so-called "Alkahest" or "Menstruum universale", as it was called by Paracelsus (1493–1541), indicates the importance given to solvents and the process of dissolution. Although the eager search of the chemists of the 15th to 18th centuries did not in fact lead to the discovery of any "Alkahest", the numerous experiments performed led to the uncovering of new solvents, new reactions, and new compounds**⁾. From these experiences arose the earliest chemical rule that "like dissolves like" *(similia similibus solvuntur)*. However, at that time, the words solution and dissolution comprised all operations leading to a liquid product and it was still a long way to the conceptual distinction between the physical dissolution of a salt or of sugar in water, and the chemical change of a substrate by dissolution, for example, of a metal in an acid. Thus, in the so-called chemiatry period (iatrochemistry period), it was believed that the nature of a substance was fundamentally lost upon dissolution. Van Helmont (1577–1644) was the first to strongly oppose this contention. He claimed that the dissolved substance had not disappeared, but was present in the solution, although in aqueous form, and could be recovered [4]. Nevertheless, the dissolution

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* "Well then, my dear listeners, let us proceed with fervor to another problem! Having sufficiently analyzed in this manner the four resources of science and nature, which we are about to leave (*i.e.* fire, water, air, and earth) we must consider a fifth element which can almost be considered the most essential part of chemistry itself, which chemists boastfully, no doubt with reason, prefer above all others, and because of which they triumphantly celebrate, and to which they attribute above all others the marvellous effects of their science. And this they call the solvent (menstruum)."

** Even if the once famous scholar J. B. Van Helmont (1577–1644) claimed to have prepared this "Alkahest" in a phial, together with the adherents of the alkahest theory he was ridiculed by his contemporaries who asked in which vessel he has stored this universal solvent.

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of a substance in a solvent remained a rather mysterious process. The famous Russian polymath Lomonosov (1711–1765) wrote in 1747: "Talking about the process of dissolution, it is generally said that all solvents penetrate into the pores of the body to be dissolved and gradually remove its particles. However, concerning the question of what forces cause this process of removal, there does not exist any somehow reasonable explanation, unless one arbitrarily attributes to the solvents sharp wedges, hooks or, who knows, any other kind of tools" [27].

The further development of modern solution theory is connected with three persons, namely the French researcher Raoult (1830–1901) [28], the Dutch physical chemist van't Hoff (1852–1911) [5], and the Swedish scientist Arrhenius (1859–1927) [6]. Raoult systematically studied the effects of dissolved nonionic substances on the freezing and boiling point of liquids and noticed in 1886 that changing the solute/solvent ratio produces precise proportional changes in the physical properties of solutions. The observation that the vapour pressure of solvent above a solution is proportional to the mole fraction of solvent in the solution is today known as Raoult's law [28].

The difficulty in explaining the effects of inorganic solutes on the physical properties of solutions led in 1884 to Arrhenius' theory of incomplete and complete dissociation of ionic solutes (electrolytes, ionophores) into cations and anions in solution, which was only very reluctantly accepted by his contemporaries. Arrhenius derived his dissociation theory from comparison of the results obtained by measurements of electroconductivity and osmotic pressure of dilute electrolyte solutions [6].

The application of laws holding for gases to solutions by replacing pressure by osmotic pressure was extensively studied by van't Hoff, who made osmotic pressure measurements another important physicochemical method in studies of solutions [5].

The integration of these three basic developments established the foundations of modern solution theory and the first Nobel prizes in chemistry were awarded to van't Hoff (in 1901) and Arrhenius (in 1903) for their work on osmotic pressure and electrolytic dissociation, respectively.

The further development of solution chemistry is connected with the pioneering work of Ostwald (1853–1932), Nernst (1864–1941), Lewis (1875–1946), Debye (1884–1966), E. Hückel (1896–1980), and Bjerrum (1879–1958). More detailed reviews on the development of modern solution chemistry can be found in references [29, 30].

The influence of solvents on the rates of chemical reactions [7, 8] was first noted by Berthelot and Péan de Saint-Gilles in 1862 in connection with their studies on the esterification of acetic acid with ethanol: "... l'éthérification est entravée et ralentie par l'emploi des dissolvants neutres étrangers à la réaction" [9]*⁾. After thorough studies on the reaction of trialkylamines with haloalkanes, Menschutkin in 1890 concluded that a reaction cannot be separated from the medium in which it is performed [10]. In a letter to Prof. Louis Henry he wrote in 1890: "Or, l'expérience montre que ces dissolvants exercent sur la vitesse de combinaison une influence considérable. Si nous représentons par 1 la constante de vitesse de la réaction précitée dans l'hexane C_6H_{14}, cette constante pour la même combinaison dans CH_3—CO—C_6H_5, toutes choses égales d'ailleurs sera 847.7. La différence est énorme, mais, dans ce cas, elle n'atteint pas encore le maxi-

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* "... the esterification is disturbed and decelerated on addition of neutral solvents not belonging to the reaction" [9].

mum.... Vous voyez que les dissolvants, soi-disant indifférents ne sont pas inertes; ils modifient profondément l'acte de la combinaison chimique. Cet énoncé est riche en conséquences pour la théorie chimique des dissolutions" [26]*⁾. Menschutkin also discovered that, in reactions between liquids, one of the reaction partners may constitute an unfavourable solvent. Thus, in the preparation of acetanilide, it is not without importance whether aniline is added to an excess of acetic acid, or *vice versa*, since aniline in this case is an unfavorable reaction medium. Menschutkin related the influence of solvents primarily to their chemical, not their physical properties.

The influence of solvents on chemical equilibria was discovered in 1896, simultaneously with the discovery of keto-enol tautomerism**⁾ in 1,3-dicarbonyl compounds (Claisen [14]: acetyldibenzoylmethane and tribenzoylmethane; Wislicenus [15]: methyl and ethyl formylphenylacetate; Knorr [16]: ethyl dibenzoylsuccinate and ethyl diacetylsuccinate) and the nitro-isonitro tautomerism of primary and secondary nitro compounds (Hantzsch [17]: phenylnitromethane). Thus, Claisen wrote: "Es gibt Verbindungen, welche sowohl in der Form $\text{—C(OH)=}\overset{|}{\text{C}}\text{—CO—}$ wie in der Form $\text{—CO—}\overset{|}{\text{CH}}\text{—CO—}$ zu bestehen vermögen; von der Natur der angelagerten Reste, von der Temperatur, bei den gelösten Substanzen auch von der Art des Lösungsmittels hängt es ab, welche von den beiden Formen die beständigere ist" [14]***⁾. The study of the keto-enol equilibrium of ethyl formylphenylacetate in eight solvents led Wislicenus to the conclusion that the keto form predominates in alcoholic solution, the enol form in chloroform or benzene. He stated that the final ratio in which the two tautomeric forms coexist must depend on the nature of the solvent and on its dissociating power, whereby he suggested that the dielectric constants were a possible measure of this "power". Stobbe was the first to review these results [18]. He divided the solvents into two groups according to their ability to isomerize tautomeric compounds. His classification reflects, to some extent, the modern division into protic and aprotic solvents. The effect of solvent on constitutional and tautomeric isomerization equilibria was later studied in detail

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* "Now, experience shows that solvents exert considerable influence on reaction rates. If we represent the rate constant of the reaction to be studied in hexane C_6H_{14} by 1, then, all else being equal, this constant for the same reaction in $CH_3\text{—CO—}C_6H_5$ will be 847.7. The increase is enormous, but in this case it has not even reached its maximum.... So you see that solvents, in spite of appearing at first to be indifferent, are by no means inert; they can greatly influence the course of chemical reactions. This statement is full of consequences for the chemical theory of dissolutions" [26].

** The first observation of a tautomeric equilibrium was made in 1884 by Zincke at Marburg [11]. He observed that, surprisingly, the reaction of 1,4-naphthoquinone with phenylhydrazine gives the same product as that obtained from the coupling reaction of 1-naphthol with benzenediazonium salts. This phenomenon, that the substrate can react either as phenylhydrazone or as a hydroxyazo compound, depending on the reaction circumstances, was called *Ortsisomerie* by Zincke [11]. Later on, the name *tautomerism*, with a different meaning however from that accepted today, was introduced by Laar [12]. For a description of the development of the concept of tautomerism, see Ingold [13].

*** "There are compounds capable of existence in the form $\text{—C(OH)=}\overset{|}{\text{C}}\text{—CO—}$ as well as in the form $\text{—CO—}\overset{|}{\text{CH}}\text{—CO—}$; it depends on the nature of the substituents, the temperature, and for dissolved compounds, also on the nature of the solvent, which of the two forms will be the more stable" [14].

by Dimroth [19] (using triazole derivatives, *e.g.* 5-amino-4-methoxycarbonyl-1-phenyl-1,2,3-triazole) and Meyer [20] (using ethyl acetoacetate).

It has long been known that UV/Vis absorption spectra may be influenced by the phase (gas or liquid) and that the solvent can bring about a change in the position, intensity, and shape of the absorption band*⁾. Hantzsch later termed this phenomenon *solvatochromism***⁾ [22]. The search for a relationship between solvent effect and solvent property led Kundt in 1878 to propose the rule, later named after him, that increasing dispersion (*i.e.* increasing index of refraction) is related to a shift of the absorption maximum towards longer wavelength [23]. This he established on the basis of UV/Vis absorption spectra of six dyestuffs, namely chlorophyll, fuchsin, aniline green, cyanine, quinizarin, and egg yolk in twelve different solvents. The – albeit limited – validity of Kundt's rule, *e.g.* found in the cases of 4-hydroxyazobenzene [24] and acetone [25], led to the realization that the effect of solvent on dissolved molecules is a result of electrical fields. These fields in turn originate from the dipolar properties of the molecules in question [25]. The similarities in the relationships between solvent effects on reaction rate, equilibrium position, and absorption spectra has been related to the general solvating ability of the solvent in a fundamental paper by Scheibe *et al.* [25].

More recently, research on solvents and solutions has again become a topic of interest because many of the solvents commonly used in laboratories and in the chemical industry are considered as unsafe for reasons of environmental protection. On the list of damaging chemicals, solvents rank highly because they are often used in huge amounts and because they are volatile liquids that are difficult to contain. Therefore, the introduction of cleaner technologies has become a major concern throughout both academia and industry [31–34]. This includes the development of environmentally benign new solvents, sometimes called *neoteric solvents* (neoteric = recent, new, modern), constituting a class of novel solvents with desirable, less hazardous, new properties [35, 36]. The term *neoteric solvents* covers supercritical fluids, ionic liquids, and also perfluorohydrocarbons (as used in fluorous biphasic systems). Table A-14 in Chapter A.10 (Appendix) collects some recommendations for the substitution of hazardous solvents, together with the relevant literature references.

For the development of a sustainable chemistry based on clean technologies, the best solvent would be no solvent at all. For this reason, considerable efforts have recently been made to design reactions that proceed under solvent-free conditions, using modern techniques such as reactions on solid mineral supports (alumina, silica, clays), solid-state reactions without any solvent, support, or catalyst between neat reactants, solid-liquid phase-transfer catalysed and microwave-activated reactions, as well as gas-phase reactions [37–42]. However, not all organic reactions can be carried out in the absence of a solvent; some organic reactions even proceed explosively in the solid state! Therefore, solvents will still be useful in mediating and moderating chemical reactions and this book on solvent effects will certainly not become superfluous in the foreseeable future.

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* A survey of older works of solvent effects on UV/Vis absorption spectra has been given by Sheppard [21].

** It should be noted that the now generally accepted meaning of the term *solvatochromism* differs from that introduced by Hantzsch (*cf.* Section 6.2).

2 Solute-Solvent Interactions

2.1 Solutions

In a limited sense *solutions* are homogeneous liquid phases consisting of more than one substance in variable ratios, when for convenience one of the substances, which is called the *solvent* and may itself be a mixture, is treated differently from the other substances, which are called *solutes* [1]. Normally, the component which is in excess is called the solvent and the minor component(s) is the solute. When the sum of the mole fractions of the solutes is small compared to unity, the solution is called a *dilute solution**⁾. A solution of solute substances in a solvent is treated as an *ideal dilute solution* when the solute activity coefficients γ are close to unity ($\gamma = 1$) [1, 171]. Solute/solvent mixtures $A + B$ that obey Raoult's law over the entire composition range from pure A to pure B are called *ideal solutions*. According to Raoult, the ratio of the partial pressure of component $A(p_A)$ to its vapour pressure as a pure liquid (p_A^*) is equal to the mole fraction of $A(x_A)$ in the liquid mixture, *i.e.* $x_A = p_A/p_A^*$. Many mixtures obey Raoult's law very well, particularly when the components have a similar molecular structure (*e.g.* benzene and toluene).

A solvent should not be considered a macroscopic continuum characterized only by physical constants such as density, dielectric constant, index of refraction *etc.*, but as a discontinuum which consists of individual, mutually interacting solvent molecules. According to the extent of these interactions, there are solvents with a pronounced internal structure (*e.g.* water) and others in which the interaction between the solvent molecules is small (*e.g.* hydrocarbons). The interactions between species in solvents (and in solutions) are at once too strong to be treated by the laws of the kinetic theory of gases, yet too weak to be treated by the laws of solid-state physics. Thus, the solvent is neither an indifferent medium in which the dissolved material diffuses in order to distribute itself evenly and randomly, nor does it possess an ordered structure resembling a crystal lattice. Nevertheless, the long-distance ordering in a crystal corresponds somewhat to the local ordering in a liquid. Thus, neither of the two possible models – the gas and crystal models – can be applied to solutions without limitation. There is such a wide gulf between the two models in terms of conceivable and experimentally established variants, that it is too difficult to develop a generally valid model for liquids. Due to the complexity of the interactions, the structure of liquids – in contrast to that of gases and solids – is the least-known of all aggregation states. Therefore, the experimental and theoretical examination of the structure of liquids is among the most difficult tasks of physical chemistry [2–7, 172–174].

Any theory of the liquid state has to explain – among others – the following facts: Except for water, the molar volume of a liquid is roughly 10% greater than that of the corresponding solid. According to X-ray diffraction studies, a short-range order of solvent molecules persists in the liquid state and the nearest neighbour distances are almost the same as those in the solid. The solvent molecules are not moving freely, as in the

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* The superscript ∞ attached to the symbol for a property of a solution denotes the property of an *infinitely dilute solution*.

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gaseous state, but instead move in the potential field of their neighbours. The potential energy of a liquid is higher than that of its solid by about 10%. Therefore, the heat of fusion is roughly 10% of the heat of sublimation. Each solvent molecule has an environment very much like that of a solid, but some of the nearest neighbours are replaced by holes. Roughly one neighbour molecule in ten is missing.

Even for the most important solvent – water – the investigation of its inner fine structure is still the subject of current research [8–15, 15a]*⁾. Numerous different models, *e.g.* the "flickering cluster model" of Franck and Wen [16], were developed to describe the structure of water. However, all these models prove themselves untenable for a complete description of the physico-chemical properties of water and an interpretation of its anomalies [304]. Fig. 2-1 should make clear the complexity of the inner structure of water.

Liquid water consists both of bound ordered regions of a regular lattice, and regions in which the water molecules are hydrogen-bonded in a random array; it is permeated by monomeric water and interspersed with random holes, lattice vacancies, and cages. There are chains and small polymers as well as bound, free, and trapped water molecules [9, 176]. The currently accepted view of the structure of liquid water treats it as a dynamic three-dimensional hydrogen-bonded network, without a significant number of non-bonded water molecules, that retains several of the structural characteristics of ice (*i.e.* tetrahedral molecular packing with each water molecule hydrogen-bonded to four nearest neighbours), although the strict tetrahedrality is lost [176]. Its dynamic behaviour resembles that of most other liquids, with short rotational and translational correlation times of the order of 0.1 to 10 ps, indicating high hydrogen-bond exchange rates [176, 305].

In principle, other hydrogen-bonded solvents should possess similar complicated structures [306]. However, whereas water has been thoroughly studied [17, 176, 307], the inner structures of other solvents are still less well known [172, 177–179]. By way of example, the intermolecular structure of acetone is determined mainly by steric interactions between the methyl groups and, unexpectedly, only to a small extent by dipole/dipole forces [308], whereas the inner structure of dimethyl sulfoxide is dictated by strong dipole/dipole interactions [309].

From the idea that the solvent only provides an indifferent reaction medium, comes the *Ruggli-Ziegler dilution principle*, long known to the organic chemist. According to this principle, in the case of cyclization reactions, the desired intramolecular reaction will be favoured over the undesired intermolecular reaction by high dilution with an inert solvent [18, 310].

The assumption of forces of interaction between solvent and solute led, on the other hand, to the century-old principle that "like dissolves like" *(similia similibus solvuntur)*, where the word "like" should not be too narrowly interpreted. In many cases, the presence of similar functional groups in the molecules suffices. When a chemical

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* The amusing story of "polywater," which excited the scientific community for a few years during the late 1960's and early 1970's, has been reviewed by Franks [175]. It turned out that polywater was not a new and more stable form of pure water, but merely dirty water. The strange properties of polywater were due to high concentrations of siliceous material dissolved from quartz capillaries in which it was produced.

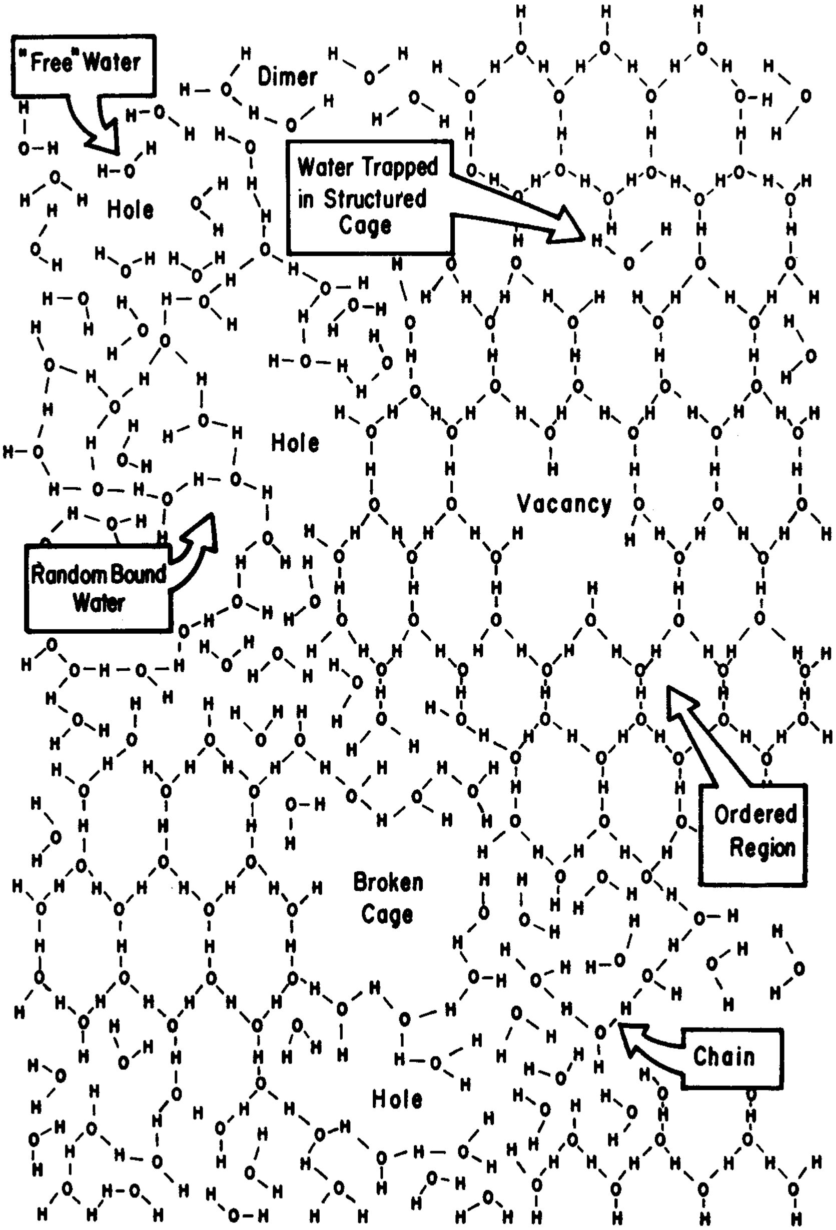

Fig. 2-1. Two-dimensional schematic diagram of the three-dimensional structure of liquid water [9].

similarity is present, the solution of the two components will usually have a structure similar to that of the pure materials (*e.g.* alcohol-water mixtures [19]). This rule of thumb has only limited validity, however, since there are many examples of solutions of chemically dissimilar compounds. For example, methanol and benzene, water and *N*,*N*-dimethylformamide, aniline and diethyl ether, and polystyrene and chloroform, are all completely miscible at room temperature. On the other hand, insolubility can occur in spite of similarity of the two partners. Thus, polyvinyl alcohol does not dissolve in ethanol, acetyl cellulose is insoluble in ethyl acetate, and polyacrylonitrile is insoluble in acrylonitrile [20]. Between these two extremes there is a whole range of possibilities where the two materials dissolve each other to a limited extent. The system water/diethyl ether is such an example. Pure diethyl ether dissolves water to the extent of 15 mg/g at 25 °C, whereas water dissolves diethyl ether to the extent of 60 mg/g. When one of the two solvents is in large excess a homogeneous solution is obtained. Two phases occur when the ratio is beyond the limits of solubility. A more recent example of a reaffirmation of the old "like dissolves like" rule is the differential solubility of fullerene (C_{60}), consisting of a three-dimensional delocalized 60π-electron system, in solvents such as methanol ($s = 0.01$ mg/mL) and 1-chloronaphthalene ($s = 50$ mg/mL) [311].

However, rather than the "like dissolves like" rule, it is the intermolecular interaction between solvent and solute molecules that determines the mutual solubility. A compound *A* dissolves in a solvent *B* only when the intermolecular forces of attraction K_{AA} and K_{BB} for the pure compounds can be overcome by the forces K_{AB} in solution [21].

The sum of the interaction forces between the molecules of solvent and solute can be related to the so-called *polarity**⁾ of *A* and *B*. Denoting compounds with large interactions $A \cdots A$ or $B \cdots B$, respectively, as polar, and those with small interactions as nonpolar, four cases allowing a qualitative prediction of solubility can be distinguished (Table 2-1).

An experimental verification of these simple considerations is given by the solubility data in Table 2-2.

Table 2-1. Solubility and polarity [22].

Solute A	Solvent B	Interaction			Solubility of A in B
		A···A	B···B	A···B	
Nonpolar	nonpolar	weak	weak	weak	can be high a)
Nonpolar	polar	weak	strong	weak	probably low b)
Polar	nonpolar	strong	weak	weak	probably low c)
Polar	polar	strong	strong	strong	can be high a)

a) Not much change for solute or solvent.
b) Difficult to break up B···B.
c) Difficult to break up A···A.

---

* For a more detailed definition of solvent polarity, see Sections 3.2 and 7.1.

Table 2-2. Solubilities of methane, ethane, chloromethane, and dimethyl ether in tetrachloro-methane (nonpolar solvent) and acetone (polar solvent) [22].

Solute	Solute polarity	Solubility/(mol · m^{-3}) at 25 °C	
		in CCl_4	in CH_3COCH_3
CH_4	nonpolar	29	25
CH_3CH_3	nonpolar	220	130
CH_3Cl	polar	1700	2800
CH_3OCH_3	polar	1900	2200

The solubilities of ethane and methane are higher in nonpolar tetrachloromethane, whereas the opposite is true for chloromethane and dimethyl ether. A survey of the reciprocal miscibility of some representative examples of organic solvents is given in Fig. 2-2.

Solubility is commonly defined as the concentration of dissolved solute in a solvent in equilibrium with undissolved solute at a specified temperature and pressure. For a deeper and more detailed understanding of the diverse rules determining the solubility of organic compounds in various solvents, see references [312–316].

The *solubility parameter* δ of Hildebrand [4, 24], as defined in Eq. (2-1), can often be used in estimating the solubility of non-electrolytes in organic solvents.

$$\delta = \left(\frac{\Delta U_{\mathrm{v}}}{V_{\mathrm{m}}}\right)^{1/2} = \left(\frac{\Delta H_{\mathrm{v}} - R \cdot T}{V_{\mathrm{m}}}\right)^{1/2} \tag{2-1}$$

In this equation, V_{m} is the molar volume of the solvent, and ΔU_{v} and ΔH_{v} are the molar energy and the molar enthalpy (heat) of vapourization to a gas of zero pressure,

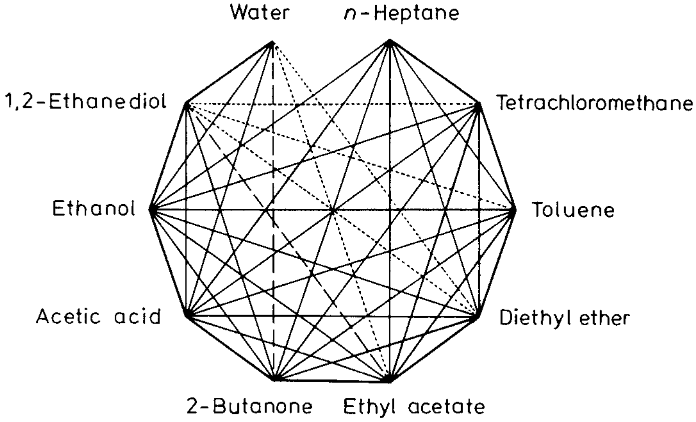

Fig. 2-2. Miscibility of organic solvents [23]. ——— miscible in all proportions; – – – – limited miscibility; .... little miscibility; without line: immiscible.

respectively. δ is a solvent property which measures the work necessary to separate the solvent molecules (*i.e.* disruption and reorganization of solvent/solvent interactions) to create a suitably sized cavity, large enough to accommodate the solute. Accordingly, highly ordered self-associated solvents exhibit relatively large δ values ($\delta = 0$ for the gas phase). As a rule, it has been found that a good solvent for a certain non-electrolyte has a δ value close to that of the solute [20, 24, 25]; *cf.* Table 3-3 in Section 3.2 for a collection of δ values. Often a mixture of two solvents, one having a δ value higher and the other having a δ value lower than that of the solute is a better solvent than each of the two solvents separately [24]; *cf.* also Section 3.2.

A nice example demonstrating mutual insolubility due to different δ values has been described by Hildebrand [180], and was later improved [181]. A system of eight non-miscible liquid layers was constructed. The eight layers in order of increasing densities are paraffin oil, silicon oil, water, aniline, perfluoro(dimethylcyclohexane), white phosphorus, gallium, and mercury. This system is stable indefinitely at 45 °C; this temperature is required to melt the gallium and phosphorus [181]. A simplified, less harmful version with five colourless liquid phases consists of mineral (paraffin) oil, methyl silicon oil, water, benzyl alcohol, and perfluoro(*N*-ethylpiperidine) (or another perfluoro-organic liquid), in increasing order of density [317]. Addition of an organic-soluble dye can colour some of the five layers.

2.2 Intermolecular Forces [26, 27, 182–184]

Intermolecular forces are those which can occur between closed-shell molecules [26, 27]. These are also called van der Waals forces, since van der Waals recognized them as the reason for the non-ideal behaviour of real gases. Intermolecular forces are usually classified into two distinct categories. The first category comprises the so-called directional, induction, and dispersion forces, which are non-specific and cannot be completely saturated (just as Coulomb forces between ions cannot). The second group consists of hydrogen-bonding forces, and charge-transfer or electron-pair donor–acceptor forces. The latter group are specific, directional forces, which can be saturated and lead to stoichiometric molecular compounds. For the sake of completeness, in the following the Coulomb forces between ions and electrically neutral molecules (with permanent dipole moments) will be considered first, even though they do not belong to the intermolecular forces in the narrower sense.

2.2.1 Ion-Dipole Forces [28, 185]

Electrically neutral molecules with an unsymmetrical charge distribution possess a permanent dipole moment μ. If the magnitude of the two equal and opposite charges of this molecular dipole is denoted by q, and the distance of separation l, the dipole moment is given by $\mu = q \cdot l$. When placed in the electric field resulting from an ion, the dipole will orient itself so that the attractive end (the end with charge opposite to that of the ion) will be directed toward the ion, and the other repulsive end directed away. The potential energy of an ion-dipole interaction is given by

$$U_{\text{ion-dipole}} = -\frac{1}{4\pi \cdot \varepsilon_0} \cdot \frac{z \cdot e \cdot \mu \cdot \cos\theta}{r^2} \qquad (2\text{-}2)^{*)}$$

where ε_0 is the permittivity of a vacuum, $z \cdot e$ the charge on the ion, r the distance from the ion to the center of the dipole, and θ the dipole angle relative to the line r joining the ion and the center of the dipole. Cos $\theta = 1$ for $\theta = 0°$, *i.e.* in this case the dipole is positioned next to the ion in such a way that the ion and the separated charges of the dipole are linearly arranged ((+ −) $\oplus$ or (− +) $\ominus$). Equation (2-2) gives the free energy for the interaction of an ionic charge $z \cdot e$ and a so-called 'point-dipole' (for which $l = 0$) in vacuum. For typical interatomic spacings ($r \approx$ 300–400 pm), the ion-dipole interaction is much stronger than the thermal energy $k \cdot T$ at 300 K. For the monovalent sodium cation ($z = +1$, radius = 95 pm) near a water molecule (radius $\approx$ 140 pm; $\mu = 5.9 \cdot 10^{-30}$ Cm), the maximum interaction energy calculated by Eq. (2-2) amounts to $U = 39k \cdot T$ or 96 kJ $\cdot$ mol^{-1} at 300 K [26b].

Only molecules possessing a permanent dipole moment should be called *dipolar molecules*. Apart from a few hydrocarbons (*n*-hexane, cyclohexane, and benzene) and some symmetrical compounds (carbon disulfide, tetrachloromethane, and tetrachloroethene) all common organic solvents possess a permanent dipole moment of between 0 and $18 \cdot 10^{-30}$ Cm (*i.e.* Coulombmeter). Among the solvents listed in the Appendix, Table A-1, hexamethylphosphoric triamide is the one with the highest dipole moment ($\mu = 18.48 \cdot 10^{-30}$ Cm), followed by propylene carbonate ($\mu = 16.7 \cdot 10^{-30}$ Cm), and sulfolane ($\mu = 16.05 \cdot 10^{-30}$ Cm). The largest dipole moments amongst fluids are exhibited by zwitterionic compounds such as the sydnones (*i.e.* 3-alkyl-1,2,3-oxadiazolium-5-olates). For example, 4-ethyl-3-(1-propyl)sydnone, a high-boiling liquid ($t_{\text{bp}} = 155$ °C/3 Torr) with a large relative permittivity ($\varepsilon_r = 64.6$ at 25 °C), has a dipole moment of $\mu = 35.7 \cdot 10^{-30}$ Cm (=10.7 D) [318]. The peculiar physical properties of such room temperature liquid sydnones make them to good nonaqueous dipolar solvents for many ionophores (electrolytes).

Ion-dipole forces are important for solutions of ionic compounds in dipolar solvents, where solvated species such as $\text{Na(OH}_2)_m^{\oplus}$ and $\text{Cl(H}_2\text{O)}_n^{\ominus}$ (for solutions of NaCl in H_2O) exist. In the case of some metal ions, these solvated species can be sufficiently stable to be considered as discrete species, such as $[\text{Co(NH}_3)_6]^{3\oplus}$ or $\text{Ag(CH}_3\text{CN)}_{2...4}^{\oplus}$.

For a comprehensive review on ion/solvent interactions, see reference [241].

2.2.2 Dipole-Dipole Forces [29]

Directional forces depend on the electrostatic interaction between molecules possessing a permanent dipole moment μ due to their unsymmetrical charge distribution. When two dipolar molecules are optimally oriented with respect to one another at a distance r as shown in Fig. 2-3a, then the force of attraction is proportional to $1/r^3$. An alternative arrangement is the anti-parallel arrangement of the two dipoles as shown in Fig. 2-3b.

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[*] It should be noted that Eqs. (2-2) to (2-6) are valid only for gases; an exact application to solutions is not possible. Furthermore, Eqs. (2-2) to (2-6) are restricted to cases with $r \gg l$.

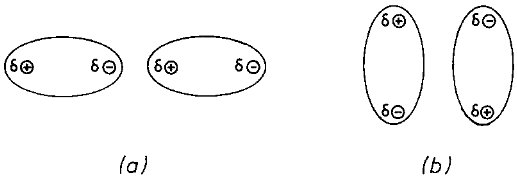

Fig. 2-3. (a) "Head-to-tail" arrangement of two dipole molecules; (b) Antiparallel arrangement of two dipole molecules.

Unless the dipole molecules are very voluminous, the second arrangement is the more stable one. The two situations exist only when the attractive energy is larger than the thermal energies. Therefore, the thermal energy will normally prevent the dipoles from optimal orientation. If all possible orientations were equally probable, that is, the dipoles correspond to freely rotating molecules, then attraction and repulsion would compensate each other. The fact that dipole orientations leading to attraction are statistically favored leads to a net attraction, which is strongly temperature dependent, according to Eq. (2-3) (k_B = Boltzmann constant; T = absolute temperature) [29].

$$U_{\text{dipole-dipole}} = -\frac{1}{(4\pi \cdot \varepsilon_0)^2} \cdot \frac{2\mu_1^2 \cdot \mu_2^2}{3k_B \cdot T \cdot r^6} \tag{2-3}$$

As the temperature increases, the angle-averaged dipole/dipole interaction energy becomes less negative until at very high temperatures all dipole orientations are equally populated and the potential energy is zero. This Boltzmann-averaged dipole/dipole interaction is usually referred to as the *orientation* or *Keesom interaction* [29]. According to Eq. (2-3), for pairs of dipolar molecules with $\mu = 3.3 \cdot 10^{-30}$ Cm (=1 D), at a separation of 500 pm, the average interaction energy is about -0.07 kJ · mol^{-1} at 25 °C. This is clearly smaller than the average molar kinetic energy of $3/2\ k \cdot T = 3.7$ kJ · mol^{-1} at the same temperature [26d].

Among other interaction forces, these dipole-dipole interactions are mainly responsible for the association of dipolar organic solvents such as dimethyl sulfoxide [30] or *N*,*N*-dimethylformamide [31].

It should be mentioned that dipoles represent only one possibility for the charge arrays in electric multipoles (*n*-poles). *n-Poles* with an array of point charges with an *n-pole moment* (but no lower moment) are *n-polar*. Thus, a monopole ($n = 1$) is a point charge and a monopole moment represents an overall charge (*e.g.* of an ion Na^+ or Cl^-). A dipole ($n = 2$; *e.g.* H_2O, H_3C—CO—CH_3) is an array of partial charges with no monopole moment (*i.e.* no charge). A quadrupolar molecule ($n = 4$; *e.g.* CO_2, C_6H_6) has neither a net charge nor a dipole moment, and an octupolar molecule ($n = 8$; *e.g.* CH_4, CCl_4) has neither charge nor a dipole or quadrupole moment. In addition to dipole/dipole interactions, in solution there can also exist such higher intermolecular multipole/multipole interactions. Therefore, to some degree, octupolar tetrachloromethane is also a kind of polar solvent. However, the intermolecular interaction energy rapidly falls off at higher orders of the multipole [26d]. The anomalous behaviour of the chair-configured, non-dipolar solvent 1,4-dioxane, which often behaves like a polar solvent even though its relative permittivity is low ($\varepsilon_r = 2.2$), is caused by its large nonideal quadrupolar charge distribution [411].

2.2.3 Dipole-Induced Dipole Forces [32]

The electric dipole of a molecule possessing a permanent dipole moment μ can induce a dipole moment in a neighbouring molecule. This induced moment always lies in the direction of the inducing dipole. Thus, attraction always exists between the two partners, which is independent of temperature. The induced dipole moment*⁾ will be bigger the larger the polarizability α of the apolar molecule experiencing the induction of the permanent dipole. The net dipole/induced dipole energy of interaction for two different molecules, each possessing a permanent dipole moment μ_1 and μ_2 and polarizabilities α_1 and α_2, often referred to as the *induction* or *Debye interaction* [32], is given by Eq. (2-4).

$$U_{\text{dipole-induced dipole}} = -\frac{1}{(4\pi \cdot \varepsilon_0)^2} \cdot \frac{\alpha_1 \cdot \mu_2^2 + \alpha_2 \cdot \mu_1^2}{r^6} \tag{2-4}$$

For a dipolar molecule of $\mu = 3.3 \cdot 10^{-30}$ Cm (1 D; *e.g.* H—Cl) separated from a molecule of polarization volume $\alpha = 10 \cdot 10^{-30}$ m^3 (*e.g.* C_6H_6) by a distance of 300 pm, the temperature-independent interaction energy is about −0.8 kJ/mol [26d].

Similarly, a charged particle such as an ion introduced into the neighbourhood of an uncharged, apolar molecule will distort the electron cloud of this molecule in the same way. The polarization of the neutral molecule will depend upon its inherent polarizability α, and on the polarizing field afforded by the ion with charge $z \cdot e$. The energy of such an interaction is given by Eq. (2-5).

$$U_{\text{ion-induced dipole}} = -\frac{1}{(4\pi \cdot \varepsilon_0)^2} \cdot \frac{z^2 \cdot e^2 \cdot \alpha}{2 \cdot r^4} \tag{2-5}$$

The importance of both of these interactions is limited to situations such as solutions of dipolar or ionic compounds in nonpolar solvents.

2.2.4 Instantaneous Dipole-Induced Dipole Forces [33, 34, 186]

Even in atoms and molecules possessing no permanent dipole moment, the continuous electronic movement results, at any instant, in a small dipole moment μ, which can fluctuatingly polarize the electron system of the neighbouring atoms or molecules. This coupling causes the electronic movements to be synchronized in such a way that a mutual attraction results. The energy of such so-called *dispersion* or *London* [33] *inter-*

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* The induced dipole moment is defined as $\mu_{\text{ind}} = 4\pi \cdot \varepsilon_0 \cdot \alpha \cdot E$ (ε_0 permittivity of vacuum; α electric polarizability of the molecule; E electric field strength).

actions can be expressed as

$$U_{\text{dispersion}} = -\frac{1}{(4\pi \cdot \varepsilon_0)^2} \cdot \frac{3\alpha_1 \cdot \alpha_2}{2r^6} \cdot \left(\frac{I_1 \cdot I_2}{I_1 + I_2}\right) \tag{2-6a}$$

where α_1 and α_2 are the polarizabilities and I_1 and I_2 are the ionization potentials of the two different interacting species [33]. When applied to two molecules of the same substance, Eq. (2-6a) reduces to Eq. (2-6b).

$$U_{\text{dispersion}} = -\frac{1}{(4\pi \cdot \varepsilon_0)^2} \cdot \frac{3\alpha^2 \cdot I}{4r^6} \tag{2-6b}$$

Dispersion forces are extremely short-range in action (depending on $1/r^6$!).

Dispersion forces are universal for all atoms and molecules; they alone are responsible for the aggregation of molecules which possess neither free charges nor electric dipole moments. Due to the greater polarizability of π-electrons, especially strong dispersion forces exist between molecules with conjugated π-electron systems (*e.g.* aromatic hydrocarbons). For many other dipole molecules with high polarizability as well, the major part of the cohesion is due to dispersion forces. For example, the calculated cohesion energy of liquid 2-butanone at 40 °C consists of 8% orientational energy, 14% inductional energy, and 78% dispersion energy [35]. Two molecules with $\alpha = 3 \cdot 10^{-30}$ m^3, $I = 20 \cdot 10^{-19}$ J, and $r = 3 \cdot 10^{-10}$ m have an interaction potential of -11.3 kJ/mol (-2.7 kcal/mol) [35a]. These values of α, I, and the average intermolecular distance r correspond to those for liquid HCl. It is instructive to compare the magnitude of these dispersion forces with that of the dipole-dipole interactions. For two dipoles, both with dipole moments of $3.3 \cdot 10^{-30}$ Cm (1.0 D), separated by a distance of $r = 3 \cdot 10^{-10}$ m and oriented as in Fig. 2-3a, the interaction energy is only -5.3 kJ/mol (-1.1 kcal/mol) [35a]. Thus, for HCl and most other compounds, the dispersion forces are considerably stronger than the dipole-dipole forces of nearest neighbour distance in the liquid state. However, at larger distances the dispersion energy falls off rapidly.

As a result of the α^2 term in Eq. (2-6b), dispersion forces increase rapidly with the molecular volume and the number of polarizable electrons. The polarizability α is connected with the molar refraction and the index of refraction, according to the equation of Lorenz-Lorentz. Therefore, solvents with a large index of refraction, and hence large optical polarizability, should be capable of enjoying particularly strong dispersion forces. As indicated in Table A-1 (Appendix), all aromatic compounds possess relatively high indices of refraction, *e.g.* quinoline ($n = 1.6273$), iodobenzene ($n = 1.6200$), aniline ($n = 1.5863$), and diphenyl ether ($n = 1.5763$); of all organic solvents, carbon disulfide ($n = 1.6275$) and diiodomethane ($n = 1.738$) have the highest indices of refraction.

Solvents with high polarizability are often good solvators for anions which also possess high polarizability. This is due to the fact that the dispersional interactions between the solvents and the large, polarizable anions like $I_3^\ominus$, $I^\ominus$, $SCN^\ominus$ or the picrate anion are significantly larger than for the smaller anions like $F^\ominus$, $HO^\ominus$, or $R_2N^\ominus$ [36]. Perfluorohydrocarbons have unusually low boiling points because tightly held electrons in fluorine have only a small polarizability.

2.2.5 Hydrogen Bonding [37–46, 187–190, 306]

Liquids possessing hydroxy groups or other groups with a hydrogen atom bound to an electronegative atom X are strongly associated and have abnormal boiling points. This observation led to the contention that particular intermolecular forces apply here. These are designated as hydrogen bridges, or hydrogen bonds, characterized by a coordinative divalency of the hydrogen atom involved. A general definition of the hydrogen bond is: when a covalently bound hydrogen atom forms a second bond to another atom, the second bond is referred to as a *hydrogen bond* [38].

The concept of hydrogen bonding was introduced in 1919 by Huggins [37]. The first definitive paper on hydrogen bonding – applied to the association of water molecules – was published in 1920 by Latimer and Rodebush [191]. All three were working in the Laboratory of G. N. Lewis, University of California, Berkeley/USA.

A hydrogen bond is formed by the interaction between the partners R—X—H and :Y—R′ according to Eq. (2-7).

$$\text{R-X-H} + \text{:Y-R}' \rightleftharpoons \text{R-X-H}\cdots\text{Y-R}' \tag{2-7}$$

R—X—H is the proton donor and :Y—R′ makes available an electron pair for the bridging bond. Thus, hydrogen bonding can be regarded as a preliminary step in a Brønsted acid-base reaction which would lead to a dipolar reaction product $\text{R—X}^{\ominus}\cdots\text{H—Y}^{\oplus}\text{—R}'$. X and Y are atoms of higher electronegativity than hydrogen (*e.g.* C, N, P, O, S, F, Cl, Br, I). Both inter- and intramolecular hydrogen bonding are possible, the latter when X and Y belong to the same molecule.

The most important electron pair donors (*i.e.* hydrogen bond acceptors) are the oxygen atoms in alcohols, ethers, and carbonyl compounds, as well as nitrogen atoms in amines and *N*-heterocycles. Hydroxy-, amino-, carboxyl-, and amide groups are the most important proton donor groups. Strong hydrogen bonds are formed by the pairs O—H $\cdots$ O, O—H $\cdots$ N, and N—H $\cdots$ O, weaker ones by N—H $\cdots$ N, and the weakest by $\text{Cl}_2\text{C—H}\cdots\text{O}$ and $\text{Cl}_2\text{C—H}\cdots\text{N}$. The π-electron systems of aromatic compounds, alkenes, and alkynes can also act as weak hydrogen bond acceptors [189].

When two or more molecules of the same type associate, so-called *homo-intermolecular* hydrogen bonds are formed (Fig. 2-4). The association of different molecules (*e.g.* $\text{R—O—H}\cdots\text{NR}_3$) results in *hetero-intermolecular* hydrogen bonds. The designations *homo-* and *heteromolecular* [192] as well as *homo-* and *heteroconjugated* hydrogen bond are also in use. A remarkable example of a competitive solvent-dependent equilibrium between homo- and hetero-intermolecular hydrogen-bond associated species has been found in solutions of 4-hydroxyacetophenone and 2-(2-hexyloxyethoxy)ethanol [319].

Hydrogen bonds can be either *inter*molecular or *intra*molecular. Both types of hydrogen bonds are found in solutions of 2-nitrophenol, depending on the Lewis basicity of the solvent [298]. The intramolecularly hydrogen-bonded form exists in non-hydrogen-bonding solvents (*e.g.* cyclohexane, tetrachloromethane). 2-Nitrophenol breaks its intramolecular hydrogen bond to form an intermolecular one in electron-pair donor (EPD) solvents (*e.g.* anisole, HMPT).

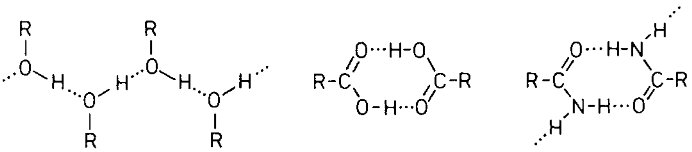
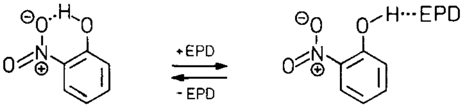


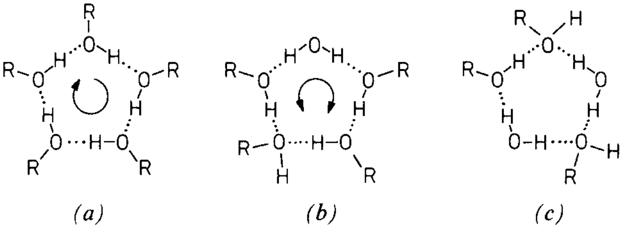
Fig. 2-4. Homo-intermolecular hydrogen bonds in alcohols, carboxylic acids, and amides (the hydrogen bonds are denoted by dotted lines).



Circular hydrogen bonds have been found in the hexahydrate of α-cyclodextrin (cyclohexaamylose) [193]. Hydration water molecules and hydroxy groups of the macromolecule cooperate to form a network-like pattern with circular O—H · · · O hydrogen bonds. If the O—H · · · O hydrogen bonds run in the same direction, the circle is called *homodromic*. Circles with the two counter-running chains are called *antidromic*, and circles with more randomly oriented chains are designated *heterodromic* [193]; *cf.* Fig. 2-4a. Such circular hydrogen bonds can be of importance with respect to the inner molecular structure of water and alcohols (*cf.* also Fig. 2-1).

The question of the exact geometry of hydrogen bonds (distances, angles, lone-pair directionality) has been reviewed [194].

The bond dissociation enthalpy for normal hydrogen bonds is *ca.* 13...42 kJ/mol (3...10 kcal/mol)*⁾. For comparison, covalent single bonds have dissociation enthalpies of 210...420 kJ/mol (50...100 kcal/mol). Thus, hydrogen bonds are approx. ten times weaker than covalent single bonds, but also approx. ten times stronger than the non-



(a) (b) (c)

Fig. 2-4a. Three types of circular hydrogen bonds: (a) homodromic, (b) antidromic, and (c) heterodromic hydrogen bonds [193].

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* Bond dissociation enthalpies outside these limits are, however, known. Examples of weak, normal, and strong hydrogen bonds are found in the following pairs: phenol/benzene ($\Delta H = -5$ kJ/mol) [47], phenol/triethylamine ($\Delta H = -37$ kJ/mol) [47], and trichloroacetic acid/triphenylphosphane oxide ($\Delta H = -67$ kJ/mol) [48]. An extremely strong hydrogen bond is found in $Me_4N^+HF_2^-$ ($\Delta H = -155$ kJ/mol) [38]. The strength of a hydrogen bond correlates with the basicity of the proton-acceptor and the acidity of the proton-donor molecule. Compounds with very strong hydrogen bonds have been reviewed [320].

specific intermolecular interaction forces. The question as to whether or not a hydrogen bond is stronger than the equivalent deuterium bond is addressed in reference [321]: the D-bond seems to be somewhat stronger than the H-bond in the case of neutral hydrogen-bonded complexes, but the reverse is true for charged complexes.

Hydrogen bonds are characterized by the following structural and spectroscopic features [39]: (a) the distances between the neighbouring atoms involved in the hydrogen bond [X and Y in Eq. (2-7)] are considerably smaller than the sum of their van der Waals radii; (b) the X—H bond length is increased and hydrogen bond formation causes its IR stretching mode to be shifted towards lower frequencies (for exceptions see reference [190]); (c) the dipolarity of the X—H bond increases on hydrogen bond formation, leading to a larger dipole moment of the complex than expected from vectorial addition of its dipolar components R—X—H and Y—R′; (d) due to the reduced electron density at H-atoms involved in hydrogen bonds, they are deshielded, resulting in substantial downfield shifts of their ^{1}H NMR signals; (e) in hetero-molecular hydrogen bonds, a shift of the Brønsted acid/base equilibrium $\mathrm{R{-}X{-}H \cdots Y{-}R' \rightleftharpoons R{-}X^{\ominus} \cdots H{-}Y^{\oplus}{-}R'}$ to the right-hand side with increasing solvent polarity is found (*cf.* Section 4.4.1 and references [195, 322] for impressive examples).

Up until now there has been no general agreement as to the best description of the nature of the forces in the hydrogen bond [42–46]. The hydrogen bond can be described as a dipole-dipole or resonance interaction. Since hydrogen bonding occurs only when the hydrogen is bound to an electronegative atom, the first assumption concerning the nature of the hydrogen bond was that it consists of a dipole-dipole interaction such as $\mathrm{R{-}X^{\delta\ominus}{-}H^{\delta\oplus} \cdots Y^{\delta\ominus}{-}R'}$. This viewpoint is supported by the fact that the strongest hydrogen bonds are formed in pairs in which the hydrogen is bonded to the most electronegative elements (*e.g.* $\mathrm{F{-}H \cdots F^{\ominus}}$, $\Delta H = -155$ kJ/mol). The greater strength of the hydrogen bond compared with non-specific dipole-dipole interactions is due to the much smaller size of the hydrogen atom relative to any other atom, which allows it to approach another dipole more closely. This simple dipole model accounts for the usual linear geometry of the hydrogen bond, because a linear arrangement maximizes the attractive forces and minimizes the repulsion.

However, there are reasons to believe that more is involved in hydrogen bonding than simply an exaggerated dipole-dipole interaction. The shortness of hydrogen bonds indicates considerable overlap of van der Waals radii and this should lead to repulsive forces unless otherwise compensated. Also, the existence of symmetrical hydrogen bonds of the type $\mathrm{F^{\delta\ominus} \cdots H \cdots F^{\delta\ominus}}$ cannot be explained in terms of the electrostatic model. When the X—Y distance is sufficiently short, an overlap of the orbitals of the X—H bond and the electron pair of :Y can lead to a covalent interaction. According to Eq. (2-8), this situation can be described by two contributing "protomeric" structures, which differ only in the position of the proton*⁾.

$$\mathrm{R{-}X{-}H \cdots Y{-}R'} \quad \xleftrightarrow{\;p\;} \quad \mathrm{R{-}X^{\ominus} \cdots H{-}Y^{\oplus}{-}R'} \tag{2-8}$$

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* The term "protomeric structure" was obviously introduced in analogy to the well-known "mesomeric structures", which are used to describe the electronic ground state of aromatic compounds such as benzene in terms of a resonance hybrid [323].

The approximate quantum mechanical description of proton states by linear combination of these protomeric structures has been called *protomerism* (symbol *p*) [323, 324]. It seems to be applicable to hydrogen bond systems in which a proton transfer may occur between two potential minima of equal depth [323, 324].

Solvents containing proton-donor groups are designated *protic* solvents [36] or *HBD* solvents [196]; solvents containing proton-acceptor groups are called *HBA* solvents [196]. The abbreviations *HBD* (hydrogen-bond donor) and *HBA* (hydrogen-bond acceptor) refer to donation and acceptance of the proton, and not to the electron pair involved in hydrogen bonding.

Solvents without proton-donor groups have been designated *aprotic* solvents [36]. However, this term is rather misleading, since, for example, solvents commonly referred to as *dipolar aprotic* (*e.g.* CH_3SOCH_3, CH_3CN, CH_3NO_2) are in fact *not* aprotic. In reactions where strong bases are employed, their protic character can be recognized. Therefore, the term *aprotic* solvents should be replaced by *nonhydroxylic* or better still by *non-HBD* solvents [197].

Typical protic or HBD solvents are water, ammonia, alcohols, carboxylic acids, and primary amides. Typical HBA solvents are amines, ethers, ketones, and sulfoxides. *Amphiprotic* solvents can act both as HBD and as HBA solvents simultaneously (*e.g.* water, alcohols, amides; *cf.* Fig. 2-4).

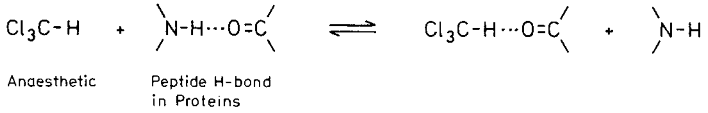
In *type-A* hydrogen bonding, the solute acts as a HBA-base and the solvent as a HBD-acid; in *type-B* hydrogen bonding, the roles are reversed [196].

Hydrogen bonding is responsible for the strong, temperature-dependent self- and hetero-association of amphiprotic solvents (*e.g.* water, alcohols, amides).

The molecular structure of binary HBD/HBA solvent mixtures is largely determined by intermolecular hydrogen bonding between the two components, which usually leads to pronounced deviations from ideal solution behaviour [306, 325–327]. Representative examples are trichloromethane/acetone [326] and trichloromethane/dimethyl sulfoxide mixtures [327], which readily form hydrogen-bonded 1:1 and 2:1 complexes, respectively, with distinct changes in their physical properties as a consequence.

Hydrogen bonding plays a particularly important role in the interactions between anions and HBD solvents. Hence, HBD solvents are good anion solvators. Due to the small size of the hydrogen atom, small anions like $F^{\ominus}$, $Cl^{\ominus}$, or $HO^{\ominus}$ are more effectively solvated by such solvents than the larger ones, *e.g.* $I_3^{\ominus}$, $I^{\ominus}$, $SCN^{\ominus}$, or the picrate ion [36]. This is also one of the reasons why the Gibbs energy of hydration, ΔG_{solv}, of the halide ions decreases in the series $F^{\ominus} > Cl^{\ominus} > Br^{\ominus} > I^{\ominus}$ [49].

Hydrogen bonding is of paramount importance for the stabilization and the shape of large biological molecules in living organisms (*e.g.* cellulose, proteins, nucleic acids). For instance, the anaesthetic properties of some halogen-containing solvents such as chloroform, halothane (CF_3—$CHClBr$), and methoxyflurane (CH_3O—CF_2—$CHCl_2$) have been connected with their ability to hinder the formation of biologically important hydrogen bonds. This is shown in the following equilibrium [300]:



Halohydrocarbon solvents containing an acidic C—H bond shift this equilibrium in favour of free or less associated species, thus perturbing the ion channels which determine the permeability of neuron membranes to $K^{\oplus}/Na^{\oplus}$ ions in the nervous system. Hydrogen bonds play a decisive role in determining the structure and dimension of these ion channels, on which this permeability depends [300].

Hydrogen-bonding also seems to be the molecular basis of sweetness. All sweet compounds seemingly have a H-bond donor and a H-bond acceptor ca. 250 ... 400 pm apart, which can form hydrogen bonds with a complementary pair on the sweet receptor in the tastebuds of the tongue [328].

The effectiveness of solvents (and solutes) as hydrogen-bond donors and/or acceptors has been studied experimentally using suitable reference compounds, comprising representative HBDs or HBAs, in order to construct quantitative scales of solvent (and solute) hydrogen-bond acidity and hydrogen-bond basicity, respectively. For reviews on their construction and application to physicochemical and biochemical processes, see references [329–334] as well as Chapter 7. Scales of hydrogen-bond acidity and basicity have mostly been set up using complex formation constants, as determined in inert solvents [329–332]. For example, the strength of HBAs has been measured from the Gibbs energy change ΔG_{HB} for the formation of 1:1 hydrogen-bonded complexes between all kinds of HBAs (bases) and the reference HBD 4-fluorophenol in tetrachloromethane at 25 °C [331, 332]. Other attempts to construct scales of HBD and HBA strengths, *e.g.* the α and β scale of Taft and Kamlet [333, 334], are described in Chapter 7. Not unexpectedly, the pK_{HB} scales derived in this way do not correspond to the common pK_a and pK_b scales, *i.e.* to the normal acidity or basicity constants.

2.2.6 Electron-Pair Donor/Electron-Pair Acceptor Interactions (EPD/EPA Interactions) [50–59, 59a, 59b]

When tetrachloromethane solutions of yellow chloranil and colourless hexamethylbenzene are mixed, an intensely red solution is formed ($\lambda_{max} = 517$ nm [50]). This is due to the formation of a complex between the two components, and is only one example of a large number of so-called *electron-pair donor/electron-pair acceptor complexes (EPD/EPA complexes)*[*]. It is generally accepted that the characteristic long-wavelength absorptions of these EPD/EPA complexes are associated with an electron transfer from the donor to the acceptor molecule. Mulliken termed these absorptions "charge-transfer (CT) absorptions" [51].

A necessary condition for the formation of an additional bonding interaction between two valency-saturated molecules is the presence of an occupied molecular

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[*] Synonyms for *EPD/EPA complex* are *electron donor acceptor (EDA) complex* [50], *molecular complex* [57, 58], and *charge-transfer (CT) complex* [51]. Since normally the term *molecular complex* is only used for weak complexes between neutral molecules, and the appearance of a charge-transfer absorption band does not necessarily prove the existence of a stable complex, the more general expression *EPD/EPA complex*, proposed by Gutmann [53], will be used here. This will comprise all complexes whose formation is due to an interaction between electron-pair donors (Lewis bases) and electron-pair acceptors (Lewis acids), irrespective of the stabilities of the complexes or the charges of the components.

orbital of sufficiently high energy in the EPD molecule, and the presence of a sufficiently low unoccupied orbital in the EPA molecule*). Based on the type of orbitals involved in bonding interactions, all EPD molecules can be divided into three groups [51, 53]: *n*-, σ-, and π-EPD. In the first group, the energetically highest orbital is that of the lone pair of *n*-electrons on the heteroatoms (R_2O, R_3N, R_2SO), in the second it is that of the electron pair of a σ-bond (R—Hal, cyclopropane), and in the third it is that of the pair of π electrons of unsaturated and aromatic compounds (alkenes, alkylbenzenes, polycyclic aromatics). Similarly, EPA molecules can also be divided into three groups [51, 53]: *v*-, σ-, and π-EPA. The lowest orbital in the first group is a vacant valency-orbital of a metal atom ($Ag^{\oplus}$, certain organometallic compounds), in the second it is a non-bonding σ-orbital (I_2, Br_2, ICl), and in the third it is a system of π-bonds (aromatic and unsaturated compounds with electron-withdrawing substituents such as aromatic polynitro compounds, halobenzoquinones, tetracyanoethene). Because, in principle, any donor is able to form a complex with any acceptor, there exist nine different types of EPD/EPA complexes. The largest number of investigations have been concerned with complexes of the type π-EPD/π-EPA (*cf.* the above-mentioned hexamethylbenzene/chloranil complex) and π-EPD/σ-EPA (*cf.* complexes of aromatic hydrocarbons and alkenes with halogens and interhalogens).

More recent interesting examples of π-EPD/π-EPA complexes can be found in references [335, 336] and of π-EPD/*v*-EPA complexes (*i.e.* π/cation interactions) in references [337, 338]. For the synthesis of the first free, non-coordinated silyl cation in solution [*i.e.* trimesitylsilylium tetrakis(pentafluorophenyl)borate], the careful selection of a *non-coordinating* solvent, which nevertheless dissolves educts and product, was of crucial importance. Only with arenes as weak EPD solvents, bulky substituents around the silicon atom, and a weak nucleophilic anion, was the synthesis of $(Mes)_3Si^+$ $(F_5C_6)_4B^-$ in solution possible [338].

The reaction enthalpies, ΔH, for the formation of strong EPD/EPA complexes, often used as a measure of the bond energies, lie between −42 and −188 kJ/mol (−10 to −45 kcal/mol) [59]. *n*-EPD/*v*-EPA complexes are particular members of this group (*e.g.* Et_2O—BF_3, $\Delta H = -50$ kJ/mol or −11.9 kcal/mol [60]). For weak complexes, ΔH is usually larger than the dispersion energies but smaller than about 42 kJ/mol (10 kcal/mol) [59]. π-EPD/π-EPA complexes between neutral molecules are examples ($-\Delta H = 0 \ldots 21$ kJ/mol or $0 \ldots 5$ kcal/mol), *e.g.* benzene/1,3,5-trinitrobenzene ($\Delta H = -8$ kJ/mol or −1.9 kcal/mol [57]).

No general agreement exists as to the relative importance of the different intermolecular forces in making up the EPD/EPA complexes. According to Mulliken's VB description of weak EPD/EPA complexes, the electronic ground state can be considered as a hybrid of two limiting structures (*a*) and (*b*) in Fig. 2-5.

The non-ionic structure (*a*) represents a state without any donor-acceptor interactions, in which only non-specific intermolecular forces hold D and A together. The mesomeric structure (*b*) characterizes a state in which an ionic bond has been formed by

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* The fundamental difference between this EPD/EPA bonding interaction and a normal chemical bond is that in an ordinary chemical bond each atom supplies one electron to the bond, whereas in EPD/EPA bonding one molecule (the donor) supplies the pair of electrons, while the second molecule (the acceptor) provides the vacant molecular orbital.

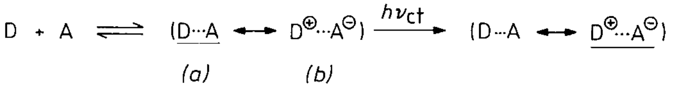

Fig. 2-5. Formation and optical excitation of an EPD/EPA complex between donor D and acceptor A (the predominating mesomeric structure in the ground and excited states is underlined).

transfer of an electron from D to A. This electron transfer will be easier the lower the ionization potential of the donor [61, 63], and the higher the electron affinity of the acceptor [62, 63]. The ionic limiting structure (*b*) is relatively energy-rich and contributes only slightly to the ground state. Nevertheless, this small contribution is sufficient in establishing an extra bonding interaction in addition to the non-specific van der Waals forces. However, subsequent investigations showed that these charge-transfer forces are weaker than was previously believed, and that the classical van der Waals forces (including electrostatic forces) suffice in explaining the stabilities of EPD/EPA complexes [59, 64, 198]. The relative importance of contributions from the electrostatic and charge-transfer forces in the ground state of EPD/EPA complexes has been studied by many authors. For a review, see reference [183; Vol. 1, p. 6ff.]. It seems that both electrostatic and charge-transfer interactions are important in the ground state of EPD/EPA complexes. Their relative contribution, however, varies widely in different EPD/EPA complexes [183].

Another description of EPD/EPA interactions, particularly useful for strong complexes, is based on the coordinative interaction between Lewis bases or nucleophiles (as EPD) and Lewis acids or electrophiles (as EPA) [53, 58]. The intermolecular bonding is seen not as a hybrid of electrostatic and charge-transfer forces, but as one of electrostatic and covalent ones. The interaction of the acceptor A with the electron pair of the donor D is a result of an overlap of the orbitals of the two molecules; consequently, a finite electron density is created between the two partners according to Eq. (2-9).

$$\mathrm{D}\colon + \mathrm{A} \rightleftharpoons \mathrm{D}^{\oplus}\text{—}\mathrm{A}^{\ominus} \tag{2-9}$$

Hence, the structure $\mathrm{D}^{\oplus}\text{—}\mathrm{A}^{\ominus}$ is a covalent one and the EPD/EPA interaction between D and A can be described as a Lewis acid/base interaction [65].

Of the solvents, aromatic and olefinic hydrocarbons are π-donors (π-EPD); alcohols, ethers, amines, carboxamides, nitriles, ketones, sulfoxides and *N*- and *P*-oxides are *n*-donors (*n*-EPD), and haloalkanes are σ-donors (σ-EPD). Boron and antimony trihalides are acceptor solvents (v-EPA), as are halogens and mixed halogens (σ-EPA), and liquid sulfur dioxide (π-EPA). In principle, all solvents are amphoteric in this respect, *i.e.* they may act as a donor (nucleophile) and an acceptor (electrophile) simultaneously. For example, water can act as a donor (by means of the oxygen atom) as well as as an acceptor (by forming hydrogen bonds). This is one of the reasons for the exceptional importance of water as a solvent.

n-Donor solvents are particularly important for the solvation of cations. Examples are hexamethylphosphoric triamide, pyridine, dimethyl sulfoxide, *N*,*N*-dimethylformamide, acetone, methanol, and water. Their specific EPD properties make them excellent cation solvators, and they are, therefore, good solvents for salts. They are also known as *coordinating solvents* [66]. The majority of inorganic reactions are carried out in coordinating solvents.

An empirical semiquantitative measure of the nucleophilic properties of EPD solvents is provided by the so-called *donor number DN* (or *donicity*) of Gutmann [53, 67] (*cf.* also Section 7.2). This donor number has been defined as the negative ΔH values for 1:1 adduct formation between antimony pentachloride and electron-pair donor solvents (D) in dilute solution in the non-coordinating solvent 1,2-dichloroethane, according to Eq. (2-10)*).

$$\mathrm{D\!:} + \mathrm{SbCl_5} \underset{\text{in Cl-CH}_2\text{CH}_2\text{-Cl}}{\overset{\text{room temp.}}{\rightleftharpoons}} \overset{\oplus}{\mathrm{D}}-\overset{\ominus}{\mathrm{Sb}}\mathrm{Cl_5} \tag{2-10}$$

Solvent Donor Number $DN = -\Delta H_{\mathrm{D\text{-}SbCl_5}}/(\mathrm{kcal \cdot mol^{-1}})$

The linear relationship between $-\Delta H_{\mathrm{D{-}SbCl_5}}$ and the logarithm of the corresponding equilibrium constant ($\lg K_{\mathrm{D{-}SbCl_5}}$) shows that the entropy contributions are equal for all the studied acceptor/donor solvent reactions. Therefore, one is justified in considering the donor numbers as semiquantitative expressions for the degree of coordination interaction between EPD solvents and antimony pentachloride. Antimony pentachloride is regarded as an acceptor on the borderline between hard and soft Lewis acids. A list of organic solvents ordered according to increasing donicity is given in Table 2-3. From this it is seen that, for example, nitromethane and acetonitrile are weak donor solvents, whereas dimethyl sulfoxide and triethylamine are very strong donors. The higher the donor number, the stronger the interaction between solvent and acceptor.

Unfortunately, donor numbers have been defined in the non-SI unit $\mathrm{kcal \cdot mol^{-1}}$. Marcus has presented a scale of dimensionless, normalized donor numbers DN^{N}, which are defined according to $DN^{\mathrm{N}} = DN/(38.8\ \mathrm{kcal \cdot mol^{-1}})$ [200]. The non-donor solvent 1,2-dichloroethane ($DN = DN^{\mathrm{N}} = 0.0$) and the strong donor solvent hexamethylphosphoric triamide (HMPT: $DN = 38.8\ \mathrm{kcal \cdot mol^{-1}}$; $DN^{\mathrm{N}} = 1.0$) have been used to define the scale. Although solvents with higher donicity than HMPT are known (*cf.* Table 2-3), it is expedient to choose the solvent with the highest directly (*i.e.* calorimetrically) determined DN value so far as the second reference solvent [200]**). The DN^{N} values are included in Table 2-3.

A visual estimate of the different donicities of EPD solvents can easily be made using the colour reaction with copper(II), nickel(II), or vanadyl(IV) complexes as acceptor solutes [204].

The donor number has proven very useful in coordination chemistry, since it can be correlated with other physical observables for such reactions, *e.g.* thermodynamic

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* An analogous approach was first used by Lindqvist and Zackrisson [67a]. The authors established a series of EPD solvents calorimetrically, based on their increasing donor capacities relative to a standard acceptor ($\mathrm{SbCl_5}$ or $\mathrm{SnCl_4}$) with which the given donor was combined in 1,2-dichloroethane.

** The donor number of $38.8\ \mathrm{kcal \cdot mol^{-1}}$ for HMPT was given by Gutmann [67]. It should be mentioned, however, that a much higher DN value of $50.3\ \mathrm{kcal \cdot mol^{-1}}$ was subsequently measured for this solvent by Bollinger *et al.* [214]. This shows that serious problems arise in measuring the Lewis basicity of this EPD solvent towards $\mathrm{SbCl_5}$.

Table 2-3. Donor numbers (donicities) *DN* [199, 200, 212, 241, 339] and normalized DN^{N} values [200] of a selection of thirty-six organic EPD solvents[a], determined calorimetrically in dilute 1,2-dichloroethane solutions at room temperature and valid for isolated EPD solvent molecules[b].

Solvents	$DN/(\mathrm{kcal \cdot mol^{-1}})$[c]	DN^{N}[d]
1,2-Dichloroethane *(reference solvent)*	*0.0*[e]	*0.00*[e]
Nitromethane	2.7	0.07
Nitrobenzene	4.4	0.11
Acetic anhydride	10.5	0.27
Cyanobenzene, Benzonitrile	11.9	0.31
Ethanenitrile, Acetonitrile	14.1	0.36
Tetrahydrothiophene-1,1-dioxide, Sulfolane	14.8	0.38
1,4-Dioxane	14.8	0.38
4-Methyl-1,3-dioxol-2-one, Propylene carbonate	15.1	0.39
(Cyanomethyl)benzene, Benzylcyanide	15.1	0.39
2-Methylpropanenitrile, *i*-Butanenitrile	15.4	0.40
Diethyl carbonate	16.0	0.41
Propanenitrile	16.1	0.41
Methyl acetate	16.3	0.42
1,3-Dioxol-2-one, Ethylene carbonate	16.4	0.42
Butanenitrile	16.6	0.43
3,3-Dimethyl-2-butanone, *t*-Butyl methyl ketone	17.0	0.44
Acetone	17.0	0.44
Ethyl acetate	17.1	0.44
3-Methyl-2-butanone, Methyl *i*-propyl ketone	17.1	0.44
2-Butanone	17.4	0.45
Diethyl ether	19.2	0.49
Tetrahydrofuran	20.0	0.52
Trimethyl phosphate	23.0	0.59
Tri-*n*-butyl phosphate	23.7	0.61
N,*N*-Dimethylformamide	26.6	0.69
1-Methylpyrrolidin-2-one	27.3	0.70
N,*N*-Dimethylacetamide	27.8	0.72
Tetramethylurea	29.6	0.76
Dimethyl sulfoxide	29.8	0.77
N,*N*-Diethylformamide	30.9	0.80
N,*N*-Diethylacetamide	32.2	0.83
Pyridine	33.1	0.85
Hexamethylphosphoric triamide	38.8	*1.00*[f]
Triethylamine	61.0	1.57

[a] A compilation of 170 resp. 134 *DN*-values taken from different sources can be found in references [200, 339]. Further 14 *DN* values, determined indirectly from the ^{1}H NMR shift of chloroform, are given in reference [293].

[b] As the basic donor numbers were measured in an inert diluent, they reflect the donicity of the isolated EPD solvent molecules. In neat, associated EPD solvents an increase in the donicity should occur [199]. For such highly-structured solvents (*e.g.* water, alcohols, amines) the term *bulk donicity* has been introduced [201] in order to rationalize the deviations of these solvents in plots of $^{23}\mathrm{Na}^{\oplus}$ NMR shifts [202] and ESR parameters [203] *vs.* the donor numbers. Because of the great discrepancies which exist between the DN_{bulk} values given in the literature, they are not included in this table. For a collection of bulk donicities, DN_{bulk}, see reference [200], Table II.

[c] For the definition of *DN cf.* Eq. (2-10). For conversion into SI units: $1\ \mathrm{kcal \cdot mol^{-1}} = 4.184\ \mathrm{kJ \cdot mol^{-1}}$.

[d] $DN^{\mathrm{N}} = DN/(38.8\ \mathrm{kcal \cdot mol^{-1}})$ [200]; $DN = 38.8\ \mathrm{kcal \cdot mol^{-}}$ for hexamethylphosphoric triamide as reference solvent.

[e] Zero by definition.

[f] Unity by definition [200].

(ΔG or K), kinetic (rates), electrochemical (polarographic half-wave and redox potentials), and spectroscopic data (chemical shifts of NMR signals) [53, 67–69, 205–207].

The donor number approach has been criticized for conceptual [208] and experimental reasons [200, 209–212]. For this and other reasons, other Lewis basicity parameters have been sought.

Another remarkable Lewis basicity scale for 75 non-HBD solvents has been established by Gal and Maria [211, 212]. This involved very precise calorimetric measurements of the standard molar enthalpies of 1:1 adduct formation of EPD solvents with gaseous boron trifluoride, $\Delta H^{\circ}_{\mathrm{D—BF_3}}$, in dilute dichloromethane solution at 25 °C, according to Eq. (2-10a).

$$\mathrm{D{:}} + \mathrm{BF_3} \underset{\text{in CH}_2\text{Cl}_2}{\overset{25\,°\mathrm{C}}{\rightleftharpoons}} \overset{\oplus}{\mathrm{D}}—\overset{\ominus}{\mathrm{B}}\mathrm{F_3} \qquad (2\text{-}10\text{a})$$

A selection of $\Delta H^{\circ}_{\mathrm{D—BF_3}}$ values is given in Table 2-4. This new Lewis basicity scale is more comprehensive and seems to be more reliable than the donor number scale. A comparison of various Lewis basicity scales has been given by Persson [301].

Persson, Sandström, and Goggin have proposed an empirical solvent scale, called the D_{S} scale, ranking the donor strength of 64 EPD solvents towards a soft acceptor

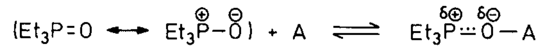
Table 2-4. Molar enthalpies of complex formation between boron trifluoride and several non-HBD solvents, determined in dichloromethane at 25 °C, according to Eq. (2-10a) [211, 212].

Solvents	$-\Delta H^{\circ}_{\mathrm{D-BF_3}}/(\mathrm{kJ\cdot mol^{-1}})$[a]
Dichloromethane	10.0
Nitrobenzene	35.79
Nitromethane	37.63
Tetrahydrothiophene-1,1-dioxide	51.32
Acetonitrile	60.39
Propylene carbonate	64.19
3-Pentanone	72.28
1,4-Dioxane	74.09
Ethyl acetate	75.55
Acetone	76.03
Di-*i*-propyl ether	76.61
Diethyl ether	78.77
Tetrahydrofuran	90.40
1,3-Dimethylimidazolidin-2-one, DMEU	98.93
Dimethyl sulfoxide	105.34
N,*N*,*N'*,*N'*-Tetramethylurea	108.62
N,*N*-Dimethylformamide	110.49
3,4,5,6-Tetrahydro-1,3-dimethylpyrimidin-2(1 *H*)-one, DMPU	112.13
1-Methylpyrrolidin-2-one	112.56
Hexamethylphosphoric triamide	117.53
Tris(pyrrolidino)phosphane oxide	122.52
Pyridine	128.08
Triethylamine	135.87
1-Methylpyrrolidine	139.51

[a] See reference [212] for a set of 75 $\Delta H^{\circ}_{\mathrm{D—BF_3}}$ values. At present, $\Delta H^{\circ}_{\mathrm{D—BF_3}}$ values for *ca.* 350 organic EPD compounds are known (J.-F. Gal and P.-C. Maria, private communication).

such as mercury(II) bromide [303]. The D_S values correspond to the Raman wavenumber shift of the symmetric IR stretching vibration on going from the gas phase to a solution of $HgBr_2$. Further measurements of $\Delta\nu(Hg—Br)$ of $HgBr_2$ and the relationships between the corresponding D_S values and other soft EPD solvent parameters can be found in reference [340]. An additional D_H scale of donor strength towards hard acceptors (*e.g.* $Na^{\oplus}$) has been derived for 24 EPD solvents [303].

An analogous empirical quantity for characterizing the electrophilic properties of EPA solvents has been derived by Gutmann and coworkers from the ^{31}P NMR chemical shifts produced by the electrophilic actions of acceptor solvents A in triethylphosphane oxide, according to Eq. (2-11) (*cf.* also Section 7.4) [70, 199, 207, 213].



$$(Et_3P{=}O \longleftrightarrow Et_3\overset{\oplus}{P}{-}\overset{\ominus}{O}) + A \rightleftharpoons Et_3\overset{\delta\oplus}{P}{\cdots}\overset{\delta\ominus}{O}{-}A \qquad (2\text{-}11)$$

$$AN = \frac{\delta_{corr}(A) - \delta_{corr}(n\text{-}C_6H_{14})}{\delta_{corr}(Et_3PO—SbCl_5) - \delta_{corr}(n\text{-}C_6H_{14})} \cdot 100 = \Delta\delta_{corr} \cdot 2.348/\text{ppm}$$

These quantities have been termed *acceptor number AN* (or *acceptivity*) and they were obtained from the relative ^{31}P NMR chemical shift values δ_{corr} (*n*-hexane as reference solvent) with respect to that of the 1:1 adduct $Et_3PO—SbCl_5$ dissolved in 1,2-dichloroethane, which has been arbitrarily taken to have the value of 100. The acceptor numbers are dimensionless numbers expressing the acceptor property of a given solvent relative to those of $SbCl_5$, which is also the reference compound for assessing the donor numbers. A compilation of organic solvents in order of increasing acceptor number is given in Table 2-5.

Acceptor numbers are less than 10 for nonpolar non-HBD solvents, they vary between about 10...20 for dipolar non-HBD solvents, and they cover a wide range of about 25...105 for protic solvents (*cf.* Table 2-5). Surprisingly, benzene and tetrachloromethane have stronger electrophilic properties than diethyl ether and tetrahydrofuran. Acceptor numbers are also known for binary solvent mixtures [70, 213].

Using the neutral Fe(II) complex $[Fe(phen)_2(CN)_2]$, the different Lewis acidities of EPA solvents can easily be visualized by its colour change: solutions of this Fe(II) complex are blue in HMPT, violet in dichloromethane, red in ethanol, and yellow in trifluoroacetic acid [204].

Another approach to the estimation of EPD/EPA interactions between a Lewis acid A and a Lewis base B was given by Drago [71]. Drago proposed the four-parameter Eq. (2-12) to correlate the standard enthalpy of the reaction of an acceptor A with a donor B to give a neutral 1:1 adduct in an inert solvent (tetrachloromethane or *n*-hexane).

$$-\Delta H^{\circ}_{AB}/(\text{kJ} \cdot \text{mol}^{-1}) = E_A \cdot E_B + C_A \cdot C_B \qquad (2\text{-}12)$$

E_A and C_A are empirical acceptor parameters and E_B and C_B are empirical donor parameters. The E parameters are measures of the tendency of an acid or a base to participate in *e*lectrostatic interactions, while the C parameters are measures of their tendency to form *c*ovalent bonds.

Table 2-5. Acceptor numbers (acceptivities) *AN* [70, 213, 339] of forty-eight organic EPA solvents, determined ^{31}P-NMR spectroscopically at 25 °C.

Solvents	*AN*[a)]
n-Hexane *(reference solvent)*	*0.0*
Triethylamine	1.4
Diethyl ether	3.9
Tetrahydrofuran	8.0
Benzene	8.2
Tetrachloromethane	8.6
Ethyl acetate	9.3
Diethylamine	9.4
Hexamethylphosphoric acid triamide	9.8
Tri-*n*-butyl phosphate	9.9
Diethylene glycol dimethyl ether	9.9
1,2-Dimethoxyethane	10.2
Methyl acetate	10.7
1,4-Dioxane	10.8
Acetone	12.5
1-Methylpyrrolidin-2-one	13.3
N,*N*-Dimethylacetamide	13.6
Pyridine	14.2
Nitrobenzene	14.8
Cyanobenzene	15.5
N,*N*-Dimethylformamide	16.0
Trimethyl phosphate	16.3
1,2-Dichloroethane	16.7
4-Butyrolactone	17.3
Morpholine	17.5
4-Methyl-1,3-dioxol-2-one, Propylene carbonate	18.3
N,*N*-Dimethylthioformamide	18.8
Ethanenitrile, Acetonitrile	18.9
Tetrahydrothiophene-1,1-dioxide, Sulfolane	19.2
Dimethyl sulfoxide	19.3
Dichloromethane	20.4
Nitromethane	20.5
1,2-Diaminoethane	20.9
Chloroform	23.1
2-Methyl-2-propanol, *t*-Butanol	27.1
N-Methylformamide	32.1
1-Butanol	32.2
2-Propanol	33.5
1-Propanol	33.7
2-Aminoethanol	33.7
Ethanol	37.1
Formamide	39.8
Methanol	41.5
Acetic acid	52.9
2,2,2-Trifluoroethanol	53.8
Water	54.8
Formic acid	83.6
$Et_3PO \cdot SbCl_5$ *in 1,2-dichloroethane as reference compound*	*100.0*
Trifluoroacetic acid	105.3

[a)] For the definition of *AN*, see Eq. (2-11). All δ values have been extrapolated to zero concentration and corrected for differences in volume susceptibilities.

Table 2-6. Some *E* and *C* parameters expressing Lewis acid/base strength according to Drago [217][a]; *cf.* Eq. (2-12).

Lewis acids	E_A	C_A	Lewis bases	E_B	C_B
$SbCl_5$	14.4[b]	1.17[b]	$[(CH_3)_2N]_3PO$	1.52	3.55
BF_3 (g)	9.88	1.62	CH_3SOCH_3	1.34	2.85
$(CF_3)_2CHOH$	5.93	0.62	$CH_3CON(CH_3)_2$	*1.32*[c]	2.58
C_6H_5OH	4.33	0.42	C_5H_5N	1.17	6.40
CF_3CH_2OH	3.88	0.45	$CH_3CO_2C_2H_5$	0.975	1.74
$CHCl_3$	3.02	0.16	CH_3COCH_3	0.94	2.33
$(CH_3)_3C$—OH	2.04	0.30	$(C_2H_5)_2O$	0.94	3.25
H_2O	1.64	0.57	CH_3CN	0.89	1.34
I_2	*1.00*[c]	*1.00*[c]	$(C_2H_5)_2S$	0.34	*7.40*[c]
SO_2	0.92	0.81	C_6H_6	0.28	0.59

[a] For a more complete list see references [71, 215, 217].
[b] Corrected values; see reference [217].
[c] Used to define the *E*/*C* scale.

The original set of *E* and *C* parameters was determined mainly with the help of enthalpies of adduct formation of iodine and phenol as acceptors with alkylamines as donors. Subsequently, the best set of *E* and *C* parameters has been obtained by computer optimization of a large data base of enthalpies and four arbitrarily fixed reference values [71, 215]: $E_A = C_A = 1$ for iodine, $E_B = 1.32$ for *N*,*N*-dimethylacetamide, and $C_B = 7.40$ for diethyl sulfane. Table 2-6 gives a selection of *E* and *C* parameters for Lewis acids and bases commonly used as solvents.

On the basis of these parameters, it is possible to predict the enthalpies of Lewis acid/base reactions, even those reactions which might be inaccessible experimentally, with remarkable accuracy (within $\pm 0.8\ \text{kJ} \cdot \text{mol}^{-1}$) [216].

Drago's *E*/*C* analysis and Gutmann's donor/acceptor approach [53, 67] have been compared [200, 217, 218]. Eq. (2-12) has been extended for specific and nonspecific interactions between solutes and polar solvents [219]. Various Lewis acidity and basicity scales for polar solvents have been examined and compared by Fawcett, who concluded that the donor/acceptor scales of Gutmann seem to be the most appropriate [341].

Finally, an attempt was made to establish a measure of the electron-donating and electron-accepting power of organic solvents by means of infrared [72, 73] and ^{1}H NMR measurements [73]. Further empirical Lewis acid and base parameters will be discussed in Chapters 7.2...7.5. A thorough and critical compilation of empirical solvent scales, including Lewis acidity and basicity scales, has recently been made for non-HBD solvents [342].

2.2.7 Solvophobic Interactions [74–77, 176, 220–225]

Hydrocarbons have extremely low solubilities in water. Accordingly, the dissolution of a hydrocarbon in water is usually associated with an increase in the Gibbs energy *G* of the system ($\Delta G > 0$). Since it is known experimentally that the dissolution of a hydrocarbon

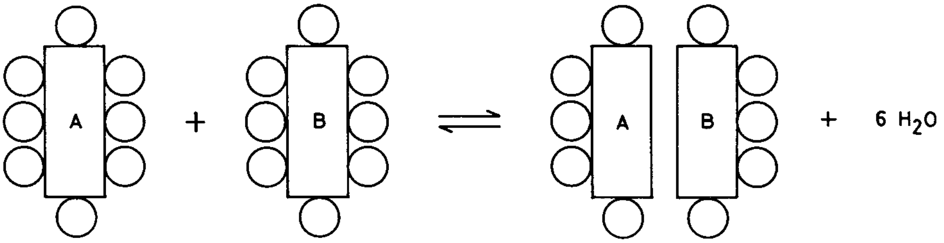


Fig. 2-6. The formation of a hydrophobic interaction between two hydrocarbon molecules A and B (the circles represent water molecules) [78].

in water is exothermic ($\Delta H < 0$) it follows from $\Delta G = \Delta H - T \cdot \Delta S$ that the entropy of the system must decrease. This can be interpreted as a consequence of the highly ordered structure of the water molecules around the dissolved hydrocarbon molecules. In other words, the water molecules are more tightly packed around the dissolved hydrocarbon molecules than in pure water. This is called a structure increase. If aqueous solutions of two hydrocarbons are mixed, the two hydrocarbons may form an aggregate with simultaneous partial reconstruction of the original undisturbed water structure. This is shown schematically in Fig. 2-6.

Due to the contact between A and B, fewer water molecules are now in direct contact with the hydrocarbon molecules. Thus, the ordering influence of the hydrophobic molecules will be diminished and the entropy increases ($\Delta S > 0$). Although thermal energy is required for the destructuring of the hydration shells around A and B ($\Delta H > 0$), the free energy diminishes upon aggregation ($\Delta G < 0$). Therefore, it is energetically advantageous for apolar molecules, or apolar groups in otherwise polar molecules, when dissolved in water, to aggregate with expulsion of water molecules from their hydration shells. In order to minimise the unfavourable solute/water interactions, the apolar solute molecules (or apolar groups) will interact preferentially, thus reducing the number of their water contacts [176]. This effect has been called *hydrophobic interaction.*[*)] The water molecules around an inert apolar solute have a higher coordination and are thus more ordered than in the bulk liquid, which is entropically unfavourable. The aggregation of apolar solutes as shown in Fig. 2-6 releases water molecules into the bulk water, which is entropically very favourable.

This hydrophobic interaction can be illustrated by considering the thermodynamic parameters for the dissolution of the archetypal apolar hydrocarbon methane in cyclohexane (an apolar, non-associated solvent) and in water (a polar, strongly self-associated solvent); Table 2-7 [225].

The unfavorable Gibbs energy ($\Delta G_s^\circ \gg 0$) for the dissolution of methane in water is the result of a strongly negative entropy of solution ($\Delta S_s^\circ \ll 0$), which prevails over

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[*] Glass beads can be used as an illustration of hydrophobia interactions. Thus, glass beads covered with dichloro-dimethylsilane can be regarded as solid hydrocarbon particles. Only hydrophobic interactions are possible. In a structured solvent such as water or formamide, the beads cluster together. When the polarity of the solvent is decreased by addition of alcohols the clusters disintegrate [79].

Table 2-7. Thermodynamic parameters for dissolution of gaseous methane in cyclohexane and water at 25 °C [225].

Solvents	$\Delta G_s^\circ/(\text{kJ} \cdot \text{mol}^{-1})$	$\Delta H_s^\circ/(\text{kJ} \cdot \text{mol}^{-1})$	$\Delta S_s^\circ/(\text{J} \cdot \text{mol}^{-1} \cdot \text{K}^{-1})$
Water	25.5	−13.8	−132
Cyclohexane	14.2	−3.0	−58

the favorable enthalpic contribution ($\Delta H_s^\circ < 0$). The negative enthalpy and entropy of transfer of methane from cyclohexane to water can be interpreted in terms of an increased degree of water-water hydrogen bonding in the solvation shell surrounding the apolar solute molecule.

Generally, the introduction of apolar molecules (such as hydrocarbons or noble gases), or apolar residues in otherwise polar molecules (such as alkyl side chains in biopolymers) into water leads to a reduction of the degrees of freedom (spatial, orientational, dynamic) of the neighbouring water molecules. This effect is called the *hydrophobic effect* or *hydrophobic hydration* [176]. *Hydrophobic* means 'water-fearing'. It should be noted that the interaction between hydrophobic molecules and water molecules is actually attractive because of the dispersion interactions. However, the water/water interaction is much more attractive. Water molecules simply love themselves too much to let some other compounds get in the way [26b]! Therefore, from the point of view of the water molecules, the term "hydrophobic" is rather a misnomer; it would be better to refer to water as being "lipophobic".

This hydrophobic hydration was first postulated by Frank and Evans in 1945. They wrote: "The nature of deviation found for non-polar solutes in water leads to the idea that the water forms frozen patches or microscopic icebergs around such solute molecules. The word 'iceberg' represents a microscopic region, surrounding the solute molecule, in which water molecules are tied together in some sort of quasi-solid structure" [226].

The model of "icebergs" around nonpolar solute molecules in aqueous solution is clearly not a very realistic one. However, if solutions of hydrocarbons (or noble gases) are cooled, then the solid phase that sometimes separates out consists of a so-called gas hydrate (clathrate), in which water provides a particular kind of hydrogen-bonded framework containing cages that are occupied by the nonpolar solute molecules. Obviously, such gas hydrates (clathrates) represent more realistic models for the phenomenon of hydrophobic hydration [176].

In principle, such interactions should also apply to other solvents resembling water, and therefore the more general term *solvophobic interactions* has been proposed [80, 343]. In fact, analogous water-like behaviour has been observed with self-associated solvents other than water, *e.g.* ethanol [81], glycerol [82], ethylammonium nitrate [227], and some dipolar non-HBD solvents [228].

Although there is overwhelming experimental evidence that the hydrophobic interaction is "entropy-driven", this classical view is still a matter of debate [79a, 167, 227, 229–231, 343–347]. For example, it has been claimed that the major contribution to the hydrophobic interaction between the methylene groups of *n*-alkanes is an enthalpic and not an entropic effect [230]. In other words, the poor solubility of nonpolar solutes in water should be due to unfavourable enthalpy and not to unfavourable entropy [227, 231].

Furthermore, what is the real origin of hydrophobicity (or solvophobicity), that is, which molecular property of water is primarily responsible for the positive Gibbs energy of hydration of nonpolar solutes and their tendency to associate? The two main physical explanations are:

(a) the high cohesive pressure of water (see Table 3-2 in Section 3.2), caused by the strong hydrogen-bonding interactions compared to the weak interactions between water and nonpolar solutes; and/or
(b) the small size of the water molecules, which increases the entropic cost of opening up a cavity to accommodate the solute. Opening up a cavity for solute molecules is entropically unfavourable in any solvent. However, the small size of water molecules exacerbates this situation and gives rise to entropies more negative that in other solvents with larger molecule size.

For a more detailed discussion of these questions, see references [76, 77, 176, 343–347] and references cited therein. More recent results [346, 347] have shown that the classical view (a) seems to be basically correct. The essential condition for solvophobicity is that solvent/solvent interactions are much stronger than solute/solvent interactions. However, the solvophobic effect is not necessarily always an entropic phenomenon; it can be enthalpic or entropic depending on the temperature and the geometrical size of the solute molecules [346].

Hydrophobic interactions are important in the aggregation of polymethine dyes [81] and in the stabilization of particular conformations of polypeptides and proteins in aqueous solution [222, 232]. They also play an important role in the biochemical complexation between an enzyme and a substrate [77, 78, 83, 84, 348].

Hydrophobicity parameters for organic substituents have been developed by Hansch *et al.* using partitioning phenomena [296], and by Menger *et al.* using kinetic measurements (hydrolysis of long-chain esters) [297]; see Section 7.2. Further results connected with the presence of hydrophobic interactions in solutions are discussed in Sections 2.5 and 5.4.8.

2.3 Solvation [49, 85–98, 98a, 233–241]

The term *solvation* refers to the surrounding of each dissolved molecule or ion by a shell of more or less tightly bound solvent molecules. This solvent shell is the result of intermolecular forces between solute and solvent. For aqueous solutions the term used is *hydration*. Intermolecular interactions between solvent molecules and ions are particularly important in solutions of electrolytes, since ions exert specially strong forces on solvent molecules. Crude electrostatic calculations show that the field experienced by nearest neighbours of dissolved ions is $10^6 \ldots 10^7$ V/cm. Fig. 2-7 shows a highly simplified picture of such an interaction between ions and dipolar solvent molecules.

The *solvation energy* is considered as the change in Gibbs energy when an ion or molecule is transferred from a vacuum (or the gas phase) into a solvent. The Gibbs

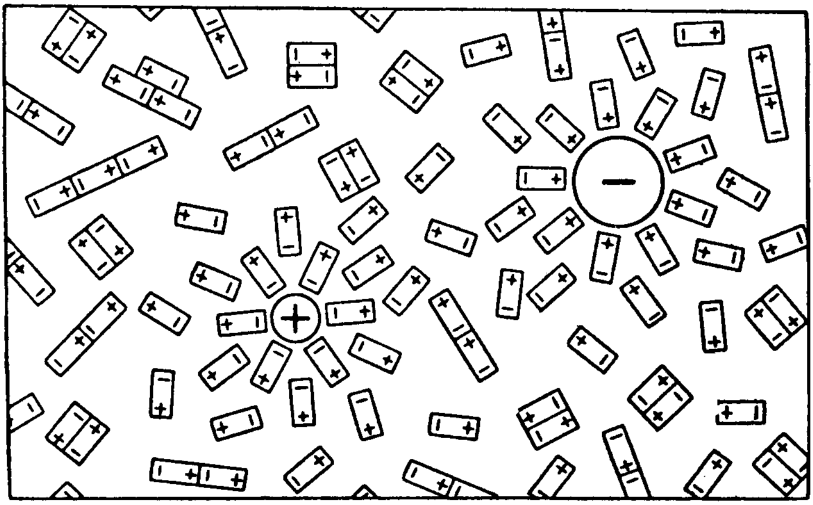

Fig. 2-7. Solvation of ions in a solvent consisting of dipolar molecules [99]. The charges of the dipolar molecules are in fact partial charges $\delta\oplus$ and $\delta\ominus$.

energy of solvation, $\Delta G^\circ_{\text{solv}}$, a measure of the solvation ability of a particular solvent, is the result of a superimposition of four principal components of a different nature [100]:

(a) the cavitation energy associated with the hole that the dissolved molecule or ion produces in the solvent;
(b) the orientation energy corresponding to the phenomenon of partial orientation of the dipolar solvent molecules caused by the presence of the solvated molecule or ion (*cf.* Fig. 2-7);
(c) the isotropic interaction energy corresponding to the unspecific intermolecular forces with a long radius of activity (*i.e.* electrostatic, polarisation, and dispersion energy);
(d) the anisotropic interaction energy resulting from the specific formation of hydrogen bonds or electron-pair donor/electron-pair acceptor bonds at well localized points in the dissolved molecules.

The dissolution of a substance requires that not only the interaction energy of the solute molecules (for crystals the lattice energy*⁾) be overcome but also the interaction energy between the solvent molecules themselves. This is compensated by the gain in Gibbs energy of solvation, $\Delta G^\circ_{\text{solv}}$. The standard molar Gibbs energy of solvation, $\Delta G^\circ_{\text{solv}}$, can be formulated as the difference between the Gibbs energy of solution, $\Delta G^\circ_{\text{soln}}$,

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* The lattice energy is the work required to separate to infinity the elements of the lattice from their equilibrium position at 0 K. For ionic lattices of the alkali halides it is of the order 628...837 kJ/mol (150...200 kcal/mol) [49]. For molecular lattices of organic compounds such as benzene, naphthalene, and anthracene it is of the order 42...105 kJ/mol (10...25 kcal/mol) [101]. The experimental heat of sublimation of benzene is 44.6 kJ/mol (10.7 kcal/mol) [102].

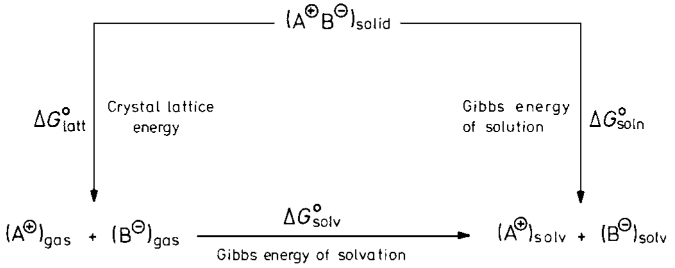

Fig. 2-8. The relationship between standard molar Gibbs energies of solvation and solution and the crystal lattice energy of an ionophore $A^{\oplus}B^{\ominus}$: $\Delta G^{\circ}_{solv} = \Delta G^{\circ}_{soln} - \Delta G^{\circ}_{latt}$.

and the crystal lattice energy, ΔG°_{latt}, as shown by means of the customary Born-Haber cycle in Fig. 2-8.

If the liberated solvation energy is higher than the lattice energy, then the overall process of dissolution is exothermic. In the opposite case the system uses energy and the dissolution is endothermic. The values for NaCl are typical: lattice energy +766 kJ/mol, hydration energy −761 kJ/mol, and energy of solution +3.8 kJ/mol. The energies of solution are generally small because interaction within the crystal lattice is energetically similar to interaction with the solvent.

The Gibbs energies of solvation of individual ions cannot be directly measured but they can be calculated [49]. The Gibbs energies of hydration of some representative ions are collected in Table 2-8. It can be seen that these values can be as high as bond energies or even higher (209...628 kJ/mol; 50...150 kcal/mol). Consequently, the solvent is often considered a direct reaction partner and should really be included in the reaction equation. The isolation of numerous solvates such as hydrates, alcoholates, etherates, and ammoniates, especially of inorganic or organometallic compounds, are examples. Between the two extremes, *viz.* the simple solvation resulting from weak

Table 2-8. Standard molar Gibbs energies of hydration, ΔG°_{hydr}, of some representative single ions at 25 °C [241, 242][a].

Cations	$\Delta G^{\circ}_{hydr}/(kJ \cdot mol^{-1})$	Anions	$\Delta G^{\circ}_{hydr}/(kJ \cdot mol^{-1})$
$H^{\oplus}$	−1056	$F^{\ominus}$	−472
$Li^{\oplus}$	−481	$Cl^{\ominus}$	−347
$Na^{\oplus}$	−375	$Br^{\ominus}$	−321
$K^{\oplus}$	−304	$I^{\ominus}$	−283
$Mg^{\oplus\oplus}$	−1838	$HO^{\ominus}$	−439
$Al^{\oplus\oplus\oplus}$	−4531	$SO_4^{\ominus\ominus}$	−1090

[a] For a comprehensive compilation of Gibbs energies of solvation, see C. M. Criss and M. Salomon: *Thermodynamic Measurements – Interpretation of Thermodynamic Data.* In A. K. Covington and T. Dickinson (eds.): *Physical Chemistry of Organic Solvent Systems*, Plenum Press, London & New York 1973, p. 253 ff. – *Cf.* also D. W. Smith: *Ionic Hydration Enthalpies*, J. Chem. Educ. *54*, 540 (1977). – A critical selection of standard molar heat capacities of hydration, $\Delta_{hyd}C^{\circ}_{p}/(J \cdot K^{-1} \cdot mol^{-1})$, of single ions has been given by M. H. Abraham and Y. Marcus, J. Chem. Soc., Faraday Trans. I *82*, 3255 (1986).

intermolecular interactions, and the *bona fide* chemical modification of the substrate by the solvent, all other possibilities exist.

The most direct measure of the energetics of ion solvation is, without doubt, their *standard molar Gibbs energy of solvation*, *i.e.* transfer from the gas phase to the solvent (*cf.* Fig. 2-8). However, this quantity is generally unknown, particularly for ions in nonaqueous solvents. Therefore, $\Delta G^\circ_{\mathrm{solv}}$ is advantageously replaced by the *standard molar Gibbs energy of transfer* of the ion X from water, W, as reference solvent, to another solvent, S, $\Delta G^\circ_{\mathrm{t}}(\mathrm{X, W \rightarrow S})$, as defined by Eq. (2-12a):

$$\Delta G^\circ_{\mathrm{t}}(\mathrm{X, W \rightarrow S}) = \mu^\infty_{\mathrm{X}}(\text{in S}) - \mu^\infty_{\mathrm{X}}(\text{in W}) = R \cdot T \cdot \ln {}^{\mathrm{W}}y^{\mathrm{S}}_{\mathrm{X}} \tag{2-12a}$$

μ^∞_{X} is the standard (*i.e.* infinite dilution) chemical potential of X and ${}^{\mathrm{W}}y^{\mathrm{S}}_{\mathrm{X}}$ the so-called *solvent-transfer activity coefficient* of X.

In order to obtain the $\Delta G^\circ_{\mathrm{t}}(\mathrm{X, W \rightarrow S})$ of individual ions from experimental data on complete electrolytes, the extrathermodynamic assumption that $\Delta G^\circ_{\mathrm{t}}(\mathrm{Ph_4As^\oplus, W \rightarrow S}) = \Delta G^\circ_{\mathrm{t}}(\mathrm{Ph_4B^\ominus, W \rightarrow S})$ for all solvents has been made, using $\mathrm{Ph_4As^\oplus Ph_4B^\ominus}$ as reference electrolyte ($\mathrm{Ph = C_6H_5}$). This seems reasonable because the large symmetrical ions of tetraphenylarsonium tetraphenylborate are of comparable size, structure, and charge, and are, therefore, similarly solvated on transfer from one solvent to another. Arguments in favour of and against this extrathermodynamic assumption have been reviewed [235, 241, 243, 244]*⁾.

Experimentally, the molar Gibbs energy of transfer of an anion $\mathrm{X^\ominus}$ is obtained from the combined results of four solubility measurements, namely of the salts $\mathrm{Ph_4As^\oplus Ph_4B^\ominus}$ and $\mathrm{Ph_4As^\oplus X^\ominus}$ in water, W, and of the same salts in the solvent S. The Gibbs energy of transfer is then:

$$\begin{aligned}\Delta G^\circ_{\mathrm{t}}(\mathrm{X^\ominus, W \rightarrow S}) = R \cdot T[&2 \cdot \ln s(\mathrm{Ph_4AsX, W}) - 2 \cdot \ln s(\mathrm{Ph_4AsX, S}) \\ &+ \ln s(\mathrm{Ph_4AsPh_4B, S}) - \ln s(\mathrm{Ph_4AsPh_4B, W})]\end{aligned} \tag{2-12b}$$

where s is the solubility, expressed on the molar scale ($\mathrm{mol \cdot l^{-1}}$).

Table 2-9 collects selected values of $\Delta G^\circ_{\mathrm{t}}(\mathrm{X, W \rightarrow S})$ obtained on this basis, taken from the extensive and critically evaluated compilations of Marcus [244, 349] and Gritzner [350]. A nice graphical representation of the changes in $\Delta G^\circ_{\mathrm{t}}$, $\Delta H^\circ_{\mathrm{t}}$, and $\Delta S^\circ_{\mathrm{t}}$ for

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* Analogously, the following extrathermodynamic "reference electrolyte" assumptions are widely used:

$$\Delta H^\circ_{\mathrm{t}}(\mathrm{Ph_4As^\oplus, W \rightarrow S}) = \Delta H^\circ_{\mathrm{t}}(\mathrm{Ph_4B^\ominus, W \rightarrow S}),$$

and similarly

$$\Delta S^\circ_{\mathrm{t}}(\mathrm{Ph_4As^\oplus, W \rightarrow S}) = \Delta S^\circ_{\mathrm{t}}(\mathrm{Ph_4B^\ominus, W \rightarrow S}),$$

for the transfer from water to all solvents at any temperature [244]. This is equivalent to assuming that the molar Gibbs energy of transfer, $\Delta G^\circ_{\mathrm{t}}(\mathrm{X, W \rightarrow S})$, at a given reference temperature (usually 298.15 K) is valid for all temperatures [244].

Table 2-9. Selected standard molar Gibbs energies of transfer of single ions X from water (W) to seven nonaqueous solvents (S), $\Delta G_t^{\circ}(\mathrm{X, W} \rightarrow \mathrm{S})/(\mathrm{kJ \cdot mol^{-1}})$[a], at 25 °C (molar scale), taken from the compilation of Marcus [244]. Values for $\mathrm{F}^{\ominus}$ were taken from G. T. Hefter, Pure Appl. Chem. *63*, 1749 (1991).

X	S						
	CH_3OH	C_2H_5OH	CH_3COCH_3	$HCON(CH_3)_2$	CH_3CN	CH_3SOCH_3	$[(CH_3)_2N]_3PO$
$H^{\oplus}$	10.4	11.1		−18	46.4	−19.4	
$Li^{\oplus}$	4.4	11		−10	25	−15	
$Na^{\oplus}$	8.2	14		−9.6	15.1	−13.4	
$K^{\oplus}$	9.6	16.4	4	−10.3	8.1	−13.0	−16
$Ag^{\oplus}$	6.6	4.9	9	−20.8	−23.2	−34.8	−44
$(CH_3)_4N^{\oplus}$	6	10.9	3	−5.3	3	−2	
$(C_6H_5)_4As^{\oplus}$[b]	−24.1	−21.2	−32	−38.5	−32.8	−37.4	−39
$F^{\ominus}$	16	26	79	85	71	73	
$Cl^{\ominus}$	13.2	20.2	57	48.3	42.1	40.3	58
$Br^{\ominus}$	11.1	18.2	42	36.2	31.3	27.4	46
$I^{\ominus}$	7.3	12.9	25	20.4	16.8	10.4	30
$CN^{\ominus}$	8.6	7	48	40	35	35	
$ClO_4^{\ominus}$	6.1	10		4	2		−7
$(C_6H_5)_4B^{\ominus}$[b]	−24.1	−21.2	−32	−38.5	−32.8	−37.4	−39

[a] A positive value of $\Delta G_t^{\circ}(\mathrm{X, W} \rightarrow \mathrm{S})$ means that the ion is better solvated by water than by solvent S; a negative value means that the ion is more strongly solvated after transfer from water to solvent S.

[b] See text for the so-called tetraphenylarsonium tetraphenylborate assumption.

the transfer of univalent single ions from water to other solvents has been given by Persson [301]. See Section 5.5.3 for further discussions.

The following three aspects are also of importance in solvation: the stoichiometry of the solvate complexes (normally described by the coordination or solvation number), the lability of the solvate complexes (usually described by the rate of exchange of the molecules of the solvent shell with those of the bulk solvent), as well as the fine structure of the solvation shell (for water often described by the simple model of ion solvation of Frank and Wen [16]).

Coordination and solvation numbers reflect the simple idea that the solvation of ions or molecules consists of a coordination of solute and solvent molecules. The *coordination number* is defined as the number of solvent molecules in the first coordination sphere of an ion in solution [103]. This first coordination sphere is composed only of solvent molecules in contact with or in bonding distance of the ion such that no other solvent molecules are interposed between them and the ion. This kind of solvation is sometimes termed *primary* or *chemical solvation*. Coordination numbers, determined by different experimental techniques [103], range in water from approx. 4 for $\mathrm{Be}^{2\oplus}$ to approx. 9 for $\mathrm{Th}^{4\oplus}$, although the majority of the values are close to 6 (*e.g.* for $\mathrm{Al}^{3\oplus}$).

The *solvation number* is defined as the number of solvent molecules per ion which remain attached to a given ion long enough to experience its translational movements [94, 97, 104]. The solvation number depends upon the reference ion and its assumed solvation number as well as upon the method of measurement. Depending on the method of measurement, solvent molecules loosely bound in the second or in a higher sphere may be included. The partial ordering of more distant solvent molecules beyond the primary solvation shell is termed *secondary* or *physical solvation*. For example, mobility measurements indicate the number of solvent molecules moving with the ion, while dielectric measurements indicate only the number of solvent molecules in the first sphere. The solvation number of $\mathrm{Li}^{\oplus}$ in water, determined using different electrolytic transference methods, varies therefore between 5 and 23. An inspection of the solvation numbers measured by electrolytic transport methods shows that the order of hydration numbers of the alkali metal cations is: $\mathrm{Li}^{\oplus} > \mathrm{Na}^{\oplus} > \mathrm{K}^{\oplus} > \mathrm{Rb}^{\oplus} > \mathrm{Cs}^{\oplus}$. The alkaline earth metal cations are more highly solvated than the alkali cations ($\mathrm{Mg}^{\oplus\oplus} > \mathrm{Ca}^{\oplus\oplus} > \mathrm{Sr}^{\oplus\oplus} > \mathrm{Ba}^{\oplus\oplus}$). The more dilute the solution the greater the solvation of a given ion. The halogen anions are hydrated in the order $\mathrm{F}^{\ominus} > \mathrm{Cl}^{\ominus} > \mathrm{Br}^{\ominus} > \mathrm{I}^{\ominus}$. Therefore, as a rule it can be stated that the smaller the ion and the greater its charge, the more highly it is solvated [94, 97, 104]. Conductance data show, that the solvation number for a given ion varies strongly with the solvent. Thus, the solvation number of $\mathrm{Li}^{\oplus}$ varies from 1.4 in sulfolane, 7 in methanol, 9 in acetonitrile to 21 in water. The conductance data also indicate that in all organic solvents used, the solvation of the alkali metal cations is in the order: $\mathrm{Li}^{\oplus} > \mathrm{Na}^{\oplus} > \mathrm{K}^{\oplus} > \mathrm{Rb}^{\oplus} > \mathrm{Cs}^{\oplus}$. The order of solvation of the halogen anions in the organic solvents studied is, in general, $\mathrm{Cl}^{\ominus} > \mathrm{Br}^{\ominus} > \mathrm{I}^{\ominus}$ [94, 97, 104].

Even in the case of strong interactions between solvent and solute, the life time of each solvate is brief since there is continuous rotation or exchange of the solvent shell molecules. The time required for reorientation of hydrates in water is of the order $10^{-10} \ldots 10^{-11}$ s at 25 °C [91]. If the exchange between bulk solvent molecules and those in the inner solvation shell of an ion is slower than the NMR time scale, then it is possible to observe two different resonance signals for the free and bound solvent. In this way, it has been shown, using ^{17}O NMR spectroscopy, that the hexaaquo hydration spheres of $Al^{3\oplus}$ and $Cr^{3\oplus}$, and the four water molecules bound by $Be^{2\oplus}$ exchange at a rate of less than $10^4/s$, while those of the alkali metal cations exchange at a rate faster than $10^4/s$ [96, 105].

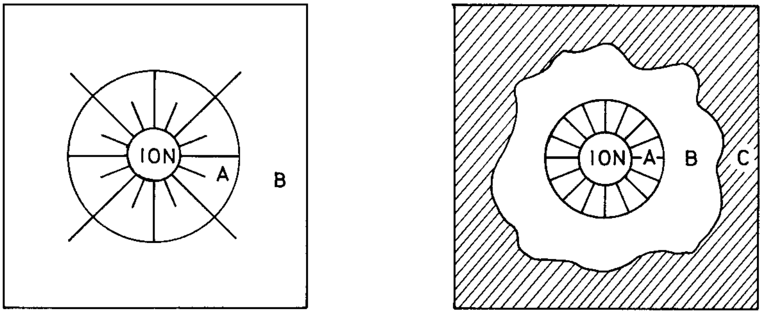
In general, since solvent molecules directly bound to an ion have different chemical shifts from those of the bulk solvent, NMR spectroscopy is a very useful method for studying solvation shells [106–111]. If the exchange rates are too high, however, the NMR signals coalesce to a single time-averaged resonance signal. It is usually assumed that solvent molecules in environments other than the first coordination sphere are exchanging at diffusion-controlled rates and therefore appear in the environmentally averaged bulk solvent resonance. A variety of different solvent nuclei have been used for this purpose: ^1H, ^{13}C, ^{17}O, and ^{31}P. As an example, the ^1H NMR spectrum of 2.1 M aqueous solution of $Al(NO_3)_3$ at −40 °C shows two signals [112]. The low-field signal arises from the coordinated solvent, and the high-field resonance from the bulk solvent. Two ^{13}C NMR signals are also observed for aqueous dimethyl sulfoxide containing $AlCl_3$ at 30 °C, one for the bulk and one for the bound solvent (1.94 ppm upfield) [113].

The ^1H NMR spectrum of an aqueous $Al(ClO_4)_3$ solution in [D_6]acetone shows nicely the two different signals of bulk water and hydration water in the $Al^{3\oplus}$ inner shell, even at room temperature [245]. The addition of acetone slows down the proton exchange rate. A primary hydration number of six for $Al^{3\oplus}$ has been obtained in this way [245].

Another approach to the study of ion-solvent interactions involves the determination of the solvent effect on the resonance frequency of the solute ion, using nuclei of spin $I \neq 0$ such as ^7Li, ^{23}Na, ^{27}Al, ^{35}Cl, ^{59}Co, ^{69}Ga, ^{133}Cs, ^{195}Pt, and ^{205}Tl [106–111, 111a, 246, 247, 294]. $^{205}Tl^{\oplus}$ is an exceptionally sensitive ion [294]. In going from water to pyridine the change in resonance frequency is approximately 782 ppm (!) [114]. In comparison, the change in chemical shift for $^{23}Na^{\oplus}$ in these two solvents is only about 1.3 ppm [115]. Therefore, $^{205}Tl^{\oplus}$ and other ions are very useful probes for the study of solvation and solvent structure. The greater the Lewis basicity of the solvent, the higher the resonance frequency of the $^{205}Tl^{\oplus}$ ion. The increase in resonance frequency with increasing solvent Lewis basicity can be considered as a measure of the strength of interaction between the solute ion and solvent molecules [294].

Other spectroscopic methods have also been used to study the statics and dynamics of solvation shells of ions and molecules [351–354]. In this respect, *solvation dynamics* refers to the solvent reorganization (*e.g.* rotation, reorientation, and residence time of solvent molecules in the first solvation shell) in response to an abrupt change in the solute properties, *e.g.* by photoexcitation of the solute with ultra-short laser-light pulses. Provided that this excitation is accompanied by an electron transfer or a change in the dipole moment, then the dynamics of this process correspond to how quickly the solvent molecules rearrange around the instantaneously created charge or the new dipole.

A number of models have been developed to describe the fine structure of the solvent shells of ions and molecules. While the agreement with experimental findings is more or less satisfactory, it is for the most part only qualitative (for reviews, see references [85, 91, 94, 95, 98]). According to the influence of the solute on the solvent structure, two different types of solvent can be distinguished (Fig. 2-9) [98]. In the former case, the pure solvent does not show a high degree of order. The directional properties of



(a) (b)

Fig. 2-9. Schematic multizone models for ion solvation in solvents: (a) with low degree of order such as hydrocarbons, consisting of solvation shell A and disordered bulk solvent B [98]; (b) in highly ordered solvents such as water, consisting of solvation shell A with immobilized solvent molecules, followed by a structure-broken region B, and the ordered bulk solvent C (Frank and Wen [16]).

the dissolved ion dominate in a rather large region around the center and decrease gradually on proceeding into the unperturbed bulk solvent. The solution consists of an ordered sphere – the primary solvation shell A – and the disordered bulk solvent B (Fig. 2-9a) [98].

In the latter case, the solvent possesses a highly ordered structure such as that found in water. Frank and Wen [16] distinguish between three different regions in the solvent surrounding a solute. In the first coordination sphere A, the solvent molecules are strongly bound to the ion and therefore appear less mobile than the molecules in the bulk solvent. At some distance from the ion there exists the normal structure of the pure ordered solvent C. Between A and C, according to Frank and Wen [16], lies an intermediate region of disorder B, with highly mobile solvent molecules. This has been introduced in order to explain the "structure making" and "structure breaking" properties of ions of different charge and size in aqueous solutions. The concept of different regions around the dissolved ion was developed by Gurney [116], who introduced the term *cosphere* for the zone surrounding a spherical ion in which significant differences in structure and properties of solvent molecules are to be expected*). In contrast to the ordinary strong *positive hydration* of small spherical ions possessing a structure-making effect on the solvent molecules (*cf.* Fig. 2-9a), water molecules around a dissolved ion are in some cases more mobile than in pure water. In other words, the exchange frequency of water molecules around the ions is greater than in regions of pure water (*cf.* region B in Fig. 2-9b). This explains the experimental observation that aqueous solutions of certain salts such as potassium iodide show a greater fluidity than pure water at the same temperature. This effect has been called *negative hydration* [85] and it is con-

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* In a liquid, the formation of temporary solvent molecule groups which have some crystalline character has been called *cybotaxis* (Greek, *κυβεύω*, dice-play, *τάξις*, an arrangement) by Stewart [116a]; see also [116b]. A *cybotactic region* may then be defined as the volume around a solute molecule in which the ordering of the solvent molecules has been influenced by the solute, including both the first solvation shell and the transition region; *cf.* [129].

nected with the structure-breaking effect of large singly-charged spherical ions on solvent molecules [91, 117]. The structure-breaking effect of large ions is not restricted to water as a solvent. Ethylene glycol and glycerol are liquids which also show this effect for a number of salts that cause structure-breaking in water [117]. To date, however, the validity of the multizone models for ion solvation proposed by Frank and Wen [16] and others has lacked direct experimental proof [117]. Consequently, owing to the lack of detailed knowledge of the solvents' structure and of satisfactory molecular theories for associated liquids, all attempts at a detailed description of solvation shells are still imperfect.

The solubility of a dissolved non-electrolyte solute can be reduced by the addition of a salt. This phenomenon, known as the *salting-out effect*, is of practical importance for the isolation of organic compounds from their solutions. In the presence of a dissolved dissociated salt, a fraction of the solvent molecules becomes involved in solvational interaction with the ions of the electrolyte, whereby their activity is diminished, leading to salting-out of the dissolved non-electrolyte solute. In other words, the salting-out can be considered as the difference in solubility in two kinds of solvents, the ion-free and the ion-containing one [248].

Theoretical chemists have developed a variety of methods and computational strategies for describing and understanding the complex phenomenon of solvation [27d, 355–358]. Altogether, three general approaches have been used for the theoretical description of solute/solvent interactions:

(a) quantum-chemical continuum models, where the solvent is treated as a structureless, *i.e.* continuous and homogeneous, medium that surrounds the solute ions or molecules like a bath, characterized solely by its relative permittivity ε_r. The solvated species (ions, polar molecules) induce polarization charges in the surrounding solvent continuum that in turn give rise to an extra electric field in the vicinity of the solute, called (Onsager) reaction field [357, 359; and references cited therein];
(b) supramolecular models, which treat the solvent molecules around the solute on the same footing as the solute, *i.e.* as discrete particles in an ensemble of solute and solvent species, using Monte Carlo statistical mechanics or molecular dynamics techniques [360, 361; and references cited therein];
(c) semicontinuum quantum-chemical models, which retain the reaction field contribution, but the direct electrostatic solute/solvent interactions in the first solvation shell are modeled differently. That is, the supermolecule (solute + first solvation shell) is surrounded by a continuum solvent [362–364; and references cited therein].

Particularly during the last decade, much progress has been made in the theoretical description of solvation. However, when applied to actual solutes, all models still have their limitations and flaws. For comprehensive reviews on theoretical treatments of solvation phenomena, see references [27d, 355–358].

2.4 Selective Solvation [89, 94, 96, 118–120, 241, 249, 250]

The description of solvation of ions and molecules in solvent mixtures is even more complicated. Besides the interaction between solvent and solute, the interaction between unlike solvent molecules plays an important supplementary role. This leads to large

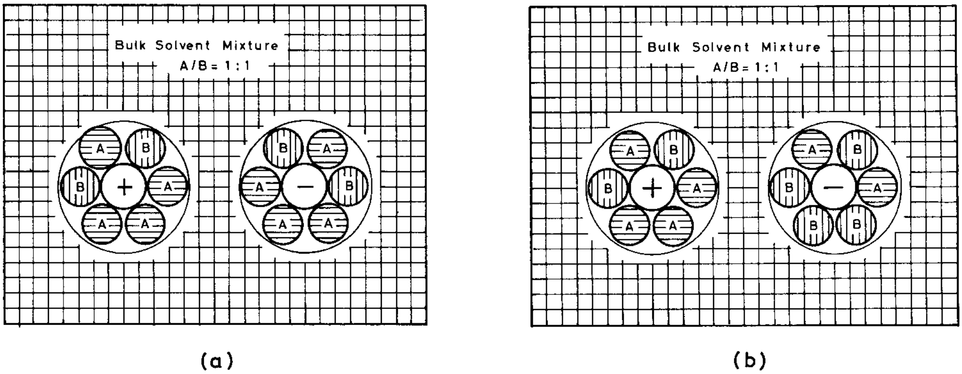

Fig. 2-10. Schematic model for the selective solvation of ions by one component of a binary 1:1 mixture of the solvents A and B [119].

(a) Homoselective solvation: both ions are preferentially solvated by the same solvent A.

(b) Heteroselective solvation: the cation is preferentially solvated by A and the anion by B.

deviations from the ideal behaviour expected from Raoult's law of vapour pressure depression of binary mixtures; see references [365, 366] for reviews on the physicochemical properties of solvent mixtures. Typical examples of the non-ideal behaviour of binary solvent mixtures are water/alcohol [19], dimethyl sulfoxide/methanol [367], as well as water/methanol and water/acetonitrile mixtures [368]. When water is mixed with methanol an exothermic mixing enthalpy is observed, whereas in the case of acetonitrile the enthalpy of mixing is endothermic [368].

From investigations of the solvation of ions and dipolar molecules in binary solvent mixtures it has been found that the ratio of the solvent components in the solvent shell can be different from that in the bulk solution. As expected, the solute is surrounded preferably by the component of the mixture which leads to the more negative Gibbs energy of solvation, ΔG°_{solv}. The observation that the solvent shell has a composition other than the macroscopic ratio is termed *selective* or *preferential solvation* (*cf.* Fig. 2-10). These terms are generally used to describe the molecular-microscopic local solute-induced inhomogeneity in a multicomponent solvent mixture. They include both (i) nonspecific solute/solvent association caused by dielectric enrichment in the solvent shell of solute ions or dipolar solute molecules, and (ii) specific solute/solvent association such as hydrogen-bonding or EPD/EPA interactions.

When in a mixture of two solvents, both ions of a binary salt are solvated preferably by the same solvent, the term applied is *homoselective solvation* (Fig. 2-10a). Similarly, the preferred solvation of the cation by one, and the anion by the other solvent, is termed *heteroselective solvation* (Fig. 2-10b) [119]. Thus, in a solution of silver nitrate in the binary solvent mixture acetonitrile/water, a preferential solvation of $Ag^\oplus$ by acetonitrile and of $NO_3^\ominus$ by water was observed (heteroselective solvation) [121, 369]*). In contrast, in solutions of calcium chloride in water/methanol mixtures, both $Ca^{2\oplus}$ and $Cl^\ominus$ are solvated largely by water (homoselective solvation) [122]. $Zn^{2\oplus}$ (from $ZnCl_2$) in

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* The reasons for preferential solvation of $Ag^\oplus$ ions by acetonitrile in acetonitrile/water mixtures and the solvation shell structure of silver ions have been discussed [251].

the solvent mixture water/hydrazine is preferentially solvated by hydrazine; in an acetonitrile/water mixture solvation is largely by water [123]. Ag_2SO_4 is heteroselectively solvated in methanol/dimethyl sulfoxide mixtures: the silver ion is preferentially solvated by dimethyl sulfoxide, whereas the sulfate ion is preferably solvated by methanol. The Ag_2SO_4 salt is only sparingly soluble in methanol and in dimethyl sulfoxide. Its solubility is higher in mixtures of the two solvents than in the neat liquids, since both the cation and the anion can be solvated with the solvent component for which it has a greater affinity [123a]. A study of silver(I) salts in the *isodielectric* mixture of methanol ($\varepsilon_r = 32.7$) and *N*-methylpyrrolidin-2-one (NMP; $\varepsilon_r = 32.2$) showed heteroselective solvation of Ag^+ by NMP and the anions ($SO_4{}^{2-}$, $BrO_3{}^-$, $IO_3{}^-$) by methanol [370]. The $Cu^{\oplus}$ ion (from $CuClO_4$) shows strong preferential solvation by acetonitrile in acetonitrile/acetone mixtures, which may be of interest in the hydrometallurgical purification of copper [252]. Even protons exhibit preferential solvation by amines in mixed water/amine ion clusters studied in the gas phase [253].*⁾

In a binary mixture of solvents S_1 and S_2, a cation $M^{z\oplus}$ with a coordination number k and charge $z^{\oplus}$ forms $(k+1)$ cations of the type $[M(S_1)_i(S_2)_{k-i}]^{z\oplus}$ with $i = 0 \ldots k$, differently solvated in the first solvation shell. These differently solvated species have been called *solvatomers* [254]. For example, with octahedrally coordinated cations ($k = 6$), $k + 1 + 3 = 10$ solvatomers are to be expected (including three *cis/trans* isomeric solvatomers with $i = 2$, 3, or 4). In favourable cases, the concentrations of all solvatomers have been obtained as a function of the solvent mole fraction by NMR measurements [254].

Preferential solvation is not restricted to ions of electrolytes dissolved in multicomponent solvent systems. Even for dipolar nonelectrolyte solutes the composition of the solvation shell can deviate from that of the bulk solvent mixture, as shown for *β*-disulfones [255] and *N*-methylthiourea [256].

Different methods for the study of selective solvation have been developed [118, 120]: conductance and Hittorf transference measurements [119], NMR measurements (especially the effect of solvent composition on the chemical shift of a nucleus in the solute) [106–109], and optical spectra measurements like IR absorption shifts [111] or UV/Vis absorption shifts of solvatochromic dyes in binary solvent mixtures [124, 249, 371]. Recently, the preferential solvation of ionic (tetralkylammonium salts) and neutral solutes (phenol, nitroanilines) has been studied particularly successfully by ^1H NMR spectroscopy through the analysis of the relative intensities of intermolecular ^1H NOESY cross-peaks [372].

A convenient measure of the degree of selective solvation is the bulk solvent composition at which both solvents of a binary mixture participate equally in the contact solvation shell. This is the solvent composition at which the NMR chemical shifts lie midway between the values for the two pure solvents. This composition has been called the *equisolvation* or *iso-solvation point* (usually expressed in mole fractions of one solvent) [125]. According to Fig. 2-10, this point describes the bulk solvent composition at which both solvents A and B participate equally in the solvation shell of the cation or the anion, respectively.

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* A comprehensive tabulation of selective solvation of ions in a number of binary solvent systems is given by Gordon [96] (p. 256).

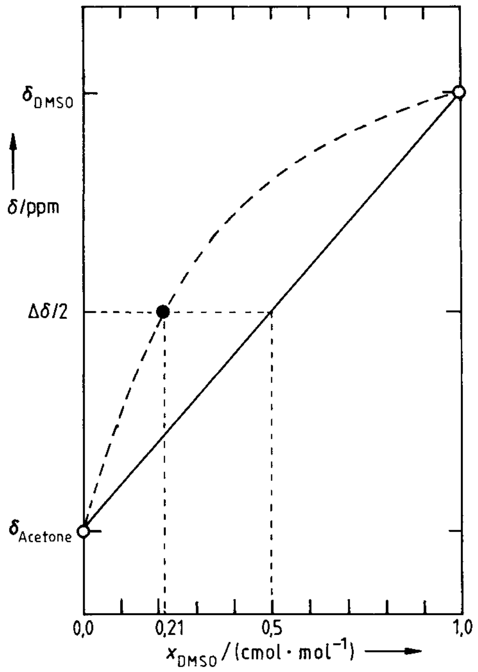
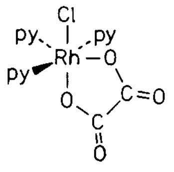


Fig. 2-11. NMR chemical shift of $^{23}Na^{\oplus}$ as a function of the mole fraction of dimethyl sulfoxide (DMSO) in a binary mixture of DMSO and acetone (according to [295]). *Straight line:* ideal case without preferential solvation, primary solvation shell of the same composition as the bulk solvent mixture. *Curved line:* real case with preferential solvation of $^{23}Na^{\oplus}$ by DMSO and iso-solvation point at $x_{DMSO}/(\mathrm{cmol \cdot mol^{-1}}) \approx 0.21$, that is, the mole fraction of the bulk solvent for which the solvated ion chemical shift is the average of the shifts obtained in the pure solvents ($\Delta\delta = \delta_{DMSO} - \delta_{Acetone}$).

A useful probe of the immediate chemical environment of solute ions is the NMR chemical shift of alkali metal ions obtained in binary solvent mixtures [111, 126, 295]. These measurements are based on the assumption that the chemical shift of the solute cation is determined in an additive fashion by the solvent molecules comprising the first solvation shell. For example (*cf.* Fig. 2-11), the iso-solvation point of $^{23}Na^{\oplus}$ in dimethyl sulfoxide/acetone mixtures occurs at $x \approx 0.21$ cmol/mol dimethyl sulfoxide, indicating the higher solvating ability of this solvent relative to acetone. As shown schematically in Fig. 2-11, the preferential solvation of $^{23}Na^{\oplus}$ by dimethyl sulfoxide displaces its chemical shift towards δ_{DMSO} and a deviation from the straight line is observed.

The iso-solvation points obtained from $^{23}Na^{\oplus}$ chemical shifts of sodium tetraphenylborate in different binary solvent mixtures indicate the following relationships between the solvating abilities of pairs of organic solvents: $CH_3SOCH_3 \gg CH_3NO_2$; pyridine > CH_3NO_2; $CH_3SOCH_3 > CH_3CN$; pyridine > CH_3CN; $C_6H_5CN > CH_3NO_2$; CH_3SOCH_3 > pyridine [126].

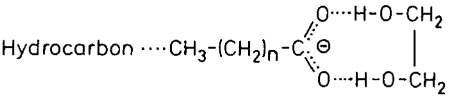
The term selective solvation also applies when one and the same dipolar molecule is preferentially solvated at two different loci by two different solvents. An example is the



(1)

chloro-oxalato-tripyridine-rhodium(III) complex (*1*), which dissolves in a 1:1 mixture of pyridine and water, but not in either pure water or pyridine [127]. Presumably, a Gibbs energy of solvation large enough to overcome the lattice forces is attained only by selective solvation of the three pyridine ligands by pyridine, and of the oxalato ligand by water.

Many macromolecular compounds dissolve in mixtures better than in pure solvents [20]. Thus, poly(vinyl chloride) is insoluble in acetone as well as in carbon disulfide, but soluble in a mixture of the two. The opposite situation is also known. Malononitrile and *N*,*N*-dimethylformamide both dissolve polyacrylonitrile but a mixture of the two does not [20]. Soaps dissolve neither in ethylene glycol nor in hydrocarbons at room temperature but are quite soluble in a mixture of the two. Here, ethylene glycol solvates the ionic end, and the hydrocarbon the apolar end of the fatty acid chain [128].



A great variety of models for a quantitative description of the composition dependence of the physicochemical properties of solutes dissolved in binary solvent mixtures have been developed [257–261, 373–378]. For example, using a rather simple two-step solvent-exchange model [374, 377], the behaviour of seventy binary solvent mixtures towards a solvatochromic betaine dye (structure see Fig. 6-2 in Section 6.2.1) can be quite precisely described, even for so-called *synergetic* solvent mixtures [377].

A binary solvent mixture exhibits *synergistic effects* on a physicochemical solute property P if for some mixtures this property P has a value higher or lower than either properties P_1 and P_2 corresponding to the neat solvents S_1 and S_2 [379]. For example, the empirically determined solvent polarity of binary mixtures of HBD and HBA solvents is often larger than the polarities of the two neat components. Clearly, the formation of hydrogen-bonded 1:1 complexes between HBD ad HBA solvent molecules leads to a new, more polar medium [124, 249, 377] (see Chapter 7 for a definition of the term *solvent polarity*).

The non-ideal behaviour of a wide selection of binary solvent mixtures has been studied experimentally mainly by means of suitable solvatochromic dyes, the UV/Vis absorptions of which are solvent-dependent (*cf.* Section 6.2.1); see references [380–385] for some more recent examples. Conversely, the largely non-ideal solute behaviour in binary solvent mixtures has been used for the quantitative determination of the compositions of such solvent mixtures, *e.g.* for the determination of small water contents in organic solvents [386–388].

2.5 Micellar Solvation (Solubilization) [96, 128, 130–132, 220, 262–267]

Special conditions are found in solutions of large cations and anions possessing a long unbranched hydrocarbon chain, *e.g.* $CH_3{—}(CH_2)_n{—}CO_2^{\ominus}M^{\oplus}$, $CH_3{—}(CH_2)_n{—}SO_3^{\ominus}M^{\oplus}$, or $CH_3{—}(CH_2)_n{—}N(CH_3)_3^{\oplus}X^{\ominus}$ (with $n > 7$). Such compounds are known as *amphiphiles*, reflecting the presence of distinct polar and nonpolar regions in the

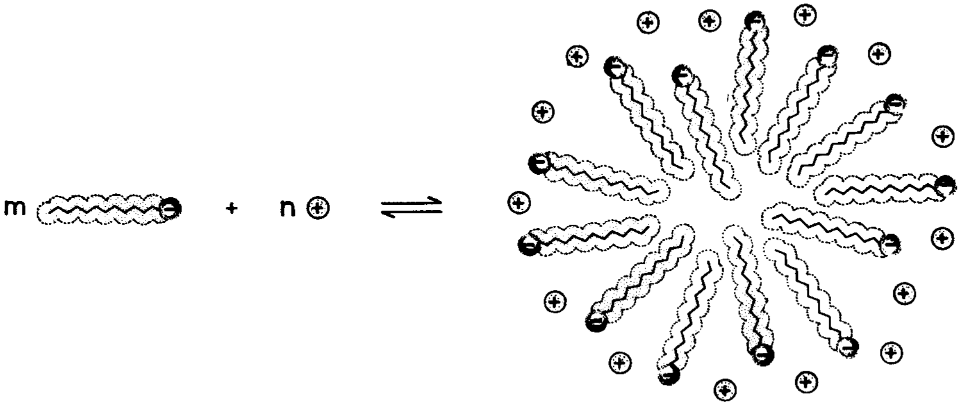


Fig. 2-12. Schematic two-dimensional representation of spherical micelle formation by an anionic amphiphile such as $CH_3—(CH_2)_{11}—CO_2^{\ominus}M^{\oplus}$ in water. The head group (⊖), the counterions (⊕), and the hydrocarbon chains are only schematically indicated to denote their relative position. The highly charged interface (ionic head groups plus bound counterions) between the micelle's hydrophobic core and the bulk solution is called the *Stern layer*. For a more realistic three-dimensional picture of a micelle, see references [264, 389].

molecule. Salts of such large organic ions are often highly aggregated in dilute aqueous solution. The resulting structured aggregates, together with counterions localized near their periphery by coulomb forces, are termed *micelles*[*]. Fig. 2-12 gives a schematic representation of the formation of a spherical micelle by an anionic amphiphile.

The hydrophobic part of the aggregate molecules forms the core of the micelle while the polar head groups are located at the micelle-water interface in contact with the water molecules. Such micelles usually have average radii of 2...4 nm and contain 50...100 monomers in water. Their geometric structure is usually roughly spherical or ellipsoidal. In non-aqueous nonpolar solvents, the micellar structures are generally the inverse of those formed in water. In these solvents, the polar head groups form the interior of the micelle while the hydrocarbon chains of the ions are in contact with the nonpolar solvent.

At very low concentrations, ionic amphiphiles behave as normal strong electrolytes, but if the concentration is raised above the so-called *c*ritical *m*icelle *c*oncentration (*cmc*; usually $10^{-4} \ldots 10^{-2}$ mol · l^{-1}), spherical aggregates are formed. Increasing the amphiphile (surfactant) concentration results in two different effects [264, 389]: (a) the increasing amphiphile concentration leads to an increased ionic strength of the aqueous bulk solution, thus decreasing the electrostatic repulsion between the head groups due to screening of their negative or positive charges; (b) for the hydrophobic hydrocarbon tails, an increase in the amphiphile concentration is unfavourable because of the increasing hydrophobic amphiphile/water interactions (see Section 2.2.7). Eventually,

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[*] The term *micelle* was introduced in 1877 by Nägeli (from the Latin *mica*, a crumb) for a molecular organic aggregate of limited size without exact stoichiometry [270]. The existence of surfactant aggregates in aqueous soap solutions was established in 1896 by Krafft [271], and the first description of a surfactant micelle was given in 1913 by Reychler [272].

Table 2-10. Some typical surfactants (*surf*ace *act*ive *a*ge*nts*) with their critical micelle concentrations (*cmc*) and aggregation numbers in aqueous solutions at 25 °C [268].

Surfactants	*cmc*/(mol · l^{-1})	Aggregation number
Anionic		
Sodium 1-dodecyl sulfate (SDS)	0.0081	62
$CH_3—(CH_2)_{11}—OSO_3^{\ominus}Na^{\oplus}$		
Cationic		
1-Hexadecyl (=Cetyl)-trimethylammonium bromide (CTAB)	0.0013	78
$CH_3—(CH_2)_{15}—\overset{\oplus}{N}(CH_3)_3Br^{\ominus}$		
Nonionic		
Hexa(oxyethylene)dodecanol	0.00009	400
$CH_3—(CH_2)_{11}—(OCH_2CH_2)_6—OH$		
Zwitterionic		
3-(*N*-1-Dodecyl-*N*,*N*-dimethylammonio)propane-1-sulfonate (SB 12)	0.003	55
$CH_3—(CH_2)_{11}—\overset{\oplus}{N}(CH_3)_2—(CH_2)_3—SO_3^{\ominus}$		

the driving force for dissolution of the amphiphile will be completely balanced by the forces working against the dissolution of the hydrophobic tails. Now, two different scenarios are possible: either a macroscopic phase separation will occur (*i.e.* formation of aggregates of infinite size), or micelles will be formed (*i.e.* formation of aggregates of finite size). Such micelles are thermodynamically stable, microheterogeneous, supramolecular species, dissolved in the aqueous bulk. They are characterized by the aforementioned *cmc* and the *micellar aggregation number*, both of which are dependent on the hydrocarbon tail length, the nature of the counter ion, and the ionic strength of the bulk solution.

Typical surfactants are listed in Table 2-10 along with their respective *cmc* values and aggregation numbers [268].

In reality, micellar systems are more complex than is implied by the simple static picture given in Fig. 2-12 (also known as the Hartley model [390]). A more realistic picture of micellar structures has been given by Menger [269]. According to his "porous cluster" or "reef" model, micelles possess rugged, dynamic surfaces, water-filled pockets, nonradial distribution of chains, and random distribution of terminal methyl groups. In fact, a micelle is a highly disorganized structure with multiple bent hydrocarbon chains, cavities, and even hydrocarbon/water contacts, and shows deviations from a precise spherical shape. A micelle is a dynamic molecular assembly which exists in equilibrium with its monomer, where monomer units are both leaving and entering the micelle. A monomer remains in a micelle for only $10^{-8} \ldots 10^{-3}$ s depending on the chain length of the surfactant molecule. Another, so-called surfactant-block model of micelles, has been given by Fromherz [273].

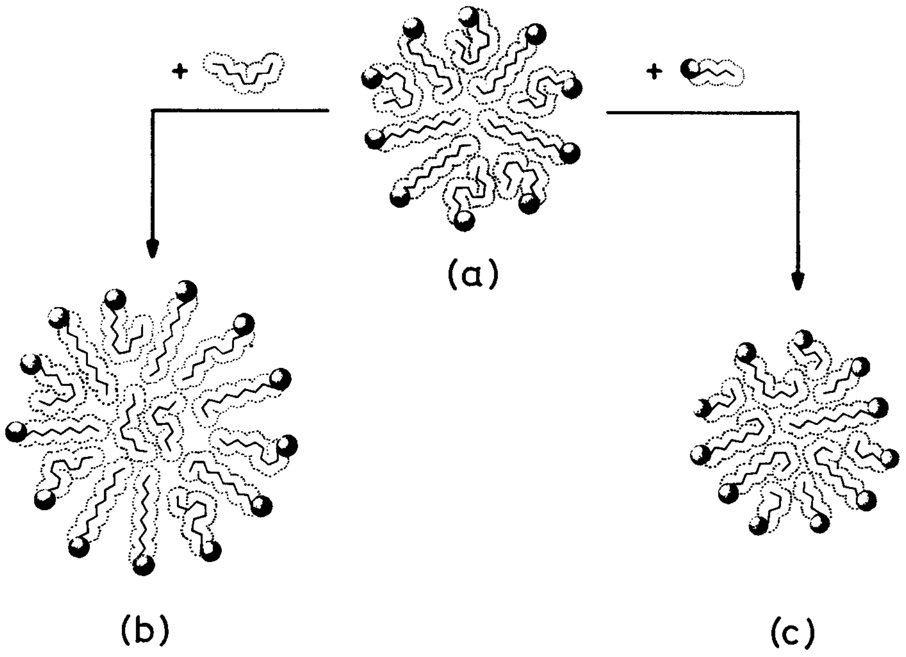

Fig. 2-13. Schematic two-dimensional representation of the solubilization of (b) *n*-nonane as a nonpolar substrate, and (c) 1-pentanol as another amphiphile, by a spherical ionic micelle (a) of an *n*-decanoic acid salt in water.

The existence of micelles in solutions of large ions with hydrocarbon chains is responsible for the observation that certain substances, normally insoluble or only slightly soluble in a given solvent, dissolve very well on addition of a surfactant (detergent or tenside). This phenomenon is called *solubilization* and implies the formation of a thermodynamically stable isotropic solution of a normally slightly soluble substrate (the *solubilizate*) on the addition of a surfactant (the *solubilizer*) [128, 133]. Non-ionic, nonpolar solubilizates such as hydrocarbons can be trapped in the hydrocarbon core of the micelle. Other amphiphilic solutes are incorporated alongside the principal amphiphile and oriented radially, and small ionic species can be adsorbed on the surface of the micelle. Two modes of solubilizate incorporation are illustrated in Fig. 2-13.

Because the micellar interior is far from being rigid, a solubilized substrate is relatively mobile. Like micelle formation, solubilization is a dynamic equilibrium process. Representative recent examples are the solubilization of benzene, naphthalene, anthracene, and pyrene in aqueous solution by the addition of 1-dodecanesulfonic acid [391], the solubilization of fullerene C_{60} in aqueous solutions of the non-ionic surfactant Triton X-100 [392], and the solubilization of a cholesteryl-group bearing pullulane (a hydrophobized polysaccharide) [393].

Essentially spherical micelles are not the only aggregates that can be formed in aqueous solution above the critical micelle concentration. Depending on the molecular structure of the amphiphile and the solution conditions (*e.g.* electrolyte concentration, pH, temperature), inverted micelles, bilayers, vesicles, and biological membranes can readily be formed by spontaneous self-association [394] of certain amphiphilic molecules [130–132, 264]. In contrast to infinite *planar* bilayers, vesicles or liposomes (vesicles formed from lipids) are closed *spherical* bilayer aggregates that are much larger than micelles. Eventually, the mutual interaction of these aggregates at high concentrations (low water content) can lead to a transition to larger and more ordered *mesophases* or *lyotropic liquid crystalline* structures [264].

Not only solubilities, but also the rates and selectivities of organic reactions can be affected by the addition of surfactants to the reaction medium. The modification of chemical reactions by incorporating the reactant molecules into organized assemblies as a kind of microreactor has been the subject of considerable attention [274–277, 395, 396] (*cf.* also Section 5.4.8).

2.6 Ionization and Dissociation [49, 96, 134–139, 241, 278, 279]

Solutions of non-electrolytes contain neutral molecules or atoms*⁾ and are non-conductors. Solutions of electrolytes are good conductors due to the presence of anions and cations. The study of electrolytic solutions has shown that electrolytes may be divided into two classes: *ionophores* and *ionogens* [134]. Ionophores (like alkali halides) are ionic in the crystalline state and they exist only as ions in the fused state as well as in dilute solutions. Ionogens (like hydrogen halides) are substances with molecular crystal lattices which form ions in solution only if a suitable reaction occurs with the solvent. Therefore, according to Eq. (2-13), a clear distinction must be made between the *ionization* step, which produces ion pairs by heterolysis of a covalent bond in ionogens, and the *dissociation* process, which produces free ions from associated ions [137, 397, 398].

$$\underset{\text{Ionogen}}{(\mathrm{A{-}B})_{\mathrm{solv}}} \overset{K_{\mathrm{Ion}}}{\rightleftharpoons} \underset{\text{Ion Pair}}{(\mathrm{A^{\oplus}B^{\ominus}})_{\mathrm{solv}}} \underset{K_{\mathrm{Assoc}}}{\overset{K_{\mathrm{Dissoc}}}{\rightleftharpoons}} \underset{\text{Free Ions}}{(\mathrm{A^{\oplus}})_{\mathrm{solv}} + (\mathrm{B^{\ominus}})_{\mathrm{solv}}} \tag{2-13}$$

$$K_{\mathrm{Ion}} = [\mathrm{A^{\oplus}B^{\ominus}}]/[\mathrm{A-B}] \tag{2-14}$$

$$K_{\mathrm{Dissoc}} = [\mathrm{A^{\oplus}}]\cdot[\mathrm{B^{\ominus}}]/[\mathrm{A^{\oplus}B^{\ominus}}] \tag{2-15}$$

The index "solv" indicates that the species in parentheses are within one solvent cage.

Ionophores may exist in solution as an equilibrium mixture containing ion pairs and free ions. *Ion pairs* are defined as pairs of oppositely charged ions with a common solvation shell, whose life times are sufficiently long to render them recognizable kinetic entities in solution and for which only electrostatic binding forces are assumed [135]. Experimentally, ion pairs behave as one unit in determining electric conductivity, kinetic behaviour, and some thermodynamic properties (*e.g.* activity coefficient; osmotic pres-

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* An example of a monoatomic un-ionized substrate solution is that of mercury in air-free water, which contains zero-valent mercury atoms [140].

sure) of electrolyte solutions. In an external electric field such paired ions do not move individually but reorient themselves as an electric dipole. The ion-pair concept was introduced in 1926 by Bjerrum [280] to account for the behaviour of ionophores in solvents of low relative permittivity.

It is possible to distinguish between free ions from associated and covalently bonded species by conductivity measurements, because only free ions are responsible for electrical conductivity in solution [136, 399]. Spectrophotometric measurements distinguish between free ions and ion pairs on the one hand, and covalent molecules on the other, because in a first approximation the spectroscopic properties of ions are independent of the degree of association with the counterion [141]. The experimental equilibrium constant K_{exp}, obtained from conductance data, may then be related to the ionization and dissociation constants by Eq. (2-16).

$$K_{\mathrm{exp}} = \frac{[\mathrm{A}^{\oplus}] \cdot [\mathrm{B}^{\ominus}]}{[\mathrm{A-B}] + [\mathrm{A}^{\oplus}\mathrm{B}^{\ominus}]} = \frac{K_{\mathrm{Ion}} \cdot K_{\mathrm{Dissoc}}}{1 + K_{\mathrm{Ion}}} \tag{2-16}$$

When the extent of ionization is small, then $K_{\mathrm{exp}} = K_{\mathrm{Ion}} \cdot K_{\mathrm{Dissoc}}$ ($K_{\mathrm{Ion}} \ll 1$ or $[\mathrm{A}^{\oplus}\mathrm{B}^{\ominus}] \approx 0$). For strong electrolytes, where $K_{\mathrm{Ion}} \gg 1$, Eq. (2-16) reduces to $K_{\mathrm{exp}} = K_{\mathrm{Dissoc}}$.

Another equation, more comprehensive than Eq. (2-16), has been developed by Izmailov according to $K_{\mathrm{exp}} = K_{\mathrm{dissoc}}/(1 + K_{\mathrm{ion}} + K^*)$, where K^* describes the equilibrium A—B + solv $\rightleftharpoons$ $(\mathrm{A—B})_{\mathrm{solv}}$ [412].

The two steps of Eq. (2-13), ionization and dissociation, are influenced in different ways by solvents. The coulombic force of attraction between two oppositely charged ions is inversely proportional to the relative permittivity of the solvent, according to Eq. (2-17). Therefore, only solvents with sufficiently high relative permittivities will be capable

$$U_{\text{ion-ion}} = -\frac{1}{4\pi \cdot \varepsilon_0} \cdot \frac{z^{\oplus} \cdot z^{\ominus} \cdot e^2}{\varepsilon_{\mathrm{r}} \cdot r} \tag{2-17}$$

(U = potential energy of an ion-ion interaction; $z \cdot e$ = charge on the ion; r = distance between the ions; ε_0, ε_{r} = permittivity of the vacuum and of the medium, resp.)

of reducing the strong electrostatic attraction between oppositely charged ions to such an extent that ion pairs can dissociate into free solvated ions. These solvents are usually called *dissociating solvents**).

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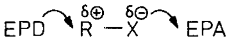
* Nernst [141a] and Thomson [141b] first showed independently that solvents of high relative permittivity promote the dissociation of ionic solutes. The term "dissociating solvent" was first used by Beckmann [141c] in connection with his ebullioscopic determination of the molecular mass of dissolved substances. Later on the term "smenogenic solvent" was proposed by Fuoss for solvents of low relative permittivity which favor the formation of ion pairs. Conversely, "smenolytic solvents" are those whose relative permittivities are high enough to prevent ion association [134]. The latter two terms have, however, found little application.

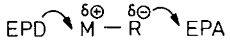
According to Eq. (2-17), for two isolated ions such as Na^+ and Cl^- in contact in vacuum ($\varepsilon_r = 1$), with $r = 276$ pm as the sum of the two ionic radii, the electrostatic binding energy is -8.4×10^{-19} J [26b]. This binding energy is of the order $200 \cdot kT$ per ion pair in vacuum, as compared to the thermal energy $kT = 4.1 \times 10^{-21}$ J at 300 K. Only at ion separation $r > 56000$ pm will the Coulomb energy fall below kT, which means that electrostatic Coulomb interactions are very strong and of long range [26b]. At ca. 500 kJ/mol ($=8.4 \times 10^{-19} \times 6.0 \times 10^{23}$), this interionic binding energy is similar to the energies of covalent bonds (*i.e.* 200–600 kJ/mol). The electrostatic interaction between oppositely charged ions can only be overcome by liberation of the molar Gibbs energy of solvation, $\Delta G^\circ_{\mathrm{solv}}$, in transferring the ion pair from the gas phase (vacuum) into a medium with $\varepsilon_r \gg 1$.

Ion association is only noticeable in aqueous solutions at very high concentrations because of the exceptionally high relative permittivity of water ($\varepsilon_r = 78.4$), but are found at much lower concentrations in alcohols, ketones, carboxylic acids, and ethers. In solvents of relative permittivities less than 10...15, practically no free ions are found (*e.g.* in hydrocarbons, chloroform, 1,4-dioxane, acetic acid); on the other hand, when the relative permittivity exceeds 40, ion associates barely exist (*e.g.* water, formic acid, formamide). In solvents of intermediate relative permittivity ($\varepsilon_r = 15\ldots20$, *e.g.* ethanol, nitrobenzene, acetonitrile, acetone, *N,N*-dimethylformamide), the ratio between free and associated ions depends on the structure of the solvent as well as on the electrolyte (*e.g.* ion size, charge distribution, hydrogen-bonded ion pairs, specific ion solvation, *etc.*) [96]. Thus, lithium halides in acetone ($\varepsilon_r = 20.6$) are very weak electrolytes, whereas tetraalkylammonium halides are strongly dissociated in the same solvent [142–144]. In solvents of very low relative permittivity like benzene ($\varepsilon_r = 2.3$), very large association constants are usually found. This indicates that most ion pairs in such solutions exist in the form of higher aggregates [96].

The ability of a solvent to transform the covalent bond of an ionogen into an ionic bond, *i.e.* its *ionizing power*, is not determined in the first instance by its relative permittivity. Rather, the ionizing power of a solvent depends on its ability to function as an electron-pair acceptor or donor [53, 137]. A dissociating solvent is not necessarily an ionizing one – and *vice versa*. In most cases, ionization of bonds of the type $H^{\delta\oplus}$—$X^{\delta\ominus}$ (*e.g.* ionization of hydrogen halides), $R^{\delta\oplus}$—$X^{\delta\ominus}$ (*e.g.* ionization of haloalkanes in S_N1 reactions), or $M^{\delta\oplus}$—$R^{\delta\ominus}$ (*e.g.* ionization of organometallic compounds) is strongly assisted by electron-pair donor (EPD) and electron-pair acceptor (EPA) solvents (*cf.* Section 2.2.6), according to (R = H, alkyl):

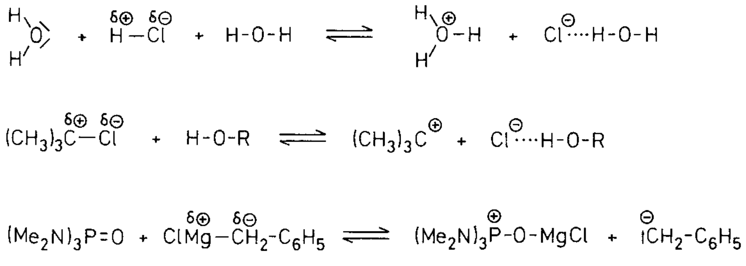


$$\mathrm{EPD} \curvearrowright \overset{\delta\oplus}{\mathrm{R}} - \overset{\delta\ominus}{\mathrm{X}} \curvearrowright \mathrm{EPA}$$



$$\mathrm{EPD} \curvearrowright \overset{\delta\oplus}{\mathrm{M}} - \overset{\delta\ominus}{\mathrm{R}} \curvearrowright \mathrm{EPA}$$

The ionization of an ionogen can therefore be regarded as a coordinative interaction between substrate and solvent [281]. The polarization of the covalent bond to be ionized can occur *via* a nucleophilic attack of the EPD solvent on the electropositive end of the bond, or by an electrophilic attack of an EPA solvent on the electronegative end. Both attacks can, of course, also occur simultaneously. The following examples are illustrative.



$$H_2O + \overset{\delta\oplus}{H}-\overset{\delta\ominus}{Cl} + H{-}O{-}H \rightleftharpoons H_2\overset{\oplus}{O}{-}H + \overset{\ominus}{Cl}\cdots H{-}O{-}H$$

$$(CH_3)_3\overset{\delta\oplus}{C}-\overset{\delta\ominus}{Cl} + H{-}O{-}R \rightleftharpoons (CH_3)_3C^{\oplus} + \overset{\ominus}{Cl}\cdots H{-}O{-}R$$

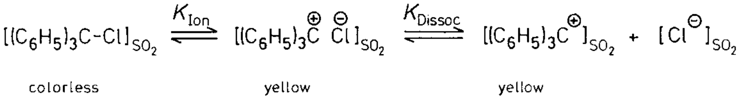
$$(Me_2N)_3P{=}O + Cl\overset{\delta\oplus}{Mg}-\overset{\delta\ominus}{CH_2}{-}C_6H_5 \rightleftharpoons (Me_2N)_3\overset{\oplus}{P}{-}O{-}MgCl + \overset{\ominus}{|CH_2}{-}C_6H_5$$

In EPD solvents, ionization depends on the stabilization of the cation through coordination and, in some solvents, on solvation of the anions as well. In EPA solvents, the anion is stabilized through coordination and, to a lesser extent, additional solvation of the cation may occur.

An evaluation of the ionizing power of a solvent requires knowledge, not only of its coordinating abilities, but also of its relative permittivity. According to Eq. (2-13), solvents of high relative permittivity promote the dissociation of ion pairs. The consequential decrease in ion pair concentration displaces the ionization equilibrium in such a way that new ion pairs are formed from the substrate. Thus, a good ionizing solvent must not only be a good EPD or EPA solvent but also possess a high relative permittivity. The donor and acceptor properties of ionizing solvents can be described empirically in a quantitative way by donor numbers [67] or acceptor numbers [70] (*cf.* Section 2.2.6).

The extraordinary ionizing ability of water is above all due to the fact that it may act as an EPD as well as an EPA solvent. Thus, water is both an ionizing and dissociating medium whereas nitromethane, nitrobenzene, acetonitrile, and sulfolane are mainly dissociating. *N*,*N*-Dimethylformamide, dimethyl sulfoxide, and pyridine are mildly dissociating but good ionizing solvents. Hexamethylphosphoric triamide is an excellent ionizing medium due to its exceptional donor properties, particularly in the case of metal-carbon bonds [145, 146]. Alcohols and carboxylic acids, as hydrogen-bond donors are good EPA solvents and, therefore, good ionizing solvents for suitable substrates.

Chloro-triphenylmethane constitutes a classical example for distinguishing the ionizing and dissociating ability of a solvent. In 1902, Walden used it in liquid sulfur dioxide in the first demonstration of the existence of carbenium ions [147]. The colourless chloro-triphenylmethane dissolves in liquid sulfur dioxide ($\varepsilon_r = 15.6$ at 0 °C), giving an intense yellow colour ($\lambda_{max} = 430$ nm). This is caused by a partial formation of ion pairs, which do not conduct electricity. At low concentrations, the ion pairs partially dissociate into free ions, which do conduct electricity [148, 149].



$$[(C_6H_5)_3C{-}Cl]_{SO_2} \overset{K_{Ion}}{\rightleftharpoons} [(C_6H_5)_3\overset{\oplus}{C}\ \overset{\ominus}{Cl}]_{SO_2} \overset{K_{Dissoc}}{\rightleftharpoons} [(C_6H_5)_3C^{\oplus}]_{SO_2} + [Cl^{\ominus}]_{SO_2} \tag{2-18}$$

$K_{Ion} = 1.46 \cdot 10^{-2}$ (0 °C); $K_{Dissoc} = 2.88 \cdot 10^{-3}$ mol/L (0 °C);

$K_{exp} = 4.1 \cdot 10^{-5}$ mol/L (0 °C) [148].

Table 2-11. Ionization equilibrium constants K_{Ion} of chloro-triphenylmethane in various solvents at 0...25 °C [150]. *Cf.* also [282].

Solvents	ε_r[a] (at 0...25 °C)	$K_{\mathrm{Ion}} \cdot 10^4$	References
Nitrobenzene	34.8 (25 °C)	Too low to measure (25 °C)[c]	[151]
Acetonitrile	35.9 (25 °C)	Too low to measure (25 °C)	[152]
Dichloromethane	8.9 (25 °C)	0.07	[153]
1,1,2,2-Tetrachloroethane	8.2 (20 °C)	0.48 (18.5 °C)	[154]
1,2-Dichloroethane	10.4 (25 °C)	0.56 (20 °C)	[154]
Nitromethane	35.9 (25 °C)	2.7 (25 °C)	[155]
Sulfur dioxide	15.6 (0 °C)[b]	146 (0 °C)	[148]
Formic acid	58.5 (16 °C)	3100 (20.5 °C)	[156]
m-Cresol	11.8 (25 °C)	5600[d] (18 °C)	[157]

[a] J. A. Riddick, W. B. Bunger, and T. K. Sakano: *Organic Solvents*, 4th edition, in A. Weissberger (ed.), *Techniques of Chemistry*, Vol. II, Wiley-Interscience, New York, 1986.

[b] A. A. Maryott and E. R. Smith: *Table of Dielectric Constants of Pure Liquids*, NBS Circular 514, Washington, 1951.

[c] Because nitrobenzene absorbs strongly at the wavelength of the carbenium ion maximum from chlorotriphenylmethane, this result was obtained with chloro-diphenyl-4-tolylmethane.

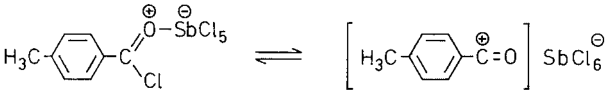
[d] This K_{Ion} value corresponds to 36 ± 4% ionization of chlorotriphenylmethane in *m*-cresol [157].

Sulfur dioxide is a π-electron-pair acceptor. The standard explanation for the strong ionizing power of SO_2 is the formation of an EPD—EPA complex between the halide anion and the sulfur dioxide molecules [148]. Table 2-11 summarizes some of the available data concerning the comparative efficiencies of various solvents in promoting the ionization of chloro-triphenylmethane [150].

The K_{Ion} of chloro-triphenylmethane varies in different solvents by at least a factor of 10^5. In the protic solvents *m*-cresol and formic acid, which have relative permittivities of 11.8 and 58.5, respectively, chloro-triphenylmethane is strongly ionized but is only slightly dissociated in the former. The remarkable ionizing power of phenols and carboxylic acids has been attributed to their EPA properties, *i.e.* their ability to form a hydrogen bond between the hydroxyl group and the halide ion. Solvents with high relative permittivities but lacking pronounced EPA properties, such as acetonitrile and nitrobenzene, are barely capable of ionizing chloro-triphenylmethane. In the case of tri(4-anisyl)-chloromethane, the K_{Ion} value in the EPA solvent sulfur dioxide at 0 °C is about $5 \cdot 10^{10}$ times greater than that in nitrobenzene at 25 °C [151].

On the other hand, the ionization of chloro-triphenylmethane is also favored by EPD solvents. Since the developing carbenium ion is an electrophilic species, it readily interacts with nucleophilic solvents. Thus, the extent of ionization of chloro-triphenylmethane in nitrobenzene increases on the addition of aprotic EPD solvents in direct relation to the donor number [158]. See reference [299] for a study of ionization and dissociation equilibria of other halo-triphenylmethanes in solution (Ph_3C—X with X = F, Cl, Br).

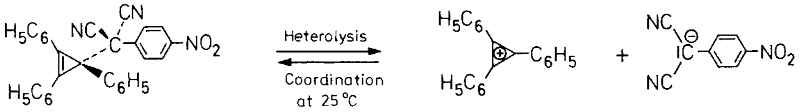
Another remarkable example of the solvent effect on the ionization of ionogens is the Friedel-Crafts intermediate antimony pentachloride/4-toluoyl chloride. It can exist as two distinct well-defined adducts depending on the solvent from which it is recrystallized, the donor-acceptor complex *(2)* or the ionic salt *(3)* [159].



(2) (3)

The donor-acceptor complex *(2)* is isolated from tetrachloromethane solution ($\varepsilon_r = 2.2$), the ionic salt *(3)* from chloroform solution ($\varepsilon_r = 4.9$). When dissolved in chloroform, the donor-acceptor complex recrystallizes as the ionic salt. Similarly, the ionic salt is converted to the donor-acceptor complex when dissolved in tetrachloromethane. This result shows that in solution an equilibrium exists between the two forms. The isolation depends on the solvent used for recrystallization. Similar results have been obtained in the case of the adduct between acetyl chloride and aluminium trichloride, which is un-ionized in chloroform, but completely ionized in nitrobenzene [160].

Other nice examples of well-studied solvent-dependent ionization equilibria of ionogens are azidocycloheptatriene $\rightleftharpoons$ tropylium azide [282, 283] and (triphenylcyclopropen-1-yl) (4-nitrophenyl)malononitrile *(2a)* $\rightleftharpoons$ triphenylcyclopropenium dicyano(4-nitrophenyl)methide *(3a)*, the latter being one of the first examples of direct heterolysis of a weak carbon-carbon bond to a carbocation and carbanion in solution [284].



(2a) (3a)

When dissolved in nonpolar solvents such as benzene or diethyl ether, the colourless *(2a)* forms an equally colourless solution. However, in more polar solvents (*e.g.* acetone, acetonitrile), the deep-red colour of the resonance-stabilized carbanion of *(3a)* appears ($\lambda = 475 \ldots 490$ nm), and its intensity increases with increasing solvent polarity. The carbon-carbon bond in *(2a)* can be broken merely by changing from a less polar to a more polar solvent. Cation and anion solvation provides the driving force for this heterolysis reaction, whereas solvent displacement is required for the reverse coordination reaction. The Gibbs energy for the heterolysis of *(2a)* correlates well with the reciprocal solvent relative permittivity in accordance with the Born electrostatic equation [285], except for EPD solvents such as dimethyl sulfoxide, which give larger $\Delta G^{\circ}_{\mathrm{het}}$ values than would be expected for a purely electrostatic solvation [284].

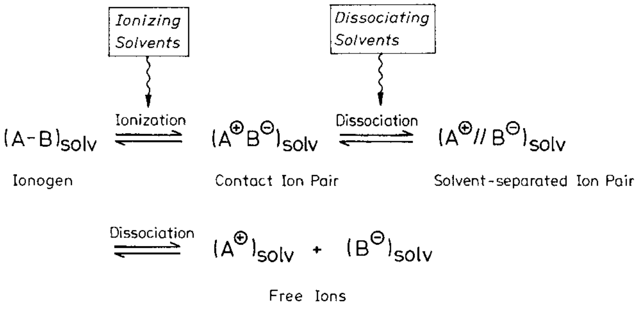
The first purely organic salt, $C_{48}H_{51}^{\oplus}C_{67}H_{39}^{\ominus}$, consisting solely of carbon and hydrogen atoms and being fully ionised in the crystalline state and in solution, was prepared by mixing tris[1-(5-isopropyl-3,8-dimethylazulenyl)]cyclopropenylium perchlorate with potassium tris(7*H*-dibenzo[*c*,*g*]fluorenylidenemethyl)methide (Kuhn's anion) in tetrahydrofuran solution [292]. An analogous green hydrocarbon salt, $C_{12}H_{15}^{\oplus}$ $C_{67}H_{39}^{\ominus}$, which consists of the tri(cyclopropyl)cyclopropenylium cation and Kuhn's anion, is completely ionized in the solid and in DMSO solution. However, in chloroform, tetrachloromethane, and benzene solutions at room temperature, a covalent hydrocarbon is formed from the two ions. Surprisingly, cooling the chloroform solution to −78 °C or evaporation of the solvent regenerates the original green hydrocarbon salt.

In acetonitrile, the ionic and covalent forms coexist in a clean equilibrium. This compound is the first hydrocarbon that only exists covalently in solution [292]. In acetone, dichloromethane, and tetrahydrofuran, a radical, derived from Kuhn's anion by single-electron transfer (SET), was detected in addition to the two ionic species. Thus, all three types of elementary organic species (ion, radical, and a covalent compound) are shown to be able to coexist in a solution equilibrium, depending on the solvent used [292]. For reviews on solvent-dependent equilibria, including radical pairs (produced by bond heterolysis) and radical ion pairs (produced by electron transfer), see references [291, 400, 401].

Another type of ion pairs, called *penetrated ion pairs* [402], has been found by studying the conductivity of tetraalkylammonium tetrafluoroborates (with variable alkyl-chain lengths) [399, 403], and the UV/Vis spectroscopic behaviour of salts with a trimethinium cyanine cation and the tetrakis(phenylethynyl)borate anion [404], in non-dissociating solvents of low relative permittivity. Clearly, in solutions of such low relative permittivity any ionic species will be highly associated. However, it has been found that the ion pairs formed can be smaller than the sum of the van der Waals radii of the components. Clearly, the ions of the ion pair interpenetrate each other depending on their molecular structure: in the first case, the BF_4^- ion penetrates into the voids between the alkyl chains of the tetraalkylammonium ion, and in the second case the cyanine cation penetrates into the crevices of the borate ion.

It should be mentioned that the ionization step in Eq. (2-13) is analogous to that involved in S_N1 and S_N2 reactions of aliphatic substrates. For example, in solvolytic reactions of haloalkanes, the process of going from a covalently bonded initial state to a dipolar or ionic activated complex (transition state) is similar to the ionization step in Eq. (2-13). Therefore, those solvent properties that promote ionization are also important in the estimation of solvent effects on nucleophilic displacement reactions [161] (*cf.* Section 5.4.1).

The ionization of an ionogen and its subsequent dissociation according to Eq. (2-13) can be further elaborated. Between the ion pair immediately formed on heterolysis of the covalent bond and the independently solvated free ions, there are several steps of progressive loosening of the ion pair by penetration of solvent molecules between the ions. At least four varieties of ion interactions representing different stages of dissociation have been postulated [96, 134, 138, 141]; *cf.* Eq. (2-19) and Fig. 2-14.



(2-19)

Based on the mutual geometric arrangement of the two ions and the solvent molecules, the following definitions of ion pairs have been given (*cf.* Fig. 2-14).

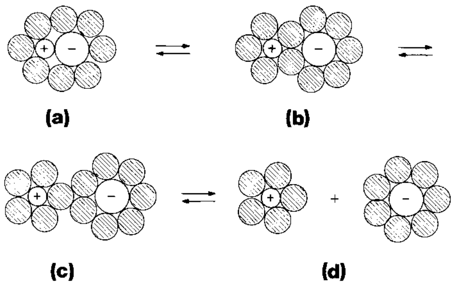


Fig. 2-14. Schematic representation of the equilibrium between (a) a solvated contact ion pair, (b) a solvent-shared ion pair, (c) a solvent-separated ion pair, and (d) unpaired solvated ions of a 1:1 ionophore in solution, according to reference [241]. Hatched circles represent solvent molecules of the primary solvation shell.

First, immediately after ionization, *contact ion pairs**⁾ are formed, in which no solvent molecules intervene between the two ions that are in close contact. The contact ion pair constitutes an electric dipole having only one common primary solvation shell. The ion pair separated by the thickness of only one solvent molecule is called a *solvent-shared ion pair**⁾. In solvent-shared ion pairs, the two ions already have their own primary solvation shells. These, however, interpenetrate each other. Contact and solvent-shared ion pairs are separated by an energy barrier which corresponds to the necessity of creating a void between the ions that grows to molecular size before a solvent molecule can occupy it. Further dissociation leads to *solvent-separated ion pairs**⁾. Here, the primary solvation shells of the two ions are in contact, so that some overlap of secondary and further solvation shells takes place. Increase in ion-solvating power and relative permittivity of the solvent favours solvent-shared and solvent-separated ion pairs. However, a clear experimental distinction between solvent-shared and solvent-separated ion pairs is not easily obtainable. Therefore, the designations solvent-shared and solvent-separated ion pairs are sometimes interchangeable. Eventually, further dissociation of the two ions leads to *free*, *i.e.* unpaired solvated *ions* with independent primary and secondary solvation shells. The circumstances under which contact, solvent-shared, and solvent-separated ion pairs can exist as thermodynamically distinct species in solution have been reviewed by Swarcz [138] and by Marcus [241].

Interestingly, theoretical calculations of Gibbs energy profiles for the separation of *tert*-butyl cation and chloride ion during the hydrolysis of 2-chloro-2-methylpropane have given support for the existence of a contact ion pair, while solvent-separated ion pairs and free, unpaired ions do not appear as energetically distinct species [302]. Monte Carlo simulations predict the occurrence of a contact ion pair at a C—Cl distance of 290 pm and the onset of the solvent-separated ion pair regime near 550 pm (*cf.* the normal C—Cl bond length of ca. 180 pm). A significant barrier of ca. 8 kJ/mol (2 kcal/mol) between the contact and solvent-separated ion pairs has been calculated [302]. For tetramethylammonium chloride in dilute aqueous solution at 25 °C, the contact and

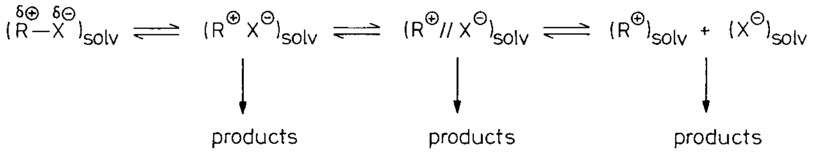
---

* Some authors use the designations *intimate ion pair*, *internal ion pair* (Winstein [162]), *cage ion pair* (Kosower [129]), or *inner-sphere ion pair* (Marcus [241]) instead of *contact ion pair*, and *external ion pair* (Winstein [162]) or *outer-sphere ion pair* (Marcus [241]) for *solvent-shared* and *solvent-separated ion pairs*. The more general designation *tight* and *loose ion pair* (Swarcz [138]) implies that, in principle, more than two different kinds of ion pairs may exist in solution. An IUPAC glossary recommends the designations *tight ion pair* (or *intimate* or *contact ion pair*) and *loose ion pair* [286].

solvent-separated ion pairs are separated by a calculated activation barrier of only 2.9 kJ/mol (0.7 kcal/mol) [302]. Analogous Monte Carlo simulations for sodium iodide ion pairs in water clusters substantiate the existence of distinct contact and solvent-separated ion pairs, showing that the Na^+ I^- contact ion pair is quite stable with respect to dissociation into free ions [405].

The suggestion that ion pairs may exist in more than one distinct form was made by Winstein [162] and by Fuoss [163] in 1954, but direct evidence for the existence of contact and solvent-separated ion pairs came from UV/Vis spectroscopic investigations of sodium fluorenide in tetrahydrofuran solution [141, 164]. Further evidence for the existence of a dynamic equilibrium between contact and solvent-separated ion pairs (*e.g.* hyperfine splitting of radical-anion ESR lines by cationic nuclei; electronic spectra of mesomeric anions; *etc.*) has been summarized by Gordon [96], Szwarc [138], and Marcus [241]. Increasing association of ions in solution greatly affects their chemical behaviour. A large variety of possible ion-pair effects on rate constants, mechanism and stereochemistry is known, especially in reactions of ion pairs containing carbenium ions [161, 165] or carbanions [166, 168, 168a].

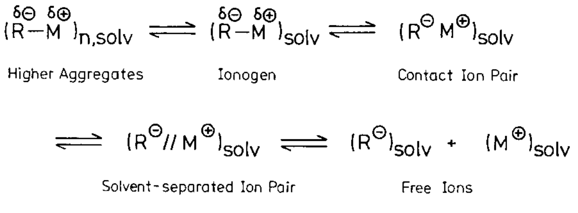
The observation that the rate of loss of optical activity during the solvolysis of certain chiral substrates $R^{\delta\oplus} - X^{\delta\ominus}$ exceeded the rate of acid production and the occurrence of a special salt effect led to the postulation of two distinct ion-pair intermediates [161, 162]. The basic Winstein solvolysis scheme is given by Eq. (2-20).



$$\begin{tikzcd}[column sep=small]
(\overset{\delta\oplus}{R}-\overset{\delta\ominus}{X})_{solv} \arrow[r, phantom, "\rightleftharpoons"] & (R^{\oplus}X^{\ominus})_{solv} \arrow[d] \arrow[r, phantom, "\rightleftharpoons"] & (R^{\oplus}/\!/X^{\ominus})_{solv} \arrow[d] \arrow[r, phantom, "\rightleftharpoons"] & (R^{\oplus})_{solv} + (X^{\ominus})_{solv} \arrow[d] \\
 & \text{products} & \text{products} & \text{products}
\end{tikzcd} \qquad (2\text{-}20)$$

According to this scheme, the solvolysis products are not only obtained from free unpaired ions, but also from the two different ion pairs, depending on the solvent-dependent degree of dissociation.

An analogous scheme holds for the reactions of certain dipolar organometallics $R^{\delta\ominus} - M^{\delta\oplus}$, according to Eq. (2-21) [138, 167, 168, 168a].



$$\underset{\text{Higher Aggregates}}{(\overset{\delta\ominus}{R}-\overset{\delta\oplus}{M})_{n,solv}} \rightleftharpoons \underset{\text{Ionogen}}{(\overset{\delta\ominus}{R}-\overset{\delta\oplus}{M})_{solv}} \rightleftharpoons \underset{\text{Contact Ion Pair}}{(R^{\ominus}M^{\oplus})_{solv}}$$

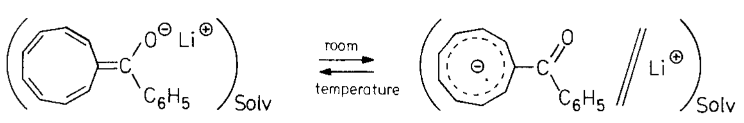
$$\rightleftharpoons \underset{\text{Solvent-separated Ion Pair}}{(R^{\ominus}/\!/M^{\oplus})_{solv}} \rightleftharpoons \underset{\text{Free Ions}}{(R^{\ominus})_{solv} + (M^{\oplus})_{solv}} \qquad (2\text{-}21)$$

Whereas the spectral behavior of solvent-separated ion pairs and free ions is very similar, the UV/Vis spectra of contact and solvent-separated ion pairs are usually different from each other, as has been shown with sodium fluorenide [141, 164]. Due to the penetration of solvent molecules between the ion-pair couples, the direct influence of the metal cation on the π-electron system of the carbanion is lost. With increasing dissociation, the absorption maximum of sodium fluorenide in tetrahydrofuran solution is shifted bathochromically in the direction of the absorption maximum of the free fluorenide ion: λ_{max} = 356 nm → 373 nm → 374 nm, for the contact ion pairs, solvent-separated ion pairs, and free fluorenide ions, respectively [164]. The equilibrium between contact and solvent-separated ion pairs is shifted in the direction of increased dissociation by the addition of cation solvators such as EPD solvents. Thus, the proportion of solvent-separated ion pairs for sodium fluorenide at 25 °C in tetrahydrofuran is 5 cmol/mol, whereas in 1,2-dimethoxyethane, a better cation solvator, it is 95 cmol/mol. In strong EPD solvents such as dimethyl sulfoxide, hexamethylphosphoric triamide, or polyethyleneglycol dimethyl ethers, most of the fluorenide salt exists as solvent-separated ion pairs only. Small quantities of dimethyl sulfoxide, when added to the sodium fluorenide solution in 1,4-dioxane, convert the contact ion pairs to dimethyl sulfoxide-separated ion pairs [141, 164].

Sodium naphthalenide behaves similarly when the solvent is changed from tetrahydrofuran to 1,2-dimethoxyethane. The formation of solvent-separated from contact ion pairs is shown by a dramatic simplification of the ESR spectrum: the 100-line spectrum of the contact ion pair, due to the spin-spin coupling of the unpaired electron with the four equal hydrogen nuclei in the α- and β-positions, together with the sodium nucleus ($I = 3/2$), collapses to a 25-line spectrum as the interaction with the sodium ion is disrupted [169, 170].

Other illustrative examples of carbanionic ion-pair dissociation/aggregation are: lithium triphenylmethide, which exists as a tight ion pair in diethyl ether and as a solvent-separated ion pair in tetrahydrofuran, as shown by UV/Vis spectrophotometric measurements [287], and lithium 10-phenylnonafulvene-10-oxide, which exists as a tight ion pair *(2b)* in tetrahydrofuran solution and as a solvent-separated ion pair *(3b)* when hexamethylphosphoric triamide or dimethyl sulfoxide are added (^{1}H and ^{13}C NMR measurements) [288].

This second case is particularly interesting since the addition of an EPD solvent is connected with a shift from the olefinic nonafulvenoxide anion in *(2b)* to the aromatic benzoyl [9] annulene anion in *(3b)*. Without association of the lithium cation with the enolate oxygen atom, the negative charge is preferably delocalized in the [9] annulene ring. Therefore, the aromatic character of this ionophore depends on its ion-pair character [288].



(2b) *(3b)*

The degree of aggregation of organolithium compounds (alkyl-, aryl-, and alkynyl-lithium compounds as well as lithium enolates) in dilute tetrahydrofuran solution at −108 °C has been determined by means of cryoscopic [289] and NMR spectroscopic measurements [290]; for a review on the solution structure of lithium enolates and phenolates, see reference [406].

The enolate and iminate ions of tetra-*n*-butylammonium salts of carbonyl compounds (*e.g.* malonates) and nitriles (*e.g.* 2-phenylpropionitrile) exhibit special dimeric molecular structures in the solid state and in solution (benzene), held together by multiple C—H···O and C—H···N hydrogen bonds, resp., with the α-methylene units of the $(n\text{-Bu})_4N^+$ cation. Thus, these anions are not truly 'naked' carbanions; they interact with one another through hydrogen bonds in a highly ordered manner, leading to another type of ion pairs, called *supramolecular ion pairs* [407]. For a review on genuine non-coordinating anions, see reference [408].

Of particular interest for regio- and stereoselective C—C bond-forming synthetic reactions are lithium organocuprates, the detailed molecular structure of which was unknown for a long time. Application of sophisticated NMR techniques has shown that a representative salt-containing lithium dimethylcuprate, $Me_2CuLi \cdot LiCN$, exists in solution (S = THF, Et_2O) in an equilibrium between homo-dimeric contact ion pairs and monomeric solvent-separated ion pairs such as $[LiS_4]^+$ $[Me—Cu—Me]^-$ [409]. A systematic X-ray study of solid-state structures of lithium organocuprates has substantiated the formation of monomeric solvent-separated ion pairs in good-solvating solvents for Li^+ (*e.g.* THF, crown ethers, amines), while in poor-solvating solvents for Li^+ (*e.g.* Et_2O, Me_2S) a dimeric contact ion pair is found. This is of practical relevance because it seems to be only the lithium organocuprate dimer of the contact-ion type that undergoes C—C bond-forming reactions such as addition to enones [409].

The ^7Li NMR spectra of solutions of the dilithium salts of the (*R*)- and (*S*)-configured (*sec*-butoxy)cyclooctatetraene dianion, $Li_2{}^+[C_8H_7—OC_4H_9]^{2-}$, in the chiral solvent 1,4-bis(dimethylamino)-2,3-dimethoxybutane (DDB; see Table A-2 in the Appendix) were found to be remarkably different. The chiral dilithium salt exists in DDB solution as a mixture of contact and solvent-separated ion pairs. Interestingly, the relative concentration of the contact ion pair is much greater for the (*R*)-enantiomer of $[C_8H_7—OC_4H_9]^{2-}$ than for the (*S*)-enantiomer, indicating a solvent/ion-pair chiral recognition. Thus, the interaction between the chiral solvent and the (*R*)- and (*S*)-*sec*-butoxy groups results in the DDB solvent being more capable of partially separating Li^+ from the (*S*)-enantiomer of $[C_8H_7—OC_4H_9]^{2-}$ than from the (*R*)-enantiomer [410].

3 Classification of Solvents

Due to the physical and chemical differences between the numerous organic and inorganic solvents it is difficult to organise them in a useful scheme. Here, five attempts at a classification of solvents are presented, which should prove useful to the chemist. Due to broad definitions, some overlapping of these is unavoidable. As has been customary in previous reviews non-aqueous organic solvents will receive particular attention [1–15, 103–108, 172, 174–177]. Extensive compilations of chemical and physical properties of non-aqueous solvents can be found in references [11–14, 104, 106, 175, 177].

3.1 Classification of Solvents according to Chemical Constitution

Solvents can be classified according to their chemical bonds: (a) molecular liquids (molecule melts; covalent bonds only), (b) ionic liquids (molten salts; only ionic bonds), and (c) atomic liquids (low-melting metals like liquid mercury or liquid sodium; metallic bonds) [16]. Numerous transitions are possible by mixing solvents of these three classes (Fig. 3-1). However, research into this area is still far from exhausted.

The customary non-aqueous organic solvents belong to the group of molecular melts and, according to their chemical constitutions, to the following classes of compounds (*cf.* Table A-1, Appendix): aliphatic and aromatic hydrocarbons and their halogen and nitro derivatives, alcohols, carboxylic acids, carboxylic esters, ethers, ketones, aldehydes, amines, nitriles, unsubstituted and substituted amides, sulfoxides, and sulfones. The classification of solvents according to chemical constitution allows certain qualitative predictions, summarized in the old rule "similia similibus solvuntur". In general, a compound dissolves far more easily in a solvent possessing related functional groups than in one of a completely different nature. A proper choice of solvent, based on the knowledge of its chemical reactivity, helps to avoid undesired reactions between solute and solvent. For example, condensations should not be carried out in solvents possessing carbonyl groups (*e.g.* ketones) or hydrolyses in carboxylic esters, amides, or nitriles.

Further well-known molecular liquids that have recently found renewed interest as solvents for many applications are water and perfluorohydrocarbons. These occupy the two extreme positions on empirical solvent polarity scales, with water being the most polar solvent and perfluorohydrocarbons being among the least polar of solvents (*cf.* Chapter 7).

Plain water has undergone a magnificent renaissance as a solvent for organic reactions, not only because it is an environmentally safe solvent, but also due to its pronounced capacity for hydrophobic hydration of apolar solutes [178–181]; *cf.* Sections 2.2.7 and 5.5.8 as well as Table A-14 in the Appendix.

Perfluorohydrocarbons are nonpolar, hydrophobic, chemically inert, and nontoxic solvents with a higher density than the corresponding hydrocarbons. They show a high capacity to dissolve gases (*e.g.* oxygen) and a temperature-dependent mutual miscibility with common organic solvents, mostly forming biphasic systems at ambient temperature [182]. These properties make them useful solvents for spectroscopic measurements [183] and for various kinds of organic reactions [184]. With different solubil-

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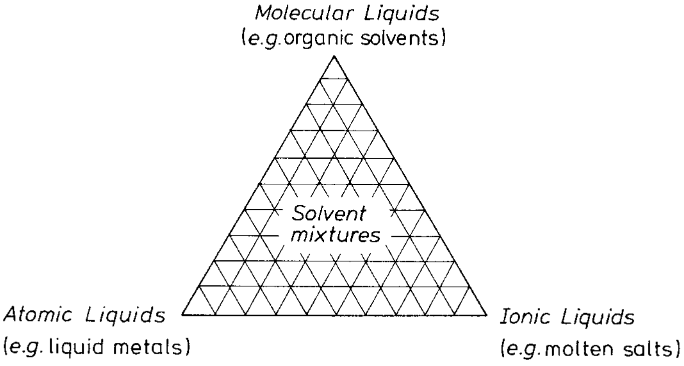
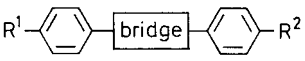
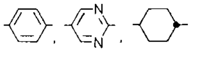


Fig. 3-1. Classification of solvents according to their characteristic chemical bonds [16].

ities for educts, reagents, products, and catalysts, biphasic solvent systems with a 'fluorous' phase can facilitate the separation of products from reaction mixtures [182, 185, 186]; *cf.* Section 5.5.13 and Table A-14 in the Appendix.

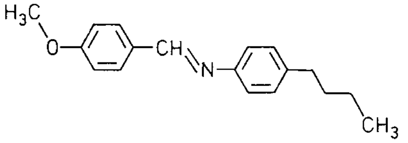
Liquid crystals or mesomorphic compounds occupy a special position [17–22, 22a, 109, 110]. Compounds capable of forming liquid crystals are long, flat, and fairly rigid along the axis of the molecule. Most known mesomorphic solvents are systems of the following general structure with polarizable aromatic nuclei held in a planar skeleton:



Common central bridges:
—CH_2—CH_2, —CH=CH—,
—C≡C—, —CH=N—,
—CH=N(O)—, —CO—O—,
—N=N—, —N=N(O)—,


Common terminal substituents:
R—, RO—, HO—, R—CO—O—,
R—O—CO—O—,
R—O—$(CH_2)_n$—O—, H_2N—,
O_2N—,
N≡C—, Cl—, Br—, I—

Unlike normal isotropic liquids, which possess a completely random arrangement of molecules, liquid crystals are considerably ordered. The degree of order in the latter lies somewhere between that of isotropic liquids and crystals. Liquid crystals are classified into lyotropic and thermotropic crystals depending on the way in which the mesomorphic phase is generated. *Lyotropic* liquid-crystalline solvents are formed by addition of controlled amounts of polar solvents to certain amphiphilic compounds. *Thermotropic* liquid-crystalline solvents, simply obtained by temperature variations, can be further classified into nematic, smectic, and cholesteric solvents depending on the type of molecular order present. In *nematic* mesophases, the long molecular axes of the component molecules are arranged, for the most part, parallel to one another. There is no further ordering present and these are the most fluid of liquid-crystalline solvents. *Cholesteric* mesophases are optically active nematic phases, additionally characterized by a gradual twist in orientational alignment as one proceeds through the bulk solvent, and forming a twisted helical macrostructure. In *smectic* mesophases, the component molecules are further arranged in layers, with their long molecular axes parallel to one another and perpendicular to the plane of the layers. As a result of this additional molecular ordering, smectic solvents are considered to be the most ordered and the less fluid liquid-crystalline solvents. A typical example of a liquid-crystalline nematic solvent, at room temperature, is *N*-(4-methoxybenzylidene)-4-*n*-butylaniline ("MBBA") [23]. At 21 °C, the crystalline structure is lost and an ordered fluid, thermally stable up to about 48 °C, is formed (nematic range 21 to 48 °C).



$$\text{Solid phase} \overset{21\ ^\circ\text{C}}{\rightleftharpoons} \text{Nematic phase} \overset{48\ ^\circ\text{C}}{\rightleftharpoons} \text{Isotropic phase}$$

Liquid crystals are usually excellent solvents for other organic compounds. Non-mesomorphic solute molecules may be incorporated into liquid-crystalline solvents without destruction of the order prevailing in the liquid-crystalline matrix. The anisotropic solute-solvent interaction leads to an appreciable orientation of the guest molecules with respect to the axis of preferred solvent alignment. The consequences may be useful as shown by the use of liquid crystals as anisotropic solvents for spectroscopic investigations of anisotropic molecular properties [166]. Ordered solvent phases such as liquid crystals have also been used as reaction media, particularly for photochemical reactions; *cf.* for example [111, 155, 163] and Section 5.5.9.

The second corner of the triangle in Fig. 3-1 is occupied by ionic liquids. Of these, molten salts are becoming increasingly important as solvents for inorganic as well as organic reactions [3, 24–30, 112–114]. High thermal stability, good electrical conductivity*), low viscosity, wide liquid range, low vapour pressure and the resulting possibility of high working temperatures, together with their excellent ability to dissolve salts and metals, make them extremely useful reaction media. Therefore, such systems are becoming increasingly important technologically. A further advantage of molten salts is their high heat conductivity, which permits a very rapid dispersal of the heat of reaction.

Often, these are the only solvents capable of dissolving salt-like hydrides such as NaH and CaH_2, carbides, nitrides, various oxides, sulfides, and cyanamides. Many metals form atomic dispersions in the melts of their halogenides, yielding extremely strongly reducing solutions. The working temperature for oxide and silicate melts lies above 1500 °C, for normal salts it is between 100 and 1000 °C, and for eutectic mixtures it is often at even lower temperatures. Salts with large organic cations such as tetraalkylammonium, tetraalkylphosphonium, 1,3- and 1,4-dialkylpyridinium, or 1,3-dialkylimidazolium ions, and with suitable inorganic anions, have melting points

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* Ionic melts possess electrical conductivities roughly a factor ten larger than those of concentrated aqueous solutions of strong electrolytes (ionophores).

Table 3-1. Melting points (t_{mp}), boiling points (t_{bp}), and liquid working ranges, $\Delta t = t_{bp} - t_{mp}$, of some fused inorganic and organic salt systems [27, 28], including a few room temperature ionic liquids (entries 17, 18, 21–28) [187–190]. For binary or ternary eutectics, the figures in parentheses give the portions in cmol/mol.

Fused salts	t_{mp}/°C	t_{bp}/°C	Δt/°C
(1) $NaCl$[a]	801	1465	664
(2) KCl[a]	771	1413	642
(3) $LiCl$[a]	610	1383	773
(4) KOH[a]	406	1327	921
(5) $NaOH$[a]	323	1388	1065
(6) $NaNO_3$[a]	308	380	73
(7) $K^+H_3C\text{—}CO_2^-$[a]	292	–	–
(8) $ZnCl_2$[a]	290	732	442
(9) $NaNH_2$[a]	210	500 (dec.)	290
(10) $ZnCl_2(60)\text{—}NaCl(20)\text{—}KCl(20)$	203	–	–
(11) $KCl(33)\text{—}AlCl_3(67)$	128	–	–
(12) *N*-Butyl-3-methylpyridinium chloride	98	–	–
(13) $AlBr_3$[a]	97	255	158
(14) $LiNO_3(25.8)\text{—}NH_4NO_3(66.7)\text{—}NH_4Cl(7.5)$	86	–	–
(15) $AgNO_3(52)\text{—}TlNO_3(48)$	82.5	–	–
(16) $(n\text{-}C_6H_{13})_4N^+NO_3^-$	69	–	–
(17) $(n\text{-}C_4H_9)_3NH^+NO_3^-$[b]	21.5	119 (dec.)	–
(18) $CH_3\text{—}CH_2\text{—}NH_3^+NO_3^-$[b,c]	12	170 (dec.)	–
(19) $[EMIM]^+Cl^-$[d]	87	–	–
(20) $[EMIM]^+PF_6^-$[d]	62	–	–
(21) $[EMIM]^+AlCl_4^-$[d]	7	–	–
(22) $[EMIM]^+F_3C\text{—}SO_3^-$[d]	−9	–	–
(23) $[EMIM]^+F_3C\text{—}CO_2^-$[d]	−14	–	–
(24) $[EMIM]^+(F_3C\text{—}SO_2)_2N^-$[d]	−15	–	–
(25) $Li^+(F_3C\text{—}SO_2)_2N^-$/Urea (1:3)[e]	−37.6	–	–
(26) $(n\text{-}C_6H_{13})_4N^+H_5C_6\text{—}CO_2^-$[f]	−50[a]	–	–
(27) $(n\text{-}C_6H_{13})(C_2H_5)_3N^+(n\text{-}C_6H_{13})(C_2H_5)_3B^-$[g]	<-75[a]	87 (dec.)	–
(28) $(CH_3)_2NH_2^+(CH_3)_2N\text{—}CO_2^-$ ("Dimcarb")[h]	–	60 (dec.)	–

[a] D. R. Lide (ed.): *CRC Handbook of Chemistry and Physics*, 77th ed., CRC Press, Boca Raton/FL, USA, 1996.

[b] C. F. Poole, B. R. Kersten, S. S. J. Ho, M. E. Coddens, K. G. Furton, J. Chromatogr. *352*, 407 (1986).

[c] H. Weingärtner, A. Knocks, W. Schrader, U. Kaatze, J. Phys. Chem. A *105*, 8646 (2001).

[d] $[EMIM]^+$ = 1-*E*thyl-3-*m*ethyl*im*idazolium ion.

[e] H. Liang, H. Li, Z. Wang, F. Wu, L. Chen, X. Huang, J. Phys. Chem. B *105*, 9966 (2001).

[f] C. G. Swain, A. Ohno, D. K. Roe, R. Brown, T. Maugh, J. Am. Chem. Soc. *89*, 2648 (1967); T. G. Coker, J. Ambrose, G. J. Janz, ibid. *92*, 5293 (1970).

[g] For other liquid tetraalkylammonium tetraalkylborides, see W. T. Ford, R. J. Hauri, D. J. Hart, J. Org. Chem. *38*, 3916 (1973).

[h] W. Schroth, J. Andersch, H.-D. Schädler, R. Spitzner, Chemiker-Ztg. *113*, 261 (1989); Z. Chem. *29*, 56, 129 (1989).

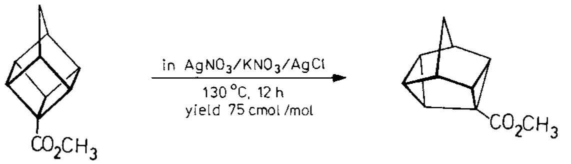
under 100 °C and are often liquid even at room temperature. Table 3-1 gives a somewhat arbitrary selection of inorganic and organic salts, eutectic salt mixtures [27, 28], and room temperature liquid salts [187–189], together with their physical constants.

Although the relative permittivities of molten salts are generally quite small ($\varepsilon_r = 2 \ldots 3$), they behave as strongly dissociating solvents! This is due to the ability of the solvent ions to exchange places with solute ions of the same charge.

Three examples of the many reactions that can be advantageously carried out in high-temperature molten salts have been selected to illustrate this molten-salt technique. When 1,1-dichloroethane is passed through a $ZnCl_2/KCl$ melt at 330 °C, chloroethene is formed in 97 cmol/mol yield by dehydrohalogenation. Likewise, the addition of hydrogen chloride to acetylene proceeds with 89 cmol/mol yield in the same melt. A combination of these two steps allows a ready synthesis of the technically important chloroethene from acetylene and 1,1-dichloroethane according to Eq. (3-1) [25, 31].

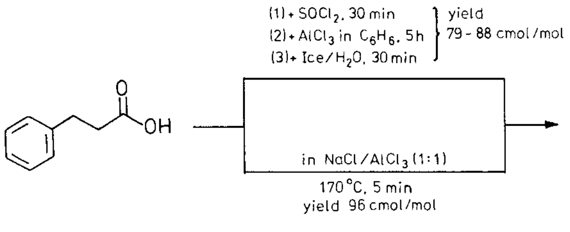
$$HC{\equiv}CH + H_3C{-}CHCl_2 \xrightarrow[\text{yield 68.5 cmol/mol}]{\text{in } ZnCl_2/KCl/HgCl_2} 2\ H_2C{=}CH{-}Cl \qquad (3\text{-}1)$$

Ionic liquids such as the eutectic $AgNO_3/KNO_3/AgCl$ (mp 113 °C) are the best solvents for effecting silver ion-catalyzed isomerizations of cage-like organic molecules, *e.g.* basketane → snoutane [31a], *cf.* Eq. (3-2).



(3-2)

Molten sodium tetrachloroaluminate (a 1:1 mixture of NaCl and $AlCl_3$) is a good reaction medium for the Friedel-Crafts acylation reaction given in Eq. (3-3) [115].



(3-3)

Whereas the classical procedure for the synthesis of 1-indanone from 3-phenylpropanoic acid consists of three reaction steps with a total reaction time of *ca.* six hours [116], the molten salt reaction is finished in five minutes and gives an even better yield [115].

Ethylammonium nitrate (entry 18 in Table 3-1) was shown in 1914 to have m.p. 12 °C and was hence the first room temperature ionic liquid [156]; this was followed in 1967 by tetra-*n*-hexylammonium benzoate with m.p. −50 °C (entry 26) [169]. Ambient-temperature ionic liquids based on 1-alkyl-3-methylimidazolium salts (entries 19–24) were first reported by Wilkes *et al.* in 1982 as tetrachloroaluminates [162a]. Replacement of this moisture-sensitive anion by the tetrafluoroborate ion and other anions led, in 1992, to air- and water-stable, room temperature ionic liquids [162b], which have since found increasing application as reaction media for various kinds of organic reactions, mainly owing to the work of Seddon [167, 190] and Hussey [187]. Suitably selected combinations of cation and anion (*cf.* entries 19–24 in Table 3-1) allow the design of ionic liquids that meet all requirements for the chemical reaction under study. Therefore, they have also been called *designer solvents.* The polarities of room temperature ionic liquids have been determined empirically using solvatochromic dyes, which revealed polarities varying between that of acetonitrile and those of lower alcohols [191, 192]. For the use of room temperature ionic liquids in synthesis and catalysis, see reviews [187–190] and Section 5.5.13. Section 5.5.13 describes applications of some *neoteric solvents* such as ionic liquids, perfluorohydrocarbons, etc., in organic synthesis. Neoteric (=recent, new, modern) indicates a class of novel reaction media that have remarkable new properties [167].

A remarkable solvent on the borderline between ionic and molecular liquids is dimethylammonium *N*,*N*-dimethylcarbamate ("Dimcarb"; see entry 28 in Table 3-1), a colourless distillable liquid that readily decomposes at its b.p. into dimethylamine and carbon dioxide, from which it is prepared at lower temperatures. Being formally an ionic liquid, owing to the weak bond between the two components, it has a variable hydrogen-bonded molecular structure with one dimethylamine moiety rapidly exchanging between the ammonium and carbamate ions. Its physical and chemical properties have been reviewed [193]. Reaction of dimethylamine with sulfur dioxide also yields an ionic liquid, presumably dimethylammonium *N*,*N*-dimethylamidosulfinate, ("Dimsulf"; b.p. 112 °C), a useful electrolyte for organic electrochemistry [194].

Another type of solvents on the borderline between ionic and molecular liquids are highly concentrated solutions of ionophores in nonpolar organic solvents, such as solutions of lithium perchlorate in diethyl ether (LPDE) [195–197]. Anhydrous lithium perchlorate is a solid with m.p. 247 °C; a 5 M solution of $LiClO_4$ in dry diethyl ether contains only about one to two ether molecules per lithium cation and can be considered as a diluted ionic liquid with the structure of a dietherate, $[Li(OEt_2)_2]^+ ClO_4^-$, below 4.25 M, and a mixture of both the dietherate and monoetherate, $[Li(OEt_2)]^+ ClO_4^-$, above 4.25 M. The lithium cation is not fully coordinated by solvent molecules and such ions are sometimes mistakenly called 'naked' ions; naked ions only exist in the gas phase. Nevertheless, the partially coordinated lithium cation is highly electrophilic and ethereal lithium perchlorate solutions can be used for many organic reactions requiring electrophilic catalysis. As early as 1959, Winstein recognized that addition of lithium perchlorate to less well coordinating organic solvents such as diethyl ether increases not only their polarity but also their Lewis acid/base properties [198]. The manifold applications of LPDE in organic synthesis have been reviewed [195–197].

The third corner of the triangle in Fig. 3-1 represents liquid metals, *e.g.* mercury or liquid sodium, which until now have received little attention as reaction media. Chemical reactions in liquid alkali metals have been reviewed [164, 199].

3.2 Classification of Solvents using Physical Constants

The following physical constants can be used to characterize the properties of a solvent: melting and boiling point, vapour pressure, heat of vapourization, index of refraction, density, viscosity, surface tension, dipole moment, relative permittivity, polarizability, specific conductivity, *etc.* A compilation of data of usual organic solvents is given in

Table A-1 (Appendix). For more comprehensive recent compilations of physical data for common organic solvents, see references [175] (260 solvents) and [177] (1141 solvents).

Solvents can be broadly classified as low, middle, or high boiling, *viz.* $t_{bp} < 100$ °C, 100…150 °C, or >150 °C at 1 bar. Similarly, liquids can be classified according to their *evaporation number* using diethyl ether as reference (evaporation number = 1 at 20 °C and 65 cL/L relative air humidity). Thus, high volatility is signified by evaporation numbers <10, moderate volatility by numbers 10…35, low volatility by numbers 35…50, and very low volatility by numbers >50 [32, 177]. Using viscosity as a criterion, solvents are of low viscosity when their dynamic viscosity is <2 mPa · s at 20 °C, of medium viscosity between 2 and 10 mPa · s, and of high viscosity above 10 mPa · s [32].

The degree of association of molecules in a liquid can be estimated by means of its *Trouton constant* [117]. At the normal boiling temperature, T_{bp}, vapourization proceeds with standard molar changes of enthalpy, ΔH°_{bp}, and entropy, ΔS°_{bp}, from which Trouton's rule is derived as given in Eq. (3-4).

$$\Delta S^{\circ}_{bp} = \frac{\Delta H^{\circ}_{bp}}{T_{bp}} \approx 21\ \mathrm{cal \cdot mol^{-1} \cdot K^{-1}}\ \text{or}\ 88\ \mathrm{J \cdot mol^{-1} \cdot K^{-1}} \qquad (3\text{-}4)^{*)}$$

This rule works best for apolar, quasi-spherical molecules. Large deviations occur when chemical association is involved (*e.g.* carboxylic acids), from molecular dipolarity (*e.g.* dimethyl sulfoxide), and from molecular asphericity (*e.g.* neopentane/*n*-pentane). Strongly associating solvents (*e.g.* HF, H_2O, NH_3, alcohols, carboxylic acids) have Trouton constants which are higher than the average value of 88 $\mathrm{J \cdot mol^{-1} \cdot K^{-1}}$ found for non-associating solvents such as diethyl ether and benzene.

In addition to Trouton's rule, some other parameters for measuring the *structuredness* of solvents have been recommended, for example a solvent dipole orientation correlation parameter [175, 200], the solvent's heat capacity density [175, 200], and a so-called S_p parameter derived from the solvent's enthalpy of vapourization minus EPD/EPA and van der Waals interactions [201]. According to these parameters, solvents can be classified as highly structured (*e.g.* water, formamide), weakly structured (*e.g.* DMSO, DMF), and practically non-structured (*e.g.* *n*-hexane and other hydrocarbons) [200, 201].

In this connection, two other physical solvent properties are important: the *cohesive pressure c* (also called *cohesive energy density*) and the *internal pressure* π of a solvent [98–100, 175].

The *cohesive pressure c* is a measure of the total molecular cohesion per unit volume, given by Eq. (3-5),

$$c = \frac{\Delta U_v}{V_m} = \frac{\Delta H_v - R \cdot T}{V_m} \qquad (3\text{-}5)$$

---

* Trouton's rule can also be written independent of units: $\Delta S^{\circ}_{bp}/R = \Delta H^{\circ}_{bp}/(R \cdot T_{bp}) \approx 11$.

where ΔU_v and ΔH_v are respectively the energy and enthalpy (heat) of vapourization of the solvent to a gas of zero pressure, and V_m is the molar volume of the solvent. On vapourization of a solvent to a non-interacting vapour, *all* intermolecular solvent-solvent interactions will be broken. Therefore, c represents the total strength of the intermolecular solvent structure. Cohesive pressure has very high values for solvents of high polarity and low values for nonpolar solvents such as perfluorohydrocarbons with weak interaction forces. Intermolecular hydrogen bonding in a solvent increases the cohesive pressure (*cf.* Table 3-2). Cohesive pressure is related to the energy required to create cavities in a liquid in order to accommodate solute molecules during the process of dissolution.

On the other hand, the *internal pressure* π is defined as the change in internal energy of a solvent as it undergoes a very small isothermal expansion, as seen in Eq. (3-6).

Table 3-2. Cohesive pressures, c, internal pressures, π, and their ratio $n = \pi/c$ for thirty organic solvents, arranged in order of decreasing n, that is, in order of increasing "structuredness", at 20 °C [99, 154, 175].

Solvents	c/MPa[a)]	π/MPa[a)]	$n = \pi/c$
Perfluoro-*n*-heptane	151	215	1.42
Perfluoro(methylcyclohexane)	161	228	1.41
1,4-Dioxane	388	494	1.27
2,2,4-Trimethylpentane	200	236	1.18
Methylcyclohexane	260	297	1.14
Cyclohexane	285	326	1.14
Hexamethylphosphoric acid triamide (HMPT)	365	403	1.10
Tetrachloromethane	310	339	1.09
Ethyl acetate	331	356	1.08
n-Hexane	225	239	1.06
Benzene	353	369	1.05
Toluene	337	355	1.05
Diethyl ether	251	264	1.05
1,2-Dichloroethane	400	419	1.05
Trichloromethane (Chloroform)	362	370	1.02
Acetylbenzene (Acetophenone)	456	457	1.00
Dichloromethane	414	408	0.99
Acetic acid	357	348	0.97
Carbon disulfide	412	372	0.90
N,*N*-Dimethylformamide (DMF)	581	480	0.83
Dimethyl sulfoxide (DMSO)	708	521	0.74
2-Methyl-2-propanol, *t*-Butanol	467	339	0.73
Acetone	488	331	0.68
Acetonitrile	581	395	0.68
1-Butanol	485	300	0.62
Ethane-1,2-diol	1050	502	0.48
Ethanol	676	293	0.43
Formamide	1568	554	0.35
Methanol	858	288	0.34
Water	2294	151	0.07

[a)] 1 MPa = 10^6 Pa = 1 J $\cdot$ cm^{-3} = 9.87 atm.

$$\pi = \left(\frac{\partial U}{\partial V_\mathrm{m}}\right)_T \tag{3-6}$$

(U = molar internal energy; V_m = molar volume; T = absolute temperature). This small expansion does not necessarily disrupt all the intermolecular solvent-solvent interactions. The internal pressure results from the forces of attraction between solvent molecules exceeding the forces of repulsion, *i.e.* mainly dispersion and dipole-dipole interactions (*cf.* Table 3-2).

Although there is obviously a close connection between cohesive pressure and internal pressure, they are not equivalent, as shown by the compilation of c and π values for some selected organic solvents shown in Table 3-2 [99, 100, 154]. It has been assumed that π is mainly a reflection of dispersion and dipole-dipole interactions within the solvent, whereas c additionally includes specific solvent-solvent interactions such as hydrogen bonding. Hydrogen bonding in a solvent increases the cohesive pressure, while the internal pressure is comparable to that of solvents without hydrogen bonding. Therefore, the hydrogen-bonding pressure or energy density contribution can be measured by the difference $(c - \pi)$ [99, 100]. Values of π approach those of c only for weakly polar solvents with dipole moments less than *ca.* $7 \cdot 10^{-30}$ Cm (*ca.* 2 D) and without specific solvent/solvent interactions. As shown in Table 3-2, the ratio $n = \pi/c$ approaches a value of unity for nonpolar solvents (*e.g.* hydrocarbons), but it can be less than or greater than unity for other solvents. High values of n are obtained for the noninteracting fluorohydrocarbons, while at the other end of the solvent spectrum HBD solvents with very low values of n are found.

The square root of the cohesive pressure c as defined in Eq. (3-5) has been termed the *solubility parameter* δ by Hildebrand and Scott [98] because of its value in correlating and predicting the solvency of solvents for non-electrolyte solutes [*cf.* Eqs. (2-1) and (5-77) in Sections 2.1 and 5.4.2, respectively]. Solvency is defined as the ability of solvents to dissolve a compound [118]. A selection of δ values is given in Table 3-3; see also references [99, 177].

The solvency increases as the δ value of the solvent approaches that of the solute. Two liquids are miscible if their solubility parameters differ by no more than *ca.* 3 units.

Because the term *solubility parameter* is too restrictive for this quantity, which can be used to correlate a wide range of physical an chemical properties (for instance, *cf.* Section 5.4.2), the term *cohesion parameter* has been proposed by Barton [99]. The term solubility parameter suggests a close relationship between the phenomenon "solubility" or "miscibility" and that of "cohesion" or "vapourization". This seems to be reasonable, considering what happens in a mixing process: the like molecules of each component in a mixture are separated from one another to an infinite distance, comparable to what happens in the vapourization process. A comprehensive review on the determination and application of solubility parameters has been given by Barton [99].

An alternative approach for the prediction of mutual miscibility of solvents has been given by Godfrey [119] (*cf.* also Appendix, Chapter A-1). As a measure of lipophilicity (*i.e.* affinity for oil-like substances), the so-called *miscibility numbers* (*M* numbers, with values between 1 and 31) have been developed. These are serial numbers of 31 classes of organic solvents, ordered empirically by means of simple test tube miscibility

Table 3-3. Hildebrand solubility parameters, δ, of thirty organic solvents at 25 °C, taken from reference [99] (Table 2 in Chapter 8).

Solvents	$\delta/\mathrm{MPa}^{1/2}$ [a]	Solvents	$\delta/\mathrm{MPa}^{1/2}$ [a]
Water	47.9	Acetic acid	20.7
Formamide	39.3	1,4-Dioxane	20.5
N-Methylformamide	32.9	Carbon disulfide	20.4
Ethane-1,2-diol	29.9	Cyclohexanone	20.3
Methanol	29.6	Acetone	20.2
Tetrahydrothiophene-1,1-dioxide	27.4	1,2-Dichloroethane	20.0
Ethanol	26.0	Chlorobenzene	19.4
N,*N*-Dimethylformamide	24.8	Trichloromethane	19.0
Dimethyl sulfoxide	24.5	Benzene	18.8
Acetonitrile	24.3	Ethyl acetate	18.6
1-Butanol	23.3	Tetrahydrofuran	18.6
Cyclohexanol	23.3	Tetrachloromethane	17.6
Pyridine	21.9	Cyclohexane	16.8
t-Butanol	21.7	*n*-Hexane	14.9
Aniline	21.1	Perfluoro-*n*-heptane	11.9

[a] $1\ \mathrm{MPa}^{1/2} = 1\ \mathrm{J}^{1/2} \cdot \mathrm{cm}^{-3/2}$.

experiments and critical solution temperature measurements. There is a close correlation between M numbers and Hildebrand's δ values [99].

The solvency of hydrocarbon solvents used in paint and lacquer formulations is empirically described by their *kauri butanol numbers*, *i.e.* the volume in milliliters at 25 °C of the solvent required to produce a defined degree of turbidity when added to 20 g of a standard solution of kauri resin in 1-butanol [120]. Standard values are $KB = 105$ for toluene and $KB = 40$ for *n*-heptane/toluene (75:25 cL/L). A high KB number corresponds to high solvent power. An approximately linear relationship exists between Hildebrand's δ values and KB numbers for hydrocarbons with $KB > 35$: $\delta = 0.06 \cdot KB + 12.9$ [99, 177].

Solvents whose molecules possess a permanent *dipole moment* are designated *dipolar* as opposed to *apolar* or *nonpolar* for those lacking a dipole moment. Unfortunately, in the literature the terms "polar" and "apolar" or "nonpolar" are used indiscriminately to characterize a solvent by its relative permittivity as well as its permanent dipole moment, even though dipole moment and relative permittivity are not directly related. Molecules possessing a centre of symmetry in all possible conformations, more than one *n*-fold axis of symmetry, or a plane of symmetry perpendicular to an *n*-fold axis of symmetry, cannot exhibit a permanent dipole moment for symmetry reasons. Therefore, only those molecules which belong to the point groups C_1, C_s, C_n, or C_{nv} can have a permanent dipole moment. The permanent dipole moments of organic solvents vary from 0 to $18.5 \cdot 10^{-30}$ Cm (0 to 5.5 D); *cf.* Appendix, Table A-1. Values of dipole moments increase steadily on going from hydrocarbon solvents to solvents containing dipolar groups such as $\mathrm{C}^{\delta+}\overset{\cdots}{-}\mathrm{O}^{\delta-}$, $\mathrm{C}^{\delta+}\overset{\cdots}{-}\mathrm{N}^{\delta-}$, $\mathrm{N}^{\delta+}\overset{\cdots}{-}\mathrm{O}^{\delta-}$, $\mathrm{S}^{\delta+}\overset{\cdots}{-}\mathrm{O}^{\delta-}$, or $\mathrm{P}^{\delta+}\overset{\cdots}{-}\mathrm{O}^{\delta-}$. The solvents with the highest dipole moments found to date are zwitterionic 3-alkyl-1,2,3-oxadiazolium-5-olates (sydnones). For example, 4-ethyl-3-(1-propyl)sydnone, a high-boiling liquid ($t_{bp} = 155$ °C/3 Torr) with a high relative permittivity ($\varepsilon_r = 64.6$ at 25 °C), exhibits a dipole moment of $\mu = 35.7 \cdot 10^{-30}$ Cm (10.7 D) [202]. The orientation of dipolar solvent molecules around the solute molecule in the absence of specific solute/solvent interactions is largely determined by the dipole moment.

It should not be forgotten that the solution value of a solute dipole moment (μ_s) differs from its gas-phase value (μ_g) and depends on the nature of the solvent. For theoretical approaches to relating the difference ($\mu_s - \mu_g$) to various physical solvent parameters (*e.g.* ε_r, n_D, *etc.*), see reference [122].

The importance of electric moments of orders higher than two (dipoles) such as quadrupoles and even octupoles in solute/solvent interactions between multipolar molecules has been stressed [121]. Depending on the charge distribution, there exist multipoles (2^n-poles) such as monopoles (n = 0; *e.g.* $Na^{\oplus}$, $Cl^{\ominus}$), dipoles (n = 1; *e.g.* HF, H_2O), quadrupoles (n = 2; *e.g.* CO_2, C_6H_6), octupoles (n = 3; *e.g.* CH_4, CCl_4), and hexadecapoles (n = 4; *e.g.* SF_6). According to Reisse [121], only neutral species with a spherical charge distribution (*e.g.* rare gases) should be designated as *apolar*. All others, with non-spherical charge distribution, should be called *polar*, *i.e.* dipolar, quadrupolar, octupolar, *etc.*, depending on the first non-zero electric moment. In this respect, methane and tetrachloromethane are polar molecules, as are *cis*- and *trans*-1,2-dichloroethene (dipolar and quadrupolar, respectively), 1,3-dioxane (dipolar) and 1,4-dioxane (quadrupolar). It has been shown that the 2^n-polar contributions ($n > 1$) to solute/solvent interactions are in many cases non-negligible [121].

The *relative permittivities* play a particular role in the characterization of solvents. Their importance over other criteria is due to the simplicity of electrostatic models of solvation and they have become a useful meaure of solvent polarity. In this connection, it is important to realize what exactly is represented by the macroscopic relative permittivity of a solvent (called relative permittivity because of $\varepsilon_r = \varepsilon/\varepsilon_0$ where ε_0 is a constant, the permittivity of vacuum). Relative permittivities are determined by inserting the solvent between the two charged plates of a condenser. The strength of the electric field E between the plates is lower than the value E_0 measured when the plates are in a vacuum, and the ratio E_0/E gives the numerical value of the relative permittivity. If the solvent molecules do not have permanent dipole moments of their own, then the external field will separate the charge within the molecules thereby inducing dipoles. Molecules with induced or permanent dipoles are forced into an ordered arrangement by the charged plates, causing what is known as polarization. The larger the polarization, the larger the drop in the electric field strength. Therefore, the relative permittivity represents the ability of a solvent to separate charge and to orient its dipoles. The relative permittivities of organic solvents vary from about 2 (*e.g.* hydrocarbons) to about 180 (*e.g.* secondary amides); *cf.* Appendix, Table A-1. Solvents with large relative permittivities may act as dissociating solvents (*cf.* Section 2.6) and are therefore called *polar* solvents, in contrast to the *apolar* or *nonpolar* solvents with low relative permittivities. Relative permittivity values often run parallel to the dissolving power of the solvent, because in the case of ionic solutes (*i.e.* ionophores) solvents of high relative permittivity facilitate dissolution by separating the ions.

Since both the relative permittivity ε_r and the dipole moment μ are important complementary solvent properties, it has been recommended that organic solvents should be classified according to their *electrostatic factor EF* (defined as the product of ε_r

and μ), which takes into account the influence of both properties [101]. Considering the *EF* values and the structures of solvents, a four-part classification of organic solvents has been established: hydrocarbon solvents ($EF\ 0 \ldots 7 \cdot 10^{-30}$ Cm), electron-donor solvents ($EF\ 7 \ldots 70 \cdot 10^{-30}$ Cm), hydroxylic solvents ($EF\ 50 \ldots 170 \cdot 10^{-30}$ Cm), and dipolar non-HBD solvents ($EF \geq 170 \cdot 10^{-30}$ Cm) [99, 101]. Another approach towards defining the polarity of solvents by means of their physical constants uses the ratio $\beta = A \cdot \mu^2 / V_\mathrm{m}$, derived from electrostatic solvation theory (A = constant, μ = dipole moment, V_m = molar volume of the solvent) [203].

The *refractive index n* of a solvent is the ratio of the speed of light of a specified wavelength (usually sodium D-line; $\lambda = 589$ nm) in vacuum, c_0, to its speed in the liquid, c, according to $n_\mathrm{D} = c_0/c$. The refractive index at a specified frequency typical of visible light is related to the relative permittivity by $n_\mathrm{D} = \varepsilon_\mathrm{r}{}^{1/2}$. The molar polarization P_m of a solvent is then given by the Lorenz-Lorentz equation: $P_\mathrm{m} = (n^2 - 1)/(n^2 + 2) \cdot M_\mathrm{r}/\rho$ (where M_r = relative molar mass, and ρ = mass density of the solvent). There is a general tendency for the refractive index to increase as the molar mass and the polarizability of the solvent increase [177, 204]. For example, diiodomethane, with $n_\mathrm{D} = 1.748$, has one of the highest refractive indices, as compared with $n_\mathrm{D} = 1.620$ for iodobenzene and 1.628 for carbon disulfide (see Table A-1 in the Appendix). This high refractive index for diiodomethane reflects a particularly high electron mobility around the two iodine atoms [205]. Solvents with high refractive indices and hence large polarizabilities are particularly suitable for solute/solvent dispersion interactions; see Section 2.2.4. The refractive index is closely related to the property of optical activity of chiral solvents. Optically active, chiral solvents (see later) rotate the plane of plane-polarized light, which arises from the differences in the refractive indices for right- and left-circularly polarized light, n_R and n_L, respectively. Therefore, it is not unexpected that specific rotations $[\alpha]_\mathrm{D}$ of chiral solutes are often solvent-dependent as well [206]; see also Section 6.2.5.

As mentioned before, relative permittivities as well as dipole moments are often used in the quantitative characterization of *solvent polarity*. However, the characterization of a solvent by means of its "polarity" is an unsolved problem since the term "polarity" itself has, until now, not been precisely defined. Polarity might be interpreted as: a) the permanent dipole moment of a compound, b) its relative permittivity, or c) the sum of all those molecular properties responsible for all the interaction forces between solvent and solute molecules (*e.g.* Coulombic, directional, inductive, dispersion, hydrogen-bonding, and EPD/EPA interaction forces) [33]. The important thing concerning the so-called polarity of a solvent is its *overall solvation ability*. This, in turn, depends on the sum of all specific as well as non-specific interactions between solvent and solute. Therefore, in the following, the term "solvent polarity" will be applied according to the definition c) above. It should be noted, however, that all interactions which lead to a chemical change of the solute are excluded under this definition (*e.g.* protonation, oxidation, reduction, and complexation).

Evidently, "solvent polarity", as so-defined, is badly described in a quantitative manner by means of individual physical constants such as relative permittivity, dipole moment, *etc.* It is no surprise therefore, that the macroscopic relative permittivities are an unsuitable measure of molecular-microscopic interactions. This has often been demonstrated experimentally. One reason is that the molecular-microscopic relative permittivity of the solvent in the vicinity of the solute is lower than that for the bulk solvent, because solvent dipoles in a solvation shell are less free to orientate themselves in a direction imposed by charged condenser plates. In the extreme case, complete dielectric saturation can occur for solvent molecules around an ionic solute.

The failure of the solvent relative permittivity to represent solute/solvent interactions has led to the definition of polarity in terms of empirical parameters. Such attempts at obtaining better parameters of solvent polarity by choosing a solvent-dependent standard system and looking at the changes in parameters of that system when the solvent is changed (*e.g.* rate constants of solvent-dependent reactions or spectral shifts of solvatochromic dyes) are treated in Chapter 7.

The aforementioned macroscopic physical constants of solvents have usually been determined experimentally. However, various attempts have been made to calculate bulk properties of liquids from pure theory. By means of quantum chemical methods, it is possible to calculate some thermodynamic properties (*e.g.* molar heat capacities and viscosities) of simple molecular liquids without specific solvent/solvent interactions [207]. A quantitative structure-property relationship treatment of normal boiling points, using the so-called CODESSA technique (*i.e. co*mprehensive *de*scriptors for *s*tructural and *s*tatistical *a*nalysis), leads to a four-parameter equation with physically significant molecular descriptors, allowing rather accurate predictions of the normal boiling points of structurally diverse organic liquids [208]. Based solely on the molecular structure of solvent molecules, a non-empirical solvent polarity index, called the *first-order valence molecular connectivity index*, has been proposed [137]. These purely calculated solvent polarity parameters correlate fairly well with some corresponding physical properties of the solvents [137].

Optically active organic solvents, consisting of chiral molecules*⁾ (chiral solvents), which rotate the plane of linearly polarized light, have become increasingly important lately [35]. In principle, diastereomeric solvates are formed when a mixture of enantiomers is dissolved in an optically active solvent. Consequently, these solvates should possess slightly different physical and chemical properties. In fact, optically active solvents have already found use in stereoselective syntheses [36–38, 123], as NMR shift reagents [39, 124], in the evaluation of the optical purity of enantiomers [40], and in the gaschromatographic separation of enantiomers on chiral phases [41, 124, 125]. A selection of such optically active solvents is given in Table A-2 (Appendix).

Some recent examples of enantioselective syntheses in chiral solvents are: the high-pressure (10^4 bar) Wagner-Meerwein rearrangement of a racemic oxirane derivative in (−)-(2*S*,3*S*)-diethyl tartrate (optical yield 6.7%) [42]; the chlorination of substituted aziridines with *t*-butyl hypochlorite to give *N*-chloroaziridines in the presence of chiral trifluoromethylcarbinols (highest enantiomeric excess, $ee = 28.7\%$) [126]; the Grignard reaction of 2,2-dimethylpropanal with phenylmagnesium bromide in (−)-menthyl methyl ether ($ee = 19.4\%$) [127] and the addition of *n*-butyllithium to benzaldehyde in the presence of (+)-(*S*,*S*)-1,4-bis(dimethylamino)-2,3-dimethoxybutane (DDB) (optical yield 30%) [128], according to the following equation:

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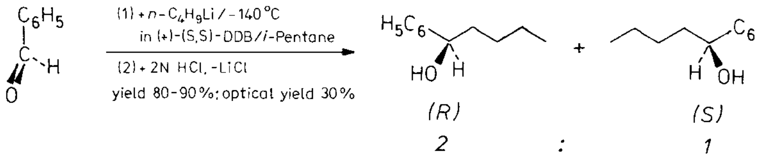
* A molecule is chiral, and hence optically active, when it does not possess planes, centres, or alternating axes of symmetry (order $n > 2$) [34].



Aldol additions between *achiral* reactants in *chiral* solvents have also been examined [157–159]. Only low asymmetric inductions ($ee = 2\ldots22\%$) have been found [158]. A twofold stereodifferentiation is observed in aldol additions between *chiral* reactants carried out in *chiral* solvents [159]. However, asymmetric inductions caused by chiral solvents or cosolvents are usually rather small [157].

In addition to the aforementioned conventional liquid organic solvents, two other types of molecular liquids have attracted much interest as supplementary or alternative media for synthesis and processing, namely *supercritical fluids* (sc-fluids) [209] and *metastable liquids* [210].

The importance of *supercritical fluids* as media for chemical reactions and in separation technology (extractions and materials processing) originates from their unique solvent properties [209, 211–217]. A fluid is termed supercritical when its temperature exceeds the so-called critical temperature, T_C. Under these experimental conditions, the two fluid phases, liquid and vapour, become indistinguishable. They exist as a single phase without any phase boundaries, possessing the favourable properties of both a liquid and a gas. The observation that above a certain temperature pure substances do not condense or evaporate, but exist only as fluids, was made as long ago as 1822 by Baron Charles Cagniard de la Tour [218]. The ability of sc-fluids to dissolve other compounds was first noted in 1879, when Hannay and Hogarth investigated the solubility of iron and cobalt chlorides in sc-ethanol [219].

Most notably, sc-fluids exhibit properties intermediate between those of gases and liquids. Their densities can be finely tuned by varying the pressure and temperature; see Fig. 3-2 [220]. The viscosities and diffusivities of sc-fluids are comparable with those of gases, yet their densities are closer to those of liquids. The low viscosity facilitates the high mass-transfer rates in sc-fluids. The density of sc-fluids is sufficiently high to allow the adequate solvation of a variety of solutes, but their solvating power is much less than that of conventional solvents. The possibility of varying the density of sc-fluids, and therefore the solubility of the solute, by adjusting the temperature and pressure, makes them ideal candidates as solvents for extraction and partitioning processes (*cf.* Section A.6 in the Appendix). The addition of normal co-solvents (modifiers, entrainers) can enhance the solubility of involatile substances in sc-fluids.

Although the unique properties of sc-fluids were known for a long time, their use as reaction media has only become more popular in recent years [211–217, 220]. Reasons for carrying out reactions in sc-fluids are [216]: (a) enhanced reaction rates for reactions with negative activation volumes; (b) homogenization of reactions that would otherwise be carried out in more than one phase (heterogeneous reactions); (c) enhanced mass transfer, important for diffusion-limited reactions; (d) increased catalyst activity in heterogeneous reactions through in situ regeneration of surfaces with tuning of the operation conditions; (e) tunable reaction rates through changing the polarities of sc-fluids by manipulating their densities; and (f) low toxicity of most sc-fluids, which makes

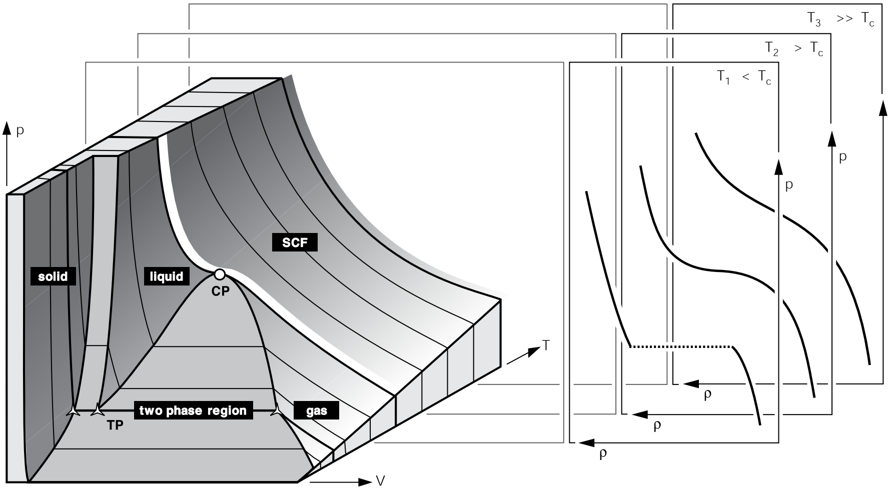


Fig. 3-2. P/V/T phase diagram of a pure substance (pure solvent) showing domains in which it exists as solid, liquid, gas (vapour), and/or sc-fluid (CP = critical point; TP = triple point; ρ = mass density). The inserted isotherms T_2 ($T_2 > T_C$) and T_3 ($T_3 \gg T_C$) illustrate the pressure-dependent density ρ of sc-fluids, which can be adjusted from that of a gas to that of a liquid. The influence of pressure on density is greatest near the critical point, as shown by the greater slope of isotherm T_2 compared to that of T_3, which is further away from T_C. Isotherm T_1 demonstrates the discontinuity in the density at subcritical conditions due to the phase change. This figure is taken from reference [220].

them ideal candidates for the replacement of environmentally problematic solvents (see Table A-14 in the Appendix). A selection of common sc-fluids is given in Table 3-4.

The most common sc-fluid for industrial processing and benchtop research is supercritical carbon dioxide, chosen because of its moderate and easily attained critical temperature and pressure and its non-toxicity. Reactions in sc-CO_2 produce similar results as reactions in nonpolar organic solvents. Its solvent polarity, empirically determined using solvatochromic dyes as polarity indicators (see Section 7.4), corresponds to that of hydrocarbons such as cyclohexane [221, 222]. Carbon dioxide has no dipole moment and only a small quadrupole moment, a small polarizability volume, and a low relative permittivity ($\varepsilon_r = 1.4$–1.6 at 40 °C and 108–300 bar) [221, 223]. Thus, sc-CO_2 is only suitable as a solvent for nonpolar substances, which unfortunately imposes considerable limitations on its practical applications. To overcome this limitation, more polar co-solvents (modifiers) such as methanol can be added to sc-CO_2.

Another environmentally benign solvent is supercritical water, which has a great potential to replace conventional solvents, although it requires rather harsh experimental conditions ($t_C = 374$ °C and $p_C = 218$ atm; see Table 3-4) [224, 225]. At the critical point of sc-H_2O, its volume is three times larger than that at ambient temperature, its relative permittivity is only 5.3 (compared to $\varepsilon_r = 78.4$ at 25 °C), and its intermolecular hydrogen-bond network is partially broken. Under supercritical conditions, water consists of small clusters, oligomers, and even monomeric gas-like water molecules [226,

Table 3-4. Critical temperature, t_C, critical pressure, p_C, critical density, ρ_C, and critical molar volume, V_C, for twenty supercritical fluids, arranged in order of increasing t_C.[a)]

Solvents	$t_C/°C$	p_C/MPa[b)]	$\rho_C/g \cdot cm^{-3}$	$V_C/cm^3 \cdot mol^{-1}$
Methane	−82.6	4.60	0.16	99
Ethene	9.2	5.04	0.22	131
Xenon	16.6	5.84	1.15	118
Trifluoromethane	26.2	4.86	0.62	133
Carbon dioxide	31.0	7.38	0.47	94
Ethane	32.2	4.87	0.20	146
Tetrafluoroethene	33.4	3.94	–	172
Dinitrogen oxide	36.4	7.26	0.45	97
Fluoromethane	44.7	5.88	–	113
Sulfur hexafluoride	45.5	3.77	0.74	199
Difluoromethane	78.5	5.83	–	121
Propane	96.7	4.25	0.22	200
1,1,1,2-Tetrafluoroethane	101.0	4.07	–	198
Dichloro-difluoromethane	111.8	4.14	0.56	217
Perfluorobutane	113.3	2.32	–	378
Ammonia	132.4	11.4	0.24	72
n-Butane	152.0	3.80	0.23	255
Methanol	239.4	8.08	0.27	117
Ethanol	240.9	6.14	0.28	168
Water	374.0	22.1	0.32	56

[a)] Values taken from (a) D. Ambrose: *Critical Constants*, in D. R. Lide (Ed.): *CRC Handbook of Chemistry and Physics*, 77th ed., CRC Press, Boca Raton/FL, USA, 1996, p. **6**-54ff.; (b) Y. Marcus: *The Properties of Solvents*. Wiley, Chichester, 1998, p. 78.

[b)] $1\ MPa = 10^6\ Pa = 1\ J \cdot cm^{-3} = 9.87\ atm$.

227]. Because oxygen, carbon dioxide, methane and other alkanes are completely miscible with dense sc-H_2O, combustion can occur in this fluid phase; even flames can burn in sc-H_2O!

In addition to supercritical water, *superheated water* can be used as a reaction medium. The reactivity of various organics in high-temperature water under autogenic pressure has been studied between 200 and 460 °C [228–230]. As the critical temperature of water is 374 °C, these experiments are both sub- and supercritical. In this particular chemistry, water participates as solvent, reactant, and catalyst. For example, ethers and esters undergo facile hydrolysis in neutral superheated water at 250–350 °C. The physical and chemical properties of water change dramatically as the temperature increases to such a large extent. For example, as the temperature rises from 25 to 300 °C, the density of water decreases from $\rho = 0.997$ to $0.713\ g/cm^3$, its relative permittivity decreases from $\varepsilon_r = 78.4$ to 19.7, and its solubility parameter decreases from $\delta = 47.9$ to 29.7 $MPa^{1/2}$ (see Table 3-3). Over the same temperature range, the ionic product of water increases by three orders of magnitude from 10^{-14} to $10^{-11.3}$. This means that water becomes both a stronger acid and a stronger base as the temperature increases. The change in the relative permittivity makes the solvent polarity properties of water at 300 °C roughly equivalent to those of acetone at 25 °C ($\varepsilon_r = 20.6$). Therefore, under superheated conditions, water can act as a powerful acid/base bicatalyst and ionic reactions are preferred over free-radical reactions. The ability of superheated water to effect condensation, cleavage, and hydrolysis reactions, as well as selective ionic reactions, is mainly due to the changes in its physical and chemical properties, which approach those of polar organic solvents at room temperature [228–230].

For the use of sc-fluids as reaction media in synthesis, see reviews [211–217, 224, 225, 228–230] and Section 5.5.13, which describes applications of some neoteric solvents such as ionic liquids, perfluorohydrocarbons, and sc-fluids in organic synthesis and catalysis.

Metastable liquids constitute another remarkable manifestation of the liquid state. Liquids can also exist in conditions under which the *stable* state is either a solid, a vapour, or a liquid of different composition. When this occurs, a liquid is said to be *metastable* with respect to the stable phase. For example, metastability with respect to crystalline or vapour phases defines *supercooled* and *superheated* liquids, respectively [210]. Water can exist as a liquid below 0 °C (=supercooled water). It is also possible to heat liquid water above 100 °C without boiling (=superheated water). However, care must be taken to prevent supercooled water from freezing and superheated water from boiling. Supercooled and superheated water exist in a kind of precarious equilibrium. The temperature range over which supercooled and superheated water can exist at atmospheric pressure extends from ca. -41 °C to ca. 280 °C [210, 231]. This possibility of superheating a liquid above its boiling point, or of supercooling it below its freezing point, is not limited to water. Supercooled and superheated liquids are said to be metastable. They are of no importance as reaction media, but supercooled water is found abundantly in Nature [210, 231]. Organisms and plants exposed to prolonged sub-0 °C conditions have developed strategies to prevent the potential freezing of their water content, as formation of ice crystals inside their cells would be lethal. To avoid its freezing in animals, there exist two possibilities: colligative depression of freezing point by so-called cryoprotectants (*e.g.* glycerol) or through the action of antifreeze proteins. Antarctic fish are protected down to -2 °C by antifreeze proteins; for a more detailed discussion and other examples of metastable liquids, see references [210, 231].

3.3 Classification of Solvents in Terms of Acid-Base Behaviour

3.3.1 Brønsted-Lowry Theory of Acids and Bases [43–50, 107, 168]

According to the Brønsted-Lowry definition, acids and bases are proton donators and -acceptors, respectively, as expressed in the following equilibrium

$$\underset{\text{Acid}}{HA^{z+1}} \rightleftharpoons \underset{\substack{\text{Conjugate}\\\text{Base}}}{A^{z}} + H^{+} \tag{3-7}$$

where $z = 0, \pm 1, \ldots$ [51, 52]. Since, in solution, the isolated proton cannot exist [129], an acid-base reaction will take place only in the presence of a base possessing a higher proton affinity than the conjugate base A^z. As most solvents possess acid or base properties, the strengths of acids and bases depend on the medium in which they are dissolved.

The equilibrium shown in Eq. (3-8) will be established when an acid HA is dissolved in a basic solvent SH.

$$\underset{\text{Acid}}{\mathrm{HA}^{z+1}} + \underset{\text{Solvent}}{\mathrm{SH}} \rightleftharpoons \underset{\substack{\text{Lyonium}\\ \text{Ion}}}{\mathrm{SH}_2^+} + \mathrm{A}^{z} \tag{3-8}$$

The strength of the acid HA in the solvent SH is given by the acidity contant K_a according to Eq. (3-9)*) [53].

$$K_a = \frac{[\mathrm{SH}_2^+]\cdot[\mathrm{A}^z]}{[\mathrm{HA}^{z+1}]} \tag{3-9}$$

In an acidic solvent SH, the acid-base equilibrium shown in Eq. (3-10) will be established.

$$\underset{\text{Base}}{\mathrm{A}^{z}} + \underset{\text{Solvent}}{\mathrm{SH}} \rightleftharpoons \mathrm{HA}^{z+1} + \underset{\substack{\text{Lyate}\\ \text{Ion}}}{\mathrm{S}^-} \tag{3-10}$$

Increasing basicity or acidity of the solvent displaces the equilibria (3-8) and (3-10) to the right. The addition of these two equations gives a new equilibrium describing the self-ionization (autoprotolysis) of the solvent.

$$\underset{\text{Solvent}}{2\,\mathrm{SH}} \rightleftharpoons \underset{\substack{\text{Lyonium}\\ \text{Ion}}}{\mathrm{SH}_2^+} + \underset{\substack{\text{Lyate}\\ \text{Ion}}}{\mathrm{S}^-} \tag{3-11}$$

Eq. (3-11) reflects both the acidic and basic properties of a solvent, which are described quantitatively by the *autoprotolysis constant* K_{auto}.

$$K_{\text{auto}} = [\mathrm{SH}_2^+]\cdot[\mathrm{S}^-] \tag{3-12}$$ **)

Autoprotolysis constants for some representative solvents are collected in Table A-12 (Appendix). The useful pH range of a solvent increases as the autoprotolysis constant decreases. The smaller the autoprotolysis constant, the greater the range of acid or base strengths which can exist in a solvent***).

Self-ionizing solvents possessing both acid and base characteristics (*e.g.* water) are designated *amphiprotic solvents*, in contrast to *aprotic solvents*, which do not self-

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* Since, in general, the solvent SH is in large excess, its concentration [SH] remains almost constant and is therefore included in the constant K_a.

** Since the solvent concentration [SH] remains practically constant due to the large excess of unionized solvent, this term is usually included in K_{auto}.

*** Thus, the magnitude of K_{auto} is an important criterion for the proper choice of solvent for titrations in non-aqueous solvents; *cf.* Section A-8 (Appendix).

Table 3-5. Classification of organic solvents according to their Brønsted acid-base behaviour [56].

Solvent designation		Relative acidity[a)]	Relative basicity[a)]	Examples
	Neutral	+	+	H_2O, CH_3OH, $(CH_3)_3COH$, $HOCH_2CH_2OH$, C_6H_5OH
Amphiprotic	Protogenic	+	−	H_2SO_4, HCOOH, CH_3COOH
	Protophilic	−	+	NH_3, $HCONH_2$, $CH_3CONHCH_3$, $H_2N—CH_2CH_2—NH_2$
	Dipolar Protophilic	−	+	$HCON(CH_3)_2$, CH_3SOCH_3, pyridine, 1,4-dioxane $(C_2H_5)_2O$, tetrahydrofuran
Aprotic	Dipolar Protophobic	−	−	CH_3CN, CH_3COCH_3, CH_3NO_2, $C_6H_5NO_2$, sulfolane
	Inert	−	−	Aliphatic hydrocarbons, C_6H_6, $Cl—CH_2CH_2—Cl$, CCl_4

[a)] − indicates weaker and + indicates stronger acid or base than water.

ionize to a measurable extent (*e.g.* aliphatic hydrocarbons, tetrachloromethane) [47, 53–55].

It is not possible to draw a sharp line between amphiprotic and aprotic solvents since, in practice, amphiprotic solvents with extremely small K_{auto} values behave like aprotic solvents. It has been suggested that solvents with K_{auto} values greater than 20 should be called aprotic rather than amphiprotic [44].

This classification of solvents was first proposed by Brønsted, who distinguished between four types of solvents on the basis of their acid and base properties [54]. Davies extended the Brønsted classification and distinguished between solvents with relative permittivities greater or smaller than 20, thus arriving at eight classes of solvents [47]. Kolthoff's classification in a slightly simplified fashion is given in Table 3-5 [56].

Water is the prototype of an amphiprotic solvent and all other solvents with similar acid-base properties are called *neutral solvents*. Solvents that are much stronger acids and much weaker bases than water are called *protogenic solvents*, while those that are much stronger bases and much weaker acids than water are designated *protophilic solvents*. This division is somewhat arbitrary since, by agreement, water is the reference taken to define neutral.

From Eq. (3-8), it is seen that the ionization of an acid depends on the basicity of the solvent. In other words, the effective strength of an acid is greater, the higher the proton affinity of the medium. However, the ionization of the acid depends not only on the basicity of the solvent, but also on its relative permittivity and its ion-solvating ability. The dependence of the acidity and basicity constants of a compound on the basicity and acidity, respectively, of the solvents, leads to a distinction between *levelling* and *differentiating solvents* [49, 57, 58].

All mineral acids ionize to the same extent in aqueous solution: they are essentially completely ionized due to almost quantitative reaction with the base water. It would be a strange coincidence, however, if all these acids had exactly the same acid

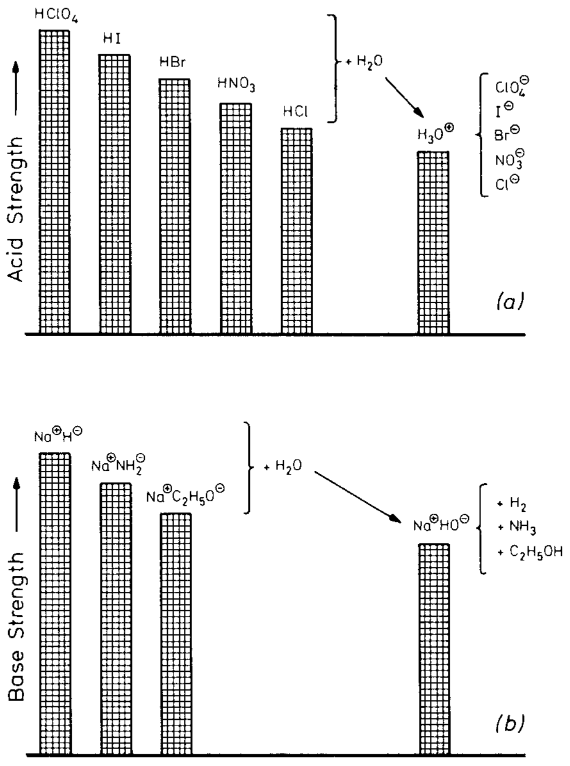

Fig. 3-3. Schematic description of the levelling effect of water on (a) acids and (b) bases in aqueous solution [2]. Relative orders of acidity and basicity are not invariable to changes of solvent and of the conjugated acid or base, respectively.

strength in spite of their different constitutions. The explanation is that water exerts a levelling effect on the acid strengths. Fig. 3-3 shows that in water the strengths of all acids stronger than H_3O^+ are adjusted to that of H_3O^+ itself. Solvents exhibiting such behaviour are called *levelling solvents**). In order to establish the relative strengths of the mineral acids, it is necessary to perform the measurements in solvents of very low basicity and ionizing ability. Logically enough, such solvents are designated *differentiating solvents*. Fig. 3-3 makes it clear that the strongest acid that can exist in a solvent is the lyonium ion $SH_2^{\oplus}$ (in case of (a) $H_3O^{\oplus}$), while the lyate ion, $S^{\ominus}$, is the strongest base that can exist in a solvent (in case of (b) $HO^{\ominus}$). Thus, in methanol, hydrochloric acid is completely ionized, whereas nitric acid is only partly so. In the less basic formic acid, hydrochloric acid is also only partially ionized, whereas the first H-atom of sulfuric acid is still completely ionized. Acetonitrile is a very weak base and an exceptionally weak acid, thus, only slight levelling of acids and bases occurs in this solvent, making it a good differentiating solvent. Perchloric acid appears to be strong in acetonitrile, whereas

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* The expression "levelling solvents" ("chemisch nivellierende Lösungsmittel") was introduced by A. Hantzsch, Z. Elektrochem. *29*, 221 (1923).

other acids are differentiated [59]: HBr $>$ H_2SO_4 $>$ HNO_3 $>$ HCl and picric acid. When the solvent is a stronger base than water, its levelling effect will apply also to weaker acids. Thus, in liquid ammonia, even the carboxylic acids are practically fully ionized.

Similarly, strong bases will also have equal basicities in sufficiently acidic solvents. As shown in Fig. (3-3b), all bases stronger than the $HO^{\ominus}$ ion are adjusted to the basicity of this ion in water. Consequently, the effective basicities of guanidines and carbanions cannot be measured in water, but only in less acidic differentiating solvents such as liquid ammonia or diethyl ether.

Evidently, in a given solvent the more highly ionized acid or base is also the strongest one. However, if the same acid is examined in different solvents, one finds, surprisingly enough, that the most acidic solution is the one in which the acid is the least ionized. For example, a solution of hydrochloric acid in benzene is a stronger acid than in aqueous solution; in the former, ionization is slight, in the latter, complete. In the aqueous solution, an indicator would have to compete with the base H_2O for the protons; however, in the benzene solution, competition involves only the much weaker base $Cl^{\ominus}$. Therefore, a larger proportion of the indicator would be transformed into its conjugate acid in benzene than in water, thus making the benzene solution of HCl the better proton donator.

Numerous acidity and basicity scales have been elaborated for water and other solvents. However, there is no one single scale of acidity and basicity, equally valid and useful for all types of solvents and applicable to both equilibrium and kinetic situations. Excellent reviews on different acidity functions are given by Boyd [60] and Bates [50].

In dilute aqueous solution, the acidity is measured using pH values. For concentrated acid solutions and non-aqueous acid solutions, pH values are no longer available. Hence, the *Hammett acidity function* H_0 is used as a measure of the acidity of such media [130]. The proton donor ability of an acid in such media is measured by studying the equilibria of a series of indicator bases B (mostly nitroanilines), the UV/Vis absorption spectra of which are markedly different from those of their conjugate acids, so that the indicator concentration ratio $I = [B]/[BH^+]$ can be measured spectrophotometrically. The acidity function H_0 is then given by $H_0 = pK_{BH+} + \lg I$, with the subscript zero indicating that the H_0 function applies only to neutral bases B [130, 170]. For dilute solutions, H_0 corresponds exactly to pH; in concentrated solutions, the two functions differ appreciably.

Brønsted acids stronger than pure (100%) sulfuric acid ($H_0 = -11.9$) are classified as *super acids* [131, 132]. Thus, perchloric acid ($HClO_4$), fluorosulfonic acid ($F—SO_3H$), and trifluoromethanesulfonic acid ($CF_3—SO_3H$) are considered as super acids. Even exceedingly weak basic solvents (*e.g.* carbonyl compounds; aromatic, olefinic, and saturated hydrocarbons) are protonated by these super acids to give the corresponding carbocations [131].

Streitwieser *et al.* [160] and Bordwell *et al.* [161] used the lyate ions of organic solvents such as cyclohexylamine and dimethyl sulfoxide in the determination of the C—H acidity of weak organic carbon acids. Using *super base* systems such as alkali metal salts of cyclohexylamine (*i.e.* lithium and cesium cyclohexylamides) [160] and dimethyl sulfoxide (sodium dimsyl) [161] in an excess of these non-HBD solvents, relative acidity scales for weak carbon acids have been established. In this way, pK_a^{DMSO} values for the ionization of over a thousand Brønsted acids in dimethyl sulfoxide have become available, covering a range of *ca.* 35 pK_a units [161]. The upper limits of measurements in cyclohexylamine and dimethyl sulfoxide are imposed by the acidities of the two solvents, corresponding to maximum determinable pK_a^{CHA} and pK_a^{DMSO} values of *ca.* 39 and 32, respectively.

The acidity and basicity of solvents can be measured in different ways [49]. Besides the usual experimental methods of measuring acid-base equilibrium constants, another possible approach is the determination of solvent basicities and acidities by measuring the change in some physical property (like an IR or UV/Vis absorption or NMR chemical shift) of the molecules of a standard substrate when transferred from a reference solvent to another solvent. For example, the shift in wavenumber of the $\equiv$C—H valence vibration band of phenylacetylene when transferred from tetrachloromethane to nineteen other solvents has been measured, giving a relative order of basicity ranging from tetrachloromethane (low) to hexamethylphosphoric triamide (high) [61]. The basicity of solvents has also been measured using the ^{1}H NMR chemical shift of the chloroform H-atom $\Delta\delta_\infty(CHCl_3)$ obtained by extrapolation to infinite $CHCl_3$ dilution in the solvent in question and in an inert reference solvent (cyclohexane), respectively. The results, summarized in Table 3-6, establish an order of solvent basicity using chloroform as the standard proton donor [62].

For other, more recent quantitative scales of the hydrogen-bond donor acidities and hydrogen-bond acceptor basicities of solvents, see the end of Section 2.2.5 (and references [329–334] cited therein).

The protonation equilibria of a variety of solvents in strong acids such as aqueous sulfuric acid at 25 °C have been measured ^{1}H NMR spectroscopically [232]. For exam-

Table 3-6. Solvent order of increasing basicity relative to chloroform, measured using the relative ^{1}H NMR chemical shift and extrapolated to infinite dilution with cyclohexane as reference solvent [62].

Solvents	$\Delta\delta_\infty(CHCl_3)$[a] ppm
Cyclohexane	0.00
Tetrachloromethane	0.18
Chloroform	0.20
Nitromethane	0.47
Acetonitrile	0.56
1,4-Dioxane	0.63
Diethyl ether	0.74
Tetrahydrofuran	0.79
Acetone	0.92
Cyclohexanone	0.97
Triethylamine	1.22
N,*N*-Dimethylformamide	1.30
Dimethyl sulfoxide	1.32
Pyridine	1.56
Hexamethylphosphoric acid triamide	2.06

[a] $\Delta\delta_\infty(CHCl_3) = \delta_\infty(CHCl_3, \text{solvent}) - \delta_\infty(CHCl_3, \text{cyclohexane})$

ple, the relative order of increasing basicity for some dipolar non-hydroxylic solvents determined this way is: nitromethane < sulfones < acetonitrile ≪ acetone < dimethyl sulfoxide < amides [232].

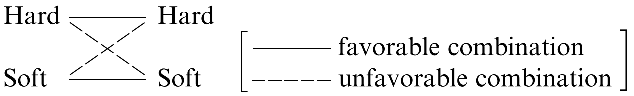
Recent gas-phase studies of proton-transfer reactions with stepwise solvation of the reactants (*i.e.* incremental addition of solvent molecules to form supermolecular clusters) have demonstrated that the acid/base behaviour of isolated solvent molecules can be dramatically different from their performance as bulk liquids. Water, the classical amphiprotic solvent, shall serve as an example.

In contrast to the acid/base behaviour of "polymeric" bulk water, "monomeric" water is a relatively weak acid and base in the gas phase compared to its substituted derivatives (R—OH, R—O—R, *etc.*), whose conjugated base or acid ions are stabilized by polarization of the alkyl groups. The gas-phase basicity of water is 138 kJ/mol (33 kcal/mol) below that of ammonia. Its gas-phase acidity is comparable to that of propene and it is less acidic than phenol by about 167 kJ/mol (40 kcal/mol). With respect to the well-known acid/base properties of water, ammonia, and phenol in aqueous solution, one has to conclude that enormous solvation energies must contribute to the difference from the behaviour of isolated water molecules. See Section 4.2.2 for further discussions and references.

3.3.2 Lewis Theory of Acids and Bases [44–65, 65a]

According to Lewis, acids are electron-pair acceptors (EPA) and bases electron-pair donors (EPD), connected through the following equilibrium [63, 65a]:

$$\begin{array}{llcl} \mathrm{A} \quad + & :\mathrm{D} & \rightleftharpoons & \mathrm{A{-}D} \\ \text{Acid} & \text{Base} & & \text{Acid-Base} \\ \text{EPA} & \text{EPD} & & \text{Complex} \\ \text{Electrophile} & \text{Nucleophile} & & \end{array} \tag{3-13}$$



The Lewis acid/base complex is formed through an overlap between a doubly occupied orbital of the donor D and a vacant orbital of the acceptor A (*cf.* also Section 2.2.6). This acid/base approach was extended by Pearson, who divided Lewis acids and bases into two groups, hard and soft, according to their electronegativity and polarizability (principle of hard and soft acids and bases; HSAB concept) [66, 67]. Hard acids (*e.g.* $H^{\oplus}$, $Li^{\oplus}$, $Na^{\oplus}$, BF_3, $AlCl_3$, hydrogen-bond donors HX) and hard bases (*e.g.* $F^{\ominus}$, $Cl^{\ominus}$, $HO^{\ominus}$, $RO^{\ominus}$, H_2O, ROH, R_2O, NH_3) are those derived from small atoms with high electronegativities and are generally of low polarizability. Soft acids (*e.g.* $Ag^{\oplus}$, $Hg^{\oplus}$, I_2, 1,3,5-trinitrobenzene, tetracyanoethene) and soft bases (*e.g.* $H^{\ominus}$, $I^{\ominus}$, $R^{\ominus}$, $RS^{\ominus}$, RSH, R_2S, alkenes, C_6H_6) are usually derived from large atoms with low electronegativities and are usually polarizable. The usefulness of this division arises from a simple rule concerning the stability of Lewis acid/base complexes: *hard acids prefer to coordi-*

nate to hard bases and soft acids to soft bases [66, 67]. This HSAB concept describes a wide range of chemical phenomena in a qualitative way and has found many applications in organic chemistry [66–70] (for a criticism of the HSAB concept, see refs. [71, 72]). Since the hard species are generally of small size and high charge density, and the soft species are large in size with a low charge density, *ionic bonding* predominates in hard/hard reactions, whereas *covalent bonding* between the reactants, involving their frontier orbitals (*i.e.* HOMO/LUMO interactions according to Fukui), predominates in soft/soft reactions [233, 234]. Based on ionization potentials and electron affinities, even numerical values of absolute hardness, *i.e.* resistance to deformation or change in the electronic charge cloud, can now be assigned to various Lewis acids and bases.

Solvents can be classified as EPD or EPA according to their chemical constitution and reaction partners [65]. However, not all solvents come under this classification since *e.g.* aliphatic hydrocarbons possess neither EPD nor EPA properties. An EPD solvent preferably solvates electron-pair acceptor molecules or ions. The reverse is true for EPA solvents. In this respect, most solute/solvent interactions can be classified as generalized Lewis acid/base reactions. A dipolar solvent molecule will always have an electron-rich or basic site, and an electron-poor or acidic site. Gutmann introduced so-called donor numbers, *DN*, and acceptor numbers, *AN*, as quantitative measures of the donor and acceptor strengths [65]; *cf.* Section 2.2.6 and Tables 2-3 and 2-4. Due to their coordinating ability, electron-pair donor and acceptor solvents are, in general, good ionizers; *cf.* Section 2.6.

The HSAB behaviour is dependent on the medium in which EPD/EPA reactions are carried out. For example, the order of stability of complexes of metal ions with halide ions in the gas phase is $F^- > Cl^- > Br^- > I^-$, which makes all metal ions appear hard in the gas phase. However, in aqueous solution, the stability order is reversed to $F^- < Cl^- < Br^- < I^-$ for those metal ions classified as soft [69].

The application of the HSAB concept to solutions leads to the rule that hard solutes dissolve in hard solvents and soft solutes dissolve in soft solvents [66]. This rule can be considered as a modern version of "similia similibus solvuntur". For example, benzene is considered a very soft solvent since it contains only a basic function. Contrary to benzene, water is a very hard solvent, with respect to both its basic and acidic properties. It is the ideal solvent for hard bases and hard acids. The hardness of water is reduced by the introduction of alkyl substituents in proportion to the size of the alkyl group. In alcohols, therefore, softer solutes become soluble. Whereas oxalate salts are quite insoluble in methanol, the corresponding softer bisthiooxalate salts are quite soluble.

Since hydrogen-bonding is a hard acid-hard base interaction, small basic anions prefer specific solvation by protic solvents. Hence, the reactivity of $F^{\ominus}$, $HO^{\ominus}$, or $CH_3O^{\ominus}$ is reduced most on going from a dipolar non-HBD solvent such as dimethyl sulfoxide to a protic solvent like methanol. Dipolar non-HBD solvents are considered as fairly soft compared to water and alcohols [66].

Similar considerations can be made in the case of cation solvation. Small, hard cations of high oxidation state will be preferably solvated by hard EPD solvents like H_2O or ROH. In principle, relative to the gas state, all ions become softer in the solute state as a result of solvation [66].

Replacement of the oxygen in hard oxygen-donor solvents (such as THF, DMF, and 1-methylpyrrolidine-2-one) by sulfur to give the corresponding sulfur-donor solvents (*i.e.* thiolane [235], *N*,*N*-dimethylthioformamide [236], and 1-methylpyrrolidine-2-thione [237]) leads to much softer EPD solvents, more suitable for the solvation of soft cations (*e.g.* Ag^+, Tl^+, Hg^{2+}, *etc.*).

Based on single-ion transfer properties, various quantitative empirical scales describing the softness of EPD solvents have been proposed; for reviews, see references [173, 238, 239].

Marcus proposed a μ scale of solvent softness (from the Greek *malakos* = soft), defined as the difference between the mean of the standard molar Gibbs energies of transfer of Na^+ and K^+ ions from water (W) to a given solvent (S), $\Delta G°_t(Me^+, W \rightarrow S)/(kJ \cdot mol^{-1})$, and the corresponding Gibbs transfer energy for Ag^+ ions, divided by 100 [171, 239]. Since water is a hard solvent, the Gibbs energy of transfer of ions from water as a reference solvent to other solvents, should depend on the softness of these EPD solvents to a different extent for hard and soft ions. Provided that the charge and size of the solvated ions are equal, hard ions prefer water and soft ions the softer solvents. The definition of μ was selected because the size of the soft Ag^+ ion ($r = 115$ pm) is intermediate between those of the hard Na^+ ($r = 102$ pm) and K^+ ions ($r = 138$ pm). The degree of softness among solvents with oxygen, nitrogen, and sulfur donor atoms increases in the sequence *O*-donor (alcohols, ketones, amides) < *N*-donor (nitriles, pyridines, amines) < *S*-donor solvents (thioethers, thioamides) [171].

The soft donor properties of EPD solvents have also been quantified by the softness parameter *SP* of Gritzner [173, 240]. This parameter is solely based on the standard molar Gibbs energies of transfer of Ag^+ ions from benzonitrile as reference solvent to other soft solvents and should be used for soft/soft interactions only.

Finally, the D_S and D_H solvent scale of Persson *et al.* should be mentioned [241]. The empirical D_S scale, ranking the EPD solvent's donor strength towards a soft acceptor, is based on the shift of the Raman IR absorption for the symmetrical stretching vibration of the Hg—Br bond of soft mercury(II) bromide in the solvent of interest relative to that in the gas phase: $D_S = \Delta\tilde{\nu}(Hg—Br)/cm^{-1} = [\tilde{\nu}(Hg—Br)_{gas} - \tilde{\nu}(Hg—Br)_{solvent}]/cm^{-1}$. D_S values are known for more than sixty solvents with widely varying solvating properties [241]. An additional solvent donor strength scale for hard acceptors, D_H, has been derived for twenty-four solvents from published molar Gibbs' energies for transfer of Na^+ from a given solvent to 1,2-dichloroethane as a reference solvent [241].

A detailed discussion and comparison of all these and further solvent softness scales can be found in references [173, 238, 239]. For other Lewis acid/base parameters of EPD and EPA solvents, derived from calorimetric measurements (*e.g.* Gutmann's donor and acceptor numbers), see reference [65] and Section 2.2.6.

The concept of the superacidity of Brønsted acids has been extended to Lewis acids [131, 132]. It is suggested that those Lewis acids stronger than anhydrous aluminium trichloride (the most commonly used Friedel-Crafts catalyst) should be designated as *super acids*. These superacidic Lewis acids include such higher-valence halides as antimony, arsenic, tantalum, and niobium pentafluorides. Frequently used conjugated Brønsted-Lewis super acids are $F—SO_3H/SbF_5$ "magic acid" and HF/SbF_5 (fluoroantimonic acid) [131]. These superacidic systems are considered to be *ca.* 10^{16} times stronger than 100 percent sulfuric acid [131].

3.4 Classification of Solvents in Terms of Specific Solute/Solvent Interactions

Parker divided solvents into two groups according to their specific interactions with anions and cations, namely *dipolar aprotic solvents* and *protic solvents* [73]. The distinction lies principally in the dipolarity of the solvent molecules and their ability to form hydrogen bonds. The origin of this solvent classification was the experimental finding that certain S_N2 reactions at saturated carbon atoms involving anions as nucleophiles are much faster in the so-called dipolar aprotic solvents than in protic solvents. This is because in dipolar aprotic solvents most anions are much less solvated and hence more reactive than in protic solvents [74]. It appears appropriate to add to these two groups a third one, namely, the *apolar aprotic solvents*, according to Fig. 3-4.

An apolar aprotic solvent is characterized by a low relative permittivity ($\varepsilon_r < 15$), a low dipole moment ($\mu < 8.3 \cdot 10^{-30}$ Cm = 2.5 D), a low E_T^N value (E_T^N *ca.* 0.0 ... 0.3); *cf.* Table A-1, Appendix), and the inability to act as a hydrogen-bond donor. Such solvents interact only slightly with the solute since only the non-specific directional, induction, and dispersion forces can operate. To this group belong aliphatic and aromatic hydrocarbons, their halogen derivatives, tertiary amines, and carbon disulfide.

In contrast, dipolar aprotic solvents*) possess large relative permittivities ($\varepsilon_r > 15$), sizeable dipole moments ($\mu > 8.3 \cdot 10^{-30}$ Cm = 2.5 D), and average E_T^N values of 0.3 to 0.5. These solvents do not act as hydrogen-bond donors since their C—H bonds are not sufficiently polarized. However, they are usually good EPD solvents and hence cation solvators due to the presence of lone electron pairs. Among the most important dipolar aprotic solvents are acetone, acetonitrile [75], benzonitrile, *N*,*N*-dimethylacetamide [76, 77], *N*,*N*-dimethylformamide [76–78], dimethylsulfone [79], dimethyl sulfoxide [80–84], hexamethylphosphoric triamide [85], 1-methylpyrrolidin-2-one [86], nitrobenzene, nitromethane [87], cyclic carbonates such as propylene carbonate (4-methyl-1,3-dioxol-2-one) [88], sulfolane (tetrahydrothiophene-1,1-dioxide) [89, 90, 90a], 1,1,3,3-tetramethylurea [91, 91a]; and tetrasubstituted cyclic ureas such as 3,4,5,6-tetrahydro-1,3-dimethyl-pyrimidin-2-(1*H*)-one (dimethyl propylene urea, DMPU) [133]. The latter is a suitable substitute for the carcinogenic hexamethylphosphoric triamide (*cf.* Table A-14) [134].

Protic solvents contain hydrogen atoms bound to electronegative elements (F—H, —O—H, —N—H, *etc.*) and are, therefore, hydrogen-bond donors *i.e.* HBD solvents (*cf.* Section 2.2.5). With the exception of acetic acid (and its homologues), the relative permittivities are usually larger than 15, and the E_T^N values lie between 0.5 and 1.0, indicating that these solvents are strongly polar. To this class of solvents belong water, ammonia, alcohols, carboxylic acids, and primary amides.

It is emphasized that this classification is not rigid. There are several solvents that cannot be unequivocally assigned to any one of these three groups, *e.g.* ethers, carbox-

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* Although widely used, the term *dipolar aprotic* solvent is in fact rather misleading. Solvents referred to as dipolar *aprotic* are in fact *not* aprotic. In reactions where strong bases are employed, their protic character can be recognized. In dimethyl sulfoxide solution, the pK_a values are, for CH_3NO_2 17.2, CH_3CN 31.3, CH_3SOCH_3 35, 1-methyl-2-pyrrolidone *ca.* 35, HMPT *ca.* 45 or above [135]. It has therefore been recommended by Bordwell *et al.* [135] that the designation *dipolar aprotic* for these solvents be replaced by *dipolar nonhydroxylic* or better still by *dipolar non-HBD* solvents. The abbreviations *HBD* (hydrogen-bond donor) and *HBA* (hydrogen-bond acceptor) refer to donation and acceptance of the proton, and not to the electron pair involved in hydrogen bonding (*cf.* Section 2.2.5).

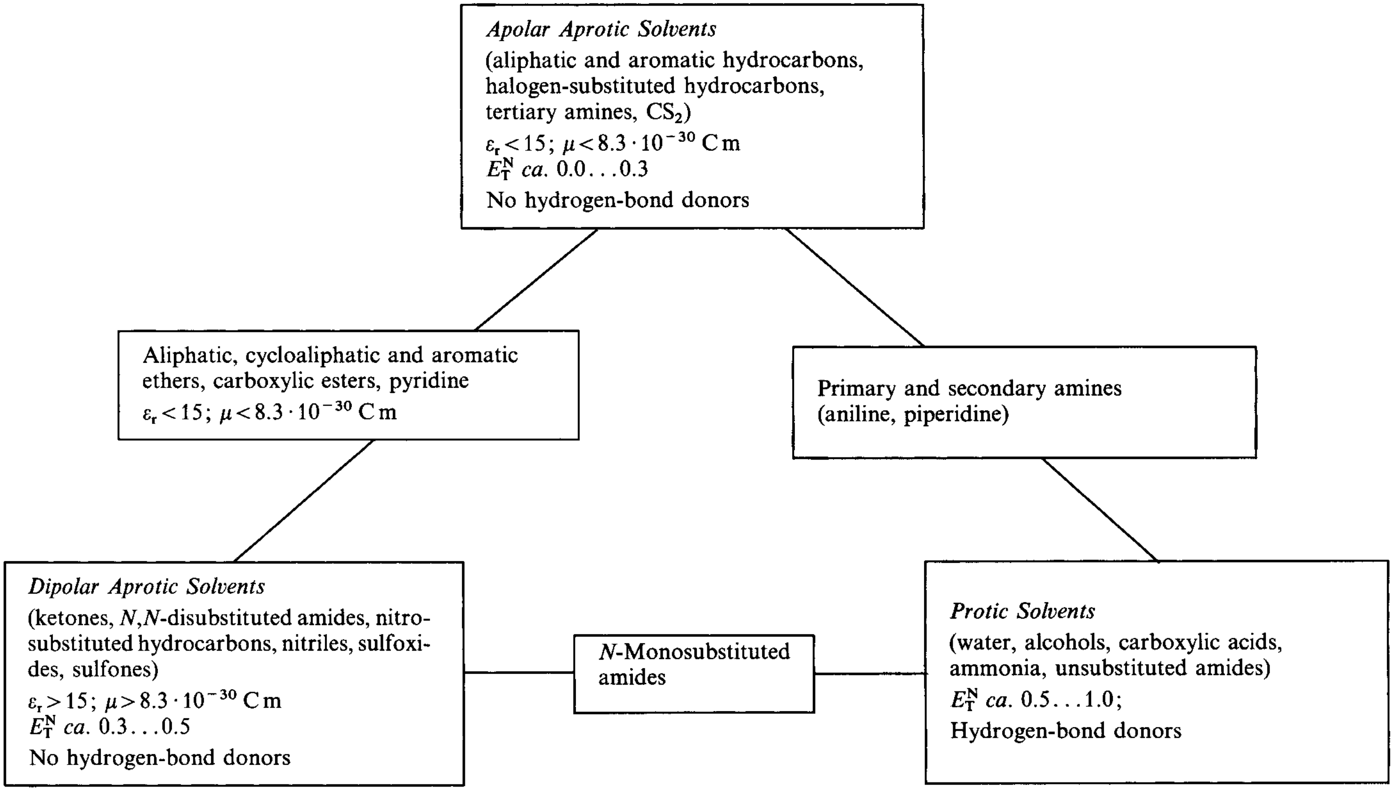

Fig. 3-4. An extension of Parker's classification of organic solvents [73] (concerning the E_T^N values, see Section 7.4).

ylic esters, primary and secondary amines, and *N*-monosubstituted amides such as *N*-methylacetamide [91b]. The choice of $\varepsilon_r = 15$ as the borderline is arbitrary but practical, since, in solvents with smaller ε_r values, ion association occurs, so that the free solvated ions can no longer be observed (*cf.* Section 2.6). This division of solvents into three classes has mainly heuristic value. Its usefulness is due to the fact that special prominence is given to the dipolar aprotic solvents with their extraordinary specific ion solvation [73, 92–96].

Protic solvents are particularly good anion solvators due to their hydrogen-bonding ability [136]. This tendency becomes more pronounced, the higher the charge density (*i.e.* ratio of charge to volume) of the anion to be solvated, and hence the greater its hardness according to the HSAB principle. It should be noted that the stronger the solvation, the more the nucleophilic reactivity of the anion will be decreased. Therefore, in protic solvents, the strongest nucleophiles will be those with lower or more diffused charge density, *i.e.*, "soft anions" (*cf.* Section 5.4.1).

In contrast, in dipolar aprotic solvents, anion solvation occurs mainly by ion-dipole and ion-induced dipole forces. The latter are important for large, polarizable, soft anions, with low charge density, in soft dipolar aprotic solvents. Therefore, although these solvents tend to be poor anion solvators, they are usually better, the larger and softer the anion. This has the consequence that the reactivity of anions is exceptionally high in dipolar aprotic solvents, and the rate constants of S_N2 reactions can increase by several powers of ten when the solvent is changed from protic to dipolar aprotic (*cf.* Section 5.4.2).

The observation that protic solvents are far better anion solvators than dipolar aprotic solvents, and that the reverse is true for cation solvation, has led to extremely valuable rules for the selection of solvents for specific reactions [73, 92–97].

3.5 Classification of Solvents using Multivariate Statistical Methods

Chemical experience suggests that more than three solvent classes, as recognized by Parker [73] (*cf.* Section 3.4 and Fig. 3-4), may be necessary to classify solute/solvent interactions for a wide range of organic solvents. Multivariate statistical methods have therefore been used in the classification and selection of organic solvents [102, 138–143]. Compilations of their physicochemical constants (*e.g.* boiling points, molar volumes, heats of vapourization, dipole moments, relative permittivities, molar refractions, *etc.*) and sometimes, additionally, empirical parameters of solvent polarity (*cf.* Chapter 7), are used as basic data sets. The extraction of chemical information contained in such a data set, *i.e.* the detection of the relative importance of individual variables in determining the data structure, can be done by two statistical methods: multiple linear regression analysis (MRA) [144] and factor (FA) or principal component analysis (PCA) [145]. This kind of analysis is part of the relatively new research field of *chemometrics**) [146, 147].

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* *Chemometrics* has been defined as the application of mathematical and statistical methods to chemical measurements, in particular in providing maximum chemical information through the analysis of chemical data. Because of the enormous increase in generating analytical data, analytical chemists were among the first to use chemometrical methods extensively [148]. The first paper mentioning the name *chemometrics* was from Wold and was published in 1972: S. Wold, Kem. Tidskr. *84*, 34 (1972).

In MRA, a dependent variable Y is described in terms of a series of explanatory variables $X_1 \dots X_n$, as given in Eq. (3-14).

$$Y = a_1 \cdot X_1 + a_2 \cdot X_2 + \cdots + a_n \cdot X_n + b \tag{3-14}$$

It is assumed that all the explanatory variables are independent of each other and truly additive as well as relevant to the problem under study [144]. MRA has been widely used to establish linear Gibbs energy (LGE) relationships [144, 149, 150]. The Hammett equation is an example of the simplest form of MRA, namely bivariate statistical analysis. For applications of MRA to solvent effects on chemical reactions, see Chapter 7.7.

The other statistical method used for seeking regularities in physicochemical data, FA, was first developed and used in psychometrics [145]. FA may be described as a mathematical method for seeking the simplest existing linear structure within a given set of multidimensional data. Starting with a matrix of such experimental data (descriptors), it is possible to extract, using sophisticated statistical methods, the minimum number of underlying, non-measurable variables (factors or principal components) necessary to describe this whole data set in multiple regression equations. After the number of factors (or components) have been found and their magnitudes have been calculated for particular solvents, often a physical or chemical meaning emerges. Although these factors are purely mathematical constructs and do not necessarily embody a direct physical significance, the advantage of FA is that an otherwise hidden physical or chemical interpretation will emerge. The two methods, FA and PCA, are coincident when PCA is used after normalizing the data set. The mathematics of fitting FA and PCA to a matrix of chemical data is well described in the literature [145, 151], and the capabilities of PCA in different fields of pattern recognition have been reviewed [152].

A clear geometrical description of solvent classification using FA or PCA can be given as follows. Common descriptors used for the classification of solvents are their physicochemical constants and empirical parameters of solvent polarity (see Chapter 7). Each descriptor defines a coordinate axis in a coordinate system. If m descriptors are used as the basic data set, they will therefore define an m-dimensional space in which each solvent can be described by a point (with coordinates equal to the m descriptors). The whole set of different solvents will then define a swarm of points in the m-dimensional descriptor space. If only three descriptors are involved, say boiling point, dipole moment, and relative permittivity, a simple right-angled three-dimensional coordinate system, as given in Fig. 3-5, results with t_{bp}, μ, and ε_r plotted along the x, y, and z axes, respectively.

FA/PCA now constitutes a projection of this swarm of points down to a space of lower dimensions in such a way that the first component vector (factor F_1) describes the direction through the swarm showing the largest variation in the data. The second component (factor F_2) shows the next largest variation, and so on. The supposition that the components (factors) should be independent of one another means that their vectors must be at right angles to one another, *i.e.* mutually orthogonal. To the extent that the solvent points in Fig. 3-5 fall into the plane defined by F_1 and F_2, the position of an individual solvent now needs only two coordinates, instead of the original three, for its localization. Thus, the intrinsic dimensionality of the three sets of solvent property data is reduced to two.

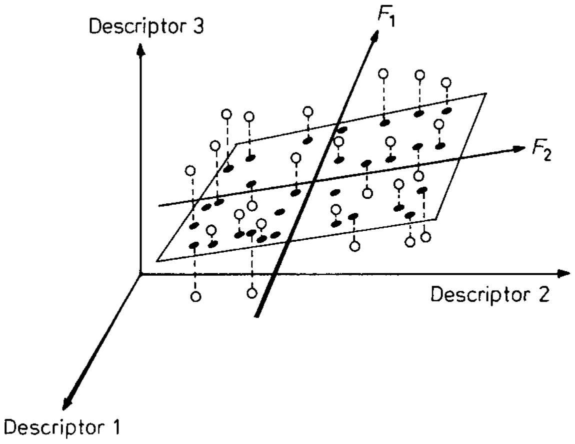

Fig. 3-5. Geometrical representation of FA. The three-dimensional property space is defined by three solvent descriptors (*e.g.* t_{bp}, μ, and ε_r) and filled with 30 solvent points, some of them already lying in the plane defined by the two factors F_1 and F_2 (according to [139] and [142]).

The coordinates of each solvent point are (i) the factor (or principal component) scores *F*, and (ii) the factor (or principal component) loadings *L*. They give the information necessary to reconstitute the original physical properties *D* of any solvent according to Eq. (3-15).

$$D = F_1 \cdot L_1 + F_2 \cdot L_2 + \cdots + F_n \cdot L_n \tag{3-15}$$

Eigenvectors and eigenvalues are the products of calculation at the beginning. They characterise the property of the square matrix (correlation or covariance) derived from the initial data matrix, and they allow calculation of the factor scores *F* and factor loadings *L*, respectively.

The advantage of this empirical model is that the systematic variation in the solvent data can now be described using fewer variables than in the original data set. Eventually, an attempt is made to explain the factors F_1 and F_2, which themselves define a new coordinate system, by considering an underlying physical or chemical meaning (*e.g.* polarity, polarizability, or Lewis acidity/basicity of the solvent molecule), thus leading finally to a new solvent classification.

Martin *et al.* [102] were the first to apply FA to solvent classification. A factor analysis for 18 organic solvents with 18 physicochemical parameters led to a solvent classification similar to Parker's classification [73], which was mainly based on chemical intuition (*cf.* Fig. 3-4).

Using PCA, Cramer [139] found that more than 95% of the variances in six physical properties (activity coefficient, partition coefficient, boiling point, molar refractivity, molar volume, and molar vaporization enthalpy) of 114 pure liquids can be explained in terms of only two parameters, which are characteristic of the solvent molecule. These two factors are correlated with the molecular bulk and cohesiveness of the individual solvent molecules, the interaction of which depends mainly upon nonspecific, weak intermolecular forces. This is closely related to nonspecific, weak solute/solvent interactions. With these factors, experimental values of 18 common physical properties for 139 additional liquids of diverse structure have been predicted with surprising accuracy [139].

FA of data matrices containing 35 physicochemical constants and empirical parameters of solvent polarity (*cf.* Chapter 7) for 85 solvents has been carried out by Svoboda *et al.* [140]. An orthogonal set of four parameters was extracted from these data, which could be correlated to solvent polarity as expressed by the Kirkwood function $(\varepsilon_r - 1)/(2\varepsilon_r + 1)$, to solvent polarizability as expressed by the refractive index function $(n^2 - 1)/(n^2 + 1)$, as well as to the solvent Lewis acidity and basicity. Thus, four solvent parameters are generally needed for the quantitative empirical description of solvent effects on chemical reactions and light absorptions: two are needed to describe the nonspecific solvation of polar and dispersion character, and two to describe specific solvation of electrophilic and nucleophilic character. For correlations of solvent effects using only one empirical solvent parameter, the best parameters are the $E_T(30)$ values, which are derived from the UV/Vis absorption of a solvatochromic dye (*cf.* Sections 6.2.1 and 7.4).

Elguero *et al.* [141] have reduced Palm's analogous tetraparametric model for the multiple correlation of solvent effects [*cf.* Eq. (7-48) in Section 7.7] to a triparametric one, with two factors explaining 94% of the data variance given in an original set of four descriptors [Y, P, E, and B of Eq. (7-48) in Section 7.7] for 51 solvents.

A data matrix of eight common descriptors of solvent properties for 82 solvents was analysed with PCA by Carlson *et al.* [142]. The eight descriptors were melting point, boiling point, density, relative permittivity, dipole moment, refractive index, $E_T(30)$ [*cf.* Eq. (7-27) in Section 7.4], and lg P (*i.e.* the logarithm of the equilibrium partition coefficient of a solvent between 1-octanol and water at 25 °C [153]). Using a two-component model of the whole data set [one component explained principally by ε_r, μ, and $E_T(30)$, the other strongly correlated to the refractive index], different strategies for a systematic selection of solvents for chemical reactions were proposed. This has been applied to the Willgerodt-Kindler reaction between acetophenone and sulfur in the presence of morpholine, in order to reveal the influence of different solvents on the optimum reaction conditions (other variables: amount of sulfur/ketone, amount of morpholine/ketone, and reaction temperature) [165].

Application of PCA to a set of five thermodynamic and spectroscopic basicity-dependent properties of 22 organic non-HBD solvents (related to hydrogen-bonding, proton-transfer, and interaction with hard and soft Lewis acids) by Maria *et al.* [143] has led to the interesting result that just two factors are sufficient to account for about 95% of the total variance of the solvent data. Physical significance has been given to these two principal factors by correlating them with intrinsic gas-phase affinities of the solvent molecules toward the proton and the potassium cation. A blend of electrostatic and charge-transfer (or electron-delocalization) character can be attributed to the first factor F_1. The second factor F_2 corresponds to an essentially electrostatic character. A third factor F_3, of marginal importance only, arises in part from steric hindrance to acid/base complexation. Thus, the inherent dimensionality of the condensed-phase basicity of organic non-HBD molecules commonly used as solvents is essentially reduced to two [143].

Further useful attempts at the classification of organic solvents by means of chemometrical methods have been made by Zalewski *et al.* [242] and by Abraham *et al.* [243], using various sets of physicochemical solvent data.

The most ambitious approach to a general classification of solvents by PCA has been that of Chastrette *et al.* [138]. His classification is based on the representation of 83 solvents as points in an eight-dimensional property space, using the Kirkwood function $(\varepsilon_r - 1)/(2\varepsilon_r + 1)$, molar refraction $V_m \cdot (n^2 - 1)/(n^2 - 2)$, Hildebrand's δ parameter [*cf.* Eq. (2-1) in Section 2.1], refractive index, boiling point, dipole moment, and the HOMO and LUMO energies as solvent descriptors. Five descriptors are the properties of bulk solvents, whereas the last three (μ, HOMO, and LUMO) are molecular properties. The calculated HOMO and LUMO energies of the solvents are included in the set of basic variables in order to take into account Lewis acid/base interactions between solute and solvent. Because some of the eight descriptors are linearly correlated to each other, the spatial dimensionality needed to describe the solvent classification should be lower than eight.

Indeed, it was possible to reduce the original eight-dimensional space by suppressing five principal components, providing an easily visualised three-dimensional solvent property space, with only an 18% loss of information. This subspace is defined by the principal components F_1 (strongly correlated with the molar refraction, refractive index, and HOMO energy), F_2 (strongly correlated with the Kirkwood function, dipole moment, and boiling point), and F_3 (strongly correlated with the LUMO energy). Therefore, F_1 can be interpreted as an index of the polarizability of the solvent, F_2 represents the polarity of the solvent, and F_3 can be explained by the electron affinity and Lewis acidity of the solvent. The Lewis basicity of the solvent seems to be included in F_1.

The 83 organic solvents have been grouped into *nine classes* from the clustering of their principal component values, using a nonhierarchical multivariate taxonomy to progressively classify solvents by means of the discriminating power of the eight descriptors (*cf.* Fig. 3-6).

Classes (1)...(3) comprise dipolar aprotic*⁾ solvents. The first class (AD) contains the usual protic solvents having a relative low dipolarity ($\mu \leq ca.\ 12 \cdot 10^{-30}$ Cm). More dipolar aprotic solvents ($\mu \geq ca.\ 12 \cdot 10^{-30}$ Cm) are found in the second class (AHD). A third class (AHDP) contains only two members, differing from the second by their high polarizability.

Classes (4)...(6) include apolar aprotic*⁾ solvents. In classes (4) and (5), ARA and ARP, are found aromatic apolar ($\mu \approx 0 \ldots 4 \cdot 10^{-30}$ Cm) and aromatic relatively dipolar solvents ($\mu \approx 4 \ldots 10 \cdot 10^{-30}$ Cm). Class (6), called EPD, consists of solvents that are typical electron pair donors ($\mu \approx 4 \ldots 10 \cdot 10^{-30}$ Cm).

Protic or HBD solvents are found in classes (7) and (8). These two classes of hydrogen-bonding solvents (HB and HBSA) are clearly separated by the degree of their intermolecular association. If a total of ten solvent classes are established, water would then constitute a subclass of class HBSA.

Lastly, class (9), labelled MISC (from miscellaneous), consists of four solvents, which have only their high polarizabilities in common.

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* Bordwell *et al.* [135] have pointed out that solvents referred to as *dipolar aprotic* are in fact not aprotic. In reactions employing strong bases their protic character can be recognized. Therefore, instead of *dipolar aprotic* the designation *dipolar nonhydroxylic* or better *dipolar non-HBD* solvents is strongly recommended. *Cf.* Section 2.2.5 and 3.4 (footnote). In order to avoid confusion, the nomenclature proposed by Chastrette *et al.* [138] is retained in Fig. 3-6.

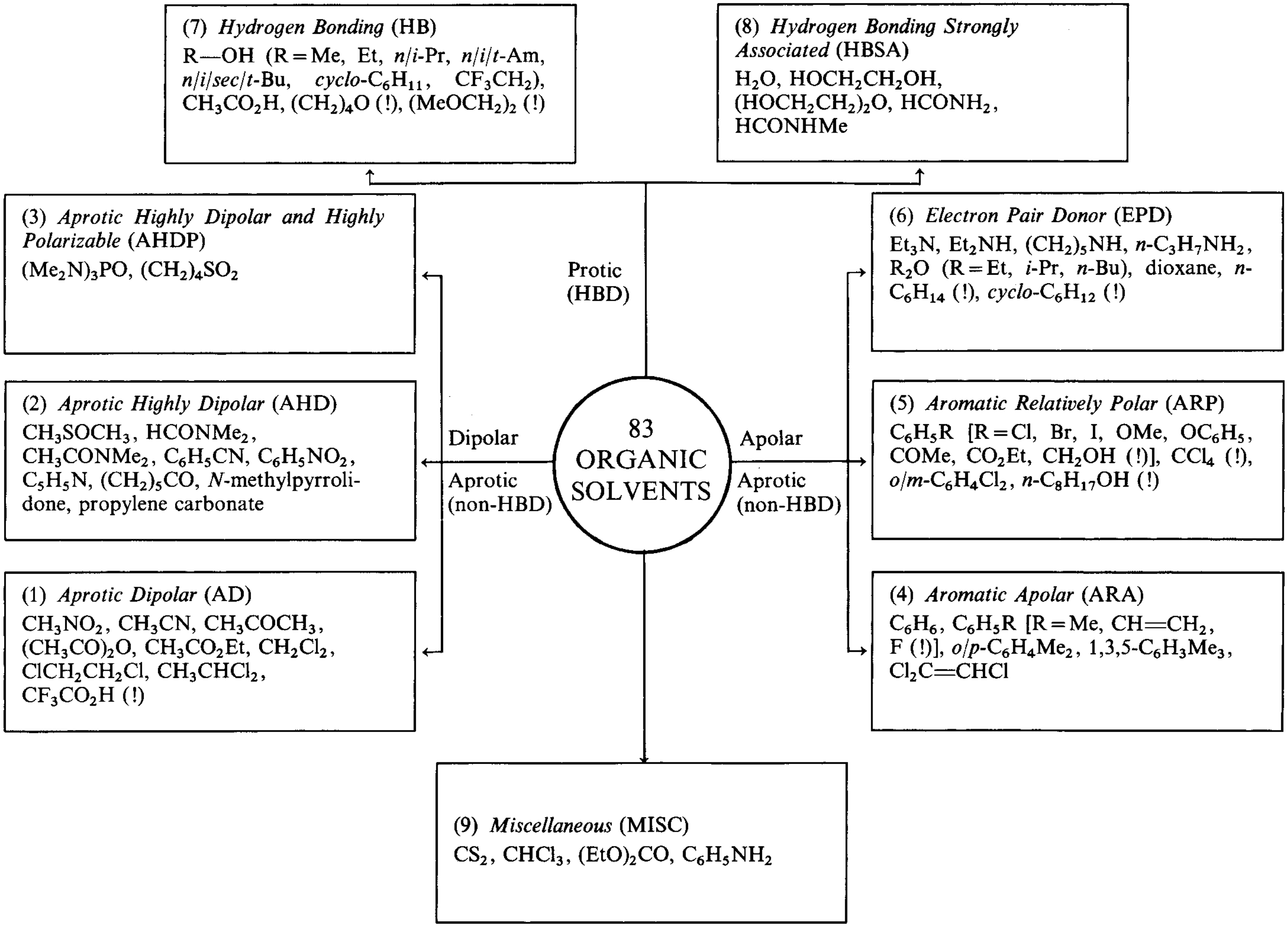

Fig. 3-6. Chastrette's classification of organic solvents [138].

It is remarkable that this overall solvent classification, obtained entirely using statistical methods (PCA), correlates strongly with the chemist's intuition! Some of the solvent classes of Parker's scheme (*cf.* Fig. 3-4) are reproduced in Fig. 3-6.

However, certain limitations are obvious. Some solvents, marked by (!) in Fig. 3-6, are not expected to be classed as found. Trifluoroacetic acid is classified as AD; benzyl alcohol, 1-octanol, and tetrachloromethane appear in the class ARP; *n*-hexane and cyclohexane in class EPD; tetrahydrofuran and 1,2-dimethoxyethane in the class HB.

The reasons for some of these irregularities may be associated with the choice of HOMO and LUMO for multifunctional solvents. For heteroatom-containing solvents such as benzyl alcohol, the HOMO of the π-electrons or the high-lying heteroatom lone-pair HOMO are available for solute/solvent interactions. The possible regiospecific interaction of the solvent frontier orbitals with solute molecules could mean that a solvent has two points in the descriptor space and hence two places in the resulting classification scheme, depending on the particular solute/solvent system under consideration. According to the classification in Fig. 3-6, benzyl alcohol is treated as an aromatic solvent, rather than as an alcohol.

This duality in the descriptor choice demonstrates the fallibility of searching for a unique, universally valid classification of all organic solvents. Further work has to be done in order to clarify this point.

Another problem that has been tackled by multivariate statistical methods is the characterization of the solvation capability of organic solvents based on empirical parameters of solvent polarity (see Chapter 7). Since such empirical parameters of solvent polarity are derived from carefully selected, strongly solvent-dependent reference processes, they are molecular-microscopic parameters. The polarity of solvents thus defined cannot be described by macroscopic, bulk solvent characteristics such as relative permittivities, refractive indices, etc., or functions thereof. For the quantitative correlation of solvent-dependent processes with solvent polarities, a large variety of empirical parameters of solvent polarity have been introduced (see Chapter 7). While some solvent polarity parameters are defined to describe an individual, more specific solute/solvent interaction, others do not separate specific solute/solvent interactions and are referred to as general solvent polarity scales. Consequently, single- and multi-parameter correlation equations have been developed for the description of all kinds of solvent effects, and the question arises as to how many empirical parameters are really necessary for the correlation analysis of solvent-dependent processes such as chemical equilibria, reaction rates, or absorption spectra.

By a quantitative structure-property relationship (QSPR) analysis of a total of 45 different empirical solvent scales and 350 solvents, the direct calculation of predicted values of solvent parameters for any scale and for any previously unmeasured solvent was possible using the CODESSA program (*i.e.* *co*mprehensive *de*scriptors for *s*tructural and *s*tatistical *a*nalysis) developed by Katritzky *et al.* [244]. The QSPR models for each of the solvent scales were constructed using only theoretical descriptors, derived solely from the molecular solvent structure. This QSPR study enabled classification of the various solvent polarity scales and ultimately allowed a unified PCA treatment of these scales. This PCA treatment, carried out with 40 solvent scales as variables (each having 40 data points for 40 solvents as objects), allowed a rational classification and grouping of both solvents and solvent scales [245]. Surprisingly, it emerged that only three major components, orthogonal (=unrelated) to each other, are sufficient to determine solvent polarity. For 36 of the solvent scales, an average of 88% of the variance is described by the first three principal components, which can be roughly related to the relative permittivities and dipolarities of the solvents, as well as to their electrophilicities (acidities) and nucleophilicities (basicities). The solvents included in this study also showed a clear clustering into five groups: (i) highly polar, strong HBD (*e.g.* formamide), (ii) polar, HBD (water, alcohols), (iii) dipolar non-HBD (DMF, DMSO), (iv) less dipolar, non-HBD (ethers, dichloromethane), and (v) apolar, non-HBD (*n*-hexane, tetrachloromethane) (*cf.* Fig. 3-6!) [245].

Another statistical treatment of a set of 32 solvent parameter scales for 45 solvents using the program SMIRC (*s*election of a set of *m*inimally *i*nter*r*elated *c*olumns) has been carried out by Palm *et al.* [246], who, incidentally, introduced the first multi(four)-parameter equation for the correlation analysis of solvent effects in 1971 [*cf.* Eq. (7-50) in Chapter 7]. The minimum sufficient set of residual descriptors for the multilinear description of solvent effects consists of nine solvent parameter scales. This set of nine (purified) descriptors has been successfully applied to an extended set of 359 different solvent-dependent processes; for more details, see reference [246].

4 Solvent Effects on the Position of Homogeneous Chemical Equilibria

4.1 General Remarks

An equilibrium is homogeneous when all components are either exclusively in the gas phase or exclusively in solution. For gas-phase equilibria, the ratio of the product concentrations for end and starting materials is constant at a given temperature (law of mass action of Guldberg and Waage, 1867). When the reaction partners are dissolved, the standard molar Gibbs energy of solvation, $\Delta G^\circ_{\text{solv}}$, is liberated due to the intermolecular interactions between solvent and solute. In general, this quantity is different for starting and end products. Thus, a displacement of the equilibrium can take place when going from the gas phase to solution [1–7]. An unchanged equilibrium constant can only be expected when $\Delta G^\circ_{\text{solv}}$ is accidently the same for starting and end products.

The effect of the medium on the position of equilibrium can be considered from two points of view: (a) comparison of the gas-phase and solution equilibrium constants, and (b) comparison of the equilibrium constants for different solvents. Unfortunately, few equilibrium reactions have been studied both in the gas and liquid phases [5, 6]. These are primarily non-ionic reactions where the interaction between reacting molecules and solvent is relatively small (*e.g.* the Diels-Alder dimerization of cyclopentadiene). In this chapter, therefore, equilibria which have been examined in solvents of different polarity will be the main topic considered (except for acid-base reactions described in Section 4.2.2).

Let us consider a simple isomerization reaction $A \rightleftharpoons B$ in the solvents I and II, whose abilities to solvate A and B are different. This corresponds to the Gibbs energy diagram shown in Fig. 4-1.

From Fig. 4-1, Eq. (4-1) can be immediately derived,

$$\Delta G^\circ(\text{II}) + \Delta G^\circ_\text{t}(\text{A}, \text{I} \rightarrow \text{II}) = \Delta G^\circ_\text{t}(\text{B}, \text{I} \rightarrow \text{II}) + \Delta G^\circ(\text{I}) \qquad (4\text{-}1)$$

which, on rearrangement, leads to Eq. (4-2) [102]:

$$\begin{aligned} \Delta G^\circ(\text{II}) - \Delta G^\circ(\text{I}) &= \Delta\Delta G^\circ(\text{I} \rightarrow \text{II}) \\ &= \Delta G^\circ_\text{t}(\text{B}, \text{I} \rightarrow \text{II}) - \Delta G^\circ_\text{t}(\text{A}, \text{I} \rightarrow \text{II}) \qquad (4\text{-}2) \end{aligned}$$

Since, for equilibria, the logarithm of the equilibrium constant is proportional to the standard molar Gibbs energy change, ΔG°, according to Eq. (4-3),

$$\Delta G^\circ = -R \cdot T \cdot \ln K \qquad (4\text{-}3)$$

it follows from Eqs. (4-2) and (4-3) that the difference in the molar transfer Gibbs energies of educt A and product B, $\Delta\Delta G^\circ_\text{t}(\text{I} \rightarrow \text{II})$, determines the solvent effect on the position of this equilibrium. In the particular case of Fig. 4-1, $\Delta G^\circ_\text{t}(\text{B}, \text{I} \rightarrow \text{II}) > \Delta G^\circ_\text{t}(\text{A}, \text{I} \rightarrow \text{II})$, so that the equilibrium is displaced towards B when the solvent is changed from I to II.

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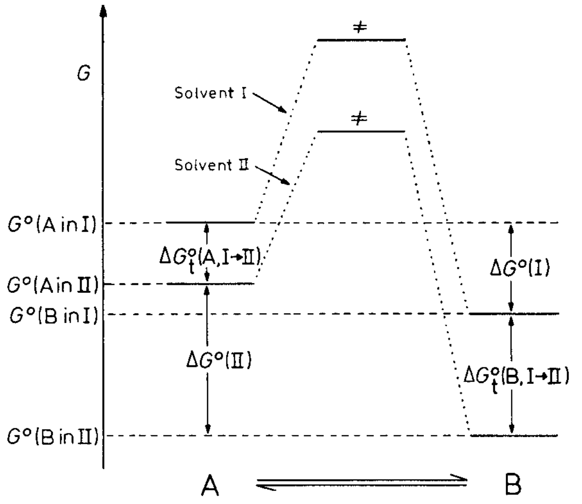


Fig. 4-1. One-dimensional Gibbs energy diagram for an equilibrium reaction A $\rightleftharpoons$ B in the solvents I and II. Ordinate: standard molar Gibbs energies of the reactants A and B in solvents I and II; Abscissa: not defined. $\Delta G^\circ(\mathrm{I})$ and $\Delta G^\circ(\mathrm{II})$: standard molar Gibbs energies of reaction in solvents I and II, respectively; $\Delta G_t^\circ(\mathrm{A, I \rightarrow II})$ and $\Delta G_t^\circ(\mathrm{B, I \rightarrow II})$: standard molar Gibbs energies of transfer of the solutes A and B from solvent I to solvent II, respectively [$\Delta G_t^\circ(\mathrm{A, I \rightarrow II}) = G^\circ(\mathrm{A\ in\ I}) - G^\circ(\mathrm{A\ in\ II})$, and $\Delta G_t^\circ(\mathrm{B, I \rightarrow II}) = G^\circ(\mathrm{B\ in\ I}) - G^\circ(\mathrm{B\ in\ II})$], *cf.* Eq. (2-12a) in Section 2.3; $\neq$ = transition state.

The required standard molar Gibbs energies of transfer can be obtained from activity coefficient measurements, using Eq. (4-3a),

$$\Delta G_t^\circ(\mathrm{X, I \rightarrow II}) = -R \cdot T \cdot \ln(\gamma_{\mathrm{I}}/\gamma_{\mathrm{II}}) \qquad (4\text{-}3a)$$

in which γ refers to activity coefficients of solute X in solvents I and II. Methods used to obtain these activity coefficients have included vapour pressure, solubility, and distribution coefficient measurements [103]. It should be stressed that solvent-transfer activity coefficients can be directly obtained only for neutral solutes. For ionophores, only the product of the γ values of the cation and anion can be determined. Values for single ions can be obtained indirectly by means of so-called extrathermodynamic assumptions; *cf.* Eq. (2-12b) and Table 2-9 in Section 2.3.

In studying solvent effects on equilibria, it is, in principle, not sufficient to investigate the ΔG° changes alone, because this term is determined by both an enthalpy and an entropy term according to Eq. (4-4).

$$\Delta G^\circ = \Delta H^\circ - T \cdot \Delta S^\circ \qquad (4\text{-}4)$$

Transfer functions can also be defined for the thermodynamic state functions ΔH° and ΔS° [102]. The ease of calorimetric measurements has made the standard molar transfer enthalpy, $\Delta H_t^\circ(\mathrm{X, I \rightarrow II})$, readily available. If both transfer Gibbs energies and transfer enthalpies are available, it should be possible to achieve a complete dissection of the effect of solvents on the various thermodynamic parameters.

Four types of reaction control can be recognized:

(a) Cooperative effects, with $\Delta\Delta H^\circ$ and $T \cdot \Delta\Delta S^\circ$ having opposite signs. Then these two terms will be additive;
(b) Enthalpy-controlled effects, in which the two terms are opposed, but the enthalpy term is larger;
(c) Entropy-controlled effects, in which the two terms are opposite but the $T \cdot \Delta\Delta S^\circ$ is larger; and
(d) Compensating effects, in which the two terms are opposed but nearly equal.

A change in temperature may interconvert categories (b), (c), and (d).

A quantitative description of the influence of the solvent on the position of chemical equilibria by means of physical or empirical parameters of solvent polarity is only possible in favourable and simple cases due to the complexity of intermolecular solute/solvent interactions. However, much progress has recently been made in theoretical calculations of solvation enthalpies of solutes that can participate as reaction partners in chemical equilibria; see the end of Section 2.3 and references [355–364] to Chapter 2. If the solvation enthalpies of all participants in a chemical equilibrium reaction carried out in solvents of different polarity are known, then the solvent influence on this equilibrium can be quantified. A compilation of about a hundred examples of the application of continuum solvation models to acid/base, tautomeric, conformational, and other equilibria can be found in reference [231].

In the following sections, the influence of solvents on chemical equilibria is treated on a more qualitative basis, using acid/base, tautomeric, and other equilibria as representative examples.

4.2 Solvent Effects on Acid/Base Equilibria [8–13]

4.2.1 Brønsted Acids and Bases in Solution

As already emphasized in Section 3.3.1, the ionization equilibrium of an acid, Eq. (4-5), or of a base, Eq. (4-6), is affected by a solvent change, not only because of the

$$\mathrm{HA^{z+1} + SH \rightleftharpoons SH_2^+ + A^z} \tag{4-5}$$

$$\mathrm{A^z + SH \rightleftharpoons HA^{z+1} + S^-} \tag{4-6}$$

acidity or basicity of the solvent, but also because of its relative permittivity and the ability of the solvent to solvate the various species of Eqs. (4-5) and (4-6). A change in relative permittivity or in solvating ability can thus influence the acidity of an acid HA or the basicity of a base A. Thus, for example, the acidity constant K_a for carboxylic acids is up to 10^6 times larger in water ($\varepsilon_r = 78.3$) than in absolute ethanol ($\varepsilon_r = 24.6$), although water is only 15 ... 20 times stronger a base than ethanol.

Eq. (4-5) shows the reaction of an acid with an amphiprotic solvent to form a solvated proton and the conjugate base of the acid, at an infinite distance from each other. Part of the energy required for this reaction comes from the electrostatic interactions between these ions and can be estimated from simple electrostatic theory. The electrostatic work necessary for gradually increasing the charge of a spherical species HA of radius r_{HA} from zero up to its full charge $z_{HA} \cdot e$, immersed in a continuous medium of relative permittivity ε_r, is given by the Born equation (4-7) (ε_0 = permittivity of vacuum; z = number of elementary charges e; N_A = Avogadro constant) [14].

$$\Delta G^\circ_{\text{electrostatic}} = \frac{1}{4\pi \cdot \varepsilon_0} \cdot \frac{N_A \cdot z^2_{HA} \cdot e^2}{2 \cdot \varepsilon_r \cdot r_{HA}} \tag{4-7}$$

The Born equation gives the electrostatic Gibbs free energy of an ion immersed in a medium of relative permittivity ε_r. However, it does not include the energy expended by solvents in forming the cavities to accommodate the ions. This energy is generally small compared to the large Born energy, which amounts to as much as ca. −1000 kJ/mol for the transfer of monovalent cations or anions (with radius $r = 140$ pm) from the gas phase ($\varepsilon_r = 1$) to water ($\varepsilon_r = 78$).

Application of this equation to acid/base reaction (4-5) leads to a net change in Gibbs energy per mol as shown in Eq. (4-8), if only pure electrostatic interactions are considered [8].

$$\Delta G^\circ_{\text{electrostatic}} = \frac{1}{4\pi \cdot \varepsilon_0} \cdot \frac{N_A \cdot e^2}{2 \cdot \varepsilon_r} \cdot \left(\frac{1}{r_{SH_2^\oplus}} + \frac{z^2_A}{r_A} - \frac{z^2_{HA}}{r_{HA}} \right) \tag{4-8}$$

Thus, the Gibbs energy difference $\Delta\Delta G$ for the ionization of a mol of HA in solvent 1 and solvent 2 with relative permittivities $\varepsilon_{r(1)}$ and $\varepsilon_{r(2)}$, respectively, provided that the radii of the reactants are the same in both solvents, is given by Eq. (4-9).

$$\begin{aligned} \Delta\Delta G^\circ &= (\Delta G^\circ_{\text{electrostatic}})_2 - (\Delta G^\circ_{\text{electrostatic}})_1 \\ &= \frac{1}{4\pi \cdot \varepsilon_0} \cdot \frac{N_A \cdot e^2}{2} \cdot \left(\frac{1}{r_{SH_2^\oplus}} + \frac{z^2_A}{r_A} - \frac{z^2_{HA}}{r_{HA}} \right) \cdot \left(\frac{1}{\varepsilon_{r(2)}} - \frac{1}{\varepsilon_{r(1)}} \right) \end{aligned} \tag{4-9}$$

Because the Gibbs energy of reaction, ΔG, is related to the equilibrium constant K_a, according to Eq. (4-3), Eq. (4-9) can be converted into Eq. (4-10).

$$\ln \frac{(K_a)_2}{(K_a)_1} = -\frac{1}{4\pi \cdot \varepsilon_0} \cdot \frac{N_A \cdot e^2}{2 \cdot RT} \cdot \left(\frac{1}{r_{SH_2^\oplus}} + \frac{z^2_A}{r_A} - \frac{z^2_{HA}}{r_{HA}} \right) \cdot \left(\frac{1}{\varepsilon_{r(2)}} - \frac{1}{\varepsilon_{r(1)}} \right) \tag{4-10}^{*)}$$

---

* A modification of Eq. (4-10) has been developed by Izmailov by expressing the specific and nonspecific solute/solvent interactions by means of a conventional division of the ΔG values into electrostatic and nonelectrostatic ones, in order to obtain a more complete equation that also contains the constants of complex formation between solutes and solvent [318].

Eq. (4-10) can be used only for solvents of equal acid and base strength, because only the effect of the solvent relative permittivity on the degree of ionization is considered. Under these conditions, Eq. (4-10) predicts that the logarithm of the ionization constant K_a of HA should be inversely proportional to the relative permittivity of the solvent in which HA is dissolved. However, one has to take into account the fact that the relative permittivities near solute ions can differ considerably because of the effect of dielectric saturation, which hinders the precise calculation of electrostatic interactions. Because of these restrictions, Eq. (4-10) can be expected to yield only semiquantitative results. Nevertheless, it allows us to predict qualitatively how the charge type of an acid affects the ionization constant in solvents of different relative permittivities.

If the acid HA in Eq. (4-5) has a charge of +1 ($z = 0$; *e.g.* NH_4^+), the right-hand side of Eq. (4-10) involves only the difference between two reciprocal radii ($z_A = 0$), and is often very nearly zero. Therefore, a change in the relative permittivity should in this case have only a small, if any, influence on the ionization equilibrium of an acid such as NH_4^+. This is plausible, because in this acid/base reaction (4-5) no charges are created or destroyed at all. Also, there is no electrostatic attraction between the positively charged species HA and the neutral conjugate base A. Indeed, the cationic acid NH_4^+ is only about 1/10 as strong in ethanol as it is in water according to the lower basicity of the solvent ethanol compared with water (*cf.* Table 4-1).

On the other hand, if HA is an uncharged acid ($z = -1$; *e.g.* $CH_3—CO_2H$), the right-hand side of Eq. (4-10) involves the sum of two reciprocal radii ($z_{HA} = 0$) and a strong influence of the relative permittivity on the ionization equilibrium is expected. Because in acid/base reactions of this charge type, neutral molecules are converted into anions and cations, which attract each other, reaction (4-5) will shift to the right with an increase in relative permittivity of the solvent in which HA is dissolved. Ionization increases when ε_r increases. This rule is qualitatively verifiable for water and alcohols as

Table 4-1. Solvent influence on the acid/base equilibrium $HA^{z+1} + SH \rightleftharpoons SH_2^+ + A^z$ for various charge types[a].

z	Acid-base charge type	pK_a change with increasing basicity of SH	pK_a change with increasing ε_r of SH	Examples	$\Delta pK_a = (pK_a)_{H_2O} - (pK_a)_{C_2H_5OH}$[a,b]
0	$HA^{\oplus}/A^0$	decrease	no or small effect	$NH_4^{\oplus}/NH_3$	−1.2
				$H_5C_6NH_3^{\oplus}/H_5C_6NH_2$	−0.4
−1	$HA^0/A^{\ominus}$	decrease	decrease	$H_3C—CO_2H/H_3C—CO_2^{\ominus}$	−5.7
				Picric acid/Picric anion	−3.3
−2	$HA^{\ominus}/A^{2\ominus}$	decrease	decrease	$HO_2C—(CH_2)_2—CO_2^{\ominus}/{}^{\ominus}O_2C—(CH_2)_2—CO_2^{\ominus}$	−5.8[d]
				$HO_2C—CH{=}CH—CO_2^{\ominus}/{}^{\ominus}O_2C—CH{=}CH—CO_2^{\ominus}$[c]	−5.5[d]

[a] See reference [11] for more examples.

[b] Relative permittivities: $\varepsilon_r = 78.4$ (H_2O), $\varepsilon_r = 32.7$ (CH_3OH), and $\varepsilon_r = 24.6$ (C_2H_5OH) at 25 °C.

[c] Fumaric acid.

[d] $\Delta pK_a = (pK_a)_{H_2O} - (pK_a)_{CH_3OH}$ in this case.

solvents. In fact, acetic acid is only about 10^{-6} times as strong an acid in ethanol (low ε_r) as in water (high ε_r) (*cf.* Table 4-1).

In the case of an anionic acid ($z = -2$; *e.g.* HSO_4^-), the acid/base equilibrium (4-5) will be shifted to the right with an increase in relative permittivity of the solvent in which HA is dissolved. Here, the ionization will increase much more quickly with an increase in relative permittivity than in the preceding case.

Table 4-1 shows the predicted solvent influence on the acidity constants K_a for various charge types of acid/base pairs.

Analogous rules apply to the basicity constants K_b according to Eq. (4-6). For example, for a pair A^0/HA^+ ($z = 0$; *e.g.* $NH_3 + ROH$), K_b increases as the relative permittivity of the solvent increases.

Because it is practically impossible to find solvents that differ only in their relative permittivities, and not in their basicity or acidity, the predictions based on Eq. (4-10) are usually not in good agreement with the experimental results. In addition, the solvation capability or polarity of a solvent is not described by its relative permittivity alone. Besides the purely electrostatic Coulomb interactions, there exist other specific and unspecific interaction forces, such as ion-dipole, dipole-dipole, hydrogen bonding, ion-pair formation, *etc.* Also, the model used to describe the coulombic effects on acid/base ionization constants ignores the actual shape and size of the individual ions. For example, in contrast to the carboxylic acids the acidity constant of picric acid increases by a factor of 1500 simply for a solvent change from ethanol to water (*cf.* Table 4-1). Because the negative charge of the picric anion is delocalized over a large molecule, the solvation enthalpy of this anion will be lower than that of the carboxylate anions. This means that its stability does not change with the solvation capability of the solvent to the same extent as for the carboxylate anions, where the negative charge is more or less localized on only two oxygen atoms.

Using activity coefficients, it is possible to examine in greater detail the effect of solvents on acid and base strengths. Equilibrium constants expressed in terms of concentration are solvent-dependent. Solvent-independent, so-called thermodynamic equilibrium constants are obtained when the concentration terms are replaced by concentration-based activity terms. The thermodynamic equilibrium constant K for the reaction $HA \rightleftharpoons H^{\oplus} + A^{\ominus}$ is given by the following equation:

$$K = \frac{a_{H^+} \cdot a_{A^-}}{a_{HA}} = \frac{[H^+]\gamma_{H^+}[A^-]\gamma_{A^-}}{[HA]\gamma_{HA}} = K_a \cdot \frac{\gamma_{H^+} \cdot \gamma_{A^-}}{\gamma_{HA}} \tag{4-11}$$

In highly dilute aqueous solution, the activity coefficients approach the value 1. That is, in aqueous solution, K and K_a become practically equal at infinite dilution. If the equilibrium constant, expressed in concentration terms, is denoted by K_{SH} for the solvent SH, and K_{H_2O} is the value of K_a in water at infinite dilution, then it follows that:

$$K = K_{SH} \cdot \frac{\gamma_{H^+} \cdot \gamma_{A^-}}{\gamma_{HA}} = K_{H_2O} \tag{4-12}$$

where the values of γ are the appropriate activity coefficients in the solvent SH. Analogously, for another acid HB with an acid/base equilibrium $HB \rightleftharpoons H^{\oplus} + B^{\ominus}$, Eq. (4-13) can be written:

$$K' = K'_{SH} \cdot \frac{\gamma_{H^+} \cdot \gamma_{B^-}}{\gamma_{HB}} = K'_{H_2O} \tag{4-13}$$

Division of Eq. (4-12) by Eq. (4-13) gives Eq. (4-14)

$$\frac{K_{SH} \cdot \gamma_{HB} \cdot \gamma_{A^-}}{K'_{SH} \cdot \gamma_{HA} \cdot \gamma_{B^-}} = \frac{K_{H_2O}}{K'_{H_2O}} \tag{4-14}$$

which can be rearranged to Eq. (4-15)

$$K_{SH} = K'_{SH} \cdot \frac{K_{H_2O}}{K'_{H_2O}} \cdot \frac{\gamma_{HA} \cdot \gamma_{B^-}}{\gamma_{HB} \cdot \gamma_{A^-}} \tag{4-15}$$

The acidity constant of a given acid in any solvent SH can then be calculated from Eq. (4-15) when its acidity constant in water at infinite dilution, the acidity constant of another acid HB in water and in solvent SH, and the activity term are all known. The values γ_{HA} and γ_{HB} can be obtained from solubilities, partial pressures, distribution coefficients, *etc.* The ratio $\gamma_{B^-}/\gamma_{A^-}$ can be determined potentiometrically, or from the solubility of salts. The values of K_{SH} calculated in this way correspond satisfactorily with the measured values.

At this point, we can only refer to the various acidity scales for different series of solvents, such as those of Hammett [15] and Grunwald [16]. The acidity functions are introduced in order to obtain expressions that are not affected by the relative permittivity and that allow a quantitative comparison of acidity in different solvents. It should be stated, however, that there exists no single scale of acidity or basicity that is universally valid in all types of solvents and applicable to both equilibrium and kinetic situations [17, 109].

Medium effects on acid/base equilibria in aqueous solutions of strong acids have been analyzed not only in terms of Hammett acidity functions, but also in terms of linear Gibbs energy relationships, first developed by Bunnett *et al.* [225]; see [226] for a review.

The ionisation constants of many acidic organic compounds determined in water [110a] and in twelve of the most popular dipolar non-HBD solvents [110b] have been compiled, as have the methods of determination [111] and prediction [112] of pK_a values. Particular attention has been paid to C—H acidic compounds [113]. Whereas the ionisation constants of Brønsted acids and bases for aqueous solutions are well known, the corresponding pK_a values for nonaqueous solutions are comparatively scarce.

4.2.2 Gas-Phase Acidities and Basicities [18–21, 114–118]

Acidities and basicities of organic compounds are expected to be different in the gas phase and in solution. Whereas in the gas phase acidity and basicity are intrinsic properties of the individual molecules, in the liquid state these properties belong to the phase as a whole due to the interaction between solute and solvent molecules. Solution-phase acidities and basicities reflect solvent properties as well as the intrinsic proton-donating and -accepting power of the solute. Therefore, acidities and basicities measured under solvent-free conditions must be available before the interplay between solute properties and solvent effects can be studied. Efforts in this direction have not made much progress until recently due to the lack of methods for measurements of gas-phase acidities and basicities.

Gas-phase acidities and basicities for many organic compounds are now available, primarily due to the development within the past decades of three new experimental techniques: pulsed high-pressure (*i.e.* 0.1 ... 1300 Pa) mass spectrometry (HPMS) [22, 23, 118], the flowing afterglow (FA) technique with a fast-flowing gas like helium in the pressure range of *ca.* $10^{-1} \ldots 10^{-2}$ Pa [119], and pulsed electron beam, trapped ion cell, ion cyclotron resonance (ICR) spectrometry, carried out at *ca.* $10^{-6} \ldots 10^{-3}$ Pa [24–26, 115].

The development of these ion-molecule equilibrium measurements has completely changed the status of acid/base reactions (and of other reactions; *cf.* Section 5.2) in the gas phase. It is now possible to compare the complex and poorly understood situation in solution with the simple state in the gas phase. It is also possible to determine the acidity of all acids in the gas phase, from the weakest such as methane to the strongest. In solution, however, due to the levelling effect of the solvent or solubility problems, only a certain range of acids can be measured in a given solvent.

Using these methods, relative intrinsic acidities and basicities of molecules in the gas phase have been determined by measuring equilibrium constants, $K = [\mathrm{A}^{\ominus}] \cdot [\mathrm{BH}]/[\mathrm{HA}] \cdot [\mathrm{B}^{\ominus}]$, for proton-transfer reactions such as

$$(\mathrm{HA})_{gas} + (\mathrm{B}^{\ominus})_{gas} \rightleftharpoons (\mathrm{A}^{\ominus})_{gas} + (\mathrm{BH})_{gas} \qquad (4\text{-}16)$$

Similar measurements for proton-transfer reactions such as (S = solvent molecules)

$$(\mathrm{HA})_{gas} + (\mathrm{B}^{\ominus}\cdot \mathrm{S}_n)_{gas} \rightleftharpoons (\mathrm{A}^{\ominus}\cdot \mathrm{S}n)_{gas} + (\mathrm{BH})_{gas} \qquad (4\text{-}17)$$

have allowed the scrutiny of the solvent influence as a function of stepwise solvation of the participating ions by sequential addition of solvent molecules ($n = 0$ up to $4 \ldots 9$), thus bridging the gap between the gas-phase and solution reaction.

The standard molar Gibbs energy change for reaction (4-16), $\Delta G^{\circ} = -RT \cdot \ln K$, is then a measure of the relative acidity of HA and BH (or of the relative basicity of $\mathrm{B}^{\ominus}$ and $\mathrm{A}^{\ominus}$). Series of acids and bases have been studied to establish a scale of relative acidities in the same manner as $\mathrm{p}K_{\mathrm{a}}$ values are determined in solution.

In addition, an absolute intrinsic acidity or basicity scale as the case may be, corresponding to the reaction (4-18),

$$(\mathrm{HA})_{gas} \rightleftharpoons (\mathrm{H}^{\oplus})_{gas} + (\mathrm{A}^{\ominus})_{gas} \qquad (4\text{-}18)$$

can be established by incorporating certain standard reactions such as $\mathrm{H}_2 \rightleftharpoons \mathrm{H}^{\oplus} + \mathrm{H}^{\ominus}$ and $\mathrm{HF} \rightleftharpoons \mathrm{H}^{\oplus} + \mathrm{F}^{\ominus}$, for which ΔH° and ΔG° can be calculated from available data, into the relative scale. These absolute gas-phase acidities are conveniently expressed in terms of the proton affinity, *PA*, of the anion $A^{\ominus}$, defined as the standard molar enthalpy change ΔH° for the gaseous deprotonation reaction (4-18): $PA(A^{\ominus}) = -\Delta H^{\circ}$. For most simple cases, the change in ΔS° for this reaction is about the same. Thus, ΔH° (and ΔG°) varies in about the same way as the proton affinity does.

From consideration of the following thermodynamic cycle,

$$\begin{array}{ll}
\mathrm{H{-}A} \longrightarrow \mathrm{H}^{\odot} + \mathrm{A}^{\odot} & D_{\mathrm{HA}}\ \text{(homolytic dissociation energy of the H—A bond)} \\
\mathrm{A}^{\odot} + e^{\ominus} \longrightarrow \mathrm{A}^{\ominus} & -EA_{\mathrm{A}}\ \text{(electron affinity of radical A)} \\
\mathrm{H}^{\odot} \longrightarrow \mathrm{H}^{\oplus} + e^{\ominus} & IP_{\mathrm{H}}\ \text{(ionization potential of atomic hydrogen, } i.e.\ \text{1312 kJ/mol)} \\
\hline
\mathrm{H{-}A} \longrightarrow \mathrm{H}^{\oplus} + \mathrm{A}^{\ominus} &
\end{array}$$

the proton affinity of $A^{\ominus}$ is given by Eq. (4-19):

$$PA = D_{\mathrm{HA}} - EA_{\mathrm{A}} + IP_{\mathrm{H}} \tag{4-19}$$

Since IP_{H} is a constant for every reaction, for the sake of simplicity this term is usually omitted; the acidities are then expressed as $D_{\mathrm{HA}} - EA_{\mathrm{A}}$. The acid strength increases as this difference decreases.

Scales of gas-phase proton affinities and gas-phase acidities for numerous organic compounds, including super bases and super acids [232], can be found in references [115, 120, 232, 233]; for comparisons of gas-phase and solution acidities, see references [124, 234–238].

In most cases, the gas-phase acidity orders differ dramatically from those observed in solution since the Gibbs energies of solvation (*ca.* 200–600 kJ/mol; *cf.* Table 2-8 in Section 2.3) are much larger than the intrinsic acidity differences for most pairs of compounds. Thus, the relative acidities in solution are often dictated by the differential Gibbs energies of solvation rather than by the intrinsic properties of the solute molecules.

The solution and gas-phase acidities of C—H acids are of particular interest because of the wide structural variations that are possible in this class of compounds [113, 123]. A qualitative ordering of a selection of C—H acids (and some O—H acids for comparison) gives the following sequence of increasing acidity in the gas phase [120]:

$$\begin{array}{l}
\mathrm{CH_4} < \mathrm{H_2O} < \mathrm{CH_3O}\mathit{H} < \mathrm{C_6H_5C}\mathit{H}_3 < \mathrm{HC{\equiv}CH} < \mathrm{CH_3SOCH_3} < \mathrm{CH_3CN} \\
< \mathrm{CH_3COCH_3} < \mathrm{C}\mathit{H}_3\mathrm{CHO} < \mathrm{C_6H_5COC}\mathit{H}_3 < \mathrm{CH_3NO_2} < \text{Cyclopentadiene} \\
< \text{Fluorene} < \mathrm{CH_3CO_2}\mathit{H} < \mathrm{CH_2(CN)_2}
\end{array}$$

Surprisingly enough, toluene is more acidic than water in the gas phase, but *ca.* 20 orders of magnitude less acidic in solution. Thus, in the gas phase, the reaction of $HO^{\ominus}$ with toluene proceeds rapidly, with the release of energy, to yield charge-delocalized $C_6H_5CH_2^{\ominus}$ and H_2O. In aqueous solution, the reaction proceeds in the opposite direction, converting the benzyl anion into toluene by water, and the latter giving charge-localized $HO^{\ominus}$.

Contrary to the behaviour in solution, malononitrile is a stronger acid than acetic acid in the gas phase, while fluorene, which is almost 10^5 times less acidic than cyclopentadiene in solution, becomes the stronger of the two in the gas phase. The reason for the reversed cyclopentadiene/fluorene acidity order is the better solvation of the smaller cyclopentadienide ion relative to the large fluorenide ion with the more delocalized negative charge, on going from the gas phase to solution. Whereas the larger, more charge-delocalized anion is preferably produced in the gas phase, in solution, the smaller anion with the higher charge density, *i.e.* the better solvated anion, is favoured.

A study of some C—H acids in dimethyl sulfoxide solution led to an acidity order that almost paralleled that found in the gas phase, whereas in protic solvents the order was different [116, 124, 125]. This result highlights the importance of specific solute/solvent interactions such as hydrogen bonding in comparing acid/base equilibria measured in the gas phase and in solution.

Some features of the solution pK_a scale are retained in the gas phase. For instance, the acidity of hydrogen halides increases in the order HF < HCl < HBr < HI, both in aqueous solution and in the gas phase [120].

The discovery of Brauman and Blair in 1968 [34] that the acidities of aliphatic alcohols are completely reversed on going from bulk solution to the gas phase was a landmark in the interpretation of solvent and substituent effects on acid/base equilibria. The gas-phase acidity of alcohols increases in the following order [34, 125, 126]:

$$\mathrm{H{-}OH} < \mathrm{CH_3{-}OH} < \mathrm{CH_3CH_2{-}OH} < \mathrm{CH_3CH_2CH_2{-}OH} < \mathrm{(CH_3)_2CH{-}OH}$$

$$< \mathrm{CH_3CH_2CH_2CH_2{-}OH} < \mathrm{(CH_3)_3C{-}OH} < \mathrm{Me_3CCH_2{-}OH} < \mathrm{C_6H_5CH_2{-}OH}$$

$$< \mathrm{(Me_3C)_2CH{-}OH} < \mathrm{CH_3{-}SH} < \mathrm{CH_3CH_2{-}SH} \ll \mathrm{C_6H_5{-}OH}$$

In the gas phase, tertiary alcohols are more acidic than secondary alcohols, and these in turn are stronger acids than primary alcohols. In other words, the anion $\mathrm{R{-}CH_2O^{\ominus}}$ is a stronger base than both $\mathrm{R_2CH{-}O^{\ominus}}$ and $\mathrm{R_3C{-}O^{\ominus}}$. This is in striking contrast to the solution behaviour, where introduction of alkyl groups at the OH-bearing carbon atom causes a significant increase in basicity of alkoxide anions [35, 127].

Prior to the availability of gas-phase data, the solution order of acidities was taken as evidence of anion destabilization through electron donation by methyl groups. Now it is clear that the liquid-phase ordering is due entirely to differential solvation of the reactants of Eq. (4-18). The effects of alkyl groups on gas-phase acidities have been considered in terms of inductive and polarization effects. It is now established that the stabilization of anions by alkyl substitution is due mostly to the role played by polarization forces between the negatively charged centre and the alkyl groups. A charged atom in an isolated ion in the gas-phase has only its attached alkyl groups to interact with, whereas in solution the polarizability of the surrounding solvent molecules is an additional factor in stabilizing the ion. Since polarizability generally increases with molecular volume, all alkyl groups are more polarizable than the hydrogen atom, and can stabilize a nearby charge whether that charge is negative or positive. Hence, the gas-phase acidities (and basicities) of alcohols should increase the greater the number and size of the alkyl groups. The reversed acidity order of alcohols obtained in bulk solution ($\mathrm{RCH_2{-}OH} > \mathrm{R_2CH{-}OH} > \mathrm{R_3C{-}OH}$) can be explained by the assumption that stabilization of the alkoxide ions through hydrogen bonding should be much better with the sterically less hindered $RCH_2—O^{\ominus}$ than with $R_2CH—O^{\ominus}$ and $R_3C—O^{\ominus}$ [128]. Since the Gibbs energies of solvation of the alkoxide ions are large compared to the difference in ionization energies according to Eq. (4-18), a reversal of the acidity order easily occurs in going from the gas phase to solution. Thus, the solution acidity order of alcohols is an artefact, and does not represent any intrinsic property of the alcohol molecules.

By quantitatively measuring the equilibrium given in Eq. (4-20), it has been shown [129] that the reversal of the relative acidities of methanol and ethanol on going from the

$$CH_3O^{\ominus}\cdots HOCH_3 + C_2H_5OH \rightleftharpoons C_2H_5O^{\ominus}\cdots HOCH_3 + CH_3OH \tag{4-20}$$

gas phase to bulk solvent is almost half completed with the first molecule of solvation. The Gibbs energy of solvation of $CH_3O^{\ominus}$ using one molecule of CH_3OH is approximately 71 kJ/mol (17 kcal/mol) [130]. Thus, the first molecule of solvent causes the behaviour of the alkoxide ion to become already "solution-like". In other cases [*cf.* Eq. (4-17)], more solvent molecules are necessary for the reactivity to approach that of the bulk solvated form. Obviously, the first few solvent molecules can contribute most of the total solvation energy. These results also show that the solvating abilities of isolated solvent molecules can be very different from their performance as bulk liquids. For example, the extremely low gas-phase acidity and basicity of "monomeric" water is completely different from its acid/base behaviour as "polymeric" water, *i.e.* as the classical amphiprotic solvent.

Other well-studied cases of acidity order changes induced by differential solvation are substituted phenols [131] and halo-substituted carboxylic acids [34a, 122, 132, 239]. For a comparison of the acid/base behaviour of oxygen-versus sulfur acids and bases (*e.g.* R—OH/R—SH) in the gas phase and in solution, see reference [214].

By comparing the gas-phase and solution acidities of substituted phenols, it has been found that the solvent not only plays a dominant role in controlling the phenol acidity, but also in modifying the effects of substituents on this acidity. Modifications due to differential substituent solvation can significantly change the order of substituent effects on phenol acidity [131]. An analogous solvent influence on the substituent effects on gas-phase and solution basicity was found in the series of 4-substituted pyridines [33].

Generally, it has been found that substituent effects on acidity or basicity are significantly attenuated by the transfer of the substituted reactant from the gas phase into solution [235, 237, 240, 241]. Substituent effects are smaller in solution and this attenuation is different for different classes of substituted organic compounds [241].

The gas-phase acidity order of haloacetic acids $X—CH_2—CO_2H$ is: $H < F < Cl < Br < I$, *i.e.* the order is reversed compared to that in aqueous solution [34a, 122, 132, 239]. Thus, the well-known aqueous acidity order is not caused by the increasing inductive substituent effect ($I < Br < Cl < F$), as is generally assumed, but rather by solvation effects.

α-Amino acids such as glycine, which are known to exist as zwitterions in the crystalline state and in aqueous solution, are not zwitterionic in the gas phase [133]. By measuring the gas-phase acidity and basicity of glycine, it has been found that in the gas phase it exists as a non-ionic molecule $H_2N—CH_2—CO_2H$! Although the zwitterionic form of α-amino acids predominates in dipolar non-HBD solvents, the ratio of the zwitterionic to the uncharged form is, at 2...40 in dimethyl sulfoxide, much smaller than the corresponding values of $10^4 \dots 10^5$ in aqueous solution [219]. This large difference can be explained by the better solvation of the carboxylate group in water compared to dimethyl sulfoxide, with solvation of the ammonium group being similar in the two solvents [219]. The reaction path for the proton transfer from the neutral to the zwitterionic form on going from the gas to the aqueous phase does not correspond to a direct intramolecular proton transfer, but probably to a proton transfer mediated by the water molecules forming the first hydration shell [242].

Structurally related to α-amino acids is sulfamic acid, which can exist as neutral ($H_2N—SO_3H$) and zwitterionic species ($^+H_3N—SO_3^-$). According to high level *ab initio* MO calculations, the neutral form is slightly more stable in the gas phase (by ca. 2 kJ/mol), whereas in polar media the zwitterion is predicted to be strongly favoured, in agreement with measurements in aqueous and DMSO solution [261].

A historically interesting example of solvent influence on basicity that has puzzled chemists for a long time will be used to conclude this section.

It has long been known that the proton-acceptor abilities of alkylamines in aqueous solution, as expressed by their pK_b values, are in the order $NH_3 < RNH_2 < R_2NH > R_3N$(!) [27]. The unexpected reduced base strength of tertiary alkylamines is found for all the common alkyl groups. However, if the basicities of methylamines are determined in the gas phase, they increase monotonically from ammonia to trimethylamine, as expected from theoretical considerations: $NH_3 < CH_3NH_2 < (CH_3)_2NH < (CH_3)_3N$ [28–30, 115]. Therefore, the "basicity anomaly" of tertiary alkylamines in aqueous solution must be related to the differential solvation of the reacting species of the corresponding acid/base equilibrium.

The reaction between the ammonium ion, $NH_4^{\oplus}$, and trimethylamine, $(CH_3)_3N$, analogous to Eq. (4-16), has been studied by pulsed ICR mass spectrometry [115]. The Gibbs energy diagram in Fig. 4-2 describes what happens to the reactants on going from

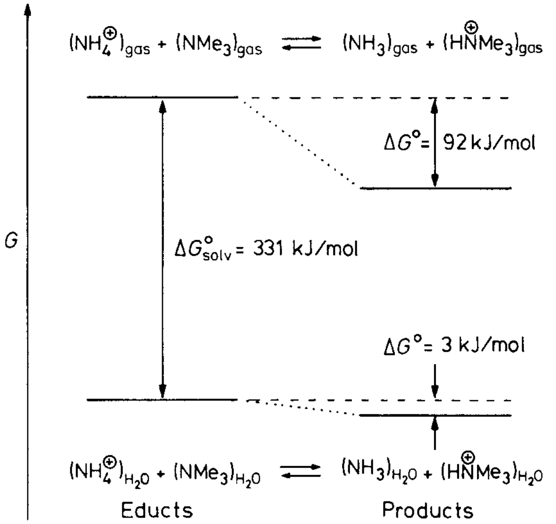
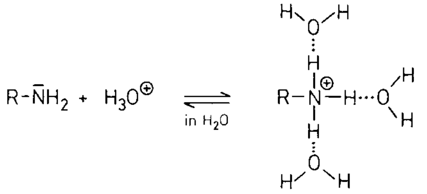


Fig. 4-2. One-dimensional Gibbs energy diagram for the acid/base equilibrium reaction between the ammonium ion and trimethylamine in the gas phase (top) and in aqueous solution (bottom) [115].

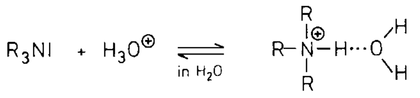
the gas phase to aqueous solution. In the gas phase, the products are more stable than the educts by 92 kJ/mol. In aqueous solution, the Gibbs energy of reaction falls to only 3 kJ/mol because of preferential solvation of the $NH_4^{\oplus}$ ion by hydrogen bonding. This means that at equilibrium in aqueous solution the concentration of the ammonium ion is higher by a factor of 10^{15} than it is in the gas phase.

Why is trimethylamine a much stronger base than ammonia in the gas phase? The increase in base strength with increasing number of alkyl substituents at the amine nitrogen atom can be considered in terms of inductive and polarization effects. The electric field of the positive charge permeates the space around the alkylammonium ion and distorts the electron clouds of the alkyl groups. Both the inductive and polarization effect make $Me_3NH^{\oplus}$ a more stable ion than $NH_4^{\oplus}$. In particular, the replacement of hydrogen atoms by the larger, more polarizable alkyl groups stabilizes charged centres. The observation that the gas-phase acidity of alcohols increases with alkyl substitution (see above) shows that alkyl groups can stabilize a charge of either sign, withdrawing or donating electrons as needed.

What happens to the same reaction in aqueous solution? Whereas the neutral reactants, ammonia and trimethylamine, are hydrated about equally well, the ammonium ion is hydrated much more strongly than is $Me_3NH^{\oplus}$. As shown by Eqs. (4-21) and (4-22), solvation through hydrogen bonding will tend to increase the base strength of all amines



(4-21)



(4-22)

in aqueous solution because the positively charged ammonium ions will be better solvated than the uncharged amines [31]. However, the solvation through hydrogen bonding will decrease with increasing alkyl substitution; *cf.* Eq. (4-22). The ammonium ion can be stabilized by four hydrogen bonds, whereas $Me_3NH^{\oplus}$ has only one acidic hydrogen atom.

The apparent basicity "anomaly" of alkylamines can now be understood in terms of two opposing influences, one base-strengthening (due to increasing alkylation of the amine), and the other base-weakening (because of reduced solvation of the ammonium ions with increasing alkylation). For solvation effects on the basicities of alkyl amines in solvents other than water, see reference [243].

Why are aniline ($pK_b = 9.4$) and pyridine ($pK_b = 8.8$) so much less basic than ammonia ($pK_b = 4.8$) in aqueous solution? For a long time, students of organic chemistry have been given reasons in terms of lone-pair delocalization and sp^2/sp^3 hybridization of the nitrogen atom. From gas-phase studies, it is now clear that aniline and pyridine are inherently much stronger bases than ammonia [116]*). Therefore, the reversed basicity order obtained in aqueous solution is caused by differential hydration! However, if more suitable reference compounds are used, cyclohexylamine ($pK_b = 3.3$) for aniline and piperidine ($pK_b = 2.9$) for pyridine, then aromatic amines are indeed less basic than saturated ones in aqueous solution. Thus, according to Arnett [213], "the right idea has been promoted over the years but for the wrong reasons, a not infrequent occurrence in chemistry".

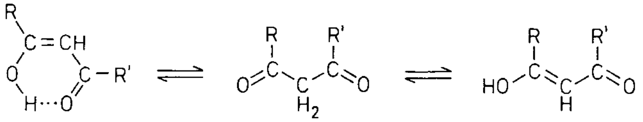
Another acid/base anomaly, the anomalous relationship between rates and equilibria for the proton-transfer reactions of nitroalkanes such as $H_3C—NO_2/H_3C—CH_2—NO_2/(H_3C)_2CH—NO_2$ found in water, does not exist in the gas phase [244]. Only in aqueous solution is the rate of proton abstraction by HO^- unexpectedly slower for the more acidic nitro compound.

Some general rules for solvation effects on acid/base equilibria as transferred from the gas phase to solution have been collected by Arnett [213].

4.3 Solvent Effects on Tautomeric Equilibria

4.3.1 Solvent Effects on Keto/Enol Equilibria [36–43, 134]

In general, 1,3-dicarbonyl compounds, which include β-dialdehydes, β-ketoaldehydes, β-diketones, and β-ketocarboxylic esters, can exist in solution or as the pure compound in three tautomeric forms**): the diketo form *(4a)*, the *cis*-enolic *(4b)*, and the *trans*-enolic form *(4c)*.



(4b) *(4a)* *(4c)*

Open-chain 1,3-dicarbonyl compounds are observed in the *trans*-enolic form only in rare cases [41] (for examples, see references [44, 45]). When the *trans*-enolic form is excluded, the keto/enol equilibrium constant K_T is given by Eq. (4-23).

$$K_T = \frac{[\text{enol}]}{[\text{diketo}]} \tag{4-23}$$

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* The much greater gas-phase base strength of aniline (and cyclohexylamine) compared with ammonia is due to the polarizability of the large carbocyclic residue. However, aniline is less basic than cyclohexylamine in the gas phase as well as in aqueous solution. The nitrogen lone-pair in aniline, unlike that in cyclohexylamine, is conjugated with the aromatic π-system of the benzene ring and is thus, to some extent, delocalized. Protonation of the aniline nitrogen atom localizes this electron pair and causes some loss of delocalization energy.

** If $R \neq R'$, two *cis*-enolic and two *trans*-enolic forms can exist.

Table 4-2. Equilibrium constants and mole fractions of enol tautomers of ethyl acetoacetate *(4a)* ($R = CH_3$, $R' = OEt$; K_T), acetylacetone *(4a)* ($R = R' = CH_3$; K'_T), and 5,5-dimethylcyclohexane-1,3-dione *(5a)* (K''_T), determined ^1H NMR spectroscopically at *ca.* 20 °C at solute concentrations of *ca.* $10^{-3} \ldots 10^{-2}$ mol/L, *i.e.* under conditions unperturbed by self-association of the solute [134], values for pure solutes excepted [47].

Solvents (deuterated)	K_T	x(enol) / (cmol · mol^{-1})	K'_T	x(enol) / (cmol · mol^{-1})	K''_T	x(enol) / (cmol · mol^{-1})
Gas phase[a]	0.74	42.5	11.7	92	–	–
Cyclohexane	1.65	62	42	98	–	–
Tetrahydrofuran	0.40	29	7.2	88	–	–
Toluene	0.39	28	10	91	0.08	7
Tetrachloromethane	0.29	22.5	29	97	–	–
Benzene	0.26	21	14.7	94	0.12	11
Ethanol	0.14	12	5.8	85	169	99.4
1,4-Dioxane	0.13	11.5	4.8	83	2.8	74
Acetone	0.13	11.5	–	–	4.2	81
Pyridine	0.10	9	3.7	79	–	–
Trichloromethane	0.09	8	5.94	86	0.05	5
Dichloromethane	0.09	8	4.2	81	–	–
Pure solute[b]	0.081	7.5	4.3	81	–	–
Methanol	0.07	6.5	2.9	74	148	99.3
Water	0.07	6.5	0.23	19	19	95
Dimethyl sulfoxide	0.05	5	2.0	67	94	99.0

[a] Values at 40 °C; see reference [38].
[b] Values at 33 °C; see reference [47].

In solution, open-chain 1,3-dicarbonyl compounds enolize practically exclusively to the *cis*-enolic form *(4b)*, which is stabilized by intramolecular hydrogen bonding. In contrast, cyclic 1,3-dicarbonyl compounds (*e.g.* cycloalkane-1,3-diones [46]), can give either *trans*-enols (for small rings) or *cis*-enols (for large rings). As the diketo form is usually more dipolar than the chelated *cis*-enolic form, the keto/enol ratio often depends on solvent polarity. This will be discussed in more detail for the cases of ethyl acetoacetate and acetylacetone [47–50, 134, 135].

The equilibrium constants, measured by ^1H NMR spectroscopy, of ethyl acetoacetate and acetylacetone [47, 48, 134] (Table 4-2) indicate a higher enol content for these *cis*-enolizing 1,3-dicarbonyl compounds in apolar aprotic than in dipolar protic or dipolar aprotic solvents.

The ratios obtained in the apolar aprotic solvents approach the gas-phase values [38]. In principle, on dissolution of β-dicarbonyl compounds in solvents of low polarity, the percentage of the *cis*-enolic form increases, whereas polar solvents displace the equilibrium towards the diketo form. Although at first sight it is surprising that increasing solvent polarity diminishes the enol content, this is understandable in terms of intramolecular chelation of the enol. The enol form is the least polar of the two tautomers because intramolecular hydrogen bonding helps reduce the dipole-dipole repulsion of the carbonyl groups; this is unreduced in the diketo form. Furthermore, the enol stabilization due to the intramolecular hydrogen bonding will be more pro-

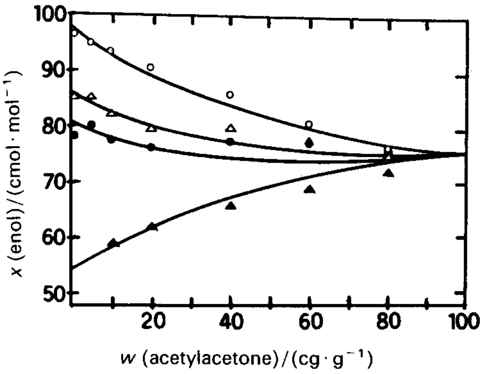


Fig. 4-3. Effect of solvent and concentration on the keto/enol equilibrium of acetylacetone in four solvents of different polarity at 37 ± 2 °C: CCl_4 (○), $CHCl_3$ (△), CH_2Cl_2 (●), and $HCON(CH_3)_2$ (▲) [50].

nounced when intermolecular hydrogen bonding with the solvent does not compete. Thus, a change to a more polar solvent, with a tendency towards intermolecular hydrogen bonding (EPD solvents), is generally associated with a decline in enol content.

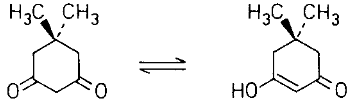
In agreement with this, the enol content also depends strongly on the initial concentration of the 1,3-dicarbonyl compound; see Fig. 4-3 [50].

As the dipolar 1,3-dicarbonyl compound acetylacetone is progressively diluted with apolar solvents, the enol content increases. Conversely, progressive dilution with a dipolar aprotic EPD solvent such as, *N*,*N*-dimethylformamide reduces the enol content of the acetylacetone solution.

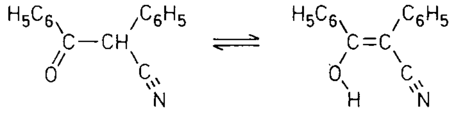
The addition of comparatively less polar alcohols to solutions of acetylacetone in water shifts its keto/enol equilibrium in favour of the less polar *cis*-enolic form *(4b)*, which has been quantitatively rationalized in terms of so-called pairwise solute/solvent interactions [245]. The keto/enol equilibrium of ethyl acetoacetate and acetylacetone has also been studied in polar supercritical fluids such as CHF_3 ($\mu = 1.65$ D) and $CClF_3$ ($\mu = 0.50$ D) [246]. In polar trifluoromethane, the dipolar keto form was found to be favoured, although the change in the equilibrium constant with increasing sc-fluid density (*i.e.* increasing pressure) was quite minor. For *ab initio* calculations of the relative stabilities of various enols of acetylacetone in the gas phase, and theoretical calculations of keto/enol equilibria in aqueous solutions, see references [247] and [248], respectively.

In contrast to the *cis*-enolizing 1,3-dicarbonyl compounds, the *trans*-enolizing cycloalkane-1,3-diones with four- to six-membered rings show exactly the opposite dependence on solvent polarity [46]. In these compounds, intramolecular hydrogen bonding is excluded on steric grounds. For example, 5,5-dimethyl cyclohexane-1,3-dione *(5a,b)* is 95% enolized in aqueous solution [51]. However, in dilute solution in toluene, an apolar solvent, it is only 7% enolized [52, 134]; x(enol) = 7 cmol/mol; *cf.* Table 4-2.

Analogously, the keto/enol equilibrium of *trans*-enolizing 2-phenylindane-1,3-dione lies far on the side of the diketo form in apolar chloroform (>95 cmol/mol), whereas the *trans*-enol form is favoured in the polar HBA solvent dimethyl sulfoxide (ca. 77 cmol/mol) [249].



(5a) (5b)



(6a) (6b)

Another example is the β-ketonitrile *(6a,b)*. Because of the linearity of the cyano group, a cyclic structure with an intramolecular hydrogen bond is impossible. As predicted, it is found that the enol content is greater in polar than in apolar solvents [53].

In general, for the protomer pairs in which the enol cannot form an intramolecular hydrogen bond, such as *(5a)* ⇌ *(5c)*, the tautomeric equilibrium seems to be controlled almost completely by the hydrogen-bond acceptor property (Lewis basicity) of the solvent. EPD solvents enhance the enol content strongly; *cf.* *(5a)* in Table 4-2.

For protomer pairs such as *(4a)* ⇌ *(4b)*, in which intramolecular hydrogen bonding is possible, the solute/solvent effect due to dipolarity/polarizability interactions dominates, although differential stabilization of the tautomers by hydrogen bonding remains significant. If there exists a substantial difference in the permanent dipole moments of the two tautomers, and both can donate a hydrogen bond to the solvent, the dipole/dipole solute/solvent interactions will dominate [134]. Similar results have been obtained for acetoacetic acid itself, for which the enol mole fraction ranges from less than 2 cmol/mol in D_2O to 49 cmol/mol in CCl_4 [136].

Open-chain β-keto carboxylic esters with two mesityl substituents, such as methyl 3-hydroxy-2,3-dimesityl-2-propenoate, exist in solution only as the (*Z*)-isomer *(4b)* and the (*E*)-isomer *(4c)*; no keto form *(4a)* has been observed [223]. The (*Z*)-form predominates in nonpolar solvents such as cyclohexane (90 cmol/mol) and benzene (87 cmol/mol). Increasing solvent polarity shifts this (*Z*)/(*E*) equilibrium in favour of the more polar (*E*)-isomer, up to 76 cmol/mol (*E*)-form in ethanol [223]. The introduction of mesityl substituents stabilizes enols of simple monocarbonyl compounds such as 2,2-dimesitylethenol, $Mes_2C{=}CH{-}OH$ [42, 224].

The influence of solvents on tautomeric equilibria has been related to the solubilities of the two tautomers. Formally, the dissolution of a solute to give a saturated solution may be regarded as an equilibrium:

$$\text{crystals} + \text{solvent} \rightleftharpoons \text{dilute saturated solution}$$

The energy of the solid phase is independent of the solvent, and thus differences in solubility on going from one solvent to another will be a measure of the solvent effect on the Gibbs energy of the dissolved compound [1, 2]. Table 4-3 shows that the variation in

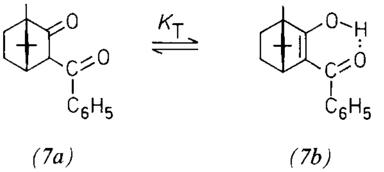
Table 4-3. Keto/enol equilibrium of 3-benzoyl camphor in five solvents at 0 °C [37].

Solvents	K_T [a]	$\frac{S_{enol}}{S_{diketo}}$ [b]	G
Diethyl ether	6.81	6.39	1.06
Ethyl acetate	1.98	1.81	1.09
Ethanol	1.67	1.57	1.06
Methanol	0.87	0.75	1.15
Acetone	0.85	0.80	1.06

[a] $K_T = [\text{enol}]/[\text{diketo}]$.

[b] Enol solubility/diketo solubility.

the equilibrium constants for the keto/enol tautomerization of 3-benzoyl camphor *(7a,b)*, in a series of solvents, is consistent with the solubilities of the two tautomers.



(7a) *(7b)*

The van't Hoff-Dimroth relationship (4-24) [37, 54] states that two interconvertible isomers are in equilibrium when the ratio of their concentrations is proportional to that of their solubilities S in the relevant solvent. In Eq. (4-24), G is a solvent-independent constant, characteristic of the 1,3-dicarbonyl compound. Therefore, the equilibrium constant, K_T equals G multiplied by the solubility ratio.

$$K_T = \frac{[\text{enol}]}{[\text{diketo}]} = G \cdot \frac{S_{enol}}{S_{diketo}} \tag{4-24}$$

From this, it follows that the concentration of an enol will be at a maximum in a solvent in which it has the highest relative solubility.

The applicability of Eq. (4-24) was demonstrated by O. Dimroth using 3-benzoyl camphor *(7a,b)* as an example [37]. This was particularly suitable, since both the diketo and the enol form are separately isolable, and the solubility of each is readily determined due to the slowness of their tautomerization. Although the ratio of the S terms varies by a factor of 8, the value of G is constant within an error of ±5%. This is understandable, since for each 1,3-dicarbonyl compound, the same characteristic difference between diketo and enol forms should, in principle, be observed.

The solubility is a reflection of how well the diketo and enol forms are solvated. Deviations from Eq. (4-24) are due mainly to the fact that the equation holds only for dilute solutions. At high concentrations, the solubility is no longer determined by solvent-solute interactions alone, but self-solvation (*i.e.* interactions between the dissolved molecules themselves) also plays a role. Thus, as already stated, the enol content of a solution also depends on the concentration of the 1,3-dicarbonyl compound [55].

From the thermodynamic point of view, the keto/enol equilibrium is determined by the change in Gibbs energy, ΔG°, which, in turn, is comprised of the enthalpy ΔH° and entropy ΔS° of enolization; *cf.* Eq. (4-4). Therefore, the position of equilibrium in solution will be determined by the differences $\Delta H^\circ_{\mathrm{solv}}$ and $\Delta S^\circ_{\mathrm{solv}}$ between the keto and enol forms, according to Eq. (4-25).

$$\Delta G^\circ_{\text{keto-enol}} = \Delta H^\circ_{\text{keto-enol}} \pm \Delta H^\circ_{\mathrm{solv}} - T \cdot \Delta S^\circ_{\text{keto-enol}} - T \cdot \Delta S^\circ_{\mathrm{solv}} \tag{4-25}$$

The values of $\Delta H_{\text{keto-enol}}$ and $T \cdot \Delta S_{\text{keto-enol}}$ can be determined from the temperature dependence of the equilibria in the gas phase [38]. However, the magnitudes and signs of the solvation terms are not well known. ΔH_{solv} will be either negative or positive when changing from a nonpolar to a polar solvent depending on which of the tautomers is the more polar. The resulting change in the equilibrium can be compensated by the corresponding entropy change. In a nonpolar solvent, stronger solvation leads to a higher degree of order of the solvent molecules and, hence, to a decrease in the entropy. In contrast, polar solvent molecules show a high degree of order even in the absence of a dipolar solute. The thermodynamic parameters for the enolization reaction of acetyl-acetone in seven solvents have been determined. The molar Gibbs energy of reaction varies from −0.25 kJ/mol in methanol to −9.1 kJ/mol in cyclohexane at 25 °C [134a].

Since these complications have prevented a quantitative estimation of the enthalpies and entropies of keto and enol forms in different solvents, a quantitative relationship between ΔG or K_{T}, and the solvating ability or polarity of the solvent (expressed in physical characteristics such as the relative permittivity ε_{r}, the dipole moment μ, the refraction index n, *etc.*) has not been possible either. Such equations would have the form of Eq. (4-26):

$$\Delta G^\circ = \mathrm{f}(\varepsilon_{\mathrm{r}}, \mu, n, \ldots) \quad \text{or} \quad K_{\mathrm{T}} = \mathrm{f}(\varepsilon_{\mathrm{r}}, \mu, n, \ldots) \tag{4-26}$$

For purely electrostatic solute/solvent interactions, the Kirkwood equation, Eq. (4-27) [56], is applicable, which relates the standard molar Gibbs free energy of transfer of spherical dipolar molecules of radius r and dipole moment μ from the gas phase ($\varepsilon_{\mathrm{r}} = 1$) to a continuous medium of relative permittivity ε_{r}.

$$\Delta G^\circ = -\frac{N_{\mathrm{A}}}{4\pi \cdot \varepsilon_0} \cdot \frac{\mu^2}{r^3} \cdot \frac{\varepsilon_{\mathrm{r}} - 1}{2\varepsilon_{\mathrm{r}} + 1} \tag{4-27}$$

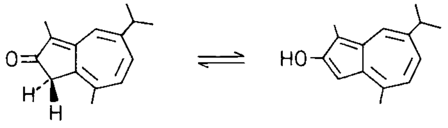
Application of this equation to keto/enol equilibria gives Eq. (4-28), derived by Powling and Bernstein [57].

$$(\Delta H^\circ)_{\mathrm{solution}} = (\Delta H^\circ)_{\mathrm{gas}} - \frac{N_{\mathrm{A}}}{4\pi \cdot \varepsilon_0} \cdot \left(\frac{\varepsilon_{\mathrm{r}} - 1}{2\varepsilon_{\mathrm{r}} + 1} \cdot \frac{\varrho}{M_{\mathrm{r}}} \right) \cdot (\mu_1^2 - \mu_2^2) \tag{4-28}$$

M_r is the molar mass and ϱ is the density of the solvent, μ_1 and μ_2 are the dipole moments of the least and more stable isomers, respectively. The proposed linear function between the enthalpy of tautomerization and the solvent quantity $[(\varepsilon_r - 1)/(2\varepsilon_r + 1)]\varrho/M_r$ gives, in the case of ethyl acetoacetate and acetylacetone, approximate straight lines (omitting the alcohols), but with considerable scattering of the points [47]. This scattering is not surprising in view of the rather concentrated solutions used, the specific interactions expected in hydrogen-bonding solvents, and the possible entropy effects in these systems.

A wide variety of different theoretical (*e.g.* Kirkwood function) and empirical (*cf.* Chapter 7) parameters of solvent polarity have successfully been tested using multivariate statistical methods in order to model the solvent-induced changes in keto/enol equilibria [134].

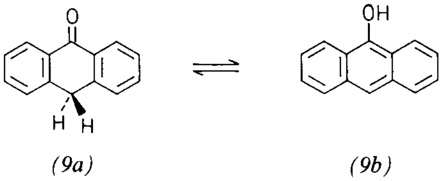
Most simple monocarbonyl compounds are enolized to such a small extent, that it is difficult to determine reliably their enol content in solution [58, 137]. The enol content of acetone, for example, is about $6 \cdot 10^{-8}$ cmol/mol at equilibrium [137]. A remarkable example of a solvent-dependent keto/enol equilibrium of a monocarbonyl compound is 2-hydroxy-7-isopropyl-1,4-dimethylazulene (2-hydroxy-guaiazulene) *(8a,b)* [59].



(8a) *(8b)*

Whereas in chloroform and water, no enol form *(8b)* is detectable, the enol content is 5 cmol/mol in cyclohexane, 20 cmol/mol in methanol, 55 cmol/mol in 1,4-dioxane, and 95 cmol/mol in dimethyl sulfoxide. Apparently, the enol is stabilized in solvents that can act as hydrogen-bond acceptors, while the keto form is favoured in protic solvents acting as hydrogen-bond donors. 6-Hydroxy-4,8-dimethylazulene behaves similarly [59a]. In polar solvents such as acetonitrile or dimethyl sulfoxide, the enolic azulenoid structure is exclusively observed, whereas in less polar solvents, dichloromethane or chloroform, a keto/enol equilibrium in a ratio of about 3:1 is detectable by ^{1}H NMR measurements [59a].

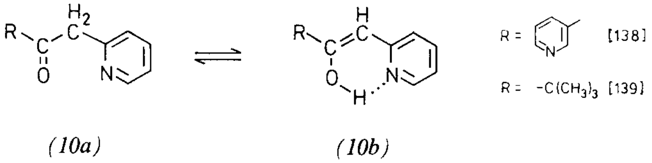
In the case of the tautomerization between 9-anthrone, *(9a)*, and 9-anthranol, *(9b)*, the equilibrium lies practically completely on the side of the keto form *(9a)* in the gas phase as well as in inert solvents such as *iso*-octane and benzene; *e.g.* in benzene at 20 °C, the enol content is 0.25 cmol/mol [60, 134].



(9a) *(9b)*

Addition of increasing amounts of triethylamine to a benzene solution of *(9a)* leads to a gradual shift of the equilibrium towards the enol form *(9b)*. This can be interpreted in terms of hydrogen-bond formation between 9-anthranol and triethylamine. In hydrogen-bond accepting solvents such as *N*,*N*-dimethylformamide (enol content 56.5 cmol/mol at 20 °C), pyridine (58 cmol/mol), and dimethyl sulfoxide (61.5 cmol/mol), the anthranol content increases further [61, 134].

Particularly well-studied tautomeric keto/enol equilibria are those of 3-pyridinyl 2-picolyl ketone [138] and *t*-butyl 2-picolyl ketone [139].



In both cases, the tautomeric equilibria are shifted to the more dipolar keto form *(10a)* with increasing solvent polarity. For instance, *t*-butyl 2-picolyl ketone (R = *t*-butyl) is the only tautomer observed in 2,2,2-trifluoroethanol [139], and 3-pyridinyl 2-picolyl ketone (R = 3-pyridinyl) dominates in water with a mole fraction of 60 cmol/mol [138].

Another illustrative example of a solvent-dependent keto/enol tautomerism of a monocarbonyl compound is given by 4-[(pent-1-ylthio)acetyl]-*N*-(4′-chlorobenzyl)-pyridinium chloride. In the HBA solvent dimethyl sulfoxide, the enol predominates (84 cmol/mol), while in the HBD solvent water it exists as the ketone (47 cmol/mol) and its hydrate (40 cmol/mol) [250]. Recrystallization of this pyridinium salt from a DMSO/ethyl acetate mixture yields the pure enolic form, with one molecule of DMSO per molecule of enol present in the crystal lattice.

Further examples of solvent-dependent keto/enol equilibria can be found in reference [41].

4.3.2 Solvent Effects on Other Tautomeric Equilibria [62–64, 140]

Solvent effects similar to those described for the keto/enol equilibria can also be found for other tautomerisms, *e.g.* lactim/lactam, azo/hydrazone, ring/chain equilibria, *etc.* [62–64]. The pecularities arising here can only be illustrated by means of a few representative examples.

One of the classic studies of *lactim/lactam tautomerism* is the determination of the 2-hydroxypyridine *(11a)* ⇌ 2-pyridone *(11b)* equilibrium [63–65, 141–145, 251–255].

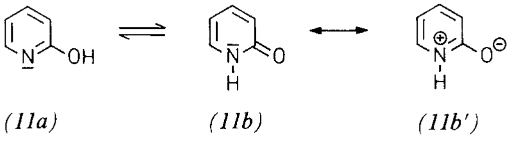


Table 4-4. Gas-phase and solution equilibrium constants $K_T = [NH]/[OH]$ of 2- and 4-hydroxypyridine at 25...30 °C unless otherwise stated [65, 67].

Solvents	2-Hydroxypyridine K_T	4-Hydroxypyridine K_T
Vapour[a)]	0.4 ± 0.25 (by UV)[c)] 0.5 ± 0.3 (by IR)[d)]	<0.1[d)]
Cyclohexane[b)]	1.7	–
Trichloromethane[b)]	6.0	1.3
Acetonitrile[b)]	148	4.6
Water[a)]	910	1900

a) Reference [65].
b) Reference [67].
c) At 130 °C.
d) At 250 °C.

IR and UV/Vis [65a], mass spectrometric [65b], photoelectron [65c], microwave [65d], as well as low-temperature matrix-isolation IR spectroscopic measurements [65e] reveal that 2- and 4-hydroxypyridine (as well as 2- and 4-mercaptopyridine [65f]) exist in the gas phase and in inert matrices (N_2, Ar) under equilibrium conditions mainly in the lactim (hydroxy or mercapto) form, in contrast to the situation in solution. While in nonpolar solvents such as cyclohexane and chloroform both tautomers exist in comparable amounts, the tautomeric equilibrium is shifted entirely in favour of the lactam (oxo or thioxo) form in polar solvents such as water, as well as in the crystalline state [66, 67, 141–145, 251–255]. Supercritical-fluid 1,1-difluoroethane can be used to adjust the tautomeric constant $K_T = [(11b)]/[(11a)]$ isothermally over a continuum from gas-phase values to those measured in polar solvents, simply by increasing the pressure [254]. The gas-phase and solution equilibrium constants of 2- and 4-hydroxypyridine are given in Table 4-4.

The gas-phase equilibrium constants differ from those in aqueous solution by as much as 10^4! The large differences between the stabilities of the tautomeric forms in the gas phase and in solution once more reveal the dominant influence of solvation on relative molecular stabilities.

By considering the equilibrium $(11a) \rightleftharpoons (11b)$ in solvents of varying polarity, it has been found that increasing solvent polarity shifts the equilibrium towards the pyridone-form. This form is more dipolar than the hydroxy-form due to the contribution of the charge-separated mesomeric form *(11b′)*. Whereas the solvent has little influence on the ground-state electronic structure of the lactim form, significant effects on the molecular geometry, charge distribution, and vibrational frequencies have been found for the lactam form *(11b)*, which are readily understood in terms of increasing importance of the dipolar mesomeric structure *(11b′)* in polar solvents [251]. Furthermore, the hydrogen-bonding ability of the solvent plays an important role since hydrogen-bond donors tend to stabilize the oxoform, whereas hydrogen-bond acceptors stabilize the hydroxy form. For example, the oxo form of 6-chloro-4-methyl-2-hydroxypyridine predominates in water, while in various other solvents the hydroxy form predominates: 67 cmol/mol in methanol, 56 cmol/mol in chloroform, 96 cmol/mol in dimethyl sulfoxide, and 95 cmol/mol in cyclohexane [66].

The precise determination of the protomeric equilibrium constants K_T for 2(4)-hydroxypyridine $\rightleftharpoons$ 2(4)-pyridone is rather difficult because of self-association even in highly diluted solutions of the tautomers in nonpolar solvents such as cyclohexane. Self-associated tautomers may have K_T values which are substantially different from those of the unassociated isomers [142, 255].

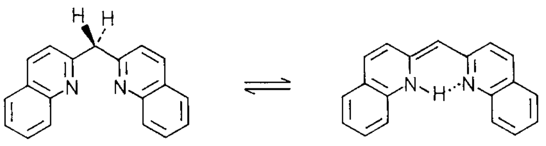
A quantitative model for the differential solvation of the hydroxypyridine/pyridone tautomer pair in terms of reaction-field and hydrogen-bonding effects, using multivariate regression analysis, has been given by Beak *et al.* [141]. *Ab initio* and other calculations correctly predict the greater stability of 2-hydroxypyridine *(11a)* as compared to 2-pyridone *(11b)* in the gas-phase [144, 251–253]. The calculated free energy difference for the lactim/lactam pair *(11a)* and *(11b)* in the gas phase at 25 °C is $\Delta G = 2.9$ kJ/mol in favour of *(11a)*, in good agreement with the experimental value [252].

In contrast to mono-hydroxypyridines and mono-hydroxypyrimidines, the lactim-lactam equilibria of uracils are not found to be markedly influenced by solvent polarity [143].

In the vapour phase, both 2- and 4-hydroxyquinoline exist as the NH forms, *i.e.* as 2- and 4-quinolones, in contrast to the results found for 2- and 4-hydroxypyridines [145].

The lactim/lactam tautomerism of hydroxamic acids and their O-alkyl and O-acyl derivatives has also been studied [146]. Hydroxamic acids exist in the solid state and in polar solvents as the lactam tautomer only, whereas in nonpolar solvents the hydroximic tautomer is also present. Further analogous solvent-dependent lactim/lactam equilibria have been observed for certain Schiff bases (prepared from anilines and 2(4)-hydroxybenzaldehyde [256] or 2-hydroxynaphthaldehyde [257]), for 3-hydroxypyrazole [258], and for 3-methyl-1-phenylpyrazolin-5-one [259].

Di-(2-quinolyl)methane exists in a solvent-dependent tautomeric equilibrium between a colourless form *(12a)* and a coloured, hydrogen-bonded form *(12b)* in solution [68].



(12a) *(12b)*

The thermodynamic data for the transformation of the two forms have been estimated and are given in Table 4-5.

In hydrogen-bond donor solvents such as alcohols and trichloromethane, the tautomeric equilibrium is shifted in favor of the colourless form *(12a)* more than in other solvents. This is obviously due to the formation of hydrogen bonds between *(12a)* and these protic solvents. In aprotic solvents, ΔH° is negative and the reaction is exothermic. Since, however, all ΔG° values are positive, the negative value of ΔH° must be over-compensated by a positive entropy change; *cf.* Eq. (4-4).

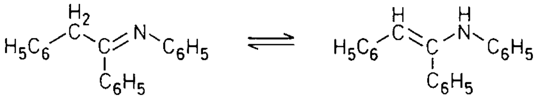
Table 4-5. Thermodynamic data for the tautomeric conversion *(12a)* → *(12b)* of di(2-quinolyl)-methane at 20 °C [68].

Solvents	$\frac{\Delta G^\circ}{(\mathrm{kJ \cdot mol^{-1}})}$ [a]	$\frac{\Delta H^\circ}{(\mathrm{kJ \cdot mol^{-1}})}$ [a]	$\frac{T \cdot \Delta S^\circ}{(\mathrm{kJ \cdot mol^{-1}})}$ [a]
Ethanol	+12.6	+9.6	−2.9
Trichloromethane	+9.6	+8.4	−1.3
tert-Butanol	+8.8	+6.7	−2.1
Benzene	+6.3	−0.4	−6.7
Tetrachloromethane	+5.4	−1.7	−7.1
N,*N*-Dimethylformamide	+4.6	−3.3	−7.9
n-Heptane	+4.2	−6.3	−10.5
Carbon disulfide	+2.9	−10.0	−13.0

[a] The energy which is added to the system is considered to be positive, and that given up by the system to be negative.

This entropy decrease for the formation of the coloured form *(12b)* may be due to the planarization of the molecule (formation of the N—H···N bridge) and the fixation of the di-*cis*-form *(12b)*, while in *(12a)* there is free rotation about the central C—C bond. In protic solvents, the colourless form *(12a)* is already stabilized by hydrogen bonding and $T \cdot \Delta S^\circ$ is small. Therefore, the ΔG° values are greater in these solvents and ΔH° is positive [68].

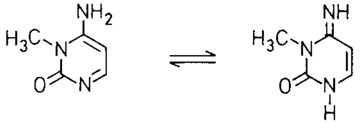
The ketimine *(13a)*, prepared from desoxybenzoin and aniline, is also subject to a solvent-dependent tautomerism called *imine/enamine tautomerism*. The enamine content of a solution of *(13a)* increases in the order tetrachloromethane (31 cmol/mol at 35 °C), [D_5]pyridine (47.5 cmol/mol at 55 °C), and [D_6]dimethyl sulfoxide (67 cmol/mol at 55 °C) [69]. Hydrogen-bond acceptor solvents favour the enamine form *(13b)* due to hydrogen-bonding, whereas in less polar and apolar solvents the equilibrium is shifted towards the imine form *(13a)* [69].



(13a) *(13b)*

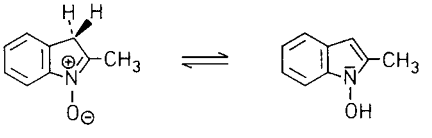
Other remarkable cases of solvent-dependent imine/enamine tautomerism have been reported by Ahlbrecht *et al.* [147], Scheffold *et al.* [69a], and Pérez-Ossorio *et al.* [211].

Compounds capable of a solvent-dependent *amino/imino tautomerism* are 3-methylcytosine *(14a,b)* and 1-alkyladenines [69b]. It has been shown by IR and UV/Vis spectroscopy that, in all cases, the imino forms such as *(14b)* predominate in nonpolar media (*e.g.* 1,4-dioxane). However, the content of the amino form *(14a)* increases with increasing solvent polarity, and in aqueous solution the amino form predominates [69b]. Further interesting examples of solvent-dependent tautomeric amino/imino equilibria are given in references [148, 149]. For a review on the solvent-dependent tautomerism of unsymmetrical acyclic and cyclic amidines, X—NH—CR=N—Y, see reference [260].



(14a) *(14b)*

An extreme case is the *nitrone/hydroxylamine tautomerism* between 2-methylindolenine-*N*-oxide *(15a)* and 2-methyl-*N*-hydroxyindole *(15b)* [70]. The position of this equilibrium depends strongly on the proton-accepting and donating abilities of the solvent: in pyridine and acetonitrile there exists 0 cmol/mol of form *(15a)*, 33 cmol/mol in tetrachloromethane, but 100 cmol/mol in phenol. Thus, it is possible to observe either *(15a)* (in phenol) or *(15b)* (in pyridine) depending on the solvent used.



(15a) *(15b)*

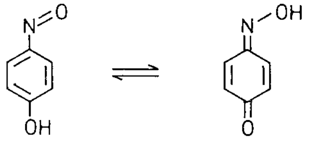
The position of the *N*-oxide/*N*-hydroxy equilibrium of 1-hydroxybenzotriazole, which is similar in structure to *(15b)*, is also solvent-dependent: approximately 6, 11, 18, and 26 cmol/mol of the *N*-oxide form is present at equilibrium in dimethyl sulfoxide, acetone, formamide, and methanol, respectively [218].

Because azo dyes are of commercial importance as colouring materials, the *azo/hydrazone tautomerism* of hydroxy-substituted azo compounds has been intensively studied [71, 228]. In the case of 4-phenylazo-1-naphthol *(16a)*, an increase in the solvent polarity displaces the tautomeric equilibrium towards the more dipolar quinone hydrazone form *(16b)* [72–74, 74a, 74b, 150–154]. In addition, the NH and OH groups of both tautomers are capable of forming hydrogen bonds with suitable solvents. Due to the stronger hydrogen-bond donor ability of the OH group compared with that of the NH group, it will be to a different degree. Thus, the formation of hydrogen bonds with HBA solvents such as pyridine should mainly stabilize the azo form, whereas the basic imino group in the hydrazone form should be more stabilized in HBD solvents such as chloroform or acetic acid. From UV/Vis spectroscopic measurements, the following order of increasing proportions of the hydrazone form *(16b)* has been found in solution

(16a) *(16b)*

(mole fractions in cmol/mol): pyridine (15) < acetone (30) < ethanol (31) < methanol (40) < benzene (56) < trichloromethane (79) < acetic acid (89) [151]. That is, the azo form *(16a)* is indeed stabilized in pyridine, acetone, ethanol, and methanol, whereas the hydrazone form dominates in trichloromethane and acetic acid. This is relative to the equilibrium in benzene, which is used as reference solvent. In *N*,*N*-dimethylformamide and dimethyl sulfoxide solutions, the azo dye *(16)* is converted into its mesomeric anion, due to the high basicities and high relative permittivities of these solvents [151]. Similar results have been obtained with 4-*alkyl*azo-1-naphthols [152]. Quantum-chemical calculations have shown that the azo form *(16a)* should be the more stable isomer in the gas phase [153, 154].

Relatively independently of solvent polarity, 4-nitrosophenol *(17a)* exists in solution mainly in the 1,4-benzoquinone monoxime form *(17b)* [75, 76]: *ca.* 83 cmol/mol monoxime in 95 cl/L aqueous ethanol [75], *ca.* 86 cmol/mol in 1,4-dioxane, and *ca.* 75 cmol/mol in acetone (at 20 °C) [76].

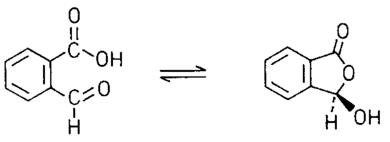


(17a) *(17b)*

In the case of 2-nitrosophenols such as 2,4-dialkyl-6-nitrosophenols, the tautomeric equilibrium is shifted towards the 1,2-benzoquinone monoxime form with increasing polarity of the solvent [76a].

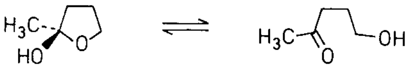
The reversible tautomeric equilibrium between phosphane oxides and ylides with a P—OH bond, *e.g.* $R_2P({=}O){-}CHR'_2 \rightleftharpoons R_2P({-}OH){=}CR'_2$ ($R = C_6H_5$; $R' = 4\text{-}Cl{-}C_6H_4{-}SO_2$), has been found to be solvent-dependent [155]. The more dipolar phosphane oxide dominates in polar solvents (90 cmol/mol in dichloromethane at 25 °C), whereas in HBA solvents such as tetrahydrofuran the P—OH form is favoured (*ca.* 54 cmol/mol).

Finally, four different examples of solvent-dependent *ring/chain tautomerism* should be mentioned [77, 210]. The equilibrium between phthalaldehydic acid *(18a)* and phthalide *(18b)*, which in decalin lies in favor of *(18b)* (90 cmol/mol phthalide at 20 °C), is strongly shifted towards the open-chain form *(18a)* in the hydrogen-bond accepting solvent dimethyl sulfoxide (only 5 cmol/mol phthalide) [78].



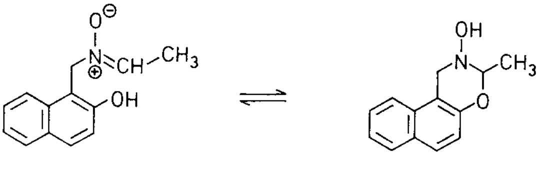
(18a) *(18b)*

In the case of 5-hydroxy-2-pentanone, there is a slight preference for the open-chain form *(19b)* over the cyclic hemiketal *(19a)* (in [D_{12}]cyclohexane 55 cmol/mol and in [D_6]dimethyl sulfoxide 61 cmol/mol *(19b)*) in most organic solvents [79].

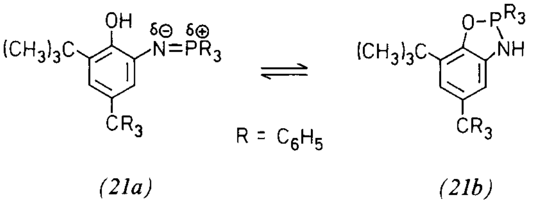

(19a) *(19b)*

An increase in solvent polarity further favours the open-chain tautomer; in water there is no evidence for any cyclic form [79]. This is remarkable in view of the fact that the furanose/pyranose equilibria of sugars, which are interconverted through the open-chain form, are also solvent-dependent [80, 81, 159]. Arabinose, for example, in [D_5]pyridine consists of 66 cmol/mol pyranose form (α:β = 33:33) and 34 cmol/mol furanose form (α:β = 21:13), compared with 95.5 cmol/mol pyranose form (α:β = 60:35.5) and 4.5 cmol/mol furanose form (α:β = 2.5:2.0) in deuterium oxide as solvent [80, 159].

In solution, the hydroxylaminomethylation product of 2-naphthol and acetaldehyde exhibits an equilibrium between the hydroxynitrone form *(20a)* and the cyclic hydroxylamine form *(20b)*, the position of which depends on the solvent: 29 cmol/mol hydroxynitrone form in [D_6]dimethyl sulfoxide, and 94 cmol/mol in [D_4]methanol [80a].


(20a) *(20b)*

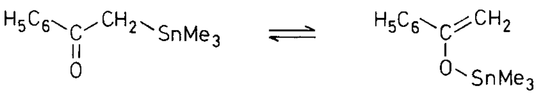
The ring/chain tautomeric equilibrium between (2-hydroxyphenylimino)phosphorane *(21a)* and 1,3,2-benzoxazaphospholine *(21b)* has been studied in thirteen solvents by NMR spectroscopy [80b]. This equilibrium is shifted towards the ring-form *(21b)* in hydrogen-bond acceptor solvents (*e.g.* tris-*n*-propylamine, dimethyl sulfoxide), compared to inert solvents such as benzene or acetone. Therefore, depending on substituents and solvents, it is possible to prepare either iminophosphoranes or benzoxazaphospholines [80b].


(21a) *(21b)*

Further remarkable examples of solvent-dependent ring/chain tautomeric equilibria can be found in references [156–158, 210].

The positions of *metallotropic tautomeric equilibria* can also be strongly solvent-dependent [160–163]. Metallotropic transformations of the σ,σ-type are related to prototropic tautomeric equilibria whereby the mobile hydrogen atom is replaced by an organometallic group. Metallotropic reactions also include π,π- and σ,π-transitions depending on the nature of the bond formed by the metal [160]. Two examples of σ,σ-type metallotropic equilibria will conclude this Section.

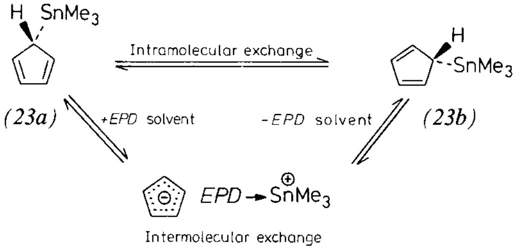
The metallotropic C → O transition of the trimethylstannyl group of liquid trimethyl-phenacyltin *(22a)* to give the O-isomer *(22b)* has been found to be solvent-dependent [161].



(22a) *(22b)*

As expected, the relative concentration of the more dipolar C-isomer *(22a)* increases with increasing solvent polarity (concentration of *(22a)* in cmol/mol): C_6H_{12} (74) < pure liquid (78) < C_6H_6 (81) < $ClCH_2CH_2Cl$ (83) < $CHCl_3$ (95) < CH_3COCH_3 (>99) [161].

Dynamic exchange of the trimethylstannyl substituent in cyclopenta-1,3-dienyl-trimethylstannane *(23a)* (and in cyclonona-1,3,5,7-tetraenyl-trimethylstannane) proceeds in less polar, weakly coordinating solvents such as tetrahydrofuran, 1,2-dimethoxyethane, trichloromethane, and dichloromethane through an intramolecular, orbital-symmetry controlled sigmatropic reaction. Addition of EPD solvents such as



(23a) *(23b)*

(23c)

hexamethylphosphoric triamide or *N*,*N*-dimethylformamide to the tetrahydrofuran solution of *(23a)* shifts the equilibrium in favour of the ion pair *(23c)*, thus facilitating an intermolecular, dissociative mechanism for the substituent exchange [162].

In general, polar but weakly coordinating solvents will facilitate intramolecular metallotropic processes. Solvents exhibiting both high polarity and high coordinating capacity (EPD solvents), capable of inducing the heterolysis of the carbon-metal bond, should accelerate metallotropic processes through an intermolecular dissociative mechanism.

4.4 Solvent Effects on Other Equilibria

Not only tautomeric equilibria are subject to considerable solvent effects. Other equilibria, such as rotational and conformational equilibria [81–83], *cis*/*trans* (or *E*/*Z*) isomerization, valence isomerization [84], ionization, dissociation, and association [85] (some of which are considered in Section 2.6), complex equilibria [86, 163, 262, 263], acid/base equilibria [264, 265] *etc.*, are also strongly affected by the medium. Only a small number of representative examples will be considered in this Section in order to give an idea of how solvents can affect these different kinds of equilibria.

4.4.1 Solvent Effects on Brønsted Acid/Base Equilibria [8–13, 104–108, 264, 265]

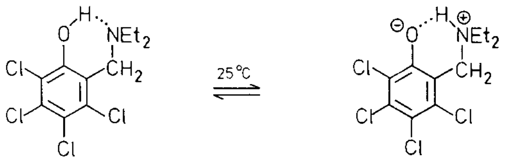
Sections 3.3.1 and 4.2.1 dealt with Brønsted acid/base equilibria in which the solvent itself is involved in the chemical reaction as either an acid or a base. This Section describes some examples of solvent effects on proton-transfer (PT) reactions in which the solvent does not intervene directly as a reaction partner. New interest in the investigation of such acid/base equilibria in non-aqueous solvents has been generated by the pioneering work of Barrow *et al.* [164]. He studied the acid/base reactions between carboxylic acids and amines in tetra- and trichloromethane. A more recent compilation of Brønsted acid/base equilibrium constants, determined in up to twelve dipolar aprotic solvents, demonstrates the appreciable solvent influence on acid ionization constants [264]. For example, the pK_a value of benzoic acid varies from 4.2 in water, 11.0 in dimethyl sulfoxide, 12.3 in *N*,*N*-dimethylformamide, up to 20.7 in acetonitrile, that is by about 16 powers of ten [264].

According to Eq. (4-29), protons can be transferred from Brønsted acids A—H to bases |B *via* the hydrogen-bonded covalent and ionic complexes *(a)* and *(b)*, depending on both the relative acidity and basic strength of A—H and |B, respectively, and the solvation capability of the surrounding medium [265, 266]. Eq. (4-29) is simplified because not only 1:1 complexes but 1:2 and higher complexes can be formed in solution.

$$\text{A-H} + |\text{B} \xrightleftharpoons{\text{Association}} \underset{(a)}{\text{A-H}\cdots\text{B}} \xrightleftharpoons[\text{Transfer}]{\text{Proton}} \underset{(b)}{\text{A}^{\ominus}\cdots\text{H-B}^{\oplus}} \xrightleftharpoons{\text{Dissociation}} \text{A}^{\ominus} + \text{H-B}^{\oplus} \tag{4-29}$$

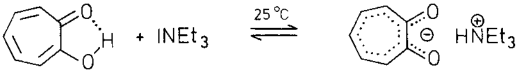
The solvent can influence all three steps of Eq. (4-29): the association, the proton-transfer, and the dissociation step. The main factor which determines the position of the acid/base equilibrium given in Eq. (4-29) is the differential solvation of the covalent and the ionic hydrogen-bonded complexes *(a)* and *(b)*. Both the hydrogen-bonded complex *(a)* and the proton-transfer ion pair *(b)* have been observed in the systems 4-nitrophenol/triethylamine [165], picric acid/triethylamine [166], chloro-substituted phenols/*N*-methylpiperidine or *n*-octylamine [167], and trifluoroacetic acid/pyridine [168]. With increasing solvent polarity, the proton-transfer equilibrium $(a) \rightleftharpoons (b)$ is shifted in favour of the ionic structure *(b)*. Thermodynamic parameters ($K, \Delta H^\circ$) for the formation of hydrogen-bonded complexes of phenol with various bases in different solvents can be found in reference [209]. The strengths of hydrogen bonds between solutes (protonated amines and phenolate ions) in aqueous solution have been studied [220]. Formation of such solute/solute hydrogen bonds in water as solvent requires that competition from hydrogen-bonding of the HBD and HBA molecules to 55 M water must be overcome.

A simple example of an *intra*molecular proton-transfer reaction (thus avoiding the association and dissociation step) is given by the Mannich base *(24)* [169, 170], which can be considered as an analogue of the corresponding intermolecular complexes between phenols and amines [163]. UV/Vis and IR spectroscopic measurements show that this proton-transfer equilibrium is shifted to the right-hand side with increasing solvent polarity (concentration of *(24b)* in cmol/mol): CCl_4 (0) < $CHCl_3$ (15) < CH_2Cl_2 (26) < $ClCH_2CH_2Cl$ (30) < CH_3CN (40) [170]. A linear relationship exists between ln K_{PT} and Onsager's reaction field parameter $(\varepsilon_r - 1)/(2\varepsilon_r + 1)$, demonstrating the presence of nonspecific solute/solvent interactions only in these non-HBD solvents.



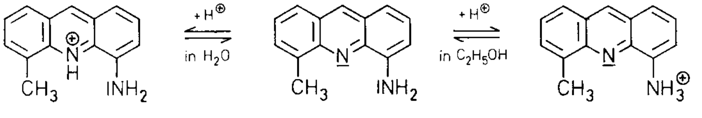
(24a) *(24b)*

Another rather simple example is the acid/base reaction between tropolone and triethylamine, which has been studied using IR and ^1H NMR spectroscopy in various solvents [171].



In non-HBD solvents such as *n*-heptane, tetrachloromethane, diethyl ether, deuterio-trichloromethane, and dimethyl sulfoxide, tropolone transfers its proton to triethylamine to give an ion pair, which is in equilibrium with the non-associated reactants. There is no formation of a hydrogen-bonded complex between tropolone and triethylamine because of the fact that tropolone itself is intramolecularly hydrogen-bonded. The extent of the ion pair formation increases with solvent polarity. In polar HBD solvents such as ethanol, methanol, and water, this proton-transfer equilibrium is shifted completely towards the formation of triethylammonium tropolonate [171].

A peculiar example of a solvent-dependent regiospecific proton-transfer equilibrium is found for 4-amino-5-methylacridine *(25)* [172]. In aqueous hydrochloric acid, the ring nitrogen atom of *(25)* is protonated to give *(25a)*, whereas in ethanolic hydrochloric acid the primary amino group preferentially accepts the proton to give *(25b)*. Without a methyl group in the 5-position (*i.e.* with 4-aminoacridine) only the ring nitrogen atom is protonated in both solvents.



(25a) *(25)* *(25b)*

Obviously, the 5-methyl substituent sterically impedes the ethanol solvation of the $NH^{\oplus}$ form *(25a)*, thus favouring reaction at the more exposed 4-amino group. In water, protonation of the ring nitrogen atom and solvation of the resulting $NH^{\oplus}$ form *(25a)* by the smaller water molecules can take place despite the methyl group [172].

The regioselectivity of protonation of various types of amides has been studied theoretically and experimentally in the gas phase and in water, showing that the site of protonation (acid residue or amide nitrogen) is often altered on going from the gas phase to aqueous solution [267].

4.4.2 Solvent Effects on Lewis Acid/Base Equilibria [106–108, 173, 174, 268]

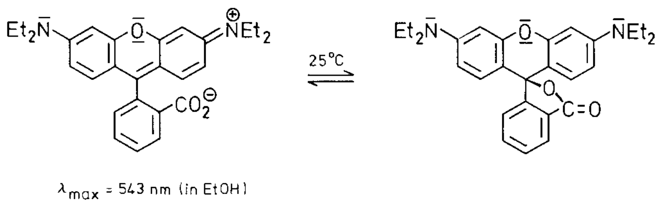
Sections 2.2.6 and 2.6 dealt with Lewis acid/base equilibria in which principally the solvent itself is involved in the chemical reaction, either as a Lewis acid (EPA solvents) or as a Lewis base (EPD solvents). This Section includes some examples of solvent-dependent Lewis acid/base equilibria in which the solvent is not directly involved as the reaction partner, but as the surrounding and interacting medium.

Formally analogous to Eq. (4-29), Eq. (4-30) describes in a simplified manner the reaction between a Lewis acid $A^{\oplus}$ and a Lewis base $|B^{\ominus}$, via tight ion pairs (which can sometimes be considered as EPD/EPA complexes), to give the covalent ionogen A—B [*cf.* also Eq. (2-13) in Section 2.6].

$$\underset{\text{Free Ions}}{A^{\oplus} + |B^{\ominus}} \underset{\text{Dissociation}}{\overset{\text{Association}}{\rightleftharpoons}} \underset{\text{Tight Ion Pair}}{\underset{(a)}{A^{\oplus}|B^{\ominus}}} \underset{\text{Ionization}}{\overset{\text{Electron transfer}}{\rightleftharpoons}} \underset{\text{Ionogen}}{\underset{(b)}{A-B}} \tag{4-30}$$

The position of this equilibrium depends on the electrophilicity or nucleophilicity of $A^{\oplus}$ and $|B^{\ominus}$, respectively, as well as the solvation capability of the surrounding medium. The solvent can influence the association as well as the electron-transfer step (or in the reverse reaction the ionization and dissociation step). The position of the Lewis acid/base equilibrium given in Eq. (4-30) will depend mainly on the differential solvation of the ionic and covalent species *(a)* and *(b)*.

A simple example of an *intra*molecular Lewis acid/base reaction (thus avoiding the association step) is the xanthene dye rhodamine B, which exists in solution either in the red-coloured zwitterionic form *(26a)* or as the colourless lactonic form *(26b)* [175, 221, 222]. Solutions of rhodamine B in non-HBD solvents such as dimethyl sulfoxide, *N,N*-dimethylformamide, 1,4-dioxane, pyridine, and hexamethylphosphoric triamide are entirely colourless, indicating complete conversion into the inner lactone *(26b)*. Protic

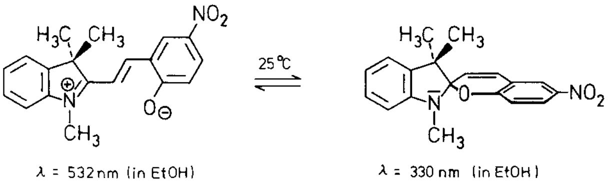


(26a) *(26b)*

solvents stabilize the zwitterion and shift the equilibrium toward the highly coloured zwitterionic form (concentration of *(26a)* in cmol/mol): $(CH_3)_3COH$ (1.6) < n-C_3H_7OH (65.2) < C_2H_5OH (70.6) < H_2O (81.5) < $HCONH_2$ (88.5) < CH_3OH (89.2) < CF_3CH_2OH (94.6) [221]. The conversion of *(26b)* to *(26a)* is sensitive to the presence of hydroxy groups to such an extent that a white piece of cellulose turns red on contact with a colourless solution of *(26b)* [175]. Addition of acids to solutions of rhodamine B in either non-HBD or protic solvents produces an intensely coloured cation ($\lambda_{max} = 553$ nm in ethanol [222]) by protonation of the carboxylate group of *(26a)* [221, 222]. The application of increasing external pressure to alcoholic solutions of rhodamine B shifts its equilibrium in favour of the zwitterion *(26a)*, which causes a larger "electrostriction" of the surrounding solvation shell than lactone *(26b)* (see Section 5.5.11) [269]. Rational design of the rhodamine B structure by fine tuning of the substituents in the 3,6-positions of the xanthylium ring can lead to compounds that form the coloured form only under certain conditions [270].

Analogous solvent-dependent intramolecular Lewis acid/base equilibria between lactonic and zwitterionic forms have also been found for the xanthene dyes fluorescein and eosin [176]. Structurally related colourless 3,3-diarylphthalides form highly coloured triarylcarbenium ions by interaction with acidic compounds such as phenols. This acid/base reaction has been used to design optochemical sensors suitable for the detection of vapours of polar solvents in the air or in waste water [271].

The colourless spiropyran *(27b)* is another important example of an intramolecular Lewis acid/base equilibrium. In solution, it is in equilibrium with the coloured zwitterionic species *(27a)* [99].



(27a) *(27b)*

The thermodynamic data presented in Table 4-6 reveal that the change in equilibrium constant is in the direction anticipated, with more ionization occurring as the

Table 4-6. Thermodynamic data for the intramolecular Lewis acid/base reaction *(27a)* $\rightleftharpoons$ *(27b)* at 25 °C [99a].

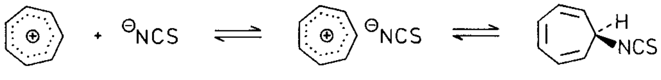
Solvents	$K \cdot 10^5$ [a]	ΔG° / (kJ · mol^{-1})	ΔH° / (kJ · mol^{-1})	$T \cdot \Delta S^\circ$ / (kJ · mol^{-1})
Benzene	4.1	25.1	18.4	−6.7
Trichloromethane	9.8	22.6	2.2	−20.0
Acetone	134	16.3	7.5	−8.8
Ethanol	843	11.7	8.8	−3.0

[a] $K = [(27a)]/[(27b)]$.

solvent becomes more polar. Accordingly, the Gibbs energy change decreases monotonically with increasing solvent polarity.

The negative entropy changes observed in all solvents are a result of an ordering of solvent molecules in the environment of the zwitterionic form. Since polar solvents are *per se* more structured than apolar solvents, proportionally less negative entropy changes are obtained in more polar solvents such as ethanol. The rate of the spiropyran/merocyanine interconversion is also solvent-dependent, as is the position of the visible absorption band of *(27a)*, which, as is typical for a merocyanine, exhibits a pronounced negative solvatochromism (see Section 6.2) [99c, 99d].

A further illustrative example is the *inter*molecular Lewis acid/base reaction between tropylium and isothiocyanate ions via tight ion pairs *(28a)* to give 7-isothiocyanatocycloheptatriene *(28b)* [177].



(28a) *(28b)*

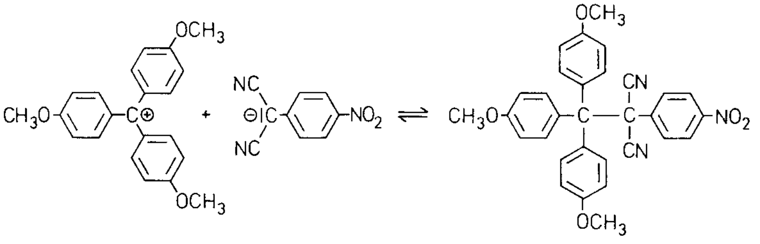
In solution, both the ionic and covalent forms of tropylium isothiocyanate have been directly observed by low-temperature ^{13}C and ^{1}H NMR spectroscopy. In deuterio-trichloromethane and in diethyl ether, the covalent form *(28b)* is exclusively present below −10 °C. With increasing temperature and with increasing solvent polarity (addition of CD_3CN to the solution of *(28b)* in $CDCl_3$), the relative concentration of the ionic *(28a)* increases. In pure acetonitrile, the ionic form *(28a)* dominates. Evidence that the ionic form is a tight ion pair in these solvents is given by NMR and UV/Vis spectra (*e.g.* the occurrence of a charge-transfer absorption between isothiocyanate and tropylium ion). Accordingly, the Gibbs energy of activation for the random migration of the isothiocyanato group around the cycloheptatriene ring decreases with increasing solvent polarity [177]. That is, the stabilization of the ionic *(28a)* by polar solvents corresponds to a similar stabilization of the preceding dipolar activated complex.

Analogous results have been obtained for the Lewis acid/base equilibrium between ionic tropylium azide and covalent 7-azidocycloheptatriene [178]. Again, in less polar solvents such as deuterio-trichloromethane and even [D_6]acetone, no ionization to give the tropylium and azide ions could be detected. Dipolar liquid sulfur dioxide, however, induces complete ionization at low temperature (−70 °C).

An interesting example of a Lewis acid/base reaction between neutral reactants is the formation of tris(*n*-butyl)phosphonium-dithiocarboxylate, $(n\text{-Bu})_3P^+{-}CS_2^-$, from tris(*n*-butyl)phosphane and carbon disulfide in solution. As expected, this equilibrium is strongly shifted in favour of the dipolar zwitterion with increasing solvent polarity (diethyl ether → dimethyl sulfoxide) [272, 273].

The examples mentioned above are characterized by heterolysis of C—O, C—N, or C—P bonds. Finally, a solvent-dependent Lewis acid/base reaction between carbocations and carbanions, produced by heterolysis of a weak C—C bond, is presented (*cf.* also Section 2.6).

A large variety of different combinations of charge-delocalized carbenium ions with carbanions has been investigated in order to find a well-balanced equilibrium mixture of free ions or ion-pairs and a neutral covalent product with clean C—C bond formation in solution [179]. The equilibrium between (4-nitrophenyl)malononitrile anions and trianisylmethyl cations [179] or triphenylcyclopropenium cations [180] was finally found to be the most useful. The Lewis acid/base equilibrium between the (4-nitrophenyl)malononitrile anion and the triphenylcyclopropenium cation has already been discussed in Section 2.6 as an example of a solvent-dependent ionization reaction. The first-mentioned reaction can be represented as:



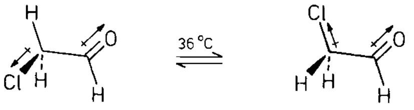
(29a) *(29b)*

A [D_2]dichloromethane solution at room temperature contains 70 cmol/mol ionic *(29a)* and 30 cmol/mol covalent *(29b)*. With decreasing solvent polarity, the equilibrium is shifted toward the right-hand side (concentration of *(29b)* in cmol/mol): CD_2Cl_2 (30) < CD_3CN (55) < CD_3COCD_3 (85) < $(CD_2)_4O$ (100). In [D_8]tetrahydrofuran solution, only the covalent *(29b)* is present [179].

4.4.3 Solvent Effects on Conformational Equilibria [81–83, 181–184]

Changing the medium has a particular effect on various conformational and rotational equilibria [83, 181–184]. Because the Gibbs energy differences between conformational isomers are almost always very small (*ca.* 0…13 kJ/mol) and the solvation enthalpies of dipolar solutes are at least as large and often much larger than this, the medium can affect conformational equilibria very considerably. It is often found that one conformer or rotamer is predominant in one medium but not in another. This has led to the long-established rule that the conformer (rotamer) of higher dipole moment is more favored in media of high relative permittivity [83].

For example, the standard molar Gibbs energy for the *rotational* equilibrium *(30a)* ⇌ *(30b)* of chloroacetaldehyde is strongly solvent-dependent, as shown in Table 4-7 [87].



(30a) *(30b)*

Inspection of Table 4-7 reveals a substantial increase in the more dipolar rotamer *(30b)* as the polarity of the solvent increases. In saturated hydrocarbon solvents (the

Table 4-7. Solvent dependence of the relative rotamer population (mole fraction of *(30b)*) and the standard molar Gibbs energy differences between rotamers of chloroacetaldehyde at 36 °C [87].

Solvents	$\dfrac{x\ (30b)}{(\text{cmol} \cdot \text{mol}^{-1})}$	$\dfrac{\Delta G^\circ}{(\text{kJ} \cdot \text{mol}^{-1})}$ for $(30a) \rightleftharpoons (30b)$
trans-Decalin	44	−1.26
Cyclohexane	45	−1.30
Tetrachloromethane	47	−1.46
Trichloromethane	55	−2.34
Benzene	58	−2.68
Dichloromethane	61	−2.97
Acetone	72	−4.18
Acetonitrile	76	−4.60
N,*N*-Dimethylformamide	79	−5.23
Dimethyl sulfoxide	84	−6.07
Formamide	85	−6.28

least polar solvents used), *(30b)* is only favored by *ca.* 1.3 kJ/mol, whereas in formamide (the most polar solvent used) it is favored by *ca.* 6 kJ/mol. In view of the higher dipole moment of *(30b)* over *(30a)*, this appears reasonable [87].

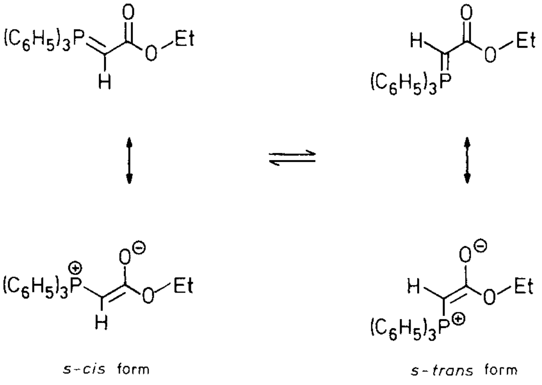
A second well-studied example of a solvent-dependent *rotational* equilibrium is that of 1,2-dichloroethane, which exists preferentially in the apolar *trans* (or antiperiplanar) form ($\mu = 0$) and the dipolar *gauche* (or synclinal) form ($\mu \approx 2.6$ D). According to thorough experimental measurements and theoretical calculations [274–279], the *trans* form is the more stable conformer in the gas phase (ca. 79%). In solution, the population of the *trans* conformer decreases with increasing solvent polarity (ca. 26% in acetonitrile) in favour of the more dipolar *gauche* conformer, as expected. Interestingly, even hydrocarbons [276] and noble gases as cryogenic solvents (liquefied Xe, Kr, and Ar) [277] shift this equilibrium slightly in favour of the *gauche* conformer because of polarization and weak dipole/induced dipole solute/solvent interactions. Thus, noble gas solutions do not behave as "pseudo gas phase" model solutions, as is often assumed; they can significantly shift rotational equilibria if the conformers have different dipolarities, as shown in this case [277].

Another remarkable example is the medium effect on the rotational equilibrium of ethoxycarbonylmethylene triphenylphosphorane $(31a) \rightleftharpoons (31b)$. As the polarity of the solvent increases, the equilibrium shifts in the direction of the *s-trans*-isomer *(31b)*, as shown by the equilibrium constants presented in Table 4-8.

In the *s-cis* rotamer *(31a)* the $P^{\oplus}/O^{\ominus}$ attraction is maximized. Increasing relative permittivity of the solvent reduces the attraction of the opposite charges, resulting in an increase in the amount of *s-trans* rotamer *(31b)*. An exception is found with trichloromethane as solvent ($\varepsilon_r = 4.9$). Here, the *s-trans* isomer is stabilized more effectively than in the more polar acetonitrile ($\varepsilon_r = 35.9$) and nitromethane ($\varepsilon_r = 35.9$). This is obviously due to the fact that trichloromethane associates with the negative oxygen atom through hydrogen bonding. Addition of a HBD solvent such as methanol to the trichloromethane solution enhances the *s-cis* → *s-trans* conversion to an even greater extent.

Table 4-8. Equilibrium constants for the *s-cis*/*s-trans*-isomerization reaction *(31a)* $\rightleftharpoons$ *(31b)* of ethoxycarbonylmethylene triphenylphosphorane in various solvents at −10 … 0 °C [95].

Solvents (deuterated)	$K = [s\text{-}cis]/[s\text{-}trans]$
Tetrachloromethane	6.2
Benzene	5.9
Nitromethane	2.4
Acetonitrile	2.3
Trichloromethane	1.8
Trichloromethane/Methanol (5:1)	0.83
Trichloromethane/LiBr	0.57



(31a) *(31b)*

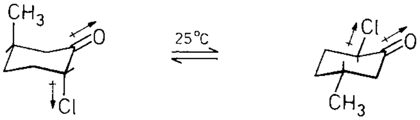
Addition of the extremely polar lithium bromide favours the formation of the *s-trans* isomer even more [95]. Analogous results were obtained with formylbenzylidene triphenylphosphorane [96].

In this context, the solvent influence on the C—N rotational barrier in *N*,*N*-dimethylformamide, $Me_2N—CH{=}O \leftrightarrow Me_2N^+{=}CH—O^-$, is noteworthy [280]. For this rotation, the Gibbs free energy of activation in the gas phase ($\Delta G^{\neq} = 81$ kJ/mol) is much smaller than in polar HBD solvents such as water ($\Delta G^{\neq} = 92$ kJ/mol). Thus, the rate of amide bond rotation decreases as the polarity and the HBD ability of the solvent increases. This can be attributed to the change in dipole moment on rotation, whereby a polar solvent stabilizes the ground state with the higher dipole moment ($\mu = 3.8$ D) in preference to the less dipolar activated complex [280].

Further well-studied examples of solvent-dependent rotational equilibria have been those of furfural [185], the *N*,*N*-dimethylamides of furoic and thenoic acids [186], benzil monoimines [187], and methyl 2-, 3-, and 4-fluorobenzoates [188].

Alicyclic compounds exhibiting *conformational* isomerism are also subject to considerable medium effects [80–83, 182, 184].

One interesting example is (+)-*trans*-2-chloro-5-methylcyclohexanone *(32)*. The sign of the Cotton effect in its ORD spectrum is reversed on transferring it from water to *n*-heptane (molar optical rotation at $\lambda = 330$ nm and 25 °C; $[\Phi]_D = +382$ and -1486, respectively) [189]. This can be ascribed to a diaxial/diequatorial conformational equilibrium *(32a)* $\rightleftharpoons$ *(32b)*, which lies more to the left-hand side in *n*-heptane than in water.



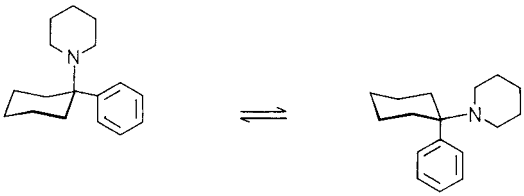
(32a) *(32b)*

Due to the nearly parallel C=O and C—Cl dipole vectors in *(32b)*, the *ee* isomer must have the larger net dipole moment and is therefore better solvated in polar solvents. In nonpolar solvents, the electrostatic repulsion between the two equatorial C=O and C—Cl dipoles in *(32b)* is unfavourable, and the molecule escapes from this situation to give the *aa* isomer *(32a)*, even at the cost of nonbonded axial repulsions [189].

The majority of results obtained for other cyclohexanone derivatives, such as 4-methoxycyclohexanone [94a], a bridged 4-oxacyclohexanone [94b], 2- and 4-halocyclohexanones [190], 2-chloro- [191] and 2-bromocyclohexanone [281] have been similar. The conformational Gibbs energy difference $\Delta G°(e \rightarrow a)$ for 4-methoxycyclohexanone has been determined in thirty-four solvents. It shows a marked sensitivity to solvent change, the axial conformer being the more stable in all but the most dipolar HBD solvents [94a]. It is interesting to note that although the equatorial conformer is the least dipolar one, it is stabilized by polar solvents more effectively than the axial isomer. This is due to the larger quadrupole moment of the equatorial conformer [197].

In the case of diaxial/diequatorial equilibria of *trans*-1,2-dihalocyclohexanes (with and without a 4-*tert*-butyl group), $\Delta G°$ $(aa \rightarrow ee)$ also shows a pronounced dependence on the medium, varying from about 4 kJ/mol in apolar solvents to about −2 kJ/mol in polar solvents [90–94, 192–194]. This is mainly due to the very different dipole moments of the two conformers. In general, the more dipolar diequatorial isomer is favoured in polar solvents.

Another remarkable example is provided by the observation of the strong influence of solvents on the conformation of phencyclidine *(33)*, a drug developed as an anaesthetic, but later withdrawn because of its psychotomimetic effects [195].



(33a) *(33b)*

Table 4-9. Solvent dependence of standard molar Gibbs energy differences between *cis*/*trans*-isomers of 2-isopropyl-5-methoxy-1,3-dioxane at 25 °C [89].

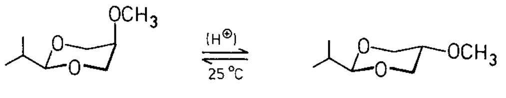
Solvents	$\Delta G^{\circ}_{OCH_3}/(kJ \cdot mol^{-1})$ for *(34a)* $\rightleftharpoons$ *(34b)*[a]
n-Hexane	−4.44
Cyclohexane	−4.31
Tetrachloromethane	−3.77
1,3,5-Trimethylbenzene	−3.64
tert-Butylbenzene	−3.47
Diethyl ether	−3.47
Toluene	−2.97
Tetrahydrofuran	−2.72
Benzene	−2.47
1,1,1-Trichloroethane	−2.43
Acetone	−1.42
Nitrobenzene	−0.84
Deuterio-trichloromethane	−0.79
Trichloromethane	−0.67
Dichloromethane	−0.42
Methanol	−0.13
Acetonitrile	+0.04

[a] $K = [trans]/[cis]$.

In dipolar non-HBD solvents such as [D_6]acetone and [D_3]acetonitrile, the equilibrium is more to the left-hand side than in the less polar [D_2]dichloromethane. Upon transfer from CD_2Cl_2 to an HBD solvent (CD_2Cl_2/CD_3OD, 1:2, cl/L), the equilibrium is shifted substantially to the right-hand side. The ratio *(33b)*/*(33a)* varies from 99:1 in CD_2Cl_2/CD_3OD at −80 °C to 1:1 in CD_3COCD_3/CD_3CN at room temperature. Obviously, conformer *(33b)* with the piperidine ring in the equatorial position is stabilized by hydrogen-bonding in HBD solvents; similar stabilization of the axial piperidine ring in *(33a)* is sterically inhibited. Consequently, it can be expected that the structure of this drug is subject to change on passing through a cell membrane [195].

A thoroughly examined case, namely that of a heterocycloalkane, which involves an axial/equatorial conformational change shall conclude this Section.

The position of the acid-catalyzed equilibrium between *cis*- *(34a)* and *trans*-2-isopropyl-5-methoxy-1,3-dioxane *(34b)* has been determined in seventeen different solvents; *cf.* Table 4-9 [89].



(34a)
axial *cis* isomer
$\mu = 9.5 \cdot 10^{-30}$ Cm

(34b)
equatorial *trans* isomer
$\mu = 4.3 \cdot 10^{-30}$ Cm

Inspection of Table 4-9 reveals that the axial *cis* isomer *(34a)*, which is the conformer with the higher dipole moment, becomes more favoured as the solvent polarity increases. In the most polar solvent studied, acetonitrile, ΔG° is nearly zero. Benzene, toluene, trichloromethane, dichloromethane, and methanol are seen to behave as more polar solvents than their relative permittivities would lead one to predict. The deviation for trichloromethane was particularly difficult to explain (for a full discussion, see reference [89]). In general, good correlations between $\Delta G^{\circ}_{\mathrm{OCH_3}}$ values and other solvent-dependent phenomena such as absorption maxima of solvatochromic dyes, rate constants of reactions involving dipolar activated complexes, *etc.*, were obtained [89]. Because of this, it was recommended that the solvent scale obtained should be used as an empirical scale of solvent polarity, useful for the prediction of medium effects on other solvent-dependent reaction rates or equilibria [89] (*cf.* Section 7.2).

The so-called *anomeric effect*, *i.e.* that polar substituents X attached to a carbon α to a heteroatom Y ($\mathrm{Y} = \mathrm{O}$, N) in a six-membered ring preferentially reside in the axial position, has been shown to be solvent-dependent [82, 83, 217, 282–286]. In general, the position of an anomeric equilibrium shifts in favour of the equatorial anomer with increasing solvent polarity. The anomeric effect is thought to be the result of either molecular orbital interactions, which stabilize the axial conformer, or electrostatic interactions, which destabilize the equatorial conformer [82, 282].

The MO explanation for the anomeric effect considers the n–σ^* overlap between the lone-pair of Y and the vacant σ^* orbital of the C—X bond. This stabilizing interaction is more effective when X is axial and thus the axial conformer is favoured. The electrostatic explanation invokes the destabilizing interaction between the dipole moment of the C—X bond and the dipole moment resulting from the C—Y bond and the lone-pairs of Y. Such dipole/dipole interactions are minimized when X is axial and again the axial conformer is preferred in the gas phase or in nonpolar solvents. It is not so easy to distinguish between the relative importance of each interaction. However, the observation that the axial preference is diminished by increasing solvent polarity is best explained by the electrostatic interaction model [82, 282–284]. The unfavourable electrostatic dipole/dipole repulsion in the equatorial anomer decreases with increasing solvent polarity, and hence the equilibrium shifts towards the equatorial conformer in polar solvents. This solvent-dependent anomeric effect has been particularly well studied with 4,6-dimethyl-2-methoxytetrahydropyran [283, 284] and 2-methoxy-1,3-dimethylhexahydropyrimidine [282].

Another well-known example is D-glucopyranose, the anomeric equilibrium mixture of which is made up of 36% of the axial α anomer and 64% of the equatorial β anomer at 20 °C in water as a polar solvent ($\varepsilon_{\mathrm{r}} = 78$), with $\Delta G(\alpha \rightarrow \beta) = -1.4$ kJ/mol [82]. This is in agreement with free-energy simulations with an empirical force field [285] and quantum-chemical calculations [286], showing that the preference of D-glucopyranose for the β-anomer in water is mainly due to electrostatic solvation and hydrogen-bonding effects, which stabilize the more dipolar β-anomer better than the α-anomer.

Numerous attempts have been made to calculate relative conformer energies in solution, using physical properties of solutes and solvents, in order to derive theoretical procedures or models with predictive ability [83, 88, 182, 188, 190, 192, 196–198, 274–281]. The methods used include quantum-chemical calculations (*e.g.* [198]), statistical mechanics and molecular dynamics calculations (*e.g.* [182]), direct dipole-dipole methods (*e.g.* [83]), and reaction field methods based on Onsager's theory [199] of dipolar molecules in the condensed phase (*e.g.* [83, 88, 188, 190, 194, 197]). In general, a quantitative description of solvent effects on conformational equilibria can be given on the basis of these methods, except in cases where specific solute/solvent interactions occur.

According to the reaction field method, the electrostatic stabilization of a solute molecule, located in the centre of a spherical cavity, with dipole moment μ and radius r in a solvent modeled as a uniform dielectric with relative permittivity ε_r, can be expressed as in Eq. (4-31) (ε_0 = permittivity of vacuum).

$$\begin{aligned}\Delta G^\circ_{\text{solv}} &= G^\circ_{\text{vapour}} - G^\circ_{\text{solution}} \\ &= -\frac{N_A}{4\pi \cdot \varepsilon_0} \cdot \frac{\varepsilon_r - 1}{2\varepsilon_r + 1} \cdot \frac{\mu^2}{r^3}\end{aligned} \tag{4-31}$$

The difference in the Gibbs energy of solvation, $\Delta G^\circ_{\text{solv}}$, for two species in equilibrium, $A \rightleftharpoons B$, is then given by Eq. (4-32), assuming that they have the same size.

$$\Delta\Delta G^\circ_{\text{solv}} = -\frac{N_A}{4\pi \cdot \varepsilon_0} \cdot \frac{\varepsilon_r - 1}{2\varepsilon_r + 1} \cdot \left(\frac{\mu_A^2}{r^3} - \frac{\mu_B^2}{r^3}\right) \tag{4-32}$$

Qualitatively, Eq. (4-32) predicts that the more dipolar isomer will be preferentially stabilized in more polar media. Quantitatively, the expression significantly overestimates the solvent effects obtained experimentally for conformational equilibria [182]. Further modifications are necessary, *e.g.* adjustment for back-polarization of the solute by its own reaction field, inclusion of the effect of the solute's quadrupole moment on the reaction field [197], *etc.* Specific solute-solvent interactions, such as those with HBD solvents, cannot be treated with this reaction field theory. For a more detailed discussion, see references [83, 182].

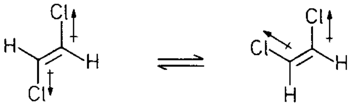
A purely empirical correlation between the $\Delta\Delta G^\circ_{\text{solv}}$ of equilibria such as $A \rightleftharpoons B$ and solvent polarity has been given by the parabolic Eq. (4–33), where $X = (\varepsilon_r - 1)/(2\varepsilon_r + 1)$ and, in the majority of cases, $C = 0.5 = \lim\limits_{\varepsilon_r \to \infty} X$ [196].

$$\Delta\Delta G^\circ_{\text{solv}} = A + B \cdot \sqrt{C - X} \tag{4-33}$$

If $X = 0$, the A parameter should be regarded as the extreme $\Delta\Delta G^\circ_{\text{solv}}$ value for solvents with infinitely large polarity, and the B parameter could be considered as a measure of the susceptibility of the equilibrium to changes of solvent polarity. Eq. (4-33) has been successfully applied to various conformational and tautomeric equilibria [196].

4.4.4 Solvent Effects on *cis/trans* or *E/Z* Isomerization Equilibria [82, 200]

One of the simplest examples of a *cis/trans* or *E/Z* isomerization equilibrium is represented by *trans-* *(35a)* and *cis*-1,2-dichloroethene *(35b)*. In the gas phase at 185 °C, the equilibrium mixture contains 63.5 cmol/mol of the thermodynamically more stable *cis*-isomer *(35b)* [201].



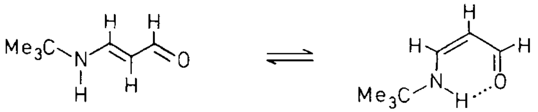
(35a) $\mu = 0\ \mathrm{C\,m}$

(35b) $\mu = 6.3 \cdot 10^{-30}\ \mathrm{C\,m}$

Due to the high activation barrier for *cis*/*trans* isomerization reactions at carbon-carbon double bonds (*ca.* 260–270 kJ/mol [82]), it is often impossible to measure directly the non-catalyzed thermal equilibration reaction in solution. For 1,2-dichloroethene, however, the relative stability of its *cis* and *trans* isomers in various solvents has been determined by means of calorimetric measurements of heats of solution [202]. Surprisingly, these measurements show a quite similar solvent effect on both diastereomers, even though the *cis* isomer is a dipolar molecule and the *trans* isomer is not. Therefore, the position of this *cis*/*trans* equilibrium should not be very solvent-dependent.

One reason for this at first sight unexpected result is the fact that probably 70...90% of the solute/solvent interaction term is caused by London dispersion forces, which are more or less equal for the *cis* and *trans* isomers. Another important reason is that one has to take into account higher electric moments: the *trans* isomer has a quadrupole moment, and the *cis* isomer also has moments of a higher order than two. Calculations of solute/solvent interactions of both diastereomers using a reaction field model led to the conclusion that the quadrupolar contribution of the *trans* isomer is comparable to the dipolar contribution of the *cis* isomer. It has been pointed out that the neglect of solute/solvent interactions implying higher electric moments than the dipole moment can lead to completely false conclusions [202].

Unlike those for *cis*/*trans* isomers, the activation barriers separating *s-cis* and *s-trans* isomers are usually small (*ca.* 40...50 kJ/mol); the Gibbs energy differences for *s-cis* and *s-trans* isomers are also small (*ca.* 4...20 kJ/mol). For example, a more easily measurable *cis*/*trans* isomerization reaction can be carried out with 3-*tert*-butylaminopropenal *(36)* [203].



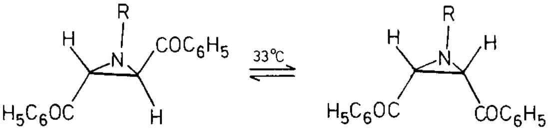
(36a) *E-s-E* form

(36b) *Z-s-Z* form

According to its ^{13}C and ^{1}H NMR spectra, this vinylogous amide exists as the *E-s-E* form in polar solvents such as [D$_4$]methanol, and as a mixture of *Z-s-Z* and *E-s-E* isomers in nonpolar solvents such as deuterio-trichloromethane (30 cmol/mol *(36a)* and 70 cmol/mol *(36b)*). As expected, the more dipolar *E-s-E* form is stabilized in polar solvents (dipole moment of the related *E-s-E* 3-dimethylaminopropenal $21 \cdot 10^{-30}$ Cm).

Experimental and theoretical studies on the solvent influence on molecular geometries and *cis/trans* isomerization processes of other so-called push-pull ethenes, $R_2N{-}CH{=}CH{-}A \leftrightarrow R_2N^+{=}CH{-}CH{=}A^-$ (with $A = NO_2$, CHO, CN, *etc.*), have been collected in references [287, 288]. The barriers to isomerization about the C=C bonds of these acceptor-substituted enamines are considerably smaller than those for simple ethenes such as 2-butene ($E_a = 259$ kJ/mol [82]), owing to a significant contribution of the mesomeric zwitterionic structure to the electronic ground state. Increasing solvent polarity increases the contribution of this dipolar mesomeric structure, and hence leads to a decrease in the barrier to C=C isomerization and a simultaneous increase in the barrier to rotation about the C—N bond [288]. The calculated sequence of solvent stabilization for such acceptor-substituted enamines is: (activated complex for C=C rotation) $\gg E$ form $> Z$ form $>$ (activated complex for C—N rotation). Obviously, the activated complex for isomerization about the C=C bond corresponds to a full zwitterion with maximal solvent stabilization [288].

Finally, a *cis/trans* isomerization process of a heterocycloalkane is presented. The *cis/trans* isomer ratios of 2,3-dibenzoyl-1-benzylaziridine *(37)* have been determined by means of ^{1}H NMR measurements [97] ($R = CH_2C_6H_5$).



(37a)
$\mu = 8.7 \cdot 10^{-30}$ Cm

(37b)
$\mu = 15.8 \cdot 10^{-30}$ Cm

This isomerization reaction passes through *cis/trans*-isomeric open-chain azomethine-ylides, which arise from conrotatory ring-opening at the C—C bond [98]. The equilibrium constants range from 5.25 in dimethyl sulfoxide to 0.32 in *tert*-butanol, as shown in Table 4-10, and approximately parallel the polarities of the solvents used. The more dipolar *cis*-aziridine *(37b)* is the more stable isomer in polar solvents; the reverse is true for the less dipolar *trans*-aziridine *(37a)*. The isomer ratio is 1.63 in methanol (corresponding to 62 cmol/mol *cis* isomer); this is in close agreement with the separately determined solubility ratio of 1.50 (corresponding to 60 cmol/mol *cis* isomer). This close agreement of the ratios of the solubilities of the two isomers with their equi-

Table 4-10. Equilibrium constants and mole fractions of *(37b)* in various solvents for the base-catalyzed *trans/cis*-isomerization *(37a)* $\rightleftharpoons$ *(37b)* of 2,3-dibenzoyl-1-benzylaziridine at 33 °C [97].

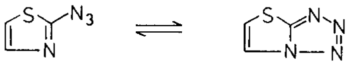
Solvents	x *(37b)*/(cmol · mol^{-1})	$K = [cis]/[trans]$
tert-Butanol	24	0.32
Ethanol	45	0.82
Methanol	62	1.63
Dimethyl sulfoxide	84	5.25

librium constants is a modern example of a long recognized phenomenon [37]; *cf.* Table 4-3 and Eq. (4-24).

4.4.5 Solvent Effects on Valence Isomerization Equilibria [84]

Valence isomerization reactions interconvert so-called valence isomers by simple reorganization of some of the bonding electrons, without any atom migration. Since both valence isomers may have different structures and thus different physical properties (*e.g.* different dipole moments) it is to be expected that solvents should influence the equilibrium between non-degenerate isomers.

For example, ^{1}H NMR measurements showed that the azido/tetrazole equilibrium of thiazolo[2,3-*e*]tetrazole *(38b)* is considerably affected by the medium [100].



(38a) *(38b)*

Whereas in the gas phase and in nonpolar solvents such as tetrachloromethane and benzene, the 2-azidothiazole *(38a)* is the more stable isomer, in polar solvents such as dimethyl sulfoxide and hexamethylphosphoric triamide the bicyclic valence isomer *(38b)* is the dominant species [100]. This result is in line with the fact that the dipole moment of phenyl azide ($\mu = 5.2 \cdot 10^{-30}$ Cm) is smaller than that of cyclic 1,2,3-benzotriazole ($\mu = 13.7 \cdot 10^{-30}$ Cm). Similar results have been obtained for the valence isomers of 3-azidopyrazine-1-oxide [204].

Another remarkable example is 2,4,6-tri-*tert*-butyl-*N*-thiosulfinylaniline *(39a)*, which is in equilibrium with its valence isomer *(39b)* in solution, while in the solid state only *(39b)* exists [205]. The equilibrium ratio *(39b)*/*(39a)* is subject to a considerable

(39a) *(39b)*

$\mu \approx 5 \cdot 10^{-30}$ Cm $\mu \approx 10 \cdot 10^{-30}$ Cm

solvent effect: the mole fraction of *(39b)* in *n*-hexane solution is 86 cmol/mol and in acetonitrile solution 96 cmol/mol. Polar solvents enhance the preference for the cyclic isomer *(39b)*, mainly due to its larger dipole moment [205]. This is noteworthy because the aromaticity of the benzene ring is destroyed in *(39b)*.

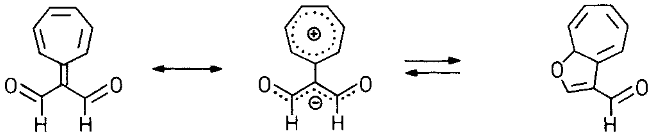
In the case of the oxepin/benzene oxide valence isomerization *(40a)* $\rightleftharpoons$ *(40b)*, it has been found by UV/Vis measurements that, with *iso*-octane as the solvent, only about 30 cmol/mol benzene oxide is present, whereas in water/methanol (85:15, cL/L) the benzene oxide portion rises to about 90 cmol/mol [101]. Increasing solvent polarity

(40a) *(40b)*

shifts this equilibrium towards the more dipolar benzene oxide isomer, in agreement with quantumchemical MNDO calculations [206]. These calculations have shown that in the gas phase *(40a)* is more stable than *(40b)*, but that *(40b)* is more stabilized in polar media.

The behaviour of the corresponding hexafluoro derivative of *(40b)* in solution is somewhat different: solutions of hexafluorobenzene oxide in nonpolar solvents are stable at room temperature. In acetonitrile or acetone, the hexafluorobenzene oxide rearranges spontaneously to hexafluorocyclohexa-2,4-dienone and not to hexafluorooxepin. However, ^{19}F NMR measurements in chlorobenzene at various low temperatures indicate the existence of a dynamic equilibrium between perfluorobenzene oxide and perfluorooxepin [289].

A further example is the reversible valence isomerization equilibrium between the dipolar 8,8-diformylheptafulvene *(41a)* and the less dipolar 8a*H*-cyclohepta[*b*]furan-3-carbaldehyde *(41b)* [212].



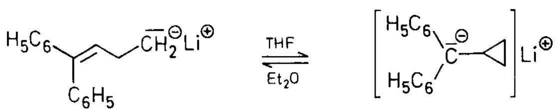
(41a) *(41b)*

$\mu = 17.5 \cdot 10^{-30}$ Cm (5.2 D)

In deuterium oxide, only *(41a)* could be detected by ^{1}H NMR spectroscopy. In less polar solvents, such as perdeuterated acetonitrile, acetone, and benzene, the mole fraction of *(41a)* decreases to $x = 69$, 58, and 54 cmol/mol, respectively. Eventually, in tetrachloromethane, the less dipolar *(41b)* predominates; $x(41b) = 63$ cmol/mol [212].

Finally, the allylcarbinyl/cyclopropylcarbinyl anion rearrangement *(42a)* $\rightleftharpoons$ *(42b)* should be mentioned as a striking example of a solvent-dependent valence isomerization [207].

The deep-red lithium cyclopropyl-diphenylmethanide *(42b)*, which is stable in tetrahydrofuran solution, opens completely to the colourless lithium (3,3-diphenylprop-2-enyl)methanide in diethyl ether. The *retro* rearrangement to *(42b)* can be achieved simply by adding tetrahydrofuran to the solution of *(42a)* in diethyl ether [207]. Obviously, tetrahydrofuran, which is the better cation-solvating EPD solvent, makes the carbon-lithium bond in *(42a)* more ionic, thus favouring the ring closure to *(42b)*, which has a more delocalized negative charge.



(42a) *(42b)*

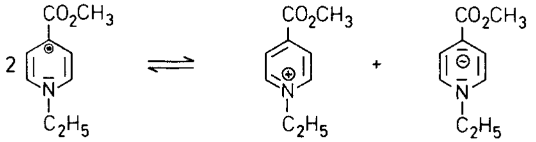
A closely related example, the equilibrium between tight and solvent-separated ion pairs of lithium 10-phenylnonafulvene-10-oxide, has already been given in Section 2.6 (formulas *(2b)* and *(3b)*). Depending on the solvent-influenced association with the lithium cation, the anion exists either as the aromatic benzoyl [9]annulene anion or as the olefinic nonafulvene oxide anion [208].

The first metallaquinone (*i.e.* a compound in which one of the 1,4-benzoquinone oxygen atoms is replaced by ruthenium) has recently been synthesized and exhibits another interesting type of solvent-dependent valence isomerization [290]. This metallaquinone interconverts between a quinoid-Ru(0) carbene form in nonpolar solvents (reddish-orange solution in benzene) and a zwitterionic Ru(II)-phenolate form in polar solvents (yellow solution in methanol).

4.4.6 Solvent Effects on Electron-Transfer Equilibria

Examples of solvent effects on electron-transfer equilibria between organic species (*i.e.* redox and disproportionation reactions) are rather scarce.

A nice example is the disproportionation reaction of the 1-ethyl-4-(methoxycarbonyl)pyridinyl radical *(43)*, which leads to the ion pair *(43a)*/*(43b)* [215, 216].



(43) *(43a)* *(43b)*

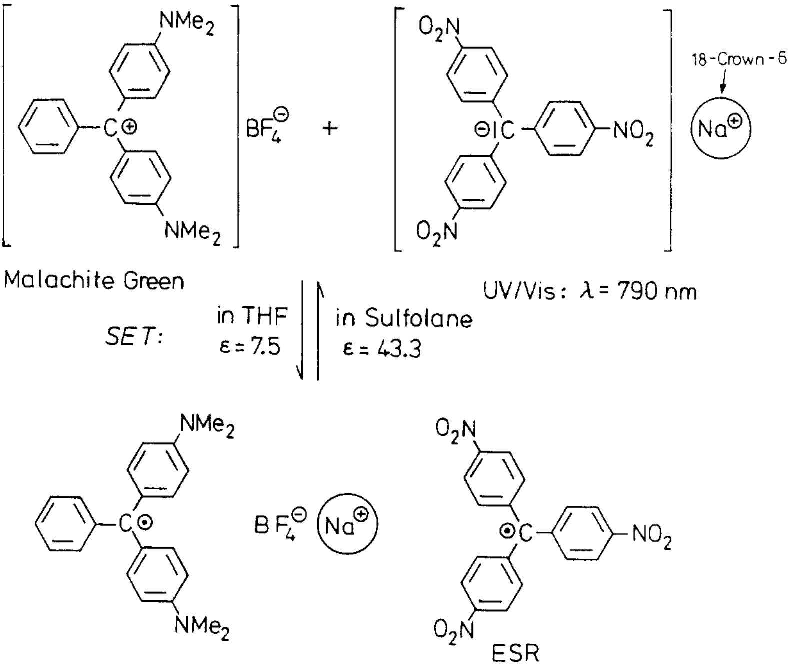
Solvent	$HCON(CH_3)_2$	CH_3CN	C_2H_5OH	$HCONH_2$	H_2O
$K=\frac{[\text{ion pair}]}{[\text{radical}]}$	$4\cdot10^{-13}$	10^{-13}	10^{-8}	10^{-6}	$5\cdot10^{-5}$

As expected, an increase in solvent polarity shifts this equilibrium from the left to the right-hand side due to the better solvation of the ion pair as compared to the neutral radical [215].

From equilibrium constants for transfer from water to vapour, determined by dynamic vapour pressure measurements, the hydrophilic character of 1,4-benzoquinone and 1,4-hydroquinone has been estimated [227]. 1,4-Benzoquinone is about 3.2 orders of magnitude less strongly solvated by water than is 1,4-hydroquinone. Because 1,4-hydroquinone is so much more strongly solvated than 1,4-benzoquinone, its reducing power in water is less by *ca.* 18 kJ/mol (0.2 V) than it would be in a medium of unit relative permittivity. Therefore, the redox potentials of biologically important hydroquinone/quinone systems should be strongly affected by the surrounding medium, particularly if the corresponding electron-transfer reaction is part of an electron transport chain embedded in mitochondrial inner membranes [227].

The redox properties of tetraphenylporphyrin have been studied in dimethyl sulfoxide (DMSO) and more polar water/DMSO mixtures. Increasing solvent polarity (*i.e.* increasing water content) shifts the reduction potentials to more positive values and makes the reduction step more favourable, since a better solvated anion is formed from a neutral species [291].

An interesting solvent-dependent, reversible electron-transfer equilibrium between a pair of resonance-stabilized carbocations and carbanions and the corresponding carbon radicals has been described by Arnett *et al.* [229]. Addition of bis(4-dimethylaminophenyl) phenylcarbenium tetrafluoroborate (malachite green) to sodium tris(4-nitrophenyl) methanide leads, in tetrahydrofuran, to the corresponding triphenylmethyl radicals by single-electron transfer, whereas in sulfolane as solvent only traces of the radicals could be detected by ESR spectroscopy. That is, in the more polar solvent sulfolane, both the carbocation and carbanion are stabilized by electrostatic ion/solvent interactions, whereas in the less polar tetrahydrofuran single-electron transfer from the carbanion to the carbocation occurs readily to produce trityl radicals. Dilution of the radical solution in tetrahydrofuran with sulfolane leads to a sharp decrease of the ESR signal and to an increase of the carbanion absorption in the UV/Vis spectrum, in accordance with a reversible electron-transfer equilibrium [229].



Another hydrocarbon salt, composed of the tri(cyclopropyl)cyclopropenylium cation and Kuhn's anion, which can exist in all three types of elementary organic species (*i.e.* as an ionic, radical, and covalent compound) in a solution equilibrium, depending on the solvent, has already been mentioned in Section 2.6 [292].

Comprehensive reviews on the solvent influence on electron- and charge-transfer reactions between organic electron-donor and acceptor compounds, resp., [230], as well as on the redox properties of predominately inorganic redox couples [293] can be found in the literature.

4.4.7 Solvent Effects on Host/Guest Complexation Equilibria [294–299]

The formation of supramolecular host/guest complexes between two or more neutral or charged species, which are held together only by comparatively weak, noncovalent intermolecular forces, has been thoroughly investigated during the last decades, not least because of its paramount importance with regard to the chemical molecular recognition found in biochemical processes [294–299]. For example, the reversible formation of such complexes is responsible for the selective recognition and high catalytic activity of enzymes, usually observed in aqueous media. However, solvents other than water are known to have a profound influence on the stabilities of all kinds of host/guest complexes [300–306].

Host/guest complex formation in solution can be simply described by the following equation,

$$(\mathrm{Host})_{\mathrm{S}} + (\mathrm{Guest})_{\mathrm{S}} \rightleftharpoons (\mathrm{Host/Guest\ complex})_{\mathrm{S}} + \mathrm{S}$$

where the first term represents solvated hosts such as acyclic and cyclic polyethers (*e.g.* podands, coronands, cryptands; see Section 5.5.5), cyclophanes, calixarenes, cyclodextrins, *etc.*, and the second term represents guests such as solvated metal ions, organic ions, neutral dipolar molecules, dyes, *etc.* The standard Gibbs free energy for host/guest complexation depends on the change in surface area as the two solvent cavities containing the host and guest collapse into a single solvent cavity containing the complex, which is usually formed in a 1:1 stoichiometry. This reaction is associated with (a) some desolvation of both the host and guest molecules in order for them to come closer together, and (b) simultaneous solvation of the newly formed complex, which is presumably accompanied by the release of solvent molecules S from the host and guest solvation shells into the bulk solvent, which then experience solvent/solvent interactions. Accordingly, by means of a thermodynamic cycle, the Gibbs free energy of complex formation in solution, $\Delta G(\mathrm{host} + \mathrm{guest})_{\mathrm{S}}$, is given by Eq. (4-34),

$$\begin{aligned}\Delta G(\mathrm{host} + \mathrm{guest})_{\mathrm{S}} = {} & \Delta G(\mathrm{host} + \mathrm{guest})_{\mathrm{G}} - \Delta G(\mathrm{host})_{\mathrm{S}} - \Delta G(\mathrm{guest})_{\mathrm{S}} \\ & + \Delta G(\mathrm{host/guest\ complex})_{\mathrm{S}} \qquad (4\text{-}34)\end{aligned}$$

and thus depends on the Gibbs free energies of (from left to right) complex formation in the gas phase, desolvation of the host and guest, as well as of solvation of the host/guest complex.

In addition, the uncomplexed, usually rather large guest molecules may have different conformations in different solvents (*e.g.* uncomplexed crown ethers may be present in oxygen-in and oxygen-out conformations depending on the solvent [295]). According to Cram [294], the principle of preorganization of the binding sites prior to complexation includes not only geometrical changes of the host, but also the minimization of solvation energy changes during complexation.

Overall, the solvent influence on such host/guest equilibria is obviously a rather complex phenomenon and has to be carefully analysed for each individual solvent-dependent complex formation. A few representative examples of solvent-dependent host/guest complexation reactions are given in the following.

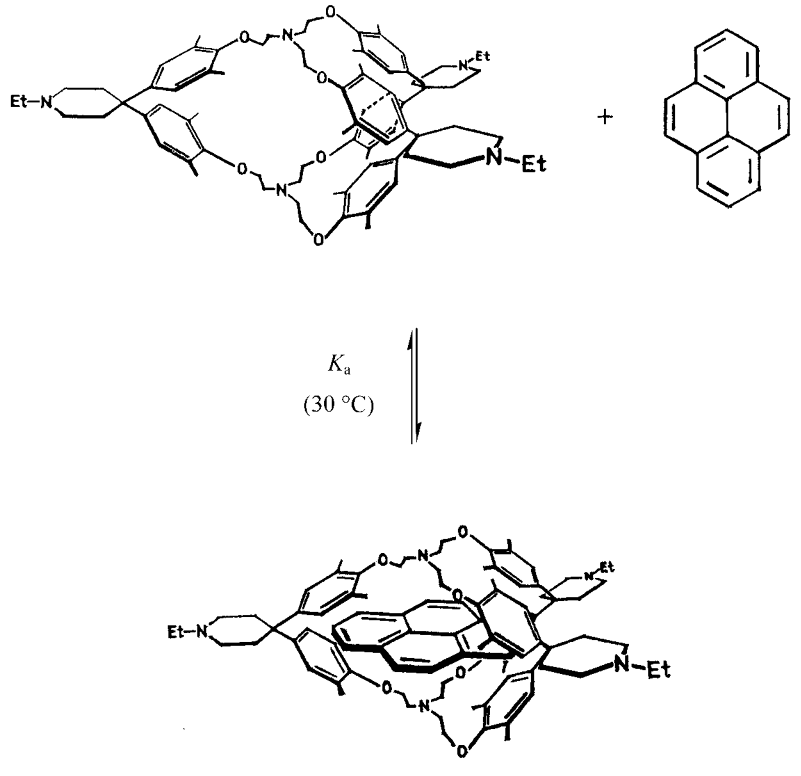
The 1:1 host/guest complexation between the cyclic polyether [18]crown-6 and potassium thiocyanate [*cf.* Eq. (5-128) in Section 5.5.5] has been studied calorimetrically in fourteen solvents of different polarity at 25 °C [300]. The complex formation (or association) constant K_a increases by a factor of $>10^4$ (!) on going from water to propylene carbonate (PC), with K_a increasing in the solvent order H_2O < HMPT < DMSO < DMF < Me_2CHOH < MeCN < $Me_2C{=}O$ < MeOH < PC. Surprisingly, a satisfactory linear correlation was found between lg K_a and the standard molar Gibbs energy of transfer of potassium cations from water to the solvents given in this sequence, $\Delta G_t^\circ(K^+, W \rightarrow S)$; *cf.* Table 2-9 in Section 2.3. Thus, the position of the complexation equilibrium between the neutral crown ether and a cationic guest is mainly determined by the desolvation energy of the metal cation, $\Delta G(\text{host})_S$ in Eq. (4-34), which is largest for the good cation solvators water, HMPT, DMSO, and DMF. This finding is in line with the much larger solvation energies obtained for charged species as compared with those of electroneutral ligands. It is also consistent with the perfect fit between the hole size of the coronand ($d = 260$ pm) and the guest diameter ($d = 266$ pm) [295]; there is practically no room left for solvent molecules inside the complex. An analysis of the thermodynamic parameters shows that the host/guest complex formation is accompanied by a considerable decrease in entropy in all solvents [300]. Obviously, the entropy increase associated with the host desolvation is more than counterbalanced by the entropy decrease caused by the host/guest complexation. The release of solvent molecules from the guest solvation shell into the bulk of highly structured solvents seems to be less important in this respect.

Analogous dramatic solvent-dependent host/guest complexation constants have been found for the inclusion of silver(I) cations (which are similar in size to K^+, but softer) into the cyclic polyether 1,10-diaza-[18]crown-6 [301]. The K_a values increase by nearly eight orders of magnitude in the solvent sequence DMSO < $H_2O \approx CH_3CN$ < DMF < MeOH < $Me_2C{=}O$ < CH_3NO_2 < PC. They are smallest in EPD solvents such as DMSO, H_2O, and CH_3CN, which are known to solvate Ag^+ ions strongly. Again, the major factor in controlling the variation in the complex formation constants K_a is the desolvation of the silver(I) cations. The HBD solvents water and methanol form hydrogen bonds to the basic nitrogen atoms of the aza-crown ether, thereby leading to somewhat lower K_a values than one might expect [301].

Not only metal cations but also organic cations such as arenediazonium ions can be complexed by polyethers. Benzenediazonium tetrafluoroborate forms 1:1 host/guest complexes with acyclic (*e.g.* pentaglyme) and cyclic polyethers (*e.g.* crown ethers) [302]. This solvent-dependent complexation increases the stability of the benzenediazonium ion in solution and determines the first-order rate constant and the outcome of its thermal decomposition, with a change from the heterolytic (in the absence of complexing agents) to the homolytic dediazoniation mechanism; *cf.* Eq. (5-149) in Section 5.5.7.

Other useful hosts for a great variety of guests are cyclic oligosaccharides such as α-cyclodextrin, composed of six α-(1 → 4)-linked D-glucopyranose units forming an *endo*-hydrophobic/*exo*-hydrophilic host with a cavity of diameter 47–60 pm [295]. The binding constants for the 1:1 host/guest complexation between α-cyclodextrin and the azo dye methyl orange ($Me_2N—C_6H_4—N{=}N—C_6H_4—SO_3H$) have been measured in water ($K_a/L \cdot mol^{-1} = 682$) and in seven water/solvent mixtures ($K_a \ll 682$), demonstrating the destabilizing effect of organic solvents on complex formation. In water, there is a hydrophobic driving force for the inclusion of the organic dye molecule into the *endo*-hydrophobic cavity of α-cyclodextrin, which is reduced upon addition of organic solvents such as dimethyl sulfoxide, acetonitrile, or acetone; this is accompanied by a decreased solvent stabilization of the *exo*-hydrophilic host/guest complex by these organic solvents as compared to water.

Cyclophanes, having at least two benzenoid rings disubstituted by closed chains of carbon atoms (usually methylene groups), constitute another class of excellent hosts with apolar hydrophobic cavities [295, 296, 299, 304]. A particularly well-studied example is the solvent-dependent 1:1 complex formation between a macrobicyclic cyclophane with two tertiary cryptand nitrogen atoms and pyrene (as well as other polycyclic arenes), as shown in the following equation [305]:



The inclusion of planar pyrene into the macrobicyclic cyclophane (which displays solubility in nonpolar *and* polar solvents) has been studied in a total of eighteen solvents of differing polarities as a kind of model reaction for molecular recognition, mimicking both the highly polar biological aqueous phases and the less polar lipid membranes. On going from water, the most polar, to carbon disulfide, the least polar of the eighteen solvents, the Gibbs free energy of host/guest complexation decreases from $\Delta G^\circ = -39.4$ kJ/mol to $\Delta G^\circ = -5.4$ kJ/mol ($\Delta\Delta G^\circ = 34.0$ kJ/mol), which corresponds to a change in K_a ($L \cdot mol^{-1}$) from 6.0×10^6 (H_2O) to 9×10^0 (CS_2) at 30 °C [305]. Calorimetric measurements of the enthalpies of formation of the host/pyrene complex show that the complex formation is enthalpy-driven in all solvents studied, with mostly unfavourable complexation entropies (*i.e.* entropy decrease).

A linear correlation has been found between the solvent-dependent ΔG° values and the empirical parameter of solvent polarity, $E_T(30)$ (see Section 7.4). Thus, the host/guest binding strength increases steadily on going from nonpolar solvents to water, thus shifting the complexation equilibrium more and more to the right-hand side with increasing solvent polarity.

All solvent molecules are small enough to easily enter and exit the large, highly preorganized host cavity, leading to a complete equilibrium solvation of the host. The host/pyrene complex is stabilized by dispersion interactions and local dipole/induced dipole interactions and, in all solvents, adopts the geometry shown, with exclusion of solvent molecules from the host interior. Consequently, the large differences in binding strength result entirely from solvation effects. Computer simulations have shown that the major contribution to the experimentally observed solvent effect is due to the different free energies of cavitation for water and less polar, less structured solvents. The stronger cohesive interactions of water facilitate the transfer of pyrene from the solution into the cyclophane cavity, whereas the free energy needed for the desolvation of the cyclophane cavity and subsequent pyrene complexation depends only slightly on the nature of the solvent. Molecules of solvents with high cohesive pressure interact more favourably with bulk solvent molecules than with the apolar surfaces of the free host and guest. Therefore, free energy is gained upon the release of surface-solvating solvent molecules into the bulk during the host/guest complexation step. Furthermore, upon complexation, the less favourable dispersion interactions between solvent molecules of low polarizability (*e.g.* water) and the highly polarizable arene surface of the guest molecule pyrene are replaced by the more favourable dispersion interactions between the complementary surfaces of host and guest [299, 305].

Similar results have been reported for the host/guest complex formation between a tetracationic cyclophane host [=cyclobis(paraquat-*p*-phenylene)] and the planar heteroarene indole. The binding constants K_a, determined in six solvents of different polarities, increase with increasing solvent polarity, being *ca.* 100-fold greater in water than in acetone [306]. Further examples of solvent-dependent cyclophane/guest complexation reactions can be found in reference [299].

Solvents can also act as a kind of template and increase the selectivity in reactions leading to more than one product. A more recent example is the synthesis of so-called glycolurils by acylation of cyclic hydrazines (tetrahydro-1,2-diazines) with active tetracarboxylic esters, leading to three diastereomeric *C*-, *S*-, and *W*-shaped products in a solvent-dependent ratio [307]. The *C*-shaped isomer is self-complementary in hydrogen-bond donor and acceptor sites and readily forms dimeric capsules in solvents that compete poorly for hydrogen bonds. While in the HBA solvent DMSO only monomeric species are found, in [D_6]benzene H-bonded dimers with the encapsulation of benzene as guest molecules are formed ($K_a \approx 3 \cdot 10^{10}$). Interestingly, in solvents that favour the formation of a dimeric capsule, the glycoluril-forming reaction between hydrazine and ester shows a higher selectivity in favour of the *C*-shaped isomer, whereas in DMSO only the statistically expected distribution of *C*-, *S*-, and *W*-shaped isomers is found. Obviously, in the reaction sequence forming the glycolurils, benzene acts as a template, directing the reaction predominantly towards the formation of the *C*-shaped isomer, which forms H-bonded dimers with encapsuled benzene molecules. Thus, in other words, the solvent controls the covalent bond formation through molecular recognition within the monomeric intermediate in the glycoluril synthesis. The intermediate with the best solvated surface, with optimally filled niches, is formed preferentially [307].

Biochemical reactions within or outside of living cells are usually catalysed by macromolecular proteins called *enzymes*, which combine high catalytic power with high specificity, *i.e.* high chemo-, regio-, enantio-, and diastereoselectivity. The rate acceleration and high selectivity of enzymatic reactions stems from a further kind of specific host/guest interaction between the active site of the large enzyme and the smaller substrate, referred to as the 'lock-and-key' interaction by Emil Fischer in 1894 [308]. To this end, the enzyme must have, or must be able to assume (by induced fit), a shape complementary to that of the substrate.

According to the Michaelis-Menten mechanism of enzyme-catalysed reactions in solution, the enzyme E binds reversibly to the substrate S in a pre-equilibrium to yield an intermediate solvated host/guest complex $(\mathrm{E} \cdot \mathrm{S})_\mathrm{S}$, which then converts the substrate to the solvated products P, according to the following equation:

$$(\mathrm{E})_\mathrm{S} + (\mathrm{S})_\mathrm{S} \rightleftharpoons (\mathrm{E} \cdot \mathrm{S})_\mathrm{S} \rightarrow (\mathrm{E})_\mathrm{S} + (\mathrm{P})_\mathrm{S}$$

In contrast to non-enzymatic chemical reactions, enzymatic reactions occur under rather mild physiological conditions, that is to say at moderate temperatures, reasonable pH values, and in *aqueous* solution. Evolution has taken place in an environment with water as one of the major components. Therefore, biochemical reactions in living cells occur in a dilute aqueous medium.

Surprisingly, it has been shown that many enzymatic reactions can advantageously be carried out in nonaqueous solutions, that is, in carefully selected organic solvents containing little or no added water, sometimes with dramatic changes in enzyme specificity as a function of solvent polarity [309–312].

An illustrative example of a change in *chemoselectivity* is the inversion of substrate specificity of the serine protease *Subtilisin Carlsberg* in the transesterification reaction of ethyl esters of *N*-acetyl-L-serine and *N*-acetyl-L-phenylalanine with 1-propanol, measured in twenty anhydrous organic solvents. The enzyme-catalysed reaction with the serine substrate is strongly favoured in dichloromethane, while the reaction with the phenylalanine substrate is preferred in *t*-butylamine, with a 68-fold change in substrate specificity [313].

An example of a solvent-dependent change in *regioselectivity* is the lipase-catalysed partial transesterification of the diester derived from 2-octyl-1,4-

dihydroxybenzene and butyric acid with 1-butanol, to give butyl butyrate and two isomeric 1,4-dihydroxybenzene monoesters. By two alternative pathways, either the monoester with the hydroxy group *ortho* to the octyl group or that with the hydroxy group *meta* to the octyl group is formed preferentially, depending on the solvent used. Thus, the regioselectivity of the lipase from *Pseudomonas cepacia* is reversed on going from toluene to acetonitrile as the reaction medium [314].

A striking example of a complete reversal of enzyme *enantioselectivity* upon a change of solvent is given by the transesterification reaction of *N*-acetyl-(L or D)-phenylalanine 2-chloroethyl ester with 1-propanol, catalysed by *Aspergillus oryzae* protease in eighteen anhydrous organic solvents [315]. Whereas in hydrophilic polar solvents such as acetonitrile, *N*,*N*-dimethylformamide, and pyridine, the L-enantiomer of the ester is much more reactive than its D counterpart, the opposite holds true for hydrophobic apolar solvents such as toluene, octane, and tetrachloromethane. The enantioselectivity (given by the ratio of initial rates v_L/v_D) changes from 7.1 in acetonitrile to 0.19 in tetrachloromethane, *i.e.* by a factor of 37. This result can be explained in terms of the variation in solvent hydrophobicity (as measured by lg $P_{o/w}$; see Section 7.2), without invoking solvent-induced conformational changes of the enzyme [315].

Another remarkable example of a solvent-induced change in *enantioselectivity* is the partial hydrolysis of achiral 4-aryl-substituted 1,4-dihydro-2,6-dimethyl-3,5-pyridine dicarboxylic diesters, catalysed by a lipase from *Pseudomonas sp.*, leading either to the (*R*)- or (*S*)-configured monoesters. Whereas in water-saturated di-*i*-propyl ether, the (*S*)-monoesters are obtained with *ee* values up to 99%, the (*R*)-monoesters are formed in water-saturated cyclohexane with *ee* values of 88–91% [316].

Many other examples of the use of enzymes in organic solvents can be found in some excellent reviews [309–312].

Attempts have been made to correlate the influence of solvents on enzyme activity, stability, and selectivity with physicochemical solvent characteristics such as relative permittivity, dipole moment, water miscibility, and hydrophobicity, as well as empirical parameters of solvent polarity. However, no rationale of general validity has been found, except the simple rule that nonpolar hydrophobic solvents are generally better than polar hydrophilic ones. The best correlations are often obtained with the logarithm of the 1-octanol/water partition coefficient, lg $P_{O/W}$, a quantitative measure of the solvent's hydrophobicity (*cf.* Section 7.2).

In the selection of suitable organic solvents for enzyme-catalysed reactions, care has to be taken that the removal of water does not denature or deactivate the protein. This leads to the question as to how much water is needed to preserve the native conformation of the enzyme-forming protein. Certainly not the entire 55.5 mol/L water that surrounds it in an aqueous solution. It seems that only a few monolayers of water around the enzyme molecule are sufficient to preserve its biological activity. As long as this water (*i.e.* constitutional water inside the protein molecule and interfacial water located on the protein surface) is available around the enzyme molecule, the bulk water can evidently be replaced by other solvents without adversely affecting the enzyme's activity. It has been found that, although enzymic proteins are denatured in water/organic solvent mixtures, their secondary structure remains essentially intact in the corresponding pure organic solvents [317].

Nonaqueous biocatalytic reactions represent significant recent progress in enzyme biotechnology. Some advantages of biocatalysis in organic solvents as opposed to water are: (a) better solubility of organic (mostly hydrophobic) substrates and products, (b) enhanced thermostability of enzymes in organic solvents, (c) the ability to carry out new reactions that are impossible in water, (d) suppression of undesirable side reactions caused by water, (e) insolubility of enzymes in organic solvents, which permits their easy recovery and reusability, and (f) as already mentioned, the possibility of controlling enzyme specificity [309–312]. A more detailed treatment of biocatalysis in organic solvents and its practical applications is beyond the scope of this book and the reader is referred to recent reviews [311, 312].

5 Solvent Effects on the Rates of Homogeneous Chemical Reactions

5.1 General Remarks [1–29, 452–463]

A change of solvent can considerably change both the rate and order of a homogeneous chemical reaction. As early as 1890, Menschutkin demonstrated in his classical study on the quaternization of triethylamine with iodoethane in 23 solvents, that the rate of reaction varied remarkably depending on the choice of solvent. Compared to the rate in *n*-hexane, the rate was found to be four times faster in diethyl ether, 36 times faster in benzene, 280 times faster in methanol, and 742 times faster in benzyl alcohol [30]. Thus, through judicious choice of solvent, decisive acceleration or deceleration of a chemical reaction can be achieved. This can be of great practical importance both in the laboratory and in the chemical industry. In some extreme cases, rate accelerations by a factor of up to *ca.* 10^9 (!) can be achieved solely by a solvent change [31]. Therefore, it is very important to establish rules and theories, enabling a rational selection of solvent and design for chemical synthesis.

The dependence of the reaction rate on the medium can, in principle, be approached from two points of view: (a) comparison of the rates of reaction in the gas phase and in solution, and (b) comparison of the rates of reaction in different solvents.

Until recently, only very few reactions which occur in solution have also been sufficiently examined in the gas phase [32]. Therefore, the comparison of solvent effects has been essentially limited to method (b). Reactions which have been studied according to method (a) are mainly non-ionic reactions, *i.e.* reactions without any charge separation or charge dispersion during the activation process, such as, for example, pericyclic reactions in which neutral reactants produce neutral products. Reactions that follow ionic mechanisms with considerable charge separation or charge dispersion during activation, such as, for example, proton-transfer or S_N2 ion-molecule reactions with charged species as reactants, have until recently only been investigated using method (b).

Three new experimental techniques, developed within the past decades, now make it possible to study ionic reactions in the gas phase as well. These are pulsed ion-cyclotron-resonance (ICR) mass spectrometry, pulsed high-pressure mass spectrometry (HPMS), and the flowing afterglow (FA) technique [469–478; see also the references given in Section 4.2.2]. Although their approaches are quite independent, the results obtained for acid/base and other ionic reactions agree within an experimental error of 0.4...1.3 kJ/mol (0.1...0.3 kcal/mol) and are considered as reliable as those obtained in solution.

In solution, ions are produced by the heterolysis of covalent bonds in ionogens. This ionization reaction is favored by solvents due to their cooperative EPD and EPA properties (*cf.* Section 2.6). In the gas phase, however, ionization of neutral molecules to form free ions is rarely observed because this reaction is very endothermic. For example, in order to ionize gaseous H—Cl into $H^{\oplus}$ and $Cl^{\ominus}$, an energy of 1393 kJ/mol (333 kcal/mol) must be provided. This considerably exceeds the 428 kJ/mol (102 kcal/mol) needed to homolytically cleave H—Cl into hydrogen and chlorine atoms. Thus, for the creation of isolated ions in the gas phase, energy must be supplied by some means other than solvation with EPD/EPA solvents. The most widely used method is ionization by elec-

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tron impact of gaseous molecules, as employed in mass spectrometry. However, whereas ions in solution are stabilized by their solvation shells, gaseous ions are immediately destroyed when they strike a solid surface. Therefore, special care has to be taken to restrict the motion of gaseous ions and to hold them long enough so that their chemical reactivity can be studied. Several methods have been developed for storing gaseous ions. In ICR mass spectrometry, a static magnetic trap is used [469].

The study of reactions of isolated ions and molecules in the gas phase without interference from solvents has led to very surprising results. Gas-phase studies of proton-transfer and nucleophilic substitution reactions permit the measurement of the intrinsic properties of the bare reactants and make it possible to distinguish these genuine properties from effects attributable to solvation. Furthermore, these studies provide a direct comparison of gas-phase and solution reactivities of ionic reactants. It has long been assumed that solvation retards the rates of ion-molecule reactions. Now, using these new techniques, the dramatic results obtained make it possible to show the extent of this retardation. For example, in a typical S_N2 ion-molecule reaction in the gas phase, the substrates react about 10^{10} times faster than when they are dissolved in acetone, and about 10^{15} (!) times faster than in water (*cf.* Table 5-2 in Section 5.2).

Clearly, the effect of the solvent on a chemical reaction is much larger than previously assumed. In solution, the behaviour of ions and molecules is dictated mainly by the solvent and only to a lesser extent by their intrinsic properties. This will be elaborated on in subsequent Sections. A comparison of gas-phase reactivities and solution reactivities is given in Section 5.2.

There are, in principle, two ways in which solvents can affect the reaction rates of homogeneous chemical reactions: through static, or equilibrium, solvent effects and through dynamic, or frictional, solvent effects [463, 465, 466].

The static influence of solvents on rate constants can be understood in terms of transition-state theory. According to this theory, solvents can modify the Gibbs energy of activation (as well as the corresponding activation enthalpies, activation entropies, and activation volumes) by differential solvation of the reactants and the activated complex. Reaction rates are very sensitive to barrier heights. For example, a change of only 8.4 kJ/mol (2 kcal/mol) in an activation barrier can alter the reaction rate at room temperature by a factor of 31. Here, it is implicitly assumed that the required reorientational relaxation of solvent molecules during the activation process is sufficiently fast and that the activated complex is in thermal equilibrium with the solvent due to the frequent collisions of the reacting system with the surrounding solvent molecules. The Hughes–Ingold rules of solvent effects on reaction rates (*cf.* Section 5.3.1) are based on equilibrium solvation of the activated complex.

This equilibrium hypothesis is, however, not necessarily valid for rapid chemical reactions. This brings us to the second way in which solvents can influence reaction rates, namely through dynamic or frictional effects. For broad-barrier reactions in strongly dipolar, slowly relaxing solvents, non-equilibrium solvation of the activated complex can occur and the solvent reorientation may also influence the reaction rate. In the case of slow solvent relaxation, significant dynamic contributions to the experimentally determined activation parameters, which are completely absent in conventional transition-state theory, can exist. In the extreme case, solvent reorientation becomes rate-limiting and the transition-state theory breaks down. In this situation, rate constants will depend on the solvent dynamics, and will vary with friction, *i.e.* with some measure of the coupling of the solvent such as density, internal pressure, or viscosity. In the opposite regime of reactions, *i.e.* those with sharp barriers and weakly dipolar, rapidly relaxing solvents, reaction rates are fairly well described by transition-state theory. At present, it seems to be difficult to quantitatively separate the influence of the dynamic and static solvent effects on the reaction rate. The importance of these less familiar frictional solvent effects on reaction rates has only recently been stressed [463, 465, 466], although the first theoretical treatment of such dynamic solvent effects was given by Kramers as early as 1940 [479].

Because the transition-state theory is essential for even a qualitative understanding of solvent effects on reaction rates, some important features of this theory are outlined below.

Arrhenius' classical theory of reaction kinetics is based on the assumption that the starting materials (reactants) have to overcome an energy barrier, the activation energy, in order to be transformed into the products. This picture has been developed and made more explicit in the theory of absolute reaction rates [2–5, 7, 8, 11, 24, 464–466, 770, 771]. The influence of solvent on reaction rates is best treated by means of this theory – also known as transition-state theory, developed almost simultaneously in 1935 by Eyring as well as Evans and Polanyi [464].

Consider a reaction between the starting compounds A and B, and suppose that during the course of the reaction these two first form an activated complex, which then decomposes to the end products, C and D. The reaction can then be described as follows:

$$\begin{array}{ccccc} \mathrm{A}+\mathrm{B} & \rightleftharpoons & (\mathrm{AB})^{\neq} & \rightarrow & \mathrm{C}+\mathrm{D} \\ \text{Reactants} & & \text{Activated Complex} & & \text{Products} \end{array} \tag{5-1}$$

The theory of absolute reaction rates is based on the following assumptions:

(a) The reactants are envisaged as being in quasi-equilibrium with the activated complex. The corresponding quasi-thermodynamic equilibrium constant is given by Eq. (5-2) (with a = activities, [ ] = molar concentrations, and γ = activity coefficients).

$$K^{\neq} = \frac{a_{(\mathrm{AB})^{\neq}}}{a_{\mathrm{A}} \cdot a_{\mathrm{B}}} = \frac{[(\mathrm{AB})^{\neq}]}{[\mathrm{A}] \cdot [\mathrm{B}]} \cdot \frac{\gamma^{\neq}}{\gamma_{\mathrm{A}} \cdot \gamma_{\mathrm{B}}} \tag{5-2}$$

The use of activity coefficients takes into account deviations from ideal behaviour in solution. The activity coefficients usually refer to the standard state of infinite dilution for the solutes: $\lim\limits_{c \to 0} \gamma = 1$.

(b) The formation of the products C and D does not significantly affect the equilibrium between reactants and activated complex.

(c) The activated complex has all the properties of a normal molecule (with N atoms) except that one vibrational degree, of the $3N$–6 vibrational degrees of freedom, is

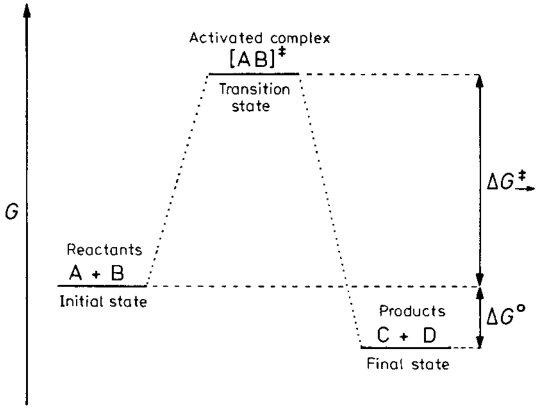

Fig. 5-1. One-dimensional Gibbs energy diagram for reaction (5-1) in solution. Ordinate: relative standard molar Gibbs energies of reactants, activated complex, and products; Abscissa*): not defined, expresses only the sequence of reactants, activated complex, and products as they occur in the chemical reaction. ΔG°: standard molar Gibbs energy of the reaction; $\Delta G^{\neq}$: standard molar Gibbs energy of activation for the reaction from the left to the right.

transformed into a translational degree of freedom, which leads to the decomposition of the activated complex.

(d) The activated complex exists at the top of an energy barrier as shown in Fig. 5-1. The activated complex represents that point in the progress of the reaction at which the reformation of reactants is as likely as the formation of products. The region in the neighbourhood of this maximum is also called the "transition state"**).

(e) The net reaction rate is determined by the rate at which the activated complex passes over the energy barrier in the direction of product formation. The probability of a forward passage through the activated complex is given by a transmission coefficient, which is usually assumed to approach unity.

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* The so-called *reaction coordinate* – often used as abscissa in such diagrams – is essentially a molecular-microscopic quantity. In the case of a unimolecular reaction it is the internuclear distance; in the case of a bimolecular reaction it represents a translational degree of freedom and in the transition state a normal mode of vibration that leads to the decomposition of the activated complex. ΔG° and $\Delta G^{\neq}$ are, however, macroscopic thermodynamic state functions, which are experimentally available only at the maxima and minima and not at configurations between them. Therefore, in order to avoid the indiscriminate mixing of macroscopic and molecular-microscopic quantities, the one-dimensional presentation of Fig. 5-1 is preferable to the smooth curves often used and called Gibbs energy "profiles". In Fig. 5-1, the reaction coordinate has no meaning. The abscissa expresses only the sequence of reactants, activated complex, reaction intermediates, and products as they occur in chemical reactions. *Cf.* also Fig. 4-1 in Chapter 4.

** The terms *activated complex* and *transition state* are often wrongly regarded as synonymous. *Activated complex* refers to the real molecular entity at the point of maximum Gibbs energy on the reaction path, whereas *transition state* describes only the set of states or energy levels at this point. The transition state has no physical existence [*cf.* K. J. Laidler, J. Chem. Educ. *65*, 540 (1988)]. In order to avoid the unnecessary confusion of state with structure (*i.e.* energy space with geometric space), it has been proposed that the configuration of atoms in the geometrical 3D space at the potential energy saddle point should be called the *critical transition structure* (CTS) [*cf.* S. H. Bauer and C. F. Wilcox, J. Chem. Educ. *72*, 13 (1995)]. Using ultrafast pulsed laser techniques with femtosecond resolution (1 fs = 10^{-15} s), it is now even possible to study directly some properties of *activated complexes* as molecular species [*cf.* A. H. Zewail, J. Phys. Chem. A *104*, 5660 (2000)].

(f) The change in the Gibbs energy of activation in going from the gas phase to solution or from one solvent to another is evaluated as the relative modification in Gibbs energy by differential solvation of the reactants and the activated complex, whereby it is implicitly assumed that in solution reactants and activated complex are in thermal equilibrium with the solvent. This equilibrium hypothesis will not be valid for rapid chemical reactions with slow reorientational relaxation of the solvent molecules. For broad-barrier reactions in slowly relaxing solvents, solvent reorientation becomes rate limiting and transition-state theory may break down [463, 465, 466].

Because the reaction rate is assumed to be proportional to the concentration of the activated complex, the specific rate constant k is proportional to $K^{\neq}$. By statistical calculations, the proportionality factor can be estimated as $k_B \cdot T/h$. Provided that each activated complex passing the transition state actually becomes product (transmission coefficient close to unity), and that the activity coefficients are close to unity, the specific rate constant of the elementary reaction is given by Eq. (5-3),

$$k = \frac{k_B \cdot T}{h} \cdot K^{\neq} \cdot (1\ \text{mol} \cdot \text{L}^{-1})^{1-n} = \frac{R \cdot T}{N_A \cdot h} \cdot K^{\neq} \cdot (1\ \text{mol} \cdot \text{L}^{-1})^{1-n} \tag{5-3}$$

where k is the rate constant including units with the dimensions $(\text{mol} \cdot \text{L}^{-1})^{1-n} \cdot (\text{time})^{-1}$, k_B the Boltzmann constant, h the Planck constant, T the absolute temperature, R the gas constant, N_A the Avogadro constant, $K^{\neq}$ the quasi-thermodynamic equilibrium constant related to a hypothetical unit molar concentration standard state for the postulated equilibrium between reactant(s) and activated complex, and n the molecularity and kinetic order of the elementary reaction (usually 1 or 2).

This simple equation predicts that the rate constant for any chemical reaction consists of an equilibrium constant multiplied by a universal frequency factor, $k_B \cdot T/h$, which varies only with the temperature.

Since $K^{\neq}$ represents an equilibrium constant, it is possible to define quantities such as $\Delta G^{\neq}$, $\Delta H^{\neq}$, and $\Delta S^{\neq}$ according to Eqs. (5-4) and (5-5), which are called the Gibbs energy, enthalpy, and entropy of activation, respectively.

$$\Delta G^{\neq} = -R \cdot T \cdot \ln K^{\neq} \tag{5-4}$$

$$\Delta G^{\neq} = \Delta H^{\neq} - T \cdot \Delta S^{\neq} \tag{5-5}$$

From Eqs. (5-3), (5-4), and (5-5), it follows that the specific rate constant for the standard state ($\gamma = 1$) can also be given by Eq. (5-6).

$$\begin{aligned} k &= \frac{R \cdot T}{N_A \cdot h} \cdot e^{-\Delta G^{\neq}/(R \cdot T)} \cdot (1\ \text{mol} \cdot \text{L}^{-1})^{1-n} \\ &= \frac{R \cdot T}{N_A \cdot h} \cdot e^{-\Delta H^{\neq}/(R \cdot T)} \cdot e^{\Delta S^{\neq}/R} \cdot (1\ \text{mol} \cdot \text{L}^{-1})^{1-n} \end{aligned} \tag{5-6}$$

Eq. (5-6) is assumed to be valid for reactions in solution, although it is probably applicable only to an ideal gas system. According to this equation, the smaller the value of $\Delta G^{\neq}$, *i.e.* the difference between the Gibbs energies of reactants and activated complex, the greater the reaction rate of a chemical reaction. The fastest reaction (with $\Delta G^{\neq} = 0$) is given by $R \cdot T/N_A \cdot h$, which corresponds to the frequency for the passage of the activated complex through the transition state. At 25 °C, this value is 6×10^{12} s^{-1}, a typical value for the frequency of molecular vibrations.

In principle, when studying solvent effects on reaction rates, it is not sufficient to investigate only the $\Delta G^{\neq}$ change because, according to Eq. (5-5), this term is determined by both an enthalpy and an entropy term. There are four types of reaction rate control [41]:

(a) Cooperative effects, with $\Delta\Delta H^{\neq}$ and $T \cdot \Delta\Delta S^{\neq}$ having opposite signs. Then these two terms will be additive;
(b) Enthalpy-controlled reactions, for which the two terms are opposed (*i.e.* $\Delta\Delta H^{\neq}$ and $T \cdot \Delta\Delta S^{\neq}$ have equal signs), but the activation enthalpy term is larger;
(c) Entropy-controlled reactions, for which the two terms oppose, but the $T \cdot \Delta\Delta S^{\neq}$ term is larger; and
(d) Compensating effects, where the two terms are opposed, but nearly equal.

If reaction (5-1) takes place in solution, then the initial reactants, as well as the activated complex, will be solvated to differing extents according to the solvating power of the solvent used. This differential solvation can retard or accelerate a reaction in the manner described in Fig. 5-2.

$\Delta G_{\mathrm{I}}^{\neq}$ in Fig. (5-2a) and (5-2b) represents the Gibbs energy of activation for a given chemical reaction in an ideal solvent I. In such a case, neither the reactants nor the activated complex are solvated. If in another solvent II only the activated complex is solvated, then $\Delta G_{\mathrm{II}}^{\neq}$ in Fig. (5-2a) results. The Gibbs energy of activation is reduced by the Gibbs energy of transfer, $\Delta G_{\mathrm{I}\to\mathrm{II}}^{\neq}$, with a consequent rate acceleration. If on the other hand, only the initial reactants are solvated, as happens in solvent III, then $\Delta G_{\mathrm{III}}^{\neq}$ in Fig. (5-2b) results. The Gibbs energy of activation is increased by the Gibbs energy of transfer, $\Delta G_{\mathrm{I}\to\mathrm{III}}^{\mathrm{R}}$, with a consequent rate deceleration. The solvation of the products does not have any influence on the reaction rate. Because in reality the initial reactants as well as the activated complex are solvated, but usually to a different extent, the difference of both Gibbs transfer energies determines the reaction rate in solution.

A dissection, therefore, of the reaction rate solvent effects into initial and transition state contributions would lead to more direct information concerning the nature of the solvent involvement [453, 467].

Fig. 5-3 shows the Gibbs energy diagram for a chemical reaction carried out in two different solvents I and II. The standard molar Gibbs energy of the reactants R in solvent I is designated $G_{\mathrm{I}}^{\mathrm{R}}$ and in solvent II as $G_{\mathrm{II}}^{\mathrm{R}}$. The difference in Gibbs energies between the two solvents, $(G_{\mathrm{I}}^{\mathrm{R}} - G_{\mathrm{II}}^{\mathrm{R}})$, is termed the Gibbs energy of transfer, $\Delta G_{\mathrm{I}\to\mathrm{II}}^{\mathrm{R}}$. Similarly, for the activated complex one obtains $\Delta G_{\mathrm{I}\to\mathrm{II}}^{\neq} = G_{\mathrm{I}}^{\neq} - G_{\mathrm{II}}^{\neq}$.

The difference in Gibbs energies of activation for the reaction in the two solvents is designated $\Delta\Delta G^{\neq}$, and from Fig. 5-3 it follows that

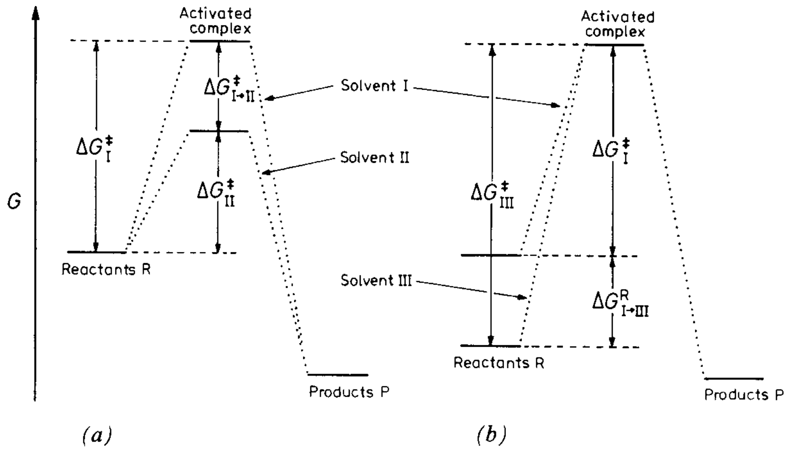

Fig. 5-2. One-dimensional Gibbs energy diagram for a chemical reaction in three different solvents I, II, and III (*cf.* Fig. 5-1). *(a)* Reaction with non-solvated (solvent I) and solvated (solvent II) activated complex (preferential solvation of the activated complex); *(b)* Reaction with non-solvated (solvent I) and solvated (solvent III) reactants (preferential solvation of the reactants). $\Delta G^{\neq}_{I}$, $\Delta G^{\neq}_{II}$, and $\Delta G^{\neq}_{III}$: standard molar Gibbs energies of activation in solvents I, II, and III, respectively; $\Delta G^{\neq}_{I\to II}$ and $\Delta G^{R}_{I\to III}$: standard molar Gibbs energies of the transfer of the activated complex and the reactants R from solvent I to solvents II and III, respectively.

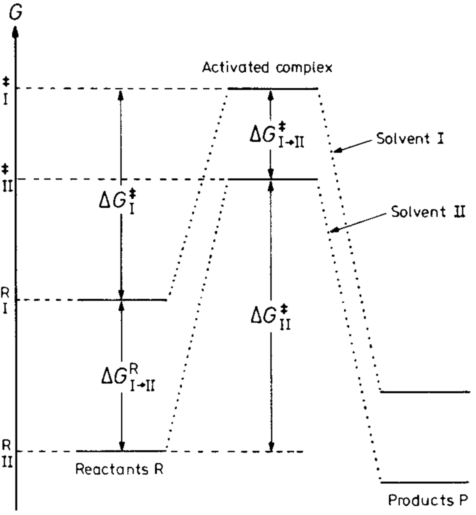

Fig. 5-3. One-dimensional Gibbs energy diagram for a chemical reaction in two different solvents I and II (*cf.* Figs. 5-1 and 5-2). $\Delta G^{\neq}_{I}$ and $\Delta G^{\neq}_{II}$: standard molar Gibbs energies of activation in solvents I and II; $\Delta G^{R}_{I\to II}$ and $\Delta G^{\neq}_{I\to II}$: standard molar Gibbs energies of transfer of the reactants R and the activated complex from solvent I to solvent II, respectively.

$$\Delta\Delta G^{\neq} = \Delta G_{\mathrm{I}}^{\neq} - \Delta G_{\mathrm{II}}^{\neq} = (G_{\mathrm{I}}^{\neq} - G_{\mathrm{I}}^{\mathrm{R}}) - (G_{\mathrm{II}}^{\neq} - G_{\mathrm{II}}^{\mathrm{R}}) \tag{5-7}$$

this can be simplified to give

$$\Delta\Delta G^{\neq} = \Delta G_{\mathrm{I}\to\mathrm{II}}^{\neq} - \Delta G_{\mathrm{I}\to\mathrm{II}}^{\mathrm{R}} \tag{5-8}$$

From Eq. (5-8), it is apparent that $\Delta G_{\mathrm{I}\to\mathrm{II}}^{\neq}$ can be evaluated from the measurable Gibbs energies of transfer of the reactants, $\Delta G_{\mathrm{I}\to\mathrm{II}}^{\mathrm{R}}$, in conjunction with the measured kinetic activation parameters, $\Delta\Delta G^{\neq}$.

The required Gibbs transfer energies, $\Delta G_{\mathrm{I}\to\mathrm{II}}^{\mathrm{R}}$, can be obtained from activity coefficient measurements according to Eq. (5-8a),

$$\Delta G_{\mathrm{I}\to\mathrm{II}}^{\mathrm{i}} = -R \cdot T \cdot \ln(\gamma_{\mathrm{I}}/\gamma_{\mathrm{II}}) \tag{5-8a}$$

where γ refers to the activity coefficients of solute i in solvents I and II. The γ values can be obtained from vapour pressure, solubility, and distribution coefficient measurements [23, 467].

Consequently, by combining the thermodynamic and kinetic measurements, values for $\Delta G_{\mathrm{I}\to\mathrm{II}}^{\neq}$ and $\Delta G_{\mathrm{I}\to\mathrm{II}}^{\mathrm{R}}$ can be obtained. Both terms can be either positive (destabilization), negative (stabilization), or zero (no solvent effect). When both terms have the same sign, a balancing situation occurs, when they are of opposite sign, a reinforcing situation. The effect of the solvent on the rate can be expected to be largest in the reinforcing situation and smallest in the balancing situation [467].

Because of the complicated interactions between solvents and solutes, the prediction of solvent effects on reaction rates, and the correlation of these effects with intrinsic solvent properties, is very difficult. Nevertheless, many authors have tried to establish – empirically or theoretically – correlations between rate constants or Gibbs energies of activation and characteristic solvent parameters such as relative permittivity, ε_{r}, dipole moment, μ, refractive index, n, solubility parameter, δ, empirical solvent polarity parameters, *etc*., as schematically shown by Eq. (5-9).

$$\lg k \quad \text{or} \quad \Delta G^{\neq} = f(\varepsilon_{\mathrm{r}}, \mu, n, \delta, \ldots) \tag{5-9}$$

An early attempt in this direction was O. Dimroth's effort in correlating rate constants k with the solubility S of the reactants in the solvents used [42]. While investigating the intramolecular rearrangement of 5-hydroxy-1-phenyl-1,2,3-triazole-4-carboxylic esters in various solvents, he found, in agreement with a rule formulated by van't Hoff [43], that the rate constants are inversely proportional to the solubility of the rearranging isomers; *cf.* Eq. (5-10).

$$k = const \cdot \frac{1}{S} \tag{5-10}$$

Relationships such as this have only a very limited application [2]. More modern attempts to correlate the solvent influence on reaction rates with physical and empirical parameters of the solvents can be found in Sections 5.4 and 7.6, respectively.

The following Sections deal first with gas-phase reactivities and then with the most important qualitative and quantitative general relationships between reaction rates and solvent properties. The next Section (5.2) begins with a comparison of reactions in the gas phase and in solution, thus demonstrating the huge changes in reaction rates obtained on going from the gas phase to solution. The following Section (5.3) deals with the qualitative Hughes–Ingold rules (and their limitations) concerning solvent effects on substitution and elimination reactions, based on a sub-classification of these reactions according to the different charge-types of the initial reactants [16]. Thereafter, further analogous examples of solvent effects on organic reactions, using a classification of reactions according to Kosower [15] and Reichardt [468], are given. Attempts at establishing quantitative relationships between reaction rates and physical solvent properties are then reviewed (Section 5.4), which is followed by a treatment of some specific solvation effects on reaction rates (Section 5.5).

5.2 Gas-Phase Reactivities

In the gas phase, bond fission is invariably homolytic and complications from solvents are absent. Reactants follow their reaction route in splendid isolation which depends only on the intrinsic (inherent) properties of the reactant molecules. On the other hand, bond fission in solution is generally heterolytic due to the EPD/EPA properties of the solvents. The ubiquitous solvent molecules perturb the reactants in their reaction course, sometimes to such an extent that the solvent is entirely responsible for the observed rate constants.

Accordingly, in the gas phase, reactions without charge separation or charge dispersion are preferred, *e.g.* radical-producing and pericyclic reactions. In solution, on the other hand, reactions involving charge separation and charge dispersion can also be carried out, *e.g.* ionization and S_N2 ion-molecule reactions. Reactions can only occur in the gas phase *and* in solution when the intermolecular interactions between reactants and solvents are so weak that the non-ionic gas-phase reaction mechanism is virtually unchanged on transferring the reactants to solution.

An example of such a reaction, which has the same mechanism in the gas phase and in solution, is the bimolecular Diels–Alder cycloaddition reaction of cyclopentadiene to give *endo*-dicyclopentadiene – a reaction between neutral reactants to give a neutral product. As the Arrhenius activation energies and the rate constants of this reaction in Table 5-1 show, there is only a slight variation on going from the gas phase to solution. The rate constants vary by only a factor of *ca.* 3, accompanied by a corresponding small change in the activation energies.

The homolytic thermolyses of di-*t*-butyl peroxide [36, 37] and diacetyl peroxide [38, 39] have roughly the same rate constants and activation energies both in the gas phase and in solution in a variety of solvents.

On the contrary, reactions involving charge separation or charge dispersion during the activation process depend strongly on the reaction medium, due to the strong intermolecular interactions between the ionic and dipolar reactants and the solvent. Examples include S_N1 and S_N2 reactions, elimination reactions, isomerizations involving polar and charged groups, as well as proton- and electron-transfer reactions.

Table 5-1. Comparison of the activation energies and specific rate constants for the bimolecular Diels–Alder cycloaddition reaction of cyclopentadiene giving *endo*-dicyclopentadiene in the gas phase and in solution at 20 °C [3, 33, 34].

Medium	$\frac{E_a}{(\text{kJ} \cdot \text{mol}^{-1})}$	$\frac{k_2}{(\text{L} \cdot \text{mol}^{-1} \cdot \text{s}^{-1})}$	k_2^{rel}
Gas phase	69.9	$6.9 \cdot 10^{-7}$	1.2
Ethanol	68.6	$19 \cdot 10^{-7}$	3.4
Nitrobenzene	63.2	$13 \cdot 10^{-7}$	2.3
Paraffin oil	72.8	$9.8 \cdot 10^{-7}$	1.8
Carbon disulfide	70.7	$9.3 \cdot 10^{-7}$	1.7
Tetrachloromethane	71.5	$7.9 \cdot 10^{-7}$	1.4
Benzene	68.6	$6.6 \cdot 10^{-7}$	1.2
Neat liquid	67.8	$5.6 \cdot 10^{-7}$	*1.0*

A typical example of such reactions is the exothermic S_N2 nucleophilic displacement reaction $Cl^{\ominus} + CH_3{-}Br \rightarrow Cl{-}CH_3 + Br^{\ominus}$. Table 5-2 provides a comparison of Arrhenius activation energies and specific rate constants for this Finkelstein reaction in both the gas phase and solution. The new techniques described above (*cf.* Sections 4.2.2 and 5.1) have made it possible to determine the rate constant of this ion-molecule reaction in the absence of any solvent molecules in the gas phase. The result is surprising: on going from a protic solvent to a non-HBD solvent and then further to the gas phase, the ratio of the rate constants is approximately $1{:}10^5{:}10^{15}$! The activation energy of this S_N2 reaction in water is about ten times larger than in the gas phase. The suppression of the S_N2 rate constant in aqueous solution by up to 15 orders of magnitude demonstrates the vital role of the solvent.

A detailed molecular-level understanding of the role of solvation on the nature of S_N2 reaction pathways has been revealed only during the last decades. Fig. 5-4 compares the gas-phase S_N2 enthalpy diagram with two minima, first proposed by Brauman *et al.* [474], with the more familiar single transition-state diagram obtained in solution.

Table 5-2. Comparison of the activation energies and specific rate constants for the bimolecular S_N2 ion-molecule reaction $Cl^{\ominus} + CH_3{-}Br \rightarrow Cl{-}CH_3 + Br^{\ominus}$ in the gas phase and in solution at 25 °C [480].

Medium	$\frac{E_a}{(\text{kJ} \cdot \text{mol}^{-1})}$	$\frac{k_2}{(\text{cm}^3 \cdot \text{molecule}^{-1} \cdot \text{s}^{-1})}$	k_2^{rel}
Gas phase (at 24 °C)	11	$2.1 \cdot 10^{-11}$	$2.5 \cdot 10^{15}$
Acetone[a)]	66	$5.5 \cdot 10^{-21}$	$6.6 \cdot 10^{5}$
N,*N*-Dimethylformamide[a)]	75	$8.3 \cdot 10^{-22}$	$1.0 \cdot 10^{5}$
Methanol[b)]		$1.0 \cdot 10^{-26}$	1.2
Water[c)]	103	$8.3 \cdot 10^{-27}$	*1.0*

[a)] D. Cook and A. J. Parker, J. Chem. Soc., Part B *1968*, 142.
[b)] R. Alexander, E. C. F. Ko, A. J. Parker, and T. J. Broxton, J. Am. Chem. Soc. *90*, 5049 (1968).
[c)] R. H. Bathgate and E. A. Moelwyn-Hughes, J. Chem. Soc. *1959*, 2642.

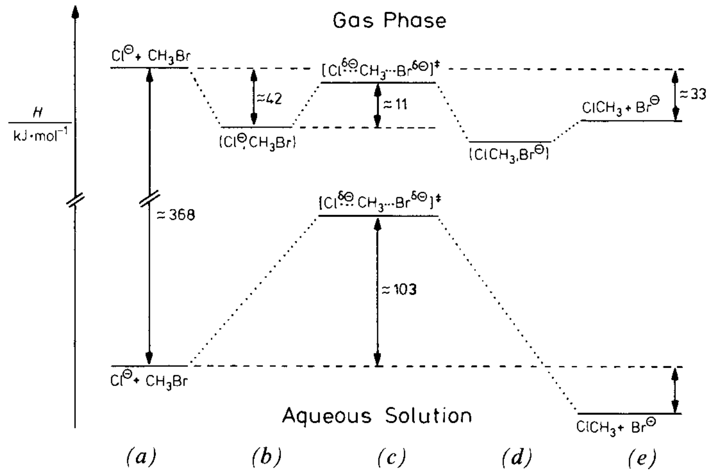

Fig. 5-4. Schematic one-dimensional enthalpy diagram for the exothermic bimolecular Finkelstein reaction $Cl^{\ominus} + CH_3—Br \rightarrow Cl—CH_3 + Br^{\ominus}$ in the gas phase and in aqueous solution [469, 474, 476]. Ordinate: standard molar enthalpies of *(a)* the reactants, *(b, d)* loose ion-molecule clusters held together by ion-dipole and ion-induced dipole forces, *(c)* the activated complex, and *(e)* the products. Abscissa: not defined, expresses only the sequence of *(a)* ... *(e)* as they occur in the chemical reaction.

The unexpected gas-phase double-minimum diagram can be best explained as follows: As the reactants approach one another, long-range ion-dipole and ion-induced dipole interactions first produce loose ion-molecule association complexes or clusters. This is related to a decrease in enthalpy prior to any chemical barrier produced by orbital overlap between the reactants. For reasons of symmetry, an analogous drop in enthalpy must exist on the product side. Because the neutral reactant and product molecules will, in general, have different dipole moments and polarizabilities, the two minima will also be different. Only in the case of degenerate identity S_N2 reactions ($X^{\ominus} + CH_3—X \rightarrow X—CH_3 + X^{\ominus}$) will the enthalpy of the two minima be equal.

Overall, the gaseous S_N2 reaction shown in Fig. 5-4 consists of a collision step, which generates reactant ion-dipole complexes *(b)*, followed by a chemical activation step forming activated complexes *(c)* that contain pentacoordinated carbon atoms. Once the transition state has been surmounted, product ion-dipole complexes *(d)* are formed, the dissociation of which yields the products *(e)*.

During the activation process, the enthalpy increases up to the central transition state level. The height of this central, intrinsic barrier is the major factor responsible for the inherent reactivities of the various reactant combinations. It is important to note that the enthalpy of the activated complex is less than that of the reactants. In other words, the enthalpy barrier for the formation of the activated complex is smaller than the lowering in enthalpy due to the attraction between the reactant ion and the dipolar reactant molecule.

This S_N2 reaction model, containing pre- and post-ion/dipole clusters that are lower in enthalpy than both the initial reactants and final products, and separated by an intrinsic barrier which localizes the transition state, has proven useful in application to other nucleophilic displacement reactions. Theoretical studies of S_N2 reaction pathways have also yielded double-minimum enthalpy diagrams of the type shown in Fig. 5-4 [481–483].

Variations in the nucleophile ($X^{\ominus}$), leaving group ($Y^{\ominus}$), and alkyl substrate (R) involved in S_N2 reactions ($X^{\ominus} + R{-}Y \rightarrow X{-}R + Y^{\ominus}$) has led to a wide range of intrinsic reactivities in the absence of the complicating effects of solvents. These reactivities have been discussed in terms of nucleophilicity, leaving group ability, and steric hindrance [474–477]. For example, the following order of increasing anionic nucleophilicity has been found in the gas phase: $Br^{\ominus} < CN^{\ominus} < Cl^{\ominus} \ll CH_3S^{\ominus} < CH_3O^{\ominus} \approx F^{\ominus} < HO^{\ominus}$ [474, 480]. According to this sequence, the intrinsic nucleophilicities follow the reverse order of the polarizabilities (*e.g.* $CH_3O^{\ominus} < CH_3S^{\ominus}$ and $F^{\ominus} < Cl^{\ominus} < Br^{\ominus}$). This is exactly opposite to the results found in solution studies. There, polarizable nucleophiles are better than non-polarizable ones because they are supposed to respond better to the demand for charge reorganization during the activation process. From the gas-phase results, it can be seen that the higher nucleophilicity of polarizable anions in solution is purely a solvation effect! Furthermore, anions with a localized charge are better gas-phase nucleophiles than those with a delocalized charge. Thus, in contrast to the phenyl anion, benzyl anions and the cyanide ion are poor nucleophiles [474, 484]. In solution, however, anions with a localized charge are generally better solvated and therefore less reactive than anions with delocalized charge.

By comparing the reaction rates in the gas phase with those obtained in solution (*cf.* Table 5-2 and Fig. 5-4), the most striking observation is the large difference in the absolute magnitudes of the rate constants. The principal reason for this rate difference is the differential solvation of the reactants, in particular the reactant anion, and the activated complex. Since the charge is more localized on the reactant anion than on the activated complex, the former will be better solvated than the charge-delocalized activated complex. This results in a greater decrease in reactant enthalpy compared to that of the activated complex. Whereas the gas-phase activation barrier lies lower than the enthalpy of the reactants, the differential solvation of the reactants and the activated complex causes an increase in this activation barrier to a value higher than the enthalpy of the reactants (*cf.* Fig. 5-4).

This differential solvation of reactants and activated complex is greater for protic solvents because protic, *i.e.* HBD solvents, are more sensitive to charge delocalization than aprotic, *i.e.* non-HBD solvents, due to reduced hydrogen-bonding with increasing charge delocalization. This is the main reason for the large rate enhancements in dipolar non-HBD solvents relative to protic solvents (*cf.* Table 5-2) [6].

Before the reactant anion and the dipolar reactant molecule can come into contact in solution, the solvation shell around the two reactants must be at least partially disrupted. Therefore, the reaction rate in solution is determined primarily by the amount of energy needed to destroy the solvation shells and not by the intrinsic properties of the reactants. The resistance to breaking the hydration shell corresponds to an activation barrier of about 103 kJ/mol for the S_N2 reaction given in Table 5-2 and Fig. 5.4.

In addition to the dramatic difference in absolute rates between gas-phase and solution reactions, there are also differences and even reversals in relative rates. For instance, the gas-phase order of increasing nucleophilicity of halogen anions is

Table 5-3. Comparison of the activation energies and specific rate constants for the bimolecular S_N2 ion-molecule reaction $HO^\ominus + CH_3—Br \rightarrow HO—CH_3 + Br^\ominus$ in the gas phase and at various degrees of hydration of the hydroxide ion at *ca.* 23 °C [485].

Medium	Nucleophile	$\frac{E_a}{(kJ \cdot mol^{-1})}$	$\frac{k_2}{(cm^3 \cdot molecule^{-1} \cdot s^{-1})}$	k_2^{rel}
Gas phase	$HO^\ominus$	*ca.* 2[a)]	$1.0 \cdot 10^{-9}$	$4.8 \cdot 10^{15}$
Gas phase	$HO^\ominus \cdot (H_2O)_1$		$6.3 \cdot 10^{-10}$	$3.0 \cdot 10^{15}$
Gas phase	$HO^\ominus \cdot (H_2O)_2$		$2.0 \cdot 10^{-12}$	$9.5 \cdot 10^{12}$
Gas phase	$HO^\ominus \cdot (H_2O)_3$		$\leq 2.0 \cdot 10^{-13}$	$\leq 9.5 \cdot 10^{11}$
Water[b)]	$HO^\ominus \cdot (H_2O)_n$	96	$2.1 \cdot 10^{-25}$	*1.0*

[a)] Estimated from the reaction probability per collision [480].

[b)] At 25 °C; *cf.* E. A. Moelwyn-Hughes, Proc. Royal Soc., Part A *196*, 540 (1949); R. H. Bathgate and E. A. Moelwyn-Hughes, J. Chem. Soc. *1953*, 2642.

$I^\ominus < Br^\ominus < Cl^\ominus < F^\ominus$, whereas in protic solvents the reverse order is found [6]. See Section 5.5.2 for further discussion.

The arguments used here for S_N2 displacement reactions can be generally applied to other ionic reactions.

It has been demonstrated that only a small number of solvent molecules are needed to bridge most of the gap between the enthalpy diagram for nucleophilic displacement reactions in the gas phase and that in solution [475, 477, 485–488].

For instance, the S_N2 displacement reaction $HO^\ominus + CH_3—Br \rightarrow HO—CH_3 + Br^\ominus$ has been carried out in the gas phase as a function of stepwise solvation of the hydroxide ion [485–487]. As Table 5-3 shows, even on the addition of just one water molecule to the nucleophile, a significant decrease in reactivity is observed. The overall decrease in reactivity amounts to at least three orders of magnitude with the addition of three molecules of water to the hydroxide ion (the solvation number of $n = 3$ represents the operational limit of the flowing-afterglow technique used for these measurements). The addition of the first solvent molecule leads to only a slight rate decrease, but further solvent addition reduces the reactivity precipitously. Eventually, in aqueous solution, a further dramatic drop in reactivity of twelve orders of magnitude is observed, accompanied by a corresponding increase in activation energy; *cf.* Table 5-3. Obviously, the solvation capability, in particular the hydrogen-bond donor ability, of three-dimensional structured "polymeric" water and of "monomeric" water is quite different.

Such a decrease in reactivity with increasing solvation can be qualitatively accounted for in terms of the double-minimum enthalpy diagram proposed for S_N2 reactions by Brauman *et al.* [474]; *cf.* Fig. 5-4. Figure 5-5 gives a schematic representation of the changes in enthalpy for the gas-phase reaction of stepwise hydrated hydroxide ions with bromomethane [485]. According to this diagram, the S_N2 reaction proceeds *via* a three-step mechanism: (i) formation of a loosely bound cluster *(b)* from the reactants *(a)*, (ii) isomerization of this cluster by methyl transfer with inversion of configuration *via* the activated complex *(c)* to cluster *(d)*, and (iii) final dissociation of the loosely bound cluster *(d)* into products *(e)*.

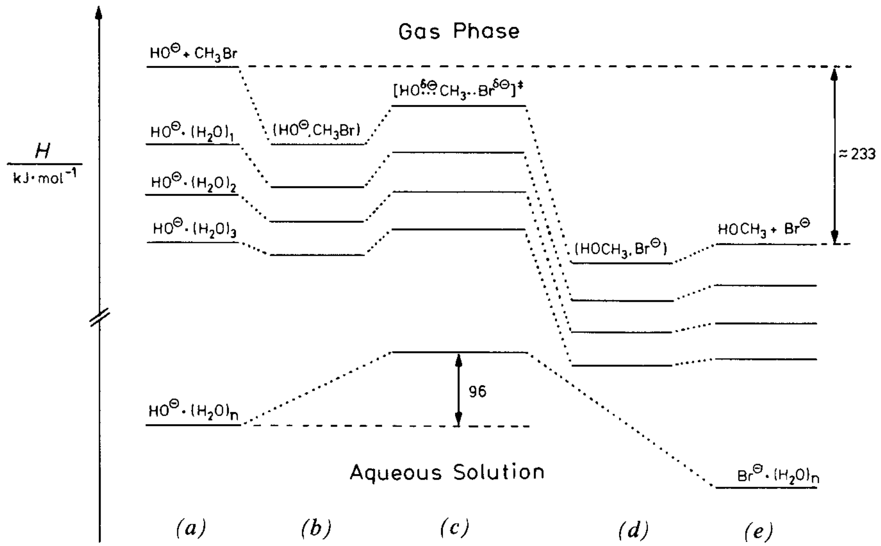

Fig. 5-5. Schematic one-dimensional relative enthalpy diagram for the exothermic bimolecular displacement reaction $HO^{\ominus} + CH_3{-}Br \rightarrow HO{-}CH_3 + Br^{\ominus}$ in the gas phase and at various degrees of hydration of the hydroxide ion [485]. Ordinate: standard molar enthalpies of *(a)* the reactants, *(b, d)* loose ion-molecule clusters held together by ion-dipole and ion-induced dipole forces, *(c)* the activated complex, and *(e)* the products. Abscissa: not defined, expresses only the sequence of *(a)* ... *(e)* as they occur in the chemical reaction. The barrier heights ascribed to the activated complex at intermediate degrees of hydration were chosen to be qualitatively consistent with the experimental rate measurements; *cf.* Table 5-3 [485]. Possible hydration of the neutral reactant and product molecules, $CH_3{-}Br$ and $HO{-}CH_3$, is ignored. The barrier height ascribed to the activated complex in aqueous solution corresponds to the measured Arrhenius activation energy. A somewhat different picture of this S_N2 reaction in the gas phase, which calls into question the simultaneous solvent-transfer from $HO^{\ominus}$ to $Br^{\ominus}$, is given in reference [487].

As the nucleophile becomes more and more solvated, the differential solvation of the reactants, the cluster, and the activated complex leads to an activated complex which becomes relatively less stable and hence to an increasingly large central reaction barrier. While the height of this central barrier may remain below the enthalpy of the reactants at low hydration numbers, thus accounting for the high reaction efficiencies observed at this degree of hydration, further solvation eventually leads to a central barrier with an enthalpy larger than that of the reactants and thus to a dramatic decrease in reaction efficiency [485]*).

Considering the product side in Fig. 5-5, there are three possible reaction pathways open to the intermediate cluster (b), formed in the gas-phase reaction of hydrated hydroxide ions with bromomethane [475].

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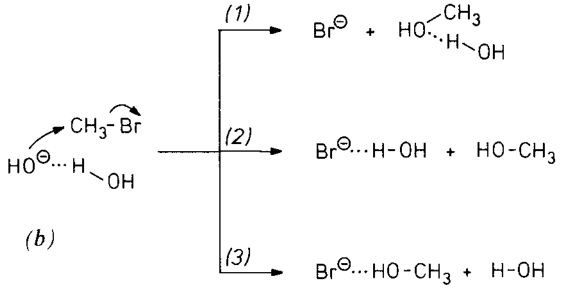
* Calculations of the interaction energies of both reactants and activated complex of simple S_N2 reactions with clusters of water molecules have shown that about sixty or even more water molecules are needed to explain the huge rate difference of about twenty orders of magnitude between gas-phase and solution S_N2 reactions; *cf.* Y. S. Kong and M. S. Jhon, Theor. Chim. Acta *70*, 123 (1986).



Option (1) gives the unsolvated and option (3) the product-solvated bromide ion. Formation of the hydrated bromide ion according to option (2) requires the concomitant transfer of a water molecule from the reactant nucleophile ($HO^{\ominus}$) to the leaving group ($Br^{\ominus}$), which can take place by simultaneous or sequential migration of H_2O and CH_3. Each of these three pathways should result in a different enthalpy diagram.

Measurements at room temperature have clearly shown that about 95% of the reaction between $HO^{\ominus} \cdot (H_2O)_1$ and CH_3—Br proceeds *via* path (1) to produce the unsolvated $Br^{\ominus}$ ion as the principal primary product and not the solvated species, $Br^{\ominus} \cdot H_2O$ and $Br^{\ominus} \cdot HOCH_3$ [487]. Thus, a sequential inversion (*i.e.* methyl transfer) and solvent transfer seems to be the preferred route for this particular reaction in the gas phase.

Ab initio SCF calculations on the degenerate S_N2 reaction $Cl^{\ominus} \cdot (H_2O)_n + CH_3—Cl \rightarrow Cl—CH_3 + Cl^{\ominus} \cdot (H_2O)_n$ provide further insight into the possible mechanisms of solvent transfer between reactant and product ions and the actual features of the intermediate enthalpy change at various degrees of solvation [489]. For the non-hydrated S_N2 reaction, the calculations produce a double-minimum enthalpy diagram analogous to that given in Fig. 5-5. The singly-hydrated reaction may proceed via *simultaneous* migration of H_2O and CH_3 through a symmetric activated complex but also *sequentially* by CH_3 transfer with subsequent migration of the H_2O molecule or *vice versa*. The doubly-hydrated reaction involves two H_2O migrations and a CH_3 transfer, which can take place in one or two discrete steps or all three simultaneously. The most favorable path involves one molecule of H_2O being transferred first with little or no barrier, followed by CH_3 transfer and then transfer of the second H_2O molecule. For large solvation numbers, when the first solvation shell of $Cl^{\ominus}$ is completed, the initial interaction between the ion-molecule reactants first involves dehydration, thus introducing a new feature into the enthalpy diagram; *cf.* the lower part of Fig. 5-5. In other words, the rate constants do not decrease monotonically with increasing solvation number and the corresponding enthalpy diagrams do not transform systematically toward that for the reaction in solution [487].

In the experiments reported in this Section, the reactions proceed in the absence of bulk solvent in an inert gaseous medium at low total pressures so that available solvent molecules are limited to those associated directly with the reactant ions. The main difference between these solvated-ion/molecule reactions in the gas phase and the corresponding reactions in solution is the kinetic role of the bulk solvent. Solvated-ion/molecule reactions carried out in the gas phase reveal the kinetic participation of the ion-solvate in the absence of bulk solvent [487].

Further examples of gas-phase measurements which reveal the influence of stepwise solvation of homo- and heteroconjugated anionic nucleophiles, $A^{\ominus} \cdot (AH)_n$ and $A^{\ominus} \cdot (BH)_n$, on the kinetics of S_N2 discplacement reactions with halomethanes can be found in references [475, 486]. In all cases, solvation of the reactant anion with up to three solvent molecules leads to a decrease in the rate constants by at least three orders of magnitude.

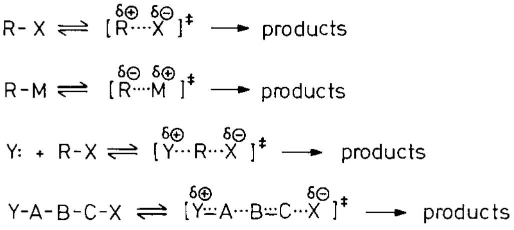
Not only reaction rates but also the kind of products obtained can be changed in going from the gas phase to solution. For instance, the reaction of the stepwise solvated hydroxide ion with acetonitrile follows three distinct pathways: bare and singly-solvated (in the gas phase) as well as bulk-solvated hydroxide ions react with acetonitrile to give three different sets of products as result of displacement, proton-transfer, and hydrolysis reactions [488]!

In conclusion, these gas-phase measurements provide new clues to the role of solvation in ion-molecule reactions. For the first time, it is possible to study intrinsic reactivities and the extent to which the properties of gas-phase ion-molecule reactions relate to those of the corresponding reactions in solution. It is clear, however, that gas-phase solvated-ion/molecule reactions in which solvent molecules are transferred into the intermediate clusters by the nucleophile cannot be exact duplicates of solvated-ion/molecule reactions in solution in which solvated reactants exchange solvent molecules with the surrounding bulk solvent [743]. For a selection of more recent experimental [772] and theoretical studies of S_N2 reactions in gas phase and solution by classical trajectory simulations [773], molecular dynamics simulations [774, 775], *ab initio* molecular orbital calculations [776, 777], and density functional theory calculations [778, 779], see the references given. For studies of reactions other than S_N2 ion-molecule processes in the gas phase and in solution, see reviews [780, 781].

5.3 Qualitative Theory of Solvent Effects on Reaction Rates

Organic reactions can be loosely grouped into three classes depending on the character of the activated complex through which these reactions can proceed: dipolar, isopolar, and free-radical transition-state reactions [15, 468].

Dipolar activated complexes differ considerably in charge separation or charge distribution from the initial reactants. *Dipolar transition-state reactions* with large solvent effects can be found amongst ionization, displacement, elimination, and fragmentation reactions such as:



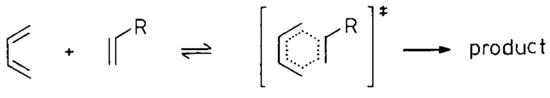
$$R-X \rightleftharpoons [\overset{\delta\oplus}{R}\cdots\overset{\delta\ominus}{X}]^{\ddagger} \longrightarrow \text{products}$$

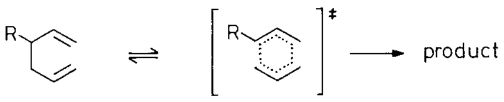
$$R-M \rightleftharpoons [\overset{\delta\ominus}{R}\cdots\overset{\delta\oplus}{M}]^{\ddagger} \longrightarrow \text{products}$$

$$Y\!: + R-X \rightleftharpoons [\overset{\delta\oplus}{Y}\cdots R\cdots\overset{\delta\ominus}{X}]^{\ddagger} \longrightarrow \text{products}$$

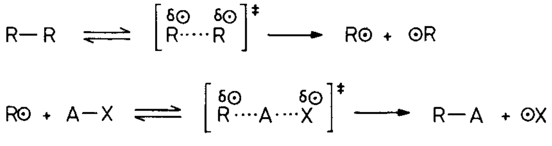
$$Y-A-B-C-X \rightleftharpoons [\overset{\delta\oplus}{Y}\mathrel{\underset{\cdots}{-}}A\cdots B\mathrel{\underset{\cdots}{-}}C\cdots\overset{\delta\ominus}{X}]^{\ddagger} \longrightarrow \text{products}$$

Isopolar activated complexes differ very little or not at all in charge separation or charge distribution from the corresponding initial reactants. *Isopolar transition-state* *reactions* with small or negligible solvent effects can be found amongst pericyclic reactions, two examples of which are Diels–Alder cycloaddition reactions and the Cope rearrangement of 1,5-hexadienes:





Free-radical activated complexes are formed by the creation of unpaired electrons during homolytic bond cleavage. *Free-radical transition-state reactions* with small or negligible solvent effects are found among radical-pair formation and atom-transfer reactions such as:



$$R{-}R \rightleftharpoons \left[\overset{\delta\odot}{R}\cdots\cdots\overset{\delta\odot}{R}\right]^{\ddagger} \longrightarrow R\odot + \odot R$$

$$R\odot + A{-}X \rightleftharpoons \left[\overset{\delta\odot}{R}\cdots A\cdots\overset{\delta\odot}{X}\right]^{\ddagger} \longrightarrow R{-}A + \odot X$$

In the following Sections, typical examples of solvent effects on dipolar, isopolar, and free-radical transition-state reactions are given.

5.3.1 The Hughes–Ingold Rules

The effect of solvent on aliphatic nucleophilic substitution and elimination reactions was investigated by Hughes and Ingold. They used a simple qualitative solvation model considering only pure electrostatic interactions between ions or dipolar molecules and solvent molecules in initial and transition states [16, 44]. Depending on whether the reaction species are neutral, positively or negatively charged, all nucleophilic substitution and elimination reactions may be divided into different charge types. Based on certain reasonable assumptions as to the extent of solvation to be expected in the presence of electric charges:

(a) increase in magnitude of charge will increase solvation;
(b) increase in dispersal of charge will decrease solvation; and
(c) destruction of charge will decrease solvation more than dispersal of charge,

the gross effect of the solvent on reactions of different charge types can be summarized as follows:

(a) An increase in solvent polarity results in an increase in the rates of those reactions in which the charge density is greater in the activated complex than in the initial reactant molecule(s).

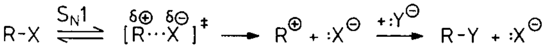
(b) An increase in solvent polarity results in a decrease in the rates of those reactions in which the charge density is lower in the activated complex than in the initial reactant molecule(s).

(c) A change in solvent polarity will have a negligible effect on the rates of those reactions that involve little or no change in the charge density on going from reactant(s) to the activated complex.

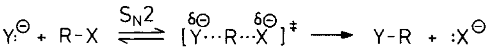
In other words, a change to a more polar solvent will increase or decrease the reaction rate depending on whether the activated reaction complex is more or less dipolar than the initial reactants. In this respect, the term "solvent polarity" was used synonymously with the power to solvate solute charges. It was assumed to increase with the dipole moment of the solvent molecules, and to decrease with increased thickness of shielding of the dipole charges.

For example, the reaction between two equally charged ions results in an increase in charge density during the activation process. Therefore, the reaction rate will increase with increasing solvent polarity. On the other hand, a reaction between oppositely charged ions will be slower in polar solvents, which are good ion solvators, because in this case a reduction of charge density occurs in going from the reactants to the activated complex. Furthermore, reactions where charge is either created or destroyed during the activation process should be affected to a greater extent by a solvent polarity change than reactions in which there is only charge dispersal. Thus, the rates of substitution reactions involving charge creation or destruction are altered by a factor of $10^3 \ldots 10^6$ in going from water to ethanol, whereas S_N reactions involving charge dispersal are increased by only a factor of 3 … 10 when the solvent is changed from ethanol to water.

These Hughes–Ingold rules can be used for making qualitative predictions about the effect of solvent polarity on the rates of all heterolytic reactions of known mechanisms. For nucleophilic substitution reactions of types (5-11) and (5-12)



$$R{-}X \overset{S_N1}{\rightleftharpoons} [\overset{\delta\oplus}{R}\cdots\overset{\delta\ominus}{X}]^{\ddagger} \longrightarrow R^{\oplus} + :X^{\ominus} \xrightarrow{+:Y^{\ominus}} R{-}Y + :X^{\ominus} \tag{5-11}$$



$$Y:^{\ominus} + R{-}X \overset{S_N2}{\rightleftharpoons} [\overset{\delta\ominus}{Y}\cdots R\cdots\overset{\delta\ominus}{X}]^{\ddagger} \longrightarrow Y{-}R + :X^{\ominus} \tag{5-12}^*$$

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* S_N2 reactions of the type shown in Eq. (5-12) have been commonly represented as occurring by attack of a lone electron pair from $Y^{\ominus}$ at the backside of R with simultaneous displacement of $X^{\ominus}$. However, this representation is misleading because electrons shift singly, not in pairs! Therefore, synchronous S_N2 displacement reactions are better represented in terms of $Y :^{\ominus} + R \cdot\cdot X \rightarrow Y \cdot\cdot R + : X^{\ominus}$, where a single electron from the donor anion $Y :^{\ominus}$ pairs with one electron from R, and an electron from R is transferred to X, accompanied by cleavage of the R—X bond [14, 483]. In certain cases, this process can merge with a single-electron transfer (SET) pathway, wherein the product Y—R is formed by coupling of an intermediate geminate radical pair according to

$$Y :^{\ominus} + R \cdot\cdot X \xrightarrow{SET} Y^{\odot} + R \cdot\cdot X^{\odot\ominus} \longrightarrow Y \cdot\cdot R + : X^{\ominus}$$

That is, the act of shifting the single electron from Y to X may occur either with or without free-radical formation. Usually, the concerted non-radicaloid process is energetically favoured. For a more detailed discussion of the various mechanisms of nucleophilic substitution reactions in aliphatic compounds and their solvent dependence, see references [14, 483, 782–785].

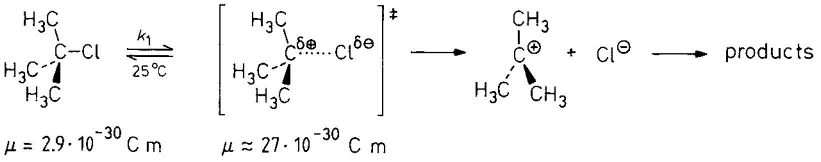
Table 5-4. Predicted solvent effects on rates of nucleophilic substitution reactions [16, 44–46].

Reaction type	Initial reactants	Activated complex	Charge alteration during activation	Effect of increased solvent polarity on rate[a]
(a) S_N1	$R—X$	$R^{\delta+}\ldots X^{\delta-}$	Separation of unlike charges	Large increase
(b) S_N1	$R—X^+$	$R^{\delta+}\ldots X^{\delta+}$	Dispersal of charge	Small decrease
(c) S_N2	$Y + R—X$	$Y^{\delta+}\ldots R\ldots X^{\delta-}$	Separation of unlike charges	Large increase
(d) S_N2	$Y^- + R—X$	$Y^{\delta-}\ldots R\ldots X^{\delta-}$	Dispersal of charge	Small decrease
(e) S_N2	$Y + R—X^+$	$Y^{\delta+}\ldots R\ldots X^{\delta+}$	Dispersal of charge	Small decrease
(f) S_N2	$Y^- + R—X^+$	$Y^{\delta-}\ldots R\ldots X^{\delta+}$	Destruction of charge	Large decrease

[a] The terms "large" and "small" arise from the theory that the effect of the dispersal of charge should be notably smaller than the effect of its creation or destruction and have therefore only relative significance.

the predictions are compiled in Table 5-4. The middle three columns show, for each charge type and mechanism, what happens to the charges on going from the initial to the transition state. The last column shows the predicted solvent effects. The conclusions derived from Table 5-4 were experimentally confirmed in a large number of substitution reactions. Some typical examples shall serve to demonstrate the application of these rules.

The solvolysis of 2-chloro-2-methylpropane is 335000 times faster in water than in the less polar solvent ethanol [40]; *cf.* reaction type (a) in Table 5-4.



(5-13)

Solvent	C_2H_5OH	CH_3OH	$HCONH_2$	HCO_2H	H_2O
k_1^{rel}*)	1	9	430	12200	335000

Comparison of the solvolysis rate constants of 2-chloro-2-methylpropane obtained in water and in benzene solution reveals a rate acceleration of *ca.* 10^{11} with increasing solvent polarity [47]**). The solvolysis rate of 1-bromoadamantane in

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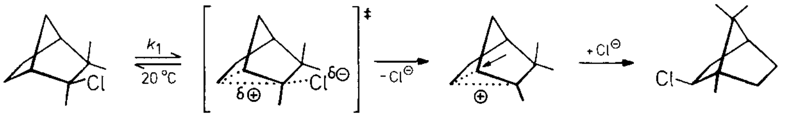
* Here, and in the following examples, only the relative rate constants, k^{rel}, with respect to the "slowest solvent" are given. The selected solvents are ordered from left to right with increasing polarity.

** In the S_N1 solvolysis reaction of 2-chloro-2-methylpropane, leading mainly to *t*-butanol and *t*-butyl ethers together with some *i*-butene, the term *solvolysis* is normally restricted to the reaction in water and other HBD solvents. In non-HBD solvents, however, the only reaction product is *i*-butene. For convenience, the term *solvolysis* is often used in the literature to cover both types of reaction, solvolysis and dehydrohalogenation of 2-chloro-2-methylpropane, because the solvent-dependent rate-determining step of both reactions, S_N1 and E1, is the same. For a detailed review on the heterolysis of tertiary haloalkanes in the gas phase and in solution, see G. F. Dvorko, E. A. Ponomareva, and N. I. Kulik, Usp. Khim. *53*, 948 (1984); Russ. Chem. Rev. *53*, 547 (1984).

ethanol/water increases by a factor of 4900 when the volume fraction of water goes from 10 to 60 cL/L [48].

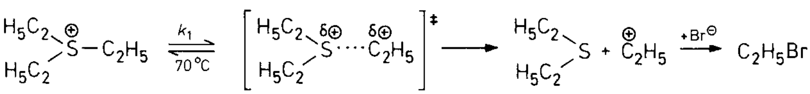
Rearrangement reactions, where the first step corresponds to the ionization of a tertiary haloalkane, also proceed faster with increasing solvent polarity, as shown by the Wagner–Meerwein rearrangement of 3-chloro-2,2,3-trimethylnorbornane to 2-*exo*-chlorobornane [49].



(5-14)

Solvent	Petroleum ether	C_6H_5Cl	$C_6H_5NO_2$	CH_3CN	CH_3NO_2
k_1^{rel}	1	20	65	200	610

In agreement with the predictions for reaction type (b) in Table 5-4, the thermolysis of triethylsulfonium bromide takes place more slowly in polar solvents, *e.g.* alcohols, than in less polar solvents, *e.g.* acetone [50].



(5-15)

Solvent	CH_3COCH_3	$CHCl_3$	$C_6H_5NO_2$	i-$C_5H_{11}OH$	$C_6H_5CH_2OH$
k_1^{rel}	290	>230	180	4.5	1

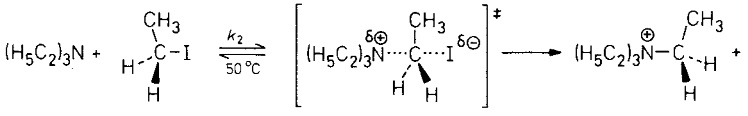
Solvolysis rates of *t*-butyl-dimethylsulfonium salts decrease with increasing solvent polarity [710]. Analogously, the rate of solvolysis of triethyloxonium salts in ethanol/water mixtures decreases with increasing water content [490]. Solvolysis rates of *N*-*t*-alkylpyridinium salts such as 1-(1-methyl-1-phenylethyl)pyridinium perchlorate are almost independent of solvent polarity, whereas *N*-*sec*-alkylpyridinium salts exhibit small decreases in rate with increasing solvent polarity [710]. The non-creation of charge in the activation process of these type (b) reactions much reduces the influence of solvent polarity on rate; *cf.* Table 5-4.

An example of reaction type (c) in Table 5-4 is the well-known Menschutkin reaction [30] between tertiary amines and primary haloalkanes yielding quaternary ammonium salts. Its solvent dependence was studied very thoroughly by a number of investigators [51–65, 491–496, 786–789]. For instance, the reaction of tri-*n*-propylamine with iodomethane at 20 °C is 120 times faster in diethyl ether, 13000 times faster in chloroform, and 110000 times faster in nitromethane than in *n*-hexane [60]. It has been estimated that the activated complex of this Menschutkin reaction should have a dipole moment of *ca.* $29 \cdot 10^{-30}$ Cm (8.7 D) [23, 64], which is much larger than the dipole moments of the reactant molecules (tris-*n*-propylamine $2.3 \cdot 10^{-30}$ Cm = 0.70 D; iodomethane $5.5 \cdot 10^{-30}$ Cm = 1.64 D) [64].

Table 5-5. Absolute and relative rate constants, Gibbs activation energies, activation enthalpies, and activation entropies of the Menschutkin reaction between triethylamine and iodoethane in twelve solvents at 50 °C [59].

Solvents	$k_2 \cdot 10^5$ $(\mathrm{L \cdot mol^{-1} \cdot s^{-1}})$	k_2^{rel}	$\Delta G^{\neq}$ $(\mathrm{kJ \cdot mol^{-1}})$	$\Delta H^{\neq}$ $(\mathrm{kJ \cdot mol^{-1}})$	$\Delta S^{\neq}$ $(\mathrm{J \cdot mol^{-1} \cdot K^{-1}})$
1,1,1-Trichloroethane	1.80	1	102.6	52.3	−156
Chlorocyclohexane	3.09	2	101.6	54.4	−146
Chlorobenzene	9.30	5	98.2	46.9	−159
1,1-Dichloroethane	11.9	7	97.1	48.1	−151
trichloromethane	15.4	9	96.2	49.0	−146
1,2-Dichlorobenzene	18.1	10	96.7	49.4	−146
Acetone	31.7	18	94.1	47.3	−145
Cyclohexanone	33.7	19	94.8	51.5	−134
1,2-Dichloroethane	42.6	24	93.4	45.2	−149
Propionitrile	59.6	33	92.3	48.5	−135
Benzonitrile	76.5	43	92.6	49.0	−135
Nitrobenzene	93.4	52	92.0	49.4	−133

Activation parameter data as a function of solvent have been published for the reaction of triethylamine with iodoethane [59]. The reaction rates obtained in dipolar aprotic solvents together with the activation parameters are given in Table 5-5 [59].



(5-16)

A solvent change from 1,1,1-trichloroethane to nitrobenzene causes a 52-fold rate acceleration for reaction (5-16), which corresponds to a decrease in $\Delta G^{\neq}$ of 10.6 kJ/mol. Bimolecular reactions such as (5-16), which produce charge during the activation process, usually show large negative entropies of activation. A negative entropy of activation indicates a greater degree of ordering in the transition state than in the initial state, due to an increase in solvation during the activation process. The $\Delta S^{\neq}$ values of Table 5-5 show that the largest decrease of activation entropy is obtained in the less polar solvents. This observation can be rationalized because polar solvents will have some structure corresponding to the orientation of the dipolar solvent molecules due to intermolecular solvent–solvent interactions. In less polar solvents, however, which have only a small or no dipole moment, the solvent molecules will be relatively unoriented and consequently have a higher entropy. Thus, nonpolar solvents will have a greater entropy loss as a result of increased solvation during the activation process. Consequently, reactions proceeding through dipolar activated complexes should have a larger negative entropy of activation in less polar solvents than in polar solvents [226].

The Menschutkin-type S_N2 reaction of triphenylphosphane with iodomethane has been studied in thirteen solvents [500]. In propylene carbonate, this reaction is 245 times faster than in di-*i*-propyl ether. In agreement with the highly dipolar activated complex, large solvent-dependent negative activation volumes, $\Delta V^{\neq}$, have been obtained as a result of charge-induced reorientation of the surrounding solvent molecules during the activation process; *cf.* also Section 5.5.11.

For many physical organic chemists, the Menschutkin reaction was a kind of "guinea pig", which has been extensively used for the study of solvent effects on chemical reactivity. A comprehensive review of this reaction has been given by Abboud *et al.* [786]. More recent theoretical treatments of the solvent influence on Menschutkin reactions can be found in references [787–789].

Another remarkable example of reaction type (c) in Table 5-4, somewhat related to the Menschutkin reaction, is the S_N2 reaction between tris(*n*-butyl)phosphane and carbon disulfide, to give zwitterionic tris(*n*-butyl)phosphonium dithiocarboxylate via a corresponding dipolar activated complex [790, 791].

$$(n\text{-Bu})_3P + CS_2 \underset{k_1}{\overset{k_2}{\rightleftharpoons}} (n\text{-Bu})_3P^+\text{—}CS_2^- \tag{5-16a}$$

The rate constants of both the forward (k_2) and the reverse reaction (k_1) are solvent-dependent, albeit to a different extent. In going from less polar diethyl ether to polar dimethyl sulfoxide, the forward reaction is accelerated by a factor of just 26, while the reverse reaction is decelerated to a larger extent. In other words, an inverted solvent change dimethyl sulfoxide → diethyl ether accelerates the reverse reaction 685-fold. This suggests that the activated complex of both reactions is located closer to the initial weakly dipolar reactants than to the zwitterionic adduct.

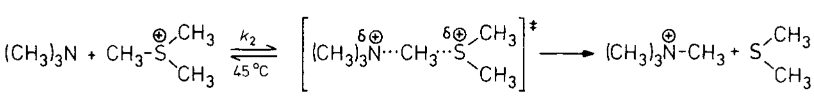
An example of reaction type (d) in Table 5-4 is the Finkelstein halide exchange reaction between iodomethane and radioactive labeled iodide ion. The rate constant for this reaction decreases by about 10^4 on going from less polar acetone to water as solvent [66].

$$\overset{*}{I}^{\ominus} + CH_3\text{-}I \underset{25\,°C}{\overset{k_2}{\rightleftharpoons}} \left[\overset{*}{I}^{\delta\ominus}\cdots CH_3\cdots I^{\delta\ominus}\right]^{\ddagger} \longrightarrow \overset{*}{I}\text{-}CH_3 + I^{\ominus} \tag{5-17}$$

Solvent	CH_3COCH_3	C_2H_5OH	$(CH_2OH)_2$	CH_3OH	H_2O
k_1^{rel}	13000	44	17	16	1

Other examples of this type of reaction are: S_N2 reactions between azide ion and 1-bromobutane [67], bromide ion and methyl tosylate [68], and bromide ion and iodoethane [497]. In changing the medium from non-HBD solvents (HMPT, 1-methylpyrrolidin-2-one) to methanol, the second-order rate constants decrease by a factor of $2 \cdot 10^5$ [67], $9 \cdot 10^4$ [68], and $1 \cdot 10^5$ [497], respectively. The large decrease in these rate constants in going from the less to the more polar solvent is not only governed by the difference in solvent polarity, as measured by dipole moment or relative permittivity, but also by the fact that the less polar solvents are dipolar aprotic and the more polar solvents are protic (*cf.* Section 5.5.2).

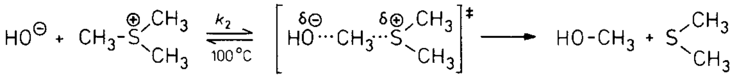
The second-order reaction between trimethylamine and the trimethylsulfonium ion gives the predicted rate decrease with increasing solvent polarity [69]; *cf.* reaction type (e) in Table 5-4.


(5-18)

Solvent	CH_3NO_2	C_2H_5OH	CH_3OH	H_2O
k_2^{rel}	119	10	6	1

Obviously, the initial reactants are more strongly solvated than the activated complex with its dispersed positive charge.

Finally, as an example of reaction type (f) in Table 5-4, the alkaline hydrolysis of the trimethylsulfonium ion demonstrates the predicted large rate decrease by increasing the proportion of water in an aqueous ethanolic reaction medium [70].

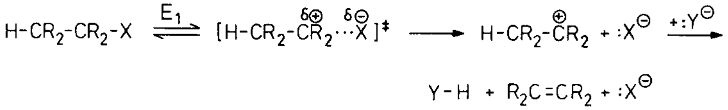

(5-19)

Solvent	Ethanol/water			
H_2O in cL/L	0	20	40	100
k_2^{rel}	19600	480	40	1

Similar findings were obtained for the alkaline decomposition of triarylsulfonium halides with ethoxide ion in aqueous ethanol at 120 °C [71]. The results indicate that the decomposition rate is decreased about 10^6-fold by increasing the water content from 2.3 to 98.2 cmol/mol [71].

It should be mentioned that a solvent change affects not only the reaction rate, but also the reaction mechanism (see Section 5.5.7). The reaction mechanism for some haloalkanes changes from S_N1 to S_N2 when the solvent is changed from aqueous ethanol to acetone. On the other hand, reactions of halomethanes, which proceed in aqueous ethanol by an S_N2 mechanism, can become S_N1 in more strongly ionizing solvents such as formic acid. For a comparison of solvent effects on nucleophilic substitution reactions at primary, secondary, and tertiary carbon atoms, see references [72, 784].

The mechanisms of nucleophilic substitution and β-elimination reactions are closely parallel with regard to the rate-determining step. The two monomolecular reactions (S_N1 and E_1) have a common rate-controlling step, whereas in the two bimolecular reactions (S_N2 and E_2), the electron transfers from the reagent to the leaving group are similar. However, they pass through a larger chain of carbon atoms in elimination than in substitution reactions. Therefore, similar rules for solvent effects on monomolecular, (5-20), and bimolecular, (5-21), β-elimination reactions of different charge-type have been obtained by Hughes and Ingold [16, 44] (*cf.* Table 5-6).


(5-20)

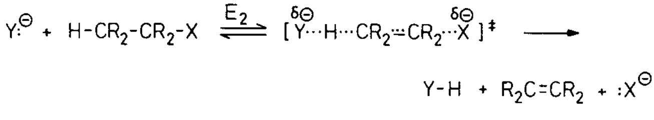

(5-21)

Table 5-6. Predicted solvent effects on rates of β-elimination reactions [16, 44, 73, 74].

Reaction type	Initial reactants	Activated complex	Charge alteration during activation	Effect of increased solvent polarity on rate[a)]
(a) E_1	$H-\overset{\vert}{\underset{\vert}{C}}-\overset{\vert}{\underset{\vert}{C}}-X$	$H-\overset{\vert}{\underset{\vert}{C}}-\overset{\vert}{\underset{\vert}{C}}{}^{\delta\oplus}\cdots X^{\delta\ominus}$	Separation of unlike charges	Large increase
(b) E_1	$H-\overset{\vert}{\underset{\vert}{C}}-\overset{\vert}{\underset{\vert}{C}}-X^{\oplus}$	$H-\overset{\vert}{\underset{\vert}{C}}-\overset{\vert}{\underset{\vert}{C}}{}^{\delta\oplus}\cdots X^{\delta\oplus}$	Dispersal of charge	Small decrease
(c) E_2	$Y: + H-\overset{\vert}{\underset{\vert}{C}}-\overset{\vert}{\underset{\vert}{C}}-X$	$Y^{\delta\oplus}\cdots H\cdots\overset{\vert}{\underset{\vert}{C}}\overset{\cdots}{=}\overset{\vert}{\underset{\vert}{C}}\cdots X^{\delta\ominus}$	Separation of unlike charges	Large increase
(d) E_2	$Y:^{\ominus} + H-\overset{\vert}{\underset{\vert}{C}}-\overset{\vert}{\underset{\vert}{C}}-X$	$Y^{\delta\ominus}\cdots H\cdots\overset{\vert}{\underset{\vert}{C}}\overset{\cdots}{=}\overset{\vert}{\underset{\vert}{C}}\cdots X^{\delta\ominus}$	Dispersal of charge	Small decrease
(e) E_2	$Y: + H-\overset{\vert}{\underset{\vert}{C}}-\overset{\vert}{\underset{\vert}{C}}-X^{\oplus}$	$Y^{\delta\oplus}\cdots H\cdots\overset{\vert}{\underset{\vert}{C}}\overset{\cdots}{=}\overset{\vert}{\underset{\vert}{C}}\cdots X^{\delta\oplus}$	Dispersal of charge	Small decrease
(f) E_2	$Y:^{\ominus} + H-\overset{\vert}{\underset{\vert}{C}}-\overset{\vert}{\underset{\vert}{C}}-X^{\oplus}$	$Y^{\delta\ominus}\cdots H\cdots\overset{\vert}{\underset{\vert}{C}}\overset{\cdots}{=}\overset{\vert}{\underset{\vert}{C}}\cdots X^{\delta\oplus}$	Destruction of charge	Large decrease

[a)] The terms "large" and "small" arise from the theory that the effect of the dispersal of charge should be notably smaller than the effect of its creation or destruction and have therefore only relative significance.

The changes undergone by the charges during the activation process are shown in the three middle columns of Table 5-6. The last column shows the predicted solvent effects.

Owing to the similarity of solvent effects for E_1 and S_N1 reactions due to the common rate-controlling step, only some examples of E_2 reactions are mentioned. Typical examples of the reaction types (c) to (f) in Table 5-6 are shown in Eqs. (5-22) to (5-25).

$$(CH_3)_3N + (CH_3)_3C{-}Br \longrightarrow (CH_3)_3\overset{\oplus}{N}{-}H + H_2C{=}C(CH_3)_2 + Br^{\ominus} \qquad (5\text{-}22)$$

$$HO^{\ominus} + CH_3{-}CH_2{-}Br \longrightarrow H_2O + H_2C{=}CH_2 + Br^{\ominus} \qquad (5\text{-}23)$$

(5-24)

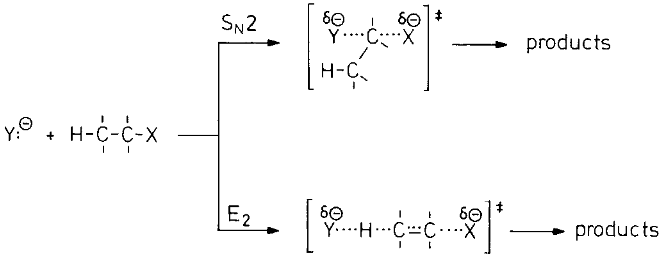
$$H_2O + O_2N{-}C_6H_4{-}CH_2{-}CH_2{-}\overset{\oplus}{N}(CH_3)_3 \longrightarrow H_3O^{\oplus} + O_2N{-}C_6H_4{-}CH{=}CH_2 + N(CH_3)_3$$

$$C_2H_5O^{\ominus} + CH_3{-}CH_2{-}\overset{\oplus}{S}(CH_3)_2 \longrightarrow C_2H_5OH + H_2C{=}CH_2 + S(CH_3)_2 \qquad (5\text{-}25)$$

In Eqs. (5-23) and (5-24), there is no net change of charge after reaction, but for Eq. (5-22) charge is created and for Eq. (5-25) it is destroyed. Further examples of observed effects for solvent changes on rates of mono- and bimolecular eliminations are given by Hughes and Ingold [16, 44]. In most cases studied, haloalkanes and *'onium* salts in ethanol/water mixtures, the observed solvent effects are in the expected direction.

According to the Hughes–Ingold rules, in E_2 and S_N2 reactions the dispersal of charge is spread over more atoms than in E_1 and S_N1 reactions, so increase in solvent polarity will generally favor the E_1 and S_N1 mechanisms over the E_2 and S_N2 mechanisms. Thus, solvent change can alter not only the rate but also the reaction mechanism.

The competition between *β*-elimination and substitution reaction determines the proportion of alkene produced. The ratio of elimination to substitution is affected by the solvent as well as other factors (concentration and strength of the attacking base, temperature, structure of substrate and attacking base). Looking at the activated complexes for S_N2 and E_2 reactions, it can be seen that the charge is more widely dispersed in the elimination transition state than in that of substitution.



From this it follows that both reactions are decelerated with increasing solvent polarity, but due to the larger charge dispersal on activation in E_2 reactions, solvent stabilization of the activated complex of elimination is less than that for substitution. Therefore, E_2 eliminations are more decelerated than S_N2 substitutions with increasing solvent polarity, and the alkene yield should fall slightly on making this solvent change. Table 5-7 gives some examples of solvent effects on the proportion in which the alkene is formed in *β*-elimination reactions.

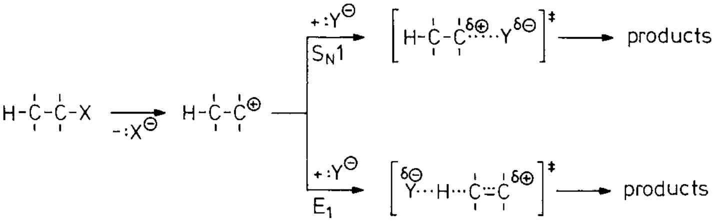
Although the solvent effects are small, the alkene formation diminishes as predicted with increasing water content (corresponding to increased solvent polarity). The S_N2/E_2 reaction of 2-phenylpropyl tosylate with sodium cyanide (in hexamethylphosphoric triamide and in *N*,*N*-dimethylformamide as solvents at 100 °C) gives *α*-methylstyrene (elimination product) and 1-cyano-2-phenylpropane (substitution product) [75]. It has been found, in accordance with the predictions of the Hughes–Ingold rules, that the elimination/substitution ratio decreases as the polarity of the solvents (measured by the relative permittivity) increases [75]. Theoretical investigations of the

Table 5-7. Observed solvent effects on the proportion of alkene formed in mono- and bimolecular *β*-eliminations in ethanol/water mixtures [16, 44].

		Water in ethanol in cL/L			
		0	20	40	100
(a) *Bimolecular reactions*	($E_2 + S_N2$)				
$HO^{\ominus} + i\text{-}C_3H_7$—Br	(55 °C)	71	59	54	–
$HO^{\ominus} + (H_5C_2)_3S^{\oplus}$	(100 °C)	–	100	100	86
(b) *Monomolecular reactions*	($E_1 + S_N1$)				
$t\text{-}C_4H_9Br$	(25 °C)	19.0	12.6	–	–
$t\text{-}C_5H_{11}$—Br	(25 °C)	36.3	26.2	–	–
$t\text{-}C_5H_{11}$—$S(CH_3)_2^{\oplus}$	(50 °C)	64.4	47.8	–	–

dichotomic S_N2/E_2 reaction between F^- and CH_3CH_2F in the presence of n HF ($n =$ 0–4) as a 'polar solvent' using the density-functional method have confirmed the experimental results: by microsolvation, the S_N2 activated complex is much more stabilized and becomes lower in energy than the *anti*-E_2 activated complex [854].

Analogously, solvent effects on alkene formation in S_N1 and E_1 reactions can be predicted [16, 44]. Owing to the fact that the first step in both reactions, the heterolysis of the C—X bond, is exactly the same, we have to consider the activated complexes which lead to either the alkene or substitution product.



Both reactions are decelerated with increasing solvent polarity. However, due to the greater dispersal of charge in the transition state of the E_1 reaction, the β-elimination is again more decelerated than the substitution reaction. This results in decreasing alkene formation with increasing solvent polarity. Similar results are obtained for reactions in which Y: represents a neutral base (*e.g.* H_2O). Some observed effects of solvent changes on alkene formation in E_1 and S_N1 reactions are given in Table 5-7. Experimental results are relatively scarce. Nevertheless, the predicted rate trends for all charge-types of *'onium* salts and haloalkanes in protic media are obtained [16, 44]. Newer studies of the competition between substitution and elimination in solvolyses of various 2-halo-2-methylpropanes in acetic acid, ethanol, and water have shown that decreasing solvent polarity favours alkene formation [76].

A further refinement of the Hughes–Ingold rules has been given by Westaway regarding the influence of solvents on the structure of S_N2 activated complexes [498]; *cf.* Eq. (5-12) and Table 5-4. His *solvation rule for* S_N2 *reactions* states that a change in solvent will not lead to a change in the structure of an S_N2 transition state if both the attacking nucleophile, Y, and the leaving group, X, have the same charge as in reaction types (d) and (e) in Table 5-4 (called *type I* S_N2 reactions). A solvent change will, however, lead to a change in the structure of the S_N2 transition state when the nucleophile and leaving group have opposite charges, as in reaction types (c) and (f) in Table 5-4 (called *type II* S_N2 reactions).

If the activated complex of *type I* S_N2 reactions is transferred from the gas phase to solution, the solvent will interact nearly equally with the two partially charged groups Y and X, thus lowering the Gibbs energy of the activated complex. The Gibbs energy of the activated complex will vary from solvent to solvent and the rate constant changes with solvent, depending on the interaction between Y and X and the solvent. However, the relative charge density of Y and X will not be altered by a solvent change, and thus the structure of the activated complex will not be changed even though its Gibbs energy has been changed.

On the other hand, in activated complexes of *type II* S_N2 reactions, the charges on Y and X are of opposite sign, and thus the nucleophile Y and the leaving group X will interact differently with the solvent. For instance, in protic solvents, the negatively charged group will be preferentially solvated *via* hydrogen-bond interactions, whereas a much weaker ion-dipole type interaction will occur at the positively charged group. As a result, the difference in solute/solvent interactions at both ends of the activated complex will be large enough to cause a shift in charge density between Y and X along the Y ... C ... X bond axis of the S_N2 transition state. In this case, not only the Gibbs energy but also the structure of the activated complex will be altered from solvent to solvent.

In other words, whether or not an S_N2 reaction has a *tight* or *loose* activated complex will not only depend upon the nature of the reactants Y and R–X, in solution it will also be affected by the nature of the solvent. Better solvation of the activated complex of a *type II* S_N2 reaction by solvents with improved EPD/EPA properties will lead to a loosening of the activated complex. Transferring this activated complex from solution to the gas phase, with subsequent loss of the charge-separation stabilizing solvation, will therefore increase its tightness; *cf.* also [499].

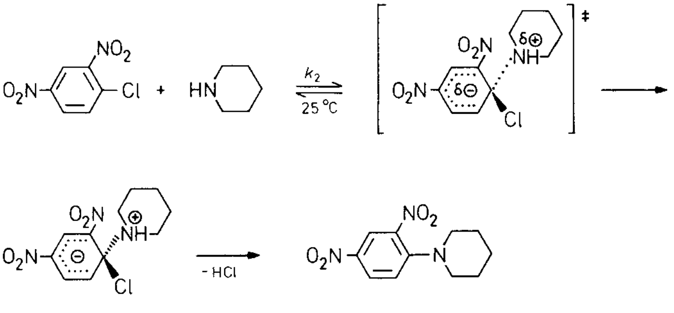
This *solvation rule for S_N2 reactions* can be useful in predicting the influence of a change in solvent on the structure of activated complexes. It is in agreement with studies involving leaving group heavy atom and secondary α-deuterium kinetic isotope effects, as well as theoretical calculations of solvent effects on transition-state structures. Possible limitations of this solvation rule have been discussed; see [498] and relevant references cited therein.

Although the Hughes–Ingold theory of solvent effects was first illustrated in the field of nucleophilic aliphatic substitutions and β-eliminations, it should be applicable to all other heterolytic reactions in solutions, where the activation processes are connected with creation, dispersal, or destruction of charge. Using Kosower's classification [15, 468], in the following Sections the solvent effects on other organic reactions will be discussed to give the reader a feeling for the expected solvent influence, and to help him or her in finding the right solvent for a particular reaction under study.

5.3.2 Solvent Effects on Dipolar Transition State Reactions

Reactions involving dipolar activated complexes are those in which, compared to the initial state, there are considerable differences in charge distribution. In addition to S_N1/S_N2 and E_1/E_2 reactions as described in Section 5.3.1, solvent effects on the following reactions involving dipolar activated complexes have been studied: aromatic nucleophilic (S_NAr) and aromatic electrophilic (S_EAr) reactions; aliphatic electrophilic substitution (S_E1/S_E2) reactions; aliphatic electrophilic (A_E) and aliphatic nucleophilic addition (A_N) reactions; cycloaddition and cycloreversion reactions; aldol addition reactions; as well as rearrangement, fragmentation, and isomerization reactions. A selection of typical and particularly instructive examples, taken from the vast number of examples given in the literature, shall demonstrate the usefulness of the simple qualitative Hughes–Ingold approach.

The simplest example of an aromatic nucleophilic substitution is the S_NAr reaction between 1-chloro-2,4-dinitrobenzene and piperidine, the two-step mechanism of which, given in Eq. (5-26), is now fully established [501–503]. It involves formation of a Meisenheimer-type zwitterionic intermediate *via* a dipolar activated complex, followed by spontaneous or base-catalysed elimination of HCl to give the reaction product. Regarding this last step, the solvent can modify the relative rates of the first and second step as well as the reaction order.

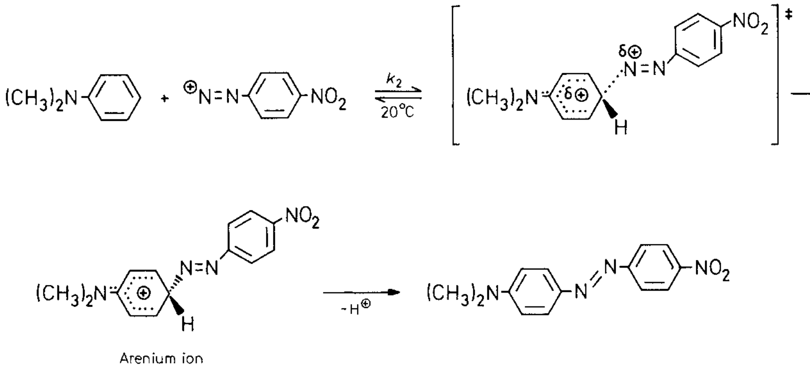


(5-26)

Solvent	c-C_6H_{12}	C_6H_6	C_6H_5Cl	CH_3COCH_3	$HCON(CH_3)_2$	CH_3SOCH_3
k_2^{rel}	1	2	5	13	29	50

In agreement with the separation of unlike charges during the activation process, an increase in rate by up to a factor of 50 with increasing solvent polarity has been found for reaction (5-26), carried out in thirteen non-HBD solvents [503]. The absence of base-catalysis suggests that specific solvent effects are negligible in non-HBD solvents. In protic solvents, however, specific solvation of the piperidine nucleophile leads to a diminution in rate with increasing HBD ability of the hydroxylic solvents [503].

As an example of a solvent-dependent electrophilic substitution reaction, the azo coupling (S_EAr) reaction of 4-nitrobenzenediazonium tetrafluoroborate with *N*,*N*-dimethylaniline is given in Eq. (5-27) [504]. According to the two-step arenium ion mechanism, the activation process of the rate-limiting first step is connected with the dispersion of the positive charge. This should lead to a decrease in rate with increasing solvent polarity.



(5-27)

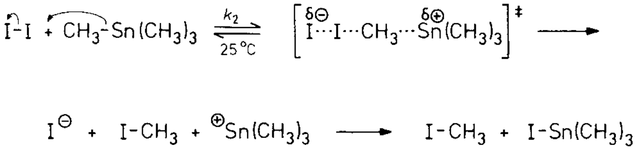
Solvent	CH_3NO_2	CH_3CN	CH_3COCH_3	$HCON(CH_3)_2$	CH_3SOCH_3	HMPT
k_2^{rel}	4748	509	110	7	4	1
DN	2.7	14.1	17.0	26.6	29.8	38.8

The solvent-induced change in rate is, however, much larger than expected from the relatively small difference in polarity between nitromethane and hexamethylphosphoric triamide. This, together with the correlation between rate decrease and increase in the solvent donor number *DN* (*cf.* Table 2-3 in Section 2.2.6), suggests that specific solvation and stabilization of the diazonium ion by EPD solvents play a dominant role in the reaction (5-27). Very likely, formation of an EPD/EPA complex between the reactants in a rapid preequilibrium step precedes the rate-controlling first step [504, 792].

The addition of bases (*e.g.* tertiary amines) can induce proton abstraction from the arenium ion intermediate in the second reaction step. Investigation of base-catalysed azo coupling reactions with *N*,*N*-dialkylanilines in different organic solvents have shown that the solvent itself can abstract the proton from the arenium ion intermediate. In solvents of relatively high basicity (CH_3OH, CH_3SOCH_3), neither base-catalysis nor a kinetic isotope effect was observed. In less basic solvents (CH_3NO_2), however, the reaction is strongly accelerated by base and exhibits a substantial deuterium isotope effect [505]. In other words, a change in solvent can also induce a change in the rate-limiting step of azo coupling reactions.

The influence of the reaction medium on azo coupling reactions has been reviewed by Zollinger *et al.* [506].

The S_E2 cleavage of tetramethyltin with iodine is an aliphatic electrophilic substitution reaction which is subject to strong solvent dependence [507–509]. The rate of iodinolysis of $(CH_3)_4Sn$ in acetonitrile at 25 °C is more than 10^5 times faster than that in tetrachloromethane (carried out at 50 °C owing to its slow rate in this solvent) [509].



(5-28)

Solvent	CCl_4	C_6H_5Cl	CH_2Cl_2	CH_3COCH_3	C_2H_5OH	CH_3CN
k_2^{rel}	1[a]	7.4	252	739	47800	274000

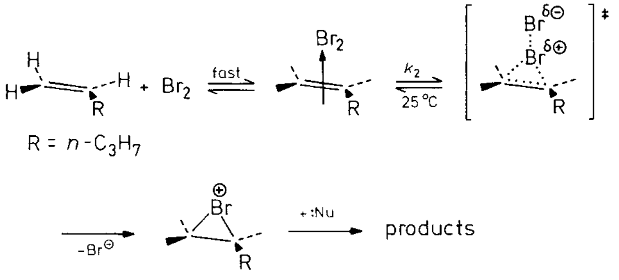
[a] at 50 °C.

The fact that the second-order rate constant is strongly solvent-dependent is in agreement with a highly dipolar activated complex as shown schematically in Eq. (5-28) by the S_E2(back) mechanism. Neither reactant has a dipole moment; the degree of charge separation in the activated complex is estimated to be between 0.8 and 1 [509]. A fast preequilibrium formation of an EPD/EPA complex between the reactants, followed by a rate-limiting iodinolysis of the alkyl metal by electron-transfer from the alkyl metal donor to the iodine moiety to give an intermediate radical ion pair, $(CH_3)_4Sn^{\oplus\cdot}$, $I_2^{\ominus\cdot}$, is also consistent with the observed solvent-dependence [509]. In S_E2 reactions, solvents not only affect the reaction rates, but also the dichotomy between S_E2(front), S_E2(back), and S_Ei mechanisms, as well as selectivity $S(R/CH_3)$ in the cleavage of unsymmetrical alkyl metals such as $(CH_3)_nSnR_{4-n}$ [508].

Solvent effects on the rates of organotin and organomercury alkyl exchange reactions have been studied and reviewed by Petrosyan [510]. It should be mentioned that the solvent influence on the reactivity of organometallic compounds was first studied by Ziegler *et al.* in 1929/30. He showed that organolithium compounds react faster in diethyl ether than in hydrocarbons such as benzene and cyclohexane [511].

Now, some addition reactions will be considered, the solvent dependences of which have been reviewed [77, 78]. Addition of uncharged electrophiles (*e.g.* Br_2, ArS—Cl, NO—Cl, R—CO_3H) to carbon–carbon multiple bonds leads to the development of a small, usually dispersed charge in the activated complex. In more polar solvents, this is accompanied by a slight rate acceleration. In reactions with substantial charge development in the activated complex, larger rate accelerations with increasing solvent polarity are observed.

A strongly solvent-dependent electrophilic reaction is the addition of halogens to alkenes [79–81] and alkynes [81a]. In a rapid equilibrium, a loose transitory EPD/EPA complex (1:1) between halogen and alkene is formed [512]. This is followed by the rate-determining step, which involves an S_N1-like unimolecular ionization to form a halonium intermediate which can be either symmetrical or unsymmetrical. This then reacts with a nucleophile Nu: to give the products; *cf.* Eq. (5-29).



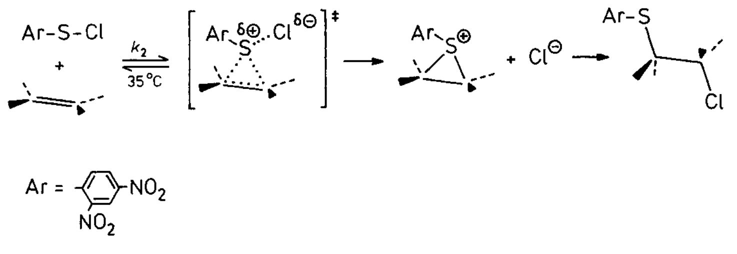
(5-29)

Solvent	CCl_4	1,4-Dioxane	CH_3CO_2H	CH_3OH	H_2O
k_2^{rel}	1	51	4860	$1.6 \cdot 10^5$	$1.1 \cdot 10^{10}$

It has been shown that in the case of bromine addition to 1-pentene in solvents of different polarity, the overall rate constant varies by a factor of 10^{10} (!) [81]. This dramatic solvent effect has been taken – together with other findings – as strong evidence for the so-called Ad_EC1-mechanism, which involves considerable charge separation in the activation step. It has also been demonstrated that protic solvents enhance this addition by a specific electrophilic solvation of the anionic part of the activated complex [81]. It appears that in the rate-determining step of alkene brominations there is also a small specific nucleophilic solvent contribution [513]. In addition it should be mentioned that, not only the rate, but also the stereospecifity of this halogen addition is strongly solvent-dependent (*cf.* Section 5.5.7) [79, 81].

The rate of the analogous bromine addition to 1-hexyne is *ca.* 10^4 times faster in methanol/water (50:50 cL/L) than in acetic acid [81a].

In the same manner, the second-order rate constant for the reaction of cyclohexene with chloro-2,4-dinitrophenylsulfane increases with increasing solvent polarity [82].



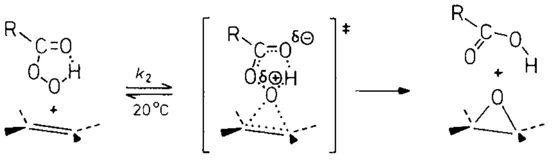
(5-30)

Solvent	CCl_4	$CHCl_3$	CH_3CO_2H	$ClCH_2CH_2Cl$	$C_6H_5NO_2$
k_2^{rel}	1	605	1370	1380	2800

Neutral reactants form a dipolar activated complex, which reacts through a thiiranium intermediate [83, 515] to give the products. Similar solvent effects have been observed in the addition of chloro-phenylsulfane to alkenes [514].

A reaction corresponding to Eq. (5-30) is the addition of nitrosyl chloride to alkenes such as cyclohexene or styrene [84, 85]. The reaction seems to be faster in polar solvents (*e.g.* nitrobenzene and trichloromethane) than in less polar solvents (*e.g.* toluene and tetrachloromethane). This is consistent with the view that the reaction involves an electrophilic attack of $NO^{\delta\oplus}—Cl^{\delta\ominus}$. The reaction was, however, also found to be very slow in diethyl ether. Presumably, this is due to strong bonding of the NO^+ cation to the ether oxygen atom [84].

The epoxidation of alkenes with peroxycarboxylic acids gives the corresponding oxirane by an electrophilic 1,1-addition mechanism as outlined in Eq. (5-31) [77, 86, 86a, 87, 516].



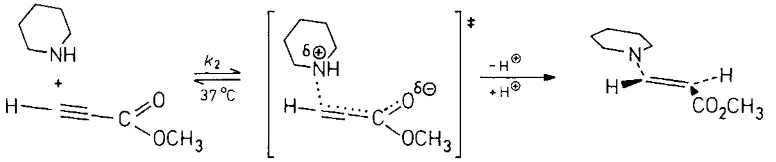
(5-31)

Solvent	$(C_2H_5)_2O$	1,4-Dioxane	n-C_6H_{14}	C_6H_6	CH_2Cl_2	$CHCl_3$
k_2^{rel} for $R = C_6H_5$ and cyclohexene [86a]	1	2.5	6.2	40	58	122

In the reactions of cyclohexene with peroxybenzoic acid ($R = C_6H_5$) [86a] and of trimethylethene with peroxyacetic acid ($R = CH_3$) [87], a moderate increase in rate with increasing solvent polarity was observed. These experimental results and recent DFT calculations [86] are in agreement with the asynchronous formation of a slightly dipolar spiro-geometrical activated complex, as proposed in Eq. (5-31). The highest rates for these reactions are obtained in non-HBD halogen-containing solvents (CH_2Cl_2, $CHCl_3$). The slowest rates are found in solvents capable of intermolecular association with the peroxycarboxylic acid (ethers). The strength of intermolecular peracid–solvent interaction increases with increasing solvent basicity [78, 87].

The addition of peroxyacetic acid to the heteronuclear C═O double bond of cyclohexanone (*i.e.* the first step of the Baeyer–Villiger oxidation reaction) also exhibits a small solvent dependence [517].

Nucleophilic additions to carbon–carbon triple bonds are also subject to solvent influence, as shown by the example given in Eq. (5-32) [88].



(5-32)

Solvent	c-C_6H_{12}	$(C_2H_5)_2O$	C_6H_6	CH_3OH	1,4-Dioxane	CH_3CN
k_2^{rel}	1	2	10	65	73	865

The second-order rate constant for the reaction between methoxycarbonylacetylene and piperidine increases with increasing solvent polarity. This can be attributed to the increased solvation of the strongly dipolar activated complex, which is formed from neutral molecules [88]. Analogous solvent effects have been observed for the nucleophilic addition of aziridine to 3-dimethylaminopropynal [89] and the addition of diethylamine to β-alkoxyvinyl methyl ketones [793].

Concerted $[_{\pi}2_s + _{\pi}2_s]$ cycloadditions are, in principle, forbidden by orbital symmetry [90]. This restriction is bypassed when these reactions occur *via* zwitterions or biradicals, or by the symmetry-allowed $[_{\pi}2_a + _{\pi}2_s]$ process. Since cycloadditions proceeding through zwitterionic intermediates or dipolar activated complexes should be affected by solvent polarity, the investigation of the solvent effects on rates can be of considerable value when considering potential models for the activated complex and the reaction mechanism [91–93]. The possible solvent effects on one-step and two-step cycloaddition reactions are shown schematically in Fig. 5-6 [92]*⁾.

In the case of one-step cycloaddition reactions involving an activated complex with a different dipolarity than the reactants, an increase in solvent polarity should enhance the reaction rate (*cf.* Fig. 5-6a). However, since two-step cycloadditions are consecutive reactions, the solvent effect depends on the relative size of $\Delta G_I^{\neq}$ and $\Delta G_I^{\neq\prime}$ or of $\Delta G_{II}^{\neq}$ and $\Delta G_{II}^{\neq\prime}$ (*cf.* Fig. 5-6b). If the formation of the zwitterionic intermediate is irreversible, and $\Delta G^{\neq} \gg \Delta G^{\neq\prime}$, then the first step is rate-determining in all solvents. Consequently, there is a rate acceleration with increasing solvent polarity. When $\Delta G^{\neq} \ll \Delta G^{\neq\prime}$, this behaviour is reversed. If ever $\Delta G^{\neq} \approx \Delta G^{\neq\prime}$, then only relatively

---

* Some definitions may be of importance for this and further discussions. A *two-step* reaction is one which takes place in two distinct kinetic steps, *via* a stable intermediate. A *one-step*, *concerted* reaction is one which takes place in a single kinetic step. A *synchronous* reaction is a concerted reaction in which all the bond-making and bond-breaking are parallel processes, having proceeded to the same extent in the activated complex. A *two-stage* reaction is a concerted but non-synchronous reaction. That is, some of the bond-making and bond-breaking processes take place mainly in the first half of the reaction (between reactants and activated complex), while the rest take place in the second half of the reaction (between activated complex and products). *Cf.* [116] and the references cited therein.

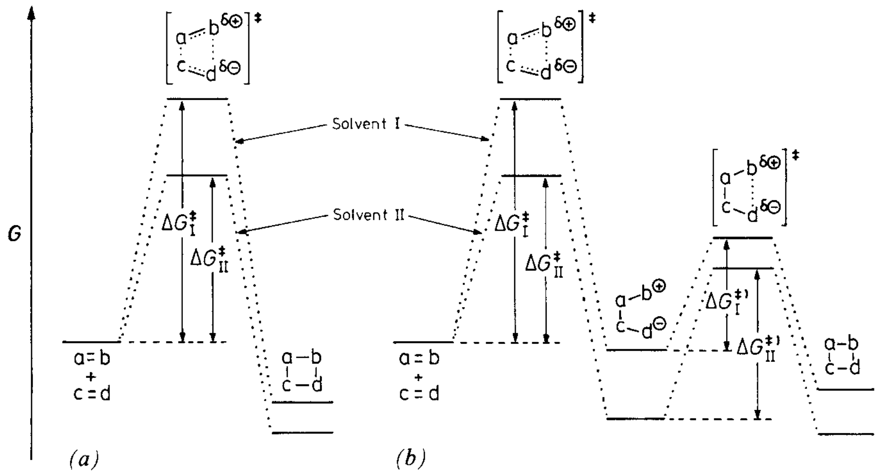


Fig. 5-6. Gibbs energy diagram for *(a)* one-step cycloaddition reactions proceeding via a dipolar activated complex, and *(b)* two-step cycloaddition reactions proceeding via a zwitterionic intermediate, in both nonpolar (solvent I) and polar solvents (solvent II) [92]. For the sake of simplicity, no notice is taken of the different solvation of the initial reactants.

small, positive or negative, solvent effects will be observed. If the formation of the zwitterionic intermediate is reversible, then a rate increase with increasing solvent polarity will always be obtained. Under these circumstances, the distinction between a one-step and a two-step mechanism can be made only (if at all) when the solvent effects are large. Additionally, the activated complexes of the first stage of two-step reactions and of one-step reactions presumably differ only slightly in structure and dipolarity. Provided that the first step in the two-step reaction is rate-determining, the expected solvent effects for both reactions should be similar in direction and extent [92]. Three typical examples shall demonstrate solvent effects on [2 + 2] cycloadditions; for more examples, see reference [92].

A prototype cycloaddition involving a zwitterionic intermediate is the reaction of *n*-butyl vinyl ether with tetracyanoethene, as shown in Eq. (5-33) [94–98].

The influence of the solvent on the cycloaddition rate constants for electron-rich alkenes is of an unusual magnitude, as shown by $k_2(\mathrm{CH_3CN})/k_2(\mathrm{C_6H_{12}}) = 2600$ for *n*-butyl vinyl ether, 10800 for 1-ethoxybutene, and 29000 for 1-methoxy-4-propenylbenzene (anethole) [94]. These ratios correspond to a $\Delta\Delta G^{\neq}$ of up to 23 kJ/mol (5.5 kcal/mol) for the increase in solvation during activation. The formation of the zwitterionic intermediate is assumed to be both reversible and rate-controlling. The dipole moments of reactants and adduct, as well as the calculated dipole moments of the activated complex and the zwitterion, reveal a notable increase in charge separation, corresponding to the large solvent effect obtained*⁾. The dipole moment of the activated

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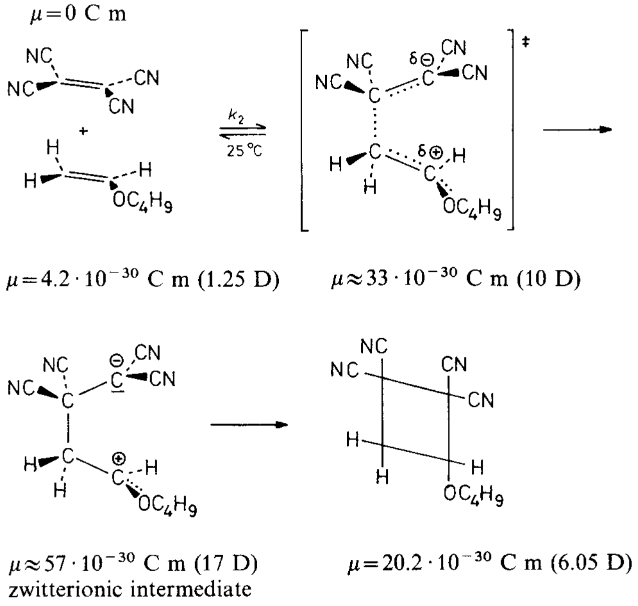
* The calculation of the dipole moment of the activated complex was based on an electrostatic model of Kirkwood, Laidler and Eyring (*cf.* Section 5.4.3) [2, 11]. The value for the dipole moment of the zwitterion was estimated as the vector sum of the partial moments [94].

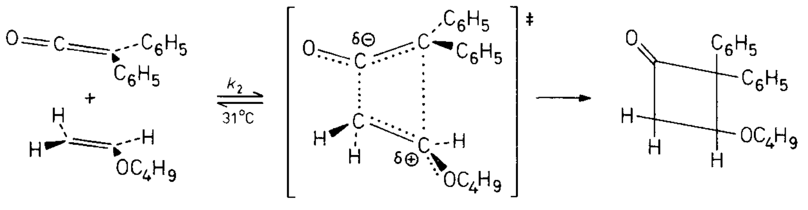


(5-33)

complex is larger than expected for the transition state of a concerted one-step cycloaddition reaction. The transition state dipole moment is two-thirds of the zwitterion dipole moment, which is reasonable because the charge separation is not yet completed in the transition state for zwitterion formation. Apart from solvent dependence of the rate constants, additional evidence for a two-step mechanism and formation of a zwitterionic intermediate in reaction (5-33) can be obtained by examining the effect of structural variation of the enol ether on the rate [94], the activation parameter [94], and the solvent dependence of the activation volume [95, 96]. The intermediate 1,4-dipole can also be trapped using alcohols or 1,4-dipolarophiles [97, 98]. Further agreement with the two-step mechanism is the lack of solvent-dependent stereospecificity for the cycloaddition reaction [94]. Rotation of the assumed zwitterionic intermediate competes with the cyclization to give the cyclobutane product. Similarly large solvent effects on rate have been observed for tetracyanoethene additions to ethyl propenyl thioether [518] and verbenene, a *trans*-fixed 1,3-diene [519]. The [2 + 2] cycloaddition of *cis*- and *trans*-1,2-bis(trifluoromethyl)-1,2-dicyanoethene to *tert*-butyl vinyl thioether also proceeds *via* a zwitterionic intermediate, corresponding to a rate acceleration of $k_2(CH_3CN)/k_2(CCl_4) = 2160$ [99]. Further 1,4-dipolar zwitterionic intermediates have been postulated for the thermal [2 + 2] cycloadditions of tetracyanoethene to styrene [99a] and 1,1-diarylbutadienes [520], as well as for the cycloaddition of tris(methoxycarbonyl)ethene to 4-(dimethylamino)styrene [521] on the basis of the rate changes observed upon altering the solvent polarity.

In contrast to reaction (5-33), the rate for the cycloaddition reaction of diphenylketene to *n*-butyl vinyl ether shows a much smaller solvent dependence; *cf.* Eq. (5-34) [100].

$\mu = 5.9 \cdot 10^{-30}$ C m (1.76 D)



(5-34)

$\mu = 4.2 \cdot 10^{-30}$ C m (1.25 D)

$\mu = 10.1 \cdot 10^{-30}$ C m (3.20 D)

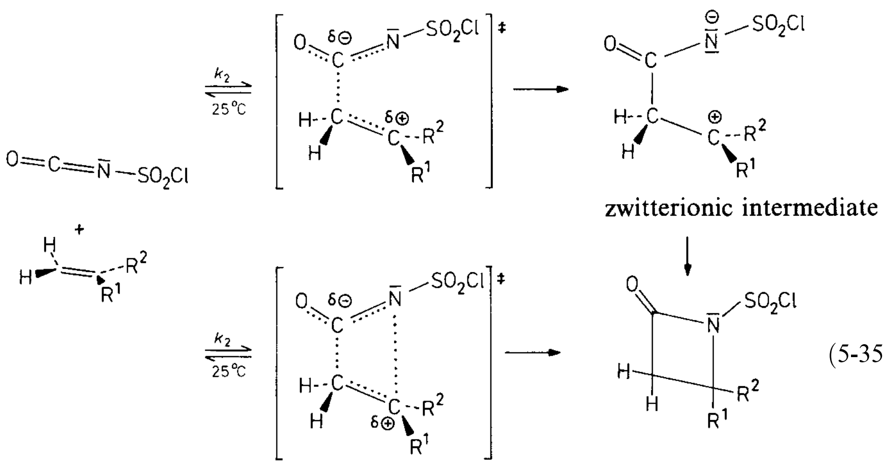
Solvent	c-C_6H_{12}	C_6H_5Cl	CH_3COCH_3	C_6H_5CN	CH_3CN
k_2^{rel}	1	13	43	63	163

The smaller rate increase with increasing solvent polarity, the large negative activation entropy, as well as electronic and steric substituent effects and the stereospecificity of this reaction, are all in agreement with a concerted, but non-synchronous one-step mechanism. The unequal bond formation in the activated complex creates partial charges, which are stabilized by increasingly polar solvents. Reaction (5-34) should be solvent-independent if the dipole moment of the activated complex approaches $10.1 \cdot 10^{-30}$ Cm (*i.e.* sum of the dipole moments of the reactants), a figure which corresponds to the dipole moment of the product. The solvent dependence obtained shows that there must be a larger charge separation in the activated complex than in the adduct [100]. A similar solvent effect was reported for the dimerization reaction of dimethyl ketene ($k_2(CH_3CN)/k_2(CCl_4) = 29$), in agreement with a concerted one-step mechanism with charge separation in the activation step [101].

In the reaction of dimethylketene with enamines such as *N*-isobutenylpyrrolidine, the two-step process *via* a zwitterion (k_I) competes successfully with the concerted one-step mechanism (k_C), leading to cyclobutanones and 2:1 adducts, respectively [102]. In contrast to the activated complex formed from vinyl ethers, there is superior stabilization of the positive charge in the zwitterion, $>C\overset{\delta\oplus}{\overline{\cdots\cdots}}NR_2$ *vs.* $>C\overset{\delta\oplus}{\overline{\cdots\cdots}}OR$; *cf.* Eqs. (5-33) and (5-34). The experimental results for the cycloaddition of dimethylketene to *N*-isobutenyl-pyrrolidine show that k_I depends to a much higher extent on solvent polarity than k_C, the rate constant of the concerted reaction. In acetonitrile, the zwitterionic 1,4-dipole is produced 560 times faster than in cyclohexane, while the same solvent change accelerates the concerted reaction only 36-fold [102].

Graf [103] originally proposed a two-step mechanism for the cycloaddition of chlorosulfonyl isocyanate to alkenes. This leads to the 1,4-dipole shown in Eq. (5-35), which can then ring close to give a β-lactam (and as by-product an unsaturated amide *via* a proton shift from R^1 or R^2 to $N^\ominus$). Moriconi [104], on the other hand, has proposed a nearly concerted, thermally allowed $[_\pi 2_s + {}_\pi 2_a]$ cycloaddition, probably initiated by a π-complex formation, and proceeding through the dipolar activated complex shown in the lower part of Eq. (5-35).

Among the evidence cited in favour of the two-step mechanism (for a review, see reference [105]) is the marked increase in reaction rate produced by polar solvents

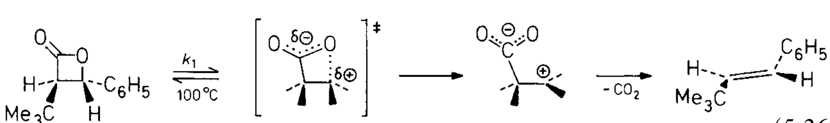


(5-35)

Solvent	n-C_6H_{14}	$(C_2H_5)_2O$	$CHCl_3$	CH_2Cl_2	$C_6H_5NO_2$	CH_3NO_2
k_2^{rel}	1	31	250	1700	5000	18800

for the reaction of chlorosulfonyl isocyanate with 2-ethyl-1-hexene ($R^1 = C_2H_5$; $R^2 = n$-C_4H_9) [106, 107]. *Ab initio* MO calculations have shown that the [2 + 2] cycloaddition between *cis*- or *trans*-alkenes and isocyanates to yield β-lactams takes place by a concerted mechanism in the gas phase, with retention of the alkene configuration in the product. However, increasing solvent polarity contributes to the asynchronicity of the reaction to such an extent that the mechanism changes from a concerted to a two-step process involving a zwitterionic intermediate, with a consequent loss of alkene stereospecificity, as observed in the reaction between chlorosulfonyl isocyanates and vinyl ethers [794].

Not only thermal [2 + 2] cycloaddition reactions but also the corresponding [2 + 2] cycloreversions are subject to large solvent effects. A good example is the thermal decarboxylation of the β-lactone *trans*-3-*t*-butyl-4-phenyloxetan-2-one, as described in Eq. (5-36).



(5-36)

$\mu \approx 14 \cdot 10^{-30}$ Cm (4.2 D) $\mu \approx 27 \cdot 10^{-30}$ Cm (8.2 D) [524] $\mu \approx 0$ Cm

Solvent	Decalin	$C_6H_5OCH_3$	C_5H_5N	Propylene carbonate	$HCONHC_6H_5$
k_2^{rel}	1	4	14	98	438

The substantial rate increase with increasing solvent polarity is consistent with a two-step route *via* a highly dipolar activated complex [522]. This mechanism is also

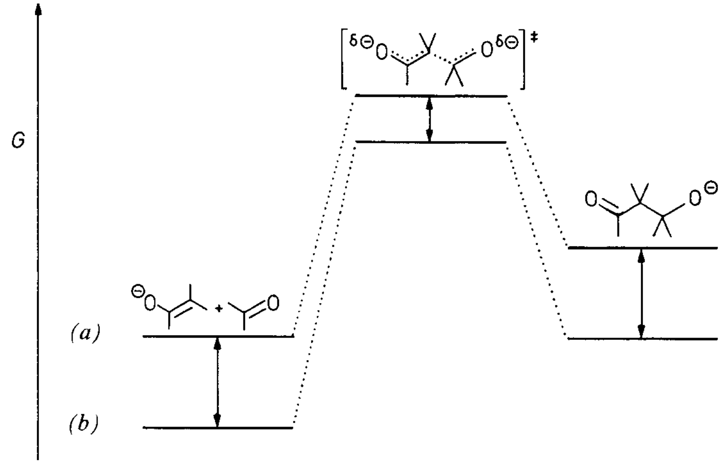
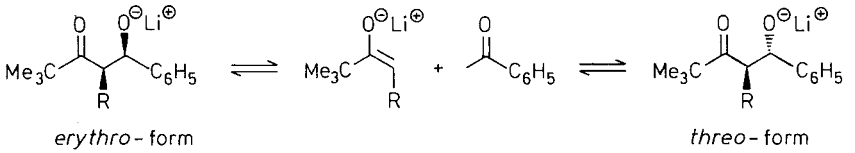


Fig. 5-7. Schematic Gibbs energy diagram for a general aldol addition of enolates to carbonyl compounds in both *(a)* nonpolar solvents, and *(b)* polar solvents, according to Heathcock [525].

supported by the negative volume of activation, $\Delta V^{\neq} = -28$ cm^3/mol, although the volume of reaction is +52 cm^3/mol! [523]. The thermal decarboxylation of 3,3-difluoro-4,4-dimethyloxetan-2-one, which could be studied in solution *and* in the gas phase, is even 3600 times faster in acetonitrile than in the gas phase [524a]. *Ab initio* MO calculations have shown that the mechanism in the gas phase is obviously quite different from that in solution. Experimental and computational kinetic data point to a concerted mechanism in the gas phase (via biradicaloid or non-Woodward–Hoffmann topological activated complexes), whereas even in moderately polar solvents zwitterionic intermediates must be involved [524a,b].

One very important addition reaction is the aldol addition of enolate ions to carbonyl double bonds to give β-hydroxy aldehydes (aldols) or β-hydroxy ketones (ketols). According to Fig. 5-7, the negative charge is localized on one oxygen atom in both the reactants and products of the aldol addition. In the activated complex, however, the negative charge is shared between two oxygen atoms. In polar solvents, reactants and products are expected to be more stabilized by solvation than the activated complex with its dispersed charge. Thus, both aldol addition and retro-aldol reaction should be faster in nonpolar than in polar solvents [525]. Enolate, activated complex, and aldolate are considered as monomeric species, which is certainly an oversimplification. Nevertheless, the arguments regarding charge delocalization during the activation process should still apply for oligomers, and the conclusion that nonpolar solvents should accelerate aldol additions (and aldol reversals) is still valid.

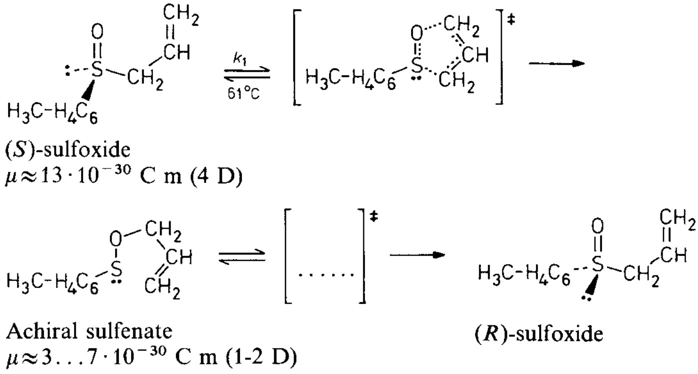
Simple, clear-cut examples of aldol reactions exhibiting such solvent effects are scarce. Heathcock *et al.* [526] have reported that the *erythro* → *threo* equilibration of lithium aldolates (*via* retro-aldol reaction) is much faster in pentane than in tetrahydrofuran or diethyl ether.



(5-37)

Thus, the *erythro* lithium aldolates given in Eq. (5-37) (R = Me, Et, *n*-Pr, *n*-Bu) equilibrate to their *threo* counterparts in less than two hours at 25 °C in pentane ($t_{1/2} = 45$ min for the aldolate with R = CH_3), whereas in diethyl ether the rate of equilibration is much slower ($t_{1/2} = 8$ hours for the aldolate with R = CH_3) [525, 526].

We shall conclude this Section with four other examples of rearrangements, fragmentations, and isomerizations for solvent-dependent reactions involving dipolar activated complexes.



(5-38)

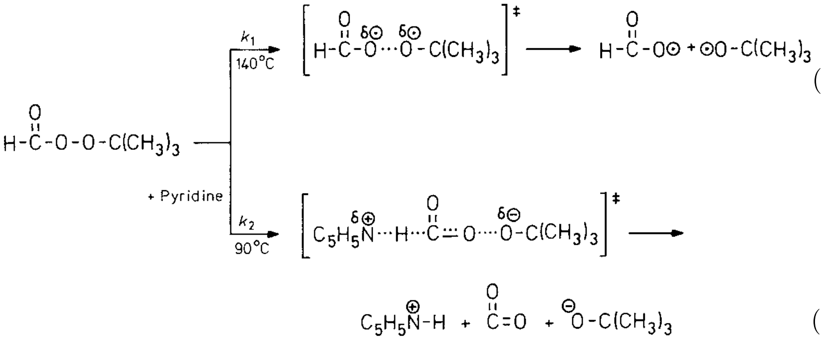
Solvent	Methylcyclohexane	C_6H_6	1,4-Dioxane	CH_3CN	C_2H_5OH	$CHF_2CF_2CH_2OH$
k_1^{rel}	332	121	73	25	11	1

A study of the solvent effects on the rate of thermal racemization of chiral allyl sulfoxides has revealed that polar solvents significantly decelerate the racemization [108]. The reaction proceeds by way of a reversible and concerted rearrangement: achiral allyl sulfenates are formed as intermediates and an intramolecular α, γ-shift of the allyl group between the sulfoxide oxygen and sulfur termini occurs as shown in Eq. (5-38).

The proposed mechanism is in accordance with the observed solvent dependence of the reaction. Whereas the dipolar sulfoxide is expected to be more strongly solvated with an increase in solvent polarity, the less dipolar sulfenate should be relatively insensitive to such a solvent change. Stabilization of the sulfoxide, relative to the less dipolar activated complex (which should be similar to the sulfenate intermediate), increases the enthalpy of activation, $\Delta H^{\neq}$. This is reflected in the necessity of breaking increasingly strong solute–solvent interactions. On the other hand, because desolvation on activation is expected to increase the degrees of freedom in the system, a more positive $\Delta S^{\neq}$ is expected to work in the opposite direction and effect a compensating increase in k_1 with increasing solvent polarity. These suppositions are confirmed by experiment [108]. The sulfenate–sulfoxide equilibrium is shifted towards the more dipolar sulfoxide with increasing solvent polarity, as measured by the corresponding equilibrium constants [108]. Monte Carlo simulations of the solvent influence on this [2,3]sigmatropic rearrangement are essentially in agreement with this mechanism, indicating that the activated complex is more product-like than reactant-like [795].

The amine-catalyzed thermal decomposition of *tert*-butyl peroxyformate [110] represents an example of a solvent-dependent heterolytic fragmentation reaction (for a review, see reference [109]). This decomposition reaction occurs *via* a radical transition state in the absence of bases, with $\Delta H^{\neq} = 159$ kJ/mol and $\Delta S^{\neq} = +63$ J/K · mol in chlorobenzene, according to Eq. (5-39a). However, in the presence of pyridine, the reaction rate increases uniformly with increasing solvent polarity. This indicates a change in reaction mechanism from a radical to a heterolytic fragmentation pathway as shown in Eq. (5-39b).

The activation parameters obtained for reaction (5-39b) in chlorobenzene are in accordance with a dipolar activated complex involving considerable charge separation:



(5-39a)

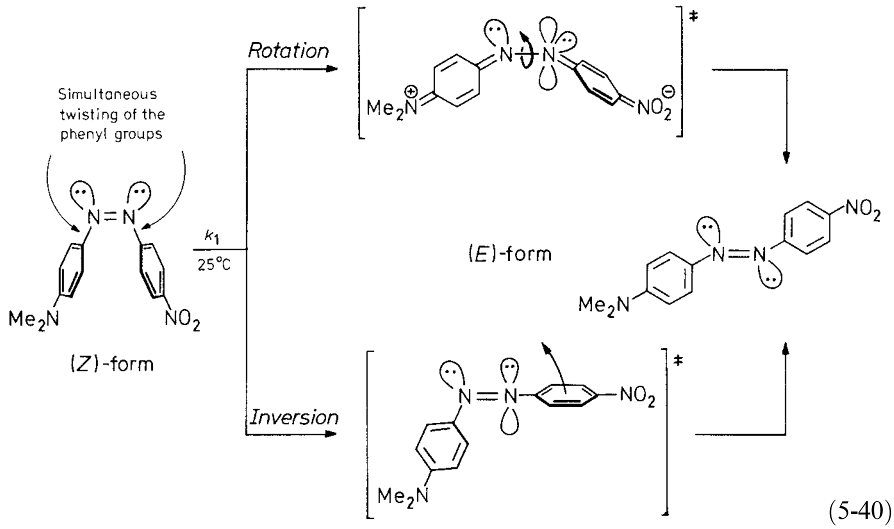
(5-39b)

Solvent	n-C_7H_{16}	CCl_4	C_6H_6	$CHCl_3$	CH_3NO_2	$C_6H_5NO_2$
k_2^{rel} for Eq. (5-39b)	1	4	14	30	110	140

$\Delta H^{\neq} = 64$ kJ/mol; $\Delta S^{\neq} = -96$ J/K · mol [110]. Thus, an increase in charge separation in the activation step should lead to more strongly orientated solvent molecules around the dipolar activated complex, as evidenced by the larger negative entropy of activation for reaction (5-39b). The solvent-dependence of the amine-catalyzed fragmentation of 2-*tert*-butylperoxy-2-methylpropanoic acid can be explained in a similar manner [111].

Push-pull substituted azobenzenes are nice examples of solvent-dependent (*E*)/(*Z*)-isomerization reactions [527–530, 561, 729]. For instance, the thermal *cis*-to-*trans* isomerization of 4-(dimethylamino)-4′-nitroazobenzene exhibits a rate enhancement of *ca.* 10^5 on changing the solvent from *n*-hexane to formamide [528].

Two mechanisms have been proposed for this isomerization reaction; *cf.* Eq. (5-40). One involves rotation around the N=N double bond and includes complete π-bond rupture to give a highly dipolar activated complex. The other involves inversion at one (or both) of the azo-nitrogen atoms with simultaneous $sp^2 \rightarrow sp$ rehybridization during the activation process. The π-bond remains intact.



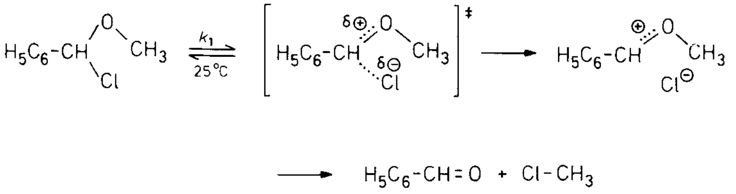
(5-40)

Solvent	n-C_6H_{14}	C_6H_6	CH_2Cl_2	CH_3COCH_3	CH_3OH	$HCONH_2$
k_1^{rel}	1	5	450	4760	$2.5 \cdot 10^4$	$8.2 \cdot 10^5$
$\Delta V^{\neq}/(cm^3 \cdot mol^{-1})$	-3[a]	-22[a]	-29	-30	-27	

[a] At 40 °C.

This huge solvent effect was first interpreted as an indication of the dipolar character of the activated complex, thus supporting the rotation mechanism. The isomerization rate is also considerably accelerated by external pressure in benzene and in polar solvents, but is little affected in n-hexane; *cf.* the negative activation volumes, $\Delta V^{\neq}$, due to electrostriction during the activation process (see Section 5.5.11 for definitions). From this, it was concluded that the isomerization mechanism changes from inversion in n-hexane to rotation in benzene and polar solvents [528]. That is, in the absence of solvational stabilization of the rotational activated complex, the inversion route becomes dominant (n-hexane; gas-phase). Other observations, however, indicate that a modification of this dual mechanism seems to be necessary. Taking into account that the inversional activated complex may also have some dipolar character due to resonance interactions of its push-pull substituents, the observed solvent, pressure, and substituent effects on rates can also be explained by means of a pure inversion mechanism [561, 729]. However, the two-route isomerization mechanism of push-pull substituted azobenzenes, *i.e.* inversion in nonpolar aprotic solvents and rotation in polar protic ones, was unequivocally proven by concave-up Arrhenius plots for reactions in solvents of medium polarity [527–529]. A change in mechanism from inversion to rotation has also been observed in supercritical (sc) carbon dioxide as solvent with small amounts of cosolvents added (1–5 cmol/mol). While in sc-CO_2/methanol the inversion mechanism dominates, the rotation mechanism is operative in more polar sc-CO_2/hexafluoro-*i*-propanol [530]. Unsubstituted and push-push substituted (Z)-azobenzenes, as well as (Z)-N-arylazomethines (*e.g.* N-benzylideneanilines), generally isomerize by way of the less solvent-dependent inversion mechanism.

We shall conclude this Section with an example of a reaction that undergoes an extreme rate acceleration with an increase in solvent polarity. Thermolysis of α-chlorobenzyl methyl ether in a series of non-nucleophilic, non-HBD solvents shows rate variations up to 10^5, encompassing a $\Delta G^{\neq}$ range of 30 kJ/mol (7 kcal/mol) [112]. This dramatic solvent effect is best explained by a mechanism involving ionization of the C—Cl bond to form an ion pair, followed by a nucleophilic attack by $Cl^{\ominus}$ on CH_3 to give an aldehyde and chloromethane; *cf.* Eq. (5-41).



(5-41)

Solvent	CCl_4	C_6H_5Cl	$CHCl_3$	$C_6H_5NO_2$	CH_3CN
k_1^{rel}	1	36	750	22000	166000

The experimental activation entropies are all negative, showing a higher degree of solvent organization in the transition state than in the initial state.

The thermal decomposition of alkyl chlorosulfites (R–O–SO–Cl → R–Cl + SO_2), the prototype of an S_Ni reaction, is also strongly accelerated in polar solvents: 353-fold upon a solvent change from *i*-octane to 1,4-dioxane [796a]. This is in agreement with a mechanism involving ionization either (a) of the S–Cl bond to yield a sulfinyl cation (R–O–SO^+) and Cl^- (with R = primary alkyl), or (b) of the R–O bond to give a carbenium ion and a chlorosulfinyl anion ($^-$O–SO–Cl) (with R = tertiary alkyl) [796b]. The generation of both ion pairs is facilitated in polar solvents, according to reaction type (a) in Table 5-4.

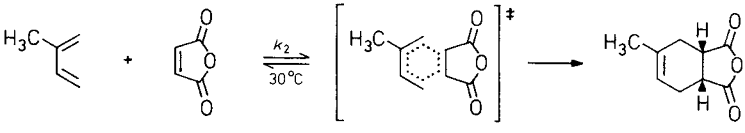
5.3.3 Solvent Effects on Isopolar Transition State Reactions

Reactions involving isopolar activated complexes (neither dipolar nor radical in nature), normally exhibit only small solvent rate effects. This is because charge distribution in the activated complexes and the reactants is very similar. Owing to the different polarizabilities of the initial and transition state molecules, there are changes in the solute/solvent dispersion interactions leading to small rate changes. Many reactions involving isopolar transition states are electrocyclic, sigmatropic, cheletropic, or cycloaddition reactions, all of which are representative of a larger class of concerted reactions known as "pericyclic reactions". Woodward and Hoffmann have suggested that the course of these reactions is controlled by the symmetry of the molecular orbitals of the reactants and products [90, 113]. Changing either the substituent or the medium usually has little effect on the rates of pericyclic reactions. This fact has been used by some chemists as a criterion for establishing the mechanism of such reactions. Examples illustrating the lack of solvent sensitivity of pericyclic and related reactions are presented. Unfortunately, because no solvent effects are expected for these reactions, thorough investigations in a large variety of solvents are lacking.

Some concerted $[m + n]$ cycloaddition reactions*⁾, however, have been well examined [90–93], *e.g.* Diels–Alder reactions [114–116] and 1,3-dipolar cycloaddition reactions [117–120, 541–543]. Both of these reactions have been established as concerted $[4 + 2]$ cycloaddition reactions.

The solvent effect on the bimolecular rate constant of a Diels–Alder reaction is usually quite small. As a rule, in going from nonpolar to polar solvents, the rate constant increases only by a factor of about 3...20 [34, 35, 121–130, 531–537].

Typical examples are the cycloaddition of isoprene and maleic anhydride as shown in Eq. (5-42) [127], and the dimerization of cyclopentadiene (*cf.* Table 5-1 in Section 5.2) [33, 34].



(5-42)

Solvent	$(i\text{-}C_3H_7)_2O$	C_6H_6	C_6H_5Cl	CH_3NO_2	$C_6H_5NO_2$	*o*-Dichlorobenzene
k_2^{rel}	1	3.5	5.0	6.6	11	13

It is clear from the above figures that the activated complex is not much more dipolar than the initial state. Neutral reactants produce a neutral product in a single, concerted, often synchronous step. Although dienes and dienophiles may have a dipole moment, these dipoles are usually incorporated unchanged into the product, and there is no reason to believe that they increase or decrease greatly during the reaction. The small solvent effects observed are in agreement with this picture of the Diels–Alder reaction.

Further examples of Diels–Alder cycloaddition reactions with small or negligible rate solvent effects can be found in the literature [531–535]. The thermolysis of 7-oxabicyclo[2.2.1]hept-5-ene derivatives is an example of a solvent-independent *retro*-Diels–Alder reaction [537]. For some theoretical treatments of the solvent influence on Diels–Alder cycloaddition reactions, which, in general, confirm their small solvent-dependence, see references [536, 797–799].

Nevertheless, there are some examples known with larger, although still moderate, solvent effects [124, 125, 129, 538–540]. Over a range of solvents from *o*-xylene to trichloromethane, the reaction rates for the addition of tetracyanoethene to anthracene have been found to increase by a factor of 70 [125]. In the case of the reaction between cyclopentadiene and acrolein, changing the solvent from ethyl acetate to acetic acid causes a 35-fold acceleration in rate [129]. A strongly dipolar activated complex is unlikely, as reflected by this small sensitivity to solvent. These data are more consistent with the following mechanism: first the diene and dienophile form an EPD/EPA com-

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* $[m + n]$-Cycloaddition reactions involve the addition of a molecule (or fragment) with m π-electrons to one with n π-electrons to produce a new ring in a concerted, but not necessarily synchronous, orbital-symmetry controlled process [90].

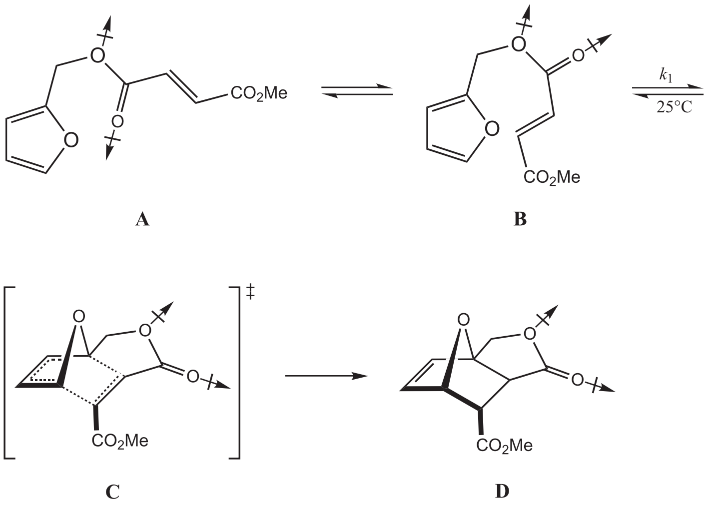
plex, this is then converted directly into the adduct *via* an electron-rich, polarizable activated complex. Some Diels–Alder reactions experience a significant change in activation enthalpy when the solvent is changed. When the relative solvation enthalpies for the reactants are determined in EPD and EPA solvents by calorimetry, it is found that in EPD solvents the reactants are stabilized, whereas the more electronegative EPA solvents stabilize the electron-rich activated complex [128]; see however references [130, 800] for a criticism of this approach.

Another explanation for enhanced solvent effects in Diels–Alder reactions in HBD solvents is that carbonyl-containing reactants and activated complexes can form R–O–H···O=C hydrogen bonds to a different extent, depending on the polarization of the C=O group, which is larger in the activated complex according to $C^+–O^-$. For example, the Diels–Alder reaction between cyclopentadiene and butenone was reported to be twelve times faster in methanol than in *i*-octane, but in water the rate is 730 times faster than in *i*-octane ($\Delta\Delta G^{\neq} \approx -16$ kJ/mol) [801]. This remarkable rate acceleration in water cannot explained simply in terms of solvent polarity differences. *Ab initio* MO calculations on the cycloaddition of cyclopentadiene and butenone have shown that during the activation process the hydrogen bond between butenone and water is enhanced by ca. 8 kJ/mol [797]. In addition to this H-bond effect, a hydrophobic effect is certainly operative in water. In the activated complex for Diels–Alder reactions, two hydrocarbon surfaces must come together, and this aggregation is facilitated in water [801]; see also Sections 2.2.7 and 5.5.8. However, there are limitations associated with the use of water as a solvent for Diels–Alder reactions because the vast majority of organic compounds are insoluble in water, and water precludes the use of water-sensitive reactants. Further examples of water-mediated Diels–Alder reactions can be found in a recent review [802].

The particular influence of water as solvent on Diels–Alder reactions can be altered by the addition of ionophores (e.g. LiCl, NaCl, $LiClO_4$, *etc.*) [801]. For the 'cyclopentadiene + butenone' reaction, the rate increases 2.5-fold on addition of LiCl (4.86 M), while a marginal decrease is observed on addition of guanidinium chloride. Obviously, lithium chloride increases the hydrophobic effect, while guanidinium chloride decreases it. The effect of aqueous salt solutions can also be understood in terms of structure-making (rate-enhancing) and structure-breaking (rate-decreasing) agents [802].

Much more impressive rate accelerations for several Diels–Alder (and other) reactions have been observed by employing solutions of lithium perchlorate (up to 5 M) in diethyl ether (LPDE solutions) [802–806]. The dramatic rate accelerations found for Diels–Alder reactions in LPDE solutions appear to stem from Lewis acid catalysis by the coordinative unsaturated Li^+ ion (see the end of Section 3.1). The Lewis acid catalysis by LPDE is applicable to those Diels–Alder reactions in which the lithium cation can coordinate with suitable functional groups in the reactants (*e.g.* Li^+···O=C). Addition of lithium-specific crown ethers (*e.g.* [12]crown-4) leads to a loss of the catalytic activity of the Li^+. For a recent extensive review of salt effects on Diels–Alder reactions, see reference [802].

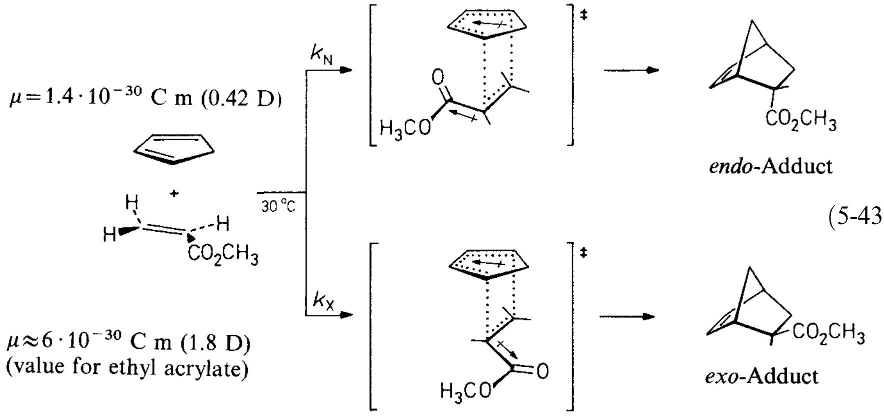
Rather large rate enhancements with increasing solvent polarity have also been found for *intramolecular* Diels–Alder reactions such as the cyclization of 2-furfuryl methyl fumarate shown in Eq. (5-42a) to yield lactone D. This first-order reaction is about 3200 times faster in dimethyl sulfoxide than in toluene as solvent [807].



(5-42a)

In order to form the activated complex required for the formation of product D, rotational changes of the less dipolar *anti*-form A to the more dipolar *syn*-conformer B are necessary, to give an activated complex C with more parallel bond dipoles, which is thus more dipolar and better solvated than the reactant molecule. In agreement with this explanation is the observation that the reverse *retro*-Diels–Alder reaction exhibits no large solvent effect, since the activated complex C is quite similar to the reactant D [807].

A very subtle solvent effect has been observed in the Diels–Alder addition of methyl acrylate to cyclopentadiene [124]. The polarity of the solvent determines the ratio of *endo* to *exo* product in this kinetically controlled cycloaddition reaction, as shown in Eq. (5-43). The more polar solvents favour *endo* addition.



(5-43)

Solvent	$(C_2H_5)_3N$	$(CH_3OCH_2)_2$	CH_3CN	CH_3CO_2H	CH_3OH
$\lg \frac{[endo]}{[exo]}$	0.445	0.543	0.692	0.823	0.845

Consideration of the dipolarity of the two activated complexes can explain the observed trend. If the reactants are pictured as lying in roughly parallel planes, the dipole moments for the *exo* orientation are seen to be nearly opposite in direction, whereas for the *endo* orientation they are parallel. Therefore, the net dipole moment for the *endo* transition state is greater than that for the *exo*. Thus, the solvation of the *endo* activated complex will be more pronounced as the polarity of the solvent increases. This leads to a lowering of the activation enthalpy and preferential formation of the *endo* adduct. The logarithm of the *endo*/*exo* product ratio in various solvents has been used to define an empirical solvent polarity scale [124] (*cf.* Section 7.3). Analogous solvent-dependent *endo*/*exo* product ratios have been obtained in [4 + 2]cycloadditions of cyclopentadiene to other acrylic acid derivatives [560]. Theoretical calculations on *exo*/*endo* structures for activated complexes of [4 + 2]cycloadditions have shown that the observed *endo* preference in polar solvents is due to the influence of the medium, and that secondary orbital interactions are not involved [808]. The solvent has the decisive influence on the *exo*/*endo* selectivity.

As measured by the criteria of stereospecificity, regioselectivity, kinetic isotope effects, and solvent effects [117–120, 541–543], 1,3-dipolar cycloaddition reactions represent orbital symmetry-allowed $[{}_{\pi}4_s + {}_{\pi}2_s]$ cycloadditions, which usually follow concerted pathways*⁾. Diels–Alder reactions and 1,3-dipolar cycloadditions resemble each other, as demonstrated by the small solvent effects on their bimolecular rate constants. In going from nonpolar to polar solvents, the rate constants of 1,3-dipolar cycloadditions change only by a factor of 2 ... 10 [120, 131–134].

The cycloaddition of *N*-methyl-*C*-phenylnitrone to ethyl acrylate yielding a substituted isoxazolidine serves to illustrate this point [132]. In solvents of increasing polarity, this reaction, shown in Eq. (5-44), exhibits only a 5.6-fold rate deceleration [132].

Similarly small rate factors were obtained for 1,3-dipolar cycloadditions between diphenyl diazomethane and dimethyl fumarate [131], 2,4,6-trimethylbenzenecarbonitrile oxide and tetracyanoethene or acrylonitrile [811], phenyl azide and enamines [133], diazomethane and aromatic anils [134], azomethine imines and dimethyl acetylenedicarboxylate [134a], diazo dimethyl malonate and diethylaminopropyne [544] or *N*-(1-cyclohexenyl)pyrrolidine [545], and *N*-methyl-*C*-phenylnitrone and thioketones [812]. Huisgen has written comprehensive reviews on solvent polarity and rates of 1,3-dipolar cycloaddition reactions [541, 542]. The observed small solvent effects can be easily explained by the fact that the concerted, but non-synchronous, bond formation in the activated complex may lead to the destruction or creation of partial charges, connected

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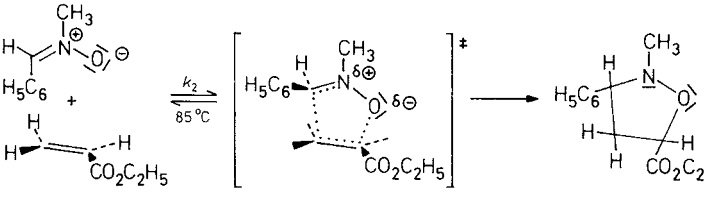
* Firestone postulated that many 1,3-dipolar cycloadditions occur by a two-step mechanism with a discrete spin-paired diradical intermediate [118], but his arguments were criticized by Huisgen [119]. Distinction between concerted and stepwise-diradical mechanisms cannot be made on the basis of the negligible small solvent effects obtained for most 1,3-dipolar cycloaddition reactions. References [90c, 543] give a fair discussion of this controversial point. Using thiocarbonyl ylides, $R_2C{=}S^{+}{-}CH_2^{-}$, and dimethyl dicyanofumarate as reaction partners, the first nonstereospecific, two-step 1,3-dipolar cycloaddition with ring-opened, equilibrating zwitterions as intermediates has been reported by Huisgen *et al.* [809]; for further examples, see reference [810]. When steric hindrance to bond formation at one end of the 1,3-dipole is particularly severe, then a stepwise, more solvent-dependent cycloaddition can obviously compete with the concerted process.

$\mu = 11.8 \cdot 10^{-30}$ C m (3.55 D)



(5-44)

$\mu = 5.9 \cdot 10^{-30}$ C m (1.76 D) $\mu = 8.3 \cdot 10^{-30}$ C m (2.48 D)

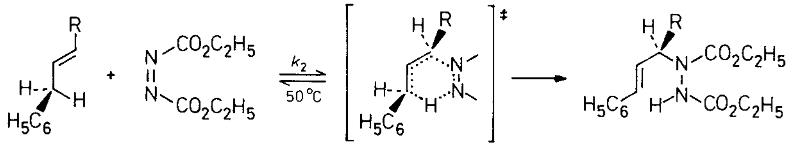
Solvent	$C_6H_5CH_3$	1,4-Dioxane	CH_3COCH_3	CH_3NO_2	CH_3CN	C_2H_5OH
k_2^{rel}	5.6	3.2	2.2	1.9	1.9	1

with the disappearance of the formal charges of the 1,3-dipole. A concerted mechanism, involving a small charge imbalance in the transition state, is characteristic of most 1,3-dipolar cycloaddition reactions. In the case of cycloadditions between diazomethane and certain aromatic anils to give substituted 1,2,3-triazolines, a specific protic/dipolar aprotic solvent effect was postulated, involving better solvation of the activated complex relative to the reactants in dipolar non-HBD solvents such as *N*,*N*-dimethylformamide [134].

Likewise, 1,3-dipolar (and other) cycloreversions have been studied in a variety of solvents [546–549]. As expected, only rather small or negligible solvent effects on rate have been observed.

Other examples of reactions closely related to the Diels–Alder cycloaddition reaction are the ene reactions between alkenes with allylic hydrogen atoms (ene) and compounds with a double bond (enophile) [135, 136], and the dye-sensitized photo-oxygenation of allylic alkenes by singlet oxygen to give allylic hydroperoxides with a shifted double bond [137–139].

The observed range of solvent effects (less than a factor of four) for the ene reaction between 3-phenyl-1-*p*-tolylpropene-(1) and diethyl azodicarboxylate, given in Eq. (5-45), is best explained by a concerted mechanism involving an isopolar six-centre transition state [136].

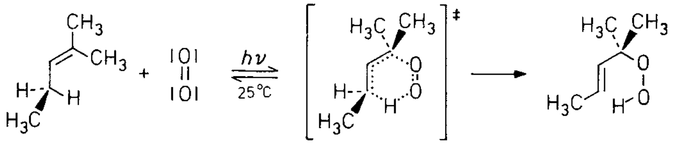


(5-45)

$R = 4\text{-}CH_3\text{-}C_6H_4$

Solvent	c-C_6H_{12}	1,4-Dioxane	$HCON(CH_3)_2$	CH_3CN	$(ClCH_2)_2$	$C_6H_5NO_2$
k_2^{rel}	1	1.1	2.0	2.2	3.1	3.9

The addition of singlet oxygen to 2-methyl-2-pentene occurs *via* a concerted "ene-type" mechanism as shown in Eq. (5-46)*). This is entirely consistent with the small solvent effect observed for this reaction [138]. When the solvent is changed from methanol to carbon disulfide, the rate changes by a factor of seven**). Thus, it would appear that the activated complex does not involve much charge separation [138].

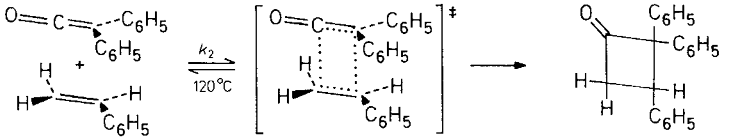


(5-46)

Solvent	CS_2	$CH_3CO_2C_2H_5$	CH_3SOCH_3	CH_3COCH_3	C_6H_6	CH_3OH
β-value*)	0.022	0.04	0.07	0.08	0.10	0.16

In the photo sensitized oxygenation reactions of alkenes, not only the influence of the solvent on the reaction rate but also the effect of solvent on product distribution (*i.e.* from competing hydroperoxide, 1,2-dioxetane, and *endo*-peroxide formation) is rather small [550, 551].

In contrast to strongly solvent-dependent [2 + 2]cycloaddition reactions, which proceed through a 1,4-dipolar zwitterionic intermediate by a two-step mechanism or through a dipolar activated complex by a one-step mechanism (*cf.* Section 5.3.2, and Eqs. (5-33) to (5-35) [92, 94–107], [2 + 2]cycloadditions are also known that exhibit concerted, nearly synchronous bond formation without significant charge separation on activation in the transition state. An example is given in Eq. (5-47). Since the rate constant for this diphenylketene/styrene addition is practically independent of solvent polarity [140], it can be classed as concerted.



(5-47)

Solvent	C_6H_5Br	*o*-Dichlorobenzene	$(ClCH_2CH_2)_2O$	$HCON(CH_3)_2$
k_2^{rel}	1.2	1.1	1.1	1

The rates of [2 + 2]cycloaddition reactions between di-*tert*-butylthioketene and azomethines [141], thiobenzophenones and keteneimines [552] as well as [2 + 2 + 2]

---

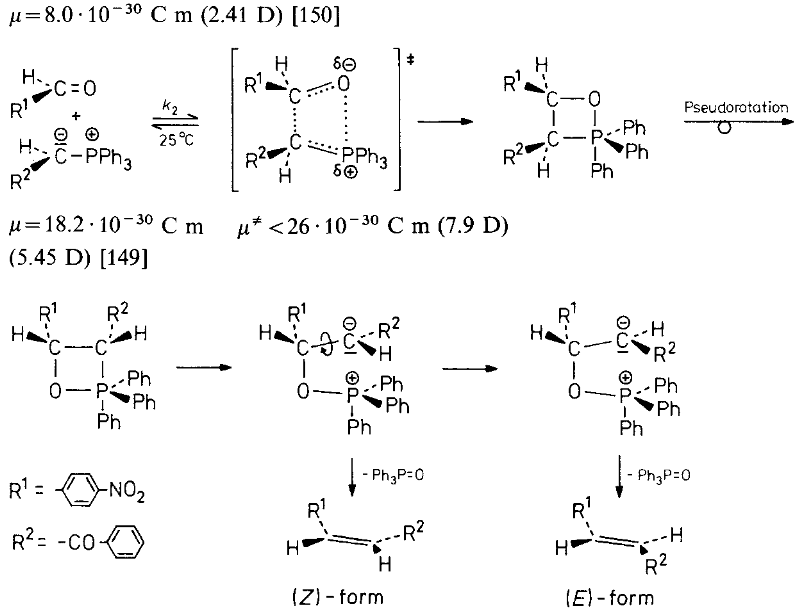
* Since there exists a second group of allylic hydrogen atoms at the other end of the 2-methyl-2-pentene molecule, two different allylic hydroperoxides are obtained in the solvent-independent ratio of *ca.* 1:1 [138].

** Only the ratio $\beta = k_d/k_A$ of the rate constant for decay of singlet oxygen to its ground-state triplet (designated k_d) and the specific rate constant for the product-forming step (designated k_A) is readily determined experimentally [137, 138]. Therefore, the β values provide an inverse measure of the reactivity of the allylic alkene.

cycloadditions between quadricyclane and, for example, acrylonitrile [553] also reveal no significant solvent dependence.

Ab initio MO calculations for the uncatalyzed [2 + 2]cycloaddition reaction between ketenes (*e.g.* chloroketene) and carbonyl compounds (*e.g.* formaldehyde) to yield oxetan-2-ones (β-lactones) predict a relatively synchronous, concerted process, with a $[_{\pi}2_{s} + (_{\pi}2_{s} + _{\pi}2_{s})]$ arrangement of the reactants in the activated complex and a negligible solvent effect [813].

Another remarkable example of a [2 + 2]cycloaddition reaction is the Wittig reaction of alkylidenephosphoranes and carbonyl compounds [142, 143, 554]. The solvent dependence of some Wittig reactions has been studied [144–148]. The relatively small inverse solvent effect found for the "salt-free" Wittig reaction between 4-nitrobenzaldehyde and the resonance-stabilized ylide benzoylmethylene-triphenylphosphorane – a 58-fold rate decrease with increasing solvent polarity [146–148] – is in agreement with a concerted, but not necessarily synchronous formation of C—C and P—O bonds in the rate-controlling first step, leading to a non-ionic cyclic oxaphosphetane intermediate such as that described in Eq. (5-48). Because C—C bond formation is more advanced than P—O bond formation in the activation process [554], small partial charges are generated. However, according to the inverse solvent effect, the activated complex must be less dipolar than the reactants. That is, the dipole moment of the activated complex should definitely be less than the sum of the reactant dipole moments. This certainly rules out the formation of a zwitterionic phosphonium betaine in



(5-48)

Solvent	CCl_4	n-C_6H_{14}	CH_3OH	CH_3CN	C_6H_6	$(HOCH_2)_2$	$HCON(CH_3)_2$
k_2^{rel}	58	16	9.5	9	3.3	1.6	1

the first, rate-determining step. In addition, the somewhat solvent-dependent activation volumes are – with values of $\Delta V^{\neq} = -20 \ldots -30$ cm^3/mol – insufficiently negative for a fully zwitterionogenic activation step [555].

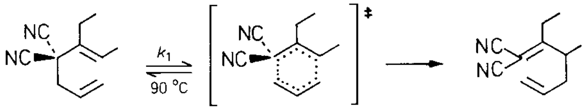
According to Bestmann [554], the initially formed 1,2-oxaphosphetane with an apical-located oxygen atom, undergoes a ligand rearrangement process (pseudorotation) thus bringing the bond necessary for alkene formation into the apical position. After this conversion, depending on the reaction conditions, alkene formation takes place either directly by an asynchronous cycloreversion of the oxaphosphetane, or by a preferred cleavage of the C–P bond to give equilibrating zwitterions which decompose to the products. The substituent R^2 determines the lifetime of this zwitterion and consequently the configuration of the alkenes formed. If R^2 is an electron-donating group, fast phosphane oxide elimination occurs and the (*Z*)-alkene is formed. Electron-withdrawing groups R^2 [*e.g.* $R^2 = COC_6H_5$ as in Eq. (5-48)] stabilize the betaine which now isomerizes to the thermodynamically more stable conformer yielding (*E*)-alkenes *via* phosphane oxide elimination.

Protic solvents shift the alkene (*E*)/(*Z*) ratio in the direction of the (*E*)-form. The alkene (*E*)/(*Z*) ratio of salt-free Wittig reactions is thus influenced not only by the electronic character of R^2, but also by the solvent and the stereochemistry of the formation of the 1,2-oxaphosphetane in the first rate-determining step. According to Eq. (5-48), the thermodynamically less stable (*Z*)-1,2-oxaphosphetane is formed in the first activation step. A conformational analysis of the activated complex leading to the 1,2-oxaphosphetane intermediate provides a reasonable explanation for this unexpected *cis*-selectivity [143, 556].

A complete analysis of the solvent influence on the Wittig reaction given in Eq. (5-48), based on Gibbs energies of transfer, $\Delta G_t^\circ(\mathrm{X, CH_3OH \rightarrow S})$, from methanol to thirteen other solvents for reactants, activated complex, and products has been given [148]. As confirmed by the kinetic results, this Wittig reaction is an example of a balanced reaction type [467] with similar solvation effects for both the initial and transition state, as well as for the final state. The activated complex appears to be reactant-like and product-like, as expected for an activated complex similar to a cyclic intermediate, without localized charges on specific ring atoms [148]. A more detailed discussion of the solvent (and salt) influence on reaction rates and (*E*)/(*Z*) alkene ratios of Wittig reactions can be found in reference [143].

Sigmatropic reactions, *i.e.* reactions involving migration of a σ-bond, flanked by one or more conjugated systems, to a new position within the system, are also pericyclic reactions [90, 113]. Solvent studies of such reactions have been carried out, *e.g.* the effect on rate of solvent polarity has been examined for some [3,3]sigmatropic reactions such as the Cope rearrangement of substituted 1,5-hexadienes [151, 152, 154] and the *ortho*-Claisen rearrangement of allyl aryl ethers [153, 154, 814]. Cope and Claisen rearrangements show little response to variation of the polarity of the solvent, in accordance with an isopolar activated complex. Some [1,3]- [557] and [1,5]sigmatropic reactions [558] can also be considered as isopolar transition state reactions involving rather small solvent effects on rate.

As an example, the rate of rearrangement of 4,4-dicyano-5-ethylhepta-1,5-diene changes only by a factor of 3.8, even when the solvent is changed drastically by going from cyclohexane to dimethyl sulfoxide (Eq. (5-49)) [151].



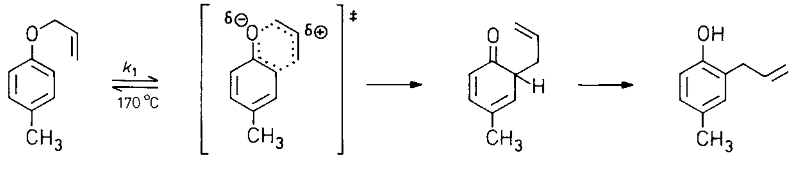
(5-49)

Solvent	c-C_6H_{12}	1,4-Dioxane	C_2H_5OH	CH_3SOCH_3
k_1^{rel}	1	2.0	2.6	3.8

It can be concluded, therefore, that there is negligible charge separation on activation, even when the compounds have two nitrile groups, which are ideal for stabilizing a potential carbanion in an ionic mechanism. Similar results were obtained for the Cope rearrangement of diethyl allylisopropenylmalonate [152]. It should be mentioned, however, that some 1,5-hexadienes, containing radical-stabilizing substituents in the 2,5-positions, seem to react *via* a diradicaloid pathway [155]. The analogous azo-Cope rearrangement of arylazo (α,α-dimethylallyl)malononitriles into N-(γ,γ-dimethylallyl)-aryl-hydrazonomalononitriles, involving simultaneous carbon–carbon bond cleavage and carbon–nitrogen bond formation, exhibits a small but significant rate increase with increasing solvent polarity (a factor of 19 on changing from CCl_4 to Me_2SO). This result suggests a concerted mechanism *via* an activated complex of low dipolarity [593].

An interesting case is the fast degenerate Cope rearrangement of the donor/acceptor-substituted 2,6-dicyano-4,8-diphenylbarbaralane, which has been studied in 26 solvents of different polarity [815]. Such degenerate Cope rearrangements are characterized by rather small activation energies in going from the reactant with a classical localized electronic structure to the activated complex with a delocalized electronic structure, corresponding to a flat double-minimum potential. The solvent-dependent thermochromism of solutions of this barbaralane suggests that dipolar polarizable solvents such as DMSO, HMPT, and DMPU stabilize the polarizable delocalized activated complex more than the less polarizable reactants. This leads to an inversion of the energetic order of reactant and activated complex, corresponding to a single-minimum potential with the former activated complex becoming the more stable species, which can be observed UV/Vis spectrophotometrically ($\lambda_{max} = 460$ nm). In most other solvents (*e.g.* cyclohexane, di-n-butyl ether, benzene), the normal order as obtained in the gas phase is maintained. Evidently, it is possible to visualize activated complexes not only by means of femtosecond spectroscopy [815], but also through the solvent-dependent thermochromism of barbaralanes (and semibullvalenes).

For the *ortho*-Claisen rearrangement of allyl p-tolyl ether shown in Eq. (5-50), the rate enhancement with increasing solvent polarity is modest, in agreement with a cyclic process involving concerted bond-making and -breaking on activation [153].



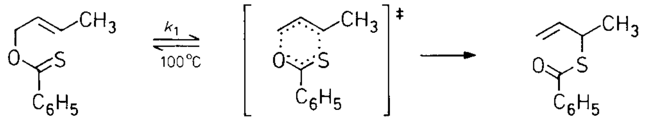
(5-50)

Solvent	n-$C_{14}H_{30}$	$(n$-$C_4H_9)_2O$	Sulfolane	$(CH_2OH)_2$	C_6H_5OH
k_1^{kel}	1	1.1	3.6	22	34

For this reaction, the rate was found to vary by a factor of 34 in going from the least polar (*n*-tetradecane) to the most polar solvent (phenol), and by a factor of 102 in going from the gas phase to the most polar solvent [153]. The small solvent and substituent effects observed suggest that a slightly dipolar activated complex must be formed during the Claisen rearrangement of this allyl aryl ether [153].

A similar slightly dipolar activated complex has been postulated for an aliphatic pendant to the aromatic Claisen rearrangement, that is for the [3,3]sigmatropic rearrangement of alkoxyallyl vinyl ethers [767]. For example, the rate of rearrangement of 6-methoxyallyl vinyl ether to 3-methoxy-4-pentenal is increased 3...68 fold upon changing the solvent from benzene to acetonitrile and methanol, respectively [767]. The first-order rate constant for the [3,3]sigmatropic rearrangement of a similar alkoxyallyl vinyl ether, methyl and sodium 8-vinyloxy-9-decenoate, increases by a factor of 56 in going from cyclohexane to trifluoroethanol [816]. A comparison with solvolytic rate data (*Y* values of Winstein; see Section 7.3) shows that the activated complexes of such [3,3]sigmatropic rearrangements are substantially less dipolar than those of S_N1 solvolysis reactions. However, in water, the rearrangement of the sodium salt is about 214 times faster than in cyclohexane. This result suggests that both hydrophobic destabilization of the reactant and H-bond stabilization of the activated complex (which contains a developing carbonyl group) are responsible for this enhanced rate acceleration [797, 814]. For a *retro*-Claisen rearrangement, a 12-fold rate increase was found for the solvent change cyclohexane → trifluoroethanol, again indicating a concerted reaction with a small partial charge separation in the activated complex [817]. A more detailed discussion of the solvent influence on Claisen rearrangements can be found in reference [814].

A reaction similar to the Claisen reaction is the [3,3]sigmatropic rearrangement of an allyl thiobenzoate into an allyl thiolbenzoate, as shown in Eq. (5-51) [156].



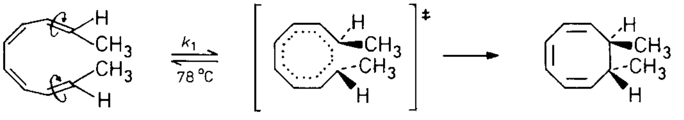
(5-51)

Solvent	c-C_6H_{12}	C_6H_5Cl	CH_3COCH_3	CH_3CN	CH_3CO_2H
k_1^{rel}	1	1.9	2.3	4.9	4.8

From the first-order rate constants obtained in different solvents (in sealed ampoules), it is apparent that this isomerization is not very sensitive to the polarity of the medium, in accordance with an isopolar, six-membered activated complex [156]. A similar small solvent effect has been observed for the [3,3]sigmatropic rearrangement of allyl S-methyl xanthate to allyl methyl dithiol carbonate [559].

Finally, the solvent dependence results for two electrocyclic reactions are mentioned. Electrocyclic reactions are generally defined as reactions involving the concerted cyclization of an n π-electron system to an $(n-2)$ $\pi + 2\sigma$-electron system, or the reverse process [90, 113, 818].

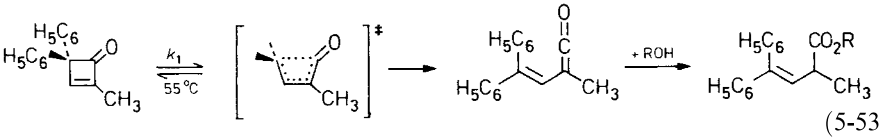
The conrotatory cyclization of *all-cis*-deca-2,4,6,8-tetraene to *trans*-7,8-dimethylcycloocta-1,3,5-triene has been studied in solvents of different polarity [157]. In agreement with a synchronous conrotatory ring closure *via* an isopolar activated complex, the solvent effect is negligible as shown by the relative first-order rate constants in Eq. (5-52).



(5-52)

Solvent	$CDCl_3$	Pyridine	CH_3CN
k_1^{rel}	1.1	1.2	1

In the case of 2-methyl-4,4-diphenylcyclobutenone, the reverse process, an electrocyclic ring opening, has also been examined in different solvents [158]; *cf.* Eq. (5-53).



(5-53)

Solvent	$c\text{-}C_6H_{12}$	C_6H_6	$CH_3CO_2C_2H_5$	C_2H_5OH	CH_3OH
k_1^{rel}	3.0	2.3	1.4	1.1	1

The small inverse dependence of the first-order rate constant on solvent polarity is in agreement with a concerted electrocyclic ring cleavage through an isopolar activated complex to vinylketene, which is converted into the corresponding ester in alcoholic solvents [158].

Desimoni *et al.* have thoroughly studied the solvent dependence of the electrocyclic ring closure of 1,2,6-triphenylhexa-1,3,5-triene (to give 1,5,6-triphenylcyclohexa-1,3-diene) and the ring opening of dimethyl 3,4-dimethyl-1,2-diphenylcyclobutene-*cis*-3,4-dicarboxylate (to yield dimethyl 2,5-dimethyl-3,4-diphenylmuconate) in 15 different solvents [819]. Both electrocyclic reactions are influenced very little by the solvent, with small rate accelerations of 1.2 and 1.8, respectively, on going from cyclohexane to methanol.

The solvent-dependence of cheletropic reactions*) has also been investigated [158a]. The thermolysis of 3-methyl-2,5-dihydrothiophene-1,1-dioxide appears to involve a concerted fission of the two σ-bonds. This is in accordance with the very small solvent effect on rate observed in six solvents of different polarity [158a].

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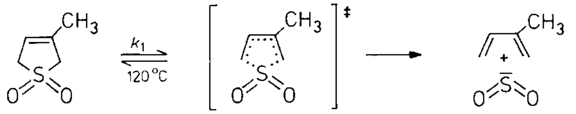
* Cheletropic reactions are defined as processes in which two σ-bonds that terminate at a single atom are made or broken in a concerted fashion.



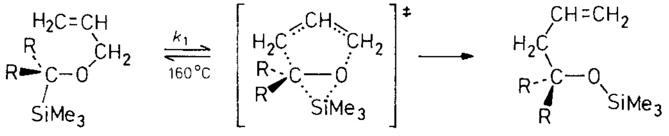
(5-54)

Solvent	n-$C_{10}H_{22}$	Triethylene glycol	$(H_5C_6)_2O$	H_5C_6—CO—C_6H_5	Sulfolane
k_1^{rel}	1	1.3	1.6	1.8	1.8

From these results, it is clear that this reaction meets the requirements for a pericyclic reaction involving an isopolar activated complex.

Another more recent example of a cheletropic reaction, studied in various solvents, is the addition of aryl-halocarbenes (generated photolytically from diazirines) to tetramethylethene to give the corresponding cyclopropane derivatives [820]. The addition of chlorophenylcarbene is only about three times faster in ethyl acetate than in pentane, as befits an isopolar activated complex.

The thermal rearrangement of allyl(silylmethyl) ethers, an example of a dyotropic reaction*⁾, in which the silyl and allyl groups exchange their positions, exhibits only a very small solvent dependence; this is as expected for a concerted reaction according to Eq. (5-55) [158b]:



(5-55)

R + R = 2,2′-Biphenylylene

Solvent	Decalin	Benzene	o-Dichlorobenzene	Propylene carbonate
k_1^{rel}	1	1.1	2.8	5.1

Finally, it should be mentioned that no strict limit between reactions with dipolar and isopolar activated complexes exists. Some borderline cases with significant but relatively small charge separation in going from the initial to the transition state, with correspondingly small solvent rate effects, have been mentioned in this Section.

5.3.4 Solvent Effects on Free-Radical Transition State Reactions

According to Kosower, a third category of reactions involving free-radical activated complexes may be defined. These complexes are formed either through the creation of unpaired electrons during radical pair formation or atom-transfer reactions [15, 468] (*cf.*

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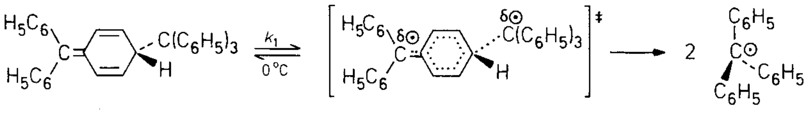
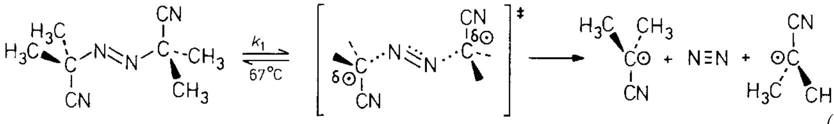
* Dyotropic rearrangements are uncatalyzed, intramolecular pericyclic reactions in which two σ-bonds simultaneously migrate [158b].

Section 5.3). These two different types of free-radical reactions have been investigated for solvent effects (for reviews, see references [159–166]). Reactions in which the medium affects the reactivity of free radicals have received greater attention than radical-forming reactions. The solvent often affects the course of free-radical reactions by participating as a reactant. This is evidenced by the incorporation of the solvent into the products of the reaction. This Section, however, will be limited to those solvent effects which are truly medium effects.

Free radicals may be generated by oxidation, reduction, or by homolytic cleavage of one or more covalent bonds, such as C—C bonds (*e.g.* dimers of triarylmethyl radicals), N—N bonds (*e.g.* tetrasubstituted hydrazines), O—O bonds (*e.g.* hydroperoxides, dialkyl and diacyl peroxides, peroxycarboxylic esters), C—N bonds (*e.g.* dialkyl azo compounds), and N—O bonds (as in the thermolysis of nitrogen pentoxide O_2N—O—NO_2). Two typical examples, which have been investigated in different solvents, are given in Eqs. (5-56) and (5-57); *cf.* also reaction (5-39a) in Section 5.3.2.



(5-56)



(5-57)

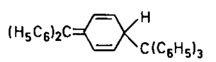
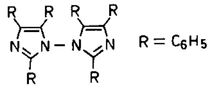
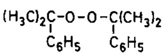
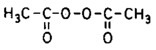
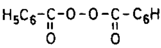
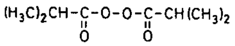
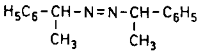
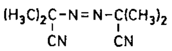
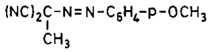
The dissociation rate of the dimer of the triphenylmethyl radical*) in 28 solvents was studied by Ziegler *et al.* [167]. The decomposition rate of azobisisobutyronitrile in 36 solvents was measured by different authors [183–185, 562]. Despite the great variety of solvents, the rate constants vary only by a factor of 2...4. This behaviour is typical for reactions involving isopolar transition states and often indicates, but does not prove, a radical-forming reaction. The lack of any marked solvent effects in most free-radical forming reactions will become more apparent after an examination of some further reactions presented in Table 5-8.

Generally, it can be said that radical-forming reactions are usually not very sensitive to medium effects, because activated complexes which produce neutral radicals normally exhibit no charge separation. Even in the case of 4-methoxyphenylazo-2-methylpropanedinitrile (*cf.* Table 5-8, last entry), which is predisposed for an ionic decomposition, there is only a modest 26-fold rate acceleration in going from *n*-decane to methanol as solvent. This rate factor can be easily explained by assuming that the cleavage of the two C—N bonds of the azo group is concerted but non-synchronous [189].

---

* Ziegler *et al.* undertook their experiments with a compound which they believed to be hexaphenylethane [167]. In 1968, it was shown that the dimer of the triphenylmethyl radical is not hexaphenylethane, but 1-diphenylmethylene-4-triphenylmethyl-2,5-cyclohexadiene [168, 169] in accordance with a proposal made by Jacobson in 1905 [170].

Table 5-8. Solvent influence on rates of monomolecular decomposition of various free-radical initiators [164].

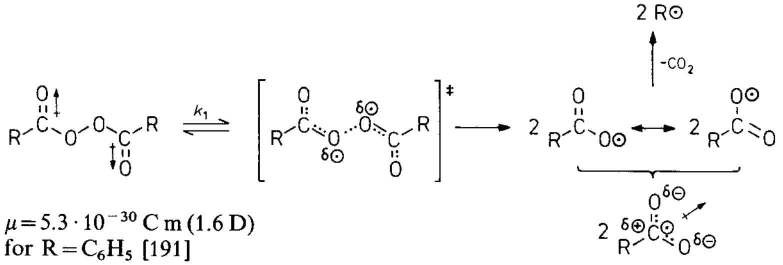
Initiators	Number of solvents	Temperature °C	Range of variation of k_1/s^{-1}	$k_1^{rel.a)}$	References
	28	0	$(1.1 \ldots 4.2) \cdot 10^{-3}$	3.9	[167]
	12	125	$(1.5 \ldots 3.5) \cdot 10^{-5}$	2.3	[172]
$(H_3C)_3C-O-O-C(CH_3)_3$	6	75	$(1.9 \ldots 5.9) \cdot 10^{-2}$	3.1	[171]
 $(H_3C)_2\underset{C_6H_5}{C}-O-O-\underset{C_6H_5}{C}(CH_3)_2$	5	140	$(2.2 \ldots 2.8) \cdot 10^{-4}$	1.3	[173]
 $H_3C-\underset{\underset{O}{\|}}{C}-O-O-\underset{\underset{O}{\|}}{C}-CH_3$	15	85.2	$(1.0 \ldots 1.7) \cdot 10^{-4}$	1.7	[174–176]
 $H_5C_6-\underset{\underset{O}{\|}}{C}-O-O-\underset{\underset{O}{\|}}{C}-C_6H_5$	40	80	$(1.8 \ldots 40) \cdot 10^{-5}$	22	[177–179]
 $(H_3C)_2CH-\underset{\underset{O}{\|}}{C}-O-O-\underset{\underset{O}{\|}}{C}-CH(CH_3)_2$	16	40	$(3.1 \ldots 68) \cdot 10^{-5}$	22	[180, 181]
 $H_5C_6-\underset{CH_3}{CH}-N=N-\underset{CH_3}{CH}-C_6H_5$	7	97.3	$(3.2 \ldots 4.1) \cdot 10^{-5}$	1.3	[182]
 $(H_3C)_2\underset{CN}{C}-N=N-\underset{CN}{C}(CH_3)_2$	36	67	$(1.0 \ldots 2.0) \cdot 10^{-4}$	2.0	[183–185, 562]
$(H_5C_6)_3C-N=N-C_6H_5$	7	25	$(1.9 \ldots 4.4) \cdot 10^{-6}$	2.3	[186–188]
 $(NC)_2\underset{CH_3}{C}-N=N-C_6H_4-p-OCH_3$	13	85	$(3.8 \ldots 100) \cdot 10^{-5}$	26	[189]

a) $k_1^{rel} = k_1$ (fastest solvent)/k_1 (slowest solvent).

Even the mesolytic scission of C—C bonds in radical cations is practically solvent-independent. The radical cations obtained by oxidation of 1,2-dimethyl-1-(4-dimethylaminophenyl)-2-phenylethane undergo unimolecular cleavage of the central C—C bond, to yield benzyl cations and benzyl radicals, with Gibbs free energies (and rate constants) that remain constant in different solvents ($\Delta G^{\neq} \approx$ 69–72 kJ/mol) [821].

Another interesting intramolecular, possibly radical-forming reaction is the thermolytic ring-opening of cyclopropanones *via* either a diradical ($\cdot H_2C—CO—CH_2\cdot$) or a zwitterionic oxyallyl intermediate [$H_2C{=}C(O^-)–CH_2^+ \leftrightarrow {}^+H_2C–C(O^-){=}CH_2$], to ultimately yield an allene oxide. The rate of racemization of enantiomerically enriched *trans*-2,3-di-*t*-butylcyclopropanone increases only by a factor of 12 on going from *i*-octane to acetonitrile as solvent [822]. This small solvent effect is incompatible with a zwitterionic intermediate and confirms, together with theoretical calculations [797, 823], the diradical nature of the oxyallyl intermediate and the preceding activated complex.

The decomposition of dibenzoyl [177–179] and diisobutyryl peroxide [180, 181] (*cf.* Table 5-8) shows relatively large enhancing effects, which may be explained by the fact that the diacyl peroxide molecule contains two mutually repelling $C^{\delta\oplus} = O^{\delta\ominus}$ dipoles. The molecule should therefore prefer the conformation shown in Eq. (5-58), with only a small net dipole moment – analogous to glyoxal, which also possesses a *transoid* conformation of the two carbonyl groups [190]. Dissociation of the diacyl peroxide leads to two independent radical dipoles, with a comparatively greater net dipole moment (for comparison, the dipole moment of methyl benzoate is $6.3 \cdot 10^{-30}$ Cm = 1.9 D). Since this dipole separation occurs on activation, the slightly better solvation of the activated complex with increasing solvent polarity leads to the 22-fold rate acceleration experimentally observed on changing the solvent from *iso*-octane to acetonitrile [180, 181]. An additional influence of the solvent on the reaction of diisobutyryl peroxide is that it favors a heterolytic product in a subsequent, product-determining step. It is believed that a common intermediate, resulting from the rate-controlling step, decomposes *via* homolytic and heterolytic pathways.

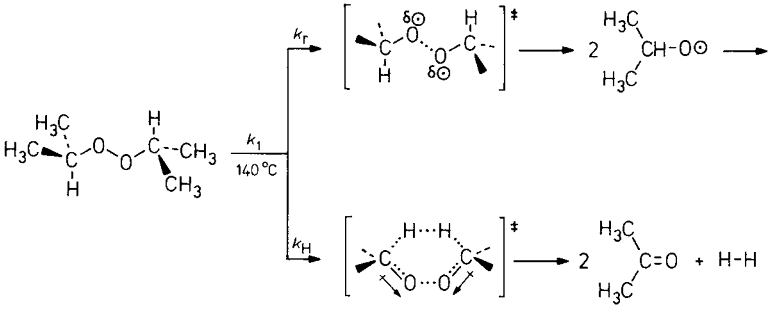


$\mu = 5.3 \cdot 10^{-30}$ C m (1.6 D) for $R = C_6H_5$ [191]

(5-58)

In the case of the thermolysis of unsymmetrical diacyl peroxides, R—CO—O_2—CO—Ar, with negatively substituted phenyl groups (*e.g.* Ar = 3-chlorophenyl), there is a moderate increase in reaction rate with increasing solvent polarity. They are generally considered to involve ion-pair intermediates (*e.g.* $R^{\oplus}\,{}^{\ominus}O_2C$—Ar), formed *via* dipolar activated complexes. A typical example is that of *endo*- and *exo*-(2-norbornyl)formyl 3-chlorobenzoyl peroxide: $k_1(CH_3CN)/k_1(\text{cyclohexane}) = 320$ for the *exo*-reactant [563].

The thermal decomposition of symmetrical dialkyl peroxides such as diisopropyl peroxide in solution has been shown to involve a competition between monomolecular homolysis (k_r) and an electrocyclic reaction yielding acetone and hydrogen (k_H); *cf.* Eq. (5-59) [564].



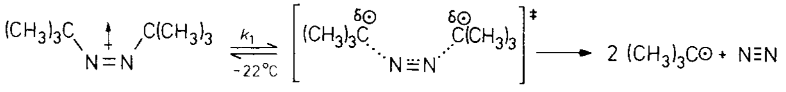
(5-59a)

(5-59b)

Whereas the activated complex for monomolecular homolysis [Eq. (5-59a)] has no dipolar character and k_r is nearly solvent-independent [$k_r(H_2O)/k_r(\text{toluene}) = 7$], k_H increases moderately with increasing solvent polarity [$k_H(H_2O)/k_H(\text{toluene}) = 59$]. This seems to be due to the development of dipolar character in the corresponding activated complex, which involves preformed dipolar acetone molecules [Eq. (5-59b)]. In the gas phase, the normal free-radical producing O–O homolysis is the preferred reaction route [564].

The rates for the thermolysis of cyclic peroxides are also only slightly solvent-dependent. For example, the first-order decomposition of acetone cyclic diperoxide (3,3,6,6-tetramethyl-1,2,4,5-tetroxane) increases only 21-fold on going from *n*-octane to acetic acid as solvent, corresponding to homolytic O–O bond rupture [824].

Azo compounds can exist in either the *cis* or *trans* form. It is reasonable to assume that the azoalkanes in Table 5-8 exhibit the *trans* configuration. Contrary to the small solvent effects obtained in the decomposition of *trans*-azoalkanes, the thermolysis of definite *cis*-azoalkanes reveals a significant solvent influence on rate. Thermolysis of aliphatic symmetrical *cis*-*tert*-azoalkanes can lead either to the corresponding *trans*-*tert*-azoalkanes, presumably *via* an inversion mechanism, or to *tert*-alkyl radicals and nitrogen by decomposition *via* a free-radical transition state [192]. An example of the first type of reaction is the (*Z*)/(*E*) isomerization of [1,1′]azonorbornane. Its rate is virtually solvent-independent, which is consistent with a simple inversion mechanism [565, 566]. The second reaction type is represented by the thermal decomposition of *cis*-2,2′-dimethyl-[2,2′]azopropane, for which a substantial decrease in rate with increasing solvent polarity has been found [193]; *cf.* Eq. (5-60).



(5-60)

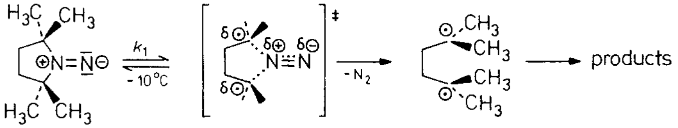
Solvent	n-C_5H_{12}	$(C_2H_5)_2O$	CH_3COCH_3	C_2H_5OH	CH_3OH
k_1^{rel}	65	31	8.4	2.1	1

Since *cis*-azoalkanes exhibit dipole moments of *ca.* $(7 \ldots 10) \cdot 10^{-30}$ Cm $(2 \ldots 3$ D) [194], this solvent effect is best rationalized by assuming a decrease and final loss of the dipole moment during activation. Due to their dipole moments, *cis*-azoalkanes are more stabilized by polar solvents than the less dipolar activated complexes. The activation process corresponds to a synchronous, two-bond cleavage, probably accompanied by widening of the C—N=N bond angles [193]. A two-step, one-bond cleavage process *via* short-lived diazenyl radicals has been discussed [567], but this mechanism seems to be important only in the case of unsymmetrical azoalkanes, in particular arylazoalkanes [192].

Cyclic *cis*-azoalkanes (*e.g.* pyrazolines, pyridazines, and others) exhibit a similar solvent effect on rate [193, 549], but angle expansion is of course impossible in these compounds.

Another explanation of these solvent effects recognizes the fact that polar solvents have a higher internal pressure [*cf.* Eq. (3-6) in Section 3.2] [549]. Since the activation volume, $\Delta V^{\neq}$, for loss of nitrogen is positive, *cis*-azoalkanes should decompose more slowly in polar solvents. This should also be true for *trans*-azoalkanes. These, however, exhibit a negligible solvent dependence of the decomposition rate; see reference [192] for further examples.

Analogous to *cis*-azoalkanes (1,2-diazenes), the thermolysis of 1,1-diazenes is also solvent-sensitive. The monomolecular decomposition rate of *N*-(2,2,5,5-tetramethylpyrrolidyl)nitrene decreases with increasing solvent polarity [568].

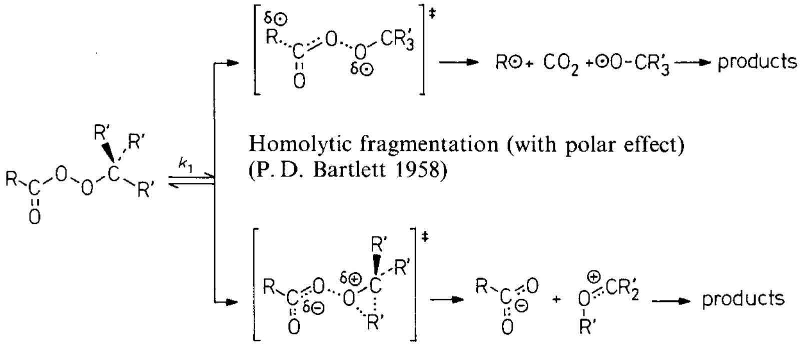


(5-61)

Solvent	n-C_6H_{12}	$(C_2H_5)_2O$	Tetrahydrofuran
k_1^{rel}	5.1	2.4	1.0

As shown by Eq. (5-61), the dipolarity of the solvated reactant molecule decreases during the activation process. Loss of nitrogen by simultaneous C—N bond-breaking produces a 1,4-biradical.

The effect of the medium on the thermolysis of peroxycarboxylic esters deserves particular mention. Some examples are compiled in Table 5-9. An interesting aspect of this reaction is that the peresters, depending on structure, substituents, and medium, can decompose by two different mechanisms given in Eqs. (5-62a) and (5-62b) [195, 196].

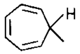
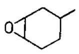
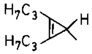
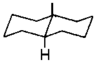
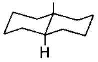
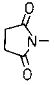


(5-62a)

(5-62b)

According to Eq. (5-62a), the perester may decompose by a concerted two-bond homolysis involving an isopolar or slightly dipolar activated complex, as established by Bartlett *et al.* [197]. The activated complex may have a slightly dipolar character resulting in a small rate increase with increasing solvent polarity (rate factors 2...11; *cf.* Table 5-9). This homolytic fragmentation, involving the so-called polar effect, is found

Table 5-9. Solvent influence on rates of monomolecular decomposition of various peroxycarboxylic esters R—CO—O—O—CR$'_3$ according to Eqs. (5-62a) and (5-62b).

No.	R	CR$'_3$	Number of solvents	Temperature °C	Slowest solvent	Fastest solvent	$k_1^{\text{rel. a)}}$	References
1	$H_5C_6{-}O{-}CH_2{-}$	$-C(CH_3)_3$	5	70	$H_5C_6{-}C_2H_5$	CH_3CN	1.6	[198]
2	$n{-}C_5H_{11}{-}$	$-C(CH_3)_3$	6	110	$CH_3(CH_2)_2CO_2H$	CH_3CO_2H	1.9	[199]
3	$H_5C_6{-}C(CH_3)_2{-}$	$-C(CH_3)_3$	3	50	n-$C_{12}H_{26}$	CH_3CN	3.5	[200]
4	$H_3CO{-}C_6H_4{-}CH_2{-}$	$-C(CH_3)_3$	3	70.4	c-C_6H_{12}	C_2H_5OH	3.8	[201]
5		$-C(CH_3)_3$	3	10.3	tetralin	CH_3OH	6.2	[202]
6		$-C(CH_3)_3$	9[b]	95	C_6H_5Cl	n-C_4H_9OH	6.4	[203]
7		$-C(CH_3)_3$	6	30	$H_5C_6{-}C_2H_5$	$H_5C_6{-}CH_2OH$	11	[204]
8	$o{-}(H_5C_6)_2C{=}CH{-}C_6H_4{-}$	$-C(CH_3)_3$	2	90	c-C_6H_{12}	CH_3OH	62	[205]
9	$o{-}H_5C_6S{-}C_6H_4{-}$	$-C(CH_3)_3$	12	40	c-C_6H_{12}	CH_3OH	692	[206]
10	$H_5C_6{-}CH_2{-}$		7	60	$H_5C_6{-}C_2H_5$	CH_3OH	31	[207]
11	$H_5C_6{-}$		11[c]	25	CH_3OH	CH_3OH/H_2O	3.5[c]	[208, 209]
12		$-C(CH_3)_3$	6	100	c-C_6H_{12}	CH_3OH	670	[210, 211]

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[a] $k_1^{\text{rel.}} = k_1$ (fastest solvent)/k_1 (slowest solvent).

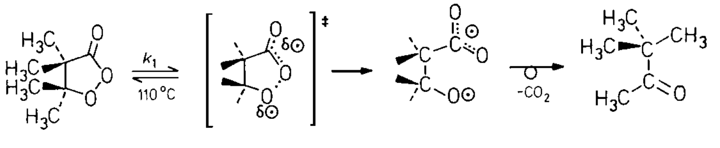
[b] Besides the two pure solvents, seven chlorobenzene/n-butanol mixtures.

[c] The reaction rate increases in the order c-C_6H_{12} < C_6H_6 < $H_3C{-}CO{-}CH_3$ < $CHCl_3$ < CH_3NO_2 < CH_3OH < CH_3CO_2H [208], but exact quantitative rate constants for this reaction are only available for eleven methanol/water mixtures up to 2.8 mmol/mol of water [209].

in reactions no. 1 ... 7 in Table 5-9. The products can be best explained by postulating a homolytic fragmentation of the peresters to form intermediate alkoxy and alkyl radicals.

Another representative example of a homolytic perester fragmentation is given by the thermal decarboxylation of β-peroxylactones such as 4,4,5,5-tetramethyl-1,2-dioxolan-3-one [569]; *cf.* Eq. (5-63).

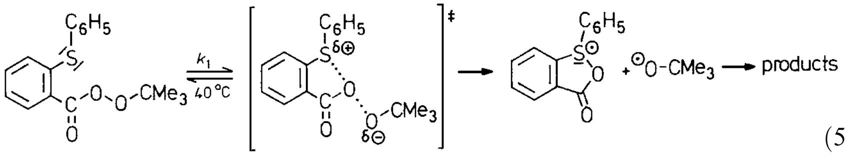
The observed rates vary only by a factor of three in the solvents used. This is consistent with a simple homolytic O—O bond cleavage leading to a short-lived 1,5-biradical, which subsequently decarboxylates with concurrent β-alkyl 1,2-migration to afford the rearranged pinacolone as the major product [569].



(5-63)

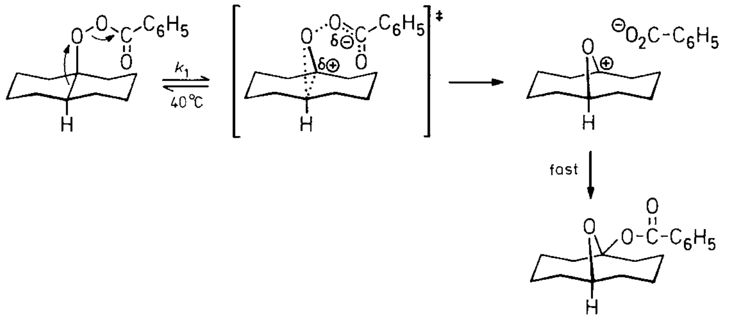
Solvent	c-C_6H_{12}	CCl_4	C_6H_6	CH_3CN
k_1^{rel}	1.0	1.2	1.8	2.8

Reactions no. 8 [205] and no. 9 [206] of Table 5-9 show special behaviour. These reactions, which show larger medium effects, involve neighbouring group participation by the alkene or phenylthio groups in the homolytic cleavage of the O—O bond, as shown for the thermolysis of *tert*-butyl 2-(phenylthio)perbenzoate in Eq. (5-64) [206]. The relatively large solvent and substituent effects observed for this anchimerically assisted reaction (rate factor 692), indicate that a large contribution to the transition state is made by a dipolar structure involving a five-membered ring. There is a concentration of positive charge on the neighbouring group involved in the displacement from oxygen and of negative charge on the oxygen leaving group. The activated complex is best described as a dipolar singlet, represented by neutral and ionic canonical mesomeric structures. Products isolated from the perester decomposition are compatible with the proposed bonding interaction in the activated complex leading to free-radical fragments. The radical nature of the intermediate – and consequently the homolytic character of the reaction – is confirmed by the products observed and by the fact that galvinoxyl solutions (a radical scavenger) are decolourized. The fraction of radicals trapped does not decrease with increasing solvent polarity. The rates of reaction (5-64), measured in various solvents, correlate well with the rates of another anchimerically assisted reaction [206], the ionization of 4-methoxyneophyl tosylate, used to establish a scale of solvent ionizing power (*cf.* Section 7.3).



(5-64)

In contrast to reactions no. 1...9 in Table 5-9, the solvent effects and products observed in reactions no. 11 [208, 209] and no. 12 [210, 211] strongly suggest that the predominant mode of decomposition of these two peresters involves heterolysis of the O—O bond and concurrent migration of the neighbouring alkyl group to the electron-deficient oxygen as described in Eq. (5-62b) [195, 196]. This ionic mechanism was first established by Criegee *et al.* [208]. Bartlett *et al.* [209] confirmed it using *trans*-9-decalyl-peroxybenzoate as substrate; *cf.* Eq. (5-65).



(5-65)

The strong rate acceleration observed in the thermal rearrangement of *trans*-9-decalyl-peroxybenzoate to 1-benzoyloxy-1,6-epoxycyclodecane with increasing solvent polarity (rate factor *ca.* 10^2) is in accordance with the postulated heterolytic O—O bond cleavage leading to a dipolar activated complex.

The decomposition of *trans*-9-decalyl-peroxyphenylacetate (no. 10 in Table 5-9) is an interesting borderline reaction. Depending on the reaction medium, either the heterocyclic Criegee mechanism or the homolytic fragmentation mechanism can be observed [207]. In alcohols, the decomposition occurs mainly by the heterolysis pathway, whereas in nonpolar solvents like ethylbenzene, the homolysis pathway predominates. In acetonitrile, both mechanisms compete, as evidenced by the product distribution. The thermolysis of this particular perester is thus an impressive example of the strong influence which solvents may have, not only on reaction rates but also on the mechanism of a chemical reaction (*cf.* Section 5.5.7 for further examples). In addition, it should be mentioned that peresters such as *tert*-butyl cycloheptatrieneperoxycarboxylate undergo heterolytic fragmentation if the reaction is acid-catalyzed [195, 212]. The base-catalyzed ionic fragmentation of *tert*-butyl peroxyformate has already been mentioned [110]; *cf.* Eq. (5-39b).

Apart from the above described radical-forming reactions, the influence of solvent on the reactions of the radicals themselves has also been thoroughly investigated [159–166]. The most important elementary reactions of radicals are atom transfer, combination, addition, disproportionation, and electron transfer, as listed in Table 5-10 [15, 213].

Most criteria for mechanisms depend upon intramolecular and extramolecular perturbation of the reacting system. A change in the medium is an extramolecular perturbation of the original system. The solvent effects produced by this perturbation can be predicted, as shown in Table 5-10, by taking into account whether or not the activated complex is dipolar or isopolar with the respect to the initial reactants. Only a small

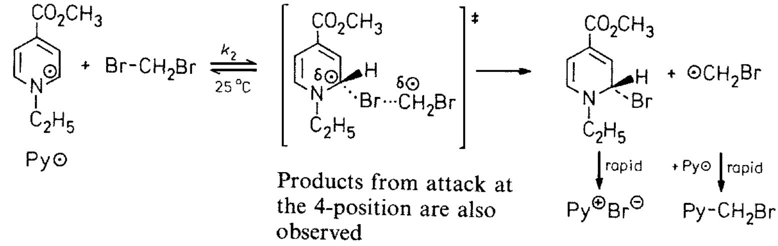
Table 5-10. Expected substituent and solvent rate effects for elementary radical reactions [15, 213].

Reaction type	Reaction scheme	Intramolecular perturbation by substituents	Extramolecular perturbation by medium
Atom transfer	$R\odot + A\text{-}X \rightleftharpoons [R^{\delta\odot}\cdots A\cdots X^{\delta\odot}]^{\ddagger} \longrightarrow R\text{-}A + \odot X$	Modest	Modest
Combination	$R\odot + \odot R \rightleftharpoons [R^{\delta\odot}\cdots R^{\delta\odot}]^{\ddagger} \longrightarrow R\text{-}R$	Small	Small
Addition	$R\odot + CH_2{=}CH\text{-}R \rightleftharpoons [R^{\delta\odot}\cdots CH_2 \overset{\delta\odot}{CH}\text{-}R]^{\ddagger}$ $\longrightarrow R\text{-}CH_2\text{-}\overset{\odot}{C}H\text{-}R$	Small	Small
Disproportionation	$R\odot + \underset{R}{C}H_2\text{-}\overset{\odot}{C}H_2 \rightleftharpoons [R^{\delta\odot}\cdots H\cdots \underset{R}{C}H \overset{\delta\odot}{C}H_2]^{\ddagger}$ $\longrightarrow R\text{-}H + \underset{R}{C}H{=}CH_2$	Small	Small
Electron transfer	$R\odot \longrightarrow R^{\oplus} + e^{\ominus}$ or $R\odot + e^{\ominus} \longrightarrow R^{\ominus}$	Large	Large

number of examples selected from the vast number of solvent-dependent free-radical reactions [159–166] shall be used to illustrate this point.

The most extensively studied reactions are those involving substitution between radicals (like halogen atoms, alkoxy or peroxy radicals, *etc.*) and a neutral molecule A—X (*cf.* first reaction in Table 5-10). In this atom-transfer reaction, the atom A, which is frequently a hydrogen atom, is transferred slowly from A—X to R·. In the isopolar activated complex of this reaction, there is no appreciable charge separation. In reactions of this type, therefore, only negligible solvent effects should be observed. However, there are also radical reactions known, in which a change in the polarity of the solvent can play an important role. For such processes, whose rate is clearly influenced by the medium, a certain charge separation during activation must be taken into account. The degree of separation of charges in an activated complex such as $[R^{\delta\ominus}\cdots A\cdots X^{\delta\oplus}]^{\neq}$ should depend on the electron affinity of the radical R· and the ionization potential of the molecule A—X.

Halogen abstraction by the stable free radical 1-ethyl-4-(methoxycarbonyl)pyridinyl (Py·) proceeds by the mechanism shown in Eq. (5-66) [214, 570]. The first step, which is rate-determining, is a transfer of the halogen atom to the pyridinyl radical.

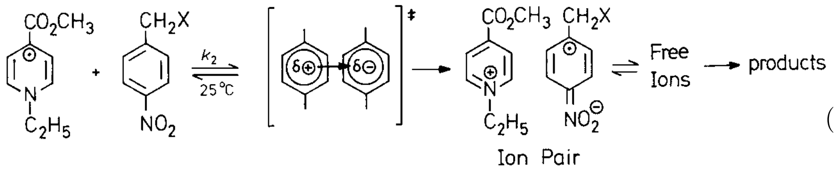


(5-66)

Solvent	CH_2Cl_2	CH_3CN	$(CH_3)_2CHOH$	C_2H_5OH
k_2^{rel}	1.0	2.1	2.0	3.5

The negligible solvent effect of this radical reaction with dibromomethane demonstrates that the activated complex for bromine atom-transfer has the same charge separation as the initial reactants. The dipole moment expected for a molecule like the pyridinyl radical is probably $(0 \ldots 10) \cdot 10^{-30}$ Cm $(0 \ldots 3$ D). Dibromomethane has a modest dipole moment of $5 \cdot 10^{-30}$ Cm (1.5 D). Consequently, in view of the negligible solvent effect upon rate, the activated complex must also have a dipole moment between $(0 \ldots 10) \cdot 10^{-30}$ Cm [214, 570].

In contrast to the preceding atom-transfer reaction, the solvent-induced rate change for the reaction between 1-ethyl-4-(methoxycarbonyl)pyridinyl and 4-(halomethyl)-nitrobenzenes is so large that a change in mechanism must be involved [215, 570]. In changing the solvent from 2-methyltetrahydrofuran to acetonitrile, the relative rate constant for 4-(bromomethyl)-nitrobenzene increases by a factor of up to 14800. This is of the order expected for a reaction in which an ion pair is created from a pair of neutral molecules [*cf.* for example, reaction (5-16)]. It has been confirmed therefore that, according to scheme (5-67), an electron-transfer process is involved [215, 570].



(5-67)

Solvent	2-Methyltetrahydrofuran	CH_2Cl_2	CH_3COCH_3	$HCON(CH_3)_2$	CH_3CN
k_2^{rel} for X = Br	1	46	278	7400	14800

It has been established that for solvents in which specific solvation is not dominant, a small solvent effect implies an atom-transfer reaction and a large solvent effect suggests an electron-transfer reaction between neutral species. The high solvent sensitivity of electron-transfer reactions between neutral molecules should provide a useful test of their occurrence [215, 570]. From Table 5-11, it can be concluded that atom-transfer, according to Eq. (5-66), is the rate-limiting step in the reaction of pyridinyl radical with

Table 5-11. Rate constant solvent effects for the reaction of haloalkanes with 1-ethyl-4-(methoxycarbonyl)pyridinyl radicals at 25 °C [215, 570].

Haloalkane	k_2^{rel} [a]	$\Delta\Delta G^{\neq}/(\mathrm{kJ \cdot mol^{-1}})$ [a]
Dibromomethane	*ca.* 0.5[b]	−1.3
(Bromomethyl)benzene	30	8.4
(Chloromethyl)benzene	63	10.3
4-(Chloromethyl)-nitrobenzene	2900	19.7

[a] Rate constant for the reaction of pyridinyl radical in acetonitrile divided by that for the reaction in 1,2-dimethoxyethane and the corresponding change in Gibbs activation energy.

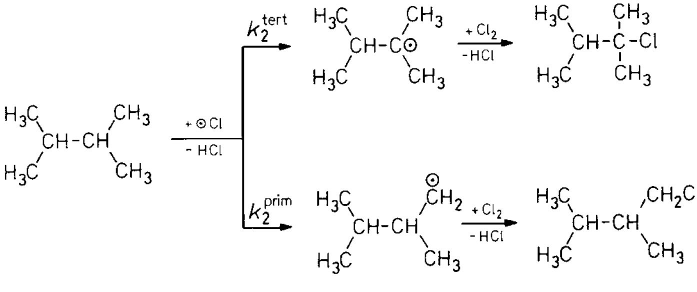
[b] $k_2^{rel} = k_2(i\text{-propanol})/k_2(\text{dichloromethane})$. This solvent polarity change is close to that used in the other cases.

(halomethyl)benzenes except for 4-(halomethyl)-nitrobenzenes, for which the solvent effect is compatible only with an electron-transfer mechanism according to Eq. (5-67) (for a more detailed discussion, see references [215, 570]).

Small but significant effects of solvent polarity were found in the autoxidation of a variety of alkenes and aralkyl hydrocarbons [216–220] (styrene [216, 218, 219], ethyl methyl ketone [217], cyclohexene [218], cumene [218, 219], tetralin [219], *etc.*). An extensive study on solvent effects in the azobisisobutyronitrile (AIBN)-initiated oxidation of tetralin in a great variety of solvents and binary solvent mixtures was made by Kamiya *et al.* [220].

Since solvent effects in radical oxidation (and autoxidation) reactions of organic compounds have been compiled and discussed in an excellent monograph by Emanuel, Zaikov, and Maizus [460], they are not discussed further here.

Another example of a solvent-dependent atom-transfer reaction is hydrogen abstraction by chlorine atoms during the photochemical chlorination of hydrocarbons with molecular chlorine; for an excellent review, see reference [571]. Russel reported that in the photochlorination of 2,3-dimethylbutane, according to reaction scheme (5-68), certain solvents do not have any effect on the selectivity of the reaction as measured by the rate ratio $k_2^{\text{tert}}/k_2^{\text{prim}}$, whereas other solvents increase this ratio significantly (*cf.* Table 5-12) [221]. The relative reactivity ratio $k_2^{\text{tert}}/k_2^{\text{prim}}$ of the tertiary hydrogen atoms, with respect to the primary hydrogens in 2,3-dimethylbutane, can be determined from the relative amounts of 2-chloro-2,3-dimethylbutane and 1-chloro-2,3-dimethylbutane



(5-68)

produced in the photochlorination of this hydrocarbon*). In the absence of any solvent, and in several aliphatic and cycloaliphatic solvents, the ratio $k_2^{\text{tert}}/k_2^{\text{prim}}$ varies from 3.3 to 9.1. In other solvents, particularly aromatic solvents and carbon disulfide, this ratio becomes comparatively large, ranging from 10 to 33 (*cf.* Table 5-12). Since the respective activated complexes leading to the primary and the tertiary haloalkane should not differ in their dipolarity, the solvation of the initial reactants must cause this selectivity. The latter group of solvents includes carbon disulfide and benzene derivatives bearing substituents that increase the electron density in the aromatic ring relative to that of benzene itself. These π-EPD solvents are able to form a loose π complex with the electrophilic chlorine radical in a reversible reaction as shown in Eq. (5-69). As might be

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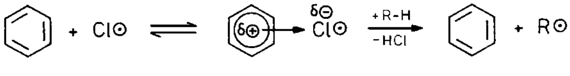
* It is necessary to multiply this product ratio by six to correct for the fact that there are twelve primary hydrogen atoms and two tertiary hydrogen atoms in the molecule.

Table 5-12. Solvent effect on the selectivity of the photochemical chlorination of 2,3-dimethylbutane at 55 °C (solvent concentration 4.0 mol/L) [221].

Solvent	Relative Reactivities $k_2^{\text{tert}}/k_2^{\text{prim}}$ [a]
2,3-Dimethylbutane	3.7[b]
Nitromethane	3.3
Tetrachloromethane	3.5
Cyclohexene	3.6
Trichloroethene	3.6
Propionitrile	4.0
Methyl acetate	4.3
tert-Butanol	4.8
Nitrobenzene	4.9
1,4-Dioxane	5.6
Di-*n*-butyl ether	7.2
N,*N*-Dimethylformamide	9.1
Chlorobenzene	10.2
Flurobenzene	10.3
Benzene	14.6
Toluene	15.4
Methoxybenzene	18.4
p-Xylene	18.6
1,3,5-Trimethylbenzene	25
Iodobenzene	31
Carbon disulfide	33[c]

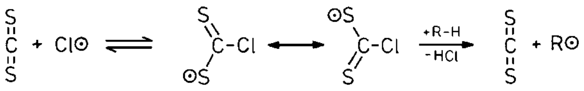
[a] *Cf.* reaction scheme (5-68).
[b] Solvent concentration 7.6 mol/L.
[c] Value at 25 °C.

expected, the complexed and therefore less reactive chlorine atoms show greater selectivity as hydrogen abstractors. The differences in the relative amounts of tertiary and primary chloroalkanes formed become more pronounced when the chlorination is performed in such complexing solvents. On the other hand, electron-withdrawing substituents on the benzene ring (*e.g.* NO_2) decrease the selectivity relative to benzene. Even in the presence of benzene, a fairly good π-EPD solvent, there is still some attack on the primary hydrogen atoms of 2,3-dimethylbutane. More direct evidence for the existence of a chlorine atom/benzene π-complex in the photochlorination of 2,3-dimethylbutane in solution in the presence of benzene has been given by Ingold *et al.* [572]. The interaction of $Cl\cdot$ with carbon disulfide, which displays a remarkably high efficiency in increasing the selectivity of the chlorine atom (*cf.* Table 5-12), probably leads to the formation of a σ-complexed radical according to Eq. (5-70), which will certainly have less energy than free $Cl\cdot$ and act as a more selective hydrogen abstractor. The comparatively small increase in selectivity caused by solvents lacking a π-electron system, but having non-bonding electrons (*n*-EPD solvents like alcohols, ethers, and *N*,*N*-dimethylformamide) might result from a complexation of the electrophilic chlorine atom by the oxygen of these solvents.



(5-69)

π-complex



(5-70)

σ-complex

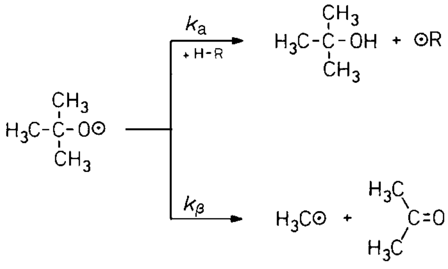
Studies of the influence of the solvent on relative selectivity in the photochlorination of 1,1-dichloroethane [573], 1-chlorobutane [574], and 2-chlorobutane [575] have shown that solvents can be divided into three classes. First, there are nonselective solvents, which are approximately as selective as the neat liquid hydrocarbon reactants (*e.g.* CCl_4, CH_2Cl_2, CH_3CN). Secondly, there are moderately selective perfluorohydrocarbon solvents (*e.g.* C_6F_{14}, C_8F_{18}, $C_{10}F_{20}O$), which exhibit selectivities similar to those in gas-phase chlorinations. Thirdly, there are solvents which lead to a greatly increased selectivity (*e.g.* C_6H_6, CS_2). The first group of solvents are relatively polarizable (as compared to the perfluorohydrocarbon solvents) and are thus able to stabilize the activated complex by solvation. This lowers the Gibbs activation energy and tends to have a levelling effect. In contrast, the inert perfluorohydrocarbons have no tendency to solvate the activated complex. Chlorinations in such solvents have a selectivity approaching that of the gas-phase reaction. The third group of solvents stabilize the chlorine atoms by specific solvation [*cf.* Eqs. (5-69) and (5-70)] and the resulting reactant/solvent complex has to be broken open before hydrogen abstraction can occur [573–575]. A detailed review on the photochlorination of alkanes in solution can be found in reference [825].

Another remarkable example of the solvent-influenced chemoselectivity of chlorine radicals is the photochlorination of cyclopropane to give, in competitive reactions, either 3-chloropropyl radicals (by S_H2 ring opening; k_C) or cyclopropyl radicals (by H abstraction; k_H) as intermediates. The rate constant ratio k_C/k_H was found to increase by a factor of 372 on going from the gas phase to 1,2-dichloroethane, presumably as a result of the internal pressure of the solvents used. Thus, solvents of high internal pressure favour the S_H2 process, while H-abstraction becomes more important in the gas phase and in solvents of low internal pressure [826].

The selectivity of free-radical side-chain bromination of toluene derivatives using *N*-bromosuccinimide and leading to mono- and dibromo-substituted toluenes has been studied in different solvents [577]. Surprisingly, yields and selectivities are much better in solvents such as methyl formate and dichloromethane than in the more commonly used tetrachloromethane.

Compared with chlorination, hydrogen abstraction reactions of alkoxy radicals are relatively insensitive to solvent effects [160, 222, 223]. The results of the AIBN-initiated radical chain chlorination of 2,3-dimethylbutane with *tert*-butyl hypochlorite indicate a solvent effect on *tert*-butoxy radical reactions of much smaller magnitude, but greater selectivity in aromatic solvents [222, 223]. The reduced solvent effect for this hydrogen abstraction reaction has been attributed to steric effects. Due to the bulky methyl groups around the electrophilic oxygen atom, complex formation involving solvent molecules and activated complex is hindered.

tert-Alkoxy radicals involved in the reactions of dialkyl peroxides and alkyl hypochlorites are not only capable of abstracting a hydrogen from a hydrocarbon yielding an alkyl radical and *tert*-alkyl alcohol, they can also decompose into a ketone and an alkyl radical, which subsequently reacts with the hydrocarbon. Changes in the rates of hydrogen abstraction (k_a) and decomposition (also called β-scission; k_β) of the radical can be determined from the relative amounts of the *tert*-alkyl alcohol and ketone produced, as shown for the *tert*-butoxy radical in Scheme (5-71) [160].



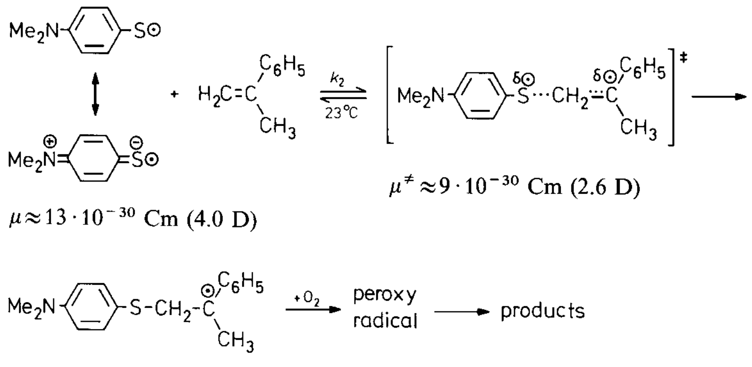
(5-71)

The ratio k_a/k_β can be solvent-dependent, as has been shown for the reaction of *tert*-butyl hypochlorite with cyclohexane in different solvents [224].

Replacement of one methyl group in the *t*-butoxy radical of Eq. (5-71) by a phenyl group leads to the cumyloxy radical, $H_5C_6{-}C(CH_3)_2{-}O\cdot$, the reaction of which has recently been studied in solvents of different polarity [827]. Analogously, cumyloxy radicals, generated photolytically from dicumyl peroxide, undergo H-abstraction reactions with cyclohexane or the solvent (k_a) and decomposition reactions (β-scission; k_β) with rate constant ratios k_a/k_β of up to 6.5 on going from polar acetic acid to apolar tetrachloromethane. The results indicate that k_a is practically solvent-independent, while k_β increases with increasing solvent polarity. This is in agreement with the results obtained for *t*-butoxy radicals [224], suggesting a decrease of k_a/k_β with increasing solvent polarity for both radicals. The increase in k_β with increasing solvent polarity is attributable to better stabilization of the activated complex for β-scission because of increased solvation of the developing dipolar ketone product (acetone or acetophenone, respectively) [827].

A free-radical addition reaction, the solvent-dependence of which has been studied in thirty-nine solvents, is the addition of the 4-(dimethylamino)benzenethiyl radical to α-methylstyrene; *cf.* Eq. (5-72) [576].

The rate of addition decreases moderately with increasing solvent polarity; there is a 35-fold rate deceleration in going from cyclohexane to dimethyl sulfoxide. In polar solvents, the dipolar reactant thiyl radical is more stabilized than the less dipolar activated complex. The stabilization of the thiyl radical by solvation has been proven by its strong positive solvatochromism (*i.e.* bathochromic shift of λ_{max} with increasing solvent polarity) [576]. Similar solvent effects on rate have been observed in the addition of the 4-aminobenzenethiyl radical to styrene [577].



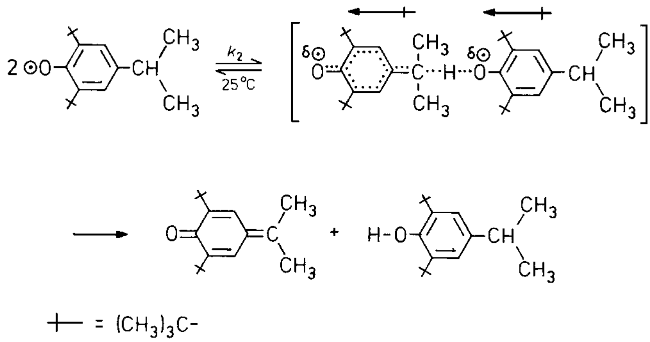
$\mu \approx 13 \cdot 10^{-30}$ Cm (4.0 D)

$\mu^{\neq} \approx 9 \cdot 10^{-30}$ Cm (2.6 D)

(5-72)

Solvent	c-C_6H_{12}	CCl_4	C_6H_6	C_2H_5OH	CH_3CN	CH_3SOCH_3
k_2^{rel}	35	19	6.8	2.8	1.7	1.0

Finally, a solvent-dependent disproportionation reaction is discussed. The 2,6-di-*tert*-butyl-4-isopropylphenoxy radical disproportionates to the corresponding quinone methide and the parent phenol in a slightly solvent-dependent reaction, according to Eq. (5-73) [225]. The enthalpies of activation vary from 21 to 32 kJ/mol in going from cyclohexane to benzonitrile, increasing as the polarity of the solvent increases. Due to the compensating changes in the entropies of activation, the reaction rates are only slightly sensitive to changes in the medium. The formation of the activated complex may be regarded as the head-to-tail joining of two dipoles. Desolvation of one of the phenoxy radicals is essential for the formation of this activated complex. Thus, in a medium in which radicals are highly solvated, the enthalpy of activation should be relatively high in order to provide the necessary desolvation energy. Such cases should be accompanied by the largest entropy increase. The linear relationship observed between $\Delta H^{\neq}$ and $(\varepsilon_r - 1)/\varepsilon_r$ strongly suggests that the solvent effect in this reaction can mainly be attributed to dipolar interactions between radical and solvent molecules [225].



(5-73)

Solvent	C_6H_6	c-C_6H_{12}	C_6H_5Cl	$C_6H_5OCH_3$	C_6H_5CN
k_2^{rel}	1	1.8	1.4	1.5	2.6
$\Delta H^{\neq}/(\text{kJ} \cdot \text{mol}^{-1})$	24	21	27	28	32

Apart from the selection of reactions involving dipolar, isopolar, or free-radical activated complexes used to demonstrate the qualitative theory of solvent effects by Hughes and Ingold [16, 44] in the preceding sections, further illustrative examples can be found in the literature (*e.g.* [14, 15, 18, 21, 23, 26, 29, 460, 468]).

5.3.5 Limitations of the Hughes–Ingold Rules

The qualitative theory of solvent effects introduced by Hughes and Ingold in 1935 [16, 44] is expressed as a set of rules that take into account the changes in charge magnitude and in charge distribution that occur between reactants and activated complex, as well as of the dielectric characteristics of solvents that enable them to solvate charges (*cf.* Section 5.3.1). Although the countless successful applications of this qualitative theory testify to its widespread use, it does contain some inherent limitations.

One of these limitations is the assumption made by Hughes and Ingold that the contribution of entropy changes ($\Delta S^{\neq}$) to changes in Gibbs energy of activation ($\Delta G^{\neq}$) are negligible. This implies that enthalpy changes ($\Delta H^{\neq}$) dominate the Gibbs energy expression $\Delta G^{\neq} = \Delta H^{\neq} - \mathrm{T} \cdot \Delta S^{\neq}$. This assumption is necessary because an increase in solvation usually decreases the entropy of a given state. Decreases in the entropy of activation counteract increasing enthalpy changes, but fortunately these decreases are relatively small for most reactions. Therefore, most but not all chemical reactions are controlled by enthalpy changes. A number of reactions in which changes in the entropy of activation govern the Gibbs energy of activation were reported by Pearson [226]. As illustrated in Table 5-5 for the reaction of iodoethane and triethylamine (*cf.* Eq. (5-16) in Section 5.3.1 [59]), the rate constants increase by a factor of 52 with increasing solvent polarity, although the enthalpies of activation show only a relatively small change of $\Delta\Delta H^{\neq} = 2.9\ \mathrm{kJ \cdot mol^{-1}}$. The entropies of activation rise by $\Delta\Delta S^{\neq} = 23\ \mathrm{J \cdot mol^{-1} \cdot K^{-1}}$ for the same sequence of solvents. Polar solvents appear to reduce the loss of entropy on passing from the reactants to the activated complex of the reaction, and it is mainly this factor that causes the rates to increase with solvent polarity. An explanation in terms of solvent orientation around the dipolar activated complex of reaction (5-16) was given in Section 5.3.1.

Another example is the $\mathrm{S_N}1$ solvolysis of 2-chloro-2-methylpropane (*cf.* Eq. (5-13) in Section 5.3.1 [40]), the rate data for which are given in Table 5-13. As the solvent is changed from ethanol to water, the rate of solvolysis increases by a factor of 335000, with a corresponding decrease in $\Delta G^{\neq}$. In going from ethanol to formic acid, the values of $\Delta S^{\neq}$ vary only from -13 to $-7\ \mathrm{J \cdot mol^{-1} \cdot K^{-1}}$. In the first five solvents, the $\Delta S^{\neq}$ values are relatively constant (*ca.* $-12\ \mathrm{J \cdot mol^{-1} \cdot K^{-1}}$), in agreement with domination of the overall solvent effects by $\Delta H^{\neq}$. Since $\Delta S^{\neq}$ is constant in these solvents, $\Delta H^{\neq}$ and $\Delta G^{\neq}$ must have a linear relationship. However, the large $\Delta S^{\neq}$ value for the reaction in water demonstrates that the $\Delta S^{\neq}$ changes are important in this case. This huge entropy effect is obviously due in part to the highly ordered structure of water.

Even in those cases where the rate constants, for a reaction in various solvents, are not significantly different, the activation parameters may indicate a significant amount of interaction between solute and solvent, as shown for the unimolecular decomposition of di-*tert*-butyl peroxide in Table 5-14 [172, 227]. The rate of decomposition of the per-

Table 5-13. Rate constants and activation parameters for the S_N1 solvolysis of 2-chloro-2-methylpropane in six solvents at 25 °C [40].

Solvents	ε_r	$\frac{k_1}{(10^5 \cdot s^{-1})}$	$k_1^{rel.}$	$\frac{\Delta G^{\neq}}{(kJ \cdot mol^{-1})}$	$\frac{\Delta H^{\neq}}{(kJ \cdot mol^{-1})}$	$\frac{\Delta S^{\neq}}{(J \cdot mol^{-1} \cdot K^{-1})}$
Ethanol	24.6	0.00860	1	113	109	−13
Acetic acid	6.2	0.0213	2.5	111	108	−10
Methanol	32.7	0.0753	9	108	104	−13
Formamide	109.5	3.72	430	98.3	93.6	−16
Formic Acid	58.5	105	12200	90.0	87.9	−7
Water	78.4	2880	335000	82.0	97.2	+51(!)

oxide does not vary by more than a factor of 2.3 in going from cyclohexane to acetonitrile, corresponding to a change in $\Delta G^{\neq}$ of only 4 $kJ \cdot mol^{-1}$. However, the activation parameters $\Delta H^{\neq}$ and $\Delta S^{\neq}$ show that the solvent apparently has a marked effect on the decomposition reaction ($\Delta\Delta H^{\neq} = 41$ $kJ \cdot mol^{-1}$; $\Delta\Delta S^{\neq} = 94$ $J \cdot mol^{-1} \cdot K^{-1}$). An evaluation of these activation parameters indicates that the compensating effects of the energy gained in solvating the radical-like activated complex, which would be expected to increase the decomposition rate, is counterbalanced by the decrease in entropy resulting from the more highly ordered arrangement of solvent molecules around the activated complex. The result is that the reaction rate is in the same range as that observed for the gas-phase reaction.

A second limitation of the Hughes–Ingold theory concerns the fact that the solvent is treated as dielectric continuum, characterized by one of the following: its relative permittivity, ε_r, the dipole moment, μ, or by its electrostatic factor, *EF*, defined as the product of ε_r and μ [27]. The term "solvent polarity" refers then to the ability of a solvent to interact electrostatically with solute molecules. It should be remembered, however, that solvents can also interact with solute molecules through specific intermolecular forces like hydrogen bonding or EPD/EPA complexation (*cf.* Section 2.2). For example, specific solvation of anionic solutes by protic solvents may reduce their nucleophilic reactivity, whereas in dipolar aprotic solvents solvation of anions is less,

Table 5-14. Rate constants and activation parameters for the decomposition of di-*tert*-butyl peroxide at 125 °C [172, 227].

Solvents	ε_r	$\frac{k_1}{(10^{-5} \cdot s^{-1})}$	$k_1^{rel.}$	$\frac{\Delta G^{\neq}}{(kJ \cdot mol^{-1})}$	$\frac{\Delta H^{\neq}}{(kJ \cdot mol^{-1})}$	$\frac{\Delta S^{\neq}}{(J \cdot mol^{-1} \cdot K^{-1})}$
Gas phase	1.00	–	–	136	159	59
Cyclohexane	2.0	1.52	1	136	171	88
Tetrahydrofuran	7.6	1.84	1.2	135	155	51
Benzene	2.3	1.99	1.3	135	148	33
Nitrobenzene	34.8	2.39	1.6	134	149	38
Acetic acid	6.2	2.98	2.0	132	140	19
Acetonitrile	35.9	3.47	2.3	132	130	−6

resulting in enormous rate accelerations [6], which cannot be explained by the simple electrostatic theory (*cf.* Section 5.5.2).

A third limitation of the Hughes–Ingold concept of solvent effects on reaction rates arises from the fact that it is based on static equilibrium transition-state solvation (*cf.* Section 5.1). That is, the reorientational relaxation of solvent molecules during the activation process is considered to be sufficiently fast so that the activated complex will be in thermal equilibrium with the surrounding solvent shell. However, this is not necessarily true in all cases, in particular not for very fast reactions. In such reactions, the rate will also depend on solvent reorientation rates and the standard transition-state theory will break down. Theoretical investigations of the S_N1 ionization reactions of $Me_3C–X$ ($X = Cl, Br, I$) in solution have shown that the calculated Gibbs energies of activation, $\Delta G^{\neq}$, decrease with increasing solvent polarity, in agreement with experiment and conventional expectations. However, a *decreasing* stabilization of the activated complexes with increasing solvent polarity has been found. That is, the activated complexes become *less* ionic in more polar solvents. This surprising result is at variance with the conventional Hughes–Ingold rules. Obviously, for S_N1 ionization reactions of tertiary haloalkanes, the conventional equilibrium reaction-rate methods cannot be applied. The S_N1 ionization process seems to be a non-equilibrium one [465]; *cf.* references [463, 465, 466] for further discussions.

It should be mentioned that an investigation of solvent rate effects is very often limited by the narrow range of solvents examined. When a particular reaction is studied in a small number of often very similar solvents, no far-reaching conclusions about the influence of solvent can be reached. As a rule, the reaction under consideration should be investigated in as many solvents of different polarity as possible. With a minimum of five different solvents, a good general picture of the reaction should be obtained. Very often, reactions have been carried out in a series of binary solvent mixtures such as alcohol/water. Solvents of such a similar structure will specifically solvate the solutes in a related manner throughout the whole solvent series, and a change of solvent mixture will mainly reflect the electrostatic influences of the solvents.

The Hughes–Ingold theory also neglects the changing solvent structure. Although solvent–solvent interactions are usually small compared to solute–solvent interactions, consideration should be given to solvent association when reactions are carried out in a highly structured solvent like water. The electrostatic theory ignores such solvent–solvent interactions.

The final limitation of the pure electrostatic theory is its inability to predict solvent effects for reactions involving isopolar transition states. Since no creation, destruction, or distribution of charge occurs on passing from the reactants to the activated complex of these reactions, their rates are expected to be solvent-independent. However, the observed rate constants usually vary with solvent, although the variations rarely exceed one order of magnitude (*cf.* Section 5.3.3). These solvent effects may be explained in terms of cohesive forces of a solvent acting on a solute, usually measured by the cohesive pressure of the solvent (*cf.* Section 5.4.2).

In spite of these limitations, the electrostatic Hughes–Ingold theory remains a good guide in predicting the solvent influence on chemical reactions, at least in a qualitative way. Exceptions can be safely assumed to involve strong specific solute–solvent interactions.

5.4 Quantitative Theories of Solvent Effects on Reaction Rates

5.4.1 General Remarks

Whereas the theoretical treatment of gas-phase reactions is comparatively simple, the calculation of rate constants for reactions in the liquid phase is very complicated. This is essentially due to the complexity of the many possible intermolecular solute-solvent interactions (*cf.* Section 2.2). When investigating solution-phase reaction kinetics, the problems to be faced include deciding which property of the solvent to use when setting up mathematical correlations with the reaction rates. Another problem is deciding which characteristics of the reacting molecules are to be considered when the effects of the solvent on their reactivity is determined. A quantitative allowance for the solvent effects on the rate constants k for elementary reactions involves establishing the following functions:

$$k = f(a, b, c, \ldots m, n, o, \ldots) \tag{5-74}$$

where a, b, and c are parameters characterizing the properties of the reactants, and m, n, and o are parameters characterizing the properties of the medium. The function thus obtained will then correctly describe the dependence of the rate constants on the medium. The problem then arises as to which reactant and solvent parameters are responsible for the observed dependences and must be included in Eq. (5-74).

When considering only pure electrostatic interactions leading to non-specific solvation, the solvent can be regarded as an isotropic continuum, with relative permittivity ε_r, and the reactants are characterized by both the magnitude and distribution of charge in the molecule. However, an analysis of solvent effects shows that not only non-specific solvation caused by electrostatic and dispersion forces, but also specific solvation caused by hydrogen bonding and EPD/EPA complexation, must be considered. The reaction kinetics for any particular reaction in a given solvent will be determined by the predominating type of solvation for that reaction.

The theoretical treatment of liquid-phase reaction kinetics is limited by the fact that no single universal theory on the liquid state exists at present. Problems which have yet to be sufficiently explained are: the precise character of interaction forces and energy transfer between reacting molecules, the changes in reactivity as a result of these interactions, and finally the role of the actual solvent structure. Despite some limitations, the absolute reaction rates theory is at present the only sufficiently developed theory for processing the kinetic patterns of chemical reactions in solution [2–5, 7, 8, 11, 24, 463–466]. According to this theory, the relative stabilization by solvation of the initial reactants and the activated complex must be considered (*cf.* Section 5.1).

Thus, the problem of making quantitative allowances for solvent-induced changes in the rate constant of a reaction $A + B \rightleftharpoons (AB)^{\neq} \rightarrow C + D$ (*cf.* Eq. (5-1) in Section 5.1) is reduced to the calculation of the difference between the partial Gibbs energies of solvation of the activated complex $(AB)^{\neq}$ and the initial reactants A and B as given in Eq. (5-75) [28].

$$\ln k = \ln k_0 - \frac{1}{R \cdot T}(\Delta G_{\mathrm{A,solv}} + \Delta G_{\mathrm{B,solv}} - \Delta G_{(\mathrm{AB})^{\neq},\mathrm{solv}}) \tag{5-75}$$

k_0 is the rate constant of the reaction in a standard solvent or in the gas phase, k is the rate constant observed in the solvent under consideration. Some progress has been made in the calculation of initial-state and transition-state solvent effects on reaction rates using thermodynamic transfer functions [453, 467]; *cf.* also Section 5.5.3.

If all possible solute–solvent interactions are taken into account, then attempts to correlate the rate constant with the medium will generally lead to such complicated equations that their experimental verification is impossible. Therefore, equations correlating rate constants with medium properties are usually derived on the basis of more or less theoretically justified models, allowing for only a limited number of dominating interaction factors. If the model adopted correctly reflects the dominating solute–solvent interactions, then a good quantitative description of the experimental data using the derived theoretical equation may be obtained. It is convenient, therefore, to distinguish between the following four reaction types:

(a) Reactions between neutral, apolar molecules (*via* isopolar activated complexes);
(b) Reactions between neutral, dipolar molecules (*via* dipolar activated complexes);
(c) Reactions between neutral, dipolar molecules and ions (*via* dipolar and charged activated complexes); and
(d) Reactions between ions (*via* dipolar and/or charged activated complexes).

The following sections will deal only with the final results of these calculations based on suitable, but rather simple models, together with some examples, which shall illustrate the proposed dependences. More detailed discussions can be found in well-known monographs [2–5, 7, 8, 11, 12, 21, 24, 25, 28, 457, 459, 460]. During the last decades, theoretical chemists have developed an impressive variety of methods and computational strategies for describing and understanding the complex phenomena of solute solvation. These can also be applied to the solvation of reactants and activated complexes, which is of particular relevance to this Chapter. These theoretical treatments of solute–solvent interactions include, amongst others, quantum-chemical continuum models, supramolecular models, and semicontinuum quantum-chemical models; see the end of Section 2.3. For recent comprehensive reviews on these topics, see references [27d, 355–358] given in Chapter 2 and references [578, 579] given in this Chapter.

5.4.2 Reactions Between Neutral, Apolar Molecules

In any solution reaction, cavities in the solvent must be created to accommodate reactants, activated complex, and products. Thus, the ease with which solvent molecules can be separated from each other to form these cavities is an important factor in solute solubility (*cf.* Section 2.1). Furthermore, because solubility and reactivity are often related phenomena, the intermolecular forces between solvent molecules must also influence rates of reaction. The overall attractive forces between solvent molecules gives the solvent as a whole a cohesion which must be overcome before a cavity is created. The degree of cohesion may be estimated using the surface tension, but a more reliable estimate is obtained by considering the energy necessary to separate the solvent molecules. This is known as the *cohesive pressure c* (also called *cohesive energy density*) [228–

232]. The cohesive pressure is defined as the energy of vapourization, ΔU_v, per unit molar volume, V_m, as shown in Eq. (5-76); *cf.* also Eq. (3-5) in Section 3.2.

$$c = \frac{\Delta U_\mathrm{v}}{V_\mathrm{m}} = \frac{\Delta H_\mathrm{v} - R \cdot T}{M_\mathrm{r} \cdot \varrho^{-1}} \tag{5-76}$$

Values of c are calculated from experimentally determined enthalpies (heats) of vapourization of the solvent to a gas of zero pressure, ΔH_v, at a temperature T, as well as from the molecular mass M_r, the density of the solvent ϱ, and the gas constant, R. The cohesive pressure characterizes the amount of energy needed to separate molecules of a liquid and is therefore a measure of the attractive forces between solvent molecules. The cohesive pressure c is related to the *internal pressure* π, because cohesion is related to the pressure within a liquid; *cf.* Eq. (3-6) in Section 3.2 for the precise definition of π*⁾.

In mixtures which are regular solutions**⁾, the mutual solubility of the components depends on the cohesive pressure, hence Hildebrand termed the square root of c the *solubility parameter* δ, according to Eq. (5-77); *cf.* also Eq. (2-1) in Section 2.1 [228, 229, 231, 238].

$$\delta = \left(\frac{\Delta U_\mathrm{v}}{V_\mathrm{m}}\right)^{1/2} = \left(\frac{\Delta H_\mathrm{v} - R \cdot T}{M_\mathrm{r} \cdot \varrho^{-1}}\right)^{1/2} \tag{5-77}$$

A good solvent for a certain nonelectrolyte solute should have a δ value close to that of the solute (*cf.* Section A.1). Extensive compilations of δ values are given in references [231, 238]; a selection of δ values for various organic solvents is given in Table 3-3 in Section 3.2.

Assuming that it is only van der Waals forces which are acting in the solute/solvent system, and that the heat of mixing is responsible for all deviations from ideal behaviour, as well as the fact that the solute/solvent interaction energy is the geometric mean of solute/solute and solvent/solvent interactions, Hildebrand [228, 229] and Scatchard [230] were able to develop the following expression for the activity coefficient f_i of the nonelectrolyte solute i dissolved in a solvent s (mole fraction basis), referred to a standard state of pure liquid solute (not infinite dilution):

$$RT \cdot \ln f_\mathrm{i} = V_\mathrm{m,i} \cdot \phi_\mathrm{s}^2 \cdot \left[\left(\frac{\Delta U_\mathrm{v,i}}{V_\mathrm{m,i}}\right)^{1/2} - \left(\frac{\Delta U_\mathrm{v,s}}{V_\mathrm{m,s}}\right)^{1/2}\right]^2 \tag{5-78}$$

---

* Since the internal pressure is actually defined in a slightly different way, values of internal pressure approach those of the cohesive pressure only for nonpolar and non-associated solvents (*cf.* Table 3-2 in Section 3.2) [228–232, 237]. Internal pressure is a measure of the instantaneous volume derivative of the cohesive pressure during isothermal expansion of a liquid (*cf.* Eq. (3-6) in Section 3.2). Because of the experimental difficulty in obtaining real internal pressures, it is usual to refer to $\Delta U_\mathrm{v}/V_\mathrm{m}$ as the internal pressure of a liquid.

** Regular solutions are characterized by a disordered distribution of solute and solvent molecules which is the same as in an ideal solution. In going from an ideal to a regular solution there is no change in entropy ($\Delta S = 0$), whereas the change in the activity coefficient f_i of the solute i is determined only by the enthalpy component of the Gibbs energy: $RT \cdot \ln f_\mathrm{i} = \Delta G = \Delta H$ [228, 229].

where $V_{\mathrm{m,i}}$ is the molar volume of solute i (as a pure liquid); $\Delta U_{\mathrm{v,i}}$ is the molar energy of vapourization of the solute (as a pure liquid); $V_{\mathrm{m,s}}$ and $\Delta U_{\mathrm{v,s}}$ are the same quantities for the solvent s; ϕ_{s} is the volume fraction of the solvent s, equal to unity for a dilute solution.

Since reactions are usually carried out in dilute solution, Eq. (5-78) can be simplified to Eq. (5-79),

$$RT \cdot \ln f_{\mathrm{i}} = V_{\mathrm{m,i}} \cdot (\delta_{\mathrm{i}} - \delta_{\mathrm{s}})^2 \tag{5-79}$$

where δ_{i} and δ_{s} are the solubility parameters of the reactant solutes and the solvent, respectively, according to Eq. (5-77) [5, 228–230].

The rate constant k of a bimolecular reaction $\mathrm{A} + \mathrm{B} \rightleftharpoons (\mathrm{AB})^{\neq} \rightarrow \mathrm{C} + \mathrm{D}$ can be expressed either as in Eq. (5-75) or in terms of the activity coefficients as shown in Eq. (5-80),

$$\ln k = \ln k_0 + \ln f_{\mathrm{A}} + \ln f_{\mathrm{B}} - \ln f_{\neq} \tag{5-80}$$

where k_0 is the rate constant in an ideal solution [5, 28].

By substituting Eq. (5-79) into Eq. (5-80), the following relationship for the rate of reaction between the nonpolar reactants A and B is obtained [5, 28]:

$$\ln k = \ln k_0 + \frac{1}{RT}[V_{\mathrm{A}}(\delta_{\mathrm{A}} - \delta_{\mathrm{s}})^2 + V_{\mathrm{B}}(\delta_{\mathrm{B}} - \delta_{\mathrm{s}})^2 - V_{\neq}(\delta_{\neq} - \delta_{\mathrm{s}})^2] \tag{5-81}$$

where V_{A}, V_{B}, and $V_{\neq}$ are the molar volumes of A, B, and the activated complex, respectively. Thus, the rate constant depends not only on the difference in molar volumes between reactants and activated complex [called the volume of activation, $\Delta V^{\neq} = V_{\neq} - (V_{\mathrm{A}} + V_{\mathrm{B}})$], but also on the relative cohesive pressure of reactants, activated complex, and solvent. If the reactants have a greater solubility in the solvent than the activated complex, the rate is lower compared to the rate in an ideal solution. The reverse is true if the activated complex is more soluble than the reactants.

Eq. (5-81), which is difficult to handle, can be changed into the linear Eq. (5-82):

$$\begin{aligned} RT \cdot \ln(k/k_0) = {} & \delta_{\mathrm{s}}^2(V_{\mathrm{A}} + V_{\mathrm{B}} - V_{\neq}) + (V_{\mathrm{A}} \cdot \delta_{\mathrm{A}}^2 + V_{\mathrm{B}} \cdot \delta_{\mathrm{B}}^2 - V_{\neq} \cdot \delta_{\neq}^2) \\ & + 2\delta_{\mathrm{s}}(V_{\neq} \cdot \delta_{\neq} - V_{\mathrm{A}} \cdot \delta_{\mathrm{A}} - V_{\mathrm{B}} \cdot \delta_{\mathrm{B}}) \end{aligned} \tag{5-82}$$

A reasonable assumption in some cases is that $V_{\neq} = V_{\mathrm{A}} + V_{\mathrm{B}}$, thus the first term in Eq. (5-82) becomes zero. The second term is constant for all solvents if molar volumes and cohesion pressures of reactants and activated complex are the same in these solvents. Thus, under certain conditions, the third term is the most important. In gas-phase reactions, only the second term is left ($\delta_{\mathrm{s}} = 0$ for the gas phase).

Intuitively, one would expect that the volume of the reactants, the volume of the activated complex, and the corresponding activation volume, as well as the internal pressure of the solvent*) will affect the reaction rate [27]. As early as 1929, Richardson and Soper [233], and later Glasstone [234], put forward rules which consider the influence of cohesion of reactants, products, and the solvent on reaction rates. They observed that reactions in which the products possessed greater (or lower) cohesion than the reactants were generally accelerated (or decelerated) by solvents with high cohesion, whereas reactions in which reactants and products were of similar cohesion, the solvent had relatively little influence on the reaction velocity. Although the reaction products are not involved in the activation process, according to the transition state theory, the above observations are still valid, since the cohesion of the activated complex may be regarded as lying somewhere between the values for the reactants and the products [27]. It has been pointed out, however, that variations in rate, caused by the internal pressure or cohesive pressure of the solvents, should be small in most solvents and generally should not exceed an order of magnitude [235].

Use of Eqs. (5-81) or (5-82) to predict solvent effects on reaction rates between nonpolar solutes is limited by the fact that there are no experimental data available for the heats of vapourization and hence for δ_i of most reacting organic compounds. However, the δ_s values are known for most organic solvents [231, 232, 236, 238]. A good approximation for the evaluation of $\delta_{\neq}$ is given by Eq. (5-83) [25, 28]:

$$\delta_{\neq} = \left(\frac{V_\mathrm{A}\delta_\mathrm{A}^2 + V_\mathrm{B}\delta_\mathrm{B}^2}{V_{\neq}} \right)^{1/2} \tag{5-83}$$

Nevertheless, it is possible to obtain correlations between reaction rates and δ_s^2, as shown in Figs. 5-8 and 5-9 (for further examples, see references [25, 126]).

Fig. 5-8 shows that there is a rough correlation of $\lg(k/k_0)$ with δ_s^2 for the Diels–Alder dimerization of cyclopentadiene [35], as predicted by Eq. (5-81). The molar volumes of cyclopentadiene and the corresponding activated complex have been determined as 83.1 and 135 cm^3, respectively [126].

Fig. 5-9 shows that there is also a very rough, inverse correlation between $\lg(k/k_0)$ and δ_s^2 for the dissociation of the dimer of the triphenylmethyl radical [167]. It can be safely assumed that in this unimolecular reaction the molar volume of the activated complex is greater than the molar volume of the reactant, since a bond breaking must occur to some extent on activation.

The scatter of the points in the two figures is not surprising in view of the simplifications made in deriving Eq. (5-81). Furthermore, the solvent effects observed in these reactions are very small with a comparatively large experimental error, and the solvents used include such dipolar and associated liquids as nitromethane and alcohols.

In principle, it is possible to distinguish between reactions with negative activation volume $\Delta V^{\neq}$ $(= V_{\neq} - V_\mathrm{reactants})$ and those with positive activation volume, since the activated complex for the former occupies less volume than the reactants, according to the schematic Eqs. (5-84) and (5-85) [239].

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* How an external pressure may affect the rate of a reaction in solution is considered in Section 5.5.11. The activation volume of a reaction is usually obtained from external pressure measurements.

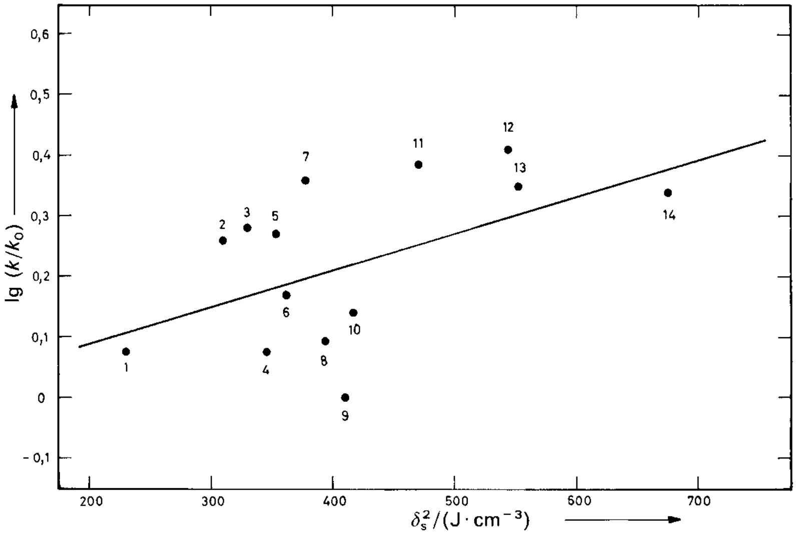
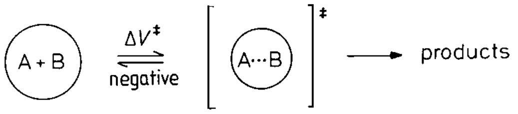
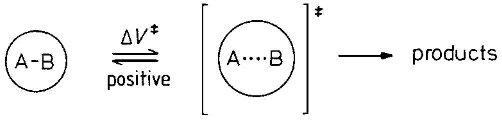


Fig. 5-8. Correlation of $\lg(k/k_0)$ [35] and the cohesive pressure δ_s^2 [238] in the Diels–Alder dimerization of cyclopentadiene at 40 °C (rate constants relative to acetone as 'slowest' solvent): 1) diethyl ether, 2) tetrachloromethane, 3) toluene, 4) tetrahydrofuran, 5) benzene, 6) trichloromethane, 7) chlorobenzene, 8) dichloromethane, 9) acetone, 10) 1,4-dioxane, 11) *tert*-butanol, 12) 1-butanol, 13) 1-propanol, and 14) ethanol. The point for methanol shows a large deviation and is not included in this figure.

Since in reaction (5-84) the reactants form a more compact activated complex, it is assumed that $(\delta_A + \delta_B) < \delta_{\neq}$. In the case of Eq. (5-85), $(\delta_{A-B}) > \delta_{\neq}$ because a loosening of bonds occurs on activation. If the nonpolar reaction is of type (5-84), *e.g.* dimerization of cyclopentadiene, ln k will increase as δ_s increases, whereas for reactions of type (5-85), such as the unimolecular dissociation of the triphenylmethyl dimer, ln k will decrease as δ_s increases. Eq. (5-81) therefore predicts that the internal pressure (or the cohesive pressure) of solvents should influence reaction rates of nonpolar reactions in the same direction as external pressure (*cf.* also Section 5.5.11) [27, 232, 239].



(5-84)



(5-85)

The solvent influence on rates of bimolecular H-atom-transfer reactions $R\cdot + H{-}X \rightarrow R{-}H + \cdot X$ has been theoretically studied [580]. Rates for the model

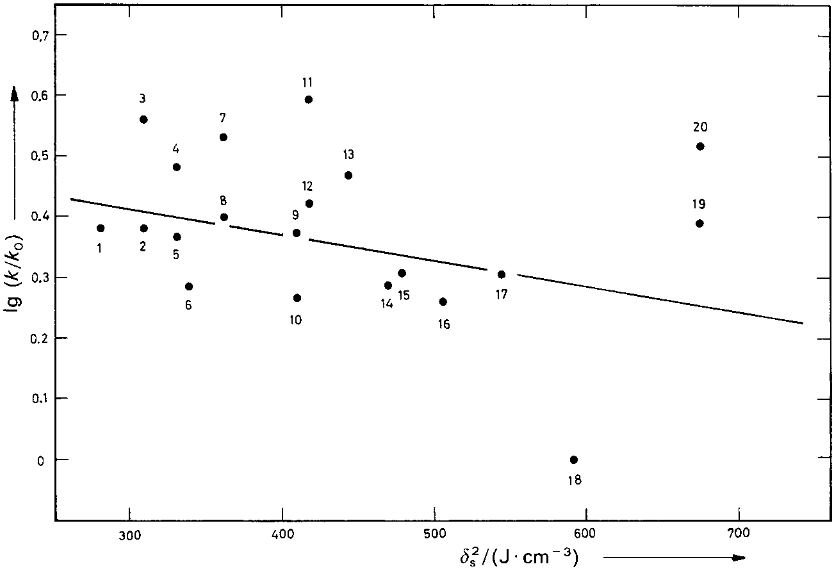


Fig. 5-9. Correlation of $\lg(k/k_0)$ [167] and the cohesive pressure δ_s^2 [238] in the dissociation of 1-diphenylmethylene-4-triphenylmethyl-2,5-cyclohexadiene ("hexaphenylethane") at 0 °C; *cf.* Eq. (5-56) in Section 5.3.4 (rate constants relative to acetonitrile as 'slowest' standard solvent):
1) ethyl benzoate, 2) diethyl oxalate, 3) tetrachloromethane, 4) 1-bromopropane, 5) toluene, 6) 4-methyl-3-penten-2-one, 7) trichloromethane, 8) styrene, 9) propionic acid, 10) *N*,*N*-diethylacetamide, 11) carbon disulfide, 12) nitrobenzene, 13) aniline, 14) methyl salicylate, 15) pyridine, 16) ethyl cyanoacetate, 17) ethylene glycol monomethyl ether, 18) acetonitrile, 19) ethanol, and 20) nitromethane.

H-exchange reaction between $CH_3\cdot$ and CH_4 have been compared in the gas-phase and in rare gas solution (compressed Ar and Xe as solvents) over a wide range of internal pressures. Depending on the solvent and its internal pressure, relatively large rate enhancements have been calculated for this methyl/methane H-abstraction reaction. The major reason for this static solvent enhancement of rate in rare gas solutions seems to be the compact (tight) character of the activated complex, $[CH_3^{\delta\ominus}\cdots H\cdots{}^{\delta\ominus}CH_3]^{\neq}$ [580].

The concept of cohesive pressure (or internal pressure) is useful only for reactions between neutral, nonpolar molecules in nonpolar solvents, because in these cases other properties of the solvents, such as the solvation capability or solvent polarity, are neglected. For reactions between dipolar molecules or ions, the solvents interact with reactants and activated complex by unspecific and specific solvation so strongly that the contribution of the cohesive pressure terms of Eq. (5-81) to $\ln k$ is a minor one. It should be mentioned that cohesive pressure or internal pressure are not measures of solvent polarity. Solvent polarity reflects the ability of a solvent to interact with a solute, whereas cohesive pressure, as a structural parameter, represents the energy required to create a hole in a particular solvent to accommodate a solute molecule. Polarity and cohesive pressure are therefore complementary terms, and rates of reaction will depend on both of them [27, 232]. The influence of solvent polarity on reaction rates will be discussed in the following Sections.

5.4.3 Reactions Between Neutral, Dipolar Molecules

In reactions between neutral, dipolar molecules, the electrostatic solute/solvent interactions such as dipole–dipole forces should above all determine the reaction rates in a manner as described qualitatively by the Hughes–Ingold theory [16, 44]. In order to describe electrostatic solvent effects, one considers the interaction between charged points separated by an isotropic dielectric continuum using functions of the relative permittivity. In rate equations involving dipolar reactants, the well-known equation of Kirkwood [240] is generally applicable. The Kirkwood expression relates the standard Gibbs free energy of transfer of a spherical dipolar molecule of radius r and dipole moment μ from the gas phase ($\varepsilon_r = 1$) to a continuous medium (with $\varepsilon_r > 1$) according to

$$\Delta G^\circ_{\text{solv}} = -\frac{N_A}{4\pi \cdot \varepsilon_0} \cdot \frac{\mu^2}{r^3} \cdot \frac{\varepsilon_r - 1}{2\varepsilon_r + 1} \tag{5-86}$$

where ε_0 is the permittivity of vacuum and N_A is the Avogadro constant. This important formula relates the changes in Gibbs solvation energy of the dipolar solute both to the relative permittivity of the solvent and to the dipole moment and radius of the solute molecule, taking into account electrostatic forces only between solute and solvent molecules*).

Applying Kirkwood's formula to the transition-state theory for the bimolecular reaction $A + B \rightleftharpoons (AB)^{\neq} \rightarrow C + D$ and combining Eq. (5-86) with Eq. (5-75), one obtains an expression for the rate constant of a reaction between two dipolar molecules A and B with moments μ_A and μ_B to form an activated complex with dipole moment $\mu_{\neq}$ [2]:

$$\ln k = \ln k_0 - \frac{1}{4\pi \cdot \varepsilon_0} \cdot \frac{N_A}{R \cdot T} \cdot \frac{\varepsilon_r - 1}{2\varepsilon_r + 1} \cdot \left(\frac{\mu_A^2}{r_A^3} + \frac{\mu_B^2}{r_B^3} - \frac{\mu_{\neq}^2}{r_{\neq}^3} \right) \tag{5-87}$$

where k is the rate constant in the medium of relative permittivity ε_r, and k_0 is the rate constant in a condensed medium with $\varepsilon_r = 1$ Eq. (5-87) predicts that, if the activated complex is more dipolar than the reactants, the rate of the reaction increases with the relative permittivity of the medium.

Based on the same premises, but with some modification of the electrostatic model introduced by Kirkwood, Laidler, and Landskroener obtained another similar

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* It should be noted that Kirkwood's formula does not appear in his first publication [240] in the form of Eq. (5-86). Nevertheless, it is this form of Kirkwood's formula which is widely known, representing only one of the terms of a more complex equation given in reference [240] with $n = 1$. Kirkwood's theory was further developed in papers by Kirkwood, Westheimer, and Tanford [241], Laidler and Landskroener [242], and Hiromi [243].

expression for the reaction of two dipole molecules in a medium as given by Eq. (5-88) [11, 242]:

$$\ln k = \ln k_0 + \frac{1}{4\pi \cdot \varepsilon_0} \cdot \frac{3 \cdot N_A}{8 \cdot R \cdot T} \cdot \left(\frac{2}{\varepsilon_r} - 1\right) \cdot \left(\frac{\mu_A^2}{r_A^3} + \frac{\mu_B^2}{r_B^3} - \frac{\mu_{\neq}^2}{r_{\neq}^3}\right) \tag{5-88}$$

This equation predicts that a plot of $\ln(k/k_0)$ versus $1/\varepsilon_r$ should give a straight line, and gives an explicit expression for the slope s of this line in terms of the radii and dipole moments as shown by Eq. (5-89):

$$s = \frac{1}{4\pi \cdot \varepsilon_0} \cdot \frac{3 \cdot N_A}{8 \cdot R \cdot T} \cdot \left(\frac{\mu_A^2}{r_A^3} + \frac{\mu_B^2}{r_B^3} - \frac{\mu_{\neq}^2}{r_{\neq}^3}\right) \tag{5-89}$$

If a reaction between neutral, dipolar molecules occurs with the formation of an activated complex with a dipole moment $\mu_{\neq}$ greater than either μ_A or μ_B, there will be an increase in the rate constant with increasing ε_r according to Eq. (5-88). This is because a medium with higher ε_r favours the production of any highly dipolar species as, in this case, the activated complex. In applying Eqs. (5-87) and (5-88) to experimental data, a model for the activated complex has to be constructed in order to evaluate reasonable values for $\mu_{\neq}$ and $r_{\neq}$. This has been done, for example, for the acid and base hydrolysis of carboxylic esters [11, 242].

Another Coulombic energy approach for the calculation of electrostatic solvent effects on reactions between dipolar molecules was made by Amis [12, 21, 244]. He related the rate constant to the energy of activation by the well-known Arrhenius equation $k = A \cdot \exp(-E_a/RT)$. It is assumed that the effect of the relative permittivity on the rate is given by Eq. (5-90):

$$\ln k = \ln k_\infty - \frac{1}{4\pi \cdot \varepsilon_0} \cdot \frac{2 \cdot \mu_A \cdot \mu_B \cdot N_A}{R \cdot T \cdot \varepsilon_r \cdot r^3} \tag{5-90}$$

where k is the rate constant in any medium of relative permittivity ε_r, k_∞ is the rate constant in a medium of relative permittivity with a value of infinity, and μ_A and μ_B are the dipole moments of the two dipolar reactants A and B in vacuum. Eq. (5-90) predicts that a plot of $\ln k$ versus $1/\varepsilon_r$ will give a straight line, the slope of which should give a reasonable value of $r = r_A + r_B$, the distance of approach for the two dipolar molecules to react.

It should be mentioned that there is no inconsistency in the fact that $\ln(k/k_0)$ is a function of $(\varepsilon_r - 1)/(2\varepsilon_r + 1)$ according to Eq. (5-87), and of $1/\varepsilon_r$ according to Eqs. (5-88) and (5-90). It can readily be seen, by carrying out explicitly the division of $(\varepsilon_r - 1)/(2\varepsilon_r + 1)$ according to Eq. (5-91), that $(\varepsilon_r - 1)/(2\varepsilon_r + 1)$ is linear in $1/\varepsilon_r$ to a good approximation [40].

$$\frac{\varepsilon_r - 1}{2\varepsilon_r + 1} = \frac{1}{2} - \frac{3}{4\varepsilon_r} + \frac{3}{8\varepsilon_r^2} - \frac{3}{16\varepsilon_r^3} + \cdots \tag{5-91}$$

For $\varepsilon_r = 8$, the error involved in neglecting terms in ε_r^2 and higher powers is less than one percent [40].

Laidler has pointed out [11, 242] that Eq. (5-88) is best considered as a semi-quantitative formulation, which gives only a rough prediction of the effect of a change in ε_r on the rate of dipole–dipole reactions. This also applies to Eqs. (5-87) and (5-90). Nevertheless, in many cases a satisfactory correlation between rate constants and function of solvent relative permittivity has been obtained, as, for instance, in the Menschutkin reaction between trialkylamines and haloalkanes forming quaternary tetra-alkylammonium salts [2, 56, 58, 60, 61, 64, 65, 245–247].

Glasstone, Laidler, and Eyring [2] were the first to correlate rate data for some Menschutkin reactions according to Eq. (5-87), and they found, in particular, that a linear correlation between $\lg(k/k_0)$ and $(\varepsilon_r - 1)/(2\varepsilon_r + 1)$ is observed in the binary solvent mixture benzene/alcohol, while in benzene/nitrobenzene a monotonous deviation from the linear dependence is observed.

Fig. 5-10 shows typical dependences of $\lg(k/k_0)$ on the Kirkwood parameter $(\varepsilon_r - 1)/(2\varepsilon_r + 1)$ obtained for the Menschutkin reaction between triethylamine ($\mu = 2.9 \cdot 10^{-30}$ Cm $= 0.9$ D) and iodoethane ($\mu = 6.3 \cdot 10^{-30}$ Cm $= 1.9$ D) in binary solvent mixtures [56].

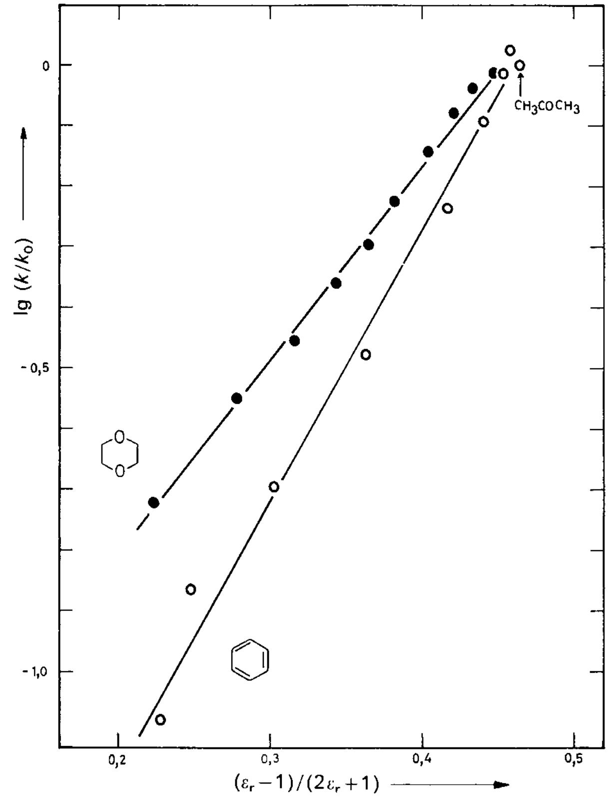

Fig. 5-10. Correlation between $\lg(k/k_0)$ [56] and the Kirkwood function $(\varepsilon_r - 1)/(2\varepsilon_r + 1)$ for the Menschutkin reaction between triethylamine and iodoethane at 40 °C in binary acetone/benzene and acetone/1,4-dioxane mixtures (rate constants relative to acetone as common standard solvent).

Binary solvent mixtures have the advantage that changing their composition will predominately change the electrostatic solute/solvent interactions, whereas non-electrostatic and specific interactions remain the same within the whole solvent series and will be cancelled out. Fig. 5-10 shows that Kirkwood's equation holds for such solvent systems, but the slopes of the straight lines are markedly different. One might, however, expect them to be the same if Eq. (5-87) were applicable.

If one compares the rate constants for the same Menschutkin reaction with Kirkwood's parameter in thirty-two pure aprotic and dipolar non-HBD solvents [59, 64], one still finds a rough correlation, but the points are widely scattered as shown in Fig. 5-11.

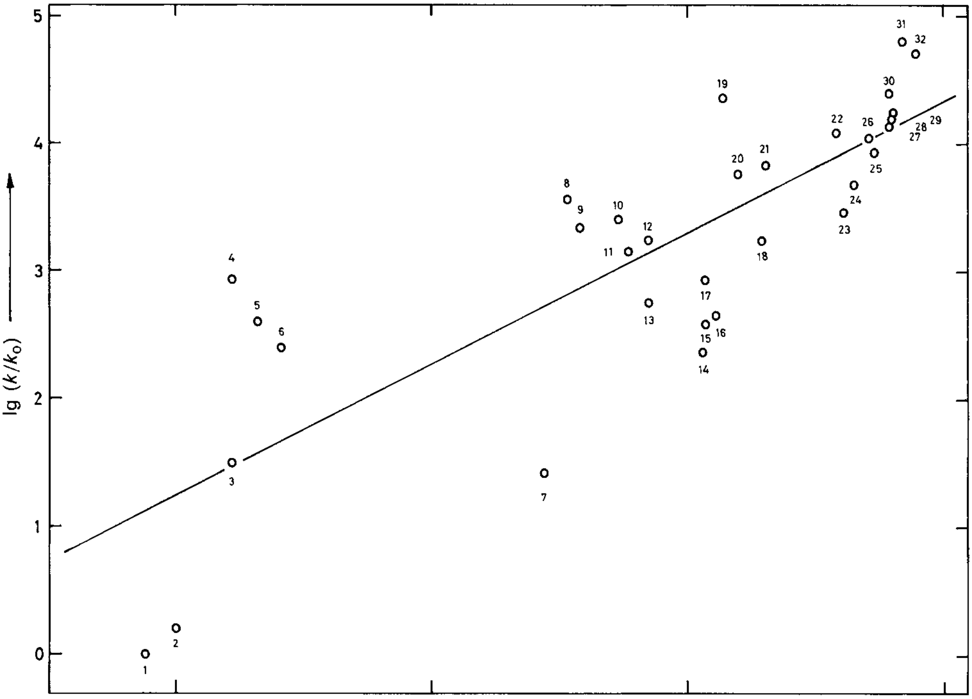

Fig. 5-11. Correlation between $\lg(k/k_0)$ [59, 64] and the Kirkwood function $(\varepsilon_r - 1)/(2\varepsilon_r + 1)$ for the Menschutkin reaction between triethylamine and iodoethane in 32 aprotic and dipolar aprotic solvents at 25 °C (rate constants relative to *n*-hexane as 'slowest' solvent):
1) *n*-hexane, 2) cyclohexane, 3) tetrachloromethane, 4) 1,4-dioxane, 5) benzene, 6) toluene, 7) diethyl ether, 8) iodobenzene, 9) trichloromethane, 10) bromobenzene, 11) chlorobenzene, 12) ethyl benzoate, 13) ethyl acetate, 14) 1,1,1-trichloroethane, 15) chlorocyclohexane, 16) bromocyclohexane, 17) tetrahydrofuran, 18) 1,1-dichloroethane, 19) 1,1,2,2-tetrachloroethane, 20) dichloromethane, 21) 1,2-dichloroethane, 22) acetophenone, 23) 2-butanone, 24) acetone, 25) propionitrile, 26) benzonitrile, 27) nitrobenzene, 28) *N*,*N*-dimethylformamide, 29) acetonitrile, 30) nitromethane, 31) dimethyl sulfoxide, and 32) propylene carbonate.

The values of the second-order rate constants are taken from the compilation made by M. H. Abraham and P. L. Grellier, J. Chem. Soc., Perkin Trans. 2 *1976*, 1735.

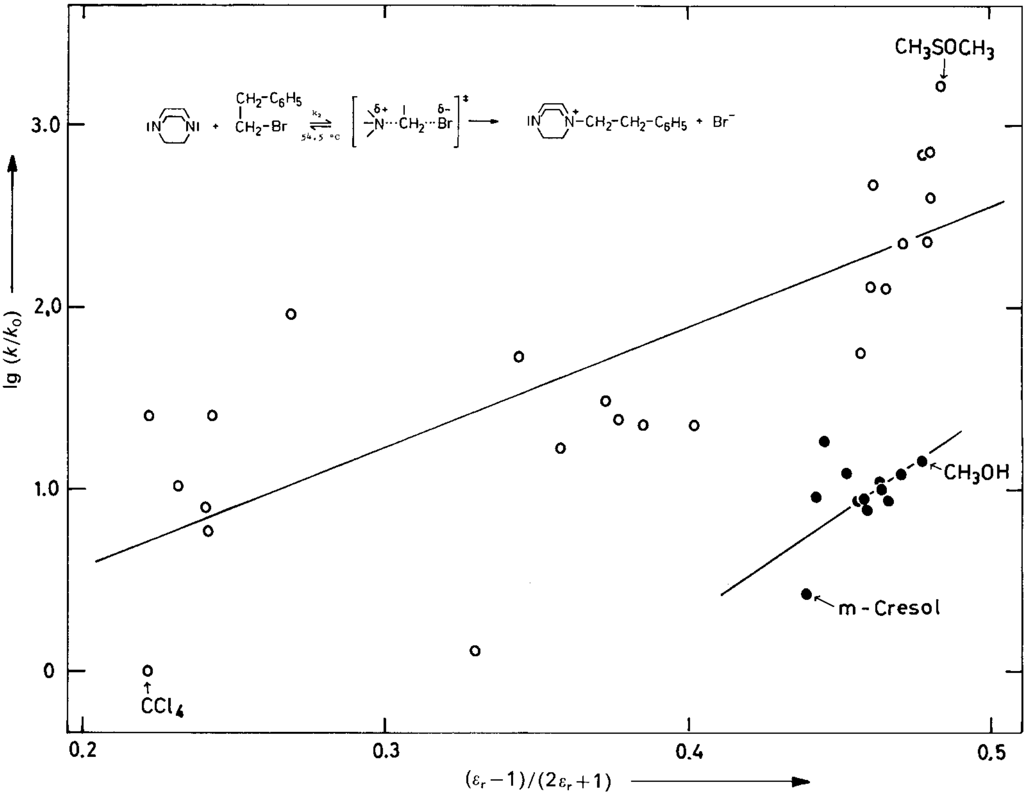

Fig. 5-12. Correlation between $\lg(k/k_0)$ [65] and the Kirkwood function $(\varepsilon_r - 1)/(2\varepsilon_r + 1)$ for the Menschutkin reaction between 1,4-diazabicyclo[2.2.2]octane and (2-bromoethyl)benzene in non-HBD (○) and HBD (●) solvents at 54.5 °C (rate constants relative to tetrachloromethane as 'slowest' standard solvent).

Extending the media used for the Menschutkin reaction to protic solvents such as alcohols leads to an even worse correlation, as shown in Fig. 5-12 for the quaternization of 1,4-diazabicyclo[2.2.2]octane with (2-bromoethyl)benzene studied in a total of thirty-six solvents [65]. The group of protic solvents is separated from the assembly of non-HBD solvents, each group showing a very rough but distinct correlation with the function of relative permittivity. Such behaviour has also been observed for several other Menschutkin reactions [60, 61].

Although Eq. (5-87) is often qualitatively obeyed, as has been frequently mentioned, there is no exact linear correlation between the rate of Menschutkin reactions and the functions of relative permittivity as in the case of Fig. 5-12 [246, 247]. A complete absence of a regular effect of changes in the dielectric properties of the solvent on the reaction rate has also been observed [248, 249]. Sometimes a satisfactory correlation has been obtained because the reaction under consideration was studied in only a limited number of solvents. It can readily be seen from Fig. 5-11 that studying this Menschutkin reaction by chance in the six solvents nos. 3, 11, 12, 26, 27, and 28 would simulate a very good correlation.

The fact that the curves of Figs. 5-10 to 5-12 (and others) have positive slopes is direct evidence for a partially ionized, dipolar activated complex. In cases for which Eq. (5-87) is reasonably well obeyed (especially for binary solvent mixtures), a reasonable value for $\mu_{\neq}$ may be calculated from the slope according to Eq. (5-89) [2, 8] (for a compilation of such calculations, see references [23, 64]). The calculated dipole moments $\mu_{\neq}$ range from *ca.* $17 \cdot 10^{-30}$ Cm (*ca.* 5 D) to *ca.* $30 \cdot 10^{-30}$ Cm (*ca.* 9 D) and show a considerable separation of charges for the activated complex of Menschutkin reactions, in agreement with the observed rate accelerations with increasing solvent polarity. However, it seems probable that if Eq. (5-87) is to hold over a substantial range of solvent compositions, rather large-scale cancellations of non-electrostatic effects must take place [23].

As the data for the Menschutkin reactions indicate, the character of the solute–solvent interactions is more complex than described by Eq. (5-87). It is evident that functions of relative permittivity alone, as given in Eq. (5-87), are not useful for describing the solvent effect on reactions between dipolar reactants, except in certain special cases, such as when a mixture of two solvents is used. In addition to electrostatic forces, non-electrostatic interactions, such as dispersion forces and hydrogen-bonding, must also be involved in Menschutkin reactions.

As seen from Fig. 5-11, although the three halobenzenes (points nos. 8, 10, and 11) have similar values of ε_r, when used as solvents they lead to different reaction rates. Iodobenzene (no. 8), with the lowest ε_r value, gives the largest rate. This observation strongly suggests that the polarizability of the solvent is an important factor in stabilizing the dipolar activated complex of this reaction. This was confirmed by Reinheimer *et al.* [57], who studied some Menschutkin reactions in benzene and its chloro, bromo, and iodo derivatives. They showed that the rate of the reaction increases with increasing polarizability of the solvent.

In case of alcoholic, protic solvents, it should be particularly noted from Fig. 5-12 that the values of $\lg(k/k_0)$ are much lower than expected on the basis of their relative permittivities. It has been pointed out [64] that hydrogen bonding between the alcohols and the trialkylamine – thus reducing the Gibbs energy of the reactants – is not the only cause of this low accelerating power. This anomalous effect of aliphatic alcohols on the rates of Menschutkin reactions is due to the fact that the activated complex for these reactions resembles a relatively nonpolar solute. Its structure lies somewhere between reactants and ion pair, probably nearer to the reactants. Compared to the situation in dipolar non-HBD solvents, which may effect stabilization through nonspecific interaction [64], such an activated complex will be destabilized by aliphatic alcohols. Within a series of aliphatic alcohols and in spite of the fact that the values of ε_r fall from 32.7 to 3.4, the reaction between bromoethane and *N*,*N*-dimethylaniline is accelerated by a factor of almost ten on going from methanol to octanol [245]. A detailed discussion of all aspects of the Menschutkin reaction, including solvent effects, can be found in an excellent review by Abboud *et al.* [786].

Eq. (5-87), which is a general rate equation predicting the effect of solvent on bimolecular reactions between dipolar molecules, can readily be modified to treat

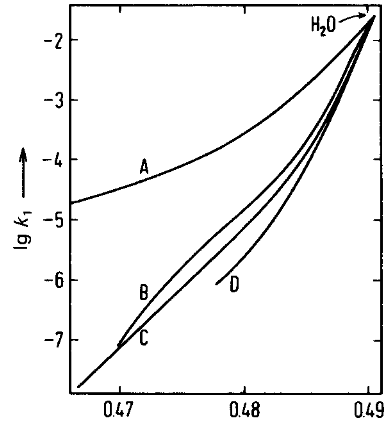

Fig. 5-13. Correlation between lg k_1 [40] and the Kirkwood function $(\varepsilon_r - 1)/(2\varepsilon_r + 1)$ for the solvolysis of 2-chloro-2-methylpropane in binary 1,4-dioxane/water (A), ethanol/water (B), acetone/water (C), and methanol/water (D) mixtures at 25 °C; *cf.* Eq. (5-13) in Section 5.3.1.

unimolecular reactions of dipolar molecules A by neglecting the term for the second reactant B. A classical example of this reaction type is the solvolysis of 2-chloro-2-methylpropane ($\mu = 7.1 \cdot 10^{-30}$ Cm = 2.1 D). This is an example of an S_N1 reaction, the solvent dependence of which has been studied in many solvents and binary solvent mixtures (*cf.* Eq. (5-13) in Section 5.3.1) [40, 47, 250].

Assuming that the influence of non-electrostatic terms and specific solute/solvent interactions are negligible, a linear relationship is expected between $\lg(k/k_0)$ and the Kirkwood parameter $(\varepsilon_r - 1)/(2\varepsilon_r + 1)$. Such plots are shown in Figs. 5-13 and 5-14 for binary solvent mixtures and pure solvents. It can be seen that there is no simple relationship between $\lg(k/k_0)$ and $(\varepsilon_r - 1)/(2\varepsilon_r + 1)$ for any of the solvents and solvent mixtures examined. As seen from Fig. 5-13, there is a large dispersion of the plot into separate lines for each solvent pair and curvature of the separate lines. Fig. 5-14 shows that there is a very poor correlation for pure solvents. In protic solvents, as a result of considerable specific solvation of the leaving anion through hydrogen bonding, the rate of solvolysis is higher than that expected from the relative permittivities of the solvents.

A somewhat better correlation using values of lg k_1 at 120 °C was obtained by Koppel and Pal'm [250], but again protic and some non-HBD solvents do not conform to the expected linear pattern. From the slope of the estimated straight line, a value of $\mu_{\neq} = 31 \cdot 10^{-30}$ Cm = 9.2 D for the activated complex was calculated, which although reasonable must treated with caution, since the slope of the line depends largely on only a few values of lg k_1 in non-HBD solvents [250]. Nevertheless, it indicates that in the activated complex the charges are considerably separated, in agreement with the qualitative considerations made in Section 5.2.1.

The breakdown of the simple linear relationship between $\lg(k/k_0)$ and $(\varepsilon_r - 1)/(2\varepsilon_r + 1)$, required by Eq. (5-87), is obviously due to the failure of the approximations involved in deriving this equation, neglection of non-electrostatic and specific solute–solvent interactions, and, in the case of binary solvent mixtures, due also to the selective solvation of the reactants and activated complex by one component of the mixture (*cf.*

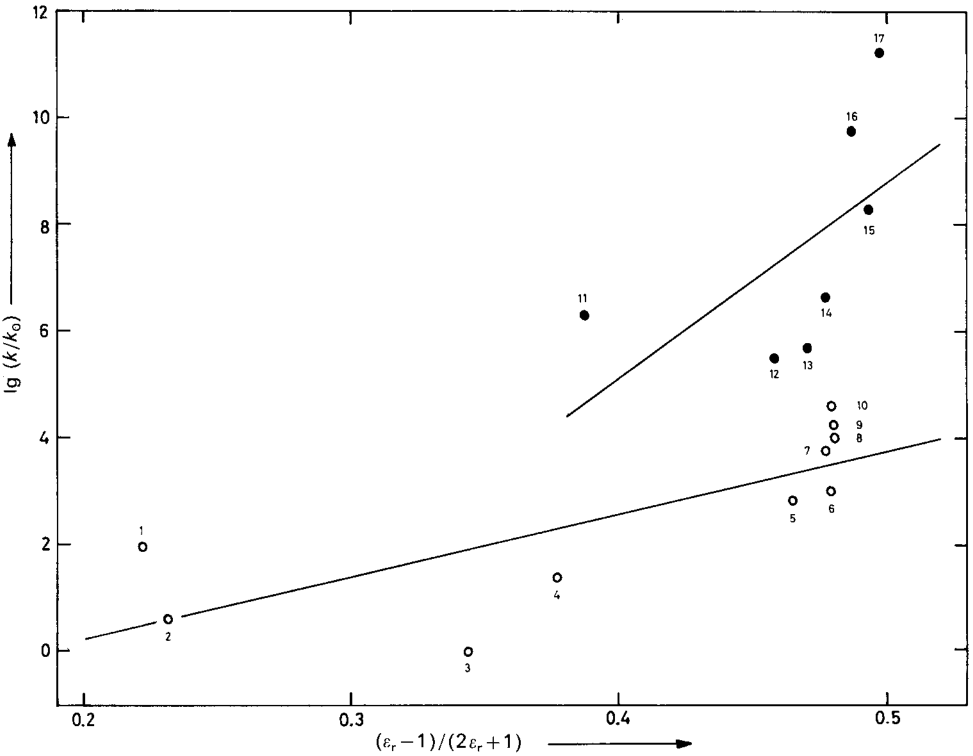

Fig. 5-14. Correlation between $\lg(k/k_0)$ [40, 47] and the Kirkwood function $(\varepsilon_r - 1)/(2\varepsilon_r + 1)$ for the solvolysis of 2-chloro-2-methylpropane in 17 pure non-HBD (○) and HBD (●) solvents at 25 °C (rates relative to diethyl ether as 'slowest' standard solvent). Values of lg k are taken from the compilation in reference [47].

1) 1,4-dioxane, 2) benzene, 3) diethyl ether, 4) chlorobenzene, 5) acetone, 6) nitrobenzene, 7) 1-methyl-2-pyrrolidinone, 8) acetonitrile, 9) *N*,*N*-dimethylformamide, 10) nitromethane, 11) acetic acid, 12) 1-butanol, 13) ethanol, 14) methanol, 15) formamide, 16) formic acid, and 17) water.

Section 2.4). It can be unequivocally concluded from a large amount of literature data, that the number of instances of deviation for reactions between dipolar molecules from the simple electrostatic relationship, given in Eqs. (5-87), (5-88), and (5-90), greatly exceeds the number of cases where the relationships hold. Thus, allowances must also be made for electrostatic, nonelectrostatic, and specific solvation effects in the general effect of the medium.

It would appear from these observations that the solvation capability might be better characterized using a linear Gibbs energy relationship approach than functions of relative permittivity. There are now numerous examples known, for which the correlation between the rates of different reactions and the solvation capability of the solvent can be satisfactorily described with the help of semiempirical parameters of solvent polarity (*cf.* Chapter 7).

5.4.4 Reactions between Neutral Molecules and Ions

Numerous organic reactions are of the ion-dipole type, as, for example, the S_N2 reactions given in Eqs. (5-17) and (5-18) in Section 5.3.1. Considering the reaction between an ion A of charge $z_A \cdot e$ and a neutral, dipolar molecule B of dipole moment μ_B according to $A^{z_A \cdot e} + B \rightleftharpoons (AB)^{\neq z_A \cdot e} \rightarrow C + D$, Laidler and Eyring [2, 251] obtained Eq. (5-92) for the rate constant in a medium of zero ionic strength:

$$\ln k = \ln k_0 + \frac{1}{4\pi \cdot \varepsilon_0} \cdot \left[\frac{z_A^2 \cdot e^2 \cdot N_A}{2 \cdot R \cdot T} \cdot \left(\frac{1}{\varepsilon_r} - 1 \right) \cdot \left(\frac{1}{r_A} - \frac{1}{r_{\neq}} \right) - \frac{N_A}{R \cdot T} \cdot \frac{\mu_B^2}{r_B^3} \cdot \left(\frac{\varepsilon_r - 1}{2\varepsilon_r + 1} \right) \right] \qquad (5\text{-}92)$$

where k and k_0 are the rate constants in media of relative permittivity ε_r and unity, respectively, and N_A is Avogadro's number. This equation predicts that $\ln k$ plotted against $1/\varepsilon_r$ for a molecule of zero dipole moment reacting with an ion of charge $z_A \cdot e$ should give a straight line, the slope of which would be $z_A^2 e^2 N_A / 2RT(1/r_A - 1/r_{\neq})$. This relationship should be especially true if the rate of the reaction is studied in mixtures of two solvents so that the relative permittivity can be varied by changing the proportions of each solvent. Since $r_{\neq}$ will be larger than r_A, the rate should be somewhat greater in a medium of lower values of ε_r. A quantitative test of Eq. (5-92) would require reasonable values of r_A and $r_{\neq}$. There seems to be no published data, however, that confirm Eq. (5-92).

A somewhat different equation relating the rate constant to the relative permittivity for a reaction $A^{z_A \cdot e} + B^{z_B \cdot e} \rightleftharpoons (AB)^{\neq (z_A + z_B)e} \rightarrow C + D$, in which the electrostatic interactions are more important than nonelectrostatic ones, was derived by Laidler and Landskroener [11, 242]:

$$\ln k = \ln k_0 + \frac{1}{4\pi \cdot \varepsilon_0} \cdot \left[\frac{e^2 \cdot N_A}{2 \cdot R \cdot T} \cdot \left(\frac{1}{\varepsilon_r} - 1 \right) \cdot \left(\frac{z_A^2}{r_A} + \frac{z_B^2}{r_B} - \frac{(z_A + z_B)^2}{r_{\neq}} \right) + \frac{3 \cdot N_A}{8 \cdot R \cdot T} \cdot \left(\frac{2}{\varepsilon_r} - 1 \right) \cdot \left(\frac{\mu_A^2}{r_A^3} + \frac{\mu_B^2}{r_B^3} - \frac{\mu_{\neq}^2}{r_{\neq}^3} \right) \right] \qquad (5\text{-}93)$$

For a reaction between two dipoles having no net charge, the second term disappears, and the solvent effect is given entirely by the last term; Eq. (5-93) then equals Eq. (5-88) in Section 5.4.3. For a reaction between an ion and a dipole (or between two charged dipoles) both terms must be included. The simplest case is for the reaction of a monovalent, structureless ion A of charge $z_A \cdot e(\mu_A = 0)$ with a neutral molecule B $(z_B \cdot e = 0)$ of dipole moment μ_B. Eq. (5-93) then has the form:

$$\ln k = \ln k_0 + \frac{1}{4\pi \cdot \varepsilon_0} \cdot \left[\frac{e^2 \cdot N_A}{2 \cdot R \cdot T} \cdot \left(\frac{1}{\varepsilon_r} - 1 \right) \cdot \left(\frac{1}{r_A} - \frac{1}{r_{\neq}} \right) + \frac{3 \cdot N_A}{8 \cdot R \cdot T} \cdot \left(\frac{2}{\varepsilon_r} - 1 \right) \cdot \left(\frac{\mu_B^2}{r_B^3} - \frac{\mu_{\neq}^2}{r_{\neq}^3} \right) \right] \tag{5-94}$$

This equation predicts that $\ln k$ will vary linearly with the reciprocal of the relative permittivity, and gives an explicit expression for the slope in terms of radii and dipole moments. If data are available for a series of mixed solvents, one procedure for the application of this equation is to plot $\ln k$ against $1/\varepsilon_r$ and to determine the slope. Then it is possible to see whether its sign and magnitude may be predicted, using reasonable values for the radii and the dipole terms, in terms of Eq. (5-94). Of course, this procedure will depend on devising a suitable model for the activated complex. For Eq. (5-94), the same restrictions are valid as for Eq. (5-88). At best, Eq. (5-94) gives a semiquantitative formulation, which allows only very rough predictions.

Another derivation of the relative permittivity dependence of $\ln k$ has been made by Amis [12, 21, 244] using a Coulomb energy approach for the ion–dipole interaction. Considering the mutual potential energy between an ion A of charge $z_A \cdot e$ and a dipole B of dipole moment μ_B at a distance r_{AB} leads eventually to Eq. (5-95):

$$\ln k = \ln k_\infty + \frac{1}{4\pi \cdot \varepsilon_0} \cdot \frac{z_A \cdot e \cdot \mu_B \cdot N_A}{R \cdot T \cdot \varepsilon_r \cdot r_{AB}^2} \tag{5-95}$$

where k_∞ is the rate constant in a medium with relative permittivity of infinite magnitude. Taking the charge of the ion into account, Eq. (5-95) predicts that a plot of $\ln k$ versus $1/\varepsilon_r$ should be a straight line of positive slope if $z_A \cdot e$ is positive, and of negative slope if $z_A \cdot e$ is negative. This equation has been applied to both positive and negative ionic reactants reacting with dipole molecules [12, 21, 57, 252]. Illustrative examples of the applicability of Eqs. (5-94) or (5-95) are the alkaline hydrolysis of methyl propionate ($\mu = 6 \cdot 10^{-30}$ Cm = 1.8 D) in acetone/water mixtures [252], and the S_N2 reaction between the azide anion and 1-bromobutane ($\mu = 7 \cdot 10^{-30}$ Cm = 2.1 D) in pure dipolar non-HBD solvents [67]. In the case of alkaline hydrolysis, the rate-determining step would be that between the negatively charged hydroxide ion and the dipolar ester. As suggested by the above mentioned equations, plots of $\lg(k/k_\infty)$ versus $1/\varepsilon_r$ give the requisite straight lines as shown for both reactions in Fig. 5-15. The positive slope of the line for the S_N2 reaction indicates that in non-HBD solvents $r_{\neq} > r_A$, according to Eq. (5-94), whereas the negative slope of the line for the ester hydrolysis in protic solvents requires that $r_A > r_{\neq}$, which can be explained in terms of specific solvation of the hydroxide ion by hydrogen bonding [67, 252]. Further examples of the application of Eq. (5-95) are given in references [12, 21].

5.4.5 Reactions between Ions

The combination of simple inorganic ions usually proceeds very rapidly and the rate of reaction is governed by the diffusion of the ions towards each other. There are, however,

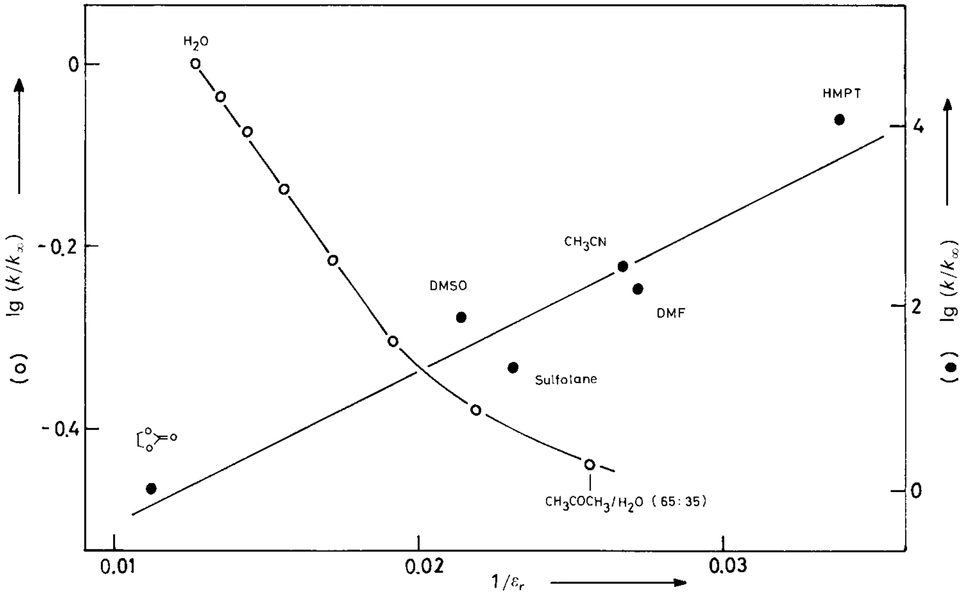

Fig. 5-15. Correlation between $\lg(k/k_\infty)$ and $1/\varepsilon_r$ for the alkaline hydrolysis of methyl propionate in eight acetone/water mixtures at 25 °C (○) [252], and for the S_N2 reaction between the azide anion and 1-bromobutane in six pure dipolar non-HBD solvents at 25 °C (●) [67] (rate constants relative to the solvent with the largest dielectric constant).

many reactions between ions which involve the making and breaking of covalent bonds or electron transfer, which may be as slow as reactions between neutral molecules (*cf.*, for example, reaction (5-19) in Section 5.3.1). Only reactions of this type will be considered in this Section.

Again, electrostatic theory will be useful in delineating the general effect of the changes on the ionic reactants and the relative permittivity of the solvent. The reaction between ions was the first reaction to which the simple electrostatic model was applied to calculate the effect of the relative permittivity and the ionic strength of the medium on the reaction rate. The change in Gibbs energy during the formation of an ion pair from the ions A and B in a standard medium with relative permittivity ε_r is equal to the electrostatic energy of the approach of two point charges $z_A \cdot e$ and $z_B \cdot e$ to a distance r_{AB} according to the following equation (N_A is Avogadro's number):

$$\Delta G_{\text{electrostatic}} = \frac{1}{4\pi \cdot \varepsilon_0} \cdot \frac{z_A \cdot z_B \cdot e^2 \cdot N_A}{\varepsilon_r \cdot r_{AB}} \qquad (5\text{-}96)$$

From this equation, which applies to infinitely dilute solutions only, it is possible to write an expression for the dependence of the rate constant on the relative permittivity at zero ionic strength:

$$\ln k = \ln k_0 + \frac{1}{4\pi \cdot \varepsilon_0} \cdot \frac{z_A \cdot z_B \cdot e^2 \cdot N_A}{R \cdot T \cdot r_{AB}} \cdot \left(1 - \frac{1}{\varepsilon_r}\right) \tag{5-97}$$

where k and k_0 are the rate constant in media of relative permittivity ε_r and unity (*i.e.* in the gas phase), respectively. r_{AB} is the distance to which the two ionic reactants must approach in order to react and can be assumed to be equal to $r_A + r_B$. Eq. (5-97), first proposed by Scatchard [253], predicts a linear plot of $\ln k$ versus $1/\varepsilon_r$ with a negative slope if the charges of the ions have the same sign, and a positive slope if the charges are of opposite sign.

For the reaction $A^{z_A \cdot e} + B^{z_B \cdot e} \rightleftharpoons (AB)^{\neq (z_A + z_B)e} \rightarrow C + D$, Laidler and Eyring [2, 251] derived another expression for the solvent dependence of rate constants using a slightly different model for the distribution of charges in the activated complex:

$$\ln k = \ln k_0 + \frac{1}{4\pi \cdot \varepsilon_0} \cdot \frac{e^2 \cdot N_A}{2 \cdot R \cdot T} \cdot \left(\frac{1}{\varepsilon_r} - 1\right) \cdot \left(\frac{z_A^2}{r_A} + \frac{z_B^2}{r_B} - \frac{(z_A + z_B)^2}{r_{\neq}}\right) \tag{5-98}$$

This equation is equivalent to the second term of Eq. (5-93). For reactions between two simple ions, the final term of Eq. (5-93) is less important and can generally be neglected. Eq. (5-98) is valid for reactions carried out in solutions of infinite dilution only, and reduces to Eq. (5-97) if $r_A = r_B = r_{\neq}$.

Some tests of Eqs. (5-97) and (5-98) have been made, particularly by carrying out a reaction between ions in a series of mixed solvents of varying values of ε_r. Examples are the reaction between bromoacetate and thiosulfate ions [11, 251], the reaction between negative divalent tetrabromophenolsulfophthalein ions and hydroxide ions [254], and the ammonium cation/cyanate anion reaction yielding urea [255]. On the whole, the relationships (5-97) and (5-98) are a good approximation, although there are usually serious deviations especially at low values of ε_r (obviously due to association between unlike ions). Deviations from linearity may be explained as being due to the failure of the simple approximations made in deriving these equations, due to selective solvation in binary solvent mixtures, and due to the neglection of such phenomena as the mutual polarization of ions or dipoles and the resulting inductive interactions, as well as specific solvation.

The entropy changes of reactions between ions deserve special mention. For reactions between ions of unlike sign there is an entropy increase in going from reactants to activated complex. This is because the activated complex will have less charge than the reactants and will become partially desolvated. For ions of the same sign, however, the activated complex will be more charged than the reactants. This one would expect to be strongly solvated. There is a loss of entropy, therefore, when the activated complex is formed. For examples which confirm these relationships, see references [5, 11, 20].

Since the activity coefficients of the reactants vary with the ionic strength I of the solution, the value of which is determined by the molar concentrations c_i of the ions i of charge z_i according to $I = 1/2 \cdot \sum_i c_i \cdot z_i^2$, the rate of reactions in solution must also depend on the ionic strength. This effect of the ionic strength of the solution on the rate constant described by Eq. (5-99) is termed the *Primary Salt Effect.*

$$\ln k = \ln k_0 + 2 \cdot z_A \cdot z_B \cdot A \cdot \sqrt{I} \tag{5-99}$$

A is a constant for a given solvent and temperature ($A = 0.51 \cdot 2.303\,\mathrm{L}^{1/2} \cdot \mathrm{mol}^{-1/2}$ for aqueous solutions at 25 °C), and k_0 is the rate coefficient extrapolated to infinite dilution. Eq. (5-99), which was first derived by Brønsted [256], Bjerrum [257], and Christiansen [258] applying the Debye–Hückel theory [259] to the influence of neutral salts upon reaction rates in solution, predicts a linear relationship if ln k is plotted against the square root of the ionic strength. Since the simple Debye–Hückel relationship does not apply at those concentrations where ion association becomes important, Eq. (5-99) is only valid for solutions below *ca.* 10^{-2} mol/L for 1-1 electrolytes. Eq. (5-99) is perfectly accurate in dilute solutions.

Its conceptual significance is closely related to the Hughes–Ingold rules as given in Table 5-4 in Section 5.3.1. An increase in the ionic strength of a solution leads to an increase in its polarity. Thus, reactions between ions of like charge ($z_A \cdot z_B$ positive) are accelerated by an increase in the ionic strength, *i.e.* the addition of electrolytes, whereas reactions between ions of opposite charge ($z_A \cdot z_B$ negative) are retarded. If one of the reactants is a neutral molecule ($z_A \cdot z_B$ zero), the rate is expected to be independent of the ionic strength to a first approximation.

However, even in reactions involving neutral molecules ($z_A \cdot z_B$ zero), electrolyte effects can be found. Such reactions between neutral, nonpolar molecules can yield ionic products *via* a dipolar activated complex. This dipolar activated complex can be stabilized by an ionic medium, and a large positive salt effect is found. In reactions such as the solvolyses of 2-halo-2-methylpropanes, ions are produced and the ionic strength increases automatically during the reaction. This can lead to a kind of autocatalytic acceleration of the solvolysis. Small negative salt effects are frequently found in reactions between ions and neutral molecules because there is a greater charge dispersion during the activation process.

Eq. (5-99) was checked in detail in a large number of studies, but an extensive treatment of primary and secondary salt effects on reaction rates is beyond the scope of this Section. The reader is referred to references [2–5, 11, 12, 19–21, 28], particularly to the excellent comprehensive reviews of Davies [260], Blandamer *et al.* [828], and Loupy *et al.* [829].

In conclusion, it can be said that the electrostatic theory of solvent effects is a most useful tool for explaining and predicting many reaction patterns in solution. However, in spite of some improvements, it still does not take into account a whole series of other solute/solvent interactions such as the mutual polarization of ions or dipoles, the specific solvation *etc.*, and the fact that the microscopic relative permittivity around the reactants may be different to the macroscopic relative permittivity of the bulk solvent. The deviations between observations and theory, and the fact that the relative permittivity cannot be considered as the only parameter responsible for the changes in reaction rates in solution, has led to the creation of different semiempirical correlation equations, which correlate the kinetic parameters to empirical parameters of solvent polarity (see Chapter 7).

5.5 Specific Solvation Effects on Reaction Rates

The intermolecular forces responsible for the association of dissolved ions or molecules with solvent molecules, consist of other forces beside the non-specific directional, inductive, and dispersion forces which formed the essential basis for the quantitative relationships discussed in the preceding chapter. This other class of intermolecular forces consists of specific interactions such as hydrogen bonding and EPD/EPA forces (*cf.* Section 2.2). In the following discussion it will be shown, with the aid of some representative examples, how a consideration of the specific solvation of the reactants as well as the activated complexes can contribute to a better understanding of the rates, mechanisms, and steric outcome of organic reactions. In this discussion, not even an approximately complete treatment of the multitude of specific solvent effects can be attempted; for further reading, see references [6, 10, 21, 26, 261–263, 452–454].

5.5.1 Influence of Specific Anion Solvation on the Rates of S_N and other Reactions

In aliphatic nucleophilic substitution reactions, the solvation of the departing anions is particularly important. In protic solvents, this takes place mainly through hydrogen bonding, thus the activated complexes may be described as in Eqs. (5-100)* and (5-101).

$$\text{R-X} + \text{H-S} \overset{S_N1}{\rightleftharpoons} [\text{R}^{\delta\oplus}\cdots\text{X}^{\delta\ominus}\cdots\text{H-S}]^{\ddagger} \longrightarrow \text{R}^{\oplus} + \text{X}^{\ominus}\cdots\text{H-S}$$

$$\xrightarrow{+\text{Y}^{\ominus}} \text{R-Y} + \text{X}^{\ominus}\cdots\text{H-S} \qquad (5\text{-}100)$$

$$\text{Y}^{\ominus} + \text{R-X} + \text{H-S} \overset{S_N2}{\rightleftharpoons} [\text{Y}^{\delta\ominus}\cdots\text{R}\cdots\text{X}^{\delta\ominus}\cdots\text{H-S}]^{\ddagger}$$

$$\longrightarrow \text{Y-R} + \text{X}^{\delta\ominus}\cdots\text{H-S} \qquad (5\text{-}101)$$

In these equations, the energy necessary for the ionization of the R–X bond will be lowered by that of the X $\cdots$ H interaction.

Therefore, protic solvents usually have an accelerating effect on S_N reactions. This is one of the main reasons why S_N reactions of haloalkanes and sulfonate esters are carried out in solvents which consist wholly or partially of water, alcohols, or carboxylic acids. The relative strengths of the hydrogen bonding in the initial and transition states often overwhelms the electrostatic effect of solvents on the Gibbs energy of activation. On the other hand, the attacking nucleophile $Y^{\ominus}$ in the S_N2 reaction (5-101) can also be specifically solvated by protic solvents, so that its reactivity, and therefore the rate of the S_N2 reaction, will be diminished. Examples of specific (electrophilic) solvation of anionic nucleophiles and leaving groups in S_N reactions can be found in references [264–269; 581–585]; see references [581, 582] for reviews.

Since the protic solvent is usually in large excess, its participation in the reaction cannot generally be established by means of kinetic measurements. However, if the reaction is carried out in a non-HBD solvent (*e.g.* C_6H_6, CCl_4), the effect of addition of small amounts of a protic solvent is easily observable. Thus, the S_N2 reaction between

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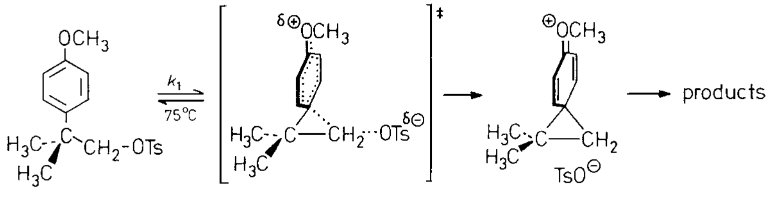
* It should be pointed out that the formation of a carbenium ion in the course of an S_N1 reaction does not in fact occur as simply as described in Eq. (5-100), but takes place *via* intermediate contact- and solvent-separated ion pairs before the free solvated ions are formed; *cf.* Eqs. (2-19) and (2-20) in Section 2.6.

bromomethane and pyridine in benzene is accelerated by the addition of small amounts of alcohols or phenols. The more acidic the added solvent, the greater its ability to form hydrogen bonds, and the greater the rate acceleration [264]. The electron-withdrawing effect of a protic solvent on the departing group X can be so pronounced that reactions that are second-order in less strongly solvating media (*e.g.* ethanol), become first-order in acidic media (*e.g.* formic acid). The protic solvents exert an electrophilic pull on the departing anions in much the same way that heavy metal ions ($Ag^{\oplus}$, $Hg^{\oplus\oplus}$) catalyze nucleophilic substitution reactions of haloalkanes.

These results are supported by the observation that dipolar non-HBD solvents such as *N*,*N*-dimethylformamide or dimethyl sulfoxide, in spite of their high relative permittivities (36.7 and 46.5) and their high dipole moments ($12.3 \cdot 10^{-30}$ and $13.0 \cdot 10^{-30}$ Cm), favour neither the ionization of haloalkanes nor S_N1 reactions (*cf.* Section 2.6). Dipolar non-HBD solvents cannot act as hydrogen-bond donors and are therefore poor at solvating the departing anions. Thus, the anchimerically assisted ionization of 4-methoxyneophyl tosylate, shown in Eq. (5-102), is nine times faster in acetic acid than in dimethyl sulfoxide. This is in spite of the fact that the relative permittivity of acetic acid is eight times smaller than that of dimethyl sulfoxide; also the dipole moment of acetic acid is smaller than that of dimethyl sulfoxide [265].



(5-102)

Solvent	$(C_2H_5)_2O$	$(CH_2)_4O$	CH_3COCH_3	$HCON(CH_3)_2$	CH_3SOCH_3
k_1^{rel}	1	17	169	980	3600

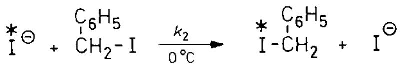
Solvent	C_2H_5OH	CH_3OH	CH_3CO_2H	H_2O	HCO_2H
k_1^{rel}	$1.2 \cdot 10^4$	$3.2 \cdot 10^4$	$3.3 \cdot 10^4$	$1.3 \cdot 10^6$	$5.1 \cdot 10^6$

It is furthermore remarkable that an approximately linear relationship between $(\varepsilon_r - 1)/(2\varepsilon_r + 1)$ and lg k_1 values for reaction (5-102), measured in 19 solvents, is found only for non-HBD solvents (*cf.* Eq. (5-87) in Section 5.4.3), whereas protic solvents are much better ionizing media than their relative permittivity would suggest [265]. For example, acetic acid and tetrahydrofuran have very similar relative permittivities (6.2 and 7.6, respectively), and yet ionization in acetic acid exceeds that in tetrahydrofuran by a factor of $2 \cdot 10^3$! The reason for this extraordinary rate acceleration is again that the departing tosylate is better solvated due to hydrogen bonding in the protic solvent. The ability of the protic solvent to form hydrogen bonds is not reflected in its relative permittivity or in the dipole moment [265].

Another instructive example of electrophilic or H-bonding assistance of protic solvents (or co-solvents) in S_N1 reactions is the accelerated acetolysis rate of 2-bromo-2-methylpropane upon the addition of phenols to a tetrachloromethane/acetic acid solution of the reactant [582]; see reference [582] for further examples. The usefulness of phenol as a solvent for S_N1 solvolysis reactions, in particular phenolysis of 1-halo-1-phenylethanes, has been stressed by Okamoto [582]. In spite of its low relative permittivity ($\varepsilon_r = 9.78$ at 60 °C), its low dipolarity ($\mu = 4.8 \cdot 10^{-30}$ Cm = 1.45 D), and its low nucleophilicity, it represents a solvent of high ionizing power due to its electrophilic driving force.

A further instructive study on the influence of protic and dipolar aprotic solvents on the rate of S_N1 heterolysis of tertiary $R_3C{-}X$ (with X = Cl, Br, I, 2,4-dinitrophenolate) shows that the rate-accelerating anion solvation due to H-bonding by protic solvents decreases dramatically on increasing the radius of the halide ions. Therefore, the differential solvation transferred from anion-solvating methanol to cation-solvating dimethyl sulfoxide as solvent is reversed on going from the chloro- to the iodoalkane: at 60 °C $k_1(\mathrm{DMSO})/k_1(\mathrm{MeOH}) = 0.05$ (*t*-BuCl) < 0.57 (*t*-BuBr) < 6.9 (*t*-BuI); the 2,4-dinitrophenolate ion behaves like the iodide [830].

While increasing anion solvation by protic solvents has an accelerating effect on S_N1 reactions as described above, it is often a decelerating factor in S_N2 reactions. Thus, reaction (5-103) between (iodomethyl)benzene and radioactively labeled sodium iodide in acetone is clearly decelerated by the addition of protic solvents such as water, ethanol or phenol, as demonstrated in Fig. 5-16 [266].



$$\overset{*}{I}{}^{\ominus} + \overset{C_6H_5}{\overset{|}{CH_2}}{-}I \xrightarrow[0\,^\circ C]{k_2} \overset{*}{I}{-}\overset{C_6H_5}{\overset{|}{CH_2}} + I^{\ominus}$$

(5-103)

The decrease in reaction rate is greatest for the addition of phenol, whereas the addition of the aprotic solvent CCl_4 leaves the reaction rate practically unchanged.

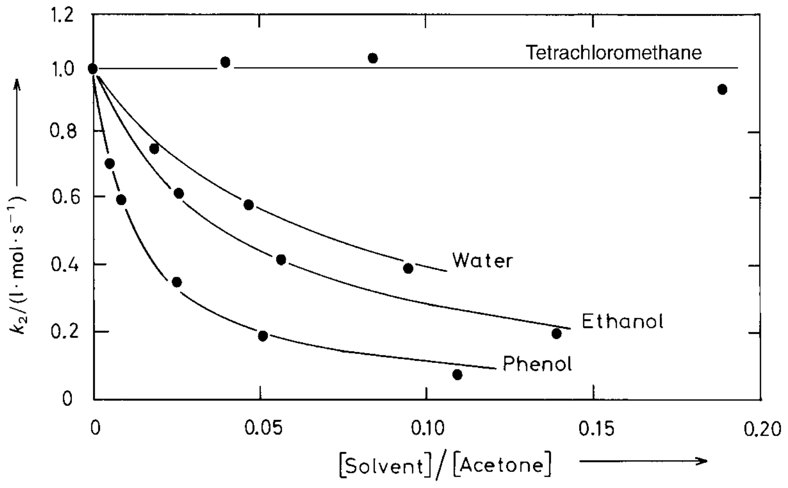


Fig. 5-16. The variation of k_2 for S_N2 reaction (5-103) with the ratio [solvent]/[acetone] [266].

The inhibitory effect of the protic solvents H–S (water < ethanol < phenol) correlates with their increasing tendency to form hydrogen bonds. This shows that the decrease in reaction rate is caused by specific solvation of the iodide ion, and depends on the position of the following equilibrium [266]:

$$(\mathrm{I}^{\ominus})_{\text{Acetone}} + \mathrm{H\text{-}S} \rightleftharpoons (\mathrm{I}^{\ominus}\cdots\mathrm{H\text{-}S}) + \text{Acetone} \qquad (5\text{-}104)$$

Similar conclusions can be drawn from specific solvent effects on the following S_N2 reactions: (a) substitution of 1-halobutanes by iodide ion in acetone in the presence of small amounts of water [267]; (b) substitution by $N_3^{\ominus}$ and $SCN^{\ominus}$ in a series of *n*-octyl derivatives (*n*-$C_8H_{17}X$ with X = Cl, Br, I, OTs, OMs as leaving groups) in different solvents (CH_3OH in contrast to CH_3SOCH_3) [583]; (c) Menschutkin reaction between 1,4-diazabicyclo [2.2.2]octane and (2-haloethyl)benzenes in binary solvent mixtures, *i.e.* a main non-HBD solvent with low concentrations of protic co-solvents [584]. (d) S_N2 reaction of *n*-octyl methanesulfonate with fluoride ions (associated with tetrahexylammonium ions) in chlorobenzene, the rate of which is dramatically reduced (by a factor of 822) on addition of small amounts of water through specific hydration of F^- to give $F^- \cdots (H_2O)_n$ (with $n = 0 \ldots 8.5$) [831].

The nucleofugacity scales observed for the S_N2 reaction (b) in nonpolar solvents (*e.g.* cyclohexane) are different from those obtained in protic solvents (*e.g.* methanol) and dipolar non-HBD solvents (*e.g.* dimethyl sulfoxide) [583]. For the Menschutkin reaction (c), specific rate inhibition has been observed on the addition of protic solvents which form hydrogen-bonds between the amine and the main solvent (*e.g.* C_6H_5OH, CH_3OH, $CHCl_3$). The retardation is proportional to the Brønsted acidity of the protic solvent added. Conversely, hydrogen-bond association between the halide nucleofuge and the protic solvent causes a specific catalytic effect, which increases as the charge density on the leaving group increases. These two effects, deactivation of the amine and activation of the halide leaving group, are always in competition and the outcome depends on the chemical nature of the reactants [584].

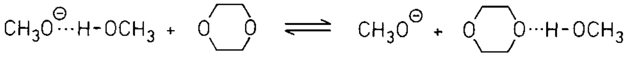
In this connection, it is noteworthy that the retarding effect of protic solvents on a given S_N2 reaction can also depend on the nature of the non-HBD solvent used [268, 269, 584]. Addition of a basic solvent may lead to a rate acceleration since the base can now compete with the nucleophile for hydrogen-bond formation with the protic solvent. Thus, the S_N2 reaction (5-105) is accelerated by addition of 1,4-dioxane to a protic solvent such as methanol as reaction medium [268].

$$\mathrm{CH_3O^{\ominus}} + \mathrm{CH_3\text{-}I} \xrightarrow[25\,^{\circ}\mathrm{C}]{k_2} \mathrm{CH_3O\text{-}CH_3} + \mathrm{I^{\ominus}} \qquad (5\text{-}105)$$

Solvent (1,4-Dioxane in cL/L)	Methanol/1,4-Dioxane			
	0	20	40	60
k_2^{rel}	1	1.9	3.4	5.0

Most probably this rate increase is due to the fact that the specific solvation of the methoxide ion is decreased because of an association between 1,4-dioxane and methanol:

$$CH_3O^{\ominus} + H\text{-}OCH_3 \rightleftharpoons CH_3O^{\ominus}\cdots H\text{-}OCH_3 \qquad (5\text{-}106)$$



(5-107)

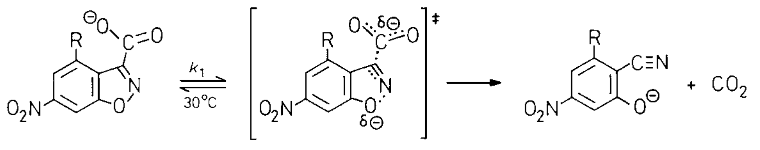
In other words, by the addition of 1,4-dioxane, the reaction medium will become richer in free, not specifically solvated methoxide ions. Accordingly, the rate of the S_N2 reaction (5-105) increases [10, 268]. This interpretation is supported by the fact that reaction (5-105) is accelerated further by addition of the more highly basic solvent dimethyl sulfoxide, although admittedly this addition also leads to an increase in the relative permittivity of the reaction medium [269].

Similar results are found for the above-mentioned Menschutkin reaction (c). The added protic solvent can also combine with the main solvent. Such solvent/solvent association leads to a diminution of the specific inhibitory and catalytic effect of protic solvents on the S_N2 reaction (c) [584]. The basicity of the main solvent determines the extent of deactivation of the protic solvent through H-bond association; this is analogous to Eq. (5-107).

There is also direct IR spectroscopic evidence that addition of a basic co-solvent to aqueous solutions reduces the percentage of non-associated "free" OH groups which are necessary for hydrogen-bonding to S_N reactants [585]. When basic co-solvents are added, they scavenge the free OH groups in water, thus lessening the specific protic solvent effect [585].

Nucleophiles with a heteroatom adjacent to the reaction center (*e.g.* $HOO^{\ominus}$, $ClO^{\ominus}$, $R_2C{=}N{-}O^{\ominus}$, $HONH_2$, NH_2NH_2) are found to be more reactive toward carbon electrophiles in S_N2 reactions in solution than would be expected from their basicities. This corresponds to a positive deviation from a Brønsted-type plot (*i.e.* $\lg k_2$ against pK_B). For instance, the hydroperoxide ion ($HOO^{\ominus}$) is 10^4 times less basic than the hydroxide ion ($HO^{\ominus}$), but it reacts *ca.* 50 times faster with (bromomethyl)benzene [459]. This behaviour is known as the *α-effect* [586] and various explanations for it have been given; *cf.* [587, 588] and references therein. If the α-effect is an intrinsic property of the anion, then it should manifest itself in the gas phase. However, it has been reported that in the gas phase $HOO^{\ominus}$ shows no evidence of enhanced nucleophilicity, compared to $HO^{\ominus}$, in its behaviour toward saturated (fluoromethane) and unsaturated carbon (methyl formate) [587]. If this is true, then the α-effect should arise because of a specific differential solvation of the α- and normal nucleophiles ($HOO^{\ominus}/HO^{\ominus}$, $NH_2NH_2/R\text{-}NH_2$, *etc.*), which would lead to reduced solvation of the α-nucleophile. It is, however, not easy to understand why α-nucleophiles should be less solvated than normal nucleophiles; see the comments given in references [588]. A thorough study of the rate of reaction of an α-nucleophile (butane-2,3-dione monooximate, Ox^-) and a normal nucleophile (4-chlorophenolate, 4-$ClPhO^-$) with a phosphorus ester (4-nitrophenyl diphenylphosphinate) in binary water/DMSO mixtures has shown that the magnitude of the α-effect [$= k(Ox^-)/k(4\text{-}ClPhO^-)$] may be due to advanced desolvation of the oximate nucleophile at the transition state relative to the O–P bond formation, corresponding to an imbalanced or asynchronous effect [832].

Our final reaction is an instructive example of specific anion solvation in a non-S_N reaction. The decarboxylation rate of 6-nitrobenzisoxazole-3-carboxylate as the tetramethylguanidinium salt exhibits a dramatic rate increase on going from protic to non-HBD solvents, as shown in Eq. (5-108) [589].



(5-108)

Solvent	H_2O	CH_3OH	C_2H_5OH	CH_2Cl_2	Et_2O	CH_3CN	CH_3SOCH_3	HMPT
k_1^{rel}	1	34	135	$6.4 \cdot 10^3$	$1.2 \cdot 10^4$	$3.9 \cdot 10^5$	$1.4 \cdot 10^6$	$9.5 \cdot 10^7$

The rate is slowest in aqueous solution and is enhanced in non-HBD solvents by a factor of up to 10^7! Obviously, specific hydrogen-bonding between protic solvent molecules and the carboxylate group suppresses the decarboxylation. This is consistent with the fact that the decarboxylation rate of *4-hydroxy*benzisoxazole-3-carboxylate ($R = OH$), a compound with its own intramolecular protic environment, is very slow and does not show a substantial solvent effect. Furthermore, not only hydrogen-bonding but also ion-pairing seems to stabilize the carboxylate ion, at least in less polar solvents such as C_6H_6, CH_2Cl_2, and Et_2O [590]. Thus, the most reactive compound is the free carboxylate ion, which lacks any specific stabilization.

Quantum-chemical calculations on the thermolysis of unsubstituted benzisoxazole-3-carboxylate, a reaction showing "an awesome solvent effect" [833], are in agreement with a concerted decarboxylation and ring-opening step. Hydration of the carboxylate increases the activation barrier (E_A) from 57 kJ/mol in the uncomplexed system to 130 kJ/mol for a model carboxylate with two bifurcated water molecules (including four hydrogen bonds to the carboxylate group), in good agreement with the experimental value of 134 kJ/mol found in water [589, 833]. The extreme solvent-dependence of this decarboxylation reaction suggests its use as a probe for many kinds of biochemical environments (*e.g.* micelles, bilayers, binding pockets of catalytic antibodies) [834–836].

In conclusion, it can be stated, according to a general rule proposed by Palit in 1947 [270], that solvents which impede the active centre of a reactant through hydrogen bonding or by some other means, will suppress the reactivity of that reactant. Conversely, solvents capable of promoting a favourable electron shift, necessary to the reaction, by specific solute/solvent interactions, will enhance the reaction rate.

It should be mentioned that specific anion solvation is not only possible through hydrogen-bonding with protic solvents and ion-pairing, it is also possible through coordination with macrocyclic organic ligands, particularly with protonated cryptands [591, 592]. For example, well-defined anion complexes, chloride ion cryptates, have been identified in aqueous solution by means of ^{35}Cl NMR spectroscopy [591]. The anion is located inside the intramolecular cryptand cavity and is held by an array of hydrogen bonds. A review on the supramolecular chemistry of anions can be found in reference [837].

5.5.2 Protic and Dipolar Aprotic Solvent Effects on the Rates of S_N Reactions

In the course of a nucleophilic substitution reaction, a new bond is formed between the attacking nucleophile and the substrate. Since the nucleophile "attacks" with a free electron pair, a reagent should be all the more nucleophilic, the more readily the electron pair can be engaged in chemical bonding. Thus, the nucleophilicity of an anion is determined – among other things – by its basicity*⁾ and its polarizability. One or the other property may dominate. While polarizability is hardly influenced by solvent, the basicity of an anion is strongly solvent dependent (*cf.* Section 4.2).

In the course of the activation process, the solvent shell of the nucleophile must be removed at the place of attack, while a new solvent shell around the activated complex is simultaneously forming. Thus, the Gibbs energy of activation will be higher, and the rate lower, the more strongly the molecules of the solvent shell are bound to the nucleophile. The less solvated a nucleophile, the more reactive it will be. Conversely, a nucleophile is stabilized by increasing solvation, its chemical potential falls, and its reactivity decreases. Since, according to Bunnett [271], nucleophilic reactivity depends on no less than seventeen factors (solvation effects included), it is very difficult to establish a general nucleophilicity order for all common nucleophiles in different solvents. Numerous attempts to establish such orders of nucleophilicities, which should be independent of any particular reaction electrophile, can be found in the literature [272–275].

When considering the solvation of anions, according to Parker [6] it is reasonable to distinguish between two classes of solvents: protic and dipolar aprotic solvents**⁾ (*cf.* Section 3.4 and Fig. 3-4). The main difference between these two classes of solvents lies in their ability to solvate anions. Small anions with a high charge density (*i.e.* the ratio of charge to volume), which are strong hydrogen-bond acceptors, are more strongly solvated in protic solvents. The hydrogen-bonding interaction is greatest for small anions (*e.g.* $F^{\ominus}$, $Cl^{\ominus}$, $HO^{\ominus}$), and least for large anions where the charge is dispersed (*e.g.* $SCN^{\ominus}$, $I^{\ominus}$, picrate). Dipolar non-HBD solvents, which are polarizable, have mutual polarizability interactions with polarizable anions. This mutual polarizability interaction should be greatest for large, polarizable anions, and least for small weakly polarizable anions. Of course, mutual polarizability is not an exclusive prerogative of dipolar non-HBD solvents; some protic solvents may also be very polarizable. From the point of view of the "principle of hard and soft acids and bases" [275], hard anions are better solvated by hard (hydrogen-bonding) solvents, and soft anions have strong interactions with soft (dipolar non-HBD) solvents (*cf.* also Section 3.3.2). In other words, small ions lose in solvation and large, polarizable anions gain in solvation on transfer from protic to dipolar non-HBD solvents [6]. These considerations are essentially confirmed by the nucleophilic reactivities observed for some S_N reactions in different media, as presented in Table 5-15 [276–287].

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[*] Basicity is measured in terms of a thermodynamic equilibrium involving coordination with H^+. Nucleophilicity is measured in terms of the rates of reaction with the most varied electrophiles. Hence, although a correlation between basicity and nucleophilicity is often found (generally S_N reactions are faster with the stronger bases), it is by no means *a priori* necessary. An example of a direct simple relationship between nucleophilicity and basicity in S_N2 reactions is the reaction of 9-substituted fluorenide ions with (chloromethyl)benzene in dimethyl sulfoxide solution [595].

[**] Solvents referred to as *dipolar aprotic* are not in fact aprotic. In reactions where strong bases are employed their protic character can be easily recognized (*e.g.* $H_3C{-}SO{-}CH_3 + NH_2^{\ominus} \rightleftharpoons H_3C{-}SO{-}CH_2^{\ominus} + NH_3$). The term dipolar *aprotic* solvent is in fact rather misleading. Therefore, it has been recommended by Bordwell *et al.* [594] that the designation *dipolar aprotic* should be replaced by *dipolar nonhydroxylic* or better still by *dipolar non-HBD* solvents. The abbreviation *HBD* stands for *hy*drogen-*b*ond *d*onor. See also Chapter 3.4 and the footnote on page 82.

Table 5-15. Relative nucleophilic reactivities of free[a] anions for S_N2 reactions in various protic and dipolar non-HBD solvents (nos. 1 … 5) as well as in molten salts (no. 6 and no. 7) and in the gas phase (no. 8).

No.	Reaction	Solvent (temperature)	Sequence of decreasing reactivity (relative reaction rates)	References
(1)	$CH_3{-}I + Me^{\oplus}X^{\ominus}$	CH_3OH (25 °C)	$C_6H_5S^{\ominus} > S_2O_3^{2\ominus} \gg I^{\ominus} > SCN^{\ominus} \approx CN^{\ominus} > CH_3O^{\ominus} > Br^{\ominus} > N_3^{\ominus} > C_6H_5O^{\ominus} > Cl^{\ominus} > CH_3CO_2^{\ominus} > F^{\ominus}$	[276]
(2)	$CH_3{-}OTos + Me^{\oplus}X^{\ominus}$	CH_3OH (25 °C)	$C_6H_5S^{\ominus} > CH_3O^{\ominus} > I^{\ominus} > SCN^{\ominus} > Br^{\ominus} > Cl^{\ominus}$	[277]
		$HCON(CH_3)_2/H_2O$[b]	$I^{\ominus} > Br^{\ominus} > Cl^{\ominus}$	[278]
		$HCON(CH_3)_2$ (0 °C)	$Cl^{\ominus} > Br^{\ominus} > I^{\ominus}$ (9:3:1)	[278]
(3)	$n\text{-}C_4H_9{-}OBros + (n\text{-}C_4H_9)_4N^{\oplus}X^{\ominus}$	CH_3COCH_3 (25 °C)	$Cl^{\ominus} > Br^{\ominus} > I^{\ominus}$ (18:5:1)	[279]
(4)	$n\text{-}C_3H_7{-}OTos + (n\text{-}C_4H_9)_4N^{\oplus}X^{\ominus}$	CH_3SOCH_3 (25 °C)	$S_2O_3^{2\ominus} > HO^{\ominus} \approx CH_3O^{\ominus} > F^{\ominus} > C_6H_5O^{\ominus} > N_3^{\ominus} > Cl^{\ominus} > Br^{\ominus} > I^{\ominus} > SCN^{\ominus}$	[280]
		CH_3SOCH_3 (50 °C)	$Cl^{\ominus} > Br^{\ominus} > I^{\ominus}$ (5.2:3.2:1)	[281]
		CH_3SOCH_3/H_2O[c]	$I^{\ominus} > Br^{\ominus} > Cl^{\ominus}$ (6.7:1.3:1)	[281]
(5)	$C_6H_5CH_2{-}OTos + K^{\oplus}X^{\ominus}$[d]	CH_3CN (30 °C)	$N_3^{\ominus} > CH_3CO_2^{\ominus} > CN^{\ominus} > F^{\ominus} > Cl^{\ominus} \approx Br^{\ominus} > I^{\ominus} > SCN^{\ominus}$ (10:9.6:2.4:1.4:1.3:1.3:1:0.3)	[282]
(6)	$CH_3{-}OTos + (C_2H_5)_4N^{\oplus} + X^{\ominus}$	$R_4N^{\oplus}R_4B^{\ominus}$[e] (35 °C)	$Cl^{\ominus} > Br^{\ominus} > I^{\ominus}$ (2.1:1.2:1)	[283]
(7)	$(n\text{-}C_5H_{11})_4N^{\oplus} + X^{\ominus}$	$(n\text{-}C_5H_{11})_4N^{\oplus}X^{\ominus}$[f] (180 °C)	$Cl^{\ominus} > Br^{\ominus} > I^{\ominus}$ (620:7.7:1)	[284]
(8)	$CH_3{-}Br + X^{\ominus}$	Gas phase	$HO^{\ominus} > CH_3O^{\ominus} \approx F^{\ominus} > CH_3S^{\ominus} \gg CN^{\ominus} > Cl^{\ominus} > Br^{\ominus}$	[285, 290]

[a] “Free” means without association with the corresponding cation, no ion pairing.

[b] 91:9 cL/L (0 °C).

[c] 70:30 cL/L (50 °C).

[d] The potassium salts are solubilized in acetonitrile with [18]crown-6, producing extremely reactive “naked” anions because of the weak anion solvation forces in acetonitrile solutions and the complete dissociation of the potassium salts [282].

[e] Molten triethyl-*n*-hexylammonium triethyl-*n*-hexyl-boride as solvent [283].

[f] Molten tetra-*n*-pentylammonium halides as solvent [284].

It is apparent that the order of anion nucleophilicity is almost completely reversed on transfer from protic to dipolar non-HBD solvents. Especially for halide ions, the relative reactivity is completely reversed in the two classes of solvents: whereas the order of reactivity is $I^{\ominus} > Br^{\ominus} > Cl^{\ominus} > F^{\ominus}$ in the protic solvent methanol (reactions no. 1 and no. 2 in Table 5-15), in dipolar non-HBD solvents such as *N*,*N*-dimethylformamide (no. 2), acetone (no. 3), dimethyl sulfoxide (no. 4), and acetonitrile (no. 5) the sequence of nucleophilicity is reversed. The traditional order of halide nucleophilicities, $I^{\ominus} > Br^{\ominus} > Cl^{\ominus}$ [261], applies only when the nucleophile is deactivated through solvation by protic solvents ($X^{\ominus} \cdots H{-}S$), whereas the natural order, $Cl^{\ominus} > Br^{\ominus} > I^{\ominus}$, is observed in dipolar non-HBD solvents. The sequences observed in dipolar non-HBD solvents give a much better picture of the true nucleophilicity of the weakly solvated anions, which also correlates better with their basicity.

With acetonitrile as solvent, there appears to be a general levelling of the nucleophilicities of anions, as indicated by the relatively small variation of rate constants obtained for reaction no. 5 in Table 5-15 [282]. Quite surprisingly, one of the best nucleophiles in acetonitrile is $CH_3CO_2^{\ominus}$, which is normally considered a very poor nucleophile in protic solvents, whereas $SCN^{\ominus}$, one of the more potent nucleophiles in aqueous solution, is approximately 30 times slower than $CH_3CO_2^{\ominus}$. Obviously, the so-called "naked", and therefore very reactive, anions in acetonitrile are solvated by much weaker forces than in protic solvents, and the variations in anion solvation in acetonitrile do not appreciably effect the relative nucleophilic reactivities of the anions [282].

Reactions no. 6 and no. 7 in Table 5-15 demonstrate that with molten quaternary ammonium salts as solvents, where deactivation by anion solvation is absent, the halide ions show the same nucleophilic order as in dipolar non-HBD solvents [283, 284]. This is in accordance with the theory of protic/dipolar non-HBD medium effects on $X^{\ominus}$ nucleophilicity [6]. It has been suggested that fused-salt experiments should provide a good model for the determination of intrinsic relative nucleophilicities of anions towards saturated carbon atoms [284].

The results for reaction no. 8 in Table 5-15 indicate that nucleophilic reactivities of anions obtained in the gas phase are essentially in the same order as in molten salts and in dipolar non-HBD solvents [285, 290]. This again suggests that specific solvation of the anions is responsible for the reversed order obtained in protic solvents relative to dipolar non-HBD solvents. Whereas the relative nucleophilicities in acetonitrile are similar to those found in the gas phase [282, 285, 290], the absolute gas-phase rates are some orders of magnitude greater than those in acetonitrile. The specific rates of displacement reactions of anions with halomethanes exceed those in solution by factors of up to $\geq 10^{10}$ [285, 290]. These large differences in absolute rates demonstrate the moderating influence of the solvent on all the reactivities [282]. See also Chapter 5.2.

In spite of evidence for increased stabilization of increasingly large anions in increasingly polarizable solvents due to dispersion interactions, there is some question as to whether the decreased reactivity of halide ions in dimethyl sulfoxide ($Cl^{\ominus} > Br^{\ominus} > I^{\ominus}$; *cf.* reaction no. 4 in Table 5-15) is due to increased solvation in the series $Cl^{\ominus} \rightarrow Br^{\ominus} \rightarrow I^{\ominus}$. Because the solvation order of these halide ions in dimethyl sulfoxide is $I^{\ominus} < Br^{\ominus} < Cl^{\ominus}$ (the same as in water!) as shown by solvation enthalpies, ΔH_{solv}, of the corresponding alkali halides in dimethyl sulfoxide and in water [281], Parker [6] suggested that the observed reactivity order $Cl^{\ominus} > Br^{\ominus} > I^{\ominus}$ in dipolar non-HBD solvents might be the order of increasing solvation in these solvents. Alternatively, this could also be the intrinsic order of nucleophilicity, which is only partially offset by decreasing solvation in the same order [281]. If the unsolvated $Cl^{\ominus}$ is a sufficiently stronger nucleophile than unsolvated $I^{\ominus}$, the more strongly solvated $Cl^{\ominus}$ in dimethyl sulfoxide may remain more reactive than the comparatively less well solvated $I^{\ominus}$. In protic solvents, however, the difference in solvation is much larger. Now the extremely strong solvation of $Cl^{\ominus}$ in protic solvents diminishes the reactivity of this anion to less than that of the more weakly solvated $I^{\ominus}$. Therefore, the reversed nucleophilic order of the halide ions in dimethyl sulfoxide relative to water must be attributed to the smaller differences in halide solvation in dimethyl sulfoxide than in water [281]. This [281] and other estimates [288, 289] are all in agreement with the observation that solvent stabilization of halide ions, although small compared to water, goes in the same direction, $Cl^{\ominus} > Br^{\ominus} > I^{\ominus}$, in dipolar non-HBD solvents.

Accordingly, gas-phase results for the clustering of $Cl^{\ominus}$, $Br^{\ominus}$, and $I^{\ominus}$ with Me_2SO and H_2O show that the bonding to dimethyl sulfoxide also decreases in the order $Cl^{\ominus} > Br^{\ominus} > I^{\ominus}$, *i.e.* with increasing ion radius [596]. Thus, anion solvation decreases with an increase in the ion radius for both protic and non-HBD solvents; however, the decrease is appreciably less in dipolar non-HBD solvents. This is the principle reason for the much higher rates of anion-molecule S_N2 reactions in dipolar non-HBD solvents [596].

An important contribution to a quantitative estimation of nucleophilic reactivity towards cations in different solvents was made by Ritchie *et al.* [274, 597]. According to Eq. (5-109),

$$\lg k = \lg k_0 + N_+ \tag{5-109}$$

where k is the rate constant for the reaction of a cation (particularly triarylmethyl cations, aryldiazonium ions, and aryltropylium cations) with a given nucleophile/solvent system, and k_0 is the rate constant for reaction of the same cation with a standard system (*e.g.* $HO^{\ominus}$ in H_2O), a parameter N_+ was defined, which represents the difference in nucleophilicity of the two systems. The N_+ values are measures of an inherent property of the (nucleophile *and* solvent) system, which is associated with the differential solvation of the nucleophile in different solvents. A selection of N_+ values is listed in Table 5-16 [597]. The higher the N_+ value, the less strongly solvated and the more reactive is the nucleophile in a given solvent. The large differences in N_+ values for the same nucleophile in protic and non-HBD solvents deserve special mention in this context; *cf.* for example entries (3), (13), and (17) for the cyanide ion, entries (15) and (19) for the monothioglycolate ion, and entries (6), (7), and (11) for hydrazine in Table 5-16.

The N_+ scale, which is derived from nucleophile/electrophile combination reactions, differs from the nucleophilicity scales generated from rates of S_N2 reactions (*cf.* Table 5-15). The N_+ equation, an example of a so-called "constant selectivity relationship", has been applied to many other electrophile/nucleophile reactions in solution, although often with only limited success.

A considerable improvement in the construction of reference scales for the quantitative characterization of nucleophiles and electrophiles in solution has been made by Mayr *et al.* [598] by means of Eq. (5-109a),

$$\lg k(20\ ^{\circ}\mathrm{C}) = s(N + E) \tag{5-109a}$$

where N and E are substrate nucleophilicity and electrophilicity parameters, respectively, and s is the nucleophile-dependent slope, measuring the susceptibility of $\lg k$ to changes in nucleophilicity of π-, n-, and σ-nucleophiles in reactions with carefully selected reference electrophiles. For example, 23 differently substituted electrophilic diarylcarbenium (benzhydryl) ions and 38 neutral nucleophilic π-systems (*e.g.* arenes, alkenes, allyl silanes, silyl enol ethers, enamines) have been used as basis sets for estab-

Table 5-16. Nucleophilic parameters N_+ for various (nucleophile + solvent) systems, based on reactions of malachite green or the tris-4-anisylmethyl cation [597].

No.	Nucleophile (solvent)	N_+
(1)	$H_2O(H_2O)$	0.73
(2)	$NH_3(H_2O)$	3.89
(3)	$CN^{\ominus}(H_2O)$	4.12
(4)	$HO^{\ominus}(H_2O)$	*4.75*[a]
(5)	$HO{-}NH_2(H_2O)$	5.05
(6)	$H_2N{-}NH_2(H_2O)$	6.01
(7)	$H_2N{-}NH_2(CH_3OH)$	6.89
(8)	$BH_4^{\ominus}(H_2O)$	6.95
(9)	$CH_3O^{\ominus}(CH_3OH)$	7.51
(10)	$N_3^{\ominus}(H_2O)$	7.54
(11)	$H_2N{-}NH_2(CH_3SOCH_3)$	8.17
(12)	$HOO^{\ominus}(H_2O)$	8.52
(13)	$CN^{\ominus}(CH_3SOCH_3)$	8.64
(14)	$N_3^{\ominus}(CH_3OH)$	8.78
(15)	$HOCH_2{-}CH_2S^{\ominus}(H_2O)$	8.87
(16)	$C_6H_5S^{\ominus}(H_2O)$	9.10
(17)	$CN^{\ominus}[HCON(CH_3)_2]$	9.44
(18)	$C_6H_5S^{\ominus}(CH_3OH)$	10.41
(19)	$HOCH_2{-}CH_2S^{\ominus}(CH_3SOCH_3)$	12.71

[a] All N_+ values are relative to $N_+ = 4.75$ for hydroxide ion in water.

lishing general reactivity scales for electrophiles and nucleophiles, which cover more than sixteen orders of magnitude [598b]. It has been shown that the reactivity parameters derived in this way from the reaction of diarylcarbenium ions with π-nucleophiles are also applicable for characterizing the reactivities of other nucleophiles such as alkynes, transition metal π-complexes, n-nucleophiles (*e.g.* amines, anions), and σ-nucleophiles (*e.g.* hydride donors such as Bu_3SnH), not belonging to the basis set [598b,c]. Most of the electrophile/nucleophile reactions were carried out in dichloromethane as reference solvent. Using the rate constants of a total of 209 combinations of diarylcarbenium ions and π-nucleophiles from the basis set, Eq. (5-109a) represents a well-founded new and helpful linear Gibbs energy relationship; for other LGE relationships, see Section 7.1.

Since anions are solvated to a much lesser extent in dipolar non-HBD solvents than in protic solvents, they exist in these solvents as more or less "naked" and therefore extremely reactive ions. For S_N2 and S_NAr reactions involving anionic nucleophiles, a change from protic to dipolar non-HBD solvent often causes a very dramatic acceleration of these reactions [6]*). Some typical examples are reactions (5-110) to (5-113), for

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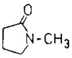
* To speak of dipolar non-HBD solvents having an accelerating effect on the rates of bimolecular substitution reactions involving anionic nucleophiles seems to be looking at things in reverse order. The view that protic solvents have a retarding effect on such reactions seems to be much more consistent with the experimental data. However, the above mentioned description of the protic/dipolar non-HBD solvent effect on reaction rates has been widely used in the literature.

Table 5-17. Relative rates of the S_N2 anion-molecule reactions (5-110) [291] and (5-111) [67], and of the S_NAr reactions (5-112) [291, 292] and (5-113) [293] in protic and dipolar non-HBD solvents at 25 °C.

Solvents	$\lg(k_2^{\text{Solvent}}/k_2^{\text{MeOH}})$[a] for reaction			
	(5-110)[b]	(5-111)[c]	(5-112)[d]	(5-113)[e]
Protic Solvents:				
CH_3OH	0	0	0	0
H_2O	0.05	0.8	–	–
$CH_3CONHCH_3$	–	0.9	–	–
$HCONH_2$	1.2	1.1	0.8	–
$HCONHCH_3$	1.7	–	1.1	–
Dipolar non-HBD Solvents:				
$(CH_2)_4SO_2$ (Sulfolane)	–	2.6	4.5	–
CH_3NO_2	4.2	–	3.5	0.8
CH_3CN	4.6	3.7	3.9	0.9
CH_3SOCH_3	–	3.1	3.9	2.3
$HCON(CH_3)_2$	5.9	3.4	4.5	1.8
CH_3COCH_3	6.2	3.6	4.9	0.4
$CH_3CON(CH_3)_2$	6.4	3.9	5.0	1.7
	6.9	–	5.3	–
$[(CH_3)_2N]_3PO$	–	5.3	7.3	–

[a] $k_2^{\text{MeOH}}/(\text{L} \cdot \text{mol}^{-1} \cdot \text{s}^{-1})$ is the second-order rate constant for the reaction in methanol; k_2^{Solvent} is for reaction in the given solvent. $\lg k_2^{\text{Solvent}} = \lg(k_2^{\text{Solvent}}/k_2^{\text{MeOH}}) + \lg k_2^{\text{MeOH}}$.

[b] $\lg k_2^{\text{MeOH}} = -5.5$.

[c] $\lg k_2^{\text{MeOH}} = -5.1$.

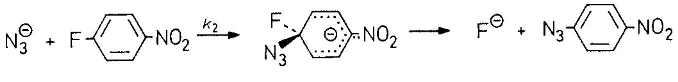
[d] $\lg k_2^{\text{MeOH}} = -7.2$.

[e] $\lg k_2^{\text{MeOH}} = -3.85$ (50 °C).

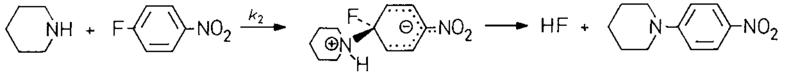
which rate data in several solvents relative to solvent methanol are reported in Table 5-17 as the logarithms of rate ratios.

$$Cl^{\ominus} + CH_3\text{-}I \xrightarrow{k_2} Cl\text{-}CH_3 + I^{\ominus} \quad (5\text{-}110)$$

$$N_3^{\ominus} + CH_3CH_2CH_2CH_2\text{-}Br \xrightarrow{k_2} CH_3CH_2CH_2CH_2\text{-}N_3 + Br^{\ominus} \quad (5\text{-}111)$$



(5-112)

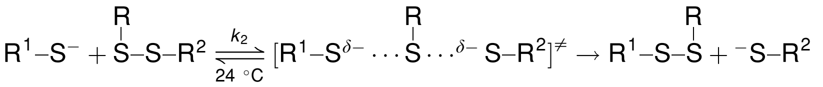


(5-113)

The rate increases (relative to methanol) involve factors in the range of 10^2 to 10^7 going from a protic to a dipolar non-HBD solvent. Even larger factors, as in the reaction $2,4\text{-}(NO_2)_2C_6H_3I$ with $Cl^{\ominus}$ in hexamethylphosphoric triamide (ca. 10^9!) are not uncommon [291]. For reaction (5-112), the solvent change from methanol to hexamethylphosphoric triamide corresponds to a decrease in the Gibbs energy of activation, $\Delta\Delta G^{\neq}$, of 36.4 kJ/mol (8.7 kcal/mol) [292]. Hexamethylphosphoric triamide is usually the "fastest" of dipolar non-HBD solvents [291]. That these protic/dipolar non-HBD solvent effects are mainly anion-solvation phenomena is confirmed by the observation that similarly large rate ratios are not observed for reaction (5-113), which involves a neutral nucleophile (piperidine). Menschutkin reactions between tertiary amines – neutral nucleophiles – and haloalkanes are also rather insensitive to protic/dipolar non-HBD solvent transfer [6, 23]. As expected for such an effect, attributed mainly to hydrogen-bonding interactions, protic/dipolar non-HBD solvent effects on the chemistry of anions are strongly temperature dependent; differences between protic and dipolar non-HBD solvents are greater at low temperatures than at high temperatures [291].

In addition, it should be mentioned that for protic/dipolar non-HBD solvent effects on S_N2 reactions $Y^{\ominus} + RX \rightleftharpoons [YRX^{\ominus}]^{\neq} \rightarrow YR + X^{\ominus}$ not only the solvation of the anion must be taken into account. An important factor in determining the rate of this reaction in different solvents may be the solvation of the reactant molecule RX and the activated complex $[YRX^{\ominus}]^{\neq}$. Although ions have much greater solvation enthalpies than nonelectrolytes, the solvation of nonelectrolytes should not be neglected, because important criteria are the differences in solvation. Many anionic activated complexes, especially those of S_NAr reactions, are expected to be highly polarizable and will have strong dispersion interactions in highly polarizable solvents such as dimethyl sulfoxide or *N*,*N*-dimethylformamide. On the other hand, due to the delocalization of the negative charge, they are weak hydrogen-bond acceptors and are not particularly well solvated by protic solvents. For example, solvation of large polarizable S_NAr transition state anions decreases in the solvent order $[(CH_3)_2N]_3PO$, $CH_3SOCH_3 > HCON(CH_3)_2 > CH_3OH > CH_3NO_2$, CH_3CN [291]. These differences in solvation of activated complexes may also contribute to the large rate accelerations obtained on protic/dipolar non-HBD solvent transfer for bimolecular substitution reactions*). However, in most cases S_N reactions are faster in dipolar non-HBD solvents because the reactant anion $Y^{\ominus}$ is much more solvated by protic than by dipolar non-HBD solvents and this outweighs any effects due to solvation of the transition state anion or reactant molecule [6].

Nucleophilic reactions with anions for which hydrogen bonding is less important are not so greatly influenced by changes from protic solvents to dipolar aprotic ones. For example, the rate constant for the degenerate thiolate/disulfane interchange reaction shown in Eq. (5-113a) is larger in dimethyl sulfoxide than in water



$$R^1{-}S^- + \overset{R}{\overset{|}{S}}{-}S{-}R^2 \underset{24\ ^\circ C}{\overset{k_2}{\rightleftharpoons}} [R^1{-}S^{\delta-}\cdots\overset{R}{\overset{|}{S}}\cdots{}^{\delta-}S{-}R^2]^{\neq} \rightarrow R^1{-}S{-}\overset{R}{\overset{|}{S}} + {}^{-}S{-}R^2 \qquad (5\text{-}113a)$$

as expected, but only by a factor of ca. 2700 (with $R^1 = R = R^2 = -CH_2CH_2OH$) [838]. In D_2O/DMSO mixtures, $\lg k_2$ is directly proportional to the mole fraction of D_2O, even at small fractions of D_2O. Evidently, thiolate ions are not specifically solvated by water, in contrast to alcoholate ions. The rate acceleration in DMSO seems to

---

* For an extensive discussion concerning the solvation of activated complexes of bimolecular substitution reactions for numerous variations of RX and $Y^{\ominus}$, as well as different mechanisms, see references [6, 23, 291].

be due to better solvation of the charge-delocalized, polarizable activated complex of this exchange reaction by DMSO, which reduces the activation barrier.

Since small anions such as $F^{\ominus}$, $HO^{\ominus}$, and $CN^{\ominus}$ are often so poorly solvated by pure dipolar non-HBD solvents, it is difficult to find a soluble salt to act as the anion source. For example, electrolytes such as KF, KOH, and KCN are only slightly soluble in pure dimethyl sulfoxide. There are two possibilities for overcoming this experimental difficulty. First, the solubility of electrolytes in dipolar non-HBD solvents can be increased by using the corresponding tetraalkylammonium salts. Among these, tetraalkylammonium fluorides are the most prominent. In solutions of tetraalkylammonium fluorides in dipolar non-HBD solvents, the fluoride ion is virtually unsolvated. These "naked" fluoride ions are both strong nucleophiles [599] and very effective bases [600]. They are more nucleophilic and basic than the fluoride ions of lower alkali metal fluorides (LiF, NaF, KF) in protic solvents; see reference [839] for reviews on the solvation of fluoride ions in nonaqueous solvents. Secondly, protic/dipolar non-HBD solvent mixtures can be used as media for substitution reactions. Mixtures of dimethyl sulfoxide with water or alcohols have proven especially useful. This is because salts such as KOH, KF, KCN, CH_3ONa, and CH_3CO_2Na are reasonably soluble in solvent mixtures such as CH_3SOCH_3/H_2O (90:10) or CH_3SOCH_3/CH_3OH (90:10). Water or alcohols in combination with pure dipolar non-HBD solvents (*e.g.* 15 cL/L water in HMPT) provide a source of nucleophilic oxygen for the conversion of haloalkanes or sulfonate esters into the corresponding alcohols or ethers [601].

All the features discussed for protic/dipolar non-HBD solvent transfer are also observed for transfer from protic to dipolar non-HBD/protic mixtures, but to a slightly lesser extent. In general, all S_N2 anion-molecule reactions are faster in mixtures than in pure protic solvents. They show a continuous, but not necessarily linear, rate increase with an increase in the dipolar non-HBD component of the protic/dipolar non-HBD mixture [6]. Even small amounts of dipolar non-HBD component may cause a considerable acceleration in reaction rate.

The use of dipolar non-HBD instead of protic solvents as reaction media often has considerable practical synthetic advantages, which have been summarized by Parker [6], Madaule-Aubry [294], Liebig [295], and Schmid [26]. A selection of common and less common dipolar non-HBD solvents is given in Table 5-18, together with some physical constants useful for their practical application. Reviews on particular dipolar non-HBD solvents have appeared; these are included in Table 5-18 (*cf.* also references [75–91] in Chapter 3).

Finally, some important examples emphasizing the versatility and synthetic utility of dipolar non-HBD solvents as reaction media will be given.

$RCO_2^{\ominus}$, an indifferent nucleophile in protic solvents, enjoys a large rate enhancement, permitting rapid alkylation with haloalkanes in hexamethylphosphoric triamide [301, 302]. When the Williamson ether synthesis is carried out in dimethyl sulfoxide [303], the yields are raised and the reaction time shortened. Displacements on unreactive haloarenes become possible [304] (conversion of bromobenzene to *tert*-butoxybenzene with *tert*-$C_4H_9O^{\ominus}$ in dimethyl sulfoxide in 86% yield at room temperature). The fluoride ion, a notoriously poor nucleophile or base in protic solvents, reveals its hidden capabilities in dipolar non-HBD solvents and is a powerful nucleophile in substitution reactions on carbon [305].

Table 5-18. A selection of twenty-one organic dipolar non-HBD solvents in order of increasing dipole moment (*cf.* also Appendix, Table A-1).

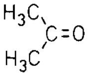
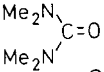
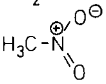
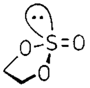
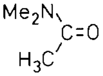
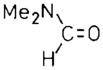
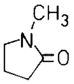
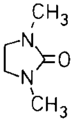
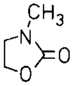
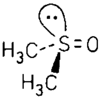
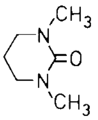
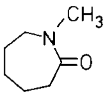
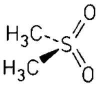
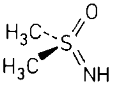
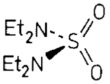
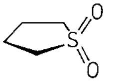
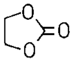
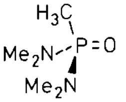
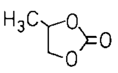
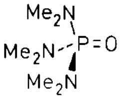
Structure (+→)$^{a)}$	Name	$\mu/(10^{-30}$ Cm)	t_{mp}/°C	t_{bp}/°C	References
 $(H_3C)_2C{=}O$	Acetone	9.0	−94.7	56.1	
 $(Me_2N)_2C{=}O$	Tetramethylurea (Temur)	11.6	−1.2	175.3	[602, 603]
 $H_3C-\overset{\oplus}{N}(=O)-O^{\ominus}$	Nitromethane	12.0	−28.6	101.2	[604]
	1,3,2-Dioxathiolane-2-oxide (Ethylene sulfite)	12.3		170–171 (dec.)	[605]
 $Me_2N(H_3C)C{=}O$	*N*,*N*-Dimethylacetamide (DMAC)	12.4	−20.1	166.1	[606]; *N*,*N*-Diethylacetamide: [633]
 $Me_2N(H)C{=}O$	*N*,*N*-Dimethylformamide (DMF)	12.7	−60.4	153.1	[606–608]
	1-Methylpyrrolidin-2-one	13.6	−24.4	202	[609]; 1-Ethyl-pyrrolidin-2-one: [633]
	1,3-Dimethylimidazolidin-2-one (*N*,*N*′-Dimethyl-ethylene urea, DMEU)	13.6	8.2	225.5	[603]
	3-Methyloxazolidin-2-one	13.7	15.9	87–90 (1.3 mbar)	[610, 611]
$H_3C-C\equiv N$	Acetonitrile	13.0	−43.8	81.6	[296, 608, 612]
	Dimethyl sulfoxide	13.5	18.5	189.0	[608, 613–616]
	3,4,5,6-Tetrahydro-1,3-dimethyl-2(1H)-pyrimidinone (*N*,*N*′-Dimethylpropylene urea, DMPU)	14.1	−23.8	246.5	[603, 617–618]
	1-Methyl-hexahydro-azepin-2-one, N-Methyl-ε-capro-lactam	14.1		12 (25 mbar)	
	Dimethylsulfone	14.2	110	238	[619]

Table 5-18. (Continued)

Structure ($\leftarrow\!\!+$)[a]	Name	$\mu/(10^{-30}$ Cm)	$t_{mp}/°C$	$t_{bp}/°C$	References
	*S,S*-Dimethylsulfoximine (DMSOI)		52–53	100 (6.5 mbar)	[620]
	Tetraethylsulfamide (TES)	14.6[b]		249–251	[621]
	Tetrahydrothiophene-1,1-dioxide (Sulfolane)	16.0	28.4	287.3	[608, 622–624]
	1,3-Dioxolan-2-one (Ethylene carbonate)	16.0	36	156	[625, 626]
	Methylphosphonic acid bis(dimethylamide)	16.0	−3.2	62–63 (4 mbar)	[627, 628]
	4-Methyl-1,3-dioxolan-2-one (Propylene carbonate)	16.5	−54.5	241.7	[608, 625, 629, 630]
	Hexamethylphosphoric acid triamide (HMPT)	18.5	7.3	233	[608, 617, 618, 631]

[a] All formulae are oriented in such a way that the dipole moment of the solvent molecule is approximately in a parallel direction with this arrow.

[b] Value for tetramethylsulfamide; H. Nöth, G. Mikulaschek, and W. Rambeck, Z. Anorg. Allg. Chem. *344*, 316 (1966).

The observation that bimolecular reactions of anions are often much faster in dipolar non-HBD solvents than in protic solvents of comparable relative permittivity is of great practical significance, not only for substitution reactions but also for elimination, proton abstraction, and addition reactions [6].

Reduced solvation of commonly used E2 bases ($HO^{\ominus}$, $RO^{\ominus}$) in dipolar non-HBD solvents may elevate their reactivities to such an extent that E2 reactions of quite inert substrates occur [306]. Halide ions in dipolar non-HBD solvents are sufficiently strong bases to promote dehydrohalogenations of haloalkanes [73, 74]. Even the fluoride ion is the most efficient in this reaction [307, 308, 600]; the elimination rates decrease in the order $F^{\ominus} > Cl^{\ominus} > Br^{\ominus} > I^{\ominus}$.

A shift from $CH_3O^{\ominus}/CH_3OH$ to *tert*-$C_4H_9O^{\ominus}/CH_3SOCH_3$ can produce dramatic increases in rates (up to a factor of 10^9) of reactions which depend on proton abstraction from a C–H bond [31, 304]. The subsequent reaction of the carbanion may involve isomerization, elimination, oxidation, and condensation, hence demonstrating the importance of the potassium *tert*-butoxide/dimethyl sulfoxide system in organic syntheses. The base-catalyzed alkene isomerization reaction (double bond migration) has been used to investigate the efficacy of a wide variety of base/dipolar non-HBD solvent systems [309, 310].

Addition of anionic nucleophiles to alkenes and to heteronuclear double bond systems (C═O, C═S) also lies within the scope of this Section. Chloride and cyanide ions are efficient initiators of the polymerization and copolymerization of acrylonitrile in dipolar non-HBD solvents, as reported by Parker [6]. Even some 1,3-dipolar cycloaddition reactions leading to heterocyclic compounds are often better carried out in dipolar non-HBD solvents in order to increase rates and yields [311]. The rate of alkaline hydrolysis of ethyl and 4-nitrophenyl acetate in dimethyl sulfoxide/water mixtures increases with increasing dimethyl sulfoxide concentration due to the increased activity of the hydroxide ion. This is presumably caused by its reduced solvation in the dipolar non-HBD solvent [312, 313]. Dimethyl sulfoxide greatly accelerates the formation of oximes from carbonyl compounds and hydroxylamine, as shown for substituted 9-oxofluorenes [314]. Nucleophilic attack on carbon disulfide by cyanide ion is possible only in *N*,*N*-dimethylformamide [315]. The fluoride ion, dissolved as tetraalkylammonium fluoride in dipolar difluoromethane, even reacts with carbon dioxide to yield the fluorocarbonate ion, $F{-}CO_2^-$ [840].

The superoxide ion, $O_2^{\ominus}$, produced by the electron-transfer reduction of dioxygen ($O_2 + e^{\ominus} \rightleftharpoons O_2^{\ominus}\cdot$), is a strong Brønsted base and an effective nucleophile. Because of rapid hydrolysis and disproportionation, the lifetime of $O_2^{\ominus}\cdot$ in aqueous solution is limited. This has led to investigations of its reaction chemistry in dipolar non-HBD solvents [632]. Under these conditions, the superoxide ion attacks haloalkanes by S_N2 displacement of the halides to eventually give dialkyl peroxides in a multi-step reaction [632].

5.5.3 Quantitative Separation of Protic and Dipolar Aprotic Solvent Effects for Reaction Rates by Means of Solvent-Transfer Activity Coefficients

By considering the changes in *standard molar Gibbs energy of solvation*, $\Delta G^{\circ}_{\text{solv}}$, of reactants and activated complexes, when a reaction is transferred from one solvent to another, it is possible to approach the problem from a quantitative point of view. The observed changes in Gibbs energy of solvation when an electrolyte $M^{\oplus}X^{\ominus}$ is transferred from a reference solvent O to another solvent S is commonly reported as the *solvent-transfer activity coefficient* ${}^{O}y^{S}$*) [6, 291, 316–319, 454, 634, 635]. This coefficient makes it possible to relate the difference in chemical potential, μ, of a solute MX at infinite dilution on transferring it from an arbitrarily chosen reference solvent O to another solvent S at temperature T according to Eq. (5-114)**):

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* Also called the *medium effect*, *solvent activity coefficient*, or *transfer activity coefficient*, and also written as $y_t^{\infty}(\text{MX, O} \rightarrow \text{S})$. It is a constant characteristic of the solute MX (or the solute ions $M^{\oplus}$ and $X^{\ominus}$) and the two solvents O and S.

** The change in standard molar Gibbs energy on transferring an electrolyte MX from one solvent to another may also be expressed as the *standard molar Gibbs energy of transfer*, ΔG_t° [6, 454, 634, 635]. The two quantities, solvent-transfer activity coefficient, ${}^{O}y^{S}$, and Gibbs energy of transfer, ΔG_t°, are related by the following simple equation:

$$\Delta G_t^{\circ}(\text{MX}, \text{O} \rightarrow \text{S}) = \mu^{\infty}_{\text{MX}}(\text{in S}) - \mu^{\infty}_{\text{MX}}(\text{in O}) = RT \cdot \ln({}^{O}y^{S}_{M^{\oplus}} \cdot {}^{O}y^{S}_{X^{\ominus}}),$$

where $\mu^{\infty}_{\text{MX}}(\text{in S})$ and $\mu^{\infty}_{\text{MX}}(\text{in O})$ are the standard chemical potentials of MX referred to at infinite dilution in solvents S and O, respectively. In this Section, results are quoted as solvent-transfer activity coefficients using the molar concentration scale; *cf.* Eq. (2-12a) in Chapter 2.3.

$$\mu^{\infty}_{MX}(\text{in S}) = \mu^{\infty}_{MX}(\text{in O}) + RT \cdot \ln {}^{O}y^{S}_{MX} \tag{5-114}$$

A positive value of $\ln {}^{O}y^{S}_{MX}$ implies that the solute MX is better solvated by solvent O than by solvent S. A negative value indicates that solvation by solvent S is greater. Values of $\ln {}^{O}y^{S}_{MX}$ are obtained from various measurements, *e.g.* solubility, distribution, vapour pressure, and electrochemical measurements. Although solvent-transfer activity coefficients can be defined for individual ions $M^{\oplus}$ and $X^{\ominus}$ they cannot be independently measured. In order to divide the solvent-transfer activity coefficient ${}^{O}y^{S}_{MX}$ into separate contributions ${}^{O}y^{S}_{M^{\oplus}}$ and ${}^{O}y^{S}_{X^{\ominus}}$, an extrathermodynamic assumption must be considered; *cf.* Chapter 2.3 and [454, 634, 635].

The most convenient and generally accepted extrathermodynamic assumption is that ${}^{O}y^{S}_{Ph_4As^{\oplus}} = {}^{O}y^{S}_{Ph_4B^{\ominus}}$, using $Ph_4As^{\oplus}Ph_4B^{\ominus}$ as the reference electrolyte ($Ph = C_6H_5$). The tetrahedral ions of tetraphenylarsonium tetraphenylboride are of comparable structure and size. It is proposed, therefore, that the anion and the cation are similarly influenced on transfer from one solvent to another. This assumption makes it possible to calculate reasonable values for single-ion solvent-transfer activity coefficients (and single-ion Gibbs energies of transfer; *cf.* Table 2-9 in Chapter 2.3) between solvent pairs. Table 5-19 shows some selected values of $\lg {}^{O}y^{S}$ for anions and cations. These have been taken from Marcus's extensive critical compilation [634, 635]. All $\lg {}^{O}y^{S}$ values are expressed relative to water as the reference solvent O at 25 °C.

The striking increase in $\lg {}^{W}y^{S}_{ion}$ values for small anions with high charge density, on going from water to any of the dipolar non-HBD solvents, is consistent with the large rate increase observed in reactions of these anions and gives quantitative significance to the qualitative discussion in Section 5.5.2. The rather large increase in the solvent-transfer activity coefficient of $CH_3CO_2^{\ominus}$, compared with $Cl^{\ominus}$, for the isodielectric solvent change from CH_3OH to CH_3CN and $HCON(CH_3)_2$, reflects the considerable stabilization of this anion through hydrogen-bonding in both methanol and water. As expected, the larger and more polarizable anions show considerably smaller increases in $\lg {}^{W}y^{S}_{ion}$ values on transfer from water to dipolar non-HBD solvents (*e.g.* $I^{\ominus}$, $SCN^{\ominus}$). An extreme example of the difference between small, non-polarizable and large, polarizable anions is seen in the $\lg {}^{W}y^{S}$ values of $F^{\ominus}$ and $(C_6H_5)_4B^{\ominus}$ for the solvent change $CH_3OH \rightarrow HCON(CH_3)_2$: $\lg {}^{W}y^{DMF}_{F^{\ominus}}$ and $\lg {}^{W}y^{DMF}_{Ph_4B^{\ominus}}$ differ by 14.7 units, which corresponds to a difference in Gibbs energy of transfer of 84 kJ/mol.

In addition, it is worth emphasizing the contrasting behaviour of anions and cations on going from water to protic and to dipolar non-HBD solvents. Cations are generally smaller and less polarizable than anions and they are not hydrogen-bond acceptors. Some cations, however, are pronounced Lewis acids and are substantially better solvated in solvents which contain basic oxygen atoms and behave like EPD solvents (*cf.* Section 3.3.2). Therefore, small closed-shell cations such as $Li^{\oplus}$, $Na^{\oplus}$, and $K^{\oplus}$ are much more extensively solvated by solvents such as $[(CH_3)_2N]_3PO$, $HCON(CH_3)_2$, and CH_3SOCH_3, as well as by water, than by methanol. The silver cation has a strong, apparently specific interaction with solvents such as $[(CH_3)_2N]_3PO$, $HCON(CH_3)_2$, CH_3SOCH_3, and CH_3CN. The interaction of $Ag^{\oplus}$ with CH_3COCH_3 and CH_3OH is much weaker. Large organic cations [*e.g.* $(CH_3)_4N^{\oplus}$, $(C_6H_5)_4As^{\oplus}$] are very poorly solvated by water but are much better solvated by dipolar non-HBD solvents.

When solvent-transfer activity coefficients are applied to reaction rates in terms

Table 5-19. Some representative values of solvent-transfer activity coefficients for anions and cations at 25 °C with water (W) as reference solvent; molar concentration scale[a]. For the corresponding Gibbs energies of transfer, see Table 2-9 in Section 2.3.

Ions	$\lg {}^{W}y^{S}$ for solvent S[b]						
	$S = CH_3OH$	$HCONH_2$	CH_3CN	CH_3COCH_3	CH_3SOCH_3	$HCON(CH_3)_2$	$[(CH_3)_2N]_3PO$
$F^{\ominus}$	2.8	4.4	12.4	13.9	12.8	14.9	–
$Cl^{\ominus}$	2.3	2.4	7.4	10.0	7.0_5	8.5	10.2
$Br^{\ominus}$	1.9_5	1.9	5.5	7.4	4.8	6.3	8.0_5
$I^{\ominus}$	1.3	1.3	2.9	4.4	1.8	3.6	5.2_5
$N_3^{\ominus}$	1.6	1.9	6.5	7.5	4.5	6.3	8.6
$CN^{\ominus}$	1.5	2.3	6.1	8.4	6.1	7.0	–
$SCN^{\ominus}$	0.98	1.2	2.5	–	1.7	3.2	3.5
$ClO_4^{\ominus}$	1.1	−2.1	0.35	–	–	0.70	−1.2
$CH_3CO_2^{\ominus}$	2.8	3.5	10.7	–	–	11.6	–
$(C_6H_5)_4B^{\ominus}$	−4.2	−4.2	-5.7_5	−5.6	-6.5_5	-6.7_5	−6.8
$Li^{\oplus}$	0.77	-1.7_5	4.4	–	−2.6	-1.7_5	–
$Na^{\oplus}$	1.4	−1.4	2.6_5	–	-2.3_5	−1.7	–
$K^{\oplus}$	1.7	−0.75	1.4	0.70	−2.3	−1.8	−2.8
$Ag^{\oplus}$	1.1_5	−2.7	-4.0_5	1.6	−6.1	-3.6_5	−7.7
$(CH_3)_4N^{\oplus}$	1.0_5	–	0.53	0.53	−0.35	−0.93	–
$(C_6H_5)_4As^{\oplus}$	−4.2	−4.2	-5.7_5	−5.6	−6.6	-6.7_5	−6.8

[a] Values recalculated from Table 2.4 in Y. Marcus, Pure Appl. Chem. *55*, 977 (1983) [634]. Some values for F^- were taken from G. T. Hefter, Pure Appl. Chem. *63*, 1749 (1991). See also G. Hefter, Y. Marcus, and W. E. Waghorne, Chem. Rev. *102*, 2773 (2002).

[b] A positive value of $\lg {}^{W}y^{S}$ indicates that the ion is better solvated by water than by solvent S; a negative value means that the ion is more strongly solvated by transferring it to the solvent S. A difference in $\lg {}^{W}y^{S}$ of unity corresponds to a difference in Gibbs energy of solvation of $\lg 10 \cdot RT \cdot \lg {}^{W}y^{S}$, *i.e.* 5.7 kJ/mol at 25 °C.

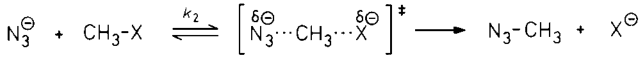
of the absolute rate theory, where reactions are considered to involve an equilibrium between the reactants and the activated complex, Eq. (5-115) is obtained for a bimolecular reaction such as $Y^{\ominus} + RX \rightleftharpoons [YRX^{\ominus}]^{\neq} \rightarrow YR + X^{\ominus}$ [6, 291, 292].

$$\lg(k^{S}/k^{O}) = \lg {}^{O}y^{S}_{Y^{\ominus}} + \lg {}^{O}y^{S}_{RX} - \lg {}^{O}y^{S}_{[YRX^{\ominus}]^{\neq}} \qquad (5\text{-}115)^{*)}$$

The specific rate constant for this bimolecular reaction in a solvent S is related to the rate constant in the reference solvent O through the appropriate solvent-transfer activity coefficients. Eq. (5-115) shows to what extent solvent effects on the reaction rate are due to changes in the solvation of reactant anions, $Y^{\ominus}$, of reactant nonelectrolytes, RX, and of anionic activated complexes, $[YRX^{\ominus}]^{\neq}$. Anionic and uncharged activated complexes will behave in exactly the same way upon solvent transfer as "real" anions and non-electrolytes of comparable structure. Anionic activated complexes such as $[YRX^{\ominus}]^{\neq}$ should behave like large polarizable anions, and, therefore, should be better solvated in polarizable, dipolar solvents than in protic solvents.

The rate constants k in the reference solvent O and in solvent S can be readily measured. Values of $\lg {}^{O}y^{S}$ for RX and $Y^{\ominus}$ are obtained as described above. Thus, by applying Eq. (5-115), $\lg {}^{O}y^{S}$ values for the activated complex can be calculated, providing information about the structure and charge distribution of activated complexes. Values of $\lg {}^{O}y^{S}_{[YRX^{\ominus}]^{\neq}}$ from Eq. (5-115) are compared with $\lg {}^{O}y^{S}$ values for relevant solutes, or for other well-established activated complexes, whose structure and charge distribution are such that they might act as models for the activated complex under consideration. The model with a $\lg {}^{O}y^{S}$ value close to $\lg {}^{O}y^{S}_{[YRX^{\ominus}]^{\neq}}$ may be used as a guide to the structure of $[YRX^{\ominus}]^{\neq}$. Parker and coworkers have estimated the $\lg {}^{O}y^{S}$ values of activated complexes for numerous variations of RX, $Y^{\ominus}$ and mechanisms (*e.g.* S_N2, S_NAr) for substitution reactions of various charge types [6, 291, 292]. Using the Gibbs energy of transfer approach*⁾, similar calculations of solvent effects on the Gibbs energy of reactants and activated complexes have been collected by Abraham [23], especially for Menschutkin reactions [64].

Examples of the use of this procedure are shown in Table 5-20. These data for the S_N2 reaction (5-116) are taken from Parker *et al.* [6, 291], whose extensive compilation compares relative rates and solvent-transfer coefficients on transfer from the reference solvent methanol to the isodielectric solvent *N,N*-dimethylformamide at 25 °C.

 (5-116)

$$N_3^{\ominus} + CH_3\text{-}X \underset{}{\overset{k_2}{\rightleftharpoons}} \left[\overset{\delta\ominus}{N_3}\cdots CH_3\cdots\overset{\delta\ominus}{X}\right]^{\ddagger} \longrightarrow N_3\text{-}CH_3 + X^{\ominus} \qquad (5\text{-}116)$$

On transfer from methanol to *N,N*-dimethylformamide, the increase in the rate of these four analogous S_N2 reactions varies from $10^{2.0}$ to $10^{4.6}$, the rate being faster in

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[*] An alternative way to analyze the solvent effect on this S_N2 reaction in terms of Gibbs energy of transfer, ΔG_t°, of reactants and activated complex from reference solvent O to another solvent S is given by the following equation [6, 23, 64, 292]:

$$\Delta G_t^{\neq} = \Delta G_t^{\circ}(Y^{\ominus}) + \Delta G_t^{\circ}(RX) - \Delta G_t^{\circ}([YRX^{\ominus}]^{\neq}).$$

For an attempt to correlate solvent transfer Gibbs energies of activation, ΔG_t°, of some S_N1 and S_N2 reactions with the donor and acceptor numbers of the solvent, see reference [292a].

Table 5-20. Relative reaction rates and solvent-transfer activity coefficients[a)] for reactants and activated complex of S_N2 reaction (5-116) upon solvent transfer from methanol (abbreviated to M) to *N*,*N*-dimethylformamide (DMF) at 25 °C [6, 291].

Leaving Group X	$\lg\left(\frac{k_2^{DMF}}{k_2^{M}}\right)$	$\lg\,{}^{M}y^{DMF}_{N_3^\ominus}$	$\lg\,{}^{M}y^{DMF}_{CH_3X}$	$\lg\,{}^{M}y^{DMF}_{[N_3CH_3X^\ominus]^{\neq}}$	$\lg\,{}^{M}y^{DMF}_{X^\ominus}$
$Cl^\ominus$	3.3	4.9	−0.4	1.2	6.5
$Br^\ominus$	3.9	4.9	−0.3	0.7	4.9
$I^\ominus$	4.6	4.9	−0.5	−0.2	2.6
$TsO^\ominus$	2.0	4.9	−0.6	2.3	3.5

[a)] The more positive the value of $\lg\,{}^{M}y^{DMF}$, the greater the solvation by methanol relative to *N*,*N*-dimethylformamide.

the dipolar non-HBD solvent. Whereas the medium has only a small effect on the CH_3X Gibbs energy (these molecules being slightly better solvated in *N*,*N*-dimethylformamide almost independently of X), the anion $N_3^\ominus$ is substantially destabilized on transfer from CH_3OH to $HCON(CH_3)_2$. The increase in rate, superimposed by a relative increase in solvation of the activated complex in *N*,*N*-dimethylformamide in the order $[N_3CH_3OTs^\ominus]^{\neq} < [N_3CH_3Cl^\ominus]^{\neq} < [N_3CH_3Br^\ominus]^{\neq} < [N_3CH_3I^\ominus]^{\neq}$, clearly reflects this destabilization. It is, however, modified by a small destabilization of the activated complex when $X = TsO^\ominus$, $Cl^\ominus$, and $Br^\ominus$, thus showing the anionic nature of the activated complex. For X = halide, this increase in stability correlates with the increasing polarizability of the activated complexes and corresponds to the increase in polarizability from $Cl^\ominus < Br^\ominus < I^\ominus$. Differences in solvation of activated complexes do not appear to contribute greatly to $\lg(k_2^{DMF}/k_2^{M})$ when halide ions are the leaving groups. However, the comparatively low rate increase obtained for methyl tosylate must be due to the more positive value of $\lg\,{}^{M}y^{DMF}_{[N_3CH_3OTs^\ominus]^{\neq}}$, because the tosylate ion itself has a less positive $\lg\,{}^{M}y^{DMF}$ value than does $Br^\ominus$ or $Cl^\ominus$, yet the activated complex containing tosylate has $\lg\,{}^{M}y^{DMF}_{\neq}$ more positive than the activated complexes containing halide. This effect has been explained by assuming that a looser activated complex with a greater localization of negative charge is present in the case of tosylate. Transition state anions with increased localization of negative charge on the leaving and incoming groups become increasingly more solvated, for the reasons already given. Departing tosylate is a better hydrogen-bond acceptor relative to free tosylate ion than is departing halide relative to free halide ion. Among other observations this leads to the generalization that, other things being equal, those $Y^\ominus + RX$ reactions possessing the "tightest" activated complex (*i.e.* most covalently bound Y and X) give the greatest accelerations on transfer from protic to dipolar non-HBD solvents. For a more detailed description of "tight and loose S_N2 activated complexes", see the reviews of Parker [6, 291].

Assuming that $\lg\,{}^{O}y^{S}_{RX} - \lg\,{}^{O}y^{S}_{[YRX^\ominus]^{\neq}}$ is roughly constant for closely related reactions, Parker obtained, from Eq. (5-115), the simple linear Gibbs energy relationship (5-117),

$$\lg(k^{S}/k^{O}) = \lg\,{}^{O}y^{S}_{Y^\ominus} + C \qquad (5\text{-}117)$$

This involves a limited number of constants C, varying only with the nature of the substrates [6, 291]. It is possible to use Eq. (5-117) to estimate the rate constant for a given reaction in a new solvent S from its value in another reference solvent O, to within a factor of two. This is very good in view of the fact that rates can vary by a factor of up to 10^{10} on switching solvents. Assuming the validity of Eq. (5-117), the easiest way of estimating $\lg {}^{\mathrm{O}}y^{\mathrm{S}}_{\mathrm{Y}^{\ominus}}$ is to measure a reaction rate for $\mathrm{Y}^{\ominus}$ in two different solvents. A test of Eq. (5-117) for the $\mathrm{S_N2}$ reaction between bromide ion and methyl tosylate in twelve solvents is given in reference [68].

Further examples of the dissection of initial state and transition state medium effects for reactions in protic and dipolar non-HBD solvents have been given by Buncel [467, 636], Abraham [23, 64, 637], Haberfield [638], and Blandamer *et al.* [639].

5.5.4 Acceleration of Base-Catalysed Reactions in Dipolar Aprotic Solvents

The specific solvation of anions in protic solvents, mediated mainly by hydrogen-bonding, diminishes not only their nucleophilic reactivity but also their basicity. All anions, therefore, are much stronger bases in dipolar non-HBD solvents than in protic solvents. This substantial increase in kinetic and thermodynamic basicity of anions in dipolar non-HBD solvents is very profitable in preparative organic chemistry in view of the activation of weakly acidic C—H, O—H, and N—H bonds. Especially useful for this purpose are solutions of potassium *tert*-butoxide in dimethyl sulfoxide, which is among the most basic media available for the organic chemist. The basicity of the *tert*-$C_4H_9O^{\ominus}/CH_3SOCH_3$ system is comparable to that of the $NH_2^{\ominus}$/liquid NH_3 system. Extremely basic solutions are also generated by the addition of dimethyl sulfoxide to aqueous or alcoholic solutions of alkali metal hydroxides or tetraalkylammonium hydroxides*⁾. Substitution of dimethyl sulfoxide for alcohols or water, not only replaces the proton donor physically, but deactivates the remaining protic solvent by virtue of its own great H-bond acceptor capability according to Eq. (5-118) [841].

$$RO^{\ominus}\cdots H{-}OR + (CH_3)_2\overset{\delta\oplus}{S}{=}\overset{\delta\ominus}{O} \rightleftharpoons RO^{\ominus} + (CH_3)_2\overset{\delta\oplus}{S}{=}\overset{\delta\ominus}{O}\cdots H{-}OR \qquad (5\text{-}118)$$

Many reactions become possible only in such superbasic solutions, while others can be carried out under much milder conditions. Only some examples of preparative interest (which depend on the ionization of a C—H or N—H bond) will be mentioned here. The subsequent reaction of the resulting carbanion may involve electrophilic substitution, isomerization, elimination, or condensation [321, 322]. Systematic studies of solvent effects on intrinsic rate constants of proton-transfer reactions between carbon acids and carboxylate ions as well as amines as bases in various dimethyl sulfoxide/water mixtures have been carried out by Bernasconi *et al.* [769].

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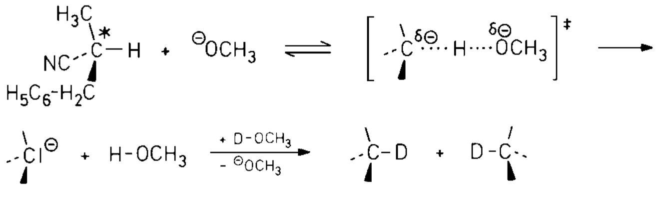
* The use of pure dimethyl sulfoxide with alkoxide ($CH_3O^{\ominus}$, *tert*-$C_4H_9O^{\ominus}$) or hydride ($H^{\ominus}$) ions leads to even more strongly basic systems which contain, in part, the very strongly basic dimethylsulfinyl ("dimsyl") anion, formed in the following equilibrium reaction:

$$RO^{\ominus} + CH_3{-}SO{-}CH_3 \rightleftharpoons RO{-}H + {}^{\ominus}|CH_2{-}SO{-}CH_3$$

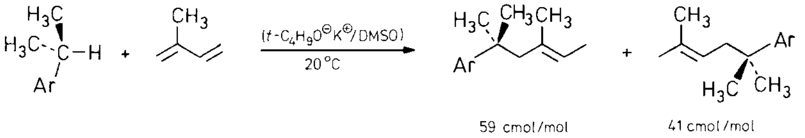
Rates of isotopic H/D exchange and racemization of optically active 2-methyl-3-propionitrile in the presence of potassium methoxide can be increased by a factor of $5 \cdot 10^7$ on going from pure methanol ($\varepsilon_r = 32.7$) to dimethyl sulfoxide ($\varepsilon_r = 46.5$) [31, 231, 304].


(5-119)

Solvent CH_3SOCH_3 in cg/g	CH_3OH/CH_3SOCH_3						
	0	25	50	76	90	98.5	100
k_2^{rel} (25 °C)	1	32	160	4900	$1.3 \cdot 10^5$	$5.0 \cdot 10^7$	ca. 10^9[a]

[a] extrapolated

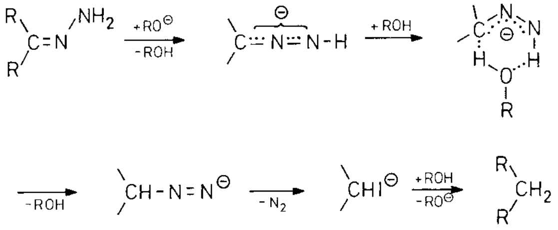
Much of the progress made in the area of base-catalysed alkene isomerization resulted from the use of dipolar aprotic solvents. Under homogeneous conditions, this brings about high reactions rates at low temperatures [309, 310, 323, 324]. For example, the base-catalysed rearrangement of allyl to propenyl ethers [325], and of allyl to propenyl amines [326] is best carried out using *tert*-C_4H_9OK/CH_3SOCH_3 as the reaction medium [323]. The alkenylation and aralkylation of a variety of alkylaromatic compounds in a homogeneous *tert*-C_4H_9OK/dipolar aprotic solvent system is greatly influenced by the solvent. In the case of the reaction between 4-isopropylpyridine (Ar = 4-pyridyl) and isoprene according to Eq. (5-120), the rate is faster in dimethyl sulfoxide ($t_{1/2} = 1.15$ min!) [324].



(5-120)

The Wittig reaction proceeds more rapidly in dimethyl sulfoxide than in other customary solvents due to the enhanced deprotonation of the phosphonium salts to alkylidenephosphoranes [327]. Even camphor, a rather unreactive ketone, undergoes the Wittig reaction easily in base/CH_3SOCH_3 systems [327].

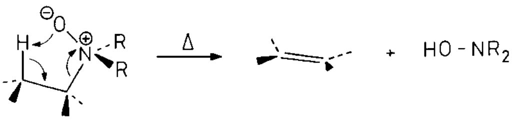
Similarly spectacular increases in rate were found for the transformation of ketone hydrazones into hydrocarbons using the Wolff–Kishner reduction. This is mainly due to the enhanced ionization of the N—H bond. This reaction occurs even at room temperature in *tert*-C_4H_9OK/CH_3SOCH_3 and proceeds by solvent-mediated transfer of a proton from nitrogen to carbon [328, 329].



(5-121)

Since the hydrazone anion is stable in the absence of a proton donor, the overall reaction must depend on the presence of an alcohol molecule in the vicinity of the hydrazone anion. This is in agreement with the observation that rate constants obtained in ROH/CH_3SOCH_3 mixtures, as a function of dimethyl sulfoxide concentration, exhibit a maximum at low alcohol concentration [330]. The rate-determining step of this reaction appears to be a concerted proton-transfer from the protic solvent to the hydrazone anion and a proton abstraction from the hydrazone anion by the basic solvent [329].

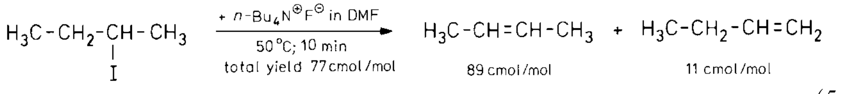
Since the Cope elimination reaction of amine oxides proceeds with intramolecular proton abstraction by the *N*-oxide group according to Eq. (5-122), it is not surprising that with dimethyl sulfoxide as solvent the reaction occurs at room temperature [328, 331]. Protic solvents require temperatures of 120 to 150 °C because hydrogen bonding of the oxygen terminal makes the reaction more difficult.



(5-122)

Further examples of strongly basic solvent systems are solutions of ionic fluorides in dipolar non-HBD solvents such as acetonitrile, *N*,*N*-dimethylformamide, dimethyl sulfoxide, and tetrahydrofuran. Tetraalkylammonium fluorides $R_4N^{\oplus}F^{\ominus}$ (R_4 = tetraethyl, tetra-*n*-butyl, benzyltrimethyl), which are soluble in dipolar non-HBD solvents, have received the most attention. Since they are highly hygroscopic, they are usually associated with varying amounts of protic solvents (mainly water). The amount of these protic solvents influences the effective basicity of the fluoride ion by hydrogen bonding ($RO{-}H\cdot\cdot F^{\ominus}$). In solutions of anhydrous tetramethylammonium fluoride in acetonitrile, dimethyl sulfoxide, trichloromethane, and dichloromethane, the fluoride ion is basic enough to abstract a proton from CH_3CN and CH_3SOCH_3, and nucleophilic enough to undergo halogen exchange with $CHCl_3$ and CH_2Cl_2 at room temperature [640].

Among the fluoride ion promoted reactions which occur in dipolar non-HBD solvents are alkylations of alcohols and ketones, esterifications, Michael additions, aldol and Knoevenagel condensations as well as eliminations; for a review, see reference [600]. In particular, ionic fluorides are useful in the dehydrohalogenation of haloalkanes and haloalkenes to give alkenes and alkynes (order of reactivity $R_4N^{\oplus}F^{\ominus} > K^{\oplus}$ ([18]crown-6) $F^{\ominus} > Cs^{\oplus}F^{\ominus} \approx K^{\oplus}F^{\ominus}$). For example, tetra-*n*-butylammonium fluoride in *N*,*N*-dimethylformamide is an effective base for the dehydrohalogenation of 2-bromo- and 2-iodobutane under mild conditions [641]; *cf.* Eq. (5-123).



$$H_3C\text{-}CH_2\text{-}\underset{\displaystyle I}{CH}\text{-}CH_3 \xrightarrow[\substack{50\,°C;\ 10\ \text{min} \\ \text{total yield } 77\ \text{cmol/mol}}]{+\ n\text{-}Bu_4N^{\oplus}F^{\ominus}\ \text{in DMF}} \underset{89\ \text{cmol/mol}}{H_3C\text{-}CH{=}CH\text{-}CH_3} + \underset{11\ \text{cmol/mol}}{H_3C\text{-}CH_2\text{-}CH{=}CH_2}$$

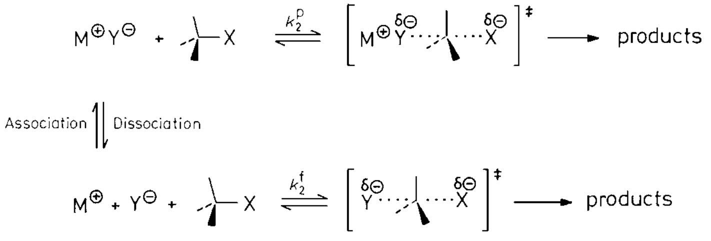
(5-123)

Wittig reactions of phosphonium fluorides in dipolar non-HBD solvents can be carried out without an additional base: *e.g.* 4-nitrobenzaldehyde reacts slowly with (4-nitrobenzyl)triphenylphosphonium fluoride in refluxing acetonitrile to give 4,4′-nitro-stilbene in good yield (84 cmol/mol) [642]. In this reaction, the fluoride ion attacks its own cation to give the corresponding Wittig ylide as intermediate.

Further examples of solvent effects on base-catalysed reactions can be found in references [297–300, 321, 322, 600].

5.5.5 Influence of Specific Cation Solvation on the Rates of S_N Reactions

The nucleophilic reactivity of an anion depends not only on the extent of its specific solvation, but also on the degree of association with the corresponding cation. An ion-pair associated anion (or cation) is much less reactive than a free, non-associated ion*). As early as 1912, Acree postulated that the reactivity of an anionic nucleophile should be depressed when its salt is incompletely dissociated [332]. Due to incomplete dissociation of the ionophore, the reaction rate constant will fall as its concentration increases. The simple model given in Eq. (5-124) is consistent with the observation that in all cases ion association deactivates the nucleophile [289].



(5-124a)

(5-124b)

Formation of the activated complex from an ion pair differs from formation from a free anion in that in reaction (5-124a) the activation process suffers from a loss in coulombic interaction energy between the centres of opposite charges. Therefore, in the presence of $M^{\oplus}$, the activation energy is increased. This model also suggests that the ratio k_2^f/k_2^p should increase with increasing intensity of cation–anion interaction [289]. Ion pairs are more stable the higher the charge densities of the component ions, and hence the stronger the electrostatic attraction. Accordingly, the nucleophilicity of anions in weakly dissociating solvents (*i.e.* solvents with low relative permittivities; *cf.* Sections 2.6 and 3.2) depends on the nature of the binary salt, and therefore on the cation. The relative reactivities of free and associated ions has been examined in detail, not only for

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* A covalent compound dissociates into free ions in stages involving the formation of at least two types of ion pairs, contact and solvent-separated ion pairs; *cf.* Section 2.6 and Eqs. (2-19) to (2-21) [289, 333].

nucleophilic aliphatic substitution [333–335], but also for electrophilic aliphatic substitution reactions. In the latter, carbanionic ion pairs or compounds are involved [321, 322, 336–339]. The reactivity of carbanions is affected in the same way by the degree of interaction between the carbanion and the counter ion. For a comprehensive review on all kinds of salt effects in organic and organometallic chemistry, see reference [829].

According to Coulomb's law [*cf.* Eq. (2-17) in Section 2.6], the interaction between cation and anion can be minimized by increasing either the relative permittivity of the medium or the interionic distance. There are several ways of separating anions from cations and thus increasing the anionic reactivity [643, 842]:

(i) enlarge the size of the opposite cation by substituting bulky 'onium cations such as quaternary tetraalkylammonium ions for the small alkali metal cations;

(ii) use EPD solvents of high Lewis basicity as reaction media or additives because they strongly solvate small alkali metal cations, thus increasing the interionic distance; they also weakly solvate anions;

(iii) encage cations by means of macro(poly)cyclic ligands such as crown ethers or cryptands. Cation complexation leads to ion-pair dissociation through formation of *ligand-separated ion pairs.*

Examples of each of these three types of anion activation*) are given.

An example of the S_N2 rate dependence on the nature of the counterion is given by the reaction of *n*-butyl 4-bromobenzene sulfonate with lithium- and tetra-*n*-butylammonium halides in the weakly dissociating solvent acetone ($\varepsilon_r = 20.6$) [279].

$$CH_3CH_2CH_2CH_2\text{-OBros} + X^\ominus \xrightarrow[25^\circ C]{k_2} CH_3CH_2CH_2CH_2\text{-X} + {}^\ominus\text{OBros} \qquad (5\text{-}125)$$

Anion $X^\ominus$		$I^\ominus$		$Br^\ominus$		$Cl^\ominus$
	$Li^\oplus$ salt[a]	6.2	>	5.7	>	1.0
k_2^{rel}		∨		∧		∧
	$(n\text{-}C_4H_9)_4N^\oplus$ salt[a]	3.7	<	18	<	68

[a] Salt concentration 0.04 mol/L

The nucleophilic reactivity of the lithium salts changes in the same order as in protic solvents ($I^\ominus > Br^\ominus > Cl^\ominus$; *cf.* Table 5-15). However, the order is completely reversed for the ammonium salts ($Cl^\ominus > Br^\ominus > I^\ominus$), and this latter order is the same as that found in dipolar non-HBD solvents such as *N,N*-dimethylformamide [278]. The small lithium cation, with its high charge density, has a strong tendency to form ion pairs with anions, whereas the electrostatic interaction between the large tetraalkylammonium ion and anions is comparatively weak. Quaternary ammonium salts, therefore, should be practically fully dissociated in acetone solution. Thus, the reactivity order obtained with these salts corresponds to that of the free, non-associated halide ions. On the other hand, the sequence obtained with the lithium salts also reflects the dissociation equilibria of these salts in acetone solution [279].

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* The term anion activation suggests that methods (i)…(iii) cause an increase in reaction rate. This does not hold for reactions in which the ion pair is more reactive than the free anion as a result of a cation-assisted reaction pathway. Methods (i)…(iii) exhibit cation *de*activation in conjunction with the anion activation!

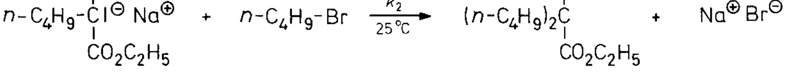
Similarly, the reactivity of phenolate ions as the tetra-*n*-butylammonium salt has been shown to be $3 \cdot 10^4$ times higher than that of the corresponding potassium salt in the S_N2 alkylation reaction with 1-halobutanes, carried out in 1,4-dioxane [340]. Whereas the rate of alkylation of the potassium salt increases by a factor of ca. 10^5 on going from 1,4-dioxane ($\varepsilon_r = 2.2$) to *N*,*N*-dimethylformamide ($\varepsilon_r = 36.7$), the alkylation rate of the quaternary phenolate is essentially insensitive to the same solvent change. Obviously, the phenolate ion combined with the larger ammonium ion is already very reactive because of the relatively weak cation–anion interaction in the ion pair. In such cases, dissociation to a truly free anion does not seem to be required in order to explain the high reactivity [340].

Examination of the S_N2 reaction between ethyl tosylate and halide ions in hexamethylphosphoric triamide ($\varepsilon_r = 29.3$) with a variety of counter ions [$Li^{\oplus}$, $(n\text{-}C_4H_9)_4N^{\oplus}$] has shown that the rates obtained with lithium salts are always higher than those with the corresponding tetra-*n*-butylammonium salts [341]. This is in contrast to the situation observed in acetone [279]. This means that, in this particular solvent, lithium salts are more dissociated than tetraalkylammonium salts. This has indeed been confirmed by conductivity measurements [341, 342]. The lithium cation apparently has specific interactions with strong EPD solvents such as $[(CH_3)_2N]_3PO$ (*cf.* Section 3.3.2).

Another effect, called the "cesium effect" [843, 844], is also connected with the observation that salts of anions with large counterions are highly dissociated in dipolar aprotic solvents, and consequently more anion-reactive. For example, the higher solubility of cesium carbonate in dipolar aprotic solvents and the fact that this salt is far more dissociated than the corresponding Li^+, Na^+, or K^+ salts, makes this carbonate a superior base in organic synthesis. Amongst the alkali metal cations, the ionic radius of Cs^+ ($r = 334$ pm) is more than twice that of Li^+ ($r = 152$ pm).

Ion-pair dissociation can be achieved not only by using large cations with correspondingly low charge densities, but also by employing EPD solvents as either reaction media or as additives to salt solutions in other solvents. EPD solvents of high Lewis basicity are particularly good specific cation solvators and weak anion solvators, thus giving rise to highly reactive anions. The cation-solvating capacity of EPD solvents can be quantitatively described in terms of their high donor numbers *DN* (*cf.* Table 2-3 in Section 2.2.6) as well as their large negative solvent-transfer activity coefficients for cations (*cf.* Table 5-19 in Section 5.5.3). Good cation-solvating EPD solvents include most of the common dipolar non-HBD solvents (*cf.* Table 5-18 in Section 5.5.2), as well as open-chain polyethers such as oligoethylene glycol dialkyl ethers ("glymes"), which contain the repeating unit $(\text{—}CH_2\text{—}CH_2\text{—}O\text{—})_n$ ($n \geq 2$) [345].

Alkali metal derivatives of CH-acidic compounds are usually highly aggregated in solvents of low relative permittivity such as benzene ($\varepsilon_r = 2.3$). The accelerating influences of a variety of EPD solvents used as additives in the alkylation of diethyl sodio-*n*-butylmalonate with 1-bromobutane in benzene according to Eq. (5-126) was discovered by Zaugg *et al.* [350]; *cf.* Table 5-21.



$$n\text{-}C_4H_9\text{-}\overset{CO_2C_2H_5}{\underset{CO_2C_2H_5}{C}}|^{\ominus}\;Na^{\oplus} + n\text{-}C_4H_9\text{-}Br \xrightarrow[25\,^{\circ}C]{k_2} (n\text{-}C_4H_9)_2\overset{CO_2C_2H_5}{\underset{CO_2C_2H_5}{C}} + Na^{\oplus}Br^{\ominus} \qquad (5\text{-}126)$$

Table 5-21. Relative rate constants of the alkylation of diethyl sodio-*n*-butylmalonate with 1-bromobutane in benzene at 25 °C with different additives [350].

Added Cation Solvator (0.648 mol/L)	$k_2^{\text{rel.}}$
No additive (benzene alone)	1
Tetrahydrofuran	1.1
CH_3COCH_3	1.3
C_2H_5OH	4.4
$CH_3O—CH_2CH_2—OCH_3$	6.4[a]
1,4-Dioxane	18
$HCON(CH_3)_2$	19
1-Methylpyrrolidin-2-one	30
$[(CH_3)_2N]_3PO$[b]	54

[a] In pure 1,2-dimethoxyethane (8.7 mol/L) the reaction is 80 times faster than in benzene.
[b] Only 0.324 mol/L added.

Table 5-21 shows that the addition of even small proportions of EPD solvents affects the reaction rate markedly. The rate acceleration thus obtained is produced by a specific solvation of sodium ion, which tends to dissociate the high-molecular mass ion-pair aggregate of the sodio-malonic ester that exists in benzene solution (degree of aggregation *n* is equal to 40...50 in benzene). This indicates that the kinetically active species is a lower aggregate of the free carbanion. Further evidence for a specific cation solvation is derived from the six-fold rate difference observed in tetrahydrofuran ($\varepsilon_r = 7.6$) and 1,2-dimethoxyethane ($\varepsilon_r = 7.2$), despite the fact that these two solvents possess nearly equal relative permittivities. The latter solvent is able to solvate sodium ions in the manner shown in Eq. (5-127). Especially noteworthy is the high reactivity exhibited on the addition of dicyclohexyl[18]crown-6. In benzene solution containing only 0.036 mol/L of this crown ether, the alkylation rate is already equal to that observed in neat 1,2-dimethoxyethane [351].

The reactivity of sodio-butyrophenone toward 1-bromo-2-methylpropane is greatly enhanced in monoglyme (2560-fold) and diglyme (11400-fold) with respect to the rate in diethyl ether according to Zook *et al.* [352]. The ethylation of sodio-butyrophenone (0.13 mol/L) by bromoethane (1.6 mol/L) in diglyme at 30 °C is 75% complete in 152 s, whereas the corresponding reaction time for a comparable ethylation in diethyl ether is 234 h [353]. Again, specific solvation of the cation in the sodium enolate aggregates may explain these results. The reactivity toward bromoethane increases in the order $Li^{\oplus} < Na^{\oplus} < K^{\oplus}$-enolate, corresponding to the decreasing charge density of the cations [353].

Finally, anion activation can also be achieved by the complexation of the cation using suitable macro(poly)cyclic ligand molecules [643]. Organic ligands that contain enforced cavities of dimensions at least equal to those of the smaller cations (and anions) have been called *cavitands* [644]. Cation complexation by such macro(poly)cyclic ligands leads to dissociation of the ion pairs as well as to salt solubilization. Complex formation with lipophilic organic ligands transforms small cations into voluminous lipophilic cationic species, which are much more soluble in organic solvents of low polarity*). Therefore, the increase in reaction rates induced by specific cation-complexing ligands usually results from an increase in the anion reactivity *as well as* an increase in the reagent concentration.

Some general examples of anion activation by different types of cation complexation are given in Eqs. (5-127)...(5-131). Among the specific multidentate complexing agents for cations are:

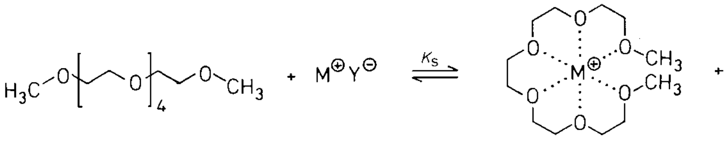
(a) open-chain *podands*, such as the oligoethylene glycol dialkyl ethers ("glymes"), investigated by Vögtle *et al.*; *cf.* Eq. (5-127) [345].

(b) cyclic *coronands*, such as the crown ethers, first introduced by Pedersen in 1967 [343]; *cf.* Eq. (5-128) [348, 645–647];

(c) macrobi-/tricyclic spherical *cryptands*, first introduced by Lehn *et al.* in 1969 [344, 648]; *cf.* Eqs. (5-129) and (5-130). Eq. (5-130) illustrates that in the case of the ammonium ion the hydrogen-bond acceptor ability of the macrotricyclic ligand can also be important [349, 648];

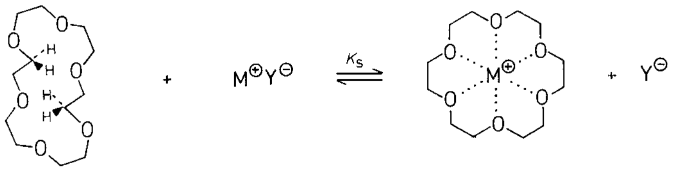
(d) cyclic *spherands*, first introduced by Cram *et al.* in 1979 [644, 649]; *cf.* Eq. (5-131).

Whereas the outside of these cationic complexes is lipophilic, the cations are held inside the hydrophilic cavity of the organic ligands. In the case of Eq. (5-127), the



(5-127)

Pentaglyme, an open-chain *podand*



(5-128)

[18]Crown-6, a cyclic *coronand*

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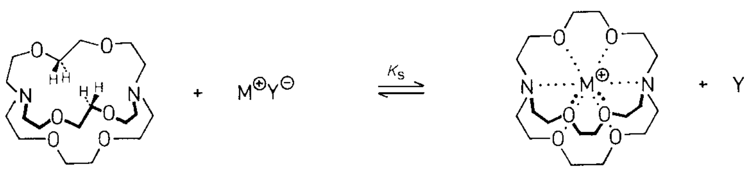
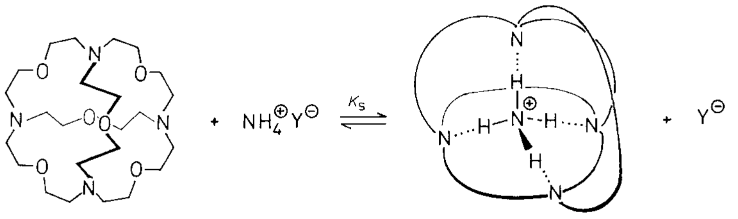
* Using water/organic solvent two-phase systems, the distribution of a salt in the organic layer is enhanced by lipophilic cation-complexing ligands. This is the basis of *liquid-liquid phase-transfer catalysis*. Phase-transfer catalysts help to transfer a water-soluble reactant salt across the interface into the organic phase where a homogeneous reaction can occur, thus enhancing the rate of reaction. For further explanations of phase-transfer catalyzed reactions, see Section 5.5.13, particularly Fig. 5-18, and reviews [656–658, 879–883].



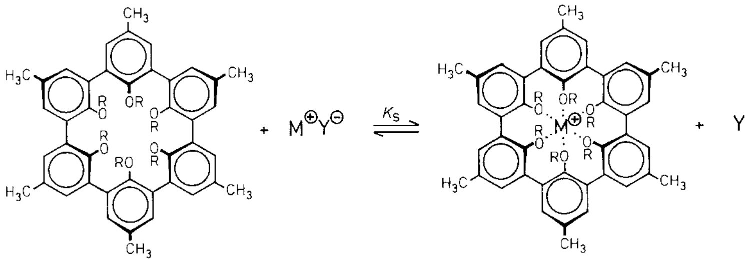
(5-129)

[2.2.2]Cryptand, a bicyclic spherical *cryptand*



(5-130)

A tricyclic spherical *cryptand*



(5-131)

A cyclic *spherand*

podands cavity is built up during complexation by a template effect. The stability constants K_S increase from Eq. (5-127) to Eq. (5-131). Typical orders of magnitudes for K_S values in methanol are $10^2 \ldots 10^4$ for podates, $10^4 \ldots 10^5$ for coronates, and $10^6 \ldots 10^8$ for cryptates*). The appropriate choice of ligand allows a selective complexation of a particular cation. For economic reasons, the simple and cheap open-chain glymes have found greater application in anion activation. Only a few representative examples of enhanced anion reactivity caused by cavitands will be mentioned here.

The effect of both podands and coronands on the S_N2 alkylation of potassium phenolate with 1-bromobutane in 1,4-dioxane ($\varepsilon_r = 2.2$) has been investigated by Ugel-

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* It should be mentioned that cation complexation by crown-type ligands can itself be solvent-dependent. For example, the dissociation rate of potassium [2.2.2]cryptate in EPD solvents increases with the donor number of the solvent [650]. Moreover, coronands themselves can interact with organic solvent molecules [651]. Such cation-solvent and ligand-solvent interactions can influence the formation of cation-ligand complexes.

stad *et al.* [354]. The addition of tetraethylene glycol dimethyl ether in concentrations equivalent to the phenolate concentration leads to an alkylation rate 11 times faster than that in pure 1,4-dioxane, whereas the same amount of dicyclohexyl[18]crown-6 causes an 8700-fold rate increase.

The base-catalysed hydrolysis of the sterically hindered ester methyl 2,4,6-trimethylbenzoate can be carried out in KOH/DMSO at room temperature in 100% yield using a [2.2.2]cryptand as the potassium-complexing ligand [652].

Liotta *et al.* [282, 355, 356, 359] investigated the chemistry of so-called "naked anions"*), *i.e.* poorly solvated fluoride, cyanide, and acetate ions, solubilized as potassium salts in acetonitrile or benzene containing [18]crown-6 as an additive. The reactivity of these naked anions in reactions with haloalkanes has been examined. According to the haloalkane structure, the reaction leads to substitution and/or elimination products. Solubilised fluoride ions are both potent nucleophiles and strong bases, whereas solubilised cyanide and acetate ions are good nucleophiles but rather weak bases. A variety of fluoroalkanes [282, 355] and nitriles [356, 361] can be prepared in good yields using crown ethers as cation solvators. The carboxylate ion is generally considered a bad nucleophile, but [18]crown-6 complexed potassium acetate (also called "bare acetate") reacts readily with haloalkanes in acetonitrile to yield the corresponding esters [359, 360]. The nitrite ion also displays a remarkable enhanced nucleophilicity in the presence of [18]crown-6. Under these conditions, nitro compounds are formed from haloalkanes in good yields [361].

Other anions ($X^\ominus = Br^\ominus, I^\ominus, HO^\ominus, CH_3O^\ominus$) also exhibit enhanced nucleophilic reactivity in crown-ether mediated reactions of $K^\oplus X^\ominus$ [357, 358]. Montanari *et al.* [653] compared the effects of phosphonium salts, coronands, and cryptands on the S_N2 reaction of *n*-octylmethanesulfonate with various nucleophiles in chlorobenzene.

Apart from these examples of nucleophilic substitution reactions, there are many more applications of reactions which are enhanced by the addition of macro(poly)cyclic ligands; examples can be found in some excellent reviews [346–348, 362, 643, 645–648].

Cation-assisted reactions, on the other hand, are hindered by complexation of the cation [648]. Reduction of carbonyl groups by metal hydrides [654] and the addition of organolithium compounds [655] are examples. This indicates that the coordination between carbonyl group and cation is an important step in these reactions. For applications of concentrated $LiClO_4/Et_2O$ (LPDE) solutions in cation-catalysed reactions, see Section 5.3.3 and references [803–806].

In this context, it should be mentioned that free cations in suitable solvents can be used as templates for the synthesis of macro(poly)cyclic compounds (*e.g.* catenanes). Such template-based syntheses are mediated by slightly solvated metal cations, which assemble the reaction partners as ligands, allowing them to easily react with each other; the desired product is obtained after removal of the template; for a review, see reference [845].

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* Completely unsolvated "naked anions" cannot be prepared in solution with coronands or even with cryptands as cation solvators. Even in this case ion-pairing still occurs leading to complexed ion pairs [646]. Totally unsolvated "naked anions" can exist only in the gas phase (*cf.* Section 5.2.).

5.5.6 Solvent Influence on the Reactivity of Ambident Anions

Ambident anions are mesomeric, nucleophilic anions which have at least two reactive centers with a substantial fraction of the negative charge distributed over these centers*)**). Such ambident anions are capable of forming two types of products in nucleophilic substitution reactions with electrophilic reactants***). Examples of this kind of anion are the enolates of 1,3-dicarbonyl compounds, phenolate, cyanide, thiocyanide, and nitrite ions, the anions of nitro compounds, oximes, amides, the anions of heterocyclic aromatic compounds (*e.g.* pyrrole, hydroxypyridines, hydroxypyrimidines) and others; *cf.* Fig. 5-17.

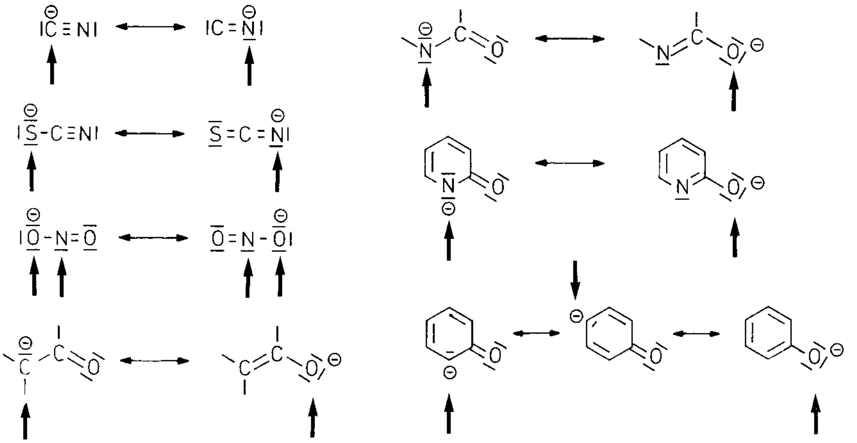

Fig. 5-17. Some ambident or ambifunctional anions. The arrows indicate the sites of dual reactivity towards electrophiles.

If the substitution reaction is kinetically controlled, then the composition of the products is determined by the relative nucleophilicity of each of the donor atoms in the ambident anion in relation to the given electrophilic reactant. Among the factors influencing the mode of reaction (counterion, additives, concentration, temperature, pressure, leaving group, structure of the alkylating agent), the solvent plays a major role in the orientation of the electrophile, and this has been examined in several reviews [364–367, 367a, 367b]. As early as 1923, Claisen noticed that the O/C alkylation ratio observed in the reaction of phenol with 3-bromopropene in the presence of potassium carbonate depends strongly on the solvent used as reaction medium [369]. In acetone, the major product formed was allyl phenyl ether, whereas in solvents such as benzene or toluene, *ortho*-allyl phenol was obtained as the main product [369].

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* The term *ambident anion* was proposed by Kornblum [363], whereas Gompper suggested that such anions should be called *ambifunctional* [364, 367].

** In principle, *ambident cations* may be defined in the same way, but the solvent dependence of their dual reactivity with nucleophiles has not yet been investigated thoroughly [368].

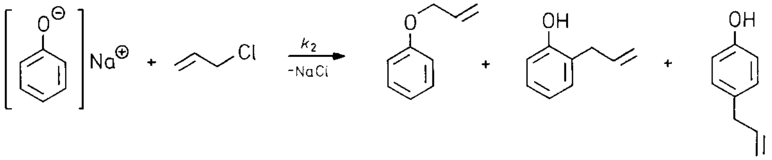
*** When a reaction can potentially give rise to two (or more) constitutional isomers but actually produces only one, the reaction is said to be *regioselective.* For example, the ambident nucleophile $NCO^{\ominus}$ usually gives only isocyanates R—NCO and not the isomeric cyanates, R—OCN.

Table 5-22. Oxygen versus carbon alkylation in the reaction of two sodium arenolates with haloalkanes at room temperature [370, 371].

Solvents	% *O*-Alkylation	% *C*-Alkylation[a]
a) *Reaction of sodium phenolate with 3-chloropropene according to equation* (5-132)		
1,4-dioxane	100	0
$(CH_3)_3COH$	100	0
C_2H_5OH	100	0
CH_3OH	100	0
$HCON(CH_3)_2$	100	0
$(CH_2)_4O$	96	0
H_2O	49	41
CF_3CH_2OH[b]	37	42
C_6H_5OH[c]	22	78
b) *Reaction of sodium β-naphtholate with (bromomethyl)benzene*		
$HCON(CH_3)_2$	97	0
CH_3SOCH_3	95	0
$CH_3O—CH_2CH_2—OCH_3$	70	22
$(CH_2)_4O$	60	36
CH_3OH	57	34
C_2H_5OH	52	28
H_2O	10	84
CF_3CH_2OH	7	85

[a] Dialkylated products included.
[b] Reaction with 3-bromopropene.
[c] At 43 °C.

Some representative data, taken from the extensive work of Kornblum *et al.* concerning the alkylation of phenolates [*cf.* Eq. (5-132)] and *β*-naphtholates, are collected in Table 5-22 [370, 371].



(5-132)

In protic solvents, the solvent effect on orientation has been interpreted in terms of preferential deactivation of the more electronegative atom by specific solvation through H-bonding*). As shown in Table 5-22, carbon alkylation competes more sig-

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* Kornblum termed this shielding of the center with maximal electron density in ambident anions by protic solvents, which prevents the reaction at this center, "selective solvation" [370]. In order to avoid confusion with selective solvation of ions or dipolar molecules in binary solvent mixtures (*cf.* Section 2.4), the designation "specific solvation" is preferred. An IR and NMR spectroscopic study of the specific solvation of OCN^-, SCN^-, and $SeCN^-$ ions has shown that, in neat protic solvents (*e.g.* MeOH, $HCONH_2$), these anions form intimate hydrogen bonds, albeit to different extents. In methanol solution, a significant proportion of the cyanate ion is hydrogen-bonded at the oxygen end, while the other two anions are much less solvated than OCN^-, forming hydrogen bonds to the nitrogen end and non-axially to the C=N *π*-bond to only a limited extent [846].

nificantly with oxygen alkylation as the protic solvents become stronger proton donors (*cf.* $CH_3CH_2OH \rightarrow H_2O \rightarrow CF_3CH_2OH \rightarrow C_6H_5OH$). In 2,2,2-trifluoroethanol, a very strong proton donor, the yield of *C*-alkylated isomers approaches 42% and 85%, respectively. Owing to H-bonding, protic solvents selectively and effectively solvate the center with the maximum electron density. As a result of this, the accessibility of this center is reduced and substitution at the other donor atom (in this case a carbon atom) may successfully compete with that at the oxygen atom. This protic solvent effect is also observed for other ambident anions. For example, in the alkylation of the enolate salt of acetoacetic ester, the yield of the *O*-alkylated isomer falls sharply on going from dipolar non-HBD solvents to protic solvents such as alcohols [372]. Even relatively small amounts of added protic solvents influence the mode of reaction. Thus, in the alkylation of the enolate salt of acetoacetic ester with ethyl tosylate in hexamethylphosphoric triamide, the addition of equimolar amounts of protic solvents such as water or *tert*-butanol significantly decreases the degree of *O*-alkylation [373]. High pressure promotes specific solvation of the more electronegative site in protic solvents, and increased alkylation occurs at the alternative position [378].

The tendency towards reaction at the center with the maximum electron density increases when dipolar non-HBD solvents are employed owing to the lack of specific solvation (*cf.* solvents $HCON(CH_3)_2$ and CH_3SOCH_3 in Table 5-22). Thus, in the alkylation of the enolate ions of 1,3-dicarbonyl compounds, the greatest yields of the *O*-alkylated isomers are obtained in hexamethylphosphoric triamide, followed by dipolar non-HBD solvents of the amide type [372–375].

In poorly cation-solvating solvents, there is also a marked dependence of reaction site on association with the corresponding cation. In non-dissociating solvents, it is likely that the cation will be preferentially coordinated to the atom in the ambident anion with the maximal electron density and this hinders reaction at this site. As shown in Table 5-22, by the results observed for the alkylation of sodium β-naphtholate, screening of the electronegative oxygen atom due to association with the accompanying sodium cation leads to an increase of *C*- *versus* *O*-alkylation in aprotic, non-dissociating solvents such as 1,2-dimethoxyethane ($\varepsilon_r = 7.2$) and tetrahydrofuran ($\varepsilon_r = 7.6$), compared with dipolar non-HBD EPD solvents. Alkylation of the less electronegative site can also be favoured by the addition of excess $M^{\oplus}$ to suppress dissociation of ambident ion pairs. The lithium enolates of 1,3-dicarbonyl compounds are an exception. They display a pronounced tendency towards *O*-alkylation (especially when compared to sodium enolates), which is not very sensitive to changes in the solvent (*e.g.* THF → DMF) [659]. It has been suggested that the tendency of lithium enolates towards *O*-alkylation is partly the result of an $Li^{\oplus}$ leaving group interaction and partly an intrinsic property of the enolate lithium ion pair [659].

The ion-pair dissociation of ambident alkali enolates, which results in increasing *O*/*C* alkylation ratios, can be promoted not only by dissociating solvents but also by specific cation solvation. In the latter case, EPD solvents (*cf.* DMF and DMSO in Table 5-22b) or macro(poly)cyclic ligands such as coronands ("crown ethers") or cryptands are used [376, 377, 660]. For example, the alkylation of sodium β-naphtholate with (bromomethyl)benzene or iodomethane in the presence of benzo[18]crown-6 gives high *O*/*C* alkylation ratios when tetrahydrofuran or benzene are the solvents [660]. In dissociating solvents such as *N*,*N*-dimethylformamide or acetonitrile, however, so far no influence of added crown ether on the *O/C* product ratio has been observed [660]. The influence of ion-pairing on the alkylation of preformed alkali metal 2,4-pentanedionates in dimethyl sulfoxide solution has been systematically studied [661]. High pressure results in a shift from paired to free ambident anions and increased *O*-alkylation in non-HBD solvents [378]. The molar *O/C* methylation ratio for the reaction of lithium, sodium, and potassium acetophenone enolates with dimethyl sulfate has been studied in fourteen aprotic solvents and correlated with solvent polarity and Lewis basicity, as well as with the ionic radii of the alkali metal cations [847].

To summarize, it can be stated that the freer the ambident anion in every respect, the larger the *O/C*-alkylation ratio in the case of 1,3-dicarbonyl compounds [365]. Thus, if *O*-alkylation products are desired in the alkylation of enolates, dipolar non-HBD and dissociating solvents such as *N,N*-dimethylformamide, dimethyl sulfoxide, or, especially, hexamethylphosphoric triamide should be used. If *C*-alkylation is desired, protic solvents like water, fluorinated alcohols, or, in the case of phenols, the parent phenol will be the best choice [365].

Taking into account the fact that the solvation of ambident anions in the activated complex may differ considerably from that of the free anion, another explanation for the solvent effect on orientation, based on the concept of hard and soft acids and bases (HSAB) [275] (see also Section 3.3.2), seems preferable [366]. In ambident anions, the less electronegative and more polarizable donor atom is usually the softer base, whereas the more electronegative atom is a hard Lewis base. Thus, in enolate ions, the oxygen atom is hard and the carbon atom is soft, in the thiocyanate ion the nitrogen atom is hard and the sulfur atom is soft, *etc.* The mode of reaction can be predicted from the hardness or softness of the electrophile. In protic solvents, the two nucleophilic sites in the ambident anion must interact with two electrophiles, the protic solvent and the substrate RX, of which the protic solvent is a hard[*)] and RX a soft acid. Therefore, in protic solvents it is to be expected that the softer of the two nucleophilic atoms (C *versus* O, N *versus* O, S *versus* N) should react with the softer acid RX.

In non-HBD, non-dissociating solvents, a corresponding proposal can be made: hard counterions (alkali metal cations) should associate preferably with the hard site, and the substrate RX with the soft site in the activated complex composed of RX and the ambident ion pair [366]. With increasing hardness of the counterion (increasing charge density), the fraction of *C*-alkylation should increase in non-HBD solvents and decrease on solvent insertion into the ion pair. Indeed, the *C*-ethylation of $M^{\oplus}$ (ethyl acetoacetate)$^{\ominus}$ in dimethyl sulfoxide or hexamethylphosphoric triamide increases in the order $M^{\oplus} = R_4N^{\oplus} < Cs^{\oplus} < K^{\oplus} < Na^{\oplus} < Li^{\oplus}$ [373].

In the gas phase, the reaction of ethyl cations, $C_2H_5^{\oplus}$, with the ambident 2,4-pentanedione (which is 92% enolized at 25 °C in the gas phase) leads predominantly (>95%) to alkylation at the hard oxygen site and not at the soft carbon atom, as predicted by the HSAB concept [662]. Accordingly, the gas-phase alkylation of the enolate ion of cyclohexanone gives only the *O*- and no *C*-alkylation product [848], and the gas-phase acylation of acetophenone enolate with trifluoroacetylchloride leads predominantly to the *O*-acylation product (*O/C* ratio = 6.0) [849].

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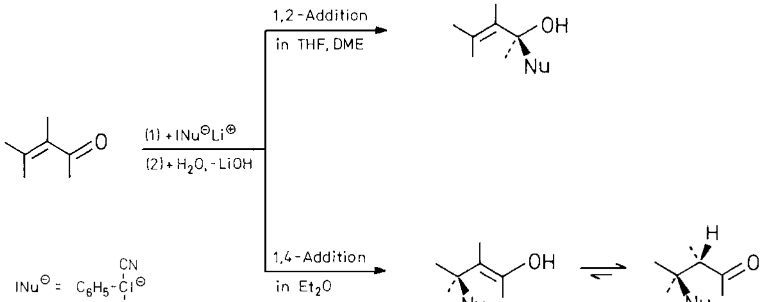
[*] Hydrogen atoms behave as hard Lewis acids in the formation of a hydrogen bond.

A theoretical explanation of the HSAB concept using quantum-chemical perturbation theory was given by Klopman [379]. He showed that the softness of a particular Lewis acid (acceptor atom) is determined by the energy of the lowest unoccupied molecular orbital and the softness of a Lewis base (donor atom) by the energy of the highest occupied molecular orbital, taking into account that the softness or hardness is influenced by the solvent. Limitations of the application of the HSAB concept to the reactivity of ambident anions have been discussed by Gompper *et al.* [367]. An alternative quantitative approach for the prediction of the dual reactivity of ambifunctional anions towards electrophiles has been proposed ("principle of allopolarization"), using so-called selectivity factors $S_f = Q_X/Q_Y$ (Q_X and Q_Y are the yields observed in reactions of ambident anions with two reaction sites X and Y) and polarity indices $P = l_X/l_Y$ (l_X and l_Y are the charge densities at reaction sites X and Y, taken from HMO calculations) as the defining parameters.

In analogy with ambident anions, mesomeric *ambident cations* do exist, but the solvent influence on their dual reactivity with nucleophiles has not been thoroughly investigated; see reference [368] for a review.

A nice example of the solvent-dependent dual reactivity of an electrophilic cryptocationic species has been given by Hünig *et al.* [663]. Ambident electrophilic α-enones react with nucleophiles such as the anion of the benzaldehyde O-(trimethylsilyl)-cyanohydrin ($Nu|^{\ominus}$) in diethyl ether exclusively by 1,4-addition. In tetrahydrofuran (THF) or 1,2-dimethoxyethane (DME), the 1,2-adduct is formed predominantly; on the addition of HMPT or [12]crown-4 it is formed exclusively; *cf.* Eq. (5-133).



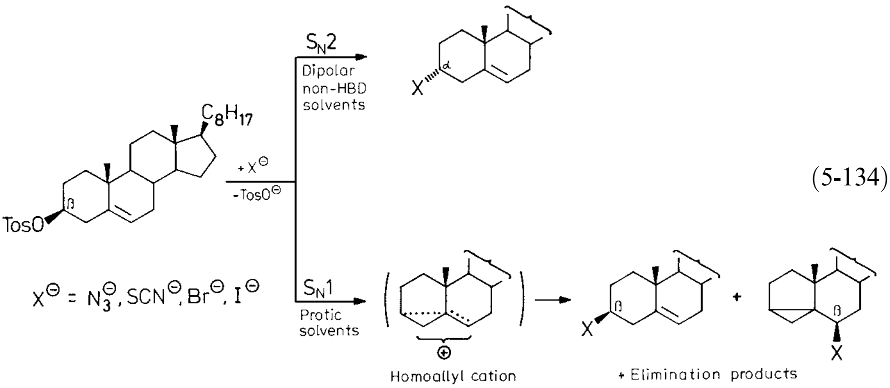
(5-133)

This dramatic solvent effect is a result of the difference in the extent of ion-pairing of $Li^{\oplus}Nu^{\ominus}$ in diethyl ether (→ contact ion pair) and THF or DME (→ solvent-separated ion pair), modified by the α-enone-$Li^{\oplus}$ complex [663].

5.5.7 Solvent Effects on Mechanisms and Stereochemistry of Organic Reactions

Elaborating on the preceding dicussion on the dual reactivity of ambident anions, this Section contains a selection of reactions of various types which have in common the fact that a change in solvent drastically changes the mechanism as well as the stereochemistry usually associated therewith. The examples are intended to demonstrate how, out of two or more alternatives, a single pathway for a reaction can be favoured through a proper choice of solvent. This, of course, is of considerable preparative interest. In this connection, it should be emphasized that alternative routes of a reaction may be separated by very small differences in Gibbs activation energy. It requires less than 12 kJ/mol (3 kcal/mol) of activation energy to change a 10:90 ratio to a 90:10 product mixture, and the sensitivity of this ratio can frequently be exploited by a proper choice of the reaction medium.

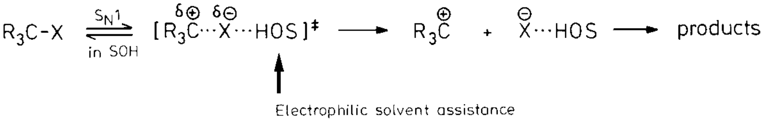
The stereochemical outcome of a nucleophilic substitution reaction at a saturated carbon is a function of the reaction mechanism (S_N1, S_N2, or S_Ni), which, in turn, can depend on the nature of the solvent, as already mentioned (*cf.* Sections 5.3.1 and 5.5.1). The fact that, in contrast to dipolar non-HBD solvents, the protic solvents diminish the nucleophilicity of anions and simultaneously favour the ionization of polarized bonds, makes it possible to displace a given reaction toward either the S_N1 or S_N2 type. A remarkable example is found in reaction (5-134) [380]. The nucleophilic substitution of cholesteryl tosylate in dipolar non-HBD solvents (*e.g.* $HCON(CH_3)_2$, CH_3SOCH_3) gives preferably the 3α-derivative with inversion of configuration. In contrast, in protic solvents (*e.g.* CH_3OH, $HCONHCH_3$), a mixture of the 3β- and 3,5-cyclo-6β derivatives is formed, corresponding to an S_N1 mechanism with initial formation of a homoallyl carbenium ion. However, a change from a protic to a dipolar non-HBD solvent never results in complete suppression of the S_N1 reaction [380].



(5-134)

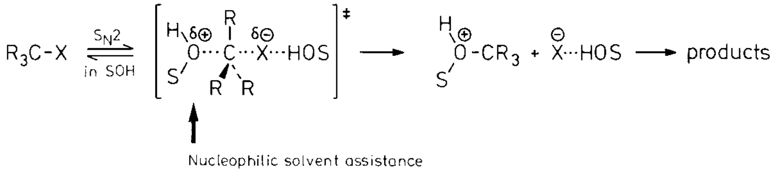
An "S_N2 (intermediate)" mechanism has been proposed as a result of the consideration of the dependence of S_N1/S_N2 solvolysis rates on electrophilic (EPA) and nucleophilic (EPD) solvent assistance [664, 665].

S_N1 reactions of secondary and tertiary substrates $R_3C—X$ (*e.g.* 2-adamantyl tosylate [665], *t*-butyl heptafluorobutyrate [666]) proceed via activated complexes with high carbenium ion character to give ion-pair intermediates. They exhibit electrophilic solvent assistance in protic solvents SOH (H-bonding to the leaving group), but they are practically insensitive to changes in solvent nucleophilicity; *cf.* Eq. (5-135).



$$R_3C\text{-}X \underset{\text{in SOH}}{\overset{S_N1}{\rightleftharpoons}} [R_3\overset{\delta\oplus}{C}\cdots\overset{\delta\ominus}{X}\cdots HOS]^{\ddagger} \longrightarrow \underset{\uparrow \text{ Electrophilic solvent assistance}}{R_3\overset{\oplus}{C} + \overset{\ominus}{X}\cdots HOS} \longrightarrow \text{products} \qquad (5\text{-}135)$$

S_N2 reactions of primary and secondary substrates $R_3C{-}X$ are accelerated relative to S_N1 reactions by additional rearside nucleophilic attack on the substrate, which reduces the carbenium ion character in the activated complex. S_N2 reactions involving a concerted mechanism are also called "S_N2 (one-stage)" reactions [665]. They span a huge spectrum of nucleophilic solvent assistance – varying from classical S_N2 processes involving strong nucleophilic solvent assistance (*e.g.* methyl tosylate) to weakly nucleophilic solvent-assisted processes with relatively high carbenium ion character in the activated complex (*e.g.* 2-propyl tosylate). This variability of S_N2 solvolysis reactions can be regarded as a solvent-dependent spectrum of intermediate mechanisms rather than a varying mixture of only two distinct processes S_N1 and S_N2. To account for this gradation in mechanism, an "S_N2 (intermediate)" mechanism has been proposed [664, 665]. This mechanism involves a pentacoordinated intermediate, which is a nucleophilically solvated ion pair similar to the activated complex in the S_N2 (one-stage) reaction. The solvent/carbocation interaction is covalent in character; *cf.* Eq. (5-136).



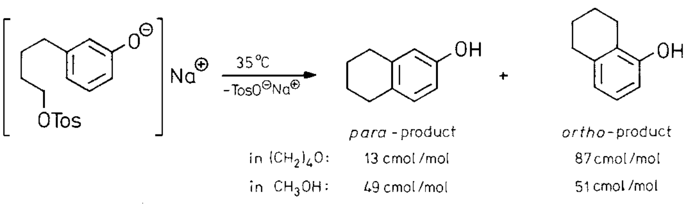
(5-136)

The heterolysis of the bond between carbon and the leaving group in $R_3C{-}X$ is supported by nucleophilic solvent assistance, the extent of which depends on the solvent and increases in the order $(CF_3)_2CHOH < CF_3CO_2H < CF_3CH_2OH < HCO_2H < H_2O < CH_3CO_2H < CH_3OH < CH_3CH_2OH$ [665]. If there is evidence for an intermediate as well as for nucleophilic solvent assistance, then the mechanism can be considered "S_N2 (intermediate)". Examples showing a gradual change of mechanism from S_N2 (one-stage) through S_N2 (intermediate) to S_N1 have been given [665].

The "S_N2 (intermediate)" mechanism has not been without criticism; see, for example, [667, 668, 784] and references cited therein. An alternative mechanism can be formulated, involving ion pairs formed by heterolysis of the $R_3C{-}X$ bond *before* rate-limiting nucleophilic solvent attack occurs. Internal return to the educt would then occur more rapidly than attack by the nucleophile to give the products. For example, the solvolyses of secondary 1-arylethyl tosylates, $ArCH(OTs)CH_3$, can be also explained in terms of an ion-pair mechanism in which nucleophilic solvent attack on the ion pair plays a major role [667]. In less nucleophilic solvents, this attack is rate-limiting, whereas attack of more nucleophilic solvents is fast, resulting in a rate-limiting initial ionization of $R_3C{-}X$. The ion pair generally interacts with the solvent, although not by a specific interaction (*i.e.* covalent bonding with a single nucleophilic solvent molecule) as in the "S_N2 (intermediate)" mechanism [667].

It is difficult to objectively prove or disprove either the S_N2 (intermediate) or the ion-pair mechanism of S_N2 solvolysis reactions. According to Olah *et al.* [669], "the S_N2 intermediate can indeed be best characterized as a trivalent carbocationic centre solvated from both sides by the negatively charged nucleophile and the leaving group". According to Tidwell *et al.* [667], "this view deemphasizes the covalent character of the solvent-carbocation interaction, and is operationally equivalent to an ion pair". A recent cluster model study of contact ion-pair formation of Me_3C–Cl in aqueous solution has shown that its S_N1 hydrolysis presumably proceeds by an S_N2 (intermediate) mechanism, involving an electrophilically *and* nucleophilically solvated activated complex, subsequent formation of the electrophilically *and* nucleophilically solvated contact ion pair, and eventual formation of the products [850]; *cf.* Eq. (5-136).

The *ortho*/*para* alkylation ratio of the intramolecular nucleophilic substitution reaction of sodio-4-(3-hydroxyphenyl)butyl tosylate, according to Eq. (5-137), was shown to be solvent-dependent [381]. In general, an increase in the *ortho*/*para* alkylation ratio resulted when the polarity of the solvent was decreased. The orientation of the reaction was explained in terms of the nature of the association between the metal and phenolate ions in different solvents [381].



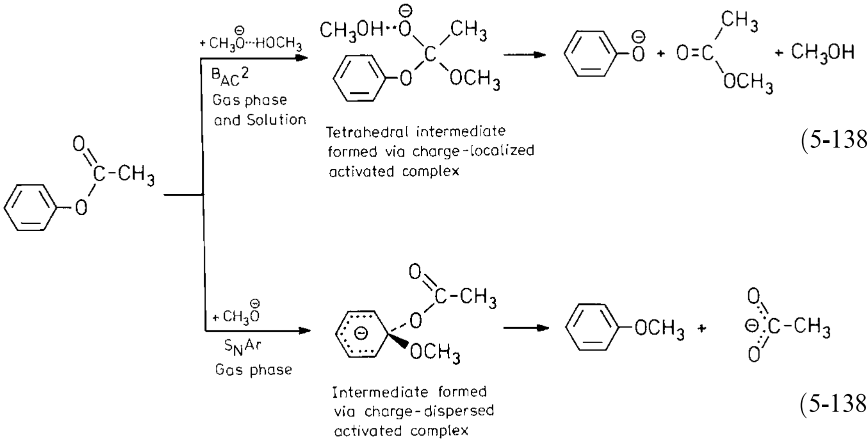
(5-137)

The α/γ alkylation ratio of the intramolecular nucleophilic substitution reaction of an α,β-unsaturated cyclohexenone tosylate can also be controlled by the right choice of solvent. The desired γ-alkylation – the final step of the total synthesis of the sesquiterpene β-vetivone – is favoured by NaOH in CH_3SOCH_3/H_2O, in contrast to $(CH_3)_3COK/(CH_3)_3COH$, which promotes α-alkylation [670].

That a single solvent molecule clustered to a nucleophile can drastically change the reaction pathway has been demonstrated by studying the reaction of phenyl acetate with methoxide ion in the gas phase [671, 672]. Alkaline hydrolysis of esters in solution is known to proceed by attack of the nucleophile at the carbonyl carbon atom to form a tetrahedral intermediate, followed by cleavage of the acyl–oxygen bond ($B_{AC}2$ mechanism); *cf.* Eq. (5-138a).

In the gas phase, however, nucleophilic aromatic substitution according to Eq. (5-138b) is the preferred pathway! Partially solvated nucleophiles such as $CH_3O^{\ominus}\ldots HOCH_3$, formed in the gas phase, again react with phenyl acetate by the $B_{AC}2$ mechanism. In the gas phase, charge-dispersed activated complexes such as those formed in the S_NAr reaction obviously have lower activation barriers than charge-localized activated complexes leading to the tetrahedral intermediate of the $B_{AC}2$ mechanism. The latter can only be stabilized by dispersing the localized negative charge over the carbonyl oxygen atom by means of H-bonding with protic solvent molecules. The attachment of even one HBD solvent molecule to the nucleophile is enough to change the reaction mechanism from S_NAr to $B_{AC}2$ [671].

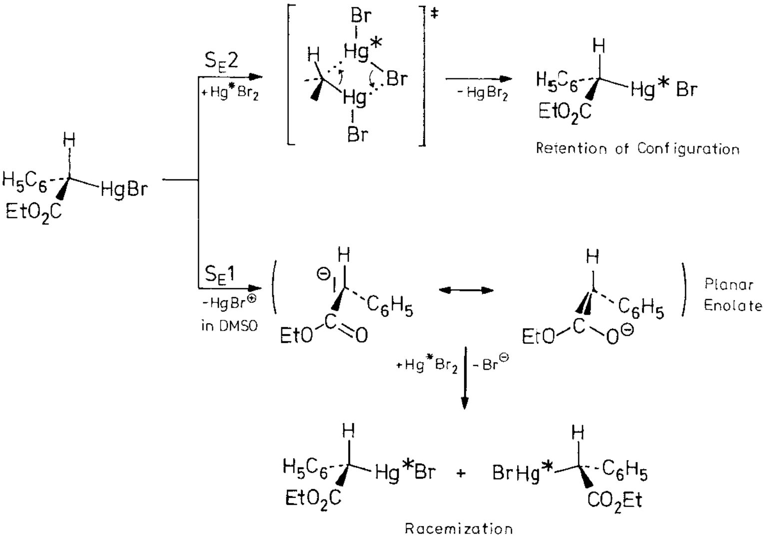
The mechanism and stereochemical course of electrophilic substitution reactions at saturated carbon atoms (S_E1, S_E2, or S_Ei) may also be affected by the medium [337, 382, 383]. This is especially true for S_E reactions of organomercury compounds, as shown by Reutov *et al.* [384], Petrosyan [673], and Hughes and Ingold [385]. The isotopic exchange reaction of (α-ethoxycarbonyl)benzylmercuric bromide with radiomercuric



(5-138a)

(5-138b)

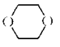
bromide in anhydrous dimethyl sulfoxide, shown in Eq. (5-139), is first-order in substrate but zeroth-order in Hg*Br$_2$ (Hg* = ^{203}Hg) and proceeds with complete racemization of the optically active substrate [384, 385]. These observations are in agreement with an S$_E$1 mechanism. This was the first time that such a mechanism was established for organomercury compounds. The ionization of the C—Hg bond is facilitated by specific solvation of the leaving group, *i.e.* $(CH_3)_2S{=}O \rightarrow HgBr^{\oplus}$. However, when the



(5-139)

same reaction is carried out in aqueous acetone, aqueous ethanol, or in pyridine, second-order kinetics are followed and the reaction occurs with retention of configuration. The reaction pathway followed in these solvents is presumably of the S$_E$2 type. Subsequent to the work of Reutov [384] and Hughes and Ingold [385], solvent-induced alterations of mechanisms have been observed for other reactions of organometallic compounds, par-

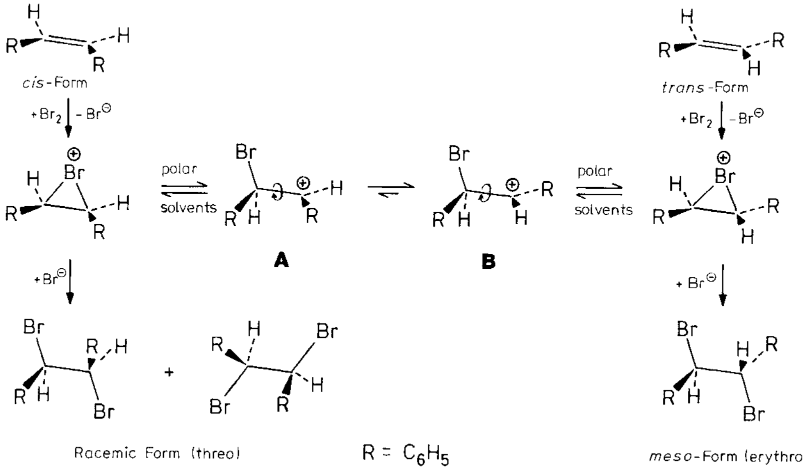
Table 5-23. Stereoselectivity of electrophilic bromine addition to *cis*- and *trans*-stilbene, carried out at 0 °C in the dark [79, 386]; *cf.* Eqs. (5-29) and (5-140).

Solvents	cmol/mol *racemic* 1,2-dibromo-1,2-diphenylethane[a)]	
	from *cis*-stilbene	from *trans*-stilbene
CS_2	81.4	5.5
CCl_4	77.0	11.0
	67.4	–
C_2H_5OH	52.0	–
$CCl_3CO_2CH_3$	51.0	21.0
CCl_3CN	34.0	18.5
$C_6H_5NO_2$	29.5	16.5

[a)] The difference to 100 cmol/mol consists of *meso*-1,2-dibromo-1,2-diphenylethane.

ticularly other organomercury compounds [337, 338, 382, 383] as well as organotin compounds [674].

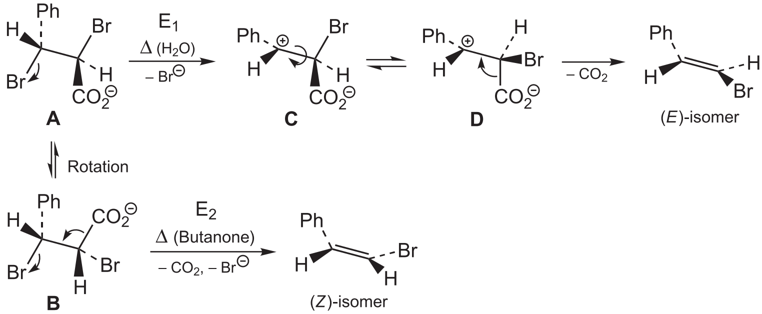
For electrophilic additions of halogens to alkenes, not only is the reaction rate strongly solvent-dependent [79–81] (*cf.* Eq. (5-29) in Section 5.3.2), but the stereochemical course may also be affected by the polarity of the medium [79, 386–388]. For example, the stereoselectivity of bromine addition to *cis*- and *trans*-stilbene according to Eq. (5-140) has been found to be solvent-dependent, as shown in Table 5-23 [79, 386].



(5-140)

Whereas in nonpolar solvents such as CS_2 and CCl_4, bromine adds to *cis*-stilbene in a highly stereoselective manner to give 81.4 cmol/mol *racemic* stilbene dibromide, and to *trans*-stilbene to give 94.5 cmol/mol *meso*-stilbene dibromide, in polar solvents, the degree of stereoselectivity is considerably reduced in both cases. Similar results have been observed for bromine addition to 1-phenylpropene [387]. These results can be interpreted in terms of reaction scheme (5-140), which involves both ethene bromonium ions (symmetrical or unsymmetrical) and α-halogeno carbenium ions as intermediates. The observed solvent dependence of this polar bromination reaction may be the result of differential solvation requirements of the bromonium ion and the carbenium ion in their equilibria, leading to more carbenium ion character, as opposed to bromonium ion character, as the solvent polarity increases. In nonpolar solvents, the increased relative bromonium ion stability may be attributed to "internal solvation" of the carbenium ion by the neighbouring bromine atom. In polar solvents, however, the carbenium ion is more stabilized, enabling it to rotate about the C—C single bond ($A \rightleftharpoons B$), particularly at higher temperatures. In other words, the cyclic halonium ion becomes relatively more stable than the carbenium ion as the solvent becomes less capable of nucleophilic solvation. The observation that there is an increase in stereoselectivity for electrophilic alkene halogenation in nonpolar solvents at low temperatures may serve as a qualitative example of solvent and temperature effects on halonium $\rightleftharpoons$ carbenium ion equilibria. These effects have been quantitatively determined by McManus and Peterson [388]. The fact that in polar solvents *racemic* and *meso*forms are not obtained in equal amounts, although the reaction seems to proceed through an α-halogeno carbenium ion in these solvents, is simply explained by the different conformational energies of A and B. The conformer B in scheme (5-140), leading to *meso*form, is sterically more favoured than A. Generally, solvent polarity plays a significant role in determining the stereochemistry of addition reactions only in borderline cases such as stilbene, where there is stabilization of the carbenium ion by the neighbouring phenyl group. Halogen addition to other alkenes, such as diethyl fumarate and diethyl maleate, also exhibits high stereoselectivity in polar solvents [79].

Examples of the solvent-dependent competition between nucleophilic substitution and β-elimination reactions (*i.e.* S_N1 versus E_1 and S_N2 versus E_2) have already been given in Section 5.3.1 (*cf.* Table 5-7). A nice example of a dichotomic β-elimination reaction, which can proceed via an E_1 or E_2 mechanism depending on the solvent used, is shown in Eq. (5-140a); *cf.* also Eqs. (5-20) and (5-21) in Section 5.3.1. The thermolysis of the potassium salt of racemic 2,3-dibromo-1-phenylpropanoic acid (**A**), prepared by bromine addition to (*E*)-cinnamic acid, yields, in polar solvents (*e.g.* water), apart from carbon dioxide and potassium bromide, the (*E*)-isomer of 1-bromo-2-phenylethene, while in solvents with low or intermediate polarity (*e.g.* butanone) it yields the (*Z*)-isomer [851].



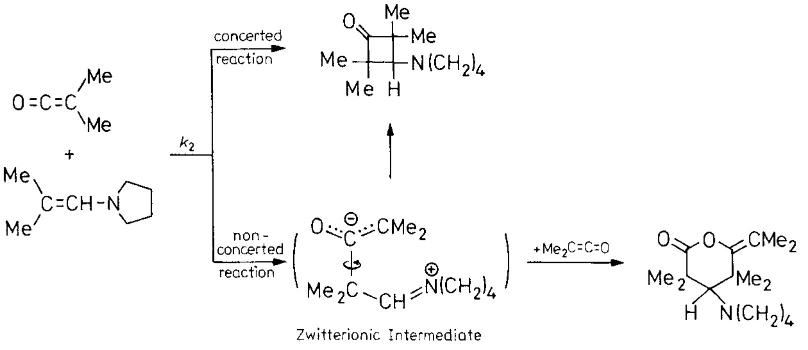
(5-140a)

In water, ionization of the C–Br bond occurs first (E_1 mechanism) to give the intermediate resonance-stabilized benzylic zwitterion **C**. After fast rotation about the C–C bond, carbon dioxide leaves conformer **D** perpendicularly to the plane of the carbenium ion, to give mainly the most stable (*E*)-isomer of *β*-bromostyrene. In butanone, after fast rotation about the C–C bond, elimination of CO_2 and Br^- occurs in a concerted single-step (E_2 mechanism) for stereoelectronic reasons (Br and CO_2^- must be *anti* to one another) to give conformer **B**, which decomposes exclusively to the thermodynamically less stable (*Z*)-isomer. In more polar solvents, the partly zwitterionic activated complex, leading to zwitterion **C** in the rate-determining step, will clearly be more stabilized by solvation than the less dipolar activated complex leading directly to the (*Z*)-isomer of *β*-bromostyrene from conformer **B** [851].

In cycloaddition and cycloreversion reactions, the mechanism and product distribution may also be strongly influenced by the reaction medium. Two examples have already been briefly mentioned in Sections 5.3.2 [102] and 5.3.3 [124]. In the reaction of dimethylketene with enamines such as *N*-isobutenylpyrrolidine, a two-step process *via* a zwitterionic intermediate, leading preferably to a *δ*-methylene *δ*-lactone as 2:1 adduct, competes with a concerted mechanism to give a cyclobutanone derivative according to Eq. (5-141) [102]. In cyclohexane, 92% of the enamine reacts concertedly to give the cyclobutanone derivative, whereas 8% goes through the zwitterionic intermediate. The path *via* the zwitterion increases in importance with increasing solvent polarity and reaches 57% in acetonitrile [102].

An interesting example of the solvent-dependent cycloreversion of a substituted 3*H*-Δ^1-pyrazoline (formed by the 1,3-dipolar cycloaddition of diazomethane to an allylic bromide) has been given by Kolsaker *et al.* [675].

The stereoselectivity of the Diels–Alder reaction between methyl acrylate and cyclopentadiene depends to some extent on solvent polarity [124]; *cf.* Eq. (5-43) in Section 5.3.3. The *endo*/*exo* ratio for the cycloaddition product has been found to vary from 74:26 cmol/mol in triethylamine to 88:12 cmol/mol in methanol at about 30 °C. It has

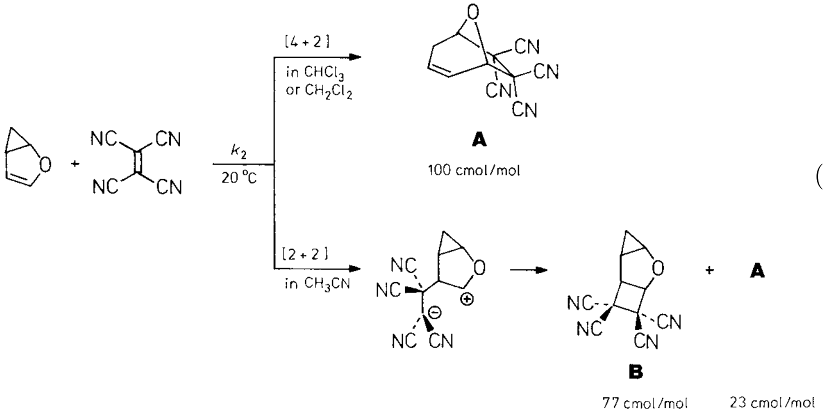


(5-141)

Solvent	c-C_6H_{12}	C_6H_6	C_6H_5Cl	$CHCl_3$	CH_3COCH_3	CH_3CN
%concerted reaction	92.0	79.4	72.8	62.3	52.1	43.0

been observed that for the same reaction not only the *exo*/*endo* stereoisomer ratio is affected by solvent polarity, but also the product ratio of *exo* (or *endo*) adduct to *endo*-dicyclopentadiene [389]. The latter is formed as a by-product in the Diels–Alder reaction. As expected, the *exo* (or *endo*) adduct/*endo*-dicyclopentadiene ratio increases with increasing solvent polarity [389]. The rate and regioselectivity of Diels–Alder reactions with inverse electron demand between the ketene aminal $CH_2{=}C(NMe_2)_2$ and 3-phenyl-1,2,4,5-tetrazine as well as substituted 1,2,4-triazines is strongly solvent-dependent [676]. The "*ortho*"/"*meta*" product ratio of regioisomers decreases with increasing solvent polarity in non-HBD solvents [676].

Examples of the solvent-influenced competition between concerted [4 + 2]Diels–Alder type cycloaddition reactions and 1,4-dipolar reaction pathways with zwitterionic intermediates can be found in references [677–679]. For example, in solvents of low polarity ($CHCl_3$, CH_2Cl_2), homofuran reacts with tetracyanoethene to form the seven-membered [4 + 2]cycloadduct **A** in quantitative yield. In solvents of high polarity (CH_3CN), however, the [2 + 2]cycloadduct **B** predominates, formed *via* a 1,4-dipolar activated complex and a zwitterionic intermediate [679]; *cf.* Eq. (5-142).

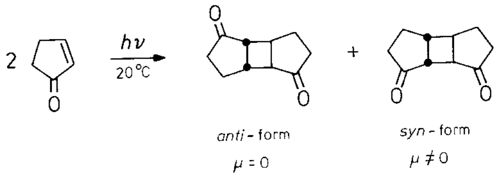


(5-142)

Appreciable solvent effects are also obtained in photochemically induced [2 + 2]-cycloadditions and cycloreversions [390–392]. Examples are given in Eqs. (5-143) [390] and (5-144) [680].

The [2 + 2]photodimerization of 2-cyclopenten-1-one leads to the regioisomeric cyclobutane derivatives shown in Eq. (5-143) [390]. The *anti*/*syn* product ratio decreases as the solvent polarity increases. This is due to the more dipolar, and hence more strongly solvated activated complex being favoured, which leads to the dipolar *syn*-cycloadduct.

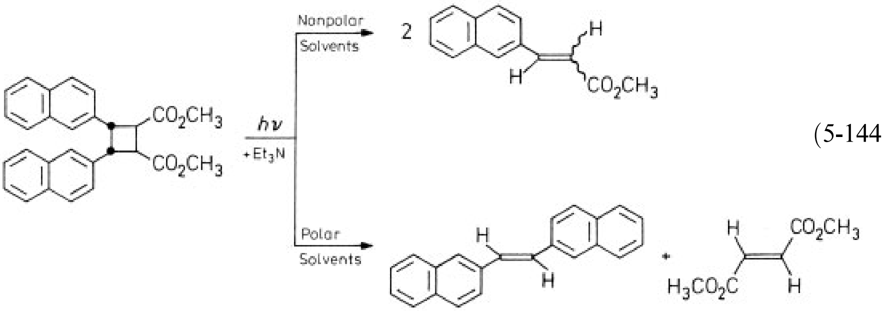
When 1,2-bis(methoxycarbonyl)-3,4-bis(2-naphthyl)cyclobutane is irradiated in solution (cyclohexane/tetrahydrofuran and tetrahydrofuran/acetonitrile mixtures) in the presence of triethylamine, it undergoes [2 + 2]cycloreversion *via* an exciplex with triethylamine [680]. Interestingly, as shown in Eq. (5-144), the mode of cycloreversion changes with the solvent polarity, reflecting the different dipolar electronic structure of the exciplex. In nonpolar solvent mixtures, a 'horizontal' cleavage of the cyclobutane



(5-143)

Solvent	C_6H_6	C_6H_5Cl	CH_2Cl_2	CH_3COCH_3	CH_3CN
$\lg \frac{[anti]}{[syn]}$	0.61	0.39	0.28	0.16	−0.14

ring takes place, in highly polar solvent mixtures a 'vertical' one. It has been assumed that in the latter case the intermediate exciplex exhibits increased charge-transfer character [680].

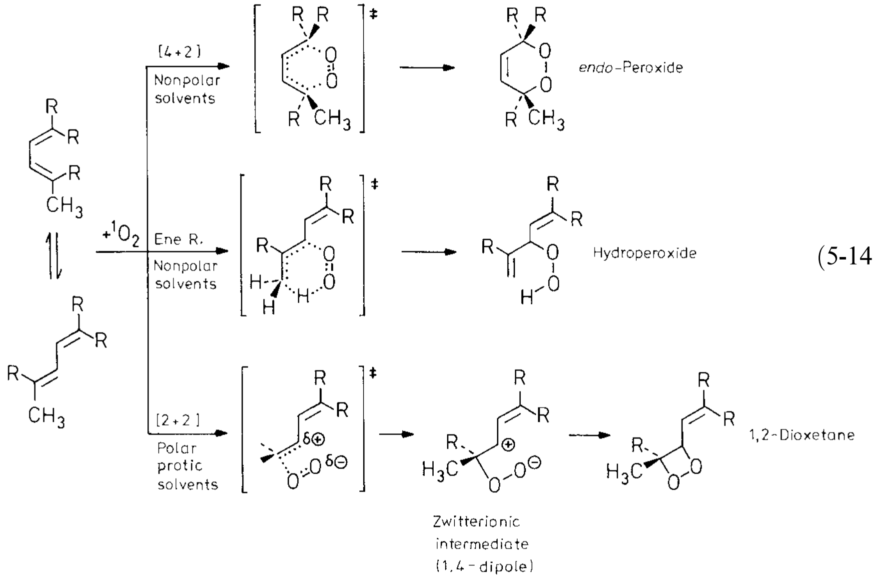


(5-144)

Photo sensitized oxygenation of alkenes with singlet oxygen can, in principle, proceed *via* three competitive reaction pathways: [4 + 2]cycloaddition to *endo*-peroxides, ene reaction of allylic hydroperoxides, and [2 + 2]cycloaddition to 1,2-dioxetanes (see reference [681] for a review). With suitable olefinic substrates, the chemical outcome of such photo-oxygenation reactions can be strongly influenced by the solvent. This is shown in the somewhat simplified Eq. (5-145).

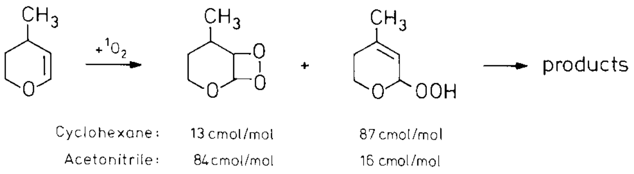
Since [4 + 2]cycloaddition and ene reactions are generally assumed to proceed in a concerted manner *via* isopolar activated complexes, they should exhibit virtually the same small, often negligible, response to changes in solvent polarity. This is what, in fact, has been found; *cf.* for example [138, 682, 683]. However, two-step [2 + 2]-cycloaddition reactions of singlet oxygen to suitably substituted electron-rich alkenes proceed *via* dipolar activated complexes to zwitterionic intermediates (1,4-dipoles or perepoxides). In this case, the relative amounts of 1,2-dioxetane and allylic hydroperoxides or *endo*-peroxides should vary markedly with solvent polarity if two or even all three of the reaction pathways shown in Eq. (5-145) are operative [681, 683, 684].

In the photo-oxygenation of enol ethers, where the ene reaction and [2 + 2]-cycloaddition compete, polar solvents favour cycloaddition whereas nonpolar solvents favour ene product formation [681, 683–685]. For example, 2,3-dihydro-4-methyl-4*H*-pyran reacts with singlet oxygen to yield both a 1,2-dioxetane and an allylic hydro-



(5-145)

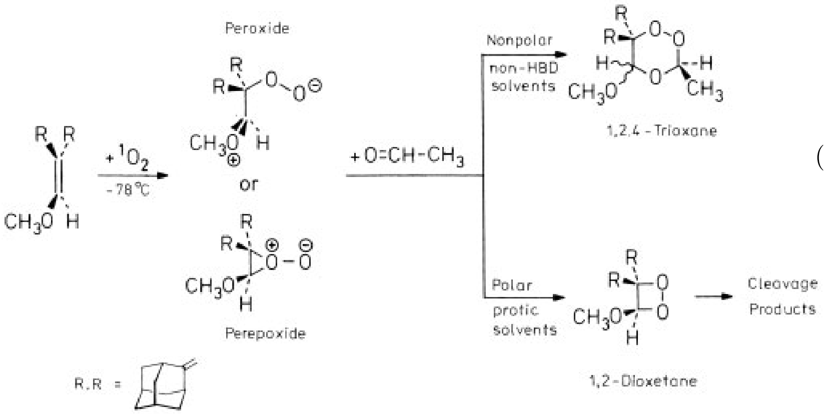
peroxide as primary products in nonpolar cyclohexane and dipolar acetonitrile, with product ratios of 13:87 and 84:16 cmol/mol, respectively, as shown in Eq. (5-146) [685].



(5-146)

Further evidence in support of zwitterionic intermediates in the [2 + 2]-cycloaddition of singlet oxygen to electron-rich alkenes has been obtained by Jefford *et al.* [684]. The photo-oxygenation of 2-(methoxymethylidene)adamantane creates a zwitterionic intermediate (peroxide or perepoxide), which can be captured by acetaldehyde to give 1,2,4-trioxanes in addition to 1,2-dioxetanes; *cf.* Eq. (5-147).

The ease of capture itself is also solvent-dependent: polar protic solvents (methanol, ethanol) stabilize the zwitterion by H-bonding, thus rendering it unreactive towards external electrophiles such as acetaldehyde, and facilitating its closure to a 1,2-dioxetane. On the other hand, nonpolar solvents (toluene, tetrahydrofuran, ethyl acetate) prevent the dispersion of charge, thus enhancing the reactivity towards aldehydes and favouring 1,2,4-trioxane formation [684]. The zwitterionic intermediate in Eq. (5-147) can be formulated as either peroxide or perepoxide (peroxirane). A distinction between these two species is difficult to make. In both cases, the positive charge is stabilized as an oxonium ion while the negative charge remains localized on the terminal oxygen atom. According to calculations, a peroxide would have a permanent dipole moment of *ca.* $34 \cdot 10^{-30}$ Cm (10.1 D) and a perepoxide a dipole moment of *ca.* $19 \cdot 10^{-30}$ Cm (5.6 D) [686].

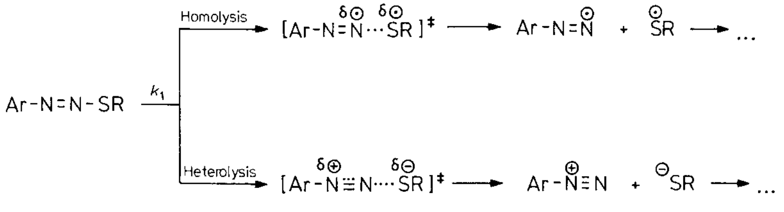


(5-147)

Further examples of solvent effects on photo-oxygenation reactions with singlet oxygen can be found in references [687–689].

Similar solvent effects can be found in fragmentation reactions [109]. Such reactions may proceed heterolytically or homolytically depending on the solvent used as reaction medium. Thus, the observed solvent effect for the thermolysis of $4\text{-}CH_3\text{–}C_6H_4\text{–}N{=}N\text{–}S\text{–}C_6H_4\text{–}4\text{-}C(CH_3)_3$ indicates that this benzenediazoaryl sulfane decomposes homolytically in apolar non-HBD solvents according to Eq. (5-148a) [393].

The marked increase in rate observed in protic solvents such as acetic acid and aqueous ethanol, however, may be due to heterolytic decomposition according to Eq. (5-148b). Suitably substituted benzenediazoaryl sulfanes such as $4\text{-}CH_3\text{–}C_6H_4\text{–}N{=}N\text{–}S\text{–}C_6H_4\text{–}4\text{-}NO_2$ should be more inclined to decompose heterolytically because of mesomeric stabilization of the diazonium and thiolate ions formed. Indeed, the thermolysis of this compound is extremely sensitive to solvent polarity, heterolysis presumably being predominant in polar solvents [393]. It was subsequently found that thermolysis of (*Z*)-benzenediazoalkyl sulfanes leads to isomerization to the (*E*)-form as well as to competing decomposition [394]. Only the decomposition is strongly accelerated with increasing solvent polarity, whereas the rate of (*Z*)/(*E*) isomerization is almost independent of the solvent.



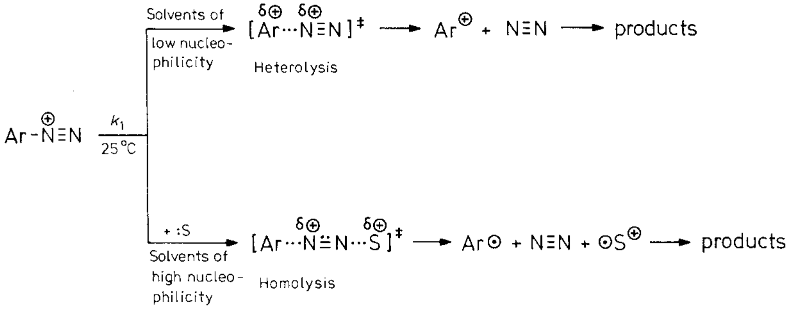
(5-148a)

(5-148b)

Solvent	$i\text{-}C_8H_{18}$	C_6H_6	C_5H_5N	CH_3SOCH_3	CH_3CO_2H	C_2H_5OH/H_2O (96:4 cL/L)
$k_1^{\text{rel a)}}$	0.32	1	0.47	0.91	47	44
$k_1^{\text{rel b)}}$	0.60	1	25	100	45	190

[a] $4\text{-}CH_3\text{–}C_6H_4\text{–}N{=}N\text{–}S\text{–}C_6H_4\text{–}4\text{-}C(CH_3)_3$
[b] $4\text{-}CH_3O\text{–}C_6H_4\text{–}N{=}N\text{–}S\text{–}C_6H_4\text{–}4\text{-}NO_2$

According to Zollinger *et al.* [690], depending on the solvent used, the thermal dediazoniation of arenediazonium ions in solution can proceed *via* competitive heterolytic and homolytic reaction pathways; *cf.* the somewhat simplified Eq. (5-149).

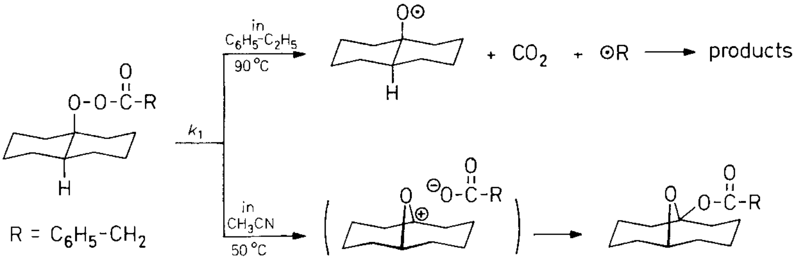


(5-149)

In solvents of low nucleophilicity (*e.g.* $(CF_3)_2CHOH$, CF_3CH_2OH, CH_3CO_2H, H_2O with pH < 1), the familiar heterolytic dediazoniation takes place to give an aryl cation and products derived therefrom. The solvent effect on heterolytic dediazoniation rates is small, the slowest (in 1,4-dioxane) and fastest rate (in 2-propanol) differing only by a factor of 9 [690].

However, in solvents of high nucleophilicity (*e.g.* DMSO, HMPT, pyridine), the formation of products derived from aryl radicals is favoured. Therefore, in these solvents, a homolytic dediazoniation must be taking place. This mechanism involves addition of a nucleophilic solvent molecule to the electrophilic β-nitrogen atom of the diazonio group, followed by homolysis to give a radical pair and nitrogen. The homolytic dediazoniation is not only enhanced by sufficiently nucleophilic solvent molecules but also by the addition of other nucleophiles, which form relatively stable radicals through electron transfer. Under comparable reaction conditions, the rates of homolytic dediazoniation are higher than the corresponding rates of heterolysis [690].

Dichotomous homolytic and heterolytic decomposition reactions can also be found in the thermolysis of peroxycarboxylic esters [195, 207–209]; *cf.* Eq. (5-62) and Table 5-9 in Section 5.3.4. An already classical example, given in Eq. (5-150), is exhibited by the decomposition of *trans*-9-decalyl peroxyphenylacetate [207].



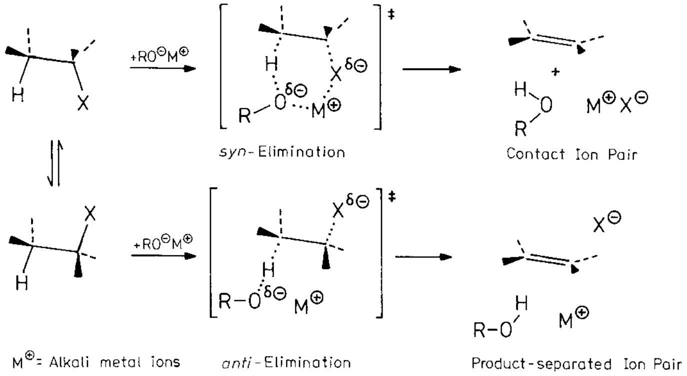
(5-150)

Product analysis and reaction-rate medium effects reveal such a change in mechanism on passing from nonpolar to polar solvents [207, 209]. The decomposition of this perester occurs by heterolysis in alcohols and mainly by homolysis in ethylbenzene, whereas in acetonitrile both mechanisms appear to compete [207].

For further examples of dichotomous solvent-influenced radical/ionic perester decompositions, see the base-catalyzed perester fragmentation shown in Eq. (5-39) in Section 5.3.2 [110], as well as the decomposition of *t*-butyl heptafluoroperoxybutyrate, C_3F_7–CO–O–O–C$(CH_3)_3$ [691]. The relative extent of monomolecular and induced thermal decomposition of disubstituted dibenzyl peroxydicarbonate, ArCH_2–O–CO–O–O–CO–O–CH_2Ar, is also substantially influenced by the reaction medium [692]. The thermolysis of suitable dialkyl peroxides can also proceed by two solvent-dependent competitive reaction pathways (homolytic and electrocyclic reaction), as already shown by Eq. (5-59) in Section 5.3.4 [564].

The solvent-influenced *syn*/*anti* dichotomy for bimolecular eliminations of acyclic and medium-ring bromides, tosylates, and 'onium salts has been reviewed [395, 693] and will be mentioned only briefly. As a rule, the *syn*-elimination pathway gains importance in non-dissociating solvents, while dissociating solvents facilitate the more common *anti*-elimination reaction. The more unusual *syn*-elimination is favoured in non-dissociating solvents because of ion-pair association, which favours a cyclic six-membered activated complex as shown in Eq. (5-151a); see reference [395].

The advantage of *syn*-elimination in solvents of low relative permittivity lies also in the formation of a contact ion pair in the product, whereas *anti*-elimination produces a product-separated ion pair according to Eq. (5-151b). Thus, reaction of free ions proceeds in standard *anti* fashion, while ion pairs (or higher aggregates) tend to react by a *syn* pathway. Solvent separation of the $RO^{\ominus}M^{\oplus}$ ion pair in the reactant state removes the driving force for *syn*-elimination (*i.e.* dissociating solvents, increase in cation size, addition of crown ethers, *etc.*).

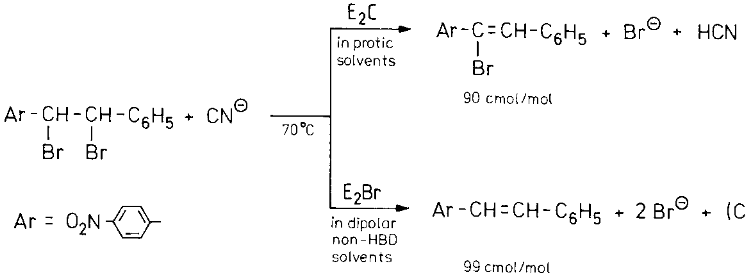


(5-151a)

(5-151b)

For example, the *syn*/*anti* product ratio of the base-promoted dehydrochlorination of *meso*-3,4-dichloro-2,2,5,5-tetramethylhexane with potassium *t*-butoxide to give (*Z*)- and (*E*)-3-chloro-2,2,5,5-tetramethyl-3-hexene changes from 92:8 in tetrahydrofuran ($\varepsilon_r = 7.6$) and 86:14 in *t*-butanol ($\varepsilon_r = 12.5$) to 7:93 in dimethyl sulfoxide ($\varepsilon_r = 46.5$) [694].

An example of extreme solvent dependence is seen in the competition between dehydrobromination (believed to be E_2C) and debromination (designated E_2Br) as shown in Eq. (5-152) [396].

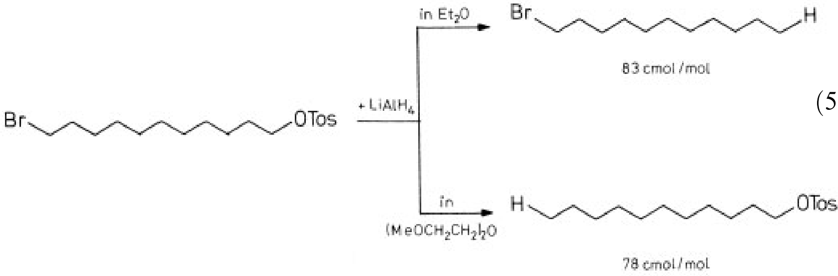


(5-152)

In *N,N*-dimethylformamide, *anti*-debromination of *erythro*-1,2-dibromo-1-(4-nitrophenyl)-2-phenylethane with $(n\text{-}C_4H_9)_4N^{\oplus}CN^{\ominus}$ gives 99 cmol/mol 4-nitro-*trans*-stilbene. As the solvent composition approaches pure ethanol, the proportion of α-bromo-4-nitro-*cis*-stilbene, the product of *anti*-dehydrobromination, increases to 90 cmol/mol. The E_2C reaction involves a looser activated complex, better solvated by protic solvents than its tighter E_2Br-like counterpart [396].

The ability of reagents to differentiate between functional groups is called *chemo-selectivity* and can be solvent-dependent. A nice clear-cut example is the reduction of the bifunctional compound 11-bromoundecyl tosylate with lithium aluminium hydride in different solvents as shown in Eq. (5-153) [695].

With diethyl ether as solvent, the reaction proceeds with the selective reduction of the tosyl group to give 1-bromo-*n*-undecane, whereas in diethylene glycol dimethyl ether ("diglyme"), the bromo substituent is selectively reduced to yield *n*-undecyl tosylate. In diethyl ether, the lithium cation is poorly solvated and $LiAlH_4$ reacts as an ion pair. In

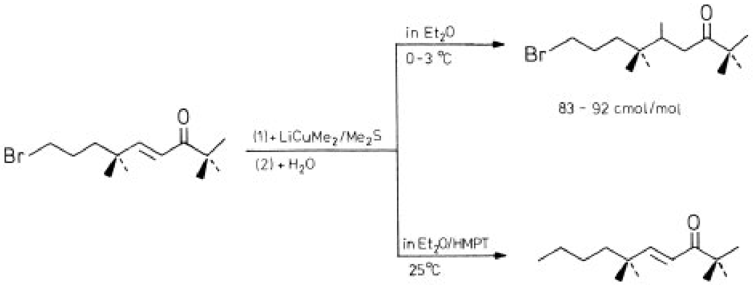


(5-153)

diglyme, the lithium cation is better solvated, forming solvent-separated ion pairs, thereby enhancing the nucleophilicity of the $AlH_4^{\ominus}$ ion, which results in rapid reduction of the bromo substituent. The high reactivity of $LiAlH_4$ toward alkyl tosylates in the weakly cation-solvating diethyl ether is presumably due to the complexation of the lithium cation to the tosyl group thereby increasing its leaving-group ability [695]. Other solvent-dependent chemoselective reductions of bifunctional compounds with lithium aluminium hydride [696, 697] and with lithium borohydride [709] have been reported.

The dissociation equilibrium of associated $Li^{\oplus}AlH_4^{\ominus}$ ion pairs in a variety of ethereal solvents has been investigated by ^{7}Li and ^{27}Al NMR spectroscopies [768]. $\delta(^{27}Al)$ is nearly independent of the solvent as is $^{1}J_{Al-H}$, whereas $\delta(^{7}Li)$ depends on the $LiAlH_4$ concentration and the EPD character of the ethereal solvent. According to this result, diglyme seems to be the solvent of choice for reactions in which the $AlH_4^{\ominus}$ should be least affected by ion-pair formation [768].

Another interesting example of solvent-dependent control of chemoselectivity is the reaction of a bromo α-enone with an organocopper reagent, as shown in Eq. (5-154) [698]. The lithium dimethylcuprate displacement reaction of haloalkanes and the conjugate addition of cuprate reagents to α-enones exhibit opposite responses on the addition of EPD solvents. An appropriate choice of substrate and reaction medium should therefore make it possible to select either the $LiCuMe_2$ coupling reaction with a haloalkane or its conjugate addition.



(5-154)

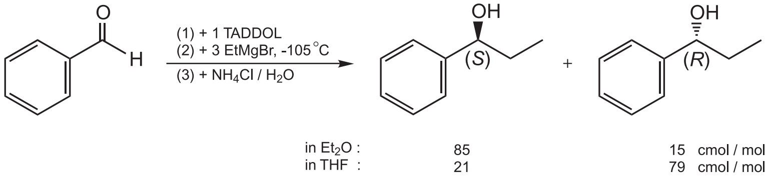
Indeed, in diethyl ether, lithium dimethylcuprate usually reacts with the α-enone group to give a methyl-substituted bromo ketone. Addition of hexamethylphosphoric triamide (HMPT), however, slows down this reaction to such an extent that displacement of the bromo substituent takes place [698]. Another remarkable example of the influence of HMPT on chemoselectivity is the reaction of an arsonium ylide, $Ph_3As{=}CH{-}CH{=}CH{-}Ph$, with benzaldehyde in tetrahydrofuran solution, yielding either an epoxide (in THF) or an alkene (in THF/HMPT) [699].

Not only chemoselectivity but also *enantioselectivity* and *diastereoselectivity* of organic reactions can be controlled by choice of solvent; for reviews on asymmetric induction, see references [700, 701].

Some examples of enantioselective syntheses, carried out in chiral media, have already been given at the end of Section 3.2, which deals with chiral solvents; *cf.* also Table A-2 (Appendix). In general, asymmetric inductions as a result of chiral solvents or chiral cosolvents are disappointingly low [700]. The reason for this is that the differential solvation by the chiral solvent of the two enantiomorphic activated complexes which lead to either the (*R*)- or (*S*)-product is not sufficient. That is, the difference in Gibbs energy of activation, $\Delta\Delta G^{\neq} = \Delta G^{\neq}_{(R)} - \Delta G^{\neq}_{(S)}$, is not large enough to favour only one of the two enantiomeric products. It should be remembered that a difference of $\Delta\Delta G^{\neq} = 10.8$ kJ/mol (2.6 kcal/mol) at 20 °C would be sufficient to get an (*S*)/(*R*) product ratio of 99:1 (*i.e.* an enantiomeric excess $ee = 98\%$).

Therefore, a more direct covalent linking of the chiral information with the reactants is necessary in order to obtain diastereomorphic activated complexes with greater differential solvation, thus leading to better diastereoselectivity.

The Grignard reaction of benzaldehyde with ethylmagnesium bromide in diethyl ether in the presence of molar amounts of (R,R)-TADDOL as a chiral additive leads predominantly to (S)-1-phenyl-1-propanol, while the same reaction carried out in tetrahydrofuran gives mostly the corresponding (R)-alcohol according to Eq. (5-154a) [852]. TADDOL is the acronym for *t*etra*a*ryl-1,3-*d*ioxolane-4,5-*d*imethan*ol*, which reacts with

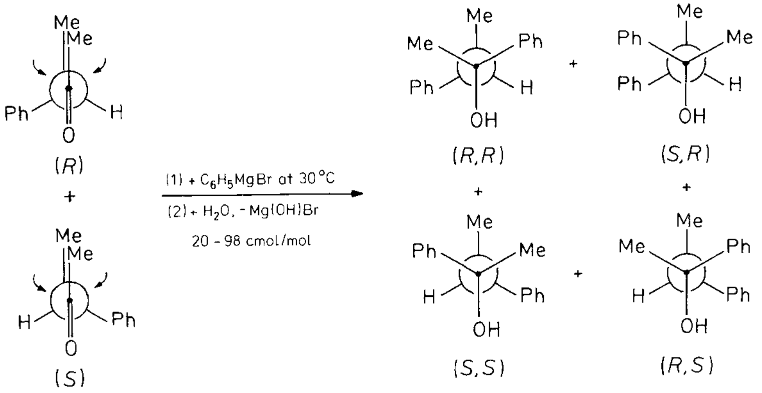


(5-154a)

the excess Grignard reagent to presumably generate a chiral magnesium alcoholate, Et–Mg–OR*. This then adds to the carbonyl group of benzaldehyde either at the *re*- or the *si*-side, depending on the ethereal EPD solvent used, which is also part of the solvation shell surrounding the magnesium ion. Otherwise, for a variety of other carbonyl compounds and Grignard reagents, this TADDOL-mediated addition reaction invariably leads to the (R)-alcohol with high enantioselectivity in tetrahydrofuran as solvent [852].

Further detailed investigations of the solvation of carbonyl compounds as the predominant factor influencing the diastereoselectivity of nucleophilic additions of various organometallics (*n*-BuLi, *t*-BuLi, *n*-BuMgBr) to α-R_3SiO-substituted aldehydes can be found in reference [853].

The Grignard reaction of (±)-3-phenylbutanone with phenylmagnesium bromide to give stereoisomeric 2,3-diphenylbutan-2-ols, shown in Eq. (5-155), represents another example [702].

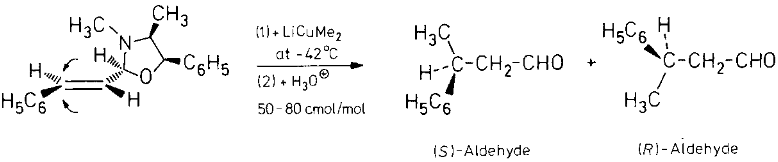


(5-155)

Solvent	Et_3N	Et_2O	1,4-dioxane	$(CH_2)_4O$	diglyme	$(MeOCH_2)_2$
$\%[(S,R)+(R,S)]$	26	36	49	61	66	73

In this particular case, the observed diastereoselectivity, *ds* = %[(*S*, *R*) + (*R*, *S*)], increases with increasing solvent polarity. The (*SR*, *RS*)-carbinol is preferentially formed in more polar solvents, whereas the (*RR*, *SS*)-carbinol dominates in less polar solvents. This result can be understood by a careful analysis of the two diastereomorphic activated complexes in terms of steric and polar effects. The activated complex which leads to the (*SR*, *RS*)-carbinol appears to be more dipolar and hence more strongly solvated; see reference [702] for details.

Another nice example is the addition of lithium dimethylcuprate to a chiral oxazolidine (prepared from (*E*)-cinnamaldehyde and (−)-ephedrine), followed by hydrolysis, to give 3-phenylbutanal; *cf.* Eq. (5-156) [703].



(5-156)

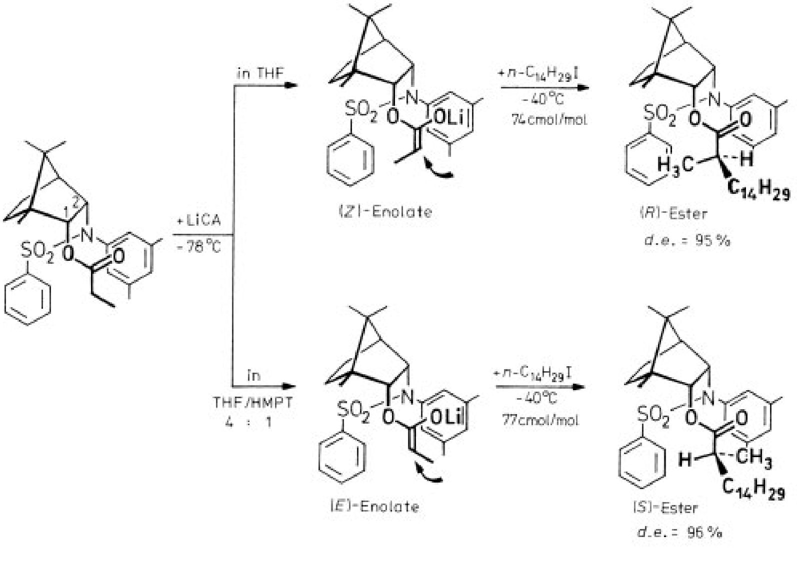
Diastereoselective addition in Et_2O/HMPT (1:1) leads to the (*S*)-aldehyde with an enantiomeric excess of 40%, whereas in *n*-hexane the (*R*)-aldehyde is formed with 80% (!) enantiomeric excess. The (*R*)-configured aldehyde is also obtained in benzene and in dichloromethane, but with lower *ee* values of 50% and 25%, respectively. Inverse results were obtained with a chiral oxazolidine prepared from (*E*)-cinnamaldehyde and (+)-ephedrine. Here, the (*S*)-aldehyde with *ee* = 79% is formed in *n*-hexane, and the (*R*)-aldehyde in Et_2O/HMPT (1:1) with *ee* = 50% [703]. This result may be due to different structures of the organocopper reagent, and hence of the diastereomorphic activated complexes, in nonpolar solvents (*n*-hexane, benzene, dichloromethane) and in EPD solvents (Et_2O/HMPT) [703].

A striking solvent effect was observed in the reduction of a chiral α-keto amide, C_6H_5–CO–CO–NR_2 (NR_2 = (*S*)-proline methyl ester), with sodium tetrahydridoborate, leading to mandelic acid after hydrolysis [704]. When the α-keto amide was reduced in pure tetrahydrofuran or methanol, the resulting enantiomeric excess of (*S*)-mandelic acid produced was 36% and 4%, respectively. However, when a tetrahydrofuran/methanol (99:1 cL/L) solvent mixture was used, the enantiomeric excess increased to 64% (!). In other solvent mixtures, a catalytic amount of a protic solvent (CH_3OH or H_2O) was found to be necessary for good asymmetric induction [704].

Extremely diastereoselective solvent-influenced alkylations were obtained with propionates of chiral alcohols derived from (+)-camphor, as shown in Eq. (5-157) [705].

Metallation of the propionate with lithium cyclohexylisopropylamide (LiCA) in a solvent-controlled reaction gives either the (*Z*)- (in THF) or (*E*)-lithium enolate (in THF/HMPT, 4:1). Rearside shielding of both diastereomeric enolates, provided by the 3,5-dimethylphenyl group attached to the sulfonamide moiety at C-2, prevents alkylation of these enolates from the backface. Hence, frontface attack with iodo-*n*-tetradecane leads to diastereomeric esters with either (*R*)- or (*S*)-configuration at the α-carbon atom of the propionate group. Using LiCA/HMPT mixtures with increasing

HMPT molar ratio in the metallation step leads to a smooth changeover from diastereoselective formation of the (*R*)-ester to diastereoselective formation of the (*S*)-ester. The turning point is at an LiCA/HMPT molar ratio of 1:1. Obviously, this configurational conversion is caused by the kinetically controlled formation of the diastereomeric enolates by deprotonation with either LiCA or the LiCA/HMPT complex. The EPD solvent HMPT acts as a lithium-solvating agent in this reaction, causing preferential formation of the (*E*)-lithium enolate. An explanation for this dramatic solvent effect has been given by analysis of the steric requirements for the enolization of esters [706]. The better solvation of $Li^{\oplus}$ in the presence of HMPT and the enhanced reactivity of the amide base favours the activated complex leading to the (*E*)-enolate. In the less coordinating solvent THF, the interaction between $Li^{\oplus}$ and the ester carbonyl oxygen atom must be strong, thus favouring the activated complex leading to the (*Z*)-enolate; see reference [706] for details. Addition of cation-solvating HMPT *after* the deprotonation step in reaction (5-157) also leads to an increase in diastereoselectivity, *i.e.* preferential formation of the (*R*)-ester. This solvent effect may be caused by disruption of conformationally unfavourable interactions between $Li^{\oplus}$ and the 3,5-dimethylphenyl group of the sulfonamide moiety; *cf.* Eq. (5-157) [705].



(5-157)

Solvent-controlled diastereoselectivities have also been observed in Diels–Alder cycloaddition reactions of cyclopentadiene with bis-(−)-menthyl fumarate [707] and with the acrylate of (*S*)-ethyl lactate, $CH_2{=}CH{-}CO{-}OCH(CH_3){-}CO_2Et$ [708]. In the latter reaction, giving four diastereomeric cycloadducts, diastereoselectivities of up to 85:15 have been obtained in *n*-hexane [708]. The diastereoselectivities decrease with increasing solvent polarity, while the *endo*/*exo* selectivity increases. This is in agreement with the pattern found for simple achiral acrylates [124]; *cf.* Eq. (5-43) in Section 5.3.3.

We shall conclude this section with reference to the (*E*)/(*Z*) isomerization of imino compounds $R_2C{=}N^{\diagup R'}$, which, in principle, may proceed by a rotation mechanism or an inversion mechanism. Determination of the solvent dependence of this isomerization has been used in deciding between the two possible reaction mechanisms [397, 398]. The small solvent effects usually observed are in agreement with an inversion mechanism [398]. An inversion mechanism was also postulated for the $(E)/(Z)$ isomerization of push-pull substituted azobenzenes [529, 561]; *cf.* Eq. (5-40) in Section 5.3.2.

Only a few representative, particularly interesting examples of solvent effects on the mechanisms and stereochemistry of organic reactions have been mentioned in this Section. The significance of these, often very specific, solvent effects is well-recognized by organic chemists, but a detailed understanding of them is frequently lacking and hence they are the subject of ongoing research.

5.5.8 Influence of Micellar and Solvophobic Interactions on Reaction Rates and Mechanisms

The modification of chemical reactions through the incorporation of the reactant molecules into aqueous micelles or other organized assemblies has received considerable attention in recent years. Reactions are known for which rates, mechanisms, and even the stereochemistry have been significantly affected by the addition of so-called *amphiphiles* to the reaction medium.

Solvophobic and especially hydrophobic interactions provide the driving force for the aggregation of organic ions known as amphiphiles in dilute aqueous solutions (*cf.* Sections 2.2.7 and 2.5) [399]. Amphiphilic ions possessing long unbranched hydrocarbon chains have both pronounced hydrophobic and hydrophilic properties and exhibit, therefore, the important property of forming, over a narrow concentration range termed the *critical micelle concentration* (*cmc*), molecular aggregates in solution, called *micelles* (*cf.* Fig. 2-12 in Section 2.5)*). These micelles, rather than individual amphiphilic ions, may cause alterations of rates and mechanisms of organic reactions in aqueous solutions of surfactants. A suitable choice of surfactant can lead to rate increases of 5- to 1000-fold compared to the same reaction in the absence of surfactant. The catalysis of organic reactions by ionic micelles can be explained in terms of electrostatic and hydrophobic interactions of the reactants and activated complexes with the micelle. The reaction substrate is partitioned between micellar and bulk aqueous phases by hydrophobic binding of the substrate to a micelle. Then, by simple electrostatics, this complex either attracts (rate acceleration) or repels (rate retardation) an incoming ionic reactant. The field of micellar catalysis has been the subject of comprehensive reviews [289, 400–403, 711–713]. Therefore in this section, only a few typical examples shall demonstrate the influence of hydrophobic interactions on organic reactions.

According to Eq. (5-158), the reaction of 1-fluoro-2,4-dinitrobenzene with phenolate or thiophenolate ions is accelerated by micelles of cetyl-trimethylammonium bromide (CTABr) in aqueous solution by factors of 230 and 1100, respectively [404].

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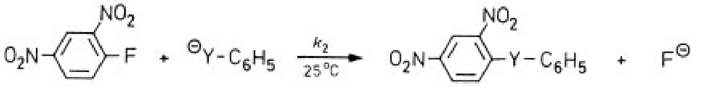
* Depending on their chemical structure, surfactants capable of forming micelles are usually classified into cationic (*e.g.* ammonium salts), anionic (*e.g.* sulfates, carboxylates), ampholytic (*e.g.* zwitterionic salts), and non-ionic surfactants (usually containing polyoxyethene chains); *cf.* Table 2-10 in Section 2.5.

This enhancement of the reaction of bulk-phase anions $C_6H_5Y^{\ominus}$ with the organic nonelectrolyte 2,4-$(NO_2)_2C_6H_3F$, the latter partitioned between the bulk and micellar phases, is expected in the presence of cationic amphiphiles such as CTABr from purely

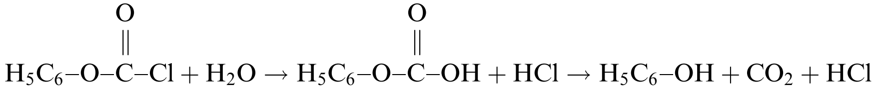


(5-158)

Surfactant	no CTABr added	with cationic CTABr
$k_2^{rel}(Y = O)$	1	230
$k_2^{rel}(Y = S)$	1	1100

electrostatic considerations. Amphiphiles with opposite charge to that of the reactant ion accelerate, whereas amphiphiles of like charge inhibit the reactions of neutral substrates. The catalytic efficiency increases with increasing diffusion of neutral substrate into the micelles, that is, with increasing lipophilicity of the reactant molecules. A compilation of micellar catalytic effects expected for organic reactions of different charge type in the presence of cationic or anionic micelles can be found in reference [289].

In contrast to reaction (5-158), addition of micelle-forming surfactants can also slow down chemical reactions. For example, the spontaneous hydrolysis of phenyl chloroformate at 25 °C according to Eq. (5-158a) is retarded by a factor of *ca.* 16 on addition of sodium dodecylsulfate (SDS) above the *cmc*. Below the *cmc*, the SDS



$$H_5C_6{-}O{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}Cl + H_2O \rightarrow H_5C_6{-}O{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}OH + HCl \rightarrow H_5C_6{-}OH + CO_2 + HCl \qquad (5\text{-}158a)$$

monomers do not have a significant effect on the observed rate constant [855]. The hydrolysis of phenyl chloroformate follows an addition/elimination pathway, the addition of water being rate-determining. The observed micellar effect can be attributed to the lower polarity of the micellar interface at which the reaction takes place and to the electrostatic destabilization of the zwitterionic activated complex by the negatively charged head groups ($-SO_3^-$) of the surfactant.

Even at reactant concentrations well below critical micelle concentrations, hydrophobic interactions may result in marked rate accelerations. Thus, the rates of bimolecular aminolysis of 4-nitrophenyl decanoate and acetate by *n*-decylamine and ethylamine have been determined in aqueous solution and a distinct rate enhancement in the aminolysis of the long chain ester by the long chain amine was reported [405, 406]. As shown in Table 5-24, the ratio $k_2^{decylamine}/k_2^{ethylamine}$ for 4-nitrophenyl decanoate is 317*). That is, *n*-decylamine attacks the long-chain ester 47 times faster than expected on the

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* Even larger rate increases (up to 10^7-fold) were observed for the corresponding amine-catalyzed termolecular reaction of 4-nitrophenyl ester with alkylamines, carried out in water or aqueous ethanol at 25 °C [406].

Table 5-24. Second-order rate constants for the aminolysis of 4-nitrophenyl esters in water/acetone (99:1) at 35 °C according to $CH_3(CH_2)_nCO\text{–}OC_6H_4\text{–}4\text{-}NO_2 + C_2H_5(CH_2)_nNH_2 \rightarrow CH_3(CH_2)_nCO\text{–}NH(CH_2)_nC_2H_5 + HOC_6H_4\text{–}4\text{-}NO_2$, with $n = 0$ and 8 [405].

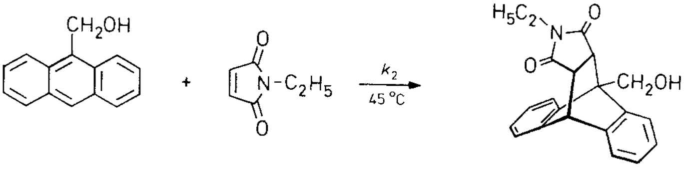
Ester	$k_2^{\text{ethylamine}}$	$k_2^{\text{decylamine}}$	$k_2^{\text{decylamine}}/k_2^{\text{ethylamine}}$
4-Nitrophenyl acetate	5.74	39.1	6.8
4-Nitrophenyl decanoate	0.42	133	317
$k_2^{\text{decanoate}}/k_2^{\text{acetate}}$	0.073	3.4	47

basis of its reactivity toward 4-nitrophenyl acetate. This rise in the observed rate constant is best explained by the association of the reactant molecules to form a kind of "micro-micelle" prior to reaction. This is due to hydrophobic interactions between the long hydrocarbon chains of both reactants in aqueous solution. In accordance with this interpretation, the ratios $k_2^{\text{decylamine}}/k_2^{\text{ethylamine}}$ fall to values near unity for both esters when the reactions are carried out in aqueous 1,4-dioxane (50:50), a medium in which hydrophobic interactions are seriously disrupted [405].

Another remarkable example is the hydrolysis of the amide ($H_{25}C_{12}\text{–}NMe_2^+\text{–}CH_2\text{–}\mathit{CO\text{–}NH}\text{–}C_6H_4\text{–}4\text{-}NO_2)Br^-$ at 25 °C, which is accelerated about 10^8-fold on addition of sodium hexadecanoate as compared to the addition of sodium acetate [856]. This dramatic rate increase under very mild reaction conditions can again be attributed to hydrophobic association between the long-chain amide and the long-chain catalyst, as well as to the electrostatic attraction between the cationic ammonium centre of the reactant and the anionic carboxylate group of the catalyst.

Diels–Alder cycloaddition reactions have undergone impressive improvements, taking advantage of hydrophobic interactions existing between the essentially nonpolar reactants in the aqueous medium. The use of water as a solvent in Diels–Alder reactions leads to greatly enhanced reaction rates and selectivities. This remarkable result has been pioneered by Breslow *et al.* [801] and further explored by Grieco *et al.* [714]; for reviews, see references [715–718].

For example, the rate of the Diels–Alder cycloaddition reaction between 9-(hydroxymethyl)anthracene and *N*-ethylmaleimide, as shown in Eq. (5-159), is only slightly altered on changing the solvent from dipolar acetonitrile to nonpolar isooctane, as expected for an isopolar transition state reaction; *cf.* Section 5.3.3. In water, however,

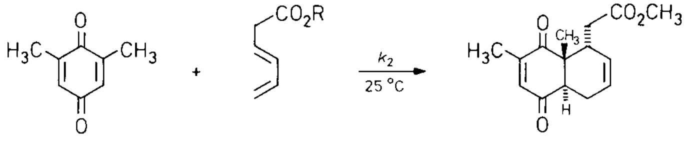


(5-159)

Solvent	$i\text{-}C_8H_{18}$	$n\text{-}C_4H_9OH$	CH_3OH	CH_3CN	H_2O	$H_2O + 4.86$ M LiCl
k_2^{rel}	7.4	6.2	3.2	1	211	528

the reaction is 211 times faster than in acetonitrile! The addition of lithium chloride, known as a solute that increases hydrophobic effects, increases the rate in water by a further 2.5-fold. This exceptional behaviour of the solvent water is best explained in terms of hydrophobic interactions, which promote the association of the diene and the dienophile during the activation process [801]. For some Diels–Alder reactions of cyclopentadiene, which can give both *endo* and *exo* addition of dienophiles, the *endo*/*exo* product ratio increases when water is used as solvent [801]. This is related to the well known influence of polar solvents on such ratios [124] as well as to the need to minimize the activated complex surface area in aqueous solution.

The Diels–Alder cycloaddition reaction of 2,6-dimethyl-1,4-benzoquinone with methyl (*E*)-3,5-hexadienoate, carried out in toluene as solvent, gives only traces of the cycloadduct shown in Eq. (5-160), even after seven days. However, when the solvent is changed to water and sodium (*E*)-3,5-hexadienoate is used as the diene, 77 cmol/mol of the desired cycloadduct is obtained after one hour and esterification with diazomethane [714]*). Again, hydrophobic interactions between diene and dienophile in the aqueous medium seem to be responsible for this remarkable and synthetically useful rate acceleration.



(5-160)

R = CH_3: in Toluene, 7d → traces only

R = $Na^{\oplus}$: in Water, 1 h → 77 cmol/mol (after esterification with CH_2N_2)

A sugar-assisted solubilization of the diene in aqueous Diels–Alder reactions has been proposed, using glucose as the hydrophilic moiety [744]. Based on the aqueous Diels–Alder cycloaddition of cyclopentadiene with diethyl fumarate, an increase in reaction rate with the increasing solvophobicity of the medium, characterized by Abraham's solvophobicity parameter *Sp* (see Section 7.3), has been found [745]. Addition of *β*-cyclodextrin to the reaction medium further promotes this cycloaddition. Increasing medium solvophobicity and the addition of *β*-cyclodextrin also influences the diastereoselectivity (*i.e.* the *exo*/*endo* product ratio) of this Diels–Alder reaction: the amount of *endo* product increases on addition of *β*-cyclodextrin and with increasing medium solvophibicity, due to the more compact activated complex leading to the *endo* adduct [745].

An interesting phenomenon related to the acceleration of Diels–Alder reactions in aqueous media is found when clays such as montmorillonite are suspended in an organic solvent (*e.g.* ethanol or dichloromethane) [719]. The layered structure of the clay enables it to trap pools of internal water, which are obviously capable of exerting hydrophobic effects.

It should also be mentioned in this context that the pressure dependence of the rate of Diels–Alder cycloaddition reactions is much less in water than in nonaqueous

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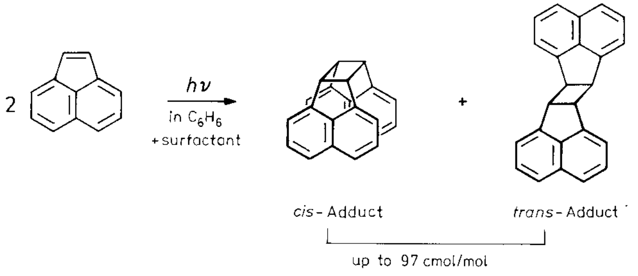
[*] Under the conditions of the aqueous Diels–Alder reaction, the initially formed *cis*-cycloadduct equilibrates to the more stable *trans*-fused ring system.

solvents, mainly because of hydrophobic interactions of the apolar reactants. A careful study of the cycloaddition of butanone to isoprene has shown that in aqueous solution the volume of activation, $\Delta V^{\neq}$, is only about -34 cm^3/mol, whereas in dichloromethane as solvent $\Delta V^{\neq}$ is close to the expected value of ca. -40 cm^3/mol [857]; see also Section 5.5.11.

Not only Diels–Alder cycloadditions but also 1,3-dipolar cycloaddition reactions can be subject to hydrophobic rate enhancements. For example, the reaction of *C,N*-diphenylnitrone with di-*n*-butyl fumarate at 65 °C to yield an isoxazolidine is about 126 times faster in water than in ethanol, while in nonaqueous solvents there is a small 10-fold rate decrease on going from *n*-hexane to ethanol as solvent – in agreement with an isopolar transition-state reaction [*cf.* Eq. (5-44) in Section 5.3.3] [858]. Because water and ethanol have comparable polarities, the rate increase in water cannot be due to a change in solvent polarity. During the activation process, the unfavourable water contacts with the two apolar reactants are reduced, resulting in the observed rate enhancement in aqueous media. Upon addition of LiCl, NaCl, and KCl (5 M) to the aqueous reaction mixture the reaction rate increases further, whereas addition of urea (2 M) leads to a rate decrease, as expected for the structure-making and structure-breaking effects of these additives on water [858].

The hydrophobicity-driven association of reactant molecules in aqueous solution has even been found in aldol reactions. The trimethylsilyl ether of cyclohexanone adds to benzaldehyde in aqueous solution at 20 °C in the absence of a catalyst to give aldol addition products with a *syn*/*anti* stereoselectivity opposite to that of the acid-catalyzed reaction carried out in dichloromethane [746].

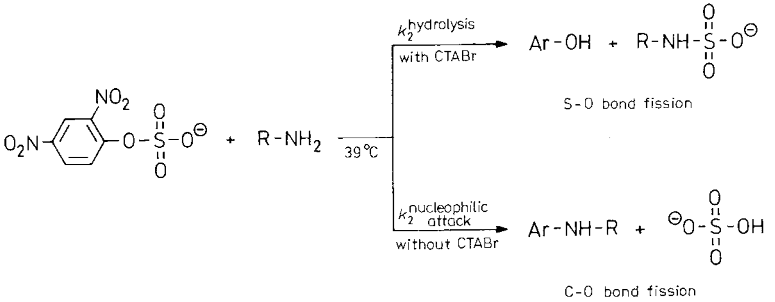
The useful ability of micelles to produce high local concentrations of bound organic reactants at low bulk concentrations has been used in photodimerization reactions; see references [712, 713] for reviews. The increase in reactant concentration per unit volume of the micelle promotes the probability of encounters between two molecules resulting in up to 1000-fold rate enhancements. The photodimerization of acenaphthylene illustrates this effect nicely; *cf.* Eq. (5-161) [720, 721].



(5-161)

At acenaphthylene concentrations as low as $2 \cdot 10^{-3}$ M, facile photodimerization takes place in benzene in the presence of nonionic or anionic surfactants, whereas in pure benzene at these concentrations no detectable amount of the two dimers is found [720]. Furthermore, the *cis*/*trans* product ratio is slightly dependent on the type of surfactant used [720, 721]. The product ratio during the course of photodimerization of 1-substituted acenaphthylenes is influenced by both solvent polarity and the addition of surfactants. The photodimerization reaction in micelles yields stereoisomer ratios similar to those obtained in polar solvents [721].

Most chemical studies in this field have concentrated on the effect of micellar surfactants on reaction rates and only a few attempts have been made to investigate the effect that micelles might have in altering the relative extent of competing reactions. For example, in studying the competitive hydrolysis and aminolysis of aryl sulfates in aqueous solution, Fendler *et al.* have found [407] that cationic micelles such as cetyltrimethylammonium bromide (CTABr) are able to alter the balance between S—O bond fission and C—O bond fission as shown in Eq. (5-162).



(5-162)

The reaction of amines with 2,4-dinitrophenyl sulfate can result in the formation of phenol and sulfate ion (by S—O bond fission), or alternatively in the production of *N*-substituted anilines and hydrogen sulfate ions (by C—O bond fission). Under non-micellar conditions, C—O bond cleavage is the dominating reaction, while cationic micelles are able to induce complete suppression of aniline formation. This dramatic effect has been explained in terms of a change in the micro-environment of both the reactants and activated complexes through contributions from hydrophobic and electrostatic interactions [407].

To summarize, solubilization of reactants in micelles can lead to the following effects: local concentration, cage, pre-orientational, microviscosity, and polarity effects [713]. *Local concentration effects* are attributable to the increase in substrate concentration per unit volume of micelle due to the tendency of hydrophobic organic substrates to be solubilized in micelles. The ability of micelles to hold reactive intermediates together long enough for intramicellar reactions between them to occur is called the *cage effect*; *cf.* Section 5.5.10. The *pre-orientational effect* is the capability of micelles to solubilize substrates in a specific orientation, thus determining the regioselectivity of their reactions. Since the viscosity inside the micelles is generally much higher compared to the surrounding aqueous solution, a substrate molecule incorporated into a micelle has less translational and rotational freedom. This could be reflected in its chemical reactivity and is called the *microviscosity effect.* Finally, the micropolarity of the hydrophobic interior of a micelle and of the micelle/solution interface is different from the polarity of the bulk aqueous solution. A change in substrate reactivity due to the variation in micropolarity is called a *polarity effect.* Solvatochromic dyes can be used as molecular probes (*e.g.* pyridinium *N*-phenolate betaine dyes) to determine directly the actual micropolarity experienced by a substrate in the region of the micelle; *cf.* [722–724].

Space limits us to only a few representative examples of this type of hydrophobic interaction in this Section.

Oil and water do not mix, but on addition of a suitable surfactant a microemulsion can be formed depending on the relative concentrations of the three components. Microemulsions (*i.e.* surfactant/water/oil mixtures) can also be used as reaction media; see references [859–862] for reviews. Microemulsions are isotropic and optically clear, thermodynamically stable, macroscopically homogeneous, but microscopically heterogeneous dispersions of oil-in-water (O/W) or water-in-oil (W/O), where "oil" is usually a hydrocarbon. The name *microemulsion*, introduced by Schulman *et al.* in 1959 [863], derives from the fact that oil droplets in O/W systems or water droplets in W/O systems are very small (ca. 10 ... 100 nm: *nanodroplets*). Unlike conventional emulsions, microemulsion domains fluctuate in size and shape with spontaneous coalescence and break-up. The oil/water interface is covered with surfactant molecules and this area can amount to as much as 10^5 m^2 per litre (!) of microemulsion.

A great variety of chemical reactions can be advantageously carried out in microemulsions [860–862]. In one of the first papers in this field, Menger *et al.* described the imidazole-catalyzed hydrolysis of 4-nitrophenyl acetate in water/octane microemulsions with AOT as an anionic surfactant [=sodium bis(2-ethyl-1-hexyl)-sulfosuccinate] [864]. The solubilized water, containing the imidazole catalyst, is confined in spherical pools encased by surfactant molecules, which have only their anionic head groups ($-SO_3^-$) immersed in the aqueous droplets. When the ester, dissolved in water-insoluble organic solvents, is added to this water/octane/AOT/imidazole system, it readily undergoes the catalysed hydrolysis under mild reaction conditions (25 °C).

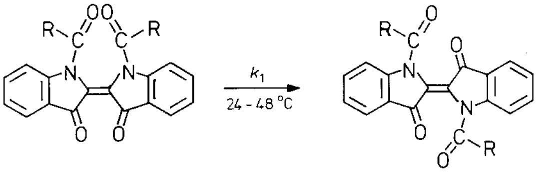
More recently, microemulsions have been developed for the oxidative/hydrolytic destruction of sulfanes (→ sulfoxides) and phosphoric acid derivatives using sodium hypochlorite and cetyl-trimethylammonium chloride (CTAC). The compounds studied serve as model compounds for chemical warfare agents such as 'mustard gas' [bis(2-chloroethyl)sulfane] and sarin (GB: *i*-propyl-methylphosphonofluoridate). Big stocks of these must now be destroyed after implementation of the Chemical Weapons Convention (CWC), which came into force in April 1997 [865].

5.5.9 Liquid Crystals as Reaction Media

Liquid crystals possess physical properties which lie somewhere between those of solids and liquids; *cf.* Section 3.1 and [725]. The rigidity which is present in a solid matrix is absent in liquid crystals, thus permitting molecular motion as well as conformational flexibility of the dissolved solute molecules. At the same time, due to the order in the liquid-crystalline phase, the randomness in motion and conformational flexibility of the dissolved solute molecules is to some extent restricted. If the structures of the solute and solvent molecules are compatible, then solute molecules can be incorporated into the liquid-crystalline phase without disrupting its order. Thus, the reactivity of substrate molecules incorporated into liquid crystals without destroying their order should be different from that in isotropic solvents. Apart from the first report on the influence of liquid crystals on chemical reactions by Svedberg in 1916 [726], the use of liquid crystals as solvents for chemical reactions has become a subject of further research only in recent decades; see references [713, 866, 867] for reviews.

For example, reactions which would lead to a product with steric demands that do not fit in the liquid-crystalline order can be retarded. That is, the rigidity of the solvent molecules can prevent uni- or bimolecular reactions which would be feasible in isotropic solvents. Alternatively, the ability of liquid crystals to orient dissolved solute molecules acts as a driving force in bimolecular reactions, particularly in entropy-controlled reactions, which are subject to severe orientational constraints in the activation process. Two factors seem to be primarily responsible in influencing the reactivity of solutes ordered in liquid crystals: (*a*) the solvation ability of the liquid-crystalline solvent, *i.e.* the efficiency with which the solute molecules are solvated, and (*b*) the degree of distortion which the reacting system must undergo during the activation process. Only a few examples showing the influence of solvent order on chemical reactions can be presented here; for reviews of organic photochemical reactions in organized media, see [713].

The rates and activation parameters for the thermal *cis* → *trans* isomerization of *N*,*N*′-distearoylindigo have been determined in both isotropic and liquid-crystalline solvents [727].



(5-163)

cis-*N*,*N*′-Diacylindigo *trans*-*N*,*N*′-Diacylindigo
R = n-$C_{17}H_{35}$

Solvent	C_6H_6 (48 °C)	$C_6H_5CH_3$ (48 °C)	isotropic BS (46 °C)	smectic BS*) (24 °C)
k_1^{rel}	68	53	31	1 (!)
$\Delta H^{\neq}/(\mathrm{kJ \cdot mol^{-1}})$	93		91	130
$\Delta S^{\neq}/(\mathrm{J \cdot K^{-1} \cdot mol^{-1}})$	−25		−33	+88

In isotropic nonpolar solvents such as benzene, toluene, and *n*-butyl stearate (BS; $t > 27$ °C), the long alkyl chains have no influence on the rate of the *cis* → *trans* isomerization reaction. However, in the smectic phase of the liquid-crystalline solvent *n*-butyl stearate, the isomerization rate is considerably slower than in isotropic solvents. The correspondingly higher activation enthalpy and the increased positive activation entropy are obviously caused by the migration of the two long stearoyl chains involved in the *cis* → *trans* isomerization. The solute alkyl chains are intertwined with ordered solvent molecules and their translocation will be resisted by nearby *n*-butyl stearate molecules. This anchoring effect, and not the shape changes of the isomerizing indigoid

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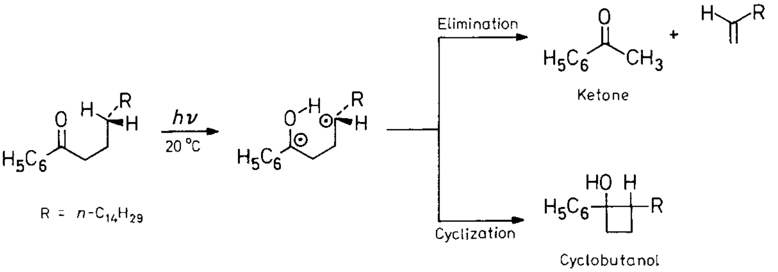
* *n*-Butyl stearate has an enantiotropic smectic B phase from 14...27 °C [727].

moiety, is what is responsible for the observed rate decrease in smectic *n*-butyl stearate [727].

Similar rate decelerations in liquid-crystalline solvents have been observed for the thermal *cis* → *trans* isomerization of a bulky tetrasubstituted ethene in cholesteric phases [728]. On the other hand, the activation parameters for the thermal *cis* → *trans* isomerization of less-dipolar substituted azobenzenes show no dependence on the solvent order. This indicates that the *cis* isomers and their corresponding activated complexes present a similar steric appearance to the solvent environment [729]. This result is more consistent with an isomerization mechanism which proceeds by inversion rather than by rotation; *cf.* Eq. (5-40) in Section 5.3.2 and [527–529, 561]. The latter reaction represents a nice example of the use of liquid-crystalline solvents as mechanistic probes [729].

As a consequence of the alignment of solute molecules in liquid-crystalline solvents, the ratio of products formed in competitive reaction pathways can be different from that observed in isotropic liquids. This is illustrated by the Norrish type II photolysis of alkyl phenyl ketones with varying alkyl chain length in the isotropic, smectic, and



(5-164)

Solvent	$n\text{-}C_7H_{16}$	$n\text{-}C_{17}H_{36}$*)	$CH_3CO_2\text{—}n\text{-}C_4H_9$	$n\text{-}C_{17}H_{35}CO_2\text{—}n\text{-}C_4H_9$**)
ketone / *cyclobutanol*	1.1	1.2	2.2	21 (!)

solid phase of *n*-butyl stearate (BS) [730]. For example, the ratio of elimination to cyclization products formed in the photolysis of *n*-heptadecyl phenyl ketone was shown to exhibit a strong phase dependence with a 10-fold increase in the smectic *n*-butyl stearate phase relative to the isotropic solvent *n*-butyl acetate; *cf.* Eq. (5-164).

The small increase in product ratio observed on changing the solvent from *n*-heptane to *n*-butyl acetate is caused by the increase in solvent polarity. When the photolysis was carried out in solid *n*-heptadecane, no specific change was observed in the ketone/cyclobutanol product ratio.

These results have been explained as follows [730]: the cyclization of the intermediate 1,4-biradical, formed after γ-H-abstraction, requires rotation of the phenyl-substituted radical centre away from its equilibrium position. That is, the phenyl group

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* Solid at 20 °C; $t_{mp} = 22.5$ °C [730].

** *n*-Butyl stearate has an enantiotropic smectic B phase from 14...27 °C [727].

must be placed in a direction perpendicular to the long axis of the alkyl phenyl ketone and the surrounding *n*-butyl stearate molecules. This should cause a disruption of the smectic solvent order and, as a consequence, cyclobutanol formation will be unfavourable in *n*-butyl stearate. For the competitive elimination reaction, the intramolecular motions required in the activation process should cause only a small distortion of the liquid-crystalline solvent order. Thus, the formation of elimination products is enhanced in the ordered solvent.

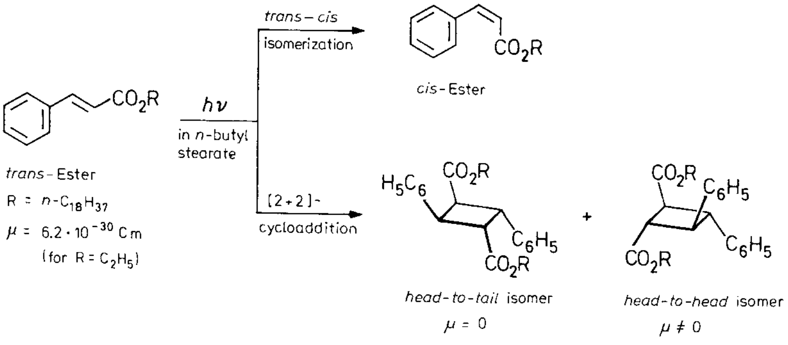
For alkyl phenyl ketones with shorter alkyl chains (*e.g.* *n*-butyl and *n*-decyl phenyl ketone), the elimination-to-cyclization ratio is virtually unaltered in the smectic solvent [730]. These ketones are not as rigidly incorporated into the liquid-crystalline lattice as *n*-heptadecyl phenyl ketone and thus are able to disrupt their local smectic environment to a greater extent. Hence, the corresponding conformations of the 1,4-biradical which lead to the elimination products are not more favourable than those which lead to cyclization products in the liquid-crystalline solvent.

In general, the greater the similarity in size and shape between the solute and liquid-crystalline solvent molecules, the easier it is for the solute to incorporate itself into the liquid-crystalline phase. If the result of a chemical reaction depends on the solvent order, then the largest effects can be expected for those solute molecules which fit best into the liquid-crystal structure. Since the structure of *n*-heptadecyl phenyl ketone is identical to *n*-butyl stearate except for the terminal phenyl and butoxy groups, it exhibits the largest solvent effect of the ketones studied [730].

Another illustrative example is the photodimerization of *n*-octadecyl *trans*-cinnamate, which has been studied in the isotropic, smectic, and crystalline phases of *n*-butyl stearate, BS [731]; *cf.* Eq. (5-165).

Irradiation of cinnamate esters leads to *trans/cis*-isomerization, dimerization, and ester cleavage reactions. The latter represents less than 5% of the total reaction pathway in this particular case. As expected, dimerization is favoured over isomerization with increasing initial solute concentrations. The *trans/cis*-isomerization involves only a relatively small perturbation of the surrounding solvent molecules. Therefore, it occurs with almost equal facility in the isotropic, smectic, and solid phases of *n*-butyl stearate. However, the regioselectivity of the photochemical $[2+2]$cycloaddition reaction is strongly phase-dependent. Of the possible dimers, only the two stereoisomers shown in Eq. (5-165) were detected in the irradiated samples. A strong preference for *head-to-tail* dimerization has been found in the smectic and solid phases. This result has been explained by assuming that not only solvent-mediated solute alignments but also dipole-dipole induced interactions between dipolar cinnamate molecules must exist in the mesophase. The dipole-dipole interaction leads to pairwise, antiparallel associations of the cinnamate molecules with interdigitation among neighbouring solute molecules. Irradiation of these antiparallel oriented solute associates preferentially yields the *head-to-tail* dimers. In summary, the regioselectivity of the photodimerization of *n*-octadecyl *trans*-cinnamate is controlled by the combination of two factors: solute alignment by ordered solvents and dipole-dipole interactions between solute molecules [731].

Similar results have been observed in the photodimerization reaction of acenaphthylene [732, 733]; *cf.* Eq. (5-161) in Section 5.5.8. A considerable increase in the production of the *trans*-adduct was reported in cholesteric liquid-crystalline media compared to the isotropic solvent benzene, in which the *cis*-adduct is the dominant product



(5-165)

Solvent	BS at 32 °C (isotropic)	BS at 18 °C*) (smectic)	BS at 8 °C (solid)
$\frac{\textit{head-to-tail}^{**)}}{\textit{head-to-head}}$	3.3	14.2	15.1

[733]. That is, the ordered structure of the cholesteric mesophase affects the formation of the *trans*-adduct advantageously. Furthermore, the *trans*/*cis* product ratio depends significantly on the initial acenaphthylene concentration. In isotropic solutions, the dimerization of singlet-excited acenaphthylene molecules is known to yield exclusively the *cis*-adduct, whereas a mixture of *cis*- and *trans*-adducts results from triplet-excited solute molecules. The lowering of *cis*-adduct production in the mesophase has been attributed to the enhanced efficiency of the triplet reaction in comparison with the singlet reaction, as shown by quantum yield measurements [732]. The increase in triplet reaction efficiencies has been ascribed to the increase in the fraction of acenaphthylene–acenaphthylene collisions which have coplanar or parallel-plane orientations with respect to the surrounding solvent molecules, and not to the increase in the total number of collisions per unit time [732]. See references [713, 732, 733] for a more detailed discussion of this photodimerization reaction.

Surprisingly, some Diels–Alder cycloaddition reactions show no variation in *endo*/*exo* product ratio with changes in solvent phase. Ordered liquid-crystalline solvents are not able to differentiate between *endo*- and *exo*-activated complexes in the Diels–Alder reaction of 2,5-dimethyl-3,4-diphenylcyclopentadienone with dienophiles of varying size (cyclopentene, cycloheptene, indene, and acenaphthylene), when it is carried out in isotropic (benzene), cholesteric (cholesteryl propionate), and smectic liquid-crystalline solvents at 105 °C [734].

Cholesteric liquid crystals are optically active nematic phases as a result of their gradual twist in orientational alignment. Therefore, cholesteric liquid-crystalline solvents are expected to induce enantioselectivity in chemical reactions; see reference [713] for a review on photoasymmetric induction by chiral mesophases. The existing results are not very promising. So far, the maximum photoasymmetric induction reported has

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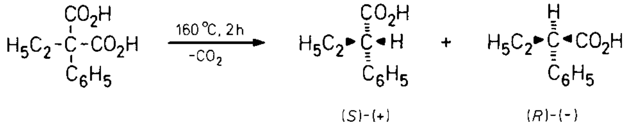
* *n*-Butyl stearate exists as an enantiotropic smectic B phase from 14…27 °C [727].

** Dimer ratios.

been for hexahelicene formation in cholesteric phases, with an enantiomeric excess of the right-handed helix of about 1% [735]. The decarboxylation of ethyl-phenylmalonic acid in cholesteryl benzoate as a liquid-crystalline solvent gave 2-phenylbutyric acid (overall yield 80 cmol/mol), which was shown to be optically active with an enantiomeric excess of 18% of the (*R*)-(−) enantiomer; *cf.* Eq. (5-166) [765]. In contrast to the



(5-166)

18% *ee* found in the cholesteric solvent, decarboxylation of ethyl-phenylmalonic acid in bornyl acetate, an isotropic chiral solvent, yielded 2-phenylbutyric acid which was essentially racemic (*ee* = 0%) [765]. Using cholesteryl 4-nitrobenzoate as a liquid-crystalline solvent, the *ortho*-Claisen rearrangement of γ-methylallyl 4-tolyl ether yielded optically active 2-(α-methylallyl)-4-methylphenol, but the absolute configuration and optical purity of the rearrangement product were unknown [766]. Various explanations for the failure of asymmetric induction in thermal reactions in liquid-crystalline media have been given in the literature [736, 737].

Not only reaction rates, but also the positions of chemical equilibria can be influenced by liquid crystals as reaction media. A nice example is the ionization equilibrium of chloro-tris(4-methoxyphenyl)methane according to $Ar_3C{-}Cl \rightleftharpoons Ar_3C^+ + Cl^-$, which is more shifted in favour of the nearly planar triarylcarbenium ion in nematic liquid crystals as compared to in an isotropic reaction medium [868]. Obviously, the disc-shaped carbenium ion fits better into the rod-like nematic phase than the tetrahedral covalent ionogen, which distorts the internal structure of the nematic liquid crystal.

All in all, liquid-crystalline media are not generally useful solvents for controlling the rates and stereochemistries of chemical reactions. In each case, careful consideration of the fine details regarding the structure of educts and activated complex, their preferred orientations in a liquid-crystalline solvent matrix, and the disruptive effects that each solute has on the solvent order has to be made. A mesophase effect can only be expected when substantial changes in the overall shape of the reactant molecule(s) occur during the activation process [734].

5.5.10 Solvent Cage Effects

When two chemical species react together at every encounter*), chemical change can take place only as fast as the reactants can diffuse together. In contrast to the gas phase, there may be many collisions per encounter in solution. Considering a pair of molecules that have just encountered each other or, what in this regard is equivalent, a pair of molecules that have just arisen from the decay of a parent molecule, these molecules can

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* The whole process of two species coming together and remaining together for a number of subsequent collisions in solution has been called an "encounter".

become separated from each other only as a result of their diffusional motion through the inert solvent. If this diffusion is comparatively slow in solution, diffusion may be answerable for the observable rates of many reactions, since the slowest step in a sequence determines the net rate of change. Such reactions are called "encounter-" or "diffusion-controlled" [18, 408, 409, 409a].

Reactions that occur with an activation energy of less than about 20 kJ/mol (5 kcal/mol) depend upon the rate at which the reactants move together through the solution. Since the movement of a molecule through an inert solvent has itself an activation energy of diffusion of about 20 kJ/mol, this movement becomes the slowest step for diffusion-controlled reactions. Almost all radical–radical recombination reactions require so little activation energy that they are usually diffusion-controlled in solvents of normal viscosity. Thus, the recombination rates for simple alkyl radicals in inert solvents lie in the range $10^8 \ldots 10^{10}$ $\mathrm{L \cdot mol^{-1}\ s^{-1}}$ at 25 °C [410]. Ion combination reactions such as the acid-base reaction between the solvated proton and solvated hydroxide ion are also known to be diffusion-controlled. This reaction has one of the largest rate constants known for liquid-phase reactions, $1.4 \cdot 10^{11}$ $\mathrm{L \cdot mol^{-1}\ s^{-1}}$ in water at 25 °C [411].

When a pair of radicals (or ions) have reached adjacent positions through diffusion, or have been generated from a single parent molecule as in the decomposition of radical initiators, they are hemmed in by a cage of solvent molecules – an effect that has been called the "solvent cage effect"*). The two species must diffuse to become statistically distributed in the solvent, but, because of the activation energy of diffusion, they collide with each other several times before they separate, and recombination may occur during these collisions**). This type of reaction is called a "cage reaction" [413].

Rate constants for diffusion-controlled reactions can be calculated from the laws of diffusion [18, 869]. For a simple cage reaction $\mathrm{A\cdot + \cdot B \rightarrow AB}$, in which $\mathrm{A\cdot}$ reacts with $\mathrm{\cdot B}$ every time the two approach one another to within a distance R, the following equation can be derived,

$$k_2 = 4\pi \cdot R \cdot N_\mathrm{A} \cdot (D_\mathrm{A} + D_\mathrm{B})$$

where k_2 represents the overall second-order rate constant for uncharged reactants, R is the average radius of the solvent cage, N_A is Avogadro's number, and D_A and D_B are

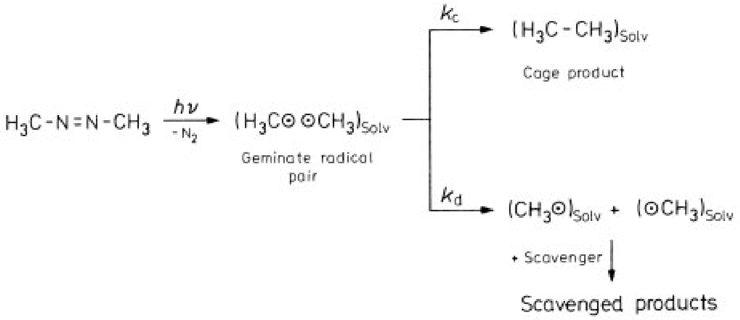
---

* The concept of a *solvent cage* restricting the separation of two reactants was first introduced by Frank and Rabinowitsch [412] in predicting a reduction in the quantum yield for photodissociation processes in solution compared with the gas phase. Thus, when iodine in solution is dissociated by a flash, the quantum yield is much less than unity indicating that most of the iodine atoms recombine before escaping from the solvent cage. The *solvent cage* is an aggregate of solvent molecules that surrounds the fragments formed by thermal or photochemical bond cleavage of a precursor species. A more imaginative description of the cage effect has been given by Houston [18]: "The difference between a reaction in the gas phase and one in solution is much like the difference between a romantic encounter on an empty beach and one on a crowded dance floor. The romance of closeness is not appreciably changed by the surrounding solvent of dancers, but it is more difficult to find one another in a crowd, and correspondingly difficult to separate once the dance has ended. The solvent tends to slow the rate of approach of the reactants, so that they must diffuse toward one another through the solution, but it also keeps them together for many 'collisions' once they come in contact. This latter phenomenon is often referred to as the *cage effect*."

** Other radical reactions which can compete with recombination inside the solvent cage are disproportionation [414] and reaction with the adjacent solvent molecules.

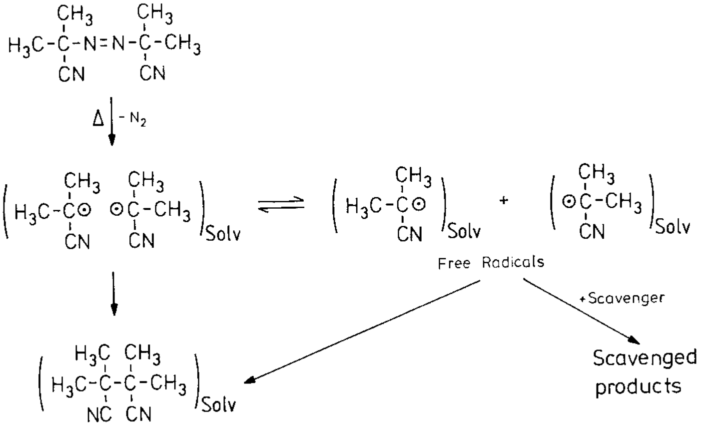
the diffusion coefficients of reactants $A\cdot$ and $\cdot B$ through the solvent under consideration. For a cage reaction between a pair of reactants whose average diameter is $R = 2.0$ nm and diffusion coefficients of $D_A \approx D_B \approx 10^{-9}$ $m^2 \cdot s^{-1}$, typical for many species in aqueous solution, a rate constant of $k_2 = 3.0 \cdot 10^{10}$ $L \cdot mol^{-1} \cdot s^{-1}$ can be calculated according to this equation [18]. For oppositely charged reactants A^+ and B^-, an additional multiplicative factor due to the mutual electrostatic attraction has to be added.

With azoalkanes, peroxides, and other initiators, varying percentages of the radicals formed react together as a geminate pair in the solvent cage, as seen, for instance, in the photolysis of azomethane according to Eq. (5-167) [415–417]. The efficiency of free-radical production, *F*, in the decomposition of azomethane can be described in terms of an effective rate constant, k_d, which approximately describes the diffusional separation of caged radical pairs to give free radicals, a process competing with radical–radical reactions within the solvent cage, the rate constant of which is designated as k_c. The combination reaction must obviously be very fast, in order to compete successfully with diffusion. It is usually assumed that k_c is nearly independent of the nature of the solvent, and that all the variation in cage products may be attributed to k_d. Very clear evidence for the existence of a cage effect in reaction (5-167) was found from the results of crossover experiments [416, 417]. When a mixture of azomethane and perdeuterioazomethane is photolyzed in the gas phase, the $CH_3\cdot$ and $CD_3\cdot$ radicals formed recombine rapidly to yield CH_3CH_3, CD_3CD_3, and CH_3CD_3 in such proportions (1:1:2) that it is clear that $CH_3\cdot$ and $CD_3\cdot$ are randomly mixed before recombination. When, however, the same experiment is repeated in the inert solvent *i*-octane, no CH_3CD_3 is detected when CH_3CH_3 and CD_3CD_3 are formed along with N_2. Evidently, solvent molecules keep methyl radicals formed from the same parent molecule together until they recombine. The cage effect can occur in the gas phase at high pressures, as has been demonstrated for the photolysis of azomethane in propane at 49 bar. Here, propane and intact reactant molecules act as a quasi-solvent and prevent formation of CH_3CD_3 [416]. For further gas-phase analogous cage effects, see reference [870].



(5-167)

Cage effects also account for the fact that not all the radicals produced from the decomposition of initiators such as azobisisobutyronitrile (AIBN) are effective in initiating radical polymerizations. In the somewhat simplified reaction Scheme (5-168) depicting the thermolysis of AIBN, two types of cyanopropyl radicals are shown, one still within the solvent cage, whereas the others have reached their statistical separation in the solution. Adding certain reactive compounds called scavengers to the solution should divert the free radicals away from dimer formation. In other words, radical



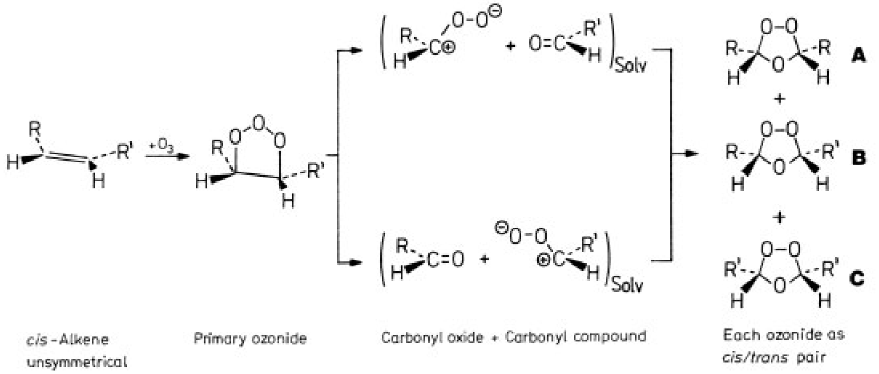
(5-168)

scavengers should reduce the yield of tetramethylsuccinonitrile derived from the free radicals (but not that formed from the caged ones) to a limiting value. This then represents the amount of product formed within the solvent cage. Indeed, the yield of tetramethylsuccinonitrile from the thermolysis of AIBN in tetrachloromethane at 80 °C falls from about 96 cmol/mol when no scavenger is present to a constant value of about 19 cmol/mol using *n*-butanethiol, a good hydrogen donor, as a scavenger [418]. This means that 19 cmol/mol of the initiator radicals are lost in solvent cage recombinations and only 81 cmol/mol of AIBN molecules are efficient in free-radical production under these reaction conditions. The initiator efficiency of AIBN is, in fact, lower under most circumstances, since only few substrates approach the reactivity of *n*-butanethiol as a scavenger. The fraction of AIBN molecules leading to initiation of styrene polymerization increases as the concentration of the monomer increases, reaching a limiting value of 68 cmol/mol above 2 mol/L styrene in an inert solvent [419]. The remaining 32 cmol/mol may be attributed to the reactions of the geminate radical pairs.

Solvent cage effects have been observed not only in the decomposition of azoalkanes, but also in the thermolysis of other compounds, such as peroxides (*e.g.* diacyl peroxides [420], peresters [421]), which generate two radicals simultaneously. For example, diacetyl peroxide initially labeled with ^{18}O in the carbonyl oxygen was partially thermolysed in *i*-octane at 80 °C and it was found that *ca.* 38 cmol/mol of all geminate radical pairs formed in the decomposition recombine to give diacetyl peroxide with scrambling of the label [420]. Solvent cage effects have even been found for ion-producing reactions, albeit only at high external pressures. The solvolysis of 2-bromopropane in a 4:1 methanol/ethanol mixture at 46 °C becomes diffusion-controlled at pressures higher than 40 kbar [738]. Liquid-crystalline solvents and micellar systems can also provide solvent cages. Liquid crystals and micelles have the capacity to hold two reactive species together for a longer period of time compared to isotropic, homogeneous solutions. Micellar aggregates are particularly effective in imposing cage constraints on chemical reactions. Photochemical examples of the consequences of restricting solute diffusion in liquid crystals and in micelles can be found in references [713, 871]; *cf.* also Sections 5.5.8 and 5.5.9.

The prediction of solvent effects on k_d, as reflected by the efficiency of free-radical production, *F*, has been attempted by considering the correlation between *F* and macroscopic solvent parameters such as solvent viscosity [413]. That the proportion of cage reactions depends on the viscosity of the solvent used was shown by Kochi [422], who decomposed a series of diacyl peroxides in *n*-pentane and decalin. In decalin, the more viscous solvent, photolysis of two different diacyl peroxides gave high yields of the symmetrical dimers and only a minor yield of cross-dimer, thus indicating the strong solvent cage effect. In the more fluid solvent *n*-pentane, the cage effect is less important and a higher proportion of the cross-products was formed. Usually, however, no simple relationship with solvent viscosity was found. Studying the photolysis of azomethane in a wide range of different media, Martin *et al.* [423] were able to correlate the observed amount of cage product ethane to macroscopic solvent parameters other than viscosity, namely solvent internal pressure and cohesive energy density (*cf.* Section 5.4.2).

We shall conclude this Section with an example of solvent cage effects of ion-molecule recombination reactions as found in the ozonolysis of alkenes in non-polar solvents [739, 740]. According to the Criegee mechanism [424], unsymmetrically



(5-169)

substituted alkenes ought to give two zwitterions and two carbonyl compounds after decomposition of the unstable primary ozonide, as shown in reaction scheme (5-169). If both scission and recombination are statistical, the three possible final ozonides *A*, *B*, and *C* should be formed in a 1:2:1 ratio, provided there is no preferred breakdown of the initial ozonide and no solvent cage. The experimentally determined values of this molar ratio differ from the statistical value, the yield of the symmetrical cross-ozonides always being lower, as observed for 2-pentene [425] and 2-hexene [426]. This means that part of the recombination reaction must occur in a solvent cage. With an increase in the initial concentration of alkene, the relative proportions of “normal” and “cross” ozonides approach the statistical values. When he failed to find cross-ozonides in the ozonolysis of 3-heptene, Criegee postulated that the zwitterion and carbonyl fragments were formed and recombined in a solvent cage, thus preventing cross-recombination [427]. The earlier failure of Criegee to obtain any cross-ozonides in the case of 3-heptene can now probably be attributed to the alkene concentration used [428]. At the concentration of alkene normally used in ozonolysis the predominant product is the normal parent ozonide of the unsymmetrically substituted alkene. A plot of the ratio of normal ozonides to cross-ozonides *versus* alkene concentration shows that cross-ozonide formation decreases with dilution [428]; *cf.* also [428a].

Reduced solvent cage effects have, however, been observed for ozonations in polar solvents such as dichloromethane and ethyl acetate, in contrast to nonpolar hydrocarbons; *cf.* [739, 740]. Increasing the polarity of the ozonation solvent leads to an increase in the ratio of cross to normal ozonides formed from unsymmetrical alkenes. Obviously, the increased solvent polarity increases the separation of the carbonyl oxide and the carbonyl compound, allowing them to react more independently rather than in a solvent cage. Accordingly, in contrast to nonpolar solvents, an increase in reaction temperature has no effect on the ozonide ratio. This is due to the fact that in polar solvents the solvent cage effect is minimal. For the ozonolysis of an equimolar mixture of ethene and tetradeuterioethene, leading to two normal and one cross-ozonide, it has been estimated that in polar solvents such as CH_2F_2 at least 90% of the final ozonide formation occurs outside the solvent cage in which the primary ozonide decomposition took place. This percentage decreases to about 10% out-of-cage recombination in a nonpolar solvent such as *i*-butane [741].

In conclusion, the relative yields of the normal and cross-ozonides are a function of initial alkene concentration, solvent polarity, and temperature. High alkene concentration, polar solvents, and high temperatures maximize the cross-ozonide yields, with proportions close to statistical amounts in favourable cases [739, 740].

For recent comprehensive reviews on the ozonation reaction, dealing not only with solvent effects on the relative yields of normal and cross-ozonides, but also with solvent effects on the total ozonide yield and the *cis*/*trans* ozonide ratio from *cis*- and *trans*-alkenes, see references [739, 740]. Supplementary solvent effects have been reported for the ozonolysis of 3-aryl-1-methylindenes yielding solvent-dependent mixtures of final *exo*- and *endo*-ozonides [742].

5.5.11 External Pressure and Solvent Effects on Reaction Rates

Not only the internal pressure of a solvent can affect chemical reactions (see Section 5.4.2 [231, 232]), but also the application of external pressure can exert large effects on reaction rates and equilibrium constants [239, 429–433, 747–750]. According to Le Chatelier's principle of least restraint, the rate of a reaction should be increased by an increase in external pressure if the volume of the activated complex is less than the sum of the volumes of the reactant molecules, whereas the rate of reaction should be decreased by an increase in external pressure if the reverse is true. The fundamental equation for the effect of external pressure on a reaction rate constant *k* was deduced by Evans and Polanyi on the basis of transition-state theory [434]:

$$\left(\frac{\partial \ln k}{\partial p}\right)_T = -\frac{\Delta V^{\neq}}{RT} \tag{5-170}$$

provided that k is expressed in pressure-independent concentration units (mole fraction or molality scale) at a fixed temperature and pressure*). The volume of activation, $\Delta V^{\neq}$, is interpreted as the difference between the partial molar volume of the activated complex including its molecules of solvation, $V^{\neq}$, and the sum of the partial molar volumes of the reactants with their associated solvent molecules, $\sum r \cdot V^{\mathrm{R}}$, at the same temperature and pressure: $\Delta V^{\neq} = V^{\neq} - \sum r \cdot V^{\mathrm{R}}$, where r is the stoichiometric number of the reactant R and V^{R} its partial molar volume.

To produce significant changes in $\ln k$, pressures of several hundred bars are commonly used. While a change in reaction rate by a factor of 2 to 4 can be anticipated for a change in temperature of 10 °C, a pressure change of about 700 bar is required to bring about the same effect even for reactions with the relatively large activation volume of $\pm 40\ \mathrm{cm}^3 \cdot \mathrm{mol}^{-1}$ [435]. Normally, the magnitude of $\Delta V^{\neq}$ lies somewhere between $+25$ and $-25\ \mathrm{cm}^3 \cdot \mathrm{mol}^{-1}$, which requires pressures of *ca.* 1200 bar to produce rate changes of a factor of 3. The minus sign in Eq. (5-170) means that pressure accelerates reactions which are characterized by a volume shrinkage in passing from the reactants through the activated complex (negative $\Delta V^{\neq}$) and retards those with a volume expansion (positive $\Delta V^{\neq}$). In many cases, a plot of ln k against pressure is linear, indicating that for these reactions the quantity $\Delta V^{\neq}$ is independent of pressure. However, above *ca.* 10 kbar, reactions do not obey the ideal rate equation (5-170) since activation volumes are pressure-dependent; the values of $\Delta V^{\neq}$ generally decrease as pressure increases. Extensive compilations of activation and reaction volumes in solution for a great variety of pressure-dependent chemical reactions can be found in references [430, 749].

The activation volume changes arise from two sources: (a) making and breaking of chemical bonds, and (b) interaction of reactants and activated complex with the surrounding solvent molecules. Therefore, $\Delta V^{\neq}$ can be considered as being composed of $\Delta V_{\mathrm{i}}^{\neq}$, the *intrinsic* change in molar volume of the reactant molecules themselves in forming the activated complex, as well as $\Delta V_{\mathrm{e}}^{\neq}$, the change in molar volume of the solvating solvent molecules during the activation process, according to Eq. (5-171)**):

$$\Delta V^{\neq} = \Delta V_{\mathrm{i}}^{\neq} + \Delta V_{\mathrm{e}}^{\neq} \tag{5-171}$$

$\Delta V_{\mathrm{e}}^{\neq}$ is related to the well-known volume contraction normally observed on dissolution of electrolytes and called *electrostriction*. The contraction of the solvent surrounding an ion is best expressed by the Drude–Nernst equation (5-172):

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* If k is expressed in the pressure-dependent molarity scale (*i.e.* $\mathrm{mol} \cdot \mathrm{L}^{-1}$), its pressure-dependence is given by

$$\left(\frac{\partial \ln k}{\partial p}\right)_T = -\frac{\Delta V^{\neq}}{RT} - \kappa(n-1)$$

where κ is the compressibility of the solution (usually that of the solvent) and n is the kinetic order of the reaction. For first-order reactions ($n = 1$), the equations for the pressure-dependence of k are identical. For reactions of higher order, however, the additional compressibility term must be taken into account.

** For modifications of the somewhat simplified Eq. (5-171) and corresponding discussions, see references [872, 873].

$$\Delta V_e = -\frac{N_A \cdot z^2 \cdot e^2}{2r \cdot \varepsilon_r^2} \frac{\partial \varepsilon_r}{\partial p} \tag{5-172}$$

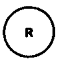
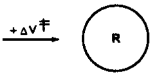
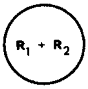
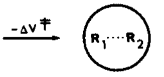
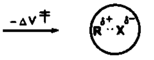
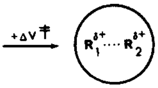
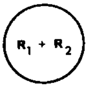
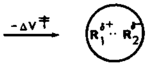
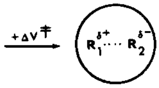
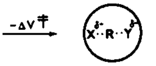
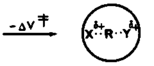
The solvent is assumed to be a continuum of relative permittivity ε_r, and the ion to be a hard sphere of radius r with charge $z \cdot e$; N_A is the Avogadro number. Eq. (5-172) represents the electrostatic contraction change in volume for a mole of ions. According to the Drude–Nernst equation, electrostriction should be proportional to the square of the charge on the ions, inversely proportional to the ionic radii, and should increase in proportion to the value of $(1/\varepsilon_r^2)/(\partial \varepsilon_r/\partial p)$, which depends on the nature of the solvent. It follows that ΔV_e will vary strongly in reactions where charges are created or neutralized, which, in turn, should show up as a solvent dependence of $\Delta V^{\neq}$.

$\Delta V_i^{\neq}$ represents the change in volume due to changes in bond lengths and angles. It is this contribution to $\Delta V^{\neq}$ that is connected to the reaction mechanism in terms of the relative positions of the atoms in reactants and the activated complex. The absolute size of $\Delta V_i^{\neq}$ has been concluded to be approximately $+10\ \text{cm}^3 \cdot \text{mol}^{-1}$ for bond cleavage and approximately $-10\ \text{cm}^3 \cdot \text{mol}^{-1}$ for bond formation in reactions of organic molecules [430].

In a reaction, $A \rightleftharpoons [X]^{\neq} \rightarrow C + D$, bonds will be stretched to form $[X]^{\neq}$, so that $\Delta V_i^{\neq}$ would be expected to be positive for unimolecular dissociative reactions and negative for the reverse bimolecular associative reaction of C and D. The $\Delta V_e^{\neq}$ contribution is caused by the rearrangement of the solvent molecules due to steric requirements of the reaction and to the change in charge density on activation. The latter effect can be predicted on the basis of the qualitative theory of solvent effects introduced by Hughes and Ingold [16, 44] (*cf.* Section 5.3.1), representing the reacting ions or dipolar molecules as spheres and the solvent as a dielectric. Creation or concentration of charge on the reacting species, on passing from the initial to the transition state, will increase the intermolecular electrostatic forces between the solute and the permanent or induced dipoles in the solvating molecules. This leads to a reduction in volume, called *electrostriction*, of the solvate complex. Since the extent of electrostriction varies as the square of the charge on the sphere according to Eq. (5-172), the association of ions with like charges will increase the electrostriction in the solvent and $\Delta V_e^{\neq}$ will be large and negative, whereas association of two oppositely charged reactants will be accompanied by a large positive $\Delta V_e^{\neq}$. Because the degree of solvation of ionic or strongly dipolar species may be extensive, the $\Delta V_e^{\neq}$ term often predominates over the $\Delta V_i^{\neq}$ term. The activation volume, therefore, reflects not only the intrinsic differences in molecular dimensions of reactants and activated complex, but also the difference in their degree of solvation. Pressure is therefore a probe uniquely suited for the study of solvation changes during a reaction.

The importance of the solvent in determining the effects of pressure on reaction rates has been recognized in general terms for a long time, but the first satisfactory discussion was given by Buchanan and Hamann in 1953 [436]. A schematic compilation of pressure and solvent effects on reactions of different charge type, established by Dack [27, 239], is given in Table 5-25. The entire basis of the effect of solvent polarity on $\Delta V^{\neq}$, as shown in Table 5-25, is that less polar solvents have higher compressibilities and are therefore more constricted by ionic or dipolar solutes than more polar solvents, which exhibit smaller compressibilities owing to the strong intermolecular interactions already present in the absence of a solute. This consideration would also suggest a cor-

Table 5-25. Effect of external pressure and solvent polarity on the rate of reactions of different charge type and on their volume of activation, $\Delta V^{\neq}$ [27, 239].

No.	Reactants	Activated Complex	Effect of increased pressure on reaction rate	Effect of increased solvent polarity on $\Delta V^{\neq}$
1			Decrease	None
2			Increase	None
3			Increase	More negative
4			Decrease	More positive
5			Increase	More negative
6			Decrease	More positive
7			Decrease	More positive
8			Decrease	More positive

relation between $\Delta V^{\neq}$ and the entropy of activation, $\Delta S^{\neq}$, because an increase in electrostriction due to an intensification of the electric field around the solute corresponds to a decrease in both volume and entropy owing to reduced freedom of motion within the solvent complex. That is, a large negative $\Delta V^{\neq}$ value should, in principle, correspond to a large negative $\Delta S^{\neq}$ value for reactions whose temperature and pressure dependence has been investigated in solvents of different polarity. Indeed, a linear relationship of $\Delta V^{\neq}$ with $\Delta S^{\neq}$ has been reported for many reactions.

Two typical examples shall illustrate the predictions made by Table 5-25. Clear-cut examples of reaction type 2 are Diels–Alder cycloaddition reactions*). The solvent

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* The first Diels–Alder reaction studied under high pressure was the dimerization of cyclopentadiene [751]. For recent, more detailed studies of the pressure-dependence of Diels–Alder cycloaddition reactions in solvents of different polarity, as well as discussions of the corresponding mechanistic aspects, see references [857, 874].

Table 5-26. Effect of external pressure and solvent polarity on reaction rate and activation volume of the Diels–Alder reaction between isoprene and maleic anhydride at 35 °C [437]; *cf.* Eq. (5-42) in Section 5.3.3.

Solvents	$k_2 \cdot 10^4/\text{s}^{-1}$ a)		$k_2^{\text{rel.}}$ b)	$\Delta V^{\neq}/(\text{cm}^3 \cdot \text{mol}^{-1})$ at 1 bar c)
	at 1 bar	at 1336 bar		
Dichloromethane	5.28	26.1	4.9	−39.8
Dimethyl carbonate	1.82	–	–	−39.3
Acetone	2.18	11.8	5.4	−39.0
Diisopropyl ether	0.597	3.56	6.0	−38.5
1-Chlorobutane	1.59	9.31	5.9	−38.0
Acetonitrile	6.25	33.9	5.4	−37.5
Ethyl acetate	1.22	6.33	5.2	−37.4
1,2-Dichloroethane	5.50	32.2	5.9	−37.0
Nitromethane	9.86	44.4	4.5	−32.5

a) Rate constants based on mol fraction scale.

b) $k_2^{\text{rel.}} = k_2(1336\ \text{bar})/k_2(1\ \text{bar})$.

c) Limit of error $\pm 0.8\ \text{cm}^3 \cdot \text{mol}^{-1}$.

$\Delta\Delta V^{\neq} = 7.3\ \text{cm}^3 \cdot \text{mol}^{-1}$

effect on the activation volumes for such a cycloaddition reaction is reported in Table 5-26 [437]. In agreement with an isopolar cyclic activated complex being intrinsically smaller than the reactants, large negative values of $\Delta V^{\neq}$ have been found for this reaction. As expected, solvent polarity has comparatively little influence on $\Delta V^{\neq}$ ($\Delta\Delta V^{\neq} = 7.3\ \text{cm}^3 \cdot \text{mol}^{-1}$ between nitromethane and dichloromethane). This suggests that the solute–solvent interactions of the activated complex are small and similar to those of the reactants. Nevertheless, the small solvent effects obtained might be explained in terms of solvent internal pressure [27, 438], this acting on the rates of nonpolar reactions in the same direction as external pressures*).

Similar pressure effects have been observed in the 1,3-dipolar cycloaddition of diazo-diphenylmethane to various alkenes. This is in agreement with a concerted mechanism involving an isopolar activated complex [752, 753]; *cf.* Section 5.3.3. For the 1,3-dipolar cycloaddition of diazo-diphenylmethane to dimethyl acetylenedicarboxylate at 25 °C in *n*-hexane ($\Delta V^{\neq} = -24\ \text{cm}^3 \cdot \text{mol}^{-1}$) and in acetonitrile ($\Delta V^{\neq} = -15\ \text{cm}^3 \cdot \text{mol}^{-1}$), the solvent-induced difference $\Delta\Delta V^{\neq}$ is only $9\ \text{cm}^3 \cdot \text{mol}^{-1}$; this corresponds to a very small rate constant solvent effect, $k_2(\text{CH}_3\text{CN})/k_2(n\text{-C}_6\text{H}_{14}) = 3.4$ [752].

Contrary to reactions going through isopolar transition states, reactions of types 3 to 8 in Table 5-25, which involve formation, dispersal or destruction of charge, should exhibit large solvent effects on their activation volumes. This is shown in Table 5-27 for the $\text{S}_\text{N}2$ substitution reaction between triethylamine and iodoethane [441], an example of the well-known Menschutkin reaction, the pressure dependence of which has been investigated thoroughly [439–445, 755].

Corresponding to reaction type 5 in Table 5-25, increasing pressure leads to an increase in reaction rate, which is more pronounced in less polar solvents. The $\Delta V^{\neq}$

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* For common organic solvents, the internal pressures range from 1800 to 5000 bar at 25 °C [438].

Table 5-27. Effect of external pressure and solvent polarity on reaction rate and activation volume of the Menschutkin reaction between triethylamine and iodoethane at 50 °C [441]; *cf.* also Table 5-5 in Section 5.3.1 [59].

Solvents	$k_2 \cdot 10^6/(\mathrm{L \cdot mol^{-1} \cdot s^{-1}})$		$k_2^{\mathrm{rel.\,a)}}$	$\Delta V^{\neq}/(\mathrm{cm^3 \cdot mol^{-1}})$ at 1 bar[b)]
	at 1 bar	at 1961 bar		
n-Hexane	0.123	1.35	11.0	−51.5
Acetone	318	2600	8.2	−48.5
Benzene	27.8	–	–	−46.2
Chlorobenzene	92.0	627	6.8	−44.6
Methanol	50.6	208	4.1	−40.6
Nitrobenzene	934	4450	4.8	−37.0

[a)] $k_2^{\mathrm{rel.}} = k_2(1961\ \mathrm{bar})/k_2(1\ \mathrm{bar})$. $\Delta\Delta V^{\neq} = 15\ \mathrm{cm^3 \cdot mol^{-1}}$

[b)] The limit of error for $\Delta V^{\neq}$ lies between ±1.6 and ±2.6 $\mathrm{cm^3 \cdot mol^{-1}}$.

values observed in solvents of different polarity demonstrate clearly that nonpolar solvents undergo more electrostriction than polar media ($\Delta\Delta V^{\neq} = 15\ \mathrm{cm^3 \cdot mol^{-1}}$ between *n*-hexane and nitrobenzene). Somewhat more positive activation volumes have been reported for the Menschutkin-type reaction of triphenylphosphane with iodomethane at 30 °C: $\Delta V^{\neq} = -28.0\ \mathrm{cm^3 \cdot mol^{-1}}$ in acetonitrile and $\Delta V^{\neq} = -17.6\ \mathrm{cm^3 \cdot mol^{-1}}$ in the slightly more polar propylene carbonate; the reaction is 245 times faster in propylene carbonate than it is in nonpolar diisopropyl ether [755].

Reaction type 3 in Table 5-25 is best represented by the S_N1 solvolysis of 2-chloro-2-methylpropane; *cf.* Eq. (5-13) in Section 5.3.1. Considering the heterolysis of the C—Cl bond, one would expect the activation volume to be positive because of the C—Cl stretching during the activation process. However, a negative activation volume of $\Delta V^{\neq} = -22.2\ \mathrm{cm^3 \cdot mol^{-1}}$ has been found for this solvolysis at 30 °C in ethanol/water (80:20 cL/L), indicating a strong volume contraction due to solvation of the dipolar activated complex (electrostriction) [756]. Typical activation volumes for haloalkane solvolyses in protic solvents are in the range of $-15 \ldots -30\ \mathrm{cm^3 \cdot mol^{-1}}$.

Both S_N1 and S_N2 solvolyses of haloalkanes have negative activation volumes at low external pressures because the activation volume is mainly determined by the electrostriction of the surrounding solvent molecules [*cf.* reaction types 3 and 7 in Table 5-25 and Eq. (5-171)]. The electrostriction of solvents is usually high at zero or low external pressures because common solvents are quite compressible [875]. However, at very high external pressures, the compressibility of solvents decreases greatly. As a consequence, the electrostriction around a solute ion or dipole, which is related to the macroscopic compressibility, drops significantly at high pressures (*i.e.* at several tens of kilobars). Under such drastic experimental conditions, an S_N1 solvolysis should now have a positive and an S_N2 solvolysis a negative activation volume, which allows a clear distinction between the two mechanisms. This has indeed been found for the solvolysis of 2-chloro-2-methylpropane (S_N1) and iodomethane (S_N2) in glycerol as solvent and nucleophile at high external pressures [738]. The S_N1 reaction now has (above 16 kbar) a positive $\Delta V^{\neq}$ because the C–Cl bond length is increased in the activated complex, while $\Delta V^{\neq}$ remains negative (up to 70 kbar) for the S_N2 reaction because a solvent molecule forms a partial

$O \cdots C$ bond in the activation process. An analogous high-pressure experiment (up to 82 kbar) showed that the solvolysis of 2-bromopropane in methanol/ethanol (4:1) follows an S_N1 mechanism, with a negative $\Delta V^{\neq}$ at low pressures ($p < 40$ kbar), and a positive $\Delta V^{\neq}$ at higher pressures ($p > 40$ kbar) [738].

Many other examples of pressure-dependent organic reactions of the types collected in Table 5-25 are given in references [239, 429–433, 747–750]. In general, the influence of external pressure and solvent polarity can be used to draw conclusions about whether or not the activated complex is more dipolar than the initial reactants, and helps to clarify reaction mechanisms in the framework of the transition-state theory (TST).

High-pressure effects can be used to study dynamic solvent effects on reactions in highly viscous liquid phases, that is, in such phases in which reactions are shifted from the equilibrium TST-valid region to the nonequilibrium TST-invalid region at high pressures; *cf.* Section 5.3.5 and a recent review by Asano [754]. Commonly, chemical transformations and the corresponding rearrangement of the solvent molecules in the solvation shell are concerted processes and reactions can be described by one reaction coordinate. If the thermal fluctuations of the solvent are not fast enough to maintain the thermal solvation equilibrium between reactants and activated complex, then the solvent rearrangement during the activation process can be rate-determining. The *cis* → *trans* isomerization reactions at N=N and C=N double bonds of azobenzenes and azomethines are effected by inversion at nitrogen [*cf.* Eq. (5-40) in Section 5.3.2] and the activation volumes are close to zero as expected. However, when azobenzene is 4,4′-donor/acceptor-substituted, the reaction proceeds by rotation through a dipolar activated complex in polar solvents, and is accompanied by the expected large negative activation volume. The rates of both reactions are independent of the viscosity of the solvent. These unimolecular isomerization reactions have activation energies of 50–70 kJ/mol and they are slow enough to proceed in the TST-valid solvation equilibrium region at normal pressure. However, in viscous solvents (*e.g.* 2-methylpentane-2,4-diol, glycerol triacetate), increasing the external pressure leads first to a normal rate behaviour, and then, at higher pressures, this becomes a strong pressure-dependent rate retardation. This is best explained by a shift of the reaction from the TST-valid region at lower pressure to the TST-invalid region at higher pressure. Under these circumstances, the reactant molecule has to wait for the formation of the solvation shell that stabilizes the activated complex before it undergoes the isomerization. The solvent rearrangement is then the rate-determining step and this rate constant was found to correlate with solvent viscosity. Thus, for the reaction systems studied, the chemical transformation and the solvent rearrangement have to be described by two independent reaction coordinates [754].

Finally, it should be mentioned that external pressure has found more and more application in organic synthesis, not least because of the increasing commercial availability of high-pressure devices. For the following types of organic reactions, a rate enhancement with increasing pressure is expected [749]: (a) associative reactions in which the number of molecules decreases in forming the products; *e.g.* cycloaddition and condensation reactions; (b) reactions which proceed via cyclic isopolar activated complexes; *e.g.* Cope and Claisen rearrangements; (c) reactions which proceed *via* dipolar activated complexes; *e.g.* Menschutkin-type S_N2 reactions, aromatic electrophilic substitution reactions; and (d) reactions with steric hindrance. Comprehensive reviews on organic syntheses under high external pressure can be found in references [430, 749].

Whilst dealing with pressure-dependent chemical reactions, the use of supercritical fluids (sc-fluids) as reaction media should be briefly mentioned here; see Table 3-4 and Figure 3-2 in Section 3.2, as well as references [757, 758]. An important property of supercritical fluids as solvents is the possibility of manipulating the physicochemical properties of these solvents through small changes in *pressure* and temperature. This can influence solubilities, mass transfer (diffusivity), and rate constants of the reacting systems which are dissolved in supercritical solvents. The effect of external pressure on reaction kinetics measured in supercritical solvents can occur through the pressure-dependence of concentrations of the reactants or through the pressure-dependence of the rate constants.

The Diels–Alder cycloaddition reaction of maleic anhydride with isoprene has been studied in supercritical-fluid CO_2 under conditions near the critical point of CO_2 [759]. The rate constants obtained for supercritical-fluid CO_2 as solvent at 35 °C and *high* pressures (>200 bar) are similar to those obtained using normal liquid ethyl acetate as the solvent. However, at 35 °C and pressures approaching the critical pressure of CO_2 (7.4 MPa), the effect of pressure on the rate constant becomes substantial. Obviously, $\Delta V^{\neq}$ takes on large negative values at temperatures and pressures near the critical point of CO_2. Thus, pressure can be used to manipulate reaction rates in supercritical solvents under near-critical conditions. This effect of pressure on reacting systems in sc-fluids appears to be unique. A discussion of fundamental aspects of reaction kinetics under near-critical reaction conditions within the framework of transition-state theory can be found in reference [759].

5.5.12 Solvent Isotope Effects

Solvent isotope effect (SIE) is a term frequently used to describe changes in kinetic and equilibrium processes produced by replacing a normal solvent by its isotopically substituted counterpart. Since replacement of hydrogen by deuterium gives the largest relative mass change and easily measurable results from a perturbation of those molecular properties which are sensitive to mass, the ratio of a measurement X in light water (H_2O) to the corresponding value in heavy water (D_2O), X_{H_2O}/X_{D_2O}, is usually what is meant by the term solvent isotope effect of that property [446–449, 760, 761]. Comparatively little is known of solvent isotope effects in solvents other than water (*e.g.* CH_3OH/CH_3OD, CH_3CO_2H/CH_3CO_2D) [447]. Kinetic solvent isotope effects (KSIE), k_{H_2O}/k_{D_2O}, range from 0.5 to about 6, with the most common values falling between 1.5 and 2.8 [447]. The isotope effect for reactions carried out in an isotopically substituted solvent can be used to indicate direct or indirect solvent participation in the reaction. Unfortunately, the observed effects are a combination of three factors: (a) the solvent can be a reactant; for instance, if an O—H or O—D bond of the solvent is broken in the rate-determining step, there will be a *primary isotope effect*; (b) the reactant molecules may become labelled with deuterium by a fast H/D exchange reaction, and then the newly labeled molecule can cleave in the rate-determining step; (c) the intermolecular solute/solvent interactions (*i.e.* the solute solvation) may be different in the labelled and

Table 5-28. Some important physical properties of light and heavy water [446, 451, 635].

Property	Unit	Value for H_2O	Value for D_2O
Relative molecular mass, M_r	$g \cdot mol^{-1}$	18.015	20.031
Melting point (at 1013 hPa), t_m	°C	0.00	3.82
Boiling point (at 1013 hPa), t_{bp}	°C	100.00	101.42
Temperature of maximal density, t	°C	4.0	11.2
Density, ρ [a]	$g \cdot cm^{-3}$	0.997047	1.10448
Molar volume, V_m [a]	$cm^3 \cdot mol^{-1}$	18.069	18.133
Viscosity, η [a]	mPa · s	0.912	1.121
Vapour pressure, p [a]	kPa	3.170	2.740
Molar heat of vaporization, ΔH_v [a]	$kJ \cdot mol^{-1}$	43.869	46.375
Refractive index, n_D [a]	1	1.33250	1.32841
Relative permittivity, ε_r [a]	1	78.46	78.06
Dipole moment, μ	C · m	$6.12 \cdot 10^{-30}$	$6.14 \cdot 10^{-30}$
Ionization constant, K_w [a]	$mol^2 \cdot L^{-2}$	$1.008 \cdot 10^{-14}$	$0.112 \cdot 10^{-14}$
Solubility parameter, δ [a]	$MPa^{1/2}$	47.9 [b]	48.7
Solubility of NaCl in moles of salt per 55.5 moles of solvent [a]	$mol \cdot kg^{-1}$	6.1	5.8
Critical temperature, t_C	°C	374.0	370.7
Critical pressure, p_C	MPa	22.055	21.941
Critical volume, V_C	$cm^3 \cdot mol^{-1}$	55.9	56.3
Critical density, ρ_C	$g \cdot cm^{-3}$	0.322	0.356

[a] At 25 °C.
[b] *Cf.* Table 3-3 in Section 3.2.

nonlabelled solvent. This can change the differential solvation of educts and activated complex and hence the Gibbs energy of activation of the reaction. This is called a *secondary isotope effect*. In many cases, not only the first and third factors, but often the second as well, are simultaneously operative and it is difficult to separate them [762].

In Table 5-28 a number of the physical properties of light and heavy water are compared [446, 451, 635].

Whereas light and heavy water have nearly identical relative permittivities and dipole moments, it can be concluded from the greater boiling point, heat of vaporization, density, and viscosity of heavy water, that liquid D_2O is more structured than the already highly structured H_2O at room temperature (*cf.* Fig. 2-1 in Section 2.1). This is also consistent with the fact that salts acting as structure-breakers are generally less soluble in D_2O than H_2O [446].

Bearing this in mind, and assuming that the direction and magnitude of medium-influenced kinetic solvent isotope effects of type (c) are determined by the different solvation of reactants and activated complex, Swain and Bader draw the following conclusion [450]*): A reaction which destroys the structure of water during formation of the activated complex (by creation of charge) will proceed more rapidly in light water. A reaction which returns structure to the solvent when the activated complex is reached (by neutralization or dispersal of charge) will exhibit an enhanced rate in heavy water.

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* Another view of the origin of solvent isotope effects has been given by Bunton and Shiner [763]; see also [764].

In addition to these non-specific effects, there also can exist differences in specific interactions such as hydrogen bonding between reactants or activated complex and the solvent. The rather scarce experimental results available confirm these simple predictions only in part. Most of the systems studied involve acid or base catalysis and consequently the participation of water as a reactant. Thus, the observed solvent isotope effects often include a composite of primary and secondary isotope effects, because any protons which are exchangeable with solvent protons or deuterons give rise to primary and secondary isotope effects. For example, in the autoprotolysis of water according to $2\ L_2O \rightleftharpoons L_3O^+ + LO^-$ (L = H, D) with $K_w(H_2O)/K_w(D_2O) = 9.0$ (*cf.* Table 5-28), the bond from oxygen to one of the isotopically substituted atoms L is broken (=primary isotope effect) and the bond from oxygen to the other hydrogen remains intact so that substitution here contributes to a secondary isotope effect. As the whole reaction takes place in water ($H_2O \rightarrow D_2O$), there is a solvent isotope effect as well.

Since proton-transfer is an integral part of kinetic solvent isotope effects in acid- and base-catalyzed reactions, and the solvent is involved in the reaction as a reaction partner, further treatment of this topic lies beyond the scope of this book. The reader is therefore referred to some excellent and comprehensive reviews relating to solvent isotope effects [20, 446–449, 760, 761].

5.5.13 Reactions in Biphasic Solvent Systems and in Neoteric Solvents

The increasing awareness about environmental protection and safety at work has led to an increasing search for safer procedures and safer solvents during the last decade. The efforts in this respect are often summarized by the key phrase *green chemistry*. Green chemistry is dedicated to environmentally benign chemical syntheses and industrial processing, and includes sustainable development as a desirable goal for achieving economic and societal objectives [876]. A few illustrative examples of these developments, that is, reactions in biphasic solvent systems and in neoteric solvents such as perfluorohydrocarbons, supercritical carbon dioxide, and room temperature liquid salts, are given in this section. Neoteric (=recent, new, modern) indicates a class of novel reaction media with remarkable new properties; see reference [167] to Chapter 3. Some chemical and physical properties of perfluorohydrocarbons, ionic liquids, and supercritical fluids have already been described in Sections 3.1 (Table 3-1) and 3.2 (Table 3-4), and recommendations for the substitution of hazardous solvents by safer ones are given in Section A.10 (Table A-14). Recent reviews on the substitution of solvents by safer media and processes can be found in reference [877].

Conventionally, organic syntheses are carried out in homogeneous media. Often, however, is it difficult to find solvents in which covalent organic compounds and ionic inorganic reagents (bases, nucleophiles, oxidizing agents, *etc.*) as well as catalysts are sufficiently soluble to obtain a homogeneous reaction mixture. Furthermore, isolation of the product(s) can entail a fairly lengthy work-up procedure, involving quenching with a large amount of water, distillative removal of the reaction solvent, followed either by isolation of the product by filtration and washing, or else multiple extraction with a water-immiscible solvent, washing the extracts with water, drying, and evaporation of the extraction solvent – to mention only a few possibilities.

One of the oldest techniques for overcoming these problems is the use of biphasic water/organic solvent systems using phase-transfer methods. In 1951, Jarrouse found that the reaction of water-soluble sodium cyanide with water-insoluble, but organic solvent-soluble 1-chlorooctane is dramatically enhanced by adding a catalytic amount of tetra-*n*-butylammonium chloride [878]. This technique was further developed by Makosza *et al.* [879], Starks *et al.* [880], and others, and has become known as liquid-liquid *phase-transfer catalysis (PTC)*; for reviews, see references [656–658, 879–882]. The mechanism of this method is shown in Fig. 5-18 for the nucleophilic displacement reaction of a haloalkane with sodium cyanide in the presence of a quaternary ammonium chloride as PT catalyst.

Sodium cyanide and the haloalkane are soluble in water and in the organic phase, respectively. In the aqueous phase, Na^+CN^- reacts with water-soluble Q^+Cl^- to produce Q^+CN^-, which is also soluble in the water-saturated organic phase. Then, this Q^+CN^- reacts in the organic phase with R–Cl to yield R–CN and Q^+Cl^-, which transfers back to the aqueous phase, ready for further reaction cycles. This procedure profits from the fact that quaternary ammonium salts (mostly chlorides, bromides, or hydrogen sulfates) with longer *N*-alkyl chains (usually with eight or more carbon atoms) have affinity for both the polar aqueous and the nonpolar organic phase. In order to minimize hydration of the nucleophiles in the organic phase, thereby achieving the best results, nonpolar solvents such as dichloromethane, 1,2-dichloroethane, toluene, or benzene are used, which are practically immiscible with water. According to Fig. 5-18, this PTC reaction involves two reactions (one in the aqueous and one in the organic phase), transfer of Q^+CN^- from the aqueous to the organic phase, and transfer of Q^+Cl^- from the organic to the aqueous phase, as well as equilibrium partitioning of Q^+CN^- and Q^+Cl^- between the aqueous and organic phases. Thus, the overall reaction rate depends on the intrinsic rate constants in the aqueous and organic phases, the mass-transfer rate of Q^+CN^- and Q^+Cl^-, and the equilibrium partition coefficients of Q^+CN^- and Q^+Cl^-, which are all affected by the interaction of the components and their environments. The organic solvent provides the medium for interaction of the reactants and plays, therefore, the dominant role in influencing the PTC reaction rate

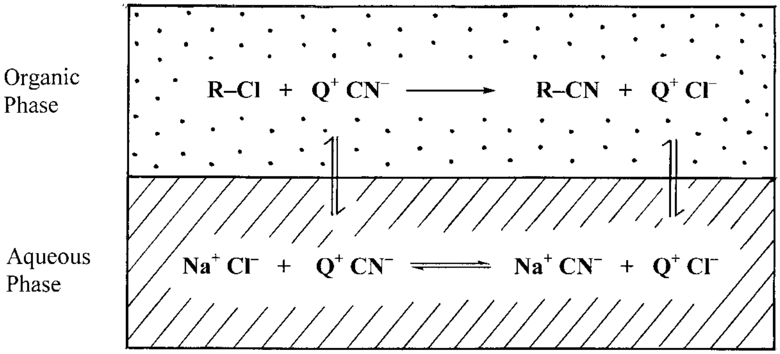

Fig. 5-18. Phase-transfer catalyzed nucleophilic displacement reaction of a haloalkane, R–Cl, with sodium cyanide, Na^+CN^-, to yield a nitrile, R–CN, in the presence of sub-stoichiometric amounts of a quaternary ammonium chloride, Q^+Cl^-, as PT catalyst.

and the degree of conversion of the reactants. The polarity of the organic phase, in conjunction with the structure of the anion and the catalyst cation, affects the selectivity of the PT catalyst partitioning into the organic phase. For example, increasing the polarity and hydrogen-bonding ability of the organic phase has a favourable effect on the extraction of anions with high charge density (=high charge/volume ratio). An excellent review on the influence of organic solvents on a great variety of PTC reactions has recently been given by Wang [882].

The advantages of PTC reactions are moderate reaction conditions, practically no formation of by-products, a simple work-up procedure (the organic product is exclusively found in the organic phase), and the use of inexpensive solvents without a need for anhydrous reaction conditions. PTC reactions have been widely adopted, including in industrial processes, for substitution, displacement, condensation, oxidation and reduction, as well as polymerization reactions. The application of chiral ammonium salts such as *N*-(9-anthracenylmethyl)cinchonium and -cinchonidinium salts as PT catalysts even allows enantioselective alkylation reactions with *ee* values up to 80–90%; see reference [883] for a review. Crown ethers, cryptands, and polyethylene glycol (PEG) dialkyl ethers have also been used as PT catalysts, particularly for solid–liquid PTC reactions; *cf.* Eqs. (5-127) to (5-130) in Section 5.5.4.

Another particularly interesting biphasic solvent system is the combination of nonpolar perfluoro-substituted alkanes, dialkyl ethers, or trialkylamines (so-called *fluorous solvents*) with more polar, conventional organic solvents. The term *fluorous* was introduced in analogy to the term *aqueous* [885]. Fluorous solvents are nonpolar, hydrophobic, chemically inert, and non-toxic, with a higher density than the corresponding non-fluorinated solvents ($\rho \approx 1.7$–$1.9\ \mathrm{g \cdot cm^{-3}}$). They usually have a limited, temperature-dependent miscibility with conventional organic solvents, forming biphasic solvent systems at ambient temperature. With different solubilities for educt, reagent, catalyst, and product, biphasic solvent systems with a fluorous phase can facilitate the separation of the product from the reaction mixture. The fluorous biphase system (FBS) consists of a fluorous phase preferentially containing fluorous-soluble nonpolar educts, reagent, and catalyst, and a second phase preferentially containing polar educts and the product, which is usually an organic solvent with limited solubility in the fluorous phase. Reagents and catalysts can be made fluorous phase-soluble by the introduction of perfluoroalkyl groups of appropriate length and number, mostly of the type $F_3C{-}(CF_2)_n{-}(CH_2)_2{-}$ (so-called *fluorous ponytails* or *fluorous tags*). The insulating ethylene spacer $-(CH_2)_2-$ is necessary to attenuate the strong ($-I$)-effect of the strongly electronegative fluorine substituents, which can otherwise change the chemical properties of the reagent and catalyst in an undesirable manner. Such fluorous biphase systems are well-suited for converting nonpolar educts to products of higher polarity, as the partition coefficients of educts and products will be higher and lower, respectively, in the fluorous phase. As a consequence, there is little or no solubility limitation on the educts and easy separation of the products. A fluorous biphase reaction can proceed either in the fluorous phase or at the interface between the two phases, depending on the solubility of the educts in the fluorous phase.

Furthermore, some fluorous biphase systems can become a single phase with increasing temperature. For example, *n*-heptane and perfluoro(methylcyclohexane) are immiscible at room temperature (*ca.* 20 °C) and form a two-phase system. At higher

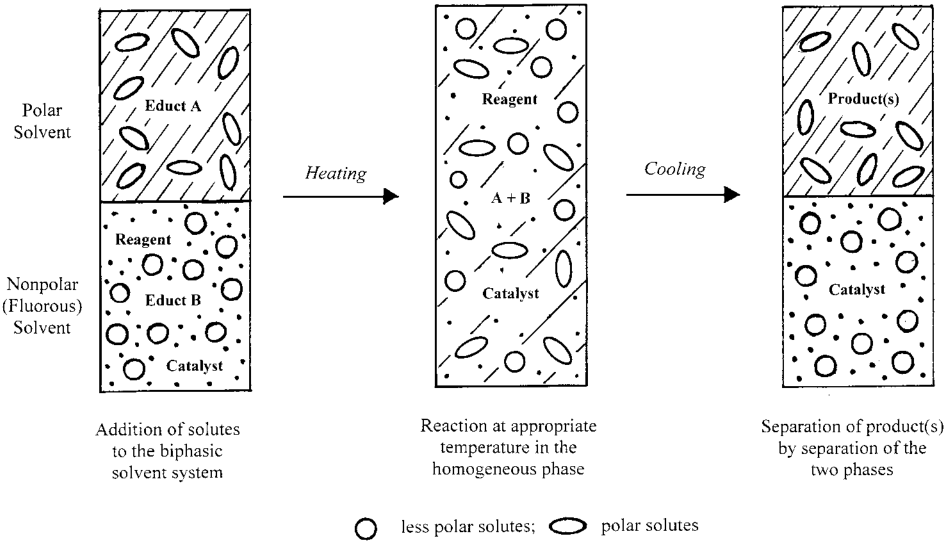

Fig. 5-19. Catalyzed chemical reaction between polar educt A and nonpolar educt B and a reagent in a biphasic solvent system with temperature-dependent mutual miscibility of the polar and nonpolar (fluorous) solvents. A more detailed illustration of the experimental possibilities for catalysis in fluorous solvents is given in reference [890].

temperatures (*ca.* 40 °C), these solvents become miscible and form a monophasic binary solvent mixture, which can serve as a homogeneous reaction medium for educts, reagent, and catalyst, and the catalytic reaction can take place. After completion of the reaction, cooling down the reaction mixture leads to formation of two separate phases once more. In the ideal case, the product is now dissolved in one phase, the remaining educts, reagent, and catalyst in the other, making the isolation of the product very easy. The isolation and re-use of the often rather expensive catalyst is also made easier by this method. For a hypothetical catalyzed reaction, this procedure is illustrated in Fig. 5-19.

This new experimental technique, using *fluorous solvents* or *fluorous biphasic systems* (FBS) with *fluorous biphase catalysis* (FBC), was developed by Vogt and Kaim [884] and by Horváth and Rábai [885] in 1991 and 1994, respectively. Since then, this method has found many applications in synthetic organic chemistry and has already been reviewed repeatedly [886–893]. Incidentally, temperature-dependent two-phase → one-phase transitions are not limited to combinations of fluorous solvents with organic solvents. For example, certain mixtures of water and 1-cyclohexylpyrrolidin-2-one form one phase at ambient temperature and a two-phase system at higher temperatures ($>$*ca.* 50 °C), also allowing interesting separation possibilities.

The reason why fluorous alkanes are immiscible with normal alkanes possibly stems from their different conformations: *n*-alkanes exist in well-known zig-zag conformations, whereas perfluoro-*n*-alkanes adopt more helical conformations because of the larger van der Waals radius of fluorine ($r = 135$ pm) as compared to that of hydrogen ($r = 120$ pm). Molecules of fluorous solvents are also subject to very weak van der Waals interactions due to the low polarizability of the electrons of the CF_2 groups. As a consequence of these particular conformations, which have many cavities to accommodate solutes, as well as the low degree of solvent/solvent interactions, perfluorohydrocarbons exhibit good solubilities for gases such as O_2, N_2, H_2, and CO_2 [*e.g.* up to 57 mL of O_2 in 100 mL of perfluoro(methylcyclohexane)]. Therefore, fluorous solvents are good media for aerobic oxidation reactions.

For example, the aerobic catalytic oxidation of alcohols ($R{-}CH_2OH$ or $R_2CHOH \rightarrow R{-}CHO$ or $R_2C{=}O$), aldehydes ($R{-}CH{=}O \rightarrow R{-}CO_2H$), sulfanes ($R_2S \rightarrow R_2SO$ or R_2SO_2), and cyclic alkenes ($R{-}CH{=}CH{-}R \rightarrow$ epoxides), using fluorous biphasic systems and specially designed perfluoroalkyl-substituted transition metal complexes (Ni, Ru, Cu) as catalysts, has been studied by Knochel *et al.* [894, 895]. The oxidation of 4-chlorobenzaldehyde with oxygen (at *ca.* 1 bar) in the presence of an Ni catalyst (3 cmol/mol) in monophasic toluene/perfluorodecalin (1:1) at 64 °C yielded, after 12 hours of stirring, 87 cmol/mol of 4-chlorobenzoic acid. After cooling to room temperature and the formation of two phases, the acid deposited as a precipitate could be isolated by filtration, and the catalyst-containing fluorous phase could be separated and re-used for further oxidations. After six reaction cycles, the yield of the acid was still 70 cmol/mol [894]. The aerobic oxidation of 4-nitrobenzyl alcohol in the presence of catalytic amounts of a perfluoroalkyl-substituted copper(I) complex and TEMPO (2,2,6,6-tetramethylpiperidine-1-oxide) has been carried out in biphasic chlorobenzene/perfluorooctane at 90 °C under a gentle stream of oxygen, to give 4-nitrobenzaldehyde in 93 cmol/mol yield. After cooling, the two phases were separated, the product was isolated from the chlorobenzene layer, and the catalyst-containing fluorous phase was directly re-used for further reaction runs. Even after eight cycles, 86 cmol/mol of analytically pure 4-nitrobenzaldehyde could still be isolated [895].

These two simple examples demonstrate the usefulness of the FBC procedure, combining the advantages of both homogeneous and heterogeneous catalysis: homogeneous reaction conditions due to the miscibility of fluorous solvents with conventional organic solvents only at higher temperatures, and the facile separation of the usually expensive catalyst from the biphasic system formed at lower temperatures, allowing its re-use for further reaction cycles. This method also avoids the contamination of the product phase with traces of metal stemming from the catalyst. In contrast to aqueous biphase catalysis, fluorous biphasic systems are compatible with moisture-sensitive compounds such as organometallics. Further examples can be found in references [885–893], particularly in [891]; a *user's guide* to practical applications of fluorous catalysts and reagents is given in reference [890].

Although perfluorinated solvents are still expensive, the advantages of FBS and FBC also make this method of interest for industrial applications. Of particular importance in this respect is the conversion of terminal alkenes into aldehydes containing one more carbon than the starting alkene, by reacting the alkene with synthesis gas (CO/H_2) in the presence of cobalt or rhodium catalysts in a homogeneous phase (hydroformylation, oxo, or Roelen reaction). According to Horváth *et al.* [885], this hydroformylation reaction can be advantageously carried out in the fluorous biphasic system toluene/perfluoro(methylcyclohexane), using conventional rhodium catalysts but with tris(perfluoroalkyl)-substituted phosphanes as ligands. The 1-alkene substrate is soluble in cold toluene and the rhodium catalyst in cold perfluoro(methylcyclohexane). By heating this reaction mixture to 100 °C in the presence of CO/H_2 in an autoclave, a homogeneous phase is formed in which the transition metal catalyzed reaction takes place. Cooling to room temperature results in separation of the aldehyde product (in the organic phase) from the fluoro-ponytailed catalyst (in the fluorous phase). This FBS-based method has some advantages over the modern aqueous biphasic oxo reaction, called the Ruhrchemie/Rhône-Poulenc process, in which water-soluble rhodium catalysts with triply-sulfonated triarylphosphane ligands are used; for a detailed discussion, see reference [896].

Another remarkable class of solvents are *ionic liquids* (molten salts), which can be used as monophasic solvents or in biphasic solvent systems. Some of their chemical and physical properties have already been mentioned in Section 3.1; see Fig. 3-1 and Table 3-1 in Section 3.1, as well as references [3, 24–30, 112–114, 167, 187–191] to Chapter 3. Ionic liquids have been known since 1914, when Walden discovered ethylammonium nitrate ($EtNH_3^+NO_3^-$), which has a melting point of just 12 °C; see reference [156] to Chapter 3. Subsequently, high-temperature melting inorganic salts and eutectic inorganic salt mixtures were used as reaction media for many inorganic and organic reactions. Three examples of the application of such inorganic eutectics as solvents for organic reactions have already been given in Section 3.1. However, for the most part, this approach has not been very successful, often because of corrosion problems with the reaction vessels. For a long time, ionic liquids were only of interest to electrochemists as electrolytes. The rediscovery of room temperature liquid salts, this time consisting of large organic cations such as 1,3-dialkylimidazolium, 1,3- or 1,4-dialkylpyridinium, tetraalkylammonium, and tetraalkylphosphonium, in combination with mostly inorganic anions such as Cl^-, Br^-, BF_4^-, PF_6^-, $F_3C{-}CO_2^-$, $F_3C{-}SO_3^-$, $(F_3C{-}SO_2)_2N^-$, and $AlCl_4^-$, with melting points under 100 °C (often below room temperature) has, during the last decade, led to a renaissance in the application of these ionic liquids as reaction media. Ambient temperature ionic liquids based on 1-alkyl-3-methylimidazolium salts were first reported by Wilkes *et al.* in 1982 as tetrachloroaluminates; see reference [162a] to Chapter 3. Replacement of the moisture-sensitive $AlCl_4^-$ ion by the BF_4^- ion and other stable anions led, in 1992, to air- and water-stable, room temperature ionic liquids (see ref. [162b] to Chapter 3), which are now finding increasing application as reaction media for a great variety of chemical reactions, mainly due to the work of Seddon, Hussey, Chauvin, and others; see references [167, 190] and reference [187] to Chapter 3, as well as [905, 906].

Ionic liquids have very good dissolution properties for most inorganic and organic compounds, high thermal stabilities, densities greater than unity ($\rho > 1\ \text{g} \cdot \text{cm}^{-3}$), no measurable vapour pressure, and they are non-flammable. The two last-mentioned properties in particular make ionic liquids promising as "green solvents for the future" [897, 898]. Further advantages are the optimization of physical solvent characteristics and coordinating abilities through a broad choice of cation/anion combinations, reaction rate enhancements because of missing reactant solvation shells, higher reaction selectivities, and often better yields. Because of the manifold cation/anion combinations, these solvents can be constructed to possess a particular set of desired properties and are therefore also called *tailor-made* or *designer* solvents [898]. For example, the miscibility of ionic liquids with water changes with their structure: 1-alkyl-3-methylimidazolium tetrafluoroborates with alkyl chain lengths of less than six carbon atoms are miscible with water at 25 °C, but at or above six carbon atoms they form a separate phase when mixed with water. The ionic liquid 1-(*n*-butyl)-3-methylimidazolium hexafluorophosphate, $[\text{BMIM}]^+\text{PF}_6{}^-$, even forms triphasic mixtures with water and alkanes. This multiphasic behaviour of some ionic liquids is analogous to that of fluorous biphasic systems and has important implications for clean synthetic processes. Using biphasic solvent systems consisting of an immiscible covalent organic solvent and ionic liquid, organic products can easily be separated from the educts, reagent, and catalysts, which remain dissolved in the ionic phase after the reaction, by decantation of the organic phase or by extraction of the ionic phase.

Ionic liquids can be used as replacements for many volatile conventional solvents in chemical processes; see Table A-14 in the Appendix. Because of their extraordinary properties, room temperature ionic liquids have already found application as solvents for many synthetic and catalytic reactions, for example nucleophilic substitution reactions [899], Diels–Alder cycloaddition reactions [900, 901], Friedel–Crafts alkylation and acylation reactions [902, 903], as well as palladium-catalyzed Heck vinylations of haloarenes [904]. They are also solvents of choice for homogeneous transition metal complex catalyzed hydrogenation, isomerization, and hydroformylation [905], as well as dimerization and oligomerization reactions of alkenes [906, 907]. The ions of liquid salts are often poorly coordinating, which prevents deactivation of the catalysts.

Only two examples will be mentioned here in more detail. The $\text{S}_\text{N}2$ alkylation reaction of ambident potassium 2-naphtholate (2-naphthol + KOH) with 1-bromobutane in $[\text{BMIM}]^+\text{PF}_6{}^-$ at room temperature proceeds at a similar rate as observed in dipolar aprotic solvents such as DMF or DMSO, to regioselectively afford 1-butyl 2-naphthyl ether in 98 cmol/mol isolated yield (*O*/*C* alkylation ratio $> 99{:}1$) [899]. In contrast to the reaction in dipolar aprotic solvents, which are difficult to remove from the product, the ether product can be simply extracted into an organic solvent such as toluene, leaving the ionic liquid behind. The by-product (potassium bromide) of the reaction can be extracted with water, and the ionic liquid can be used again.

For Friedel–Crafts acylations of aromatic compounds, a Lewis acid catalyst (*e.g.* AlCl_3) is necessary, which can be delivered by the chloroaluminate(III) ion of the ionic liquid used as the reaction medium [902, 903]. Mixing 1-ethyl-3-methylimidazolium (EMIM) chloride with aluminium trichloride results in the equilibrium formation of the ambient-temperature ionic liquid $[\text{EMIM}]^+\text{AlCl}_4{}^-$. The Lewis acid/base properties of this system are described by the equilibrium $2\,\text{AlCl}_4{}^- \rightleftharpoons \text{Al}_2\text{Cl}_7{}^- + \text{Cl}^-$, where $\text{Al}_2\text{Cl}_7{}^-$ is the Lewis acid and Cl^- the Lewis base. The composition of such tetrachloroaluminate(III) ionic liquids is best described by the apparent mole fraction x of added AlCl_3: ionic liquids with $x(\text{AlCl}_3) < 0.5$ contain an excess of Cl^- ions over $\text{Al}_2\text{Cl}_7{}^-$ ions and are called 'basic', those with $x(\text{AlCl}_3) > 0.5$ containing an excess of $\text{Al}_2\text{Cl}_7{}^-$ over Cl^- are called 'acidic', and salt melts with $x(\text{AlCl}_3) = 0.5$ are called 'neutral'. In Lewis acidic mixtures of $[\text{EMIM}]^+\text{Cl}^-$ and AlCl_3 with $x(\text{AlCl}_3) > 0.5$, benzene reacts quantitatively with acetyl chloride at room temperature to give acetylbenzene as the only product in less than five minutes [902]. The proposed reaction mechanism includes the formation of the intermediate electrophile according to $\text{H}_3\text{C–CO–Cl} + \text{Al}_2\text{Cl}_7{}^- \rightleftharpoons \text{H}_3\text{C–CO}^+ + 2\,\text{AlCl}_4{}^-$. Acylation of naphthalene with acetyl chloride in $[\text{EMIM}]^+\text{Cl}^-/\text{AlCl}_3$ with $x(\text{AlCl}_3) = 0.67$ within 5 min at 0 °C regioselectively affords 89 cmol/mol of 1-acetylnaphthalene and only 2 cmol/mol of the corresponding 2-isomer [903].

Further illustrative examples of the application of ionic liquids as reaction media can be found in the recent reviews of Welton (ref. [188] to Chapter 3), Wasserscheid and Keim (ref. [189] to Chapter 3), Seddon [897], and Freemantle [898].

In addition to fluorous solvents and ionic liquids, *supercritical fluids* (*sc-fluids*, *scf's*), such as supercritical carbon dioxide (sc-CO_2), constitute a third class of neoteric solvents that can be used as reaction media. Although sc-fluids have been known for a long time and have been advantageously used as eluants in extraction and chromatography processes (see Sections A.6 and A.7 in the Appendix), their application as reaction media for chemical processes has become more popular only during the last decade. Some of their physical properties and the supercritical conditions necessary for their existence have already been described in Section 3.2 (see Figure 3-2 and Table 3-4); see also references [209, 211–220, 224–230] to Chapter 3 for reviews on sc-fluids and their applications (particularly for sc-CO_2 and sc-H_2O).

When carbon dioxide is heated beyond its critical point, with a critical temperature of $t_C = 31.0$ °C, a critical pressure of $p_C = 7.38$ MPa, and a critical density of $\rho_C = 0.47\ \text{g} \cdot \text{cm}^{-3}$, the gaseous and the liquid phase merge into a single supercritical phase (sc-CO_2) with particular new physical properties: very low surface tension, low viscosity, high diffusion rates, pressure-dependent adjustable density and solvation capability ("solvation power"), and miscibility with many reaction gases (H_2, O_2, *etc.*). It can dissolve solids and liquids. The relative permittivity of an sc-fluid varies linearly with density, *e.g.* for sc-CO_2 at 40 °C, $\varepsilon_r = 1.4 \rightarrow 1.6$ on going from 108 to 300 bar. This small change in the already low relative permittivity, together with the empirical determination of solvent polarity by solvatochromic dyes, indicates that pure sc-CO_2 is always a fluid of very low polarity, comparable with that of hydrocarbons such as cyclohexane (see refs. [221, 222] to Chapter 3). The polarity of sc-CO_2 can be substantially increased by the addition of even small amounts of polar co-solvents. Carbon dioxide has no permanent dipole moment, but a significant quadrupole moment, which contributes to solute dipole/solvent quadrupole interactions. Quadrupolar solvent effects on solvation and reactivity of solutes dissolved in sc-CO_2 have been studied in detail [908].

It should be noted that the local density of an sc-fluid around solute molecules is subject to large fluctuations and can differ considerably from its bulk density. The region near a solute molecule is quite dynamic, with solvent molecules rapidly entering and leaving this area, but nonetheless enhancing the local density. As a result, the solubility of reactants in sc-fluids can be varied by adjusting the pressure and temperature, whereby higher density generally corresponds to higher solubility. Appreciable solubilities in pure sc-fluids usually require densities of $\rho > \rho_C$, and supercritical fluids are only suitable as reaction media if they fulfil this criterion. For the solubility of reactants in sc-fluids, three factors are important. The solubility increases with increasing vapour pressure of the solute. Solutes of low polarity are more soluble than polar or ionic compounds. The solubility in sc-CO_2 can be enhanced by the introduction of "CO_2-philic" perfluoroalkyl or polysiloxane substituents into the reactants, reagents, and/or catalysts [909]. Many polyfluoro-substituted polymers are highly soluble in both liquid and sc-CO_2. Addition of reactants, reagents, and catalysts to an sc-fluid can change its phase behaviour. Therefore, visual control of the reaction mixture in a window-equipped reactor is always necessary, in order to make sure that a single homogeneous phase is still present after addition of the substrates.

The high compressibility of sc-fluids allows continuous variation of their densities and related properties from gaseous to liquid-like values with comparatively small variations in temperature and/or pressure. In this way, the positions of equilibria and the rates of chemical reactions can be continuously changed ("reaction tuning"), as shown by the following two examples.

The azo/hydrazone tautomeric equilibrium 4-phenylazo-1-naphthol $\rightleftharpoons$ 1,4-naphthoquinone-1-phenylhydrazone [*cf.* *(16a)* $\rightleftharpoons$ *(16b)* in Section 4.3.2] has been studied in various liquids and in liquid and supercritical carbon dioxide [910]. The less dipolar azo tautomer ($\mu \approx 6 \cdot 10^{-30}$ Cm) is dominant in the dilute gas phase, in compressed ethane, and in liquid *n*-hexane. However, in liquid and in sc-CO_2 (at 35 °C and 27 MPa), the tautomeric equilibrium is shifted towards the more dipolar hydrazone form ($\mu \approx 17 \cdot 10^{-30}$ Cm), to give similar amounts of the two tautomers. This shift can be attributed to the quadrupole moment of CO_2 and its Lewis acidity. If only dipole/induced dipole forces were operative, similar results would be expected for sc-CO_2 and ethane [910]. Incidentally, the electron-accepting, Lewis acidic property of CO_2 is nicely demonstrated by its chemical reaction with dimethylamine to yield the ionic liquid dimethylammonium dimethylcarbamate (Dimcarb; *cf.* Section 3.1, Table 3-1, entry 28).

The rate constants of the unimolecular thermolysis of α-chlorobenzyl methyl ether to yield benzaldehyde and chloromethane [*cf.* Eq. (5-41) in Section 5.3.2] have been determined in supercritical 1,1-difluoroethane ($t_C = 113$ °C; $p_C = 4.5$ MPa). Near the critical point at 130 °C, the rate constant increases by about two orders of magnitude on increasing the pressure from 4.48 to 345 MPa [911]. At 130 °C and 30 MPa, the rate constant is comparable to that obtained in conventional tetrachloromethane. The activation volume found for this reaction is $\Delta V^{\neq} = -6$ L/mol, which suggests that the sc-solvent clusters are more ordered around the activated complex than around the reactant. This is in agreement with the formation of a highly dipolar activated complex, which is stabilized by solvation through dipolar $H_3C{-}CHF_2$. The rate constant of this reaction can be adjusted over a continuum with a single sc-fluid instead of a series of common liquid solvents. Thus, this example nicely demonstrates how supercritical solvents can be used to bridge, over a continuum, the gap between gas-phase and liquid-phase kinetics [911]. For reviews on solvation in supercritical fluids and on homogeneous organic reactions used as mechanistic probes in sc-fluids, see references [912, 913].

Supercritical fluids as solvents for *synthetic* organic reactions have found increasing interest only during the last decades. The earliest reported sc-fluid organic reaction seems to be the hydrolysis of aniline in sc-H_2O to give phenol and ammonia [914]. Meanwhile, a great variety of other organic reactions have been studied in sc-fluids, predominately in sc-CO_2 and sc-H_2O. Supercritical carbon dioxide and water are obviously the most attractive solvents for organic syntheses in both the laboratory and on a technical scale from the point of view of a "green chemist" [876]. They are environmentally and toxicologically benign, non-flammable, comparatively inert, inexpensive, and easy to recycle. However, the use of sc-H_2O demands rather harsh reaction conditions because of its high critical temperature and pressure ($t_C = 374$ °C; $p_C = 22.1$ MPa). Therefore, mainly sc-CO_2 has been used as an sc-fluid for organic syntheses, in particular for homogeneously and heterogeneously catalyzed hydrogenation reactions, hydroformylation of 1-alkenes, Pd-catalyzed C–C coupling reactions between haloarenes and vinylic substrates (including the Heck reaction), alkene metathesis reactions, oxidation reactions with molecular oxygen or peroxides, Diels–Alder cycloaddition reactions, homogeneous and heterogeneous polymerization reactions, free-radical chain reactions, enzymatically catalyzed reactions, and reactions with simultaneous use of CO_2 as an sc-fluid and a C_1 reaction partner. More recent compilations of synthetic organic reactions carried out in sc-fluids can be found in references [909, 915, 916]; see also references [211–220, 224–230] to Chapter 3. Only a few illustrative examples can be mentioned here.

The laboratory-scale hydrogenation of unsaturated organic compounds is usually slow because H_2 is only sparingly soluble in common solvents. In contrast, the high miscibility of sc-CO_2 with H_2 makes this sc-fluid very useful for such hydrogenation reactions using heterogeneous noble metal catalysts. Thus, the hydrogenation of cyclohexene in sc-CO_2 with a polysiloxane-supported Pd catalyst (5% Pd) in a continuous flow reactor is extremely rapid and gives cyclohexane in practically quantitative yield [917]. In addition to the high miscibility of sc-CO_2 and H_2, the reduced viscosity of sc-fluids and the increased diffusion rates therein enhances the transport to and from the catalyst, which is no longer a limiting factor. The ability to control the reaction conditions with great precision can be used to manipulate the selectivity of reactions carried out in sc-fluids. For example, the hydrogenation of acetylbenzene in sc-CO_2 (at 12 MPa) at 90 °C and a H_2/substrate ratio of 2:1 predominantly affords 1-phenylethanol (yield 90 cmol/mol) as the product. However, at 300 °C and a H_2/substrate ratio of 6:1, the more hydrogenated product ethylcyclohexane is formed (yield 90 cmol/mol) [917]. An excellent review on sc-fluids in heterogeneous catalysis can be found in reference [220] to Chapter 3.

A nice example of a homogeneous catalytic hydrogenation is the reduction of carbon dioxide to formic acid, carried out in sc-CO_2 in the presence of a soluble ruthenium(II)-trimethylphosphane catalyst and triethylamine at 50 °C and 21 MPa [918]. The turnover frequency (TOF = mole of product per mole of catalyst per hour) of this rapid reaction is rather high, with values up to 1400. This reaction, carried out at 50 °C in sc-CO_2, is 18 times faster than in conventional tetrahydrofuran under otherwise identical reaction conditions. This formic acid synthesis can be coupled with subsequent reactions: by addition of methanol or dimethylamine, this supercritical reaction system provides a highly efficient one-pot route to methyl formate and *N*,*N*-dimethylformamide, respectively [918]. Another example of a reaction in which carbon dioxide acts as both reactant and reaction medium is the formation of tetraethyl-2-pyranone from hex-3-yne and CO_2 in the presence of an Ni(II)-diphosphane catalyst at 102 °C under supercritical reaction conditions [919].

A further useful application of sc-CO_2 as a reaction medium is the free-radical side-chain bromination of alkylaromatics, replacing conventional solvents such as tetrachloromethane or chlorofluorohydrocarbons having no abstractable hydrogen atoms [920]. For example, bromination of ethylbenzene in sc-CO_2 at 40 °C and 22.9 MPa yields 95 cmol/mol (1-bromoethyl)benzene, with practically the same regioselectivity as obtained in conventional tetrachloromethane as the solvent. Even the classical Wohl–Ziegler bromination of benzylic or allylic substrates using *N*-bromosuccinimide (NBS) can be conducted in sc-CO_2 [920]. Irradiation of a solution of toluene, NBS, and AIBN (as initiator) in sc-CO_2 at 40 °C and 17.0 MPa for 4 hours gave (bromomethyl)-

benzene in quantitative yield, with no detectable amount of the potential side product 4-bromotoluene. In neither case is there any change in reaction mechanism on going from tetrachloromethane to sc-CO_2 as solvent [920].

The first Diels–Alder reaction conducted in sc-CO_2 was reported by Hyatt in 1984 [921]: cycloaddition of cyclopentadiene to methyl acrylate gave a mixture of methyl *endo*- and *exo*-5-norbornene 2-carboxylate in high yield at ambient temperature [*cf.* Eq. (5-43) in Section 5.3.3]. The solvent-dependent *endo*/*exo* product ratio found in sc-CO_2 (at 40 °C and 8.5 MPa) was of the same order as that found for liquid CO_2 and for hydrocarbons such as cyclohexane. According to Eq. (7-24) in Section 7.3, the logarithm of the *endo*/*exo* product ratio (called the Ω value) was introduced by Berson as an empirical measure of solvent polarity. A comparison of the Ω values from the *endo*/*exo* ratios obtained in sc-CO_2 places this sc-fluid close to hydrocarbons with respect to its polarity, in agreement with solvatochromic measurements (*cf.* references [221, 222] to Chapter 3). Numerous other Diels–Alder cycloaddition reactions have since been successfully studied in sc-CO_2. The reaction between cyclopentadiene and ethyl acrylate has been explored in dichloromethane, tetrahydrofuran, and *n*-hexane, as well as in sc-CO_2. The reaction rates found in the three nonpolar conventional solvents were slightly higher, but within a factor of two of those in sc-CO_2 [922]. For a more recent reinvestigation of the well-studied Diels–Alder reaction between isoprene and maleic anhydride in sc-CO_2, see reference [923].

As an example of the use of sc-CO_2 in an enzymatic reaction, the lipase-catalyzed esterification of oleic acid with racemic (±)-citronellol should be mentioned. At 31 °C and 8.4 MPa, the (−)-(*S*)-ester is formed enantioselectively in sc-CO_2 with an optical purity of nearly 100% [924]. The reaction rate is enhanced by increasing pressure, *i.e.* by increasing the solvation capability or solvent polarity of sc-CO_2. A linear correlation has been found between reaction rate and the solvatochromic solvent polarity parameter $E_T(30)$; see Section 7.4 for the definition of $E_T(30)$.

A great variety of chemical reactions have also been conducted advantageously in sc-H_2O, *e.g.* the hydrolysis of esters, amides, and nitriles, dehydration of alcohols (cyclohexanol → cyclohexene, glycerol → propenal, butane-1,4-diol → THF), partial oxidation with molecular oxygen (cyclohexane → cyclohexanone), to mention only a few possibilities. Excellent reviews on the chemistry in supercritical water can be found in references [224, 225, 228–230] to Chapter 3, as well as in a special report [925]. Some physical properties of sc-H_2O have already been described in Section 3.2. A gradual decrease of the density and relative permittivity of water with increasing temperature is paralleled by increasing water solubility of organic compounds. At 300 °C, the polarity and density of water roughly approach those of acetone at room temperature. The enhanced self-ionization of water at high temperatures makes it a stronger acid and a stronger base, thus promoting acid- and base-catalyzed reactions at higher temperatures. Thus, sc-H_2O frequently participates not only as a solvent and reactant, but also as a catalyst. The properties of supercritical ionophore (electrolyte) solutions have been studied by geochemists in order to understand mineral-forming processes deep in the Earth, where conditions can be supercritical. Because oxygen, carbon dioxide, methane, and other alkanes are completely miscible with sc-H_2O, even combustion (flameless or with flames!) can occur in this sc-fluid. Thus, oxidation in sc-H_2O can be used to detoxify hazardous organic materials (all kinds of waste, chemical warfare agents, *etc.*) nearly quantitatively in short times. As the main oxidation products are water, carbon dioxide, and (for halo-organics) simple acids, the final aqueous mixture can mostly be disposed of without further treatment. Because of the rather harsh reaction conditions in sc-H_2O ($t_C = 374$ °C, $p_C = 22.1$ MPa = 218 atm), the most promising application of sc-H_2O as a reaction medium seems to lie not in synthesis, but in the destruction of hazardous organic compounds [925].

In addition to supercritical water (sc-H_2O), *superheated water* (SHW) or *high-temperature water* (HTW) has recently attracted attention as a new medium for organic reactions. High-temperature water can be broadly defined as liquid water above 200 °C under autogenic pressure. The physical properties of superheated water, which are quite different from those of ambient liquid water, have already been described at the end of Section 3.2. Superheated water has a lower relative permittivity, fewer and weaker intermolecular hydrogen bonds, and a higher isothermal compressibility than normal liquid water. The solvent polarity of water at 300 °C is roughly equivalent to that of acetone at 25 °C ($\varepsilon_r = 20.6$), as measured by its relative permittivity. Whereas the solubility of most gases in ambient liquid water initially decreases with increasing temperature, at higher temperature a minimum is soon reached, and then the gas solubility increases. The physical and chemical properties of high-temperature water vary with temperature and pressure over wide ranges, approaching those of polar organic solvents at ambient temperature. Therefore, high-temperature water can support dipolar, isopolar, and free-radical transition state reactions, depending on the reaction conditions. In addition, high-temperature water can be used as medium for chemical syntheses, waste destruction, plastics recycling, coal liquefaction, and biomass processing. For recent reviews on the application of superheated or high-temperature water for scientific and engineering purposes see references [228–230] to Chapter 3.

6 Solvent Effects on the Absorption Spectra of Organic Compounds

6.1 General Remarks

When absorption spectra are measured in solvents of different polarity, it is found that the positions, intensities, and shapes of the absorption bands are usually modified by these solvents [1–4]. These changes are a result of physical intermolecular solute–solvent interaction forces (such as ion-dipole, dipole-dipole, dipole-induced dipole, hydrogen bonding, *etc.*), which above all tend to alter the energy difference between ground and excited state of the absorbing species containing the chromophore*). The medium influence on absorption spectra can be considered by comparing the spectral change observed (a) on going from the gas phase to solution, or (b) simply by changing the nature of the solvent. Because in most cases it is not possible to measure the absorption spectrum in the gas phase, the treatment of this topic will be restricted to approach (b) in this chapter. This is possible, because there is increasing evidence that there is no lack of continuity between the magnitude of spectral changes, in going from an isolated molecule in the gas phase to a weakly interacting or to a strongly interacting liquid medium, provided there are no specific interactions like hydrogen bonding or EPD/EPA complexation [3].

All those spectral changes which arise from alteration of the chemical nature of the chromophore-containing molecules by the medium, such as proton or electron transfer between solvent and solute, solvent-dependent aggregation, ionization, complexation, or isomerization equilibria lie outside the scope of this chapter. Theories of solvent effects on absorption spectra assume principally that the chemical states of the isolated and solvated chromophore-containing molecules are the same and treat these effects only as a physical perturbation of the relevant molecular states of the chromophores [435–437].

Thus, solvent effects on absorption spectra can be used to provide information about solute-solvent interactions [1–4]. On the other hand, in order to minimize these effects, it would be preferable to record absorption spectra in less interacting nonpolar solvents, such as hydrocarbons, whenever solubility permits. Suitable choice of a spectral solvent may be facilitated by consulting Tables A-4 (UV/Vis), A-5 (IR), A-6 (^{1}H NMR), and A-7 (^{13}C NMR) in the Appendix, which list some of the more common solvents and their absorption properties.

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* A *chromophore* is generally regarded as any grouping of an organic molecule (sometimes the whole molecule itself) which is responsible for the light absorption under consideration. O. N. Witt introduced this term, although it had a different meaning from that accepted today; *cf.* Ber. Dtsch. Chem. Ges. *9*, 522 (1876). For example, the C=C group of ethene or 1-hexene, responsible for their $\pi \rightarrow \pi^*$ UV absorption, is the chromophore of these alkenes, although their absorption maxima lie in the far ultraviolet ($\lambda_{max} = 162$ and 179 nm for ethene and 1-hexene, respectively). For *β*-carotene, the whole polyene chain with eleven conjugated C=C bonds represents the chromophore ($\lambda_{max} = 454$ nm). In the IR spectrum of acetaldehyde, the absorption band at $\tilde{\nu} = 1748$ cm^{-1} stems from the stretching vibration of the C=O group as the chromophore.

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6.2 Solvent Effects on UV/Vis Spectra [5–17]

6.2.1 Solvatochromic Compounds

The term *solvatochromism* is used to describe the pronounced change in position (and sometimes intensity) of a UV/Vis absorption band that accompanies a change in the polarity of the medium. A hypsochromic (or blue) shift with increasing solvent polarity is usually called *negative solvatochromism.* The corresponding bathochromic (or red) shift is termed *positive solvatochromism.**) What kind of compounds exhibit this response to changes in solvent polarity?

To begin with, the solvent effect on spectra, resulting from electronic transitions, is primarily dependent on the chromophore and the nature of the transition ($\sigma \rightarrow \sigma^*$, $n \rightarrow \sigma^*$, $\pi \rightarrow \pi^*$, $n \rightarrow \pi^*$, and charge-transfer absorption). The electronic transitions of particular interest in this respect are $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$, as well as charge-transfer absorptions. Organic compounds with chromophores containing π-electrons can be classified into three different groups according to their idealized π-electronic structure: *aromatic compounds*, *polyenes* (and *polyynes*), and *polymethines* (*cf.* Fig. 6-1 [18, 19]).

In contrast to compounds of aromatic and polyene-like electronic structure, polymethines are conjugated chain molecules with equal bond lengths and charge alternation along the methine chain [18, 19]. They exhibit the following common structural features:

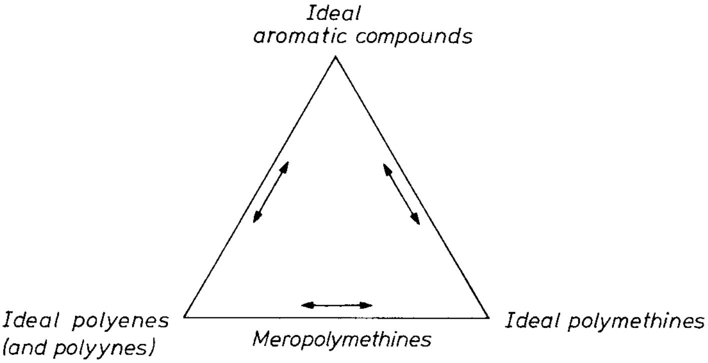

Fig. 6-1. Classification of organic compounds with π-electron systems, according to Dähne [18, 19].

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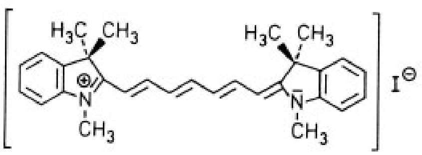
* The UV/Vis absorption of solute molecules can be influenced not only by surrounding solvent molecules but also by other environments, *e.g.* embedment in solids, polymers, glasses, micelles, or proteins, as well as adsorption on solid surfaces. Therefore, the more general term *perichromism* (from the Greek *peri* = around and *chroma* = colour) has been recommended (Prof. E. M. Kosower, Tel Aviv/Israel, private communication to the author). Solvatochromic shifts caused by dye inclusion into protein interiors have been called *enzymichromism* [438].

$\ldots(n+3)\pi\ldots$ $n = 1, 3, 5, 7, \ldots$
$X{-}(CR)_n{-}X'$ $R = H$ or substituents
X, X' = terminal chain atoms (N, O, P, S) or atom groups
$X = X'$ polymethine dyes ($X = X' = N$: cyanines; $X = X' = O$: oxonoles)
$X \neq X'$ meropolymethine dyes ($X = N$ and $X' = O$: merocyanines)

Of particular interest are the intramolecularly ionic *meropolymethine dyes* (especially the *merocyanines*), whose electronic structure lies somewhere between that of polyenes and that of polymethines depending on the nature of X and X′ as well as on solvent polarity [20]. These are systems in which an electron-donating group, D, is linked by a conjugated system, R, to an electron-accepting group, A. Their intermediate π-electronic structure can be described in terms of two mesomeric structures, D—R—A $\leftrightarrow$ $D^{\oplus}$—R—$A^{\ominus}$, as, for example, this special vinylogous merocyanine dye $(n = 0, 1, 2, \ldots)$:

Its electronic transition is associated with an intramolecular charge-transfer between donor and acceptor group, producing an excited state with a dipole moment (μ_e) appreciably different from that in the ground state (μ_g).

It has been established experimentally that only those molecules with π-electrons for which the charge distribution (and consequently the dipole moment) in the electronic ground state is considerably different from that in the excited state exhibit a pronounced solvatochromism. Thus, for the following organic compounds, only a comparatively small solvent dependence of their UV/Vis absorption spectra is observed: *aromatic compounds* (without electron donor and/or acceptor groups, *e.g.* benzene [21, 22]), *polyenes* (*e.g.* lycopene [23], carotinoids [24]), *polyynes* (*e.g.* polyacetylenes [25]), and symmetrical *polymethine dyes* [26–28, 292, 293]. A remarkable *aromatic* compound with a large three-dimensional π-electron network is fullerene C_{60}. The energy of its A_0 electronic transition around $\lambda_{max} = 405$ nm varies only by $\Delta\tilde{\nu} = 360\ \mathrm{cm}^{-1}$ on going from *n*-hexane to carbon disulfide as solvent [463]. A representative example of *polyenic* π-systems is β-carotene. Its long-wavelength $\pi \rightarrow \pi^*$ absorption at around $\lambda_{max} = 454$ nm is shifted only by $\Delta\tilde{\nu} = 239$ cm^{-1} $(\Delta\lambda = 5$ nm) with a solvent change cyclohexane → methanol [464]. An example of a *polymethinic* π-system is the heptamethinium cyanine dye shown below.



Solvent	$CHCl_3$	CH_3SOCH_3	CH_3OH
λ_{max}/nm	757	750	740
$\Delta\lambda$/nm		17 (only!)	
Solvent polarity	⟶		

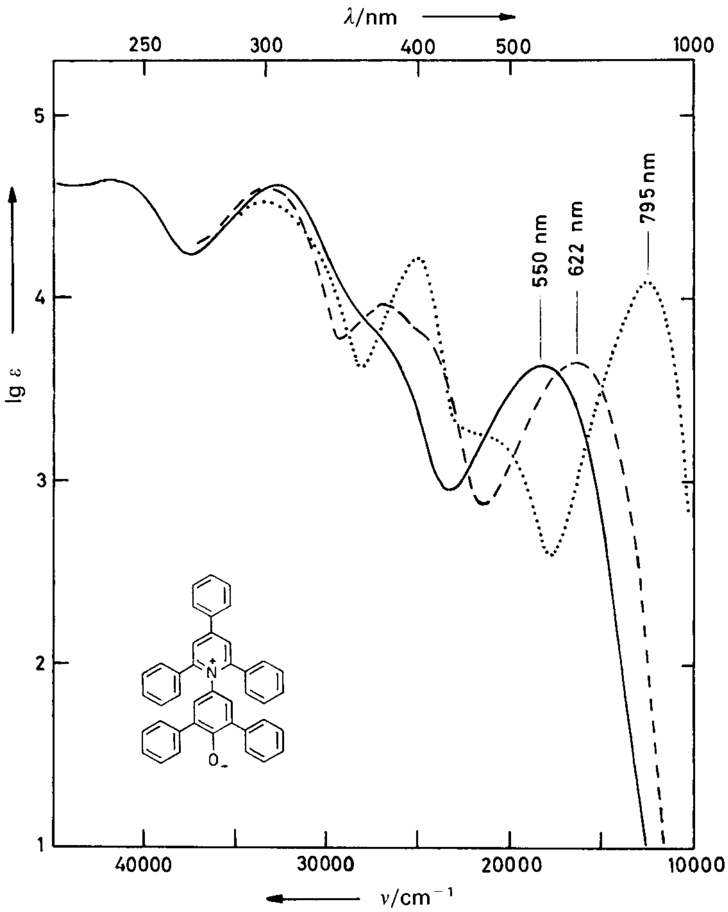
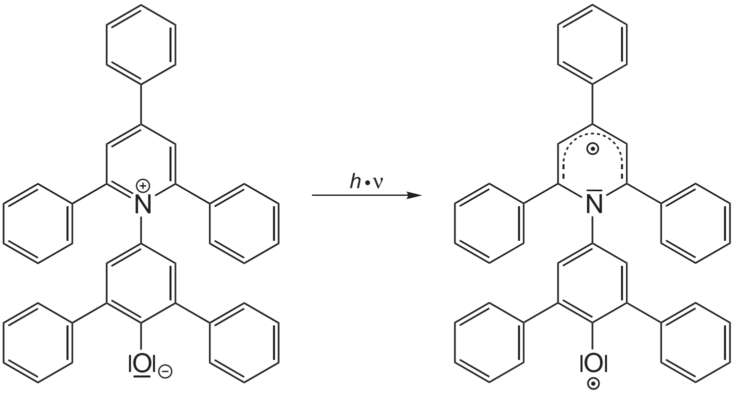


Fig. 6-2. UV/Vis absorption spectrum of 2,6-diphenyl-4-(2,4,6-triphenylpyridinium-1-yl)phenolate in ethanol (——), acetonitrile (----), and 1,4-dioxane (· · · · ·) at 25 °C [10, 29].

A solvent change from methanol to trichloromethane causes a bathochromic shift of only $\Delta\tilde{\nu} = 304\,\text{cm}^{-1}$ ($\Delta\lambda = 17$ nm) in its long-wavelength $\pi \rightarrow \pi^*$ absorption band [293].

In contrast to these nonpolar compounds, very dramatic solvent effects on UV/Vis spectra have been observed for dipolar meropolymethine dyes, especially merocyanines, due mainly to the change in their dipole moments on electronic transition. An example is the following negatively solvatochromic pyridinium *N*-phenolate betaine, which exhibits one of the largest solvatochromic effects ever observed (*cf.* Fig. 6-2 [10, 29]).

Its long-wavelength band is shifted by $\Delta\tilde{\nu} = 9730\ \text{cm}^{-1}$ ($\Delta\lambda = 357$ nm) on going from diphenyl ether to water as solvent. Solutions of this betaine dye are red-colored in methanol, violet in ethanol, blue in isoamyl alcohol, green in acetone, and yellow in anisole, thus comprising the whole visible region. This extraordinarily large solvent-induced shift of the visible $\pi \rightarrow \pi^*$ absorption band of intramolecular charge-transfer character has been used to introduce an empirical parameter of solvent polarity, called the $E_T(30)$ value [10, 29, 294]; *cf.* Section 7.4. It can also be used for the UV/Vis spectroscopic determination of water or other polar solvents in binary mixtures of solvents of different polarity [30, 31, 295, 296]. Applications of the solvatochromism of this pyridinium-*N*-phenolate betaine dye in analytical chemistry have been reviewed [297].



Solvent	$(C_6H_5)_2O$[a]	$C_6H_5OCH_3$	CH_3COCH_3	i-$C_5H_{11}OH$	C_2H_5OH	CH_3OH	H_2O[a]
λ_{max}/nm	810	771	677	583	550	516	453
Solution colour	–	yellow	green	blue	violet	red	–
Solvent polarity	⟶						

[a] Solubility very low.

As shown by the two formulae, the long-wavelength visible absorption of this betaine dye is connected with an intramolecular charge-transfer from the phenolate to the pyridinium moiety. Differential solvation of the highly dipolar, zwitterionic electronic ground state and and the less dipolar first excited state leads to the large negative solvatochromism observed. There is direct experimental proof for this intramolecular charge-transfer: the electromagnetic radiation that is emitted from oriented betaine molecules on photoexcitation has been directly measured. The dipole moment decreases and changes direction upon photoexcitation (from *ca.* 15 D in the ground state to *ca.* −6 D in the excited state) [439].

Convenient, rapid classroom demonstrations of solvent polarities, using test tubes or overhead projectors and the beautifully coloured solutions of the pyridinium-*N*-phenolate betaine dye in various solvents or binary solvent mixtures, have been described [440–442].

The extreme sensitivity of the visible absorption spectrum to small changes in the surrounding medium has made this betaine dye a useful molecular probe in the study of micellar systems [298, 299, 443–445], microemulsions and phospholipid bilayers [299], model liquid membranes [300], polymers [301, 446], organic-inorganic polymer hybrids [447], sol-gel matrices [448], surface polarities [449–451], and the retention behaviour in reversed-phase liquid chromatography [302]. Using polymer membranes with embedded betaine dyes, even an optical alcohol sensor has been developed [452].

Not only the position of the long-wavelength absorption band of the pyridinium *N*-phenolate betaine dye is strongly solvent-dependent but also its bandwidth and bandshape. A thorough band-shape analysis of a betaine dye with *tert*-butyl groups instead of the phenyl groups in *o,o′*-position to the phenolic oxygen atom has been performed [431]. Because of its extraordinary solvatochromism, this betaine dye has been subject to other more sophisticated experimental measurements (*e.g.*, IR, Raman, resonance Raman spectroscopy [453, 454]; ultrafast transient pump-probe spectroscopy [455–457]) as well as to quantum-chemical calculations at various levels of theory [454, 458–462]. All results have been in agreement with an $S_0 \rightarrow S_1$ charge-transfer transition and they reveal valuable details on the geometrical structure of the S_1 state and the excited-state dynamics.

A representative selection of some thoroughly investigated positive and negative solvatochromic compounds is given in Table 6-1. Further interesting recent examples of solvatochromic dyes can be found in references [311–314]. A compilation of 78 solvatochromic compounds that have been proposed as probes for measuring empirically the polarity of solvents is given in reference [10]; see also Chapter 7.

Table 6-1 reveals that the long-wavelength absorption band undergoes a bathochromic shift as the solvent polarity increases (positive solvatochromism), if the excited state is more dipolar than the ground state ($\mu_g < \mu_e$; dyes no. 1...11). If the ground state is more dipolar than the excited state ($\mu_g > \mu_e$), the opposite behaviour, a hypsochromic shift, occurs (negative solvatochromism; dyes no. 12...22). In valence-bond theory language, the extent and direction of solvatochromism depends on whether the zwitterionic mesomeric structure is more important in the ground state or in the excited state. The quadrupole-merocyanines nos. 8 and 10 represent special cases for which the dipole moments μ_g and μ_e must be zero due to the presence of a center of symmetry. Some of the dyes included in Table 6-1 have been used to derive empirical scales of solvent polarity (nos. 1, 2, 4, 12, and 13; *cf.* Section 7.4) [10, 294].

Further to the first part of Table 6-1 dealing with positive solvatochromic dyes, three new dyes must be mentioned the positive solvatochromism of which exceeds that of Brooker's merocyanine dye (entry 1) considerably. The long-wavelength $\pi \rightarrow \pi^*$ absorption of 5-(dimethylamino)-5′-nitro-2,2′-bithiophene is shifted bathochromically by $\Delta\tilde{\nu} = 4710\ \text{cm}^{-1}$ ($\Delta\lambda = 131$ nm) on going from *n*-hexane to formamide/water (1:1) as solvent [465]. Replacement of the dimethylamino-substituted thiophene ring by a selenophene ring extends the solvent dependence even more [466]. Lastly, an amino-substituted benzodifuranone has been reported to exhibit a positive solvatochromism of $\Delta\tilde{\nu} = 5875\ \text{cm}^{-1}$ ($\Delta\lambda = 206$ nm) upon a solvent change from nonafluoro-*t*-butanol to HMPT [467].

Not only intramolecularly ionic compounds such as dipolar meropolymethine dyes, but also EPD/EPA complexes (*cf.* Section 2.2.6) with an intermolecular charge-transfer (CT) absorption can exhibit a pronounced solvatochromism. The CT transition also involves ground and excited states with very different dipole moments. This suggests that the CT absorption band should exhibit marked solvent polarity effects [17, 63, 64].

A striking example is the negatively solvatochromic effect observed for 1-ethyl-4-(methoxycarbonyl)pyridinium iodide, the UV/Vis spectra of which in a variety of solvents are shown in Fig. 6-3 [65–67]. The longest-wavelength band of the ground-state ion-

Table 6-1. A selection of 22 representative solvatochromic compounds showing their dipole moments in the ground (μ_g) and excited state (μ_e) [32, 33] and their long-wavelength π–π^* absorption maxima in two solvents of widely different polarity.

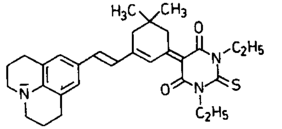
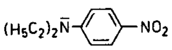
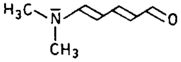
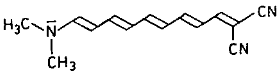
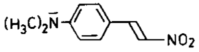
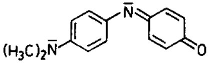
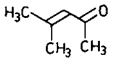
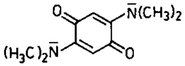
No.	Formula	$\frac{\mu_g \cdot 10^{30\,a)}}{\mathrm{C\,m}}$	$\frac{\mu_e \cdot 10^{30\,a)}}{\mathrm{C\,m}}$	$\tilde{\nu}/\mathrm{cm}^{-1}$ (nonpolar solvent)	$\tilde{\nu}/\mathrm{cm}^{-1}$ (polar solvent)	$\Delta\tilde{\nu}/\mathrm{cm}^{-1\,b)}$	References
(a) *Positive solvatochromic compounds*							
1		–	–	17 790 (*iso*-octane)	13 390 (lutidine-water 20:80)	4400	[34]
2		$17^{c)}$	$43^{c)}$	27 400 (cyclohexane)	23 230 (water)	4170	[35]
3		26	–	30 170 (*n*-hexane)	26 140 (water)	4030	[37]
4		46	99	18 800 (methyl-cyclohexane)	14 810 (ethanol)	3990	[36]
5		26	60	25 440 (*n*-heptane)	21 320 (water)	4120	[38, 432]
6	 **Phenol blue**	19	25–30	18 120 (cyclohexane)	14 970 (water)	3150	[23, 39–41]
7		9	–	43 370 (*iso*-octane)	41 220 (water)	2150	[42]
8		0	0	20 830 (*n*-hexane)	18 830 (water)	2000	[43]

Table 6-1. (Continued)

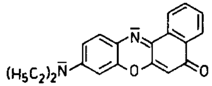
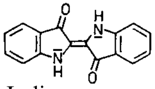
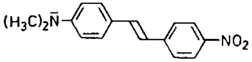
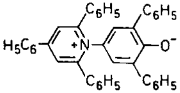
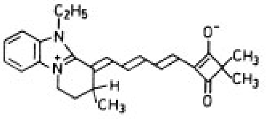
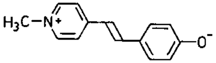
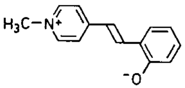
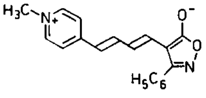
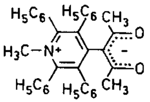
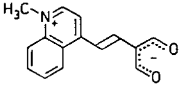
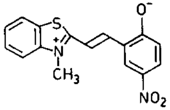
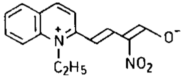
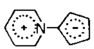
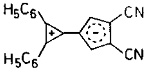
No.	Formula	$\frac{\mu_g \cdot 10^{30}}{\text{C m}}$ [a)]	$\frac{\mu_e \cdot 10^{30}}{\text{C m}}$ [a)]	$\tilde{\nu}$/cm^{-1} (nonpolar solvent)	$\tilde{\nu}$/cm^{-1} (polar solvent)	$\Delta\tilde{\nu}$/cm^{-1} [b)]	References
9		–	–	19 190 (benzene)	18 180 (methanol)	1010	[44, 45]
10	 Indigo	0	0	17 010 tetrachloromethane	16 130 (dimethyl sulfoxide)	880	[46]
11		25	78	24 100 (cyclohexane)	23 500 (methanol)	600	[47, 47a, 303e]
(b) *Negative solvatochromic compounds*							
12		49[d)]	20[d)]	12 350 (diphenyl ether)	22 080 (water)	–9730	[29, 30]
13		–	–	14 600 (toluene)	24 100 (water)	–9500	[34]
14		87	–	16 130 (trichloromethane)	22 620 (water)	–6490	[48–50, 50a, 304–309]
15		–	–	16 080 (trichloromethane)	22 170 (water)	–6090	[51]
16		97	63	16 390 (pyridine)	21 280 (water)	–4890	[52, 53]

Table 6-1. (Continued)

No.	Formula	$\frac{\mu_g \cdot 10^{30}}{\text{C m}}$ [a]	$\frac{\mu_e \cdot 10^{30}}{\text{C m}}$ [a]	$\tilde{\nu}$/cm^{-1} (nonpolar solvent)	$\tilde{\nu}$/cm^{-1} (polar solvent)	$\Delta\tilde{\nu}$/cm^{-1} [b]	References
17		–	–	18 520 (benzene)	23 150 (methanol)	−4630	[54]
18		–	–	17 000 (benzene)	21 550 (water)	−4550	[55]
19		–	–	16 640 (toluene)	19 760 (methanol)	−3120	[56, 310]
20		35	–	19 010 (benzene)	22 080 (water)	−3070	[57]
21		44	–	19 560 (trichloromethane)	22 060 (water)	−2500	[58, 59]
22		48	–	27 250 (cyclohexane)	28 820 (acetonitrile)	−1570	[60]

[a] Dipole moments in Coulombmeter (Cm). 1 Debye = $3.336 \cdot 10^{-30}$ Cm. Methods of determination of μ_e and results have been reviewed [32, 33, 303].

[b] $\Delta\tilde{\nu} = \tilde{\nu}$ (nonpolar solvent) − $\tilde{\nu}$ (polar solvent).

[c] Value for 1-dimethylamino-4-nitrobenzene.

[d] Value for 2,6-di-*t*-butyl-4-(2,4,6-triphenylpyridinium-1-yl)phenolate [61, 62].

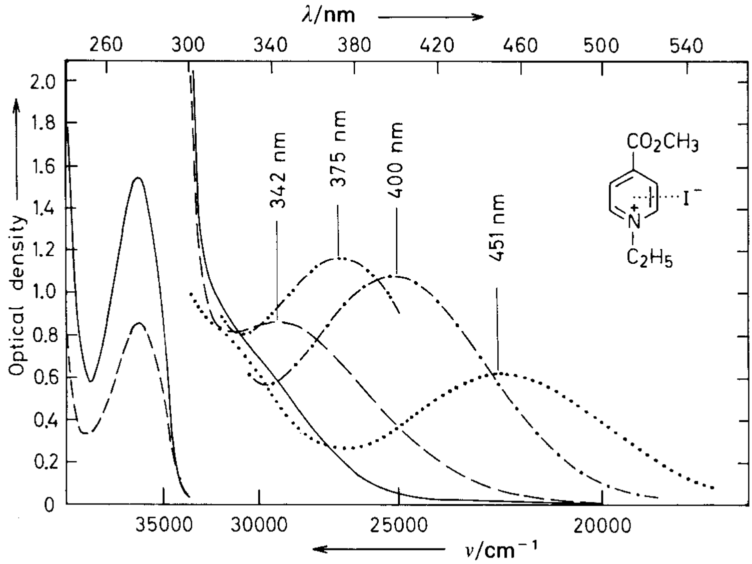
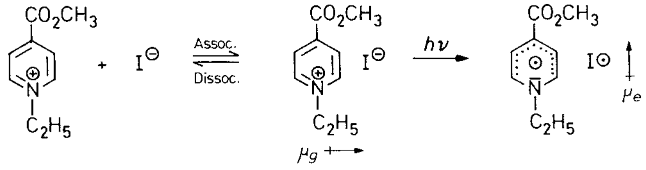


Fig. 6-3. The first charge-transfer band in the UV/Vis absorption spectrum of 1-ethyl-4-(methoxycarbonyl)pyridinium iodide in water (——), methanol (----), 2-propanol (— · · — · · — · · —), acetonitrile (— · — · — · —), and *cis*-1,2-dichloroethene (· · · · ·) at 25 °C [65–67].

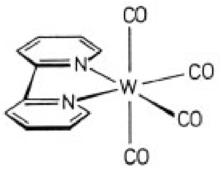
pair complex corresponds to an intermolecular transfer of an electron from the iodide to the pyridinium ion with annihilation of charge during the transition. The large dipole

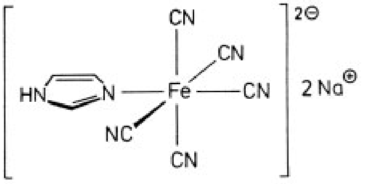


moment of the ground state is at right angles to the pyridinium ring. In the excited state, however, it is much smaller and will lie, at least that part resulting from the pyridinyl radical, in the plane of the ring ($\mu_g > \mu_e$; $\mu_g \perp \mu_e$). The corresponding dipole moments for the ground and excited state have been calculated as $\mu_g = 46 \cdot 10^{-30}$ Cm (13.9 D) and $\mu_e = 29 \cdot 10^{-30}$ Cm (8.6 D) [315]. The large negative solvatochromism of this pyridinium iodide has been explained in terms of the stabilization of the more dipolar ground state and destabilization of the less dipolar excited state on transfer of the ion pair to more polar solvents [65–67]. Alternatively, the negative solvatochromism may have arisen from both states being destabilized on transfer to more polar solvents, with a relatively greater destabilization of the excited state [315]. The pronounced negative solvatochromism of this pyridinium iodide has been used to establish an empirical scale of solvent polarity, the so-called *Z*-scale [65–67]; *cf.* Section 7.4.

Less pronounced, but nevertheless significant solvent shifts of the CT band are observed for EPD/EPA complexes, if the ground state is not ionic and the excited state is ionic ($\mu_g < \mu_e$). An example is the CT absorption band of the acenaphthene/3,5-dinitrophthalic anhydride complex, which shows a bathochromic shift with increasing solvent polarity [64].

Organometallic complexes composed of a central metal atom and organic ligands containing a π-electron system exhibit two kinds of solvent-dependent charge-transfer absorptions, depending on the relative electron-donor/electron-acceptor properties of metal and ligand: (i) metal-to-ligand charge-transfer absorption (MLCT), and (ii) ligand-to-metal charge-transfer absorption (LMCT). The strong solvatochromism observed for both types of charge-transfer absorptions has been thoroughly investigated for a variety of group VI metal complexes with different organic ligands (mainly diimine derivatives, —N=C—C=N—, and their heterocyclic counterparts); see references [423, 424] for recent reviews. Only two representative examples can be mentioned here: the negative solvatochromic 2,2′-bipyridine tetracarbonyl-tungsten(0) complex with MLCT absorption [425, 426], and the positive solvatochromic imidazole pentacyano-ferrate(III) complex with LMCT absorption [427].





Solvent	i-C_8H_{18}	CH_3OH
λ_{max}/nm	574	474
$\Delta\lambda$/nm	−100	

Solvent	$HCONMe_2$	H_2O
λ_{max}/nm	427	500
$\Delta\lambda$/nm	+73	

In the MLCT case, upon excitation an electron is transferred from the electron-rich tetracarbonyl-tungsten(0) moiety to the electron-accepting 2,2′-bipyridine system ($d \rightarrow \pi^*$ transition), with a simultaneous change in polarizability and dipole moment, leading to an excited state with a reduced dipole moment. In the LMCT case, upon excitation an electron jumps from the electron-rich imidazole ring to the electron-accepting pentacyanoferrate(III) fragment ($\pi \rightarrow d$ transition) with similar but opposite changes in polarizability and dipole moment. The MLCT absorption of centrosymmetric binuclear coordination compounds without a permanent dipole moment such as bis(pentacarbonyl-tungsten)pyrazine, $(CO)_5W$-pyrazine-$W(CO)_5$, experiences an even stronger solvatochromism than that of their mononuclear, non-centrosymmetric, dipolar analogues, thus demonstrating the importance of solvent dipole/solute induced-dipole and dispersion interactions in solutions of such complexes [426]; *cf.* the analogous solvatochromism of the centrosymmetric organic dyes nos. 8 and 9 in Table 6-1.

A consistent model permitting rationalization and prediction of the solvatochromic behaviour of coordination compounds with MLCT absorption has been described [428]. According to this qualitative model, the changing relationship between the metal-ligand bond dipolarities in the ground and MLCT excited state determines whether the complex is negatively, positively, or not solvatochromic [428]. For comprehensive reviews on solvent effects on electronic spectra of metal complexes, see references [15, 17].

Special cases of charge-transfer spectra are the so-called charge-transfer-to-solvent (CTTS) spectra [17, 68]. In this type of CT transitions, solute anions may act as electron-donors and the surrounding solvent shell plays the role of the electron-acceptor. A classical example of this kind of CTTS excitation is the UV/Vis absorption of the iodide ion in solution, which shows an extreme solvent sensitivity [68, 316]. Solvent-dependent CTTS absorptions have also been obtained for solutions of alkali metal anions in ether or amine solvents [317]. Quantum-mechanical molecular simulations of the CTTS spectra of halide ions in water are given in reference [468].

6.2.2 Theory of Solvent Effects on UV/Vis Absorption Spectra

A qualitative interpretation of solvent shifts is possible by considering (a) the momentary transition dipole moment present during the optical absorption, (b) the difference in permanent dipole moment between the ground and excited state of the solute, (c) the change in ground-state dipole moment of the solute induced by the solvent, and (d) the Franck–Condon principle [69]. According to Bayliss and McRae, four limiting cases can be distinguished for intramolecular electronic transitions in solution [69, 318]:

(1) *Nonpolar solute in a nonpolar solvent.* In this case, only dispersion forces contribute to the solvation of the solute. Dispersion forces, operative in any solution, invariably cause a small bathochromic shift, the magnitude of which is a function of the solvent refractive index n, the transition intensity, and the size of the solute molecule. The function $(n^2 - 1)/(2n^2 + 1)$ has been proposed to account for this general red shift [69, 70]. Corresponding linear correlations between this function of n and $\Delta\tilde{\nu}$ have been observed for aromatic compounds (*e.g.* benzene [22], phenanthrene [71]), polyenes (*e.g.* lycopene [23], β-carotene [464]), and symmetrical polymethine dyes (*e.g.* cyanines [26, 27, 292, 293]).

(2) *Nonpolar solute in a polar solvent.* In the absence of a solute dipole moment there is no significant orientation of solvent molecules around the solute molecules, and again a general red shift, depending on the solvent refractive index n, is expected. Solute quadrupole/solvent dipole interactions also have to be taken into account in this case, as shown for nonpolar aromatic solutes (*e.g.* anthracene) [469].

(3) *Dipolar solute in a nonpolar solvent.* In this case, the forces contributing to solvation are dipole-induced dipole and dispersion forces. If the solute dipole moment increases

during the electronic transition, the Franck–Condon excited state*) is more solvated by dipole-solvent polarization, and a red shift, depending on the solvent refractive index *n* and the change in solute dipole moment, is expected. The Franck–Condon excited state is less solvated if the solute dipole moment decreases during the electronic transition, and a blue shift, again proportional to the two above mentioned factors, is expected. In the latter case, the resultant shift may be red or blue depending on the relative magnitude of the red shift caused by polarization and the blue shift.

(4) *Dipolar solute in a polar solvent.* Since the ground-state solvation results largely from dipole-dipole forces in this case, there is an oriented solvent cage around the dipolar solute molecules, resulting in a net stabilization of their ground state. If the solute dipole moment increases during the electronic transition ($\mu_g < \mu_e$), the Franck–Condon excited state is formed in a solvent cage of already partly oriented solvent dipoles. The better stabilization of the excited state relative to the ground state with increasing solvent polarity will result in a bathochromic shift. Its magnitude will depend on the extent of the change in the solute dipole moment during the transition, the value of the solvent dipole moment, and the extent of interaction between the solute and solvent molecules. This situation is schematically illustrated in Fig. 6-4a.

If the dipole moment of the solute decreases during the electronic transition, the Franck–Condon excited state is formed in a strained solvent cage of oriented dipoles not correctly disposed for its efficient stabilization. Thus, with increasing solvent polarity, the energy of the ground state is lowered more than that of the excited state, and this produces a hypsochromic shift (*cf.* Fig. 6-4b). The superimposed bathochromic shift due to polarization will usually be less, resulting in a net hypsochromic shift. For intermolecular charge-transfer transitions (except charge-transfer-to-solvent) the direction of the solvent-induced wavelength shift may be determined in a similar manner.

For strongly solvatochromic compounds (see Table 6-1), the observed solvent-induced wavelength shifts cannot be explained only in terms of a change in the permanent dipole moment on electronic transition ($\mu_g \neq \mu_e$). The change in ground-state dipole moment of the solute, induced by the surrounding solvent cage ($\mu_g \rightarrow \mu_g'$) must also be taken into account [20, 36, 72–79]. The dipolar solute molecules cause an electronic polarization of the surrounding solvent molecules, creating a so-called reaction

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* The Franck–Condon principle states that since the time required for a molecule to execute a vibration (*ca.* 10^{-12} s) is much longer than that required for an electronic transition (*ca.* 10^{-15} s), the nuclei of the chromophore (and of the surrounding solvent molecules) do not appreciably alter their positions during an electronic transition; *cf.* J. Franck, Trans. Faraday Soc. *21*, 536 (1926), and C. U. Condon, Phys. Rev. *32*, 858 (1928). Therefore, at the instant of its formation, the excited solute molecule is momentarily surrounded by a solvent cage whose size and orientation are those suited to the ground state, a situation which is usually called the Franck–Condon state [69]. The equilibrium excited state is subsequently reached by a process of relaxation. The Franck–Condon excited molecule and its solvent cage are in a strained state, whose energy is necessarily greater than that of the equilibrium state. Because the Franck–Condon excited state is directly reached, the magnitude of the solvent effect does not correspond exactly to the extent of charge-transfer on electronic activation, as was proposed for reaction rates, where the activated complex is supposed to be in thermal equilibrium with its environment.

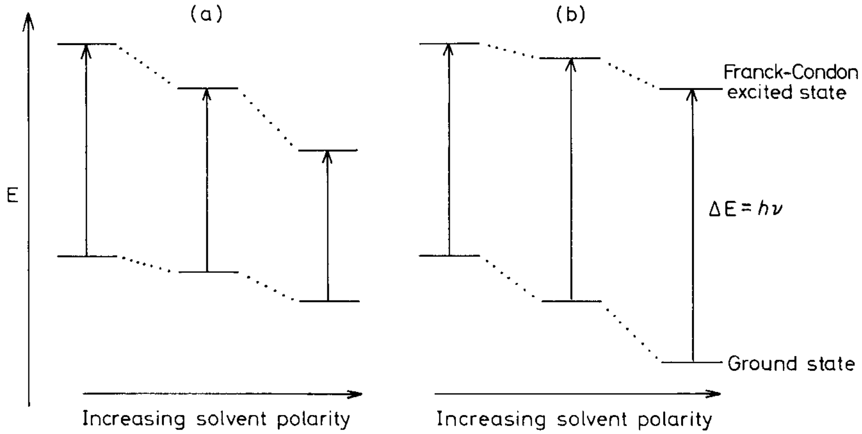
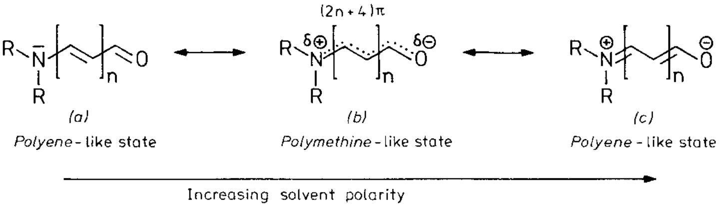


Fig. 6-4. Schematic qualitative representation of solvent effects on the electronic transition energy of dipolar solutes in polar solvents [2, 69]. (a) $\mu_g < \mu_e$, *i.e.* the dipole moment of the Franck–Condon excited state of the solute is larger than those of its ground state; (b) $\mu_g > \mu_e$.

field*) which affects the solute's ground-state dipole moment μ_g. That is, the interaction of the dipolar solute molecules with this induced reaction field, due to the total dipole moment (permanent and induced) of the solvent molecules, may cause an alteration of the electronic structure of the chromophore**). For meropolymethine dyes such as the positively solvatochromic merocyanine described below, this implies that increasing solvent polarity should shift the electronic structure from a polyene-like state *(a)* to a more polymethine-like state *(b)* [20, 74–79, 470].



The effects of such a change in electronic ground-state structure on the position of the absorption band were calculated by Förster in 1939 [72]. According to his calcu-

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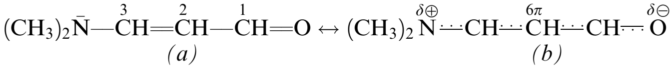
* According to Onsager, a reaction field is the electric field arising from an interaction between an ideal nonpolarizable point dipole and a homogeneous polarizable dielectric continuum in which the dipole is immersed [80]. The reaction field is the electric field felt by the solute molecule due to the orientation and/or electronic polarization of the solvent molecules by the solute dipole.

** This reaction field, caused by the solvent molecules surrounding the dipolar solute molecule, is of the order of 10^7 V/cm and can influence an absorption spectrum in the same manner as an externally applied electric field. The spectral changes produced by means of a homogeneous external electric field have been termed *electrochromism*. Thus, solvatochromism is closely related to electrochromism [13, 81, 82].

Table 6-2. ^{13}C and ^{15}N chemical shifts [77], $^{3}J_{HH}$ coupling constants [73], and C=O stretching vibrations [20] of 3-(dimethylamino)propenal in solvents of increasing polarity.



$$(CH_3)_2\overset{-}{N}-\overset{3}{C}H=\overset{2}{C}H-\overset{1}{C}H=O \leftrightarrow (CH_3)_2\overset{\delta\oplus}{N}\cdots CH\cdots\overset{6\pi}{C}H\cdots CH\cdots\overset{\delta\ominus}{O}$$

(a) (b)

$\mu_g = 21 \cdot 10^{-30}$ Cm a)
(benzene; 25 °C)

Solvents	CCl_4	CS_2	$CDCl_3$	CD_3SOCD_3	CD_3CN	D_2O
$\delta_{^{13}C}$/ppm C-1	187.6	–	–	188.4	–	190.5
C-2	101.2	–	–	101.3	–	100.3
C-3	160.1	–	–	161.6	–	164.4
$\delta_{^{15}N}$/ppm b),c)	56.8	–	62.4	64.9	–	85.4
$^{3}J_{1-H/2-H}$/Hz	–	7.95	8.22	–	8.25	9.32
$^{3}J_{2-H/3-H}$/Hz	–	12.7	12.5	–	12.5	12.2
$\tilde{\nu}_{C=O}/cm^{-1}$ b)	1633 d)	–	1620	1620	1624	1592

a) M. H. Hutchinson and L. E. Sutton, J. Chem. Soc. *1958*, 4382.
b) Values for non-deuterated solvents.
c) R. Radeglia, R. Wolff, B. Bornowski, and S. Dähne, Z. Phys. Chem. (Leipzig) *261*, 502 (1980).
d) Value for c-C_6H_{12}.

lations, an intermediate meropolymethine *(b)* with equal contribution of both mesomeric structures *(a)* and *(c)* will have the longest-wavelength absorption. Therefore, a chromophore with a polyene-like electronic structure *(a)* will exhibit a bathochromic shift with increasing solvent polarity (positive solvatochromism), whereas a chromophore with a polymethine-like electronic structure *(b)* will show a hypsochromic shift on the same solvent change (negative solvatochromism) [72].

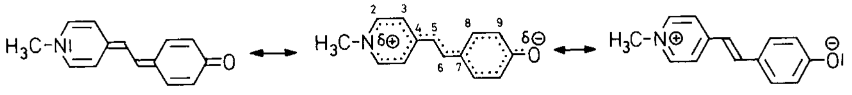
That the electronic ground-state structure of a dipolar solute is indeed affected by solvent polarity has been independently shown by ^{1}H NMR [20, 50, 73, 75, 78], ^{13}C NMR [77], and IR measurements [20] of merocyanines. Some of these results observed with the positively solvatochromic 3-(dimethylamino)propenal are presented in Table 6-2.

The transition from polyene-like state *(a)* (with a balanced π-electron density) to polymethine-like state *(b)* (with strongly alternating π-electron density along the methine chain) with increasing solvent polarity can clearly be seen from the ^{13}C and ^{15}N chemical shifts and from the increasing equalization of the $^{3}J_{HH}$ coupling constants, as well as from the decreasing wavenumber of the C=O stretching vibration. Furthermore, it has been shown that the electronic polarizability of this merocyanine also depends strongly on solvent polarity [79, 83]. In non-polar solvents, the polarizability is similar to that of polyenes, whereas in polar solvents, it very nearly reaches that of ideal polymethines [79].

Recent theoretical calculations on 3-aminopropenal and 5-(dimethylamino)penta-2,4-dienal are essentially in agreement with the observed bathochromic band shift, the increasing dipole moment, and the decreasing bond-length alternation as solvent polarity increases [471, 472]. Not unexpectedly, an enhanced solvatochromic effect is obtained for water as solvent because of hydrogen bonding to the carbonyl ↔ enolate oxygen atom of these vinylogous amides [471, 472]. The molecular electronic structure of such donor/acceptor- or push-pull-substituted polyenes can be tuned from the polyene-like (bond-alternated) state *(a)*, through the polymethine-like (non-alternated) state *(b)*, to the fully reversed zwitterionic (bond-alternated) state *(c)*, as a function of the donor/acceptor strength, the *solvent polarity*, and static external electric fields [470]. The permanent dipole moment increases in response to these structural changes and the linear polarizability reaches a maximum at the polymethine-like state *(b)*. This remarkable behaviour is of importance in optimizing organic materials for nonlinear optical (NLO) applications [470].

As shown by the ^{1}H NMR chemical shifts of negatively solvatochromic meropolymethine dyes (*e.g.* phenol blue), the electronic ground-state structure of these dyes changes from a polymethine-like state *(b)* in non-polar solvents to a polyene-like state *(c)* in polar solvents [50, 78].

A particularly interesting solvatochromic merocyanine dye is 1-methyl-4-[(4-oxocyclohexadienylidene)ethylidene]-1,4-dihydropyridine also called Brooker's merocyanine [48]. First it exhibits a bathochromic and then a hypsochromic shift of the long-wavelength $\pi \rightarrow \pi^*$ absorption band as the solvent polarity increases [309]; *cf.* also entry 14 in Table 6-1.



(a) (b) (c)

Solvent	c-C_6H_{12}		$CHCl_3$		H_2O
λ_{max}/nm	592		620		442
$\Delta\lambda$/nm		+28		−178	
Solvent polarity			→		

This surprising inverted solvatochromism seems to indicate that the ground-state electronic structure of this merocyanine dye changes, with increasing solvent polarity, from the quinonoid structure *(a)* to the benzenoid structure *(c)* via the intermediate polymethine-like structure *(b)*. The longest-wavelength absorption is near the balanced valence structure *(b)*, that is in trichloromethane as solvent. In agreement with this inverted solvatochromism, the calculated dipole moments of the ground and excited states show the following evolution: $\mu_g < \mu_e$ in nonpolar and $\mu_g > \mu_e$ in polar solvents for the $\pi \rightarrow \pi^*$ transition [308]. Increasing solvent polarity also causes a dramatic change in molecular geometry, as shown by both the calculated bond lengths and the net π-electron charges [308]. In a solvent of medium polarity, the merocyanine dye adopts an ideal polymethine valence structure with intermediate bond lengths of *ca.* 140 pm along the methine chain C-4/C-5/C-6/C-7. The experimentally not observed *trans* → *cis* photoisomerization of this transoid stilbazolium merocyanine dye can also be explained in terms of the contribution of both the benzenoid and quinonoid mesomeric structures to its ground-state electronic structure [430]. Whereas semiempirical MO calculations are in agreement with this inverted solvatochromism [308], recent, more sophisticated, theoretical calculations, as well as ^{1}H and ^{13}C NMR measurements in a range of solvents have shown that Brooker's merocyanine does indeed exist as a resonance hybrid, which is, however, weighted toward the zwitterionic pyridinium phenolate structure, even in solvents of low polarity [304]. The large hypsochromic band shifts observed for this merocyanine in HBD solvents (*e.g.* water) arises from both a dielectric effect and a strong hydrogen-bonding effect of the type $\mathrm{Ar{-}O^- \cdots H{-}OR}$. Thus, the HBD ability of the solvent is most probably the key factor behind the experimentally observed negative solvatochromism in protic solvents [308, 477]. For similar merocyanine dyes exhibiting a negative solvatochromism in polar HBD solvents and a solvatochromic reversal in media of low polarity, see references [473–477].

In addition to changes in ground-state electronic structure and changes in dipole moment on electronic transition, a third possibility responsible for solvatochromism has been discussed [84]: if the potential curves (Morse curves) of the ground and excited states of a meropolymethine are shifted towards one another by solvent interaction, then, according to the Franck–Condon principle, the relative intensity of the vibronic transitions should be altered, with a net shift or change of shape of the absorption band as a consequence [84]. It has been shown, however, that this effect contributes to solvatochromism only to a minor extent, if at all [37]. A remarkable solvent effect influencing the shape of $\pi \rightarrow \pi^*$ absorption bands, attributed to solvent-induced changes in vibronic interactions, has been reported for an unsymmetrical pyrylothiacyanine dye [319].

Sometimes, external solvent polarization interactions can lift internal symmetry restrictions in the solute molecule and can induce new bands not observable in the gas-phase spectrum. A well-known example is the vibrationally forbidden $0 \rightarrow 0$ vibrational component of the long-wavelength $\pi \rightarrow \pi^*$ absorption of benzene (at 262 nm in *n*-hexane), which appears when benzene is dissolved in organic solvents, but not in the gas phase [320].

It should be mentioned that solvent effects on the intensity of UV/Vis absorption bands cannot be interpreted in a simple qualitative fashion as is the case for the band position shifts [85, 308, 309, 321–323].

Quantitative calculations of the solvent dependence of UV/Vis absorption spectra, based on different models, have been carried out by Bayliss and McRae [69], Oshika [86], McRae [70], Lippert [47], Bakhshiev [87], Bilot and Kawski [88], Weigang and Wild [71], Abe [89], Liptay [90, 94], Kuhn and Schweig [59, 91], Nicol *et al.* [16, 92], Suppan [93], Kampas [95], Germer [95a], Nolte and Dähne [95b], Bekárek [324], Mazurenko [325], Suppan [16, 478], Ågren and Mikkelsen [479], and Klamt [480]. The underlying theory has been repeatedly reviewed [1, 4, 13–17], and critical discussions of the differences in the results of previous calculations can be found in references [1, 15, 16, 90, 318]. A detailed discussion of all these approaches is beyond the scope of this book. Recent overviews of state-of-the-art theoretical treatments of solvent effects on electronic spectra are given in references [435–437].

According to the McRae-Bayliss model of solvatochromism [69, 70] which is directly evolved from Onsager's reaction field theory [80], the electronic transition from ground (g) to excited state (e) of a solvatochromic solute is given by Eq. (6-1) [318]:

$$\begin{aligned}\tilde{\nu}_{\mathrm{eg}}^{\mathrm{sol}} = \tilde{\nu}_{\mathrm{eg}}^{0} &- [(\mu_{\mathrm{g}} \cdot \mu_{\mathrm{e}} \cdot \cos\varphi - \mu_{\mathrm{g}}^2) \cdot 1/a_{\mathrm{w}}^3] \cdot [L(\varepsilon_{\mathrm{r}}) - L(n^2)] \\ &- [(\mu_{\mathrm{e}}^2 - \mu_{\mathrm{g}}^2) \cdot 1/a_{\mathrm{w}}^3] \cdot [L(n^2)]\end{aligned} \tag{6-1}$$

where $\tilde{\nu}$ is the solute transition energy in the gas phase ($\tilde{\nu}_{\mathrm{eg}}^{0}$) and in solution ($\tilde{\nu}_{\mathrm{eg}}^{\mathrm{sol}}$), a_{W} the solute cavity radius, μ_{g} and μ_{e} the permanent dipole moments of the ground and excited-state molecule, and φ the angle between the ground and excited-state dipoles. $L(\varepsilon_{\mathrm{r}})$ and $L(n^2)$ are reaction field functions defined by $L(x) = 2(x-1)/(2x+1)$ with $x = \varepsilon_{\mathrm{r}}$ or n^2; ε_{r} and n are the bulk static relative permittivity and refractive index of the solvent, respectively. $[L(\varepsilon_{\mathrm{r}}) - L(n^2)]$ and $L(n^2)$ are the relevant solvent variables, whereas the remaining terms $(\mu_{\mathrm{g}}, \mu_{\mathrm{e}}, \varphi, a_{\mathrm{W}})$ are assumed to be solute-dependent constants and independent of the solvent. As already mentioned, this is not strictly correct since any real solute dipole is polarizable and therefore affected by the reaction field.

This McRae-Bayliss model of solvatochromism as well as modifications thereof have been carefully reexamined and tested by Brady and Carr [318] and by Ehrenson [318]. The inadequacies of the McRae-Bayliss approach to solvatochromism are outlined. Alternative reaction field models have been tested, albeit with only limited success [318].

A more rigorous approach to general UV/Vis absorption/solvent correlations has been given by Liptay [33, 90, 94]. According to Liptay, the solvent-dependent wavenumber shift for an absorption corresponding to an electronic transition from ground- (g) to excited-state (e) molecules can be described by Eq. (6-2)*):

$$\begin{aligned}
hca\Delta\tilde{\nu}_{\mathrm{eg}}^{\mathrm{sol}} &= hca(\tilde{\nu}_{\mathrm{eg}}^{\mathrm{sol}} - \tilde{\nu}_{\mathrm{eg}}^{0}) \\
&= (W_{\mathrm{Ce}}^{\mathrm{FC}} - W_{\mathrm{Cg}}) + (W_{\mathrm{De}}^{\mathrm{FC}} - W_{\mathrm{Dg}}) \\
&\quad - \tfrac{1}{2}(\tilde{\boldsymbol{\mu}}_{\mathrm{e}} - \tilde{\boldsymbol{\mu}}_{\mathrm{g}})\mathbf{f}'(\mathbf{1} - \mathbf{f}'\boldsymbol{\alpha}_{\mathrm{e}})^{-1}(\boldsymbol{\mu}_{\mathrm{e}} - \boldsymbol{\mu}_{\mathrm{g}}) \\
&\quad - (\tilde{\boldsymbol{\mu}}_{\mathrm{e}} - \tilde{\boldsymbol{\mu}}_{\mathrm{g}})\mathbf{f}(\mathbf{1} - \mathbf{f}\boldsymbol{\alpha}_{\mathrm{g}})^{-1}\boldsymbol{\mu}_{\mathrm{g}} \\
&\quad - \tilde{\boldsymbol{\mu}}_{\mathrm{g}}(\mathbf{1} - \mathbf{f}'\boldsymbol{\alpha}_{\mathrm{e}})^{-1}(\mathbf{1} - \mathbf{f}\boldsymbol{\alpha}_{\mathrm{g}})^{-2}\mathbf{f}(\boldsymbol{\alpha}_{\mathrm{e}} - \boldsymbol{\alpha}_{\mathrm{g}}) \\
&\quad \times \left[\tfrac{1}{2}(\mathbf{1} - \mathbf{f}'\boldsymbol{\alpha}_{\mathrm{g}})\mathbf{f}\boldsymbol{\mu}_{\mathrm{g}} + (\mathbf{1} - \mathbf{f}\boldsymbol{\alpha}_{\mathrm{g}})\mathbf{f}'(\boldsymbol{\mu}_{\mathrm{e}} - \boldsymbol{\mu}_{\mathrm{g}})\right] \qquad (6\text{-}2)
\end{aligned}$$

$\tilde{\nu}_{\mathrm{eg}}^{0}$ and $\tilde{\nu}_{\mathrm{eg}}^{\mathrm{sol}}$ are the absorption wavenumbers of the transition considered in the gas phase and in solution, respectively, h is Planck's constant, c is the speed of light in vacuum, and a ($=10^2\ \mathrm{m}^{-1} \cdot \mathrm{cm}$) is a conversion constant (thus the unit of $\tilde{\nu}_{\mathrm{eg}}$ is cm^{-1}).

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* The tensors $\mathbf{f}$ and $\mathbf{f}'$ in Eq. (6-2) may be represented by Eqs. (6-3) and (6-4) [33, 90], assuming that the solvent can be approximated to a homogeneous and isotropic dielectric, where the solute molecules are localized in a spherical cavity (then the tensor $\mathbf{f}_{\mathrm{e}}$ is reduced to the scalar f_{e}), and approximating the dipole moment of the solute molecule by a point dipole localized in the center of this sphere:

$$\mathbf{f} = f\mathbf{1} = [2(\varepsilon_{\mathrm{r}} - 1)/4\pi\varepsilon_0 a_{\mathrm{w}}^3(2\varepsilon_{\mathrm{r}} + 1)]\mathbf{1} \qquad (6\text{-}3)$$

$$\mathbf{f}' = f'\mathbf{1} = [2(n^2 - 1)/4\pi\varepsilon_0 a_{\mathrm{w}}^3(2n^2 + 1)]\mathbf{1} \qquad (6\text{-}4)$$

In these Eqs., ε_{r} represents the relative permittivity of the solution, ε_0 the permittivity of vacuum, n the refractive index of the solution (for $\tilde{\nu} \to 0$), and a_{W} is the radius of the sphere.

The first term on the right-hand side of Eq. (6-2) represents the differences of the energies required to form a cavity in the solvent for the ground state and Franck–Condon excited-state molecules. Since, for most transitions, its change in size during the excitation process is small, it is usually assumed that $W_{\mathrm{Ce}}^{\mathrm{FC}} - W_{\mathrm{Cg}} = 0$. The second term represents the dispersion interaction between the solute molecule and the surrounding solvent molecules, approximated by $W_{\mathrm{De}}^{\mathrm{FC}} - W_{\mathrm{Dg}} = -hcaD_{\mathrm{eg}}f'$, where D_{eg} is a quantity almost independent of the solvent. According to Eq. (6-4), the dispersion interactions are dependent on the refraction index n of the solvent. The third and fourth terms of Eq. (6-2) represent the energy change due to the change in the permanent dipole moment of the solute molecule during excitation. The third term depends on the change in the dipole moment and essentially on the refractive index of the solvent used; the fourth term depends on the ground-state dipole moment, the change of dipole moment, and the relative permittivity of the solvent. The fifth and last term depends on the change of the polarizability $(\alpha_e - \alpha_g)$ of the solute molecule on excitation*⁾.

In the case of nonpolar solute molecules, the third and fourth as well as the fifth term in Eq. (6-2) is zero, thus the solvent dependence will be determined by dispersion interactions and only the second term is essential. The solvent shift, compared to the vapour state, will be approximately 70 to 3000 cm^{-1} to lower wavenumbers (general red shift) depending only on the function $\mathbf{f}'$ (*cf.* Eq. (6-4)). If, on excitation, there is a sufficiently large change in dipole moment, the third and fourth terms have to be taken into account. In the case of an increase in the dipole moment, these terms cause a bathochromic shift, and in the case of a decrease, a hypsochromic shift of the absorption band. It has been calculated that for a molecule with an interaction radius $a_{\mathrm{W}} = 6 \cdot 10^{-8}$ cm, a dipole moment $\mu_g = 20 \cdot 10^{-30}$ Cm (6 D), and a dipole change $(\mu_e - \mu_g) = 100 \cdot 10^{-30}$ Cm (30 D), the shift between the vapour state and a nonpolar solvent ($\varepsilon_r = 2$) will be *ca.* 4000 cm^{-1}, and the shift from a nonpolar to a medium polar solvent ($\varepsilon_r = 30$) will be *ca.* 12000 cm^{-1} [90]. The last term in Eq. (6-2) will be important only if μ_g or $(\mu_e - \mu_g)$ is also large. In this case, the two preceding terms are usually much larger and will essentially determine the solvent dependence. Therefore, in an approximation, the last term may usually be neglected [33, 90]. Finally, it should be mentioned that because of the approximations made in deriving Eq. (6-2), one cannot expect that this equation for the solvent dependence of UV/Vis absorptions will be fully accurate [33, 90].

Combining the idea of solvent-induced changes in molecular structure with the concept of a solvent continuum around the solvatochromic molecule, a microstructural model of solvatochromism has been developed by Dähne *et al.*, which reproduces, qualitatively correctly and quantitatively satisfactorily, the solvatochromic behavior of simple merocyanine dyes [95b]. The results obtained with this model for 5-(dimethylamino)penta-2,4-dienal are in good agreement with the solvent-dependent experimental data such as transition energies, oscillator strengths, π-electron densities, and π-bond energies [95b]; *cf.* also [326, 327].

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* For the addition of a sixth and a seventh term depending on the fluctuation of the reaction field, see references [33, 94].

6.2.3 Specific Solvent Effects on UV/Vis Absorption Spectra

In principle, the general rules for solvent effects on the position of $\pi \rightarrow \pi^*$ absorption bands are also valid for $n \rightarrow \pi^*$ (and $n \rightarrow \sigma^*$) absorption bands of *N*-heterocycles and of compounds with heteronuclear double bonds such as $>\!C{=}X$ or $-N{=}X$ (with $X = O$, S, N, *etc*). For instance, the $n \rightarrow \pi^*$ excited state of a carbonyl group*) is less dipolar but more polarizable than the ground state. During the process of excitation, one *n*-electron is promoted from a nonbonding orbital on the oxygen atom to an antibonding π^* orbital, which is delocalized over the carbonyl group. Removal of an electron from the oxygen atom implies a considerable contribution from the $>\!\bar{C}^{\ominus}{-}\underline{\bar{O}}^{\oplus}$ mesomeric structure, with a decrease or even reversal in direction of the excited-state dipole moment. Indeed, it has been found that the dipole moment of the lowest singlet $n \rightarrow \pi^*$ excited state of benzophenone, at $\mu_e(n \rightarrow \pi^*) = 5 \cdot 10^{-30}$ Cm (1.5 D), is only half as large as the dipole moment of the ground state, $\mu_g = 10 \cdot 10^{-30}$ Cm (3 D) [32, 33, 96]. This dipole diminution leads to a *hypsochromic* (or blue) shift of the $n \rightarrow \pi^*$ absorption band with increasing solvent polarity, because the electrostatic dipole/dipole interactions stabilize the dipolar S_0 ground state more than the less dipolar S_1 excited state.

As one *n*-electron is promoted to a more diffuse π^* orbital, which is more polarizable, the excited S_1 state usually has a larger polarizability than the S_0 ground state. Thus, the dispersion interaction of the excited carbonyl solute with the solvent will be larger than the dispersion interaction of the less polarizable ground-state solute with the solvent. The electronic excitation energy decreases, resulting in a *bathochromic* (or red) shift of the $n \rightarrow \pi^*$ absorption band.

In addition, protic solvents are capable of hydrogen-bond formation with the oxygen lone pairs of the carbonyl group, lowering the energy of the *n*-state, whereas to a first approximation the energy of the π^* state is not modified by intermolecular hydrogen bonding. Thus, this specific carbonyl solute/solvent interaction should lead to a *hypsochromic* (or blue) shift of the $n \rightarrow \pi^*$ absorption band [97–106].

Overall, the band shifts experimentally observed for all kinds of $n \rightarrow \pi^*$ absorptions are the net results of three, partly counteracting contributions: electrostatic (dipole/dipole; dipole/induced dipole → blue shift), dispersion (→ red shift), and specific hydrogen-bonding (→ blue shift). Which of these solute/solvent interactions are dominant for the solute under study depends on the solvents used. For example, the results obtained for pyridazine, as shown in Fig. 6-5, clearly implicate hydrogen-bonding as the principle cause of the observed hypsochromic band shift that occurs when the HBD solvent ethanol is added to solutions of pyridazine in nonpolar *n*-hexane [98]. The intensity of $n \rightarrow \pi^*$ absorption bands is usually very low because they correspond to symmetry-forbidden transitions, which are made weakly allowed by vibronic interactions (*cf.* Fig. 6-5).

An example with varying contributions to the observed solvent effect of all three terms is the UV absorption of acetone, a prototype $n \rightarrow \pi^*$ excitation. On going from the gas phase ($\tilde{\nu}_{max} = 36100$ cm^{-1}; $\lambda_{max} = 277$ nm) to solution spectra, the absorption

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* Again, the excited state referred to here is the Franck–Condon excited state, which has a solvent shell identical to that of the ground state.

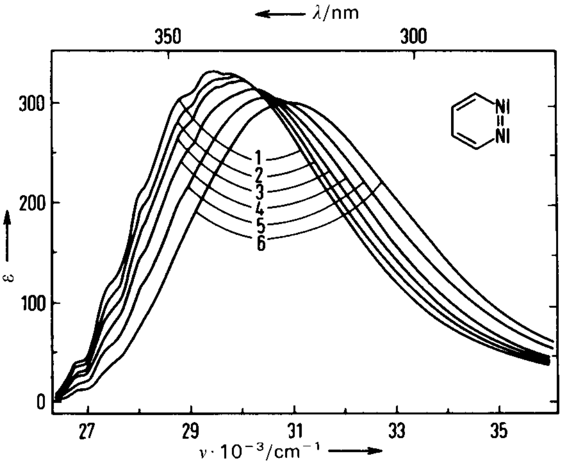


Fig. 6-5. The $n \rightarrow \pi^*$ band in the UV/Vis absorption spectrum of pyridazine in *n*-hexane/ethanol mixtures from zero to 3.2 cL/L ethanol ($c = 1.01 \cdot 10^{-2}$ mol/L pyridazine) [98]. Ethanol concentrations: curve (1) zero, (2) 0.0343, (3) 0.0686, (4) 0.137, (5) 0.274, and (6) 0.549 mol/L.

band is red-shifted in apolar solvents such as cyclohexane ($\Delta\tilde{\nu} = -400$ cm^{-1}; $\Delta\lambda = +3$ nm) and benzene ($\Delta\tilde{\nu} = -650$ cm^{-1}; $\Delta\lambda = +5$ nm). A blue band shift is found in dipolar HBD solvents such as methanol ($\Delta\tilde{\nu} = +850$ cm^{-1}; $\Delta\lambda = -6$ nm) and water ($\Delta\tilde{\nu} = +1700$ cm^{-1}; $\Delta\lambda = -12$ nm) [481, 482]. The red shift observed in apolar solvents is mainly caused by solute/solvent dispersion interactions, whereas the blue shift in dipolar HBD solvents is due to electrostatic and hydrogen-bond interactions, which overcompensate for the red shift caused by dispersion forces. Recent theoretical calculations of the solvatochromic shifts observed for acetone in nine solvents in terms of electrostatics, dispersion, and hydrogen-bonding are in excellent agreement with the experimental data [328, 329]. It is even possible to quantify the various individual contributions to the observed total band shift for each solvent.

The UV/Vis spectra of aromatic ketones such as benzophenone are composed of $n \rightarrow \pi^*$ and π–π^* absorption bands, which show opposite solvent effects; see Table 6-3 and Fig. 6-6 [102, 104, 108]. For the $n \rightarrow \pi^*$ transition of benzophenone ($\tilde{\nu}_{max} = 28860$ cm^{-1}; $\lambda_{max} = 347$ nm in *n*-hexane), a small blue shift of $\Delta\tilde{\nu} = +680$ cm^{-1} ($\Delta\lambda = -8$ nm) is observed on going from apolar *n*-hexane to dipolar aprotic acetonitrile as solvent. This blue shift is significantly enhanced on going further to protic solvents such as water ($\Delta\tilde{\nu} = +1520$ cm^{-1} and $\Delta\lambda = -17$ nm for $CH_3CN \rightarrow H_2O$). This larger band shift is again mainly due to hydrogen bonding to the carbonyl group. Incidentally, the $n \rightarrow \pi^*$ transition energies of carbonyl groups in different solvents are found to vary linearly with the infrared C=O stretching frequencies measured in the same solvents, indicating the importance of the ground-state stabilization by solvents [102].

In contrast to the $n \rightarrow \pi^*$ absorption of carbonyl compounds, for their $\pi \rightarrow \pi^*$ absorption $\mu_e(\pi \rightarrow \pi^*)$ is not only colinear with μ_g but also has increased magnitude with respect to μ_g (*e.g.* benzophenone: $\mu_g = 10 \cdot 10^{-30}$ Cm; $\mu_e(\pi \rightarrow \pi^*) = 16 \cdot 10^{-30}$ Cm [107]). Consequently, in going from a nonpolar to a polar solvent, the $\pi \rightarrow \pi^*$ absorption should undergo a bathochromic shift, while the $n \rightarrow \pi^*$ absorption undergoes a hypsochromic shift. This contradictory behaviour of absorption bands with changes

Table 6-3. The $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ band maxima in the UV/Vis absorption spectrum of benzophenone in solvents of increasing polarity [104].

Solvents	$\tilde{\nu}(n \rightarrow \pi^*)/\mathrm{cm}^{-1}$	$\tilde{\nu}(\pi \rightarrow \pi^*)/\mathrm{cm}^{-1}$
n-Hexane	28 860	40 400
Cyclohexane	28 860	40 240
Diethyl ether	29 070	40 160
1,2-Dichloroethane	29 370	39 600
Dimethyl sulfoxide	29 370	–
N,*N*-Dimethylformamide	29 330	–
Acetonitrile	29 540	39 920
1-Butanol	29 990	39 600
1-Propanol	29 900	39 600
Ethanol	30 080	39 680
Methanol	30 170	39 600
Water	*ca.* 31 060 (sh)	38 830
	$\Delta\tilde{\nu} = +2200\ \mathrm{cm}^{-1}$ $\Delta\lambda = -25$ nm	$\Delta\tilde{\nu} = -1570\ \mathrm{cm}^{-1}$ $\Delta\lambda = +10$ nm

in solvent polarity, illustrated for benzophenone in Fig. 6-6 and Table 6-3, is of diagnostic importance in order to distinguish between the $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ transitions of carbonyl compounds [98, 109]. For the distinction of $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ transitions of substituted azobenzenes see, for example, reference [331]. It should be mentioned that in strongly acidic media $n \rightarrow \pi^*$ bands disappear because of protonation of the heteroatom.

In the UV spectrum of 4,4′-bis(dimethylamino)benzophenone (also called Michler's ketone), the low-intensity $n \rightarrow \pi^*$ band is superimposed by the strong $\pi \rightarrow \pi^*$ band ($\tilde{\nu}_{\max} = 30000\ \mathrm{cm}^{-1}$ and $\lambda_{\max} = 333$ nm in *n*-hexane), which exhibits one of the largest known positively solvatochromic band shifts. Its UV spectrum has been mea-

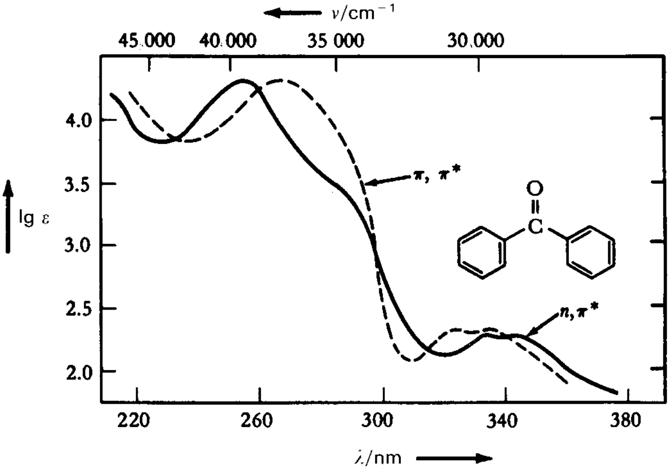
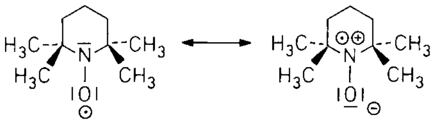


Fig. 6-6. UV/Vis absorption spectrum of benzophenone in cyclohexane (——) and ethanol (---) at 25 °C [104, 108].

sured in 73 different solvents, showing a band shift of $\Delta\tilde{\nu} = -5080\ \text{cm}^{-1}$ ($\Delta\lambda = +68$ nm) on going from *n*-hexane to 3-methoxyphenol as solvent [106]. Surprisingly, there is a disproportionately large red shift on going from protic methanol to protic 3-methoxyphenol ($\Delta\tilde{\nu} = -2160\ \text{cm}^{-1}$; $\Delta\lambda = +32$ nm), which cannot be explained in terms of specific hydrogen-bonding alone. It seems that there is an additional specific EPD/EPA interaction between the aromatic phenol and the aromatic ketone [106].

The solvent-dependences of the $n \rightarrow \pi^*$ transitions of chromophores other than the carbonyl group, such as $\rangle C{=}S$ in thiocarbonyl compounds [332], $\rangle\overset{\oplus}{N}{-}\overset{\ominus}{O}$ in *N*-oxides [65, 333], $\rangle\overset{\odot\oplus}{N}{-}\overset{\ominus}{O}$ in aminyl oxide radicals [334–336], and $\rangle\overset{\oplus}{N}{=}\overset{\ominus}{N}$ in 1,1-diazenes [337], have also been investigated. One example, the 2,2,6,6-tetramethylpiperidine-1-oxyl radical, exhibits a comparatively large negative solvatochromism of the weak $n \rightarrow \pi^*$ absorption band, whereas the intense $\pi \rightarrow \pi^*$ transition in the ultraviolet region is not sensitive to solvent changes [334, 336].



Solvent	n-C_6H_{14}	CH_3CN	CH_3OH	H_2O
$\lambda_{\text{max}}^{n\rightarrow\pi^*}$/nm	477	461	446	424
$\Delta\lambda$/nm	−53			

The visible $n \rightarrow \pi^*$ absorption band is shifted hypsochromically by $\Delta\lambda = 53$ nm on changing the medium from *n*-hexane to water. Based on the negative solvatochromism of this aminyloxide radical, a spectroscopic solvent polarity scale, called the E_B scale of Lewis acidity has been proposed [336]. Because of its pronounced negative solvatochromism, 4-nitropyridine-1-oxide has been recommended as an empirical indicator of the HBD acidity of solvents [330]; *cf.* Section 7.4. The solvatochromic range of this *N*-oxide, measured in 48 different solvents, amounts to $\Delta\tilde{\nu} = +2840\ \text{cm}^{-1}$ ($\Delta\lambda = -31$ nm) for the solvent change *n*-hexane → water.

The marked solvent-dependence of the $n \rightarrow \pi^*$ transition of benzophenone [110] and of 2,2,6,6-tetramethylpiperidine-1-oxyl [338] when solubilized by micellar surfactants, has also been used to investigate the molecular-microscopic polarity of the micellar environment in which the transition takes place.

Specific hydrogen bonding is also involved in the solvation of saturated compounds with heteroatoms carrying lone pairs of electrons, which give rise to $n \rightarrow \sigma^*$ transitions. These transitions also undergo a significant blue shift with increasing solvent polarity, especially in protic solvents [111]. Direct evidence of the general validity of the concept of a blue shift of $n \rightarrow \sigma^*$ absorption bands is provided by a comparison of the vacuum UV bands of water, ammonia, hydrogen sulfide, and phosphane in aqueous solution relative to the location of these bands in the gas phase or in non-HBD nonpolar solvent solution spectra [111].

6.2.4 Solvent Effects on Fluorescence Spectra

When excited states of a molecule are created in solution by continuous or flash excitation, the excited-state molecule interacts to a varying degree with the surrounding solvent molecules, depending on their polarity, before returning to the ground state. These excited-state solute/solvent interactions found in fluorescent molecules are often reflected in the spectral position and shape of the emission bands as well as in the lifetimes of the excited-state molecules. The solvent-dependence of the position of emission bands in fluorescence spectra is commonly included in the term *solvatochromism*. Sometimes, the solvent-dependence of fluorescence spectra has been called *fluorosolvatochromism* [26] or *solvatofluorochromism* [27]. Because of the close connection between spectral absorption and emission (see Figs. 6-4 and 6-7), there is no need for special terms for the fluorescence-based solvatochromism [16].

Fluorescence usually occurs from the S_1 to the S_0 electronic state by emission of photons. The $0 \rightarrow 0$ transition is generally the same for absorption and fluorescence. According to Stokes' rule, the fluorescence maximum is always located at lower wavenumbers (higher wavelengths) than the absorption maximum because of the loss in energy due to vibrational relaxation (see Fig. 6-7). The gap between the maximum of the first absorption band and the maximum of the corresponding fluorescence band is called the *Stokes shift*, and is usually expressed in wavenumbers as $\Delta\tilde{\nu} = \tilde{\nu}_a - \tilde{\nu}_f$. This Stokes' shift provides valuable information on the excited state. When the dipole moment of a fluorescent molecule is larger in the excited state than in the ground state (*i.e.* $\mu_e > \mu_g$), then the differential solvation of the two states by solvents of varying polarity gives rise to an increase in the Stokes' shift with increasing solvent polarity [112–116, 339, 340].

When considering the solvent dependence of the position of emission bands, the finite relaxation time τ_R for the rearrangement of the solvent molecules surrounding the solute molecule in the Franck–Condon excited state and the finite lifetime τ_e of the molecule in the excited state have to be taken into account.

In the case of $\tau_R \gg \tau_e$*), the emission will occur before any rearrangement of solvent molecules in the solvation shell takes place. The initial state of the emission process is the Franck–Condon excited state and the final state is the equilibrium ground state. Hence, the wavenumber of emission will be equal to the wavenumber of the corresponding absorption. In the case of $\tau_R \ll \tau_e$ (*cf.* Fig. 6-7)*), reorientation of the solvent molecules can take place after electronic excitation and a relaxed excited state is obtained in which another solvation equilibrium has been established. It is from this equilibrium state that fluorescence occurs at room temperature. By analogy, there is a

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* In liquid solutions, the rotational relaxation time τ_R for the solvent molecules is in the range 10^{-12} to 10^{-10} s at room temperature; the lifetime τ_e of an excited singlet state is of the order of 10^{-8} s. Hence, under these circumstances $\tau_R \ll \tau_e$ will be generally valid. τ_R increases strongly with decreasing temperature, while τ_e is only slightly temperature dependent. Therefore, at lower temperatures the case where $\tau_R \approx \tau_e$ can occur. In solid solutions $\tau_R \gg \tau_e$ is the norm. Promotion of an electron to the antibonding molecular orbital upon excitation (light absorption) takes about 10^{-15} s, which is very fast compared to the time for molecular vibrations ($10^{-10} \ldots 10^{-12}$ s). The spontaneous emission of a photon from the excited state is usually as fast as the absorption of a photon. These findings are the basis for the Franck–Condon principle; see footnote on p. 341 in Section 6.2.2.

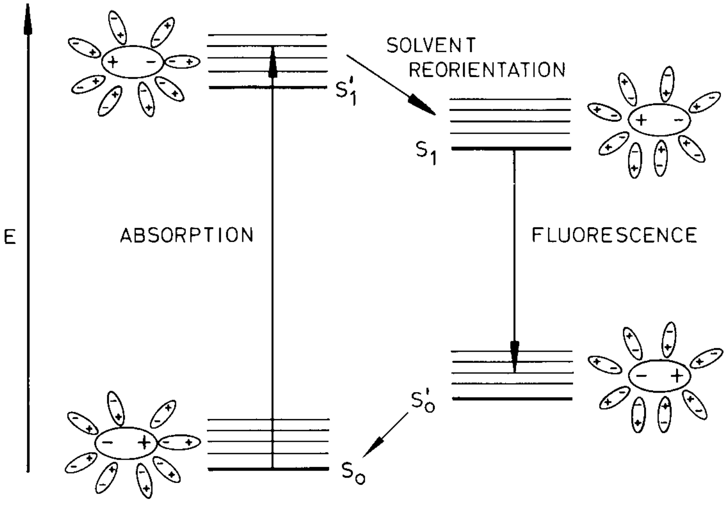


Fig. 6-7. Effect of solvent reorientation in the excited state on the fluorescence band of a dipolar molecule with dipole flip on excitation. S_1' and S_0' are the Franck–Condon excited and ground states, respectively; S_1 and S_0 are the corresponding equilibrium states; $\tau_R \ll \tau_e$.

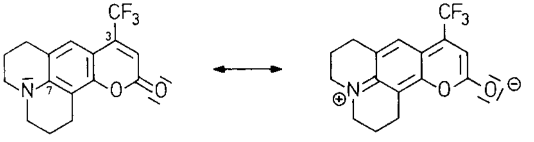
Franck–Condon ground state after emission, which persists momentarily until the solvent molecules reorganize to the equilibrium arrangement for the ground state.

A general explanation of solvent effects on fluorescence spectra is based on the differential solvation of the fluorescent molecules (also called *fluorophores*) in their ground and excited states, mediated by the various non-specific and specific intermolecular forces acting between the solute and solvent [16, 47, 112–114]. When the ground and excited states of an apolar fluorophore differ only in their polarizabilities and not in their dipolarities, then only solute/solvent dispersion interactions exist and rather small or no solvent-induced band shifts are observed. As an example, for benzo[*a*]pyrene, an apolar planar aromatic 20 π hydrocarbon with negligible dipole moments μ_g and μ_e, no discernible solvent dependence of the Stokes' shift was observed in 15 solvents of different polarity [483]. Accordingly, the calculated excited-state polarizability of benzo[*a*]pyrene is only 1.4 times larger than the value for the ground state [483].

However, most fluorophores undergo an intramolecular charge transfer upon excitation so that usually $\mu_e > \mu_g$. In such cases, the relaxed excited state S_1 will be energetically stabilized relative to the ground state S_0 (Fig. 6-7) and a significant red shift of the fluorescence band will be observed. The stronger the solute/solvent interaction, the lower the energy of the excited state, and the larger the red shift of the emission band and the corresponding Stokes shift. A well-known example is the donor/acceptor-substituted 4-(dimethylamino)-4′-nitro-stilbene (entry 11 in Table 6-1), which exhibits a large red shift of its long-wavelength fluorescence emission band of $\Delta\tilde{\nu} = -7600$ cm^{-1} ($\Delta\lambda = +302$ nm) on going from cyclohexane to acetone as solvent, *i.e.* with increasing solvent polarity [47]. This observation is in agreement with the large, *ca.* 3-fold increase in dipole moment on optical excitation ($\mu_g = 25 \cdot 10^{-30}$ C m; $\mu_e = 78 \cdot 10^{-30}$ C m [47a, 303e]).

The solvent-induced shifts of absorption and emission bands can be used to calculate dipole moments of electronically excited molecules [32, 33, 47, 303]. Excited-state dipole moments have also been obtained by the measurement of fluorescence polarization caused by external electric fields [32, 33].

An illustrative example of solvent effects on absorption and emission spectra is given by the following positive solvatochromic laser dye 7-dialkylamino-4-(trifluoromethyl)coumarin ("coumarin-153"), in which the rotation of an amino group is restricted by incorporating it into a hexahydroquinolizine ring [341].



(a) (b)

Solvent	c-C_6H_{12}	C_6H_6	CH_3CN	C_2H_5OH	$HCONH_2$	$\Delta\lambda$/nm	$\Delta\tilde{\nu}$/cm^{-1}
$\lambda_{max}^{Abs.}$/nm	385	404	410	415	426	+41	−2490
$\lambda_{max}^{Fluor.}$/nm	460	500	545	552	564	+104	−4030

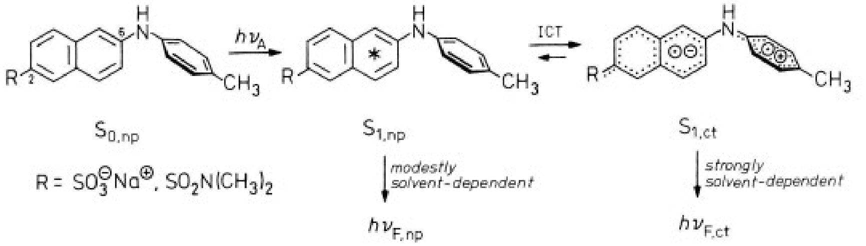
With increasing solvent polarity, both absorption and emission bands undergo a bathochromic shift, the latter being more pronounced than the former. This indicates an *i*ntramolecular *c*harge-*t*ransfer (ICT) absorption of the less dipolar ground-state molecule with *(a)* as the dominant mesomeric structure, leading to highly dipolar excited-state molecule with *(b)* as the prominent structure. It is this planar ICT excited-state molecule from which the emission occurs. Increasing solvent polarity stabilizes the ICT excited-state molecule relative to the ground-state molecule with the observed red shift of the fluorescence maximum as the experimentally observed result [341c]. The large solvatochromic red shifts observed for the absorption and emission spectra of coumarin-153 are in agreement with the large 2.3-fold increase in dipole moment from $\mu_g \approx 22 \cdot 10^{-30}$ Cm to $\mu_e \approx 50 \cdot 10^{-30}$ Cm [341c].

In the case of 7-diethylamino-4-(trifluoromethyl)coumarin ("coumarin-35"), which has an amino group that is free to rotate, another competitive solvent-dependent decay path has been proposed: rotation of the amino group of the planar ICT excited-state molecule can lead to a *t*wisted *i*ntramolecular *c*harge-*t*ransfer (TICT) excited-state molecule, from which a radiationless decay to the ground-state molecule occurs [341]. Solvent-dependent rate constants for both the radiative and nonradiative decay of excited-state coumarin dyes have been determined [341]. For critical discussions concerning the electronic structure of the excited states of 7-(dialkylamino)coumarins and 7-aminocoumarin ("coumarin-151"), see references [341d, 341e].

The existence of two interconvertible ICT and TICT excited-state molecules can lead to a dual, variable solvent-dependent fluorescence. This dual fluorescence was first discovered by Lippert *et al.* [342] using 4-(dimethylamino)benzonitrile as the fluorescent compound, and then correctly interpreted by Grabowski *et al.* [343]. They identified the

TICT excited state as the origin of the long-wavelength solvent-dependent fluorescence of this nitrile; see also references [484, 485]. The large number of organic molecules with two fluorescent states and the underlying concepts of the TICT excited state have been extensively reviewed [116, 344].

Particularly well studied examples of another solvent-dependent dual fluorescence are 6-(arylamino)-2-naphthalene sulfonates (ANS), whose absorption and emission characteristics are as follows (np = nonplanar; ct = charge transfer) [119, 120, 340]:

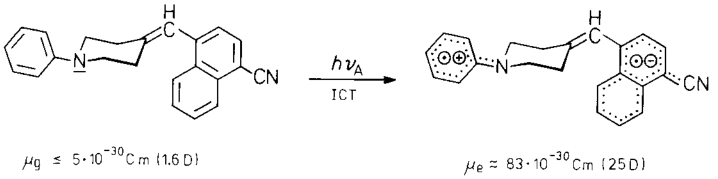


In contrast to the absorption maxima of ANS, the fluorescence maxima are sensitive to solvent changes, but to a different extent in solvents of varying polarity. The fluorescence of ANS arises from two different excited-state molecules, the apolar locally excited state $S_{1,np}$ and the zwitterionic excited state $S_{1,ct}$, which emerges from $S_{1,np}$ by intramolecular electron or charge transfer. The first emission, predominant in nonpolar solvents, varies only modestly with solvent polarity, as expected for a transition $S_{1,np} \rightarrow S_0$ between two states of similar charge separation. The second emission, observed in more polar solvents, is quite sensitive to solvent polarity, as anticipated for a transition $S_{1,ct} \rightarrow S_0$ between two states of very different charge separation [119, 120, 340].

The conversion of the initially formed $S_{1,np}$ state to the $S_{1,ct}$ state by intramolecular electron transfer is very fast and varies in a way that parallels but does not exactly correspond to the dielectric relaxation time for the solvent used. This is because the local environment around the excited-state molecule is different from that surrounding a solvent molecule [120, 340]. That is, the ICT process is to a large extent determined by the dielectric relaxation processes of the solvent surrounding the ANS molecule. Thus, solvent motion seems to be the controlling factor in the formation and decay of the ICT excited state of ANS and other organic fluorophores [120, 340]. A detailed mechanism for fast intramolecular electron-transfer reactions of ANS and 4-(dimethylamino)benzonitrile, using two simplified molecular-microscopic models for the role of the solvent molecules, has been given by Kosower [340]; see also reference [116].

Dielectric friction is the measure of the dynamic interaction of a charged or dipolar solute molecule with the surrounding polar solvent molecules. This concept has been applied, by Hynes *et al.* [339] and others [486], to solvent- and time-dependent fluorescence shifts resulting from the electronic absorption by a solute in polar solvents. If the solvent molecules are strongly coupled to the charge distribution in ground- and excited-state molecules, the relatively slow solvent reorientation can lead to an observable time evolution of the fluorescence spectrum in the nano- to picosecond range. This time-dependent fluorescence (TDF) has been theoretically analysed in terms of dynamic non-equilibrium solvation of excited-state molecules in polar solvents. It was shown that the TDF shift is proportional to the time-dependent dielectric friction on the absorbing dipolar molecule. That is, the relaxation rate of the fluorescence spectrum directly reflects a dynamic solvent property, namely the reorientation rate of the surrounding polar solvent molecules closest to the fluorescent solute molecule. This is analogous to studies of dynamic polar solvent effects on chemical reactions; *cf.* Chapter 5.1 and reference [463] cited therein. In fast chemical reactions, dielectric friction leads to deviations from the rate constants predicted by transition-state theory. This assumes that equilibrium solvation holds throughout the passage from educts via the activated complex to the products. The closest possible correlation between time-dependent fluorescence and fast solvent-dependent chemical reactions should be seen for electron-transfer reactions that involve a large charge separation similar to those encountered in absorbing molecules with subsequent ICT processes as mentioned above [339, 340]. For reviews on dynamic solvent effects and electron-transfer reactions, see references [117, 118, 453].

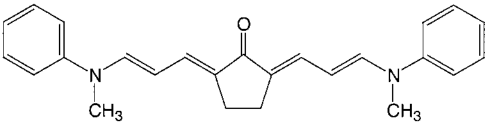
An extreme example of solvent-dependent fluorescence of an ICT excited-state molecule is shown by 1-phenyl-4-(4-cyano-1-naphthylmethylene)piperidine, a bichromophoric rod-shaped molecule containing electron-donor (D) and -acceptor groups (A) separated by an elongated cycloalkyl spacer, also called "Fluoroprobe" [345]. The absorption spectrum of this piperidine derivative is virtually independent of solvent polarity and closely resembles the expected sum of the spectra of the two separate chromophores, that is, *N*,*N*-dialkylaniline (D) and 1-vinylnaphthalene (A). The fluorescence spectrum does not exhibit any emission caused by the two separate, locally excited chromophores D and A. Instead a single, rather broad emission band is observed, the maximum of which undergoes a dramatic bathochromic shift with increasing solvent polarity of $\Delta\tilde{\nu} = -10160\ \text{cm}^{-1}$ ($\Delta\lambda = +287$ nm) for the solvent change *n*-hexane → acetonitrile. The position of the fluorescence maximum covers almost the entire visible spectral region if the solvent polarity is varied, thus making this compound a visual probe of solvent polarity. This behaviour is characteristic of an emission originating from a highly dipolar or zwitterionic ICT excited-state molecule. The dipole moment of this excited-state molecule, $\mu_e = 83 \cdot 10^{-30}$ Cm, corresponds to a full charge separation over the distance between the centers of the electron-donor and -acceptor groups. This indicates an almost complete electron transfer on excitation, despite the lack of either direct D/A contact or mesomeric coupling via a π-electron system between D and A [345]. The combination of strong solvatochromism with high fluorescence quantum yield makes this bichromophoric piperidine derivative attractive as a fluorescent solvent polarity probe [345].



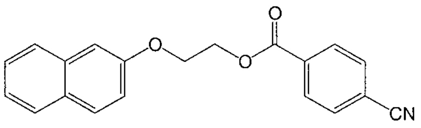
Solvent	n-C_6H_{14}	C_6H_6	$CHCl_3$	CH_2Cl_2	C_5H_5N	CH_3CN	$\Delta\lambda$/nm	$\Delta\tilde{\nu}$/cm^{-1}
$\lambda_{\max}^{\text{Fluor.}}$/nm	407	478	531	579	627	694	+287(!)	−10160(!)

A small selection of other strongly solvatochromic fluorophores, recommended as solvent polarity probes because of their large solvent-induced shifts of the long-wavelength emission band, is given in Scheme 1; further examples can be found in references [10, 16, 112, 486].

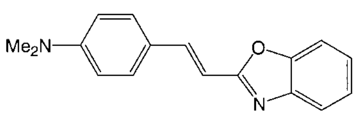
Fluorescence measurements on short-lived (<1 ns) and long-lived (>10 ns) electronically excited organic molecules in binary solvent mixtures have been used to study



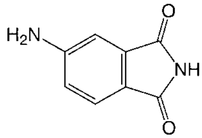
2,5-Bis[3-(*N*-methyl-*N*-phenylamino)propen-1-yliden]cyclopentanone
$\Delta\tilde{\nu} = -3970\ \mathrm{cm}^{-1}$ ($\Delta\lambda = +119$ nm) for toluene → water [346, 347]



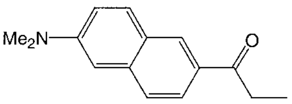
2-(2-Naphthoxy)ethyl 4-cyanobenzoate
$\Delta\tilde{\nu} = -4000\ \mathrm{cm}^{-1}$ ($\Delta\lambda = +88$ nm)
for cyclohexane → *t*-butanol [348]



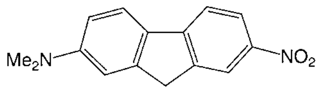
2-[4-(Dimethylamino)styryl]benzoxazole
$\Delta\tilde{\nu} = -4050\ \mathrm{cm}^{-1}$ ($\Delta\lambda = +92$ nm)
for *n*-hexane → water [349]



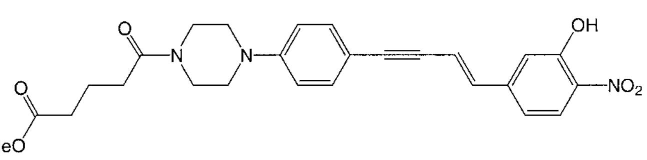
4-Aminophthalimide
$\Delta\tilde{\nu} = -5010\ \mathrm{cm}^{-1}$ ($\Delta\lambda = +115$ nm)
for diethyl ether → water [350–353]



2-(Dimethylamino)-6-propanoylnaphthalene (PRODAN)
$\Delta\tilde{\nu} = -6100\ \mathrm{cm}^{-1}$ ($\Delta\lambda = +130$ nm)
for cyclohexane → water [354, 355]



2-(Dimethylamino)-7-nitrofluorene
$\Delta\tilde{\nu} = -7020\ \mathrm{cm}^{-1}$ ($\Delta\lambda = +260$ nm)
for triethylamine → dimethyl sulfoxide [429]



A representative molecular fluorescence marker
$\Delta\tilde{\nu} = +3600\ \mathrm{cm}^{-1}$ ($\Delta\lambda = -105$ nm)
for *n*-heptane → methanol [433]

Scheme 1. Fluorescent solvent polarity probes, together with the maximum solvent-induced red shift of the long-wavelength emission band.

the phenomenon of *selective* or *preferential solvation* of dipolar solute molecules [353, 394]. Even in ideal solvent mixtures, the $\pi^* \rightarrow \pi$ emission energy is often highly nonlinear with the mole fraction of polar solvent. This nonlinearity results from both (i) the nonspecific solute/solvent association described as dielectric enrichment in the solvent shell of dipolar solute molecules, and (ii) specific solute/solvent associations such as hydrogen-bonding or EPD/EPA interactions. Both types of solute/solvent interaction lead to molecular-microscopic local solute-induced inhomogeneities in the binary solvent mixture, generally called selective or preferential solvation; *cf.* Section 2.4.

Differential solvent interactions with ground- and excited-state molecules not only lead to shifts in the fluorescence maxima but also to perturbation of the relative intensities of the vibrational fine structure of emission bands. For instance, symmetry-forbidden vibronic bands in weak electronic transitions can exhibit marked intensity enhancements with increasing solute/solvent interaction [320, 359]. A particularly well-studied case is the solvent-influenced fluorescence spectrum of pyrene, first reported by Nakajima [356] and later used by Winnik *et al.* [357] for the introduction of an empirical solvent polarity parameter, the so-called *Py* scale; *cf.* Section 7.4.

The $\pi^* \rightarrow \pi$ emission spectrum of monomeric pyrene exhibits five well-resolved major vibronic bands between 370 and 400 nm, labelled I...V in progressive order (the $0 \rightarrow 0$ band being labelled I, *etc.*). Peak I ($0 \rightarrow 0$ band) shows significant intensity enhancement with increasing solvent polarity compared with peak III ($0 \rightarrow 2$ band). Thus, the ratio of emission intensities of the vibronic bands I and III serves as a quantitative measure of solvent polarity ($Py = I_{\mathrm{I}}/I_{\mathrm{III}}$), although it is difficult to determine exactly [358]. The origin of the relative changes in intensity of the vibronic bands in the fluorescence spectrum of pyrene seems to be the varying degree of vibronic coupling between the weakly allowed first excited state and the strongly allowed second excited state [359]. The main solvent/pyrene interaction is the dipole/induced dipole interaction. Thus, solvent polarity determines the extent to which the induced dipole moment is formed by vibrational distortion of the pyrene skeleton [359].

Fluorescent organic compounds have been widely used as molecular-microscopic probes in biophysical studies of the local environment in micelle-forming surfactant solutions, in phospholipid dispersions, and in membranes. It is assumed that the nature of the probe environment is reflected in its emission characteristics (*i.e.* position and intensity of emission maxima, vibrational fine structure, quantum yields, excited-state lifetime, polarization of the fluorescence); *cf.* [112, 115, 360] for reviews.

Numerous theoretical and experimental studies of solvent effects on the fluorescence spectra of organic molecules (fluorophores) have led to a variety of quantitative expressions similar to Eq. (6-2) [4, 13, 16, 90, 112, 487]. Among the existing relationships describing how a change in dipole moment ($\Delta\mu = \mu_{\mathrm{e}} - \mu_{\mathrm{g}}$) correlates with electronic excitation and emission, the most popular are based on a linear correlation between the difference in wavenumbers of the absorption and fluorescence maxima ($\Delta\tilde{\nu} = \tilde{\nu}_{\mathrm{a}} - \tilde{\nu}_{\mathrm{f}} =$ Stokes shift) and a solvent polarity function, which usually involves the relative permittivity (ε_{r}) and the refractive index (n) of the medium.

Liptay has developed Eq. (6-5a) for the solvent dependence of the difference between the wavenumbers $\tilde{\nu}_{\mathrm{eg}}^{\mathrm{sol}(a)}$ of the absorption ($g \rightarrow e$) and $\tilde{\nu}_{\mathrm{eg}}^{\mathrm{sol}(f)}$ of the corresponding emission ($e \rightarrow g$) for the limiting case when $\tau_{\mathrm{R}} \ll \tau_{\mathrm{e}}$ [33, 90]. All terms depending on polarizability change are neglected.

$$
\begin{aligned}
hca\Delta\tilde{\nu} &= hca(\tilde{\nu}_{\mathrm{eg}}^{\mathrm{sol}(a)} - \tilde{\nu}_{\mathrm{eg}}^{\mathrm{sol}(f)}) \\
&= hca(\tilde{\nu}_{\mathrm{eg}}^{0(a)} - \tilde{\nu}_{\mathrm{eg}}^{0(f)}) \\
&\quad + \frac{2}{4\pi\varepsilon_0 a_{\mathrm{W}}^3}\left[\frac{\varepsilon_{\mathrm{r}}-1}{2\varepsilon_{\mathrm{r}}+1} - \frac{n^2-1}{2n^2+1}\right]|\mu_{\mathrm{e}} - \mu_{\mathrm{g}}|^2 \qquad \text{(6-5a)}
\end{aligned}
$$

$\tilde{\nu}_{\mathrm{eg}}^{0(a)}$ and $\tilde{\nu}_{\mathrm{eg}}^{0(f)}$ are the wavenumbers of the electronic transitions for absorption and fluorescence in the gas phase, respectively; the other terms are as in Eq. (6-2). Eq. (6-5a) has been widely used for the determination of dipole moment changes from the solvent dependence of spectra. The main source of error is the limited accuracy of the estimated value for the interaction radius a_{W} of the solute molecule since $\Delta\tilde{\nu}$ is a cubic function of a_{W}.

The expression most commonly used in fluorescence spectroscopy is, however, the somewhat simplified Eq. (6-5b), first developed by Lippert [47, 488] and Mataga [14, 489]. It is based on Onsager's reaction-field theory, which assumes that the fluorophore is a point dipole residing in the center of a spherical cavity with radius a_{w} in a homogeneous and isotropic dielectric with relative permittivity ε_{r}. The so-called Lippert–Mataga equation is as follows:

$$
\Delta\tilde{\nu} = \tilde{\nu}_{\mathrm{a}} - \tilde{\nu}_{\mathrm{f}} = \frac{1}{4\pi\cdot\varepsilon_0}\cdot\frac{2}{h\cdot c\cdot a_w^3}\cdot(\mu_{\mathrm{e}} - \mu_{\mathrm{g}})^2\cdot\Delta f + \text{const.} \qquad \text{(6-5b)}
$$

with $\Delta f = f(\varepsilon_{\mathrm{r}}) - f(n^2) = [(\varepsilon_{\mathrm{r}}-1)/(2\varepsilon_{\mathrm{r}}+1)] - [(n^2-1)/(2n^2+1)]$ representing the solvent's orientation polarization, since $f(\varepsilon_{\mathrm{r}})$ describes the total polarization and $f(n^2)$ represents the induction polarization. Δf ranges from 0.002 in cyclohexane to 0.320 in water, within the limits of $\Delta f = 0$ for vacuum and $\Delta f = 1$ for a medium with infinite ε_{r} or n. In another approach by McRae [70], the solute polarizability was included, and in this case the solvent function in Eq. (6-5b) had to be replaced by $\Delta f = [(\varepsilon_{\mathrm{r}}-1)/(\varepsilon_{\mathrm{r}}+2)] - [(n^2-1)/(n^2+2)]$. Based on Eq. (6-5b), the change in dipole moment, $\Delta\mu$, can simply be estimated from the slope of a plot of $\Delta\tilde{\nu}$ against Δf. However, it should be mentioned that both Eqs. (6-5a) and (6-5b) are no longer applicable when, in addition to the non-specific interactions, specific fluorophore/solvent interactions such as hydrogen bonding or EPD/EPA interactions also contribute significantly to the overall solute/solvent interaction in the case under study. A further limitation results from the cavity radius, which is difficult to estimate for elongated molecules with a more ellipsoidal form.

6.2.5 Solvent Effects on ORD and CD Spectra

Optical rotatory dispersion (ORD) involves the measurement of the rotation of plane-polarized light by a chiral compound as a function of the wavenumber. Circular dichroism (CD) is the unequal absorption of right and left circularly-polarized light as a function of its wavenumber. CD and anomalous ORD curves observed for chiral solute molecules are different manifestations of the so-called *Cotton effect* [121–124]. A necessary condition for the appearance of a Cotton effect is the absorption of light in the UV/Vis spectral range by the chiral solute. The position of the maximum of the UV/Vis absorption corresponds fairly well to the position of the CD maximum and to the wavenumber at which the ORD curve crosses the zero rotation line. Therefore, all solute/solvent interactions that influence position and intensity of UV/Vis absorption bands will also affect the ORD and CD spectra [121–124].

Most of the research on ORD and CD has involved chiral ketones, because the carbonyl chromophore has a convenient weak $n \rightarrow \pi^*$ absorption band in the 33 300 cm^{-1} (300 nm) region*). The Cotton effect, as observed in either ORD or CD curves of molecules containing a carbonyl chromophore, varies with a change of solvent. This variation occurs both in the wavenumber of the ORD extrema or of CD maxima, and in the intensity of the Cotton effect, as measured by the rotational strength (R), ellipticity (θ), differential absorption ($\Delta\varepsilon$), or the ORD amplitude (a) [361]. Thus, the hypsochromic shift observed for $n \rightarrow \pi^*$ transitions of carbonyl chromophores with increasing solvent polarity and increasing solvent capacity for hydrogen-bond formation (*cf.* Section 6.2.3) gives rise to a corresponding blue shift of the CD and ORD curves. Typical wavelengths for the maximum of the $n \rightarrow \pi^*$ CD band are: $\lambda_{max} = 297$ nm in *n*-hexane, 295 nm in 1,4-dioxane, 293 nm in acetonitrile, 290 nm in ethanol or methanol, and 283 nm in 2,2,2-trifluoroethanol [361]. This hypsochromic shift of the $n \rightarrow \pi^*$ band of carbonyl chromophores with increasing solvent polarity is largely a result of the stabilization of the solute *n*-orbital by solvation, particularly hydrogen bonding in protic solvents. However, intensity redistributions among the vibrational sub-bands of the $n \rightarrow \pi^*$ absorption band with increasing solute/solvent interaction can also be responsible for the observed blue shifts [328, 329]. In addition, an enhanced Cotton effect is usually observed with increasing solvent polarity. This change in $\Delta\varepsilon$ can be reasonably explained by the assumption that the total symmetry of a tightly bonded solute/solvent complex should be greater than that of a weakly solvated solute molecule [361]. Typical examples of solvent-dependent Cotton effects for carbonyl and other heteronuclear X=O compounds can be found in references [125] (camphor derivatives), [126] and [328] (keto steroids), [127] (α-silyl ketones), [128] (cyclic lactones and lactams), [129] (uracil nucleosides), and [130] (α-chloro sulfoxides).

The CD spectrum of the thiolactam (R)-5-methylpyrrolidine-2-thione reveals a pronounced solvent dependence [490]. Its long-wavelength $n \rightarrow \pi^*$ thiocarbonyl CD band at $\lambda_{max} = 326$ nm (in cyclohexane) undergoes a large solvent- *and* concentration-dependent blue shift of $\Delta\tilde{\nu} = +4880$ cm^{-1} ($\Delta\lambda = -54$ nm) on going from cyclohexane to water. This corresponds to the blue shifts usually observed for $n \rightarrow \pi^*$ bands in UV absorption spectra (see Section 6.2.3) and is best explained in terms of a monomer → dimer equilibrium of the thiolactam involving the formation of intermolecular solute/solute hydrogen bonds in nonpolar solvents. In HBA solvents (*e.g.* DMSO) and HBD solvents (*e.g.* EtOH), this equilibrium is disturbed by competitive solute/solvent H-

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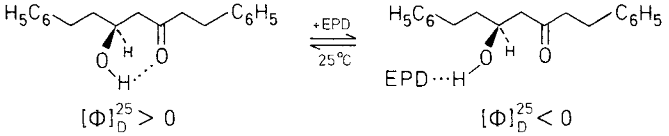
* Chiral compounds with chromophores that absorb light strongly in the UV/Vis region are usually unsatisfactory for ORD and CD measurements as insufficient incident light is transmitted to permit the measurements.

bonding with the thiolactam, which can donate or accept hydrogen bonds depending on the solvent type.

For some carbonyl compounds, a reverse in optical rotation sign has been observed when the ORD spectra were measured in solvents of different polarity. For example, (*S*)-5-hydroxy-1,7-diphenyl-3-heptanone is dextrorotatory in trichloromethane (molar optical rotation $[\Phi]_D^{25} = +39.6$) and levorotatory in methanol ($[\Phi]_D^{25} = -7.6$), whereas its acetate is dextrorotatory in both solvents [363]. This observation suggests that the interaction between the *β*-ketol moiety and the solvent is responsible for the change and reversal in optical rotation with increasing solvent polarity.



Solvent	CCl_4	$CHCl_3$	C_6H_6	1,4-Dioxane	CH_3COCH_3	CH_3CN	CH_3OH
$[\Phi]_D^{25\,a)}$	+48.8	+39.6	+39.6	+13.5	−2.5	−7.6	−7.6

a) $c = 0.025$ mol/L; $[\Phi]_D = ([\alpha]_D \cdot M_r)/100$, with M_r = relative molar mass.

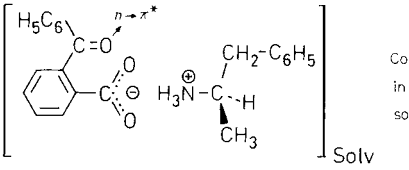
The solvent-induced variations in the optical rotation of the *β*-ketol moiety are presumably caused by conformational changes, associated with the formation and breaking of the intramolecular hydrogen bond. In non-EPD solvents, the intramolecularly hydrogen-bonded conformer with coplanar hydroxyl and carbonyl groups dominates. Increasing EPD character of the solvents causes breaking of the intramolecular hydrogen bond, followed by competitive intermolecular hydrogen bonding and nonspecific solvation of the *β*-ketol moiety; *cf.* references [363, 364] for further discussions.

Another reason for the solvent-dependent Cotton effects on $n \rightarrow \pi^*$ absorption bands is the solvent-induced alteration of equilibria between distinct conformers of the carbonyl compound; *cf.* Section 4.4.3. Differential solvation of equilibrating conformers can change the position of the equilibrium and thus the intensity and even the sign of the Cotton effect. An illustrative example is (+)-*trans*-2-chloro-5-methylcyclohexanone, the Cotton effect of which reverses its sign on transfer from water to *n*-hexane [362]; *cf.* equilibrium (*32a*) $\rightleftharpoons$ (*32b*) in Section 4.4.3. The molar optical rotations of this conformationally mobile α-chloro ketone, taken from its ORD spectrum measured in twenty-eight solvents, manifest huge changes with increasing solvent polarity: $[\Phi]_{330}^{25}$ at $\lambda = 330$ nm equals −1819 in cyclohexane, −428 in diethyl ether, +382 in water, and +680 in dimethyl sulfoxide [362]. This is obviously due to a shift of the diaxial/diequatorial equilibrium in favour of the more dipolar diequatorial conformer with increasing solvent polarity; see Section 4.4.3 and reference [364] for further discussions.

Structurally symmetric achiral compounds may show optical activity in the presence of chiral solvent molecules owing to asymmetry induced by the chiral solvent. For example, the achiral carbonyl compounds benzil and benzophenone surprisingly show optical activity in the region of the $n \rightarrow \pi^*$ absorption in the CD spectrum when dissolved in the chiral solvent (*R*, *R*)-(−)-2,3-butanediol [131, 365]. This phenomenon, first recorded for organic molecules by Bosnich [131], has been named *induced optical activity* [365]. Obviously, the optical activity will be induced in the carbonyl chromophore by the surrounding chiral and protic solvent molecules, leading to a dissymmetric environment, even if there is a completely random distribution of the chiral solvent molecules in the solvation shell [365].

Conversely, it has been shown that a chiral solute, dissolved in an achiral solvent, can induce a chiral distribution of the solvent molecules around the solute even though the solvent molecules themselves are achiral. This allows the achiral solvent to contribute significantly to the CD spectrum, as has been shown for solutions of (+)-camphor. Measurements and calculations have shown that 5–10% of the intensity of the $n \rightarrow \pi^*$ carbonyl CD band of camphor are contributed by its solvation shell [491].

When 2-benzoylbenzoic acid and chiral (*R*)-(−)-amphetamine are dissolved together in equimolar proportions in nonpolar solvents, a strong CD is induced in the region of the $n \rightarrow \pi^*$ carbonyl absorption [132]. The sign of the CD is positive and its magnitude is reduced with increasing solvent polarity: the molar ellipticity $[\theta]$ at $\lambda \approx 320$ nm equals +1320 in tetrachloromethane, +229 in acetonitrile, and nearly zero in methanol.



Contact ion pair
in non-dissociating
solvents

Contact ion pairs derived from salt formation between the keto acid and the chiral amine appear to be responsible for this observation. The proximity of the counter ions of the tight ion pair in non-dissociating solvents is the origin of the induced CD. Increasing dissociation of the ion pair in more polar solvents should then reduce the strength of the induced CD, in agreement with the experimental observations [132].

In this context, one should recall that not only the ORD and CD spectra, but also the optical rotations ($[\alpha]_D$ or $[\Phi]_D$) of chiral compounds dissolved in isotropic achiral solvents can change in magnitude, and sometimes in sign, with a change in solvent polarity; see Section 3.2 and references [123, 492–495]. An exceptional example is the optical rotation of (*S*)-(−)-nicotine and (2*R*, 3*R*)-(+)-diethyl tartrate, the magnitude and sign of which depends strongly on the solvent and concentration [492]. The reasons for this solvent dependence are rather complicated since physical as well as chemical and conformational effects are at work. Earlier work connects the decrease in $[\alpha]_D$ observed with increasing solvent polarity with the increasing dipole moment of the solvent [493], while quantum-chemical calculations relate the rotatory strength of chiral solute molecules with solvent field corrections for the solute dipole [494]. A related example is given by the optical rotations of some axially chiral biaryls, which undergo remarkable variations on going from ordinary achiral solvents (*e.g.* benzonitrile) to isotropic biaryl-type solvents (*e.g.* 2-methylbiphenyl) [495]. In this case, the chiral solute induces chiral conformations in the neighbouring solvent molecules of the solvation shell, which contribute to the observed optical rotation. Therefore, experimental descriptions of optical rotations without reporting *solvent*, concentration, and temperature are useless.

6.3 Solvent Effects on Infrared Spectra

The vibrational spectrum of a molecule A—B depends not only on the strength of the bond between A and B, but may also be markedly affected by environmental factors. Such intermolecular interactions modify the infrared spectra in a number of ways: the wavenumber of the normal vibrational modes of a molecule may be shifted to higher or lower values, the intensities can be altered, and the half-width of bands may be greatly increased. A typical example, exhibiting two parts of the infrared spectrum of 1,1-dichloroethene, is illustrated in Fig. 6-8. With increasing solvent polarity, the two absorption bands are shifted to lower [$\tilde{\nu}_{as}(CH_2)$] and higher wavenumbers [$\gamma(CH_2)$], respectively. At the same time, both the absorption intensity and the half-width of the two bands increase steadily with increasing solute/solvent interaction. Obviously, the two infrared vibrations of 1,1-dichloroethene are influenced by nonspecific and specific solute/solvent interactions to a different extent.

The measurement of such solvent-induced IR spectral changes has been extensively used in spectroscopic studies of solute/solvent interactions [1–4, 367], especially

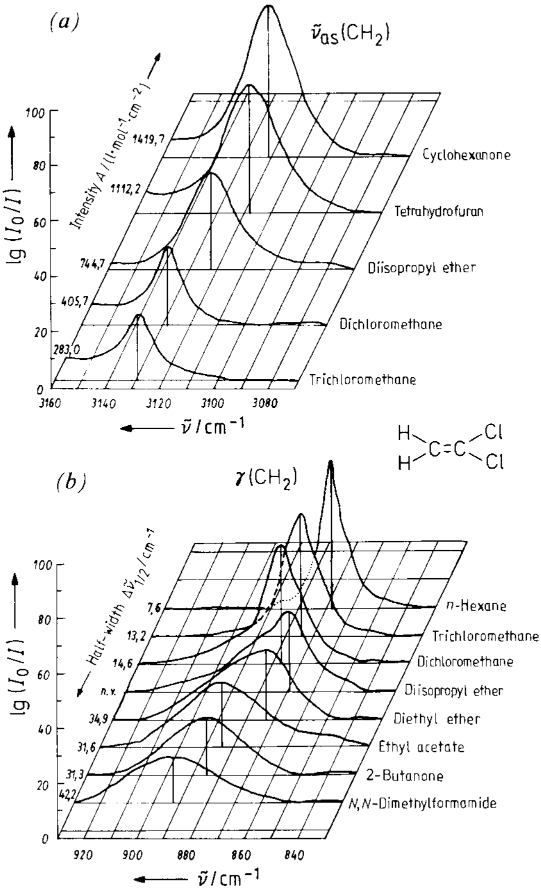


Fig. 6-8. Infrared spectrum of 1,1-dichloroethene, $H_2C{=}CCl_2$. Solvent effect on *(a)* the wavenumber $\tilde{\nu}$ and intensity A of the antisymmetrical stretching vibration $\tilde{\nu}_{as}(CH_2)$; and *(b)* the wavenumber $\tilde{\nu}$ and half-width $\Delta\tilde{\nu}_{1/2}$ of the out-of-plane bending vibration $\gamma(CH_2)$ [366].

hydrogen-bond (HBD/HBA) interactions [134, 135, 367]. Experimental solvent effect studies and solvent shift theories have been previously reviewed [1–4, 136–144]. The IR transmission characteristics of solvents commonly used in IR spectroscopy can be found in Table A-5 (Appendix).

The wavenumber shift, $\Delta\tilde{\nu}$, is generally represented as the difference between the absorption in the vapour phase ($\tilde{\nu}^0$) and in the solvent under consideration ($\tilde{\nu}^s$). When measured in solution, the band maxima of all simple stretching vibrations are displaced to lower wavenumbers (*e.g.* stretching vibration $\tilde{\nu}_{C=O}$ of carbonyl compounds) whereas those of bending vibrations are shifted to higher wavenumbers (*e.g.* out-of-plane deformation γ_{C-X} of halobenzenes). The most solvent-sensitive infrared stretching vibrations are those of $\mathrm{X}^{\delta\oplus}{=}\mathrm{O}^{\delta\ominus}$ bonds (X = C, N, P, S), $\mathrm{X}^{\delta\ominus}{-}\mathrm{H}^{\delta\oplus}$ bonds (X = C, N, O, S, halogens), and $\mathrm{C}^{\delta\oplus}{-}\mathrm{X}^{\delta\ominus}$ bonds (X = halogens). Three typical examples are given in Table 6-4 [145–150, 368]. In all three cases, the C=O, O—D, and C—Cl stretching vibrations are shifted to lower wavenumbers with increasing solvent polarity. Excessive shifts of $\tilde{\nu}_{C=O}$ in HBD solvents (*e.g.* H_2O) and of $\tilde{\nu}_{O-D}$ in HBA solvents (*e.g.* Et_3N), caused by hydrogen-bonding are observed. When the solute/solvent interaction is non-

Table 6-4. Absorption band maxima in the infrared spectra of acetone [145–148, 368] (C=O stretch), methan[^{2}H]ol [149] (O—D stretch), and 1-chloropropane [150] (C—Cl stretch) in a selection of solvents of increasing polarity.

Solvents	$\tilde{\nu}_{C=O}/\mathrm{cm}^{-1}$ of $\mathrm{Me_2C{=}O}^{a)}$	$\tilde{\nu}_{O-D}/\mathrm{cm}^{-1}$ of $\mathrm{CH_3O{-}D}^{b)}$	$\tilde{\nu}_{C-Cl}/\mathrm{cm}^{-1}$ of $n\text{-}\mathrm{C_3H_7Cl}^{a,c)}$
Vapour ($\tilde{\nu}^0$)	1738	2720	743
n-Hexane	1721.5	2696	735
Triethylamine	1719.5	2406 (!)	–
Tetrachloromethane	1718	2689	–
Carbon disulfide	1718	–	730
Benzene	1717	2668	725
Tetrahydrofuran	1716.5	2575	–
Ethyl acetate	–	2631	723.5
1,4-Dioxane	1715	2592	722.5
Acetone	1715	2597	721
Acetonitrile	1713.5	2617	720
N,*N*-Dimethylformamide	1713	2554	–
Nitromethane	1711.5	2661	719 (!)
Dichloromethane	1711.5	2677	–
Dimethyl sulfoxide	1709	2528	–
Ethanol	1708.5$^{d)}$	–	–
Methanol	1707.5$^{e)}$	–	–
Ethane-1,2-diol	1703.5	–	–
Aniline	1703	2511	–
Water (D_2O)	1697.5 (!)	–	–
	$\Delta\tilde{\nu} = \tilde{\nu}^0 - \tilde{\nu}^{H_2O} = 40.5\ \mathrm{cm}^{-1}$	$\Delta\tilde{\nu} = \tilde{\nu}^0 - \tilde{\nu}^{Et_3N} = 314\ \mathrm{cm}^{-1}$	$\Delta\tilde{\nu} = \tilde{\nu}^0 - \tilde{\nu}^{CH_3NO_2} = 24\ \mathrm{cm}^{-1}$

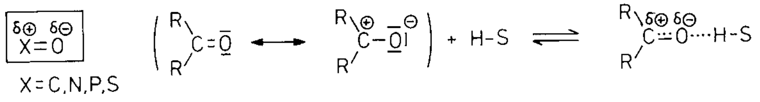
a) Dilute solution.
b) 0.04 mol/L CH_3OD.
c) *trans*-Conformer.
d) With shoulder at 1718 cm^{-1}.
e) With shoulder at 1717 cm^{-1}.

specific as in non-HBD and non-HBA solvents, the bands shift monotonically from one extreme to the other.

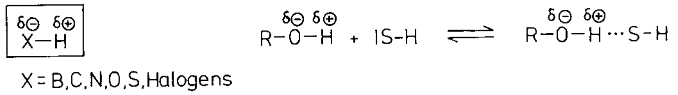
Solvents effects on the infrared stretching vibrations of the following organic compounds have been studied in depth: $\tilde{\nu}_{C=O}$ of 4-pyridones [151], tropone and tropolones [152], benzophenone and *N*,*N*-dimethylformamide [154], acetophenone [155], aliphatic aldehydes [157], *N*-methylacetamide [369], *N*-cyclohexylpyrrolidin-2-one [496], urea [497], esters and dialkyl carbonates [370]; $\tilde{\nu}_{N=O}$ for a nitrosyl protoporphyrin derivative [371]; $\tilde{\nu}_{P=O}$ for triarylphosphane oxides [153] and triethylphosphane oxide [372]; $\tilde{\nu}_{S=O}$ for dimethyl sulfoxide [154, 373]; $\tilde{\nu}_{C-H}$ for chloroalkanes [160], trichloromethane [374], and *n*-octane [375]; $\tilde{\nu}_{\equiv C-H}$ of 1-alkynes [133, 138]; $\tilde{\nu}_{C-Cl}$ for haloalkanes [150, 161]; $\tilde{\nu}_{C\equiv N}$ for acetonitrile [156]; $\tilde{\nu}_{Si-H}$ for silanes [159]; $\tilde{\nu}_{N-H}$ of pyrrole [158], *N*-methylacetamide [369], and *N*-methylanilines [376], as well as $\tilde{\nu}_{O-H}$ of *tert*-butyl hydroperoxide [377]. Opposite band shifts of the $\tilde{\nu}_{C=O}$ and $\tilde{\nu}_{C\equiv O}$ stretching vibrations with increasing solvent polarity have been observed for the paramagnetic cobalt complex $Co(C\equiv O)_3L_2$ [with L_2 = 2,3-bis(diphenylphosphanyl)maleic anhydride]. The frequency of the two C=O bands of the maleic anhydride moiety decreases with increasing solvent polarity, while the three C≡O bands increase in frequency; this has been explained in terms of increased delocalization of the unpaired electron from the ligand to the $Co(CO)_3$ moiety with increasing solvent polarity [498]. A comprehensive list of earlier publications on solvent effects on infrared absorptions is given by Hallam (see page 420 of reference [134]).

The wavenumber displacement of a solute vibration is a complex function of both solute and solvent properties and can be explained in terms of weak nonspecific electrostatic interactions (dipole-dipole, dipole-induced dipole, *etc.*) and of strong specific association of solute with solvent molecules, usually of the hydrogen-bond type [140]. It should be realized that the duration of vibrational transitions is very short with respect to motion of the solvent molecules (*e.g.* for an O—H stretching vibration, the frequency is *ca.* 10^{14} s^{-1}). Thus, it is possible to observe such transitions even for short-lived entities such as may arise after a collision in the liquid phase (collision complexes) [140].

To a first approximation, the bathochromic shift observed for the C═O stretching vibration of acetone (*cf.* Table 6-4) in non-HBD solvents may be explained by the degree of C═O dipolarity as determined by the relative contribution of the two mesomeric forms in Eq. (6-6).



(6-6)



(6-7)

A change in the external environment produces small alterations in the relative contribution of the two mesomeric structures, and affects the wavenumbers of absorption in much the same way as do changes in the internal chemical environment [146]. Accordingly, the $\tilde{\nu}_{C=O}$ absorption band of acetone is displaced from 1721.5 cm^{-1} in

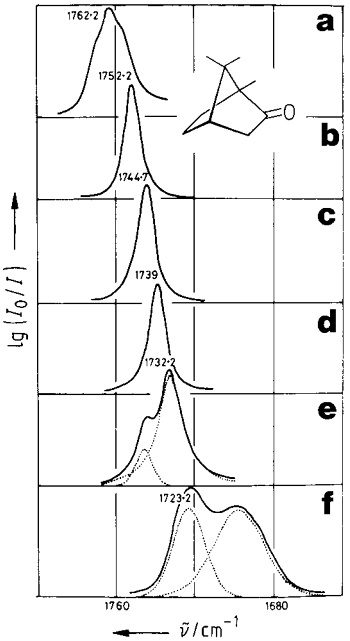


Fig. 6-9. The $\tilde{\nu}_{C=O}$ stretching absorption band in the infrared spectrum of camphor (a) in the gas phase, (b) in *n*-heptane, (c) in tetrachloromethane, (d) in pyridine, (e) in methanol, and (f) in 1,1,1,3,3,3-hexafluoro-2-propanol [378].

n-hexane to 1709 cm^{-1} in the dipolar non-HBD solvent dimethyl sulfoxide [368]; *cf.* Table 6-4. In protic solvents, however, hydrogen-bonding superimposes this nonspecific solvent effect according to Eq. (6-6). Even the less dipolar HBD solvent aniline causes a larger bathochromic shift of the $\tilde{\nu}_{C=O}$ band than dimethyl sulfoxide, up to 1703 cm^{-1}; this is only surpassed by water [368].

In this respect, camphor is a particularly well-studied example [378]; *cf.* Fig. 6-9. The IR absorption band of the C=O stretching vibration of camphor shows that the carbonyl group exists free in the gas-phase and experiences nonspecific solute/solvent interactions in *n*-heptane, tetrachloromethane, and pyridine, as shown by the sharp, single bands in Figs. (6-9b)...(6-9d). However, in protic solvents such as methanol, two absorption bands are present; *cf.* Fig. (6-9e). These bands are attributed to the presence of both nonspecifically solvated camphor ($\tilde{\nu}_{C=O} = 1745.4$ cm^{-1}) and a specific equimolar 1:1 camphor/methanol complex ($\tilde{\nu}_{C=O} = 1732.2$ cm^{-1}), according to the equilibrium given in Eq. (6-6). In the strong HBD solvent 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP), two carbonyl bands are observed as well. That at higher wavenumbers ($\tilde{\nu}_{C=O} = 1723.2$ cm^{-1}) is assigned to the 1:1 camphor/HFIP complex, whereas the band at lower wavenumbers is due to complexes of higher order [378].

The differentiation between effects due to specific solute/solvent interactions and bulk dielectric solvent effects is not easy to visualize and is often a matter of debate [367]. The experimental data indicate that the solvent sensitivities of $\tilde{\nu}_{X=O}$ vibrations are complex functions of several factors, including contributions from bulk dielectric effects, non-specific dispersion and induction forces, specific HBD/HBA interactions, as well as steric effects [134]. Solvent effects on the $\tilde{\nu}_{C=O}$ IR stretching absorption have been linearly correlated with the solvent shifts of $n \rightarrow \pi^*$ UV/Vis absorptions [102] and with ^{13}C NMR chemical shifts ($^{13}C{=}O$) [367, 368] of some carbonyl compounds.

Contrary to $X^{\delta\oplus}{=}O^{\delta\ominus}$, in $X^{\delta\ominus}{-}H^{\delta\oplus}$ groups, the free end of the dipolar X—H bond available for specific solvent association is of the opposite sign. Consequently, the largest solvent-induced $\tilde{\nu}_{X-H}$ shifts do not occur in HBD solvents but in HBA (=EPD) solvents of Lewis-base type [162, 163]. Thus, in accordance with Eq. (6-7), the $\tilde{\nu}_{O-D}$ IR stretching absorption band of CH_3OD undergoes the largest bathochromic shift in the less dipolar HBA solvent triethylamine, as compared to the shifts observed in dipolar non-HBA solvents such as nitromethane and acetonitrile [149]; *cf.* Table 6-4. Since $\tilde{\nu}_{O-D}$ measures the strength of the HBD solute/EPD solvent interaction, empirical solvent scales of Lewis basicity have been introduced, based on the solvent dependence of $\tilde{\nu}_{O-D}$ for CH_3OD [149] or $\tilde{\nu}_{O-H}$ for phenol; *cf.* Sections 2.2.5 and 7.4.

In order to test whether the factors responsible for solvent shifts are the same for different compounds, the so-called Bellamy–Hallam–Williams (BHW) plot is often used [162]. If the dipoles in a given family such as X═O, X—H, or C–halogen exhibit a common pattern of solvent effects, then the $\Delta\tilde{\nu}/\tilde{\nu}^0$ values of any one compound measured in a range of solvents can be plotted against the corresponding values of any other compound containing the same grouping to give a straight line. Consequently, the method of solvent variation is often useful for the identification of group frequencies of dipolar links (for examples, see references [164, 165]).

The first theoretical treatment of infrared solvent shifts was given in 1937 by Kirkwood [166] and by Bauer and Magat [167]. Eq. (6-8) – known as the Kirkwood-Bauer-Magat (KBM) relationship – has been derived on the basis of Onsager's reaction field theory [80] using the simple model of a diatomic oscillator within a spherical cavity in an isotropic medium of macroscopic relative permittivity ε_r.

$$\frac{\Delta\nu}{\nu^0} = \frac{\nu^0 - \nu^s}{\nu^0} = C \cdot \frac{\varepsilon_r - 1}{2\varepsilon_r + 1} \tag{6-8}$$

ν^0 is the vibrational frequency in the gas phase, ν^s is the frequency in the solvent of relative permittivity ε_r, and C is a constant depending upon the molecular dimensions and electrical properties of the vibrating solute dipole. The electrostatic model leading to Eq. (6-8) assumes that only the electronic contribution to the solvent polarization can follow the vibrational frequencies of the solute (*ca.* 10^{14} s^{-1}). Since molecular dipole relaxations are characterized by much lower frequencies (10^{10} to 10^{12} s^{-1}), dipole orientation cannot be involved in the vibrational interaction, and Eq. (6-8) may be written in the following modified form [158, 168]:

$$\frac{\Delta\nu}{\nu^0} = \frac{\nu^0 - \nu^s}{\nu^0} = C \cdot \frac{n^2 - 1}{2n^2 + 1} \tag{6-9}$$

Here, n is the refractive index of the solvent. Both equations have been widely used and tested for a large number of compounds [136–144] and have proved to be valid only in a very limited range in dilute solutions of nonpolar solvents, where specific interactions can be neglected. In polar solvents, the points of the KBM plot are usually shifted toward higher values of $\Delta\nu/\nu^0$. The deviations from the KBM equation have been attributed to hydrogen bonding and formation of molecular complexes and such interactions are not taken into account by the KBM equation.

The relationships (6-8) and (6-9) have subsequently been modified and improved by a number of workers [169–172]; see [1] for a review. Eqs. (6-10) and (6-11), derived by Buckingham [170],

$$\frac{\Delta\nu}{\nu^0} = C_1 + C_2 \cdot \frac{\varepsilon_r - 1}{2\varepsilon_r + 1} + C_3 \cdot \frac{n^2 - 1}{2n^2 + 1} \quad \text{(for polar solvents)} \tag{6-10}$$

$$\frac{\Delta\nu}{\nu^0} = C_1 + \frac{1}{2}(C_2 + C_3) \cdot \frac{\varepsilon_r - 1}{2\varepsilon_r + 1} \quad \text{(for nonpolar solvents)} \tag{6-11}$$

give better agreements than Eqs. (6-8) and (6-9) for solvent shifts in infrared spectra in the absence of specific interactions. C_1, C_2, and C_3 are constants for the solute under consideration and may be evaluated by applying Eq. (6-11). Plotting the observed relative shifts in nonpolar solvents against the dielectric function $(\varepsilon_r - 1)/(2\varepsilon_r + 1)$ yields values of C_1 from the intercept and of $(C_2 + C_3)$ from the slope. C_2 and C_3 can then be evaluated from Eq. (6-10) using shifts in polar solvents.

The Buckingham Eq. (6-10) takes into account the fact that the influence of solvent dipolarity [characterized by $f(\varepsilon_r) = (\varepsilon_r - 1)/(2\varepsilon_r + 1)$] and solvent polarizability [characterized by $f(n^2) = (n^2 - 1)/(2n^2 + 1)$] on the solute IR vibrations are two independent effects. Based on the assumption that solute/solvent collision complexes are formed in solution, which should lead to a mutual correlation in dipolarity/polarizability changes, Bekárek *et al.* have added a third cross-term $f(\varepsilon_r) \cdot f(n^2)$ to the two terms of Eq. (6-10) [379]. Indeed, using the modified three-term Eq. (6-12),

$$\frac{\Delta\nu}{\nu^0} = C_1 + C_2 \cdot f(\varepsilon_r) + C_3 \cdot f(n^2) + C_4 \cdot f(\varepsilon_r) \cdot f(n^2) \tag{6-12}$$

surprisingly better correlations have been obtained for a variety of experimental solvent-dependent IR stretching vibrations [379]. Even with the cross-term $f(\varepsilon_r) \cdot f(n^2)$ alone, the correlations were better than those obtained with Eq. (6-10), thus demonstrating its predominant influence on solvent-induced IR band shifts [380].

The application of eight different reaction-field models to the solvent-induced shift of the carbonyl IR absorption band of 2-butanone, determined in 27 non-HBD solvents, has shown that in this group of solvents the dipolarity and polarizability are the dominating solvent properties responsible for the observed band shift ($\Delta\tilde{\nu}_{C=O} = -16\ \text{cm}^{-1}$ for *n*-hexane → sulfolane) [499]. Among the various reaction-field functions tested, a two-parameter equation with the Kirkwood-Bauer-Magat function $f(\varepsilon_r)$ and the cross function $f(\varepsilon_r, n^2)$ was the most successful one.

Other more sophisticated approaches to the calculation of medium effects on IR absorption bands can be found in the comprehensive, excellent review of Lutskii *et al.*

[1]. According to Lutskii, even for quite simple molecules, acceptably precise calculations of $\Delta\nu/\nu^0$ still present insuperable difficulties. This explains the growing practice of correlating $\Delta\nu/\nu^0$ with empirical parameters of solvent polarity within the framework of linear Gibbs energy relationships. Some of these empirical parameters are even derived from solvent-dependent IR absorptions as reference processes as, for example, the *G*-values of Schleyer *et al.* [154]; *cf.* Section 7.4.

Attention has also been given to the change in intensities of infrared absorption bands in going from the gas phase to solution from theoretical [168, 170, 173–175] and experimental points of view [176–181]. In general, infrared absorption intensities are relatively little altered by a solvent change. Usually, an increase of the integrated band intensity A is obtained in passing from vapour to solution in a nonpolar solvent and further to a polar solvent; *cf.* Fig. (6-8a) [366]. A fair correlation is often found between solvent effects on intensity A and on relative absorption shifts $\Delta\nu/\nu^0$. A striking example is the C=O stretching absorption of acetone [179]. When specific interactions occur, the solvent effect on intensity A is more pronounced. For instance, the C—D stretching vibration of deuteriochloroform increases 36-fold in going from tetrachloromethane to triethylamine solution [182]. Many equations have been proposed to predict the ratio of the intensities observed in the gas and liquid phase [168, 170, 173–175]. All theories predict an increase in intensity but none is able to give the precise magnitude of the solvent effect.

6.4 Solvent Effects on Electron Spin Resonance Spectra

From the point of view of the solvent influence, there are three features of an electron spin resonance (ESR) spectrum of interest for an organic radical measured in solution: the g-factor of the radical, the isotropic hyperfine splitting (HFS) constant a of any nucleus with nonzero spin in the molecule, and the widths of the various lines in the spectrum [2, 183–186, 390]. The g-factor determines the magnetic field at which the unpaired electron of the free radical will resonate at the fixed frequency of the ESR spectrometer (usually 9.5 GHz). The isotropic HFS constants are related to the distribution of the π-electron spin density (also called spin population) of π-radicals. Line-width effects are correlated with temperature-dependent dynamic processes such as internal rotations and electron-transfer reactions. Some reviews on organic radicals in solution are given in reference [390].

An illustrative example of a strongly solvent-dependent ESR spectrum is given in Fig. 6-10. It shows low-field portions of the ESR spectra of the stable, distillable (!) 4-(methoxycarbonyl)-1-methylpyridinyl radical, measured in three solvents of increasing polarity [381]. The different patterns of the ESR lines observed in different media arise from the solvent influence on the spin distribution, as measured by the HFS constants $a(^1\mathrm{H})$ and $a(^{14}\mathrm{N})$. This change in spin distribution results from solvent-induced polarization of the carbonyl group, which is coplanar and conjugated with the pyridinyl ring.

Whereas solvent effects on line-widths and g-factors have been studied only in a small number of cases, there are numerous data on the solvent dependence of the HFS

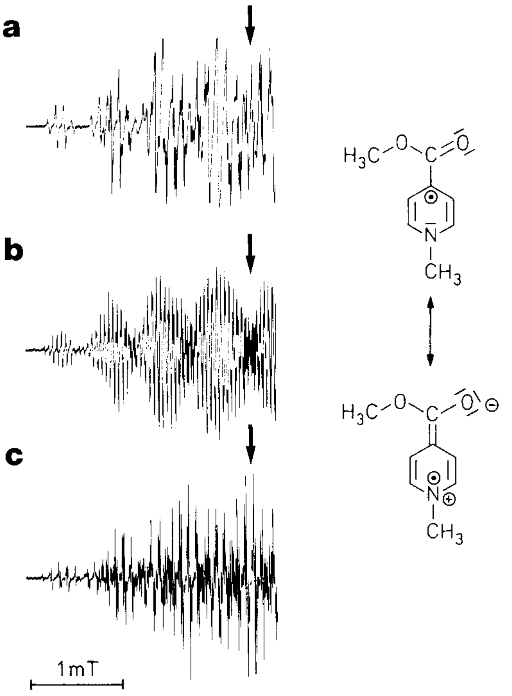


Fig. 6-10. Low-field parts of the ESR spectra of 4-(methoxycarbonyl)-1-methylpyridinyl radical in (a) 2-methylpentane, (b) benzene, and (c) *N,N*-dimethylformamide. The arrows indicate the center of the ESR spectra [381].

constants in the ESR spectra of organic free radicals. The sensitivity of nuclear HFS constants of free radicals to changes in solvent polarity have been noted for ketyls [187–188], 1,2- and 1,4-benzosemiquinone anion radicals [183, 189–195, 382], semidiones*⁾ [196], phenoxyl radicals [197–200], vinylogous carboxyl radicals [500], nitroaromatic anion radicals [201–205, 383], dialkyl and diaryl aminyloxides (nitroxides) [206–218, 335, 384–388], acyl aminyloxides [219], azomethine aminyloxides [220], thioindigo radicals [221], and pyridinyl radicals [222, 381, 389].

The solvent dependence of *g*-factors has been studied for 1,4-benzosemiquinone anion radical [191], di-*t*-butyl aminyloxide [212], 2,2,6,6-tetramethyl-4-piperidone-1-oxyl [216], and nitrosyl protoporphyrin derivatives [371]. Apparently, changes in distribution of the unpaired electron and changes in spin-orbit coupling in going from one solvent to another are reflected in the *g*-factor changes. A dramatic line width alteration has been observed for the nitrobenzene anion radical in hexamethylphosphoric triamide upon addition of methanol [205].

Table 6-5 illustrates the influence of the medium on the *g*-factors and HFS constants for the following ^{17}O-labelled aminyloxide radical [216]:

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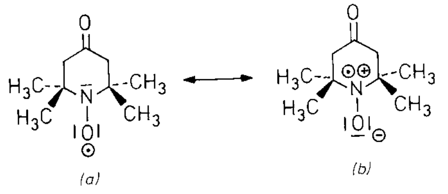
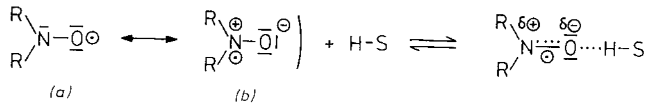
* Semidiones are vinylogues of the superoxide anion radical, $\odot\underline{\overline{O}}-\underline{\overline{O}}|^{\ominus} \leftrightarrow {}^{\ominus}|\underline{\overline{O}}-\underline{\overline{O}}\odot$, in the same way that benzosemiquinones are phenylogues of the same radical anion. Semidiones may be obtained by a one-electron reduction of conjugated aliphatic or cycloaliphatic diketones [196].

Table 6-5. g-Factors and isotropic nitrogen and oxygen hyperfine splitting constants, $a(^{14}N)$ and $a(^{17}O)$, of 2,2,6,6-tetramethyl-4-piperidone-1-oxyl in ten solvents of increasing polarity [216].

Solvents	g-Factor	$a(^{14}N)$/mT[a)]	$a(^{17}O)$/mT[a)]
Benzene	2.0062	1.445	1.929
Toluene	2.0063	1.447	1.952
N,*N*-Dimethylformamide	2.0062	1.466	1.940
Dichloromethane	2.0061	1.477	1.936
Dimethyl sulfoxide	2.0060	1.490	1.974
1-Butanol	2.0060	1.501	1.911
Formamide	2.0060	1.528	1.888
Ethane-1,2-diol	2.0061	1.540	1.872
Diethyl ether	–	1.594	1.784
Water	2.0058	1.601	1.786
[a)] mT = milliTesla	$\Delta g = 0.0005$ $\hat{=}\ 0.02\%$	$\Delta a(^{14}N) = -0.156$ mT $\hat{=}\ 11\%$	$\Delta a(^{17}O) = +0.143$ mT $\hat{=}\ 7\%$


(a) (b)

Both the g-factors and the HFS constants of this neutral aminyloxide radical depend on the solvent. The $a(^{14}N)$ values are largest in dipolar protic solvents such as water and smallest in nonpolar non-HBD solvents such as benzene. The reverse is true for the $a(^{17}O)$ values. That is, solvents which reduce $a(^{14}N)$ increase $a(^{17}O)$. This opposing behaviour of the HFS constants with increasing solvent polarity may be rationalized in terms of valence-bond theory by considering the relative contribution of the two main mesomeric structures, *(a)* and *(b)* in Eq. (6-13), to the actual electronic structure.


(6-13)

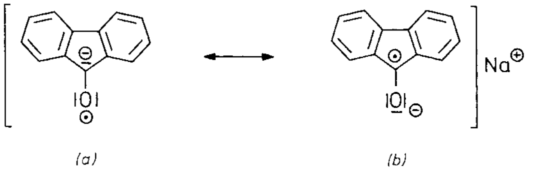
Since $a(^{14}N)$ and $a(^{17}O)$ are determined by the unpaired π-electron spin density at the nitrogen and oxygen nuclei respectively, effects that favor the dipolar structure *(b)* relative to *(a)* will be associated with an increase in the magnitude of $a(^{14}N)$ and with a decrease in the magnitude of $a(^{17}O)$. Both solvent polarity and hydrogen bonding capability will exert a similar influence on the relative contributions of *(a)* and *(b)* because hydrogen bonding is expected to occur predominantly with an oxygen lone pair in structure *(b)*, according to Eq. (6-13). Thus, the greater the polarity and hydrogen bonding capability of the solvent, the greater the increase in the electron density on oxygen and the spin density on nitrogen, and the more favoured is structure *(b)*. The corresponding very small decrease in the g-factors in polar solvents is also attributed to the redistribution of the spin density, as well as to the decrease in spin-orbit coupling which would accompany a decrease in unpaired electron density on the oxygen atom [216]. As spin density diminishes around the oxygen atom with increasing solvent polarity, the g-factor of the aminyloxide is shifted towards the free-spin value of $g_e = 2.00232$ (*cf.* Table 6-5).

Similar solvent effects on HFS constants have been observed for other aminyloxides such as diphenyl aminyloxide [207, 212], di-*t*-butyl aminyloxide [218, 385], *t*-butyl aminyloxide [213, 217], and 2,2,6,6-tetramethylpiperidyl-1-oxide [384, 387, 388]. The $a(^{14}N)$ constants of di-*t*-butyl and two other aminyloxides have been proposed as an empirical solvent polarity parameter because $a(^{14}N)$ is easily measured in most solvents [218, 389]; *cf.* Section 7.4.

A comparison of the $a(^{14}N)$ values, the $\tilde{\nu}$ values of the N—O IR stretching vibration, and the $\tilde{\nu}_{max}$ values of the $n \rightarrow \pi^*$ UV/Vis absorption of di-*t*-butyl aminyloxide reveals that the mode of solvation for the $>$C=O and $>$N—O· groups is similar [335]. For example, the $a(^{14}N)$ values of di-*t*-butyl aminyloxide in a range of solvents are linearly correlated to the $\tilde{\nu}_{max}$ values of its $n \rightarrow \pi^*$ absorption [335].

Semiquinones were among the first radicals to be studied in solution by ESR spectroscopy. Semiquinones have been observed as anion radicals [189, 191, 193–195, 382] and as protonated neutral radicals [192] in solution. 1,4-Benzosemiquinone is of particular interest because it is possible to label the carbonyl carbon atom with ^{13}C and the carbonyl oxygen atom with ^{17}O. Together with the four remaining carbon atoms, which all have a hydrogen bonded to them, it is possible to obtain three solvent-dependent HFS constants [$a(^{1}H)$, $a(^{13}C)$, and $a(^{17}O)$]. It has been shown, for example, that the carbon atoms of the 1,4-benzosemiquinone anion radical which are adjacent to the oxygen atoms exhibit marked changes in $a(^{13}C)$ constants with changes in solvent polarity [189]. The latter is 0.213 mT for both acetonitrile and dimethyl sulfoxide, but in water the splitting is only 0.04 mT [189]. Just as for aminyloxides, the redestribution of spin density within the semiquinone leads to a modification of the g-factor [191]. For the 1,4-benzosemiquinone anion radical in water solution, $g = 2.00469$, and in dimethyl sulfoxide $g = 2.00541$ [191].

A particularly well-studied anion radical is the sodium 9-fluorenone ketyl radical shown in Eq. (6-14). The solvent influence on the $a(^{13}C)$ HFS constant of the ^{13}C-enriched 9-fluorenone ketyl group was examined in dipolar non-HBD solvents and their binary mixtures with toluene and tetrahydrofuran [391].



(6-14)

Solvents	$(Me_2N)_3PO$	*N*-Methyl-pyrrolidone	CH_3CONMe_2	$HCONMe_2$	CH_3SOCH_3
$a(^{13}C)$/mT	0.176	0.224	0.230	0.275	0.320

With the increasing anion solvation power of the pure solvents, the $a(^{13}C)$ value of the free anion radical increases from 0.176 mT in HMPT to 0.320 mT in DMSO. The negatively charged oxygen atom of the carbonyl group attracts the positive end of the dipolar solvent molecules, which on their part inductively reduce the electron density around the carbon nucleus. This corresponds to a greater contribution of the mesomeric structure *(b)* to the electronic ground state; consequently, there is an increase in the ^{13}C splitting.

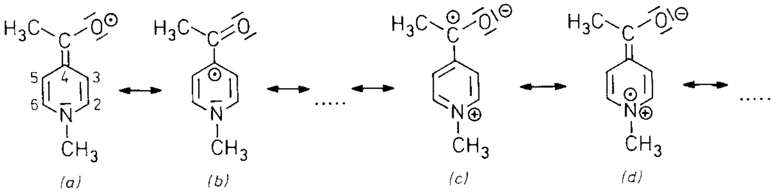
Addition of small amounts of dipolar non-HBD solvents to solutions of the sodium 9-fluorenone ketyl radical in toluene, in which diamagnetic dimers or higher aggregates are present, gives rise to well-resolved HFS patterns. The ^{13}C splitting first decreases with an increase in the mole fraction of the dipolar non-HBD solvent. A limiting $a(^{13}C)$ value is reached at mole fraction $x = 0.2 \ldots 0.3$, due to dissociation into monomeric contact ion-pairs. The $a(^{13}C)$ value keeps constant until the ion pairs finally dissociate into free ions at a mole fraction of greater than 0.6 (the concentration of the anion radical being *ca.* 10^{-4} mol/L). Then, the $a(^{13}C)$ values vary with the solvent as given in Eq. (6-14) [391]. Thus, the solvent dependence of the ^{13}C splitting can be used to follow the formation and dissociation of ion pairs between cations and anion radicals; *cf.* Section 2.6.

Gendell, Freed, and Fraenkel [183] proposed a theory (GFF theory) to account for these solvent effects. It is based on the assumption that the solvent forms localized complexes with the oxygen atoms (or other heteroatoms), altering their electronegativity and consequently redistributing the spin density within the π-system of the free radical. In constructing a model for these complexes, Fraenkel *et al.* focused their attention on radicals containing dipolar substituents (or heteroatoms) and postulated that each substituent was able to form a localized complex with one solvent molecule. This theory, together with HMO calculations of spin densities applied to the solvent effects on proton HFS constants of the 1,4-benzosemiquinone anion radical, gave good quantitative agreement [183]. The GFF theory has been tested, however, with limited success by Luckhurst and Orgel [187], who examined the ESR spectrum of 9-fluorenone ketyl in mixtures of *N*,*N*-dimethylformamide and methanol.

Various solvent effect theories concerning HFS constants in ESR spectra using various reaction field approaches have been developed by Reddoch *et al.* [385] and Abe *et al.* [392]. According to Reddoch *et al.*, none of the continuum reaction field models is entirely satisfactory. Therefore, a dipole-dipole model using a field due only to a dipole moment of one solvent molecule instead of various reaction fields was proposed, and applied to di-*t*-butyl aminyloxide [385]. However, Abe *et al.* found that the HFS constants are proportional to the reaction field of Block and Walker [393] when protic solvents are excluded [392]. This relationship has been successfully applied to di-*t*-butyl and diaryl aminyloxides, to the 4-(methoxycarbonyl)-1-methylpyridinyl radical (*cf.* Fig. 6-10), and to the 4-acetyl-1-methylpyridinyl radical (see below) [392]. For another theoretical approach to the calculation of *g*-values and HFS constants for di-*t*-butyl aminyloxide, see reference [501].

Finally, an example which exhibits extraordinarily large variations of the HFS constants with solvent should be mentioned. The neutral 4-acetyl-1-methyl-pyridinyl radical shown in Eq. (6-15) exhibits variations of the $a(^{1}H)$ constants, caused by the H-atoms of the heteroaromatic ring and the acetyl group, of the order of 200 to 300%

[222, 381, 389]. The greatest changes of HFS constants with solvent obtained so far with aminyloxides [216, 218] and some nitroaromatic anions [204] are at most of the order of 50%.



(6-15)

Solvents	$(CH_2)_4O$	$(Me_2N)_3PO$	CH_3SOCH_3	CH_3OH	H_2O
$a(^1H)$/mT of C-2	0.294	0.270	0.252	0.210	0.164
$a(^1H)$/mT of C-3	0.048	0.073	0.086	0.138	0.185
$a(^1H)$/mT of $COCH_3$	0.195	0.231	0.261	0.410	0.541

It is also noteworthy that the magnitude of the $a(^1H)$ constants caused by the 2-H and 3-H hydrogen atoms is reversed on going from tetrahydrofuran to water. Again, this unusual solvent dependence of the HFS constants may be best explained in terms of valence-bond theory, considering the relative contribution of the nonpolar mesomeric structures *(a)*, *(b)*, *etc.*, and the dipolar mesomeric structures *(c)*, *(d)*, *etc.*, to the actual electronic structure of the radical. In solvents of low polarity, large spin densities are observed at the C-2, C-4, and C-6 positions, while the methyl of the acetyl group and the H-atoms at C-3 and C-5 cause relatively small splitting constants. However, in solvents of higher polarity, which strongly favour the dipolar mesomeric structures, an increase in the acetyl and 3-H and 5-H splittings and a concomitant decrease in the 2-H and 6-H couplings is observed [222]. An additional stabilization of the dipolar structures in protic solvents may come from hydrogen bonding to the negatively charged carbonyl oxygen atom.

Another remarkable example showing opposite solvent-induced trends of the nitrogen and hydrogen HFS constants is given by the 2-[4-(dimethylamino)phenyl] indane-1,3-dionyl radical. Its electronic ground state can again be described by a less dipolar or a zwitterionic mesomeric structure, depending on the solvent used [500]. The paramagnetic cobalt complex $Co(C{\equiv}O)_3L_2$ [L_2 = 2,3-bis(diphenylphosphanyl)maleic anhydride] also exhibits a strongly solvent-dependent ESR spectrum, with increasing $a(Co)$ coupling constants as the solvent polarity decreases. The increase in the cobalt coupling constants reflects a larger cobalt 3d spin density, which is indicative of an increased ligand → metal delocalisation of the unpaired electron [498].

A completely different medium influence on ESR spectra has been observed for radical anions dissolved in non-dissociating solvents. In non-dissociating solvents of low relative permittivity, ion pairing can lead to the appearance of hyperfine features in the ESR spectra of radical anions. These are caused by interactions between the unpaired electron and the nuclei of the diamagnetic cationic gegenion [204, 223–225, 391]. For example, in the ESR spectrum of the ion pair $Na^{\oplus}A^{\ominus}$, every absorption line in the ESR spectrum of $A^{\ominus}$ will be split into a quartet of lines resulting from coupling to the ^{23}Na nuclei, which have a nuclear spin of $I = 3/2$. Generally, the stronger the solvation of the cation and accordingly the dissociation of the ion pair, the smaller will be the HFS constants. Strong coordination by the solvent will decrease the effective electron affinity of the cation. Ultimately, there may be an insertion of solvent molecules between cation and anion, leading to solvent-separated ion pairs (*cf.* Fig. 2-14 in Section 2.6). This process may be quantized or may appear as a more continuous pulling-off process. Both processes are especially favoured by solvents which are good cation solvators, such as the oligoethylene glycol dialkyl ethers (glymes) (*cf.* Section 5.5.5).

With respect to these solvent effects, it is unfortunate that in most cases ethers have been used as solvents for determining ESR spectra of radical anions. In these solvents, metal coupling due to ion pair formation is almost always obtained. In general, in coordinating solvents of relatively high relative permittivity such as acetone, *N*,*N*-dimethylformamide, or acetonitrile, metal ion hyperfine splitting has not been detected. In binary solvent mixtures, gradual changes in the HFS constants resulting from an increased proportion of the better cation-solvating solvent have been reported for naphthalenides [204] and 9-fluorenides [391]. The use of tetraalkylammonium salts in ESR studies of radical anions often serves to overcome the difficulties associated with ion-pair formation. Lowering the temperature corresponds to an increase in ionic solvation. Therefore, on cooling, the ESR spectra of free radical anions often appear, in addition to those of the ion pairs. A compilation of solvent and cation dependences of metal hyperfine splittings for ion pairs has been given by Sharp and Symons [204].

6.5 Solvent Effects on Nuclear Magnetic Resonance Spectra

6.5.1 Nonspecific Solvent Effects on NMR Chemical Shifts

The positions and linewidths of nuclear magnetic resonance (NMR) signals, as well as the magnitudes of the spin-spin coupling constants in the high-resolution NMR spectrum of a particular molecule in solution, are affected by the surrounding molecules of the same or different species. In solution, the position of the resonance signal is often found to be concentration dependent. This effect of neighbouring solute molecules can be easily eliminated by carrying out the measurements at different concentrations and extrapolating to infinite dilution. The solvent-dependence of NMR chemical shifts is most conveniently referred to the shift values, extrapolated to infinite dilution in a nonpolar solvent having as nearly isotropic molecular properties (in particular shape, polarizability, and magnetic susceptibility) as possible. Tetrachloromethane, *n*-hexane, and cyclohexane are commonly used as inert reference solvents. The characteristic ^{1}H and ^{13}C NMR resonance signals of commonly used NMR solvents are compiled in Tables A-6 and A-7 (Appendix).

In general, two different solvent effects on NMR spectra can be distinguished: (a) shifts due to a difference in the bulk volume magnetic susceptibility χ of the solute and the solvent; (b) shifts arising from intermolecular interactions between solute and solvent molecules. Since the bulk susceptibility effect depends on the shape of the sample and, therefore, is not of chemical interest, some form of correction for it is applied. For two coaxial cylindrical samples with axes perpendicular to the applied magnetic field and differing in magnetic susceptibility by $\Delta\chi$, the bulk susceptibility correction is given by Eq. (6-16):

$$\begin{aligned}\delta_{\text{corr}} &= \delta_{\text{exp}} + \frac{2\pi}{3} \cdot \Delta\chi \cdot 10^6 \\ &= \delta_{\text{exp}} + \frac{2\pi}{3} \cdot (\chi^{\text{reference}} - \chi^{\text{solution}}) \cdot 10^6 \qquad (6\text{-}16)\end{aligned}$$

Only shifts observed in excess of this amount may then be attributed to intermolecular interaction effects. Use of an internal standard provides an automatic compensation for the bulk susceptibility effect, but for comparison of shifts measured in this way in different solvents it must be kept in mind that the standard itself may be subject to solvent effects. These are minimized in ^{1}H and ^{13}C NMR spectroscopy by the use of tetramethylsilane (TMS) as an internal standard.

The intermolecular solute/solvent interactions may arise from nonspecific interaction forces such as dispersion, dipole-dipole, dipole-induced dipole, *etc.*, as well as from specific interactions found in protic and aromatic solvents. Solvent effects on NMR spectra were first observed by Bothner-By and Glick [226] and independently by Reeves and Schneider [227] in 1957. Since then, the influence of solvent on chemical shifts (and coupling constants) has been extensively studied by scores of workers and has been thoroughly reviewed by several specialists [1–4, 288–237].

Some illustrative examples of solvent-dependent NMR chemical shifts for several different nuclei in a cation [238, 239], two dipolar molecules [240, 241], and an apolar molecule [242, 243] are given in Table 6-6.

Whereas the solvent influence on the ^{1}H and ^{13}C chemical shifts of the apolar tetramethylsilane is comparatively small ($\Delta\delta$ *ca.* 0.5 ... 1.5 ppm), much greater effects are observed in the case of dipolar molecules such as 4-fluoro-nitrosobenzene and triethylphosphane oxide ($\Delta\delta$ *ca.* 3 ... 25 ppm) as well as for the thallium(I) ion ($\Delta\delta > 2000$ ppm!).

Amongst the cations, $^{205}\text{Tl}^{\oplus}$ is exceptionally sensitive to its solvent environment. The solvent-dependent chemical shift observed for this cation is over 2600 ppm [238, 239]. In comparison, the known solvent chemical shift for $^7\text{Li}^{\oplus}$ is only 6 ppm [244], for $^{23}\text{Na}^{\oplus}$ 20 ppm [245, 396], and for $^{133}\text{Cs}^{\oplus}$ it is only 130 ppm [246]. The remarkable solvent sensitivity of the chemical shift of $^{205}\text{Tl}^{\oplus}$ makes it an exceptionally useful probe for the study of common and preferential solvation [247]; *cf.* Section 2.4. Similar huge solvent-induced chemical shifts have been found for ^{59}Co salts and complexes [395]. No single bulk property of the solvent has been shown responsible for these large shifts. A correlation between cation chemical shifts and Gutmann's donor number, which is a measure of solvent Lewis basicity (*cf.* Table 2-3 in Section 2.2.6), has often been found [245, 246]. The solvent-induced chemical shifts can be viewed as a measure of the strength of cation/solvent interaction, with the solvent acting as Lewis base and interacting electrostatically and covalently with the cation. Relatively large solvent-induced ^{1}H chemical shifts have been also observed for organic cations such as 1-methylpyridinium [248], 1,4-diethylpyridinium [249], 1-methylquinolinium [250], and tropylium ion [250].

Table 6-6. A selection of solvent-dependent NMR chemical shifts[a] of the thallium(I) ion ($^{205}Tl^{\oplus}$) [238, 239], triethylphosphane oxide (^{31}P) [240, 367], 4-fluoro-nitrosobenzene (^{19}F) [241], and tetramethylsilane (^{13}C and ^{1}H) [242, 243].

Solvents	$\delta(^{205}Tl)$ of $Tl^{\oplus}X^{\ominus}$[b]	$\delta(^{31}P)$ of $(C_2H_5)_3PO$[c]	$\Delta\delta(^{19}F)$ of 4-FC_6H_4NO[d]	$\delta(^{13}C)$ of $(CH_3)_4Si$[e]	$\delta(^{1}H)$ of $(CH_3)_4Si$[f]
n-Hexane	–	0.00	–	0.19	–
Cyclohexane	–	–	10.50	0.16	−0.04
1,2-Diaminoethane	2147	–	–	–	–
1-Aminobutane	1896	–	–	–	–
Benzene	–	3.49	11.50	−0.26	0.30
Tetrachloromethane	–	3.64	11.10	−0.82	−0.16
1,4-Dioxane	–	4.59	11.60	−0.07	–
Acetone	–	5.33	12.45	0.09	0.03
Pyridine	644	6.04	12.55	−0.34	0.34
N,*N*-Dimethylformamide	126	6.82	12.85	−0.11	–
Dimethyl sulfoxide	369	8.22	13.20	–	–
Dichloromethane	–	8.67	12.90	−0.18	−0.08
Trichloromethane	–	9.83	12.95	−0.53	−0.14
Formamide	96	16.95	13.05	–	–
Methanol	–	17.60	12.45	0.51	–
Water	0	23.35	–	–	–
	$\Delta\delta = 2147$ ppm	$\Delta\delta = 23.35$ ppm	$\Delta\Delta\delta = 2.70$ ppm	$\Delta\delta = 1.33$ ppm	$\Delta\delta = 0.50$ ppm

[a] Shifts in ppm; a positive sign corresponds to paramagnetic downfield shifts.

[b] Shifts are extrapolated to zero anion concentration and are in units of ppm from water.

[c] Shifts extrapolated to infinite dilution, referred to *n*-hexane and corrected for the difference in volume susceptibilities between *n*-hexane and the respective solvent.

[d] Shifts relative to fluorobenzene as internal standard, at high dilution ("shielding parameters" [241]).

[e] Apparent ^{13}C shift of TMS (20 mL/100 mL) with respect to the resonance of ^{13}C in neat TMS.

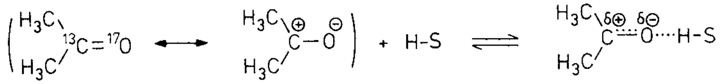
[f] Intrinsic ^{1}H shift of TMS (20 mL/100 mL) with respect to the resonance of ^{1}H in neat TMS.

In the case of the dipolar molecules included in Table 6-6, parts of the solvent-induced chemical shifts may be qualitatively explained in terms of valence-bond theory, as shown for 4-fluoro-nitrosobenzene [241]. Its ^{19}F signal is increasingly shifted to lower field strengths with increasing solvent polarity. The greater the solvent polarity, the greater the charge separation in the dipolar molecule due to an increasing contribution of the dipolar mesomeric structure to the electronic ground state, and the greater the

deshielding of the fluorine atom. This corresponds to the downfield ^{19}F chemical shifts observed in polar solvents.

An analogous interpretation explaining part of the large downfield ^{31}P chemical shift of triethylphosphane oxide, $Et_3P{=}O \leftrightarrow Et_3P^{\oplus}{-}O^{\ominus}$, which is observed with increasing solvent polarity, has also been given [240, 367]. The high ^{31}P NMR shift sensitivity of triethylphosphane oxide makes this dipolar compound particularly useful as a probe molecule in the study of solute/solvent interactions. Indeed, Gutmann *et al.* have used ^{31}P chemical shifts to measure solvent Lewis acidity, also called the acceptor number [240]; *cf.* Table 2-5 in Section 2.2.6, and Section 7.4. The ^{31}P chemical shifts of triethylphosphane oxide, measured in a variety of solvents, are linearly correlated to the corresponding IR wavenumber shifts $\tilde{\nu}(P{=}O)$ of its P=O stretching vibration [367].

The solvent influence on X=O dipolarity (X = C, N, P, S) has been also studied, particularly for carbonyl compounds such as aliphatic ketones and esters [251–254, 367, 397, 398]. For example, the ^{13}C and ^{17}O chemical shifts of the carbonyl atoms are very sensitive to solvents, especially to protic solvents capable of hydrogen-bonding to the carbonyl oxygen atom, as shown for acetone in Eq. (6-17) [251, 253, 367, 397].


(6-17)

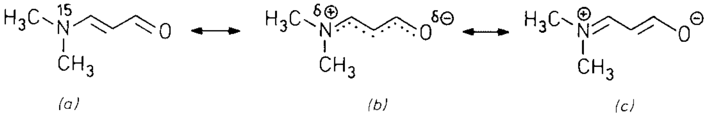
Solvents	CCl_4	C_6H_6	CH_3COCH_3	$HCONMe_2$	CH_3CN	CH_3OH	H_2O	HCO_2H
$\Delta\delta(^{13}C{=}O)$/ppm[a,b]	−1.3	−0.8	0	+0.7	+2.1	+3.7	+9.1	+9.1
$\Delta\delta(C{=}^{17}O)$/ppm[a,c]	+5	0	0	−2	−4	−12	−37	−40

[a] Chemical shifts relative to neat acetone; a negative sign corresponds to diamagnetic highfield shifts.
[b] At 15.1 MHz [251].
[c] At 7.65 MHz [254].

The shift data given in Eq. (6-17) demonstrate that, as the ^{13}C shielding decreases with increasing solvent polarity, the corresponding ^{17}O shielding increases [254]. A monotonic relationship is seen to exist between the ^{13}C and ^{17}O solvent-induced chemical shifts of acetone. This behaviour has been interpreted qualitatively in terms of the altered dipolarity of the carbonyl group as represented by the relative importance of the two mesomeric structures in the valence-bond description of acetone. Furthermore, these solvent effects on ^{13}C chemical shifts can be linearly correlated with the corresponding infrared C=O stretching frequencies measured in the same variety of solvents, as has been shown for acetone, acetophenone, and ethyl acetate [253, 367].

Other representative dipolar compounds for which solvent-induced chemical shifts have been thoroughly studied are dipolar aliphatic compounds (^{13}C) [399], substituted aromatic hydrocarbons (^{1}H) [252, 255, 400], heterocyclic aromatic compounds (^{1}H) [255, 256], *N*,*N*-dimethylbenzamide (^{13}C) [401], acetonitrile [502] and acetone *O*-methyloxime [503] (^{14}N), meropolymethine dyes (^{1}H, ^{13}C, and ^{15}N) [20, 50, 73, 75, 77, 78, 402], pyridinium-*N*-phenolate betaine dyes (^{13}C) [403, 404], trichloromethane (^{13}C) [257], pyridine-1-oxide (^{13}C) [258], fluoropyridines (^{19}F) [259], fluorobenzene (^{19}F) [260], trimethyl phosphate (^{31}P) [504], and triphenylphosphane oxide (^{31}P) [261]. Leading references for further examples are [248–261]; *cf.* also [1–4, 228–237].

A particularly well-studied dipolar example of solvent-induced NMR chemical shifts is 3-(dimethylamino)propenal. As shown by ^{1}H- [20, 50, 73, 75, 78], ^{13}C- [77, 402], and ^{15}N NMR investigations [402], this vinylogous amide exhibits a polyene-like π-electron structure *(a)* in nonpolar solvents, and a dipolar polymethine-like structure *(b)* in polar solvents; *cf.* Eq. (6-18) and Table 6-2 in Section 6.2.2.



(6-18)

Solvents	C_6H_6	1,4-Dioxane	CH_3COCH_3	$HCONMe_2$	CH_3SOCH_3	CH_3OH	H_2O
$\delta(^{15}N)$/ppm[a)]	55.6	57.0	59.2	62.2	64.9	72.9	85.4

[a)] $c = 0.5$ mol/L; aqueous saturated $^{15}NH_4Cl$ solution as external reference.

Accordingly, the ^{15}N signal of the ^{15}N-labelled merocyanine exhibits a large downfield shift of $\Delta\delta \approx 30$ ppm with increasing solvent polarity, corresponding to increased deshielding of the ^{15}N atom. These solvent-induced ^{15}N chemical shifts correlate linearly with the Gibbs energy of activation, $\Delta G^{\neq}_{\text{rot}}$, for the rotation of the dimethylamino group around the ^{15}N—C bond [402]. This can be rationalized in terms of the π-electron distribution along the N—C fragment of 3-(dimethylamino)propenal: increasing solvent polarity favours nitrogen lone-pair delocalization with downfield ^{15}N chemical shifts and increasing $\Delta G^{\neq}_{\text{rot}}$ values as a consequence.

Compared with the pronounced solvent-induced chemical shifts observed with ionic and dipolar solutes, the corresponding shifts of nonpolar solutes such as tetramethylsilane are rather small; *cf.* Table 6-6. A careful investigation of ^{13}C chemical shifts of unsubstituted aromatic, as well as alternant and nonalternant, unsaturated hydrocarbons in aliphatic and aromatic non-HBD solvents by Abboud *et al.* has shown that the differential solvent-induced chemical shift range (relative to benzene as reference) is of the order of only $-1.4 \ldots +1.0$ ppm (positive values representing downfield shifts) [405]. The ^{13}C NMR spectra of these aromatic compounds have been shown to be sensitive to solvent dipolarity and polarizability, except in aromatic solvents, for which an additional specific aromatic solvent-induced shift (ASIS; see later) has been found. There is no simple relationship between the solvent-induced chemical shifts and the calculated charge distribution of the aromatic solute molecules. This demonstrates the importance of quadrupoles and higher multipoles in solute/solvent interactions involving aromatic solutes [405].

In conclusion, the shielding constant of a nucleus in a particular molecule is not only determined by the electronic distribution within the molecule, but also by the nature of the surrounding medium. The observed shielding constant, σ_{obsd}, is the sum of the shielding constant for the isolated molecule, σ_{o}, and a contribution σ_{medium}, arising from the surrounding medium, according to

$$\sigma_{\text{obsd}} = \sigma_{\text{o}} + \sigma_{\text{medium}} \tag{6-19}$$

The shielding constant σ_{medium} is given by Eq. (6-20),

$$\sigma_{\text{medium}} = (H_0 - H)/H_0 \tag{6-20}$$

where H_0 is the applied magnetic field strength producing resonance in an isolated gaseous molecule, and H is the field required to produce resonance in the medium. Buckingham, Schaefer, and Schneider [262] have suggested that σ_{medium} contains contributions from five different sources according to the generally accepted Eq. (6-21).

$$\sigma_{\text{medium}} = \sigma_{\text{b}} + \sigma_{\text{a}} + \sigma_{\text{w}} + \sigma_{\text{e}} + \sigma_{\text{s}} \tag{6-21}$$

σ_{b} arises if an external reference is used, and is due to the bulk magnetic susceptibility differences between the solution and reference sample. The magnitude of σ_{b} depends on the shape of the sample; *cf.* Eq. (6-16). It is zero for a spherical sample or when an internal reference is used. σ_{a} is derived from the anisotropy of the molecular magnetic susceptibility of the solvent molecules. It is particularly important for disc-shaped molecules of aromatic solvents and rod-like molecules such as carbon disulfide. σ_{a} has been detected experimentally by major deviations from the expected behaviour of methane based on σ_{b} and σ_{w}. σ_{w} is a downfield shift, thought to arise from weak dispersion interactions between solute and solvent molecules (van der Waals forces) [263]. This effect is measured by the use of nonpolar, isotropic solutes (*e.g.* methane) in nonpolar, isotropic solvents (*e.g.* tetrachloromethane) and an external reference, followed by a susceptibility correction. Its magnitude increases with increasing molecular polarizability of the solvent molecules. σ_{e} represents the contribution of a polar effect caused by the charge distribution in the dipolar solute molecule [262, 264, 265]. Dipolar molecules induce a dipole moment in the surrounding solvent molecules. The electric field thus created (the reaction field according to Onsager [80]) produces a small change in the solute chemical shift. This effect should therefore depend on the dipole moment and polarizability of the solute and the relative permittivity of the solvent, *i.e.* $(\varepsilon_{\text{r}} - 1)/(2\varepsilon_{\text{r}} + 1)$ [262, 264]. The solvent shifts experienced by dipolar molecules include all the terms described so far. They are commonly reported as the solvent-induced difference in the chemical shifts of the solute of interest and the internal reference compound (usually TMS) in a nonpolar dilute reference phase such as cyclohexane. Finally, a fifth term, σ_{s}, may be added on the right side of Eq. (6-21) to account for specific solute/solvent interactions such as hydrogen-bonding or EPD/EPA interactions. With EPD solutes in protic solvents (or *vice versa*), σ_{s} is usually by far the largest term.

Each of the contributions to σ_{medium} has been the subject of several separate investigations. It is usually found that σ_{b} and σ_{w} cause paramagnetic shifts (that is, they lead to resonance at lower applied field). σ_{a} leads to diamagnetic shifts for disc-shaped solvent molecules such as benzene, and to paramagnetic shifts for cylindrically symmetric, rod-shaped ones such as carbon disulfide, whereas σ_{e} can be responsible for either diamagnetic or paramagnetic shifts, depending on the position of the nucleus relative to the polar group in the solute molecule [262].

Fig. 6-11 illustrates the dissection of the solvent-induced ^{1}H NMR shift into various terms using the rather elementary example of methane [3, 266].

Since screening constant σ and chemical shift δ are related to each other, in practice a modified Eq. (6-21), Eq. (6-22), is often used,

$$\Delta\delta = \delta_{\text{obsd}} - \delta_0 = \delta_{\text{b}} + \delta_{\text{a}} + \delta_{\text{w}} + \delta_{\text{e}} + \delta_{\text{s}} \tag{6-22}$$

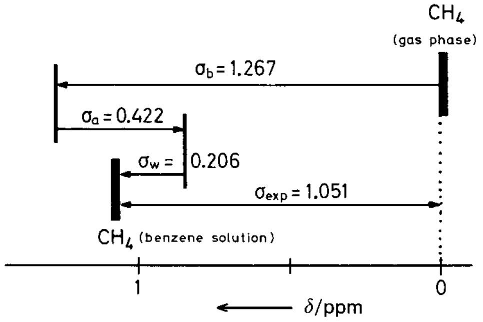


Fig. 6-11. Solvent-induced ^1H NMR chemical shift for methane on going from the gas phase to benzene solution [3, 266].

where $\Delta\delta$ represents the chemical shift increment caused by the medium in going from the gaseous (δ_0) to the condensed state (δ_{obsd}).

In gas-to-solution NMR spectra of ^{129}Xe $\left(I = \frac{1}{2}\right)$, the observed range of chemical shifts is rather large, at $\Delta\delta \approx 250$ ppm. The solvent-induced chemical shift of the signals of spherical, highly polarizable xenon is dominated by the dependence of δ_w on the surrounding medium (*i.e.* van der Waals interactions). For neutral monoatomic species such as xenon, δ_e and δ_s are zero [505]. For the ^{17}O NMR chemical shifts of water ($H_2{}^{17}O$), dissolved in various media, the solvent influence is much more complicated. The sequence of changes vapour phase → *n*-pentane → methanol → neat liquid water → aqueous HCl (11.3 M) corresponds to downfield shifts of the ^{17}O signal of $-36.1 \rightarrow -19.1 \rightarrow -12.3 \rightarrow 0 \rightarrow +26.7$ ppm, measured relative to water as an external reference [506]. In this case, *all* non-specific and specific solute/solvent interactions contribute significantly to the observed solvent effect, with major contributions from the solute/solvent and solvent/solvent hydrogen-bonding interactions [506, 507].

The numerous attempts and several proposed models for calculating and describing the first four quantities of Eq. (6-21) or Eq. (6-22) in a quantitative way have been thoroughly reviewed [1, 3, 232, 233, 235, 267, 268, 398, 406, 407], and will therefore not be mentioned here. For a promising recent effort to calculate solvent effects on nuclear magnetic shielding parameters derived from NMR spectroscopy, see reference [508]; for spectra, see the general references [435, 436]. Comparison of experimental and calculated solvent-induced chemical shifts is often hampered by the fact that most of the experimental results are obtained with liquid samples. It would be preferable to have chemical shifts (and spin-spin coupling constants) quoted relative to the isolated probe molecule in the gas-phase [406]. The crux of the matter is that, by definition, chemical shifts are differential quantities and may contain contributions from several different solvent effects which cannot be separated *a priori* [235].

6.5.2 Specific Solvent Effects on NMR Chemical Shifts

Specific solvent effects on the resonance positions of the nuclei of dissolved compounds consist mainly of hydrogen-bonding effects and aromatic solvent-induced shifts (ASIS effects). The interactions between the solute and the surrounding solvent molecules lead, in these cases, to molecular species which are more or less definable entities. If the residence-time of a given nucleus in each of the distinct species present in the solution is sufficiently short, a single averaged resonance signal is observed.

Since the discovery, in 1951, that H-atoms involved in hydrogen bonds experience large shifts in their resonance signals [268, 269], the behaviour of ^{1}H NMR chemical shifts, as affected by hydrogen-bond interactions, has been widely studied and thoroughly reviewed [232–235, 270–272]. Hydrogen bonding usually results in a paramagnetic downfield shift of the resonance signal of the H-atom involved; the solvents most effective in causing this are those with strong EPD properties. There is a general observation that the magnitude of the change in the ^{1}H NMR chemical shift which occurs when a hydrogen bond is formed is related to its strength. Since hydrogen bonds are usually made and broken very rapidly relative to the NMR timescale, despite the chemical shift difference between bonded and nonbonded forms, separate lines are not observed for the different species.

Hydrogen-bond donors possessing OH, NH, SH, and CH functional groups have been employed. Processes ranging from self-association of trichloromethane to inter- and intramolecular hydrogen bonding of ambifunctional species (*e.g.* carboxylic acids, 2-aminophenols) have been examined. A great variety of examples is given in recent reviews [270–272]. In particular, the behaviour of the hydroxy-H-atom shift, because of its extreme sensitivity to hydrogen-bonding interaction, has been widely studied. In almost all cases, formation of the hydrogen bond causes the resonance signal of the bonded OH H-atom to move downfield by as much as $\Delta\delta \approx 10$ ppm. Intramolecularly hydrogen-bonded enols and phenols display resonances at especially low field. In solutions of dipolar compounds in protic solvents such as water, hydrogen bonding is the most important kind of intermolecular interaction.

Another illustrative example is that of phenylacetylene. Table 6-7 summarizes the ^{1}H NMR chemical shifts of its alkyne H-atom in a variety of solvents [273]. Most solvents (except aromatic solvents) decrease the shielding of the acetylenic hydrogen nuclei. The corresponding low-field shifts have been interpreted in terms of weak specific association between the alkyne as hydrogen-bond-donor and electron pair-donor groupings of the solvent [273]. The high-field shifts in aromatic solvents arise from the magnetic anisotropy of the solvent molecules (see below). The order of effectiveness of the solvent

Table 6-7. ^{1}H NMR chemical shifts of the alkyne H-atom of phenylacetylene in various solvents at infinite dilution [273].

Solvents	$\delta(\equiv\text{C–H})$/ppm	$\Delta\delta$/ppm[a]
Toluene	2.64	−0.10
Benzene	2.71	−0.03
Cyclohexane	2.74	0.00
Nitromethane	3.26	0.52
Acetonitrile	3.35	0.61
Nitrobenzene	3.44	0.70
1,4-Dioxane	3.50	0.76
Acetone	3.61	0.87
Pyridine	4.10	1.36
N,*N*-Dimethylformamide	4.35	1.61

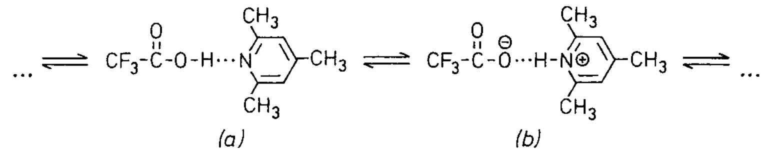
[a] $\Delta\delta = \delta(\text{solvent}) - \delta(\text{cyclohexane})$.

in shifting the $\equiv$C—H signal is qualitatively the same as that observed for the shifts of the infrared NH stretching frequencies of pyrrole in dilute solutions [162]. The basicity of a variety of EPD solvents has been measured by the ^{1}H NMR chemical shift of the trichloromethane H-atom at infinite dilution in the solvent of interest and in cyclohexane as inert reference solvent (*cf.* Table 3-5 in Section 3.3.1) [143, 274, 275].

The reason for the pronounced shifts of hydrogen-bonded H-atoms cannot be completely explained by simple electrostatic considerations. First, it is evident that the electron distribution in the X—H covalent bond in the hydrogen-bonded system X—H$\cdots$|Y is altered by the electric field of |Y in such a way that the H-atom is deshielded. But, in addition, the H-atom may experience an anisotropy effect of the neighbouring group |Y. When the H-atom is bonded more or less to the centre of the π-electron cloud of an aromatic solvent, the ring current effect leads to a large upfield shift (*cf.* Table 6-7), which predominates over any deshielding due to other factors. A hydrogen bond to π-electrons of an aromatic or heteroaromatic ring is the only type of hydrogen bond that results in an upfield, rather than a downfield, shift.

The effect of hydrogen bonding on the chemical shift of the H-bond-acceptor atom |Y (and of X) has also been studied. For example, hydrogen bonding affects the ^{17}O chemical shift of hydroxy groups. The effect of solvent on the ^{17}O chemical shift of water, methanol, and acetic acid has been investigated [276, 506, 507]. It appears that the hydroxylic oxygen experiences greater downfield shifts when it acts as a hydrogen-bond donor than when it serves as a hydrogen-bond acceptor [276]. The ^{13}C and ^{17}O chemical shifts of acetone [251, 254] (*cf.* Eq. (6-17) in the preceding section), and the ^{31}P chemical shift of triethylphosphane oxide [240] (*cf.* Table 6-6) also reveal a comparatively large medium effect in protic solvents, obviously due to hydrogen bonding. The large solvent-induced ^{59}Co chemical shift of $(n\text{-Bu})_4N^{\oplus}$ $Co(CN)_6^{\ominus}$ observed in protic solvents has been recommended as a measure of the HBD capacity of protic solvents [395]. In protic solvents, a downfield shift of the ^{59}Co resonance occurs upon hydrogen-bonding to the cyanide ligand, according to ^{59}Co—C$\equiv$N$\cdots$H—S. A ^{59}Co chemical shift difference of *ca.* 1 ppm is even observed between the solvents H_2O and D_2O; D_2O being the weaker HBD solvent [395].

Solvent-induced ^{1}H chemical shifts of hydrogen-bonded H-atoms are not only found for hydrogen-bonded *solute/solvent* complexes but also for hydrogen-bonded *solute/solute* complexes. A well-studied example is the intermolecularly hydrogen-bonded 1:1 complex between trifluoroacetic acid (as HBD) and 2,4,6-trimethylpyridine (as HBA), as shown in Eq. (6-23) [408]; *cf.* also Eq. (4-29) in Section 4.4.1.



(6-23)

Solvents	C_6H_6	C_6H_5Cl	CH_2Cl_2	$ClCH_2CH_2Cl$	CH_3CN
δ(OH)/ppm[a]	19.02	18.92	18.10	18.00	16.95

[a] Equimolar solution with $c = 0.15$ mol/L [408].

In this case, the solvent-induced ^{1}H chemical shift of *ca.* 2 ppm is best explained by assuming a double-minimum potential model of the hydrogen-bond, *i.e.* the existence of a rapid solvent-dependent proton-transfer equilibrium between *(a)* the covalent and *(b)* the ionic hydrogen-bonded complex. With increasing solvent polarity, the proton-transfer equilibrium is shifted in favour of the ionic complex *(b)*.

In conclusion, ^{1}H NMR spectroscopy has proven to be one of the most sensitive spectroscopic methods, both qualitatively and quantitatively, for studying hydrogen bonds [270–272, 277]; *cf.* also Section 2.2.5.

When a dipolar molecule is dissolved in a magnetically anisotropic solvent consisting of disc-shaped molecules, *e.g.* benzene, the NMR signals of the solute H-atoms are usually shifted upfield with respect to their positions in an isotropic solvent such as 2,2-dimethylpropane (neopentane) or tetrachloromethane; *cf.* the preceding discussion of σ_a in Eq. (6-21). The specific solvent-induced ^{1}H NMR chemical shift of a solute H-atom signal when the solvent is changed from a reference aliphatic solvent to an aromatic solvent is called *aromatic solvent-induced shift* (ASIS)*⁾ and is defined according to Eq. (6-24) [278, 279],

$$\Delta\delta(\text{ASIS}) = \delta_{\text{AS}} - \delta_{\text{S}} \qquad (6\text{-}24)$$

where δ_{AS} is the position of a H-atom signal in the aromatic solvent (*e.g.* C_6H_6 or C_6D_6) and δ_{S} is the value for the same signal in the aliphatic solvent (*e.g.* CCl_4 or $CDCl_3$). A positive value of $\Delta\delta$(ASIS) indicates a downfield shift relative to the signal position in the aliphatic solvent. $\Delta\delta(^1$H-ASIS) values can be as large as ±1.5 ppm and have proven to be a powerful tool in the elucidation of structural, stereochemical, and conformational problems [3, 232–234, 408]. The utility of $\Delta\delta(^{13}$C-ASIS) is still unknown since ^{13}C NMR chemical shifts cover a far greater range than ^{1}H chemical shifts and, therefore, contributions due to solvent anisotropies become relatively insignificant in ^{13}C NMR spectroscopy [409].

The pronounced magnetic anisotropy of benzene helps to reveal subtle solute–solvent interactions which otherwise could not be detected. For example, ASIS's can be used to differentiate between axial and equatorial H-atoms or methyl groups adjacent to carbonyl groups. A typical shift for an axial 2-methyl group in a cyclohexanone is 0.2…0.3 ppm upfield, in benzene relative to tetrachloromethane as solvent, while that of the corresponding equatorial 2-methyl group is 0.05…0.10 ppm downfield [3]. This can be used to determine the configuration at the 2-position and to assess the position of the conformational equilibrium in 2-methylcyclohexanone.

The so-called carbonyl plane rule permits the locating of H-atoms behind or in front of a keto group [408, 410, 411]. Assuming a reference plane perpendicular to the C_α—CO—$C_{\alpha'}$ plane and passing through the carbonyl carbon atom, the value of $\Delta\delta$(ASIS) is positive for H-atoms lying in front of this perpendicular plane (toward the oxygen atom), and negative for those H-atoms lying behind the perpendicular plane. For example, the $\Delta\delta$(ASIS) values for the terpene ketone pulegone are positive for the 10-methyl group and negative for the 7- and 9-methyl groups as the former lies in front

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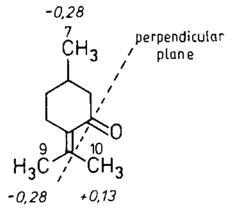
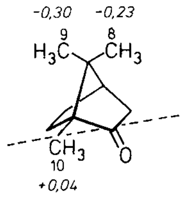
* Somewhat related to the ASIS's are the lanthanide-induced NMR chemical shifts. These involve addition of a lanthanide salt to form a complex, rather than a solvent effect. In fact, aromatic solvents are of the same class as the diamagnetic lanthanide shift reagents; *cf.* reference [415].

of the carbonyl reference plane and the latter behind the reference plane [412]. Analogous results have been observed for camphor, whose 10-methyl group signal experiences a downfield shift whereas the signals of the 8- and 9-methyl groups are shifted upfield in benzene relative to tetrachloromethane [412]; see reference [408] for further examples of the carbonyl plane rule. Interestingly, when the aromatic solvent is hexafluorobenzene instead of benzene, the carbonyl plane rule is exactly reversed [412, 413].



$\Delta\delta$(^{1}H-ASIS) of pulegone in ppm



$\Delta\delta$(^{1}H-ASIS) of camphor in ppm

For both terpene ketones, pulegone and camphor, the $\Delta\delta$(^{13}C-ASIS) has been estimated by a chemical shift comparison method using *t*-butylcyclohexane as an additional reference compound [409]. By comparing the $\Delta\delta$(ASIS) of both ^{1}H and ^{13}C nuclei it seems that the carbonyl plane rule is also valid for aromatic solvent-induced ^{13}C NMR chemical shifts of carbonyl compounds [409]. Obviously, the particular geometrical arrangement of the aromatic solvent molecules around the carbonyl dipole influences both the ^{1}H and ^{13}C nuclei in the same way.

The ASIS for many other classes of organic compounds have also been studied and plane rules for lactones, lactams, and acid anhydrides have been suggested; *cf.* reference [3] for a comprehensive selection of successful applications of ASIS.

In an investigation of the origin of the ASIS phenomenon, camphor has been studied in a variety of solvents [279]. It was found that there is an excellent linear correlation between the $\Delta\delta$(^{1}H-ASIS) values of the 8- and 9-methyl group for more than fifty different aromatic solvents. This is in accordance with a formulation of the type

$$\Delta\delta(\text{ASIS}) = (\text{solute property}) \cdot (\text{solvent parameter}) \tag{6-25}$$

The solute property was identified with a site factor which depends only on the geometry of the solute. The solvent parameter is simply proportional to the concentration of benzene rings in the medium [279]. Based on these results, Laszlo *et al.* proposed a solute/solvent cluster model which is the most accepted ASIS approach [279]. This model considers ASIS as resulting from a slight organization of aromatic solvent molecules around the dipolar site of the solute molecule due to weak intermolecular interactions between solute dipoles and solvent quadrupoles [413]. The lifetime of such transient solute/solvent complexes must be very short on the NMR time scale and the resultant NMR spectrum will be a weighted average among all solute/solvent species involved. The exact stoichiometry and geometry of these transient complexes are not known, but the flat surface of benzene molecules is likely to face the positive end of the solute dipole. Thus, benzene molecules induce upfield shifts due to their magnetic anisotropy for H-atoms near the positive dipole end. The peripheral part of benzene molecules is likely to face the negative end of the solute dipole. Thus, downfield shifts are induced for H-atoms near the negatively charged end of the solute dipole; *cf.* reference [413] for a picture of the most stable orientation of benzene molecules around a solute dipole. The opposite ASIS observed with hexafluorobenzene as aromatic solvent can then easily be explained in terms of the different charge distribution in hexafluorobenzene as compared to benzene [413]. The strong H—F dipoles cause the fluoro-substituted solvent to present its negatively charged fluorine atoms to the positive end of the solute dipole. That is, hexafluorobenzene would take up the edgeway stance whereas benzene would be face-on [413].

A multivariate data analysis of $\Delta\delta(^1\text{H-ASIS})$ of ethereal solutes, using tetramethylsilane as internal reference, has shown that ASIS can be described by a single solvent parameter model [414]. This statistically calculated single parameter can be correlated to Laszlo's solvent parameter, given in Eq. (6-25) and derived from the ASIS of camphor. These results are in favour of the time-averaged transient cluster model, where ASIS is a product of a solute-specific site parameter and a solvent parameter; *cf.* Eq. (6-25). This solvent parameter has been interpreted as being composed of solvent molar volumes and electronic effects caused by substituents in the aromatic solvent molecules [414, 417]. Since the intermolecular solute/solvent interactions causing ASIS are weak, solvent/solvent interactions can compete with them. Thus, it seems reasonable that solvent packing effects, as expressed by molar volumes, can influence the value of $\Delta\delta(\text{ASIS})$.

The solvent clustering model as well as other attempts at explaining the ASIS phenomenon (not given here) have been reviewed and criticized, but no descriptive alternative model has been given [416].

Liquid crystals provide another kind of magnetically anisotropic solvents which have been used in NMR spectroscopy [281–283]. Liquid crystals are known to form partially ordered structures; *cf.* Sections 3.1 and 5.5.9 [280]. Small anisotropic solute molecules dissolved in liquid-crystalline solvents experience partial orientation. Thus, rapid tumbling of the solute molecule about only two of the three axes is possible. This results in some averaging but still allows coupling between the magnetic dipoles of the nuclei as well as chemical shift anisotropies. If the solute molecules are not free to tumble rapidly enough for dipole/dipole averaging, as they usually do in the gas or liquid phase, rather complex NMR spectra with line broadening are observed. However, from the positions and the number of lines observed in the NMR spectra of solutes dissolved in a liquid-crystalline solvent, it is possible to determine their bond angles, relative bond lengths, and the sign of spin-spin coupling constants. For example, this restricted tumbling results in magnetic nonequivalence of the ^{1}H chemical shifts of benzene and normal coupling constants between the 1,2-, 1,3-, and 1,4-H-atoms can be obtained.

Finally, an interesting application of chiral solvents in the determination of the optical purity and the absolute configuration of solutes by NMR spectroscopy should be mentioned. Experimental observations indicate that the NMR spectra of enantiomeric mixtures in certain optically active solvents show small splittings of some of the peaks (*cf.* Table A-2 in the Appendix for chiral solvents). For example, Pirkle *et al.* [284] have examined the ^{1}H and ^{19}F NMR spectra of enantiomeric 2,2,2-trifluoro-1-phenylethanol in optically active 1-(1-naphthyl)ethylamine. In the chiral solvent, the solute gives rise to distinct signals for each enantiomer. These observations are explained as the result of strong specific and non-specific interactions which produce labile diastereomeric solvates. In these solvates, each isomer is sufficiently different for some of the enantiomeric nuclei to be in magnetically different environments. Another nice example of the formation of ^{1}H NMR spectroscopically different diastereomeric solvates are solutions of (−)-cocaine in (*R*)- and (*S*)-methyl phenylcarbinol [418].

A different extent of ion association of salts dissolved in various solvents can also influence the ^{1}H NMR chemical shifts of the H atoms of the cation (or anion) of this salt, as has been found for the room temperature ionic liquids 1-*n*-butyl-3-methylimidazolium tetrafluoroborate and 1-*n*-butyl-3-methylimidazolium hexafluorophosphate, $[BMIM]^+BF_4^-$ and $[BMIM]^+PF_6^-$, measured in nine deuterated solvents [509]. These salts differ only in their anions: BF_4^- is a small and hard anion with high charge density, while PF_6^- is a large polarizable soft anion with low charge density. The solvent-induced ^{1}H NMR chemical shift changes of the signal of 2-H of the aromatic imidazolium ring are somewhat larger for $[BMIM]^+PF_6^-$ than for $[BMIM]^+BF_4^-$. Obviously, owing to the more intimate interaction of the ions of $[BMIM]^+BF_4^-$ as compared to those of $[BMIM]^+PF_6^-$, the H atoms of the former salt are less sensitive to solvent interactions [509].

6.5.3 Solvent Effects on Spin-Spin Coupling Constants

Variation of solvent not only affects chemical shifts in NMR spectra of dissolved compounds, but also the spin-spin coupling or splitting constants. Splitting occurs when there is isotropic coupling of nuclear spins through the bonding electrons. When the signals of two nuclei A and B are split by one another, the magnetic field experienced by A is modified through the effects on the bonding electrons of the $(I + 1)$ nuclear spin orientations of B, and *vice versa.* Therefore, solvent-induced changes in a coupling constant must reflect changes in the electronic structure of the solute molecule. The best way to change the electronic structure of a ground-state molecule is to subject it to an external electric field. Some of the known intermolecular solute/solvent interaction mechanisms (*cf.* Section 2.2) are expected to produce such electric fields in the solute cavity (reaction fields). Thus, solvent effects on coupling constants have been observed frequently, but attempts to derive widespread correlations and generalizations have not been very successful. Reviews by Smith [236], Barfield and Johnston [237], and Hansen [419] give comprehensive information concerning solvent effects on coupling constants as well as on the underlying theories used to explain the observed results.

In one of the earliest publications devoted primarily to solvent effects on coupling constants, Evans [285] reported a 9.6 Hz increase for the one-bond coupling constant $^1J_{^{13}C-H}$ of trichloromethane in thirteen solvents ranging from cyclohexane ($J = 208.1$ Hz) to dimethyl sulfoxide ($J = 217.7$ Hz). Additional values of $^1J_{^{13}C-H}$ for trichloromethane in N- and O-containing heterocyclic solvents have been provided by Laszlo [286] ($J = 215.0$ Hz in pyridine; $J = 213.0$ Hz in 1,4-dioxane). The changes in $^1J_{^{13}C-H}$ observed in solvents of increasing basicity and polarity have been attributed to hydrogen bonding and reaction-field effects. Hydrogen bonding might lengthen the C—H bond of trichloromethane, which ought to result in a decrease in $^1J_{^{13}C-H}$, but through an electrostatic repulsion mechanism the carbon 2*s* contribution is increased resulting in an increase in $^1J_{^{13}C-H}$, the result actually observed [285, 286]. A shift of electrons away from hydrogen towards carbon produces an increase in the contribution of the carbon 2*s* orbital to the C—H bond and a corresponding increase in $^1J_{^{13}C-H}$. Further support for the primacy of hydrogen-bonding effects on $^1J_{^{13}C-H}$ have been provided by examining tribromomethane in thirty solvents [287]. Solvent effects on $^1J_{^{13}C-H}$ coupling constants have been calculated by the finite perturbation theory [420]. According to these calculations, solvent effects on $^1J_{^{13}C-H}$ arise mainly from electronic changes in the solute molecule caused by intermolecular solute/solvent interactions [420]. $^1J_{^{13}C-H}$ for pyridine 1-oxide is also solvent-dependent [258]. In summary, although the solvent effects are rather small, $^1J_{^{13}C-H}$ and most other one-bond coupling constants always increase in solvents of increasing polarity and basicity. Solvent-induced changes in ^1J of at most 7% have been observed, and for long-range couplings they are even smaller [236, 419].

Geminal two-bond couplings between H-atoms, $^2J_{H-H}$, may change from 2 to 80%, always decreasing (in the absolute sense) in solvents of increasing polarity [236, 288]. A typical example is 1-chloro-1-cyanoethene, the $^2J_{H-H}$ solvent dependence of which has been studied in various solvents [289, 290]. For trifluoromethane, the $^2J_{H-F}$ coupling constant varies only by 1% in a range of solvents, decreasing algebraically with increasing van der Waals solute/solvent interactions [421]. Geminal $^2J_{H-H}$ coupling constants may be either positive or negative. Therefore, it must be recognized that positive geminal coupling constants which apparently decrease and negative geminal coupling constants which apparently increase are, in fact, showing exactly the same behaviour in the absolute sense: the coupling constants become more negative or decrease algebraically.

Vicinal three-bond couplings, $^3J_{A-B}$, present rather ambiguous results [236, 237]. When changes do occur, $^3J_{A-B}$ often increases as the polarity of the solvent increases. An example of this behaviour, $^3J_{H^1-H^2}$ of 3-(dimethylamino)propenal [20, 73], has been already mentioned in Table 6-2 (*cf.* discussion in Section 6.2.2). A detailed study of H—H, H—F, and F—F three-bond coupling constants of difluoroalkenes has been given [291]. The dielectric solvent effects on $^3J_{F-H}$ of mono-, di-, and trifluoroethanes have been calculated and satisfactorily compared with the experimental results [422]. Observed vicinal coupling constants in some ethane derivatives are also found to vary with solvent. In such cases, however, vicinal couplings may be altered as a result of conformational changes in an adjacent part of the molecule. Three-bond coupling constants are known to vary with the dihedral angle between the C—H bonds.

An illustrative example of the $^3J_{H-H}$ solvent dependence caused by conformational changes is given by 1,1,2-trichloroethane, the ^1H NMR spectrum of which has been reported in 32 protic and aprotic solvents [510]. In solution, 1,1,2-trichloroethane exists in two preferred staggered conformations with different dipole moments. On going from *n*-pentane to dimethyl sulfoxide as solvent, the $^3J_{H-H}$ coupling constant changes from 6.265 to 5.126 Hz (a reduction of 18%). The two major solvent influences on the ^3J values are solvent dipolarity and solvent HBA basicity. These arise because the conformational equilibrium is shifted in favour of the more dipolar stereoisomer with increasing solvent polarity, and because the H atom in the $-CHCl_2$ moiety is slightly acidic and is thus capable of forming weak hydrogen bonds to HBA solvents [510]. Another well-studied case is the solvent influence on the intrinsic $^3J_{H-H}$ coupling constants of cyclic hydroxy ethers with a fixed conformation [511].

7 Empirical Parameters of Solvent Polarity

7.1 Linear Gibbs Energy Relationships

Solvent effects on organic reactivity (*cf.* Chapters 4 and 5) and on absorption spectra (*cf.* Chapter 6) have been studied for more than a century (*cf.* Chapter 1). Organic chemists have usually attempted to understand these solvent effects in terms of the *polarity* of the solvent. Solvent polarity is a commonly used term related to the capacity of a solvent for solvating dissolved charged or neutral, apolar or dipolar, species. This concept of solvent polarity is easily grasped qualitatively, but it is difficult to define precisely and even more difficult to express quantitatively. Attempts to express it quantitatively have mainly involved physical solvent properties such as relative permittivity, dipole moment, or refractive index (*cf.* Section 3.2). From idealized theories, the solvent dielectric constant (*i.e.* the relative permittivity ε_r) is often predicted to serve as a quantitative measure of solvent polarity. However, this approach is often inadequate since these theories regard solvents as a non-structured isotropic continuum, not composed of individual solvent molecules with their own solvent/solvent interactions, and they do not take into account specific solute/solvent interactions such as hydrogen-bonding and EPD/EPA interactions, which often play a dominant role in solute/solvent interactions. Similarly, solvent dipole moments are inadequate measures of solvent polarity since the charge distribution of a solvent molecule may not only be given by its dipole moment but also by its quadrupole or higher multipole moments, leading to dipolar, quadrupolar, octupolar, *etc.* solvent molecules [121]. Therefore, a more general definition of the commonly used term *solvent polarity* would be useful.

The author stated in 1965 [1, 3] that the polarity of a solvent is determined by its solvation capability (or solvation power) for reactants and activated complexes as well as for molecules in their ground and excited states. This, in turn, depends on the action of *all* possible, specific and nonspecific, intermolecular forces between solvent and solute molecules. These intermolecular forces include Coulomb interactions between ions, directional interactions between dipoles, inductive, dispersion, hydrogen-bonding, and charge-transfer forces, as well as solvophobic interactions (see Chapter 2). Only those interactions leading to definite chemical alterations of the solute molecules through protonation, oxidation, reduction, complex formation, or other chemical processes are excluded. This more pragmatic definition of solvent polarity has meanwhile been included in the 'IUPAC Recommendations 1994' for terms used in physical organic chemistry [291].

It is obvious that such a definition of solvent polarity cannot be measured by an individual physical quantity such as the relative permittivity. Indeed, very often it has been found that there is no correlation between the relative permittivity (or its different functions such as $1/\varepsilon_r$, $(\varepsilon_r - 1)/(2\varepsilon_r + 1)$, *etc.*) and the logarithms of rate or equilibrium constants of solvent-dependent chemical reactions. No single macroscopic physical parameter could possibly account for the multitude of solute/solvent interactions on the molecular-microscopic level. Until now the complexity of solute/solvent interactions has also prevented the derivation of generally applicable mathematical expressions that would allow the calculation of reaction rates or equilibrium constants of reactions carried out in solvents of different polarity.

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In such a situation other indices of solvent polarity are sought. The lack of simple theoretical expressions for calculating solvent effects and the inadequacy of defining "solvent polarity" in terms of single physical constants has stimulated attempts to introduce empirical scales of solvent polarity, based on convenient, well-known, solvent-sensitive reference processes. A common approach is to assume that some particular reaction rate, equilibrium, or spectral absorption is a suitable model for a large class of other solvent-dependent processes. If one carefully selects an appropriate, sufficiently solvent-sensitive reference process, one can assume that this process reflects all possible solute/solvent interactions that are also present in related solvent-influenced processes. It should therefore give an empirical measure of solvent polarity – or, more precisely, an empirical measure of the solvation capability of a particular solvent for the given reference process. This reference process can be considered as a probe of the solvation shell of the standard solute – a probe that sums up a wide variety of possible intermolecular interactions such as ion-dipole, dipole-dipole, dipole-induced dipole, hydrogen-bonding, interactions, *etc.* Naturally, the most useful model processes should be those best understood on a molecular basis. Model processes used to establish empirical scales of solvent polarity have been reviewed [1–9, 122–124, 289]. More recent reviews on empirical solvent polarity scales can be found in references [292–296].

At best, this approach provides a quantitative index to solvent polarity, from which absolute or relative values of rate or equilibrium constants for many reactions, as well as absorption maxima in various solvents, can be derived. Since they reflect the complete picture of all the intermolecular forces acting in solution, these empirical parameters constitute a more comprehensive measure of the polarity of a solvent than any other single physical constant. In applying these solvent polarity parameters, however, it is tacitly assumed that the contribution of intermolecular forces in the interaction between the solvent and the standard substrate is the same as in the interaction between the solvent and the substrate of interest. This is obviously true only for closely related solvent-sensitive processes. Therefore, an empirical solvent scale based on a particular reference process is not expected to be universal and useful for all kinds of reactions and absorptions. Any comparison of the effect of solvent on a process of interest with a solvent polarity parameter is, in fact, a comparison with a reference process.

This kind of procedure, *i.e.* empirical estimation of solvent polarity with the aid of actual chemical or physical reference processes, is very common in chemistry. The well-known Hammett equation for the calculation of substituent effects on reaction rates and chemical equilibria, was introduced in 1937 by Hammett using the ionization of *meta*- or *para*-substituted benzoic acids in water at 25 °C as a reference process in much the same way [10]. Usually, the functional relationships between substituent or solvent parameters and various substituent- or solvent-dependent processes take the form of a *linear Gibbs energy relationship*, frequently still referred to as a *linear free-energy* (LFE) *relationship* [11–15, 125–127].

Let us consider a certain reaction series, one in which only small changes are involved in going from one reaction to another. These changes may be structural, such as a series of differently substituted compounds, or may involve a single reaction carried out in a series of different solvents or solvent mixtures. It has been found that the changes in rate and in equilibrium constant occurring in one reaction series can be often related to those in another, closely related series. Thus, plotting the logarithms of rate or equilibrium constants for one reaction series against the corresponding constants for a second, related series frequently gives a straight line, which can be expressed by Eq. (7-1).

$$\lg k_\mathrm{i}^\mathrm{B} = m \cdot \lg k_\mathrm{i}^\mathrm{A} + c \tag{7-1}$$

k_i^A and k_i^B are rate or equilibrium constants of two reaction series *A* and *B*, which are subject to the same changes in the structure or the surrounding medium.

Since the relationship between the equilibrium constant, *K*, for a reaction and the difference between the standard molar Gibbs energies of the products and reactants, ΔG°, is given by Eq. (7-2),

$$\lg K = -\frac{\Delta G^\circ}{\ln 10 \cdot R \cdot T} \tag{7-2}$$

and a similar expression using the standard molar Gibbs energy of activation, $\Delta G^{\neq}$, for the rate constant *k* of a reaction can be written as in Eq. (7-3),

$$\lg\left(\frac{k}{R \cdot T/N_\mathrm{A} \cdot h}\right) = -\frac{\Delta G^{\neq}}{\ln 10 \cdot R \cdot T} \tag{7-3}$$

Eq. (7-1) essentially describes a relationship between standard molar Gibbs energies*). It is often convenient to express linear Gibbs energy relationships in terms of ratios of constants by referring all members of a reaction series to a reference member of the series; thus, the correlation in Eq. (7-1) can also be expressed by Eq. (7-4).

$$\lg(k_\mathrm{i}^\mathrm{B}/k_0^\mathrm{B}) = m \cdot \lg(k_\mathrm{i}^\mathrm{A}/k_0^\mathrm{A}) \tag{7-4}$$

where k_0^A and k_0^B are the constants for the reference substituent or the reference solvent.

Such relationships are useful in two ways. The first application is in the study of reaction mechanisms. The correlation of data for a new reaction series by means of a linear Gibbs energy relationship establishes a similarity between the new series and the reference series. The second use of linear Gibbs energy equations is in the prediction of reaction rates or equilibrium constants dependent on substituent or solvent changes. Let us consider a reaction between a substrate and a reagent in a medium *M*, which leads, *via* an activated complex, to the products**).

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* Linear Gibbs energy relationships are manifestations of so-called extrathermodynamic relationships. Extrathermodynamic approaches are combinations of detailed models with the concepts of thermodynamics. Since it involves model building, this kind of approach lacks the rigour of thermodynamics, but it can provide information not otherwise accessible. Although linear Gibbs energy relationships are not a necessary consequence of thermodynamics, their occurrence suggests the presence of a real connection between the correlated quantities, and the nature of this connection can be explored.

** The designation of one reactant as the *substrate* and another as the *reagent* is arbitrary but useful in considering chemical reactivity. The substrate always undergoes some change in the reaction series, the reagent does not. A catalyst is always considered to be a reagent.

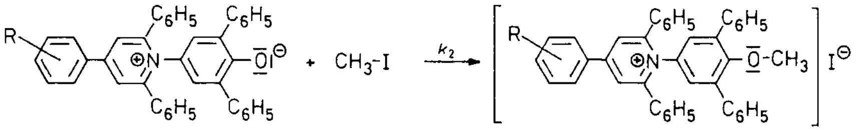
$$(\text{Substrate})_M + (\text{Reagent})_M \rightleftharpoons [\text{S}\cdots\text{R}]^{\neq}_M \rightarrow (\text{Products})_M \tag{7-5}$$

There are three ways of introducing small changes in order to establish a reaction series:

(a) First, we can change the substrate by introducing different substituents. In the case of *meta*- and *para*-substituted benzene derivatives, this leads to the well-known Hammett equation (7-6), where k_X is a rate or equilibrium constant for *meta*- or *para*-

$$\lg k_X - \lg k_0 = \lg(k_X/k_0) = \sigma \cdot \varrho \tag{7-6}$$

substituted substrates, σ is the substituent constant, and ϱ is the reaction constant ($\varrho = 1$ for the standard reaction by definition) [10]. A typical Hammett correlation is shown in Fig. 7-1 for the S_N2 alkylation reaction of substituted pyridinium-*N*-phenolate betaines with iodomethane [16]. As expected for this S_N2 reaction (negative ϱ-value), electron-releasing substituents increase the reaction rate, whereas electron-withdrawing groups have a decelerating effect.



(b) Second, we can change the reagent to give, for example, a Gibbs energy relationship called the Brønsted–Pedersen catalysis equation, developed as a result of studies on the base-catalyzed decomposition of nitroamide [17]. This equation establishes a quantitative relationship between acid and base strengths and their effectiveness as catalysts in reactions subject to general acid or base catalysis: the stronger the acid (or base), the better it is as a catalyst. This Brønsted catalysis law, introduced in 1924, was the first linear Gibbs energy relationship.

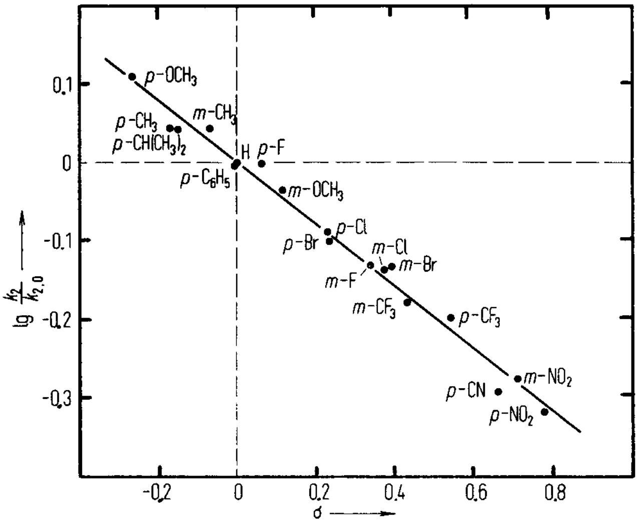


Fig. 7-1. Hammett correlation between σ-values and the logarithms of the relative rate constants of the S_N2 alkylation reaction of substituted pyridinium *N*-phenolate betaines with iodomethane in trichloromethane at 25 °C [16].

(c) Finally, we can change the surrounding medium M while leaving the other reaction parameters unchanged. Provided the selected reaction is sufficiently solvent-sensitive, this gives us the desired empirical solvent parameters [1–9, 122–124, 292–296]. Thermodynamically, solvation may be considered in the same general terms as the modification of the properties of the substrate molecule by substituent changes, the solvating molecules being equivalent to loosely attached substituents [18]. One important difference between substituent and solvent effects on chemical reactivity is that substituents may change the chemical reactivity of a given substrate only in a discontinuous manner, whereas solvents, especially solvent mixtures, allow a continuous modification of the substrate reactivity. Empirical parameters of solvent polarity based on solvent effects on chemical equilibria and reaction rates will be described in Sections 7.2 and 7.3.

In principle, the same considerations as in Eq. (7-5) can be made for the spectral excitation of a substrate, dissolved in a medium M, with photons $h \cdot \nu$. Although linear Gibbs energy relationships usually deal only with relative reactivities, in the form of reaction-rate and equilibrium data, this approach can be extended to various physical measurements such as spectroscopic investigations of the members of a reaction series in various spectral ranges (UV/Vis [19], IR [19], NMR [20], *etc.*). Spectroscopic measurements can very often be obtained under conditions of greater precision and variety than available in reactivity measurements.

$$\underset{\text{Ground state}}{(\text{Substrate})_M} + h \cdot \nu \rightarrow \underset{\text{Excited state}}{(\text{Substrate})^*_M} \qquad (7\text{-}7)$$

In order to establish a reaction series, the substrate in Eq. (7-7) can be altered in two ways:

(a) Variation by substituents leading to spectroscopic Hammett equations in the form presented in Eq. (7-8),

$$\frac{E_{\mathrm{T,X}} - E_{\mathrm{T,O}}}{\ln 10 \cdot R \cdot T} = \sigma \cdot \varrho_{\mathrm{A}} \qquad (7\text{-}8)$$

and first introduced by Kosower, Hofmann, and Wallenfels [21]. $E_{\mathrm{T,X}}$ and $E_{\mathrm{T,O}}$ are the transition energies in kJ/mol (or kcal/mol) of the substituted and unsubstituted substrate, respectively; σ is the Hammett substituent constant, and ϱ_{A} has been denoted as an absorption constant [22, 23]. The transition energies are divided by ($\ln 10 \cdot RT$) in order to convert them into an appropriate form for Hammett substituent constants, which are commonly derived from equilibrium or rate constants. A representative example of this kind of Hammett correlation for the long-wavelength π–π^* absorption of substituted pyridinium *N*-phenolate betaines is shown in Fig. 7-2 [23].

As expected, electron-withdrawing substituents cause a bathochromic shift of this absorption band, which exhibits a strong intramolecular charge-transfer character (*cf.* Section 6.2.1), whereas electron-releasing substituents give rise to a corresponding hypsochromic shift.

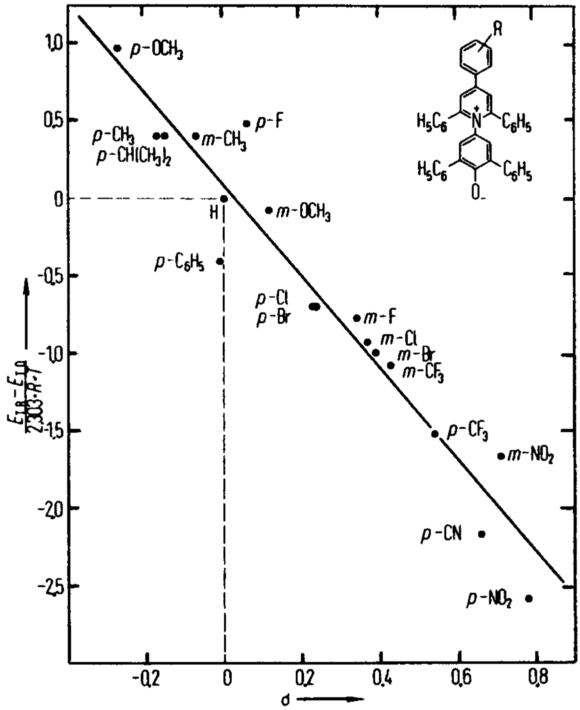


Fig. 7-2. Hammett correlation between σ-values and the modified transition energies of the long-wave-length charge-transfer $\pi \rightarrow \pi^*$ absorption of substituted pyridinium *N*-phenolate betaines in methanol at 25 °C [23]; *cf.* Fig. 6-2 in Chapter 6.

(b) Provided the position of the absorption band is sufficiently solvent-sensitive, changing the medium *M*, in which the substrate is to be dissolved, permits the introduction of spectroscopic solvent polarity scales. Empirical parameters of solvent polarity based on spectroscopic measurements will be described in Section 7.4. The most comprehensive solvent polarity scale is based on solvatochromic pyridinium *N*-phenolate betaines, already mentioned in Section 6.2.1 and in Figs. 7-1 and 7-2 [293].

In the early use of linear Gibbs energy relationships, simple single-term equations such as the Hammett equation were considered sufficient to fit given sets of experimental data from reaction series. Later on, more complicated multi-term equations with more than one product term were formulated in order to model the simultaneous influence of several effects on chemical reactions or optical excitations; one product term per effect [15]. The connection between such multiparameter relationships and solvent effects will be described in Section 7.7.

Simple and multiple linear Gibbs energy relationships can be generally interpreted in two distinct ways [126, 127]:

(a) Traditionally, as relationships expressing combinations of fundamental chemical or physical effects, universally present in chemical reactions. Deviations from such relationships have to be explained by new effects in addition to the old, known effects. If all such effects are discovered and quantified, retrospective rationalization and prediction of chemical processes (*i.e.* chemical reactions and equilibria) is fully possible and it is conceivable that at some time in the future basic research will no longer be needed. The main problems are to find reaction series which are best suited to discovering all these fundamental effects, and to establish how large a deviation can be tolerated before another fundamental effect has to be postulated.

(b) Chemometrically*⁾, as locally valid linearizations of very complicated unknown functional relationships using empirical models of similarity. That is, linear Gibbs energy relationships are considered as approximate models with local validity for similar reaction series only, *e.g.* one model for reactions of substituted benzene derivatives, another model for reactions of substituted aliphatic compounds. In the case of solvent effects, one model would apply to solvatochromic non-HBD, another to solvatochromic HBD reference dyes. In contrast to the traditional interpretation (a), this means that a given linear Gibbs energy relationship is not necessarily universally valid. In any new chemical reaction series there will be regularities in the observed data that *cannot* be predicted from the behaviour of previously investigated chemical model processes. In other words, the data observed in a chemical reaction series can be divided into two parts: one part which will coincide with other known reaction series, and another part which will be system-specific. The latter part is often not negligible and can sometimes be substantial. The larger the common part, the closer the similarity between a new reaction series and the reference reaction series previously investigated. The mathematics of fitting PC and FA models to a matrix of chemical data permits one to judge objectively the applicability of a given linear Gibbs energy relationship, without making assumptions about a single term model fitting part of the data matrix.

A fascinating discussion on the problem of whether linear Gibbs energy relationships are (a) fundamental laws of chemistry, or (b) only local empirical rules, can be found in references [126, 127]. Attempts at discriminating between these two kinds of interpretation of linear Gibbs energy relationships based on an evaluation of the practicality of models derived from either view are described. It seems that from a more rigorous mathematical point of view, interpretation (b), stressed by Wold and Sjöström [126], appears to be the correct one, whereas from a more practical, descriptive point of view, interpretation (a), stressed by Taft and Kamlet [127], will be the one preferred by experimental chemists. The final answer is ambiguous.

Another question now seems to be more pertinent. Are empirical parameters of solvent polarity still necessary in view of the great progress that has been made during the last decades in the development of theoretical methods and computational strategies for describing and understanding the complex phenomenon of solvation of reactants, activated complexes, and products, as well as of molecules in their ground and excited states? Essentially, three general approaches have been used for the theoretical description of solute/solvent interactions: quantum-chemical methods, supramolecular methods, and semicontinuum quantum-chemical methods (see the end of Section 2.3 and

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[*] Chemometrics stands in this context for analysis of multivariate chemical data by means of statistical methods such as principal component analysis (PCA) or factor analysis (FA); *cf.* Section 3.5.

references [27d, 355–361] to Chapter 2 for recent reviews). The results obtained from all these theoretical calculations are very impressive. However, when applied to actual chemical or physical processes in a solution under study, all methods still have their limitations and flaws, particularly concerning the inclusion of nonspecific solute/solvent interactions. Therefore, for obtaining comparatively simple and quick information about how a solvent change may influence a particular reaction under study, both qualitatively and quantitatively, the use of linear Gibbs energy relationships still seems to be a good choice. A chemist in his daily laboratory work is often faced with simple questions such as: would the reaction under study profit from a change from solvent A to solvent B, would the reaction run faster in B than in A, and if yes to what extent, 10-fold or 100-fold? For these decisions, the comparison with other analogous, well-studied solvent-dependent processes and the empirical parameters derived therefrom will certainly continue to be as useful as it has been up to now.

7.2 Empirical Parameters of Solvent Polarity from Equilibrium Measurements

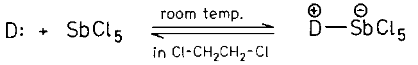
The first attempt to introduce an empirical relationship between an equilibrium constant and solvent polarity was made in 1914 by K. H. Meyer [24]. Studying the solvent-dependent keto-enol tautomerism of 1,3-dicarbonyl compounds, he found a proportionality between the equilibrium constants of various tautomeric compounds in the same set of different solvents (*cf.* Table 4-2 in Section 4.3.1). He therefore split the tautomeric equilibrium constant K_T into two independent factors according to Eq. (7-9).

$$K_T = \frac{[\text{enol}]}{[\text{diketo}]} \equiv L \cdot E \tag{7-9}$$

E is the so-called enol constant and measures the enolization capability of the diketo form ($E = 1$ for ethyl acetoacetate by definition). Thus, the so-called *desmotropic constant* L is a measure of the enolization power of the solvent. By definition, the values of L are equal to the equilibrium constants of ethyl acetoacetate ($E = 1$), determined in different solvents [24]. This desmotropic constant seems to be the first empirical solvent parameter. It describes the relative solvation power of a solvent for diketo and enol forms of 1,3-dicarbonyl compounds. It was measured only for a few solvents and was soon forgotten.

In contrast to this early empirical solvent scale, one of the more recent, introduced by Eliel and Hofer in 1973 [25] and based on the solvent-dependent conformational equilibrium of 2-*i*-propyl-5-methoxy-1,3-dioxane, should be mentioned (*cf.* Table 4-9 in Section 4.4.3). In general, polar solvents shift this conformational equilibrium towards the more dipolar *axial cis* isomer. The authors proposed calling the standard molar Gibbs energy changes associated with this equilibrium, $-\Delta G^\circ_{\mathrm{OCH_3}}$, the D_1 scale (D for dioxane, 1 for the number of carbons in the alkoxy group). They also recommended the use of this solvent scale, known for seventeen solvents, in the estimation of other solvent-dependent equilibria and reaction rates [25].

Another approach to a new solvent scale was introduced by Gutmann in 1966 [26, 27]. Based on the fact that many chemical reactions are influenced primarily by coordination interactions between an electron-pair acceptor (EPA) substrate and electron-pair donor (EPD) solvents (*cf.* Sections 2.2.6 and 2.6), he provided an empirical measure of the Lewis basicity of solvents using the so-called *donor number DN* (or *donicity*). Antimony pentachloride was chosen as a reference compound in order to obtain a measure of the nucleophilic properties of a solvent since the antimony is readily coordinated on the acceptance of an electron-pair from an EPD solvent. According to Eq. (7-10), the donor number is defined as the negative value of the molar enthalpy for adduct



$$\mathrm{D{:}} + \mathrm{SbCl_5} \underset{\text{in Cl-CH}_2\text{CH}_2\text{-Cl}}{\overset{\text{room temp.}}{\rightleftharpoons}} \overset{\oplus}{\mathrm{D}}-\overset{\ominus}{\mathrm{Sb}}\mathrm{Cl_5}$$

$$\text{Solvent Donor Number } DN \equiv -\Delta H_{\mathrm{D-SbCl_5}}/(\mathrm{kcal \cdot mol^{-1}}) \qquad (7\text{-}10)$$

formation between antimony pentachloride and EPD solvents, D, measured calorimetrically in highly diluted solutions of 1,2-dichloroethane as an inert solvent at room temperature [26]. Corresponding enthalpy measurements in the reference solvent tetrachloromethane have led to analogous results [28].

Donor numbers vary from 2.7 for nitromethane, which is a weak EPD solvent, to 38.8 for hexamethylphosphoric triamide, a strong EPD solvent; *cf.* Table 2-3 in Section 2.2.6. The donor number was measured directly, *i.e.* calorimetrically, for *ca.* fifty solvents [26–28, 128]. It has also been estimated by other means such as ^{23}Na [29, 129], ^{27}Al [130], and ^{1}H NMR [131] spectroscopy. Visual estimates of the varying donor numbers of EPD solvents can easily be made using the colour reactions with copper(II), nickel(II), or vanadyl(IV) complexes as acceptor solutes instead of $SbCl_5$ [132]. A selection of donor numbers has already been given in Table 2-3 in Section 2.2.6. A discussion of methods for the determination of donor numbers and critical compilations of *DN* values for 170 and 134 solvents can be found in references [133] and [294], respectively.

Since donor numbers are defined in the non-SI unit kcal · mol^{-1}, Marcus has recommended the use of dimensionless normalized donor numbers DN^{N}, which are defined as $DN^{\mathrm{N}} = DN/(38.8\ \mathrm{kcal \cdot mol^{-1}})$ [133]. The non-donor solvent 1,2-dichloroethane ($DN = DN^{\mathrm{N}} = 0.0$) and the strong donor solvent hexamethylphosphoric triamide (HMPT: $DN = 38.8\ \mathrm{kcal \cdot mol^{-1}}$; $DN^{\mathrm{N}} = 1.0$) have been used to fix the DN^{N} scale. Although solvents with higher donicity than HMPT are known, it is expedient to choose this EPD solvent with the highest directly, *i.e.* calorimetrically, determined *DN* value as the second reference solvent [133]. The normalized DN^{N} values are also included in Table 2-3 in Section 2.2.6.

Since the donor numbers were measured in dilute solution in inert 1,2-dichloroethane*$^{)}$, they reflect the donicity of *single* EPD solvent molecules. However, in neat, associated EPD solvents an increase in the donicity occurs [134]. For such highly

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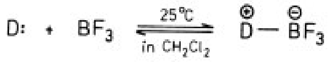
* 1,2-Dichloroethane is obviously not a chemically inert solvent under all circumstances. For example, the EPD solvent triethylamine is rapidly quaternized by 1,2-dichloroethane under the catalytic action of $SbCl_5$, leading to an overestimated donor number for triethylamine [128]. Even solutions of HMPT and $SbCl_5$ in 1,2-dichloroethane contain non-negligible amounts of charged species, the formation of which contributes to the measured enthalpy [138].

structured neat EPD solvents (*e.g.* water, alcohols, amines) the term *bulk donicity* has been introduced [135] in order to rationalize the deviations of these solvents in plots of $^{23}\mathrm{Na}^{\oplus}$ NMR chemical shifts [136] and ESR parameters [137] *vs.* the donor number. Unfortunately, great discrepancies exist between the DN_{bulk} values given in the literature when estimated by different methods. For this reason, they are not included in Table 2-3 in Section 2.2.6; see reference [133] for a collection and discussion of bulk donicities, DN_{bulk}.

Donor numbers are considered as semiquantitative measures of solute/EPD solvent interactions, and are particularly useful in the prediction of other EPD/EPA interactions in coordination chemistry. Numerous examples of the application of donor numbers have been given by Gutmann [26, 27, 30]; *cf.* also [113, 133]. It has been shown that donor number correlations are parallel with correlations based on the highest occupied molecular orbital (HOMO) eigenvalues of EPD solvent molecules [139]. For non-HBD solvents, a fair correlation has been obtained between their donor numbers and their gas-phase proton affinities PA, indicating that the DN values do indeed reflect the intrinsic molecular properties of EPD solvents [140].

The donor number approach has been criticized for both conceptual [141] and experimental reasons [28, 133, 138, 265]. Therefore, the search for other empirical Lewis-basicity parameters has continued.

Another remarkable Lewis basicity scale for 75 non-HBD solvents has been established by Gal and Maria [138, 142]. This involved very precise calorimetric measurements of the standard molar enthalpies of 1:1 adduct formation of EPD solvents with gaseous boron trifluoride, $\Delta H^{\circ}_{\mathrm{D-BF_3}}$, in dilute dichloromethane solutions at 25 °C, according to Eq. (7-11).



$$\mathrm{D{:}} + \mathrm{BF_3} \xrightleftharpoons[\text{in } \mathrm{CH_2Cl_2}]{25\,^{\circ}\mathrm{C}} \overset{\oplus}{\mathrm{D}}-\overset{\ominus}{\mathrm{B}}\mathrm{F_3} \qquad (7\text{-}11)$$

A selection of $\Delta H^{\circ}_{\mathrm{D-BF_3}}$ values has already been given in Table 2-4 in Section 2.2.6. This new Lewis basicity scale is more comprehensive and seems to be more reliable than the donor number scale. Analogously, a Lewis basicity scale for 88 carbonyl compounds (esters, carbonates, aldehydes, ketones, amides, ureas, carbamates) has been derived from their standard molar enthalpies of complexation with gaseous boron trifluoride in dichloromethane solution [143]. The corresponding $\Delta H^{\circ}_{\mathrm{CO-BF_3}}$ values range from 33 $\mathrm{kJ \cdot mol^{-1}}$ for di-*t*-butyl ketone to 135 $\mathrm{kJ \cdot mol^{-1}}$ for 3-diethylamino-5,5-dimethylcyclohexen-2-one.

Solution calorimetry of the molecular probes pyrrole, *N*-methylpyrrole, benzene, and toluene in 35 solvents has been used by Catalán *et al.* to determine a solvent HBA basicity scale, ranging from the gas phase to HMPT [31a]. Analogously, a solvent HBD acidity scale was derived calorimetrically using *N*-methylimidazole and *N*-methylpyrrole as probe molecules in 36 solvents, ranging from the gas phase to 2,2,2-trifluoroethanol [31b].

Another, more general approach for the estimation of EPD/EPA interactions between Lewis acids and bases, not restricted to the solvent as a reaction partner, was given by Drago [32]; *cf.* Eq. (2-12) and Table 2-6 in Section 2.2.6.

A compilation and critical comparison of various Lewis basicity scales for EPD solvents has been given by Persson *et al.* [144, 292].

The solvent-dependent tautomerization of a pyridoxal 5′-phosphate Schiff base has been shown to be another appropriate model process for the measurement of solvent polarities [32a]. This model process seems to be particularly useful for the determination of the polarities of sites of proteins at which pyridoxal 5′-phosphate is bound [32a].

Furthermore, an empirical hydrophobicity parameter derived from measurements of the distribution of a solute between two immiscible liquids should be mentioned; *cf.* Section 2.2.7 dealing with hydrophobic interactions. The hydrophobic or lipophilic character of organic compounds plays an important role in their ability to interfere with biochemical systems. Therefore, systematic efforts have been made to obtain numerically defined constants to assess the hydrophobic character of organic compounds. A hydrophobicity parameter which has proven quite valuable in the fields of toxicology, pharmacology, and environmental science is the *Hansch–Leo 1-octanol/water partition coefficient* $K_{o/w}$ or $P_{o/w}$ as defined in Eq. (7-12),

$$K_{o/w} = \frac{c_i(\text{1-octanol})}{c_i(\text{water})} \equiv P_{o/w} \tag{7-12}$$

where c_i(1-octanol) and c_i(water) are the molar equilibrium concentrations of the solute i in the two immiscible phases 1-octanol and water, respectively [145–147]. The 1-octanol/water partition coefficients are often used as hydrophobicity parameters in the Gibbs energy-based form of lg $P_{o/w}$. They are known for a vast number of organic compounds, particularly for those compounds normally used as organic solvents. A lg $P_{o/w}$ value of 3.90 for *n*-hexane means that this hydrophobic solvent is preferably found in the 1-octanol phase, whereas a lg $P_{o/w}$ value of -1.35 for dimethyl sulfoxide reveals the hydrophilicity of this particular solvent. A compilation of lg $P_{o/w}$ values for 102 organic solvents can be found in reference [149], which also deals with correlations of lg $P_{o/w}$ with some solvatochromic solvent parameters. 1-Octanol/water partition coefficients have served as the basis for many papers in a field of biochemistry known as *q*uantitative *s*tructure/*a*ctivity *r*elationship (QSAR), inspired by Hansch's original observation that distribution of a solute between these two solvents provides an accurate measure of lipophilic/hydrophilic interactions. For example, lg $P_{o/w}$ is a good measure of the ease with which drugs penetrate membranes and bind to hydrophobic surfaces. The interrelation between the narcotic potencies of various substances and the partition coefficient has long been known. Many applications of this hydrophobicity parameter in the framework of linear Gibbs energy relationships have been reported [145–147].

It should be mentioned that water and 1-octanol are not completely immiscible. The solubility of water in 1-octanol is $s = 2.46$ mol/L at 25 °C [= mole fraction $x(H_2O) = 0.289$], and that of 1-octanol in water is $s = 3.29 \cdot 10^{-3}$ mol/L [$= x(\text{1-octanol}) = 9.32 \cdot 10^{-4}$] [148]. In the application of $K_{o/w}$ values, it is tacitly assumed that the solvent properties of 1-octanol saturated with water are not different from those of neat 1-octanol. In practice, the presence of water in 1-octanol should increase the concentration of polar and H-bonding solutes and decrease the concentration of nonpolar solutes. However, solvatochromic studies by Carr *et al.* have shown that the water saturation of 1-octanol has only a very small effect on the properties of bulk 1-octanol. The water is almost completely associated with the hydroxy group of 1-octanol and scarcely affects the properties of this medium [148].

Using 1-octanol/water partition coefficients for aromatic solutes, Hansch also defined a hydrophobicity parameter π_X for organic substituents X according to Eq. (7-12a) [145–147].

$$\pi_X = \lg P_{o/w}^{C_6H_5X} - \lg P_{o/w}^{C_6H_6} \tag{7-12a}$$

$P_{o/w}^{C_6H_5X}$ and $P_{o/w}^{C_6H_6}$ are the partition coefficients between 1-octanol and water for C_6H_5X and C_6H_6, respectively. A positive π_X, such as +0.56 for $X = CH_3$, means that these substituents favour the organic phase relative to the hydrogen atom ($X = H$). If substituents X have negative values of π_X, such as -0.67 for OH, then they cause partitioning into water. The π_X substituent parameters have also been widely used in quantitative structure/activity relationships, particularly in pharmacology.

Another *m*icroscopic *h*ydrophobicity substituent parameter *MH* was evaluated by Menger *et al.* [150]. Addition of ammonium salts $R\text{-}NMe_3^{\oplus}\ X^{\ominus}$ (R = alkyl, aryl; $X^{\ominus}$ = halide ions) to 10^{-5} M 4-nitrophenyl laurate in water destroys or disrupts the ester aggregates formed in aqueous solution. The corresponding shift of the aggregation equilibrium deshields the laurate ester group, resulting in enhanced rate constants for the basic hydrolysis of 4-nitrophenyl laurate. The more hydrophobic the R group of the ammonium salt, the greater its disaggregation power, and the greater the rate enhancement [150].

A further quantitative measure of the solvent solvophobic effect*) has been introduced by Abraham *et al.* [282]. It has been shown that the standard molar Gibbs energies of transfer of nonpolar, hydrophobic solutes X (X = argon, alkanes, and alkane-like compounds) from water (W) to other solvents (S) can be linearly correlated through a set of equations such as Eq. (7-12b),

$$\Delta G_t^{\circ}(X, W \rightarrow S) = M \cdot R_T + D \tag{7-12b}$$

where R_T is a solute parameter, and *M* and *D* characterize the solvent. *M* values are referred to water, *i.e.* $M = 0$ for water by definition. With another fixed point, *i.e.* the *M* value of the most hydrophobic solvent *n*-hexadecane ($M = -4.2024$), a scale of solvophobic power *Sp* has been defined according to Eq. (7-12c),

$$Sp = 1 - \frac{M(\text{solvent})}{M(n\text{-hexadecane})} = 1 + \frac{M(\text{solvent})}{4.2024} \tag{7-12c}$$

where the *Sp* values of water and *n*-hexadecane are arbitrarily taken as unity and zero. The *Sp* values provide a simple quantitative measure of the solvophobic power of solvents, relative to the two reference solvents water ($Sp = 1$) and *n*-hexadecane ($Sp = 0$)

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* The solvophobic or hydrophobic effect is simply regarded as the experimental observation of the relative insolubility in water (or other highly structured liquids) of certain organic solutes, as compared to their solubility in nonaqueous solvents. The so-defined solvophobic (hydrophobic) *effect* should be distinguished from the solvophobic (hydrophobic) *interaction* between two or more solute molecules in solution; *cf.* Section 2.2.7. The solvophobic (hydrophobic) *effect* is only related to solute/solvent interactions [282].

at 298 K. For pure solvents, the following order of decreasing solvophobic power has been obtained [282]: water > formamide > 1,2-ethanediol > methanol > ethanol > 1-propanol > 2-propanol > 1-butanol $\gg$ *n*-hexadecane. Good correlations between *Sp* values and the rate constants as well as stereoselectivities of several Diels–Alder cycloaddition reactions, carried out in hydrophobic media, have been reported [283, 297]; *cf.* also Section 5.5.8.

In this context, another empirical solvent parameter called *SI* should be mentioned. *SI* stands for *S*olvent *I*nfluence (in Russian, *BP* for *В*лияние *Р*астворителя). This parameter was introduced by Shmidt *et al.* in 1967 and was derived from the study of many different extraction equilibria, *i.e.* of the distribution of organic and inorganic compounds between two immiscible liquid phases [298–301]. It was found that in the extraction of metal salts using various extraction reagents, the distribution coefficients of the extractable compound depend on the specific electrophilic and/or nucleophilic properties of the solvents used as diluent. From a large number of well-studied extraction systems, Eq. (7-12d) has been derived,

$$\lg(K/K_0) = a \cdot SI + b \tag{7-12d}$$

where K is the extraction constant for the extraction under consideration with a given solvent as diluent, K_0 is the extraction constant for the same system with a standard diluent (*e.g.* benzene), and a is a constant coefficient for a series of extraction systems differing only in the nature of the solvent used as diluent. For numerous extraction systems, linear correlations have been found between $\lg K$ and the diluent *SI* parameter [298–301]. This and other linear Gibbs energy relationships applicable in the correlation analysis of distribution and extraction constants have been reviewed by Makitra [302].

Finally, a parameter describing the *softness* of solvents should be mentioned. In terms of Pearson's principle of hard and soft acids and bases, the hardness of an ion or molecule is understood as resistance to a change or deformation in the electronic cloud (*cf.* Section 3.3.2). This property, or its complement, the softness of solvents, is expected to play a role in the solvation of hard and soft solutes. Marcus defined a μ scale of solvent softness (from *malakos* = soft in Greek) according to Eq. (7-12e) as the difference between the mean of the standard molar Gibbs energies of transfer of sodium and potassium ions from water (W) to a given solvent (S) and the corresponding transfer energy for silver ions, divided by 100 [285].

$$\mu = \left\{\frac{1}{2}[\Delta G_t^\circ(\mathrm{Na}^\oplus, \mathrm{W} \rightarrow \mathrm{S}) + \Delta G_t^\circ(\mathrm{K}^\oplus, \mathrm{W} \rightarrow \mathrm{S})] - \Delta G_t^\circ(\mathrm{Ag}^\oplus, \mathrm{W} \rightarrow \mathrm{S})\right\} \cdot \frac{1}{100} \tag{7-12e}$$

Since water is a hard solvent, the Gibbs energy of transfer of ions from water as a reference solvent to other solvents should depend on the softness of these solvents in a different manner for hard and soft ions. For ions of equal charge and size, hard ions should prefer water and soft ions the softer solvents. The definition of μ by Eq. (7-12e) has been given because the size of the soft $\mathrm{Ag}^\oplus$ ion is intermediate between those of hard $\mathrm{Na}^\oplus$ and $\mathrm{K}^\oplus$. The μ values for 34 organic solvents have been determined; *e.g.* $\mu = -0.12$ for 2,2,2-trifluoroethanol, 0.00 for water (by definition), 0.64 for pyridine, and 1.35 for *N,N*-dimethylformamide. The degree of softness among solvents with oxygen, nitrogen, and sulfur donor atoms increases in the series O-donor (alcohols, ketones, amides) < N-donor (nitriles, pyridines, amines) < S-donor solvents (thioethers, thioamides). Applications of this softness scale of solvents have been reported [285].

The donor properties of soft EPD solvents have also been described by the softness parameter *SP* of Gritzner [290, 303]. This parameter is based on the standard molar Gibbs energies of transfer of soft Ag^+ ions from benzonitrile as a reference solvent to other soft solvents and should only be used for soft solute/soft solvent interactions. Further solvent softness parameters based on the Raman IR absorption of the symmetrical stretching vibration of the Hg–Br bond in $HgBr_2$ have been developed by Persson *et al.* [287, 292]; *cf.* also Section 3.3.2. The relationships between these solvent softness scales have recently been reviewed [304].

7.3 Empirical Parameters of Solvent Polarity from Kinetic Measurements

Since reaction rates can be strongly affected by solvent polarity (*cf.* Chapter 5), the introduction of solvent scales using suitable solvent-sensitive chemical reactions was obvious [33, 34]. One of the most ambitious attempts to correlate reaction rates with empirical parameters of solvent polarity has been that of Winstein and his co-workers [35–37]. They found that the S_N1 solvolysis of 2-chloro-2-methylpropane (*t*-butyl chloride, *t*-BuCl) is strongly accelerated by polar, especially protic solvents; *cf.* Eq. (5-13) in Section 5.3.1. Grunwald and Winstein [35] defined a solvent "ionizing power" parameter *Y* using Eq. (7-13),

$$Y = \lg k^{t\text{-BuCl}} - \lg k_0^{t\text{-BuCl}} \tag{7-13}$$

where $k_0^{t\text{-BuCl}}$ is the first-order rate constant for the solvolysis of *t*-butyl chloride at 25 °C in aqueous ethanol (80 cL/L ethanol and 20 cL/L water; $Y = 0$) as reference solvent, and $k^{t\text{-BuCl}}$ is the corresponding rate constant in another solvent. This reaction was selected as the model process because it was believed to occur by an essentially pure S_N1 mechanism, with ionization of the C—Cl bond as the rate-determining step. Choosing a standard reaction and a reference solvent, a linear Gibbs energy relationship is then written in the familiar form of Eq. (7-14):

$$\lg(k/k_0)_{RX} = m \cdot Y + c \tag{7-14}$$

In Eq. (7-14), k and k_0 are the specific rate constants for the S_N1 solvolysis of RX (in this case *t*-BuCl) in a given solvent and in the standard solvent, respectively, m is the sensitivity of the specific rate of solvolysis of RX to changes in the solvent "ionizing power" (Y), Y is a parameter characteristic of the given solvent, and c is the intercept (zero for an ideally behaved solvolysis). Eq. (7-14) is expected to be applicable to reactions very similar to the standard reaction, that is, S_N1 substitutions. The similarity between Y and m of Eq. (7-14), and σ and ϱ of the Hammett equation (7-6) is obvious. Y values are known for some pure, mainly protic solvents and for various binary mixtures of organic solvents with water or a second organic solvent [35, 36]. Typical Y values are indicated in Table 7-1. It should be noted that the Y value of the standard solvent lies about midway between the extremes. Y values of binary mixtures are not related to solvent composition in a simple manner.

The solvolysis of *t*-butyl chloride at 120 °C was also chosen as a solvent-dependent model reaction by Koppel and Pal'm [38] in order to calculate a solvent polarity scale which is restricted to nonspecific interactions only. In order to confirm the limiting S_N1 mechanism for the solvolysis of *t*-butyl chloride, Schleyer and his co-workers [39] compared the solvolysis rates of *t*-butyl chloride and 1-bromoadamantane in a large series of solvents. They reasoned that any rate-determining elimination or nucleophilic solvent assistance in *t*-butyl chloride solvolysis will result in a failure to correlate with 1-bromoadamantane. In 1-bromoadamantane, backside nucleophilic solvent attack and elimination are impossible. An excellent correlation between solvolysis data for *t*-butyl chloride and 1-bromoadamantane has been found, indicating that *t*-butyl chloride seems to solvolyze by a limiting S_N1 mechanism, free from nucleophilic solvent participation and from rate-determining elimination. Similarly good correlations have been observed between the solvolysis rates of *t*-butyl chloride and 1-adamantyl tosylate [40] as well as 2-adamantyl tosylate [41]. The absence of any S_N2 character in the solvolysis of *t*-butyl heptafluorobutyrates in aqueous ethanol and similar solvents has been confirmed [151]. In most cases, the solvolysis rate data of *t*-butyl substrates are best explained by an S_N1 process with electrophilic solvent assistance of the leaving group in protic solvents through the formation of strong hydrogen bonds. That is, the ionization rates of *t*-butyl halides should be mainly dependent on solvent polarity and solvent electrophilicity, but not on solvent nucleophilicity [152]; *cf.* Eqs. (5-135) and (5-136) in Section 5.5.7. However, according to Bentley *et al.* [153], Kevill *et al.* [155], and Bunton *et al.* [156] it is now thought that *t*-butyl chloride reacts solvolytically with weak but significant nucleophilic solvent assistance. Only 1- and 2-adamantyl substrates seem to react by an S_N1 (limiting) mechanism due to their cage structure, which absolutely precludes nucleophilic attack by solvents from the rear. This has been concluded from the observation that the relative reactivities of *t*-butyl chloride and 1-chloroadamantane are different in nucleophilic solvents and in weakly nucleophilic solvents such as trifluoroacetic acid, hexafluoro-2-propanol, or trifluoroethanol, in which *t*-butyl chloride is abnormally unreactive [153]. See also reference [157] for a nice picture of the solvolysis of 1-bromoadamantane as compared to that of *t*-butyl bromide with and without backside solvent assistance.

The Grunwald–Winstein equation (7-14) is fairly successful in a large number of cases. Good linear relationships between $\lg k_1$ and Y are found for the solvolysis of various tertiary haloalkanes and secondary alkyl sulfonates, *i.e.* reactions which proceed by an S_N1 mechanism, as found for the standard reaction. For reactions involving borderline mechanisms (*e.g.* solvolysis of secondary haloalkanes) and for S_N2 reactions (*e.g.* solvolysis of primary haloalkanes), the application of Eq. (7-14) is less satisfactory. When solvolysis rates for different binary mixtures of solvents are correlated using Eq. (7-14), the well-known phenomenon of dispersion is often observed, that is, lines or curves of slightly different slopes are observed for each solvent system [35, 36]. In other words, the substrate parameter m is solvent dependent in these cases. If Eq. (7-14) were strictly obeyed, all the points should lie on a single straight line. These observations indicate that the reaction rate depends not only on the ionizing power of the solvent (for

Table 7-1. Empirical parameters based on kinetic measurements for solvents of decreasing polarity.

Solvents	Y [35, 36]	$\lg k_1$[a]	X [51]	$\mathscr{S}$[b]	Ω [52]
Water	3.493	−1.180	–	–	0.869[k]
Formic Acid	2.054	−0.929	–	–	–
2,2,2-Trifluoroethanol	1.045[c,d]	–	–	–	–
Formamide	0.604	–	–	–	0.825[k]
Methanol/Water (80 cL/L + 20 cL/L)	0.381	–	–	–	–
Ethanol/Water (80 cL/L + 20 cL/L)	0.000	−2.505	–	–	–
Tetra-*n*-hexylammonium benzoate	−0.39[e]	–	–	–	–
Acetone/Water (80 cL/L + 20 cL/L)	−0.673	–	–	–	–
1,4-Dioxane/Water (80 cL/L + 20 cL/L)	−0.833	–	–	–	–
Methanol	−1.090	−2.796	0.91	−1.89	0.845
Acetic acid	−1.675	−2.772	0.00	–	0.823
Ethanol	−2.033	−3.204	–	−2.02	0.718
2-Propanol	−2.73	–	–	–	–
t-Butanol	−3.26	–	–	–	–
Dimethyl sulfoxide	–	−3.738	1.6	–	–
Nitromethane	–	−3.921	–	0.041	0.680
Acetonitrile	–	−4.221	0.04	−0.328	0.692
N,*N*-Dimethylformamide	−3.5[f]	−4.298	0.8	−0.222	0.620
Acetic anhydride	–	−4.467	–	–	–
1,2-Dichloroethane	–	–	–	−0.420	0.600
Dichloromethane	–	–	–	−0.553	–
Pyridine	–	−4.670	–	–	0.595
Acetone	–	−5.067	–	−0.824	0.619
Trichloromethane	–	–	–	−0.886	–
Chlorobenzene	–	–	−1.9	−1.15	–
1,2-Dimethoxyethane	–	–	–	–	0.543
1,4-Dioxane	–	–	–	−1.43	–
Ethyl acetate	–	−5.947	–	−1.66	–
Tetrahydrofuran	–	−6.073	–	−1.54	–
Benzene	–	–	–	−1.74	0.497[g]
Tetrachloromethane	–	–	−4.8	−2.85	–
Diethyl ether	–	−7.3	–	−2.92	0.466[i]
Cyclohexane	–	–	–	−4.15	0.595[g]
Decalin	–	–	–	–	0.537[h]
Triethylamine	–	–	–	–	0.445
n-Hexane	–	–	–	*ca.* −5	–

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[a] Ionization of 4-methoxyneophyl tosylate at 75 °C [37].

[b] S_N2 reaction of tris(*n*-propyl)amine with iodomethane at 20 °C [49, 50].

[c] V. J. Shiner, W. Dowd, R. D. Fisher, S. R. Hartshorn, M. A. Kessick, L. Milakofsky, and M. W. Rapp, J. Am. Chem. Soc. *91*, 4838 (1969).

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[i] R. Braun and J. Sauer, Chem. Ber. *119*, 1269 (1986); value at 20 °C.

[k] A. Lattes, I. Rico, A. de Savignac, and A. A. Samii, Tetrahedron *43*, 1725 (1987).

which Y is a measure), but also on the nucleophilicity of the solvent. Obviously, nucleophilic solvent assistance may be relevant in reactions with increasing S_N2 characteristics. Therefore, the trends in m values suggest their usefulness in determining the extent of solvent nucleophilic participation. Those reactions which are S_N1 exhibit m values near 1.00, while values for S_N2 substrates range from 0.25 to 0.35. Values of m between these extremes are typical for secondary substrates lying in the borderline area between limiting S_N1 and pure S_N2 mechanisms. The term "S_N2(intermediate) mechanism" has been suggested for reactions where there is evidence of nucleophilic solvent assistance and evidence for a nucleophilically solvated ion pair reaction intermediate; *cf.* Eq. (5-136) in Section 5.5.7. Thus, a gradual change in mechanism going from S_N2(one-stage) through S_N2(intermediate) to an S_N1(limiting) mechanism has been postulated [41, 153]; *cf.* Section 5.5.7 for a discussion of this solvent-influenced S_N2/S_N1 mechanistic spectrum.

To account for nucleophilically solvent-assisted processes, Grunwald, Winstein *et al.* [42] later provided a four-parameter equation of the type shown in Eq. (7-15)*⁾:

$$\lg(k/k_0)_{RX} = m \cdot Y + l \cdot N + c \tag{7-15}$$

In Eq. (7-15), the additional term $l \cdot N$ involves the sensitivity l, this indicating the substrates response to changes in solvent nucleophilicity (N). As in Eq. (7-14), Y denotes the solvent ionizing power, and ethanol/water (80:20 cL/L) is again chosen as the standard solvent with $N = 0$ (and $Y = 0$) for this binary solvent mixture. The intercept c should be zero for well-behaved solvolyses. It is somewhat unfortunate that m has been retained as the sensitivity to solvent ionizing power, since, in reactions where $l \neq 0$, different values for m will be obtained depending on whether the correlation analysis is in terms of Eq. (7-14) or (7-15). Obviously, the simple Grunwald–Winstein equation (7-14) can only be used when the $l \cdot N$ term of the extended equation (7-15) makes either a negligible ($l = 0$) or constant contribution, which is then included in c. The extended Grunwald–Winstein equation (7-15) has been explicitly evaluated by both Peterson *et al.* [43] and Bentley, Schleyer *et al.* [44], using two reference substrates, one with a high sensitivity to solvent nucleophilicity (*e.g.* bromomethane [43] or methyl tosylate [44]; $l = 1.00$), and the other with a low sensitivity to solvent nucleophilicity (*e.g.* *t*-butyl chloride [43] or 2-adamantyl tosylate [44]; $l = 0.00$ and $m = 1.00$). Eq. (7-15) correlates solvolysis data for such widely varying substrates as methyl and 2-adamantyl tosylates [44].

The evaluation of the bulk nucleophilicity of solvents (N) in terms of Eq. (7-15) is more difficult than the establishment of the Y scale of solvent ionizing power according to Eq. (7-14) [305]. As already mentioned, for substrates RX which ionize without

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* The original equation was expressed as the partial differential equation [42]:

$$d \lg k = \left(\frac{\partial \lg k}{\partial Y}\right)_N dY + \left(\frac{\partial \lg k}{\partial N}\right)_Y dN$$

If the partial derivatives are constant and equal to m and l, respectively, this expression leads to Eq. (7-15).

nucleophilic solvent assistance, one can assume that $l = 0$ for solvolysis of this substrate and Eq. (7-15) simplifies to Eq. (7-14). This requirement is closely satisfied by substrates RX with R = 1- or 2-adamantyl. However, for the solvolysis of a neutral substrate RX with an anionic leaving group X^-, there is no corresponding system where $m \rightarrow 0$. In order to establish an N scale for the solvolysis of a standard substrate RX, Eq. (7-15) can be rearranged to give Eq. (7-16a), if one takes $l = 1$ by definition for this substrate:

$$N_{RX} = \lg(k/k_0)_{RX} - m_{RX} \cdot Y_x \tag{7-16a}$$

Y_x values are available for the common leaving groups X [306] and the value of $\lg(k/k_0)_{RX}$ can be determined experimentally. The difficulty is to obtain the appropriate sensitivity value m_{RX} for use in Eq. (7-16a).

Based on the reasonable assumption that primary methyl substrates should be subject to the most pronounced nucleophilic solvent assistance towards their solvolyses, methyl tosylate (MeOTs) was chosen by Bentley, Schleyer *et al.* as a standard substrate ($l = 1$) for the evaluation of N_{RX} [44, 154]. Methyl tosylate solvolyzes cleanly in a wide variety of solvents without steric hindrance. From a plot of $\lg(k/k_0)_{MeOTs}$ against Y_{OTs}, a value of $m_{RX} = 0.3$ was chosen to give Eq. (7-16b) [44, 154, 305, 307]:

$$N_{OTs} = \lg(k/k_0)_{MeOTs} - 0.3 \cdot Y_{OTs} \tag{7-16b}$$

Values of N derived in this way are designated as N_{OTs} [158] or N_{BS} [305] values; they range from −5.56 (CF_3CO_2H) to +0.2 (2-propanol). The values of Y in this equation are based on 2-adamantyl tosylate (2-AdOTs) instead of *t*-butyl chloride solvolysis in order to retain the same leaving group (TsO^-). Although it is a secondary substrate, 2-adamantyl tosylate solvolyzes according to an S_N1(limiting) or k_c mechanism*) through the rate-determining formation of contact ion pairs without detectable nucleophilic solvent assistance [154]. The Y_{OTs} scale of solvent ionizing power spans a rate range of over eight orders of magnitude, from $Y_{OTs} = +4.57$ (CF_3CO_2H) to −3.74 (*t*-butanol) [158], and can even be extended to aqueous sulfuric acid as the ionizing medium [159]. The Y_{OTs} scale correlates *non*linearly with the original $Y_{t\text{-BuCl}}$ values [158]. Using the extended Eq. (7-16c), N_{OTs} values in conjunction with Y_{OTs} values gave good to excellent correlations for the solvolyses of a great variety of sulfonates [44, 154].

$$\lg(k/k_0)_{ROTs} = m \cdot Y_{OTs} + l \cdot N_{OTs} + c \tag{7-16c}$$

In spite of these successful correlations, the choice of $m_{RX} = 0.3$ for use in Eq. (7-16b) was criticized for some reasons; see references [160, 305] for details. Therefore, Kevill *et al.* have introduced a considerable improvement by making a fundamental

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* According to Winstein, real solvolyses are either nucleophilically solvent assisted (designated k_s and including both substitution and elimination processes) or anchimerically assisted (designated k_Δ), with k_c representing the hypothetical limit which is reached when nucleophilic solvent assistance and anchimeric assistance approach zero. *Anchimeric* assistance (from the Greek *anchi* + *meros*, neighbouring parts) means neighbouring group participation during the ionization step; *cf.* Eq. (7-20) for an example.

change in the type of substrate undergoing S_N1 solvolysis; see [160, 305] and references cited therein. Using substrates of the type RX^+ (*i.e.* sulfonium and oxonium salts), the anionic leaving group X^- of RX is replaced by a neutral molecule leaving group according to $R{-}X^+ \rightarrow R^+ + X$. With a neutral leaving group X, the mY term in Eq. (7-16b) can be ignored. According to the Hughes–Ingold rules, the positive charge is dispersed during the activation process and a small but significant rate decrease with increasing solvent polarity is to be expected; see reaction type (b) in Table 5-4 in Section 5.3.1. Among the 'onium salts studied (*e.g.* triethyloxonium hexafluorophosphate [160], *etc.*), the *S*-methyl-dibenzothiophenium ion ($MeDBTh^+$; as its trifluoromethanesulfonate) has been found to be the most useful because of its structural analogy to methyl tosylate (MeX compared to MeX^+); *cf.* Eq. (7-16b). With this new standard substrate, a new solvent nucleophilicity scale (N_T) was defined by Kevill *et al.* [305, 308], as expressed in Eq. (7-17):

$$N_T = \lg(k/k_0)_{MeDBTh^+} \tag{7-17}$$

In Eq. (7-17), k and k_0 are the specific rate constants of S_N1 solvolysis of the *S*-methyl-dibenzothiophenium ion in a given solvent and in a standard solvent ($EtOH/H_2O$, 80:20 cL/L; $N_T = 0$), respectively. N_T values are known for 37 pure and binary solvents and span a range from $N_T = -5.26$ [$(CF_3)_2CHOH/H_2O$, 97:3 cg/g] to +0.37 (EtOH) [305, 308]. The N_T solvent nucleophilicity scale can be used directly to correlate the solvolytic behaviour of other RX^+ substrates with a neutral nucleofuge, and also in applications of the extended Grunwald–Winstein equation (7-15). Many examples of the use of N_T values in the correlation of specific rates of solvolysis of a variety of RX and RX^+ substrates are given in reference [305].

Interestingly, an analysis of the specific rate constants for *t*-butyl chloride solvolysis in 46 solvents based on the extended Grunwald–Winstein equation (7-15), using Y_{Cl} and N_T, gives a very good correlation (correlation coefficient $r = 0.988$) with values of $m = 0.86$, $l = 0.38$, and $c = 0$ [309]. This result confirms the involvement of nucleophilic solvation of the developing carbocation in the S_N1 solvolysis of *t*-butyl chloride, in addition to the strong electrophilic solvation of the anionic leaving group [305].

Very precise experimental studies clearly show that Winstein's original Y values, as defined by Eq. (7-14), do not apply to leaving groups other than the *chloride* ion [153, 158–166], most probably due to the variable amount of specific solvation of different leaving groups by solvent molecules. If allowance is made for different leaving groups X, the solvolytic rate data of substrates RX can be correlated with data for a reference compound according to the general Eq. (7-18).

$$\lg(k/k_0)_{RX} = m \cdot Y_X \tag{7-18}$$

Y_X values for different leaving groups X have been defined using $m = 1.00$ for the solvolyses of 1-adamantyl substrates (X = Cl [153], Br [153], I [161], picrate [162], and $^{\oplus}SMe_2$ [163]) and 2-adamantyl substrates (X = OTs [44, 158], $OClO_3$ [162, 166], OSO_2CF_3 = OTf [164, 166], and picrate [166]). Additional Y_{OTs} values have been obtained from solvolyses of 1-adamantyl tosylate (X = OTs [158, 162]). Further Y_{OTf} values for trifluoromethanesulfonates (triflates) have been determined from the solvolysis of 7-norbornyl triflate [165]. This range of Y_X values ensures that specific leaving group solvation effects do not interfere with mechanistic deductions from the solvolysis rate data. Sufficient data are now available to evaluate trends in the various Y_X scales. A comparison of the Y_X scales and a discussion of the correlations between them can be found in references [166, 306]. For example, the relative rates for the S_N1 solvolyses of different bridgehead substrates *having the same leaving group* are found to be almost solvent-independent [167].

An analysis of Winstein's Y and N values and their modifications in terms of Kamlet and Taft's linear solvation energy relationship (*cf.* Section 7.7) has been given by Abraham *et al.* [288].

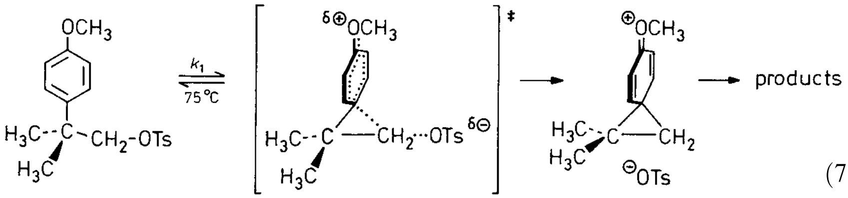
The medium influence on the solvolyses of a variety of further substrates, *i.e.* benzylic [310–313], allylic and propargylic compounds [312], as well as very crowded tertiary haloalkanes [314], has been studied and analyzed in the framework of the extended Grunwald–Winstein equation (7-15).

A four-parameter relationship (7-19) similar to Eq. (7-15) was proposed by Swain *et al.* in 1955 [45].

$$\lg(k/k_0) = c_1 \cdot d_1 + c_2 \cdot d_2 \tag{7-19}$$

d_1 and d_2 are measures of solvent nucleophilicity and electrophilicity, respectively, and c_1 and c_2 measure the substrate's sensitivity to these solvent properties. The rate constant k_0 refers to the reaction in the standard solvent, 80:20 cL/L ethanol/water. This approach is essentially statistical since, in contrast to Eq. (7-15), four rather than two parameters (m and l) are varied. Numerous values of d_1, d_2, c_1, and c_2 were calculated, using scales based on certain standard systems, in such a way as to fit a large number of experimental rate constants [45]. Although a satisfactory correlation was achieved for a wide range of solvents and substrates, this approach has been criticized for a lack of connection with chemical reality [42, 46]. Thus, the substrate factors c_1 and c_2 are of little mechanistic significance, *e.g.* *t*-butyl chloride has a higher c_1 value than bromomethane, suggesting that bromomethane (S_N2 substrate) should be less sensitive to solvent nucleophilicity than *t*-butyl chloride (S_N1 substrate). Overall, this treatment was not very successful and Swain *et al.* later conceded that the quantitative justification for the critical subsidiary conditions chosen for the iterative calculation technique used was questionable [265].

An alternative model system, potentially superior to *t*-butyl chloride in the evaluation of solvent ionizing power, is based on the specific rate of anchimeric, β-aryl assisted solvolysis or decomposition of 4-methoxyneophyl tosylate at 75 °C according to Eq. (7-20) [37]. Use of this compound avoids some practical disadvantages of *t*-butyl



(7-20)

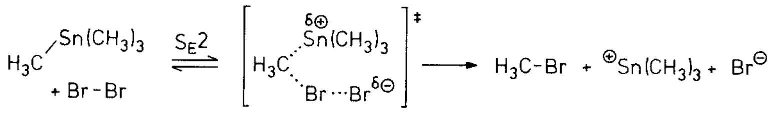
chloride: *t*-butyl chloride, being rather volatile, is troublesome to weigh accurately; it reacts extremely rapidly in highly polar solvents, and its solvolysis rate constant cannot usually be determined in nonhydroxylic solvents. Therefore, Winstein *et al.* [37] put forward the values of lg k_1 for the ionization of 4-methoxyneophyl tosylate as a reference reaction suitable for measuring solvent polarity even in fairly nonpolar and non-HBD solvents (*cf.* Table 7-1)[*]. The lg k_1 (or lg k_{ion}) scale is equivalent to the Y scale for protic solvents and has been extended to non-HBD solvents, for which Y values are not available. Although a primary substrate, 4-methoxyneophyl tosylate is believed to solvolyze through concerted anchimeric β-aryl participation without nucleophilic solvent interference and internal ion-pair return [37]. A more sophisticated picture of solvent effects on β-arylalkyl tosylate solvolyses has been given by Schleyer *et al.* He demonstrated that primary and secondary β-arylalkyl substrates solvolyze through competition between discrete β-aryl assisted (k_Δ) and β-aryl non-assisted reaction pathways (k_s), each of which leads to distinct sets of products [168]. This is due to the fact that the neighbouring aryl group and the solvent molecules are in competition to displace the leaving group. By decreasing the solvent nucleophilicity as well as introducing electron-releasing substituents in the aryl group, the kinetic influence of the β-aryl group becomes more noticeable. Therefore, the lg k_1 (or lg k_{ion}) values, as measures of the solvent ionizing power, are subject to the same limitations as found for the Y values; *cf.* the preceding discussion of Eq. (7-14).

In addition to the application of S_N1 reactions as model reactions for the evaluation of solvent polarity, Drougard and Decroocq [48] suggested that the value of lg k_2 for the S_N2 Menschutkin reaction of tri-*n*-propylamine and iodomethane at 20 °C – termed "$\mathscr{S}$" according to Eq. (7-21) – should also be used as a general measure of solvent polarity.

$$\mathscr{S} = \lg k_2[(CH_3CH_2CH_2)_3N + CH_3I] \tag{7-21}$$

The second-order rate constants of this quaternization reaction have been determined for seventy-eight solvents by Lassau and Jungers [49, 50]. A selection from this relatively extensive solvent scale is given in Table 7-1.

Analogous to the Y scale and based on a nucleophilic substitution reaction, Gielen and Nasielski [51] suggested that a solvent polarity scale could be based on electrophilic aliphatic substitution reactions such as the reaction of bromine with tetramethyltin shown in Eq. (7-22).



(7-22)

This model reaction probably passes through a non-cyclic dipolar activated complex (S_E2 mechanism) in polar solvents, while in less polar solvents a cyclic activated complex gains importance (S_F2 mechanism) [51]. The linear Gibbs energy relationship

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[*] In his appreciation of Winstein's scientific work, Bartlett [47] proposed the term W for "Winstein parameter" for these values commonly referred to as "lg k_1" or "lg k_{ion}".

given by these authors is as follows:

$$\lg(k/k_0) = p \cdot X \tag{7-23}$$

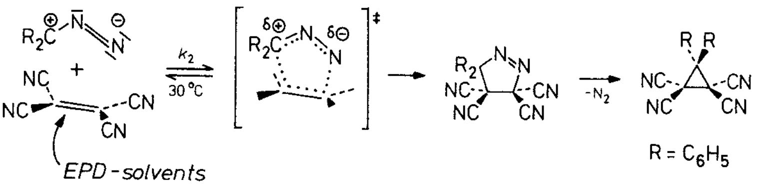
k and k_0 are the rate constants of reaction (7-22) in a given solvent and in glacial acetic acid, respectively. The latter is used as the reference solvent ($X = 0$ by definition). X is a parameter characteristic of the given solvent, and p is a parameter characteristic of the given reaction; $p = 1$ for Eq. (7-22) by definition. X values have only been determined for seven solvents to date (see Table 7-1). The two solvent scales, X and Y, are not quite in harmony, since the reaction rate is influenced by the electrophilic and nucleophilic character of the solvent to differing degrees. The electrophilic substitution reaction (7-22) is probably supported by a nucleophilic pull of the solvent on the leaving group ($-SnMe_3$). The coupling constants $^2J_{^{117}Sn-^1H}$ obtained from ^1H NMR spectra of $(CH_3)_3SnBr$ in various solvents, which can be taken as a measure of the nucleophilic character of the solvent with respect to tin, show a correlation with the X values, in agreement with this assumption [51].

The fact that the rate of some Diels–Alder [4 + 2] cycloaddition reactions is affected, albeit only slightly, by the solvent was used by Berson *et al.* [52] in establishing an empirical polarity parameter called Ω. These authors found that, in the Diels–Alder addition of cyclopentadiene to methyl acrylate, the ratio of the *endo* product to the *exo* product depends on the reaction solvent. The *endo* addition is favoured with increasing solvent polarity; *cf.* Eq. (5-43) in Section 5.3.3. Later on, Pritzkow *et al.* [53] found that not only the *endo*/*exo* product ratio but also the absolute rate of the Diels–Alder addition of cyclopentadiene to acrylic acid derivatives increases slightly with increasing solvent polarity. The reasons for this behaviour have already been discussed in Section 5.3.3. Since reaction (5-43) is kinetically controlled, the product ratio [*endo*]/[*exo*] equals the ratio of the specific rate constants, and Berson *et al.* [52] define

$$\lg(k_{endo}/k_{exo}) = \lg[endo]/[exo] \equiv \Omega \tag{7-24}$$

The values of Ω lie between 0.445 (triethylamine) and 0.869 (water), and are known for fourteen solvents (*cf.* Table 7-1). Owing to the low solubility of the reactants in polar media, an extension of this scale is limited.

Related to Diels–Alder [2 + 2]cycloadditions are 1,3-dipolar cycloadditions, which are known to be far less solvent-dependent; *cf.* Eq. (5-44) in Section 5.3.3. Nagai *et al.* [169] found that the 1,3-dipolar cycloaddition reaction of diazo-diphenylmethane to tetracyanoethene (TCNE) is an exception; it is 180 times faster in nonbasic trichloromethane than in the EPD solvent 1,2-dimethoxyethane; *cf.* Eq. (7-25). The second-order



(7-25)

rate constant decreases with increasing solvent basicity. This solvent effect can be interpreted in terms of the solute/solvent interaction between the soft Lewis acidic π-acceptor TCNE and basic EPD solvents. Thus, one of the educts is stabilized through specific solvation resulting in a corresponding rate deceleration. Using reaction (7-25) as the reference process, an empirical parameter D_π of solvent Lewis basicity for interactions with soft π-acceptors has been proposed according to Eq. (7-26):

$$\lg(k_0/k) = D_\pi \tag{7-26}$$

k_0 and k are the rate constants of reaction (7-25) at 30 °C in benzene (reference solvent with $D_\pi = 0$) and other solvents, respectively [169]. D_π values are known for 34 solvents [169]. They are relatively large for aromatic solvents (*i.e.* soft EPD solvents) compared to other empirical Lewis basicity parameters that have been determined by employing rather hard Lewis acid probes, *e.g.* $SbCl_5$-derived DN values [*cf.* Eq. (7-10)], CH_3OD-derived B values [*cf.* Eq. (7-34)], and 4-nitrophenol-derived β values [*cf.* Eq. (7-51)]. The D_π values have been applied successfully to reactions of diazo-diphenylmethane with various soft π-acceptors such as other cyano-substituted alkenes as well as quinones [170].

Finally, it should be mentioned that the solvent-dependent intramolecular Beckman–Chapman rearrangement of *anti*-methylketoxime *O*-picrates, $H_3C(R)C{=}N{-}OX$ (*e.g.* with $R = 1$-adamantyl and $X = 2,4,6$-trinitrophenyl), has been proposed as a standard reaction for measuring solvent polarities [315]. This anionotropic sextet rearrangement proceeds 62 times faster in dimethyl sulfoxide than in tetrahydrofuran. The solvent-dependent rate-determining step is the migration of R to nitrogen with simultaneous loss of the phenolate XO^- as a leaving group, to yield a nitrilium ion as an intermediate. The advantages of this probe reaction have been discussed [315].

7.4 Empirical Parameters of Solvent Polarity from Spectroscopic Measurements

Spectroscopic parameters of solvent polarity have been derived from solvent-sensitive standard compounds absorbing radiation in spectral ranges corresponding to UV/Vis, IR, ESR, and NMR spectra (*cf.* Chapter 6) [1–9]. The first suggestion that solvatochromic dyes should be used as indicators of solvent polarity was made by Brooker *et al.* [54] in 1951, but Kosower [5, 55] in 1958 was the first to set up a comprehensive solvent scale.

Since then, solvent-dependent absorptions of a great variety of compounds have been studied as potential reference processes for establishing empirical scales of solvent polarity. Most approaches include negatively or positively solvatochromic dyes because they are experimentally easy to handle. The use of solvatochromic dyes as solvent polarity indicators has been reviewed [1, 2, 293–296, 316], see, in particular, reference [293]; only a few of these dyes can be mentioned in this Section.

Kosower [5, 55] has taken the longest-wavelength intermolecular charge-transfer (CT) transition of 1-ethyl-4-(methoxycarbonyl)pyridinium iodide as a model process. It exhibits a marked negative solvatochromism; *cf.* the formula of this dye and its UV/Vis absorption spectra in Fig. 6-3 in Section 6.2.1. A solvent change from pyridine to methanol causes a hypsochromic shift of the longest-wavelength CT band of $\Delta\lambda = -88$ nm ($\Delta\tilde{\nu} = +5960\ \text{cm}^{-1}$). This is due to stabilization of the electronic ground state, which is an ion pair, relative to the first excited state, which is a radical pair, with increasing solvent polarity. The general conditions for the appearance of solvatochromism have already been discussed in Section 6.2.2. Kosower defined his polarity parameter, Z, as the molar transition energy, E_T, expressed in kcal/mol, for the CT absorption band of 1-ethyl-4-(methoxycarbonyl)pyridinium iodide in the appropriate solvent according to Eq. (7-27):

$$E_T/(\text{kcal}\cdot\text{mol}^{-1}) = h\cdot c\cdot\tilde{\nu}\cdot N_A = 2.859\cdot 10^{-3}\cdot\tilde{\nu}/\text{cm}^{-1} \equiv Z \tag{7-27}$$

h is Planck's constant, c is the velocity of light, $\tilde{\nu}$ is the wavenumber of the photon which produces the electronic excitation, and N_A is Avogadro's number. A Z value of 83.6 for methanol means that a transition energy of 83.6 kcal is necessary to promote one mole of the standard dye, dissolved in methanol, from its electronic ground state to its first excited state*). The stronger the stabilizing effect of the solvent on the ground-state ion-pair as compared with the less dipolar radical pair in the excited state, the higher this transition energy and, thus, the Z value. A high Z value corresponds to high solvent polarity. The basis for the use of Z as a measure of solvent polarity has already been given in Section 6.2.1; *cf.* also [5, 55, 171, 172]. An alternative explanation for the negative solvatochromism of substituted pyridinium iodides has been given [171].

Z values cover a range from 94.6 (water) to about 60 kcal/mol (*i*-octane) and were originally measured for 21 pure solvents and 35 binary solvent mixtures [5, 56], as well as some electrolytes [57] and surfactant solutions [58]. Various authors have since gradually extended this to include 45 pure solvents. Z values for a further 41 pure solvents have been determined by Griffiths and Pugh [172], who also compiled all available Z values and their relationships with other solvent polarity scales. A selection of Z values together with some other spectroscopic solvent polarity parameters is given in Table 7-2.

There are some serious limitations in the determination of Z values. First, Z values can only be obtained by direct measurement over the solvent range trichloromethane ($Z = 63.2$ kcal/mol) to 70:30 cL/L ethanol/water ($Z = 86.4$ kcal/mol). In highly polar solvents, the long-wavelength charge-transfer band moves to such short wavelengths that it cannot be observed underneath the much stronger $\pi \rightarrow \pi^*$ absorption band of the pyridinium ion. Therefore, the Z value for water was obtained by extra-

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* For conversion according to the International System of Units, the following equations can be used:

$$1\ \text{kcal}\cdot\text{mol}^{-1} = 4.184\ \text{kJ}\cdot\text{mol}^{-1};$$

$$E_T/(\text{kJ}\cdot\text{mol}^{-1}) \quad \text{or} \quad Z/(\text{kJ}\cdot\text{mol}^{-1}) = 1.196\cdot 10^{-2}\cdot\tilde{\nu}/\text{cm}^{-1}.$$

The choice of $\text{kcal}\cdot\text{mol}^{-1}$ as unit for the Z scale is related to the usefulness of this quantity for comparison to chemical reactions and their activation energies. Since this and other parameters have been widely used in the literature, conversion of the units into $\text{kJ}\cdot\text{mol}^{-1}$ has been avoided in order to avert confusion.

polating the Z values measured for acetone/water, ethanol/water, and methanol/water mixtures to zero organic component in a plot against Winstein's Y values. Because the lines were extrapolated a considerable distance, the original Z value for water (94.6 kcal/mol) has been reexamined and a lower Z value (91.8 kcal/mol) is advocated by Griffiths and Pugh [172]. Secondly, the standard pyridinium iodide is not soluble in many nonpolar solvents. By using the more soluble 4-(*t*-butoxycarbonyl)-1-ethylpyridinium iodide and pyridine-1-oxide as secondary standards, it was possible to calculate Z values of nonpolar solvents [5, 55].

Z values are both temperature- and pressure-dependent. The CT absorption band of substituted pyridinium halides is shifted hypsochromically as the temperature of the solution is decreased [59]. Thus, Z values decrease with increasing temperature due to a lowering of the solute/solvent interactions at the higher temperature. Furthermore, it has been shown that the CT absorption band of 1-ethyl-4-(methoxycarbonyl)-pyridinium iodide is shifted bathochromically for solutions in methanol and ethanol with increasing pressure (up to 1920 bar), while for other solvents such as acetone and *N*,*N*-dimethylformamide it is shifted hypsochromically [60]. Except for the lower alcohols, the bulk solvent polarity generally increases with pressure [60].

Z values have been widely used to correlate other solvent-sensitive processes with solvent polarity, *e.g.* the $n \rightarrow \sigma^*$ absorption of haloalkanes [61], the $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ absorption of 4-methyl-3-penten-2-one [62], the $\pi \rightarrow \pi^*$ absorption of phenol blue [62], the CT absorption of tropylium iodide [63], as well as many kinetic data (Menschutkin reactions, Finkelstein reactions, *etc.* [62]). Copolymerized pyridinium iodides, embedded in the polymer chain, have also been used as solvatochromic reporter molecules for the determination of microenvironment polarities in synthetic polymers [173]. No correlation was observed between Z values and the relative permittivity ε_r or functions thereof [317]. Measurement of solvent polarities using empirical parameters such as Z values has already found favour in textbooks for practical courses in physical organic chemistry [64].

Brownstein suggested Eq. (7-28) analogous to the Hammett equation (7-6), for the general description of solvent effects [65]:

$$\lg k - \lg k_0 = \lg(k/k_0) = S \cdot R \tag{7-28}$$

k is the rate constant, equilibrium constant, or the function of a spectral shift for a reaction or absorption in the relevant solvent, and k_0 is the corresponding quantity for dry ethanol as reference solvent ($S = 0.00$ for dry ethanol by definition). S is characteristic of the solvent and R gives the susceptibility of the given property towards a change of solvent. As a standard process, Brownstein [65] chose the CT absorption of Kosower's dye [55], and assigned to it an R value of 1.00. Having chosen a standard solvent and a standard reaction, it was then possible to calculate R and S values for other reactions and solvents, respectively. From Kosower's work, 58 S values were used to determine R values for 9 reactions. In a continuation of this process, 158 S values and 78 R values were deduced, including R values for solvent-dependent UV/Vis, IR, and NMR absorptions, rates of reactions, and positions of equilibria [65]. The S values represent statistical averages of a variety of different solvent polarity parameters, including Z and Y, and therefore, cannot be related to a specific model process. In principle, this is

Table 7-2. Empirical parameters based on spectroscopic measurements for solvents of decreasing polarity (25 °C; 1013 hPa).

Solvents	$Z/(\mathrm{kcal \cdot mol^{-1}})$ [5, 55, 172]	S [65]	$\chi_R/(\mathrm{kcal \cdot mol^{-1}})$ [77]	$\chi_B/(\mathrm{kcal \cdot mol^{-1}})$ [77]	Φ [79]	G [85]	$a(^{14}\mathrm{N})/\mathrm{mT}$ [89]
Water	94.6	0.1540	–	68.9	0.545	–	1.7175
2,2,2-Trifluoroethanol	–	–	–	–	0.475	–	–
2,2,3,3-Tetrafluoro-1-propanol	86.3	–	–	–	–	–	–
1,2-Ethanediol	85.1	0.0679	40.4	–	0.295	–	1.6364
Ethanol/Water 80:20 cL/L	84.8	0.0650	–	–	–	–	–
2-Aminoethanol	84.4a)	–	–	–	–	–	–
Methanol	83.6	0.0499	43.1	63.0	0.285	–	1.6210
Formamide	83.3	0.0463	–	–	0.245	–	–
Ethanol	79.6	0.0000	43.9	60.4	0.255	–	1.6030
Acetic acid	79.2	0.0050	–	–	0.37	–	1.6420
2-Octanol	78.6a)	–	–	–	–	–	–
1-Propanol	78.3	–0.0158	44.1	–	–	–	–
Diethyleneglycol monomethyl ether	78.1a)	–	–	–	–	–	–
N-Methylacetamide	77.9b)	–	–	–	–	–	–
1-Butanol	77.7	–0.0240	44.5	56.8	–	–	1.6018
Tetrahydrothiophene-1,1-dioxide	77.5b)	–	–	–	–	–	–
2-Propanol	76.3	–0.0413	44.5	56.1	0.19	–	1.5973
Propylene carbonate	72.4a)	–	–	–	–	–	–
2-Methyl-2-propanol, *t*-Butanol	71.3	–0.1047	–	–	0.130	–	1.5860
Acetonitrile	71.3	–0.1039	45.7	53.7	0.135	93	1.5666
Nitromethane	71.2c)	–0.134	44.0	–	–	99	1.5759
Dimethyl sulfoxide	70.2	–	42.0	–	0.115	–	1.5692
N,*N*-Dimethylformamide	68.4	–0.1416	43.7	51.5	0.135	–	1.5635
N,*N*-Dimethylacetamide	66.9b)	–	43.0	–	–	–	–
Tri-*n*-hexyl-*n*-heptylammonium iodide (mp. 95.7 °C; in molten form)	66.4d)	–	–	–	–	–	–
Acetone	65.5	–0.1748	45.7	50.1	–	–	1.5527
Nitrobenzene	–	–0.218	42.6	–	–	100c)	–
Diethyleneglycol diethyl ether	65.2a)	–	–	–	–	–	–
Benzonitrile	65.0c)	–	43.3	–	–	–	–
Dichloromethane	64.7	–0.1890	44.9	47.5	–	100	1.5752

1,1,2,2-Tetrachloroethane	64.3[f]	−0.083	–	–	–	–	–
Pyridine	64.0	−0.1970	43.9	50.0	–	94	1.5608
cis-1,2-Dichloroethene	63.9[e]	–	–	–	–	–	–
1,2-Dichloroethane	63.4[f]	−0.151	–	–	–	95	1.5655
Trichloromethane	63.2	−0.2000	44.2	–	0.095	106	1.5863
Hexamethylphosphoric triamide	62.8[g]	–	–	–	0.115	–	–
1,1-Dichloroethane	62.1[f]	–	–	–	–	–	–
Triethyleneglycol dimethyl ether	61.3[c]	–	–	–	–	90[c]	–
Fluorobenzene	60.2[e]	–	–	–	–	–	–
Di-*n*-butyl ether	60.1[a]	−0.286	48.6	–	–	61	–
1,2-Dichlorobenzene	60.0[e]	–	–	–	–	–	–
Ethyl acetate	59.4[f]	−0.210	47.2	–	–	–	–
Bromobenzene	59.2[e]	−0.164	44.6	–	–	–	1.5479
1,2-Dimethoxyethane	59.1	–	–	–	–	–	1.5424
Ethoxybenzene, Phenetole	58.9[c]	–	–	–	–	89[c]	–
Tetrahydrofuran	58.8[c]	–	46.6	–	0.10	–	1.5373
Chlorobenzene	58.0[e]	−0.182	45.2	–	–	–	1.5472
2-Methyltetrahydrofuran	55.3	–	–	–	–	–	–
1,4-Dioxane	–	−0.179	48.4	–	0.115	86	1.5452
Diethyl ether	–	−0.277	48.3	–	0.08	64	1.5334
Benzene	54	−0.215	46.9	–	0.02	80	1.5404
Toluene	–	−0.237	47.2	41.7	–	74	1.5347
Carbon disulfide	–	−0.240	–	–	–	74	1.5289
Tetrachloromethane	–	−0.245	48.7	–	−0.01	69	1.5331
Triethylamine	–	−0.285	49.3	–	–	62	–
n-Hexane	–	−0.337	50.9	–	0.07	44	1.5134
Cyclohexane	–	−0.324	50.0	–	0.035	49	–
Gas phase	–	−0.556	–	–	–	0	–

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[a] W. N. White and E. F. Wolfarth, J. Org. Chem. *35*, 2196 (1970).

[b] R. S. Drago, D. M. Hart, and R. L. Carlson, J. Am. Chem. Soc. *87*, 1900 (1965); R. S. Drago and K. F. Purcell, in T. C. Waddington (ed.): *Non-Aqueous Solvent Systems*, Academic Press, London, New York, 1965, p. 211 ff.

[c] J. F. King and R. G. Pews, Can. J. Chem. *43*, 847 (1965).

[d] J. E. Gordon, J. Am. Chem. Soc. *87*, 4347 (1965).

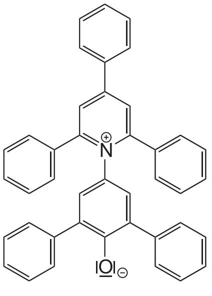
[e] C. Walling and P. J. Wagner, J. Am. Chem. Soc. *86*, 3368 (1964).

[f] P. H. Emslie and R. Foster, Rec. Trav. Chim. Pays-Bas *84*, 255 (1965).

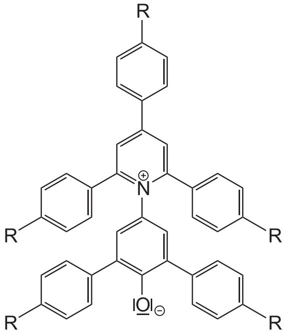
[g] J. E. Dubois and A. Bienvenüe, Tetrahedron Lett. *1966*, 1809.

an interesting attempt at generalization but many of the correlations used to calculate *R* and *S* values are rather poor. It would seem that too many different solvent-dependent processes are being mixed-up and treated in an oversimplified way.

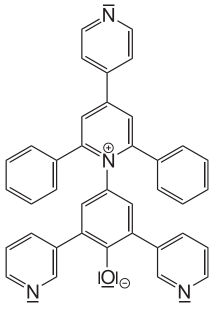
The practical limitations in the *Z*-value approach can be overcome by using pyridinium *N*-phenolate betaine dyes such as *(44)* as the standard probe molecule. They exhibit a negatively solvatochromic $\pi \rightarrow \pi^*$ absorption band with intramolecular charge-transfer character; *cf.* discussion of this dye in Section 6.2.1, its UV/Vis spectrum in Fig. 6-2, and its dipole moment in the electronic ground and excited states mentioned in Table 6-1, dye no. 12.



(44)



(45): R= $-C(CH_3)_3$
(46): R= $-CF_3$



(47)

Dimroth and Reichardt [66] have proposed a solvent polarity parameter, $E_T(30)$, based on the transition energy for the longest-wavelength solvatochromic absorption band of the pyridinium *N*-phenolate betaine dye *(44)* (dye no. 30 in reference [66]). According to Eq. (7-27), the $E_T(30)$ value for a solvent is simply defined as the transition energy of the dissolved betaine dye *(44)* measured in kcal/mol [2, 66–68, 293] (for conversion into SI units, see the footnote on page 412). The major advantage of this approach is that the solvatochromic absorption band is at longer wavelengths for *(44)* than for Kosower's dye, generating an extraordinarily large range for the solvatochromic behaviour: from $\lambda = 810$ nm, $E_T(30) = 35.3$ kcal/mol, for diphenyl ether, to $\lambda = 453$ nm, $E_T(30) = 63.1$ kcal/mol, for water. Since the greater part of this solvatochromic range lies within the visible region of the spectrum, it is even possible to make a visual estimation of solvent polarity. For example, the solution colour of *(44)* is red in methanol, violet in ethanol, green in acetone, blue in isoamyl alcohol, and greenish-yellow in anisole [66]. A remarkable feature of these solution colour changes is that nearly every colour of the visible spectrum can be obtained by employing suitable binary mixtures of solvents of different polarity. A description of nice illustrative test-tube experiments and visual classroom demonstrations of solvent polarities by means of betaine dye *(44)* (which is commercially available) is given in a series of papers published in the *Journal of Chemical Education* [318–322]. To date, the betaine dye *(44)* holds the world record in solvatochromism with a direct experimentally observed hypsochromic shift of $\Delta\lambda = -357$ nm (ΔE_T *ca.* 28 kcal/mol = 117 kJ/mol) for a solvent change from diphenyl ether to water. Owing to this exceptionally large displacement of the solvatochromic absorption band, the $E_T(30)$ values provide an excellent and very sensitive characterization of the polarity of solvents, high $E_T(30)$ values corresponding to high solvent polarity.

$E_T(30)$ values have been determined for more than 360 pure organic solvents [66, 174–176, 293] and for a great number of binary solvent mixtures [68–72, 124, 177–192, 293]. A collection of $E_T(30)$ values for pure organic solvents, representing the most comprehensive empirical solvent polarity scale so far known, is given in Table 7-3*). Some discrepancies between the $E_T(30)$ values given in Table 7-3 and those published in earlier papers [66, 174] can be explained by improved techniques for the purification of organic solvents and obtaining UV/Vis spectra of highly diluted betaine solutions [175, 176]. $E_T(30)$ values are also known for various binary solvent mixtures: alcohols/water [68, 124, 177–181], ethers/water [68, 70, 72, 180, 182], dipolar non-HBD solvents/water [68, 70, 178, 180, 181, 183, 184], alcohols/alcohols [180, 184–186], dipolar non-HBD solvents/alcohols [183–187], and numerous other solvent/solvent combinations [68–72, 124, 177–190]. $E_T(30)$ values of binary solvent mixtures with limited mutual miscibility have also been investigated [191]. A compilation of about 40 publications dealing with $E_T(30)$ values of binary solvent mixtures and others concerning the $E_T(30)$ values of electrolytes as well as microheterogeneous media (*e.g.* micellar solutions) is given in reference [293]. For other reviews on the polarity of binary solvent mixtures, see references [192].

The primary standard betaine dye *(44)* is only sparingly soluble in water and less polar solvents; it is insoluble in nonpolar solvents such as aliphatic hydrocarbons. In order to overcome the solubility problems in nonpolar solvents, the more lipophilic penta-*t*-butyl-substituted betaine dye *(45)* has additionally been used as a secondary reference probe [174]. The excellent linear correlation between the E_T values of the two dyes allows the calculation of $E_T(30)$ values for solvents in which the solvatochromic indicator dye *(44)* is not soluble. Introduction of electron-withdrawing substituents (*e.g.* Cl [323], F, CF_3, C_6F_{13} [324]) in the betaine molecule reduces the basicity of its phenolate moiety, which allows the direct determination of $E_T(30)$ values for somewhat more acidic solvents. Moreover, the lipophilic and fluorophilic penta(trifluoromethyl)-substituted betaine dye *(46)* is more soluble in nonpolar solvents (*e.g.* hexafluorobenzene) than the standard dye *(44)* [324]. Conversely, the solubility in aqueous media can be improved through replacement of some of the peripheral hydrophobic phenyl groups in *(44)* by more hydrophilic pyridyl groups, to yield the more water-soluble betaine dye *(47)* [325]. The E_T values of these new secondary standard betaine dyes correlate linearly with the $E_T(30)$ values of *(44)*, which allows the calculation of $E_T(30)$ values for solvents in which only betaine dyes *(45)–(47)* are sufficiently stable and soluble for the UV/Vis spectroscopic measurements [324, 325].

Unfortunately, $E_T(30)$ values have by definition the dimension of kcal/mol, a unit which should be abandoned in the framework of SI units. Therefore, the use of so-called normalised E_T^N values has been recommended [174]. They are defined according to Eq. (7-29), using water and tetramethylsilane (TMS) as extreme reference solvents.

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* A compilation of the 100 most important organic solvents together with their physical constants in order of decreasing E_T^N values can be found in the Appendix (Table A-1).

Table 7-3. Empirical parameters of solvent polarity, $E_T(30)$ [*cf.* Eq. (7-27)] and normalized E_T^N values [*cf.* Eq. (7-29)], derived from the long-wavelength UV/Vis charge-transfer absorption band of the negatively solvatochromic pyridinium *N*-phenolate betaine dyes *(44)* and *(45)*, measured at 25 °C and 1013 hPa, for a selection of 288 solvents, taken from reference [293].

Solvents	$E_T(30)$/(kcal · mol^{-1})a)	E_T^N
Gas phase	(27.1)b)	(−0.111)
Tetramethylsilane (TMS)	(30.7)c)	*0.000*d)
Alkanes, Alkenes, Cycloalkanes, and Cycloalkenes		
2-Methylbutane	(30.9)c)	(0.006)
n-Pentane	(31.0)c)	(0.009)
n-Hexane	(31.0)c)	(0.009)
1-Hexene	(32.4)c)	(0.052)
n-Heptane	(31.1)c)	(0.012)
n-Octane	(31.1)c)	(0.012)
n-Nonane	(31.0)c)	(0.009)
n-Decane	(31.0)c)	(0.009)
n-Dodecane	(31.1)c)	(0.012)
Cyclohexane	(30.9)c)	(0.006)
Cyclohexene	(32.2)c)	(0.046)
cis-Decahydronaphthalene, *cis*-Decalin	(31.2)c)	(0.015)
1,2,3,4-Tetrahydronaphthalene, Tetralin	33.5	0.086
Vinylbenzene, Styrene	34.8	0.127
Haloalkanes and Haloalkenes		
Dichloromethane	40.7	0.309
Dibromomethane	39.4	0.269
Diiodomethane	36.5	0.179
Trichloromethane, Chloroform	39.1	0.259
Trichloro[^{2}H]methane, Deuteriochloroform	39.0	0.256
Tribromomethane, Bromoform	37.7	0.216
Tetrachloromethane	32.4	0.052
Bromoethane	37.6	0.213
1,1-Dichloroethane	39.4	0.269
1,2-Dichloroethane	41.3	0.327
1,2-Dibromoethane	38.3	0.235
1,1,1-Trichloroethane	36.2	0.170
1,1,2-Trichloroethane	40.3	0.296
1,1,2,2-Tetrachloroethane	39.4	0.269
Pentachloroethane	36.4	0.176
1,1-Dichloroethene	37.0	0.194
(*E*)-1,2-Dichloroethene	(34.2)c)	(0.108)
(*Z*)-1,2-Dichloroethene	(41.9)c)	(0.346)
Trichloroethene	35.9	0.160
Tetrachloroethene	(32.1)c)	(0.043)
1-Chloropropane	37.4	0.207
1,3-Dichloropropane	40.2	0.293
2,2-Dichloropropane	37.9	0.222
1,2,3-Trichloropropane	40.4	0.299
1,4-Dichlorobutane	39.5	0.272
Chlorocyclohexane	36.2	0.170
Arenes and Alkylarenes		
Benzene	34.3	0.111
Methylbenzene, Toluene	33.9	0.099

Table 7-3. (Continued)

Solvents	$E_T(30)/(\text{kcal} \cdot \text{mol}^{-1})$[a]	E_T^N
(Trifluoromethyl)benzene	(38.5)[c]	(0.241)
1,4-Dimethylbenzene, *p*-Xylene	33.1	0.074
1,3,5-Trimethylbenzene	(32.9)[c]	(0.068)
1,2,3,4-Tetramethylbenzene	(33.0)[c]	(0.071)
Ethynylbenzene, Phenylacetylene	37.2	0.201
Cyclohexylbenzene	34.2	0.108
1-Methylnaphthalene	(35.3)[c]	(0.142)
Haloarenes		
Fluorobenzene	37.0	0.194
1,2-Difluorobenzene	39.3	0.265
1,3-Difluorobenzene	37.3	0.204
1,4-Difluorobenzene	36.4	0.176
1,3,5-Trifluorobenzene	(33.2)[c]	(0.077)
Pentafluorobenzene	(38.4)[c]	(0.238)
Hexafluorobenzene	34.2	0.108
Chlorobenzene	36.8	0.188
1,2-Dichlorobenzene	38.0	0.225
1,3-Dichlorobenzene	36.7	0.185
1,2,4-Trichlorobenzene	36.2	0.170
Bromobenzene	36.6	0.182
Iodobenzene	36.2	0.170
1-Chloronaphthalene	37.0	0.194
Pyridines and other Heteroarenes		
Azine, Pyridine	40.5	0.302
2-Methylpyridine, 2-Picoline	38.3	0.235
4-Methylpyridine, 4-Picoline	39.5	0.272
3,4-Dimethylpyridine, 3,4-Lutidine	38.9	0.253
2,6-Dimethylpyridine, 2,6-Lutidine	36.9	0.191
2,6-Di-*t*-butylpyridine	(34.0)[c]	(0.102)
2,4,6-Trimethylpyridine, Collidine	36.4	0.176
2-Fluoropyridine	42.4	0.361
2-Chloropyridine	41.9	0.346
3-Bromopyridine	39.7	0.278
2,6-Difluoropyridine	43.3	0.389
Pentafluoropyridine	36.3	0.173
2-Cyanopyridine (30 °C)	44.2	0.417
Benzo[*b*]pyridine, Quinoline	39.4	0.269
Aliphatic and Cycloaliphatic Alcohols		
Methanol	55.4	0.762
Benzyl alcohol	50.4	0.608
Ethanol	51.9	0.654
Ethanol/Water (80:20 cL/L)	53.7	0.710
(±)-1-Phenylethanol	46.7	0.494
2-Phenylethanol	49.5	0.580
2-Methoxyethanol	52.0	0.657
2-Ethoxyethanol	51.0	0.627
2-(*n*-Butoxy)ethanol	50.0	0.596
2-Mercaptoethanol	53.6	0.707
2-Aminoethanol	51.8	0.651
2-Cyanoethanol	59.6	0.892

Table 7-3. (Continued)

Solvents	$E_T(30)/(\text{kcal} \cdot \text{mol}^{-1})$[a)]	E_T^N
2-Chloroethanol	55.1	0.753
2,2,2-Trifluoroethanol	59.8	0.898
2,2,2-Trichloroethanol	54.1	0.722
1-Propanol	50.7	0.617
2,2,3,3-Tetrafluoro-1-propanol	59.4	0.886
3-Phenyl-1-propanol	48.5	0.549
2-Propen-1-ol, Allyl alcohol	51.9	0.654
2-Propyn-1-ol, Propargyl alcohol	55.7	0.772
2-Propanol	48.4	0.546
1,1,1,3,3,3-Hexafluoro-2-propanol, HFIP	62.1[e)]	0.969
(±)-1-Methoxy-2-propanol	48.6	0.552
(±)-1-Amino-2-propanol	50.1	0.599
1-Butanol	49.7	0.586
(±)-2-Amino-1-butanol	50.2	0.602
(±)-2-Butanol	47.1	0.506
2-Methyl-1-propanol, *i*-Butanol	48.6	0.552
2-Methyl-2-propanol, *t*-Butanol (30 °C)	43.3	0.389
1-Pentanol, *n*-Amyl alcohol	49.1	0.568
(±)-2-Pentanol, *sec*-Amyl alcohol	46.5	0.488
3-Pentanol	45.7	0.463
(±)-2-Methyl-1-butanol	48.0	0.534
3-Methyl-1-butanol, *i*-Amyl alcohol	49.0	0.565
2-Methyl-2-butanol, *t*-Pentanol	41.0	0.318
(±)-3-Methyl-2-butanol	45.7	0.463
1-Hexanol	48.8	0.559
1-Heptanol	48.5	0.549
3-Ethyl-3-pentanol	38.5	0.241
2,4-Dimethyl-3-pentanol	40.1	0.290
1-Octanol	48.1	0.537
1-Nonanol	47.8	0.528
3-Ethyl-2,4-dimethyl-3-pentanol	37.9	0.222
1-Decanol	47.7	0.525
1-Undecanol	47.6	0.522
1-Dodecanol	47.5	0.519
Cyclopentanol	47.0	0.503
Cyclohexanol	47.2	0.509
2-(Hydroxymethyl)furan, Furfuryl alcohol	(50.3)[c)]	0.605
2-(Hydroxymethyl)tetrahydrofuran	50.3	0.605
Aliphatic Polyalcohols		
Ethane-1,2-diol, Glycol	56.3	0.790
(±)-Propane-1,2-diol	54.1	0.722
Propane-1,3-diol	54.9	0.747
Propane-1,2,3-triol, Glycerol	57.0	0.812
(±)-Butane-1,2-diol	52.6	0.676
(±)-Butane-1,3-diol	52.8	0.682
Butane-1,4-diol	53.5	0.704
Butane-2,3-diol (mixture of *meso* and *rac* form)	51.8	0.651
Pentane-1,5-diol	51.9	0.654
Diethylene glycol	53.8	0.713
Triethylene glycol	52.8	0.682
Tetraethylene glycol	52.2	0.664
Tris(2-hydroxyethyl)amine, Triethanolamine	55.4	0.762

Table 7-3. (Continued)

Solvents	$E_T(30)/(\text{kcal} \cdot \text{mol}^{-1})$[a)]	E_T^N
Aromatic Alcohols (Phenols)		
Hydroxybenzene, Phenol	53.4	0.701
2-Methylphenol, *o*-Cresol	51.9	0.654
3-Methylphenol, *m*-Cresol	52.4	0.670
4-Methylphenol, *p*-Cresol	53.3	0.697
2,4-Dimethylphenol, 2,4-Xylenol	50.3	0.605
2,4-Di-*t*-butylphenol	46.2	0.478
2,6-Di-t-butylphenol	41.8	0.343
2-Chlorophenol	54.7	0.741
4-Chlorophenol	54.4	0.731
2-(Methoxycarbonyl)phenol, Methyl salicylate	45.4	0.454
2-(Phenoxycarbonyl)phenol, Phenyl salicylate	41.9	0.346
Aliphatic, Cycloaliphatic and Aromatic Ethers, Thioethers, and Acetals		
Diethyl ether	34.5	0.117
Ethyl vinyl ether	36.2	0.170
Di-*n*-propyl ether	34.0	0.102
Di-*i*-propyl ether	(34.1)[c)]	(0.105)
Di-*n*-butyl ether	(33.0)[c)]	(0.071)
t-Butyl methyl ether	34.7	0.124
Dimethoxymethane	35.8	0.157
Diethoxymethane	33.9	0.099
1,2-Dimethoxyethane	38.2	0.231
Diethylene glycol dimethyl ether, Diglyme	38.6	0.244
Diethylene glycol diethyl ether	37.5	0.210
Triethylene glycol dimethyl ether, Triglyme	38.9	0.253
(±)-Methyloxirane, Propylene oxide	39.8	0.281
(±)-2-(Chloromethyl)oxirane, Epichlorohydrin	44.5	0.426
Oxole, Furan	(36.0)[c)]	0.164
Oxolane, Tetrahydrofuran	37.4	0.207
(±)-Tetrahydro-2-methylfuran	36.5	0.179
Thiole, Thiophene	35.4	0.145
Thiolane, Tetrahydrothiophene	36.7	0.185
1,3-Dioxolane	43.1	0.383
Oxane, Tetrahydropyran	36.2	0.170
1,4-Dioxane	36.0	0.164
Methoxybenzene, Anisole	37.1	0.198
(Methylthio)benzene, Thioanisole	37.0	0.194
Ethoxybenzene, Phenetole	36.6	0.182
1,2-Dimethoxybenzene, Veratrole	38.4	0.238
Dibenzyl ether	36.3	0.173
Diphenyl ether (30 °C)	35.3	0.142
Aliphatic, Cycloaliphatic, and Aromatic Ketones		
Propanone, Acetone	42.2	0.355
1,1,1-Trichloroacetone	45.9	0.469
2-Butanone	41.3	0.327
2-Pentanone	41.1	0.321
3-Pentanone	39.3	0.265
3-Methyl-2-butanone, *i*-Propyl methyl ketone	40.9	0.315
2-Hexanone	40.1	0.290
4-Methyl-2-pentanone, *i*-Butyl methyl ketone	39.4	0.269

Table 7-3. (Continued)

Solvents	$E_T(30)/(\text{kcal} \cdot \text{mol}^{-1})$[a)]	E_T^N
3,3-Dimethyl-2-butanone, *t*-Butyl methyl ketone	39.0	0.256
4-Heptanone	38.9	0.253
2,4-Dimethyl-3-pentanone, Di-*i*-propyl ketone	38.7	0.247
5-Nonanone, Di-*n*-butyl ketone	37.5	0.210
2,6-Dimethyl-4-heptanone, Di-*i*-butyl ketone	38.0	0.225
Cyclopentanone	39.4	0.269
Cyclohexanone	39.8	0.281
Phenylethanone, Acetophenone	40.6	0.306
Pentane-2,4-dione, Acetylacetone	49.2	0.571
Carboxylic acids		
Formic acid	(54.3)[f)]	(0.728)
Acetic acid	(51.7)[f)]	(0.648)
Propionic acid	(50.5)[f)]	(0.611)
Aliphatic, Cycloaliphatic, and Aromatic Esters		
Methyl formate	41.9	0.346
Ethyl formate	40.9	0.315
Methyl acetate	38.9	0.253
Methyl trichloroacetate	39.6	0.275
Ethyl acetate	38.1	0.228
Ethyl chloroacetate	39.4	0.269
Ethyl trichloroacetate	38.7	0.247
Vinyl acetate	38.0	0.225
n-Propyl acetate	37.5	0.210
n-Butyl acetate	38.5	0.241
Methyl acrylate	38.8	0.250
Methyl methacrylate	37.9	0.222
4-Butyrolactone	44.3	0.420
Dimethyl carbonate	38.2	0.232
Diethyl carbonate	36.7	0.185
1,3-Dioxolane-2-one, Ethylene carbonate (40 °C)	48.6	0.552
(±)-4-Methyl-1,3-dioxolane-2-one, (±)-Propylene carbonate	46.0	0.472
Glycerol triacetate, Triacetin	40.4	0.299
Ethyl benzoate	38.1	0.228
Dimethyl phthalate	40.7	0.309
Di-*n*-butyl phthalate	39.5	0.272
Ethyl acetoacetate	49.4	0.577
(*S*)-(−)-Ethyl lactate	51.1	0.630
Amides, Thioamides, and Cyanamides		
Formamide	55.8	0.775
N-Methylformamide	54.1	0.722
N,*N*-Dimethylformamide, DMF	43.2	0.386
N,*N*-Dimethylthioformamide	44.0	0.410
N-Methylformanilide	40.8	0.312
N-Methylacetamide (30 °C)	52.0	0.657
N,*N*-Dimethylacetamide, DMAC	42.9	0.377
N,*N*-Diethylacetamide	41.4	0.330
1-Methylpyrrolidine-2-one	42.2	0.355
1-Methylpyrrolidine-2-thione	42.8	0.373
1-Ethylpyrrolidine-2-one	41.6	0.336

Table 7-3. (Continued)

Solvents	$E_T(30)/(\text{kcal} \cdot \text{mol}^{-1})$[a)]	E_T^N
1-Cyclohexylpyrrolidine-2-one	40.4	0.299
N,*N*-Dimethylcyanamide	43.8	0.404
N,*N*-Diethylcyanamide	43.3	0.389
N,*N*-Di-*i*-propylcyanamide	42.0	0.349
1-Pyrrolidinecarbonitrile, *N*-Cyanopyrrolidine	42.6	0.367
1-Piperidinecarbonitrile, *N*-Cyanopiperidine	42.1	0.352
4-Morpholinecarbonitrile, *N*-Cyanomorpholine	42.8	0.373
Tetra-N-alkyl-substituted Ureas		
1,1,3,3-Tetramethylurea	40.9	0.315
1,1,3,3-Tetramethylguanidine	39.3	0.265
1,3-Dimethylimidazolin-2-one, Dimethyl ethylene urea, DMEU	42.5	0.364
Hexahydro-1,3-dimethyl-2-oxopyrimidine, Dimethyl propylene urea, DMPU	42.1	0.352
Aliphatic and Aromatic Nitriles		
Ethanenitrile, Acetonitrile	45.6	0.460
Trichloroacetonitrile	40.0	0.287
Propanenitrile, Propionitrile	43.6	0.398
Cyanoethene, Acrylonitrile	46.7	0.494
n-Butanenitrile, Butyronitrile	42.5	0.364
(Cyanomethyl)benzene, Phenylacetonitrile	42.7	0.370
Cyanobenzene, Benzonitrile	41.5	0.333
Nitroalkanes and Nitroarenes		
Nitromethane	46.3	0.481
Nitroethane	43.6	0.398
Nitrocyclohexane	39.6	0.275
Nitrobenzene	41.2	0.324
Aliphatic, Cycloaliphatic, and Aromatic Amines		
2-Amino-2-methylpropane, *t*-Butylamine	(36.5)[c)]	(0.179)
1,2-Diaminoethane	42.0	0.349
Diethylamine	35.4	0.145
Triethylamine	(32.1)[c)]	(0.043)
Tris(*n*-butyl)amine	(32.1)[c)]	(0.043)
Azolidine, Pyrrolidine	39.1	0.259
Hexahydropyridine, Piperidine	35.5	0.148
Tetrahydro-1,4-oxazine, Morpholine	41.0	0.318
Aminobenzene, Aniline	44.3	0.420
N-Methylaniline	42.5	0.364
N,*N*-Dimethylaniline	36.5	0.179
Phosphorus Compounds (Phosphates)		
Trimethyl phosphate	43.6	0.398
Triethyl phosphate	41.7	0.324
Tri-*n*-propyl phosphate	40.5	0.302
Tri-*n*-butyl phosphate	38.9	0.253
Hexamethylphosphoric acid triamide, HMPT	40.9	0.315
Hexamethylphosphorothioic acid triamide, HMPTS (30 °C)	39.5	0.272
Methylphosphonic acid bis(dimethylamide)	42.3	0.358

Table 7-3. (Continued)

Solvents	$E_T(30)/(\text{kcal} \cdot \text{mol}^{-1})$[a]	E_T^N
Sulfur Compounds (Sulfoxides, Sulfones, Sulfamides)		
Carbon disulfide	32.8	0.065
Dimethyl sulfoxide, DMSO	45.1	0.444
Tetrahydrothiophene 1,1-dioxide, Sulfolane	44.0	0.410
(±)-Tetrahydro-3-methylthiophene 1,1-dioxide, 3-Methylsulfolane	43.0	0.380
N,*N*,*N′*,*N′*-Tetraethylsulfamide, TES	41.0	0.318
Miscellaneous Solvents		
Dimethylammonium *N*,*N*-dimethylcarbamate, Dimcarb	57.2	0.818
Carbon dioxide (in its liquid and supercritical state):		
At 24 °C and 69 bar	(34.5)[c,g]	(0.117)
At 40 °C and 400 bar	(32.2)[c,h]	(0.046)
t-Butyl hydroperoxide	49.7	0.586
3-Methyloxazolidin-2-one	44.9	0.438
3-Methyl-1,2,3-oxazolium-5-olate, 3-Methylsydnone (40 °C)	49.2	0.571
3-*n*-Propyl-1,2,3-oxadiazolium-5-olate, 3-*n*-Propylsydnone	50.1	0.599
(+)-(2*S*,3*S*)-Bis(dimethylamino)-2,3-dimethoxybutane, DDB	36.6	0.182
Water and Heavy Water		
Water	63.1	*1.000*[d]
Deuterium oxide (99.75 cg/g)	62.8	0.991

[a] Since the standard betaine dye *(44)* was numbered 30 in the first publication [66], its molar *t*ransition *e*nergies were designated as $E_T(30)$ values.

[b] Extrapolated value. Because of the low volatility of betaine dye *(44)*, its gas-phase UV/Vis spectrum is not experimentally available; see also reference [174].

[c] The $E_T(30)$ values in parentheses are secondary values, determined by means of the more lipophilic penta-*t*-butyl-substituted betaine dye *(45)*, and calculated according to: $E_T(30)$ $[\text{kcal} \cdot \text{mol}^{-1}] = [28591/\lambda_{max}(45)(\text{nm}) - 1.808]/0.9424$, which is derived from the correlation equation: $E_T(45) = 0.9424 \cdot E_T(30) + 1.808$ ($n = 16$, $r = 0.999$, $s = 0.17$); see reference [175].

[d] By definition; *cf.* Eq. (7-29).

[e] See reference [324] for the determination of the $E_T(30)$ value for HFIP.

[f] These $E_T(30)$ values in parentheses are secondary values, calculated from Kosower's Z values by means of the correlation equation: $E_T(30) = 0.752 \cdot Z - 7.87$ ($n = 15$, $r = 0.998$); see reference [172].

[g] See J. A. Hyatt, J. Org. Chem. *49*, 5097 (1984).

[h] See R. Eberhardt, S. Löbbecke, B. Neidhart, and C. Reichardt, Liebigs Ann./Recueil 1195 (1997).

$$E_T^N = \frac{E_T(\text{solvent}) - E_T(\text{TMS})}{E_T(\text{water}) - E_T(\text{TMS})} = \frac{E_T(\text{solvent}) - 30.7}{32.4} \tag{7-29}$$

Hence, the corresponding E_T^N scale ranges from 0.000 for TMS, the least polar solvent, to 1.000 for water, the most polar solvent. These E_T^N values are dimensionless numbers which are included in Table 7-3. For example, an E_T^N value of 0.500 for cyclohexanol means that this solvent exhibits 50% of the solvent polarity of water, as empirically measured by means of the standard dye *(44)*.

The major limitation of the $E_T(30)$ values is the fact that they cannot be measured for acidic solvents such as carboxylic acids. Addition of traces of an acid to solutions of *(44)* or *(45)* immediately changes the colour to pale yellow due to protonation at the phenolic oxygen atom of the dye. The protonated form no longer exhibits the long-wavelength solvatochromic absorption band. The excellent linear correlation between $E_T(30)$ and Kosower's Z values, which are available for acidic solvents, allows the calculation of $E_T(30)$ values for such solvents [174]. A further limitation has been the fact that it has not been possible to measure the absorption maximum of the standard betaine dye *(44)* in the gas phase as a reference state.

The solvents in Table 7-3 can be roughly divided into three groups according to their $E_T(30)$ or E_T^N values depending on their specific solvent/solute interactions: (i) protic (HBD) solvents (E_T^N *ca.* 0.5 ... 1.0), (ii) dipolar non-HBD solvents (E_T^N *ca.* 0.3 ... 0.5), and (iii) apolar non-HBD solvents (E_T^N *ca.* 0.0 ... 0.3). This solvent classification is confirmed by other solvent characteristics; *cf.* Fig. 3-3 in Section 3.4.

Because of the rather localized negative charge at the phenolic oxygen atom*), the standard dye *(44)* is capable of specific HBD/HBA and Lewis acid/base interactions. Therefore, in addition to the nonspecific dye/solvent interactions, the betaine dye *(44)* predominately measures the specific HBD and Lewis acidity of organic solvents. On the other hand, the positive charge of the pyridinium moiety of *(44)* is delocalized. Therefore, the solvent Lewis basicity will not be registered by the probe molecule *(44)*. If this solvent property is relevant for the system under study, other empirical measures of Lewis basicity should be used; *cf.* Section 7.7.

An analysis of the $E_T(30)$ values, using multivariate statistical methods, has been carried out by Chastrette *et al.* [193]. According to this analysis, the $E_T(30)$ values of non-HBD solvents are measures of the dipolarity and polarizability as well as the cohesion of the solvents. Another analysis of $E_T(30)$ values in terms of functions of the dielectric constant (ε_r) and refractive index (n_D) of forty non-HBD solvents has been given by Bekárek *et al.*; he emphasizes the predominant influence of the $f(\varepsilon_r)$ term on the $E_T(30)$ parameter of those solvents [194]. For further correlations of the $E_T(30)$ values with other empirical parameters of solvent polarity, see Section 7.6.

The $E_T(30)$ values of binary solvent mixtures are not related to their composition in a simple linear manner [68–72, 124, 177–192]. Most binaries behave as more or less

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* X-ray analysis of bromo-substituted betaine dye *(44)* shows that it is not planar. Not only are the five peripheral phenyl groups twisted, but also the pyridinium and phenolate rings, the latter with a mutual interplanar angle of about 65° [75a]. For the X-ray analysis of 4-(2,4,6-triphenylpyridinium-1-yl)phenolate (*i.e.* betaine dye *(44)* without the two 2,6-phenyl rings at the phenolate moiety), see reference [75b]. In this less substituted betaine dye, the pyridinium/phenolate interplanar angle is 60°.

non-ideal solvent mixtures. A monotonous, but not always linear change in $E_T(30)$ with mole fraction of one solvent component (x_s) is obtained for some alcohol/water mixtures such as CH_3OH/H_2O [68, 124, 177–178, 181], for alcohol/alcohol mixtures such as CH_3OH/C_2H_5OH [185], for dipolar non-HBD/dipolar non-HBD mixtures such as CH_3CN/DMSO [185], and for apolar non-HBD/apolar non-HBD mixtures such as C_6H_6/C_5H_5N [185].

However, addition of a small amount of a polar solvent to the betaine dye *(44)* in nonpolar solvents causes a disproportionately large hypsochromic band shift, which corresponds to an excessively large increase in $E_T(30)$. This phenomenon can easily be explained by strong preferential or selective solvation of the dipolar betaine dye by the more polar component of the binary solvent mixture; *cf.* Section 2.4. Typical examples of solvent mixtures with preferential solvation of *(44)* are 1,4-dioxane/H_2O [68, 124, 177–178, 180], C_5H_5N/H_2O [68, 124, 177], *t*-BuOH/H_2O [180], 2-(*n*-butoxy)ethanol/H_2O [180], CH_3CN/H_2O [183], *c*-C_6H_{12}/C_2H_5OH [190] and C_6H_6/C_2H_5OH [190]. More recently, a great variety of further binary solvent mixtures have been thoroughly studied by means of solvatochromic betaine dye *(44)*; see references [326–331] for a representative selection. In these cases, the $E_T(30)$ values do not in fact measure the polarity of the bulk solvent mixture but rather the micropolarity of the solvation shell on the molecular-microscopic level. Solvatochromic dyes such as *(44)* are thus a simple means for the study of the phenomenon of preferential solvation [192].

A particular interesting synergistic solvent effect has been found for some binary solvent mixtures composed of HBA and HBD solvents. For example, a graph of $E_T(30)$ against composition for the binaries $(RO)_3PO/CHCl_3$ [68], $CH_3COCH_3/CHCl_3$ [68, 183], CH_3COCH_3/CH_2Cl_2 [183], DMSO/ROH (R = *i*-Pr, *t*-Bu) [185] and CH_3CN/ROH (R = Et, *i*-Pr, *t*-Bu) [185] shows a pronounced maximum. This means that the binary solvent mixtures behave as more polar media than either of their two components! The deviations in $E_T(30)$ in these synergistic solvent mixtures are attributable to specific intermolecular solvent/solvent hydrogen bond interactions (*e.g.* $P{=}O\cdots HCCl_3$, $C{=}O\cdots HCCl_3$, $S{=}O\cdots HOR$, *etc.*), which create a new, more polar solvent system [68, 184, 187]. Relatively strong interactions between acetone and trichloromethane have been recognized many times on the basis of a variety of experimental evidence. This synergistic polarity behaviour of HBA/HBD solvent mixtures can be of particular interest in the acceleration of solvent-dependent chemical reactions.

The polarities of binary solvent mixtures with limited mutual miscibility such as *n*-BuOH/H_2O and *c*-C_6H_{12}/DMF [191] as well as of solid polymer mixtures (organic glasses) [195] have also been studied using solvatochromic probes such as the betaine dye *(44)*.

According to Langhals [184, 191, 192, 196], the $E_T(30)$ values of binary solvent mixtures can be quantitatively described by the two-parameter equation (7-30a).

$$E_T(30) = E_D \cdot \ln(c_p/c^* + 1) + E_T^\circ(30) \qquad (7\text{-}30a)$$

c_p is the molar concentration of the more polar component (*i.e.* the solvent with the higher $E_T(30)$ value) and $E_T^\circ(30)$ is the $E_T(30)$ value of the pure component with lower polarity. E_D and c^* are adjustable parameters specific for the binary solvent system under study. c^* is a threshold value defining a transition between two regions. For low concentrations of the more polar solvent ($c^* \gg c_p$), a good approximation of Eq. (7-30a) is $E_T(30) = E_D \cdot (c_p/c^*) + E_T^\circ(30)$, and the $E_T(30)$ values increase linearly with the molar concentration of the more polar solvent c_p. For high concentrations of the more polar solvent ($c^* \ll c_p$), Eq. (7-30a) can be written as $E_T(30) = E_D \cdot \ln(c_p/c^*) + E_T^\circ(30)$, and values of $E_T(30)$ correlate linearly with the logarithm of the molar concentration of the more polar solvent ln c_p. Eq. (7-30a) is valid with high precision for about 80 investigated solvent mixtures and can even be applied to more complicated solvent systems than those mentioned above [191, 192].

In contrast to Eq. (7-30a), which describes the $E_T(30)$ behaviour in binary solvent mixtures in a rather empirical way, a more rational preferential solvation model has been developed by Connors *et al.* [327] as well as by Bosch and Rosés *et al.* [328], based on the following simple two-step solvent exchange model:

$$\mathbf{I}(\mathrm{S1})_2 + 2\ \mathrm{S2} \rightleftharpoons \mathbf{I}(\mathrm{S2})_2 + 2\ \mathrm{S1}$$

$$\mathbf{I}(\mathrm{S1})_2 + \mathrm{S2} \rightleftharpoons \mathbf{I}(\mathrm{S12})_2 + \mathrm{S1}$$

where S1 and S2 indicate the two pure solvents being mixed, and S12 represents a solvent formed by interaction of solvents 1 and 2. $\mathbf{I}(\mathrm{S1})_2$, $\mathbf{I}(\mathrm{S2})_2$, and $\mathbf{I}(\mathrm{S12})_2$ represent the solvatochromic indicator betaine dye *(44)* solvated by solvents S1, S2, and S12. The two solvent-exchange processes can be characterized by two preferential solvation parameters, $f_{2/1}$ and $f_{12/1}$. They measure the tendency of the indicator dye **I** to be solvated by solvents S2 and S12 with reference to solvation by solvent 1. The preferential solvation parameters are defined as $f_{2/1} = (x_2^S/x_1^S)/(x_2^0/x_1^0)^2$ and $f_{12/1} = (x_{12}^S/x_1^S)/(x_2^0/x_1^0)$, where x_1^S, x_2^S, and x_{12}^S are the mole fractions of solvents S1, S2, and S12, respectively, in the solvation shell of the indicator dye, and x_1^0 and x_2^0 are the mole fractions of the two solvents S1 and S2 in the bulk binary solvent mixture. The normalized E_T^N polarity of the binary solvent mixture is then calculated as an average of the E_T^N values of solvents S1, S2, and S12 as follows:

$$E_T^N = x_1^S \cdot E_{T1}^N + x_2^S \cdot E_{T2}^N + x_{12}^S \cdot E_{T12}^N$$

From these equations, a general equation that relates the E_T^N value of a binary solvent mixture to the E_T^N values of the two pure solvents, the preferential solvation parameters, and the solvent composition can be derived, viz.:

$$E_T^N = \frac{E_{T1}^N(1-x_2^0)^2 + E_{T2}^N f_{2/1}(x_2^0)^2 + E_{T12}^N f_{12/1}(1-x_2^0)x_2^0}{(1-x_2^0)^2 + f_{2/1}(x_2^0)^2 + f_{12/1}(1-x_2^0)x_2^0} \tag{7-30b}$$

The general equation (7-30b) has been successfully applied by Bosch, Rosés *et al.* to a great variety of binary solvent mixtures (>70), even to solvent mixtures showing synergistic behaviour due to HBD solvent/HBA solvent interactions [328].

It should be mentioned that an equation analogous to Eq. (7-30a) has been successfully applied to salt effects on reaction rates arising from variations in solvent polarity on the addition of electrolytes (ionophores) [197]; *cf.* also Eq. (5-99) in Section 5.4.5. For electrolyte solutions, the added salt can be treated as a more polar "cosolvent" [197].

The strong dependence of $E_T(30)$ values on the composition of binary mixtures of solvents with different polarity can be used for the quantitative UV/Vis spectroscopic determination of water in organic solvents [68, 192, 198, 199, 321, 322].

In general, the $E_T(30)$ values exhibit a good, mostly linear correlation with a large number of other solvent-sensitive processes such as light absorption, reaction rates, and chemical equilibria [2]. Applications of $E_T(30)$ values to chemical reactivity [124, 200–202] and analytical chemistry [203] have been reviewed. Their application to photochemical processes has been discussed [204, 205]. Its extreme sensitivity to small changes in the surrounding medium has made the betaine dye *(44)* a useful molecular probe in the study of micellar systems, microemulsions, phospholipid bilayers, model liquid membranes, polymers, organic–inorganic polymer hybrids, sol–gel matrices, surface polarities, and the retention behaviour in reversed-phase liquid chromatography; see page 333 and references [298–302, 443–451] of Chapter 6. Even standard molar Gibbs energies of transfer of chloride ions, ΔG_t° ($Cl^\ominus$, $H_2O \rightarrow S$), could be linearly correlated to the $E_T(30)$ values [206]. $E_T(30)$ values have also been used to calculate acceptor numbers, AN_E, which are not otherwise available by direct measurements [207]; *cf.* Table 2-5 in Section 2.2.6.

It should be mentioned that the pyridinium *N*-phenolate betaine dye *(44)* is not only very sensitive to changes in solvent polarity, but in addition its longest-wavelength solvatochromic absorption band also depends on changes in temperature [73, 175, 180, 208] and pressure [74, 182, 208], on the addition of electrolytes (ionophores) [209–213], as well as on the introduction of substituents in the peripheral phenyl groups; *cf.* Fig. 7-2 in Section 7.1 and reference [332] for a review.

The *thermo-solvatochromism* of *(44)* can be easily observed by means of a betaine solution in ethanol: at −75 °C the solution is red-colored, while at +75 °C it is blue-violet, corresponding to absorption maxima of $\lambda_{max} = 513$ and 568 nm, respectively [73]. The reason for this thermo-solvatochromism is the increased stabilization of the dipolar electronic ground state of *(44)* relative to the less dipolar excited state with decreasing temperature, due to better solute/solvent interactions at low temperature. It can be stated that, the lower the temperature, the higher the $E_T(30)$ value.

Tamura and Imoto [74] and Hendrickson, Drickamer *et al.* [182] observed pressure effects on the solution spectra of *(44)*. In all solvents used they found a hypsochromic shift of the longest-wavelength absorption band with increasing pressure. The observed hypsochromic shift of a betaine solution in methanol amounts to $\Delta\lambda = -15$ nm ($\Delta\tilde{\nu} = +600$ cm^{-1}; $\Delta E_T = +1.7$ kcal/mol) on raising the pressure from 1 to 10 kbar [182]. On the supposition that this *piezo-solvatochromism* results from better solute/solvent interactions with increasing pressure, it can be stated that, the higher the pressure, the more polar the solvent, and the higher the $E_T(30)$ value.

The addition of electrolytes (ionophores) to solutions of *(44)* causes hypsochromic shifts of its solvatochromic absorption band [197, 209–213]. This phenomenon can be designated as *halo-solvatochromism**). For example, the addition of KI, NaI,

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* The *halo-solvatochromism* of *(44)* can be considered as the only genuine halochromism, *i.e.* a colour change with increasing ionic strength of the medium *without* chemically changing the chromophore. The term *halochromism*, as introduced by Baeyer *et al.* [214], denotes the trivial colour change of a dye on addition of acids or bases. This is simply caused by the creation of a new chromophore in an acid/base reaction whereby a colourless compound is rendered coloured on salt formation, *e.g.*

$$(C_6H_5)_3C\text{—}Cl \text{ (colourless)} + AlCl_3 \rightleftharpoons (C_6H_5)_3C^\oplus \text{(yellow)} + AlCl_4^\ominus.$$

LiI, BaI_2, $Ca(SCN)_2$, and $Mg(ClO_4)_2$ to solutions of *(44)* in acetonitrile leads to a differential hypsochromic band shift which increases with this ionophore order, *i.e.* with increasing charge density of the cation [211]. Obviously, salts act similarly to other polar compounds (solvents) when added to solutions of *(44)*. The polarity of binary ionophore/solvent mixtures as a function of composition can be quantitatively described in a manner similar to other binary solvent/solvent mixtures [197, 213].

It should be noted that the polarity of the medium also influences the ^1H and ^{13}C NMR chemical shifts of dye *(44)* [215, 216]; *cf.* Section 6.5.1. The sites in the betaine molecule most influenced by the solvent are those nearest to the positive and negative charges within the dye molecule, and this is reflected in the NMR chemical shifts.

The solvent, temperature, pressure, ionophore, and substituent effects on the UV/Vis spectra of the pyridinium *N*-phenolate betaine dyes indicate the extreme sensitivity of this class of compounds to small changes in the environment. Their behaviour may be compared to that of the Princess and the Pea in one of H. C. Andersen's fairy-tales [76]*). Their utility for setting up linear Gibbs energy relationships is demonstrated by the fact that the same betaine dye can be used for establishing kinetic and spectroscopic scales of substituents (*cf.* Figs. 7-1 and 7-2) as well as a spectroscopic scale of solvent polarity (*cf.* Table 7-3).

Further solvent polarity scales based on UV/Vis absorption as well as fluorescence spectra have been proposed by Brooker *et al.* [77], Dähne *et al.* [78], de Mayo *et al.* [217], Dubois *et al.* [79], Mukerjee *et al.* [218] and Wrona *et al.* [219], Walter *et al.* [220], Walther [81] and Lees *et al.* [82], Zelinskii *et al.* [80], Winnik *et al.* [222], Kamlet and Taft [84, 84a, 224, 226]. Buncel *et al.* [333], and Catalán *et al.* [296, 334–337]. In addition to these scales, a great variety of further positively and negatively solvatochromic dyes have been recommended as solvent polarity indicators. A review describes about 60 organic and inorganic compounds, the solvatochromism of which is sufficiently large for their potential application as empirical solvent polarity probes [293].

The solvent dependence of the $\pi \rightarrow \pi^*$ transition energies of two meropolymethine dyes was used by Brooker *et al.* [77] to establish the solvent polarity parameters χ_R and χ_B (*cf.* Table 7-2). χ_R is based on the positively solvatochromic merocyanine dye no. 1 in Table 6-1 of Section 6.2.1 (red shift with increasing solvent polarity), while χ_B represents the transition energies of the negatively solvatochromic merocyanine dye no. 13 in Table 6-1.

Dähne *et al.* [78] proposed the positively solvatochromic 5-(dimethylamino)penta-dien-2,4-al (dye no. 3 in Table 6-1) as a solvent polarity indicator and recommended a relative polarity function *RPM* (from the German "Relatives Polaritätsmaß").

The $\pi \rightarrow \pi^*$ transition energy E_{sp} of a spiropyran zwitterion of the type described in Section 4.4.2 [$(27a) \rightleftharpoons (27b)$] has been used by de Mayo *et al.* to characterize the polarity of solid oxide surfaces such as that of silica gel [217].

Dubois *et al.* [79] formulated Φ values (formerly F values) as solvent polarity parameters based on the position of the solvent-sensitive $n \rightarrow \pi^*$ transition of certain saturated aliphatic ketones, as shown in Eq. (7-31)

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* The princess was so sensitive to her surroundings that she was able to feel a pea through 20 mattresses and 20 eider-down quilts in her bed. This extreme sensitivity corresponds in some way to the sensitivity of the pyridinium-*N*-phenolate betaine dye *(44)*.

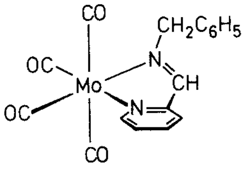
$$\Delta\tilde{\nu}_{\mathrm{H}}^{\mathrm{S}} = \tilde{\nu}^{\mathrm{S}} - \tilde{\nu}^{\mathrm{H}} = \Phi(\tilde{\nu}^{\mathrm{H}} - 32637) - 174 \tag{7-31}$$

Solvents are characterized by deviations from unity of the slope of plots of $\tilde{\nu}^{\mathrm{S}}$ values (wavenumber of absorption for various ketones in solvent S) against $\tilde{\nu}^{\mathrm{H}}$ (for various ketones in *n*-hexane as reference solvent); *cf.* Table 7-2.

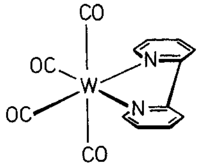
Mukerjee *et al.* [218] and Wrona *et al.* [219] have used the highly solvatochromic $n \rightarrow \pi^*$ transition energy of the stable 2,2,6,6-tetramethylpiperidine-1-oxide radical (TMPNO) for the development of a solvent polarity scale. So-called $E_{\mathrm{B}}^{\mathrm{N}}$ values, as empirical measures of solvent Lewis acidity, have been determined for 53 pure organic solvents and some binary solvent/water mixtures [219].

Using the negative solvatochromism of the $n \rightarrow \pi^*$ absorption of *N*,*N*-(dimethyl)-thiobenzamide *S*-oxide, an $E_{\mathrm{T}}^{\mathrm{SO}}$ solvent scale has been proposed by Walter *et al.* [220]. This scale comprises of 36 solvents and three binary solvent/water mixtures and is thought to be particularly useful for characterizing protic solvents.

Furthermore, the E_{K} scale of Walther [81] and the E_{MLCT}^* scale of Lees *et al.* [82] should be mentioned. Both rather comprehensive solvent scales are based on the negatively solvatochromic metal-to-ligand charge-transfer absorption (MLCT; $d \rightarrow \pi^*$) of the two zero-valent group VI metal complexes *(46)* and *(47)* of the common formula $\mathrm{M(CO)_4}$(diimine). A consistent explanation for the solvatochromic behaviour of such coordination compounds with MLCT absorption has been given by Kaim *et al.* [83]; *cf.* also Section 6.2.1.



(46)



(47)

For a review of the use of solvatochromic metal complexes as visual indicators of solvent polarity, see reference [221].

Solvatochromic fluorescent probe molecules have also been used to establish solvent polarity scales. The solvent-dependent fluorescence maximum of 4-amino-*N*-methylphthalimide was used by Zelinskii *et al.* to establish a "universal scale for the effect of solvents on the electronic spectra of organic compounds" [80, 213]. More recently, a comprehensive *Py* scale of solvent polarity including 95 solvents has been proposed by Winnik *et al.* [222]. This is based on the relative band intensities of the vibronic bands I and III of the $\pi^* \rightarrow \pi$ emission spectrum of monomeric pyrene; *cf.* Section 6.2.4. A significant enhancement is observed in the $0 \rightarrow 0$ vibronic band intensity I_{I} relative to the $0 \rightarrow 2$ vibronic band intensity I_{III} with increasing solvent polarity. The ratio of emission intensities for bands I and III serves as an empirical measure of solvent polarity: $Py = I_{\mathrm{I}}/I_{\mathrm{III}}$ [222]. However, there seems to be some difficulty in determining precise *Py* values, as shown by the varying *Py* values from different laboratories; the reasons for these deviations have been investigated [223].

An interesting approach, called the *solvatochromic comparison method*, used to evaluate a β scale of solvent hydrogen-bond acceptor (HBA) basicities, an α scale of solvent hydrogen-bond donor (HBD) acidities, and a π^* scale of solvent dipolarity/polarizability using UV/Vis spectral data of solvatochromic compounds, was employed and further developed by Kamlet, Taft *et al.* [84, 84a, 224, 226]. Magnitudes of enhanced solvatochromic shifts, $\Delta\Delta\tilde{\nu}$, in HBA solvents*) have been determined for 4-nitroaniline relative to homomorphic**) *N*,*N*-diethyl-4-nitroaniline (compound no. 2, Table 6-1, Section 6.2.1). Both standard compounds are capable of acting as HBA substrates (at the nitro oxygens) in HBD solvents, but only 4-nitroaniline can act as a HBD substrate in HBA solvents. Taking the $\Delta\Delta\tilde{\nu}$ value of 2800 cm^{-1} for hexamethylphosphoric triamide (a strong HBA solvent) as a single fixed reference point ($\beta_1 = 1.00$), a β scale of solvent HBA basicities for HBA solvents was developed [84]. Using the same solvatochromic comparison method, *i.e.* the enhanced solvatochromic shifts, $\Delta\Delta\tilde{\nu}$, in HBD solvents for 4-nitroanisole and the pyridinium *N*-phenolate betaine dye *(44)*, an α scale of HBD acidities was evaluated. Taking the $\Delta\Delta\tilde{\nu}$ value of 6240 cm^{-1} for methanol (a strong HBD solvent) as a fixed reference point ($\alpha_1 = 1.00$), an α scale of solvent HBD acidities for HBD solvents was established [84].

The same authors also introduced a π^* scale of solvent dipolarity/polarizability [84a]. This π^* scale is so named because it is derived from solvent effects on the $\pi \rightarrow \pi^*$ electronic transitions of a selection of seven positively solvatochromic nitroaromatics of the type $D{-}C_6H_4{-}A$, where D and A stand for electron-donor (*e.g.* NMe_2) and electron-acceptor (*e.g.* NO_2) groups, respectively: 4-nitroanisole, *N*,*N*-diethyl-3-nitroaniline, 4-methoxy-β-nitrostyrene, 1-ethyl-4-nitrobenzene, *N*-methyl-2-nitro-*p*-toluidine, *N*,*N*-diethyl-4-nitroaniline, and 4-(dimethylamino)benzophenone. Given a solvatochromic indicator compound, the π^* value for a solvent S was defined according to Eq. (7-32):

$$\pi^*(\mathrm{S}) = [\tilde{\nu}(\mathrm{S}) - \tilde{\nu}(c\text{-}\mathrm{C_6H_{12}})]/[\tilde{\nu}(\mathrm{DMSO}) - \tilde{\nu}(c\text{-}\mathrm{C_6H_{12}})] \qquad (7\text{-}32)$$

where $\tilde{\nu}(S)$ corresponds to the wavenumber of the maximum of the long-wavelength solvatochromic absorption band of the indicator measured in the various solvents. Cyclohexane and dimethyl sulfoxide were used as reference solvents by taking $\pi^*(c\text{-}C_6H_{12}) = 0.00$ and $\pi^*(\mathrm{DMSO}) = 1.00$ by definition. Solvent effects on the $\tilde{\nu}_{max}$ values of these seven primary solvatochromic indicators were employed in the initial construction of the π^* scale, which was then expanded and refined by multiple least-squares correlations with additional solvatochromic indicators. In this way, an averaged π^* scale of solvent dipolarity/polarizability was established, which measures the ability of the solvent to stabilize a charge or a dipole by virtue of its dielectric effect [84a]. A normalized range of 0.00 (for cyclohexane) to 1.00 (for dimethyl sulfoxide) for the π^* values of common solvents has been chosen so that, taken together with the α scale of

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* The term hydrogen-bond acceptor (HBA) refers to the acceptance of the proton of a hydrogen-bond. Therefore, HBA solvents are also electron-pair donor (EPD) solvents. Hydrogen-bond donor (HBD) refers to the donation of the proton. Therefore, HBD solvents behave as protic solvents.

** The term *homomorphic* molecules was introduced by Brown *et al.* [225]. Molecules having the same or closely similar molecular geometry are *homomorphs*, *e.g.* ethane is a homomorph of methanol, toluene of phenol, 4-aminobenzenesulfonamide of 4-aminobenzoic acid, and *N*,*N*-diethyl-4-nitroaniline of 4-nitroaniline.

solvent HBD acidities and the β scale of solvent HBA basicities (which have also been scaled to range from 0.00 to 1.00), these parameters can be used in a multiparameter equation (*cf.* Section 7.7).

In 1994, a review on the further development and improvement of the π^* scale was given by Laurence, Abboud *et al.* [227]. They redetermined π^* values for a total of 229 solvents, this time using only two (instead of seven) solvatochromic nitroaromatics as indicator compounds, *i.e.* 4-nitroanisole and *N*,*N*-dimethylamino-4-nitroaniline, for good reasons; see later and reference [227] for a more detailed discussion. A thermodynamic analysis of the π^* scale [and the $E_T(30)$ scale] has been reported by Matyushov *et al.* [228]. Using six novel diaza merocyanine dyes of the type R–N=N–R′ (R = *N*-methylpyridinium-4-yl or *N*-methylbenzothiazolium-2-yl, and R′ = 2,6-disubstituted 4-phenolates or 2-naphtholate) instead of nitroaromatics as positively solvatochromic probe compounds, an analogous $\pi^*{}_{azo}$ scale was developed by Buncel *et al.*, which correlates reasonable well with the π^* scale, but has some advantages; for a detailed discussion, see references [333]. Another π^* scale, based solely on naphthalene, anthracene, and β-carotene, was constructed by Abe [338]. π^* values are mixed solvent parameters, measuring the solvent dipolarity and polarizability. The differences in the various π^* scales are caused by the different mixture of dipolarity and polarizability measured by the respective indicator. The π^* scale of Abe is practically independent of the solvent dipolarity, whereas Kamlet–Taft's π^* and Buncel's $\pi^*{}_{azo}$ reflect different contributions of both solvent dipolarity and polarizability.

A selection of Kamlet and Taft's solvatochromic parameters α, β, and π^* for 40 organic solvents, taken from a more recent comprehensive and improved collection [227, 294], is given in Table 7-4.

The parameters in Table 7-4 were arrived at by averaging the multiple normalized solvent effects on a variety of solvent-dependent properties involving various types of solvatochromic indicator dyes. Therefore, the solvatochromic parameters of Table 7-4 are no longer directly based on the solvent effects indicated by a distinct single solvatochromic indicator dye. Rather, they are statistically averaged values resulting from a series of successive approximations [226][*]. Kamlet and Taft's solvatochromic parameters have been used in different combinations in one-, two-, and three-parameter correlations known as *linear solvation energy relationships* (LSERs). An impressive series of more than 40 articles entitled "Linear solvation energy relationships" has been published: Part 1 [229]...Part 41 [230]; see Section 7.7 for a further discussion of such multiparameter correlations.

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[*] There is a discussion in the literature concerning the use of averaged and statistically optimized "constant" solvent polarity parameters (*e.g.* α, β, π^*) instead of experimentally derived parameters which are based on a distinct, single, and well-understood solvent-dependent reference process [*e.g.* Y_{OTs}, Z, $E_T(30)$]. There are some practical reasons in favour of the experimentally derived solvent parameters. They are related to a distinct chemical or physical reference process and the corresponding solvent scale can easily be enlarged by new precise measurements. Averaged and statistically optimized solvent parameters are no longer directly related to a distinct reference process and are thus ill-defined. New data may be difficult to incorporate into the existing framework, and even if they are, then this can lead to a modification of the already calculated "constant" solvent parameters. It has been pointed out "that it is better to study one good model with precision than to take the average of results obtained from many poor models" [237]; *cf.* also [153].

Table 7-4. A selection of Kamlet and Taft's solvatochromic parameters α, β, and π^* for 40 organic solvents, taken mainly from references [227, 294] as well as from references [226, 295].

Solvents	α	β	π^*
Gas phase	0.00	0.00	−1.23
n-Hexane	0.00	0.00	−0.11
Cyclohexane	*0.00*[a)]	*0.00*[a)]	*0.00*[a)]
Carbon disulfide	0.00	0.07	0.51
Dichloromethane	0.13	0.10	0.73
Trichloromethane, Chloroform	0.20	0.10	0.69
Tetrachloromethane	0.00	0.10	0.21
Benzene	0.00	0.10	0.55
Methylbenzene, Toluene	0.00	0.11	0.49
Chlorobenzene	0.00	0.07	0.68
Nitrobenzene	0.00	0.30	0.86
Pyridine, Azine	0.00	0.64	0.87
Diethyl ether	0.00	0.47	0.24
Tetrahydrofuran	0.00	0.55	0.55
1,4-Dioxane	0.00	0.37	0.49
Triethylamine	0.00	0.71	0.09
Propanone, Acetone	0.08	0.48	0.62
Cyclohexanone	0.00	0.53	0.68
Ethyl acetate	0.00	0.45	0.45
Ethyl benzoate	0.00	0.41	0.68
(±)-Propylene carbonate	0.00	0.40	0.83
Dimethyl sulfoxide	0.00	0.76	*1.00*[a)]
Tetrahydrothiophene-1,1-dioxide, Sulfolane	0.00	0.39	0.90
Acetonitrile	0.19	0.40	0.66
Nitromethane	0.22	0.06	0.75
Hexamethylphosphoric acid triamide, HMPT	0.00	*1.00*[a)]	0.87
N,*N*-Dimethylformamide, DMF	0.00	0.69	0.88
N-Methylformamide	0.62	0.80	0.90
Formamide	0.71	0.48	0.97
t-Butanol	0.42	0.93	0.41
Cyclohexanol	0.66	0.84	0.45
1-Butanol	0.84	0.84	0.47
2-Propanol	0.76	0.84	0.48
1-Propanol	0.84	0.90	0.52
Ethanol	0.86	0.75	0.54
Ethane-1,2-diol, Glycol	0.90	0.52	0.92
Methanol	0.98	0.66	0.60
Acetic acid	1.12	0.45	0.64
2,2,2-Trifluoroethanol	1.51	0.00	0.73
1,1,1,3,3,3-Hexafluoro-2-propanol	1.96	0.00	0.65
Water	1.17	0.47	1.09

a) By definition.

An extension of the β scale of solvent HBA basicity, using only 4-nitroaniline and *N*,*N*-diethyl-4-nitroaniline as solvatochromic indicators (B_{KT} scale), has been described by Krygowski *et al.* [231, 232]. Some further improvements of Kamlet and Taft's solvatochromic parameters have been proposed by Kolling [233] and Bekárek [234]. According to Bekárek, better correlations are obtained using modified β_n, α_n, and π_n^*

values, which are derived from the original β, α, and π^* values by dividing them by the refractive index function $(n^2 - 1)/(2n^2 + 1)$. This is in order to eliminate the polarization contribution of the solvent molecules in the cybotactic solvation sphere during the electronic excitation of the solvatochromic indicators. According to Bekárek, the original β, α, and π^* values are adequate for correlating certain types of spectral properties (*e.g.* HFS constants in ESR spectra), but their applicability to other types of solvent effects could be improved by using the modified β_n, α_n, and π^*_n values [234]. However, this modification has been strongly criticized by Kamlet, Taft, and Abboud for conceptual and computational reasons. This leads to the conclusion that in *all* correlations the original solvatochromic parameters are in fact best [235].

Interestingly, a statistical principal component analysis of the solvatochromic shift data sets previously used by Kamlet and Taft in defining the π^* scale has shown that, rather than one (π^*), two solvent parameters (θ_{1k} and θ_{2k}) are necessary to describe the solvent-induced band shifts of the studied solvatochromic indicators [236]. This is not unexpected since the π^* parameters are assumed to consist of a blend of dipolarity and polarizability contributions to the solute/solvent interactions.

Laurence *et al.* [237–239] have tried to improve Kamlet and Taft's solvatochromic comparison method [224] by introducing a new *thermosolvatochromic comparison method*. In doing this, they tried to eliminate various shortcomings including sometimes insufficiently precisely determined solvatochromic parameters. According to the solvatochromic comparison method, the π^* value of a solvent S is measured by the bathochromic shift relative to cyclohexane, $-\Delta\tilde{\nu}_S$, of the $\pi \rightarrow \pi^*$ transition of a non-HBD indicator dye (*e.g.* 4-nitroanisole); *cf.* Eq. (7-32). The basicity parameter β of the same solvent is measured by the supplementary bathochromic shift $-\Delta\Delta\tilde{\nu}_S$ obtained using a second HBD indicator dye (*e.g.* 4-nitrophenol), which is a homomorph of the first dye. Plotting the absorption wavenumbers of the HBD indicator dye i against the wavenumbers of its non-HBD homomorph j, for non-HBD and non-HBA solvents, leads to the linear reference line given in Fig. 7-3.

Because of the specific HBD solute/HBA solvent interaction, all HBA solvents fall below this line, the higher the basicity the lower their position. The Kamlet–Taft β values are the means of the normalized values $-\Delta\Delta\tilde{\nu}_S(i-j)$ for several indicator dyes j

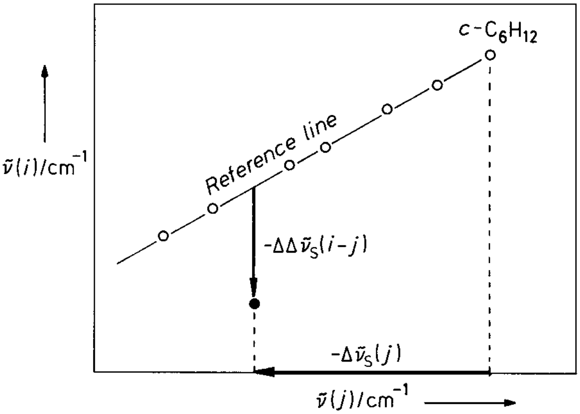

Fig. 7-3. Illustration of the solvatochromic comparison method according to [237]. Reference line equation: $\tilde{\nu}(i) = a_{ij} \cdot \tilde{\nu}(j) + b_{ij}$. Reference solvent: cyclohexane. ○ non-HBA and non-HBD solvents; ● an HBA solvent.

and various homomorph pairs i/j, according to Eq. (7-33) [237].

$$-\Delta\Delta\tilde{\nu}_{\mathrm{S}}(i-j) = [\mathrm{a}_{ij} \cdot \tilde{\nu}_{\mathrm{S}}(j) + \mathrm{b}_{ij}] - \tilde{\nu}_{\mathrm{S}}(i) \tag{7-33}$$

It is obvious that the accuracy of the determination of $-\Delta\Delta\tilde{\nu}_{\mathrm{S}}(i-j)$ depends strongly on the precision with which the reference line of Fig. 7-3 is established.

Laurence *et al.* [237, 238] have shown that some of the absorption bands of the solvatochromic indicator dyes previously used by Kamlet and Taft to fix the reference lines exhibit a solvent- and temperature-dependent vibrational fine structure, which makes the determination of the band maxima, $\tilde{\nu}_{\max}$, difficult. Furthermore, the indicator dyes used are thermo-solvatochromic, *i.e.* $\tilde{\nu}_{\max}$ is temperature-dependent. No allowance for this temperature-dependence of the α, β, and π^* values has been made previously.

Finally, the right choice of solvent on going from the gas phase to the most polar non-HBA and non-HBD solvents has to be made in order to fix the reference line as given in Fig. 7-3. Taking all these difficulties into account, and using 4-nitrophenol/4-nitro-anisole and 4-nitroaniline/*N*,*N*-dimethyl-4-nitroaniline as distinct solvatochromic indicator couples i and j, as well as a carefully selected set of non-HBA and non-HBD solvents, Laurence *et al.* [237, 238] have determined more precise reference lines. From these, it was possible to derive new solvent dipolarity/polarizability and solvent HBA basicity parameters, which they believe to be more correct than the original π^* and β parameters; see also reference [227]. In particular, the β scale seems to be mainly a scale of solvent HBA basicity against NH donor solutes and does not have the degree of general validity as originally claimed [84].

Other spectroscopic measurements of solvent polarity use as standard processes solvent-sensitive infrared stretching absorptions of groups such as X=O and X—H $\cdots$ B, where X may be C, S, N, O, or P, and B is a hydrogen-bond acceptor (HBA) [*cf.* Eqs. (6-6) and (6-7) in Section 6.3]. Schleyer *et al.* [85] proposed the relationship (7-34) for the correlation of solvent-sensitive IR vibrations.

$$\frac{\tilde{\nu}^0 - \tilde{\nu}^{\mathrm{s}}}{\tilde{\nu}^0} = a \cdot G \tag{7-34}$$

If X—H $\cdots$ B vibrations are being examined, $\tilde{\nu}^0$ refers to its gas-phase value. The value for a is a measure of solvent susceptibility of a particular IR vibration, and G*) is a function of the solvent only. Since solvent shifts of $\tilde{\nu}_{\mathrm{C=O}}$ and $\tilde{\nu}_{\mathrm{S=O}}$ are proportional to solvent shifts of $\tilde{\nu}_{\mathrm{X-H \cdots B}}$, G values are calculated from the solvent shifts of the carbonyl bands of *N*,*N*-dimethylformamide and benzophenone and the sulfonyl band of dimethyl sulfoxide. An arbitrary value of 100 was assigned to dichloromethane to fix the scale ($G = 0$ for the gas phase) [85]. Values of G are given in Table 7-2. Further G values have been determined by Somolinos *et al.* [240] and their relationships to other solvent polarity parameters have been investigated [241].

Kagiya *et al.* [86] have measured the IR wavenumbers of the O—D and C=O stretching vibrations of monodeuteriomethanol (CH_3OD) and acetophenone, respec-

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* The abbreviation *G* was chosen from the name of a close aquaintance of one of the authors [85]; private communication to C. R.

tively, in various solvents. Taking benzene as the reference solvent, they used the wavenumber shift relative to the maximum found in benzene as a measure of the electron-pair donating power and the electron-pair accepting power of a given solvent. Measurements of the O—D stretching band of CH_3OD, $\tilde{\nu}_{MeOD}$, have been greatly extended (up to 55 aprotic solvents) and improved by Shorter *et al.* [87]. Based on the measurements of Kagiya *et al.* [86], Koppel and Pal'm [6] have defined a Lewis basicity parameter B_{MeOD} using Eq. (7-35),

$$B_{MeOD}/\mathrm{cm}^{-1} = \Delta\tilde{\nu}_{OD} = \tilde{\nu}^0_{MeOD} - \tilde{\nu}_{MeOD\cdots B} \tag{7-35}$$

where $\tilde{\nu}^0_{MeOD}$ and $\tilde{\nu}_{MeOD\cdots B}$ refer to the O—D stretching vibration of CH_3OD measured in the gas phase ($\tilde{\nu}^0_{MeOD} = 2720\ \mathrm{cm}^{-1}$ [87]) and in a given HBA solvent B. A comprehensive collection of B_{MeOD} values can be found in reference [87].

In a similar way, another set of solvent Lewis-basicity parameters, B_{PhOH}, based on band shifts of the O—H stretching vibration of phenol in tetrachloromethane induced by hydrogen-bond formation with added HBA solvents B, was used by Koppel and Paju [88] to classify 198 solvents, according to Eq. (7-36) ($B_{PhOH} = 0$ for CCl_4):

$$B_{PhOH}/\mathrm{cm}^{-1} = \Delta\tilde{\nu}^{CCl_4}_{OH} = \tilde{\nu}^{CCl_4}_{PhOH} - \tilde{\nu}^{CCl_4}_{PhOH\cdots B} \tag{7-36}$$

This B_{PhOH} scale was further extended by Makitra *et al.* [242]. It has been shown that the spectroscopically determined B_{PhOH} values correlate well with Gutmann's calorimetrically measured donor numbers *DN* [243]; *cf.* Eq. (7-10).

Another remarkable IR spectroscopic parameter of solvent Lewis basicity has been introduced by Laurence *et al.* [239], using the so-called *infrared comparison method* analogous to Kamlet and Taft's solvatochromic comparison method [224]. The band maxima wavenumbers of the C═O stretching vibration of the two homomorphs CCl_3CO_2H and $CCl_3CO_2CH_3$ have been measured in the gas phase as well as in non-HBD and non-HBA solvents in order to establish a reference line that conforms to Eq. (7-37); *cf.* Fig. 7-3.

$$\tilde{\nu}^{CCl_3CO_2H}_{C=O} = 1.171 \cdot \tilde{\nu}^{CCl_3CO_2CH_3}_{C=O} - 293 \tag{7-37}$$

This linear relationship demonstrates the similarity of the polarity effects on both homomorphic vibrators, trichloroacetic acid and its methyl ester. For HBA solvents B, however, the $\tilde{\nu}_{C=O}$ data points are displaced below the reference line of Eq. (7-37). These deviations are caused by the formation of solute/solvent hydrogen bonds $CCl_3CO_2H\cdots B$, resulting in a decrease in the C═O vibration wavenumber. The hydrogen-bond induced wavenumber shift $\Delta\tilde{\nu}_{C=O}$ for a HBA solvent is then calculated by Eq. (7-38); *cf.* Eq. (7-33).

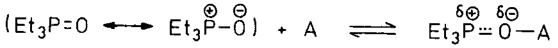
$$\begin{aligned}\Delta\tilde{\nu}_{C=O} &= \tilde{\nu}^{CCl_3CO_2H}_{C=O}\ [\text{calc. from Eq. (7-37)}] - \tilde{\nu}^{CCl_3CO_2H}_{C=O}\ [\text{observed}] \\ &= [1.171 \cdot \tilde{\nu}^{CCl_3CO_2CH_3}_{C=O} - 293] - \tilde{\nu}^{CCl_3CO_2H}_{C=O}\end{aligned} \tag{7-38}$$

Due to this subtraction, the nonspecific polarity effect of the solvent is disentangled from its basicity effect on the C═O vibrator of CCl_3CO_2H in HBA solvents. $\Delta\tilde{\nu}_{C=O}$ values range from 1.4 cm^{-1} for benzene to 29.3 cm^{-1} for tri-*n*-butyl phosphate [239]. The $\Delta\tilde{\nu}_{C=O}$ displacements correlate well with the $\Delta\tilde{\nu}_{OD}$ values of Eq. (7-35). However, this $\Delta\tilde{\nu}_{C=O}/\Delta\tilde{\nu}_{OD}$ relationship is family-dependent, *i.e.* different linear correlations are obtained for different classes (families) of organic HBA solvents such as π, S, O, and N bases [239]. Unfortunately, $\Delta\tilde{\nu}_{C=O}$ values are not available for carbonyl-containing solvents because of insufficient solvent transparency, and for more basic solvents such as water, DMSO, and HMPT because of decarboxylation and proton-transfer reactions. An excellent review on solvatochromic scales derived from various similarity models employed in IR and UV/Vis spectroscopy has been given by Laurence [339]. The similarity principle simply states that similar changes in molecular structure or medium should produce similar changes in the solvatochromic properties of the solutes under study.

Electron spin resonance (ESR) and nuclear magnetic resonance (NMR) measurements have also been used to establish solvent polarity scales. Knauer *et al.* [89] determined the nitrogen hyperfine splitting constants, $a(^{14}N)$, of several aminyloxide radicals (nitroxides), such as di-*t*-butyl aminyloxide, in 31 solvents. It has been known for some time that the ^{14}N isotropic HFS constant in the ESR spectrum of an aminyloxide free radicals is sensitive to the polarity of the solvent in which it is dissolved (*cf.* Table 6-5 and the discussion in Section 6.4). Since $a(^{14}N)$ is easily measured in almost all solvents, it may prove to be useful as an empirical solvent polarity parameter, especially in cases where the other parameters are difficult to determine owing to limited solubility. Only very low radical concentrations are usually needed to obtain an ESR spectrum. The $a(^{14}N)$ values of di-*t*-butyl aminyloxide are included in Table 7-2. Further $a(^{14}N)$ values of di-*t*-butyl aminyloxide have been determined by Kolling [244], Reddoch *et al.* [245], and Symons *et al.* [246], who also discussed their solvent-dependence, their applicability as solvent parameters, and their correlations with other solvent parameters in more detail. The $a(^{14}N)$ values of 2,2,6,6-tetramethylpiperidine-1-oxide (TMPNO) [247, 248] and 4-acetyl-1-methylpyridinyl free radicals [244] have also been discussed as potential solvent polarity probes. A critical comparison of the TMPNO $a(^{14}N)$ values with other physical and empirical solvent parameters has been given by Kecki *et al.* [248]. For example, the $a(^{14}N)$ values of aminyl oxides correlate well with the $E_T(30)$ and *AN* values, but not with the solvent relative permittivities or dipole moments or functions thereof [245, 248].

Interesting solvent scales based on NMR measurements have been proposed by Taft *et al.* [90] and by Gutmann, Mayer *et al.* [91]. A solvent polarity parameter, designated as *P*, has been defined by Taft *et al.* [90] as the ^{19}F chemical shift (in ppm) of 4-fluoro-nitrosobenzene in a given solvent, relative to the same quantity in the reference solvent cyclohexane (*cf.* Table 6-6 and the discussion in Section 6.5.1). These parameters define a scale ranging from $P = 0.0$ in cyclohexane to $P = 2.7$ in sulfolane, and can easily be measured in a wide variety of solvents. The *P* values appear to be related to the ability of the solvents to form specific 1:1 complexes with the nitroso group of the standard compound. A compilation of *P* values can be found in reference [92]. In addition, ^{13}C chemical shifts of (trifluoromethyl)benzene and phenylsulfur pentafluoride have been used by Taft *et al.* to study nonspecific dipolar interactions with HBD solvents and utilized to define π^* values of solvent dipolarity/polarizability for protic solvents [249].

Complementary to the donor numbers *DN* [*cf.* Eq. (7-10)], Gutmann, Mayer *et al.* introduced so-called acceptor numbers *AN* as measures of the Lewis acidity or EPA property of organic solvents [91, 134, 207, 251]. Acceptor numbers are derived from the relative ^{31}P NMR chemical shift values, δ_{corr}, of triethylphosphane oxide, related to those of the 1:1 adduct Et_3PO—$SbCl_5$. δ_{corr} is the observed ^{31}P chemical shift corrected for concentration effects and for differences in magnetic volume susceptibility.



$$(Et_3P{=}O \longleftrightarrow Et_3\overset{\oplus}{P}{-}\overset{\ominus}{O}) + A \rightleftharpoons Et_3\overset{\delta\oplus}{P}{\cdots}\overset{\delta\ominus}{O}{-}A$$

With *n*-hexane as the reference solvent, values of *AN* for a given solvent A are calculated according to Eq. (7-39).

$$AN = \frac{\delta_{\text{corr}}(\text{A}) - \delta_{\text{corr}}(n\text{-}C_6H_{14})}{\delta_{\text{corr}}(Et_3PO\text{—}SbCl_5) - \delta_{\text{corr}}(n\text{-}C_6H_{14})} \cdot 100 \tag{7-39}$$

The *AN* scale was set up by defining $AN = 0$ for *n*-hexane, and $AN = 100$ for Et_3PO—$SbCl_5$ dissolved in 1,2-dichloroethane. The term $[\delta_{\text{corr}}(Et_3PO\text{—}SbCl_5) - \delta_{\text{corr}}(n\text{-}C_6H_{14})]$ was experimentally found to be 42.58 ppm; Eq. (7-39) reduces therefore to Eq. (7-40).

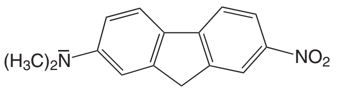
$$AN = \frac{\delta_{\text{corr}}(\text{A}) - \delta_{\text{corr}}(n\text{-}C_6H_{14})}{42.58 \text{ ppm}} \cdot 100 = \Delta\delta_{\text{corr}} \cdot 2.348/\text{ppm} \tag{7-40}$$

A selection of *AN* values has already been given in Table 2-5 of Section 2.2.6; *cf.* also Table 6-6 in Section 6.5.1. The observed solvent-dependent ^{31}P chemical shifts result mainly from the polarization of the dipolar P═O group, induced by the interaction with electrophilic solvents A, particularly HBD solvents. The decrease in electron density at the phosphorus atom results in a deshielding proportional to the strength of the probe/solvent interaction. In solutions of protic acids, the ^{31}P chemical shift of the *O*-protonated triethyl hydroxyphosphonium salt is observed. Since Et_3PO is very hygroscopic and therefore not very suitable from an experimental point of view, the use of $(n\text{-}Bu)_3PO$ instead of Et_3PO as probe molecule has been recommended [250].

The *AN* values represent dimensionless numbers expressing the Lewis acidity properties of a given solvent A relative to those of $SbCl_5$, which is also the standard compound for setting up the donor number scale. Owing to the good solubility properties of triethylphosphane oxide, acceptor numbers are available for many types of coordinating and non-coordinating solvents. They are particularly useful in characterizing the Lewis acidities of protic solvents and protonic acids. Relationships have been found between the acceptor number and other empirical parameters such as *Z*, $E_T(30)$, and *Y* values, as well as many thermodynamic solvation quantities and other solvent-dependent processes [91, 139, 140, 207, 250–253]. The fairly good linear correlations of *AN* with *Z* and $E_T(30)$ reveal that the latter represent, to a large extent, measures of the electrophilic properties of the solvents, and therefore of necessity fail when applied to reactions which are mainly influenced by the nucleophilic properties of the solvents. The acceptor numbers are linearly correlated with the $E_T(30)$ parameter according to

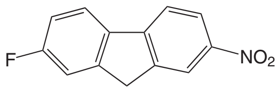
$AN = 1.850 \cdot E_T(30) - 59.5$, as established for 51 solvents ($r = 0.944$) by Marcus [294]. This satisfactory linear correlation has been used to calculate *AN* values from $E_T(30)$ values for such solvents, for which the former are difficult to measure [207].

Finally, the ambitious approach of Catalán *et al.* to introduce complete new comprehensive scales of solvent dipolarity/polarizability (*SPP* scale), solvent basicity (*SB* scale), and solvent acidity (*SA* scale) must be mentioned [296, 335–337]. These three UV/Vis spectroscopic scales are based on carefully selected positively solvatochromic and homomorphic pairs of probe dyes and include values for about 200 organic solvents; for a recent review, see reference [296]. The molecular structures of the three pairs of homomorphic indicator dyes proposed are as follows:

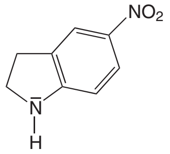


(48) (DMANF)

and

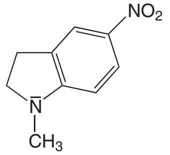


(49) (FNF)

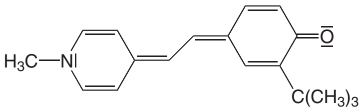


(50) (NI)

and

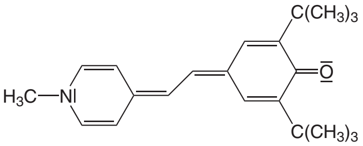


(51) (MNI)



(52) (TBSB)

and



(53) (DTBSB)

Based on the well-known strong solvent-dependent UV/Vis absorption and fluorescence of 2-amino-7-nitrofluorene (see Section 6.2.4), the donor/acceptor-substituted fluorenes 2-dimethylamino-7-nitrofluorene *(48)* (DMANF) and its homomorph 2-fluoro-7-nitrofluorene *(49)* (FNF) were selected as positively solvatochromic indicator dyes for measuring the solvent dipolarity and polarizability. The long-wavelength intramolecular charge-transfer absorption of *(48)* is connected with an increase in dipole moment of $\Delta\mu \approx 60 \cdot 10^{-30}$ Cm (18 D; $\mu_g < \mu_e$), and is thus sensitive to solute/solvent dipole/dipole and dipole/induced dipole interactions. The rigid and highly conjugated 16 π electron system of *(48)*, a phenylogous nitramide, is readily polarizable, and is thus capable of registering solute/solvent polarizability interactions. It is further assumed that the basicity of *(48)* does not change very much upon electronic excitation. In order to remove specific solute/solvent interactions, the homomorph *(49)* was used as a secondary probe dye and it is believed that the use of difference $\Delta\tilde{\nu}$ of the absorptions of *(48)* and *(49)* will cancel many spurious effects. Both compounds exhibit a significant positive solvatochromism, that of *(49)* being smaller than that of *(48)*. A solvent change from perfluoro-*n*-hexane to dimethyl sulfoxide results in bathochromic band shifts of $\Delta\lambda = +67$ nm ($\Delta\tilde{\nu} = -4038\ \text{cm}^{-1}$) and $\Delta\lambda = +26$ nm ($\Delta\tilde{\nu} = -2380\ \text{cm}^{-1}$), for *(48)* and *(49)* respectively [335]. The difference $\Delta\tilde{\nu} = \tilde{\nu}(49) - \tilde{\nu}(48)$, taken as a measure of *s*olvent di*p*olarity/*p*olarizability (*SPP* scale), varies from $\Delta\tilde{\nu} = 4692\ \text{cm}^{-1}$ for the gas phase to 6811 cm^{-1} for dimethyl sulfoxide. Using these two media as references to fix the scale from 0.000 (gas phase) to 1.000 (dimethyl sulfoxide, DMSO), the *SPP* scale is then defined as [296, 335]:

$$SPP(\text{solvent}) = \frac{\Delta\tilde{\nu}(\text{solvent}) - \Delta\tilde{\nu}(\text{gas})}{\Delta\tilde{\nu}(\text{DMSO}) - \Delta\tilde{\nu}(\text{gas})} = \frac{\Delta\tilde{\nu}(\text{solvent}) - 4692}{2119} \tag{7-40a}$$

A selection of *SPP* values is collected in Table 7-5 for nearly the same set of solvents as given in Table 7-4. Whereas cyclohexane is often used as a nonpolar reference solvent in other solvent scales, the *SPP* scale shows a considerable gap between cyclohexane and the gas phase (0.557 units), which is nearly as wide as that between cyclohexane and polar hexafluoro-2-propanol (0.457 units). Therefore, the choice of cyclohexane as a reference solvent to define a solvent scale has been called into question [335]. For a comparison of the *SPP* scale with Kamlet and Taft's π^* scale, see reference [338].

For the construction of a solvent hydrogen-bond acceptor (HBA) basicity scale (*SB* scale), the positive solvatochromism of 5-nitroindoline *(50)* (NI) and its homomorph 1-methyl-5-nitroindoline *(51)* (MNI) has been used by Catalán *et al.* [296, 336]. 5-Nitroindoline *(50)* can act as a hydrogen-bond donor (HBD), forming H-bonds to HBA solvents, whereas its *N*-methyl derivative *(51)* no longer has this property. The two homomorphs have the same HBA properties as well as similar dipole moments and polarizabilities. Thus, they exhibit the same sensitivity to changes in solvent dipolarity/polarizability and should only register a change in the solvent's HBA basicity. A solvent change from tetramethylguanidine (TMG; a strong HBA solvent) to hexafluoro-2-propanol (a non-HBA solvent) leads to bathochromic band shifts of $\Delta\lambda = +22$ nm ($\Delta\tilde{\nu} = -1253\ \text{cm}^{-1}$) and $\Delta\lambda = +56$ nm ($\Delta\tilde{\nu} = -2963\ \text{cm}^{-1}$) for *(50)* and *(51)*, respectively [336]. In order to cancel spurious effects accompanying solute-specific HBD solute/HBA solvent interactions, the difference $\Delta\tilde{\nu} = \tilde{\nu}(50) - \tilde{\nu}(51)$ is taken as a measure of the solvent HBA basicity. This difference varies from $\Delta\tilde{\nu} = 1570\ \text{cm}^{-1}$ for the gas phase to $-165\ \text{cm}^{-1}$ for TMG. Using these two media as references to normalize the scale between 0.000 (gas phase) and 1.000 (TMG), the *SB* scale is then defined as [296, 336]:

$$SB(\text{solvent}) = \frac{\Delta\tilde{\nu}(\text{solvent}) - \Delta\tilde{\nu}(\text{gas})}{\Delta\tilde{\nu}(\text{TMG}) - \Delta\tilde{\nu}(\text{gas})} = \frac{\Delta\tilde{\nu}(\text{solvent}) - 1570}{1735} \tag{7-40b}$$

A selection of *SB* values is collected in Table 7-5. Not unexpectedly, a satisfactory linear correlation exists between Catalán's *SB* values and Kamlet and Taft's β values (see Table 7-4) for 98 solvents ($r = 0.928$), with deviations for some aliphatic amines and ethers with long alkyl chains. For comparisons of the *SB* scale with further solvent basicity scales, see reference [336].

Table 7-5. A selection of Catalán's solvatochromic parameters *SA*, *SB*, and *SPP* for 40 solvents, taken from reference [296].

Solvents	*SA*	*SB*	*SPP*
Gas phase	0a)	*0.000*b)	*0.000*b)
Perfluoro-*n*-hexane	0a)	0.057	0.214
n-Hexane	0a)	0.056	0.519
Cyclohexane	0a)	0.073	0.557
Dichloromethane	0.040	0.178	0.876
Trichloromethane, Chloroform	0.047	0.071	0.786
Tetrachloromethane	0a)	0.044	0.632
Benzene	0a)	0.124	0.667
Methylbenzene, Toluene	0a)	0.128	0.655
Chlorobenzene	0a)	0.182	0.824
Nitrobenzene	0.056	0.240	0.986
Pyridine	0.033	0.581	0.922
Diethyl ether	0a)	0.562	0.694
Tetrahydrofuran	0.0	0.591	0.838
1,4-Dioxane	0.0	0.444	0.701
Triethylamine	0a)	0.885	0.617
Propanone, Acetone	0.0	0.475	0.881
Cyclohexanone	0.0	0.482	0.874
Ethyl acetate	0.0	0.542	0.795
Ethyl benzoate	0.0	0.417	0.835
(±)-Propylene carbonate	0.106	0.341	0.930
Dimethyl sulfoxide	0.072	0.647	*1.000*b)
Tetrahydrothiophene-1,1-dioxide, Sulfolane	0.052	0.365	1.003
Acetonitrile	0.044	0.286	0.895
Nitromethane	0.078	0.236	0.907
Hexamethylphosphoric acid triamide, HMPT	0a)	0.813	0.932
N,*N*-Dimethylformamide, DMF	0.031	0.613	0.954
N-Methylformamide	0.444	0.590	0.920
Formamide	0.674	0.414	0.833
2-Methyl-2-propanol, *t*-Butanol	0.145	0.928	0.829
Cyclohexanol	0.258	0.854	0.847
1-Butanol	0.341	0.809	0.837
2-Propanol	0.283	0.762	0.848
1-Propanol	0.367	0.727	0.847
Ethanol	0.400	0.658	0.853
Ethane-1,2-diol, Glycol	0.565	0.534	0.932
Methanol	0.605	0.545	0.857
Acetic acid	0.689	0.390	0.781
2,2,2-Trifluoroethanol	0.893	0.107	0.912
Hexafluoro-2-propanol	1.00	0.014	1.014
Water	1.062	0.025	0.962

a) Assumed value.

b) By definition.

Finally, a solvent hydrogen-bond donor (HBD) acidity scale (*SA* scale) was developed by Catalán *et al.*, using the homomorphic merocyanines *(52)* and *(53)* as positively solvatochromic indicator dyes, *i.e.* 1-methyl-4-[(4-oxocyclohexadienylidene)-ethylidene]-1,4-dihydropyridine with one (TBSB) and two *t*-butyl groups (DTBSB) in the positions α- and α,α′- to the carbonyl group, respectively [296, 337]. The acronyms TBSB and DTBSB stand for *o*-*t*-butyl- and *o*,*o*′-di-*t*-butyl-stilbazolium betaine, respectively, *i.e.* names valid for the zwitterionic mesomeric ground-state structures of these dyes. The positive solvatochromism observed is more in agreement with the less dipolar 1,4-dihydropyridine structure ($\mu_g < \mu_e$). At least one of the two lone-pairs of the carbonyl group in dye *(52)* can interact with HBD solvents by hydrogen bonding. In dye *(53)*, the carbonyl group is shielded on both sides by bulky *t*-butyl groups and thus specific solute/solvent interactions are hindered. A solvent change from tetrahydrofuran (a non-HBD solvent) to methanol (a strong HBD solvent) results in bathochromic band shifts of $\Delta\lambda = +84$ nm ($\Delta\tilde{\nu} = -2537$ cm^{-1}) and $\Delta\lambda = +15$ nm ($\Delta\tilde{\nu} = -379$ cm^{-1}) for dyes *(52)* and *(53)*, respectively. As expected, the solvatochromic shift observed for the sterically hindered dye *(53)* is much less than that for *(52)*, the latter resulting from non-specific solute/solvent interactions only.

The *SA* scale was established using the solvatochromic comparison method of Kamlet and Taft [224, 226]. A good linear correlation ($r = 0.961$) has been found between the wavenumbers of the absorption maxima of dyes *(52)* and *(53)*, measured in fifty non-acidic or non-HBD solvents, according to Eq. (7-40c):

$$\tilde{\nu}(52) = 1.405 \cdot \tilde{\nu}(53) - 6289 \tag{7-40c}$$

It describes a reference line that can be used to quantify the deviations from this line found for acidic or HBD solvents. These deviations, $\Delta\tilde{\nu}$ (solvent), are then given by Eq. (7-40d) [*cf.* Fig. 7-3 and Eq. (7-33)]:

$$\Delta\tilde{\nu}(\text{solvent}) = \tilde{\nu}(52) - [1.405 \cdot \tilde{\nu}(53) - 6289] \tag{7-40d}$$

In going from tetrahydrofuran to ethanol, these $\Delta\tilde{\nu}$ values increase from −39 to 1300 cm^{-1}. In order to obtain a normalized scale of near-zero HBD acidity for non-HBD solvents and a value of roughly unity for HBD solvents, the *SA* scale was defined as follows [296, 337a]:

$$SA(\text{solvent}) = \frac{\Delta\tilde{\nu}(\text{solvent})}{\Delta\tilde{\nu}(\text{ethanol})} \cdot 0.4 = \frac{\Delta\tilde{\nu}(\text{solvent})}{1300} \cdot 0.4 \tag{7-40e}$$

The direct determination of *SA* values for more acidic solvents was not possible because in such solvents the indicator dyes *(52)* and *(53)* are protonated at the carbonyl oxygen atom. For such acidic solvents, 3,6-diethyl-1,2,4,5-tetrazine (DETZ) was introduced as a third probe dye [337b]. This aromatic tetrazine exhibits a solvent-dependent $n \rightarrow \pi^*$ absorption in the visible region: a change from methylcyclohexane ($\lambda_{max} = 550$ nm) to hexafluoro-2-propanol ($\lambda_{max} = 517$ nm) leads to a hypsochromic band shift of $\Delta\lambda = -33$ nm ($\Delta\tilde{\nu} = +1160$ cm^{-1}), mainly due to the HBD acidity of the solvent (see Section 6.2.3). Analogous application of Kamlet and Taft's solvatochromic comparison method made it possible to extend the *SA* scale to more acidic solvents; see reference [337b] for details. A selection of *SA* values is included in Table 7-5. For HBD solvents with known α and *SA* values, a rather good linear correlation between Kamlet and Taft's α values and Catalán's *SA* values has been found ($n = 7$, $r = 0.951$) [337a].

The general *SPP* scale of solvent dipolarity/polarizability and the specific *SB* and *SA* scales of solvent HBA basicity and HBD acidity, respectively, are orthogonal to one another and they can be used in the correlation analysis of solvent effects in single- or, in combination with the others, in two- or three-parameter correlation equations, depending on the solvent-influenced process under consideration; see also Section 7.7. Examples of the correlation analysis of a variety of other solvent-dependent processes by means of *SPP*, *SB*, and *SA* values, including those used for the introduction of other solvent polarity parameters, can be found in references [335–337, 340–342]. In particular, comparisons with Kamlet and Taft's π^* scale [340] and Winstein and Grunwald's *Y* scale [341] have been made.

7.5 Empirical Parameters of Solvent Polarity from Other Measurements

An important measure of the total molecular cohesion per unit volume of liquid is the *cohesive pressure c* (also called *cohesive energy density*), which characterizes the energy associated with all the intermolecular solvent/solvent interactions in a mole of the solvent. The cohesive pressure is defined as the molar energy of vapourization to a gas at zero pressure, ΔU_v, per molar volume of the solvent, V_m, according to Eqs. (3-5) and (5-76) in Sections 3.2 and 5.4.2, respectively [93, 94]. The cohesive pressure c is related to the *internal pressure* π; *cf.* Eq. (3-6) and Table 3-2 in Section 3.2.

The square root of the cohesive pressure has been termed by Hildebrand and Scott the solubility parameter δ because of its value in correlating and predicting solubility behaviour of non-electrolytes (ionogens) [93, 94]; *cf.* Eqs. (2-1) and (5-77) in Sections 2.1 and 5.4.2, respectively. Comprehensive lists of δ values are given in references [94, 95, 343]; *cf.* Table 3-3 in Section 3.2 for a selection. Correlations of δ values with other solvent polarity parameters have been attempted, but in most cases only relatively poor mutual relationships were found [96, 97, 255, 256]. Since δ values, which are characterized by the energy needed to separate molecules of the liquid, give only a measure of the attractive forces between the solvent molecules, they need not necessarily be a measure of the solute/solvent interaction forces. It could be that some of the solvent/solvent interaction forces are also of relevance in particular solute/solvent interactions. Rather, the δ values are related to the energy necessary to form a cavity in the solvent, which can then accommodate the solute molecule. In accordance with this is the experimental observation that a good solvent for a certain non-electrolyte solute should have a δ value close to that of the solute [93, 94]. Depending on the solvent, creation of a cavity in an organic solvent requires about 20...40 kJ/mol (5...10 kcal/mol).

Sometimes, Hildebrand's solubility parameter δ has been incorrectly used in linear Gibbs energy relationships; *cf.* for example [96, 97, 226, 255]. Since in linear Gibbs energy relationships the correlated solvent-dependent solute properties (*e.g.* $\lg K$, $\lg k$, $h \cdot \nu$) are proportional to Gibbs energy changes of reaction or activation (ΔG, $\Delta G^{\neq}$) and excitation energies (E_T), all the terms of a regression equation should include an energy dimension; *cf.* Eqs. (7-2) and (7-3) in Section 7.1. Therefore, it is unjustified to use δ values in such regression equations because they have the dimension of the square root of the energy ($J^{1/2} \cdot cm^{-3/2}$). Instead of δ, the cohesive pressure c, which is equal to δ^2, should be used, as has been demonstrated in work dealing with the inclusion of cavity terms in multiparameter regression equations [256–258].

It has been shown that gas-liquid chromatographic methods are particularly suitable for a quantitative characterization of the polarity of solvents. In gas-liquid chromatography it is possible to determine the solvent power of the stationary liquid phase very accurately for a large number of substances [98, 99, 259, 260]. Many groups of substances exhibit a certain dependence of their relative retention parameters on the solvation characteristics of the stationary phase or of the separable components. In determining universal gas-chromatographic characteristics, the so-called *retention index*, *I*, introduced by Kováts [100], is frequently used. The elution maxima of individual members of the homologous series of *n*-alkanes (C_nH_{2n+2}) form the fixed points of the system of retention indices. The retention index is defined by means of Eq. (7-41),

$$I = 100 \cdot \frac{\lg V_x - \lg V_n}{\lg V_{n+1} - \lg V_n} + 100 \cdot n \tag{7-41}$$

where V_x is the specific retention volume of solute x and V_n and V_{n+1} are the retention volumes of two *n*-alkanes with n and $n+1$ carbon atoms, respectively; hence, $V_n < V_x < V_{n+1}$. The retention index is independent of the gas-chromatographic equipment used, and depends only on the solute x, the temperature, and the stationary phase. The retention index specifies with which *n*-alkane a solute leaves the separation column, whereby the number of carbon atoms of the respective *n*-alkane is multiplied by 100. In other words, a retention index of 800 or 1100 means that the solute leaves the column simultaneously with either *n*-octane or *n*-undecane, respectively. A retention index of 732 implies that the solute exhibits the same retention time as a hypothetical *n*-alkane with 7.32 carbon atoms.

Kováts and Weiß [101] used these retention indices to examine the polarity of stationary liquid phases. If the total Gibbs energy of dissolution is determined by the work of separating the solvent molecules to form a hole, by a dispersion term, a polar term, and the energy of the donor/acceptor interaction, the sum of the last two terms is proportional to the difference between the retention indices of the solute on the column with a given liquid phase X (I_T^X) and with a standard nonpolar stationary phase (*i.e.* a hydrocarbon; $I_T^{St\,Ap}$) at temperature T. This difference, $\Delta I_T^X = I_T^X - I_T^{St\,Ap}$, is then proposed as the polarity parameter. Using 1-chloro- and 1-bromo-*n*-hexadecane as the standard dipolar stationary phase, and *n*-hexadecane as the standard nonpolar stationary phase, $\Delta I_{50}^{Cl/Br}$ was defined as the new polarity parameter according to Eq. (7-42) [101].

$$\Delta I_{50}^{Cl/Br} = I_{50}^{\text{1-chloro or 1-bromo-}n\text{-hexadecane}} - I_{50}^{n\text{-hexadecane}} \tag{7-42}$$

The $\Delta I_{50}^{Cl/Br}$ values show correlations with other empirical solvent polarity parameters, such as Z, $E_T(30)$, and $\lg k_1$ of 4-methoxyneophyl tosylate solvolysis [101].

Another more rigorous approach based on retention indices, taking into account the fact that the polarity of the column depends not only on the nature of the stationary phase but also on the type of substance being analyzed, has been suggested by Rohrschneider [98, 102]. The polarity of a stationary phase must therefore be assessed simultaneously with respect to a whole group of compounds possessing varying donor/acceptor properties. Rohrschneider proposed the five-term equation (7-43) for the solute retention, which has found widespread use in gas-chromatography [98, 99, 259, 260].

$$\Delta I = a \cdot x + b \cdot y + c \cdot z + d \cdot u + e \cdot s \tag{7-43}$$

a, b, c, d, and e are polarity factors of the stationary liquid phase, and x, y, z, u, and s are polarity factors of the substances undergoing analysis. Having determined the polarity factors of 22 different stationary phases with respect to chosen standard substances (benzene, ethanol, butan-2-one, nitromethane, and pyridine), and those of 30 other solutes, Rohrschneider calculated 660 retention indices with only small limits of error.

Using a different set of standard substances, *i.e.* substituting 1-butanol, pentan-2-one, and 1-nitropropane for the rather volatile ethanol, butan-2-one, and nitromethane, McReynolds developed an analogous approach [103]. Altogether, he characterized over 200 liquid stationary phases using a total of 10 probes. A statistical analysis of the McReynolds retention index matrix using the principal component analysis method has shown that only three components are necessary to reproduce the experimental data matrix [262]. The first component is related to the polarity of the liquid phase, the second depends almost solely on the solute, and the third is related to specific interactions with solute hydroxy groups [262].

Both of these approaches used in the characterization of stationary liquid-phase polarities by means of retention indices have been further explored and expanded [104, 259–261]. For a review on the characterization of solvent properties of phases used in gas-liquid chromatography by means of the retention index system, see reference [344]. Similar methods for the characterization of solvent polarity in liquid-liquid and liquid-solid chromatography can be found in references [105–107]; *cf.* also Section A-7 and Tables A-10 and A-11 in the Appendix.

7.6 Interrelation and Application of Solvent Polarity Parameters

From the previous Sections, we can conclude that there are many empirical solvent scales, the most comprehensive of which are the solvatochromic ones; *cf.* for example Table 7-3. Unfortunately, too many solvent scales have been proposed during the last decades. Around 35 different solvent scales are known*). Only about ten of them have found wider application in the correlation analysis of solvent effects, *i.e.* Y, Z, $E_T(30)$, α,

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* At present, the situation is not quite as bad as in the correlation analysis of substituent effects, where even more substituent parameters than common substituents seem to be known. It has been suggested that new solvent polarity scales should only be introduced into the literature if they exhibit significant advantages over existing solvent scales [235].

β, π^*, *DN* and *AN*, as well as *SPP*, *SA*, and *SB*. The application of most solvent scales is restricted by the fact that they are known only for an insufficient number of solvents. The catalogue of common organic solvents available to the chemist numbers about 300, not to speak of the infinite number of solvent mixtures! The extension of most solvent scales is restricted by the inherent properties of the selected reference process, which exclude the determination of solvent parameters for certain, often important solvents (*e.g.* chemical reactions between solute and solvent, solubility problems, *etc.*). For this reason, the most comprehensive solvent polarity scales are those derived from spectroscopic reference processes, which are the most easily measured for a large set of organic solvents.

In general, all these parameters constitute more comprehensive measures of solvent polarity than the relative permittivity or any other single physical characteristic, since they reflect more reliably the complete picture of all intermolecular forces acting between solute and solvent molecules. The solvent-dependent processes used to define solvent polarity parameters may be regarded as probes that permit a purely empirical investigation of solvent effects. In applying these parameters, however, it is tacitly assumed that the intermolecular interactions in the reference system used to develop a particular solvent scale are similar to those in the system the prediction of whose solvent effects is being raised. This is obviously true only for closely related solvent-dependent processes. Therefore, the use of single solvent parameters to predict solvent effects on equilibria, reaction rates, and spectral absorptions should be very restricted. One cannot expect a parameter to be universally useful for all kinds of solvent-sensitive processes, since any correlation of solvent effects of a particular process with a solvent polarity parameter is, in fact, a comparison with the effect of solvent on a reference process. However, if one compares the various empirical solvent scales (*cf.* Tables 7-1 to 7-5), based on very different solvent-sensitive reference processes, varying strongly in the energies involved, one finds, surprisingly, that most of the existing empirical solvent scales agree with each other very well qualitatively and even sometimes quantitatively. In spite of the large energy changes connected with a solvent change from methanol to hydrocarbon solvents for Z (*ca.* 100 kJ/mol), $E_T(30)$ (*ca.* 105 kJ/mol), $\lg k_1$ of 4-methoxyneophyl tosylate solvolysis ($-\ln 10 \cdot RT \cdot \lg k_1$ *ca.* 29 kJ/mol), and Ω values ($-\ln 10 \cdot RT \cdot \Omega$ *ca.* 2 kJ/mol), in all four cases one obtains similar polarity orders for the solvents. This led Berson to observe that "... in this respect a set of solvents behaves like an elephant, which can lift a log or a peanut with equal dexterity" [52].

In particular, there are good linear correlations between the $E_T(30)$ values and some other empirical solvent polarity parameters according to Eq. (7-44),

$$y = a \cdot E_T(30) + b \quad \text{or} \quad y = a \cdot E_T^N + b \tag{7-44}$$

where a and b were determined by the method of least squares. Compilations of such linear correlations between $E_T(30)$ values and other solvent polarity parameters can be found in references [124, 294b]. For example, there is a satisfactory linear correlation between the values of $E_T(30)$ and Z according to Eq. (7-45) ($n = 60$ solvents; correlation coefficient $r = 0.972$) [294b].

$$Z/(\text{kcal} \cdot \text{mol}^{-1}) = 1.27 \cdot E_T(30)/(\text{kcal} \cdot \text{mol}^{-1}) + 13.0 \tag{7-45}$$

The excellent $Z/E_T(30)$ correlation for a selected set of 15 solvents common to both scales has been used to calculate $E_T(30)$ values from Z values for acidic solvents for which $E_T(30)$ values are not available [172]; *cf.* footnote$^{f)}$ of Table 7-3. A similar satisfactory linear correlation between $E_T(30)$ values and acceptor numbers allows the calculation of AN values that are not directly available [207, 294b].

Of particular interest are the correlations between $E_T(30)$ or E_T^N values and the solvatochromic parameters π^*, α, and β of Kamlet and Taft [84a, 226, 235] as well as the SPP, SA, and SB parameters of Catalán *et al.* [335–337].

For 166 solvents, a satisfactory correlation between $E_T(30)$ or E_T^N values and Kamlet and Taft's solvatochromic parameters π^* and α has been obtained by Marcus [294b], according to Eqs. (7-46a) and (7-46b) ($n = 166$, $r = 0.979$):

$$E_T(30)/(\text{kcal}\cdot\text{mol}^{-1}) = 11.5\cdot\pi^* + 15.2\cdot\alpha + 31.2 \tag{7-46a}$$

$$E_T^N = 0.36\cdot\pi^* + 0.47\cdot\alpha + 0.01 \tag{7-46b}$$

An analogous satisfactory correlation has been found by Catalán [296] between $E_T(30)$ or E_T^N values and the solvatochromic parameters SPP, SA, and SB for 138 solvents, according to Eqs. (7-47a) and (7-47b) ($n = 138$, $r = 0.965$):

$$E_T(30)/(\text{kcal}\cdot\text{mol}^{-1}) = 20.1\cdot SPP + 24.9\cdot SA + 3.9\cdot SB + 20.7 \tag{7-47a}$$

$$E_T^N = 0.62\cdot SPP + 0.77\cdot SA + 0.12\cdot SB - 0.31 \tag{7-47b}$$

Eqs. (7-46) and (7-47) are in agreement with the observation that $E_T(30)$ and E_T^N values measure not only a blend of solvent dipolarity and solvent polarizability (as described by π^* and SPP, respectively), but for HBD solvents the solvent HBD acidity as well. In HBD solvents, the HBD acidity can even be the dominating solvent property: the quotients of the corresponding regression coefficients in Eqs. (7-46b) and (7-47b) are $0.47/0.36 = \mathit{1.31}$ and $0.77/0.62 = \mathit{1.24}$, respectively, *i.e.* greater than unity, which would be expected for equal contributions of both types of solute/solvent interactions. For non-HBD solvents, for which α and SA values are equal to zero, the $E_T(30)$ and E_T^N values essentially reflect only a blend of solvent dipolarity and polarizability. Not unexpectedly, the solvent HBA (or EPD) basicity (as described by β and SB, respectively) is not measured by the $E_T(30)$ or E_T^N values: the β and SB parameters make little or no contribution in the correlation equations (7-46) and (7-47). This is in agreement with the molecular structure of the pyridinium *N*-phenolate indicator dye *(44)*, which has no functional groups capable of interaction with HBA solvents. In the correlation analysis of solvent effects with significant contributions of HBD solute/HBA solvent interactions, a combination of $E_T(30)$ values and solvent donor numbers DN can considerably improve the correlations; see Eq. (7-60) in Section 7.7.

For attempts to improve the $E_T(30)/\pi^*$ correlations using modified Kamlet–Taft parameters (π_n^* and α_n), see references [234, 235].

The solvatochromic polarity parameter $E_T(30)$ or E_T^N is also related to some physical solvent properties beyond the solvent dipole moment, provided that solvents capable of specific solute/solvent interactions are excluded. In particular, Bekárek *et al.*

[194] and Makitra *et al.* [345] have tried to correlate $E_T(30)$ values with various functions of the solvent relative permittivities ε_r and solvent refractive indices n. For a selection of 50 aliphatic non-HBD solvents, the correlation equations (7-48a,b) have been established by Makitra *et al.* [345] ($n = 50$, $r = 0.952$):

$$E_T(30)/(\text{kcal} \cdot \text{mol}^{-1}) = 43.70 \cdot f(\varepsilon_r) + 4.12 \cdot f(n^2) + 20.63 \tag{7-48a}$$

$$E_T^N = 1.349 \cdot f(\varepsilon_r) + 0.127 \cdot f(n^2) - 0.311 \tag{7-48b}$$

where $f(\varepsilon_r)$ is equal to the Kirkwood function $(\varepsilon_r - 1)/(2\varepsilon_r + 1)$ and $f(n^2)$ represents the electronic polarizability term $(n^2 - 1)/(n^2 + 2)$, taken from the Lorenz–Lorentz equation. From the magnitudes of the respective regression coefficients, it can easily be seen that the $f(\varepsilon_r)$ term describes the predominant influence on the $E_T(30)$ or E_T^N parameter, provided that only non-specific solute/solvent interactions are considered [194, 345]. Somewhat different correlation equations have been found for aromatic solvents [194, 345]. For further correlation equations, including cross-terms such as $f(\varepsilon_r, n^2) = (\varepsilon_r - 1)(n^2 - 1)/(2\varepsilon_r + 1)(2n^2 + 1)$, see references [194, 345]. However, it was not possible to find relationships between $E_T(30)$ and various functions of permittivity and polarizability that are statistically valid for *all* groups of solvents.

Further single- and multi-parameter equations for correlations between $E_T(30)$ values and other empirical solvent polarity parameters, between various other empirical solvent parameters (*e.g.* α/Z, α/AN, β/DN, *etc.*), and between empirical solvent parameters and macroscopic physical solvent properties have been collected in the reviews of Marcus [294b], Abboud and Notario [295], and Catalán [296].

The application of single solvent parameters such as the $E_T(30)$ values in correlating other solvent-dependent processes has proved to be surprisingly successful. This means that the blend of different solute/solvent interaction forces, as measured by the solvatochromic pyridinium *N*-phenolate betaine dye *(44)*, is nearly the same as in numerous other solvent-dependent chemical reactions and spectral absorptions. It seems, therefore, that the blend of solute/solvent interactions as measured by the $E_T(30)$ values represents a kind of "mean solvent polarity", representative of many solvent-sensitive processes. As indicated by Eqs. (7-46) and (7-47), $E_T(30)$ values represent a combined measure of solvent dipolarity/polarizability and solvent HBD acidity (Lewis acidity), the latter property only being significant for protic (HBD) solvents. $E_T(30)$ correlations for more than 100 solvent-sensitive processes have been collected in references [2, 124, 200–203, 294b]. Three typical examples are given in Figs. 7-4 to 7-6.

Fig. 7-4 shows an excellent correlation between $E_T(30)$ values and the π–π^* transition energies of the open-chain form of a merocyanine dye obtained by irradiation of the corresponding photochromic benzthiazolospiropyran [108] (*cf.* the related spiropyran *(27a)*/merocyanine *(27b)* equilibrium in Section 4.4.2).

The structure of the open-chain form was assigned on the basis of its negative solvatochromic behaviour, which is similar to that of other meropolymethines such as the pyridinium *N*-phenolate betaines [108]. The correlation shown in Fig. 7-4 allows one to calculate absorption maxima of the merocyanine dye in other solvents for which $E_T(30)$ values are known.

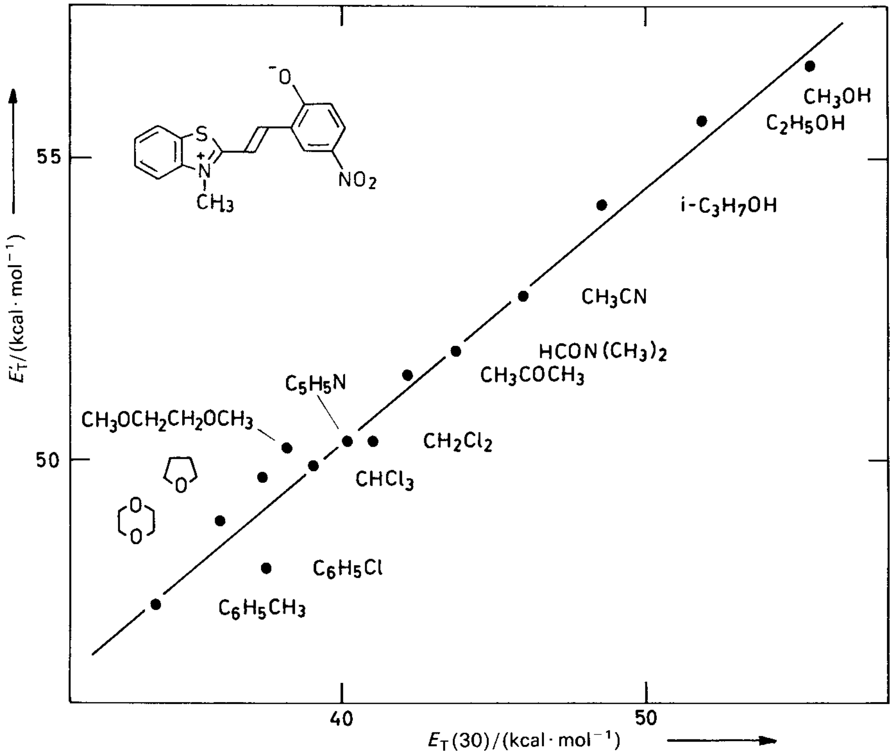

Fig. 7-4. Correlation between $E_T(30)$ [66] and the π–π^* transition energy, E'_T, of a merocyanine dye [108]. $E'_T = 0.42 \cdot E_T(30) + 33.5$ ($n = 14$; $r = 0.986$; $s = 0.482$).

A correlation between $E_T(30)$ values and the rate of thermal racemization of chiral allyl *p*-tolyl sulfoxide according to Eq. (5-38) in Section 5.3.2 is shown in Fig. 7-5 [109].

The linear decrease in reaction rate with increasing solvent polarity has been considered as evidence in support of the proposed reaction mechanism, involving a less dipolar cyclic activated complex (*cf.* discussion of this reaction in Section 5.3.2).

Fig. 7-6 demonstrates the correlation between $E_T(30)$ and the relative rates for the S_N2 Menschutkin reaction between a tertiary amine and a haloalkane in non-HBD solvents. The values of the second-order rate constants are taken from the compilation made by Abraham and Grellier [110].

A comparison of Fig. 7-6 with Fig. 5-11 in Section 5.4.3 reveals some improvement of the poor correlation between $\lg(k/k_0)$ and the Kirkwood function $(\varepsilon_r - 1)/(2\varepsilon_r + 1)$. If HBD solvents are included in the $E_T(30)/\lg(k/k_0)$ correlation, two lines are obtained as in Fig. 5-12, one for non-HBD and one for HBD solvents. This demonstrates the utility of such correlations in discovering specific solute/solvent interactions such as hydrogen-bonding.

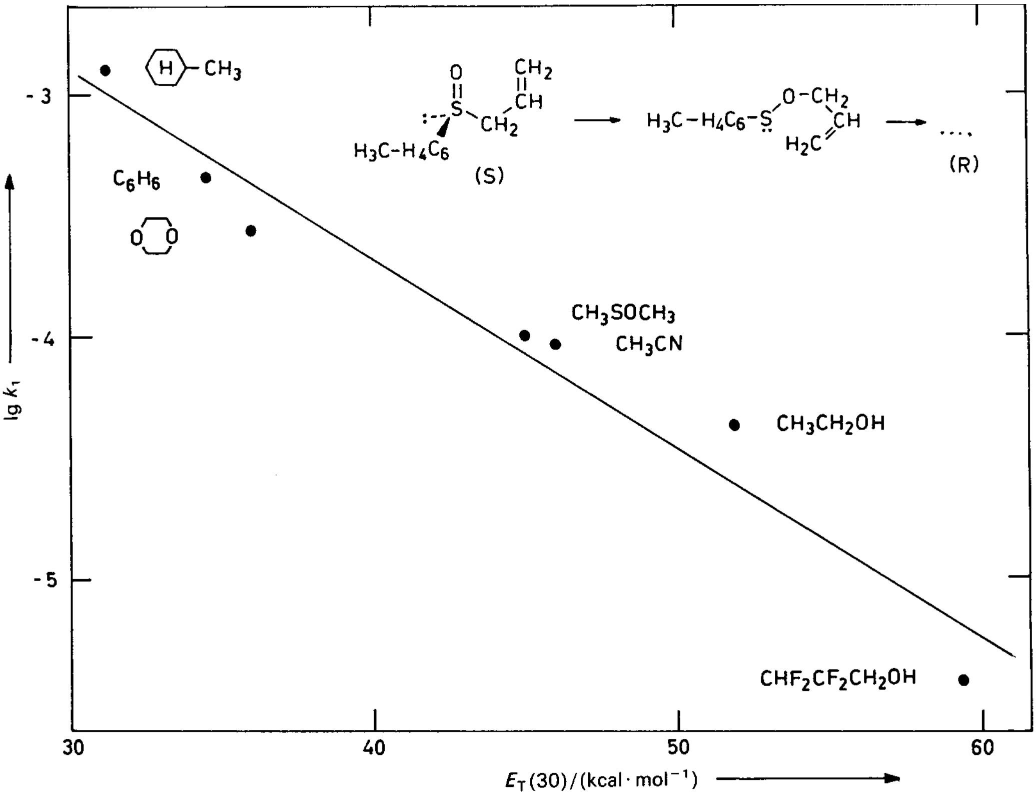

Fig. 7-5. Correlation between $E_T(30)$ [66] and lg k_1 for the thermal racemization of chiral allyl *p*-tolyl sulfoxide at 60.7 °C [109]; *cf.* Eq. (5-38). lg $k_1 = -0.078 \cdot E_T(30) - 0.55$ ($n = 7$; $r = -0.976$; $s = 0.222$).

It has been stated that, when specific hydrogen-bonding effects are excluded, and differential polarizability effects are similar or minimized, the solvent polarity scales derived from UV/Vis absorption spectra ($Z, S, E_T(30), \pi^*, \chi_R, E_K$), fluorescence spectra (*Py*), infrared spectra (*G*), ESR spectra [$a(^{14}N)$], ^{19}F NMR spectra (*P*), and ^{31}P NMR spectra (*AN*) are linear with each other for a set of select solvents, *i.e.* non-HBD aliphatic solvents with a single dominant group dipole [263]. This result can be taken as confirmation that all these solvent scales do in fact describe intrinsic solvent properties and that they are to a great extent independent of the experimental methods and indicators used in their measurement [263]. That these empirical solvent parameters correlate linearly with solvent dipole moments and functions of the relative permittivities (either alone or in combination with refractive index functions) indicates that they are a measure of the solvent dipolarity and polarizability, provided that specific solute/solvent interactions are excluded.

Applying a quantitative structure–property relationship (QSPR) analysis of 45 different empirical solvent scales and 350 solvents, a direct calculation of predicted

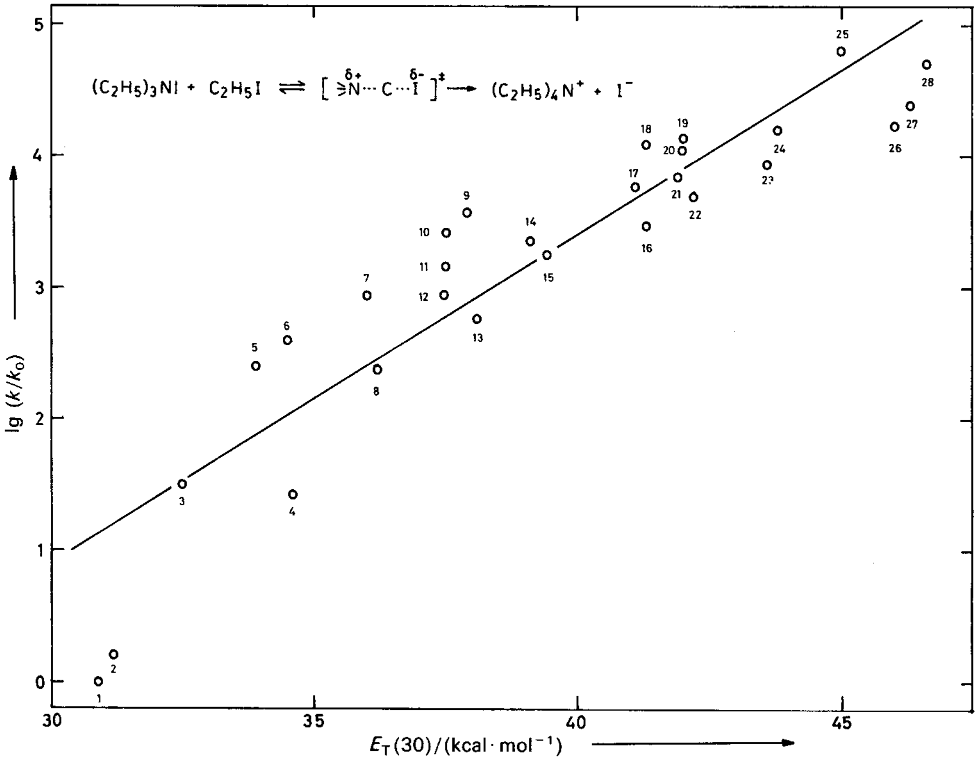

Fig. 7-6. Correlation between $E_T(30)$ [66] and $\lg(k/k_0)$ for the reaction between triethylamine and iodoethane in apolar and dipolar non-HBD solvents at 25 °C (rate constants relative to *n*-hexane as 'slowest' solvent) [110].

$\lg(k/k_0) = 0.248 \cdot E_T(30) - 6.54$ ($n = 28$; $r = 0.920$). (1) *n*-hexane, (2) cyclohexane, (3) tetrachloromethane, (4) diethyl ether, (5) toluene, (6) benzene, (7) 1,4-dioxane, (8) 1,1,1-trichloroethane, (9) iodobenzene, (10) bromobenzene, (11) chlorobenzene, (12) tetrahydrofuran, (13) ethyl acetate, (14) trichloromethane, (15) 1,1-dichloroethane, (16) 2-butanone, (17) dichloromethane, (18) acetophenone, (19) nitrobenzene, (20) benzonitrile, (21) 1,2-dichloroethane, (22) acetone, (23) propionitrile, (24) *N*,*N*-dimethylformamide, (25) dimethyl sulfoxide, (26) acetonitrile, (27) nitromethane, and (28) propylene carbonate.

values of empirical solvent parameters for any scale and for any previously unmeasured solvent is possible by means of the CODESSA program (*i.e.* *co*mprehensive *de*scriptors for *s*tructural and *s*tatistical *a*nalysis), developed by Katritzky *et al.* [346]. The QSPR models for each of the solvent scales are constructed using only theoretical descriptors, derived solely from the molecular solvent structure. This QSPR study has enabled a classification of the various empirical solvent scales, which provides considerable insight into the physicochemical background of these solvent scales [346]. Furthermore, a principal component analysis (PCA) has been carried out with 40 solvent scales as variables, each of them having 40 data points for 40 solvents as objects [347]. This PCA treatment allows a rational classification and grouping of both solvents and solvent scales. For 36 of the solvent polarity scales, an average of 88% of the variance is already described by the first three principal components, which can be roughly correlated to the solvent relative permittivity and dipolarity, as well as to their electrophilicity (HBD acidity) and nucleophilicity (HBA basicity) [347]; see also the end of Section 3.5. Another statistical treatment of a set of 32 solvent polarity scales for 45 solvents, using the program SMIRC (*i.e.* *s*election of a set of *m*inimally *i*nter*r*elated *c*olumns), has been carried out by Palm *et al.* [348], who introduced the first multi(four)-parameter equation for the correlation analysis of solvent effects; see Section 7.7.

There has been some criticism of the method of linear solvation Gibbs energy relationships. Using simulated solvatochromic correlation analyses by modeling dipole/dipole and dipole/induced-dipole interactions with a single combined parameter, Carr *et al.* have shown that, although good correlations can be obtained, the regression coefficients can be incorrect and not representative of the system under study [264]. Therefore, caution against overinterpretation of solvatochromic regression equations has been strongly recommended [264].

In conclusion, it is fair to say that the method of linear Gibbs energy correlations is still the most practical and simple method for predicting solvent effects on reaction rates, equilibria, and spectral absorptions, as well as for predicting substituent effects for reactions in solution. In so far as one understands why the model process responds to a solvent or substituent change, something can be learnt about the particular process under study. This kind of procedure has been criticized as being too empirical. However, one should take into account that not only the basic postulates of linear Gibbs energy relationships (*i.e.* additivity and separability) are of theoretically acceptable form, but the choice of a suitable reference process also requires intensive application of theory since the solute/solvent interaction of the model process and the process under investigation must be closely related.

7.7 Multiparameter Approaches

In spite of the observation that single empirical parameters, such as those mentioned in the foregoing Sections, may serve as good approximations of solvent polarity in the sense defined in Section 7.1 [1, 3], there are many examples of solvent-sensitive processes known which cannot be correlated to only one empirical solvent parameter. It has been repeatedly found that the simple concept of "polarity" as a universally determinable and applicable solvent characteristic is a gross oversimplification. The solvation capability or solvation power of a solvent, which has been roughly divided into non-specific and specific solute/solvent interactions, is the result of many different kinds of interaction mechanisms between the molecules of the solute and the solvent (*cf.* Section 2.2). Solvent effects are basically more complicated and often more specific than substituent effects. In the latter case, linear Gibbs energy relationships such as the Hammett equation are well-established and are known to work very well. In order to take into account two or more aspects of solvation, a multiparameter approach of the general form

$$A = A_0 + b \cdot B + c \cdot C + d \cdot D + \cdots \tag{7-49}$$

has been tried, where A is the value of a solvent-dependent physicochemical property ($\lg K$, $\lg k$, $h \cdot \nu$, *etc.*) in a given solvent, and A_0 is the statistical quantity corresponding to the value of this property in the gas phase or in an inert solvent. $B, C, D, \ldots$ represent independent but complementary solvent parameters, which account for the different solute/solvent interaction mechanisms; $b, c, d, \ldots$ are the regression coefficients describing the sensitivity of property A to the different solute/solvent interaction mechanisms. Such an equation can be applied only to data for a large number of wellchosen solvents, and its success must be examined by proper statistical methods [14, 15]. The separation of solvent polarity into various solute/solvent interaction mechanisms is purely formal and may not even be theoretically valid as the interactions could be coupled, *i.e.* not operate independently of each other. Nevertheless, if this separation can be reasonably accomplished, the resultant parameters may be used to interpret solvent effects through such multiple correlations, thus providing information about the type and magnitude of interactions with the solvent. On the basis of Eq. (7-49), the often observed failure of single solvent parameters can readily be understood. Any single empirical solvent parameter must have a fixed relative sensitivity to each of the various interaction mechanisms implied in Eq. (7-49). Thus, only application to processes that have the same relative sensitivity to various interaction mechanisms as the single solvent parameter will give a good correlation. Studies of multiparameter approaches to solvent effects on physical and chemical properties based on the general Eq. (7-49) have been made by Katritzky *et al.* [111], Koppel and Palm [6, 112], Kamlet and Taft [84a, 224, 226], Krygowski and Fawcett [113], Swain *et al.* [265], Mayer [266, 251], Dougherty [114], Pytela [349], Famini and Wilson [350, 364–369], Drago [351], and Catalán [296, 335–337]. Multiparameter treatments of solvent effects have been reviewed [293, 294, 296, 316, 339, 352].

Katritzky *et al.* [111] tested various multiparameter equations using linear combinations of existing empirical solvent parameters. The most successful treatment combines the $E_T(30)$ values (*cf.* Table 7-3) with functions of relative permittivity and index of refraction. Using $E_T(30)$ and the Kirkwood function $(\varepsilon_r - 1)/(2\varepsilon_r + 1)$, a two-parameter equation was constructed which allows independent variation of dipole/dipole and hydrogen-bonding forces. This equation is based on the assumptions that the Kirkwood function adequately represents dipole/dipole interactions and that $E_T(30)$ values are sensitive to both dipolar interactions and the interaction between solute and hydrogenbond donor (HBD) solvents. It could be shown that correlations of rates, equilibria, and spectral properties are indeed significantly improved by such multiparameter treatment, which implicitly allows for various independent interaction mechanisms between solvent and solute ground, transition, and excited states [111]. For a recent quantitative structure–property relationship (QSPR) analysis and a principal component analysis (PCA) of a large variety of different solvent scales by Katritzky *et al.*, see references [346, 347] and the end of Section 3.5.

A more rigorous approach has been suggested by Koppel and Palm [6, 112], who argue that a complete description of all solute/solvent interactions must include both non-specific and specific effects. They proposed the general four-parameter equation (7-50), which relates the variation of a given property A to two non-specific (Y and P) and two specific characteristics of the solvent (E and B).

$$A = A_0 + y \cdot Y + p \cdot P + e \cdot E + b \cdot B \tag{7-50}$$

A and A_0 are defined as in Eq. (7-49); by definition, A is equal to A_0 for the gas phase. The non-specific parameters Y*⁾ and P measure solvent polarization and polarizability, respectively, according to classical dielectric theory. E and B are specific parameters measuring the Lewis acidity (electrophilic solvating power) and Lewis basicity (nucleophilic solvating power) of the solvent, and y, p, e, and b are the corresponding regression coefficients indicating the sensitivity of A to the four different solvent parameters. Relative permittivities, ε_r, are the basis of Y, and were used in the form of the Kirkwood function, $(\varepsilon_r - 1)/(2\varepsilon_r + 1)$, or as $(\varepsilon_r - 1)/(\varepsilon_r + 2)$, a function based on the expression for molar polarization. The functions $(n^2 - 1)/(2n^2 + 1)$ or $(n^2 - 1)/(n^2 + 2)$ of the refractive index for sodium light were used for the polarizability parameter, P. In the effective numerical range, these pairs of functions are approximately co-linear, and the choice between the two functions $f(\varepsilon_r)$ and the two functions $f(n^2)$, respectively, is largely arbitrary.

A scale of Lewis acidity, E, was based on the $E_T(30)$ values discussed in Section 7.4 (*cf.* Table 7-3), but these were corrected for the influence of non-specific effects, and adjusted to an origin $E = 0$ for the gas phase by means of Eq. (7-51) [6, 112, 115].

$$
\begin{aligned}
E &= E_T(30) - E_T^0(30) - y \cdot Y - p \cdot P \\
&= E_T(30) - 25.10 - 14.84 \cdot Y - 9.59 \cdot P
\end{aligned}
\tag{7-51}
$$

The subtraction of the polarization $(y \cdot Y)$ and polarizability $(p \cdot P)$ contributions from the total solvent effect allows an estimation of the contribution from specific solute–solvent interactions. This correction of $E_T(30)$ values was made using least-squares regression analysis by correlating the data for suitably selected non-specifically and specifically interacting solvents. E values derived in this way from $E_T(30)$ values are presented in references [6, 115]; they range from zero (gas phase, saturated hydrocarbons) to about 22 kcal/mol for water. By definition, $e = 1$ in Eq. (7-50) for the reference process, *i.e.* the $\pi \rightarrow \pi^*$ transition of the pyridinium *N*-phenolate betaine dye *(44)*. The reason for assuming that $E_T(30)$, and thus E, largely relates to Lewis acidity in protic solvents has already been mentioned**⁾.

A scale of Lewis basicity, B, was based on the O—D infrared stretching band of CH_3OD, according to Eq. (7-35) in Section 7.4 [6, 87, 112]. EPD solvents reduce $\tilde{\nu}_{O-D}$ through hydrogen-bonding and the wavenumber shift measures the strength of the HBD solute/EPD solvent interaction. For use in Eq. (7-50) the shifts were adjusted to an origin $B = 0$ for the gas phase. By definition, $b = 1$ in Eq. (7-50) for the reference process, the IR wavenumber shifts of CH_3OD.

A detailed analysis of solvent effects on various solvent-sensitive processes by means of Eq. (7-50) has been presented by Koppel and Palm [6, 112]. If Eq. (7-50)

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* Not to be confused with the Y values of Grunwald and Winstein in Eq. (7-14).

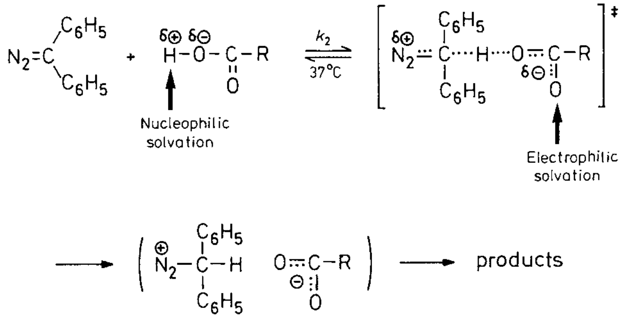
** The procedure for parameterization of solvent electrophilicity has been criticized, mainly because it was found that the use of $E_T(30)$ instead of E in the multiple regression treatment of solvent effects is often quite successful; see reference [15, 116] for examples. It has been shown that values of $E_T(30)$ and E are linearly correlated, at least for solvents with an $E_T(30)$ value of greater than *ca.* 40 kcal/mol [178]. This calls into question the value of Koppel and Palm's division of $E_T(30)$ into pure electrophilicity effects and non-specific effects by means of Eq. (7-51).

quantitatively reflects the influence of all basic types of solute/solvent interactions, it should be possible to correlate any solvent-dependent kinetic or spectral data in terms of *Y*, *P*, *E*, and *B* solvent parameters. This has been done for more than sixty solvent-sensitive processes [6]. Surprisingly, the majority of the processes investigated by Koppel and Palm [6] depend only on a single specific solvent parameter: in fifty cases, only electrophilic solvation is important (thus confirming the wide applicability of single $E_T(30)$ values), while in seven cases, nucleophilic solute/solvent interaction is the predominant solvation mechanism. Only one representative example will be mentioned in more detail in order to demonstrate what conclusions for any particular case can be drawn from Eq. (7-50). For a critical discussion of the Koppel–Palm treatment of solvent effects and valuable comments on its applicability, see reference [15].

The rate of reaction between benzoic acid and diazo-diphenylmethane in 44 non-HBD solvents correlates significantly with all four Koppel–Palm parameters of Eq. (7-50), according to Eq. (7-52) with $n = 44$, $r = 0.976$, and standard deviation $s = 0.188$ [15, 116]; *cf.* also [117].

$$\lg k_2 = -3.13 + 4.58 f(\varepsilon_r) + 11.96 f(n^2) + 0.195 E - 0.018 B \qquad (7\text{-}52)$$

The regression coefficients *e* and *b* are of opposite sign, and the order of decreasing significance of the four terms is $B > f(\varepsilon_r) > E > f(n^2)$, as shown by the stepwise regression. This result supports the mechanism given in the following reaction scheme:



The rate-determining step involves a proton-transfer from the carboxylic acid to form a diphenylmethyldiazonium/carboxylate ion-pair, which rapidly reacts in subsequent product-determining steps to give esters (or ethers in the case of alcoholic solvents). The negative sign of the basicity term of Eq. (7-52) indicates nucleophilic stabilization of the initial carboxylic acid, *i.e.* rate deceleration with increasing solvent basicity. The positive sign of the acidity term, however, indicates electrophilic stabilization of the activated complex, resulting in rate acceleration with increasing solvent acidity. Thus, the two counteracting solvent effects are nicely unravelled by this kind of treatment.

Recently, a statistical treatment of 31 different solvent parameter scales was carried out by Palm *et al.* [348], in order to find the minimum number of solvent parameters necessary for an adequate multiparameter description of solvent-dependent processes. Numerous applications of the Koppel–Palm Eq. (7-50) and modifications thereof to the correlation analysis of many solvent-dependent processes, taken from different areas of chemistry (*e.g.* kinetics [353, 354], extraction [302], partitioning [355], and solubility [356]), have been described by Makitra *et al.*

Another important treatment of multiple interacting solvent effects, in principle analogous to Eq. (7-50) but more precisely elaborated and more generally applicable, has been proposed by Kamlet, Abboud, and Taft (KAT) [84a, 224, 226]. Theirs and Koppel and Palm's approaches have much in common, *i.e.* that it is necessary to consider non-specific and specific solute/solvent interactions separately, and that the latter should be subdivided into solvent Lewis-acidity interactions (HBA solute/HBD solvent) and solvent Lewis-basicity interactions (HBD solute/HBA solvent). Using the solvatochromic solvent parameters α, β, and π^*, which have already been introduced in Section 7.4 (*cf.* Table 7-4), the multiparameter equation (7-53) has been proposed for use in so-called *linear solvation energy relationships* (LSER).

$$A = A_0 + s(\pi^* + d\delta) + a\alpha + b\beta \qquad (7\text{-}53)$$

The solute property A can represent, for example, the logarithm of a rate or equilibrium constant, as well as a position of maximal absorption in a UV/Vis, IR, NMR, or ESR spectrum*); A_0 is the regression value of this solute property in cyclohexane as reference solvent.

π^* is an index of solvent dipolarity/polarizability, which measures the ability of the solvent to stabilize a charge or a dipole by virtue of its dielectric effect. For a set of *select solvents*, *i.e.* non-HBD aliphatic solvents with a single dominant group dipole, the π^* values are proportional to the dipole moment of the solvent molecule. The π^* scale was selected to run from 0.00 for cyclohexane to 1.00 for dimethyl sulfoxide. The π^* values correspond to the use of relative permittivity and refractive index in the Koppel–Palm equation (7-50) as measures of polarization and polarizability interactions. Therefore, functions of ε_r and n^2 are not included in the KAT equation (7-53). The advantage of using π^* values instead of the functions $f(\varepsilon_r)$ and $f(n^2)$ is that the latter terms are properties of the *bulk* solvent, whereas the π^* values are derived from electronic transitions occuring on a *molecular-microscopic level* in solute-organized cybotactic regions, *i.e.* within the solvation shell of the solute [84a]. For later improvements of the π^* scale, see reference [227].

δ is a discontinuous polarizability correction term equal to 0.0 for non-chloro-substituted aliphatic solvents, 0.5 for poly-chloro-substituted aliphatics, and 1.0 for aromatic solvents. The δ values reflect the observation that differences in solvent polarizability are significantly greater between the three solvent classes than within the individual classes. Thus, the sign and magnitude of the δ term is related to the variable dipolarity/polarizability blend observed in the solvent influence on the solute property A.

α is a measure of the solvent hydrogen-bond donor (HBD) acidity and corresponds to Koppel and Palm's Lewis-acidity parameter E. It describes the ability of a solvent to donate a proton in a solvent-to-solute hydrogen bond. The α-scale was

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* In the original papers, the symbols XYZ and $(XYZ)_0$ were used instead of A and A_0 [84a]. For the sake of consistency with the general Eq. (7-49), A and A_0 are used in Eq. (7-53).

selected to extend from zero for non-HBD solvents (*e.g.* cyclohexane) to about 1.0 for methanol.

β is a measure of the solvent hydrogen-bond acceptor (HBA) basicity and corresponds to Koppel and Palm's Lewis-basicity parameter *B*. It describes the solvent's ability to accept a proton (or, *vice versa*, to donate an electron pair) in a solute-to-solvent hydrogen bond. The β-scale was selected to extend from zero for non-HBD solvents (*e.g.* cyclohexane) to about 1.0 for hexamethylphosphoric acid triamide (HMPT).

The regression coefficients *s*, *d*, *a*, and *b* in Eq. (7-53) measure the relative susceptibilities of the solvent-dependent solute property *A* to the indicated solvent parameters. Due to the normalization of the α, β, and π^* scale (from *ca.* 0.0 to *ca.* 1.0), the a/s, b/s, and a/b ratios are assumed to provide quantitative measures of the relative contribution of the indicated solvent parameters.

Eq. (7-53) has been used in the correlation analysis by multiple regression of numerous reaction rates and equilibria, spectroscopic data, and various other solvent-dependent processes. An impressive series of 46 articles entitled "Linear Solvation Energy Relationships" (LSER) has been published: Part 1 [229]... Part 46 [230]; see also the summarizing articles [127, 224, 227] and the critical compilation of solvent parameters (*e.g.* π^* and β) by Abboud and Notario [295].

Eq. (7-53) was subsequently extended to Eq. (7-54) by the introduction of two further solvent parameters, the δ_{H}^2 term*⁾ and the ξ term [226]

$$A = A_0 + s(\pi^* + d\delta) + a\alpha + b\beta + h\delta_{\mathrm{H}}^2 + e\xi \qquad (7\text{-}54)$$

δ_{H}^2 represents Hildebrand's solubility parameter squared and corresponds to the cohesive pressure *c*, which characterizes the energy associated with the intermolecular solvent/solvent interactions; *cf.* Eqs. (3-5) and (5-77) in Sections 3.2 and 5.4.2, respectively, for the definition of *c* and δ. Thus, δ_{H}^2 is considered as a measure of the enthalpy or Gibbs energy input required to separate solvent molecules to provide a suitably sized cavity for the solute. This solvent cavity term is important for multiple correlations dealing with enthalpies or Gibbs energies of solution, Gibbs energies of transfer between two solvents, or gas-liquid chromatographic partition coefficients. In most cases, the δ_{H}^2 term is only significant for highly structured solvents such as water, formamide, and 1,2-ethanediol.

In addition to the β parameter of solvent Lewis basicity, the coordinate covalency parameter ξ has been found to be useful in correlating certain types of so-called family-dependent solute basicity properties [226, 267]. Family-independent (FI) basicity properties are defined as those which have a linear relationship with β when *all* solute bases are considered together. Family-dependent (FD) basicity properties are those which exhibit a linear relationship with β only when different families of solutes having similar HBA sites are considered separately. Thus, FD properties can be correlated to FI properties if an empirical coordinate covalency parameter ξ is used in correlation equa-

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* The subscript H is used to distinguish the Hildebrand solubility parameter δ from the polarizability correction term δ in Eq. (7-54). In earlier formulations of Eq. (7-54), δ_{H} instead of δ_{H}^2 was wrongly used [96, 97, 226, 255]. In linear Gibbs energy relationships, all the terms of the regression equation should have the dimension of an energy, but δ_{H} has the dimension of the square root of the energy ($\mathrm{J}^{1/2} \cdot \mathrm{cm}^{-3/2}$); *cf.* Section 7.5 and references [256–258].

tions such as $A = A_0 + b\beta + e\xi$. Values of ξ are equal to -0.2 for P=O bases (*e.g.* HMPT), 0.0 for C=O and S=O bases (arbitrary reference value), 0.1 for triple-bonded nitrogen bases (*e.g.* nitriles), 0.2 for single-bonded oxygen bases (*e.g.* ethers), 0.6 for sp^2-hybridized nitrogen bases (*e.g.* pyridines), and 1.0 for sp^3-hybridized nitrogen bases (*e.g.* amines). The ξ values are interpreted as being approximate measures of the relative coordinate covalencies of the bonds which are formed between solute and solvent at the base centres of the solvent. Coordinate covalencies of solute/solvent adducts of a given solute acid decrease in strength (ξ decreases) as the electronegativity of the solvent base centre increases, because the positive charge created by coordinate covalency on an increasingly electronegative atom is unfavourable. The ξ values have been found to be useful in correlating the basicity behaviour of neutral oxygen and nitrogen bases of widely differing properties [267]. It has been stressed that the correlation equation $A = A_0 + b\beta + e\xi$ formally and conceptually resembles the Drago E/C treatment, with b and β corresponding to E_A and E_B, and e and ξ corresponding to C_A and C_B; *cf.* Eq. (2-12) in Section 2.2.6.

The multiparameter equation (7-54) seems to be rather difficult to apply. However, in practice, most of the linear solvation energy relationships that have been reported are simpler than indicated by Eq. (7-54) since one or more terms are inappropriate. For example, if the solute property A does not involve the creation of a cavity or a change in cavity volume between initial and activated or excited states (as is the case for solvent effects on spectral properties), the δ_H^2 term is dropped from Eq. (7-54). If the solvent-dependent process under study has been carried out in non-HBD solvents only, the α term drops out. On the other hand, if the solutes are not hydrogen-bond donors or Lewis acids, the β term drops out of Eq. (7-54). Thus, for many solvent-dependent processes, Eq. (7-54) can be reduced to a more manageable one-, two- or three-parameter correlation equation by a judicious choice of solutes and solvents [226].

The KAT equations (7-53) and (7-54) have been widely and successfully applied in the correlation analysis of all kinds of solvent-dependent processes; a review on their use in chromatography has been given by Carr [357]. Only two representative examples will be mentioned. Multiple regression of lg k_2 for the reaction between benzoic acid and diazo-diphenylmethane using the KAT equation (7-53), for the same set of 44 non-HBD solvents as used in the Koppel–Palm treatment of this reaction given in Eq. (7-52), leads to Eq. (7-55a), with $n = 44$, $r = 0.980$, and $s = 0.171$ [15, 268].

$$\lg k_2 = 0.20 + 1.21\pi^* + 2.71\alpha - 3.70\beta \tag{7-55a}$$

A comparison of Eqs. (7-52) and (7-55a) shows that both treatments give similar results, with opposite signs of the solvent Lewis-acidity and basicity parameters. This is in agreement with the given reaction mechanism, involving simultaneous nucleophilic and electrophilic solvent assistance.

Multiple regression analysis of lg k_1 of the strongly solvent-dependent solvolysis/dehydrohalogenation of 2-chloro-2-methylpropane (*t*-BuCl) for $n = 21$ solvents using the KAT equation (7-54) leads to Eq. (7-55b), with $r = 0.997$, and $s = 0.242$ [288]:

$$\lg k_1(t\text{-BuCl}) = -14.60 + 5.10 \cdot \pi^* + 4.17 \cdot \alpha + 0.73 \cdot \beta + 0.0048 \cdot \delta_H^2 \tag{7-55b}$$

From this correlation equation, it is immediately obvious that the first-order rate constant k_1 is increased by dipolar solvents (with large π^* values) and HBD solvents (with large α values). The small but statistically significant $b \cdot \beta$ term in Eq. (7-55b) is consistent with a weak nucleophilic solvent assistance in the solvolysis of 2-chloro-2-methylpropane. Increasing cohesive pressure (as given by δ_{H}^2) increases k_1 to a very small extent because of the electrostriction of the substrate solvation shell in going from the educt to the more dipolar activated complex; *cf.* Eq. (5-13) in Section 5.3.1. The complex solvent influence on 2-chloro-2-methylpropane solvolysis as described by Eq. (7-55b) is of relevance for its use as the standard reaction for the determination of Grunwald–Winstein's *Y* values as measures of solvent ionizing power; *cf.* the discussion of this topic and the question of nucleophilic solvent assistance in S_N1 reactions in the first part of Section 7.3.

A few comments of the KAT treatment of solvent effects should be made. Some shortcomings and the sometimes insufficient precision in the determination of the solvatochromic parameters have been discussed by Laurence *et al.* [167, 237, 238], who also recommended improvements by virtue of a new *thermosolvatochromic comparison method*; *cf.* Section 7.4 for a further discussion of this method. A study of linear Gibbs energy relationships (LGER) in a homologous series of *n*-alkane and *n*-alkylnitrile solvents, using Kamlet and Taft's solvatochromic indicator solutes, has shown that a single-lumped parameter of solvent dipolarity/polarizability such as the π^* values cannot be applied simultaneously to *n*-alkanes and *n*-alkylnitriles [269]. Therefore, it has been concluded by Carr *et al.* [269] that the hypothesis that solvent dipolarity and polarizability can be represented by a single parameter is certainly not generally valid. Kamlet, Abboud, and Taft have tried to consider this observation by incorporating the solvent polarizability correction term $d\delta$ in Eq. (7-53), which has different values for groups of aliphatic, chlorine-substituted aliphatic, and aromatic solvents*⁾, but the important distinction to be made is that the *solute* sensitivity to the two types of polarization can be quite different [269]. In this context, reference has to be made to Sjöström and Wold's results [236], who recommended, on statistical grounds, the use of a two-parameter equation of the form $A = A_0 + s_0\pi_0^* + s_d\pi_d^*$, where π_0^* and π_d^* represent solvent orientational and distortional polarizability scales, respectively.

Furthermore, there has been considerable discussion on the question as to whether or not linear Gibbs energy relationships (LGER), such as linear solvation energy relationships (LSER), are really fundamental laws of chemistry, reflecting simple physicochemical relationships, or rather local empirical rules of similarity, *i.e.* only locally valid linearizations of more complicated relationships [126, 127]; *cf.* Section 7.1 for a further discussion of this dialogue. Both parties, the chemometricians and the physical organic chemists, have tried to exemplify the merits of the two types of treatment of solvent effects, *i.e.* principal component analysis (PCA) and linear solvation energy relationships (LSER), by means of the correlation and rationalization of solvent effects on the ^{13}C NMR chemical shifts of lithium indenide, a planar delocalized carbanion,

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* The description of different solvent polarizabilities by means of three discontinuous polarizability correction terms δ ($\delta = 0.0$, 0.5, or 1.0 for three solvent groups) as in Eqs. (7-53) and (7-54) is surely an oversimplification [167].

measured in a set of 13 solvents; see references [270, 271] as well as [126, 127] for this lengthy discussion.

Kamlet, Taft, Abraham *et al.* have further modified Eq. (7-54) in order to correlate the solubility and distribution behaviour of nonelectrolyte solutes with solvent properties, according to Eq. (7-56) [271, 272],

$$A = A_0 + A'(\delta_{\mathrm{H}}^2)_1(V_2/100) + B\pi_1^*\pi_2^* + C\alpha_1\beta_2 + D\beta_1\alpha_2 \tag{7-56}$$

where subscript 1 refers to the solvent and subscript 2 to the solute, and A', B, C, and D are the regression coefficients for the endoergic cavity term, the exoergic dipolarity/polarizability term, and the exoergic hydrogen-bonding terms of adduct formation between HBD solvents and HBA solutes (measured by α_1 and β_2) as well as between HBA solvents and HBD solutes (measured by β_1 and α_2), respectively. V_2 is the molar volume of the solute, taken as its molecular mass divided by its liquid density at 20 °C. Whereas $(\delta_{\mathrm{H}}^2)_1$ represents the solvent's contribution to the cavity term, $V_2/100$ represents the solute's contribution to the cavity term. Instead of V_2, $V_2/100$ is used so that the parameter describing the cavity term will roughly cover the same numerical range as the other independent variables α, β, and π^* (*ca.* 0.0 ... 1.0). This simplifies the evaluation of the relative contributions of the various terms of Eq. (7-56) to the property A.

When dealing with the effects of different solvents on the properties of a single solute (*e.g.* solvent effects on reaction rates), the factors relating to the solute can be subsumed into the regression coefficients of Eq. (7-56), and the following equation results:

$$A = A_0 + h(\delta_{\mathrm{H}}^2)_1 + s\pi_1^* + a\alpha_1 + b\beta_1 \tag{7-57}$$

In Eq. (7-57), the dependence of the solute property A on each term is now given solely by solvent parameters. Furthermore, when the solute property A does not involve cavity formation or a cavity change, the cavity term drops out, and Eq. (7-57) takes the form of Eq. (7-53) (with $d = 0$).

Conversely, when dealing with solubilities or other properties of a set of different solutes in a single solvent, or with distributions of different solutes between a certain pair of solvents, the resulting Eq. (7-58) relates property A only to the solute parameters V_2, π_2^*, α_2, and β_2, and the solvent parameters are now subsumed into the regression coefficients.

$$A = A_0 + m(V_2/100) + s\pi_2^* + a\alpha_2 + b\beta_2 \tag{7-58}$$

For example, this equation has been successfully used to correlate the Hansch-Leo 1-octanol/water partition coefficient, $K_{\mathrm{o/w}}$, of 102 aliphatic and aromatic solutes according to Eq. (7-59) with the indicated solute properties ($n = 102$, $r = 0.989$, $s = 0.175$) [149]; *cf.* Eq. (7-12) in Section 7.2 for the definition of $K_{\mathrm{o/w}}$ [145–148].

$$\lg K_{\mathrm{o/w}} = 2.74(V_2/100) - 0.92\pi_2^* - 3.49\beta_2 + 0.20 \tag{7-59}$$

Dealing with this type of multiparameter correlation analysis, a series of twelve articles entitled "Solubility Properties in Polymers and Biological Media" was published by Kamlet, Taft, Abraham *et al.* (Part 1 [273]...Part 12 [274]), as well as another series entitled "Solute–Solvent Interactions in Chemical and Biological Systems" (Part 4 [358]...Part 7 [359]). The application of the LSER equation (7-58) to the prediction of solubilities of organic nonelectrolytes in water, blood, and other body tissues has been reviewed [286].

The KAT equation (7-58) for the correlation analysis of *solute* properties (*e.g.* solubility, partitioning, gas-chromatographic behaviour, *etc.*) has been further developed and refined by Abraham [360]. Abraham's multiparameter LSER equation consists of five *solute* descriptors, specified as follows: a combined dipolarity/polarizability descriptor (π_2^{H}), two descriptors for the effective HBD acidity (α_2^{H}) and HBA basicity (β_2^{H}), the excess molar refraction (R_2), and the solute gas/*n*-hexadecane partition coefficient ($\lg L$) or McGowan's characteristic volume (V_{x}). This multiparameter equation describes the properties of a series of *solutes* in a given solvent. That is, the solvent properties remain constant and only the solute is varied. Because solvent parameters are not needed, a more detailed consideration of this widely applied and highly successful approach is beyond the scope of this book. For some leading references, see [361] (correlation of gas-liquid chromatographic data), [362] (water/1-octanol partitioning, brain penetration, skin permeability), and [363] (solubility of C_{60} fullerene).

In formal analogy to the KAT equation (7-53), Catalán has combined his solvatochromically derived solvent parameters *SPP*, *SA*, and *SB* in the three-parameter equation (7-60) [296, 335–337]:

$$A = A_0 + a \cdot SPP + b \cdot SA + c \cdot SB \tag{7-60}$$

where *SPP* corresponds to the solvent dipolarity/polarizability, *SA* to the solvent HBD acidity, and *SB* to the solvent HBA basicity; for their precise definition, see Eqs. (7-40a), (7-40b), and (7-40e) as well as Table 7-5 in Section 7.4. This equation has been used to investigate some other reported solvent polarity scales [296]. For example, it has been shown that the $E_{\mathrm{T}}(30)$ scale correlates well with Eq. (7-60), which gives some insight into the various solute/solvent interactions contributing to this empirical solvent polarity scale; see Eqs. (7-47a,b) in Section 7.6.

Multiple regression analysis of $\lg k_1$ for the solvent-dependent solvolysis/dehydrohalogenation of 2-chloro-2-methylpropane (*t*-BuCl) by means of Eq. (7-60) leads, for $n = 148$ solvents and binary solvent mixtures to Eq. (7-61), with $r = 0.990$ and $s = 0.40$ [341]:

$$\lg k_1(t\text{-BuCl}) = -20.07 + 10.62 \cdot SPP + 7.89 \cdot SA + 1.71 \cdot SB \tag{7-61}$$

In analogy to Eq. (7-55b), all three individual solvent parameters contribute to the overall solvent effect, increasing the first-order rate constant k_1 with increasing *SPP*, *SA*, and *SB* values. Again, a small but significant accelerating effect results from the solvent HBA basicity term $c \cdot SB$, in agreement with a weak nucleophilically assisted S_N1 reaction; *cf.* also Eq. (7-55b) and the discussion of the mechanism of this S_N1 reaction in connection with the *Y* values of Grunwald and Winstein.

A more simplified but likewise successful empirical two-parameter approach for the description of solvent effects has been proposed by Krygowski and Fawcett [113]. They assume that only specific solute/solvent interactions need to be considered. These authors postulated that the solvent effect on a solute property A can be represented as a linear function of only two independent but complementary parameters describing the Lewis acidity and Lewis basicity of a given solvent. Again, for reasons already mentioned, the $E_T(30)$ values were chosen as a measure of Lewis acidity. In addition, Gutmann's donor numbers DN [26, 27] were chosen as a measure of solvent basicity (*cf.* Table 2-3 and Eq. (7-10) in Sections 2.2.6 and 7.2, respectively). Thus, it is assumed that the solvent effect on A can be described in terms of Eq. (7-62)*⁾.

$$A = A_0 + \alpha \cdot E_T(30) + \beta \cdot DN \tag{7-62}$$

α and β are regression coefficients describing the sensitivity of the solute property A to electrophilic and nucleophilic solvent properties, respectively. Since α and β are not necessarily on the same scale, due to the fact that $E_T(30)$ and DN do not vary over the same range for a given set of data, the regression coefficients were normalized to give $\bar{\alpha}$ and $\bar{\beta}$. Application of Eq. (7-62) involves the supposition that non-specific solute/solvent interactions are negligible or nearly constant and can be included in the solvent Lewis acidity and basicity terms. Obviously, this is a serious simplification. However, in spite of this simplification, the Krygowski–Fawcett treatment of solvent effects has been successfully applied in many cases [113]. Satisfactory correlations were obtained in 90% of the cases involving ion/solvent and ion/ion interactions, and in 75% of those involving dipole/dipole interactions [113]; see references [118–120, 232] for applications of Eq. (7-62) and its modifications.

A further interesting two-parameter treatment of solvent effects has been given by Swain *et al.* [265]. It is based on a computer calculation involving 1080 data sets for 61 solvents and 77 solvent-sensitive reactions and physicochemical properties, taken from the literature (*e.g.* rate constants, product ratios, equilibrium constants, UV/Vis, IR, ESR, and NMR spectra). According to these calculations, all solvent effects can be rationalized in terms of two complementary solvent property scales, *i.e.* A_j, measuring the solvent's anion-solvating tendency or *acity***⁾, and B_j, measuring the solvent's cation-solvating tendency or *basity***⁾, which are combined in Eq. (7-63)***⁾ [265].

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* In the original paper, Q and Q_0 were used instead A and A_0 [113]. For the sake of consistency with the general Eq. (7-49), A and A_0 are used in Eq. (7-62).

** The new names *acity* and *basity* were chosen because, although they are obviously kinds of acidity and basicity, they are neat (bulk) solvent properties involved in solute solvations. Such solvent properties cause specific local electrostatic solute/solvent interactions without major covalency changes and, therefore, are usually omitted from equations describing chemical reactions [265].

*** In the original publication, Eq. (7-63) takes the form

$$p_{ij} = c_i + a_i \cdot A_j + b_i \cdot B_j$$

with p_{ij} representing the solvent-dependent solute property i in solvent j, and c_i representing the predicted value for a reference solvent for which $A_j = B_j = 0$ [265]. For the sake of consistency with the general Eq. (7-49), A and A_0 instead of p_{ij} and c_i are used in Eq. (7-63), in spite of the unfortunate cumulation of the letter A.

$$A = A_0 + a_i \cdot A_j + b_i \cdot B_j \tag{7-63}$$

A_j and B_j characterize the solvent *j*. A and A_0 as well as the multiple regression coefficients a_i and b_i depend only on the solvent-sensitive solute property *i* under study. Constants a_i and b_i represent the sensitivity of solute property *i* to a solvent change. A nonlinear least-squares procedure, using equal statistical weighting of the 1080 data, has been used to evaluate and to optimize all 353 $[=(2 \cdot 61) + (3 \cdot 77)]$ constants A_j, B_j, a_i, b_i, and A_0 in order to get the best possible fit consistent with Eq. (7-63). In order to obtain values of A_j and B_j which represent physically significant solvent influences that are cleanly separated, some scale-setting subsidiary conditions have to be fixed. As trivial, arbitrary conditions that set zeros and scale factors but do not affect rank orders, $A_j = B_j = 0.00$ for *n*-heptane and $A_j = B_j = 1.00$ for water have been chosen. As two non-trivial, critical conditions, $A_j = 0.00$ for hexamethylphosphoric acid triamide (HMPT) and $B_j = 0.00$ for trifluoroacetic acid (TFA), have been chosen. This choice is equivalent to the assumption that HMPT is almost as poor an anion solvator, and TFA is almost as poor a cation solvator, as *n*-heptane.

Table 7-6 lists a selection of A_j and B_j values in order of their sum $(A_j + B_j)$, which may be considered as a measure of "solvent polarity" in terms of the overall solvation capability of a solvent; *cf.* Section 7.1 and references [1, 3] for this definition of solvent polarity. A plot of A_j against B_j shows that both parameters are highly variable, but there is no correlation between A_j and B_j, an essential condition for the application of Eq. (7-63). Interestingly, the overall correlation coefficient between the 1080 input data and the predictions made by Eq. (7-63) is excellent, at $r = 0.991$. That means that the two unrelated solvent parameters A_j and B_j alone account for over 98% of the solvent effects in the set of 77 solvent-sensitive processes that have been examined by Swain *et al.* [265]. Since, for the 1080 diverse input data, the solvent properties can be adequately represented by only two parameters A_j and B_j, there must be a correlation among the three neat solvent properties, *i.e.* anion-solvating tendency, hydrogen-bonding acidity (HBD acidity), and electrophilicity, and likewise cation-solvating tendency, hydrogen-bonding basicity (HBA basicity), and nucleophilicity, respectively.

The coefficients a_i and b_i, calculated for the 77 solvent-sensitive processes used to establish Eq. (7-63) as well as for 11 further solvent-dependent reactions (including another 75 data), have been discussed in detail in reference [265]. For example, $a_i = 1.87$ and $b_i = -0.05$ for the $n \rightarrow \pi^*$ absorption of benzophenone. With the high value of a_i and the negligible value of b_i, this solvent-dependent UV/Vis absorption comes close to measuring A_j in pure form. The $E_T(30)$ values (*cf.* Table 7-3) are characterized by $a_i = 30.36$ and $b_i = 4.45$ $(a_i/b_i = 6.8)$, in agreement with other observations showing that the $E_T(30)$ values are mainly related to the solvent Lewis acidity, and not to the solvent Lewis basicity. Application of Eq. (7-63) to several hundred increasingly diverse additional solvent-dependent reactions has led to satisfactory correlations (with $r > 0.965$); four explanations for non-agreement have been found and discussed by Swain *et al.* [265].

In view of the success in correlating so many solvent effects by only two solvent parameters according to Eq. (7-63), Swain *et al.* concluded that not all four solvent parameters of the KAT Eq. (7-53) are necessary; additional parameters do not improve the fits already observed with Eq. (7-63), and, for example, the β parameter of Eq. (7-53)

Table 7-6. Selection of values of solvent acity, A_j, and solvent basity, B_j, for 34 solvents, calculated according to Eq. (7-63) [265].

Solvents *j*	A_j	B_j	$(A_j + B_j)$[a]
n-Heptane	*0.00*	*0.00*	0.00
Cyclohexane	0.02	0.06	0.09
Triethylamine	0.08	0.19	0.27
Tetrachloromethane	0.09	0.34	0.43
Diethyl ether	0.12	0.34	0.46
Carbon disulfide	0.10	0.38	0.48
Toluene	0.13	0.54	0.67
Benzene	0.15	0.59	0.73
Ethyl acetate	0.21	0.59	0.79
Tetrahydrofuran	0.17	0.67	0.84
Chlorobenzene	0.20	0.65	0.85
1,4-Dioxane	0.19	0.67	0.86
t-Butanol	0.45	0.50	0.95
Methoxybenzene	0.21	0.74	0.96
2-Butanone	0.23	0.74	0.97
2-Propanol	0.59	0.44	1.03
Acetone	0.25	0.81	1.06
Acetic acid	0.93	0.13	1.06
Hexamethylphosphoric acid triamide	*0.00*	1.07	1.07
1-Propanol	0.63	0.44	1.08
Ethanol	0.66	0.45	1.11
1,2-Dichloroethane	0.30	0.82	1.12
Dichloromethane	0.33	0.80	1.13
Trichloromethane	0.42	0.73	1.15
Pyridine	0.24	0.96	1.20
Acetonitrile	0.37	0.86	1.22
N,*N*-Dimethylformamide	0.30	0.93	1.23
Methanol	0.75	0.50	1.25
Nitromethane	0.39	0.92	1.31
Dimethyl sulfoxide	0.34	1.08	1.41
Ethane-1,2-diol	0.78	0.84	1.62
Formamide	0.66	0.99	1.65
Trifluoroacetic acid	1.72	*0.00*	1.72
Water	*1.00*	*1.00*	2.00

[a] The solvents are listed in order of their sum $(A_j + B_j)$, which is considered as reasonable measure of "solvent polarity" in terms of the overall solvation capability of a solvent [265].

is rendered superfluous [265]. These conclusions, as well as Swain *et al.*'s general approach, have been criticized by Taft, Abboud, and Kamlet [275], leading to a reply by Swain [276] dismissing this criticism. The reader is referred to references [275, 276] and to the June issue of the *Journal of Organic Chemistry* in 1984 for this interesting discussion (issue no. 11, p. 1989–2010).

Both Kamlet, Abboud, and Taft *et al.*'s [224, 226] and Swain *et al.*'s [265] multiparameter solvent effect treatments have an inherent weakness in so far as the solvent parameters α, β, and π^* as well as A_j and B_j are averaged and statistically optimized parameters: the former are derived from various types of solvatochromic indicator dyes, while the latter are calculated from a selection of 77 solvent-sensitive processes. Thus, they are no longer directly related to a distinct, carefully selected, well-understood single reference process [as, for example Y_{OTs}, Z, and $E_{\mathrm{T}}(30)$]; *cf.* footnote on page 379. The significance of such averaged and statistically optimized solvent parameters depends above all on (i) the right choice of the various solvent-dependent processes used in the averaging procedure, which has to be done with a skillful hand, and (ii) the right choice of the critical subsidiary conditions, which have to be defined and justified in order to get solvent parameters with a clear physical meaning at the molecular-microscopic level*). For example, concerning point (i), according to Taft, Abboud, and Kamlet [275], most of the 77 solvent-dependent processes selected by Swain *et al.* [265] involve only non-HBD solutes (reactants or indicator dyes). Therefore, Swain *et al.*'s finding that Kamlet, Abboud, and Taft's β parameter of solvent HBA basicity is superfluous may have resulted from a somewhat unfortunate data selection. As far as point (ii) is concerned, Swain criticizes that in three-parameter equations such as (7-53) the six critical subsidiary conditions needed to assure that the derived solvent parameters are physically significant are often not properly defined. It has been stressed that optimization of the correlations through adjustment of the solvent parameters is not enough and has nothing to do with the physical significance of these calculated solvent parameters [276].

Another semiempirical multiparameter relationship for the description of solvent effects on the statics and kinetics of chemical reactions, according to Eqs. (7-64) and (7-65), has been introduced by Mayer [266].

$$\Delta G^S - \Delta G^R = a \cdot (DN^S - DN^R) + b \cdot (AN^S - AN^R) + c \cdot (\Delta G_{vp}^{0S} - \Delta G_{vp}^{0R}) \quad (7\text{-}64)$$

$$\Delta\Delta G = a \cdot \Delta DN + b \cdot \Delta AN + c \cdot \Delta\Delta G_{vp}^{0} \quad (7\text{-}65)$$

ΔG represents the Gibbs energy of reaction or activation ($\Delta G^{\neq}$), DN the donor number [26, 27], AN the acceptor number [91], and ΔG_{vp}^{0} the standard molar Gibbs energy of vapourization of a solvent S and a reference solvent R, respectively. Acetonitrile ($\Delta G_{vp}^{0} = 5.31$ kJ/mol) has been used as a reference solvent [266]. The coefficients a and b are correlated to the donor and acceptor strengths of the reaction partners relative to those of the reference compounds $SbCl_5$ and $(C_2H_5)_3PO$, respectively. This approach is based on a model developed for calculating the Gibbs energy change associated with the creation of cavities in the solvent, the size of which corresponds to the volume occupied by the solute molecules. Experimental equilibrium and rate data, including solubility measurements, complex-formation equilibria, ion-pair equilibria, and an S_NAr reaction,

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* For a two-parameter treatment of solvent effects (with two independent solvent vectors), only two critical subsidiary conditions must be defined in order to force the two solvent parameters to represent physically significant solvent properties. Four other trivial arbitrary conditions have to be defined in order to fix zero reference points and scale-unit sizes. However, for a three-parameter treatment (with three independent solvent vectors), already six critical subsidiary conditions must be defined, in addition to the six trivial reference or scale-factor conditions. On the contrary, single-parameter treatments require no definition of critical subsidiary conditions, but only one reference (zero) condition and one standard (unit) condition, whose arbitrary assignment changes only the reference solvent and the scale-unit size [265, 276].

have been successfully used to test Eqs. (7-64) and (7-65) by the method of multiple linear regression analysis [266]. In a remarkable application of Eq. (7-65) (with $c = 0$), it has been shown that for non-HBD solvents the logarithm of their relative permittivities can be represented by a linear combination of the acceptor number and the donor number [134, 207]; *cf.* also [139].

Finally, a multiparameter correlation equation based solely on theoretically determined solvent descriptors, introduced by Famini and Wilson, deserves attention [350]. Linear solvation energy relationships (LSERs), such as the KAT equation (7-54) and its successors, can be summarized by the general form shown in Eq. (7-66):

$$\begin{aligned} A = A_0 &+ \text{dipolarity/polarizability term(s)} \\ &+ \text{hydrogen-bonding term(s)} + \text{bulk/cavity term} \end{aligned} \tag{7-66}$$

where A and A_0 are the values of the solvent-dependent physicochemical property in a given solvent and in the gas phase or in an inert solvent, respectively; *cf.* also Eq. (7-49). As mentioned before, the dipolarity/polarizability terms are measures of solute/solvent dipole and induced dipole interactions (exoergic). The hydrogen-bonding terms give a measure of the energy of interaction (exoergic) when hydrogen-bonded HBA solute/HBD solvent and/or HBD solute/HBA solvent complexes are formed. The bulk or cavity term is a measure of the energy needed to overcome the cohesive solvent/solvent interactions (endoergic) to form cavities for the solute molecules. The regression coefficients of the LSER equation provide chemical insight into the specific molecular properties or solute/solvent interactions that impact most strongly on the solvent-dependent process under study. Usually, not all terms of an LSER equation are statistically significant.

The solvent descriptors in LSER equations mentioned so far have been experimentally obtained using carefully selected solvent-dependent reference processes, in most cases the UV/Vis absorption of solvatochromic indicator dyes. In addition to these experimentally based LSER equations, a new theoretical set of solvent parameters has been developed by Famini and Wilson [350]. Termed the theoretical linear solvation energy (TLSER) descriptors, these parameters are determined solely from computational methods permitting an *a priori* prediction of solvent properties. The TLSER descriptors were developed so as to give TLSER equations with correlation coefficients and standard deviations close in value to those for normal LSERs, and to be as widely applicable to solvent-dependent processes as the normal LSER set. A set of six TLSER descriptors has been developed by Famini and Wilson and the resulting generalized TLSER equation for solutes in a given solvent is shown in Eq. (7-67) [350]:

$$A = A_0 + a \cdot V_{\mathrm{mc}} + b \cdot \pi_{\mathrm{I}} + c \cdot \varepsilon_{\alpha} + d \cdot \varepsilon_{\beta} + e \cdot q_{-} + f \cdot q_{+} \tag{7-67}$$

In this equation, V_{mc} represents the molecular van der Waals volume (in Å^3) and indicates the cavity size needed in the solvent matrix to accommodate the solute. The polarizability index, π_{I}, is obtained by dividing the polarizability volume by the molecular volume, to give a alternatively size-independent quantity that indicates the ease with which electrons may move throughout the solvent molecule. The solvent HBD acidity and HBA basicity are modeled by covalent terms ε_α and ε_β, and electrostatic terms q_- and q_+. The ε_α and ε_β terms are derived from linear functions of the highest occupied molecular orbital (HOMO) energy and the lowest unoccupied molecular orbital (LUMO) energy, respectively. The covalent HBD acidity term, ε_α, is defined as a linear transformation of the energy difference between E_{HOMO} of water and E_{LUMO} of the solute, according to $0.30 - [0.01|(E_{\text{LUMO(solute)}} - E_{\text{HOMO(water)}})|]$. This transformation provides a 'zero-point' reference for the scale and corrects the scale to be positive with increasing acidity. The covalent HBA basicity term, ε_β, is likewise defined, but uses the LUMO energy of water and the HOMO energy of the solute, according to $0.30 - [0.01|(E_{\text{LUMO(water)}} - E_{\text{HOMO(solute)}})|]$. The water energies have been included for 'aesthetic reasons' [350c]: the smaller these differences are, the greater is the ability to form a hydrogen bond with water. The electrostatic contribution to the HBA basicity, q_-, is the magnitude of the largest negative formal charge on a nonhydrogen atom of the solvent molecule. The electrostatic contribution to the HBD acidity, q_+, is defined as the magnitude of the charge on the most positive hydrogen atom in the solvent molecule. A table of TLSER descriptors for a selection of 30 solvents can be found in reference [351].

The TLSER methodology has been successfully applied to develop correlation equations for a wide variety of solvent-dependent properties and processes [350, 364–369]. Some examples are the characterization of other solvent polarity, acidity, and basicity scales [364], the acidities of substituted acetic acids in various solvents [365], the basicities of substituted dimethylamines in various solvents [366], the decarboxylation kinetics of 3-carboxybenzisoxazole [367], the C=O stretching frequencies of substituted pyrrolidin-2-ones [368], and gas–water distribution coefficients [369].

Of particular interest is the analysis of other, experimentally determined empirical solvent polarity scales by means of the theoretically derived TLSER equation (7-67). For example, correlation of the solvatochromic E_{T}^{N} scale [see Eq. (7-29) in Section 7.4] with the TLSER descriptors of Eq. (7-67) leads to Eq. (7-68) for $n = 29$ solvents, with $r = 0.937$ and $s = 0.075$ [351]:

$$E_{\text{T}}^{\text{N}} = 0.8585 - 0.3662 \cdot V_{\text{mc}} - 4.0 \cdot \pi_{\text{I}} + 0.3202 \cdot q_- + 1.5164 \cdot q_+ \qquad (7\text{-}68)$$

According to this equation, the E_{T}^{N} values include both the molecular volume and the polarizability index, which is indicative of solute/solvent dispersion interactions. The negative sign of a and b means that increasing dispersion interactions decrease the E_{T}^{N} values, in agreement with the red shift usually observed in UV/Vis spectra with increasing dispersion interactions. The covalent acidity and basicity terms drop out ($c = d = 0$). However, E_{T}^{N} has significant contributions from both the electrostatic acidity and basicity terms q_+ and q_-, which is indicative of dipolar interactions and a permanent dipolarity contribution. That the electrostatic acidity term q_+ is clearly more significant than q_- further indicates that there are additional acidity factors being included in this empirical solvent polarity scale. This is in agreement with the molecular structure of the solvatochromic indicator dye (see betaine dye *(44)* in Section 7.4) and other observations that have been already mentioned.

A more detailed discussion of this E_{T}^{N} correlation and the TLSER correlations of other experimentally derived solvent scales can be found in reference [351]. Obviously, the computationally based TLSER parameters can be used in the same way as the experimentally based LSER parameters. The advantage of the TLSER descriptors is that they are obtained from computation and not from experiment. This permits the prediction of properties and correlations for compounds for which the solvatochromic or other solvent parameters are not readily available.

Finally, some special multiparameter correlations of solvent effects will be mentioned. A common multiple regression equation with seven fitting constants has been derived for the relationship between the Gibbs energy of transfer of ions from water to polar solvents, $\Delta G_t^\circ(\mathrm{X, W} \rightarrow \mathrm{S})$, and the properties of solvents *and* ions. Almost 200 data points can be described in terms of four solvent properties (DN, $E_T(30)$, ε_r, and δ_H^2) and three ionic solute properties (charge, size, and softness) [277]. The substituent and solvent influence on the cationic polymerization of 4-substituted styrenes can be described by four-parameter correlation equations involving terms for the substituent and solvent influence as well as the initiator activity [278, 279]. Such correlations are especially useful for controlling industrial polymerization processes as well as specific product formation [278, 279]. Modified multiparameter equations involving solvent viscosity parameters have been used to correlate the solvent influence on quantum yields of radiative electronic deactivation processes [280]. The dependence of the optical resolution of phenylglycine derivatives with L-(+)-tartaric acid on racemate structure and solvent polarity has been successfully described with multiparameter correlation equations [281]. The solubility of fullerene C_{60} in 113 organic solvents has been successfully correlated with a four-parameter equation using the LSER approach [370]. Increasing molar volume and solvent polarity [as measured by $E_T(30)$] diminished the solubility of C_{60}, whereas solvent polarizability and EPD ability enhanced its solubility. Using an analogous LSER approach, the rate constants for a Menschutkin reaction ($\mathrm{Et_3N + EtI}$) and solvolyses of several tertiary haloalkanes have been successfully correlated by multiparameter equations; see reference [371] for details.

Many different solvent parameters and multiparameter equations have been introduced in this Chapter 7. Certainly, only a few of them will survive the test of applicability and acceptance by organic chemists. Indeed, the preference for certain time-tested solvent scales and multiparameter treatments is already clearly discernible. Amongst the one-parameter scales, the $E_T(30)$ or E_T^N scale and the DN scale have frequently been used, while the Kamlet–Abboud–Taft (KAT) LSER approach seems to be the most widely applied multiparameter approach.

The multiparameter treatment of solvent effects can be criticized from at least three complementary points of view. First, the separation of solvent effects into various additive contributions is somewhat arbitrary, since different solute/solvent interaction mechanisms can cooperate in a non-independent way. Second, the choice of the best parameter for every type of solute/solvent interaction is critical because of the complexity of the corresponding empirical solvent parameters, and because of their susceptibility to more than one of the multiple facets of solvent polarity. Third, in order to establish a multiparameter regression equation in a statistically perfect way, so many experimental data points are usually necessary that there is often no room left for the prediction of solvent effects by extrapolation or interpolation. This helps to get a sound interpretation of the observed solvent effect for the process under study, but simultaneously it limits the value of such multiparameter equations for the chemist in its daily laboratory work.

In this context, one should be aware of the important remark made by the Austrian philosopher Karl Popper in his autobiography [284]: “It is always undesirable to make an effort to increase precision for its own sake ... since this usually leads to loss of clarity.... One should never try to be more precise than the situation demands.... Every increase in clarity is of intellectual value in itself; an increase in precision or exactness has only a pragmatic value as a means to some definite end.”

Appendix

A. Properties, Purification, and Use of Organic Solvents

A.1 Physical Properties

A selection of one-hundred useful organic solvents are listed according to decreasing polarity in Table A-1. Also given are their physical constants, *viz.* melting point, boiling point, relative permittivity, dipole moment, and index of refraction. The measure of polarity used is the empirical solvent parameter E_T^N, derived from the solvatochromism of a pyridinium *N*-phenolate betaine (*cf.* Section 7.4). Further physical data, including those of technically useful solvents, are found in references [1–8, 97–100]. Particularly useful collections of all kinds of solvent properties, relevant for a great variety of solvent applications, can be found in the handbooks of Marcus [8] and Wypych [99].

In Table A-2, a selection of chiral organic solvents is given, together with some physical data. Such chiral solvents have received much attention because of their use in determining optical purities [9, 134], as media for stereoselective syntheses [10–12, 135, 136], and as NMR shift reagents [13].

Another important property of organic solvents is their miscibility with other organic liquids (*cf.* Fig. 2-2 in Chapter 2). The farther two solvents are located from each other in Hecker's "mixotropic" series of solvents [51], given in Table A-10, the less miscible they are.

According to Hildebrand's solubility parameter approach [101], two liquids are miscible if their solubility parameters δ differ by no more than 3.4 units [101, 102]; *cf.* Eqs. (2-1) and (5-77) for the definition of δ. That is, mutual miscibility decreases as the δ values of two solvents become farther apart. Higher mutual solubility will follow if the δ values of the solvents are closer. A comprehensive collection of δ values has been given by Barton [100].

An alternative, more empirical but more accurate method for predicting miscibility has been given by Godfrey [103], using so-called *miscibility numbers* (*M*-numbers). These are serial numbers of 31 classes of organic solvents, ordered empirically by means of their lipophilicity (*i.e.* their affinity for oil-like substances), using simple test-tube miscibility experiments. All pairs of solvents whose *M*-numbers differ by 15 units or less are miscible in all proportions at 25 °C; a difference of ≥17 corresponds to immiscibility, and an *M*-number difference of 16 units indicates borderline behaviour (limited mutual miscibility) [103]. The central class of solvents with *M*-number equal to 16 (*e.g.* 2-*n*-butoxyethanol) comprises "universal" solvents, which are miscible with less lipophilic as well as with more lipophilic solvents.

A.2 Purification of Organic Solvents

Normally it is necessary to purify a solvent before use. Naturally, the purity that can be achieved depends on the nature of the impurities [14, 15] and the desired purity is

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Table A-1. Compilation of one-hundred important organic solvents together with their physical constants[a], arranged in order of decreasing E_T^N value, as empirical parameter of solvent polarity[b].

Solvents	$t_{mp}/°C$[c]	$t_{bp}/°C$[d]	ε_r[e]	$\mu \cdot 10^{30}/Cm$[f]	n_D^{20}[g]	E_T^N[h]
(1) Water	0.0	100.0	78.36	6.2	1.3330	1.000
(2) 1,2-Ethanediol[i]	−12.6	197.5	37.70	7.7	1.4318	0.790
(3) Formamide	2.55	210.5	109.50	11.2	1.4475	0.775
(4) Methanol[k]	−97.7	64.5	32.66	9.6	1.3284	0.762
(5) *N*-Methylformamide	−3.8	200	182.40	12.9	1.4319	0.722
(6) Diethylene glycol	−7.8	245.7	31.69 (20 °C)	7.7	1.4475	0.713
(7) Triethylene glycol	−4.3	288.0	23.69 (20 °C)	10.0	1.4558	0.682
(8) Tetraethylene glycol	−6.2	327.3	19.7	10.8	1.4577	0.664
(9) 2-Methoxyethanol	−85.1	124.6	16.93	6.8	1.4021	0.657
(10) *N*-Methylacetamide[l]	30.6	206.7	191.3 (32 °C)	12.8	1.4253 (35 °C)	0.657
(11) Ethanol[k]	−114.5	78.3	24.55	5.5	1.3614	0.654
(12) 2-Aminoethanol	10.5	170.9	37.72	7.6	1.4545	0.651
(13) Acetic acid	16.7	117.9	6.17 (20 °C)	5.6	1.3719	0.648
(14) 1-Propanol[m]	−126.2	97.2	20.45	5.5	1.3856	0.617
(15) Benzyl alcohol	−15.3	205.4	12.7	5.5	1.5404	0.608
(16) 1-Butanol	−88.6	117.7	17.51	5.8	1.3993	0.586
(17) 1-Pentanol	−78.2	138.0	13.9	5.7	1.4100	0.568
(18) 3-Methyl-1-butanol	−117.2	130.5	15.19	6.1	1.4072	0.565
(19) 2-Methyl-1-propanol	−108.2	107.9	17.93	6.0	1.3959	0.552
(20) 2-Propanol[m]	−88.0	82.2	19.92	5.5	1.3772	0.546
(21) Cyclohexanol	25.15	161.1	15.0	6.2	1.4648 (25 °C)	0.509
(22) 2-Butanol	−114.7	99.5	16.56	5.5	1.3971	0.506
(23) 2-Pentanol	−50	119.0	13.71	5.5	1.4064	0.488
(24) Nitromethane[n]	−28.55	101.2	35.87	12.0	1.3819	0.481
(25) Propylene carbonate[l]	−54.5	241.7	64.92	16.5	1.4215	0.472
(26) 3-Pentanol	−8	115.3	13.35	5.5	1.4104	0.463
(27) Acetonitrile[l]	−43.8	81.6	35.94	13.0	1.3441	0.460
(28) Dimethyl sulfoxide[l]	18.5	189.0	46.45	13.5	1.4793	0.444
(29) Aniline	−6.0	184.4	6.98	5.0	1.5863	0.420
(30) Sulfolane[l]	28.45	287.3	43.3 (30 °C)	16.0	1.4816 (30 °C)	0.410
(31) Acetic anhydride	−73.1	140.0	20.63	9.4	1.3904	0.407
(32) Propanenitrile	−92.8	97.3	28.26	13.4	1.3658	0.398
(33) 2-Methyl-2-propanol[m]	25.6	82.3	12.47	5.5	1.3877	0.389
(34) *N*,*N*-Dimethylformamide (DMF)[l]	−60.4	153.1	36.71	12.7	1.4305	0.386

Table A-1. (Continued)

Solvents	t_{mp}/°C[c]	t_{bp}/°C[d]	ε_{r}[e]	$\mu \cdot 10^{30}$/Cm[f]	n_{D}^{20}[g]	$E_{\mathrm{T}}^{\mathrm{N}}$[h]
(35) *N*,*N*-Dimethylacetamide (DMAC)	−20.1	166.1	37.78	12.4	1.4384	0.377
(36) 1,3-Dimethylimidazolidin-2-one, (DMEU)[o]	8.2	225.5	37.60	13.6	1.4707 (25 °C)	0.364
(37) 1-Methylpyrrolidin-2-one[p]	−24.4	202	32.2	13.6	1.4700	0.355
(38) Acetone[n]	−94.7	56.1	20.56	9.0	1.3587	0.355
(39) 1,3-Dimethyl-2-oxohexahydropyrimidine (DMPU)[o]	−23.8	246.5	36.12	14.1	1.4881 (25 °C)	0.352
(40) 1,2-Diaminoethane[l]	11.3	116.9	12.9	6.3	1.4568	0.349
(41) Cyanobenzene[q]	−12.7	191.1	25.20	13.9	1.5282	0.333
(42) 1,2-Dichloroethane[q]	−35.7	83.5	10.36	6.1	1.4448	0.327
(43) 2-Butanone	−86.7	79.6	18.11	9.2	1.3788	0.327
(44) Nitrobenzene	5.8	210.9	34.78	14.0	1.5562	0.324
(45) 2-Pentanone	−76.9	102.3	15.38 (20 °C)	9.0	1.3908	0.321
(46) 2-Methyl-2-butanol	−8.8	102.0	5.78	5.7	1.4050	0.318
(47) Morpholine	−4.8	129.0	7.42	5.2	1.4542	0.318
(48) Tetramethylurea[o]	−1.2	175.3	23.60	11.6	1.4493 (25 °C)	0.315
(49) Hexamethylphosphoric triamide (HMPT)[l]	7.3	233	29.30	18.5	1.4588	0.315
(50) 3-Methyl-2-butanone	−92.2	94.9	15.87 (30 °C)	9.2	1.3880	0.315
(51) Dichloromethane[q]	−94.9	39.6	8.93	3.8	1.4242	0.309
(52) Acetophenone	19.7	202.0	17.39	9.8	1.5342	0.306
(53) Pyridine[l]	−41.5	115.3	12.91	7.9	1.5102	0.302
(54) Cyclohexanone	−32.1	155.7	15.50	10.3	1.4510	0.281
(55) 4-Methyl-2-pentanone	−84.2	117.5	13.11 (20 °C)	9.0	1.3958	0.269
(56) 1,1-Dichloroethane[q]	−97.0	57.4	10.0 (18 °C)	6.1	1.4164	0.269
(57) Quinoline	−14.9	237.2	8.95	7.3	1.6273	0.269
(58) 3-Pentanone	−39.0	102.0	17.00 (20 °C)	9.4	1.3923	0.265
(59) Trichloromethane	−63.6	61.2	4.89	3.8	1.4459	0.259
(60) 3,3-Dimethyl-2-butanone	−52.5	105.9	12.60	9.2	1.3952	0.256
(61) Methyl acetate	−98.1	56.9	6.68	5.6	1.3614	0.253
(62) Triethylene glycol dimethyl ether	−45	216	7.6	7.4	1.4224	0.253
(63) 2,4-Dimethyl-3-pentanone	−69.0	125.3	17.2 (20 °C)	9.1	1.3999	0.247
(64) Diethylene glycol dimethyl ether	−64.0	162.0	5.8	6.6	1.4078	0.244
(65) 1,2-Dimethoxyethane[r]	−69.2	84.6	7.20	5.7	1.3796	0.231
(66) Ethyl acetate	−83.6	77.2	6.02	5.9	1.3724	0.228
(67) 1,2-Dichlorobenzene	−17.1	180.5	9.93	8.3	1.5515	0.225
(68) 2,6-Dimethyl-4-heptanone	−46.0	168.2	9.91 (20 °C)	8.9	1.4122	0.225
(69) Diethylene glycol diethyl ether	−44.3	188.9	5.70	6.6	1.4115	0.210

Table A-1. (Continued)

Solvents	$t_{\mathrm{mp}}/^{\circ}\mathrm{C}$[c]	$t_{\mathrm{bp}}/^{\circ}\mathrm{C}$[d]	ε_r[e]	$\mu \cdot 10^{30}/\mathrm{Cm}$[f]	$n_D{}^{20}$[g]	E_T^N[h]
(70) Tetrahydrofuran[s]	−108.4	66.0	7.58	5.8	1.4072	0.207
(71) Methoxybenzene	−37.5	153.7	4.33	4.2	1.5170	0.198
(72) Fluorobenzene	−42.2	84.8	5.42	4.9	1.4684 (15 °C)	0.194
(73) 1,1-Dichloroethene	−122.6	31.6	4.82 (20 °C)	4.3	1.4247	0.194
(74) Chlorobenzene	−45.6	131.7	5.62	5.6	1.5248	0.188
(75) Diethyl carbonate	−43.0	126.9	2.82 (20 °C)	3.0	1.3837	0.185
(76) Bromobenzene	−30.9	156.0	5.40	5.2	1.5568	0.182
(77) Ethoxybenzene	−29.6	169.9	4.22 (20 °C)	4.5	1.5074	0.182
(78) Iodobenzene	−31.4	188.4	4.49 (20 °C)	4.7	1.6200	0.170
(79) 1,1,1-Trichloroethane	−30.4	74.1	7.25 (20 °C)	5.7	1.4380	0.170
(80) 1,4-Dioxane[s]	11.8	101.3	2.21	1.5	1.4224	0.164
(81) Trichloroethene	−86.4	87.2	3.42 (16 °C)	2.7	1.4773	0.160
(82) Piperidine	−10.5	106.3	5.8 (20 °C)	4.0	1.4525	0.148
(83) Diethylamine	−49.8	55.5	3.78	4.0	1.3846	0.145
(84) Diphenyl ether	26.9	258.1	3.60	3.9	1.5763 (30 °C)	0.142
(85) *t*-Butyl methyl ether	−108.6	55.2	4.5 (20 °C)	4.1	1.3690	0.124
(86) Diethyl ether	−116.3	34.5	4.20	3.8	1.3524	0.117
(87) Benzene[t]	5.6	80.1	2.27	0.0	1.5011	0.111
(88) Di-*n*-propyl ether	−123.2	90.1	3.39 (26 °C)	4.4	1.3805	0.102
(89) Toluene[t]	−95.0	110.6	2.38	1.0	1.4969	0.099
(90) 1,4-Dimethylbenzene	13.3	138.4	2.27 (20 °C)	0.0	1.4958	0.074
(91) Di-*n*-butyl ether	−95.2	140.3	3.08 (20 °C)	3.9	1.3992	0.071
(92) Carbon disulfide[u]	−111.6	46.3	2.64 (20 °C)	0.0	1.6275	0.065
(93) Tetrachloromethane	−22.9	76.7	2.24	0.0	1.4602	0.052
(94) Triethylamine	−114.7	88.9	2.42 (20 °C)	2.2	1.4010	0.043
(95) Tri-*n*-butylamine	−70.0	214.1	2.29	2.6	1.4291	0.043
(96) *cis*-Decahydronaphthalene	−43.1	195.8	2.20 (20 °C)	0.0	1.4810	0.015
(97) *n*-Heptane	−90.6	98.5	1.92 (20 °C)	0.0	1.3876	0.012
(98) *n*-Hexane	−95.4	68.7	1.88	0.0	1.3749	0.009
(99) *n*-Pentane	−129.8	36.1	1.84 (20 °C)	0.0	1.3575	0.009
(100) Cyclohexane	6.8	80.8	2.02 (20 °C)	0.0	1.4262	0.006

[a] The physical constants were taken from the following references: (1) R. C. Weast, M. J. Astle: *CRC Handbook of Data on Organic Compounds*, Vols. I and II, CRC Press, Boca Raton/FL, USA, 1985; (2) D. R. Lide (ed.): *Handbook of Chemistry and Physics*, 82nd edition, CRC Press, Boca Raton/FL, USA, 2001; (3) J. A. Riddick, W. B. Bunger, T. K. Sakano: *Organic Solvents, Physical Properties and Methods of Purification*. 4th edition, in: A. Weissberger (ed.): *Techniques of Chemistry*, Vol. II, Wiley-Interscience, New York, 1986; (4) A. L. McClellan: *Tables of Experimental Dipole Moments*, Vols. 1–3, Freeman, San Francisco, 1963; Rahara Enterprises, El Cerrito/CA, USA, 1974 and 1989; (5) A. A. Maryott, E. R. Smith: *Table of Dielectric Constants of Pure Liquids*, NBS Circular 514, Washington DC, 1951; (6) Y. Marcus: *The Properties of Solvents*, Wiley, Chichester, 1998; (7) G. Wypych (ed.): *Handbook of Solvents* (+Solvent Database on CD-ROM), Chem Tec Publishing, Toronto, and William Andrew Publishing, New York, 2001; (8) M. J. O'Neil et al. (eds.): *The Merck Index*, 13th ed., Merck and Co., Whitehouse Station/NJ, USA, 2001.

[b] C. Reichardt, Chem. Rev. *94*, 2319 (1994); *cf.* also Table 7-3 in Chapter 7.

[c] Melting point.

[d] Boiling point at 1013 hPa.

[e] Relative permittivity ("dielectric constant") of the pure liquid at 25 °C, unless followed by another temperature in parentheses.

[f] Dipole moment in Coulombmeter (Cm), measured in benzene, tetrachloromethane, 1,4-dioxane, or *n*-hexane at 20…30 °C. 1 Debye $= 3.336 \cdot 10^{-30}$ Cm.

[g] Refractive index at the average *D*-line of sodium (16969 cm^{-1}) at 20 °C, unless followed by another temperature in parentheses.

[h] Normalised E_T^N values, derived from the transition energy at 25 °C of the long-wavelength visible absorption of a standard pyridinium *N*-phenolate betaine dye, $E_\mathrm{T}(30)$[b]; *cf.* Eqs. (7-27) and (7-29) in Section 7.4.

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Table A-2. Selection of thirty-four chiral solvents and cosolvents (in alphabetical order)[a].

Solvents	$t_{\mathrm{fp}}/^{\circ}\mathrm{C}$	$t_{\mathrm{bp}}/^{\circ}\mathrm{C}$ (hPa)	$[\alpha]_{\mathrm{D}}^{20}$ [b]	Configuration
(1) 2-Amino-1-butanol	−2	178	−10 (neat)	(*R*)
		(1013)	+10 (neat)	(*S*)
(2) 2-Amino-1-propanol (Alaninol)	–	174.5	−18 (neat)	(*R*)
		(1013)	+18 (neat)	(*S*)
(3) 1-Amino-2-propanol	24…26	160	−18 (water)	(*R*)
		(1013)	+18 (water)	(*S*)
(4) 1,4-Bis(dimethylamino)-	43	68…70	+34 (benzene)	(2*R*, 3*R*)
butane-2,3-diol (DBD)[c]		(0.7)	−35 (benzene)	(2*S*, 3*S*)
(5) 1,4-Bis(dimethylamino)-2,3-	–	62…64	−15 (neat)	(2*R*, 3*R*)
dimethoxybutane (DDB)[d]		(4)	+15 (neat)	(2*S*, 3*S*)
(6) 1,3-Butanediol	<−50	207.5	−31 (ethanol)	(*R*)
		(1013)	+30 (ethanol)	(*S*)
(7) 2,3-Butanediol	16	183	−13 (neat; 23 °C)	(2*R*, 3*R*)
		(1013)	+13 (neat; 23 °C)	(2*S*, 3*S*)
(8) 2-Butanol	−114	99.5	−13 (neat)	(*R*)
		(1013)	+13 (neat)	(*S*)
(9) 2-Chlorobutane	−131	68	−31 (neat)	(*R*)
		(1013)	+31 (neat)	(*S*)
(10) Diethyl tartrate[e]	18	280	+8.5 (neat)	(2*R*, 3*R*)
		(1013)	−8.5 (neat)	(2*S*, 3*S*)
(11) 2,3-Dimethoxybutane[f,g]	−84	109…110	+3.7 (neat)[f]	(2*R*, 3*R*)
		(1000)		
(12) 1-Dimethylamino-1-	–	81	+62 (neat; 26 °C)	(*R*)
phenylethane[h]		(16)	−64 (neat)	(*S*)
(13) 2,3-Dimethylpentane	−135	90	−11 (neat)	(*S*)
		(1013)		
(14) Ethyl lactate	−25	154	+11 (neat)	(*R*)
		(1013)	−11 (neat)	(*S*)
(15) 2-Heptanol	–	160	−9.5 (neat)	(*R*)
		(1013)	+10 (neat; 24 °C)	(*S*)
(16) 3-Heptanol	−70	157	+5 (neat; 25 °C)	(*S*)
		(1013)		
(17) 2-(Hydroxymethyl)oxirane	–	167 (dec.)	+15 (neat; 23 °C)	(*R*)
(Glycidol)		(1013)	−15 (neat)	(*S*)
(18) 2-Methyl-1-butanol	−70	129	−6 (neat)	(*S*)
		(1013)		
(19) 3-Methyl-2-butanol	–	113	+5 (neat)	(*S*)
		(1013)		
(20) 3-Methylhexane	−119	92	+9 (neat)	(*S*)
		(1013)		
(21) 4-Methyl-2-pentanol	−90	132	−21 (neat)	(*R*)
		(1013)	+21 (neat)	(*S*)
(22) *N*-Methyl-(1-phenylethyl)amine	–	184	+70 ($\mathrm{CHCl_3}$)	(*R*)
		(973)	−75 ($\mathrm{CHCl_3}$)	(*S*)
(23) 2-Methyltetrahydrofuran[i,j]	−137	80	−27 (neat)	(*R*)
		(1013)	+27 (neat)	(*S*)
(24) 1-(1-Naphthyl)ethylamine[k]	–	153	+83 (neat; 17 °C)	(*R*)
		(11)	−81 (neat; 25 °C)	(*S*)
(25) 2-Octanol[l]	−32	180	−9.5 (neat; 17 °C)	(*R*)
		(1013)	+9.5 (neat)	(*S*)
(26) 2-Pentanol	−73	119	−13 (neat; 25 °C)	(*R*)
		(1013)	+13 (neat; 25 °C)	(*S*)

Table A-2. (Continued)

Solvents	t_{fp}/°C	t_{bp}/°C (hPa)	$[\alpha]_D^{20}$ [b]	Configuration
(27) 1-Phenylethanol[m,n]	20	204	+44 (neat)	(*R*)
		(1013)	−44 (neat)	(*S*)
(28) (1-Phenylethyl)amine[o,p]	−10	187	+39 (neat)	(*R*)
		(1013)	−40 (neat)	(*S*)
(29) *N*-(1-Phenylethyl)formamide[q,r]	46...47	175...178	+180 (neat)	(*R*)
		(20)	−172 (neat)	(*S*)
(30) 1-Phenyl-1-propanol	–	218...220	+48 (hexane)	(*R*)
		(1013)	−47 (hexane)	(*S*)
(31) 1,2-Propanediol	−60	188	−15 (neat; 24 °C)	(*R*)
		(1013)	+17 (neat)	(*S*)
(32) 1,2,3,4-Tetramethoxybutane[s]	–	70 (19)	−6 (neat)	(2*S*, 3*S*)
(33) 2,2,2-Trifluoro-1-(1-naphthyl)-ethanol[t]	52...53	83...85 (0.03)	−26 (ethanol)	(*R*)
(34) 2,2,2-Trifluoro-1-phenylethanol[u]	20	73...76	−41 (neat; 25 °C)	(*R*)
		(9)	+31 (neat)	(*S*)

[a] The physical constants are taken from the following references: (1) *Beilstein's Handbuch der organischen Chemie*, 4th ed., Springer, Berlin; (2) J. A. Riddick, W. B. Bunger, T. Sakano: *Organic Solvents, Physical Properties and Methods of Purification*, in: A. Weissberger (ed.): *Techniques of Chemistry*, Vol. II, Wiley-Interscience, New York, 1986; (3) Fluka Chemie AG: *Chiral Compounds Chemistry*, Buchs/Switzerland, 1994; (4) Sigma-Aldrich Co.: *Chiral Nonracemic Compounds*, Milwaukee/WI, USA, 1998; (5) Merck-Eurolab GmbH: *Der Laborkatalog Merck®*. Darmstadt, 2001.

[b] Specific rotation (dimension $10^{-1} \cdot \mathrm{deg} \cdot \mathrm{cm}^2 \cdot \mathrm{g}^{-1}$), measured at the average *D*-line of sodium (16969 cm^{-1}) at 20 °C, unless followed by another temperature in parentheses. Because of different enantiomeric purities of the solvents studied, the literature values of $[\alpha]_D$ often vary; therefore, only rounded values are given.

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[u] W. H. Pirkle, S. D. Beare, T. G. Burlingame, J. Org. Chem. *34*, 470 (1969), W. H. Pirkle, P. L. Rinaldi, J. Org. Chem. *42*, 3217 (1977).

determined by the intended use [16]. The following is a practical definition of the purity of a solvent: "A material is sufficiently pure if it does not contain impurities of such nature and in such quantity as to interfere with the use for which it is intended" [1]. Detailed prescriptions for purification are available in standard texts [1, 17, 104, 105]. The most frequently found impurity in organic solvents is water. A water content of only 20 μg/g (20 ppm) is equivalent to the total amount of solute in a 10^{-3} molar solution! Since water interferes undesirably with many reactions, its removal is one of the basic laboratory operations. Drying agents may bind water either physically or chemically [18, 19]. The best method depends in each case on the chemical nature of the solvent and the desired degree of dryness [20]. All organic solvents possessing a relative permittivity of less than 15 can be freed almost completely from water, alcohols, peroxides, and traces of acid, by simple adsorptive filtration through aluminium oxide (activity I) or silica gel (activity I), *e.g.* using a chromatography column 2 ... 5 cm in diameter and 40 ... 150 cm long [19, 21–24].

Another safe and nonhazardous, general, large-scale procedure for the purification of solvents without distillation for their use in air- and moisture-sensitive reactions has been developed by Grubbs *et al.* [137]. The solvent, slightly pressurized with nitrogen, is passed through two sequential purification columns. The first contains activated alumina (removing water, peroxides, and inhibitors), and the second, optional, column contains a supported copper redox catalyst as an oxygen scavenger. A simplified modification of this distillation-free solvent purification system has also been described [138].

Comparative studies of the drying efficiencies of a number of common desiccants for different types of organic solvents have been carried out by Burfield and coworkers [106–117]. Using a new and very sensitive tritiated water tracer method for determining water content, they obtained rather unexpected results concerning the drying efficiencies of commonly used desiccants. The results of this study, together with other recommended physical and chemical drying methods [1, 17, 18, 104, 105], are compiled in Table A-3. In particular, Burfield's results draw attention to the almost universal applicability of zeolite molecular sieves as desiccants, which are capable of drying even the most difficult organic solvents [107].

The classical method for the determination of low water contents in organic solvents is the nonaqueous iodometric titration introduced by Karl Fischer in 1935, using a solution of sulfur dioxide, iodine, and pyridine in a benzene/methanol mixture [139, 140]. By replacing some of the toxic ingredients (pyridine, benzene, methanol), this titration method has more recently been developed into a simple and environmentally safe standard procedure [141].

Another UV/Vis spectroscopic method for the determination of water in organic solvents involves the use of solvatochromic dyes (such as the pyridinium *N*-phenolate betaine dye *(44)* in Chapter 7.4), and is based on the observation that water has a very high polarity compared with most organic solvents [142–145]. Even small amounts of water cause a strong hypsochromic band shift of the dissolved solvatochromic dye, which can be related to the water content by a calibration curve. A typical detection limit of this method is of the order of 1 mg water in 1 mL solvent for routine spectrophotometers [142]. An analogous solvatochromic method has been developed for the determination of aqueous ethanol mixtures [146].

A.3 Spectroscopic Solvents

Solvents used in ultraviolet, visible, infrared, microwave, and radiowave spectroscopy must meet the following requirements: transparency and stability toward the radiation used, solubility and chemical stability of the substance to be examined, and a high and reproducible purity ("optical constancy"). Normally, intermolecular interaction with the solute should be minimal. On the other hand, important information about the solute can be obtained from the changes in the absorption spectrum arising from such interactions.

A collection of UV/Vis, IR, as well as ^{1}H and ^{13}C NMR spectra of common organic solvents can be found in reference [147]. A comprehensive list with "UV and IR spectroscopic windows" of organic solvents is given in reference [8].

The number of solvents useful in UV/Vis spectroscopy decreases with decreasing wavelength (increasing wavenumber) since the absorption of all substances increases in this direction. The *cut-off point* depends on the chemical nature and to a large extent on the purity of the solvent. Hence, numerous procedures for the production of optically pure solvents have been developed [25–29]. Solvents for the measurement of fluorescence spectra must often be particularly pure [30]. The cut-off points of the solvents normally used in UV/Vis spectroscopy are collected in Table A-4. Saturated hydrocarbons are among the most useful because of the weak intermolecular interactions and the lack of excitable π-electrons. Perfluorinated hydrocarbons are recommended for the far-UV region (<200 nm) [31–33]. The UV spectra of the more important organic solvents are reproduced in the "DMS UV Atlas of Organic Compounds" [34].

Solvents for infrared spectroscopy must meet the additional requirement that they do not attack the absorption cells themselves (normally made from alkali metal halides such as NaCl, KBr, and CsBr) [35]. The transparency regions of the IR solvents within the mid-IR region (2...16 µm; 5000...625 cm^{-1}) are given in Table A-5. Complete IR spectra of organic solvents can be found in the "DMS Working Atlas of Infrared Spectroscopy" [36], in the "Sadtler IR Spectra Handbook of Common Organic Solvents" [118], as well as in "The Sprouse Collection of Infrared Spectra" [148]. Transmission characteristics of organic solvents in the near-IR region (1...3 µm; 1000...3333 cm^{-1}) are given in references [37, 38], and for the far-IR region (15...35 µm; 667...286 cm^{-1}) in references [39, 40]. The IR spectra of deuterated organic solvents between 2.5 and 16.7 µm (4000...600 cm^{-1}) have also been measured [41]. The number of IR absorption bands active in a covalent compound decreases with the number of atoms and with increasing symmetry of the molecule. Therefore, small molecules of high symmetry are particularly useful IR solvents, *e.g.* carbon disulfide (point group $D_{\infty \mathrm{h}}$) and tetrachloromethane (point group T_{d}).

In ^{1}H NMR spectroscopy, one uses solvents which either contain no hydrogens (*e.g.* CS_2, CCl_4, $Cl_2C{=}CCl_2$, hexachlorobutadiene) or deuterated solvents (*e.g.* C_6D_6, $CDCl_3$, D_2O, CD_3SOCD_3). Table A-6 gives the characteristic ^{1}H NMR absorption bands of common organic solvents. More complete collections of ^{1}H NMR chemical shifts of organic solvents are available in the literature [42, 43]. Table A-7 contains the ^{13}C NMR absorption bands of compounds used as solvents as well as reference substances in ^{13}C NMR spectroscopy [44]. In order to use ^{1}H and ^{13}C NMR chemical shifts diagnostically for certain functional groups, all solvent effects should be eliminated

Table A-3. Some recommended simple physical and chemical drying methods for thirty-three common organic solvents: ++ method gives superdry solvents with less than 1 ppm water; + solvent sufficiently dry for most chemical applications; (+) often used but less efficient; – explosive hazard (!) or other chemical reaction; no entry means not recommended or no information in the literature. For extensive compilations of more sophisticated purification methods, see references[a–f)].

Drying methods		Static drying[k)] with															Dynamic[l)] drying with					Fractional distillation[m)] [Other methods]
Solvents[Ref.]	$S^{g)}_{H_2O}$ 25 °C	M.S. 0.3 nm[n)]	M.S. 0.4 nm[n)]	M.S. 0.5 nm[n)]	P_4O_{10}	Na	Al/Hg[a,c,d)]	$LiAlH_4$[α)]	CaH_2	Al_2O_3 B–I	B_2O_3	KOH (powder)	$CaCl_2$	$CaSO_4 \cdot 0.5\ H_2O$[w)]	Na_2SO_4	K_2CO_3	M.S. 0.3 nm[n)]	M.S. 0.4 nm[n)]	M.S. 0.5 nm[n)]	Al_2O_3 B–I[i)]	Al_2O_3 N–I[i)]	
Acetic acid[a,b,d)]	∞				$+^{d}$	–	–	–	–	–		–	–			–				–	–	+ (from Ac_2O or P_4O_{10})[b)] [fractional freezing]
Acetone[a–d,p,q,β)]	∞	$(+)^{q}$	$(+)^{q}$		–	–	–	–	–	–	$+^{q}$	–	–	(+)	(+)	–				–	–	+ (from $CaSO_4 \cdot 0.5\ H_2O$)
Acetonitrile[a–e,i,o,p,w)]	∞	$+^{o,p}$			$+^{o}$	–		–	$+^{d}$		$+^{o}$	–	$(+)^{o}$	$(+)^{w}$	$(+)^{a}$	$(+)^{o}$	$+^{e,f}$				$+^{e,i}$	+ (from P_4O_{10} and then from K_2CO_3)
Benzene[a–d,i,o,p)]	(0.63)		$++^{o,p}$	$+^{c}$	$+^{a}$	$+^{o}$		$++^{o}$	$++^{o}$	$++^{o}$			$++^{o}$	$+^{d}$	(+)			$+^{f}$		$+^{i}$		+ (from Na)[a)] [fractional freezing]
tert-Butanol[a,b,d,γ)]	∞	$+^{u}_{*}$	$(+)^{u}$		–	$(+)^{u}$	+	–	$(+)^{u}$				–	$(+)^{d}$		$(+)^{d}$						+ (from Mg/I_2)[d)] [fractional freezing]
2-Butanone[a–d)]	120.0				–	–	–	–	–	–		–	–	$+^{c}$	$+^{d}$	$+^{c}$				–	–	+
Chloroform[a–d,i,x,y)]	0.6		$+^{y}$	$+^{x,y}$	$+^{f}$	–!	–			$+^{y}$		–	$+^{y}$	$+^{a}$	$+^{d}$	$+^{a}$		$+^{f}$		$+^{i}$		+ (from M.S. 0.4 nm[n)])[d)]
Cyclohexane[a,b,d,i)]	0.1		$+^{d}$		$+^{d}$	$+^{d}$				+			$+^{d}$					$+^{f}$		$+^{i}$		+ (from Na or $LiAlH_4$)[d,α)]
1,2-Diaminoethane[b,d,e)]	∞			$+^{e}$	–	$+^{e}$		–				$+^{e}$	–									+ (from Na or M.S. 0.5 nm under N_2)[d,e)]
1,2-Dichloroethane[b,d)]	1.5				$+^{d}$	–!	–		$+^{d}$	$+^{b}$			$+^{d}$	$+^{d}$	$+^{b}$	$+^{b}$				+		+ (from P_4O_{10})
Dichloromethane[a–d,i,p,r)]	2.0		$++^{p}$		$+^{d}$	–!	–		$+^{d}$	+		–	$+^{c}$	$+^{d}$				$+^{f}$		$+^{i}$		+ (from P_4O_{10})
Diethyl ether[a–d,i,p,t,w,y,z)]	13.0		$+^{p,t,z}_{*}$	$+^{y}$	–	$+^{c}$		+		+			$(+)^{c,t}$	$(+)^{w}$		$(+)^{t}$		$+^{f}$		$+^{i}$		+ (from Na or $LiAlH_4$ under N_2)[α)]
1,2-Dimethoxyethane[b–d)]	∞				–	$+^{c}$		$+^{c}$	$+^{c}$	+			+							+		+ (under N_2)[c)]
Di-*i*-propylamine[b,d,s)]	(400)	$+^{s}$	$+^{s}$		–	$+^{s}$		–	$+^{s}$			$(+)^{s}$	–									+ (from NaOH)[d)]
N,*N*-Dimethylformamide[a–e,p,q)]	∞	$+^{q}$	$+^{p,q}$		$+^{q}$	–		–	$+^{q}$			–	–					$+^{f}$				+ (i. vac. under N_2 or as benzene azeotr.)
Dimethyl sulfoxide[a–e,i,q)]	∞	$+^{q}$	$+^{q}$	$+^{e}$		–	–	–	$+^{d,e}$				–	$+^{c,d}$				$+^{d}$				+ (i. vac. from CaH_2)[e,q)] [fractional freezing]
1,4-Dioxane[a–e,i,o,p,r,w,z)]	∞	$+^{w}$	$+^{p,z}_{o}$	$+^{f}$	–	$+^{o}$			$+^{o}$	+		$+^{o}$	$(+)^{w}$	$(+)^{w}$			$+^{e}$	+	$+^{f}$	$+^{i}$		+ (from Na under N_2)[c,e)]
1,2-Ethanediol[a,b,d,u)]	∞	$+^{u}_{*}$			–	–		–					–	$(+)^{d}$	$(+)^{f}$			$+^{d}$				+ (from Mg/I_2 or as benzene azeotr.)[u)]
Ethanol[a–d,u,v)]	∞	$+^{u}_{*}$			–	–	$+^{a,d}$	–	$+^{d,u}$				–				$+^{f,v}$					+ (from Mg/I_2 or as benzene azeotr.)[u)]
Ethyl acetate[a–d,i,p)]	(29.4)		$+^{p}$		$+^{d}$	–	–	–	$+^{d}$			–	–	$+^{d}$	$+^{f}$	$+^{c}$		$+^{f}$			$+^{i}$	+ (from P_4O_{10})[a)]
HMPT[b–e,q)]	∞	$+^{q}$	$+^{q}$						$+^{q}$			$+^{q}$					$+^{e}$					+ (i. vac. from CaH_2, under Ar)[e,q)]

Methanol[a–d,u)]	∞	+[u]	–	–	–	–	+[a]	–	+[u]				–	+[d]			+[f]					+ (from Mg/I_2)[u)]
N-Methylacetamide[b,d,e)]	∞				+[e]	–		–				–	–									+ (i. vac.)[e)] [fractional freezing][e)]
1-Methyl-2-pyrrolidinone[a–d)]	∞					–		–				–	–									+ (i. vac. or as benzene azeotrope)[c)]
Nitromethane[a,b,d,i,δ)]	19.0		+[f]		–[d]	–	–	–				–	+[d]	+[d]	+[d]							+ (from M.S. 0.4 nm)
Propylene carbonate[d,e)]	(83)		+[e]	+[e]		–		–				–							+[e,d]			+ (i. vac.)[e,d)]
2-Propanol[a–d,γ)]	∞	+[f]		+[c]	–	–	+[a]	–	+[d]				–	+			+[f]					+ (from Mg/I_2)[a)]
Pyridine[a–e,i,s)]	∞	+[s]	+[s]					+[d]	+[s]	+		+[e,s]	–					+[f]		+[i]		+ (from M.S. 0.5 nm/KOH)[e)]
Sulfolane[a–e)]	∞		+[c]							+		+		+[e]						+[e]		+ (i. vac. from CaH_2)[e)]
Tetrachloromethane[a–d,i)]	0.1		+[f]	+[c]	+[i]	–!	–			+			+[i]		+	+[a]		+[f]		+[i]		+ (from P_4O_{10})[d)]
Tetrahydrofuran[a–e,i,p,z)]	∞		+[p,z]	+[f]	–	+[d]		+[c,d]	+[d]	+		–![c]	+[c]	+[c]			+[e]	+	+[f]	+[i]		+ (from $LiAlH_4$ or Na under N_2)[e,α)]
Toluene[a–d,p,r)]	0.5		++[p]	+[c]	+[d]	+[d]		+	+[d]	+			+[d]	+[d]				+[f]		+		+ (from Na)[d)]
Trichloroethene[a,b,d,i)]	(0.25)					–!	–					–	+[d]		+[f]	+[d]				+[i]		+

[a)] Houben-Weyl-Müller: *Methoden der organischen Chemie*, 4th edition, Thieme, Stuttgart, 1959, Vol. I/2, p. 765–868 (W. Bunge: *Eigenschaften und Reinigung der wichtigsten organischen Lösungsmittel*) and p. 869–885 (H. Rickert and H. Schwarz: *Trockenmittel*).

[b)] J. A. Riddick, W. B. Bunger, T. K. Sakano: *Organic Solvents. Physical Properties and Methods of Purification*, 4th ed., in A. Weissberger (ed.): *Techniques of Chemistry*, Vol. II, Wiley-Interscience, New York, 1986.

[c)] B. S. Furniss, A. J. Hannaford, P. W. G. Smith, A. R. Tatchell: *Vogel's Textbook of Practical Organic Chemistry*, 5th ed., Longman, London, New York, 1989, p. 395–413.

[d)] W. L. F. Armarego, D. D. Perrin: *Purification of Laboratory Chemicals*, 4th ed., Butterworth-Heinemann, Oxford/UK, 1996.

[e)] J. F. Coetzee (ed.): *Recommended Methods for Purification of Solvents and Tests for Impurities*, Pergamon Press, Oxford 1982; Pure Appl. Chem. *57*, 634 (1985).

[f)] Merck–Eurolab GmbH: *Der Laborkatalog Merck® – Chemikalien und Reagenzien*. D-64293 Darmstadt/Germany, 2001, p. 1285 (Lösungsmittel – Eigenschaften und Trocknung).

[g)] Maximum solubility of water in solvent in g/L, except values in parentheses which are in g/kg; ∞ means completely miscible with water[b,h,i)].

[h)] K. Schwetlick et al.: *Organikum – Organisch-chemisches Grundpraktikum*, 21st ed., Wiley-VCH, Weinheim/Germany, 2000, p. 741–762.

[i)] B. P. Engelbrecht: *Adsorptives Reinigen von Lösungsmitteln für die Chromatographie und Spektroskopie*, GIT Fachz. Lab. *23*, 681 (1979); Chem. Abstr. *91*, 133523y (1979); see also ICN Biomedicals GmbH (formerly Woelm Pharma GmbH): *Lösungsmittel-Reinigung mit ICN Adsorbentien*, D-37269 Eschwege/Germany.

[k)] Treatment with *ca.* 50 . . . 100 g/L desiccant at ambient temperature for about 24 h. Gentle agitation or stirring has an accelerating effect on drying. Sequential drying, accomplished by decanting monosiccated solvent onto a fresh charge of *ca.* 50 g/L desiccant, is more effective.

[l)] Column drying by percolating the solvent through the desiccant contained in a glass column of 2 . . . 5 cm diameter and 40 . . . 150 cm long, and collecting the eluent in a storage container protected from atmospheric moisture by a drying tube filled with molecular sieve.

[m)] Fractional distillation is often combined with static drying before or after the distillation.

[n)] Zeolite molecular sieves (sodium and calcium aluminosilicates) of nominal pore size 0.3 . . . 0.5 nm, normally used as beads except in cases where the use of powdered molecular sieve is essential (marked with an asterisk).

[o)] D. R. Burfield, K.-H. Lee, R. H. Smithers, J. Org. Chem. *42*, 3060 (1977).

[p)] D. R. Burfield, G.-H. Gan, R. H. Smithers, J. Appl. Chem. Biotechnol. *28*, 23 (1978); Chem. Abstr. *89*, 12551f (1978).

[q)] D. R. Burfield, R. H. Smithers, J. Org. Chem. *43*, 3966 (1978).

[r)] D. R. Burfield, R. H. Smithers, J. Chem. Technol. Biotechnol. *30*, 491 (1980); Chem. Abstr. *94*, 66822s (1981).

[s)] D. R. Burfield, R. H. Smithers, A. S. C. Tan, J. Org. Chem. *46*, 629 (1981).

[t)] D. R. Burfield, R. H. Smithers, J. Chem. Educ. *59*, 703 (1982).

[u)] D. R. Burfield, R. H. Smithers, J. Org. Chem. *48*, 2420 (1983); Y. Marcus, S. Glikberg, Pure Appl. Chem. *57*, 855, 860 (1985).

[v)] D. R. Burfield, G. T. Hefter, D. S. P. Koh, J. Chem. Technol. Biotechnol., Chem. Technol. Part A *34*, 187 (1984); Chem. Abstr. *101*, 133117u (1984).

[w)] D. R. Burfield, J. Org. Chem. *49*, 3852 (1984).

[x)] D. R. Burfield, J. Chem. Educ. *56*, 486 (1979); D. R. Burfield, E. H. Goh, E. H. Ong, R. H. Smithers, Gazz. Chim. Ital. *113*, 841 (1983).

[y)] D. R. Burfield, R. H. Smithers, Chem. Ind. (London) 240 (1980).

[z)] D. R. Burfield, J. Org. Chem. *47*, 3821 (1982); Deperoxidation of ethers with self-indicating molecular sieves 0.4 nm.

[α)] *Caution*: solutions of $LiAlH_4$ in oxygen-containing solvents may decompose at elevated temperatures (≧160 °C). Therefore, distillation should never be carried out to dryness, and solvents boiling above 100 °C should be distilled under reduced pressure.

[β)] J. F. Coetzee, T.-H. Chang, Pure Appl. Chem. *58*, 1535 (1986).

[γ)] Y. Marcus, Pure Appl. Chem. *58*, 1411 (1986).

[δ)] J. F. Coetzee, T.-H. Chang, Pure Appl. Chem. *58*, 1541 (1986).

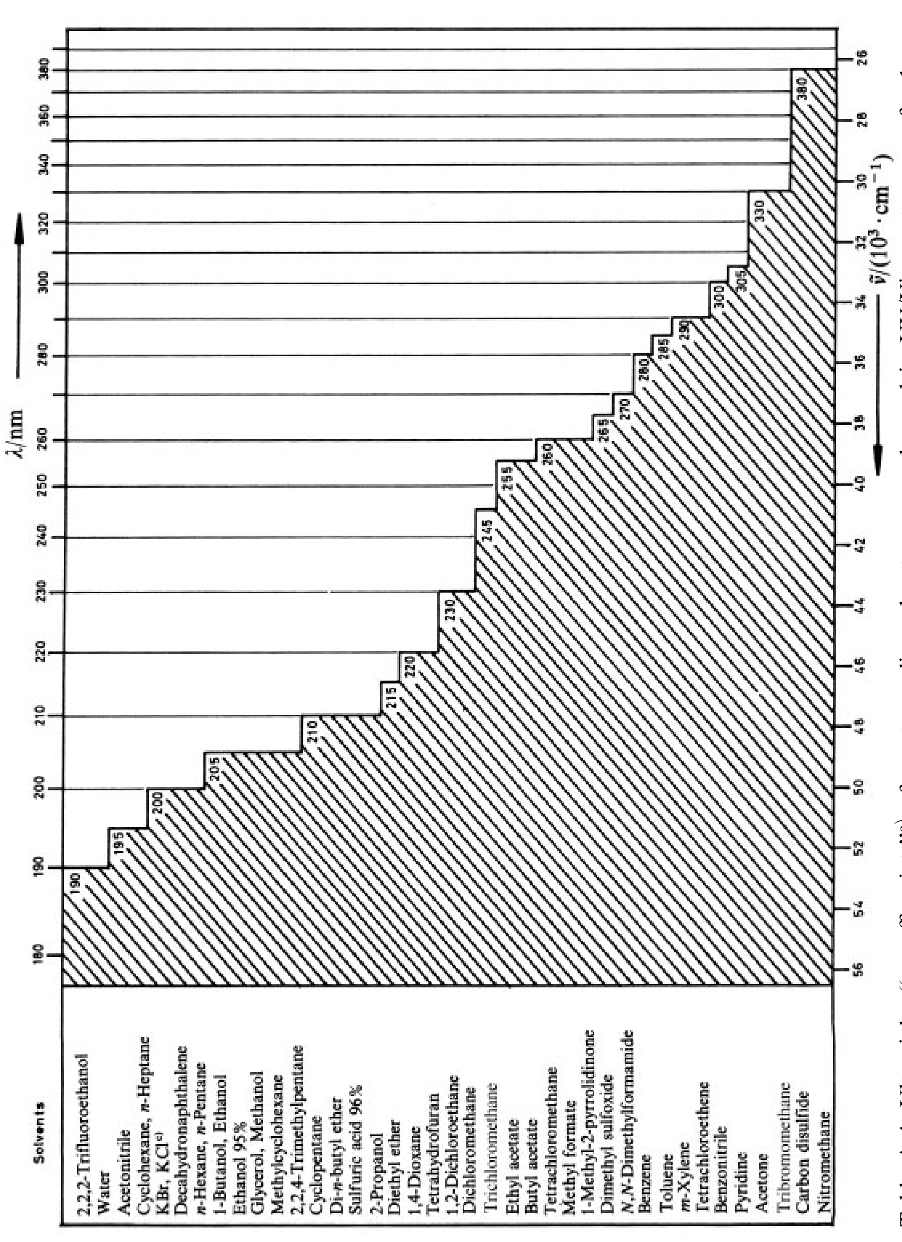


Table A-4. Ultraviolet "cut-off points"[a] of spectroquality solvents commonly used in UV/Vis spectroscopy, for 1 cm pathlengths (accuracy *ca.* ±5 nm)[b].

[a] The "cut-off point" in the ultraviolet region is the wavelength at which the absorbance approaches 1.0 using a 1-cm cell path with water as the reference. Solvents should not be used for measurements below the cut-off point, even though a compensating reference cell is employed. The cut-off points are very dependent on the purity of the solvent used. Most of the solvents listed above are available in highly purified "spectrograde" quality.

[b] Compiled from the following references:

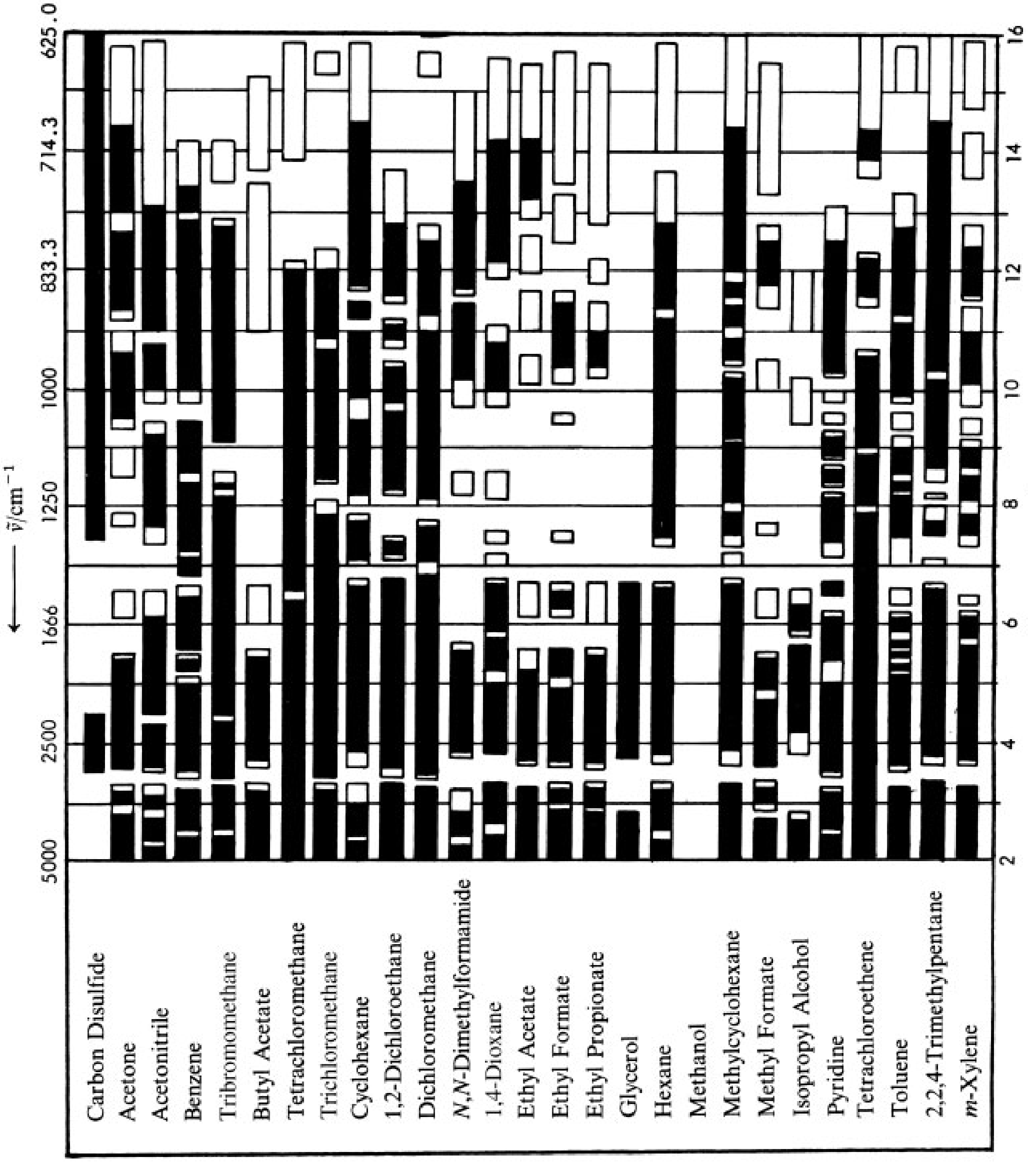
(1) Eastman Kodak Company: *Spectrophotometric Solvents*, Dataservice Catalog JJ-282, Rochester, New York 14650, USA, 1977;

(2) E. Merck: *UVASOLE® – Lösungsmittel und Substanzen für die Spektroskopie*, D-64293 Darmstadt, Germany;

(3) and from the reviews of Gordon and Ford [4] (p. 167), Pestemer [25], and Hampel [34].

[c] Values for solid, as used in a pellet for example.

Table A-5. Infrared transmission characteristics[a] of spectroquality solvents commonly used in infrared spectroscopy in the 2...16 μm region (5000...625 cm^{-1}) for 0.1 mm solvent thickness[b].



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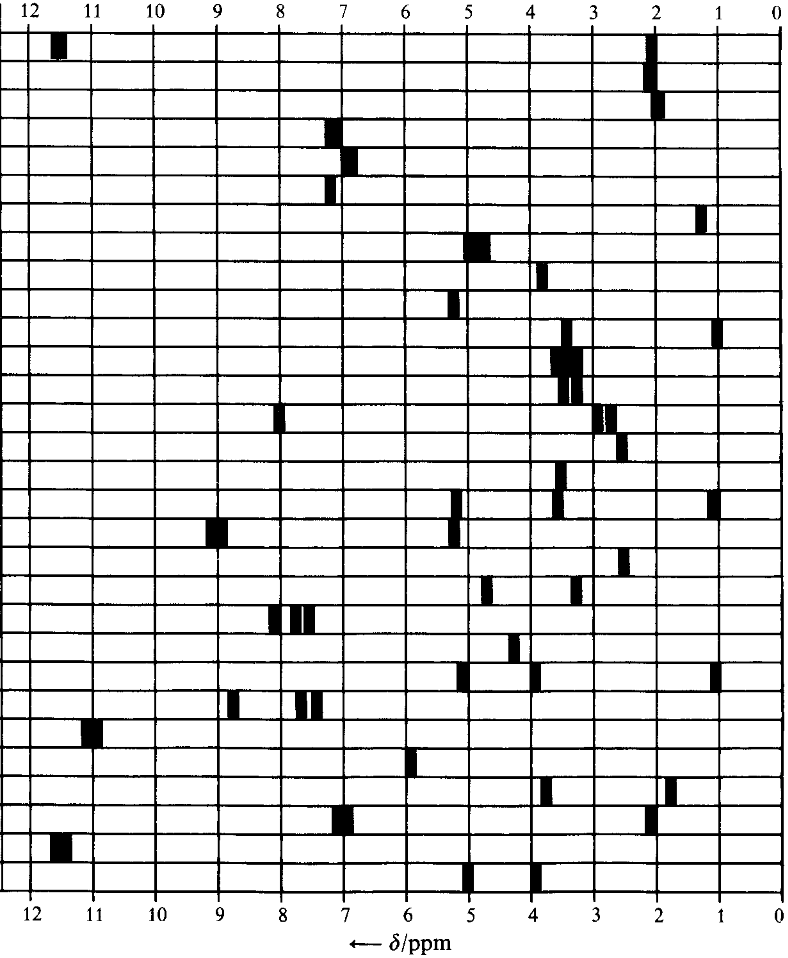
[a] ■ 80...100% Transmission; □ 60...80% Transmission. The black lines represent the useful regions. In the areas where the solvent has absorption bands that are totally absorbing, no information can be obtained about the sample, even though a compensating reference cell is employed. There is no solvent that is completely transparent over the entire wavenumber range. The most useful solvents are tetrachloromethane and carbon disulfide.

[b] N. L. Alpert, W. E. Keiser, and H. A. Szymanski: *IR – Theory and Practice of Infrared Spectroscopy*. 2^{nd} edition, first paperback printing, Plenum Publishing Corporation, New York, 1973, p. 326.

Table A-6. Characteristic ^{1}H NMR absorption bands[a] of thirty spectroquality solvents, commonly used in ^{1}H nuclear magnetic resonance spectroscopy[b] (δ scale: Tetramethylsilane $\delta_H = 0$ ppm).

Solvents	δ/ppm (multiplicity)[a]
Acetic acid-d_4	11.53(1)[c], 2.03(5)
Acetone-d_6	2.04(5)
Acetonitrile-d_3	1.93(5)
Benzene-d_6	7.15(br)
Tribromomethane-d_1	6.85(1)
Trichloromethane-d_1	7.24(1)
Cyclohexane-d_{12}	1.38(br)
Deuterium oxide	*ca.* 4.8[c]
1,2-Dichloroethane-d_4	3.72(br)
Dichloromethane-d_2	5.32(3)
Diethyl ether-d_{10}	3.34(m), 1.07(m)
Diethylene glycol dimethyl ether-d_{14}	3.49(br), 3.40(br), 3.22(5)
1,2-Dimethoxyethane-d_{10}	3.40(m), 3.22(5)
N,N-Dimethylformamide-d_7	8.01(br), 2.91(5), 2.74(5)
Dimethyl sulfoxide-d_6	2.49(5)
1,4-Dioxane-d_8	3.53(m)
Ethanol-d_6 (anhydrous)	5.19(1)[c], 3.55(br), 1.11(m)
Hexafluoroacetone · 3/2 D_2O	*ca.* 9.0(br)[c], 5.26(1)
Hexamethylphosphoric triamide-d_{18}	2.53(2 × 5)
Methanol-d_4	4.78(1)[c], 3.30(5)
Nitrobenzene-d_5	8.11(br), 7.67(br), 7.50(br)
Nitromethane-d_3	4.33(5)
2-Propanol-d_8	5.12(1)[c], 3.89(br), 1.10(br)
Pyridine-d_5	8.71(br), 7.55(br), 7.19(br)
Sulfuric acid-d_2	*ca.* 11.0[c]
1,1,2,2-Tetrachloroethane-d_2	5.91(1)
Tetrahydrofuran-d_8	3.58(br), 1.73(br)
Toluene-d_8	7.09(m), 7.00(br), 6.98(m), 2.09(5)
Trifluoroacetic acid-d_1	11.50(1)[c]
2,2,2-Trifluoroethanol-d_3	5.02(1)[c], 3.88(4 × 3)



[a] The ^{1}H chemical shifts of the residual hydrogen atoms are in ppm relative to tetramethylsilane, determined with solutions containing 5 mL/100 mL tetramethylsilane as the internal standard. The multiplicity of the peaks is given in parentheses; br indicates a broad peak without resolvable fine structure, while m denotes one with fine structure. Partial deuterium labeling results in broadening or splitting of the residual peaks, due either to deuterium-hydrogen coupling or non-equivalence of the residual hydrogens. If undeuterated solvents are used, the region obscured might be as wide as 2 . . . 3 ppm.

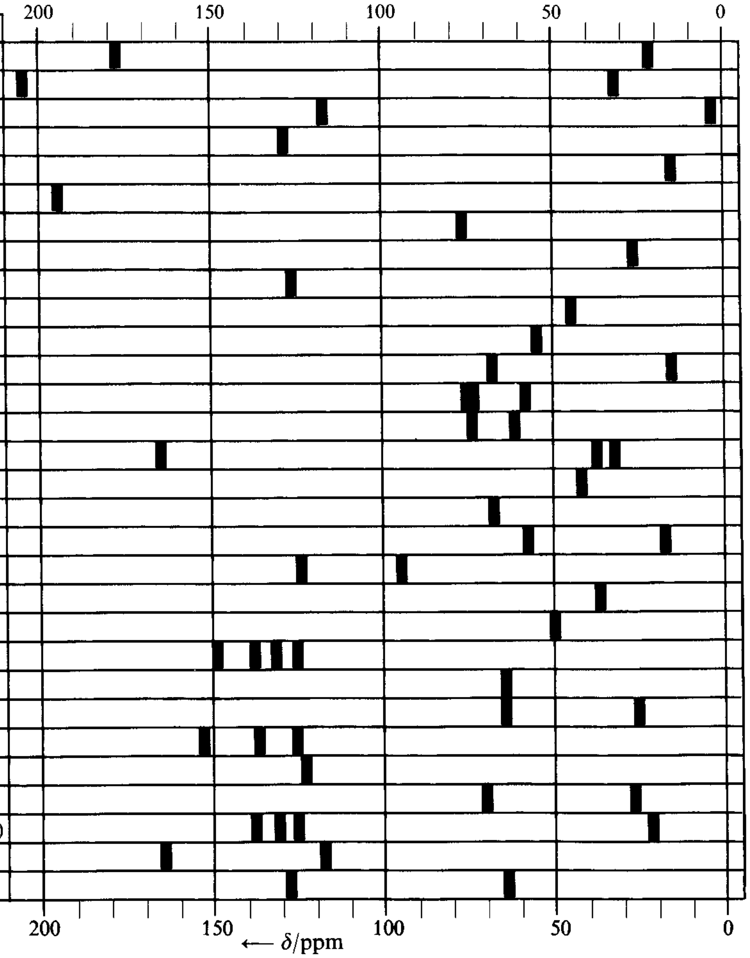
[b] Compiled from the following references:

(1) Merck, Sharp & Dohme Canada Ltd., Isotope Division: *Deuterated Solvents – Handy Reference Data*, Quebec/Canada, 1990;
(2) H.-O. Kalinowski, S. Berger, S. Braun: *Carbon–13 NMR Spectroscopy*, Wiley, Chichester, 1988;
(3) E. Pretsch, P. Bühlmann, C. Affolter: *Structure Determination of Organic Compounds – Tables of Spectral Data*. 3rd ed., Springer, Berlin, 2000 (p. 240–243).

[c] These peak positions may vary considerably depending on solute, concentration, and temperature.

Table A-7. Characteristic ^{13}C NMR absorption bands[a)] of thirty spectroquality solvents, commonly used in ^{13}C nuclear magnetic resonance spectroscopy[b)] (δ_C scale: tetramethylsilane $\delta_C = 0$ ppm).

Solvents	δ/ppm (multiplicity)[a)]
Acetic acid-d_4	178.4(br), 20.0(7)
Acetone-d_6	206.0(13), 29.8(7)
Acetonitrile-d_3	118.2(br), 1.3(7)
Benzene-d_6	128.0(3)
Tribromomethane-d_1	12.4(3)
Carbon disulfide	192.7(1)
Trichloromethane-d_1	77.0(3)
Cyclohexane-d_{12}	26.4(5)
Dichlorodifluoromethane	126.2(3)
1,2-Dichloroethane-d_4	43.6(5)
Dichloromethane-d_2	53.8(5)
Diethyl ether-d_{10}	65.3(5), 14.5(7)
Diethylene glycol dimethyl ether-d_{14}	70.7(5), 70.0(5), 57.7(7)
1,2-Dimethoxyethane-d_{10}	71.7(5), 57.8(7)
N,*N*-Dimethylformamide-d_7	162.7(3), 35.2(7), 30.1(7)
Dimethyl sulfoxide-d_6	39.5(7)
1,4-Dioxane-d_8	66.5(5)
Ethanol-d_6 (anhydrous)	56.8(5), 17.2(7)
Hexafluoroacetone · 3/2 D_2O	122.5(4), 92.9(7)
Hexamethylphosphoric triamide-d_{18}	35.8(7)
Methanol-d_4	49.0(7)
Nitrobenzene-d_5	148.6(1), 134.8(3), 129.5(3), 123.5(3)
Nitromethane-d_3	62.8(7)
2-Propanol-d_8	62.9(3), 24.2(7)
Pyridine-d_5	149.9(3), 135.5(3), 123.5(3)
Tetrachloroethene	121.4(1)
Tetrahydrofuran-d_8	67.4(5), 25.3(br)
Toluene-d_8	137.5(1), 128.9(3), 128.0(3), 125.2(3), 20.4(7)
Trifluoroacetic acid-d_1	164.2(4), 116.6(4)
2,2,2-Trifluoroethanol-d_3	126.3(4), 61.5(4 × 5)



[a] The ^{13}C chemical shifts are in ppm relative to tetramethylsilane, determined with solutions containing 5 mL/100 mL tetramethylsilane as the internal standard. The multiplicity of the peaks is given in parentheses; br indicates a broad peak without resolvable fine structure. The chemical shifts can be dependent on solute, concentration, and temperature.

[b] Compiled from the following references:
(1) Merck, Sharp & Dohme Canada Ltd., Isotope Division: *Deuterated Solvents – Handy Reference Data*, Quebec/Canada, 1990;
(2) H.-O. Kalinowski, S. Berger, S. Braun: *Carbon–13 NMR Spectroscopy*. Wiley, Chichester, 1988.
(3) E. Pretsch, P. Bühlmann, C. Affolter: *Structure Determination of Organic Compounds – Tables of Spectral Data*, 3rd ed., Springer, Berlin, 2000 (p. 157–160).

as far as possible. The ideal situation can be approached by extrapolation to infinite dilution from measurements at different concentrations. Solvent effects can generally be ignored in inert solvents such as CCl_4 or CS_2 at solute concentrations of $\leq$50 mg/g.

Concerning solvents for matrix isolation see Section A.4.

A.4 Solvents as Reaction Media

The following criteria can be used in the proper choice of solvents for chemical reactions and kinetic investigations: a maximum working range between melting and boiling point, chemical and thermal stability in this temperature range, good solubility of reactants and products (or sometimes insolubility of the products), compatibility with the analytical methods employed, and usually high degree of purity. The most useful solvents for some common reaction types are indicated in Table A-8. When a solvent is used for technical purposes, other factors may play an additional role [45]: price, flammability (ignition point, flash point), explosiveness (upper and lower explosion limit), viscosity, miscibility (*e.g.* blending with extenders or diluents), toxicity, corrosive action, and feasibility of recycling.

More recently, two-phase solvent systems, sometimes with temperature-dependent mutual miscibility of the two components, have gained interest as reaction media [149–156]. Having different solubilities for educts, products, reagents, and catalysts, biphasic solvent combinations can facilitate the separation of products from reaction mixtures. Since perfluorohydrocarbons [149–154] and room temperature ionic liquids [155, 156] are immiscible with many common organic solvents, they are particularly suitable for the formation of such biphasic solvent systems; see also Section 5.5.13.

Another interesting area concerning solvents as reaction media as well as for spectroscopy is the technique of *matrix isolation*, used when the molecule of interest is extremely unstable. Matrix isolation involves the trapping of the molecule in a rigid cage of a chemically inert solvent (the matrix) at low temperature. The main requirements are that the unstable molecule must have a stable precursor from which it can be liberated (usually by irradiation), and that the fragments so produced must not react with it or with the matrix. The reaction products can then be studied by IR or UV/Vis spectroscopy. Typical matrix materials are the noble gases (especially argon), the lighter hydrocarbons and halohydrocarbons, nitrogen, carbon dioxide, and other solvents and solvent mixtures that produce clear glasses when cooled to low temperatures. The properties of a number of matrix solvents can be found in references [93–96]. The temperature has to be sufficiently low to prevent diffusion of the solute into the matrix lattice. The useful temperature range is from 1.5 K to about 0.6 K of the matrix melting point. It should be remembered that the properties of a matrix-isolated molecule may be different from those in the commonly used solvents because of the low temperature and unusual environment.

A.5 Solvents for Recrystallization

The following requirements must be met by a solvent used for the recrystallization of an organic compound [46–48]: high solubility at high temperatures and low solubility at

Table A-8. Compilation of solvents commonly used for some important chemical reactions[a,b].

Reactions / Solvents	S_N1 Reactions[c]	S_N2 Reactions[c]	Oxidation reactions[d]	Ozonization reactions	Epoxidation reactions	Catalytic Hydrogenation[d,e]	Metal Hydride Reductions[f]	Aldol Reactions[d,g]	Wittig Reactions[h]	Diels-Alder Cycloadditions	Grignard Reactions	Friedel-Crafts Acylation and Alkylation Reactions	Halogenation	Nitration	Sulfonation	Diazotization	Diazo Coupling
Acetic acid	+		+	+	+	+		+					+	+	+	+	+
Acetone		+			+					+							
Acetonitrile		+							+	+							
Benzene			+		+		+	+	+	+		(+)				+	
t-Butanol	+		+						+								
Carbon disulfide												+					
Trichloromethane			+	+	+					+					+		
Cyclohexane						+											
Dichloromethane			+	+					+	+		+		+			
Diethyl ether					+		+	+	+	+	+						
Di-*n*-butyl ether											+						
1,2-Dichloroethane				+						+		+					
1,2-Dichlorobenzene										+		+	+	+			
1,2-Dimethoxyethane							+	+	+								
N,N-Dimethylformamide		+				+			+							+	
Dimethyl sulfoxide		+						+	+								
1,4-Dioxane			+		+	+	+			+					+		
Ethanol	+					+		+	+	+						+	+
Ethyl acetate			+	+		+											
HMPT		+							+								
Methanol	+			+		+		+	+	+							+
Nitrobenzene			+									+	+	+	+		
Nitromethane		+										+					
Petroleum ether						+						+			+		
Pyridine			+					+									+
Sulfuric acid			+											+	+	+	
Tetrachloroethene										+							
Tetrachloromethane				+	+								+	+	+		
Tetrahydrofuran						+	+	+	+	+	+						
Tetramethylene sulfone		+	+									+					
Toluene							+	+	+	+							
Trichloroethene										+		+					
Water	+		+			+		+		+						+	+

[a] *Cf.* A. K. Doolittle: *The Technology of Solvents and Plasticizers*, Wiley, New York, 1954.

[b] Table A-8 contains a more arbitrary selection from a plurality of possibilities. If more than one solvent is given for a reaction, then binary mixtures of these solvents can also be used as reaction media.

[c] C. K. Ingold: *Structure and Mechanism in Organic Chemistry*, 2nd edition, Cornell University Press, Ithaca/N.Y., and London, 1969.

[d] H. O. House: *Modern Synthetic Reactions*, 2nd edition, Benjamin, Menlo Park/California, 1972.

[e] P. N. Rylander: *Solvents in Catalytic Hydrogenation*, in W. H. Jones (ed.): *Catalysis in Organic Synthesis*, Academic Press, New York, London, 1980.

[f] H. C. Brown: *Organic Syntheses via Boranes*, Wiley-Interscience, New York, 1985.

[g] A. T. Nielsen and W. J. Houlikan: *The Aldol Condensation*, Org. React *16*, 1 (1968); *cf.* p. 76–77. – C. H. Heathcock: *Stereoselective Aldol Condensations*, in E. Buncel and T. Durst (eds.): *Comprehensive Carbanion Chemistry*, Part B, Chapter 5, p. 177ff., Elsevier, Amsterdam, 1984; *cf.* p. 199.

[h] I. Gosney and A. G. Rowley in J. I. G. Cadogan (ed.): *Organophosphorus Reagents in Organic Synthesis*, Academic Press, London, 1979, p. 24–25 and 41.

low temperatures of the substance to be recrystallized; impurities should be either highly soluble or totally insoluble; the boiling point should be as high as possible; the solvent should be chemically inert; the solvent must favor crystal growth, and be easily separated from the pure crystals by washing or drying. Hence, it should be either volatile or very soluble in a more volatile solvent and not form clathrates or solvates. In the first instance, the choice of solvent can be made according to the old rule "like dissolves like". The following list gives some guidelines [49]; a more complete collection of organic solvents used for recrystallization is given in Table A-9. When a compound is too soluble in one, and not soluble enough in another solvent, a binary mixture of the two may be a useful medium for recrystallization (*e.g.* acetic acid/water, ethanol/water, ethanol/benzene, acetone/petroleum ether, or trichloromethane/petroleum ether). For solvent selection, see also references [119, 120, 157].

Crystallization of a solid from solution cannot only be effected by changing the temperature (decreasing solubility with decreasing temperature) but also by changing the solvent polarity (decreasing solubility with decreasing solvent polarity) at constant temperature. A "cold" crystallization technique, using pairs of solvents of different polarity (*e.g.* methanol/water, acetone/water) has been considered in reference [121].

Compound to be recrystallized		Well soluble in
Hydrocarbons	*hydrophobic*	Hydrocarbons, Ethers,
Halohydrocarbons		Halohydrocarbons
Ethers		
Amines		Carboxylic Esters
Esters		
Nitrohydrocarbons		
Nitriles		Alcohols, 1,4-Dioxane
Ketones		Acetic Acid
Aldehydes		
Phenols		Alcohols, Water
Amides		
Alcohols		
Carboxylic Acids		
Sulfonic Acids	↓	
Salts	*hydrophilic*	Water

A.6 Solvents for Extraction and Partitioning (Distribution)

The partitioning of a substance between two liquid phases (multistage partitioning, partition chromatography) and the extraction of solids require similar properties of a solvent [50–55]. When a substance has to be partitioned, a solvent system with limited miscibility of the components is required in order that the substance dissolves to a different extent in the two phases. The greater the chemical differences between any two solvents, the more limited their miscibility. Other requirements that the solvent system must fulfil are, *inter alia*, a favorable partition coefficient (the average partition coefficient of the component mixture should be between *ca.* 0.2 and 5), as high a separation

Table A-9. Compilation of solvents commonly used for crystallization of organic compounds[a], listed in order of decreasing solvent polarity as measured by the E_T^N values[b].

Solvent	E_T^N	$t_{bp}/°C$	Suitable solvent for	Second solvent for mixture[c]
Water	1.000	100.0	Salts, amides, some carboxylic acids	Acetone, alcohols, 1,4-dioxane, acetonitrile
Methanol	0.762	64.5	General, esters, nitro and bromo compounds	Water, diethyl ether, benzene
2-Methoxyethanol	0.657	124.6	Sugars	Water, benzene, diethyl ether
Ethanol	0.654	78.3	General, esters, nitro and bromo compounds	Water, hydrocarbons, ethyl acetate
Acetic acid	0.648	117.9	Salts, amides, some carboxylic acids	Water
Acetonitrile	0.460	81.6	Dipolar compounds	Water, diethyl ether, benzene
Acetone	0.355	56.1	General, nitro and bromo compounds, osazones	Water, hydrocarbons, diethyl ether
Dichloromethane	0.309	39.6	General, low-melting compounds	Ethanol, hydrocarbons
Pyridine	0.302	115.3	High-melting, poorly soluble compounds	Water, methanol, hydrocarbons
Trichloromethane	0.259	61.2	General, acid chlorides	Ethanol, hydrocarbons
Methyl acetate	0.253	56.9	General, esters	Water, diethyl ether
Ethyl acetate	0.228	77.1	General, esters	Diethyl ether, benzene, hydrocarbons
1,4-Dioxane	0.164	101.3	Amides	Water, benzene, hydrocarbons
Diethyl ether	0.117	34.5	General, low-melting compounds	Acetone, hydrocarbons
Benzene	0.111	80.1	Aromatics, hydrocarbons, molecular complexes	Diethyl ether, ethyl acetate, hydrocarbons
Toluene	0.099	110.6	Aromatics, hydrocarbons	Diethyl ether, ethyl acetate, hydrocarbons
Tetrachloromethane	0.052	76.7	Apolar compounds, acid chlorides, anhydrides	Diethyl ether, benzene, hydrocarbons
Ligroin	–	90–110	Hydrocarbons	Ethyl acetate, benzene, dichloromethane
Petroleum ether	–	40–60	Hydrocarbons	Any solvent on this list from ethanol down
n-Hexane	0.009	68.7	Hydrocarbons	Any solvent on this list from ethanol down
Cyclohexane	0.006	80.8	Hydrocarbons	Any solvent on this list from ethanol down

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[a] *Cf.* A. J. Gordon and R. A. Ford: *The Chemist's Companion – A Handbook of Practical Data, Techniques, and References*. Wiley, New York, London, Sydney, Toronto, 1972, p. 442.

[b] C. Reichardt, Chem. Rev. *94*, 2319 (1994).

[c] Trial and error is usually required in selecting a second solvent for a mixture. There are some generally successful mixtures, such as diethyl ether/methanol (or ethanol) for highly associated solids (especially amides and alcohols) and many natural products, and diethyl ether/petroleum ether (or benzene) for dipolar compounds (especially esters and alcohols) and hydrocarbons[a]. *Cf.* also J. B. Baumann: *Solvent Selection for Recrystallization*. J. Chem. Educ. *56*, 64 (1979); R. E. R. Craig: *Rapid, Efficient Determination of Recrystallization Solvents at the Microscale Level*, J. Chem. Educ. *66*, 88 (1989).

factor as possible (the ratio of the partition coefficients should not, in general, be smaller than 1.5), linearity of the partition isotherm (*i.e.* concentration independence of the partition isotherm), a sufficiently large capacity, high selectivity, no tendency for emulsion formation and rapid separation of the phases (this requires low viscosity, a large density difference, and a sufficient surface tension), absence of irreversible reactions between solvent and solute, and ease of recovery of the substance [51]. The optimization of these various requirements is difficult. Generally, a compromise between these, sometimes competing, factors must be made in the choice of phase partners. The solvents used most frequently in partitioning have been divided into five classes according to the intermolecular interactions between the solvent molecules. The difference lies predominantly in the number and strength of the intermolecular hydrogen bonds [51]. Typical representatives of these five classes of solvents are water, methanol, pyridine, trichloromethane, and *n*-heptane. Within each class the solvents can be ordered according to increasing solubility in water or decreasing solubility in *n*-heptane. Thus, a "mixotropic" series of solvents has been established [51], an extended version of which is presented in Table A-10. This series gives valuable information concerning both the miscibility of solvents and their use in partitioning methods (paper, column, and thin-layer chromatography). The farther that two solvents are from each other in Table A-10, the less miscible they are. More than 400 liquid stationary phases for gas-liquid chromatography are commercially available. The selection of the proper stationary phase for a separation problem is often done by "trial and error"; here again, the rule "like dissolves like" is often useful. Collections of established liquid stationary phases can be found in references [4, 56]. Methods for assessing the polarity and selectivity of stationary phases in gas-liquid chromatography have been reviewed [133].

For the optimization of solvent composition in high-performance liquid chromatography (HPLC), see references [122–125].

In addition to common organic solvents, supercritical fluids (scf's) can be used for a great variety of extraction processes [158–165]. Supercritical fluid extraction (SFE), mostly carried out with sc-CO_2 as eluant, has many advantages compared to extractions with conventional solvents. The solvent strength of a supercritical fluid can easily be controlled by the pressure and temperature used for the extraction: at a constant temperature, extraction at lower pressures will favour less polar analytes, while extraction at higher pressures will favour more polar and higher molar mass analytes. As supercritical fluids such as CO_2 and N_2O have low critical temperatures ($t_c = 31$ °C and 36 °C, respectively), SFE can be performed at moderate temperatures to extract thermolabile compounds. Typical industrial applications using sc-CO_2 include caffeine extraction from coffee beans [158] as well as fat and oil extraction from plant and animal tissues [165]. For some physical properties of supercritical solvents, see Section 3.2.

A.7 Solvents for Adsorption Chromatography

The accumulation of an organic substance on the surface of an adsorbent is determined by its dipolarity as well as its polarizability and molecular size. This is also true for solvents, which are adsorbed more strongly the more dipolar their molecules. The mole-

Table A-10. Mixotropic Solvent Series[a–e].

(1) Water
(2) Lactic acid
(3) Formamide
(4) Morpholine
(5) Formic acid
(6) Acetonitrile
(7) Methanol
(8) Acetic acid
(9) Ethanol
(10) 2-Propanol
(11) Acetone
(12) 1-Propanol
(13) 1,4-Dioxane
(14) Propanoic acid
(15) Tetrahydrofuran
(16) *t*-Butanol
(17) 2-Methylpropanoic acid
(18) 2-Butanol
(19) 2-Butanone
(20) Cyclohexanone
(21) Phenol
(22) *t*-Amyl alcohol
(23) 1-Butanol
(24) 3-Methylphenol
(25) Cyclohexanol
(26) *i*-Amyl alcohol
(27) 1-Pentanol
(28) Benzyl alcohol
(29) Ethyl acetate
(30) 1-Hexanol
(31) 2,4,6-Trimethylpyridine
(32) Pentanoic acid
(33) Ethyl formate
(34) 3-Methylbutanoic acid
(35) Furan
(36) Diethyl ether
(37) 1-Octanol
(38) Diethoxymethane
(39) Hexanoic acid
(40) Butyl acetate
(41) Di-*i*-propoxymethane
(42) Nitromethane
(43) 1-Bromobutane
(44) Di-*i*-propyl ether
(45) Butyl butyrate
(46) 1-Bromopropane
(47) Di-*n*-butyl ether
(48) Dichloromethane
(49) Trichloromethane
(50) Di-*i*-amyl ether
(51) 1,2-Dichloroethane
(52) Bromobenzene
(53) 1,1,2-Trichloroethane
(54) 1,2-Dibromethane
(55) Bromoethane
(56) Benzene
(57) 1-Chloropropane
(58) Trichloroethene
(59) Toluene
(60) Xylenes
(61) Tetrachloromethane
(62) Carbon disulfide
(63) Decalin
(64) Cyclopentane
(65) Cyclohexane
(66) *n*-Hexane
(67) *n*-Heptane
(68) Kerosene
(69) Petroleum ether
(70) Petroleum
(71) Paraffin oil

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[a] This series applies generally to partition separations by paper-, column-, or thin-layer chromatography. The solvents listed go from most to least hydrophilic behaviour.

[b] E. Hecker, Chimia *8*, 229 (1954); E. Hecker: *Verteilungsverfahren in Laboratorien*, Verlag Chemie, Weinheim, 1955, p. 92 and 139.

[c] E. Heftmann (ed.): *Chromatography*, 2nd ed., Reinhold Publishing Company, New York, 1967.

[d] O. Mikeś: *Laboratory Handbook of Chromatographic Methods*, Van Nostrand, London, 1970.

[e] *Cf.* also A. J. Gordon and R. A. Ford: *The Chemist's Companion – A Handbook of Practical Data, Techniques, and References*, Wiley-Interscience, New York, 1972, p. 379.

cules of the adsorbed compound and the solvent compete for the active sites on the adsorbent surface. Thus, an organic compound will be adsorbed more strongly from an apolar than from a polar solvent. Conversely, a previously adsorbed material can only be replaced by a solvent when the latter has a higher affinity for the adsorbent [24, 52, 57–60, 126, 127].

The following requirements are desirable when choosing an eluant: high purity (in particular, the absence of water and other strongly polar compounds), solubility of the crude mixture, low viscosity, ease of regeneration, and suitability for analytical methods employed (*e.g.* when using UV/Vis detection during elution, the solvent itself must be transparent at the wavelength used). Furthermore, the eluant must be chemically inert to the adsorbate; *e.g.* acetone and ethyl acetate on an alkaline adsorbent such as aluminium oxide are readily transformed into diacetone alcohol and acetic acid, respectively. The success of a separation problem often depends more on the proper choice of solvent than on the choice of stationary phase. The solvents used as eluants can be arranged according to their increasing eluting power, the so-called "eluotropic" series of solvents, by an empirical determination of the retention times for a constant adsorbent and test mixture [24, 52, 57–61]. The shorter the retention time of the test sample, the higher the eluting power and hence the polarity of the solvent. Oxide adsorbents such as aluminium oxide and silica give almost identical eluotropic series. A generalised eluotropic series according to Pusey [61] is as follows: saturated hydrocarbons < aromatic hydrocarbons < halogenated hydrocarbons < ethers < esters < ketones < alcohols < carboxylic acids. Table A-11 gives the eluotropic series for standard solvents in conjugation with hydrophilic adsorbents according to Snyder [59, 60]. For hydrophobic adsorbents such as charcoal and polyamides, the eluotropic series is almost reversed. Often, mixtures of two or three solvents of different polarity lead to a better separation than a pure solvent. Again, the multicomponent eluants can be ordered in an eluotropic series [59, 60]. For example, the eluting power increases steadily in the series: petroleum ether, petroleum ether/benzene (100, 200, and 500 mL/L), benzene, benzene/ethanol (20, 50, 100, and 200 mL/L). Since the eluting power of a solvent is the result of interactions between adsorbent, solvent, and sample, eluotropic series are generally valid only for the substance class for which they have been established. The mixotropic (Table A-10) as well as the eluotropic series (Table A-11) reflect, approximately, the series of increasing polarity given by the empirical polarity parameter E_T^N (*cf.* Table A-1).

The most common approach to solvent characterization used by chromatographers is the 'solvent-triangle classification method' introduced by Snyder [166, 167]. Three solvent selectivity factors, x_i, representing the solvent's dipolarity, HBD acidity, and HBA basicity contributions to the total polarity, P', are plotted on a triangular diagram, allowing a classification of the many solvents used in liquid chromatography into eight classes with distinctly different selectivities.

In addition to conventional liquid chromatography, supercritical fluid chromatography (SFC), using a supercritical fluid as mobile phase (mostly scf-CO_2), has attracted attention in the last decades [58, 164, 168, 169]. Supercritical fluids provide a favourable medium for the transport of solutes through a chromatographic column because they resemble a gas in terms of viscosity, a liquid in terms of density, and are intermediate between these two phases in terms of diffusivity. For some physical properties of supercritical solvents, see Section 3.2.

Table A-11. Eluotropic solvent series for hydrophilic adsorbents such as alumina or silica, listed in order of increasing eluting power of the solvent[a–e], quantitatively measured by Snyder's empirical eluant strength parameter ε°[f].

Solvents	ε° (Al_2O_3)[f]	Solvents	ε° (Al_2O_3)[f]
(1) Fluoroalkanes (1,1,2-Trichloro-1,2,2-trifluoroethane)	−0.25	(20) 2-Butanone	0.51
		(21) Triethylamine	0.54
(2) *n*-Pentane	*0.00*	(22) Acetone	0.56
(3) *n*-Hexane	0.01	(23) 1,4-Dioxane	0.56
(4) 2,2,4-Trimethylpentane	0.01	(24) Tetrahydrofuran	0.57
(5) Cyclohexane	0.04	(25) Ethyl acetate	0.58
(6) Cyclopentane	0.05	(26) Diethylamine	0.63
(7) Carbon disulfide	0.15	(27) Nitromethane	0.64
(8) Tetrachloromethane	0.18	(28) Acetonitrile	0.65
(9) 1,1,1-Trichloroethane	0.19	(29) Pyridine	0.71
(10) *t*-Butyl methyl ether	0.20	(30) Dimethyl sulfoxide	0.75
(11) Xylene	0.26	(31) 1- and 2-Propanol	0.82
(12) Di-*i*-propyl ether	0.28	(32) Ethanol	0.88
(13) Toluene	0.29	(33) Methanol	0.95
(14) Chlorobenzene	0.30	(34) 1,2-Ethanediol	1.11
(15) Benzene	0.32	(35) Acetic acid	High ($\gg$1)
(16) Diethyl ether	0.38	(36) Water	Higher
(17) Trichloromethane	0.40	(37) Aqueous salt solutions, buffers	Highest
(18) Dichloromethane	0.42		
(19) 1,2-Dichloroethane	0.44		

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[a] The term *eluotropic series* for solvents arranged in the order of increasing elution strength was introduced by W. Trappe, Biochem. Z. *305*, 150 (1940).

[b] As the relative elution power depends not only on the adsorbent, but in many cases on the compound types being separated, there exists no universal eluotropic series of solvent strengths. This series was given by L. R. Snyder[d]. For another eluotropic solvent series, see J. C. Touchstone: *Practice of Thin-Layer Chromatography*, 2nd ed., Wiley, Chichester, 1983.

[c] In binary solvent mixtures, addition of a small amount of one solvent to another less polar solvent rapidly increases the eluting power. The further away in the series the solvent pair is, the more drastic the change.

[d] For reversed-phase adsorbents such as charcoal or completely silanized silica, this eluotropic solvent series is valid in the reverse order. In this case, the eluting power increases in the following sequence: water < methanol < ethanol < acetone < 1-propanol < 1-butanol ≈ diethyl ether ≈ ethyl acetate < benzene < *n*-hexane[d].

[e] L. R. Snyder: *Principles of Adsorption Chromatography*, Dekker, New York, 1968; L. R. Snyder: *Solvent Selection for Separation Processes*, in E. S. Perry and A. Weissberger (eds.): *Techniques of Chemistry*, 3rd ed., Vol. XII, p. 25–75, Wiley-Interscience, New York, 1978; L. R. Snyder and J. J. Kirkland: *Introduction to Modern Liquid Chromatography*, 2nd ed., Wiley-Interscience, New York, 1979.

[f] The solvent strength ε° is a dimensionless number and indicates the free energy of adsorption of the solvent per unit area of adsorbent with unit activity, defined as $\varepsilon^{\circ} = 0$ for *n*-pentane on alumina[d]. For silica (SiO_2) as adsorbent, the ε° values are smaller by a factor of ca. 0.8 [$\varepsilon^{\circ}(SiO_2) \approx 0.8 \cdot \varepsilon^{\circ}(Al_2O_3)$], but the ranking of solvents remains the same.

The organization of solvents for analytical and preparative thin-layer chromatography also appears to be related to their viscosities [58, 126, 127].

A.8 Solvents for Acid/Base Titrations in Non-Aqueous Media

Many acids and bases are too weak to be titrated in aqueous solution (ionization constants $<10^{-8}$). The use of non-aqueous amphiprotic differentiating titration solvents (*cf.* Section 3.3.1), however, often permits one to reach a sharp titration end-point [62–70]. Non-aqueous solvents for the titration of weak acids and bases should be obtainable water-free and in a high state of purity, be chemically inert to the titrant and the substance under investigation, readily dissolve the substance and its titration product, or if the latter precipitates favour the formation of compact, crystalline, non-voluminous material. Weak bases are frequently titrated with perchloric acid in acetic acid, and weak acids with tetraalkylammonium hydroxide in 1,2-diaminoethane, alcohols, or pyridine [62–70]. The autoprotolysis constant is a particularly important criterion for solvent selection, since this constant determines the acidity or basicity region available in the solvent used. The smaller the autoprotolysis constant, the greater the range of acid or base strengths that can exist in a solvent and the greater the likelihood that it will be a differentiating solvent. Hence, acid-base titrations are best carried out in solvents with small K_{auto} values [64, 70]. The autoprotolysis constants, K_{auto}, of some amphiprotic solvents are given in Table A-12. These were often determined by conductivity measurements. It should be noted that the measured K_{auto} values often represent only a minimum value since, for extremely weakly basic or acidic solvents, it is difficult to distinguish between electrical conductivity caused by autoprotolysis and by impurities. A solvent is amphiprotic when it shows well-defined self-ionization, such that an autoprotolysis constant can be reproducibly measured. It is recommended that the term aprotic be used in place of amphiprotic for solvents with $K_{\text{auto}} < 10^{-20}$ ($\text{p}K_{\text{auto}} > 20$) [71]. In Table A-12 are also listed some solvents whose self-ionization cannot be due to protolysis, *e.g.* acetic anhydride. Just as it is possible to define pK areas, one can also evaluate intervals of electrochemical potential for various solvents useful for titrations with glass and calomel electrodes [72].

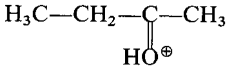
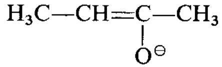
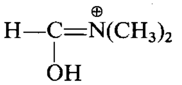
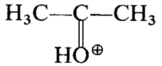
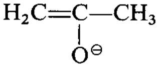
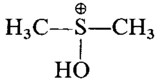
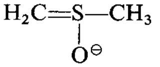
A.9 Solvents for Electrochemistry

Many electrochemical reactions, especially of organic compounds, are better carried out in non-aqueous solvents and may not even proceed in water. The following requirements should be met by these solvents [73–77]: sufficient solubility of the compounds to be examined and, of necessity, of the supporting electrolyte as well (usually tetraalkylammonium salts), chemical inertness towards the electrolyte and the reactive intermediates formed (*e.g.* the frequently formed radical anions would immediately be protonated by protic solvents), and as high a relative permittivity as possible (usually $\varepsilon_r > 10$). The latter will increase the electrical conductivity by favoring the dissociation of the electrolyte and hence decreasing the electrical resistance of the solution. Nevertheless, even solvents of low relative permittivity ($\varepsilon_r < 5$) can be used for electrochemical

Table A-12. Autoprotolysis constants (auto-ionization ionic products) of some amphiprotic solvents at 25 °C[a)] according to $2\ SH \rightleftharpoons SH_2^{\oplus} + S^{\ominus}$; $K_{auto} = [SH_2^{\oplus}] \cdot [S^{\ominus}]$[b)].

Solvents	Lyonium Ion	Lyate Ion	$pK_{auto} = -\lg[K_{auto}/(mol^2 \cdot L^{-2})]$	References
Sulfuric acid	$H_3SO_4^{\oplus}$	$HSO_4^{\ominus}$	3.33	[c]
2-Aminoethanol	$HO{-}CH_2CH_2{-}NH_3^{\oplus}$	$H_2N{-}CH_2CH_2{-}O^{\ominus}$	5.7	[d]
Formic acid	$HC(OH)_2^{\oplus}$	$HCO_2^{\ominus}$	6.2	[e]
N-Methylformamide	$CH_3{-}\overset{\oplus}{N}H{=}CH{-}OH$	$CH_3{-}N{=}CH{-}O^{\ominus}$	10.74	[v]
Hydrogen fluoride	$H_2F^{\oplus}$	$F^{\ominus}$	12.5 (0 °C)	[w]
Water	$H_3O^{\oplus}$	$HO^{\ominus}$	14.00	[f]
Acetic acid	$CH_3C(OH)_2^{\oplus}$	$CH_3CO_2^{\ominus}$	14.45	[g]
Acetic anhydride	$CH_3CO^{\oplus}$	$CH_3CO_2^{\ominus}$	*ca.* 14.5 (20 °C)	[h]
Acetamide	$CH_3CO{-}NH_3^{\oplus}$	$CH_3CO^{\ominus}{=}NH$	14.6 (98 °C)	[i]
Deuterium oxide	$D_3O^{\oplus}$	$DO^{\ominus}$	14.96	[k]
1,2-Diaminoethane	$H_2N{-}CH_2CH_2{-}NH_3^{\oplus}$	$H_2N{-}CH_2CH_2{-}NH^{\ominus}$	15.2	[l]
1,2-Ethanediol	$HO{-}CH_2CH_2{-}OH_2^{\oplus}$	$HO{-}CH_2CH_2{-}O^{\ominus}$	15.84	[m]
Formamide	$HCO{-}NH_3^{\oplus}$	$HCO^{\ominus}{=}NH$	16.8 (20 °C)	[n]
Methanol	$H_3C{-}OH_2^{\oplus}$	$H_3C{-}O^{\ominus}$	17.20	[o]
Ethanol	$H_5C_2{-}OH_2^{\oplus}$	$H_5C_2{-}O^{\ominus}$	18.88	[p]
1-Propanol	$H_7C_3{-}OH_2^{\oplus}$	$H_7C_3{-}O^{\ominus}$	19.43	[p]
Hexamethylphosphoric triamide	$[(CH_3)_2N]_3\overset{\oplus}{P}{-}OH$		20.56	[o]
1-Pentanol	$H_{11}C_5{-}OH_2^{\oplus}$	$H_{11}C_5{-}O^{\ominus}$	20.65	[q]
2-Propanol	$(H_3C)_2C{-}OH_2^{\oplus}$	$(H_3C)_2C{-}O^{\ominus}$	20.80	[p]
1-Butanol	$H_9C_4{-}OH_2^{\oplus}$	$H_9C_4{-}O^{\ominus}$	21.56	[q]
Ethyl acetate	$H_3C{-}\underset{OH}{\underset{\mid}{C}}{=}\overset{\oplus}{O}C_2H_5$	$H_2C{=}\underset{O^{\ominus}}{\underset{\mid}{C}}{-}OC_2H_5$	22.83	[o]
N,*N*-Dimethylacetamide	$H_3C{-}\underset{OH}{\underset{\mid}{C}}{=}\overset{\oplus}{N}(CH_3)_2$	$H_2C{=}\underset{O^{\ominus}}{\underset{\mid}{C}}{-}N(CH_3)_2$	23.95	[o]
1-Methyl-2-pyrrolidinone			24.15	[o]
Tetrahydrothiophene-1,1-dioxide			25.45	[o]

Table A-12. (Continued)

Solvents	Lyonium Ion	Lyate Ion	pK_{auto} = $-\lg[K_{auto}/(mol^2 \cdot L^{-2})]$	References
2-Butanone	 $H_3C-CH_2-\underset{HO^{\oplus}}{\underset{\Vert}{C}}-CH_3$	 $H_3C-CH=\underset{O^{\ominus}}{\underset{\vert}{C}}-CH_3$	25.94	[o]
2-Methyl-2-propanol	$(H_3C)_3C-OH_2^{\oplus}$	$(H_3C)_3C-O^{\ominus}$	26.8	[r]
N,*N*-Dimethylformamide	 $H-\underset{OH}{\underset{\vert}{C}}=\overset{\oplus}{N}(CH_3)_2$		29.4	[r]
Ammonia	$H_4N^{\oplus}$	$H_2N^{\ominus}$	32.5 (−33 °C)	[s]
Acetone	 $H_3C-\underset{HO^{\oplus}}{\underset{\Vert}{C}}-CH_3$	 $H_2C=\underset{O^{\ominus}}{\underset{\vert}{C}}-CH_3$	32.5	[r]
Dimethyl sulfoxide	 $H_3C-\underset{HO}{\underset{\vert}{\overset{\oplus}{S}}}-CH_3$	 $H_2C=\underset{O^{\ominus}}{\underset{\vert}{S}}-CH_3$	33.3	[t]
Acetonitrile	$H_3C-C\equiv NH^{\oplus}$	$H_2C=C=N^{\ominus}$	≥33.3	[u]

[a] Values at 25 °C unless stated otherwise.

[b] For more extensive compilations of autoprotolysis constants, see:

1. A. P. Kreshkov, Talanta *17*, 1029 (1970);
2. E. J. King: *Acid-Base Behaviour*, in A. K. Covington and T. Dickinson (eds.), *Physical Chemistry of Organic Solvent Systems*, Plenum Press, London, New York, 1973, p. 342 and 391.
3. B. Trémillon: *Chemistry in Non-Aqueous Solvents*, Reidel Publishing Company, Dordrecht, Boston, 1974, p. 70ff.
4. S. Rondinini, P. Longhi, P. R. Mussini, and T. Mussini, Pure Appl. Chem. *59*, 1693 (1987);
5. Y. Marcus: *The Properties of Solvents*, Wiley, Chichester, 1998, Table 4.5 on p. 167–172.

[c] P. A. H. Wyatt, Trans. Faraday Soc. *65*, 585 (1969).

[d] P. W. Brewster, F. C. Schmidt, and W. B. Schaap, J. Phys. Chem. *65*, 990 (1961).

[e] M. Bréant, C. Beguin, and C. Coulombeau, Anal. Chim. Acta *87*, 201 (1976).

[f] H. S. Harned, J. Am. Chem. Soc. *47*, 930 (1925); H. S. Harned and B. B. Owen: *The Physical Chemistry of Electrolytic Solutions*, 3rd edition, Reinhold, New York, 1958; see also S. J. Hawkes, J. Chem. Educ. *72*, 799 (1995).

[g] S. Bruckenstein and I. M. Kolthoff, J. Am. Chem. Soc. *78*, 2974 (1956).
[h] G. Jander and H. Surawski, Z. Elektrochem., Ber. Bunsenges. Physik. Chem. *65*, 527 (1961).
[i] S. Guiot and B. Trémillon, J. Electroanal. Chem. *18*, 261 (1968).
[k] A. K. Covington, R. A. Robinson, and R. G. Bates, J. Phys. Chem. *70*, 3820 (1966).
[l] W. B. Schaap, R. E. Bayer, J. R. Siefker, J. Y. Kim, P. W. Brewster, and F. C. Schmidt, Record Chem. Progr. *22*, 197 (1961); Chem. Abstr. *56*, 12664 (1962).
[m] K. K. Kundu, P. K. Chattopadhyay, D. Jana, and M. N. Das, J. Phys. Chem. *74*, 2633 (1970).
[n] F. H. Verhoek, J. Am. Chem. Soc. *58*, 2577 (1936).
[o] A. P. Kreshkov, N. Sh. Aldarova, and B. B. Tanganov, Zh. Fiz. Khim. *44*, 2089 (1970); Russian J. Phys. Chem. *44*, 1186 (1970); Chem. Abstr. *73*, 124160 d (1970); *cf.* also A. P. Kreshkov, N. T. Smolova, N. Sh. Aldarova, and N. A. Gabidulina, Zh. Fiz. Khim. *46*, 667 (1972); Chem. Abstr. *77*, 33798 j (1972).
[p] R. Schaal and A. Tézé, Bull. Soc. Chim. Fr. 1783 (1961).
[q] A. P. Kreshkov, N. Sh. Aldarova, and N. T. Smolova, Zh. Fiz. Khim. *43*, 2846 (1969); Chem. Abstr. *72*, 54413 s (1970).
[r] L. N. Bykova and S. I. Petrov, Zh. Anal. Khim. *27*, 1076 (1972); Chem. Abstr. *77*, 93626 m (1972); *cf.* also [o].
[s] L. V. Coulter, J. R. Sinclair, A. G. Cole, and G. C. Roper, J. Am. Chem. Soc. *81*, 2986 (1959).
[t] J. Courtot-Coupez and M. Le Démézet, Bull. Soc. Chim. Fr. 1033 (1969); *cf.* also [r].
[u] I. M. Kolthoff and M. K. Chantooni, J. Phys. Chem. *72*, 2270 (1968); *cf.* also [r].
[v] T. Oncescu, A.-M. Oancea, and L. de Maeyer, J. Phys. Chem. *84*, 3090 (1980).
[w] R. Gut, J. Fluorine Chem. *15*, 163 (1980).

investigations [170]. Furthermore, the solvent should be of low viscosity in order to guarantee rapid mass transport of ions to the electrodes. An absence of conducting impurities, especially water, is particularly important when measuring electrical conductivities [78, 79]. In addition, the solvent should have a large anodic and cathodic voltage limit, which defines the "window" of accessible electronic levels available for electron-transfer processes. Although organic solvents have intrinsic limits based on their chemical oxidation-reduction properties, the practical working limits also depend on the nature of the working electrode material and the composition of the supporting electrolyte. Therefore, the voltage limits are a system property and not only a solvent property [77]. Practical working limits in organic solvents are given in the literature [8, 73, 74, 77, 80, 81]. The electrochemical windows of a range of ionic liquids, *i.e.* liquid at room temperature, can be found in reference [171].

The rather narrow electrochemical window of water, limited by the discharge of hydrogen and oxygen, has stimulated the use of nonaqueous solvents for electrochemical reactions. Procedures for measuring and reporting electrode potentials in nonaqueous solvents are presented in reference [128]. The solvent influence on the redox properties of cations and anions has been reviewed [172], as have applications of ion-selective electrodes in nonaqueous solvents [129] and the influence of nonaqueous solvents on the polarographic half-wave potentials of cations [173].

A.10 Toxicity of Organic Solvents

Organic solvents show varied physiological and toxicological properties, which all too often are neglected in the laboratory. All solvents influence the human organism to a greater or lesser extent [82–89, 130–132]. The extent of this influence depends on the time of exposure. High doses over short time intervals can lead to acute poisoning; small doses over prolonged periods can induce chronic damage.

Solvents can be ingested through the skin and the respiratory organs. Inhalation of solvent vapours affects not only the lungs but the whole circulatory system and hence the whole body. They accumulate principally in lipid and fat-rich cells in the nervous system, brain, bone marrow, liver, and body fat. Acute poisoning manifests itself by derangement of the central nervous system (euphoria, dizziness, unconsciousness). Chronic poisonings occur initially without any obvious symptoms and damage of the organs characteristic of the different solvents appears only later.

Many solvents are absorbed not only through the respiratory organs but also through the skin (*e.g.* tetrachloromethane, dimethyl sulfoxide, benzene). This leads to dehydration of the skin due to the removal of water and fat, thereby allowing the invasion of bacteria and dirt.

Hence, organic solvents should be handled with care. In the USA, the *threshold limit values* (*TL* values) are used as a measure of the inhalation toxicity for chronic interaction with solvent vapours [90]. In the Federal Republic of Germany, the *maximum concentration values at the workplace* (*MAK* values) are used [91, 92]. Threshold limit values refer to airborne concentrations of substances and represent conditions under which it is believed that workers may be repeatedly exposed daily without adverse effect. They refer to time-weighted average concentrations for a normal 8-hour workday

Table A-13. *TL* Values[a], *MAK* Values[b,c], and Vapour Pressures[b,c] for seventy-seven organic solvents.

Solvents[d]	*TL* Values (TWA)[e]		*MAK* Values[f]		Vapour pressure at 20 °C in hPa
	mL/m^3	mg/m^3	mL/m^3	mg/m^3	
Acetic acid	10	25	–	–	15.3
Acetic anhydride	5	21	5	21	4
Acetone	500	1200	500	1200	240
Acetonitrile (skin)	20	34	20	34	97
1-Aminobutane (skin)	–	–	5	15	122 (25 °C)
2-Aminoethanol	3	7.5	2	5.1	0.53
Ammonia	25	17	20	14	8570
Aniline (skin)[g]	2	7.6	2	7.7	0.4
Benzene (skin)[h]	0.5	1.6	–	–	101
n-Butane	800	1900	1000	2400	2137 (21 °C)
1-Butanol (skin)	20	61	100	310	6.3
2-Butanol	100	303	–	–	–
t-Butanol	100	303	20	62	40.8
2-Butanone (skin)	200	590	200	600	105
1-Butyl acetate	150	713	100	480	13.3
t-Butyl methyl ether[g]	50	180	50	180	270
Carbon disulfide (skin)	10	31	5	16	400
Chlorobenzene	10	46	10	47	12
Cyclohexane	100	344	200	700	104
Cyclohexanol (skin)	50	205	50	210	1.2
Cyclohexanone (skin)[g]	25	100	–	–	5
1,2-Diaminoethane (skin)	10	25	10	25	12
1,1-Dichloroethane	100	405	100	410	240
1,2-Dichloroethane[h]	10	40	–	–	87
1,1-Dichloroethene[g]	–	–	2	8	667
1,2-Dichloroethene (*cis* + *trans*)	200	793	200	800	220
Dichloromethane[g]	50	174	–	–	475
Diethylamine (skin)	5	15	5	15	260
Diethylene glycol	–	–	10	44	0.027
Diethylene glycol dimethyl ether (skin)	–	–	5	28	2
Diethyl ether	400	1213	400	1200	587
Dimethoxymethane	1000	3112	1000	3200	440
Di-*i*-propyl ether	250	1045	200	850	180
N,*N*-Dimethylacetamide (skin)	10	36	10	36	1.3
N,*N*-Dimethylformamide (skin)	10	30	10	30	3.5
2,6-Dimethyl-4-heptanone	25	145	–	–	2.2 (25 °C)
1,4-Dioxane (skin)	20	72	20	73	41
Diphenyl ether (vapour)	1	7	1	7.1	0.3 (25 °C)
1,2-Ethanediol (skin)	–	–	10	26	–
Ethanol	1000	1884	500	960	59
2-Ethoxyethanol (skin)	5	18	5	19	ca. 5
Ethyl acetate	400	1441	400	1500	97
Ethyl benzene (skin)[g]	100	434	–	–	9
Ethyl formate (skin)	100	303	100	310	256
Formic acid	5	9.4	5	9.5	42
n-Heptane	400	1640	500	2100	48

Table A-13. (Continued)

Solvents[d]	*TL* Values (TWA)[e]		*MAK* Values[f]		Vapour pressure at 20 °C in hPa
	mL/m^3	mg/m^3	mL/m^3	mg/m^3	
Hexamethylphosphoric triamide[h] (skin)	–	–	–	–	0.04
n-Hexane (skin)	50	176	50	180	160
Methanol (skin)	200	262	200	270	128
2-Methoxyethanol (skin)	5	16	5	16	ca. 11
Methyl acetate	200	638	200	610	220
3-Methyl-1-butanol	100	361	100	370	4
Methylcyclohexane	400	1606	200	810	48
Methyl formate (skin)	100	266	50	120	640
2-Methyl-1-propanol	50	152	100	310	11.7
1-Methylpyrrolidin-2-one (vapour) (skin)	–	–	19	80	0.3
Morpholine (skin)	20	72	10	36	10
Nitrobenzene (skin)[g]	1	5	–	–	0.2
Nitromethane (skin)[g]	20	50	–	–	37
n-Octane	300	1400	500	2400	15
n-Pentane	600	1770	1000	3000	573
3-Pentanone	200	705	–	–	–
Phenol (skin)[g]	5	19	–	–	0.47
2-Propanol	400	983	200	500	44
2-Propen-1-ol (skin)[g]	0.5	1.2	–	–	24
i-Propylbenzene, Cumene (skin)	50	246	50	250	4
Pyridine	5	14	5	16	20
1,1,2,2-Tetrachloroethane (skin)[g]	1	7	1	7	7
Tetrachloroethene (skin)[g]	25	170	–	–	19
Tetrachloromethane (skin)[g]	5	31	0.5	3.2	120
Tetrahydrofuran (skin)	200	590	50	150	200
Toluene (skin)	50	188	50	190	29
1,1,1-Trichloroethane (skin)	350	1910	200	1100	133
Trichloroethene[h]	50	269	–	–	77
Trichloromethane (skin)	10	49	0.5	2.5	210
Triethylamine (skin)	1	4.2	1	4.2	72
Xylene (all three isomers) (skin)	100	434	100	440	15

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[a] *2002 Threshold Limit Values (TLVs®) for Chemical Substances and Physical Agents*, adopted by the American Conference of Governmental Industrial Hygienists (ACGIH®), available by ACGIH, 1330 Kemper Meadow Drive, Cincinnati/Ohio, 45240–1634, USA [90].

[b] *Maximale Arbeitsplatzkonzentration und Biologische Arbeitsstofftoleranzwerte 2002 (Maximum Concentrations and Biological Tolerance Values at the Workplace)*, Report No. 38 of the "Senatskommission zur Prüfung gesundheitsschädlicher Arbeitsstoffe" of the Deutsche Forschungsgemeinschaft (DFG), D-53170 Bonn/Germany; Wiley-VCH, Weinheim/Germany, 2002 [91].

[c] L. Roth, U. Weller: *Sicherheitsfibel Chemie*, 5th ed., Ecomed Verlagsgesellschaft, München, 2001.

[d] Where solvents are followed by the designation "skin", this refers to the potential significant contribution to the overall exposure by the cutaneous route, including mucous membranes and the eyes, either by contact with vapours or, of probable greater significance, by direct skin contact with

Table A-13. (Continued)

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the solvent. This attention-calling designation is intended to suggest appropriate measures for the prevention of cutaneous absorption so that the threshold limit is not invalidated.

[e] Adopted *T*hreshold *L*imit *V*alues – Time Weighted Average (TLV–TWA) – in parts of vapour or gas per million parts of contaminated air by volume (mL/m^3; ppm) at 25 °C and 1013 hPa, and in approximate milligrams of substance per cubic metre of air (mg/m^3).

[f] *M*aximale *A*rbeitsplatz*k*onzentrationen (maximum concentrations at the workplace) in parts of vapour or gas per million of contaminated air by volume (mL/m^3; ppm) at 20 °C and 1013 hPa, and in approximate milligrams of substance per cubic metre of air (mg/m^3).

[g] Solvent suspect of carcinogenic potential in humans.

[h] Solvent recognized as having carcinogenic potential, *i.e.* capable of inducing malignant tumors as shown through experience with animals and/or humans. – See also L. Roth, G. Rupp: *Krebserzeugende Stoffe*, 3rd ed., Wissenschaftliche Verlagsgesellschaft, Stuttgart/Germany, 2000.

and a 40-hour working week. *MAK* values represent the highest allowed airborne concentrations of gaseous, vapourous, or dusty chemical substances within a work area, which will neither, as far as is known, adversely affect the health of the workers nor disturb them, even by repeated long-term exposure. They refer to time-weighted average concentrations for an 8-hour workday and a 40-hour working week [91, 92]. Table A-13 gives the *TL* and *MAK* values of frequently used organic solvents. These values are based on the best available information from industrial experience and from experimental human and animal studies. The basis on which the *MAK* values are established is given in reference [92]. Since the amount and nature of the information available for establishing *TL* and *MAK* values varies, the precision of the estimated *TL* and *MAK* values is also subject to variation and the latest information should be consulted. The *TL* and *MAK* values in Table A-13 refer to those issued in 2002.

The vapour pressures of organic solvents are also listed in Table A-13, since these give an additional indication of their potential dangers caused by their volatility.

The designation "skin" is used to indicate that there is also a danger through skin ingestion either by airborne or by direct contact with the chemical substance [90–92]. When handling such compounds, meticulous care in avoiding contact with the skin, hair, and clothing is imperative for health protection.

The *TL* and *MAK* values should be used as guides in the control of health hazards. They are not constants that can be used to draw fine lines between safe and dangerous concentrations. Nor is it possible to calculate the *TL* or *MAK* values of solvent mixtures from the data in Table A-13, because antagonistic action or potentiation may occur with some combinations. It should be noted that occupational exposure limits such as the *TL* and *MAK* values are not intended for use as a comparative measure of one solvent against another. The values set airborne concentration limits on chemical exposure, but do not describe the ease with which that airborne limit is achieved. In addition, the vapour pressure of the solvent must also be considered. The lower the vapour pressure, the lower the airborne concentration. In order to better compare the safety of volatile compounds such as organic solvents, the use of the *vapour hazard ratio (VHR)* has been recommended as a feasible measure [175]. The vapour hazard ratio is defined as the quotient of the saturation concentration of a solvent (in mg/m^3; at a given temperature and pressure) and its occupational exposure limit (in mg/m^3; *e.g. TL* or *MAK* values), according to:

Table A-14. Some recommendations for the substitution of hazardous solvents by safer ones.

New safer solvent	Substitute for	Chemical reactions[a]	References
Perfluoroalkanes [*e.g.* perfluorohexane (bp. 57 °C), perfluoro(methylcyclohexane) (bp. 76 °C), perfluorodecalin (bp. 142 °C)]	Tetrachloromethane	Alkene brominations, reactions in fluorous biphasic systems (FBS)	[b] . . . [f]
(Trifluoromethyl)benzene (bp. 102 °C)	Benzene, dichloromethane	Friedel–Crafts reactions acylations, tosylations, silylations, Swern oxidations, radical reactions	[g]
Supercritical fluids (*e.g.* sc-CO_2: $t_c = 31$ °C, $p_c = 73$ bar)	Many other less polar solvents	Many types of organic reactions, *e.g.* isomerizations, hydroformylations, Diels–Alder reactions, oxidations	[h] . . . [l]
t-Butyl methyl ether (bp. 55 °C)	Et_2O, 1,4-Dioxane, THF, other ethers, benzene	Grignard reactions; as an octane booster in gasoline	[m] . . . [o]
Dimethoxymethane (bp. 42 °C), Diethoxymethane (bp. 88 °C)	Et_2O, 1,4-dioxane, THF, other ethers, benzene, $CHCl_3$	Organometallic reactions, preparation of Grignard reagents and organolithium derivatives, Schmidt reaction	[p] . . . [r]
1,3-Dimethylimidazolidin-2-one (DMI, DMEU) (bp. 225 °C)	HMPT	Organometallic reactions, S_N reactions, Wittig-Horner reactions, Birch reductions	[s] . . . [t]
1,3-Dimethylpropyleneurea (DMPU) (bp. 246 °C)	HMPT	Organometallic reactions, Enolate and Michael additions, S_N and Wittig-Horner reactions	[u]
N,*N*,*N*′,*N*′-Tetraethylsulfamide (TES) (bp. 85–88 °C/0.5 Torr)	HMPT, ethers	Many types of organometallic reactions, *e.g.* Grignard reactions	[v]
(−)-(*S*)-Ethyl lactate (bp. 154 °C)	Many solvents, *e.g.* xylene, glycol ethers, 1-methylpyrrolidone	Many types of reactions, compatible with the ester group	[w]
Water (bp. 100 °C)	Many other polar solvents	Many types of reactions, *e.g.* Diels–Alder reactions, Claisen rearrangements, carbonyl additions, transition metal-catalyzed reactions (Suzuki, Stille, and Heck coupling reactions), redox reactions	[x] . . . [z] [α] . . . [γ]
Ionic liquids [*e.g.* 1-ethyl-3-methylimidazolium triflate (mp. −9 °C); 1-*n*-butyl-3-methylpyridinium chloride (mp. 98 °C); tetra-*n*-butylammonium bromide (mp. 130 °C)]	Many other polar solvents	Many types of reactions, *e.g.* transition metal-catalyzed reactions, Heck, Diels–Alder, hydrogenation, hydroformylation and S_E reactions, alkene polymerizations	[δ] . . . [θ]

Table A-14. (Continued)

New safer solvent	Substitute for	Chemical reactions[a]	References
No solvent at all (*i.e.* solvent-free reactions)	All solvents	Many types of reactions, using the following techniques: Reactions on solid mineral supports (alumina, silica, clays); without any solvent, support, or catalyst between neat reactants; solid-liquid phase-transfer-catalyzed and microwave-activated reactions	[*ι*] . . . [*ξ*]

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$$VHR = \frac{\text{Saturation concentration (mg/m}^3\text{)}}{\text{Exposure limit (mg/m}^3\text{)}}$$

$$= \frac{\text{Sättigungskonzentration (mg/m}^3\text{)}}{\text{Grenzwert (mg/m}^3\text{)}} = GZ$$

In Germany, the vapour hazard ratio is described and recommended as the *Gefährdungszahl (GZ)* in the Technical Guidelines of the German 'Gefahrstoffverordnung' (TRGS No. 420) [176]. According to this definition, a solvent with a lower *vapour hazard ratio* or *Gefährdungszahl* is the safer one. For example, the *GZ* values for methanol and toluene (with *MAK* values of 270 and 190 mg/m^3, respectively) are (168000 mg/m^3)/(270 mg/m^3) = *622* and (110000 mg/m^3)/(190 mg/m^3) = *579*, respectively. Thus, compared to methanol, toluene is the safer solvent, in spite of the fact that methanol has the higher exposure limit. This is because the *GZ* (and *VHR*) value reflects the potential health risk of a solvent not only in terms of the exposure limit, but also the potential ease with which that limit is achieved under a given set of conditions. *VHR* values can range from 50 (for 1-methylpyrrolidin-2-one; low exposure risk) to 17644 for dichloromethane (high exposure risk). Different *GZ* and *VHR* values can be calculated under different conditions since the vapour pressure changes with temperature and pressure. A collection of *VHR* values, calculated according to the national exposure limits of many countries, can be found at http://www.dbe.dupont.com.

So-called *odor threshold values* are not included in Table A-13 since these often show great discrepancy in the literature. They depend strongly on the experimental technique and individual sensitivity. Nevertheless, an unpleasant smell together with any irritation should be taken as a warning signal.

As organic solvents can be released into the environment by air emissions, industrial and waste-treatment effluents, accidental spillages, leaking tanks, and the land disposal of solvent-containing wastes, considerable emphasis has also been placed on the environmental impact of solvents. Investigations concerning the fate of organic solvents in water, soil, and air; the methods of solvent detection and solvent recycling; and the substitution of hazardous solvents by safer ones, as well as the national and international regulations concerning solvents as volatile organic compounds and hazardous air pollutants have recently been extensively reviewed [174].

The replacement of hazardous organic solvents by safer ones is of particular interest for chemists in their routine daily laboratory work. Table A-14 collects a selection of more recent recommendations for such solvent substitutions, together with relevant references.

Of special interest is the renaissance of water as a useful solvent for many organic reactions, as well as the increasing importance of supercritical fluids and ionic liquids. In the context of sustainable chemistry and clean technology, the best solvent is no solvent at all. In following this axiom, increasing efforts have recently been made to develop solvent-free synthetic reactions using various modern techniques. The results are interesting, but not so promising that this book on solvent effects will become superfluous in the foreseeable future.

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Introduction

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Chapter 3

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Chapter 4

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Chapter 5

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Chapter 6

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Chapter 7

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