

**Supramolecular Chemistry –
Fundamentals and Applications**
Advanced Textbook

Katsuhiko Ariga · Toyoki Kunitake

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Advanced Textbook

With 173 Figures

 Springer

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Library of Congress Control Number: 2006920777

ISBN-10 3-540-01298-2 Springer Berlin Heidelberg New York
ISBN-13 978-3-540-01298-6 Springer Berlin Heidelberg New York
DOI: 10.1007/b84082

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Printed in Germany

CHOBUNSHI KAGAKU HE NO TENKAI
By Katsuhiko Ariga and Toyoki Kunitake
Copyright © 2000 by Katsuhiko Ariga and Toyoki Kunitake
Originally published in Japanese in 2000
By Iwanami Shoten, Publishers, Tokyo
This English edition published 2006
By Springer-Verlag Heidelberg

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Cover design: *design & production* GmbH, Heidelberg
Typesetting and production: LE-TeX Jelonek, Schmidt & Vöckler GbR, Leipzig, Germany
Printed on acid-free paper 2/3141/YL - 5 4 3 2 1 0

Preface

Molecules are created by the covalent bonding of atoms. However, although a molecule is created from a multitude of atoms, it behaves as an individual entity. A vast number of molecules of different sizes and structures are known, ranging from the simplest hydrogen molecule to high-molecular-weight man-made polymers and sophisticated biological macromolecules such as proteins and DNA. Indeed, all living matter, natural minerals and artificial materials, however complex and numerous they are, are combinations of some of these tens of millions of molecules. We may therefore be tempted to believe that the structures and properties of these materials and compounds can be directly related to those of the individual molecules that comprise them in a straightforward way. Unfortunately, this notion is not correct. However deeply we understand the nature of individual molecules, this knowledge is not enough to explain the structures and functions of materials and molecular assemblies that are derived as a result of organizing individual molecules. This is particularly true with biological molecular systems that are derived from the spatial and temporal organization of component molecules.

In this book we delve into the field of supramolecular chemistry, which deals with supermolecules. A supermolecule in this sense can be defined as a “molecule beyond a molecule” – a large and complex entity formed from other molecules. The molecules that comprise the supermolecule interact with each other via weak interactions such as hydrogen bonding, hydrophobic interactions and coordination to form new entities with novel properties and functions that cannot be deduced by a simple summation of the properties of the individual molecules. This monograph is intended to convey the relevance and fascination of the fast-growing field of supramolecular chemistry to advanced undergraduate students, and to provide an overview of it to young scientists and engineers. Readers will find that supramolecular chemistry is associated with many attractive disciplines of chemistry, including molecular recognition, molecular topology, self-organization, ultrathin films, molecular devices and biomolecular systems. As described in Chap. 1, supramolecular chemistry is still a very young field, and so it is difficult to predict its future, but it has already secured a firm position in the chemical sciences. For example, biotechnology and nanotechnology are expected to lead to technological revo-

lutions in near future that will dramatically affect our lifestyles and economies. Supramolecular chemistry is an indispensable tool in these technologies.

This book was originally written as part of a series of Japanese chemistry textbooks. The authors hope that this book be warmly accepted by English-language readers as well.

Ibaraki and Saitama, January 2006

*Katsuhiko Ariga,
Toyoki Kunitake*

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1 Overview – What is Supramolecular Chemistry?

“Supramolecular chemistry” is often defined as being “chemistry beyond the molecule”, which is rather vague and mysterious expression. Therefore, in order to get across the basic concepts of “supermolecules” and “supramolecular chemistry”, it is worth using an analogy from daily life. Many sports involve teams of players. One of the main objectives in such sports is to organize the team such that the performance of the team is significantly greater than that the sum of the performances of each team-member. This concept of a “good team being greater than the sum of its parts” can also be applied to a supermolecule. According to Dr. Lehn, who invented the term, a supermolecule is an organized, complex entity that is created from the association of two or more chemical species held together by intermolecular forces. Supermolecule structures are the result of not only additive but also cooperative interactions, including hydrogen bonding, hydrophobic interactions and coordination, and their properties are different (often better) than the sum of the properties of each individual component. The purposes of this book is to explore fundamental supramolecular phenomena and to explain highly sophisticated characteristics and functions of supramolecular systems. We will see that good organization and a well-selected combination of supramolecular elements leads to systems with incredible performance. The huge variety of supermolecules available may surprise many readers. In this section, we give an outline of supramolecular chemistry and relate it to the contents of this book (Fig. 1.1).

Supramolecular chemistry is still a young field, meaning that it can be rather difficult to define exactly what it encompasses – indeed it is a field that has developed rapidly due to contributions from a variety of related fields. Therefore, the subject needs to be tackled from various points of view. In this book, supramolecular chemistry is classified into three categories: (i) the chemistry associated with a molecule recognizing a partner molecule (molecular recognition chemistry); (ii) the chemistry of molecules built to specific shapes; (iii) the chemistry of molecular assembly from numerous molecules. This classification is deeply related to the size of the target molecular system. Molecular recognition chemistry generally deals with the smallest supramolecular systems, and encompasses interactions between just a few molecules. In contrast,

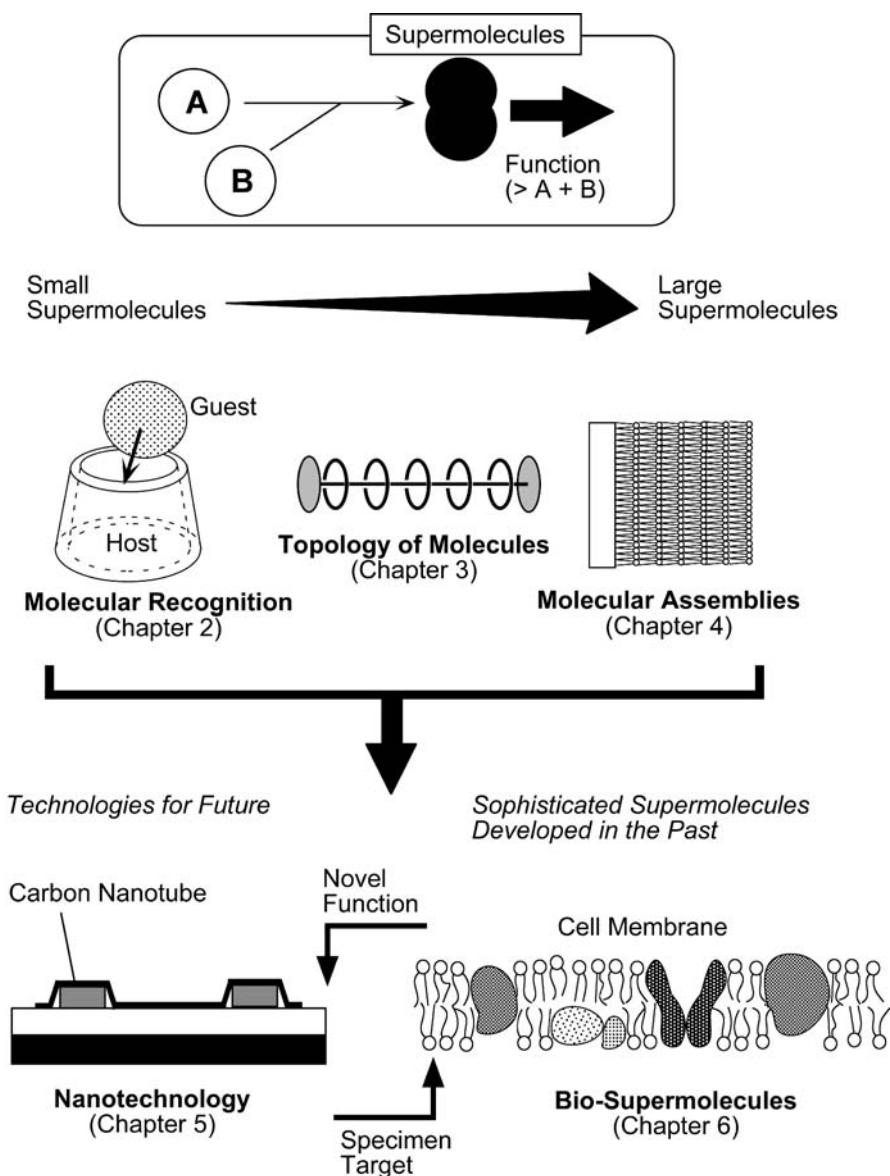


Figure 1.1. World of supermolecules

the chemistry of molecular assemblies can include molecular systems made from countless numbers of molecules. This classification scheme is reflected in Chaps. 2 to 4, which cover the basics of supramolecular chemistry, from small supermolecules in Chap. 2 to large ones in Chap. 2.

In Chap. 2, we discuss molecular recognition chemistry and describe various kinds of host molecules and related functions. The molecular recognition described in Chap. 2 can be regarded in many ways as the most fundamental kind of supramolecular chemistry, because all supramolecular chemistry is based on how to recognize molecules, how to influence molecules, and how to express specific functions due to molecular interactions. The importance of molecular recognition first came to light in the middle of the nineteenth century – considerably before the concept of supermolecules was established. For example, Pasteur noticed during microscopic observations that crystals of tartaric acid occurred in two types, that were mirror images of each other, and found that mold and yeast recognize and utilize only one of these types. The origin of “molecular recognition” is often said to be the “lock and key” principle proposed by Emil Fischer in 1894. This concept proposed that the mechanism by which an enzyme recognizes and interacts with a substrate can be likened to a lock and a key system. The presence of natural products that can recognize particular molecules was already known by the 1950s: for example, the recognition capabilities of the cyclic oligosaccharide cyclodextrin and those of the cyclic oligopeptide valinomycin.

In 1967, Pedersen observed that crown ether showed molecular recognition – the first artificial molecule found to do so. Cram developed this concept to cover a wide range of molecular systems and established a new field of chemistry, host–guest chemistry, where the host molecule can accommodate another molecule, called the guest molecule. In 1978, Lehn attempted to organize these novel chemistries, and first proposed the term “supramolecular chemistry”. This represented the moment that supramolecular chemistry was clearly established. Together, Pedersen, Cram and Lehn received the Nobel Prize for Chemistry in 1987.

In Chap. 3, medium-sized supermolecules composed from a small number of molecules are introduced. Such supermolecules have geometrically specific shapes, and readers may well be impressed by their uniqueness and variety. The supermolecules that appear in this chapter have interesting characteristics from a topological viewpoint: for example, rotaxane contains cyclic molecules that are threaded by linear molecules, and catenane contains entangled molecular rings. These entangled molecules can be obtained (with quite low yields) as the products from accidental phenomena. Introducing a strategy based on supramolecular chemistry drastically improves their yield. Fixing specific supramolecular interaction sites that give controlled ring closure results in as-designed entangled molecules. Relatively large single molecules with geometrically attractive shapes are also introduced in this chapter. Fullerenes are closed spheres formed from carbon pentagons and carbon hexagons, some of which could be described as “molecular soccer balls”. Fusing carbon pentagons and hexagons also yields carbon nanotubes, which are molecular tubes with nanoscale diameters. Controlled branching in molecules results

in the formation of dendrimers. The shapes of these supermolecules are attractive, and shape control is very important for function design. Functions can be defined by controlling shape. For example, signals can be transmitted along certain directions of a supermolecule. Some of the supermolecules described in Chap. 3 are closely associated with the nanotechnology described in Chap. 5.

In Chap. 4, supermolecules that are constructed from many molecules are explained. Controlled molecular association results in the spontaneous formation of supermolecules with specific shapes and characteristics. This process is called self-assembly or self-organization. Self-assembling processes are classified into two types. The first type involves “strict” associations formed through hydrogen bonding for example. Assemblies are constructed from blocks of a defined shape, and these blocks are used to build the final supermolecule shape according to a specific construction program.

Another type of self-assembly mode is based on “looser” molecular interactions, where one of the main binding forces comes from hydrophobic interactions in aqueous media. Amphiphilic molecules (amphiphiles) that have a hydrophilic part and a hydrophobic part form various assemblies in water and on water. The simplest example of this kind of assembly is a micelle, where amphiphiles self-assemble in order to expose their hydrophilic part to water and shield the other part from water due to hydrophobic interactions. A similar mechanism also leads to the formation of other assemblies, such as lipid bilayers. These molecules form spherical assemblies and/or two-dimensional membranes that are composed of countless numbers of molecules. These assemblies are usually very flexible. When external signals are applied to them, they respond flexibly while maintaining their fundamental organization and shape. This research field was initiated by the work of Bangham in 1964. It was found that dispersions of lipid molecules extracted from cells in water spontaneously form cell-like assemblies (liposomes). In 1977, Kunitake and Okahata demonstrated the formation of similar assemblies from various artificial amphiphiles. The latter finding showed that natural lipids and artificial amphiphiles are not fundamentally different.

In Chaps. 5 and 6, the functions, applications and future developments of supermolecules are explored using recent examples. Nanotechnology and molecular devices are described in Chap. 5. Nanotechnology deals with substances on the nanoscale – billionths of a meter. This size corresponds to the sizes of molecules or molecular associates, as well as those of supermolecules. Therefore, supermolecules provide a significant contribution to nanotechnology. Various microfabrication techniques currently play crucial roles in nanotechnology. Using these techniques, ultrafine structures have been prepared from larger structures, in what is known as the “top-down” approach. However, this approach is limited in terms of the smallest size that can be produced, and as the sizes of devices (such as microchips) continue to decrease, this limit is set to be encountered in the near future. In contrast, a fabrication approach based

on supramolecular chemistry builds structures from molecules and does not have this problem of a lower limit on structural size (and therefore structural precision). This approach is called the “bottom-up” approach, where rational designs and strategies for constructing highly functional supermolecules are the most important factor. Devices based on molecular-sized mechanisms are called molecular devices. In Chap. 5, various kinds of molecular devices are introduced, such as molecular electronic devices, molecular photonic devices, molecular machines and molecular computers.

The field of molecular devices is in its infancy. It is still not completely clear that the fine devices desired can be constructed using supramolecular approaches. However, we can see the great potential of supermolecules from the huge number of examples of them around us. Indeed, ourselves and all other living creatures are constructed by assembling molecules and supermolecules in highly organized and hierarchical ways. The material conversion, energy conversion and signal sensing accomplished in nature are often far superior to those of corresponding artificial systems. Nature has developed such high-performance supramolecular systems through a long process of evolution. The superior properties observed for biological supermolecules suggest the future potential of artificial supermolecules. Learning and mimicking biological supermolecules is a highly effective approach to designing artificial supermolecules. Biological supermolecules provide good specimens for artificial supermolecules.

In Chap. 6, biological supermolecules are explained and classified by function. Artificial supramolecular systems that mimic biological ones are also described. Biomimetic chemistry, which mimics the essence of a biosystem and then develops an artificial system that is better than the biological one, is widely used in this field. Functional developments, such as molecular transport, information transmission and conversion, energy conversion and molecular conversion (enzymatic functionality) based on biomimetic chemistry are described. New methodologies such as combinatorial chemistry and *in vitro* selection mimic evolutionary processes in nature. We leave this topic until the end of the book because we want to show that there is still lots to do in supramolecular chemistry, and that supramolecular chemistry has huge future potential.

Therefore, to summarize, Chaps. 2, 3, and 4 explain the basics of supramolecular chemistry in a hierarchical way, while the applications of this field are described in Chaps. 5 and 6. New findings in supramolecular chemistry appear each day: it is a highly exciting area of research.

While we have attempted to show many examples of supramolecular systems in this book, we have also tried to organize the contents of the book in a logical way, moving from the basics to cutting-edge research, making the content easy to follow and interesting to read. We hope that the book conveys the exciting (and often surprising!) nature of this field to the reader.

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2 The Chemistry of Molecular Recognition – Host Molecules and Guest Molecules

Our bodies are continually exposed to numerous kinds of molecules, but only some of these molecules are actually accepted by our bodies. On a molecular level, receptors in our body selectively catch the accepted molecules, in a process that is called “molecular recognition”. Molecular recognition forms the basis for supramolecular chemistry, because the construction of any supramolecular systems involves selective molecular combination. In this chapter, we display various examples in which specific molecules recognize other molecules in efficient and selective ways. The molecules that do the recognizing are called host molecules, and those that are recognized are known as guest molecules. Therefore, molecular recognition chemistry is sometimes called host–guest chemistry.

Molecular recognition is fundamental to all supramolecular chemistry, which is why this topic occurs so early in the book. Long before the field of supramolecular chemistry was initiated, there was a field of research known as molecular recognition chemistry (host–guest chemistry), where various host molecules were proposed to show molecular recognition. Another area of research focused upon the chemistry of molecular assemblies and molecular associations. Combining these chemistries, Jean-Marie Lehn proposed an united research field that was termed “supramolecular chemistry”: the chemistry of molecular systems beyond individual molecules. Therefore, the origins of supramolecular chemistry are strongly linked to molecular recognition chemistry, which investigates how host molecules recognize guests and how molecules associate. The main concept associated with molecular recognition is the “lock and key” concept proposed by Emil Fisher at the end of the nineteenth century. In the latter part of this book, although we study the design of complicated supramolecular systems, these complex systems are still based on this same simple concept. Therefore, we need to learn about molecular recognition if we are to grasp the essence of supramolecular chemistry.

In this chapter, the design and the functions of crown ethers (the origin of artificial hosts) and cyclodextrins (well-known hosts from nature) are first explained. After introducing these fundamental host systems, various host–guest systems are then discussed. Some of them appear again in other chapters, where their functions are explained in detail.

Contents of This Chapter

2.1 Molecular Recognition as the Basis of Supramolecular Chemistry The origin of supramolecular chemistry lies in molecular recognition chemistry, which studies how molecules recognize their partner. It is based on the “lock and key” principle.

2.2 Molecular Interactions in Molecular Recognition Molecular recognition occurs due to various molecular interactions such as electrostatic interaction and hydrogen bonding. Selective and efficient recognition is sometimes achieved by cooperative contributions from these interactions.

2.3 Crown Ethers and Related Hosts – The First Class of Artificial Hosts Crown ethers are macrocyclic polyethers with crown-like shapes. Various cations are selectively bound to the crown ether, depending on the size of the macrocyclic ring. More precise recognition can be accomplished using modified crown ethers such as lariat ethers and cryptands.

2.4 Signal Input/Output in Crown Ether Systems Recognition efficiency is regulated by structural changes in the crown ethers when photons and electrons are introduced to the system. Conversely, some types of molecular recognition can induce signal output, such as light emission.

2.5 Chiral Recognition by Crown Ethers Chiral recognition is one of the most important topics in host–guest chemistry. Crown ethers with axis chirality result in chiral guest molecules.

2.6 Macrocyclic Polyamines – Nitrogen-Based Cyclic Hosts Protonated macrocyclic polyamines can be good hosts for various anions. Macrocyclic polyamines also form complexes with transition metal anions.

2.7 Cyclodextrin – A Naturally Occurring Cyclic Host Cyclodextrins are cyclic hosts made from oligosaccharides. They provide a hydrophobic microenvironment in an aqueous phase.

2.8 Calixarene – A Versatile Host Calixarenes are macrocyclic host molecules made from phenol units linked through methylene bridges. The great freedom to structurally modify calixarenes allows us to create various types of host structures.

2.9 Other Host Molecules – Building Three-Dimensional Cavities Cyclophanes are cyclic hosts made from aromatic rings that mainly recognize hydrophobic guest molecules. Three-dimensional cavities can be constructed by attaching tails, walls and caps to the cyclic hosts.

2.10 Endoreceptors and Exoreceptors Host molecules with surface receptor sites are called exoreceptors, while hosts with receptor sites inside cavities are called endoreceptors. Exoreceptors yield a wide array of possibilities when constructing host systems.

2.11 Molecular Recognition at Interfaces – The Key to Understanding Biological Recognition Molecular recognition at the air–water interface is more efficient than recognition in bulk water. This has important implications for understanding biological molecular recognition, because most biological recognition occurs at aqueous interfaces.

2.12 Various Designs of Molecular Recognition Sites at Interfaces Various recognition sites, such as those for sugar recognition and nucleobase recognition, can be constructed at the air–water interface. Sophisticated recognition sites are prepared by mixing relatively simple host amphiphiles.

2.1

Molecular Recognition as the Basis for Supramolecular Chemistry

From a color change in a flask to highly sophisticated biological mechanisms, every action that occurs around us is the result of chemical reactions and physicochemical interactions occurring in various combinations. These reactions and interactions often seem to occur randomly, but this is rarely true. They often occur between selected partners – especially when the reactions and interactions occur in a highly organized system such as those found in biological settings – as the molecule recognizes the best (or better) partner. This mechanism is called “molecular recognition”. The importance of molecular recognition was realized around the middle of the nineteenth century. Pasteur noticed that there are two kinds of crystals of tartaric acid that are mirror images of each other, and these *chiral isomers* spontaneously self-recognize, resulting in the separate crystallization of each type. Living creatures such as mold and yeast recognize and utilize only one of these chiral isomers. Emil Fischer proposed that enzymes recognize substrates by a “lock and key” mechanism, where the structural fit between the recognizing molecule and the recognized molecule is important. In the 1950s, Pauling presented a hypothesis about the complementary nature of antigen and antibody structures. These works led to the research field of molecular recognition. Indeed, in 1994, an international symposium on host–guest chemistry and supramolecular chemistry was held at Mainz in Germany as a 100-year celebration of the lock and key principle.

The cyclic oligosaccharide cyclodextrins and the cyclic oligopeptide valinomycin were recognized as naturally occurring host molecules in the 1950s. Pedersen’s discovery of crown ether in 1967 opened the door to research on

artificial host molecules. Cram applied the concept of artificial hosts to various kinds of molecules, and developed the research field of host–guest chemistry, referring to chemistry where a molecule (the host) accepts another particular molecule (the guest). Lehn combined the molecular assembly and host–guest chemistries into a unified concept, “supramolecular chemistry”, reflecting the fact that this field deals with the complex entities – supermolecules – formed upon the association of two or more chemical species held together by intermolecular forces. The functionality of a supermolecule is expected to exceed a simple summation of its individual components. Lehn, Pedersen and Cram were jointly awarded the Nobel Prize in 1987.

This brief summary of the history of the field of supramolecular chemistry clearly indicates that molecular recognition is the most fundamental concept in supramolecular chemistry. In this chapter, we focus on recognition systems composed of relatively small molecules as the starting point for supramolecular chemistry.

2.2

Molecular Interactions in Molecular Recognition

In molecular recognition, a molecule selectively recognizes its partner through various molecular interactions. In this section, these interactions are briefly overviewed.

Electrostatic interactions occur between charged molecules. An attractive force is observed between oppositely charged molecules, and a repulsive force between molecules with the same type of charge (both negative or both positive). The magnitude of this interaction is relatively large compared to other noncovalent interactions, which means that the contributions from electrostatic interactions in molecular recognition systems cannot usually be ignored. The strength of this interaction changes in inverse proportion to the dielectric constant of the surrounding medium. Therefore, in a more hydrophobic environment with a smaller dielectric constant, the electrostatic interaction becomes stronger. If a functional group is in equilibrium between ionized and neutral forms, the population of the latter form decreases in a hydrophobic medium, resulting in a decreased contribution from the electrostatic interaction. Dipole–dipole and dipole–ion interactions play important roles in neutral species instead of electrostatic interactions.

Hydrogen bonding sometimes plays a crucial role during recognition, although a hydrogen bonding interaction is weaker than an electrostatic interaction. Hydrogen bonding only occurs when the functional groups that are interacting are properly oriented. This is why hydrogen bonding is the key interaction during recognition in many cases. The importance of hydrogen bonding to molecular recognition is illustrated by the base-pairing that occurs in DNA strands, where nucleobases recognize their correct partners in a highly specific way. Hydrogen bonding is one type of dipole–dipole interaction, where posi-

tively polarized hydrogen atoms in hydroxyl (OH) groups and amino groups ($-\text{NH}-$) contribute. Because the a polarized hydrogen atom has a small radius, it strongly interacts with other electron-rich atoms (C in $\text{C}=\text{O}$, N in CN) located nearby. This results in relatively strong direction-specific hydrogen bonding between these functional groups.

Coordinate bonding is another type of direction-specific interaction. This type of interaction occurs between metal ions and electron-rich atoms and is of moderate strength. Such interactions have also been utilized in the formation of supramolecular assemblies, and several examples are given in Chap. 3.

The van der Waals interaction is weaker and less specific than those described above, but it is undoubtedly important because this interaction generally applies to all kinds of molecules. It is driven by the interactions of dipoles created by instantaneous unbalanced electronic distributions in neutral substances. Although individual interactions are negligible, the combined cooperative contributions from numerous van der Waals interactions make a significant contribution to molecular recognition. When the interacting molecules have surfaces with complementary shapes, as in the lock and key concept, the van der Waals interaction becomes more effective. This interaction is especially important when the host molecule recognizes the shape of the guest molecule.

In an aqueous medium, the hydrophobic interaction plays a very important role. It is the major driving force for hydrophobic molecules to aggregate in an aqueous medium, as seen in the formation of a cell membrane from lipid-based components. The hydrophobic interaction is not, as its name may suggest, an interaction between hydrophobic molecules. This interaction is related to the hydration structure present around hydrophobic molecules. Water molecules form structured hydration layers that are not entropically advantageous. It is believed that hydrophobic substances aggregate to minimize the number water molecules involved in hydration layers. However, the mechanism and nature of the hydrophobic interaction is not that clear. Unusual characteristics, such as incredible interaction distances, have been reported for the hydrophobic interaction, and the fundamentals of hydrophobic interaction are still under debate even today.

$\pi-\pi$ interactions occur between aromatic rings, and these sometimes provide important contributions to molecular recognition. When the aromatic rings face each other, the overlap of π -electron orbitals results in an energetic gain. For example, the double-strand structure of DNA is partially stabilized through $\pi-\pi$ interactions between neighboring base-pairs.

In the molecular recognition systems that appear in the following sections, selective and effective recognition is achieved through various combinations of the above-mentioned molecular interactions. When several types of molecular interaction work together, a cooperative enhancement in molecular association is often observed. Finding an appropriate combination of molecular interactions is the key to designing efficient molecular recognition systems.

2.3

Crown Ethers and Related Hosts – The First Class of Artificial Host

Crown ethers were the first artificial host molecules discovered. They were accidentally found as a byproduct of an organic reaction. When Pedersen synthesized bisphenol, contaminations from impurities led to the production of a small amount of a cyclic hexaether (Fig. 2.1). This cyclic compound increased the solubility of potassium permanganate in benzene or chloroform. The solubility of this cyclic compound in methanol was enhanced in the presence of sodium ion. Based on the observed phenomena, Pedersen proposed that a complex structure was formed where the metal ion was trapped in a cavity created by the cyclic ether. At that time, it was already known that naturally occurring ionophores such as valinomycin incorporated specific metal ions to form stable complexes; because of this, compounds able to selectively include metal ions were the source of much attention from researchers. Pedersen called the cyclic compound a *crown ether*, because the cyclic host “wears” the ion guest like a crown.

Figure 2.2 summarizes the structures and sizes of various crown ethers. Crown ethers are named as follows: the number before “crown” indicates the total number of atoms in the cycle, and the number after “crown” gives the number of oxygen atoms in the cyclic structure. For example, 18-crown-6 is a cyclic compound with twelve carbon atoms and six oxygen atoms. The oxygen atom, which has a high electronegativity, can act as a binding site for metal ions and ammonium ions through dipole–ion interactions. The cyclic arrangement of these binding sites is advantageous to ion recognition through cooperative interaction. Therefore, matching the ion size and crown size is critical to efficient binding behavior. In Fig. 2.2, binding constants of the crown ethers to alkali cations are summarized; a greater number implies more

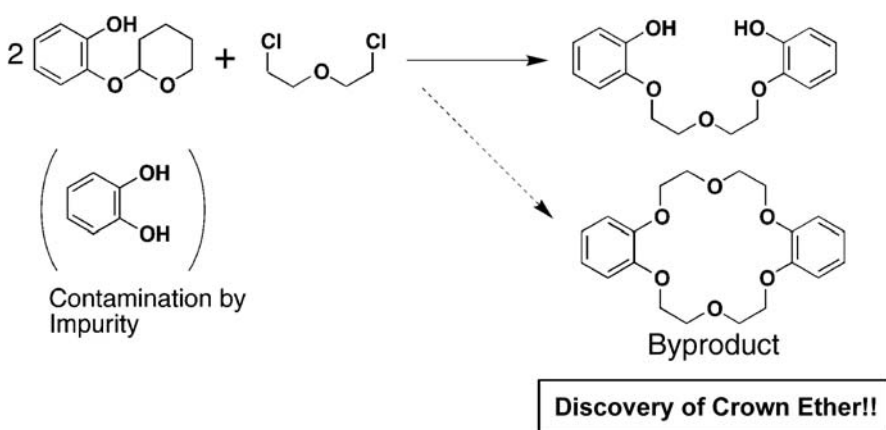


Figure 2.1. Discovery of crown ether

efficient binding. Crown ethers with larger inner cores can bind larger ions and smaller ions are accommodated by smaller crown ethers. Although these crown ethers are relatively simple molecules, they can recognize ion size.

Because the rings of the crown ethers are rather flexible, there is some degree of structural freedom during complexation. When the metal ion is larger than the crown ether, 2:1 complex formation is possible through a sandwich-type

	12-Crown-4	15-Crown-5	18-Crown-6	21-Crown-7
Inner Diameter / nm	0.12– 0.15	0.15– 0.22	0.26– 0.32	0.34– 0.43
Li^+ (0.136 nm)	-0.57	1.21	0.00	-
Na^+ (0.194 nm)	1.67	3.32	4.28	2.12
K^+ (0.266 nm)	1.60	3.50	5.67	4.30
Cs^+ (0.334 nm)	1.63	2.74	4.50	5.01
Binding Constant in Methanol ($\log K_a$)				

Figure 2.2. Selective ion recognition using crown ethers

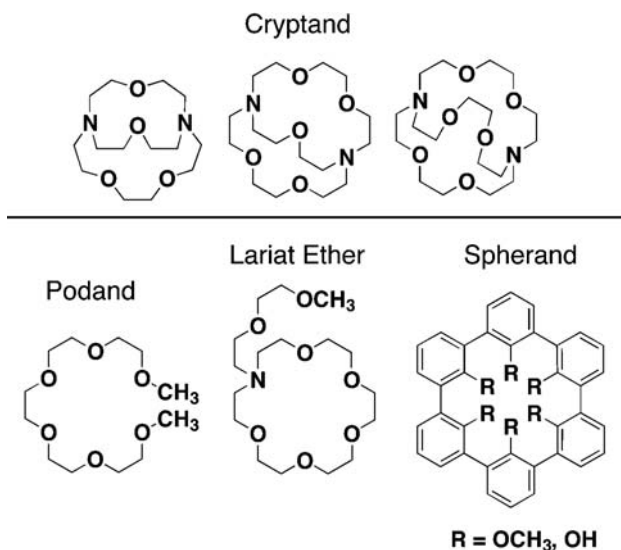


Figure 2.3. Cyclic host molecules

binding motif. However, the flexible nature of the host structure is not always advantageous to selective binding, and so improvements to the basic crown ether structure have been considered. Some hosts with improved structures are summarized in Fig. 2.3. They are classified by structural types: noncyclic hosts are known as *podands*; monocyclic hosts including crown ethers are called *coronands*; oligocyclic hosts are termed *cryptands*.

Cryptands have a motion-restricted cyclic structure; this rigid structure does not allow flexible structural changes to accommodate various guest sizes. Therefore, they can accommodate only strictly size-matched guest molecules. The binding cavity of a cryptand is defined three-dimensionally, resulting in higher binding selectivity than achieved with simple crown ethers. The attachment of a podand arm to a two-dimensional crown ether also produces a host with a three-dimensional cavity. This type of host is called a *ariat ether*, because the host structure reminds us of a *ariat* (a lasso). A *spherand* is a rigid cycle with a binding site that points to the cavity inside.

2.4 Signal Input/Output in Crown Ether Systems

Controlling the recognition ability of a crown ether through an external stimulus permits novel kinds of responsive systems to be designed. This type of stimuli-controlled mechanism is commonly seen in many biological systems. Figure 2.4 shows one example, where the host consists of oligoethylene glycol with bipyridyl units at both terminals. The bipyridine unit and the oligoethylene glycol chain have different affinities to two metal ions (ion A and ion B). Two bipyridine units sandwich a copper ion (ion A), inducing a change in the oligoethylene chain from a linear to a pseudo-cyclic (*podand*) form. This means that an alkali ion (ion B) can be accommodated by the oligoethylene loop. In this system, the binding efficiency of the alkali ion to this host is regulated by the bonding of the copper ion.

However, controlling the recognition behavior via physical stimuli such as light and electricity would be more useful, because these stimuli do not generally contaminate the solution. Figure 2.5(a) shows a photo-switching molecular recognition system. This host possesses a photosensitive azobenzene part at its center with crown ethers on both sides. UV and visible light irradiation induces a switch between the *cis* and *trans* forms of azobenzene, respectively. This photoinduced change in azobenzene conformation leads to a drastic change in relative orientations of the two crown ethers. A sandwich-type binding site is only formed when the azobenzene moiety is in the *cis* form.

Electron-driven recognition control has also been proposed. The host molecules shown in Fig. 2.5(b) and (c) gain and lose binding ability through redox reactions between thiol and disulfide groups. In Fig. 2.5(b), disulfide bonding upon oxidation causes the two crown ethers in the host molecule to face each other, resulting in a sandwich-type binding site. In Fig. 2.5(c), two thiol groups

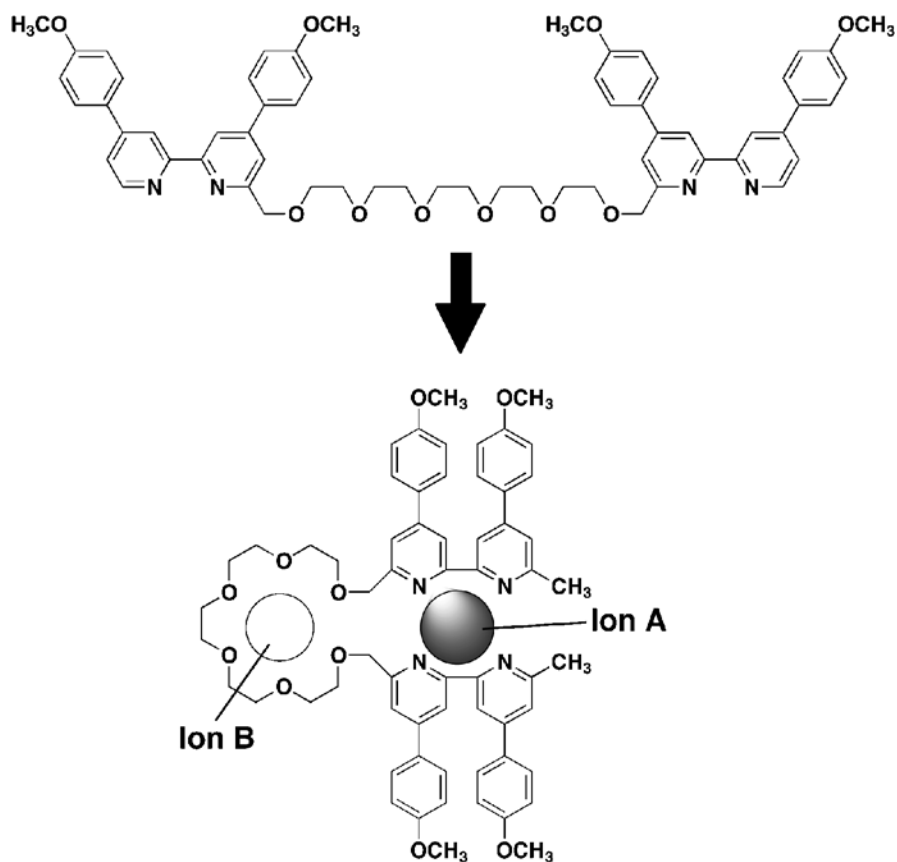


Figure 2.4. Binding of ion A to the host induces the binding of ion B

are introduced into the cavity of the host crown ether upon oxidation. In this case, however, disulfide formation decreases guest binding ability because it blocks guest insertion into the crown ether cavity. Since the thiol groups only exist inside the cavity, intermolecular disulfide formation is also efficiently suppressed.

Inverse response systems – systems where molecular recognition induces the emission of physical signals such as light – have been also developed. Very useful sensing systems can be designed based on guest binding phenomena that result in the generation of color. In the host molecule depicted in Fig. 2.6, an anthracene chromophore is connected to a crown ether binding site via a tertiary amine. When the anthracene of a free host molecule is photoexcited, light emission is quenched by the electron-donating tertiary amine (photoinduced electron transfer). Interestingly, binding a potassium ion to the crown ether enhances the emission of the crown ether. The lone pair on the tertiary amine contributes to the potassium binding, and electron transfer from the

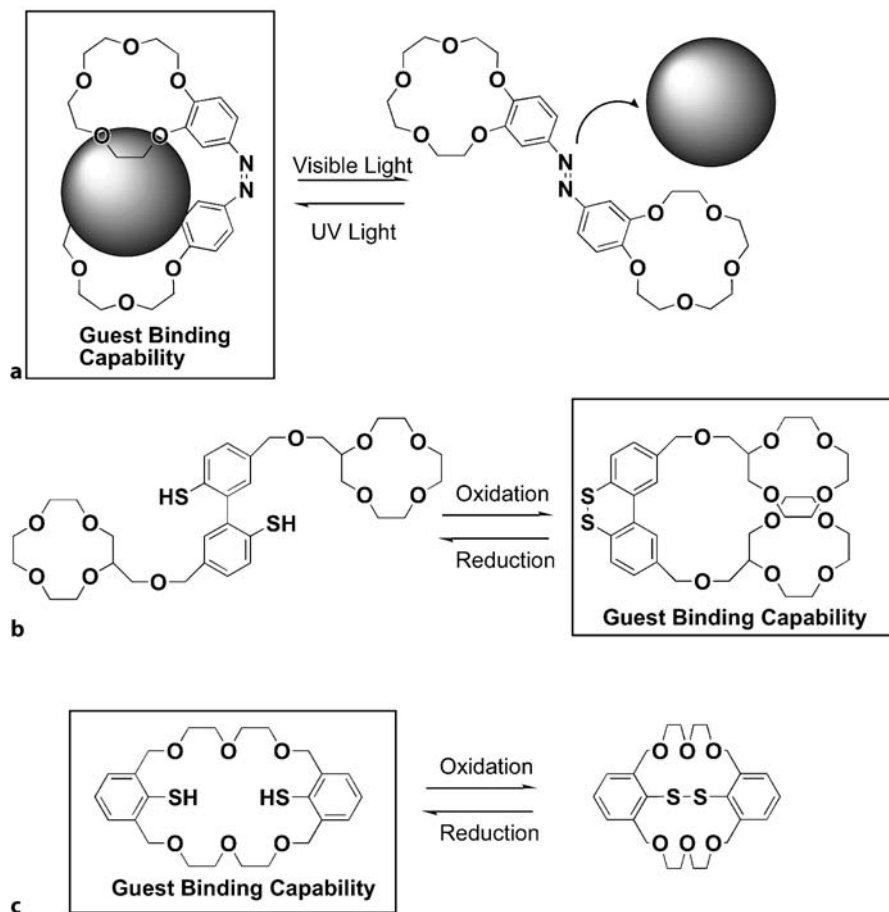


Figure 2.5. Photoinduced and electron-driven guest binding

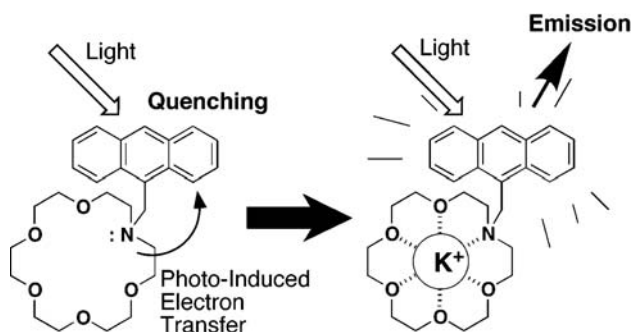


Figure 2.6. Light emission upon the binding of a potassium ion to a crown ether

amine to the excited anthracene is effectively suppressed. As a result, the anthracene can only emit in the presence of a potassium ion. Therefore, in this system, potassium ion binding can be easily detected due to the light emission. We will explore such systems again in Chap. 5 in our discussion of photonic molecular devices.

2.5 Chiral Recognition by Crown Ethers

One of the most important aims of molecular recognition is chiral recognition, because it is commonly achieved in biological systems. Receptors in our body

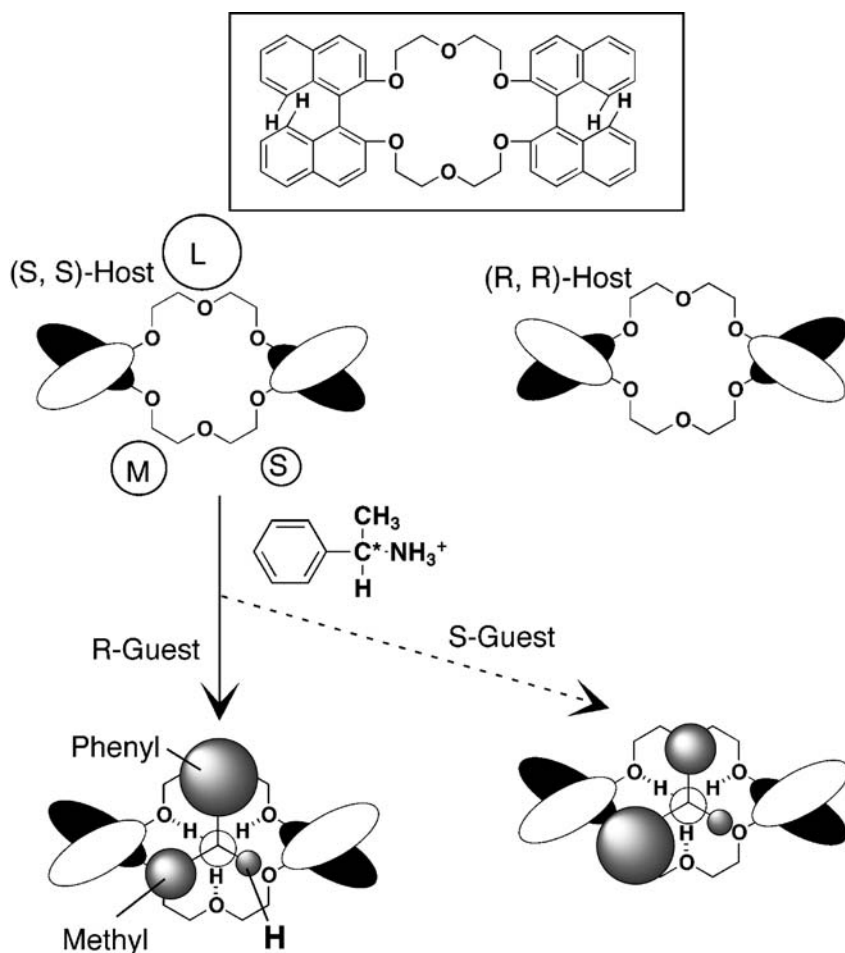


Figure 2.7. Chiral recognition using a crown ether

easily distinguish between two molecules that have same chemical composition but different structures around a chiral carbon atom. For example, we sense a sweet taste for D-glucose, but *L*-glucose tastes totally different. Generally speaking, such chiral discrimination is quite difficult to replicate using artificial hosts because chiral isomers have the same thermodynamic properties and exhibit only a few physical properties that are different, such as their optical rotatory characteristics. However, this situation can be improved by interacting a chiral additive with the chiral isomers. When a D-additive is added to the L- and D-guests, the two complexes formed (the D-D complex and the D-L complex) exhibit different thermodynamic properties, and so it becomes easier to discriminate between them. Therefore, introducing a chiral host is a good way to distinguish between chiral guest substances.

Cram demonstrated the chiral recognition of an ammonium guest using a crown ether with axis-chiral binaphthyl groups. Figure 2.7 shows top views of the complex formed. When the (*S,S*)-host binds to a chiral guest (*S*- and *R*- α -phenylethylammonium ions), the complexes formed are thermodynamically different. When the ammonium group attaches to the host crown ether, the spatial orientations of the phenyl group, the methyl group and the hydrogen atom change in an isomer-dependent way. This results in these complexes having different stabilities.

In the host shown in Fig. 2.7, the crown ether is divided in two by the two binaphthyl groups. Different regions of the cycle then interact with a large site (L), a medium site (M) and a small site (S) on the guest. Which sites interact with which regions of the host cycle depends on the stereochemistries of the host cycle and the guest. Binding of the *R*-guest to the (*S,S*)-host satisfies steric requirements, because the phenyl group, the methyl group and the hydrogen can occupy the L, M, and S sites, respectively. This complex should be stable. In contrast, the *S*-guest cannot fill the sites in this desirable manner due to its different stereochemistry. The *R*-guest is therefore selectively recognized by this host.

2.6

Macrocyclic Polyamines – Nitrogen-Based Cyclic Hosts

Replacing the oxygen atoms in the crown ethers by nitrogen atoms leads to a novel class of cyclic hosts that are called *macrocyclic polyamines*. Their structures are analogous with those of crown ethers, but the strongly basic nature of the amine group results in unique host properties. Protonation of the amines makes this type of host capable of binding anions (Fig. 2.8). Since some of the macrocyclic polyamines have elliptic shapes, linear anions such as the azide anion (N_3^-) are efficiently recognized. A macrocyclic polyamine with hydrophobic alkyl chains can be immobilized onto the surface of an electrode to create an anion sensing device. The binding of anions to the macrocyclic amines on the electrode are detected as a change in the surface potential. Macrocyclic

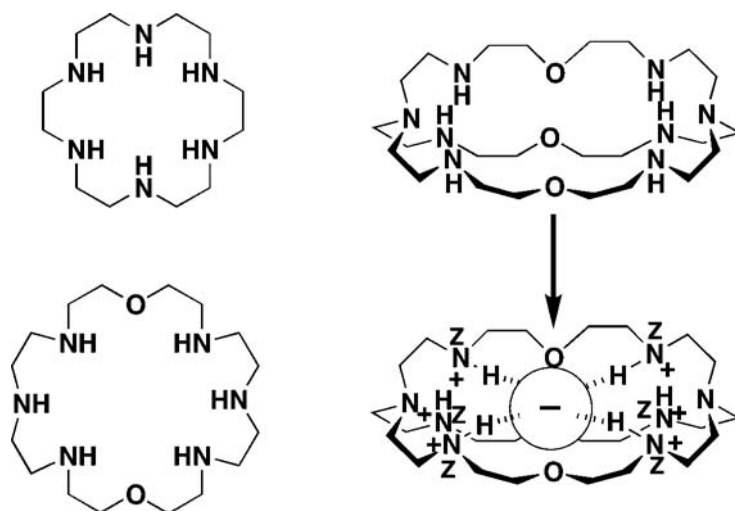


Figure 2.8. Macrocyclic polyamines

polyamines also show high affinities to multivalent phosphates such as nucleotides. As illustrated in Fig. 2.9, the biologically important molecule ATP (adenosine triphosphate) is recognized by a macrocyclic polyamine. Bound ATP is hydrolyzed into ADP (adenosine diphosphate). In the reverse reaction, the synthesis of ATP from ADP is also catalyzed by this host with the aid of Mg^{2+} . Such catalytic hosts are known as artificial enzymes, and they are described in more detail in Chap. 6.

Nitrogen and sulfur atoms are softer (they have more charge delocalization) than oxygen atom. Therefore, macrocyclic hosts containing nitrogen atoms or sulfur atoms preferentially recognize soft ions. Thioether-type crown com-

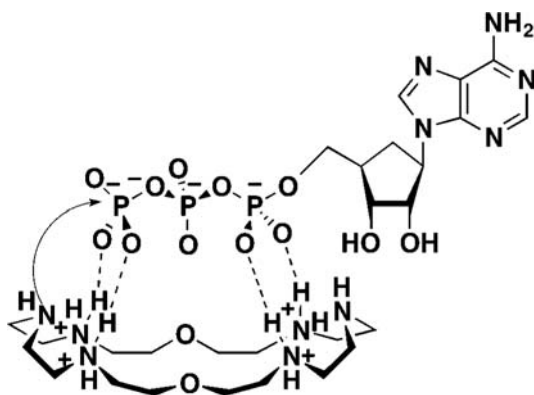


Figure 2.9. Binding of ATP by a macrocyclic polyamine

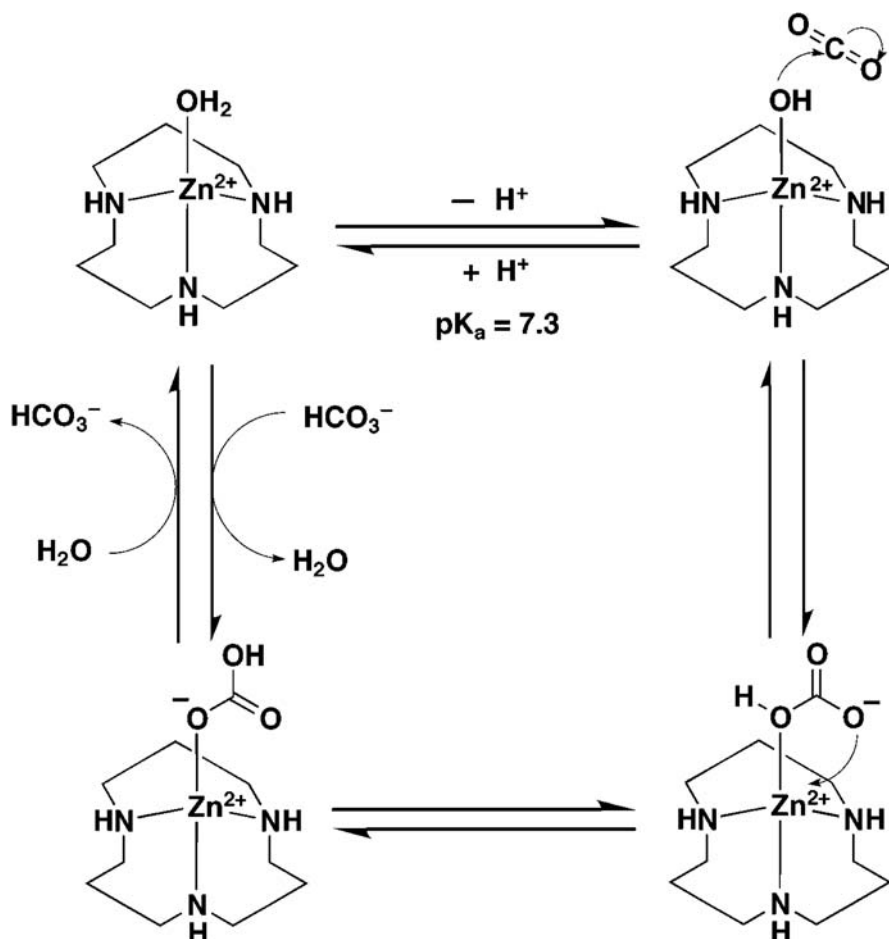


Figure 2.10. Dehydration of carbonate by 1,5,9-triazacyclodecane (electron transfer is shown in the clockwise reaction)

pounds (crown ethers with sulfur atoms instead of oxygen atoms) are called as thiacrowns. Macrocyclic polyamines (in nonprotonated form) and thiacrowns preferentially accommodate soft ions such as transition metal ions, while normal crown ethers with hard oxygen atoms have high affinities to hard ions such as alkali metal ions. The macrocyclic polyamine shown in Fig. 2.10 immobilizes Zn ion, and the complex formed can mimic carbonic anhydrase. The Zn ion located in the center of this complex has a tetrahedral coordination, similar to that seen in natural carbonic anhydrase. The water molecule coordinated to the zinc ion dissociates at neutral pH. Therefore, the complex can trap a bicarbonate ion and catalyze the dissociation of the trapped bicarbonate into carbon dioxide and water. The reverse reaction, the hydration of carbon dioxide, is also catalyzed by this complex.

2.7 Cyclodextrin – A Naturally Occurring Cyclic Host

As mentioned above, some naturally occurring cyclic hosts that possess molecular recognition capabilities were known before crown ethers (the first artificial host molecules) were discovered. For example, the cyclic oligopeptide valinomycin and the cyclic oligosaccharide cyclodextrin were found to bind to specific guest molecules. The chemical modification of cyclodextrin was particularly well-researched, and artificially modified cyclodextrins became one of the most important compounds used in host–guest chemistry.

Cyclodextrins can be obtained from starch via certain enzymes. Starch is a polysaccharide with an α 1–4 linkage of glucose, and it has a left-handed spiral structure. The enzyme changes this polysaccharide into a cyclic oligomer with an appropriate number of glycopyranoside units. The cyclic oligomers with six, seven and eight glycopyranoside units are the most common and are called α -, β - and γ -cyclodextrin, respectively. This cyclic structure is shown in Fig. 2.11; Fig. 2.11b shows a top view of an α -cyclodextrin with six glycopyranoside units, where the glycopyranoside units stand up vertically (perpendicular to the plane of the paper), so these units form the wall of an open cylinder. This structural motif can be schematically expressed as shown in Fig. 2.12. Primary hydroxyl groups are located at the side of a narrow inlet, while secondary hydroxyl groups are found on the reverse side (at the side of a wide inlet). Therefore, no hydroxyl groups exist on the wall, and so the cavity of the cyclodextrin is hydrophobic. Cyclodextrins dissolved in an aqueous phase can accommodate hydrophobic guests such as aromatic hydrocarbons in their cavities. However, inorganic ions and gas molecules can also be included. The most important factor in the guest selectivity of the cyclodextrin is that the size of the cyclodextrin cavity matches that of the guest molecule. For example, a benzene ring is a good fit to α -cyclodextrin. As listed in Fig. 2.12, the cavity size depends significantly on

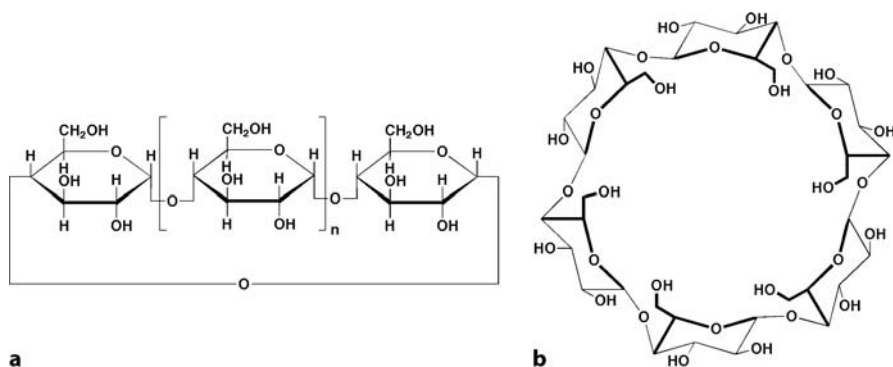


Figure 2.11. Cyclodextrin

the number of saccharide units that the cyclodextrin contains. Therefore, the guests selected depend on the size of the cavity.

The hydroxyl groups on the cyclodextrin can be modified using an appropriate organic reaction, and various types of functionalized cyclodextrins have been proposed. A cyclodextrin that emits light upon guest inclusion is exemplified in Fig. 2.13; here β -cyclodextrin with two naphthyl groups was used as the host. One of the naphthyl groups is included in the cavity of the β -cyclodextrin in the absence of external guest molecules. When an appropriate guest molecule enters the cyclodextrin cavity, the previously included naphthyl group is pushed out, forming a dimer with the other naphthyl group. This dimer formation results in strong excimer emission. In this recognition system, guest inclusion can be detected by a change in fluorescence at around 400 nm.

Cyclodextrins provide a hydrophobic micromedium in an aqueous phase. This characteristic is analogous to the reaction pockets of enzymes. Enzymes provide size-selective hydrophobic cavities and catalyze the reactions of bound substrates. As one might therefore expect, artificial enzymes based on cy-

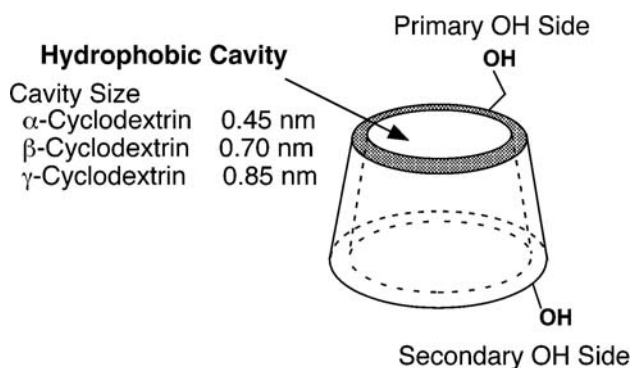


Figure 2.12. Structure of a cyclodextrin and some pore diameters

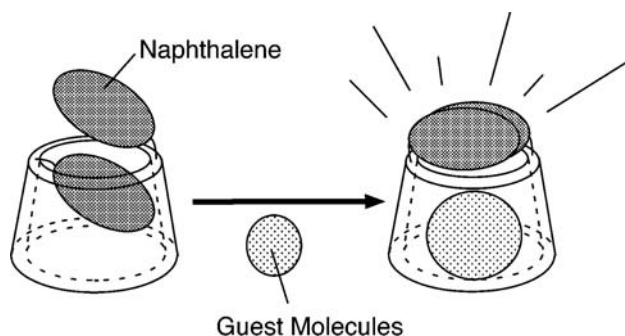


Figure 2.13. Inclusion of a guest inside the cavity of a cyclodextrin induces light emission

clodextrins have been extensively researched (see also Chap. 6). Figure 2.14 shows an example of an artificial enzyme where a cyclodextrin cavity works as a hydrophobic binding site and hydroxyl groups play the role of a catalytic residue. When phenyl acetate is used as a substrate, the phenyl ring is incorporated into the cyclodextrin cavity and the carbonyl group exposed to outer side is nucleophilically attacked by the anionic form of a secondary hydroxyl group. The acetyl group is transferred to the hydroxyl group to form an ester, and subsequent hydrolysis of the ester completes the reaction, regenerating a hydroxyl anion on the cyclodextrin. As a result, the substrate is hydrolyzed into phenol and acetate. Because the secondary hydroxyl group of the cyclodextrin forms hydrogen bonds with neighboring hydroxyl groups, it can be deprotonated at a lower pH than is usual for hydroxyl groups.

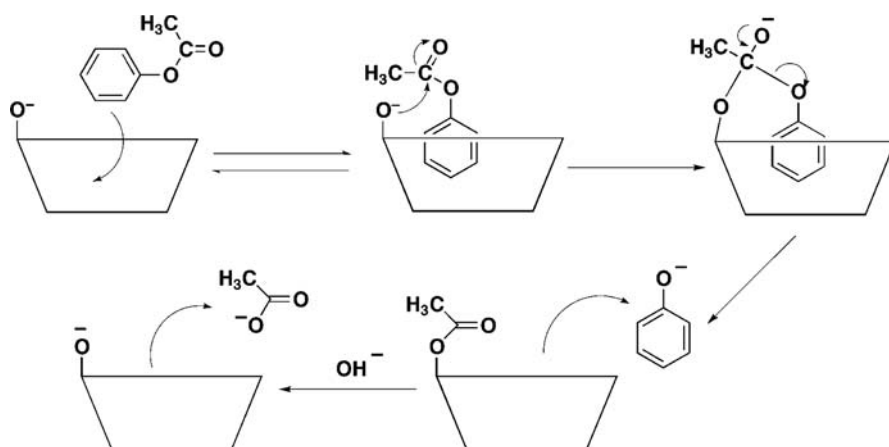


Figure 2.14. Hydrolysis of phenyl acetate by cyclodextrin

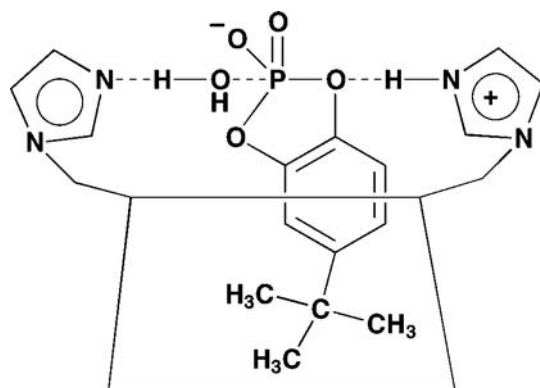


Figure 2.15. Hydrolysis of a phosphodiester by modified cyclodextrin

Another example of a cyclodextrin-based artificial enzyme is shown in Fig. 2.15. A phosphodiester is hydrolyzed through cooperative interactions with two imidazolyl groups. The relative positions of the imidazolyl groups and the inclusion geometry of the hydrophobic substrate are structurally well-matched. This artificial enzyme can be regarded as a model of ribonuclease A.

2.8

Calixarene – A Versatile Host

Calixarenes were developed later than crown ethers and cyclodextrins but have still been extensively researched. Macrocycles of calix[n]arenes are constructed by linking a number of phenol residues via methylene moieties (Fig. 2.16). Like crown ethers, the name “calixarene” reflects the structures of these molecules, since a calix is a chalice. Calixarenes with various cavity sizes have been designed, each of which has conformation isomers, and their phenolic hydroxyl groups are often modified. These structural characteristics allow us to create calixarene derivatives with various structural modifications.

The conformational isomers of a calixarene with four phenol residues are shown in Fig. 2.17. The isomers vary in terms of the orientations of their phenol groups: (a) has a cone structure with all of the phenols pointing to the same direction; (b) has a partial cone structure with one phenol pointing in a different direction to the others; (c) has a 1,3-alternate structure with neighboring phenols pointing in opposite directions. These isomeric hosts have different selectivities for metal ion inclusion in the upper cavity and the lower cavity. Of course, changing the number of phenol residues alters the guest size appropriate for effective inclusion.

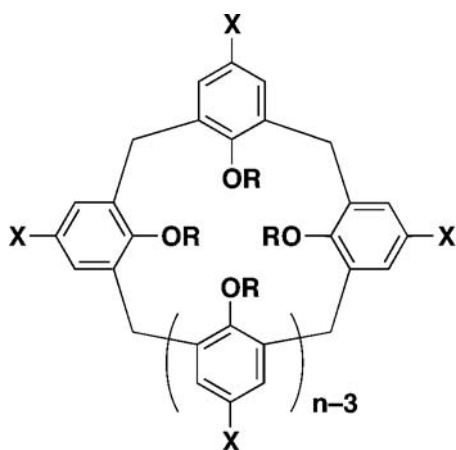


Figure 2.16. Calix[n]arene

The calix[8]arene depicted in Fig. 2.18 can bind fullerenes (see Chap. 3); the fullerene “soccer ball” is trapped in the calix. Fullerenes are usually prepared as mixture of C_{60} , C_{70} , C_{76} , and so on, and separating them is not always easy. The calix[8]arene has a cavity with an inner diameter of ~ 1 nm, which is therefore suitable for C_{60} , since it has a diameter of ~ 0.7 nm. When the calixarene is added to a toluene solution of a mixture of fullerenes, a 1:1 complex of the calixarene and C_{60} selectively precipitates. Isolation of the precipitates followed by dispersion of them in chloroform results in the precipitation of dissociated C_{60} . Repeating these processes results in C_{60} with high purity.

Since the phenolic hydroxyl groups can be modified in various ways, we can design an array of functionalized hosts. Figure 2.19 shows the structure of calixcrown, in which two hydroxyl groups in calix[4]arene are bridged by an oligoethylene glycol chain. The flexibility of the crown part is highly restricted in this structure, resulting in highly selective molecular recognition. The size of this binding site is quite close to the size of a sodium ion. The binding affinity of the calixcrown to a sodium ion is 100 000 times greater than that observed for a potassium ion.

Another interesting example involves a calixarene that exhibits a color change upon the binding of a chiral guest. When converting the chiral recognition phenomenon into a change of color, the design of the host molecule attaching to the chromophore is critical. The host molecule shown in Fig. 2.20

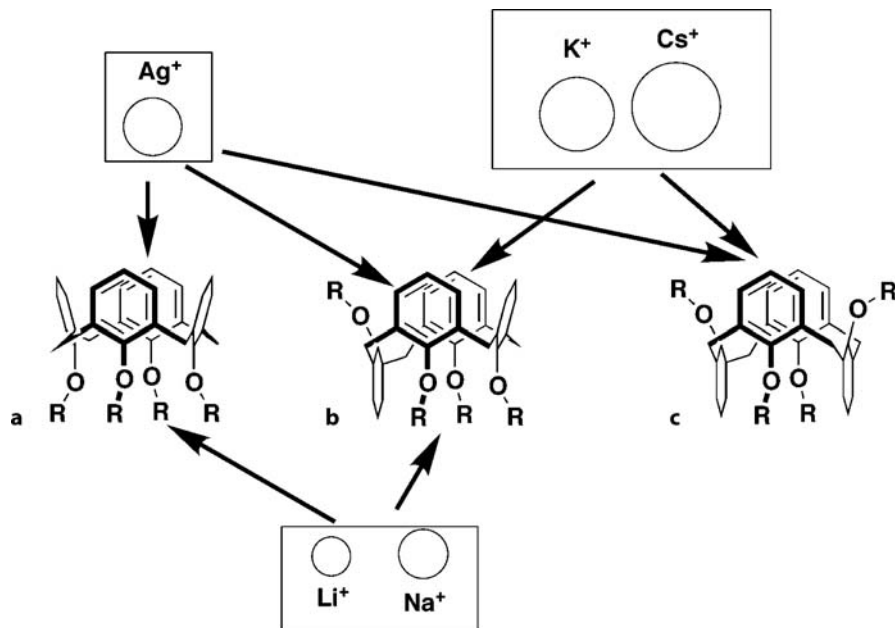


Figure 2.17. Conformation isomers and ion binding behavior of calix[4]arene

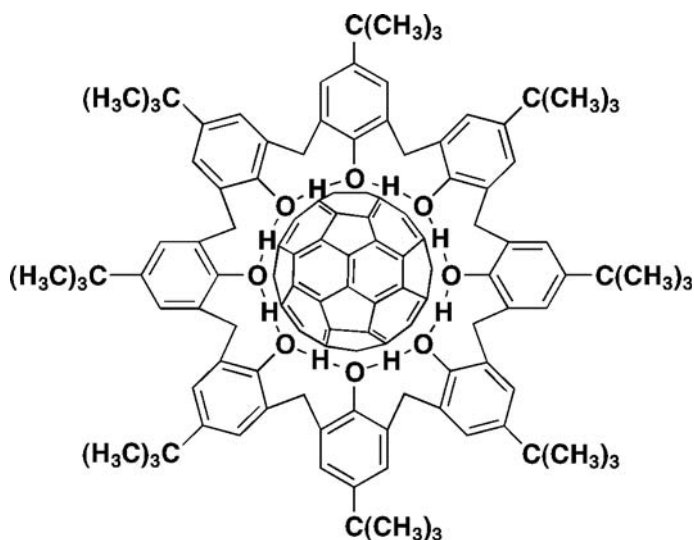


Figure 2.18. Binding of fullerene by calix[8]arene

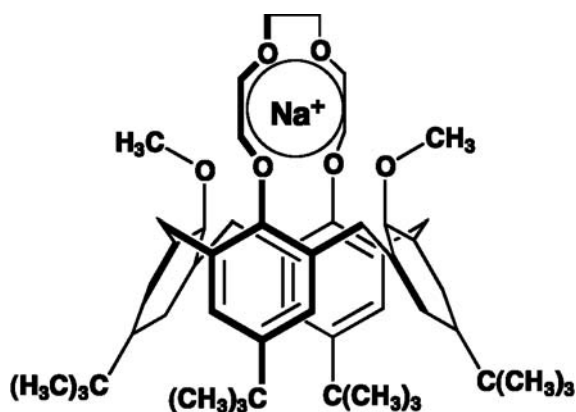


Figure 2.19. Calixcrown

possesses two dye moieties and a chiral binaphthyl group. When a guest molecule (phenyl glycinol) is added to the host (dissolved in ethanol), the solution color changes depending on the chirality of the guest. The original color of the guest-free host is red; addition of *R*-phenyl glycinol changes the color to blue-purple. In contrast, the solution color remains red upon the addition of *S*-phenyl glycinol. When *R*-phenyl glycinol is bound to the host, the left-hand indophenol (dye A) in the host is deprotonated and the right-hand indophenol (dye B) interacts more with the hydrophobic environment of the binaphthyl group. These changes cause the complex to change color. In con-

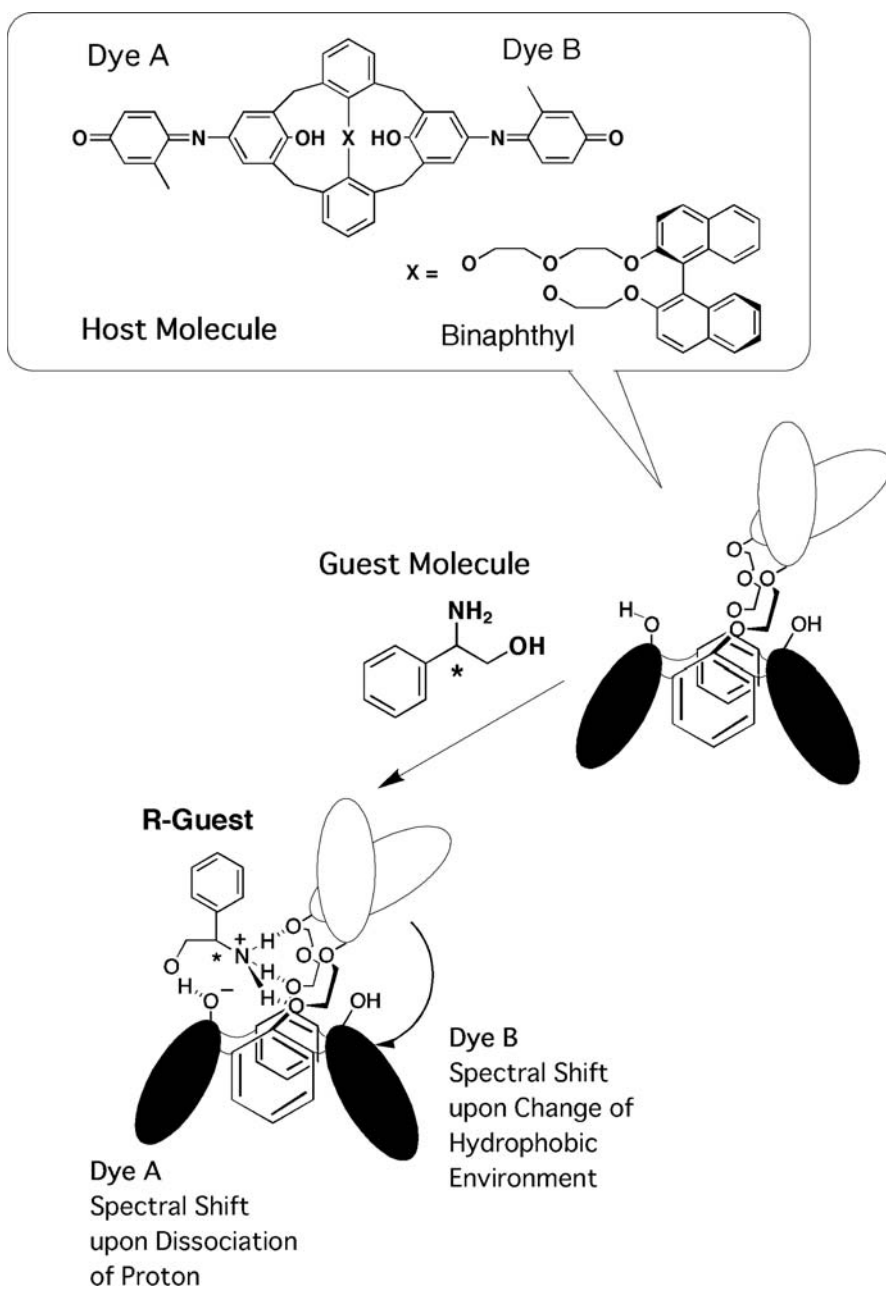


Figure 2.20. Chiral recognition by a dye-carrying calixarene

trast, binding *S*-phenyl glycinol to the same host produces a complex with a different geometry, especially in terms of the relative positions of the phenyl group and the binaphthyl group. The spectral shift in dye B is suppressed and the color change is not so pronounced. In this system, differences in the interactions between the guest and the binaphthyl group lead to different color changes depending upon the chirality of the guest.

2.9

Other Host Molecules – Building Three-Dimensional Cavities

As seen in the examples shown above, the attachment of an additional part to a two-dimensional cyclic host can be an effective way to improve the recognition ability of the host. Therefore, well-designed three-dimensional hosts show superior molecular recognition properties. In this section we introduce some three-dimensionally designed hosts.

Cyclophanes are cyclic hosts made by linking aromatic rings. Several examples of cyclophanes are depicted in Fig. 2.21. While the cyclophane in (a) is a simple two-dimensional cyclophane, the cyclophane in (b) has four alkyl chains attached. Using a similar molecular design process, a cyclophane with eight alkyl chains can be synthesized and is called an octopus-type cyclophane. The alkyl chains self-assemble in an aqueous phase and form a three-dimensional cavity. Cyclophanes with rigid steroidal walls are called steroid

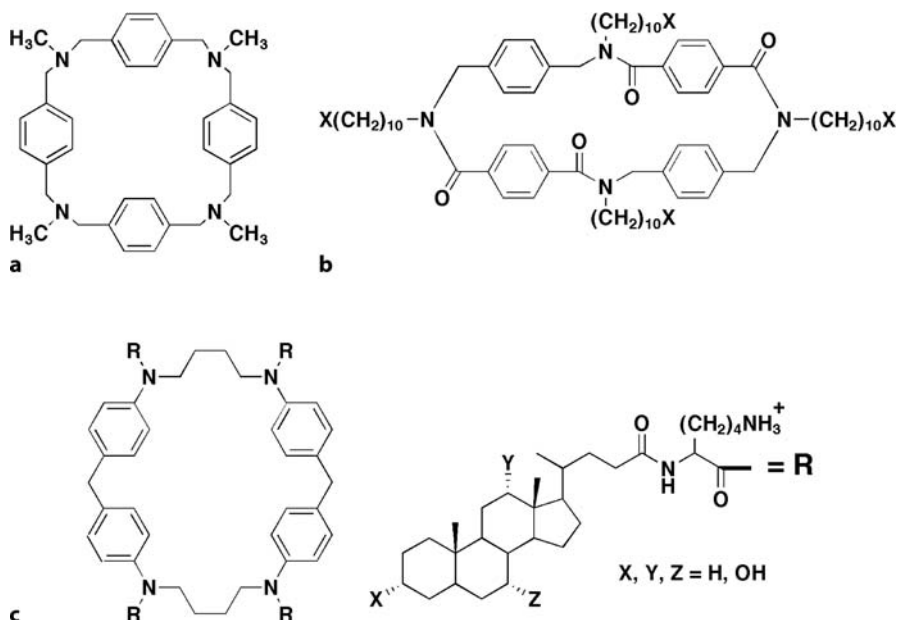


Figure 2.21. Cyclophane

cyclophanes (Fig. 2.21(c)). Four steroidal moieties are expected to stand up from the cyclophane ring, creating a three-dimensional cavity. If the steroid is composed of colic acid derivatives, it is possible to create both hydrophobic and hydrophilic cavities. Because three polar hydroxyl groups are located on one side of the cholic plane, the wall has a hydrophobic face and a hydrophilic face. The orientation of the cholic face on the cyclophane ring dictates whether a hydrophobic or a hydrophilic cavity is formed.

Adding legs or walls to the two-dimensional cyclic cavity leads to the formation of three-dimensional cavities. Further addition of a cap to the cavity creates an enclosed cavity space. Such spaces are called molecular capsules, and the trapped guest is shielded from the outer environment. If unstable species are trapped in the molecular capsule, their lifetimes can be extended and their properties are easily measured. An example of an unstable species that is stabilized inside a molecular capsule is shown in Fig. 2.22. Photoirradiation of the benzocyclobutendiol in the molecular capsule at -196°C converts it to benzyne via benzocyclopropenone. Although benzyne is usually quite unstable, benzyne trapped in the molecular capsule can be characterized with $^1\text{H-NMR}$ and $^{13}\text{C-NMR}$ at -75°C .

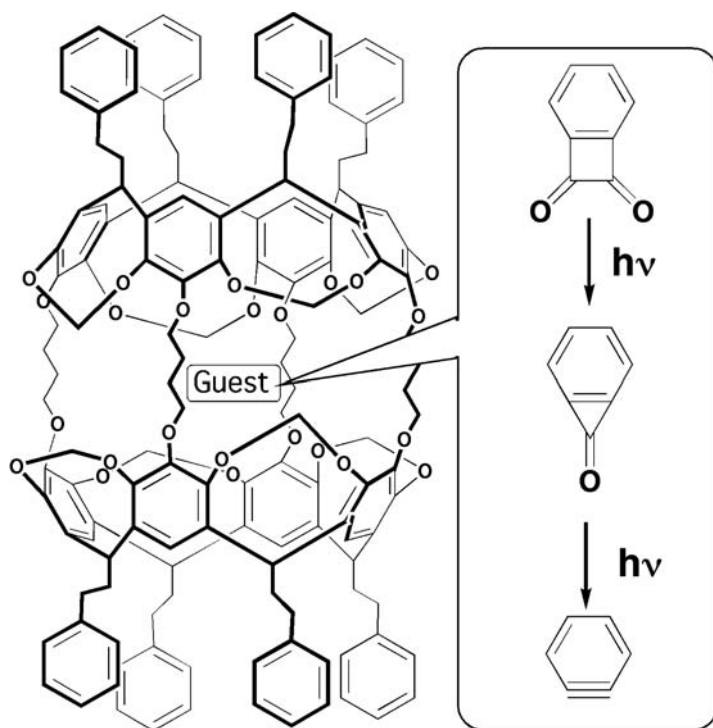


Figure 2.22. A molecular capsule stably preserves *o*-benzyne

2.10 Endoreceptors and Exoreceptors

According to Lehn's definition, host molecules that have binding sites inside their molecular structures are called *endoreceptors*. For example, enzymes are generally endoreceptors, because they recognize the guest substrate in a reaction pocket located inside the enzyme. Host molecules with guest binding sites on their surfaces are defined as *exoreceptors*. Antibodies are classified as the exoreceptors because they recognize antigen on the terminal surface.

Most of the cyclic hosts described in the previous sections can trap guest molecules inside their structures and so they are regarded as endoreceptors. If specific interactions such as hydrogen bonding are applied to guest recognition, cyclic and cavity structures are not always necessary. Using stronger, more specific interactions, it is possible to design various exoreceptor hosts; indeed, exoreceptors allow more design freedom than endoreceptors. Molecular clefts are host molecules designed according to this concept. In this kind of host, several binding sites, such as hydrogen bonding sites, are arranged on the surface of a cleft-like structure. Exoreceptor design is advantageous when preparing molecular assemblies. If the host molecule has multiple sites for molecular recognition on its surface, one host can bind two or more guest molecules at once. Extending this strategy results in the design of specifically connected molecular assemblies. Such supermolecules are introduced in the later sections.

Figure 2.23 shows one example of an acyclic host that can recognize a guest molecule through the cooperative effects of different types of molecular interaction. The recognized guest in this case is L-tryptophan, and three different

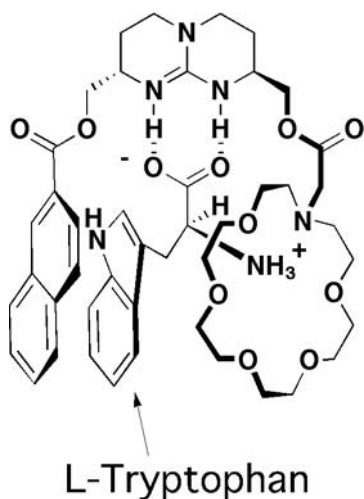


Figure 2.23. Chiral recognition by an acyclic host

parts are cooperatively recognized: ammonium binds to crown ether; carboxylate hydrogen bonds with guanidinium; an aromatic side chain interacts with a naphthyl group through a π - π interaction. The host molecule used here has (*S,S*)-configuration and only forms the desirable binding geometry with *L*-tryptophan. Similarly, the (*R,R*)-host selectively recognizes *D*-tryptophan.

Another interesting example of recognition at a molecular surface is shown in Fig. 2.24. Here, a recognition system based on an adenosine guest (A) and a Kemp's acid host (B) is modified into a self-replication system. Coupling between the amino group in A and the carboxyl group in B results in the amide C. The resulting molecule C can bind A and B through hydrogen bonding: the adenine moiety of C recognizes the imide part of B and the imide in C recognizes the adenine in A. When molecules A and B are bound to C they are in a good geometry for a condensation reaction. Therefore, the coupling reaction between A and B to give C is promoted by the presence of C. In this system, C acts as a template for self-replication. It may be surprising that a simple host-guest system like this mimics the fundamental activity associated with life, self-replication.

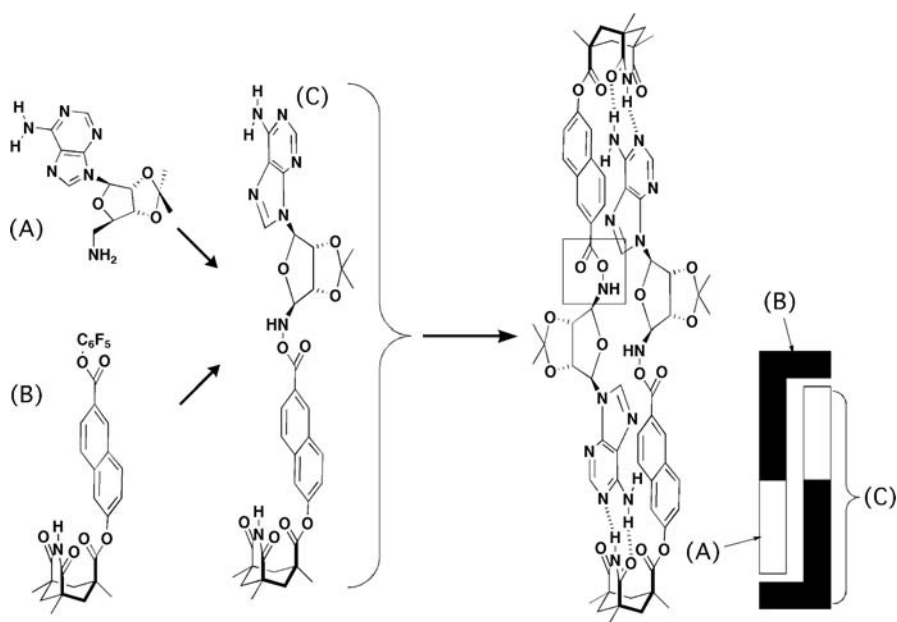


Figure 2.24. Self-replication upon molecular recognition

2.11

Molecular Recognition at Interfaces – The Key to Understanding Biological Recognition

If we extend the concept of an endoreceptor to larger dimensions, we obtain an array of binding sites located at a macroscopic interface. A monolayer of host molecules at an air–water interface (see Chap. 4) is an example of such a situation. Such recognition sites might show different characteristics to binding sites dissolved in bulk solution. Interfaces are usually formed at the boundary between two media with quite different dielectric constants. Because many forms of molecular interaction are significantly influenced by the dielectric constant of the medium, host and guest molecules at interfaces may show unique characteristics compared to when those molecules are in simple bulk phase. Molecular recognition at interfaces is an attractive research target from the point of view of fundamental science. In addition, biological systems are composed of many kinds of interfaces. Investigating molecular recognition at the interfaces could lead an understanding of various unusual properties of the molecular recognition seen in biological systems.

As a first example, consider the recognition of phosphate by a guanidinium function at the air–water interface. Guanidinium can bind phosphate and carboxylate through both hydrogen bonding and electrostatic interactions. In order to study an interface, a monolayer of amphiphilic guanidinium was spread on an aqueous phase containing guest molecules such as AMP (adenosine monophosphate) and ATP. The binding motifs of these guests are shown schematically in Fig. 2.25. The monolayers were transferred as Langmuir–Blodgett (LB) films (see Chap. 4) onto a solid support and subjected to elemental analysis by X-ray photoelectron spectroscopy (XPS). This analytical method quantitatively yields the efficiency of the guest binding from the observed P/N ratio. It was found that AMP and ATP bind one guanidinium and three guanidiniums, respectively. Complementary recognition occurs between the guest phosphate group and host guanidinium site. The most important finding of this experiment was the magnitude of the binding constant (the strength of binding). The binding constants of the guanidinium in the monolayer to AMP and ATP were $3.2 \times 10^6 \text{ M}^{-1}$ and $1.7 \times 10^7 \text{ M}^{-1}$, respectively (20°C). These values are somewhat surprisingly greater than the corresponding binding constant for guanidinium–phosphate recognition in the aqueous phase (1.4 M^{-1}).

Similar increases in binding constants have been observed for many other kinds of recognition pairs. The air–water interface is a medium where molecular interactions are more efficient than in bulk aqueous medium. This knowledge has important implications for our understanding of biological molecular recognition. In biological systems, many types of molecular recognition are selectively and efficiently achieved through complementary hydrogen bond formation. For example, DNA replication, enzyme–substrate recognition and specific protein folding are all supported by hydrogen bond-assisted molecu-

lar recognition. Surprisingly, most of these occur in aqueous phase. Water has a large dielectric constant and provides a medium that suppresses electrostatic interactions and hydrogen bonding. It is still not entirely clear how biological systems achieve efficient hydrogen bonding in a polar water phase. Biological systems are composed of various kinds of interfaces, such as cell surfaces and protein surfaces, and most recognition sites are located at these interfaces. Quantum chemical calculations of molecular interactions at interfaces suggest that effects from the nonaqueous phase (the medium with the lower dielectric constant) play some part in enhancing molecular interaction.

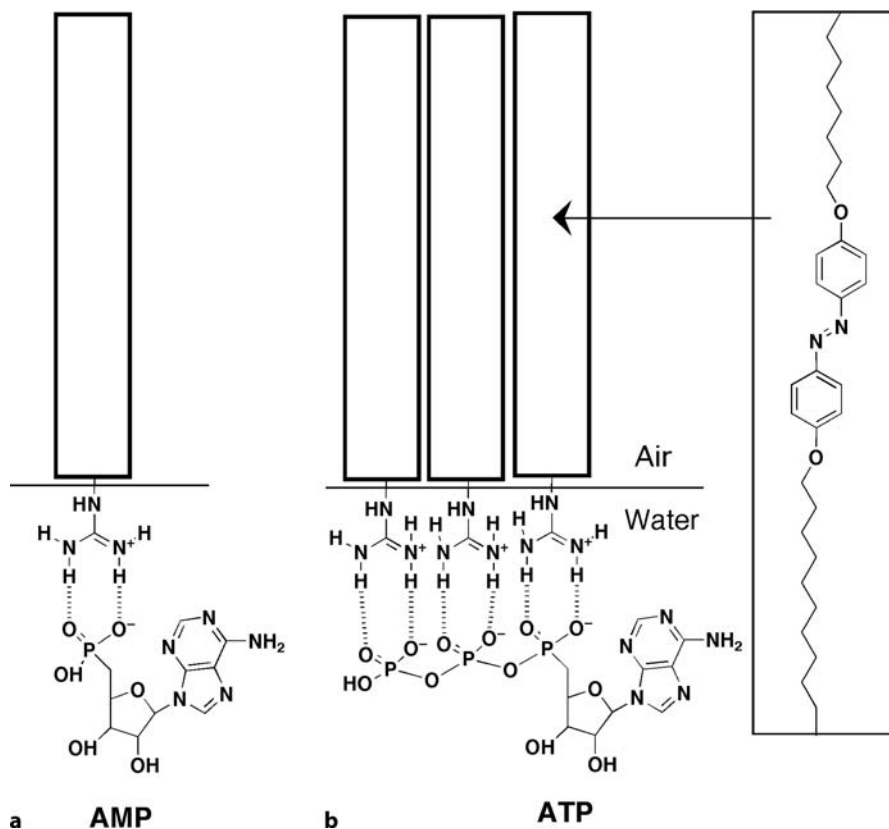


Figure 2.25. Binding of a nucleotide by a guanidinium amphiphile at the air–water interface with an enhanced binding constant

2.12

Various Designs of Molecular Recognition Sites at Interfaces

The binding between nucleobase monomers in water is usually negligible, and recognition is only achieved in a nonpolar medium. However, molecular recognition between nucleobase mimics occurs efficiently at the air–water interface. Figure 2.26(a) shows the binding of aqueous thymine to a monolayer of diaminotriazine, which is an analog of thymine's partner base, adenine. The binding constant observed for this recognition pair is comparable to the value observed for a similar recognition pair (diamidepyridine receptor)

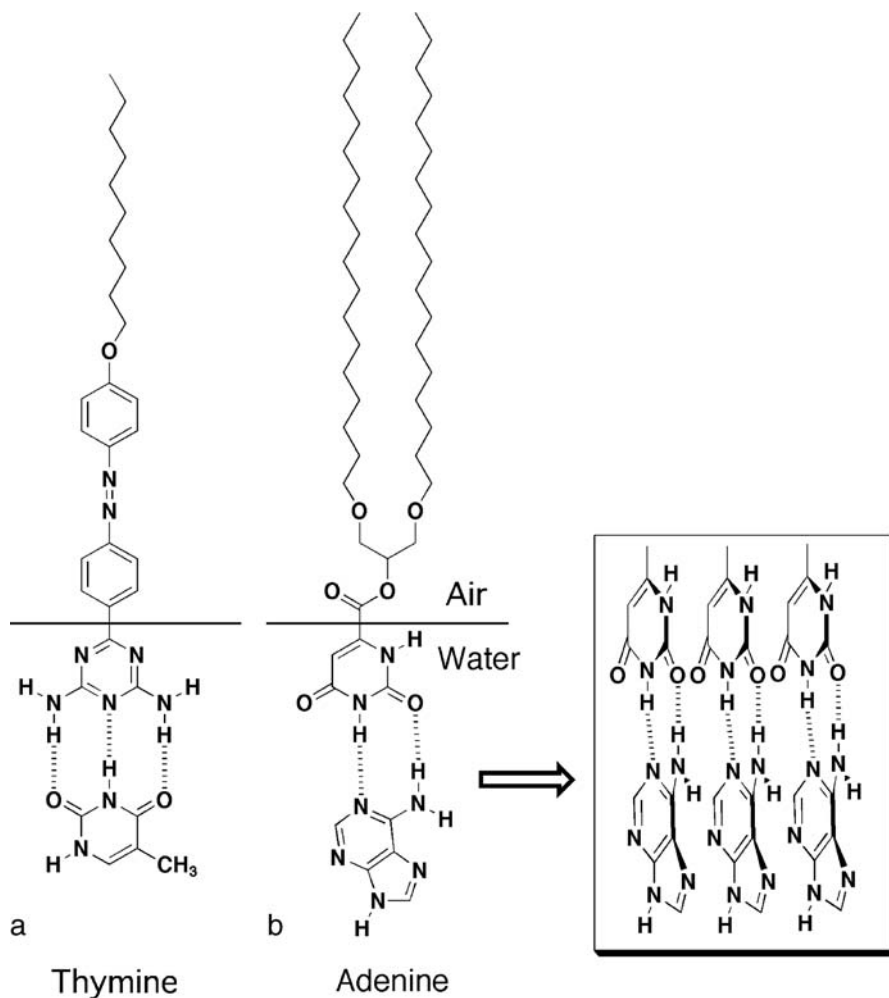


Figure 2.26. Mimicking a base-pair at the air–water interface

and butylthymidine guest) in organic solvent. Molecular recognition with the reversed pair was demonstrated between a monolayer of the cyclic imide orotate and aqueous adenine (Fig. 2.26(b)). In the latter case, a cooperative enhancement of binding efficiency was also detected. Stacking between the bound adenines stabilizes the binding. This effect is advantageous in molecular assembly-type receptor sites.

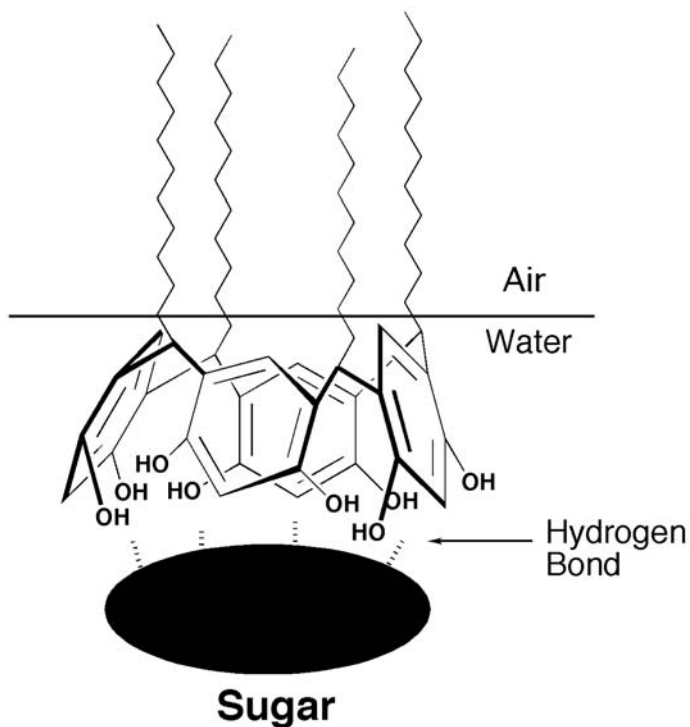
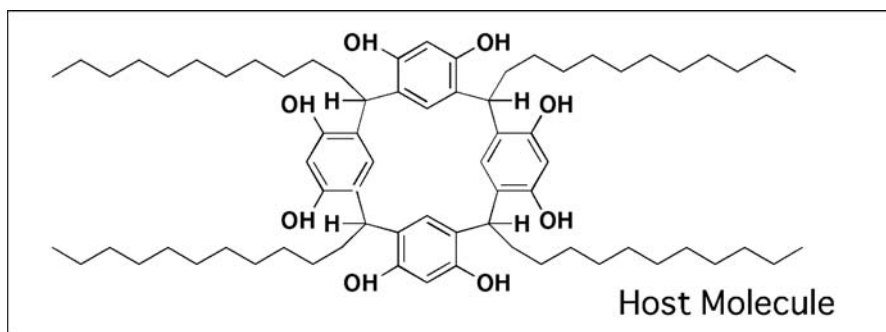


Figure 2.27. Binding of sugar by a calixresorcinarene monolayer

Calixresorcinarene is a host that is known to extract sugar molecules from an aqueous phase to an organic phase via specific hydrogen bonding. Long alkyl tails were attached to this unique host, and the hydrophobic host ob-

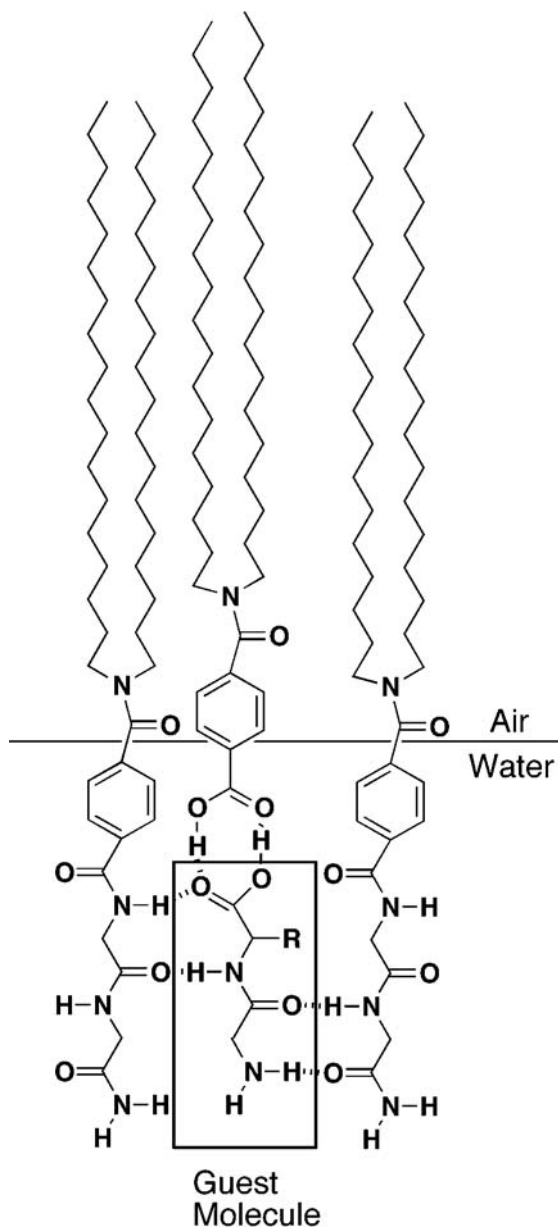


Figure 2.28. Recognition of peptide by a mixed host at the air–water interface

tained was spread on water containing sugar guests (Fig. 2.27). The binding of various sugars to the monolayer was investigated systematically. The binding efficiencies observed for the monolayer system exhibit unique selectivity: glucose < fucose \approx galactose \approx arabinose < xylose < ribose. This tendency is apparently different to the observed order of extraction from the aqueous phase to the organic phase: xylose < galactose \approx glucose < arabinose < ribose < fucose. These phenomena can be rationalized by invoking the stability of the complexes formed in the two kinds of medium. At the air–water interface, the formation of complexes that expose the hydrophilic face of the bound guest to the bulk water phase is preferable. Xylose forms a hydrophilic complex with the calixresorcinarene and shows strong binding at the air–water interface and a low efficiency for extraction into the hydrophobic phase. A hydrophobic complex formed when fucose was used as a guest. The binding selectivity to fucose at the air–water interface was low but it was efficiently extracted into the organic phase. Ribose possesses both a hydrophobic face and a hydrophilic face and it is therefore capable of forming both hydrophobic complexes and hydrophilic complexes. Therefore, fucose exhibited a high binding efficiency at both the air–water interface and in organic solvent.

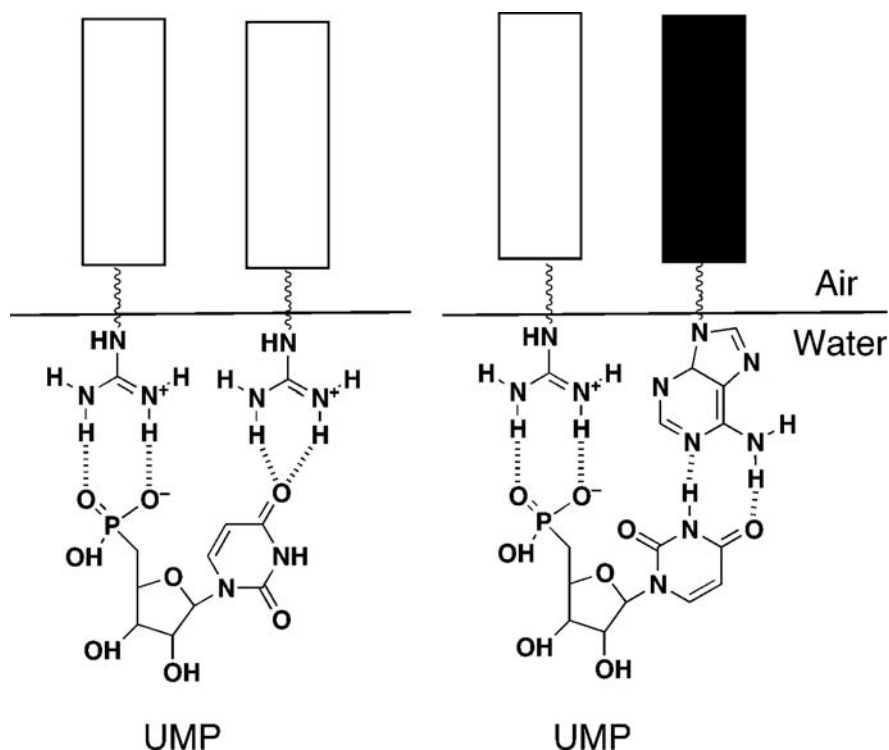


Figure 2.29. Binding of UMP by single and mixed hosts at the air–water interface

Constructing a host molecule containing various types of recognition sites is often a difficult task. Such complicated recognition sites can be formed spontaneously from rather simple host molecules at the air–water interface via a self-assembling process. An example of multiple recognition sites for aqueous peptides on a host assembly is given in Fig. 2.28. Two glycyglycinamide chains supply hydrogen bonding sites to bind to a guest peptide linkage through an antiparallel β -sheet structure, and the amphiphilic benzoic acid host fixes the C-terminal of the guest. The binding selectivity is determined by the bulkiness and the hydrophobicity of the side chain of the guest dipeptide.

In the example shown in Fig. 2.29, two guanidinium host amphiphiles bind to one uridine monophosphate (UMP). The guanidinium can form hydrogen bonds with the carbonyl group and the phosphate of UMP. However, when an equimolar amount of adenine amphiphile is mixed with the guanidinium host, the UMP carbonyl/guanidinium interaction is replaced by a uracil/adenine base pairing. Therefore, we can easily imagine that various nucleotides can be recognized by suitable combinations of host amphiphiles. Synthesizing complicated host molecules is sometimes very difficult, but self-assembly from a simple host at the air–water interface provides an easy path to the construction of sophisticated recognition sites.

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3 Controlling Supramolecular Topology – The Art of Building Supermolecules

In the previous chapter we introduced host–guest chemistry based on specific molecular interactions, which is the bedrock of supramolecular chemistry. It is worth noting at this point that complexation between appropriate hosts and guests can also be used to form large aggregates. However, before we dive into the subject of large assemblies in the next chapter, we are first going to investigate medium-size supermolecules.

Various families of novel supermolecules obtained via spontaneous or designed covalent linkages have been attracting a great deal of attention recently. These supermolecules have interesting and unique geometric features and provide the key to many tailored supramolecular topologies, and it is these molecules that we explore in this chapter. Some examples include the following. *Fullerenes* are closed spheroid structures created from carbon pentagons and hexagons. Some of them can be described as “molecular soccer balls”. Tubular structures – carbon nanotubes – can also be created by combining hexagons and pentagons of carbon. Systematic molecular branching and extension results in the stepwise formation of dendrimers, which can trap other molecules or ions. Threading rod molecules through rings (cyclic molecules) results in rotaxanes, and interlocking ring-like molecules together creates catenanes. Some of these molecules are obtained through spontaneous processes while the others are constructed via well-designed synthetic strategies.

Contents of This Chapter

3.1 Fullerenes – Carbon Soccer Balls As described above, fullerenes are closed structures constructed from pentagonal and hexagonal carbon units. The fullerene consisting of sixty carbon atoms has a structure similar to a soccer ball. Fullerenes possess very different properties to diamond and graphite; some of their electronic properties are somewhat similar to those of a semiconductor.

3.2 Carbon Nanotubes – The Smallest Tubular Molecules A carbon nanotube is carbon-based tube with a diameter that is measured in nanometers and a length of several micrometers. Nanotubes have interesting electronic characteristics that are expected to lead to their widespread use in molecular electronics.

3.3 Dendrimers – Molecular Trees Dendrimers have systematic branching structures and they are built in a stepwise manner. Supermolecules from this family can be used to shield functional groups and to collect energy.

3.4 Rotaxanes – Threading Molecular Rings Rotaxanes are obtained by threading linear polymers through molecular rings such as cyclodextrins, crown ethers and cyclophanes. Molecular shuttles based on the rotaxane structure have been proposed.

3.5 Catenanes and Molecular Capsules – Complex Molecular Associations Interlocking several rings results in a catenane structure. Catenanes can be obtained efficiently using supramolecular concepts. The spontaneous formation of a palladium coordination complex is an elegant process that is used in the synthesis of catenanes and molecular capsules.

3.1

Fullerenes – Carbon Soccer Balls

We used to believe that there are three allotropic forms of carbon: graphite, diamond, and amorphous carbon. However, an important new carbon allotrope, the fullerenes, was discovered as recently as the 1980s. The most famous fullerene is buckminsterfullerene, C_{60} , which is depicted in Fig. 3.1. The structure of this “soccer ball-shaped” molecule consists of a sphere of sixty carbon atoms arranged in pentagons and hexagons; each carbon pentagon is surrounded by five carbon hexagons.

This molecular soccer ball was discovered in 1985, as a result of studies into the structures formed by carbon atoms in space, which were in turn prompted by unexplained features in interstellar spectra.

Harold Kroto expected that chained carbon atoms were present near red giant stars. In order to experimentally demonstrate this hypothesis, he suggested to Richard Smalley, who was investigating clusters generated by irradiating solid materials with laser beams, that they might perform some joint research. Smalley was said to be somewhat reluctant to do so at first, because silicon and germanium were more attractive materials for research than carbon at that time.

However, mass spectral analysis on some products obtained from irradiating graphite with a powerful laser indicated the presence of an unknown allotrope

of carbon, C_{60} . They found that the structure of graphite was broken apart by strong energy, and high-temperature plasma containing mainly C_2 was generated. Cooling of this plasma resulted in clusters composed of sixty carbon atoms (C_{60}). Based on these findings, Smalley proposed a spherical structure made up of carbon pentagons and hexagons. The carbon atoms in C_{60} were shown to be equivalent by the fact that ^{13}C -NMR spectrum of C_{60} exhibits a single peak at 142.7 ppm.

The name buckminsterfullerene was given to this molecule by Kroto; due to his knowledge of art and architecture, he noticed that the structure of the molecule was the same as that of the geodesic domes popularized by the famous architect Richard Buckminster Fuller. Over the years, a simplified version of this name – fullerene – became popular.

Because fullerenes are closed polyhedrons they obey Euler's equation:

$$(\text{number of edges}) = (\text{number of apices}) + (\text{number of faces}) - 2$$

Because three edges meet at each apex (sp^2 carbon) and each edge links two apices, the ratio (number of edges):(number of apices) is fixed at 3:2. The total number of faces is given by the total number of pentagons and hexagons in the structure. Because each edge is shared by two faces, if we simply assign five edges to each pentagon and six to each hexagon and then total up all of the edges in the structure, we actually get twice as many as there actual are. This can be described mathematically as follows.

$$\begin{aligned} 2 \times (\text{number of edges}) &= 3 \times (\text{number of apices}) \\ (\text{number of faces}) &= (\text{number of pentagons}) + (\text{number of hexagons}) \\ 2 \times (\text{number of edges}) &= 5 \times (\text{number of pentagons}) \\ &\quad + 6 \times (\text{number of hexagons}) \end{aligned}$$

Upon combining these equations, several parameters can be erased and the number of pentagons is fixed at 12. The number of apices – in other words the number of carbon atoms – is then given by a relation involving the number of the hexagons:

$$(\text{number of apices}) = 2 \times (\text{number of hexagons}) + 20$$

Therefore, the fullerenes C_{60} , C_{70} , C_{76} , C_{78} , C_{80} , C_{90} , and C_{96} have 20, 25, 28, 29, 31, 35, and 38 hexagons, respectively.

Fullerenes show quite different electronic properties to other carbon allotropes. The carbon in diamond has a nonconductive sp^3 hybrid orbital, while that in graphite is conductive since it has an sp^2 hybrid orbital. Fullerene carbons have orbitals that are intermediate between sp^2 and sp^3 , and so the fullerenes behave like semiconductors. Graphite can be oxidized and reduced. In contrast, fullerenes are easily reduced but difficult to oxidize. Fullerenes can also be doped with metal ions (Fig. 3.2). In doped fullerenes, the metal ion is

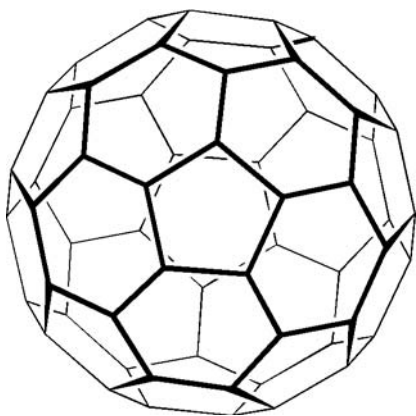


Figure 3.1. C₆₀

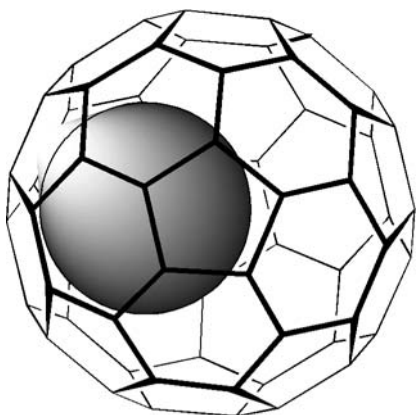


Figure 3.2. Metal-doped fullerene

located inside the fullerene. This structure consisting of an inner cation and a reducible fullerene outer framework is somewhat reminiscent of an “atom”; the metal-doped fullerene can therefore be regarded as a “superatom”. Doped fullerenes are also known to exhibit superconductivity.

Fullerenes have also been chemically modified. The reactivity of C₆₀ is closer to that of an olefin rather than a benzene ring. Solid-state reaction of the fullerene with potassium cyanide results in a fullerene dimer (a dumbbell-shaped fullerene; see Fig. 3.3). Because the fullerene intermediate anion (with a CN substituent) is reactive in the solid state, dimerization of the fullerene occurs. In contrast, this anion is stabilized by solvation, and so dimerization does not proceed.

Appropriate substitution will stabilize C₆₀ containing charged groups, allowing the C₆₀ to have an amphiphilic nature. This modified C₆₀ is soluble in

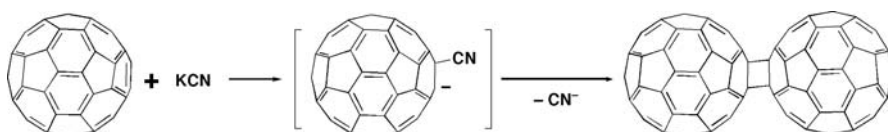


Figure 3.3. Dumb-bell shaped fullerene

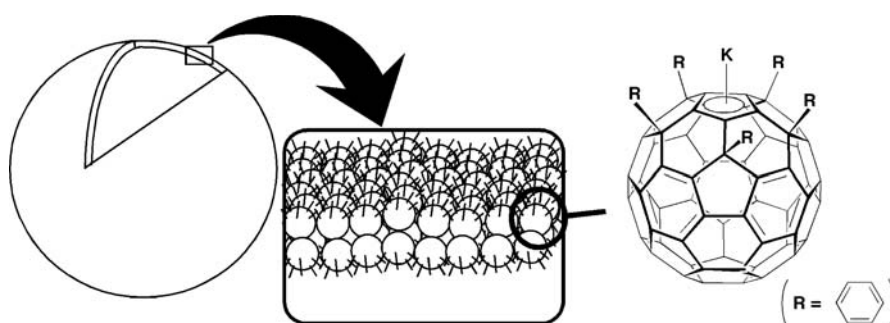


Figure 3.4. Fullerene vesicle

water, forming large aggregates known as bilayer vesicles (Fig. 3.4; see also Chap. 4). This behavior has inspired various proposed biological applications of fullerenes. Chemical modification of fullerenes should open the door to many other new applications of fullerenes too.

3.2

Carbon Nanotubes – The Smallest Tubular Molecules

Like fullerenes, carbon nanotubes are constructed from joining together (mostly) hexagons and (a few) pentagons of carbon, but they are long tubes (see Fig. 3.5) that generally include a much larger number of carbon atoms than closed fullerenes. They are 1 – 10 μm in length but only nanometers in diameter. Like buckminsterfullerene, they were also found accidentally. Their discoverer, Sumio Iijima, had already found onion-like graphite particles during observations made with an electron microscope five years before C_{60} was discovered. The structures he observed consisted of multiple layers of graphite around

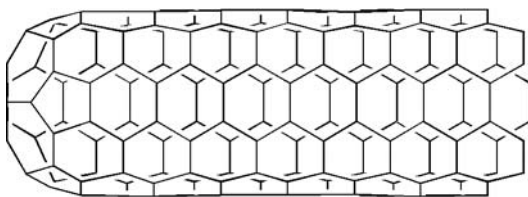


Figure 3.5. A carbon nanotube

a C_{60} core. In later research, he investigated the products of carbon rod arc discharge in order to investigate the mechanism of formation of the onion-like molecules. During these investigations, he accidentally found a long tube-like form of carbon: a carbon nanotube. There are many different kinds of carbon nanotube, including simple single-walled tubes, multiwalled tubes consisting of tubes inside tubes, and spiral nanotubes. Their electron conductivity ranges from metallic to semiconductive, depending on the tube diameter and the rolling angle (which governs the tightness of the spiral). This range of electronic characteristics are anticipated to lead to their extensive use molecular electronic devices in the future.

Various applications have been proposed for carbon nanotubes, covering a wide range of scientific fields. Carbon nanotubes can store huge volumes of gas. This could be an important property, because hydrogen is expected to be a major source of energy in the near future, which will require novel improved methods for hydrogen storage and transport. Since single-walled carbon nanotubes can adsorb as much as ten times the volume of hydrogen that active carbon can, they are considered to be a strong candidate for a new hydrogen storage technology. The tubular shape of a nanotube can be used for template synthesis. Immobilization of guest material in a carbon nanotube template and subsequent oxidative destruction of the carbon nanotube would produce tailored nanosized materials.

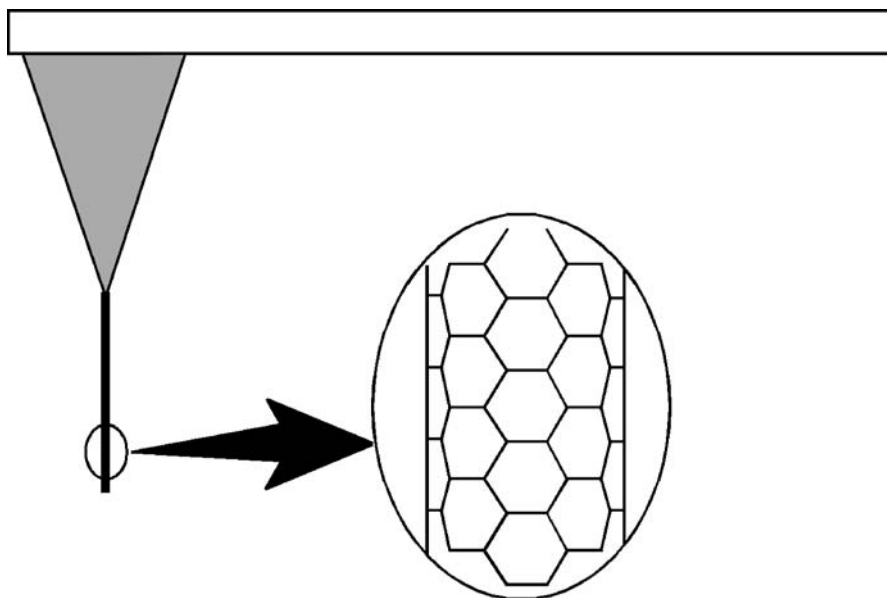


Figure 3.6. Application of a carbon nanotube as a novel type of scanning probe microscope tip

Carbon nanotubes can also be used as tips in probe microscopy (Fig. 3.6). Probe microscopy detects the morphology of a sample surface through atomic-level interactions between tip and sample. The resolution of the technique strongly depends upon the sharpness of the tip. Attaching a carbon nanotube to the top of a conventional tip dramatically improves the sharpness of the tip. Furthermore, introducing a functional group at the top of the carbon nanotube through chemical modification could lead to the ability to probe chemical distributions on sample surfaces at the atomic level, based on specific interactions and molecular recognition between the modified tip and the sample.

Another interesting application of nanotubes is the nanothermometer (Fig. 3.7). A carbon nanotube (about $10\mu\text{m}$ long and 75nm in diameter) is filled with liquid gallium, which expands in the tube as the temperature increases. Therefore, the level of the gallium in the nanotube changes in proportion to temperature, similar to the mercury in a macroscale thermometer. This nanothermometer should be suitable for use in a wide variety of microenvironments.

The fabrication of carbon nanotubes is important for future applications. One example, the formation of a “nanoring” (a ring made from a nanotube) is illustrated in Fig. 3.8. Ultrasonication single-walled carbon nanotubes in concentrated $\text{H}_2\text{SO}_4/\text{NHO}_3$ is known to break carbon nanotubes into many short pieces. The nanotube pieces are then etched lightly in $\text{H}_2\text{SO}_4/\text{H}_2\text{O}_2$ to afford oxygen-containing groups at both ends, some of which are phenolic hydroxides and others carboxylic acids. Treating these pieces with dicyclohexylcarbodiimide leads to ring closure. Indeed, a simpler way of fabricating nanorings – mixing carbon nanotubes with an ionic liquid, giving a gel – was

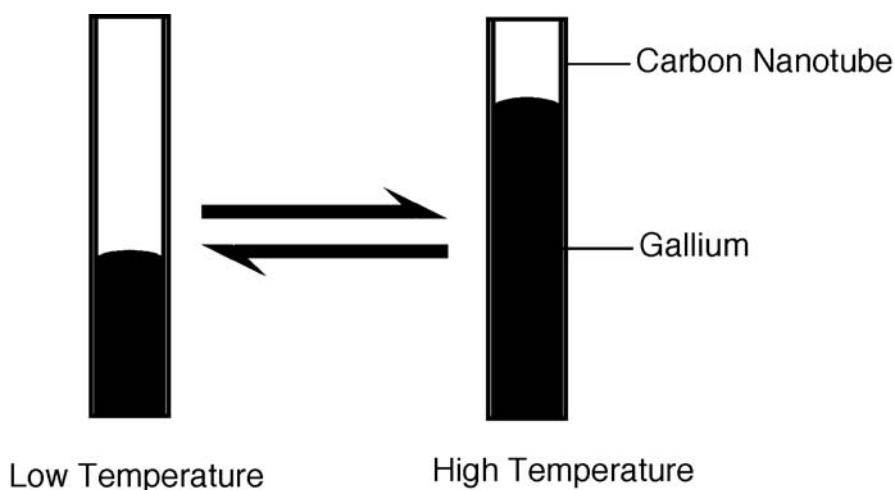


Figure 3.7. Nanothermometer based on a carbon nanotube filled with liquid gallium

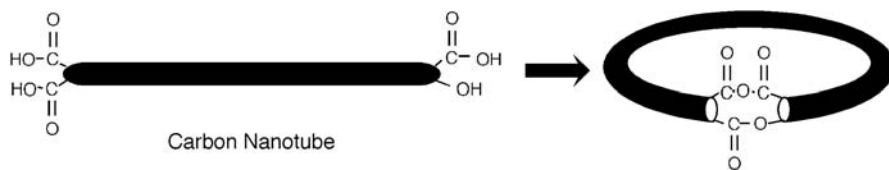


Figure 3.8. Carbon nanoring

recently reported. Using this method, materials containing carbon nanotubes could be fabricated into desirable shapes.

3.3

Dendrimers – Molecular Trees

Fullerenes and carbon nanotubes are formed spontaneously based on the restricted rules of carbon linkage. Therefore, their fundamental frameworks are not easily redesigned. Superstructures where we are free to design their sizes and shapes are sometimes more attractive prospects. In this section, the *dendrimer* family is introduced, as examples of artificially controllable superstructures. The word “dendrimer” contains the root “dendr-”, which means tree, an accurate reflection of the structures of dendrimers – molecular trees. The first dendrimer was proposed by Tomalia. After several groups had

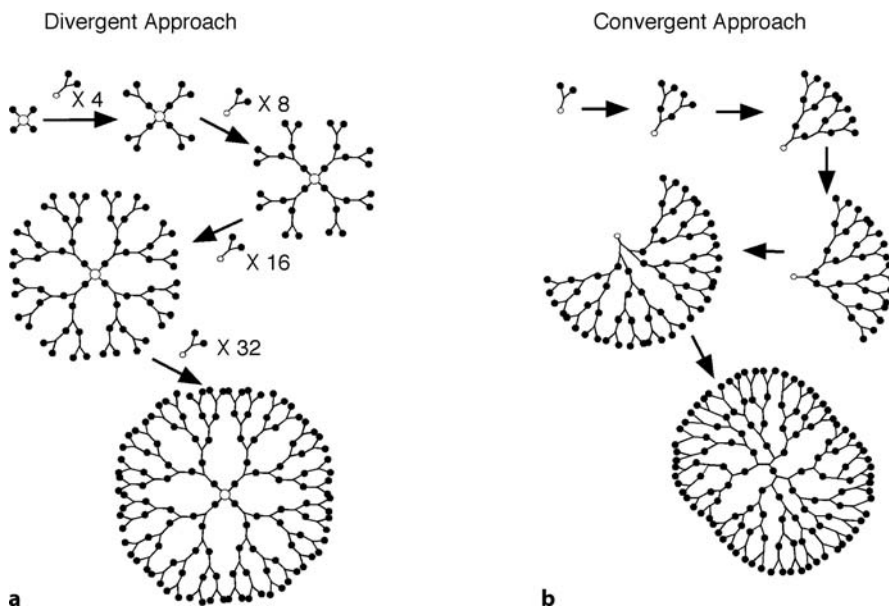


Figure 3.9. Strategies for dendrimer synthesis

demonstrated their functional utility, the number of researchers working in dendrimer chemistry rapidly increased.

Dendrimers are usually nanometers to tens of nanometers in size, which is larger than a typical closed fullerene (diameter, ~ 0.7 nm) and smaller than a microsphere (diameter, $0.1 - 10 \mu\text{m}$). Dendrimers are constructed by stepwise connection of several parts. Therefore, their sizes are defined by the number of steps taken to build them. Typical synthetic routes to complete dendrimers are illustrated in Fig. 3.9. One route starts from the center (a). Branched parts are introduced step-by-step in order to control the size and the number of branches, like trees. This type of synthetic pathway is called a *divergent method*. Another route builds dendrimer structures starting from the outside (b). In the example shown, three monomeric units are connected in the first step. Next, two of these three-monomer units are connected to another monomeric unit. After stepwise coupling into increasingly large parts, the parts are finally fused together into a spherical dendrimer. The latter method is called a *convergent method*. Divergent methods are advantageous for larger-scale synthesis, but in this case we have to be careful not to leave branches uncompleted. In contrast, the convergent method is a better way to prepare a defect-free dendrimer, but the purification process associated with this method is sometimes time-consuming.

When we do not care much about obtaining a product with precise size and structure, branched monomers can be condensed randomly. The polymeric materials obtained in this way are called *hyperbranched polymers* (Fig. 3.10).

Dendrimers have various useful properties. The number of branches increases with the step number (the dendrimer generation). The branches are crowded at the outer surface while the inner part of the dendrimer has more empty space. Therefore, the dendrimer can behave like a capsule. Size-matched functional guest molecules become entrapped in this nanometer-scale capsule.

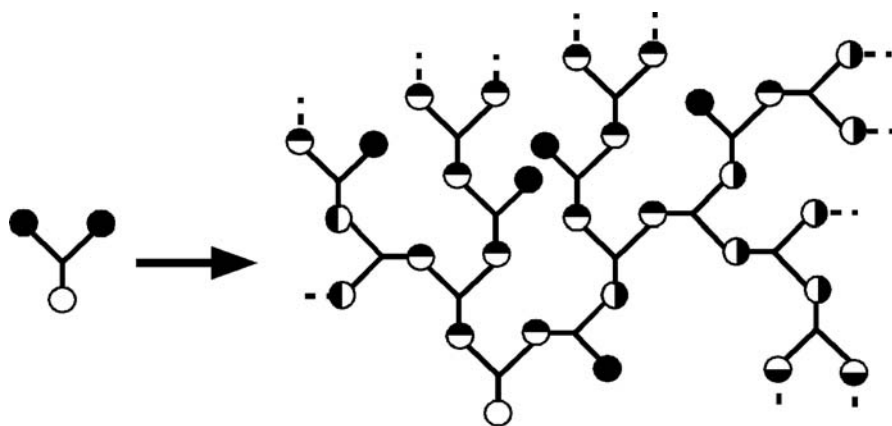


Figure 3.10. Building a hyperbranched polymer

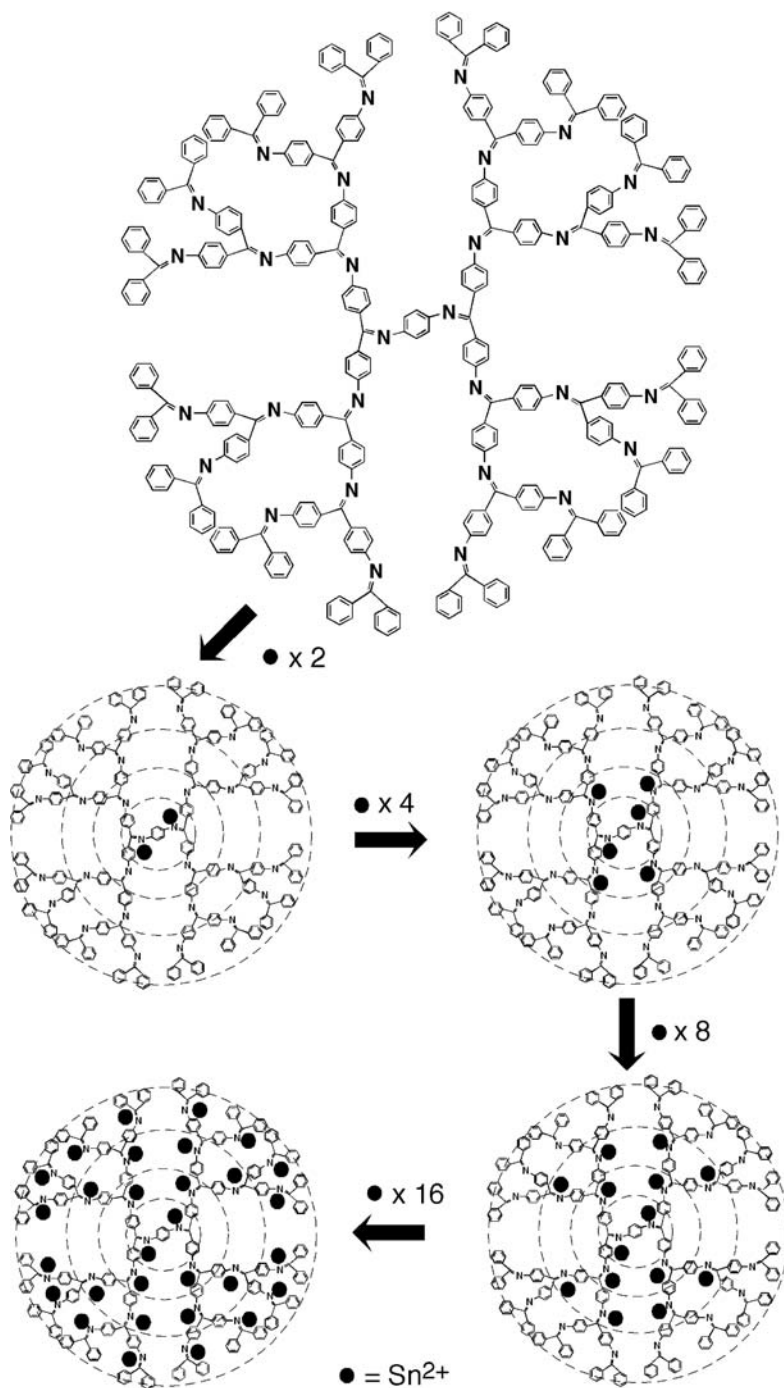


Figure 3.11. Stepwise encapsulation of tin ions in a dendrimer

The dendrimer shown in Fig. 3.11 has imide groups that can trap tin ions site-specifically. Interestingly, the tin ions bind to this dendrimer in a stepwise fashion according to the electron density gradient.

Specific functional units can be immobilized at the center of a dendrimer. In the example depicted in Fig. 3.12, a porphyrin unit is immobilized in a dendrimer (which is called a dendrimer porphyrin). Because the porphyrin unit is buried deep in the dendrimer structure, the dendrimer porphyrin is a good model of a heme protein. The environment of the dendrimer can be evaluated via the spectral characteristics of the central porphyrin. If the size of the dendrimer is large enough, the adsorption spectrum of the porphyrin shows that it is basically independent of surrounding solvent molecules: the central porphyrin is shielded by the dendrimer cage. The structural mobility of the inner part of the dendrimer porphyrin has been evaluated via NMR

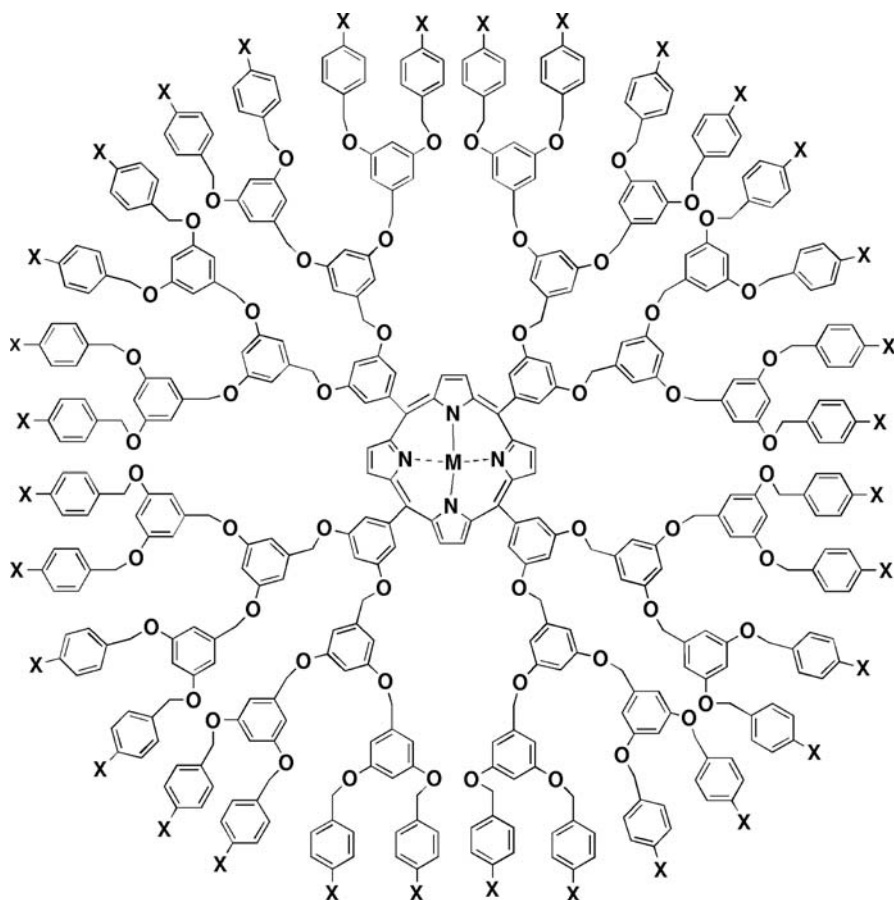


Figure 3.12. Dendrimer porphyrin

measurements. The motions of the outer parts of the porphyrin become more restricted as the size of the dendrimer increases. In contrast, the movement of the central area of the porphyrin was almost independent of the size of the dendrimer.

These structural characteristics mean that the dendrimer porphyrin can be used to mimic the function of the heme protein – its ability to bind to oxygen. A dendrimer porphyrin with an Fe(II) ion can stably trap oxygen via coordination with imidazole ligands. The oxygen was reversibly trapped within the dendrimer, and it can be released when the oxygen in the surrounding solvent was removed. The dendrimer sphere shields the porphyrin part from the outer environment. Therefore, side effects such as irreversible oxidation of the porphyrin by water and dimerization of the oxygen-bound porphyrins can be suppressed.

Since dendrimers can be designed and synthesized in stepwise processes, various structures of dendrimers can be prepared. The synthesis of a block-type dendrimer is depicted in Fig. 3.13. In this strategy, one side of the central molecule is first activated, and so a hemispherical dendrimer is selectively formed. Then the other side of the center is activated, causing another kind of

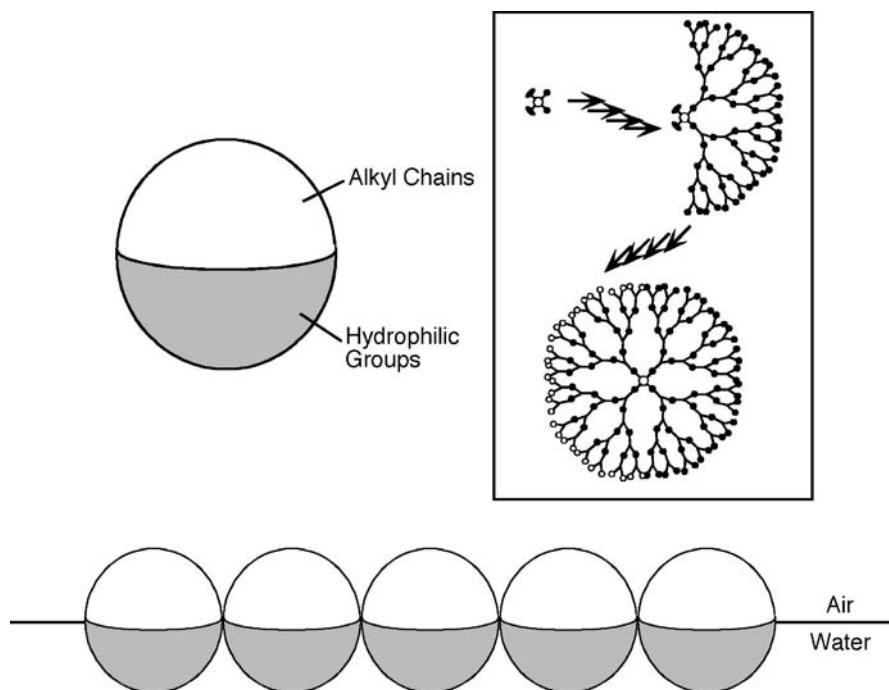


Figure 3.13. Structure and synthesis of a block dendrimer, and schematic showing a block dendrimer monolayer on the surface of water

dendrimer to grow. These processes result in a “half & half”-type dendrimer. If the hydrophilic groups and hydrophobic groups are introduced separately, an amphiphilic block dendrimer can be obtained. This type of dendrimer forms a monolayer on the surface of water.

Star-shaped dendrimers can also be synthesized, using stepwise dendrimer growth and subsequent linear polymerization (Fig. 3.14). A dendrimer with oligosaccharide chains on its outer surface was produced using this synthetic strategy. This has a ball-like shape that is densely covered with sugar residues, and is therefore known as a sugar ball. Sugar residues are known to play important roles in biological recognition processes such as virus binding. Since sugar cluster formation is key to such recognition processes, the sugar ball is expected to be a useful model for investigating sugar-based biological recognition.

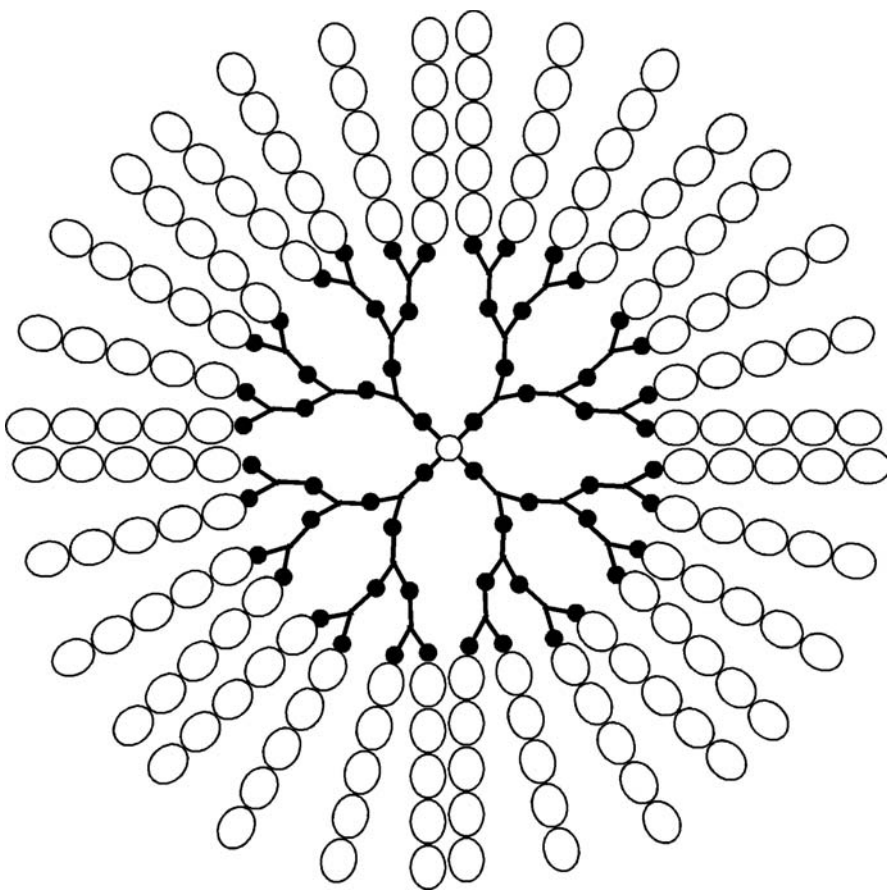


Figure 3.14. Star-shaped dendrimer

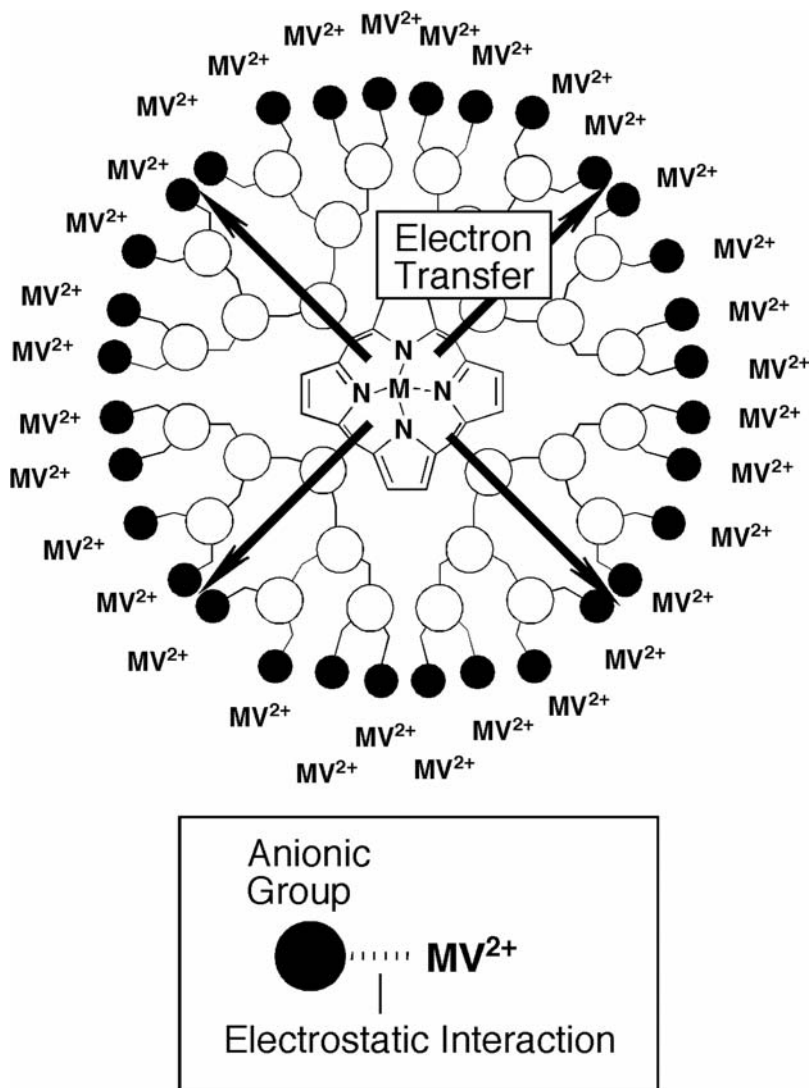


Figure 3.15. Electron transfer via a dendrimer core

Introducing ionized groups onto the outer surface of a dendrimer induces the adsorption of counterionized functional molecules. A porphyrin dendrimer with anionic groups on the outer surface has been shown to adsorb the electron acceptor methylviologen (MV²⁺) (Fig. 3.15). Photoexcitation of the central porphyrin induces electron transfer to the adsorbed methylviologens. As the size of the dendrimer was increased, electron back-transfer was effectively suppressed and a long-lived electron separation state was achieved.

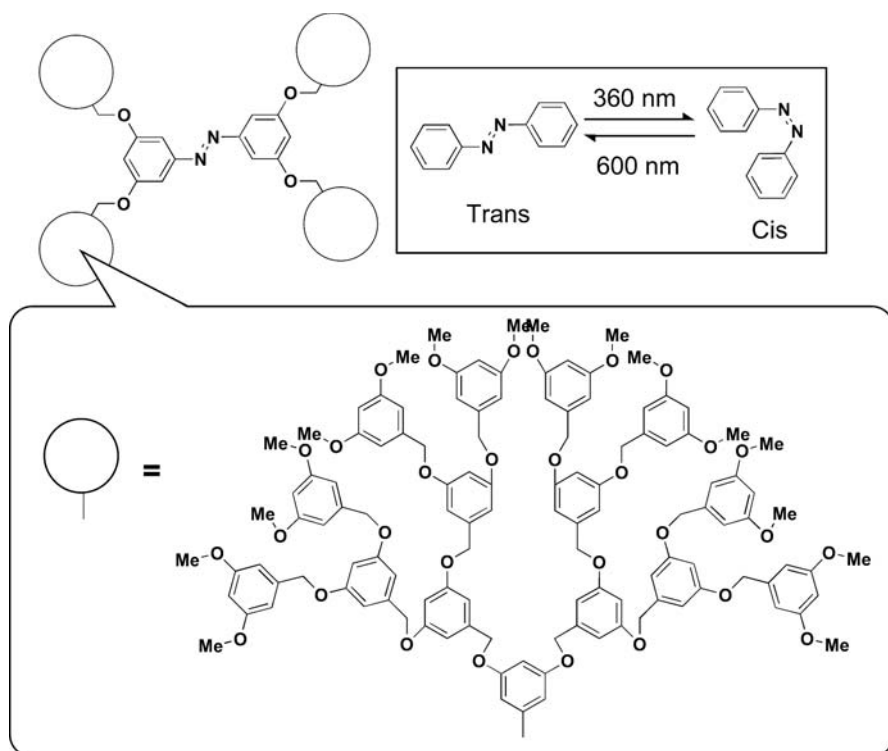


Figure 3.16. Azobenzene isomerization via energy collection

In the dendrimer structure, the number of units increases as we progress toward the outside of the molecule. Therefore, this structure is useful for functions such as accumulating energy on the outside and passing it to the center. This dendrimer function mimics the light-harvesting process associated with photosynthesis. In the dendrimer depicted in Fig. 3.16, infrared light irradiation excites the benzene groups in each unit. The energy collected induces the transformation of the central azobenzene from a *cis* configuration to a *trans* form. This transformation cannot be achieved by irradiating azobenzene without a dendrimer shell, because not enough of the energy passed to the azobenzene is accumulated by it to cause the transformation, due to energy loss through molecular collisions.

3.4

Rotaxanes – Threading Molecular Rings

Dendrimer chemistry shows that we can prepare a confined volume by designing and synthesizing an appropriate arrangement of segments. The *rotaxanes* described in this section and the *catenanes* described in the next section have

even more unique shapes and structures than dendrimers. They are prepared, respectively, by threading molecular wires through molecular rings or by interlocking molecular rings.

Some rotaxanes are depicted diagrammatically in Fig. 3.17. The word “rotaxane” means wheel axle (rota = wheel, axis = axle). Structurally, they consist of molecular rings threaded by molecular wires that have stoppers at both ends to keep the rings in place. When more than one ring is threaded by a single wire, the structure is called a polyrotaxane. Sometimes we encounter a rotaxane with no stoppers; these molecules are called pseudo-rotaxanes. These structures occur in naturally-occurring systems – some DNA enzymes are ring-shaped, and the DNA chain passes through the enzyme ring.

Researchers attempted to design and synthesize artificial rotaxane structures long before biological rotaxanes were discovered. A stepwise process involving the fixation of cyclic molecules, insertion of a linear molecule and then stopper fixation at both ends of this linear molecule, produced rotaxane structures in low yields, was reported in the 1960s. When supramolecular concepts were

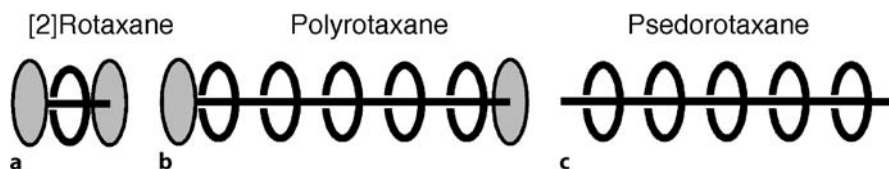


Figure 3.17. Structures of rotaxanes

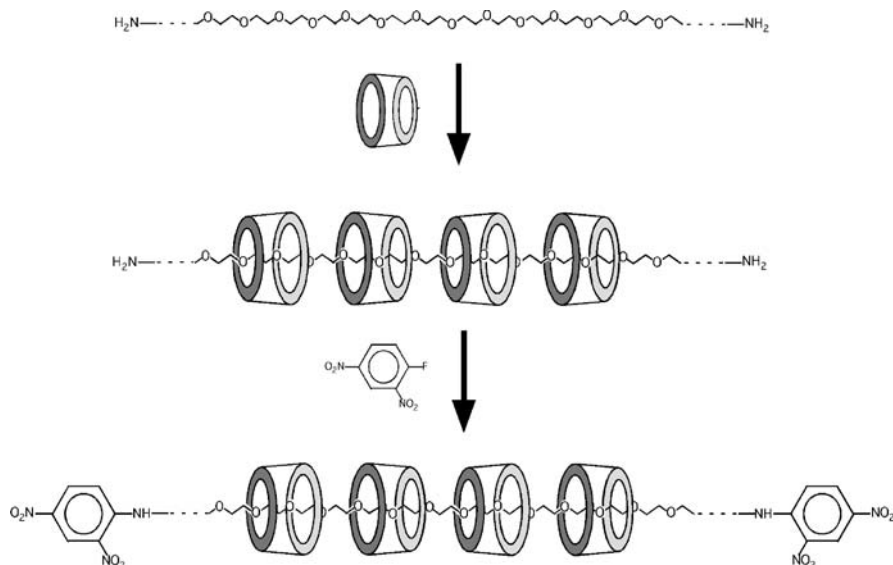


Figure 3.18. Cyclodextrin-based rotaxane

applied to rotaxane synthesis, the preparation efficiency increased. Threading wires into rings using intentional molecular interactions is a much more advantageous approach than accidental complexation.

Among the various cyclic molecules used in rotaxanes, cyclodextrin and crown ethers are the most useful due to their well-known molecular recognition properties. In particular, cyclodextrin can accommodate linear polymer such as polyethylene glycol in an aqueous phase. Therefore, a combination of cyclodextrin and a linear polymers as the ring and the wire, respectively, is one of the most useful candidates for rotaxane synthesis (Fig. 3.18). Harada reported that polymer chains thread cyclodextrin rings upon the addition of a water-soluble polymer into an aqueous cyclodextrin solution. Subsequent introduction of the stoppers results in the realization of rotaxanes. This rotaxane synthesis utilizes the fact that the polymer chains will be incorporated into the cyclodextrin rings. In the rotaxane structure obtained, the cyclodextrins align in a head-to-head (tail-to-tail) arrangement. Hydrogen bond formation between primary hydroxyl groups and between secondary hydroxyl groups stabilizes the cyclodextrin array.

If the cyclodextrins in the rotaxane structure are linked covalently, then the cyclodextrin array is maintained even after the stoppers and the polymer chain have been removed (Fig. 3.19). Reacting the cyclodextrins with epichlorohydrin under weak alkali conditions induces crosslinking between facing hydroxyl groups. The stoppers are then removed under stronger alkali

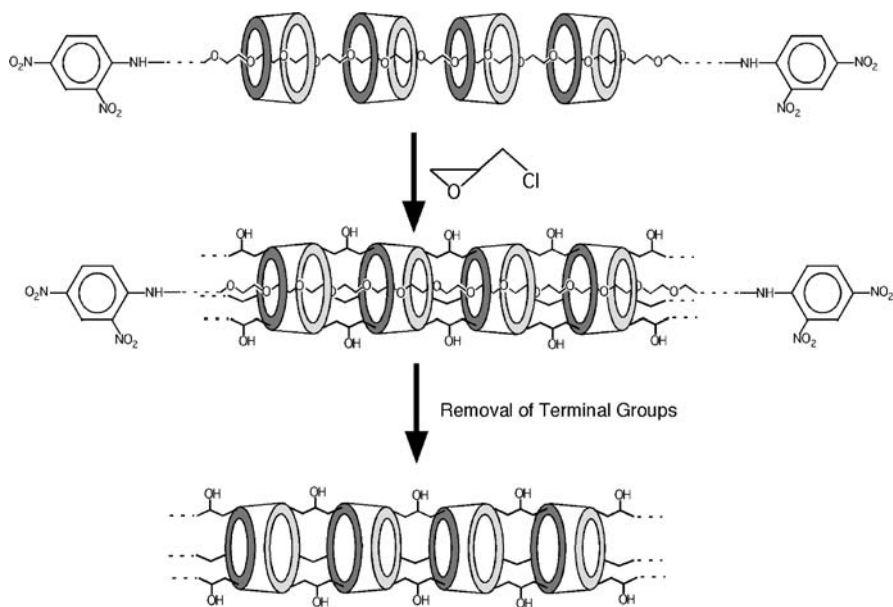


Figure 3.19. Cyclodextrin tube

conditions, and the chain is dissociated, giving a cyclodextrin tube. The tube obtained accommodates various guest molecules; slender guests have especially high affinity to the inside of the tube. Because the components of the tube are sugar units, the tube is soluble in water, unlike the carbon nanotubes previously described. Therefore, these cyclodextrin tubes have great potential in bio-related fields.

Other cyclic molecules can be also used for rotaxane formation. Figure 3.20 shows a rotaxane created via the molecular recognition of an ammonium salt by a crown ether. Cyclophane-based rotaxane has also been reported (Fig. 3.21).

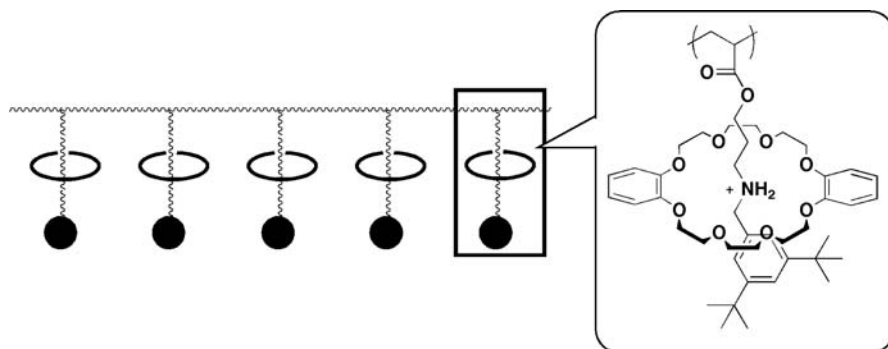


Figure 3.20. Rotaxane with a crown ether ring

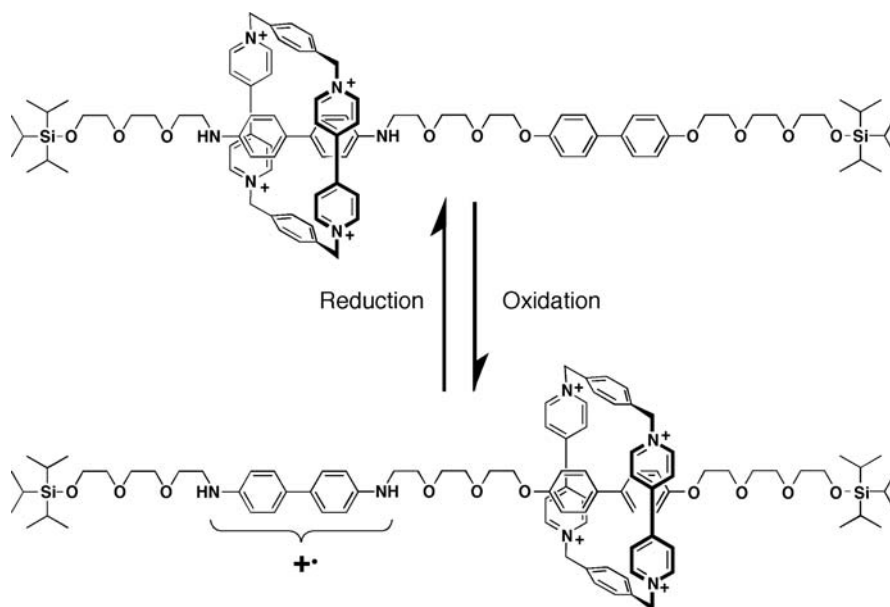


Figure 3.21. Molecular shuttle

In this structure, a cyclophane ring based on cationic viologens (an electron acceptor) is threaded by molecular wire with two kinds of biphenyl moieties. When the wire molecule is in a neutral state, the viologen ring positions itself near the benzidine moiety on the wire due to its stronger electron-donating ability. Oxidation of the benzidine unit to a cation radical form induces the viologen ring to move to the biphenol part of the wire due to electrostatic repulsion. This supermolecule is called a *molecular shuttle*, because the ring molecule shuttles between two biphenyl stations. The molecular shuttle is switched via redox-type external stimuli. This concept should prove useful in molecular device design (see Chap. 5).

3.5

Catenanes and Molecular Capsules – Complex Molecular Associations

While rotaxanes are composed of wires and rings, catenanes consist of two or more interlocked rings. The word “catenan” comes from the Latin word “catena”, which means linked chains. Although the interlocked rings in catenanes are not bonded together by covalent bonds, they cannot be separated from each other. The molecule is stabilized simply by spatial interlocking. This characteristic is different to other supermolecules, where specific interactions play crucial roles when fixing the structures of complexes.

Catenanes were first synthesized by Wasserman in 1960. The process relied upon accidental interlocking during macrocycle formation, meaning that reaction yields were low and large amounts of reactants were required. Around the same time, van Gulick proposed a more elegant strategy for catenane synthesis. The concepts behind this catenane preparation process were summarized from the view of topology. At first, van Gulick’s paper was not accepted and Wasserman was therefore recognized as the discoverer of catenane synthesis. Later on, however, van Gulick’s strategies of catenane synthesis were rediscovered by researchers, and his foresight was recognized. In 1993, the original paper written by van Gulick was officially revived.

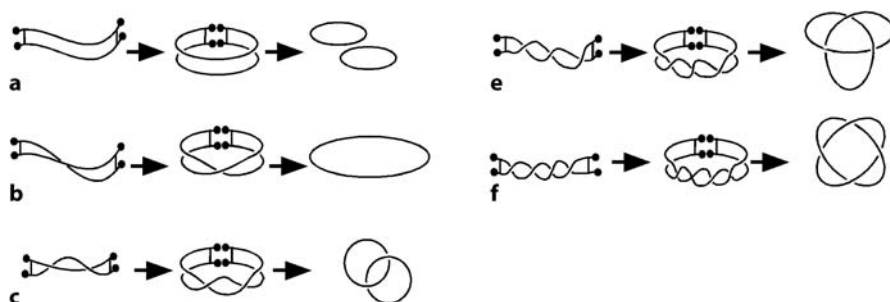


Figure 3.22. Strategies for catenane synthesis

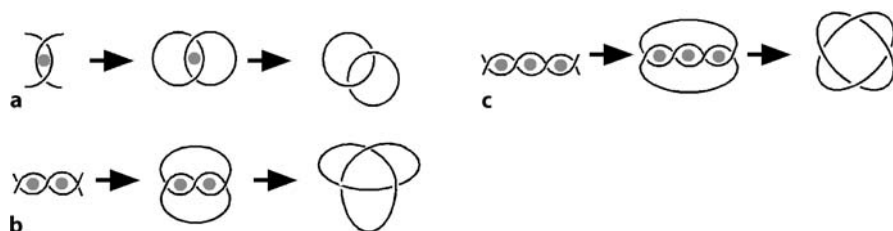


Figure 3.23. Catenane synthesis via molecular recognition

Van Gulick's concepts are briefly explained in Fig. 3.22. Consider two lines that are first fixed in space and then their ends are joined together (in other words, one of the ends of one line is joined to the nearest end of the other line, and then the other two ends are linked): step 1. Both ends of each line are then connected too (creating a loop): step 2. Finally, the bonds between the lines (created during step 1) are broken: step 3. The structures we obtain at the end of this process depend on the relative positions of the lines in the first place. If the lines do not cross (scenario a in Fig. 3.22), then two small rings are obtained. If the two lines cross once (scenario b), one large ring is obtained at the end. However, if the lines cross twice (the strings are twisted around each other; scenario c), we obtain two interlocked rings (a catenane). Crossing three or more times (even more twisting) produces even more complicated interlocking structures (scenarios d and e; these structures are called a molecular knot and a doubly-locked catenane, respectively).

As described above, the fixation of two lines that twist around each other is a key process. Complexation through appropriate molecular recognition satisfies these geometrical requirements. Strategies for catenane synthesis based on molecular recognition are summarized in Fig. 3.23. The recognition of one guest by the two different chains introduces two twisting points. Cyclization of these chains results in the formation of catenane. Two-guest recognition and three-guest recognition lead to the formation of a molecular knot and a doubly-locked catenane, respectively. It is necessary to fix the molecular geometry of the recognition system, and so interactions with defined molecular geometries, such as metal coordination, hydrogen bonding and $\pi-\pi$ interactions are often used for these designs.

The example shown in Fig. 3.24 illustrates catenane preparation via tetrahedral coordination of Cu(I). In the first process, two phenanthroline ligands coordinate to Cu(I). Each ligand is individually cyclized via hydroxyl groups attached to the ligand unit. Removal of Cu(I) completes catenane formation. In this strategy, each step is logically designed. Therefore, the yield is much better in this case than for the method relying on accidental interlocking. Syntheses of molecular knots and doubly locked catenanes based on a similar strategy have also been reported. Furthermore, molecules with five interlocked rings (similar to the symbol used for the Olympic Games) have also been achieved.

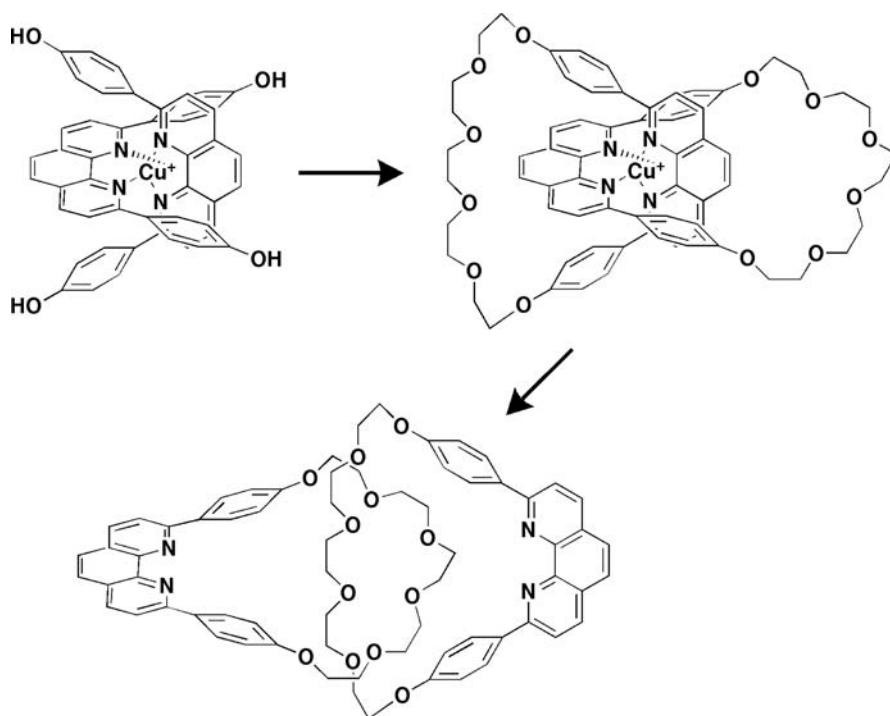


Figure 3.24. Catenane synthesis via Cu^+ coordination

Instead of using a metal ion as a “clasp”, it is also possible to use weak interactions between ring components for catenane interlocking. In the example shown in Fig. 3.25, a C-shaped precursor containing viologen-type cyclophane was complexed to a cyclophane with benzene ring moieties. The cationic bipyridine moiety in the C-shaped component was then sandwiched by electron-rich benzene units. Cyclization of the C-shaped precursor using a dibromo compound resulted in interlocked catenanes. This electronic interaction between two kinds of species results in more efficient catenane formation.

Supramolecular interactions are an important factor in catenane formation. Such interactions can be disrupted after the catenane has been built, making the catenane structure more flexible. This flexible nature can be an advantage because the catenane structure is then free to respond when external stimuli are applied. The catenane shown in Fig. 3.26 is one example where this structural flexibility is utilized. One of the rings of this catenane contains two kinds of ligands, and the nature of the coordination to the copper ion depends on the oxidation number of the copper. When the copper ion is in the $\text{Cu}(\text{I})$ state, four-way coordination is stabilized. However, five-way coordination becomes more favorable upon oxidation to $\text{Cu}(\text{II})$, and to accommodate this, the ring rotates

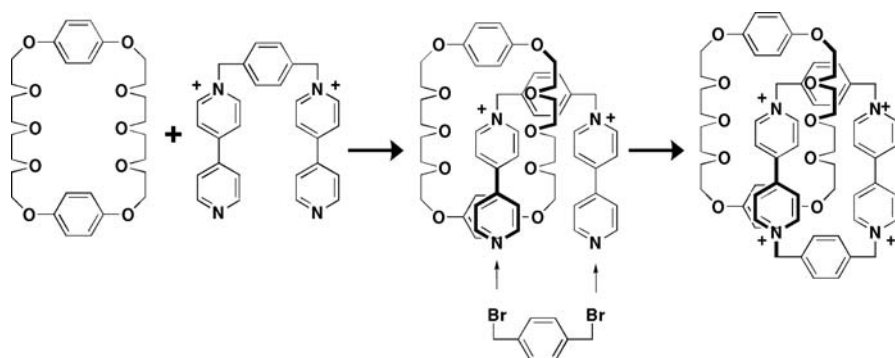


Figure 3.25. Catenane synthesis from a polyether ring and a C-shaped cyclophane precursor

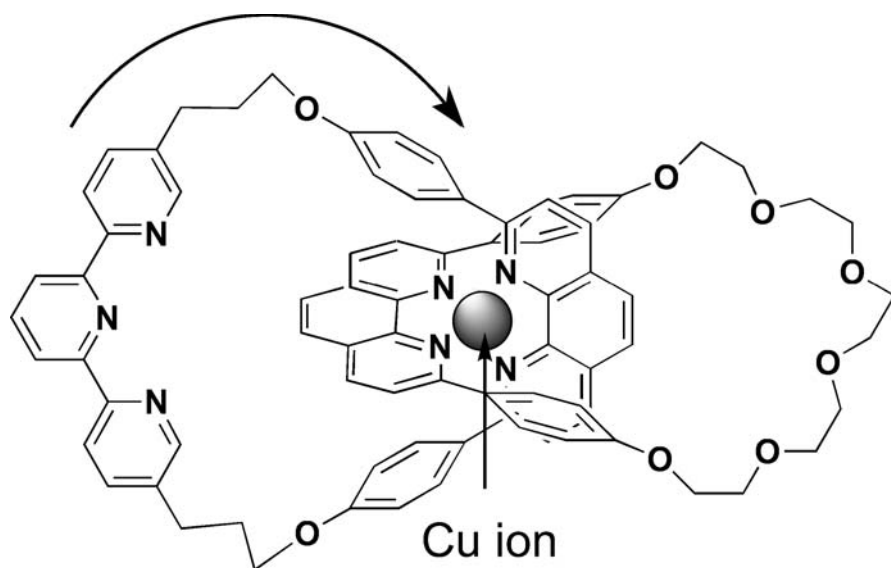


Figure 3.26. Molecular motor based on a catenane structure

so that the other ligand (which is a ligand with three coordination sites) ligates with the copper. This ring rotation upon oxidation means that the system can be regarded as a molecular motor driven by redox stimuli.

Catenane synthesis can be also achieved by dynamic molecular association. Figure 3.27 shows an example of catenane preparation through the dynamic formation of a palladium (Pd) complex. Mixing the Pd complex with pyridine-type ligands in water induces the formation of both a monocyclic structure and an interlocked catenane. An equilibrium exists between these two structures, and the catenane structures are more favorable at higher concentrations. In the catenane structure, the benzene rings stack next to each other due to favorable

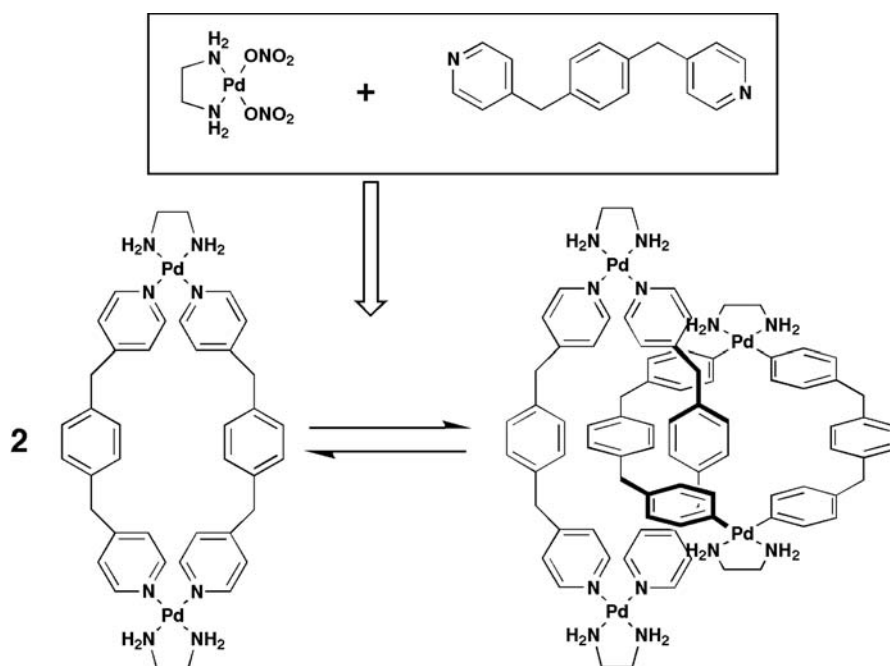


Figure 3.27. Catenane formation through a self-assembled process

hydrophobic interactions. Therefore, increasing the polarity of the medium induces more efficient formation of the catenane structure. In this system, catenane formation is based on a spontaneous molecular association that can be controlled by adjusting the surrounding environment. This strategy is an elegant use of the concepts of supramolecular chemistry.

The key to the formation of this catenane is the highly-defined structure, where the ligand–Pd–ligand coordination angle is fixed at 90° . If we extend this concept, complexes of various shapes can be formed. The structure of the complex formed depends significantly on the geometry of the ligands. This represents an attractive approach in supramolecular chemistry. Figure 3.28 shows the formation of a supramolecular complex from a planar tris-pyridine-type ligand with a coordination angle of 120° . Four ligands and six palladium atoms provide a cage structure. This structure can be obtained quantitatively in a spontaneous process by simply mixing two components in water, and organic guest molecules can be trapped inside it. Specific reactions required to trap molecules have also been reported.

Many complexes of various shapes can be obtained through the appropriate design and use of ligands. When a rectangular ligand with pyridine groups pointing in opposite directions was used, a tube-shaped complex was obtained by connecting four rectangle panels (Fig. 3.29). Simply mixing the two kinds of

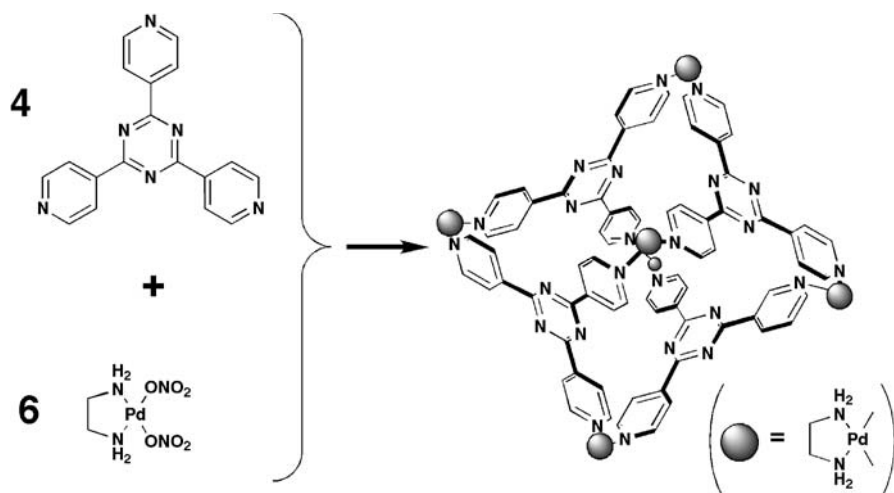


Figure 3.28. Molecular cage realized upon coordination between Pd ion and ligand

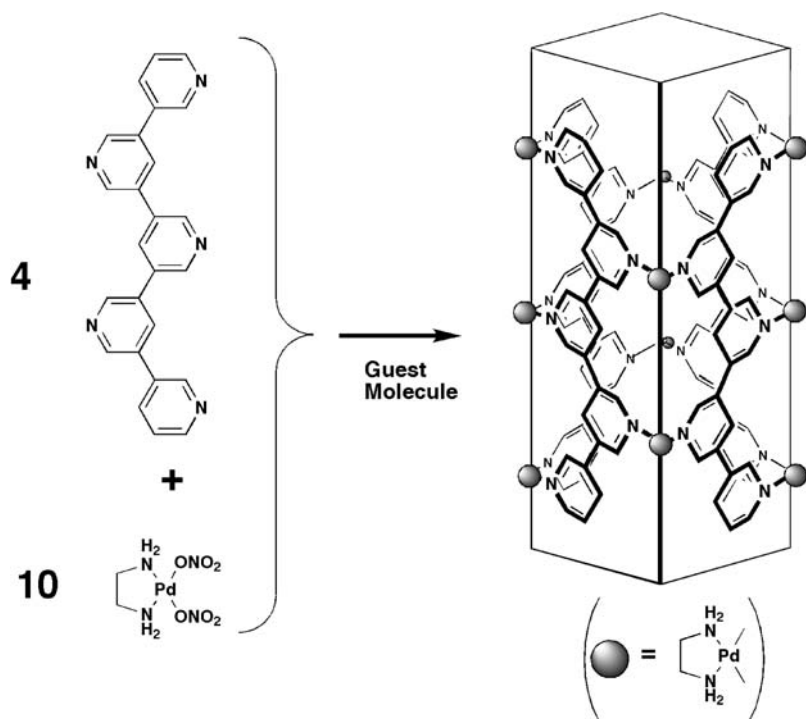


Figure 3.29. Molecular tube

components gives a mixture of randomly complexed oligomers. Interestingly, the addition of biphenyl guests converged the mixture into a single component – the tube. This process can be regarded as template synthesis. Use of a pyrimidine unit instead of pyridine also changes the complex formation. As shown in Fig. 3.30, a ligand with three pyrimidine units induces the formation of a huge molecular capsule comprising 24 components.

In another example of molecular capsule synthesis, DNA-based capsule formation has been reported. In the example shown in Fig. 3.31, a three-way junction was formed from an equimolar mixture of three programmed oligo-DNA chains. Since this junction had attractive “sticky ends”, the mixture then further self-assembled into a nanocage.

To summarize, in this chapter we have discussed medium-sized supermolecules with unique shapes. Some of them (fullerenes and carbon nanotubes) are found in nature, while others (dendrimers, rotaxanes and catenanes) can be synthesized via artificial molecular design. As seen from palladium-based molecular capsule formation, spontaneous association can sometimes also provide highly sophisticated supramolecular structures. Indeed, as

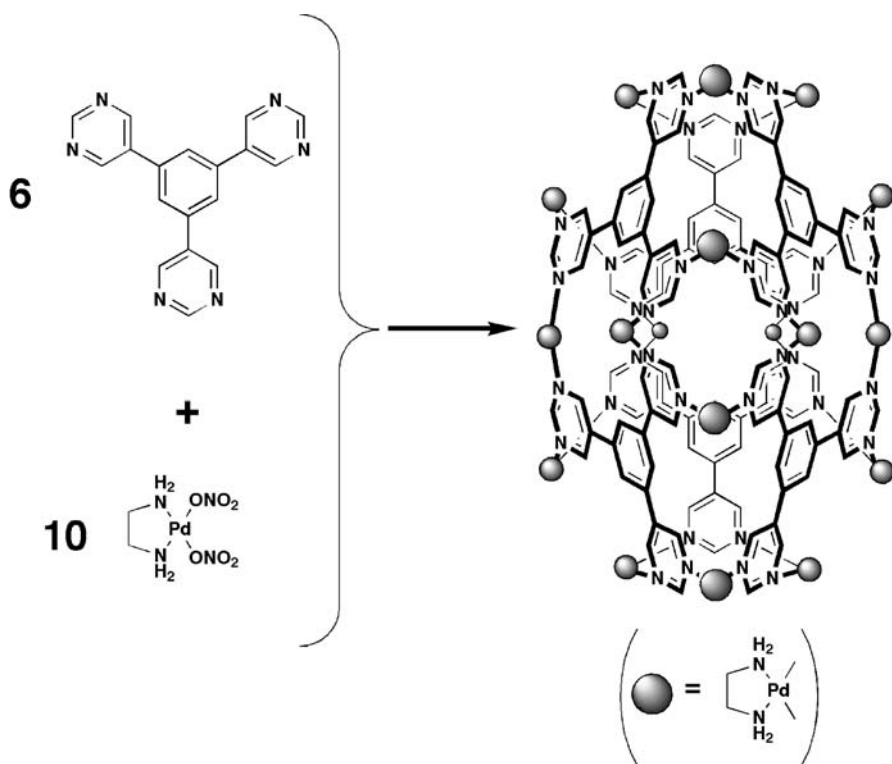


Figure 3.30. Molecular capsule

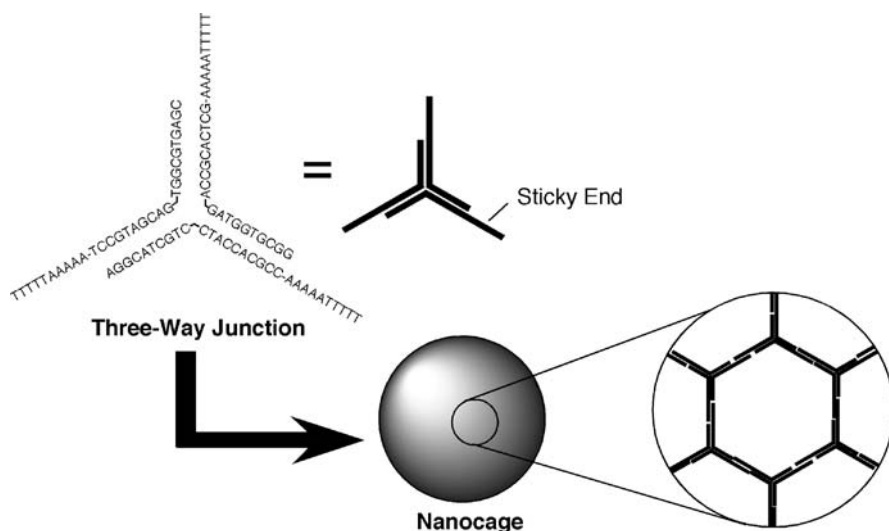


Figure 3.31. DNA nanocage

we will see in the next chapter, spontaneous association – self-assembly – is an indispensable tool when building large-scale highly-organized supramolecular systems.

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4 Molecular Self-Assembly – How to Build the Large Supermolecules

In the previous chapters, we discussed supermolecules formed from relatively small numbers of component molecules are discussed. Since the resulting supermolecules are therefore also quite small, isolating the individual supermolecules is often a tough task, which makes it difficult to apply these supermolecules to practical fields. Although sophisticated techniques for treating individual supermolecules are under development, a more realistic approach might be to design and build larger supermolecules.

In this chapter, structures and techniques that can be used to fabricate supermolecules created from huge numbers of component molecules are introduced. The supermolecules described in this chapter result from self-assembling (or self-organizing) processes, and are thus called supramolecular assemblies. The driving forces for these self-assembling processes have classified into two categories: precisely defined recognition and fuzzy molecular interaction. In this chapter, supramolecular assemblies are classified according to the precision of the forces driving assembly. Methods for controlling molecular assembly and arrangement are also explained.

Contents of This Chapter

4.1 Programmed Supramolecular Assembly Precise molecular recognition between molecules produces a well-defined complex. Multiple complex formation therefore leads to a supramolecular assembly with a defined shape and structure. The structure of the supramolecular assembly formed can be regarded as being “programmed” by structural information in the unit structure.

4.2 Supramolecular Crystals Using molecular recognition via specific interactions such as hydrogen bonding and metal coordination, it is possible to form well-designed crystal structures. Specific recognitions and reactions can be achieved in these supramolecular crystals.

4.3 Macroscopic Models of Supramolecular Assembly By controlling interactions between specific surfaces in millimeter-sized structures, it is possible to mimic molecular assembly and specific assembly.

4.4 Supramolecular Assembly via Fuzzy Interactions The driving force for molecular assembly is not always precise and specific. Molecular self-assemblies can also be formed through fuzzy interactions, and these assemblies are relatively flexible.

4.5 Structures and Formation Mechanisms of Cell Membranes Cell membranes are molecular assemblies driven by rather weak and nonspecific interactions. However, they are flexible in nature and express incredibly high functionality.

4.6 Micelles – Dynamic Supramolecular Assemblies The micelle is the simplest molecular assembly. It is composed of amphiphilic molecules and has a dynamic nature.

4.7 Liposomes, Vesicles and Cast Films – Supramolecular Assemblies Based on Lipid Bilayers Amphiphilic molecules or lipid molecules sometimes form double-layer structures. This structure is called a bilayer structure, and it can be used to model a cell membrane.

4.8 Monolayers and LB Films – Controllable Layered Assembly Some types of amphiphile form monolayer structures on the surface of water. These compressed monolayers can be transferred onto a solid support in a layer-by-layer manner. This permits well-oriented multilayers to be created with defined numbers and sequences of layers.

4.9 Self-Assembled Monolayers – Monolayers Strongly Bound to Surfaces Well-oriented self-assembled monolayers can be prepared on a solid support using strong interactions between an amphiphile and a solid surface. Self-assembled monolayers are often used for surface modification and functionalization.

4.10 Alternate Layer-by-Layer Assembly – Supramolecular Architecture Obtained with Beakers and Tweezers The alternate layer-by-layer assembly technique allows us to prepare molecularly controlled films using very simple and inexpensive techniques. This method is applicable to a wide range of substances, such as polyelectrolytes, proteins and colloidal particles.

4.11 Hierarchical Higher Organization – From Bilayers to Fibers and Rods Amphiphile assembly sometimes results in higher order supramolecular assemblies. Fibrous structures and helical ribbons with molecular dimensions are formed spontaneously.

4.12 Artificial Molecular Patterns – Artificially Designed Molecular Arrangement

Patterned arrangements of crystals and carbon nanotubes can be prepared by combining a patterning technique with self-assembly or self-growth processes.

4.13 Artificial Arrangement of Molecules in a Plane – Two-Dimensional Molecular Patterning

Artificial molecular arrangement via specific molecular recognition can be used to create two-dimensional patterns. Assembling rigid molecules known as molecular tiles results in regular molecular patterns on water.

4.1 Programmed Supramolecular Assembly

In the previous chapters, we have concerned ourselves with molecular recognition via hydrogen bonding and coordination interactions where a host molecule interacts precisely with a guest molecule to form a relatively small supermolecule. The geometry of the host-guest complex is dictated by the relative positions of the interacting functional groups, and applying many of these recognition pairs leads to the construction of assemblies with well-defined shapes. One way of looking at this process is that the structure of the supramolecular assembly is programmed in the molecular units that it is constructed from. Interestingly, this concept is widely seen in nature. For example, the three-dimensional structures of proteins are defined by their amino acid sequences; in other words, the structure of a protein is programmed in its amino acid sequence.

We can find examples of programmed supermolecules among those described in the former chapters. For example, molecular capsules composed of palladium and pyridine-type ligands (see Figs. 3.28 to 3.30) can be regarded as programmed supermolecules. The shape and structure of the molecular capsule formed is determined by the structures of the ligands in the initial complex (the number of pyridine units and their geometries). Therefore, the final assembled structures are programmed in the structures of the ligands.

In programmed systems, the structural information in the units must be transferred precisely to the assembly. An interesting example of this is shown in Fig. 4.1, where the formation of supermolecules composed of Cu^+ ions and ligands with two, three and four pyridine units is depicted. Each Cu^+ ion coordinates with two pyridine units, inducing a helical complex that is called a helicate. When Cu^+ ions are added to a mixture of the ligands, complexes with random ligand combinations are initially formed, but then spontaneous ligand exchange occurs, forming size-matched helicates. The size-matched helicates use all of the binding sites and should therefore be more stable. Therefore, less stable hetero-ligand complexes are gradually weeded out. This process

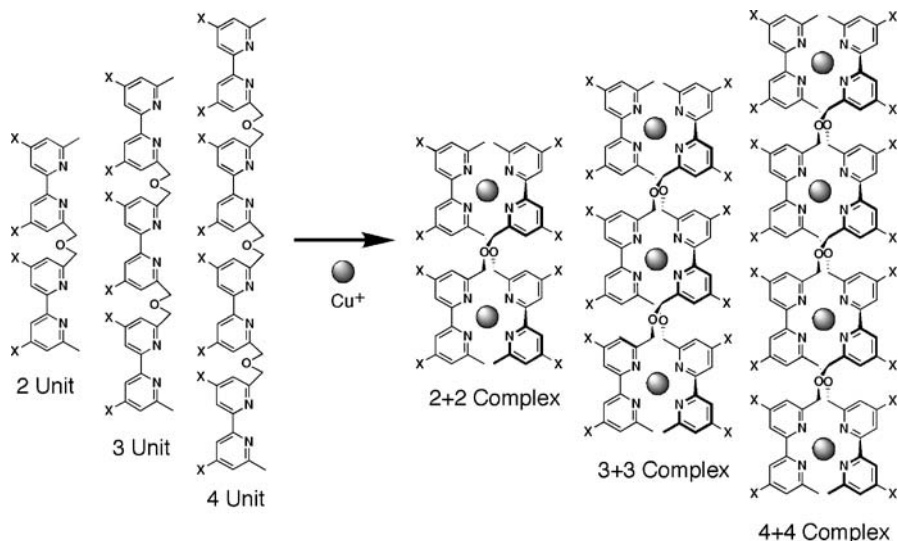


Figure 4.1. Selective formation of helicates

can be regarded as the natural selection of programmed supermolecules from random mixture.

This helicate formation mechanism can be extended to interactions with other materials. In the example shown in Fig. 4.2, ligands carrying nucleobases are used. The helicate forms a helical structure similar to the double helix of DNA, where the nucleobases in the helicate are on the outside of the helix. This helicate can form complexes with actual nucleic acid through complementary base pairing. The artificial supramolecular complex can “read the programs” of naturally-occurring molecules.

The structures of metal–ligand supermolecules can be controlled by selecting appropriate components. In the example shown in Fig. 4.3, a grid-type supermolecule was formed from Ag^+ and another type of ligand. Changing the program (changing the unit structure) results in a drastic change in the assembled structure.

The formation of shape-defined supermolecules requires direction-specific molecular interactions. Metal–ligand interactions satisfy this requirement. Hydrogen bonding is another good candidate because hydrogen bonding requires a specific geometry for the pair of interacting components. When a hydrogen-donating group (donor, D) and a hydrogen-accepting group (acceptor, A) are oriented favorably to each other at an appropriate distance, a hydrogen bond is formed. Therefore, hydrogen bonding is important interaction when precise recognition of molecules is required. Two molecules with complementary sites of donor groups and acceptor groups form particularly strongly interacting pairs. Nature makes good use of this concept. For example, ex-

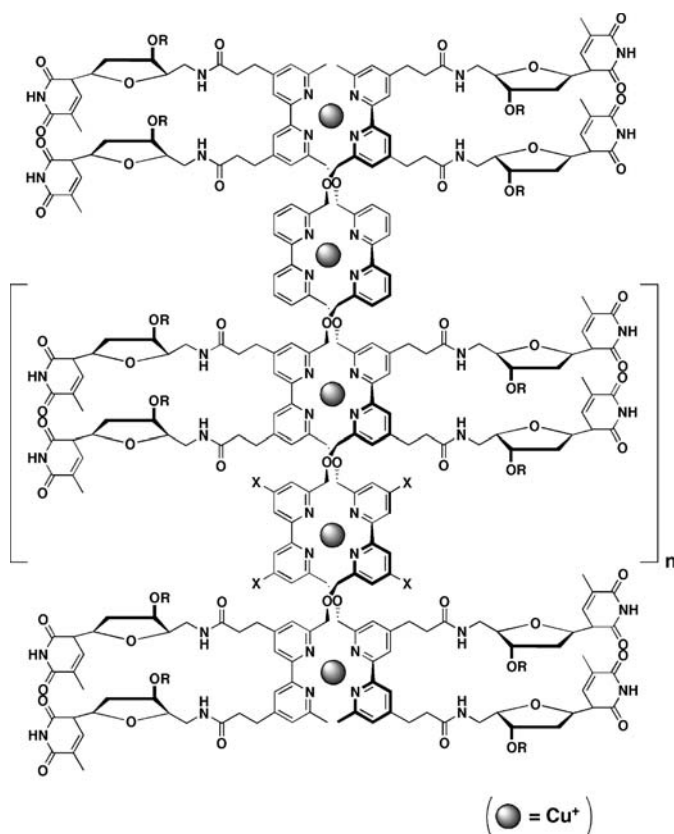


Figure 4.2. A helicate with a nucleobase-type ligand

act DNA replication relies upon complementary hydrogen bonding between nucleobases.

Figure 4.4 shows the formation of supramolecular assemblies from pairs of molecules that have complementary hydrogen bonding sites. Molecule a has two ADA sites (A, hydrogen-accepting site; D, hydrogen-donating site), while two DAD sites exist on molecule b. Therefore, molecules a and b form complementary hydrogen bonding pairs (ADA–DAD). The presence of two bonding sites on each molecule means that each molecule can bond to two others, which can lead to the formation of extended supramolecular assemblies. However, the molecules a and b can also bond in two different geometries due to their particular shapes, leading to different supramolecular assemblies. An infinitely extended supramolecular ribbon structure (c) is formed when a and b always hydrogen-bond in a geometry where the R and R' groups are facing in opposite directions. However, when a and b always bond with a relative angle of 60° between the R and R' groups, a closed circular assembly is formed (d).

When both bonding geometries are present in the same supermolecule, the assembly has a winding tape-like structure. The proportions of the different assemblies produced depends on the bulkiness of the substituent groups R and R'. In order to increase the “programming precision”, the sequences of hydrogen bonding sites on the molecules need to be rearranged. For example, the molecule shown in Fig. 4.5 contains both an AAD face and a DDA face. This molecule can self-assemble via hydrogen bonding, but in this case only one binding mode is possible, resulting in a ribbon-like supermolecule.

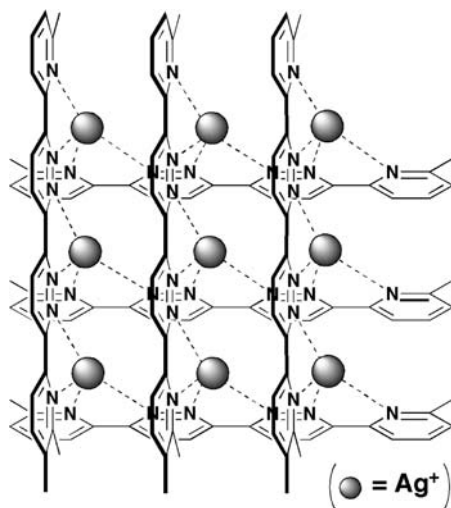


Figure 4.3. Molecular grid

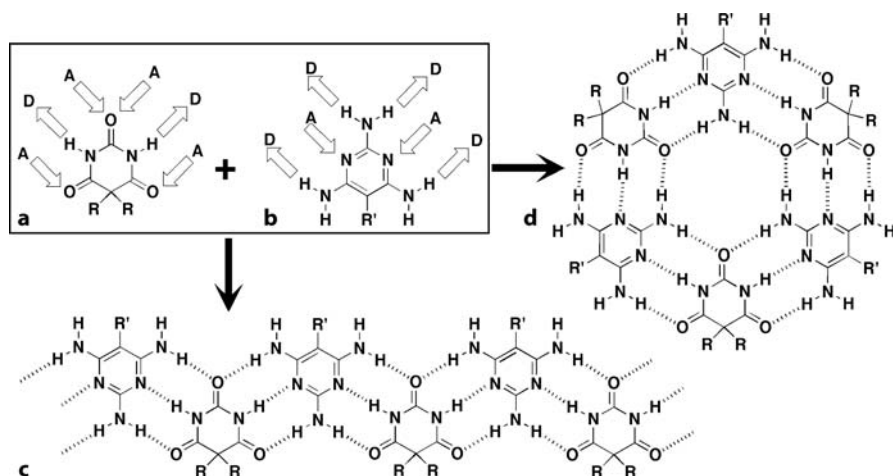


Figure 4.4. Supramolecular assemblies formed via complementary hydrogen bonding

In the above-mentioned examples, the recognition sites exist on the same aromatic ring. However, molecules containing two recognition sites in different parts of the molecule, connected through spacer unit, are also possible. The structures of the assemblies created from such molecules are dependent upon the design of the spacer part. In the example shown in Fig. 4.6, the spacer is a tartaric acid derivative that possesses two chiral centers. Two components with diamidepyridine (DAD type) and uracil (ADA type) binding sites were prepared separately. Because these binding sites form a complementary hydrogen bonding pair, mixing of these components resulted in the formation of a tape-like supramolecular assembly. The assemblies formed arranged themselves into helical filaments. Right-handed and left-handed helices were obtained according to the chiral sense of the tartarate spacer moiety.

Melamine and cyanuric acid is a typical combination used to obtain hydrogen-bonded assemblies. An investigation of the formation of this complex revealed the importance of thermodynamic factors during supramolecular formation (Fig. 4.6). Three melamine units can form a closed cyclic complex with three cyanuric units (a). Fixation of the melamine units is advantageous when forming the closed complex and the efficiency of complex formation was found to depend on the flexibility of the spacer chains. Use of a tris-melamine unit with a rigid spacer (c) resulted in a more stable complex than that yielded by a tris-melamine unit with flexible spaces (b). In general, such supramolecular complex formation is enthalpically favorable but is sometimes entropically unfavorable upon conformational freezing. If the latter entropic disadvantage is suppressed, complex formation becomes more favorable thermodynamically. The conformational freedom in the tris-melamine unit with

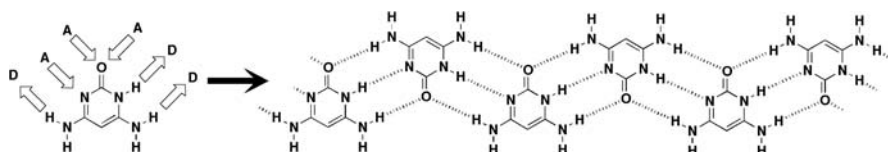


Figure 4.5. Hydrogen-bonded assembly from one component

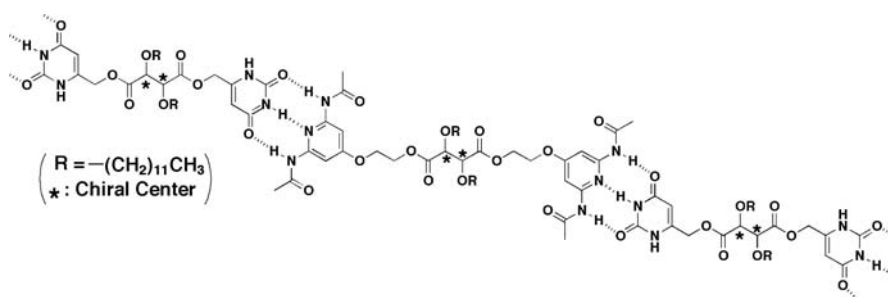


Figure 4.6. Supramolecular assembly with chiral centers

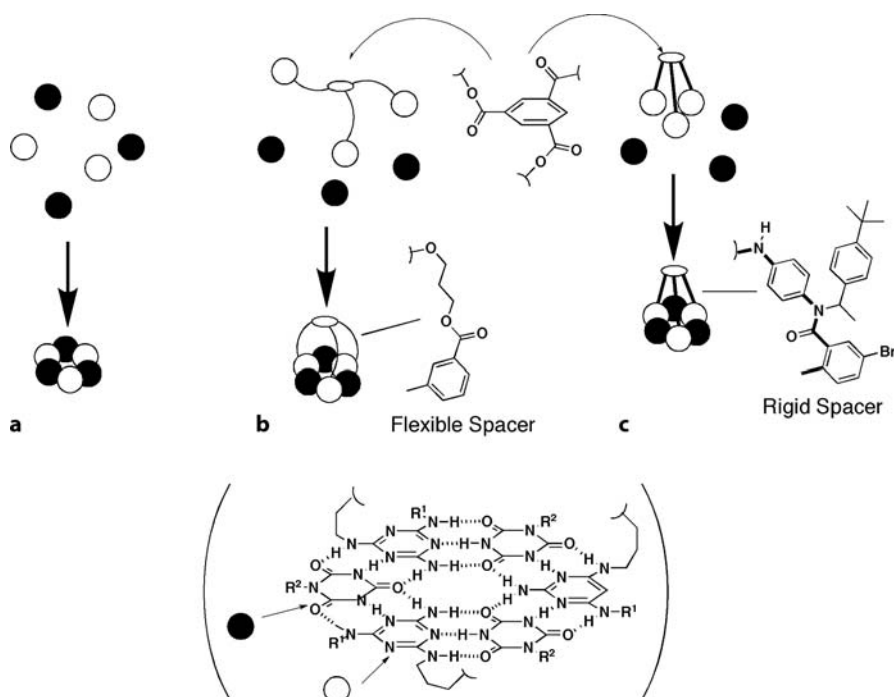


Figure 4.7. A molecule with rigid spacers forms a stable complex

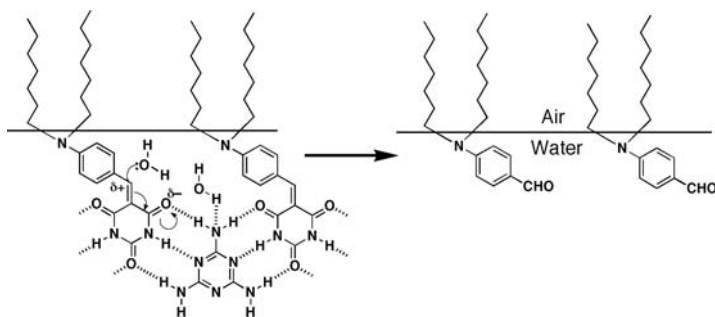


Figure 4.8. Water trapped in a hydrophobic environment near a hydrogen bonding network has high nucleophilicity

rigid spacers is restricted. Therefore, the loss of entropy upon binding with cyanuric acids is not as great as for the tris-melamine unit with flexible spaces, and so complex formation is more favorable. These examples show the importance of constructing the molecular units appropriately before supramolecular assembly.

An enzyme-like specific environment was mimicked using a supramolecular assembly based on a hydrogen bonding network. In the example depicted in

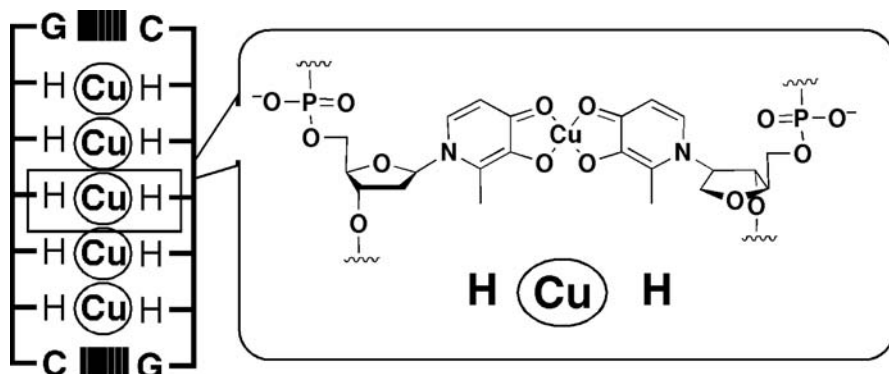


Figure 4.9. Metal–ligand coordination inserted in a DNA sequence

Fig. 4.8, a monolayer of a barbituric acid derivative forms a hydrogen bonding network with aqueous triaminopyridine. Interestingly, cleavage of carbon–carbon double bonds was detected in this system. Upon the formation of the hydrogen bonding network, a few water molecules were trapped in a hydrophobic environment at the air–water interface. This enzyme-like behavior was explained by the enhanced nucleophilicity of the trapped water in this environment and the geometry associated with the reaction.

As mentioned above, metal–ligand coordination and hydrogen bonding play important roles in the formation of programmed assemblies. In fact, these interactions can sometimes be exchanged. The base-pairing in DNA is supported by hydrogen bonding, which is replaced by metal–ligand coordination in the example in Fig. 4.9. The nucleobase part of the DNA is substituted by ligand H, and they are coupled through copper. Since various metal–ligand combinations are available, this makes it possible to add new alphabets in DNA sequences.

4.2 Supramolecular Crystals

In the previous section, we described the formation of supramolecular assemblies via precise programs based on metal coordination and hydrogen bonding. When sizes of assemblies created in this way become significantly large, they become practical materials with structures that can provide interesting functionality. For example, regular crystalline structures provide intermolecular spaces with defined sizes and shapes where specific recognition and the other related functionality can be expected.

Various supramolecular crystals have been reported. Several examples of unit molecules used to build supramolecular crystals are summarized in Fig. 4.10. Perhydrotriphenylene (a), 9,9'-bianthryl (b), cyclophosphazene (c)

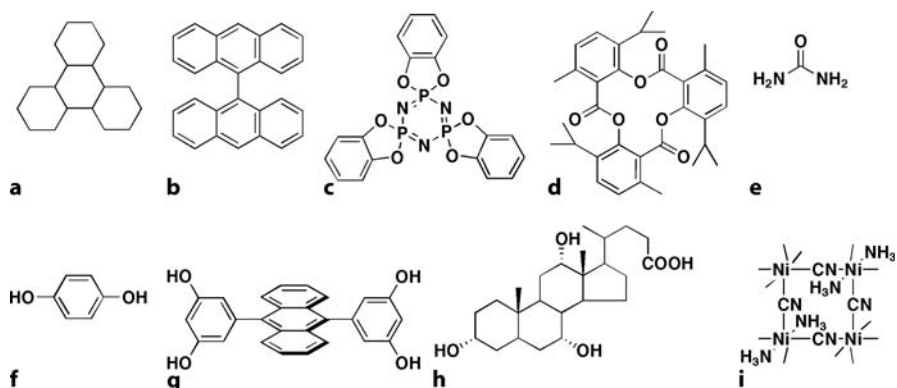


Figure 4.10. Unit molecules that form supramolecular crystals

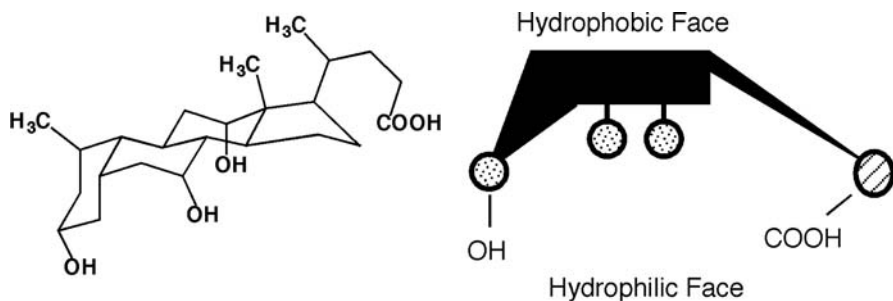


Figure 4.11. Cholic acid

and tri-*o*-thymotide (d) form crystals through van der Waals interactions. The first two molecules crystallize in such a way as to give cylinder-shaped intermolecular spaces and the latter two cage-type intermolecular spaces. Urea (e), hydroquinone (f), anthracene bisresorcinol (g) and cholic acid (h) form crystals through hydrogen bonding. Unique intermolecular spaces are formed due to the lattice-type metal–ligand linkages observed in the Hoffman complex (i).

Of these examples, crystals of cholic acid are amongst the most well-known. Cholic acid has a rigid shape and a hydrophilic face and a hydrophobic face located back-to-back (Fig. 4.11). The four hydrogen bonding sites in this molecule cannot form intramolecular hydrogen bonds and crystal structures are formed via intermolecular hydrogen bonding. Several combinations of hydrogen bonding pairs are possible. Depending on the hydrogen bonding mode, polymorphous crystals with various types of intermolecular spaces are created. Because the cholic unit has both hydrophilic and hydrophobic faces, these intermolecular spaces have unique polar characteristics. Guest accommodation modifies the intermolecular spaces, as shown in Fig. 4.12. Without any guests, the cholic acid forms the crystals depicted schematically in (a),

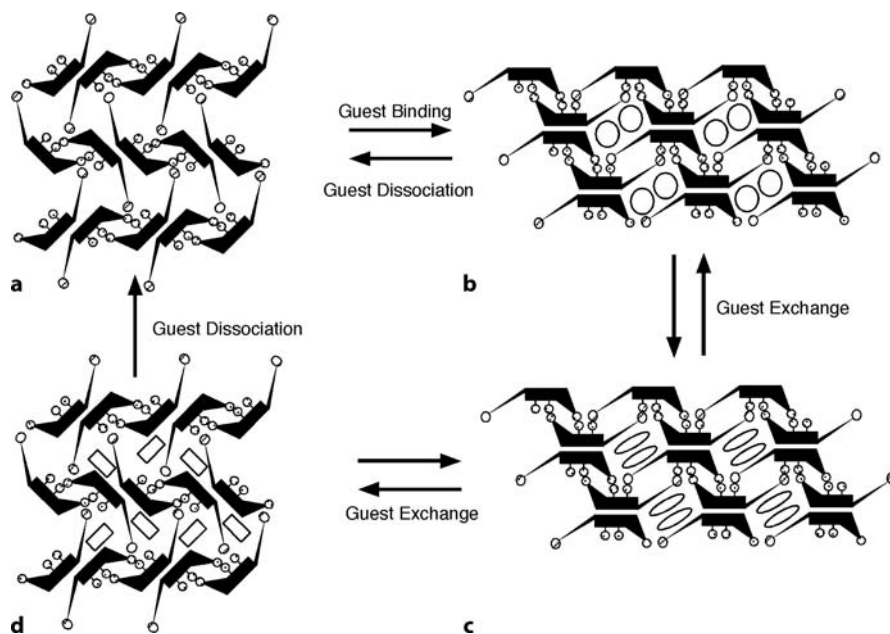


Figure 4.12. Presence of guests change the crystal structure

but the presence of some types of guest alters this morphology to another (b) because the hydrogen bond pairings are swapped. The interactions between hydrophobic faces is only based on relatively weak van der Waals interactions. Therefore, guest exchange without the need to rearrange the hydrogen bonding pattern is possible (c), although the binding of some types of guest can induce a change back to the original crystal structure due to another swap of hydrogen bonding pairs (d).

Anthracene and porphyrin molecules with resorcinol functions on both sides are known to form supramolecular crystals. As shown in Fig. 4.13, hydrogen bonds are formed between the hydroxyl groups of the resorcinol moieties. The rigid backbones (anthracene or porphyrin) are almost perpendicular to the hydrogen bonding network. Therefore, guest-accepting spaces with hydrogen-donating sites are created periodically in the structure. For example, molecules with hydrogen-accepting group such as ketones and esters are stoichiometrically trapped in these spaces. Guest molecules trapped in the molecular spaces have limited mobility and specific orientations. These characteristics lead to the regulation of reactivity and selectivity during reactions between trapped molecules. For example, the Diels–Alder reaction between an acrolein derivative and 1,3-cyclohexadiene was accelerated in this way. The selectivity of the endo-product over the exo-product was enhanced (Fig. 4.14).

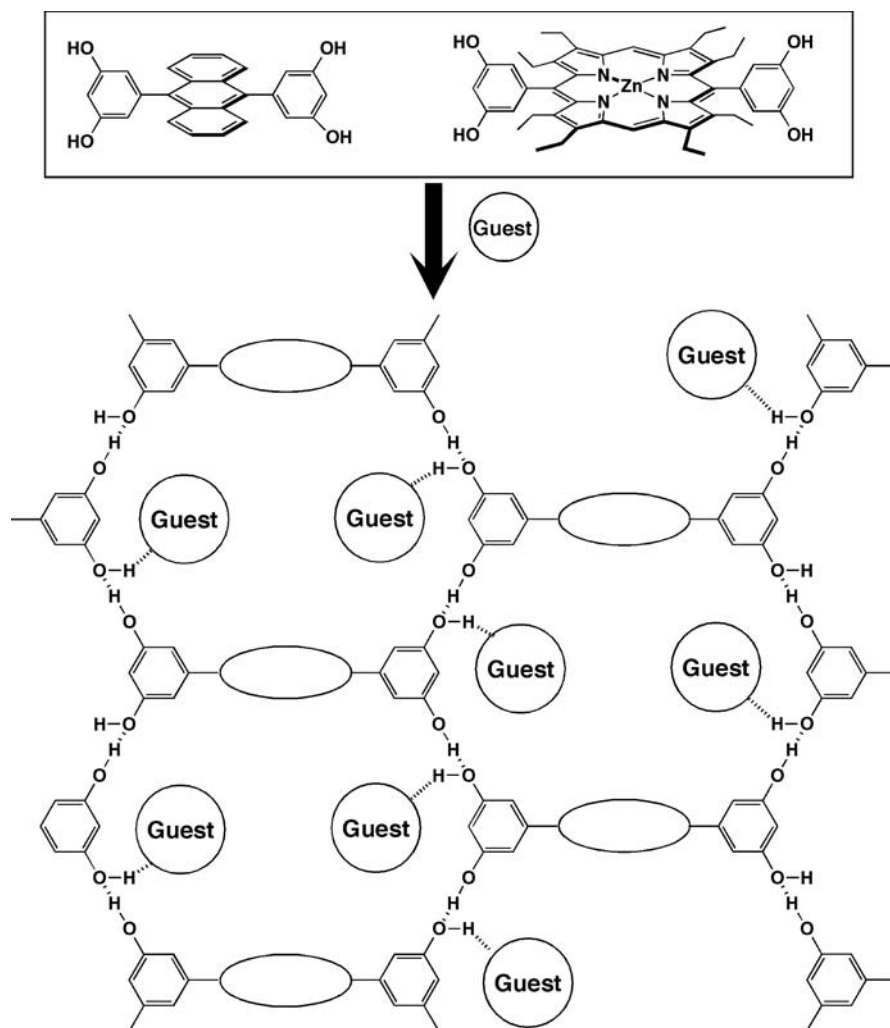


Figure 4.13. Guest molecules trapped in a crystalline cavity

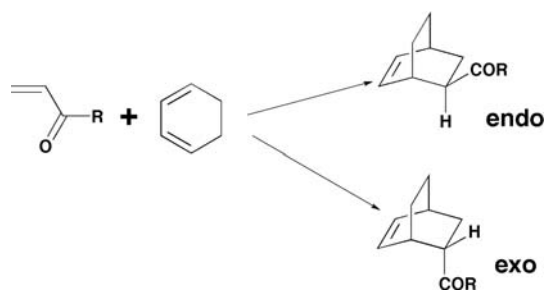


Figure 4.14. Diels-Alder reaction performed in a supramolecular crystal

4.3 Macroscopic Models of Supramolecular Assembly

Before we change topic from precisely programmed assemblies to fuzzy assemblies, we will first digress to consider some unique models. The models described in this section are artificial assemblies that are large enough to be visible, but they still have the characteristics of a molecular assembly. At the molecular level, geometric and sequential matching of interacting functional groups is crucial to specific guest recognition. As we have noted in previous chapters, this feature can be compared to a lock and key mechanism. However, inverting this comparison, a real lock and key can also imitate molecular recognition: we can create visible models of supramolecular assembly. One example is shown in Fig. 4.15, based on millimeter-sized hexagonal pieces with hydrophilic and hydrophobic faces in arranged alternately. When these pieces were placed at the interface of hydrophobic perfluorodecalin and water, the pieces spontaneously assembled in such a way as to group hydrophobic faces together in order to avoid the unfavorable exposure of the hydrophobic

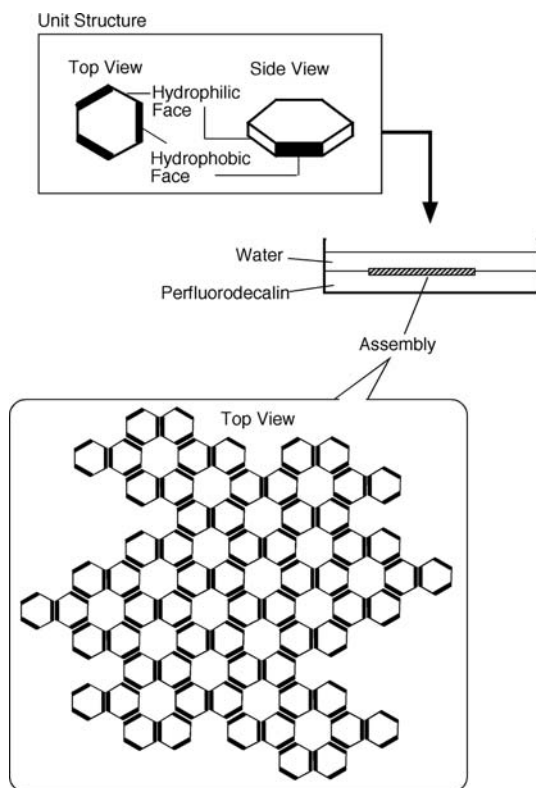


Figure 4.15. Millimeter-sized model of supramolecular assembly

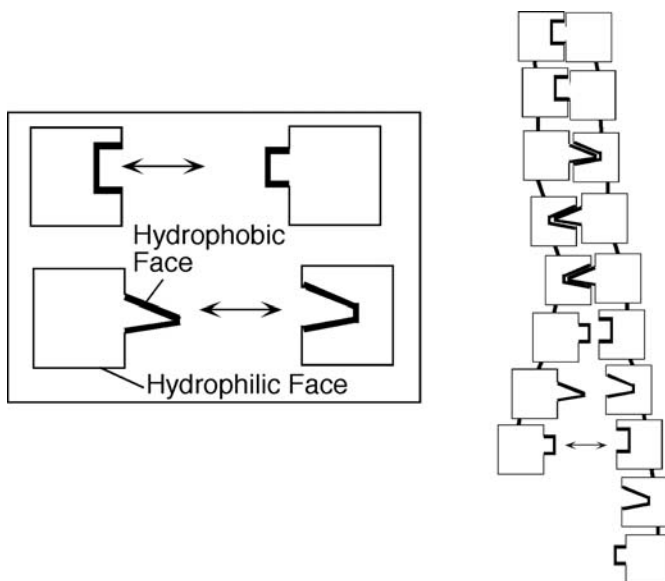


Figure 4.16. Millimeter-sized model of DNA hybridization

faces to water. This can be regarded as recognition between specific faces. This assembly process results in the formation of a regular honeycomb structure. Changing the shape of the unit piece and the arrangement of the hydrophobic faces leads to the creation of various regular macroscopic assemblies. This process is reminiscent of the formation of supramolecular assemblies from programmed molecular units.

A more interesting model is depicted in Fig. 4.16, where four different pieces with different shapes of hydrophobic faces are used. These four pieces form two kinds of pairs through contact between complementary shapes. These pieces are linearly connected in a specific sequence and floated on water. This macromodel of a polymer can form pairs most efficiently with another macromodel with a complementary sequence. This macromodel mimics hybridization processes of nucleic acids. Although these visible macromodels are not actual supermolecules, they do still imitate the mechanism of supramolecular recognition.

4.4

Supramolecular Assembly through Fuzzy Interactions

We have seen that multiple use of a precise recognition process leads to well-designed supramolecular assemblies. The structure of the assembly formed is programmed in the original pieces. Highly precise design of the recognition pair should lead to the formation of a precisely defined structure. Such

a precise structure would be expected to yield highly precise functionality. However, high precision is not always advantageous for some kinds of function. Supramolecular assemblies based on less precise recognition processes sometimes produce more flexible, sensitive and adaptable functionality. Such systems can be termed *fuzzy* supramolecular systems.

Living creatures can be regarded as ultimate examples of supermolecules, because they are formed from a huge number and variety of molecules through supramolecular interactions. However, the functionality observed in living creatures, including those used in our daily life, are not always based on precise recognition. Combinations of ambiguous recognition and control processes result in highly sophisticated overall functionality. The component molecules used in living systems are mainly assembled through rather ambiguous molecular interactions, but they combine to form well-balanced and well-controlled systems. The functions expressed by such ambiguous assemblies are highly flexible and adaptable. Since we can see the highly successful results of fuzzy interactions in nature, supermolecules formed through fuzzy recognition are worth studying in the hope that we can achieve similar highly functionalized systems. In the following sections we take a closer look at supramolecular systems based on fuzzy interactions. First, we discuss cell membranes, which provides an example of a natural supramolecular assembly based on fuzzy molecular interactions. Then we consider some artificial mimics of cell membranes – several kinds of ultrathin films.

4.5

Structures and Formation Mechanisms of Cell Membranes

Figure 4.17 is a schematic illustration of a cell membrane formed through the spontaneous assembly of mainly lipids and proteins. The structure of the cell membrane comprises lipids that form a double-layer structure containing floating proteins. The lipid layer is in a fluidic liquid crystalline state in living systems, and behaves like a solvent for the proteins. Oligosaccharide chains on the membrane surface play an important role in bioactive recognition, and some proteins are positioned at the inner surface in order to immobilize membrane components. All of the components assemble through fuzzy interactions that result in flexible supramolecular assembly. The most basic structure of the cell membrane is the double layer structure composed of lipids, which is called the lipid bilayer. The complex structure where proteins float in the lipid bilayer was proposed as a fluid mosaic model by Singer and Nicolson in 1972.

The major driving force for lipid bilayer formation is hydrophobic interaction. This interaction is much less specific and less directional than the hydrogen bonding and metal coordination interactions that are used in precisely programmed supramolecular assemblies. A simplified lipid structure is depicted in Fig. 4.18. A lipid molecule consists of a hydrophilic head and

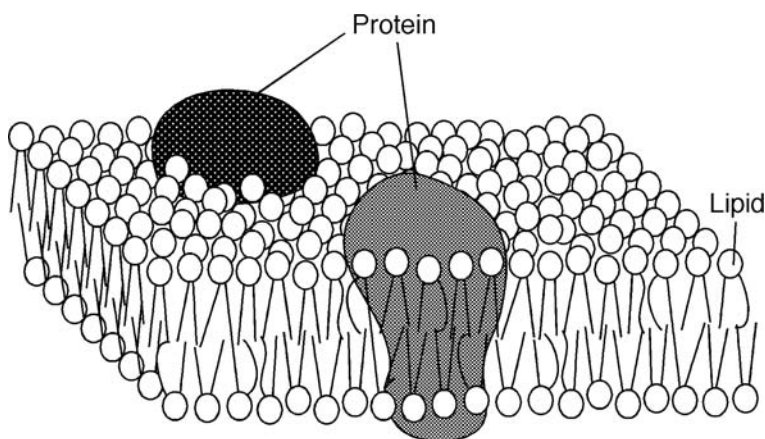


Figure 4.17. Simplified illustration of a cell membrane

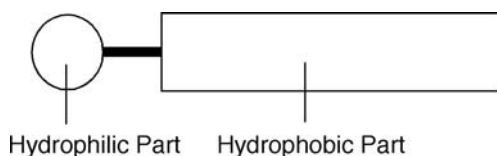


Figure 4.18. Conceptual structure of an amphiphile

a hydrophobic tail. The head has a high affinity to water, while contact of the tail with water is energetically unfavorable and this part is preferably solvated by nonpolar solvents. Molecules that have affinities for both hydrophilic and hydrophobic media are called amphiphiles. Lipids are typical amphiphiles, and many kinds of artificial amphiphiles are reported to form membrane-like structures in aqueous media. When amphiphilic molecules are molecularly dispersed in water, the polar part of the amphiphile tends to expose itself to bulk water while the hydrophobic part shields itself from the aqueous phase. As a result, amphiphilic molecules spontaneously form various types of assembly through hydrophobic interactions.

4.6 Micelles – Dynamic Supramolecular Assemblies

The simplest kind of supramolecular assembly formed by amphiphiles is the *micelle* (Fig. 4.19). Amphiphiles that form micelles usually have low hydrophobicity and are sometimes called surfactants or detergents. Such molecules show relatively high solubility and easily disperse in water up to a certain concentration level, above which they form micelles. This concentration is called the critical micelle concentration (CMC). The micelle structure depicted in

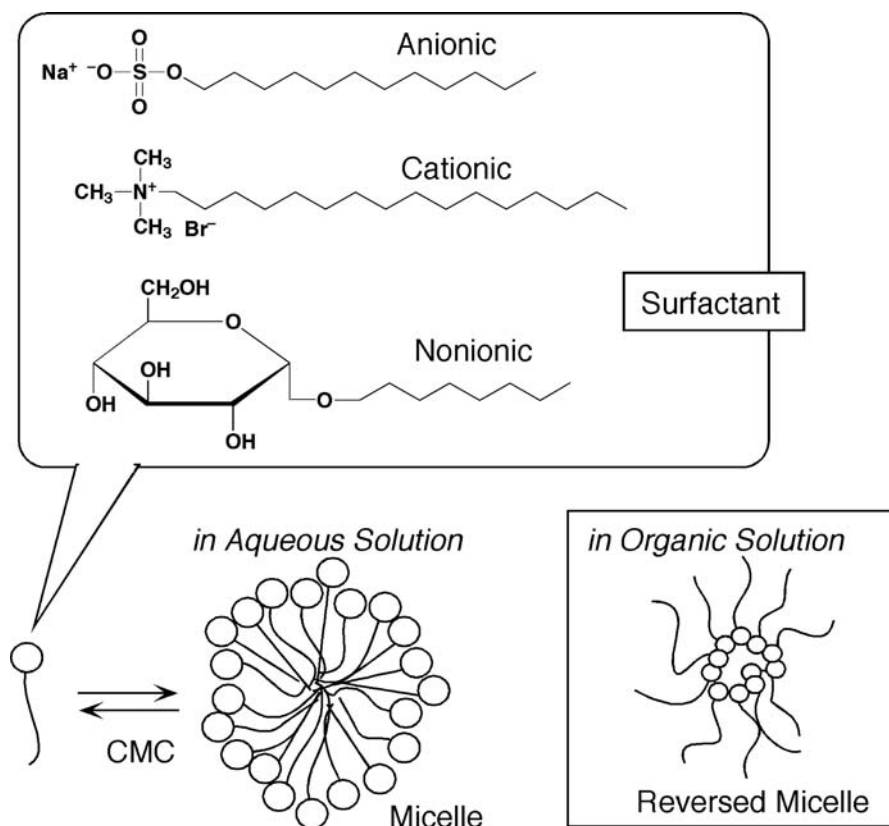


Figure 4.19. Micelle and reversed micelle

Fig. 4.19 is a cross-section; the actual micelle structure is three-dimensional. The assembled structure is completely nonregular; rapid exchange between micelle molecules and monomeric soluble molecules occurs. Therefore, a micelle can be regarded as a disordered dynamic supramolecular assembly. In a micellar structure, the hydrophilic part of the component molecule is located on the outer surface of the micelle, in contact with the aqueous phase, which minimizes the unfavorable contact of the hydrophobic part with water. Micelles can trap organic materials like oils in the inner hydrophobic core, so micelle formation is used in many cleaning agents.

A similar structure, but with the roles of the hydrophilic part and the hydrophobic part exchanged, can occur in nonpolar media, such as organic solvents. This structure is called a reversed micelle. The hydrophobic part of the amphiphile is exposed to the outer medium, shielding the polar head inside the assembly. Reversed micelles can trap small amounts of water inside them. Water-soluble molecules such as enzymes can therefore be dissolved in the

reversed micelle. This strategy is useful for enabling enzymatic reactions to occur in organic solvents.

In concentrated solutions of surfactants, micelles can form various phases, such as lamellar, cubic and hexagonal phases. These phases can be moved and placed onto solid materials (Fig. 4.20). Under selected conditions, surfactants form rod-like micelles that further assemble into hexagonal arrangements. Solidifying the surroundings of the hexagonally packed micellar rods using a sol-gel reaction with an appropriate silica reagent results in hexagonally arranged solid silicates. The organic micelles are subsequently removed by calcination, and porous material is obtained. This is called mesoporous silica.

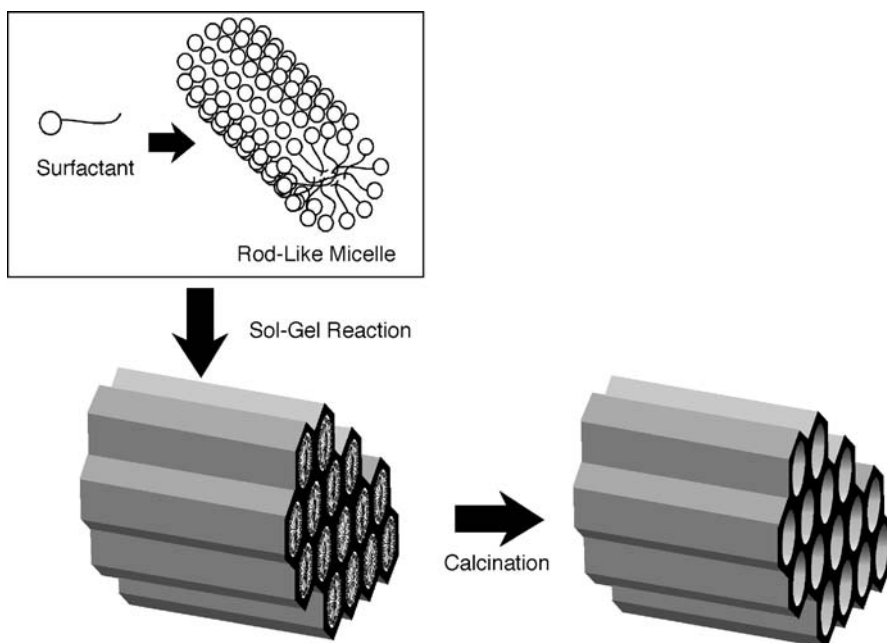


Figure 4.20. Formation of mesoporous silica

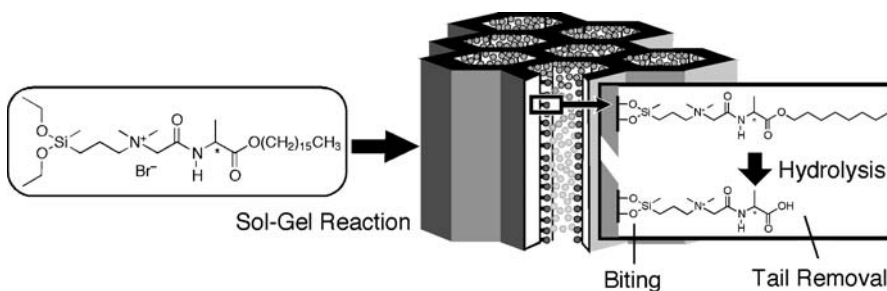


Figure 4.21. Lizard templating

Because mesoporous silica has an oriented regular pore structure with large surface area, it can be used as a catalyst support.

Designing the surfactant appropriately can result in the mesoporous silica having an interior surface that is uniquely modified. In the example shown in Fig. 4.21, a surfactant with an alkoxysilane head is covalently connected to the inner surface of a mesoporous silica through a sol-gel reaction. Selective removal of the alkyl tail by acid hydrolysis leaves open pores densely populated with functional groups. Since the surfactant bites the silica wall and removes its tail, this method is called “lizard templating”.

4.7

Liposomes, Vesicles, and Cast Films – Supramolecular Assembly Based on Lipid Bilayers

The micelle structure described in the previous section is highly dynamic, with rapid exchanges occurring between free and assembled components. This behavior is quite different from the structural stability and component mobility of a cell membrane. In order to mimic a cell membrane, we need more stable amphiphilic assemblies. The key to achieving a stable design is an appropriate design for the structure of the amphiphile.

Figure 4.22 shows examples of some lipid structures that are found in actual cell bilayer membranes. Some of them possess a phosphate moiety and are

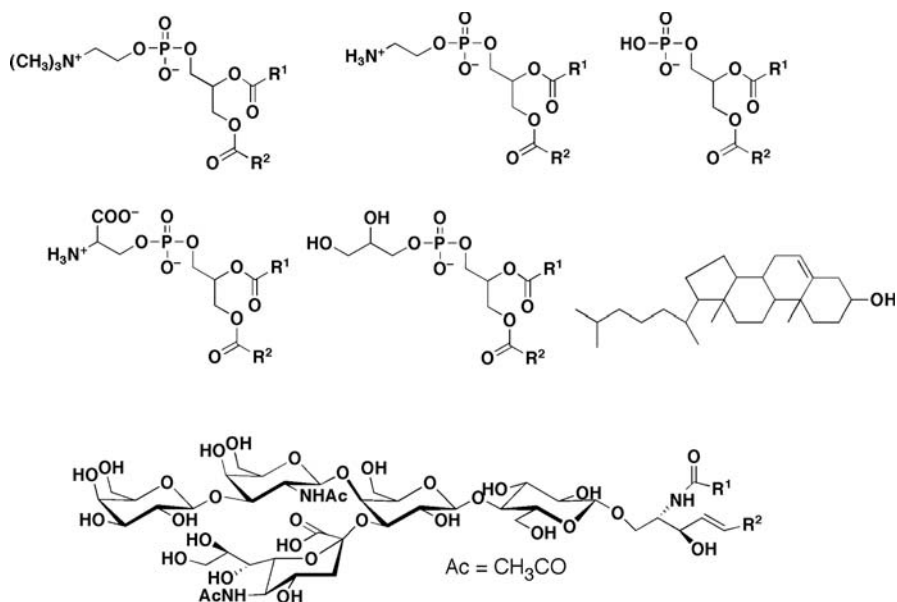


Figure 4.22. Examples of lipids that form cell membranes

therefore called phospholipids. Glycolipids (which have heads carrying sugar moieties) and cholesterol are two other important components of the cell membrane. Most of these lipids have two alkyl chains. In these lipid structures, the ratios between the sizes of the hydrophilic heads and the hydrophobic tails are different to those for micelle-forming surfactants. Amphiphiles that form bilayer structures tend to have larger tails than heads. When these amphiphiles are dispersed in water, they assemble in order to avoid unfavorable contact of the hydrophobic parts with the water. However, they cannot form micelle-like small assemblies because of their large hydrophobic tails. Therefore, the phospholipid-like amphiphiles form double-layer structures (lipid bilayers) by contacting the hydrophobic faces of two leaf-like monolayer amphiphile assemblies. This lipid bilayer structure extends two-dimensionally and forms the “skin” of a closed sphere that has a water pool inside (Fig. 4.23). This capsule-like structure can be thought of as a simplified model of a cell. This capsule-like structure is called a *liposome*. As seen in the cross-sectional image of the lipid bilayer structure, the alkyl chains are densely packed compared to the micellar assembly. Therefore, a liposome is a much more stable structure than a micelle, and liposomes are widely used as artificial cells. Cholesterol is sometimes added to increase the stability of the lipid bilayer membrane. When studying the specific recognition of particular bioactive molecules on the liposome surface, glycolipid is often incorporated into the membrane of the liposome.

Phospholipids exhibit an excellent ability to form liposome structures and are common in naturally-occurring cell membranes. The reason that nature uses phospholipids in the cell membrane is partly based on evolution-related biosynthetic requirements. From a physicochemical point of view, an amphiphile can form a liposome-like supramolecular assembly as long as the amphiphile satisfies various structural requirements. Indeed, it has been found that a much simpler molecule – an ammonium salt with two long alkyl tails – can also form liposome-like assemblies. Therefore, structures simi-

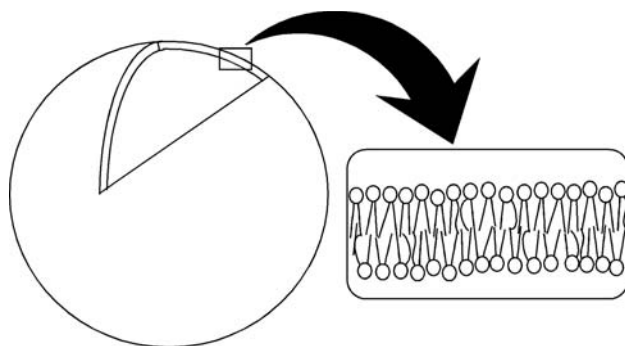


Figure 4.23. Liposome (or vesicle) with a lipid bilayer membrane

lar to cell membranes are not only produced by biological components; they can also be created from artificial amphiphiles through good molecular design.

This finding triggered research into amphiphiles that could form liposome-like structures. It was concluded that an amphiphile with an appropriate balance of polarity and size for its hydrophilic and hydrophobic parts will generally form liposome-like assemblies. Examples of artificially designed amphiphiles are shown in Fig. 4.24. Cationic, anionic, nonionic and zwitterionic groups are used in the polar heads. A dialkyl structure is often used for the tail, but trialkyl structures, tetraalkyl structures and azobenzene-type rigid structures are also available. Instead of hydrocarbon structures, a fluorocarbon structure that is highly immiscible with water has also been used as a hydrophobic tail. It was reported that introducing an amino acid residue between the hydrophilic head and hydrophobic tail increases bilayer stability. Hydrogen bonding associated with the amino acid part helps to improve the structural stability of the bilayer structure. Liposome-like structures formed from various kinds of amphiphiles are sometimes called “vesicles”, while the term “liposome” is sometimes limited to assemblies from phospholipids.

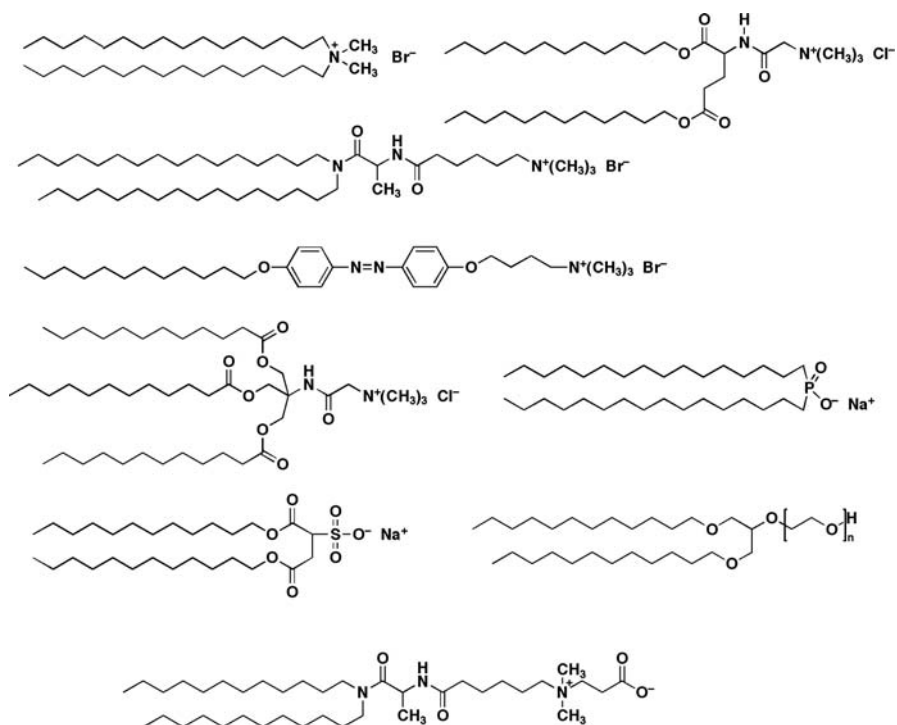


Figure 4.24. Examples of artificial lipids that form vesicles

The lipid bilayer structure, the fundamental structural unit of liposomes and vesicles, is a supramolecular assembly based on fuzzy interactions. The structural regularity of the bilayer structure is not as high as that observed for crystalline supermolecules. However, the lipid bilayer has structural ordering similar to that seen in liquid crystals. The lipid bilayer shows phase transition behavior depending on the ambient temperature. Therefore, the lipid bilayer behaves as a thermotropic liquid crystal (Fig. 4.25). At low temperature, the lipid bilayer is in a gel (or crystalline) state with motional freezing of the alkyl chains. As the temperature rises, the alkyl chains melt and attain a flexible motional state although the bilayer structure is maintained. This state is a liquid crystalline state, and the temperature at which the change in state occurs is called the gel (or crystalline)–liquid crystalline phase transition temperature. This gel–liquid crystalline phase transition temperature depends upon the water content of the system containing the lipid bilayer structure. The water content controls the state of the lipid bilayer at fixed temperature. Therefore, the lipid bilayer also behaves as lyotropic liquid crystal.

In actual cell membranes, phospholipids with various alkyl tails are mixed together and thus the crystallinity of the bilayer is quite low. Therefore, lipid bilayers in living cells have a phase transition temperature that is lower than ambient temperature, and so they are kept in the liquid crystalline state. This characteristic is crucial to life. If the cell membrane were to crystallize, the proteins and sugar chains would not work properly. In contrast, the phase transition behavior of an artificial bilayer membrane is easily controlled through appropriate design of the structure of the amphiphile, especially the lengths of the alkyl chains. The transport of materials through the bilayer membrane significantly depends upon the state of the bilayer. The release of drugs trapped in the inner water phase of the vesicle can be controlled via thermal stimuli with knowledge of the bilayer's phase transition temperature. This controlled release is an important concept in the development of drug delivery systems.

Liposomes and vesicles are usually very small – invisible to the unaided eye. However, free-standing materials containing lipid bilayer units of a size large enough to be seen without a microscope can be very useful from a functional

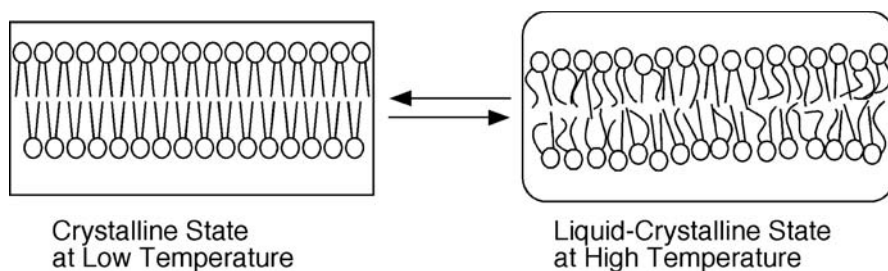


Figure 4.25. The gel (or crystalline) to liquid-crystalline transition

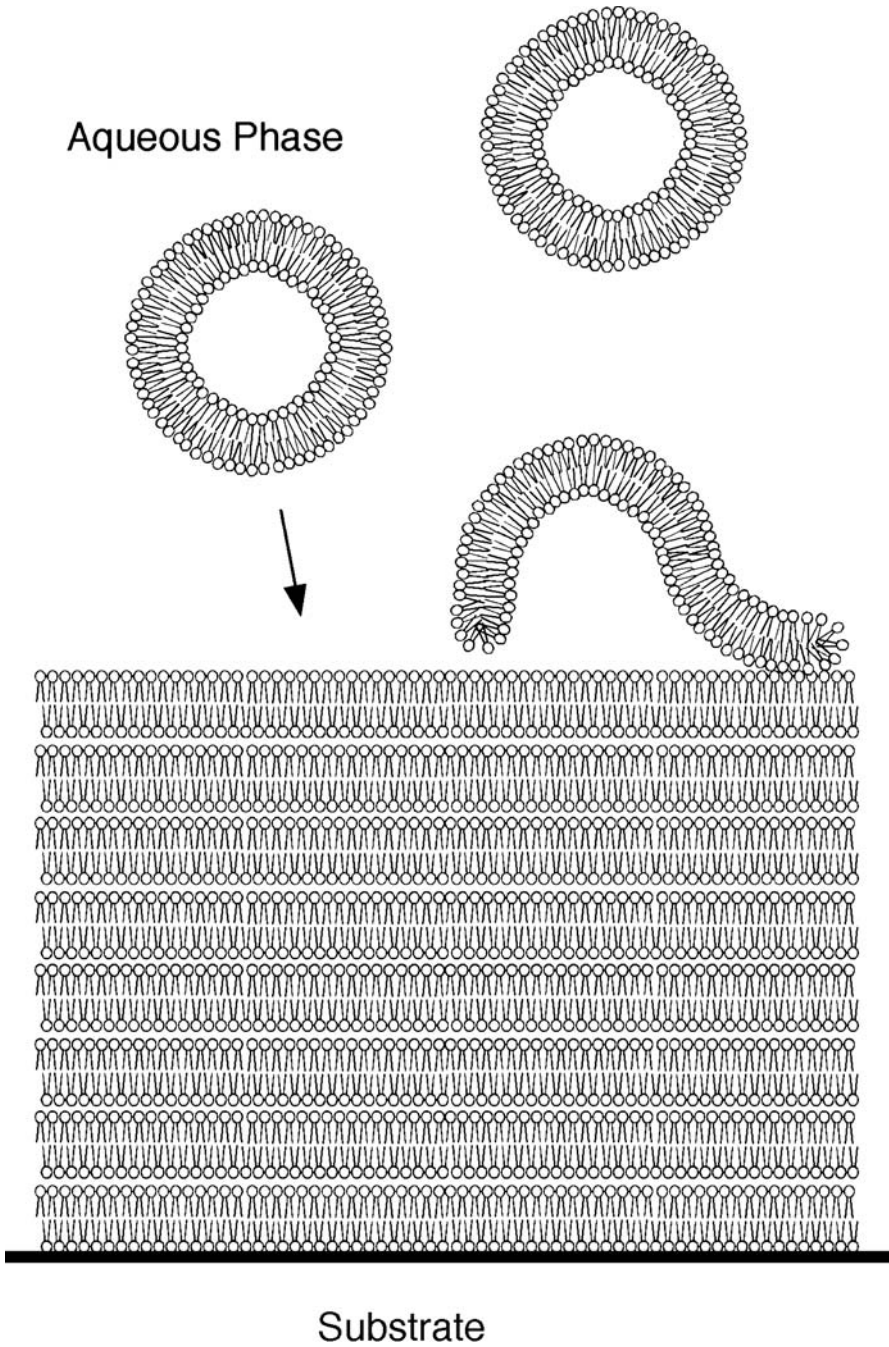


Figure 4.26. Cast film with a multibilayer structure

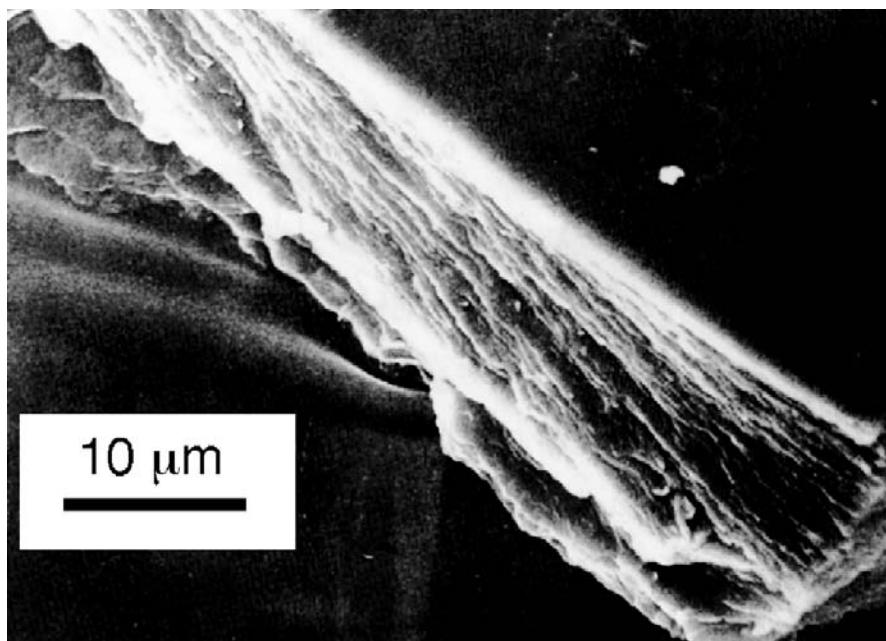


Figure 4.27. Cross-section of a cast film

point of view. Such materials can be obtained by casting an aqueous solution of bilayer-forming amphiphiles. The thin film obtained, which is called *cast film*, has a multilayered lipid bilayer structure. It is prepared by gradual evaporating water from a solution of aqueous vesicles on a solid support. If the evaporation conditions and material used as a solid support are properly chosen, the resulting thin film can be separated from the support. Such films can actually be held, and are sometimes transparent. A cross-section of the cast film is shown in Fig. 4.26 (an image of a cast film taken using an electron microscope is shown in Fig. 4.27). Sheets of the lipid bilayer structure extend in two dimensions and lots of sheets are stacked on top of each other. Therefore, the cast film has a structurally anisotropic nature. It can provide an anisotropic medium for material syntheses. Using cast film as a template, structurally anisotropic materials can be synthesized. Figure 4.28 demonstrates the synthesis of an anisotropic polymer. The hydrophilic monomer can be selectively condensed in the hydrophilic interlayers of the multibilayer structure. Polymerization and extraction of the bilayer component results in the preparation of a two-dimensionally extended sheet-like polymer.

Sophisticated amphiphile designs allow us to develop bilayer-based organic–inorganic hybrids. In the example shown in Fig. 4.29, amphiphiles with alkoxy-silane heads are used as bilayer-forming components. At the surface of the vesicle formed, cross-linked silanol groups form an inorganic silica-like structure.

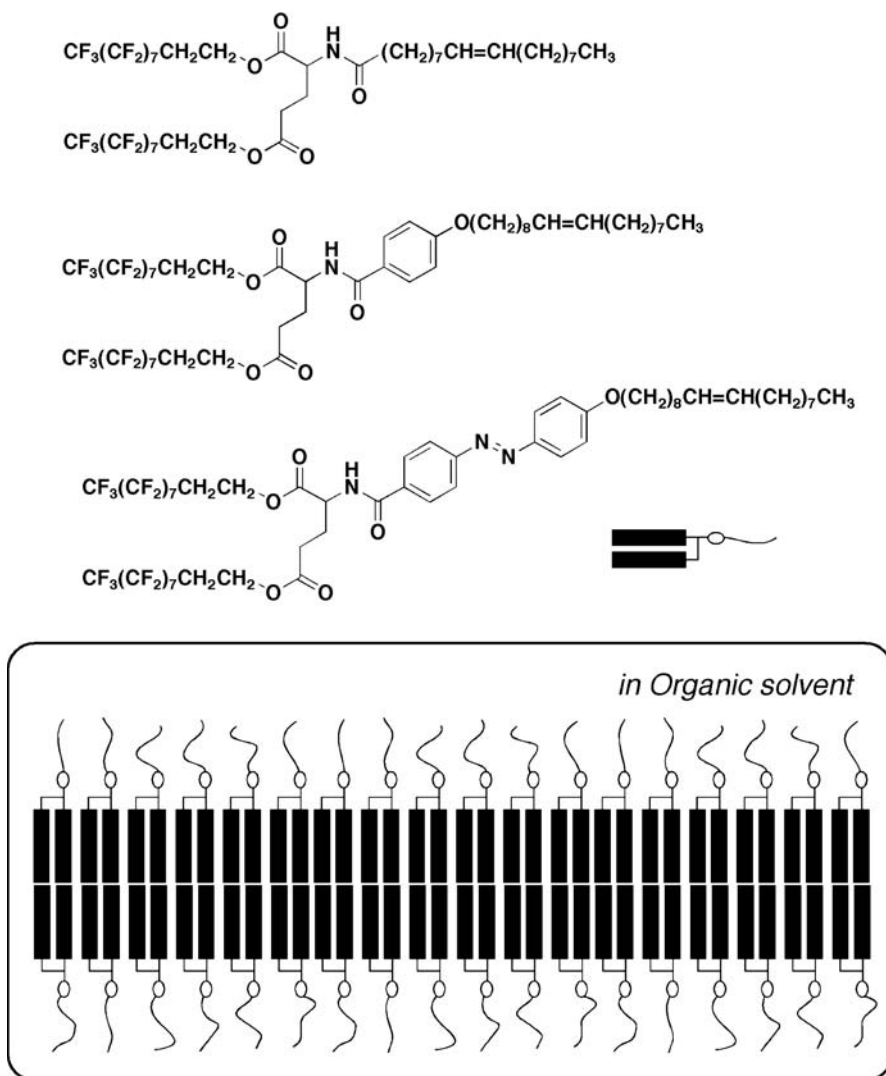


Figure 4.30. Formation of a lipid bilayer in an organic solvent

and the solvophobic part, bilayer structures are formed. So, although studies of lipid bilayers and vesicle formation were originally initiated in order to mimic cell membranes in aqueous media, appropriate molecular design has extended this concept to a wide range of molecules. The bilayer structures created in organic media may even potentially mimic the cell membranes of extraterrestrial life!

Another fundamental question about bilayer formation is whether amphiphilic molecules are really necessary. The answer to this question is “yes

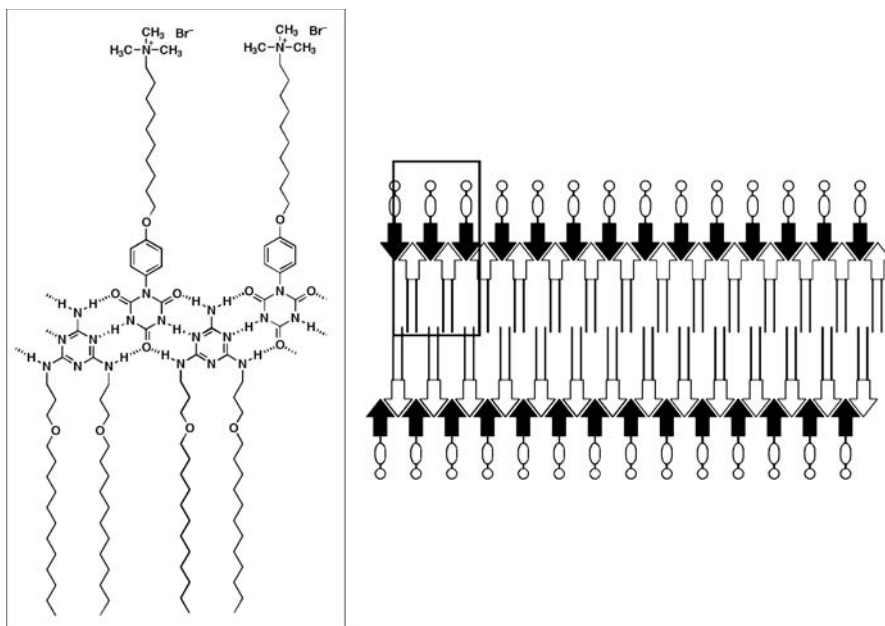


Figure 4.31. Bilayer formation from separated polar head and tails

and no”. Although amphiphilicity is required, it does not have to exist in a single molecule. Separate molecules, one of which is hydrophilic (or solvophilic) and the other hydrophobic (or solvophobic), can construct amphiphilic units through supramolecular associations. Figure 4.31 introduces one example of this, where cyanuric acid (containing a hydrophilic part) and melamine (which has hydrophobic tails) are the two components. These components assemble through complementary hydrogen bonding, resulting in the formation of a bilayer structure.

Formation of a bilayer structure is therefore driven by the self-assembling behavior of amphiphilic molecules or molecular complexes. This research topic started from the dispersion of naturally-occurring phospholipids in aqueous media, but the development of molecular design and systematic research has led to the study of bilayer chemistry in various media.

4.8

Monolayers and LB Films – Controllable Layered Assembly

While bilayer cast films are oriented assemblies of amphiphiles, the number of layers in the films cannot be controlled. However, precise control over the number of layers and the layering sequence is a crucial factor for many functional materials. Such functional materials have attracted much attention from re-

searcher working on molecular devices (see Chap. 5). One of the most powerful methods of achieving molecular assemblies with precisely layered structures is the LB technique. “LB” is an abbreviation of Langmuir and Blodgett, who were the two scientists that developed this technique. In this method, an insoluble monolayer of amphiphile molecules is first spread on the surface of a water phase that is sometimes called the subphase. After compressing the monolayer into a highly condensed state, the monolayer is transferred onto a solid support in a layer-by-layer manner.

In the LB method, the monolayer-forming amphiphile must have an appropriate hydrophilic–hydrophobic balance. When the amphiphile is too hydrophilic, the amphiphile spontaneously dissolves in water. For example, quaternary ammonium salts with single long tails easily dissolve in water. In contrast, an amphiphile that is too hydrophobic leads to the formation of a three-dimensional solid or an oil droplet on the water. A typical example of this group is an alkyl halide. The general guidelines for choosing an amphiphile structure that is suitable for creating monolayers is summarized in Fig. 4.32. Long hydrocarbon chains are often used for the hydrophobic part. Similar to bilayer-forming amphiphiles, an alkyl tail with an aromatic ring, a steroidal structure or a fluorocarbon can be also used as the hydrophobic part. The hydrophilic part of a monolayer-forming amphiphile is generally less polar than that of a bilayer-forming amphiphile because a water-insoluble nature (or a kinetically insoluble nature) is required for monolayer formation. A carboxyl group or hydroxyl group are generally used for the monolayer. Less polar amides or esters are also frequently used. The most important factor is the balance between the hydrophobic part and the hydrophilic part. Therefore, ionic

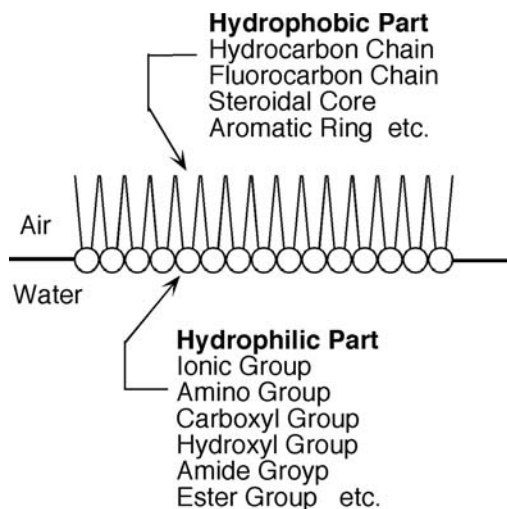


Figure 4.32. Compounds appropriate for monolayer formation

groups such as ammonium and sulfonate can be used if the hydrophobic parts are very hydrophobic. Various dialkyl amphiphiles, including phospholipids, can form both monolayers and bilayers.

The monolayer of amphiphile spread on water is then compressed into a well-packed state. The profile of monolayer compression is recorded as surface pressure–molecular area (π -A) isotherm. Typical examples of π -A isotherms are shown in Fig. 4.33. The transverse axis of the isotherm represents the molecular area, which can be obtained by dividing the total surface area by the number of amphiphile molecules. The surface pressure is derived by subtracting the surface tension of the monolayer-covered water surface from that of pure water. This has dimensions corresponding to two-dimensional pressure. Surface pressure cannot be regarded as a normal three-dimensional pressure. For convenience, when discussing the phase of two-dimensional monolayer here, the surface pressure is treated as a two-dimensional pressure.

In actual experiments, the amphiphile, dissolved in appropriate organic solvent, is dropped carefully onto the surface of water. After evaporation of the solvent, the amphiphile molecules remain on the surface of the water in a monolayer. At this stage, the amphiphile molecules are usually scattered over the surface. In this state, the monomer is an expanded phase (Fig. 4.33(a)). As the monolayer is compressed, the surface pressure gradually increases until it reaches a constant value. When the pressure levels off, the condensed monolayer and the expanded monolayer are in equilibrium. Further compression of the monolayer leads to an abrupt increase in surface pressure. When the monolayer is compressed high enough, the density of amphiphile molecules in the monolayer reaches solid-like levels. This phase is called the condensed phase. Finally, when the pressure is increased further, the monolayer cannot retain its two-dimensional nature and some of the amphiphile molecules are forced out of the monolayer plane: the monolayer collapses. Figure 4.33(b) shows another π -A isotherm, which is observed for a monolayer of amphiphiles with high condensing ability. When such amphiphiles are spread on water, the amphiphile molecules sponta-

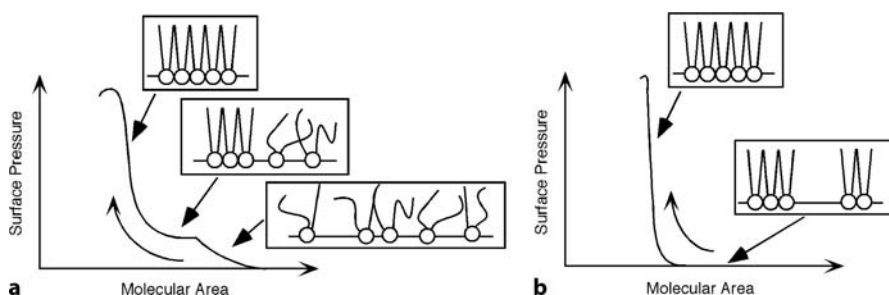


Figure 4.33. Typical surface pressure versus molecular area (π -A) isotherms

neously assemble to form islands of condensed phase on water. When such a monolayer is compressed, the surface pressure does not increase initially, but it does abruptly increase after the gaps between the condensed islands are filled.

In the LB method, multilayered films are prepared through the layer-by-layer transfer of the condensed monolayer onto a solid support. This procedure allows us to prepare ultrathin films with a controlled number of layers and layering sequence. During the transfer process, a constant surface pressure is continuously applied to maintain the condensed state of the monolayer. In the most common method, a solid support is first pushed down and pulled up through the condensed monolayer. As the support is first pushed down, the monolayer is transferred to the support, with the hydrophobic tail side of the monolayer facing the support. As the support is pulled back up, the monolayer is again transferred but with the opposite orientation (head-side of the monolayer in the direction of the support). The decrease in pressure produced by the transfer of the monolayer from the water surface to the solid support can be compensated for by applying a constant surface pressure. This transfer method is called the *vertical dipping method*.

The mode of monolayer transfer achieved depends on the polarity of the hydrophilic head of the amphiphile and the surface pressure. If monolayer transfer occurs on both the down stroke and the up stroke, head-to-head and tail-to-tail orientations of the monolayers are achieved (Fig. 4.34). This transfer mode is called Y-type, and the LB film obtained is called Y film. When the

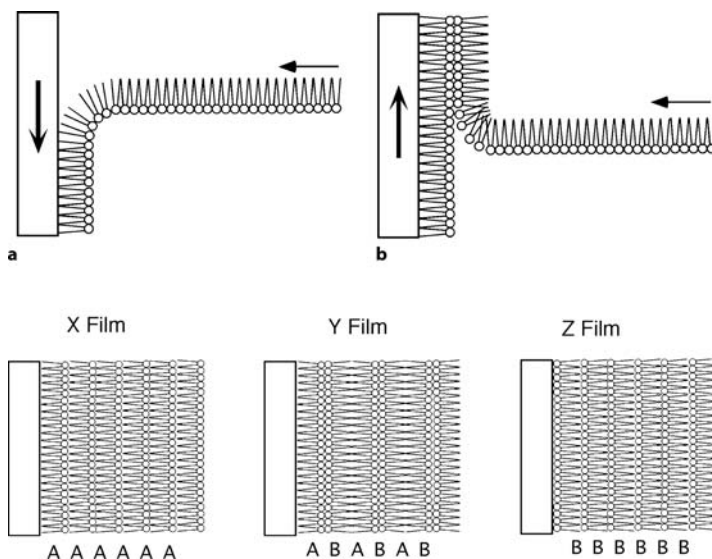


Figure 4.34. Langmuir–Blodgett (LB) film

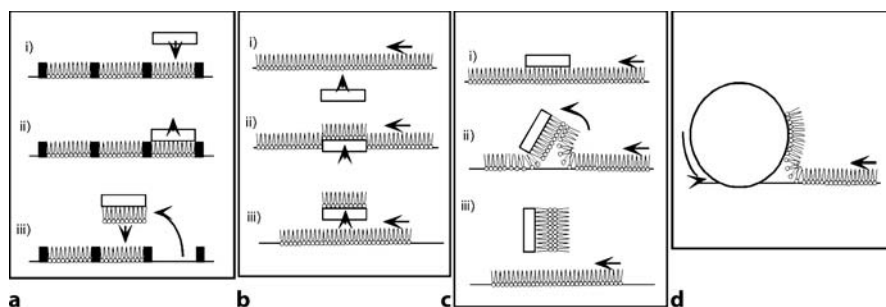


Figure 4.35. Modified methods of LB transfer

monolayer is only transferred during the down stroke of the solid support, the transfer mode is X-type. The opposite type of monolayer transfer, transfer only during the up stroke, is called Z-type. In the X film and Z film, the monolayer orients in a particular direction to form an asymmetric assembly. Such asymmetric LB films are attractive materials for nonlinear optics. However, sometimes the monolayer unit folds over during the transfer process, changing the X or Z film into a symmetric Y film. Therefore, special techniques are required to ensure asymmetrically assembled LB films.

Various modified versions of this transfer technique have been proposed. Figure 4.35a shows a horizontal lifting method where the condensed monolayer is divided into several compartments and monolayers are transferred horizontally by stamping the solid support on the monolayer compartment. The LB films obtained are ideally X film. Because the hydrophilic face of the monolayer is exposed to air, amphiphiles with weaker polarities are more suited to this method. In the method depicted in Fig. 4.35b, a solid support is pulled up through a monolayer from the water phase. If the surface of the support is hydrophilic, a single monolayer is transferred from the water onto the support with minimum disturbance. Because this method does not require lateral motion of the monolayer, rigid monolayers are easily transferred. The film obtained with this transfer method sometimes provides a portion of monolayer suitable for detailed characterizations of the main monolayer. A similar situation can be achieved by gradually lowering the water level relative to the solid support. The method shown in Fig. 4.35c is a kind of combination of the vertical dipping method and the horizontal lifting method. A solid support is initially placed on an uncomparted monolayer, and is then gradually pulled up at an appropriate angle. This method provides Y film. Because immersion of the solid support is not necessary in this method, only small amounts of subphase are needed, which is sometimes advantageous. Note that the solid supports used in these techniques do not have to be flat. As shown in Fig. 4.35(d), a drum-type support can be used to continuously transfer monolayer.

4.9

Self-Assembled Monolayers – Monolayers Strongly Bound to Surfaces

The LB method allows us to prepare multilayered films from oriented monolayers. However, the absence of a strong interaction between the film and the solid support is a problem in some applications due to its mechanical instability. For example, immersion of the LB film in organic solvent can result in the destruction of the film. In order to overcome this problem, a monolayer strongly immobilized on a solid support was proposed. This type of film is called a self-assembled monolayer (SAM). The self-assembled monolayer is prepared by utilizing the strong interaction between the heads of the amphiphiles and the surface of the solid support. Covalent linkages between silanol amphiphiles with long alkyl tails and a glass or metal oxide surface and strong interactions between thiol amphiphiles (again with long alkyl tails) and a gold surface are often used in this method. The preparation method is quite simple. Immersion of the support into a solution containing the corresponding amphiphiles induces self-assembly of the amphiphile components as a monolayer on the support surface. Washing the support removes excess adsorbent, resulting in a strongly immobilized monolayer.

The strong interaction with the solid surface sometimes compensates for a lack of self-assembling ability for some components (Fig. 4.36). Molecules whose structures are much different to those of typical amphiphiles can be used in this method. In addition, immobilizations of dyes, proteins and nucleic acid are possible using this self-assembled monolayer technique. These self-assembled monolayers have great potential for a wide range of applications.

Preparation of a multilayer is possible using the self-assembled monolayer method and appropriate molecular design (Fig. 4.37). In this method, a trichlorosilane amphiphile with a long chain terminated in a double bond was used as the monolayer component. This compound was hydrolyzed to silanol to provide a self-assembled monolayer that covalently immobilized to

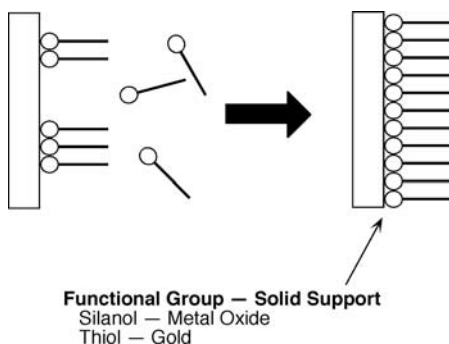


Figure 4.36. Self-assembled monolayer

a solid with surface hydroxyl groups. The terminal double bond was oxidized to a hydroxyl group. A second monolayer can then be covalently immobilized to the freshly prepared hydroxyl surface.

The formation of self-assembled monolayers is a powerful tool for surface modification, and it is useful when we need to control surface hydrophilicity or prepare functional electrodes, for example. Surface modification with belts composed of monolayers of various hydrophilicities can yield surfaces with hydrophilicity gradients. Liquid droplets can move across such surfaces against gravity due to favorable interactions with the monolayer surface (Fig. 4.38).

In the example shown in Fig. 4.39, a photoisomerizable “command” monolayer was immobilized on a solid surface and liquid crystalline layers were then deposited on the monolayer. Photoisomerization of the command monolayer can then change the orientation of the thick liquid crystalline layer.

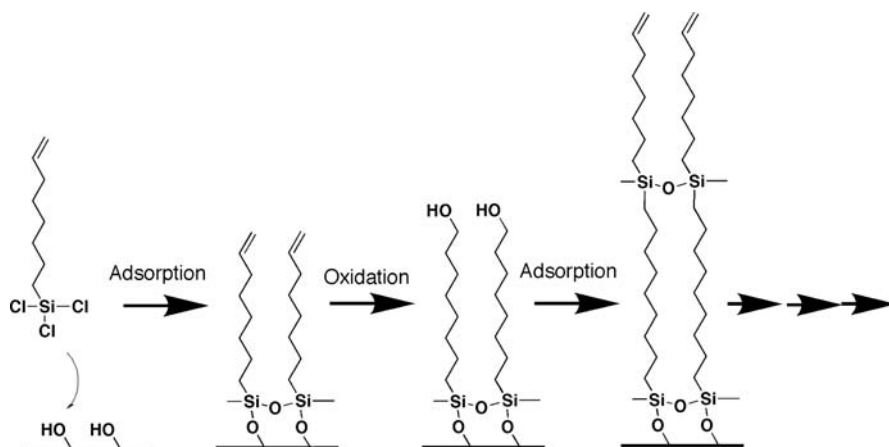


Figure 4.37. Formation of a multilayer film based on the self-assembly method

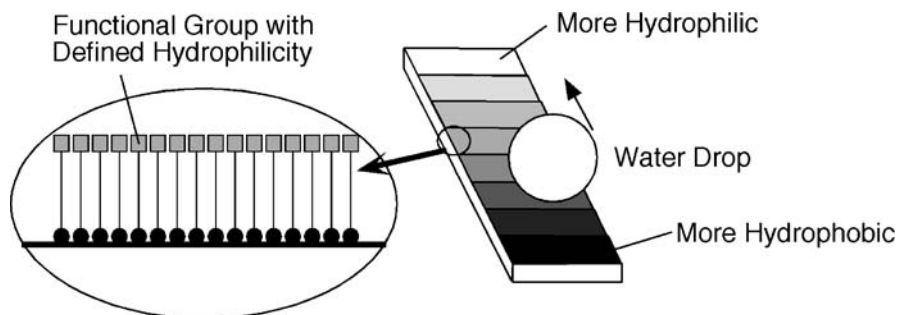


Figure 4.38. Uphill movement of a water droplet along a surface with a hydrophilicity gradient

information is therefore amplified into bulk structural change. This concept could be used in the development of display devices.

The application of a host-type molecule as a monolayer-forming component leads to the preparation of a sensor device. If the monolayer is immobilized on an electrode, guest binding can be detected as an electric signal. In the example shown in Fig. 4.40, a self-assembled monolayer of α -cyclodextrin was immobilized on a gold electrode. Because the α -cyclodextrin can accommodate hydroquinone, the binding behavior of the hydroquinone to the α -cyclodextrin monolayer was detected by a redox signal from the hydroquinone. Using the hydroquinone as a competitive guest, the binding of another guest molecule can be analyzed from the decrease of the hydroquinone response. For example, methyl red is capable of binding with α -cyclodextrin, and its binding

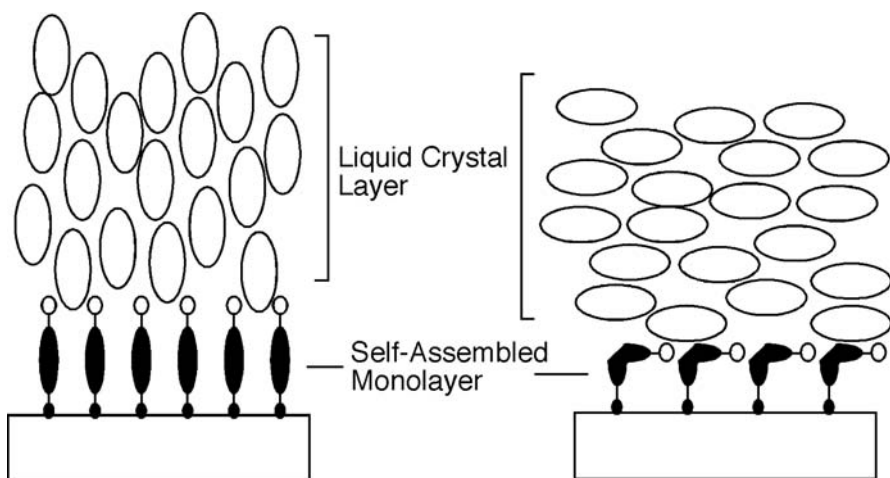


Figure 4.39. Controlling the orientation of a liquid-crystalline phase using a command surface

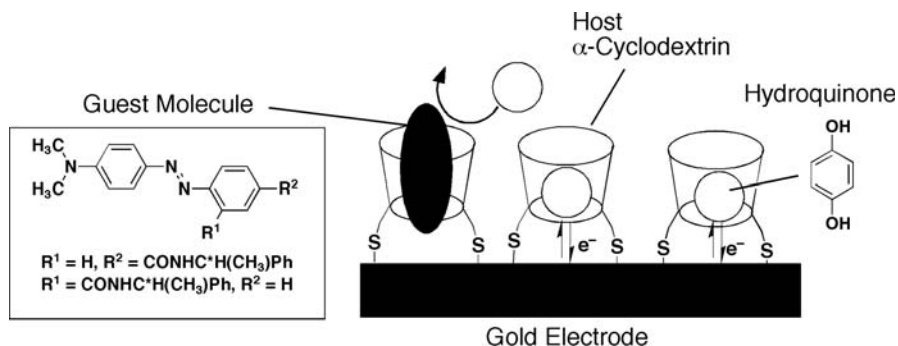


Figure 4.40. Electrochemical evaluation of guest inclusion

behavior was quantitatively determined by analyzing the suppression of the hydroquinone current. Systematic analyses revealed that the *p*-isomer binds more strongly than the *o*-isomer (regioselectivity) and the *R*-isomer binds more strongly than the *S*-isomer (stereoselectivity).

Instead of cyclodextrin, calixarene has also been used as the monolayer-forming component in sensor preparation. In the example shown in Fig. 4.41, a self-assembled monolayer of calixarene was immobilized on an electrode of a quartz crystal microbalance. The quartz crystal microbalance is a mass-sensing device capable of nanogram-level precision (see Chap. 5). When the monolayer-covered microbalance was exposed to guest gas, the guest bonding

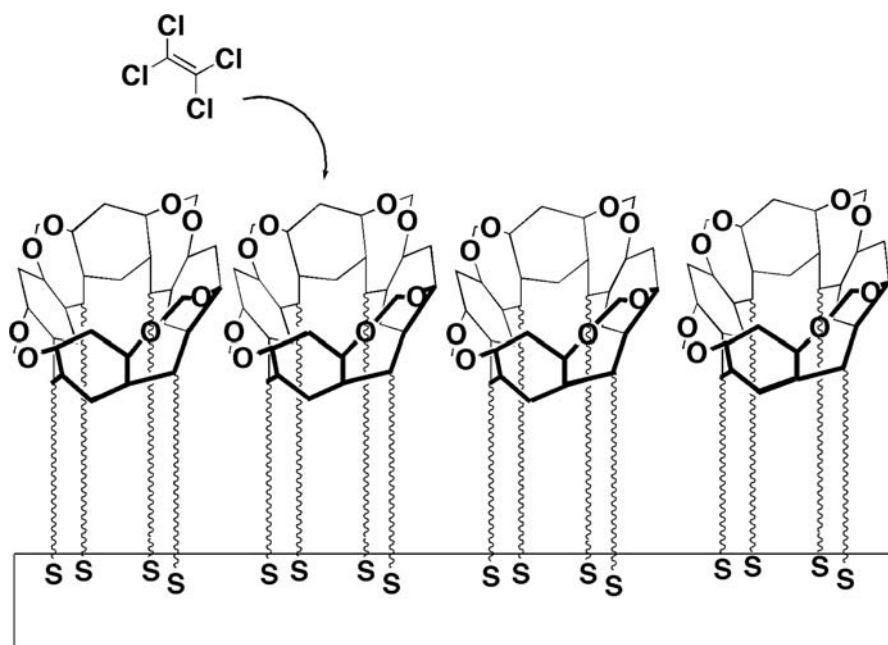


Figure 4.41. Self-assembled monolayer of calixarene host

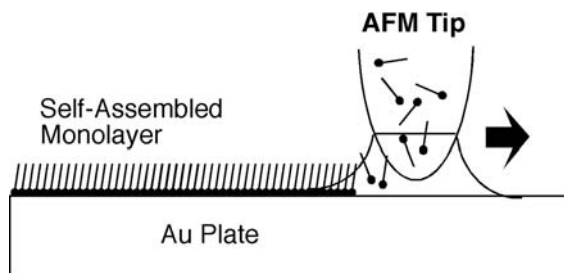


Figure 4.42. Dip-pen nanolithography

caused a change in the resonant frequency. In this case, tetrachloroethylene gave a large response.

Combining this self-assembled monolayer chemistry with AFM tip apparatus yields a new AFM-based soft lithography technique, which is often called dip-pen nanolithography (Fig. 4.42). It can be used to write very fine patterns on metal and semiconductor surfaces using a solution of monolayer-forming materials as ink.

4.10

Alternate Layer-by-Layer Assembly – Supramolecular Architecture Obtained with Beakers and Tweezers

The LB method is an elegant method of preparing well-oriented ultrathin films with a defined number of layers and layering sequence. However, this method usually requires rather expensive apparatus, and water-soluble molecules are not usually appropriate targets. In this section, another type of technique that can be used to build structures layer-by-layer is introduced. This method is called *alternate layer-by-layer assembly*. It does not provide oriented films, as obtained with the LB method, but it can be conducted using a very simple procedure: alternate layer-by-layer assembled film can be prepared using only beakers and tweezers. This method is also applicable to a wide range of water-soluble substances. The fundamental concepts behind this method are schematically explained in Fig. 4.43. The method uses a solid support that usually bears charges. In this example a negatively charged support is used. When the support is immersed in an aqueous solution containing polycations, the polycations adsorb onto the support surface through electrostatic attractions. The key to this process is overadsorption: so many polycations are adsorbed that the surface is not only neutralized but the excess amount of polycations results in a residual positive charge on the surface. In the next step, the surface covered with polycations is immersed into an aqueous solution of polyanions. Adsorption of the polyanions then induces the surface charge to flip again. This alternate adsorption of polycations and polyanions can be repeated again and again. A variety of polyions can be used in this technique. Reports have de-

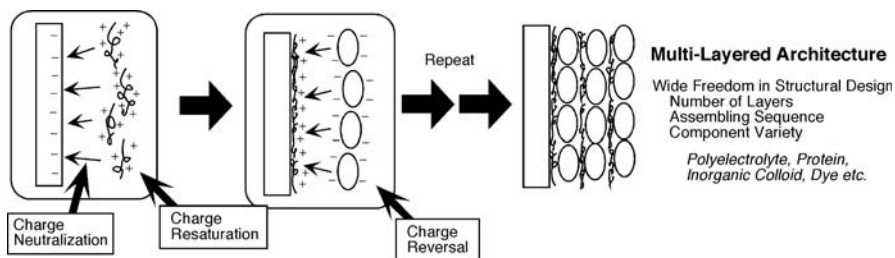


Figure 4.43. Basic concepts behind alternate layer-by-layer assembly

scribed the use of conventional polyelectrolytes, biopolymers such as charged proteins and nucleic acid, inorganic materials such as charged colloidal particles, charged molecular assemblies of dye and lipid bilayers, and complicated substances such as viruses, among others.

The advantages of alternate layer-by-layer assembly can be seen in the following example. Figure 4.44 shows the procedure used to perform the alternate layer-by-layer assembly of proteins and polyelectrolytes. In the first step, a solid support with a negative surface charge was immersed in an aqueous solution of polycations. The adsorption of the polycations was almost complete after an immersion time of 10 to 20 minutes. After sufficient washing, the support was then immersed in an aqueous solution of anionic protein, resulting in the adsorption of an anionic protein layer on the polycation-covered support. Repeating these procedures allows us to prepare multilayered protein/polyelectrolyte film. The number of protein layers in the film is dictated by the number of immersion cycles used. As long as alternate polyanion and polycation adsorption steps are applied, various kinds of proteins can be assembled in desired sequences. Because the adsorption process is conducted at mild ambient conditions and the solvent used is water, protein denaturation is minimized. As illustrated in Fig. 4.44, this procedure requires only beakers (or suitable bottles) and tweezers.

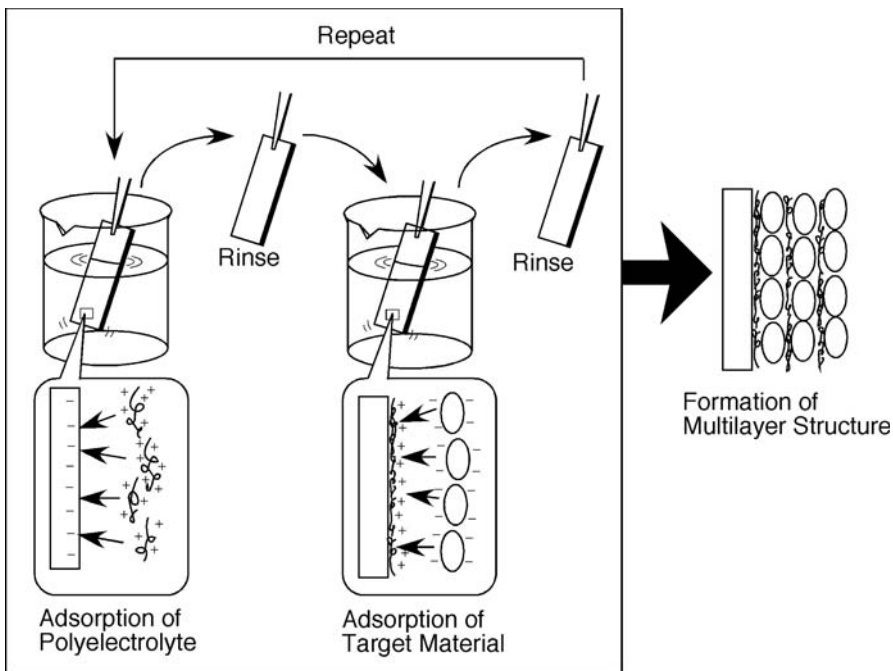


Figure 4.44. Procedure for creating alternately assembled films of protein and polyelectrolyte

Figure 4.45 shows an example of a microreactor in which glucoamylase (GA) and glucose oxidase (GOD) were used as components of an enzyme. Instead of the conventional plate, an ultrafilter was used as a solid support and GA and GOD were assembled in various layering sequences. A wide range of supports to select from is another advantage of this method. Aqueous starch (substrate) solution was placed on top of the enzyme film and pressure was applied. The starch was hydrolyzed into glucose by GA, and the glucose formed was oxidized to gluconolactone by GOD. Hydrogen peroxide was produced by the second reaction. These products passed through the ultrafilter, but the substrate starch cannot pass through due to its high molecular weight. The amount of hydrogen peroxide produced was quantified via a colored reaction with dye and peroxidase. The reactor performance can be judged from the color change of the filtrate.

The efficiency of this sequential reaction significantly depends on the layering sequence used for the two kinds of enzymes. When GA and GOD are applied in the correct order for the reaction to occur (GA in the first layer and GOD in the second layer), the reaction efficiency is high. Reversing the en-

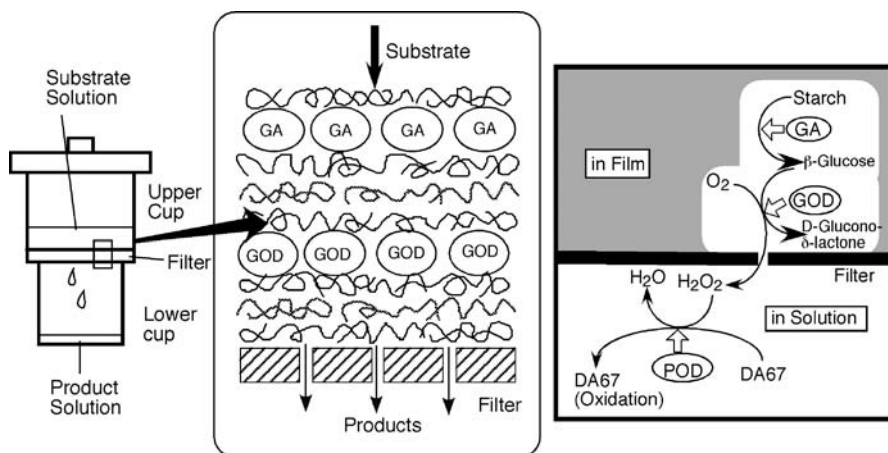


Figure 4.45. Nanoreactor used to generate an enzymatic reaction

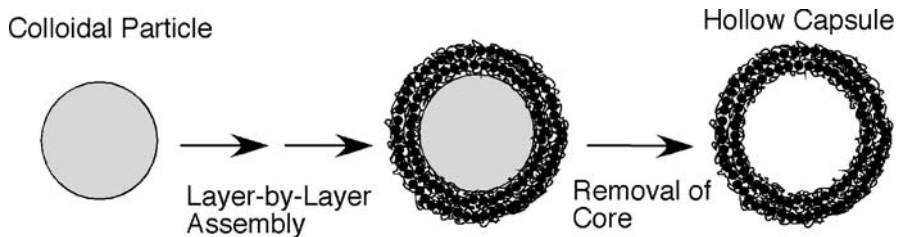


Figure 4.46. 3-D layer-by-layer assembly

zyme sequence results in a lower reaction efficiency. Separating the two types of enzyme layers also affects the reaction efficiency. These facts suggest that reactor performance depends strongly upon the order that the enzymes are applied. Alternate layer-by-layer assembly permits free selection of the layering sequence and is useful for optimizing reactor structure. Various reactors with remarkable functions, such as controlling the product using the reaction sequence, are easily designed with this assembling technique.

The use of this method is not limited to smooth solid supports because of its simplicity. Figure 4.46 shows a multilayer assembly on a colloidal particle. Destruction of the template particle provides a hollow capsule with a skin made from the layer-by-layer film.

4.11

Hierarchical Higher Organization – From Bilayers to Fibers and Rods

In the previous sections, we have focused on molecular assemblies with relatively simple structures and shapes. However, amphiphiles possess the potential to form higher order structures with unique shapes through self-assembly

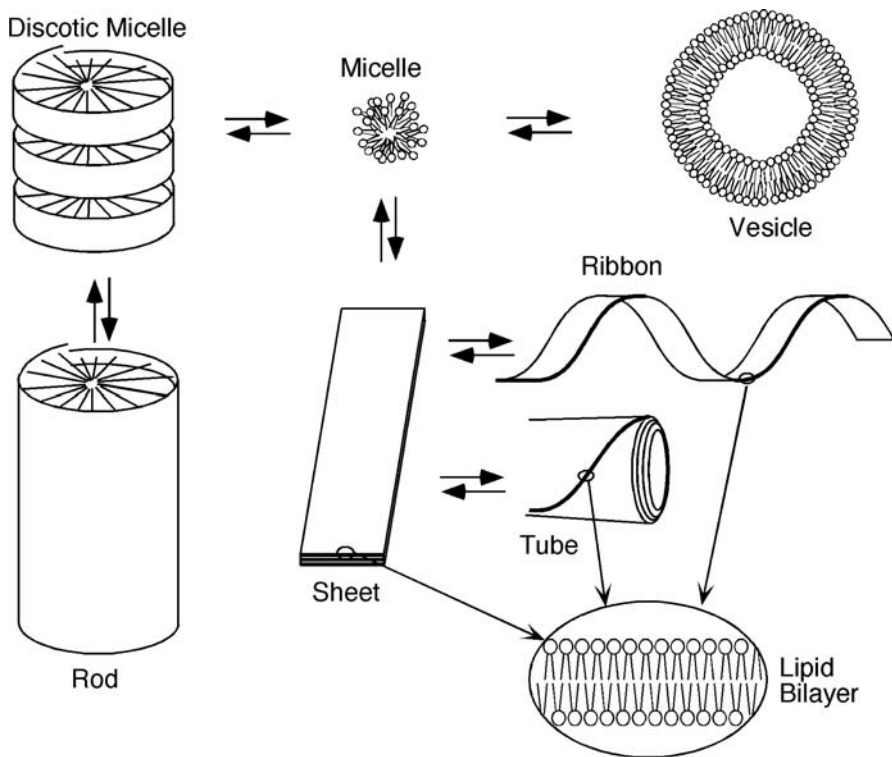


Figure 4.47. Superassembly of lipids and related compounds

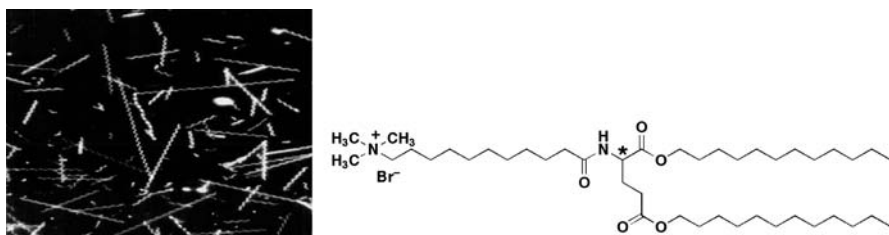


Figure 4.48. Molecular ribbon (N. Nakashima, S. Asakuma, T. Kunitake, *J. Am. Chem. Soc.*, 107, 509 (1985))

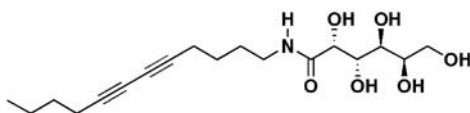
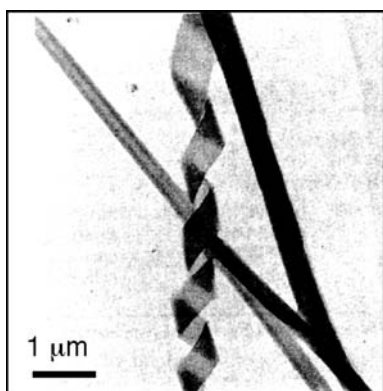


Figure 4.49. Twisted ribbon (D.A. Frankel, D. F. O'Brien, *J. Am. Chem. Soc.*, 116, 10057 (1994))

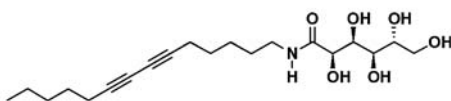
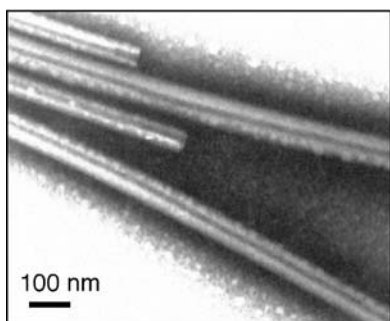


Figure 4.50. Molecular tube (J.-H. Fuhrhop, P. Blumtritt, C. Lehmann, P. Luger, *J. Am. Chem. Soc.*, 113, 7437 (1991))

processes. Some such structures are summarized in Fig. 4.47. These structures include disk-like micelles and rod-like supermolecules are illustrated. Further development of micellar and vesicle structures sometimes results

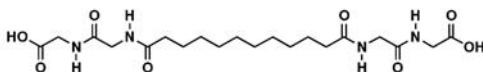


Figure 4.51. Vesicles trapped in a lipid tube (T. Shimizu, S. Ohnishi, M. Kogiso, *Angew. Chem. Int. Ed.*, 37, 3260 (1998))

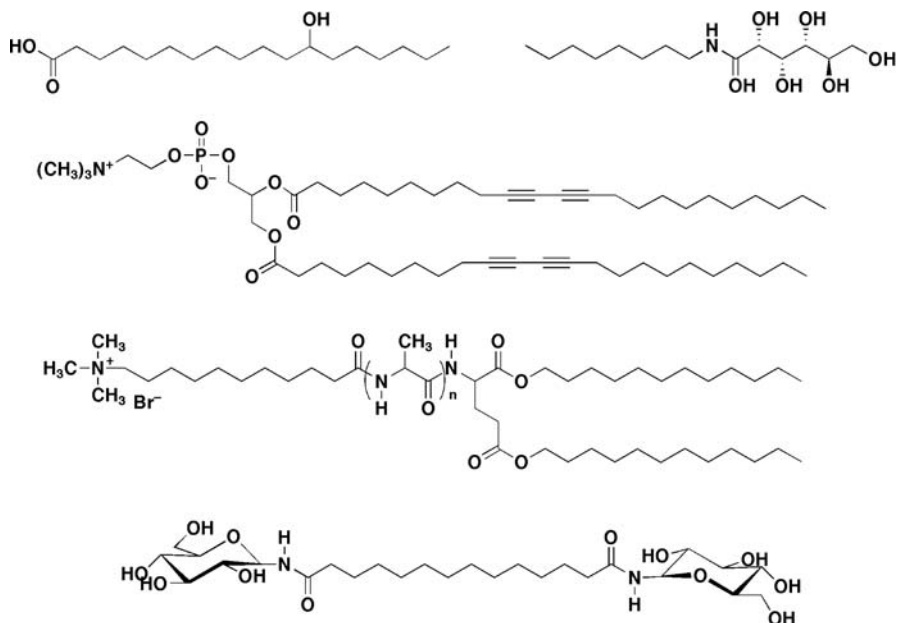


Figure 4.52. Examples of amphiphiles that form superstructures

in sheet structures consisting of a bilayer unit. When the sheet has curvature, helical ribbons and tubules are formed by twisting and rolling the sheets.

Figure 4.48 shows helical ribbon-like structures that exhibit high regularity and are formed from glutamate-based amphiphiles. The chirality of the glutamate α -carbon determines their helical sense. The fact that the information required to create this micrometer- or millimeter-sized structure is contained in such a small component molecule is astonishing. The superstructures shown in Figs. 4.49 and 4.50 were formed through the self-assembly of amphiphiles with polar heads containing sugar residues and hydrophobic tails of diacetylene. In the first example, a ribbon-like structure is formed where the helical

sense is again determined by the chirality of the sugar residue. When the ribbon structure is fused, a hollow tubular structure results, which is observable in Fig. 4.50. The internal diameter of the latter supramolecular tube is only around 10 nm. Figure 4.51 shows supramolecular assemblies formed from amphiphiles with glycylglycine units at both terminals. In this structure, the vesicles are trapped in the lipid tubes like frog's eggs.

Many types of amphiphile can form these supramolecular structures (see Fig. 4.52). Most of these have the ability to form hydrogen bonds – hydrogen bond formation significantly increases the stability of a supramolecular assembly. The presence of a chiral center sometimes leads to the formation of ribbon-like structure and twisted fibers.

These supramolecular structures can grow to sizes of microns, which is within the range of microfabrication techniques. In the future, these types of supramolecular assembly will be used in electrical circuits and semiconductor devices. Indeed, Fig. 4.53 shows a coaxial cable formed through molecular self-assembly. Its component molecule has a phthalocyanine at the center, and this is surrounded by four crown ethers and eight alkyl chains. These molecules assemble into rod-like structures, as confirmed by images obtained using an electron microscope. It was proposed that the structure of the cable consists of a electron-conducting phthalocyanine core column surrounded

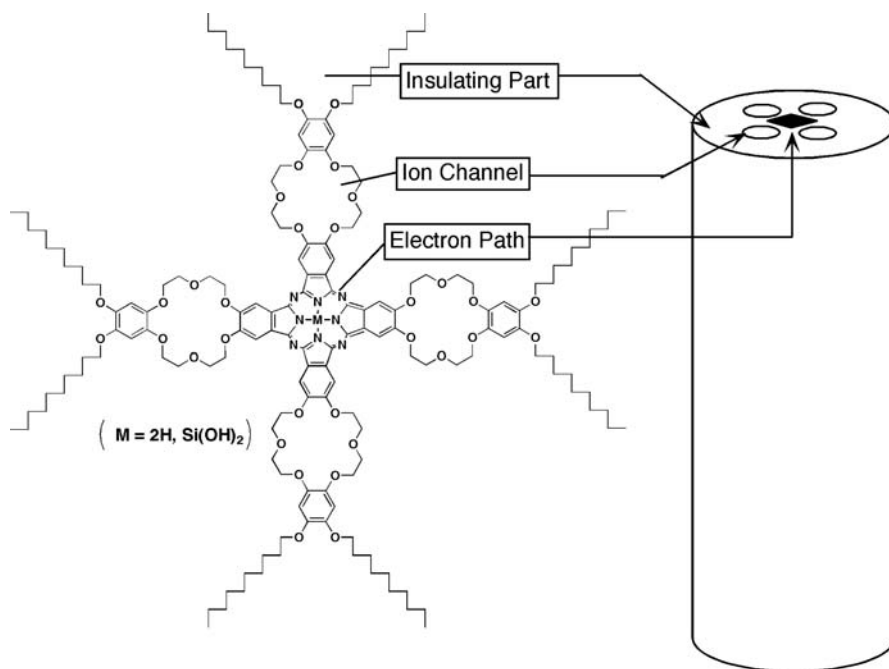


Figure 4.53. Molecular coaxial cable

by ion-conducting crown ether columns and an insulating hydrocarbon assembly. This system can therefore be regarded as multifunctionalized coaxial cable.

4.12 Artificial Molecular Patterns – Artificially Designed Molecular Arrangement

As described later in Chap. 5, the development of molecular devices requires enhanced control over the molecular arrangements of assemblies. Methodologies used to prepare fine structures are conceptually summarized in Fig. 4.54. So far, practical engineering has been largely based on microfabrication techniques, where fine structure is prepared from large bulk materials in what is called the “top-down” approach. However, although the top-down approach has been gradually fine-tuned over many years to be able to create smaller and smaller devices, it is believed that this approach will reach the limits of its precision in the near future. It will therefore be necessary to adopt an alternate strategy – structure formation based on self-assembly (the “bottom-up” approach) – if we wish to make devices smaller than the top-down approach is capable of (nanosized devices). If we can control and/or design the self-assembling process with more precision, it would enhance the range of desirable structures that could be prepared using the bottom-up approach. In other words, improving our control over self-assembly processes would significantly contribute to the development of nanotechnology. Even beyond the potential benefits to nanotechnology, there are many physical phenomena that exist on

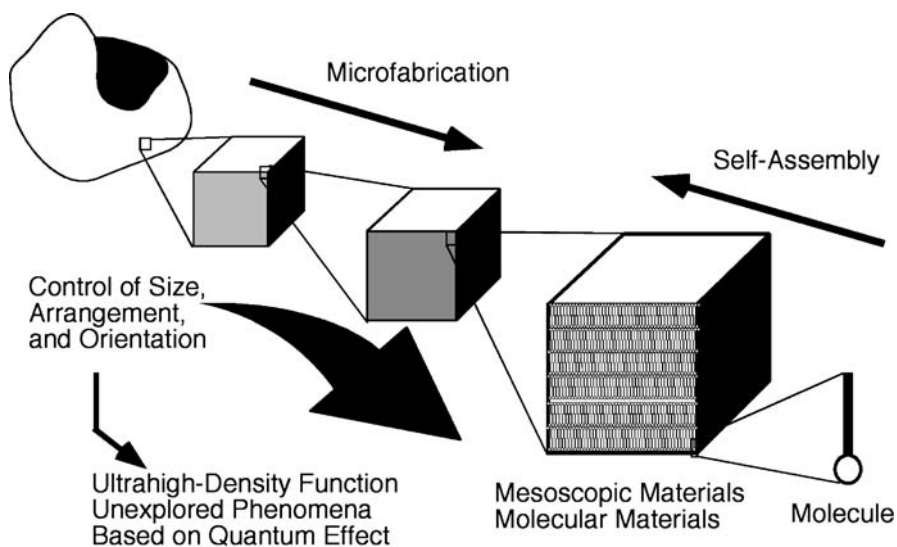


Figure 4.54. Approaches to creating fine structure

small (nanoscopic and mesoscopic) scales that are yet to be explored. Therefore, attempts to improve control over structure formation at small scales have attracted a great deal of attention from researchers working in fundamental science.

Figure 4.55 shows a technique for achieving patterned crystal growth on the surface of patterned self-assembled monolayer. This process is a combination of a conventional fabrication technique and a self-assembly process. In the first step, a patterned stamp containing a thiol compound with a polar group (such as a carboxylate group) was pushed onto a gold surface. A self-assembled monolayer of these molecules was therefore selectively formed on the parts contacted with the stamp. Next, the remaining bare surface was covered with

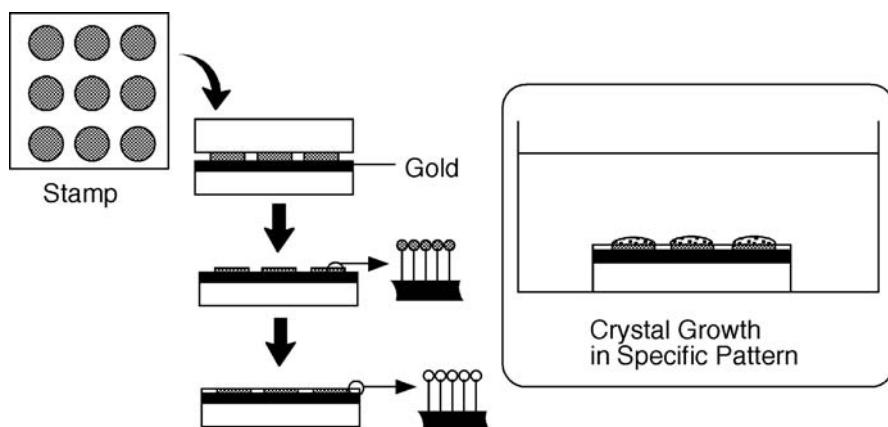


Figure 4.55. Patterned crystal growth

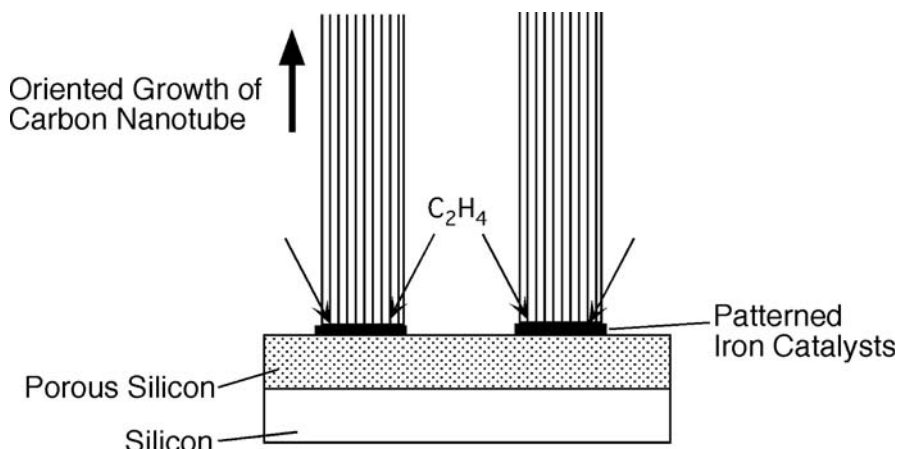


Figure 4.56. Patterned growth of carbon nanotubes

another thiol compound that did not have a polar group attached, resulting in a pattern of two polar and nonpolar thiols on the surface. Then the surface was immersed in a supersaturated calcite solution. Highly oriented calcite crystals grew on the areas covered with the polar thiol, but not on the areas covered with the nonpolar thiol. Since a wide range of patterns and functionalities can be used with this technique, various kinds of highly oriented crystal patterns could be prepared.

Because it is believed that carbon nanotubes will play an important role in ultrasmall device preparation in the future (see Chap. 5), fabricating regular supramolecular assemblies of carbon nanotubes represents an important challenge. One example is shown in Fig. 4.56. A layer of porous silicon is first prepared on a silicon support, and iron is then deposited on the porous silicon using an appropriate mask and an electron beam. When the patterned surface is exposed to ethylene gas, carbon nanotubes grow selectively on the sites covered with the iron catalyst. Again, this technique allows a range of different catalysts and patterns to be used, and various patterns of carbon nanotube arrays are easily fabricated.

4.13

Artificial Arrangement of Molecules in a Plane – Two-Dimensional Molecular Patterning

The patterns described in the previous section were fabricated using man-made templates such as stamps and masks, which does not have molecular level resolution and precision. Although some techniques for producing structures in a controlled, layer-by-layer manner to molecular level precision do exist (such as the LB method and alternate layer-by-layer assembly), it is difficult to artificially control the molecular arrangement in a single layer. There do not appear to be any general methods for controlling two-dimensional molecular arrangement. While amphiphile molecules do form regular arrangements in a monolayer, this arrangement is dictated by the nature of the molecules; it is not controlled artificially. However, if we were able to successfully control amphiphile arrangement in a plane – a monolayer – it could aid the development of new kinds of molecular devices. In the following, we describe molecular patterning on a two-dimensional plane – the air–water interface – using molecular recognition.

Among the different aspects of molecular arrangement, the sequential ordering of different amphiphile molecules is potentially the most difficult to control. The strategy that can be used to control the sequential ordering in a monolayer is schematically depicted in Fig. 4.57. When three types of molecule are mixed in a monolayer, they usually arrange themselves randomly. However, the addition of an appropriate template molecule to the aqueous subphase is expected to change this situation: amphiphiles bind to specific sites in the template molecule, and so artificial arrangement of the amphiphiles is achieved.

The complexes formed between the template and the amphiphiles can then align to give a regular two-dimensional molecular pattern. As described in Chap. 2, molecular recognition through hydrogen bonding at the air–water interface is efficient and selective. Therefore, the molecular arrangement can be defined very precisely via the template structure.

Figure 4.58 shows an example where flavin adenine dinucleotide (FAD) was used as a template molecule. Guanidinium amphiphiles, orotate amphiphiles and diaminotriazine amphiphiles were selectively recognized by phosphate, adenine, and isoalloxazine moieties, respectively. Here, we focus on a simpler two-component system containing guanidinium and orotate amphiphiles. π -A (surface pressure–molecular area) measurements and XPS (X-ray photoelectron spectroscopy) elemental analysis of various mixed monolayers of guanidinium and orotate amphiphiles confirmed stoichiometric complex formation (two guanidinium and one orotate bind to one FAD). The monolayer formed on the surface of the water was transferred onto a molecularly flat mica surface. Observation of the monolayer surface using atomic force microscopy (AFM) revealed an interesting effect of the FAD template on the structure of the molecular pattern (Fig. 4.59). When the guanidinium/orotate mixed monolayer was transferred from pure water (with no FAD), a monolayer surface with an even height of alkyl chains was observed. As illustrated in Fig. 4.60, the alkyl tails of the two types of component assemble to maximize the contact between the alkyl chains, resulting in even surface morphologies of alkyl chains. In contrast, binding of the FAD to the mixed monolayer led to the formation of regular patterns consisting of periodic changes in height (with an amplitude of angstroms). The binding of the two amphiphiles to the same FAD molecules introduced discrepancies into the molecular arrangement due to the difference

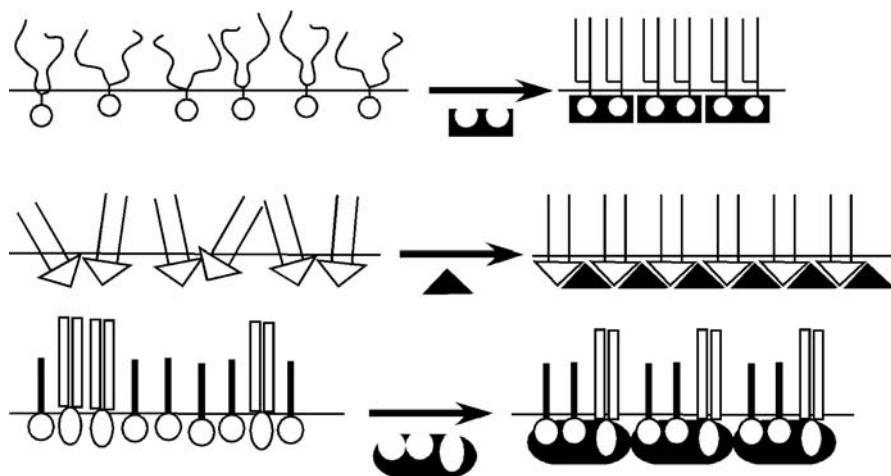


Figure 4.57. Concepts behind two-dimensional molecular patterning

in molecular length between the guanidinium amphiphile and the orotate amphiphile. This example demonstrates how to prepare a surface with a pattern consisting of periodic changes in height with high precision through specific molecular recognition.

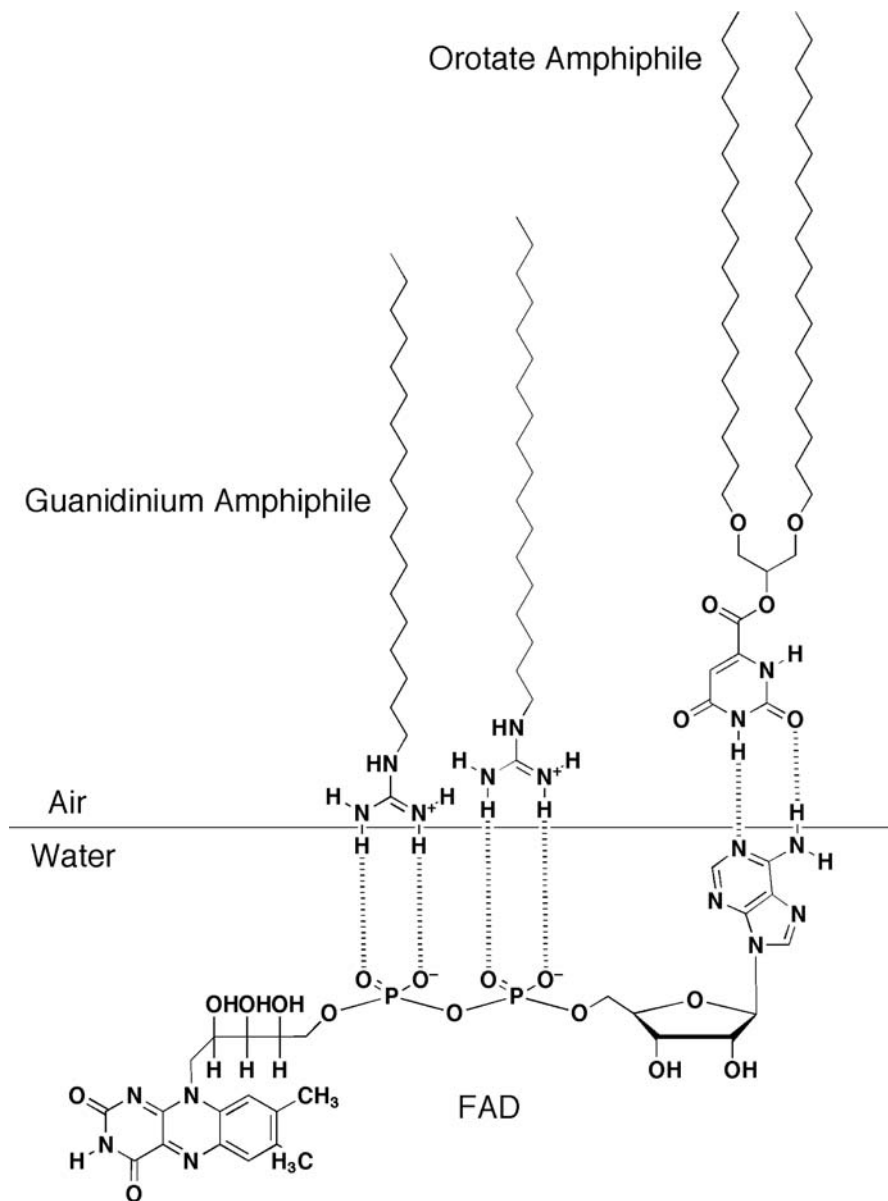


Figure 4.58. Array of amphiphiles templated by aqueous FAD

More extended supramolecular patterns can also be fabricated in two dimensions. In an example described in Fig. 4.61, the molecular ribbon formed by melamine and barbituric acid was used for two-dimensional molecular patterning. The monolayer of dialkylmelamine transferred from pure water was not strong enough to permit imaging. The addition of guest barbituric acid to the subphase led to the formation of one-dimensional melamine/barbituric acid supermolecules through complementary hydrogen bonding, which further assembled into regular two-dimensional patterns. AFM observations of the complexed monolayer showed a regular arrangement of alkyl chains. This concept could be extended to incorporate a nucleic acid template with a specific sequence. The information stored in the DNA can therefore be transferred into two-dimensional structural patterns.

In the examples mentioned above, the molecules self-assemble into specific patterns based on various molecular recognitions. However, predicting the shape of the resulting complex is not always easy because its flexibility could result in an unintentional change in shape. However, if amphiphiles with rigidly defined structures were spread on the surface of water, the molecules should assemble like tiles, providing highly predictable two-dimensional patterns. In the first models of such systems, simple unit shapes were initially considered. Among them, regular polygons such as triangles, squares and hexagons can

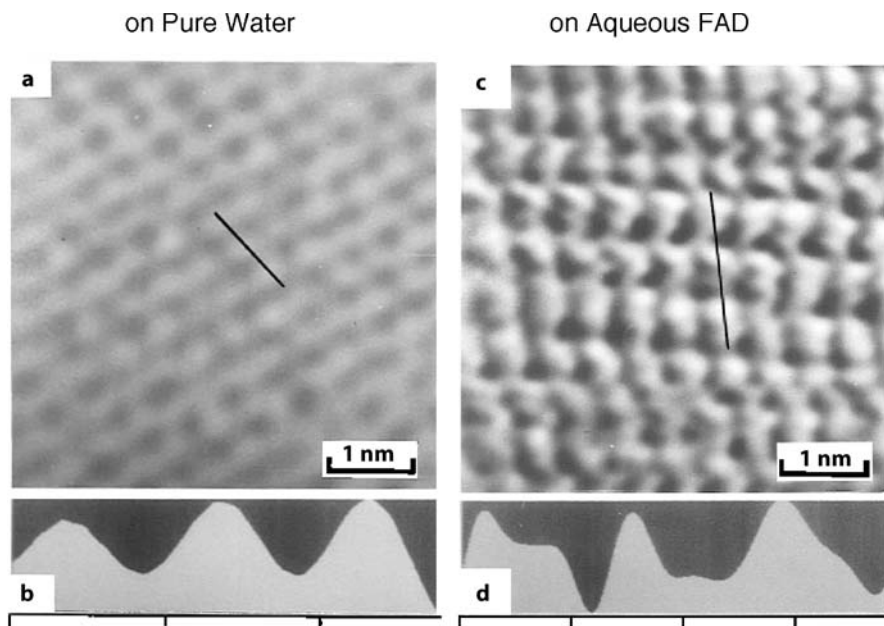


Figure 4.59. Molecular images of patterned surfaces (Y. Oishi, Y. Torii, T. Kato, M. Kuramori, K. Suehiro, K. Ariga, K. Taguchi, A. Kamino, H. Koyano, T. Kunitake, *Langmuir*, 13, 519 (1997))

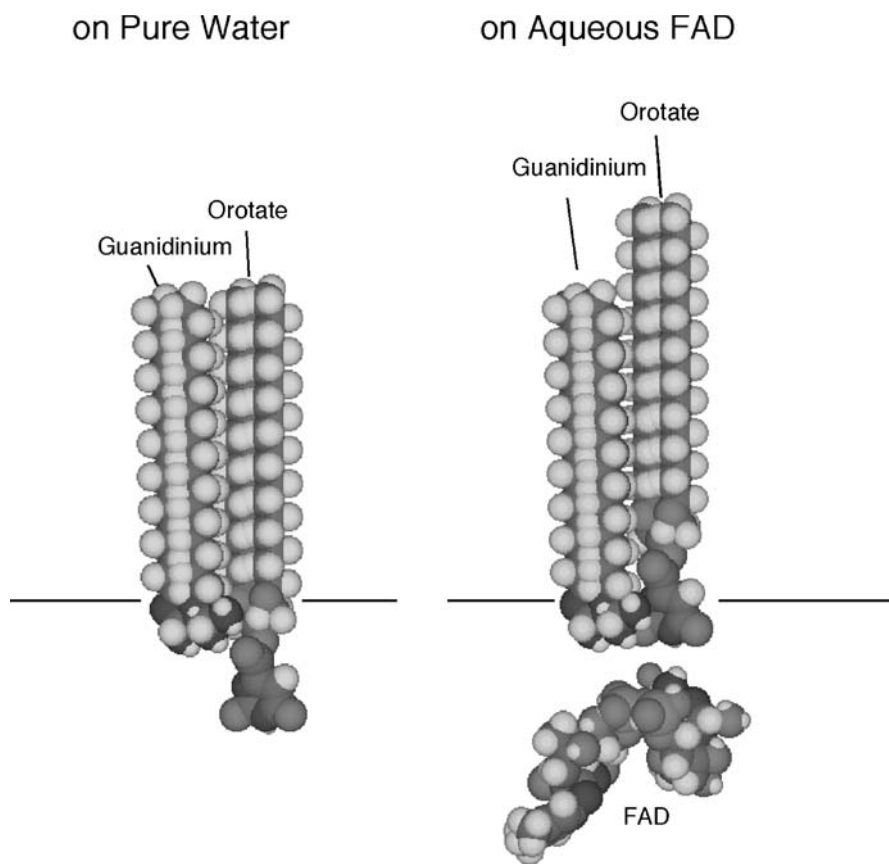


Figure 4.60. Molecular model of the origin of patterns (Y. Oishi, Y. Torii, T. Kato, M. Kuramori, K. Suehiro, K. Ariga, K. Taguchi, A. Kamino, H. Koyano, T. Kunitake, *Langmuir*, 13, 519 (1997))

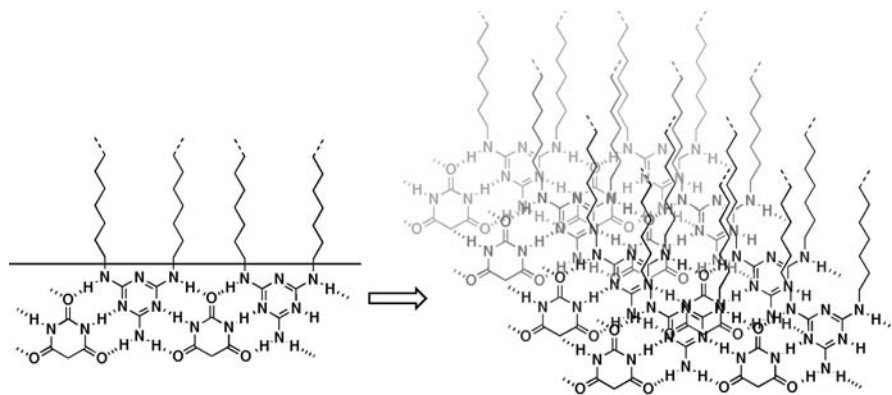


Figure 4.61. Regular molecular arrangement based on molecular ribbons

completely fill a two-dimensional plane. Hexagons have the highest symmetry and they can minimize rotational motion within the plane. Therefore, molecules with seven alkyl chains (six chains arranged around a central chain) were designed and implemented as hexagonal amphiphiles (see Fig. 4.62). This amphiphile was able to fill a plane. Because the center chain does not need to be equivalent to the others, it can form isolated tip or dip structures with a regular arrangement.

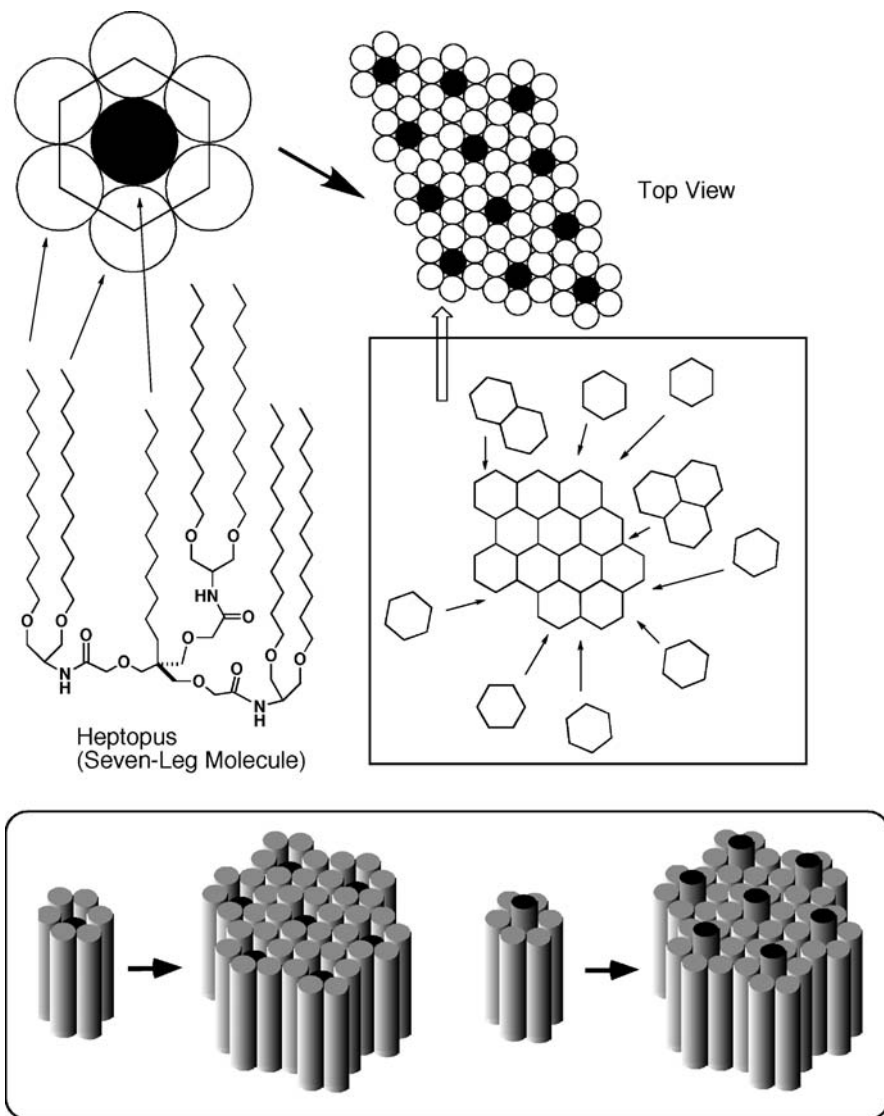


Figure 4.62. Pattern formation using hexagonal molecular units

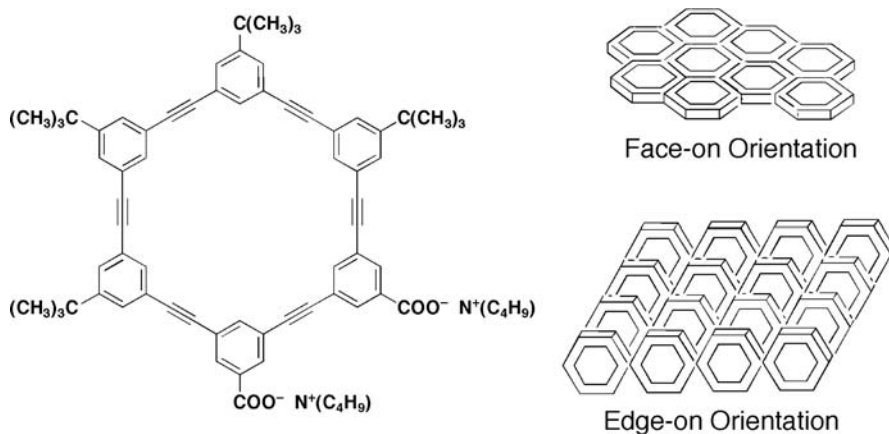


Figure 4.63. Patterned array of rigid molecular units

Figure 4.63 shows another approach to realizing monolayers of rigid-shaped molecules. A rigid macrocyclic compound was modified with hydrophobic and hydrophilic functional groups. This compound is amphiphilic and forms monolayer structures on the surface of water. Although either the face-on or the edge-on orientation is possible on water, the used compound was thought to have the edge-on one, judging from experimental data.

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5 Applications of Supermolecules – Molecular Devices and Nanotechnology

Up to now, we have discussed the formation of various molecular structures and assemblies – supermolecules – via supramolecular concepts. In this chapter, we move away from supermolecule preparation and consider practical applications of supermolecules. Approaches to functionalizing supramolecular systems are explained as various *molecular devices* are introduced. Molecular devices are functional materials that are structurally precise down to the molecular level that are constructed using the concepts of supramolecular chemistry. Supermolecules capable of electron conduction and electrical switches (molecular electronic devices), supermolecules that respond to light and manipulate photonic information (molecular photonic devices), supermolecules that can be used for information processing and calculations (molecular computer), and supermolecules that move, rotate, and catch targets (molecular machines) are introduced as examples of molecular devices. Well-defined molecular assemblies provide useful devices for direction-controlled information transfer. These examples suggest that supramolecular chemistry will be the main tool used in the development of nanotechnology – technology based on devices with nanoscale features – which is predicted to revolutionize our lives in the near future.

Contents of This Chapter

5.1 What is a Molecular Device? The development of ultras-small functional systems is predicted to enhance our standard of living. The ultimate goal of ultras-small technology is device preparation using supermolecules.

5.2 Reading Signals from Molecular Devices In order to make use of the output from a molecular device we need ways to evaluate the state of such a device. Often this is equivalent to reading the signal from the device. Various external devices, from simple electrodes to STM tips, can be used to read signals from molecular devices.

5.3 Molecular Electronic Devices – Controlling Electricity Using Supermolecules

Molecular wires and molecular switches have been developed for molecular electronics. In particular, much of the progress made in the field of molecular electronics is based on the application of carbon nanotubes.

5.4 Molecular Photonic Devices – Controlling Light with Supermolecules

It is expected that photonics will be used in many applications in the near future. Molecular recognition can be used to control light emission from molecules in molecular photonic devices.

5.5 Molecular Computers – Supermolecules that can Think and Calculate

Molecular logic devices that can process multiple signals have been combined into a molecular calculator. A DNA-based computer with parallel information processing has also been proposed.

5.6 Molecular Machines – Supermolecules that can Catch Objects, Move and Rotate

Molecules that rotate in a certain direction and actuators based on carbon nanotubes are explained. Mechanical control of molecular recognition and mechanical movement based on molecular recognition are also discussed.

5.7 Molecular Devices with Directional Functionality – Supermolecules That Transmit Signals in a Desired Direction

The ability to direct the flow of information in a desired direction is crucial to molecular device development. Controlled organization of functional molecules, mainly using the LB method, was used to prepare molecular devices regulating electron or energy flow.

5.8 Supramolecular Chemistry and Nanotechnology – Looking Ahead

Nanotechnology, including molecular devices, are expected to play a major role in many future technologies, such as those associated with space exploration. However, the ultimate examples of nanosized systems are seen in nature.

5.1**What is a Molecular Device?**

If we could create a molecular-size object that worked like an IC chip, incredibly small computers with very high information densities could be constructed. Such a dream arouses our scientific curiosity, and could also significantly enhance our standard of living. Some of the most serious problems faced by the world today, such as environmental pollution and energy production, are at least partially due to the large sizes of various important devices, machines and apparatus. As well as resulting in poor energy efficiency, a large device/machine size limits portability. Therefore, to use such devices/machines, we have to travel to the places where they are located, which can result in traffic (and

its associated problems, such as pollution) and can encourage overpopulation in some areas. If the sizes of the devices were reduced to make them more portable, we would not need to travel to use it; we could carry the devices around with us. Therefore, the development of highly functional devices of a size comparable to cellular phones and watches would revolutionize our lifestyles and standard of living.

One of the ultimate goals of those developing new devices is the preparation of molecular devices, where molecules or molecular systems replace functional units. Molecular devices are expected to provide the key to the development of nanotechnology.

Concepts of molecular devices were first proposed in the 1970's. The example shown in Fig. 5.1 was proposed by Forrest L. Carter of the US Naval Research Laboratory. He proposed a molecular device where functional moieties were bridged by conductive links. When an electron is added from the input terminal, the positive charge at the end of conductive $(SN)_n$ chain is neutralized, which is accompanied by a change in potential. This potential change suppresses electron tunneling and affects the conduction of electrons between the $V(-)$ terminal and the output terminal. Introducing a variety of input terminals would lead to the development of a system where the signal output was controlled by the pattern of inputs to the system.

This example is based on a covalently linked, complicated molecule which is difficult to synthesize. We can overcome this difficulty by using supramolecular concepts. Complicated functional systems can be constructed through the supramolecular assembly of relatively simple components. The supramolecular approach has the additional advantage of permitting us great freedom in terms of combining functional parts.

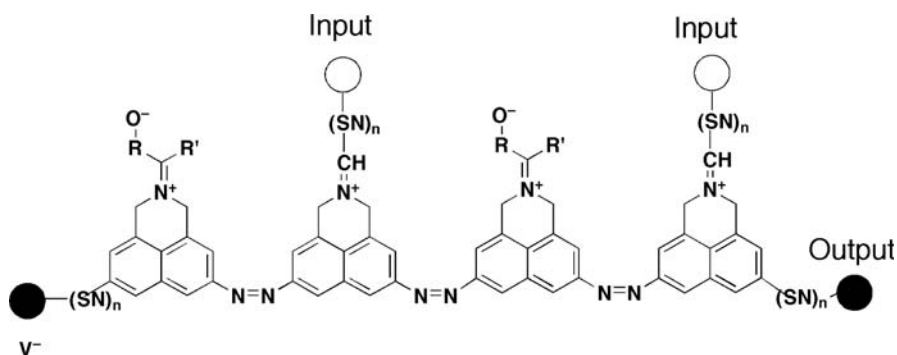


Figure 5.1. Example of a proposed molecular device

5.2

Reading Signals from Molecular Device

Before we look at the preparation and functionality of various molecular devices, we will first consider how evaluate the state of a molecular device. Evaluating the state of a molecular device is often deeply connected to an important process: reading the signal from a device. Molecular devices are usually combined with external devices that can take in signals from the device and convert them into a form that we can understand and interpret. Therefore, it is important to understand the methods used to evaluate molecular device state.

There are actually a large number of ways to evaluate the state of a supramolecular system used in a molecular device, and so only a few – the most important – are explained here (Fig. 5.2). When the targets are supermolecules dissolved in solution, spectral methods are widely used. Molecular interactions sometimes induce various changes in the nature of the supramolecular system. For example, changes in electronic state are detected by UV-Vis absorption spectroscopy and fluorescence spectroscopy. Changes in enantiomeric structure and the environment of the molecule are evaluated by circular dichroism (CD) spectroscopy. Nuclear magnetic resonance (NMR) spectroscopy and infrared (IR) spectroscopy, which are usually used to determine the chemical structure, are also useful for evaluating molecular interactions. For example, these methods provide powerful ways to determine hydrogen bond formation: hydrogen bonding causes shifts in the NMR and IR spectra, meaning that they can be used to determine the sites involved and the strength of the bonding.

Analyses of ultrathin films are also conducted via spectroscopic methods, but higher sensitivity is usually required. π -A isotherm measurement

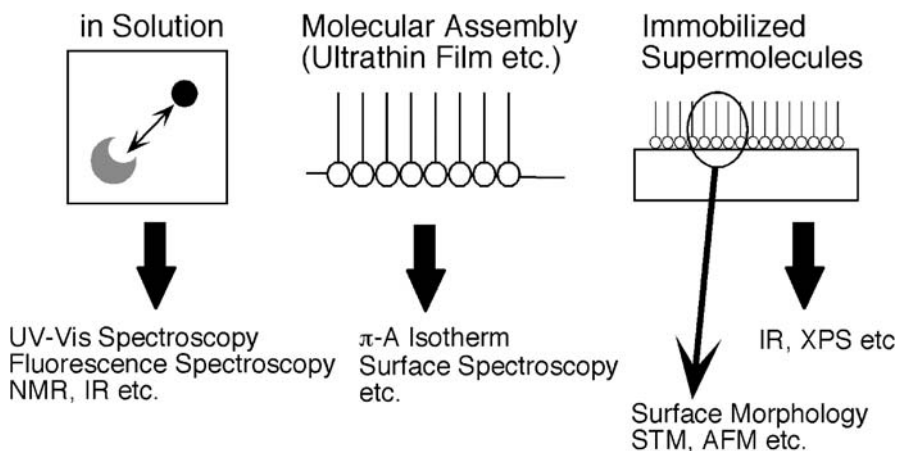


Figure 5.2. Methods of evaluating supramolecular state

is a unique way to evaluate the state of a molecular assembly. Layered LB structures or films and layered films on solid supports are typically investigated via X-ray diffraction (XRD). Elemental analyses on ultrathin films are carried out using X-ray photoelectron spectroscopy (XPS). This method is a powerful way of quantifying guests binding to the ultrathin film, as described in Chap. 2.

Methods for directly observing supermolecules have recently been developed. Scanning probe microscopy (SPM) has become a particularly useful method in the field of nanotechnology. The general concept of SPM is summarized in Fig. 5.3. A very fine tip is used in this method. As the tip approaches the sample surface, various interactions occur between the tip and the surface which result in various kinds of forces (such as atomic forces). These forces are felt by the tip and converted into electrical signals.

There are various forms of scanning probe microscopy. Among the most popular are atomic force microscopy (AFM) and scanning tunneling microscopy (STM). In AFM, the tip is scanned across the surface in such a way that the atomic force felt by the tip is kept constant (which is equivalent to saying that the tip is always the same distance from the surface). During the scan, any change in the surface topography (surface feature) produces a change in the atomic force. Therefore, to keep the atomic force constant, the tip is moved closer to or further from the surface. Therefore, the movement of the tip directly reflects the topography of the surface in AFM. STM works on a similar principle but monitors the electron tunneling current instead of the atomic force. These methods supply the surface topology to atomic-level precision. Images of supermolecules can be obtained directly. Other forces, such as those related to friction, magnetism and electrostatics, can also be monitored in other variants of SPM. High spatial resolution spectral imaging can also be performed based on near-field optical effects.

In practical molecular devices, the supramolecular system is sometimes immobilized on an external device which reads the output from the system. An electrode is a typical example of this kind of external device. Various electrodes with ultrasmall dimensions are available, and are therefore well-suited to molecular device preparation. Electrodes can also be used as a solid support for LB films and self-assembled monolayers. In the example shown

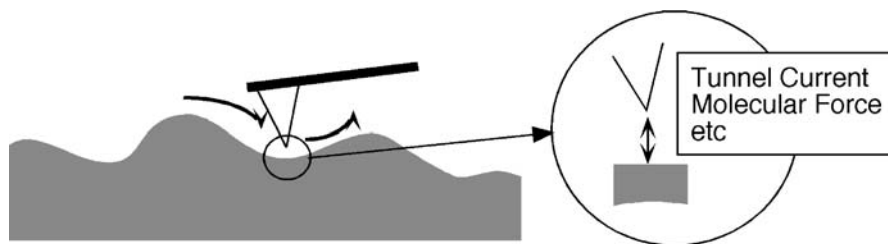


Figure 5.3. Scanning probe microscopy

in Fig. 5.4, a supramolecular component immobilized on an electrode and based on a cyclodextrin derivative is used as a sensing site for a specific guest molecule. Cyclodextrin derivatives with long alkyl chains are immobilized on the surface of an electrode using a LB or SAM method (see Fig. 4.40 for a similar example). The SAM method provides particularly stable immobilization of the monolayer component. The modified electrode was immersed in an aqueous solution of marker ions such as ferrocyanate ion. The marker ions can reach the surface of the electrode and produce redox signals when the solution does not contain the guest molecules. However, the presence of guest molecules in the solution suppresses the redox signals from the marker ion because the guest molecules bind to the cyclodextrin and block the path to the surface of the electrode. Recognition of the guest molecules by cyclodextrin was converted to a quantitative electric signal.

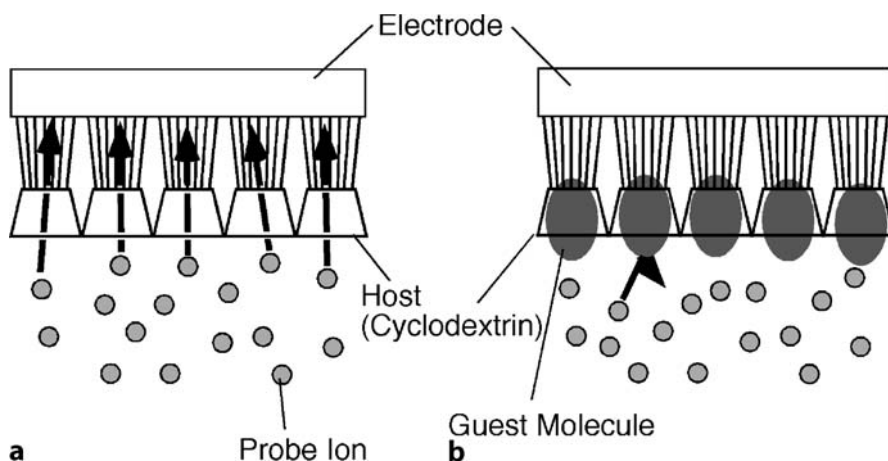


Figure 5.4. Electrical detection of guest recognition

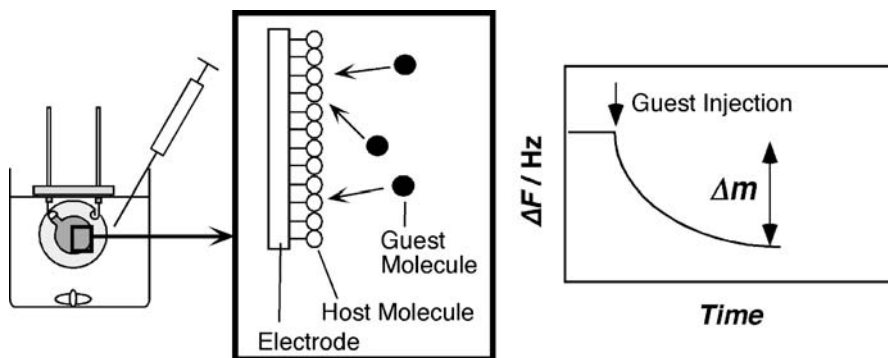


Figure 5.5. Sensitive mass detection using a quartz crystal microbalance

Other external devices are used if different output signals are required. For example, immobilizing ultrathin films of functional molecules on optical fibers allows us to detect photonic responses of functional supramolecular systems. Adsorption of specific molecules on supramolecular assemblies can be sensitively detected by surface plasmon resonance (SPR). Coupling supramolecular systems to semiconductor devices is advantageous way to prepare ultrasmall devices. Use of a field-effect transistor (FET) as an external device is a powerful method of fabricating small sensing devices. The current between the source and the drain is regulated by the gate potential. Functional supermolecules were immobilized on the gate electrode, and the surface potential changes resulting from specific guest binding to the supermolecules induced a change in the source–drain current. These sensing systems can be integrated via microfabrication techniques.

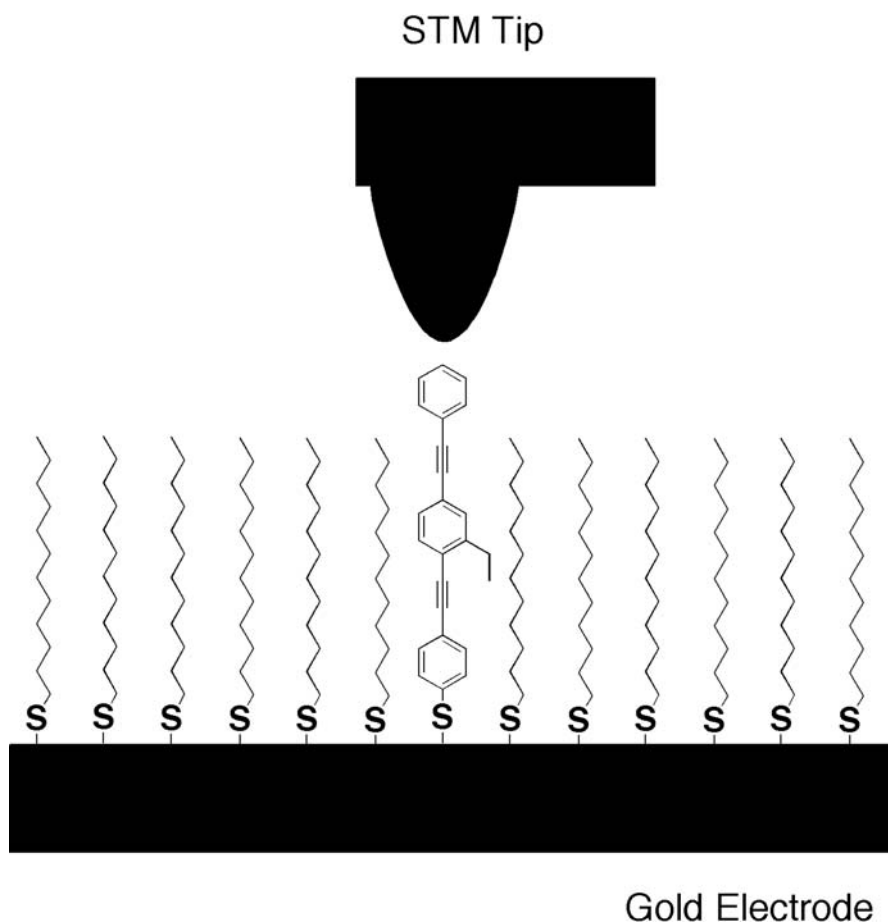


Figure 5.6. Measuring the conductivity of a single molecule

Figure 5.5 shows a unique external device, a quartz crystal microbalance (QCM). A thin plate of quartz crystal with a specific face generates piezoelectricity and exhibits a very stable resonance frequency upon the application of a voltage (this phenomenon means that quartz is widely used in timing mechanisms – in clocks for example). Metal electrodes were deposited on both sides of the quartz plate in the QCM. When some material was adsorbed onto the electrode, the resonant frequency decreased in proportion to the change in mass. In the case of a 9 MHz AT-cut QCM, a frequency change of 1 Hz was observed for a mass change of ~ 1 ng. Measuring frequencies to a precision of 1 Hz is not too difficult, while measuring masses to a precision of 1 ng using other methods is usually very difficult. Therefore, the QCM is very useful device for detecting tiny changes in mass. Figure 4.5 shows an example where host supermolecules were immobilized on the surface of QCM electrode. Inclusion of the guest by the host induces a decrease in frequency, and the adsorption behavior can be monitored in real time. The frequency reaches a constant value when the adsorption equilibrates.

Note that the QCM detects a very general parameter, the change in mass. Therefore, QCM sensing systems can be applied to a wide range of substances independent the properties of the guest. With appropriate immobilized supramolecular system design, QCM systems can be used to check for various guest molecules, such as nucleic acid, rectin and viruses.

Reading signals from individual molecules or supermolecules requires the use of ultrasmall external devices. Figure 5.6 shows one example of an ultrasmall external device, an STM tip. The conductive molecule is coimmobilized as a self-assembled monolayer along with an insulating thiol compound on the surface of conductive material. Scanning the surface of the SAM using the STM tip enables us to detect the current that passes through the molecule of interest. Recent progress in measuring techniques means that we can also detect signals from a single molecule using other methods.

5.3

Molecular Electronic Devices – Controlling Electricity Using Supermolecules

In the following sections, we will discuss various examples of molecular devices that have been actually developed. Most modern machines contain electrical circuits. In order to mimic but highly miniaturize such machines, it is very important to first develop molecular sized electronic parts and then find a way to combine them into molecular electronic devices.

Electron-conducting wire is the first requirement for molecular electronics. Molecules with conjugated linkages, such as conductive polymers, are strong candidates for this “molecular wire”. Especially when used in supramolecular systems, A regulated conjugation length is sometimes advantageous. Figure 5.7 shows an example of a molecular wire where two pyridinium moieties are connected by a conjugated chain. The length of this molecular wire fits

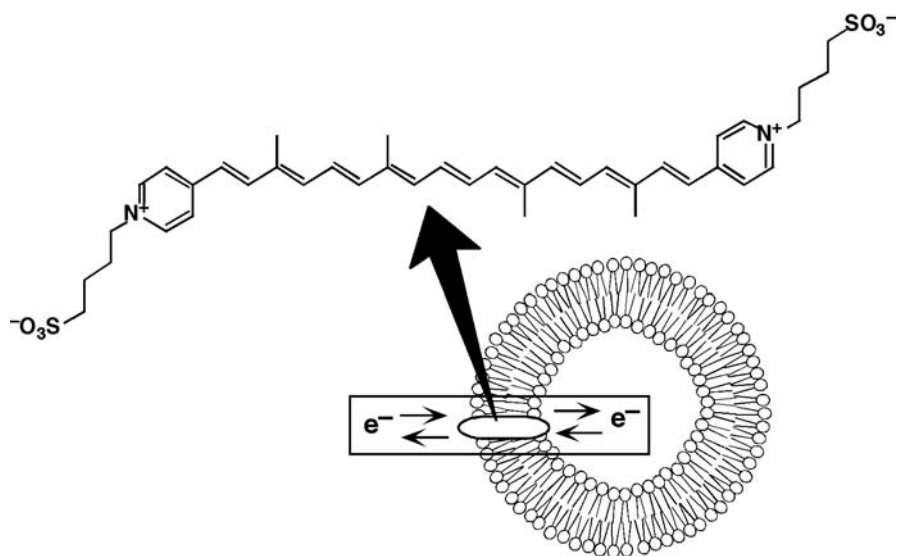


Figure 5.7. Molecular wire in a lipid bilayer

the width of a phospholipid bilayer, and the wire is accommodated effectively into the bilayer skin of a liposome. Because the surrounding bilayer was basically insulating, the molecular wire acts as an isolated conductive wire. When reduction and oxidation reactions are performed separately in the inner liposomal phase and the outer bulk phase, electrons are transmitted through this molecular wire. This system can therefore be regarded as a form of molecular wiring.

The ability to connect electronic parts is crucial to the construction of circuit-like molecular devices. However, it is quite difficult to connect components solely through covalent linkage. Therefore, it would be better to connect the electronic parts through supramolecular interactions. In fact, biological systems use a similar concept. Information is transmitted as electrical signals through nerve systems, but nerve cells are not connected to each other covalently. There is a synapse junction between the nerve cells where signals are transmitted via a chemical mediator.

Electron transfer via a noncovalent junction was achieved artificially using the example shown in Fig. 5.8. In this system, the electron donor zinc porphyrin was covalently connected to guanosine, and an electron-accepting quinone was linked to the cytosine. These two parts associate through complementary hydrogen bonding between the guanosine and cytosine. When this pair were irradiated with light of an appropriate wavelength, electron transfer occurred from the zinc porphyrin to the quinone. This example demonstrates that electrical connections can be achieved between molecular parts via noncovalent supramolecular interactions.

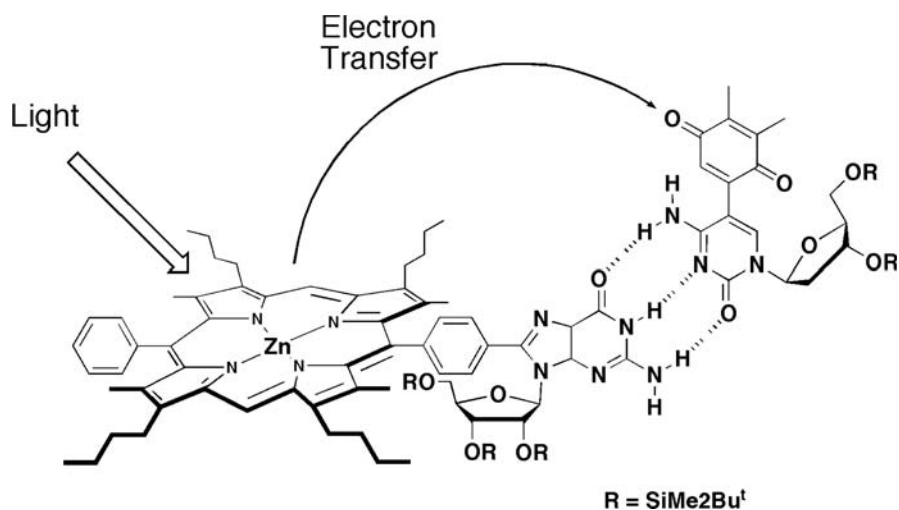


Figure 5.8. Electron transfer between a pair of supermolecules

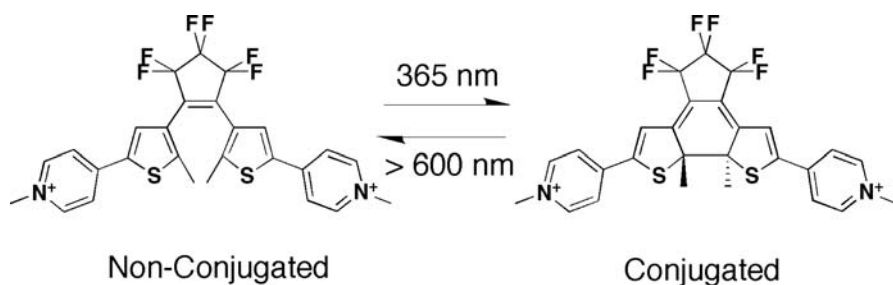


Figure 5.9. Molecular switch

An electrical switch is another important element for regulating electron flow. Direct connection and disconnection between lead wires is usually used to regulate electricity flow. The molecule shown in Fig. 5.9 mimics this kind of switch. When the center of the molecule is uncyclized, a fully conjugated path through the molecule is not available and so the molecular switch is in the OFF state. Irradiating the molecule with light at 365 nm induces cyclization of the molecule. When it is cyclized, a fully conjugated path through the molecule becomes available, and so the molecular switch is turned ON. The molecule can revert its OFF state by irradiating it with light of > 600 nm. If this kind of molecular switch was introduced into a supramolecular system, molecular electric circuits switched by photoirradiation could be constructed.

Various molecular conductive wires and molecular switches should become available in the near future. Connecting them in a logical way would

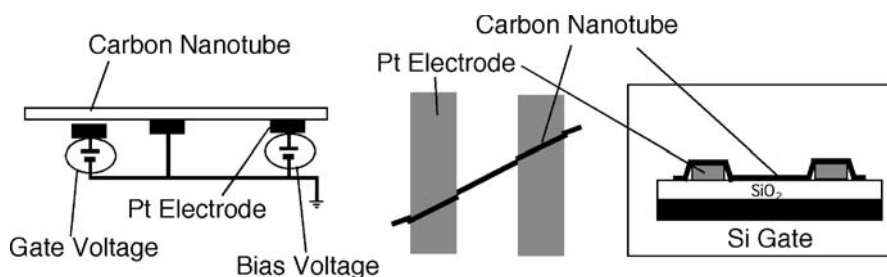


Figure 5.10. Transistor based on a carbon nanotube

result in the construction of molecular electrical circuits. However, current technologies make the construction of such circuits very difficult, and so connecting molecular devices to artificial fabricated structures could provide a more realistic approach. Such objects could be fabricated by engineering tools and connected to artificial structures such as ultrasmall electrodes. Supermolecules with sizes comparable to those of microfabricated structures would be especially useful when creating these objects. Carbon nanotubes satisfy this requirement. For example, single-walled carbon nanotubes have diameters measured in the nanometers (1–2 nm), but they are microns in length. In addition, the electronic state of a carbon nanotube can be estimated theoretically. These advantages mean that carbon nanotubes currently play a central role in molecular device preparation. When the nanotube structure is completely symmetric, it can be used as a one-dimensional quantum wire. In the following, a few examples of molecular electronic devices based on carbon nanotubes are introduced.

An ultrasmall transistor can be prepared from a carbon nanotube and some microelectrodes. Figure 5.10 shows the structure of the transistor, where a carbon nanotube bridges two platinum electrodes that were deposited on a plate of Si/SiO₂. The current induced upon the application of a voltage between the two electrodes was measured at very low temperatures. Maintaining the bias voltage between the two measuring electrodes, the gate voltage applied to the third electrode was altered, resulting in a current pulse. A plausible mechanism for this phenomenon is shown in Fig. 5.11. Electron transfer between different energy levels by thermal excitation was suppressed by the very low temperatures. Current flow is possible only when the Fermi potential of the electrode matches the energy level of the carbon nanotube. When the electrostatic potential of the carbon nanotube was gradually changed by scanning the gate voltage, at some point the electrode Fermi level and the nanotube energy level matched, resulting in a current pulse. Here, the quantization of the energy levels of the carbon nanotube at low temperatures is reflected in the discontinuous current response. At elevated temperatures, this quantum effect is far less noticeable, but even at room temperature the state of the nanotube

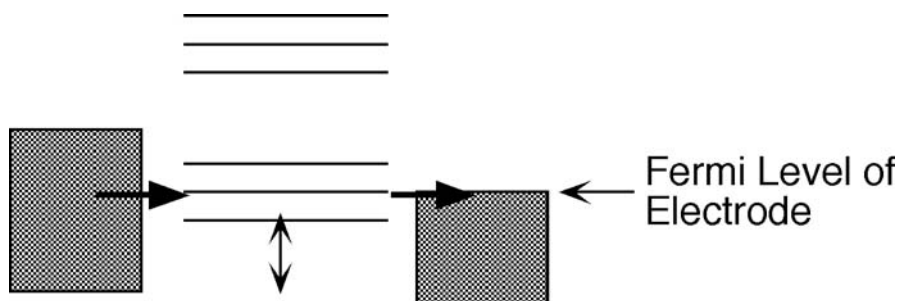


Figure 5.11. Electron conduction by matching energy levels

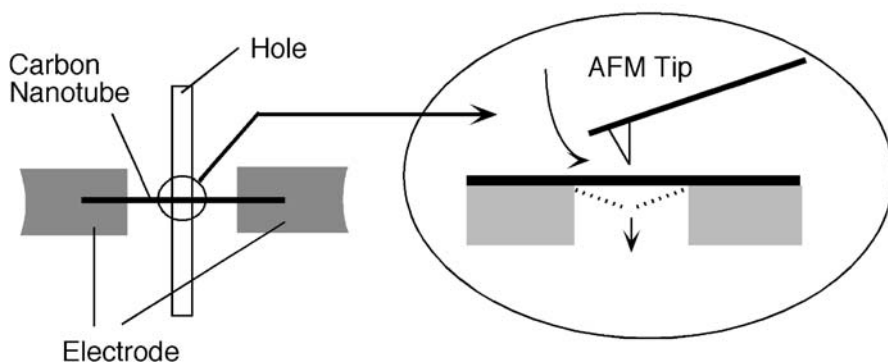


Figure 5.12. Mechanical switch based on altering the conductivity of a carbon nanotube

can still be switched (between conductive and insulating) by altering the gate voltage. This system can be regarded as a field effect transistor (FET), and the resulting molecular device is called a TUBEFET device.

Mechanically deforming the carbon nanotube alters its electric properties. In the example shown in Fig. 5.12, a carbon nanotube was bridged between two electrodes separated by a gap. When the middle of the carbon nanotube was pushed by an AFM tip, the nanotube was bent and its conductivity dropped. The electron conductivity was correlated with the degree of bending, which was measured from the position of the AFM. This process was repeatable. The bending of the carbon nanotube induced the formation of some nonconductive SP^3 orbitals within its structure, altering its conductivity. This behavior is somewhat reminiscent of a switch.

One serious issue with the construction molecular devices is how difficult it is to precisely place each supramolecular element into the correct position. It would be much easier to draw nanocircuits if we could create supermolecules at desired positions. In the example shown in Fig. 5.13, molecular wires of conductive poly(diacetylene) are drawn by an STM tip in a highly controlled

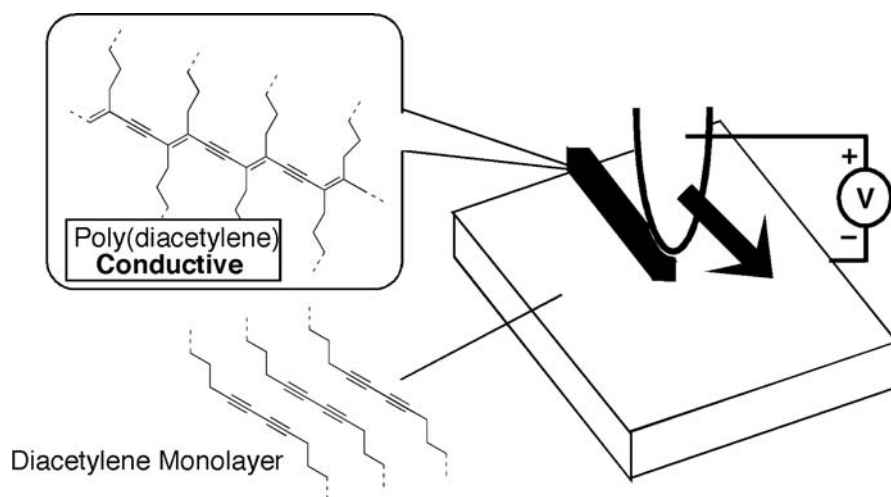


Figure 5.13. Drawing a conductive line using an STM tip

manner. The tip is used to apply an appropriate voltage to a monolayer of diacetylene derivative, forming the conductive poly(diacetylene) at the point of contact. This method would be very useful for preparing miniaturized electric circuits at desired positions on a solid support.

5.4

Molecular Photonic Devices – Controlling Light with Supermolecules

It is expected that the number of devices utilizing photonics (the optical equivalent of electronics) will increase dramatically in the near future. Light is usually a mixture of visible wavelengths that all travel at the same incredibly fast speed. Therefore, photonic systems allow us to transmit huge amounts of information within an incredibly short period of time. Photonic technology has been recently applied to various devices, such as compact discs (CDs), photocopiers and barcode readers. Rapid communication of large amounts of data between different parts of the world has been made possible through fiber optic cables, and fiber optic communication look sets to become more important than communication via electric cables in the near future. As explained in previous chapters, molecular recognition or supramolecular interactions sometimes result in spectral changes, which suggests that supermolecules would make good materials for use in photonics. Supramolecular chemistry is therefore expected to play an important role in the development of photonic devices with huge information densities.

Figure 5.14 shows an example of a molecular photonic switch in which a Ru complex and an Os complex are bridged by an azobipyridine ligand. The emission of this complex changes depending on the redox state of the

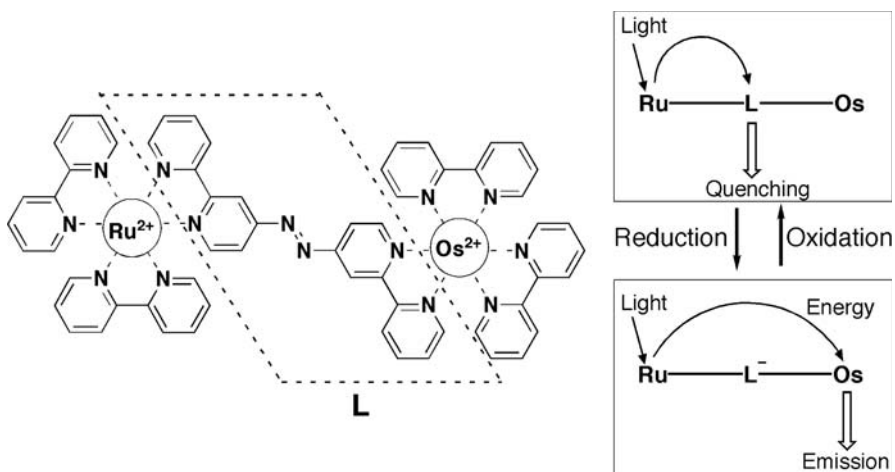


Figure 5.14. Controlling emission via redox reactions

bridging ligand. The azobipyridine is an electron acceptor in its neutral state. In this case, exciting the Ru complex with light causes the complex to pass an electron to the azobipyridine, which then relaxes thermally. In contrast, if the azobipyridine ligand is reduced, the electron-accepting nature of the ligand is suppressed. Excitation of the Ru complex then results in energy transfer to the Os complex, resulting in the emission of light. In other words, the emission behavior of the Os complex is controlled via azobipyridine redox reactions. This system can be regarded as a molecular photonic switch.

A molecular switch that responds to several kinds of stimuli has also been proposed. The molecule shown in Fig. 5.15 contains both a photoresponsive anthracene moiety and a crown ether connected via a tertiary amino group. This molecule shows switching properties based on a photoinduced electron transfer (PET) mechanism. An electron donor will quench excited anthracene, and both the tertiary amino group and the crown ether have this ability. The anthracene will therefore only emit when electron transfer is prohibited from both the amino group and the crown ether, and this can be achieved by protonating the amine and introducing sodium ions (accommodated by the crown ether). This molecular switch is therefore controlled by two inputs, and output (light emission) only occurs if both of these inputs are ON; in other words, this is an AND-type molecular logic gate.

5.5

Molecular Computers – Supramolecules That can think and Calculate

The example described at the end of the previous section is the simplest model of an information converter, because its output is controlled by the states of its

multiple inputs. Combining such molecular systems leads to the preparation of more sophisticated molecular devices.

Figure 5.16 shows two types of molecular logic devices that can be used for simple mathematics. Molecule A in Fig. 5.16 has bonding sites for a proton and a calcium ion. Light (with a wavelength of 419 nm) is only emitted from this molecule when both stimuli (protons and calcium ions) are introduced into the system. Addition of either protons or calcium ions does not induce significant emission. Therefore, again, this can be regarded as an AND-type logic gate. In contrast, the absorption behavior of molecule B shows a different dependence on these stimuli. This molecule normally absorbs at 390 nm. This behavior is also observed when both protons and calcium ions are present. However, adding either protons or calcium ions significantly suppresses the absorption (increasing transmittance). Therefore, if the transmittance at 390 nm was measured as the output signal, this system can be regarded as a XOR-type logic gate.

Combining these two logic gates yields a binary molecular calculator. Let us now denote an positive (ON) input by “01”, and a negative (OFF) input by “00”. We shall also use 0 and 1 to denote negative and positive gate outputs, respectively. In this case, when both inputs are OFF (00 + 00), the AND gate output is negative (0) and the XOR gate output is negative (0), giving a combined output of 00. When only one of the inputs is ON (01 + 00 or 00 + 01), the AND gate output is negative while the XOR gate output is positive, so the combined output here is 01. On the other hand, when both inputs are ON (01 + 01), the

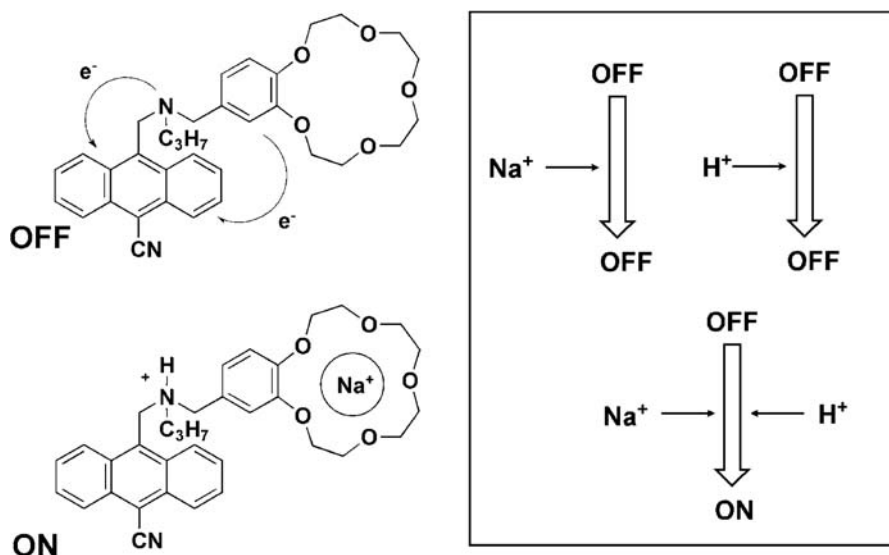
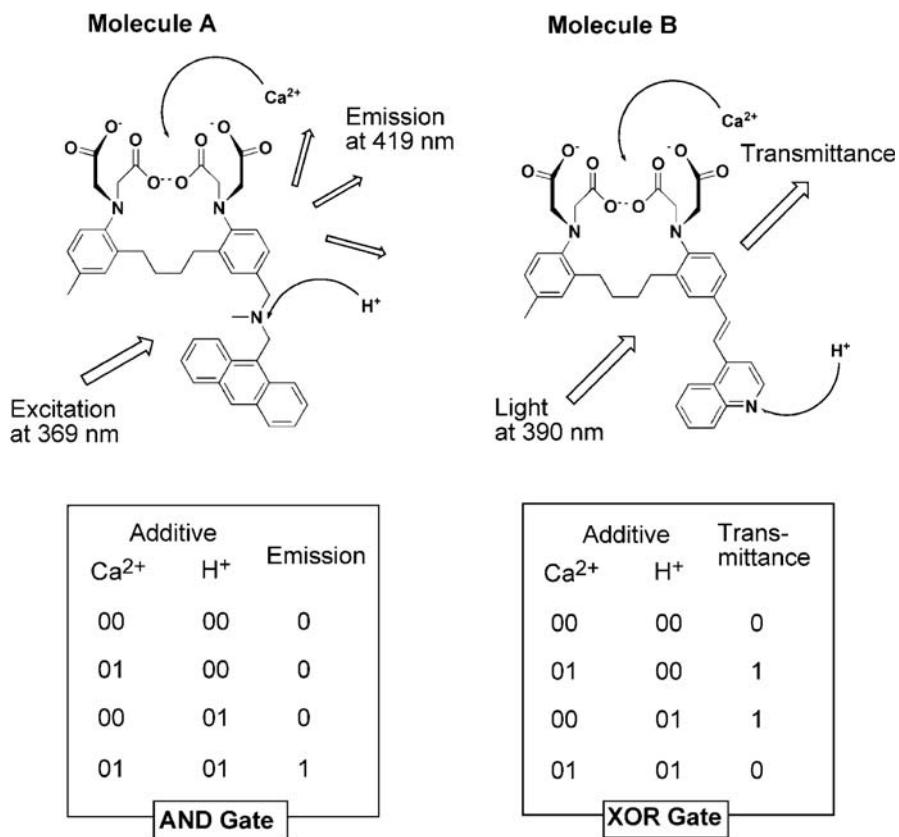


Figure 5.15. Addition of both H^+ and Na^+ induces optical emission



Input (Ca²⁺ and H⁺): 00 negative input; 01 positive input

Output (Emission and Transmittance): 0 negative output; 1 positive output

Figure 5.16. Molecular logic gates

AND gate gives a positive output and the XOR gate a negative output, which is a combined output of 10. This binary logic is summarized below:

$$00 + 00 = 00 \quad (\text{No input})$$

$$01 + 00 = 01 \quad (\text{Proton input ON only})$$

$$00 + 01 = 01 \quad (\text{Ca}^{2+} \text{ input ON only})$$

$$01 + 01 = 10 \quad (\text{Both inputs ON and negative XOR output})$$

This can be translated into the decimal system of $0 + 0 = 0$, $1 + 0 = 1$, $0 + 1 = 1$, and $1 + 1 = 2$, respectively. A supramolecular system containing molecules A and B therefore performs mathematics.

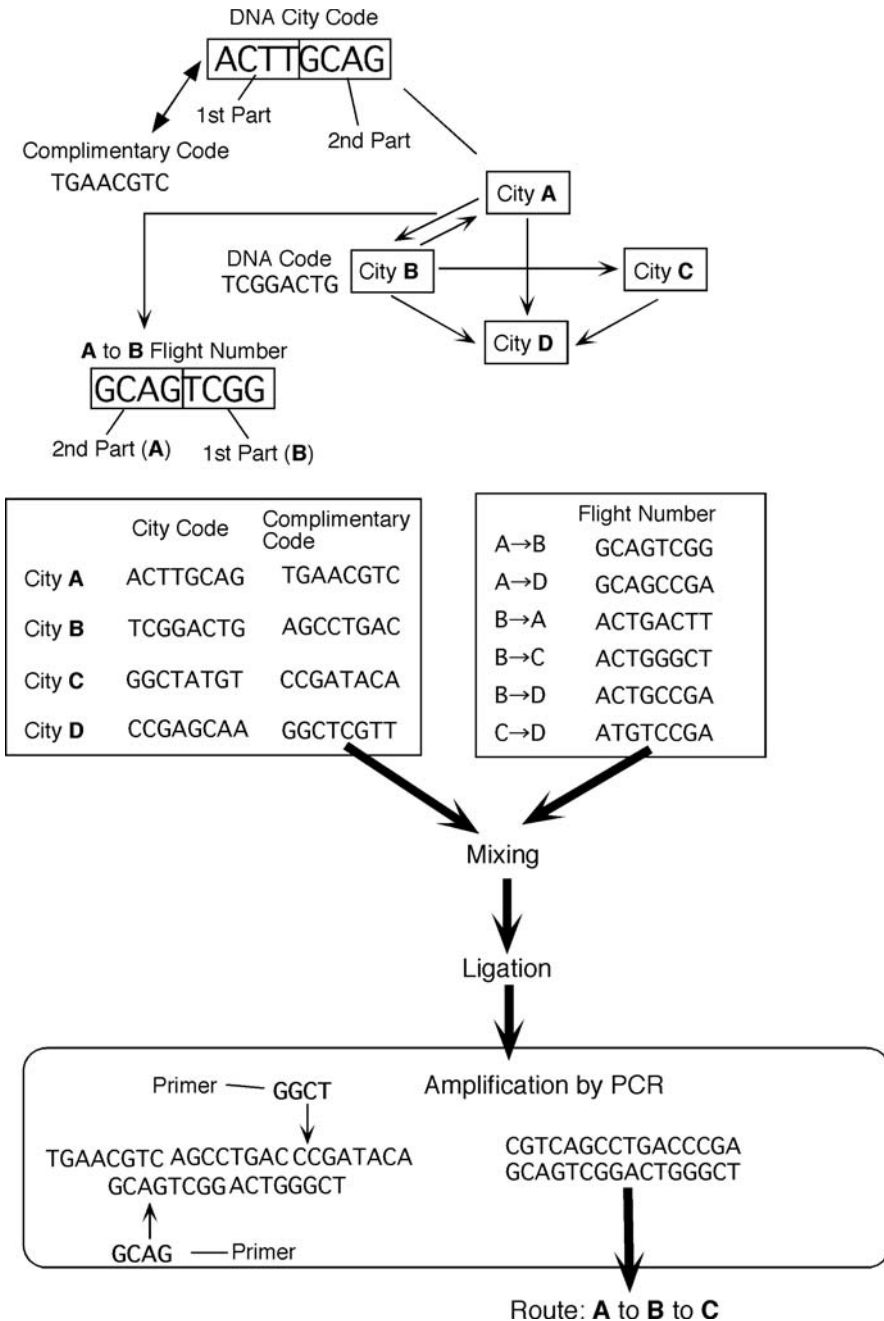


Figure 5.17. Example of DNA computing

In our body, huge amounts of information are accumulated in deoxyribonucleic acid (DNA) with incredibly high density. The blueprints of the structures of biologically important molecules – proteins – are written in DNA sequences. It is often said that the elegant and sophisticated functions seen in living creatures are programmed into the DNA strands. There have therefore been proposals to utilize the DNA molecules as a molecular computer. One example is shown in Fig. 5.17. The target of this example is to specify the correct flight route via DNA selection processes. DNA has a backbone composed of sugars, and phosphates and nucleobases are attached to every sugar unit. Adenine (A) selectively binds to thymine (T) and guanine (G) forms a specific pair with cytosine (C) between nucleobases. Two DNA strands form a complex that adopts the shape of a double helix due to these base pairings, with high precision.

DNA codes were first assigned for points. City A has a DNA city code of ACTT-GCAG. A DNA sequence of TGAA-CGTC can form a complementary pair with this code and so it is defined as a complementary code of City A. City B has a different DNA city code (TCGG-ACTG). The flight number from City A to City B is defined as GCAG-TCGG, which is derived by connecting the second part of the sequence for City A (GCAG) with the first part of the sequence of City B (TCGG). The city codes for other cities were similarly defined as GGCT-ATGT (City C) and CCGA-GCAA (City D). The corresponding complementary codes and several flight number codes are summarized in Fig. 5.17.

As an example, the selection of a flight route from City A to City C is demonstrated below. By mixing together all of the complementary codes and flight number codes, various DNA pairs were formed. The number of particular DNA pairs can be selectively amplified using the polymerase chain reaction (PCR) method. In the PCR method, short DNA segments known as primers are added and the DNA sequence between the primer sequences is selectively duplicated by the DNA polymerase. Repeating the PCR cycle allows us to selectively increase the number of desired DNA sequences. In this example, the second part of the complementary code of City A (CGTC) and the first part of the city code of City C (GGCT) were used as primers. As shown in Fig. 5.17, the PCR treatment resulted in an increase in the sequence GCAGTCGG-ACTGGGCT, which corresponds to a sequential flight from A to B and then from B to C. When we go to City C from City A, we must go via City B.

Upon describing the simplified example above, the advantages of using such a DNA system are not immediately clear. However, increasing the complexity of the problem would reveal the advantages of the DNA system. The DNA pairing occurs at once, even if the length of the DNA is increased. This is equivalent to saying that the processing time of this DNA computer does not increase as the calculations become more complicated, whereas the computers that we are used to require more processing time for more complicated calculations. This DNA computer is based on parallel processing, because the DNA pairing occurs simultaneously.

5.6 Molecular Machines – Supermolecules that can Catch Objects, Move and Rotate

Tweezers, scissors and screwdrivers are primitive tools compared to computers, but their importance and wide applicability to daily life cannot be ignored. Similarly, molecular scale mechanical devices would be very useful in nanotechnology. For example, a molecular robot that fabricates molecular wires and molecular machines that could penetrate deep inside the body would provide huge contribution in the fields of molecular electronics and medicine, respectively.

In our first example of a molecular machine, we consider a rotating molecule (a molecular bearing). The molecule shown in Fig. 5.18 has three naphthalene rings connecting to a central benzene ring; this molecule has a diameter of ~ 1.5 nm including the *tert*-butyl groups at the outside, and a twisted propeller-like shape because of steric hindrance. It was adsorbed onto the face of Cu(100) and it formed a monolayer structure, as observed by STM. Well-packed monolayers provided static images with clear molecular shapes. On the other hand, low coverage resulted in an ambiguous image: the motions of the molecules were too fast, resulting in unclear molecular images. Random nanometer defects were observed in the monolayer at a coverage of a little less than 100%. Interestingly, a molecule trapped in one of these asymmetric defects gave an unclear molecular image, even when the surrounding well-packed molecules were clearly observed. This suggests that the molecules in the defect were rotating due to weak interactions with the surrounding molecules. This molecular propeller has a tiny weight (1.33×10^{-24} kg) and only very small inertia. Its molecular motion can be easily controlled using an external energy supply (heat). This motional mechanism is obviously quite different to that usually used in macroscopic wheels.

A molecule that can be rotated to a particular direction by external stimuli is shown in Fig. 5.19. In this molecule, two of the same structures are connected through a double bond and the molecule has a twisted structure due to steric hindrance. Four steps involving light irradiation and thermal treatment

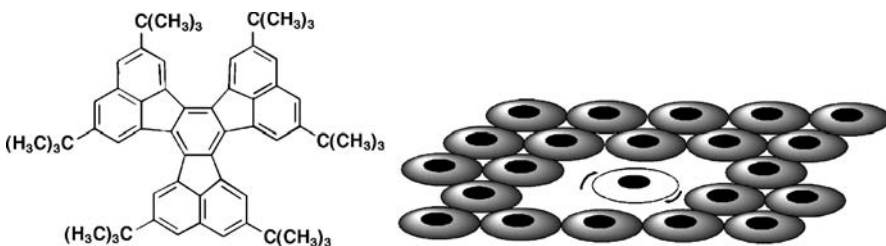


Figure 5.18. A molecule rotates within a defect

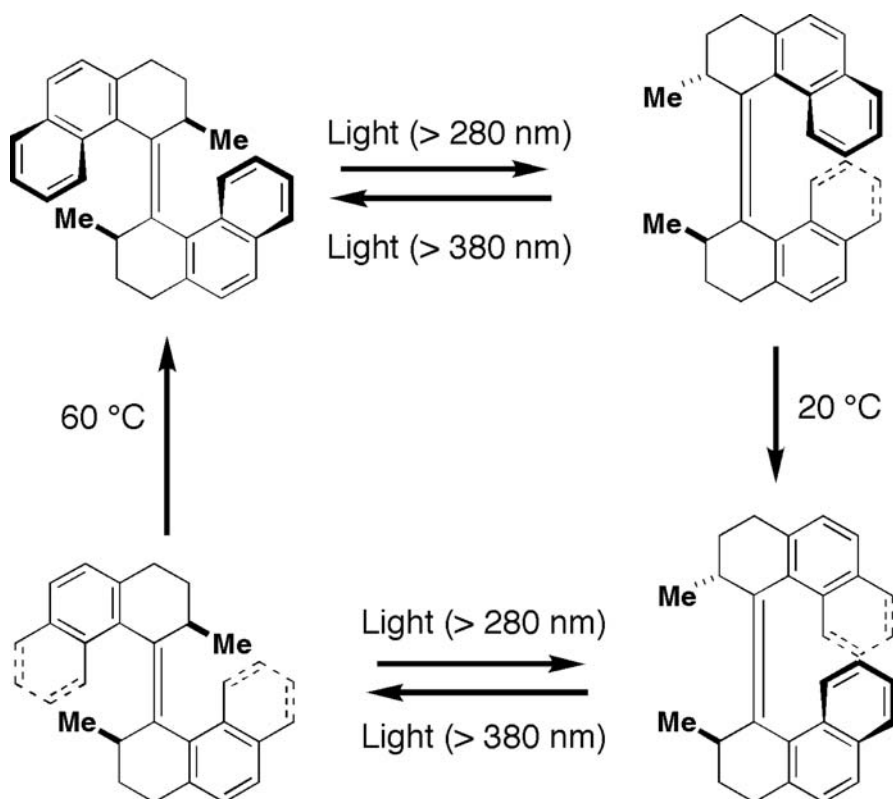


Figure 5.19. Unidirectional rotation of molecule upon irradiation with light irradiation

caused this molecule to rotate in a particular direction (counter-clockwise when viewing from the top).

The molecule in Fig. 5.20 undergoes unidirectional rotation upon certain chemical reactions. This molecule also has a twisted structure due to steric hindrance. The addition of phosgene to a system containing this molecule induced the conversion of the amino group to isocyanate. The upper half of the molecule rotated and reacted with the hydroxyl group of the lower part to form a urethane linkage. The formation of the covalent urethane linkage prohibits rotation in the reverse direction. With maintaining the urethane linkage, the upper part rotated further to achieve a more stable conformation. Finally, breaking the urethane linkage via $\text{NaBH}(\text{OC}_2\text{H}_5)_3$ caused the upper part of the molecule to undergo a half-rotation. In this example, the use of irreversible chemical reactions induces unidirectional rotation of the molecule.

Rotaxanes are unique supermolecules where cyclic molecules are threaded by linear molecules. They are powerful candidates for molecular machines,

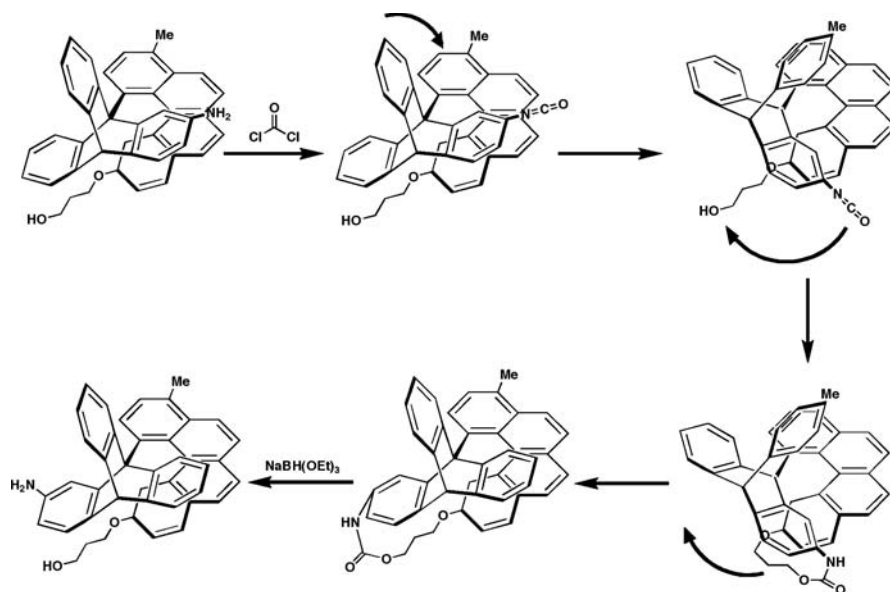


Figure 5.20. Unidirectional rotation of a molecule due to chemical reactions

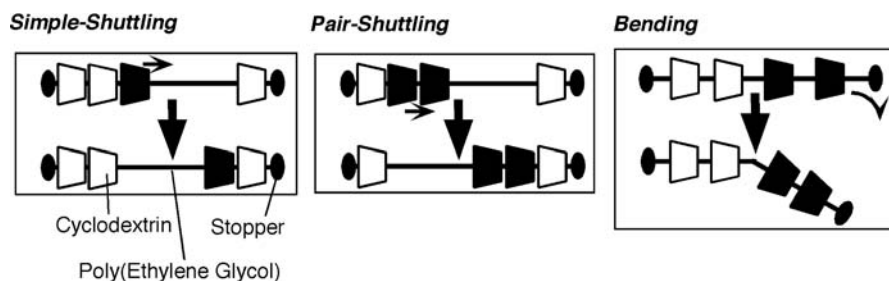


Figure 5.21. Molecular abacus based on rotaxane

and molecular shuttles based on rotaxanes have been proposed. The example described in Chap. 3 (see Fig. 3.21) shows the movement of a cyclophane along its axis molecule upon redox reaction. However, the ability to control the motions of particular cyclic molecules in a rotaxane containing many of them would be more useful in nanotechnology. Direct contact with the molecule is required for this useful task. Mechanical control of a single rotaxane molecule is shown in Fig. 5.21. A rotaxane composed of cyclodextrin rings and a polyethyleneglycol chain was nudged by an STM tip. Simple shuttling of one cyclodextrin, pair shuttling of two cyclodextrins and bending of the rotaxane molecule were all reported. This molecular shuttling is reminiscent of a Japanese abacus, so it could be called a molecular abacus.

Actuators based on the swelling and shrinking of gels are the subject of much research. They can be regarded as modeling muscle systems. However, the response times of such systems are limited, because actuator motion occurs with molecular diffusion in the gel. If each molecule could expand and shrink instead, motional response times would significantly improve. Carbon nanotubes are known to expand or shrink upon injections of electrons or

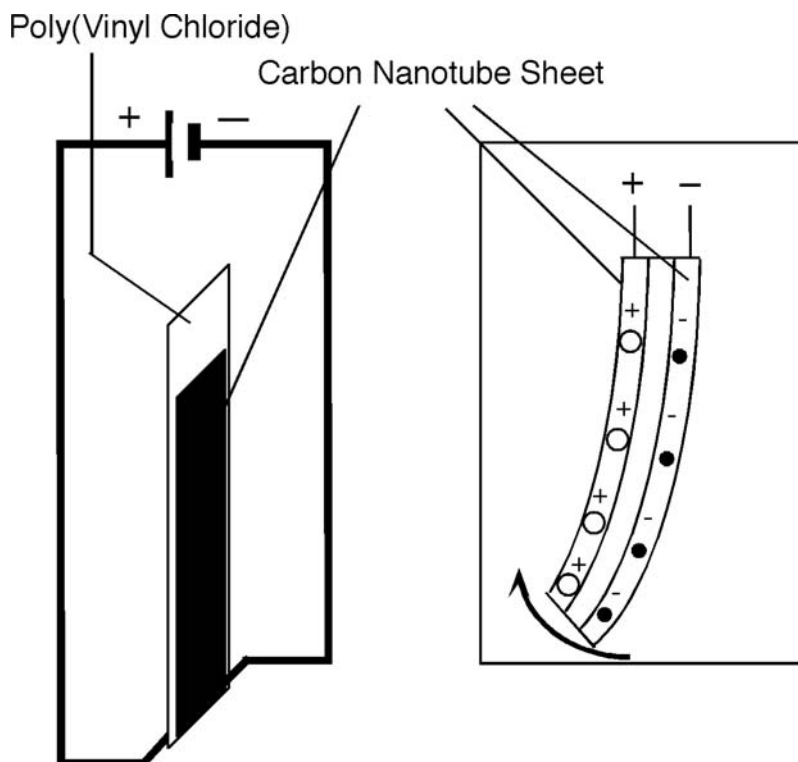


Figure 5.22. Carbon nanotube actuator

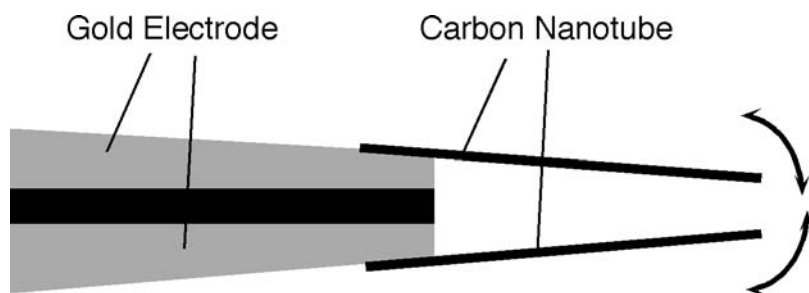


Figure 5.23. Molecular tweezers

holes. This behavior is explained by quantum effects due to changes in orbitals and band structures. This mechanical property of carbon nanotubes was utilized in the preparation of a molecular actuator (Fig. 5.22). A sheet of carbon nanotubes was first prepared by filtration, and these nanotube sheets were then attached to both sides of an insulating polymer sheet. Applying a voltage across both of the carbon nanotube sheets causes one sheet to expand and the other to shrink, which means that the total three-sheet system bends. This happens because applying a voltage across them causes a charge imbalance in the sheets, which is compensated for by the movement of counterions towards the charge. This charge compensation occurs mainly at the surfaces of the sheets, and so the counterions do not tend to diffuse deeper into the sheet. These characteristics result in a very quick mechanical response for this actuator.

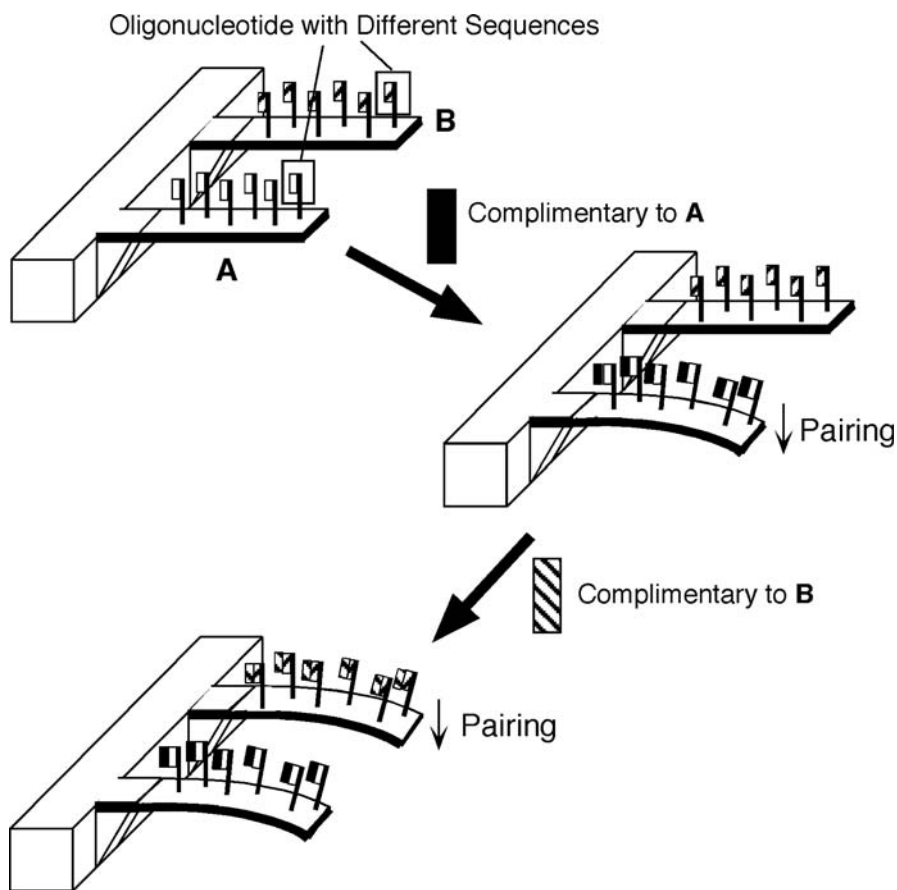


Figure 5.24. Mechanical motion upon DNA hybridization

Tools for microfabrication have also been prepared based on the unique characteristics of carbon nanotubes. In the microtool shown in Fig. 5.23, two carbon nanotubes are fixed on gold electrodes that are deposited either side

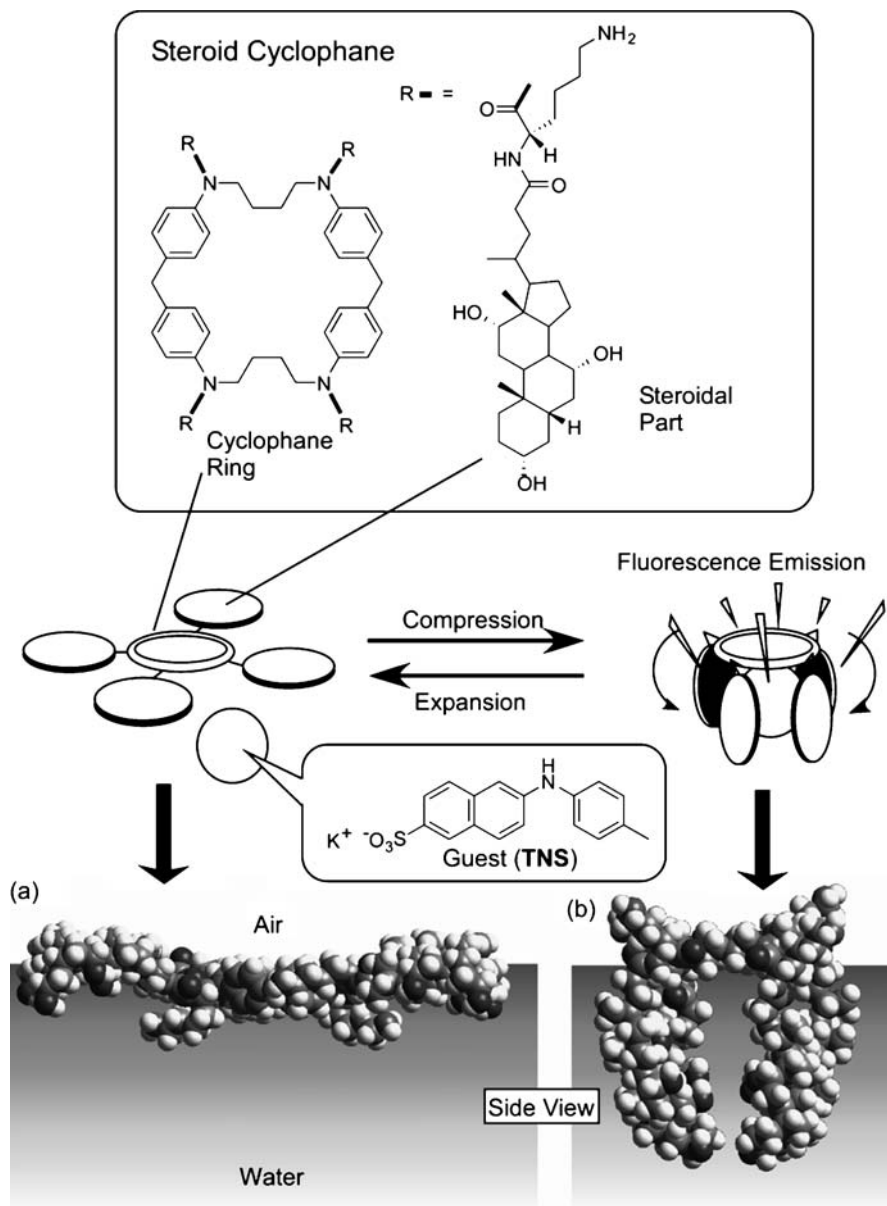


Figure 5.25. Pressure-induced emission upon molecular recognition

of a glass micropipette. Applying a voltage between these two electrodes induces opposite charges in the nanotubes (as with the sheets in the actuator described above). The oppositely charged nanotubes are attracted to each other, causing them to move towards each other and finally contact. Grounding the electrodes (and therefore the nanotubes) removes the charge and therefore causes the tweezers to move apart again. This microtool can therefore be regarded as a pair of molecular tweezers. Molecular tweezers like this have been used to catch and move clusters of tiny polystyrene spheres. This microtool has also been used as a nano-sized tester electrode; the conductivities of SiC clusters and GaAs nanowires have been directly measured in this way.

Molecular recognition is an event that occurs at the molecular level, but a large number of such recognitions can lead to macroscopic changes in substances. In the system shown in Fig. 5.24, the surface of silicon board (width $100\ \mu\text{m}$; length $500\ \mu\text{m}$; thickness $1\ \mu\text{m}$) was coated with gold, and oligonucleotides with thiol terminals were immobilized on the gold surface. If a guest oligonucleotide with a complementary sequence is introduced, it binds to the immobilized oligonucleotide to form a double helix structure. The cumulative strain induced by all of these hybridizations caused the support board to bend. In a similar way, a mechanical change was triggered in a macroscopic substance by molecular recognition between proteins.

Figure 5.25 shows the reverse of the type of conversion system described above. In this case, molecular recognition is controlled by visible mechanical changes. A host molecule with four cholic acid planes and a cyclophane ring was spread as a monolayer on the surface of water. Because the cholic moiety has a hydrophilic face and a hydrophobic face, the host molecule adopted an open conformation, contacting the hydrophilic faces to the surface of the water, at low pressure. However, compression of the host monolayer induced a change to a closed host conformation where the four cholic planes flip up from the surface of the water. The latter host conformation provides a binding medium with a high affinity to a naphthalene guest. Therefore, molecular recognition of a guest in the water phase was induced by monolayer compression. Guest binding was monitored using the associated change in surface fluorescence. In this system, the visible mechanical change (made at the $10^{-1}\ \text{m}$ level) was converted to a molecular event (at the $10^{-9}\ \text{m}$ level) – this concept bridges a huge difference in scale.

5.7

Molecular Devices with Directional Functionality – Supermolecules that Transmit Signals in a Desired Direction

An advanced molecular device would require a separate signal input and signal output. To achieve this, it is necessary to organize the functional molecules in a particular way that will lead to directional information transfer through the

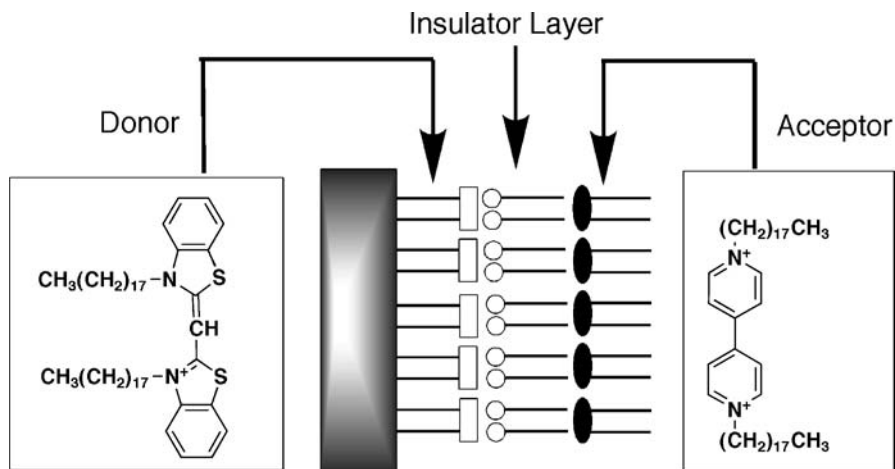


Figure 5.26. LB film for direction-specific electron transfer

supramolecular system. Techniques that can provide layered structures, such as the LB method and the alternate layer-by-layer technique, are useful for preparing molecular devices that can perform direction-specific information conversion.

Figure 5.26 shows an LB film that regulates electron transfer. Monolayers of an electron donor layer, an insulating fatty acid layer and an electron acceptor layer were transferred in a defined sequence. In this hetero-layered LB film, electron transfer only occurs from the inside to the outside, and the structure of the insulator layer determines the efficiency of electron transfer. Swapping around the donor layer and the acceptor layer reverses the direction of electron transfer. Simply controlling the layering structure therefore enables us to modulate the direction and efficiency of electron flow.

Photoinduced electron transfer devices have also been constructed using the LB method (see Fig. 5.27). Excitation of the photosensitizer pyrene induces the transfer of an excited electron to viologen (an electron acceptor) and the transfer of an electron from ferrocene (an electron donor) to the ground state of the pyrene. These processes result in charge separation, a process that occurs during photosynthesis. Reversing the layering sequence causes charge separation to occur in the opposite direction. Efficient photoinduced electron transfer therefore requires the creation of organized sequences of donor, sensitizer and acceptor in order to suppress electron back-transfer, and this is easily realized using the LB technique.

A similar functional device can be constructed through the orientation-controlled assembly of molecules with donor, acceptor and sensitizer parts. Three kinds of dye – ferrocene, viologen and pyrene – were covalently con-

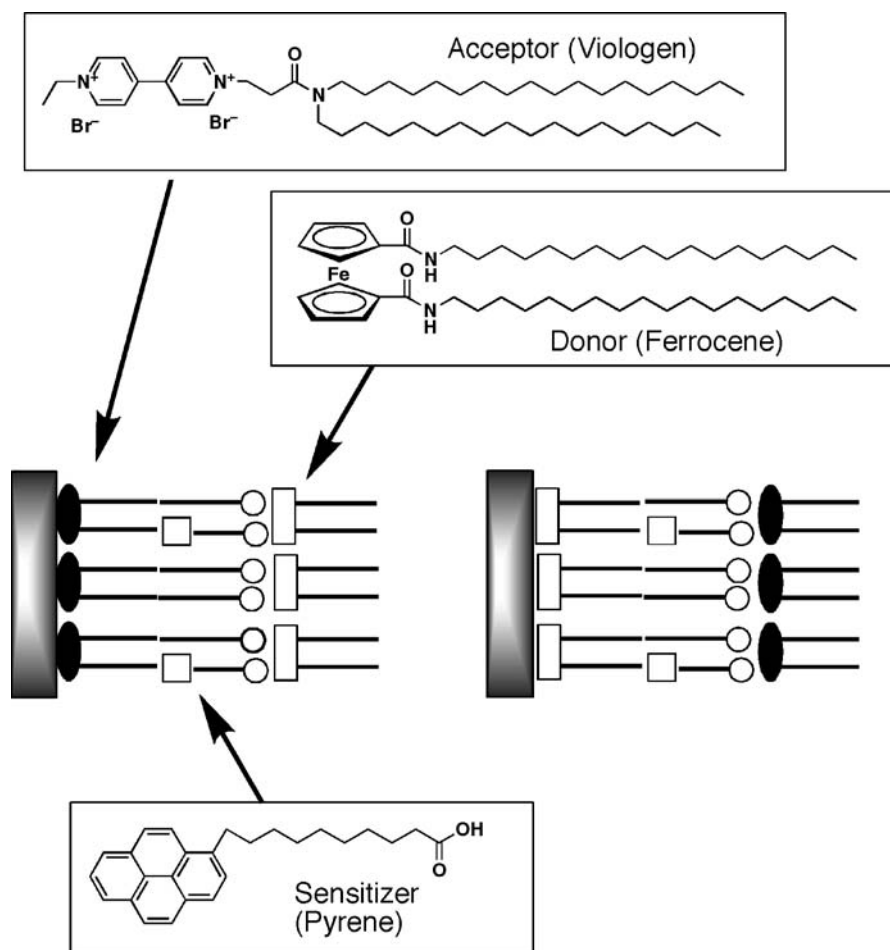


Figure 5.27. Design of LB films that exhibit photoinduced charge separation

nected in one amphiphile molecule, and a monolayer of this molecule was transferred onto an electrode. This system also shows directional photoinduced electron transfer.

Figure 5.28 shows a system used for the photocontrol of electron conductivity within a monolayer. A monolayer of an amphiphile containing azobenzene (the photocontrolled part) and tetracyanoquinone (TCNQ, which conducts electrons) was spread on water, resulting in two-dimensional photocontrolled and electrically conductive layers. Isomerizing the azobenzene part between its *trans* and *cis* isomer by alternate photoirradiation induced periodic changes in the electrical conductivity of the TCNQ part. The electrical conductivity is limited to a two-dimensional plane here, which embues a different

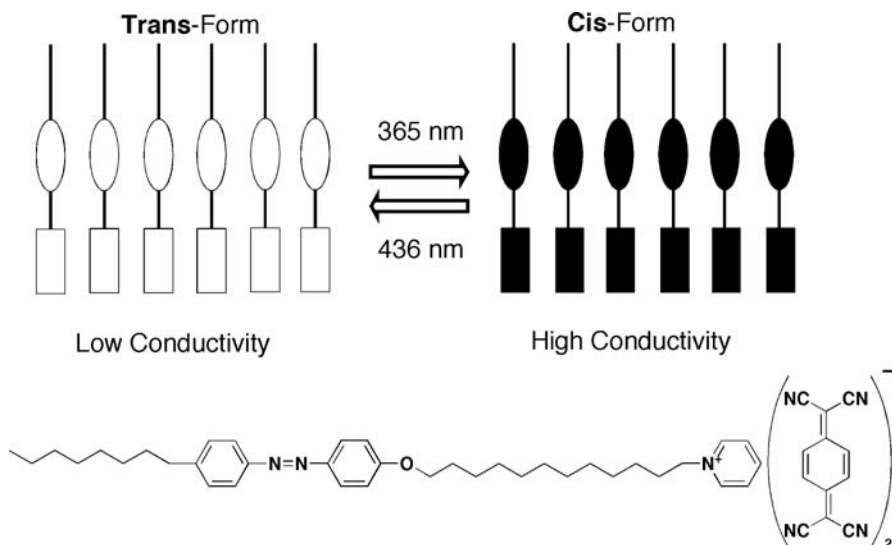


Figure 5.28. Photocontrol of conduction within a monolayer

direction-specificity to the electron flow to those described for the previous systems.

The LB film shown in Fig. 5.29 is an energy transfer device with a photo-switching layer. The switching layer is in its merocyanine form when the system is irradiated with UV light. In this case, excited thiocyanine molecules in the donor layer can transfer energy via the merocyanine to the indocarbocyanine in the acceptor layer. This results in strong indocarbocyanine fluorescence at 725 nm (λ_2). On the other hand, irradiating the system with visible light changes the switching layer into its spiropyran form, which cannot accept energy from thiocyanine. Since this cuts off the flow of energy to indocarbocyanine, it stops fluorescing and fluorescence from the thiocyanine is mainly observed at 480 nm (λ_1) instead. The energy flow from the donor layer to the acceptor layer was regulated by the photoisomerization of the switching layer. The wavelength of the input light controls the wavelength of the output signal.

In Fig. 5.30, a multilayered self-assembled film of an aminostilbazorium derivative is depicted, where the multilayer does not have a symmetric structure (the aminostilbazorium units adopt a specific orientation against the solid surface). In this aminostilbazorium derivative, the electron-donating part and the electron-accepting part are connected through conjugated linkages. Aligning this kind of molecule in a particular direction results in nonlinear optical effects. Irradiating it with light with an electric field of E and a frequency of ω induces polarization, which is expressed by polynomial equation in E . Terms greater than second-order can usually be ignored, and the main com-

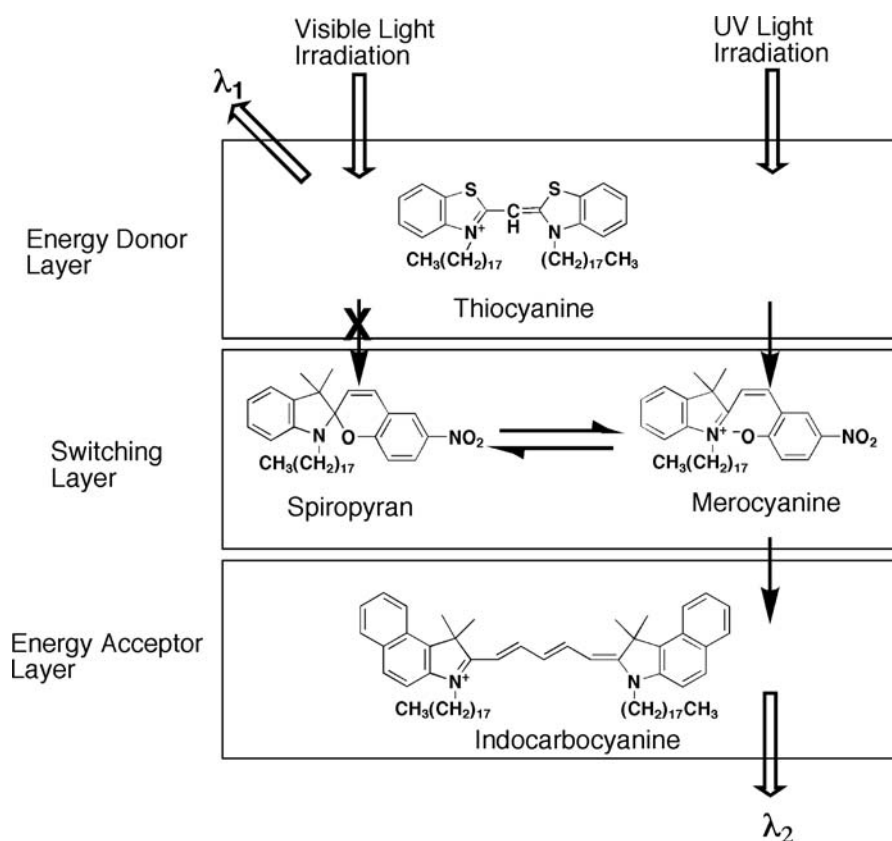


Figure 5.29. Switching device based on appropriate LB film design

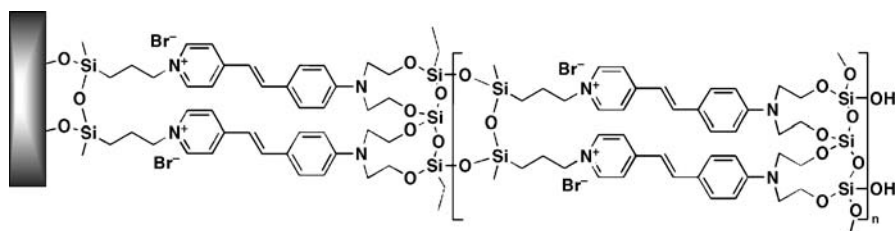


Figure 5.30. Asymmetric self-assembled monolayer used for nonlinear optics

ponent of the emitted light has a frequency of ω . At high light intensity, the contributions of higher order components with frequencies 2ω , 3ω and so on (harmonic waves) cannot be neglected. There is a significant contribution from the second-order component to the emission from the asymmetric structure. When light of frequency ω was directed onto the film shown in Fig. 5.30, the emitted light contained components of frequency 2ω . This phenomenon

is called *second harmonic generation* (SHG). This film can be regarded as molecular device that can alter the wavelength of light shone upon it.

5.8

Supramolecular Chemistry & Nanotechnology toward Future

We have discussed various molecular devices created from supermolecules in this chapter. Molecular level techniques and science will play an important roles in the development of nanotechnology in the twenty-first century. Ultrasmall devices with huge information densities will minimize pollution and energy waste, and improve our lifestyles. Tiny robots will be used in medical applications. Excursions into space – manned and unmanned – will benefit enormously from the use of nanomachines and the products of nanotechnology, which should lead to much cheaper and safer space missions.

In the issue of the regular magazine of the American Chemical Society, Chemistry & Engineering News, from February 28th, 2000, there was a special article entitled “NASA goes NANO”, which described the importance of nanotechnology to space programs. For example, Mars Pathfinder, which explored Mars in 1997, was several hundreds of kilograms in weight, and the rovers Spirit and Opportunity, which were launched towards Mars in 2003, each weighed around 180 kilograms. Huge amounts of energy and money are used in Mars missions. Therefore, reducing the size and weight of the spacecraft is highly desirable from a financial point of view. For example, reducing the size of a spacecraft to that of a can of soft drink would result in massive savings. NASA has stated a goal to reduce the size of a typical space probe by 1/100, and to increase reliability by a factor of 1000 by 2020. As space probes venture further and further from Earth to perform ever more complex tasks, it becomes increasingly difficult to guide the actions of the probe by remote control, given the increasing time delay taken for signals to reach (and return from) the probe. What is needed is a “thinking spacecraft” that can fly, walk and escape based on its own judgment and that can adapt to its environment (it can “learn”). This would require onboard systems with superhigh information densities. NASA is therefore interested in the following technologies that could permit this approach: (1) nanocomputers based on organic materials and carbon nanotubes; (2) quantum computers with atomic or quark-level precision; (3) biocomputers with DNA and artificial nerves; (4) photonic computers (computers driven by photons). Some of the examples described in this chapter already provide the first steps toward some of these targets.

However, in “Nanotechnology Research Directions” (a report published by the US government in 1999), it was pointed out that current nanoscale technologies are still highly inferior to those seen in natural systems. The efficiency of the energy conversion that occurs in mitochondrial and photosynthetic systems far exceeds those obtained in artificial systems. A dog can smell and a bat can hear far more sensitively than most artificial sensors. The information pro-

cessing exhibited by brain and nerve systems is far more sophisticated than that exhibited by current computers. Nature developed superior nanotechnologies to our own several billion years ago, and most of them are based on molecular interactions – supramolecular chemistry. There are huge numbers of natural supermolecules all around us. We have a lot to learn from nature and biology. In the next chapter, some natural supramolecular systems are reviewed as well as ways to mimic them, and we suggest how biological materials may be used in new technologies in the future.

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6 Biological Supermolecules – Learning from Nature

In the previous four chapters, we described studies of a wide variety of artificial supramolecular systems, from very basic ones to those used in sophisticated devices, although we must recognize that the field of supramolecular chemistry has huge potential and so current accomplishments are just the beginning. For the field to develop as far as many expect it to, however, we will almost certainly need good target molecules to aim for. Luckily, we have easy access to huge numbers of such target molecules, since nature uses them extensively in the biological world. Because of the high complexity and functionality of biological supermolecules, the ability to build and control build biological supermolecules is often said to be the ultimate goal of supramolecular chemistry. The structures of biological systems are built up through the accumulation of various kinds of functional molecules that are assembled through weak interactions. Indeed, living things – including ourselves – can be regarded as incredibly complex biological supramolecular systems.

Therefore, in this chapter we will describe various kinds of biological supermolecules and their artificial mimics. The field of chemistry that focuses on mimicking biological functions and creating materials obtained from studying biological supermolecules is called *biomimetic chemistry*. In this chapter we will cover various aspects of this field, including material transport, information conversion and transfer, energy conversion and material conversion (enzymatic function). New kinds of supramolecular and combinatorial chemistry, as well as evolutionary molecular engineering, which mimics natural evolutionary processes, are also introduced as methods of selecting better supermolecules with enhanced functionality.

Contents of This Chapter

6.1 Supramolecular Systems Seen in the Biological World The superior designs of biological supermolecules quickly become apparent upon studying them. The bacterial flagellar motor is a well-organized protein assembly and can be regarded as an ultras-small high-performance motor. The lipid bilayer of a cell membrane provides a fluidic medium for proteins that express various functions.

6.2 Controlling Material Transport – Ion Channels Ion channels maintain two different ion compositions outside and inside a cell via active transport. The immobilization of appropriately designed molecules in a lipid bilayer membrane leads to the formation of artificial ion channels.

6.3 Information Conversion and Amplification – Signal Transduction When an extracellular signal is recognized by a receptor on a cell membrane, the G-protein activates the enzyme inside the cell. The activation of an enzyme by external chemicals can be mimicked using a system consisting of an artificial receptor and an enzyme immobilized on an artificial lipid bilayer membrane.

6.4 Energy Conversion – Photosynthesis During the process of photosynthesis, a well-organized dye array in the cell membrane accomplishes photoinduced charge separation that eventually leads to ATP synthesis. This system has been mimicked by immobilizing a functional dye molecule and ATP synthase in a lipid bilayer membrane.

6.5 Material Conversion – Natural and Artificial Enzymes Enzymes perform highly selective and highly efficient molecular conversion based on sophisticated three-dimensional arrangements of amino acids. Artificial enzyme mimics can be constructed using cyclodextrins and lipid bilayer membranes.

6.6 Cleaving Genes – Restriction Enzymes Restriction enzymes can cleave nucleic acids at specific sequences. Artificial restriction enzymes can be prepared by combining oligo(nucleic acids) and supramolecular catalytic sites.

6.7 Tailor-Made Enzymes – Catalytic Antibodies There are antibodies that catalyze reactions by mimicking their transition states. A catalytic antibody can be regarded as a tailor-made artificial enzyme.

6.8 Key to the Origin of Life – Ribozymes Ribozymes are nucleic acids with catalytic capabilities. The discovery of ribozymes led to the *RNA world hypothesis* for the origin of life.

6.9 Combinatorial Chemistry and Evolutionary Molecular Engineering Combinatorial chemistry is a methodology for selecting the best substance from a library of randomly assembled candidates. Evolutionary molecular engineering mimics the selection of the best molecule for a particular task via natural evolutionary processes.

6.1 Supramolecular Systems Seen in the Biological World

The highly sophisticated functions seen in biological systems originate from their well-designed molecular arrangements, which are formed through self-assembly and self-organization. The characteristics of biological supermolecules mean that they provide good targets to aim for and good design rules to use when designing artificial functional systems. We now consider several examples of biological supermolecules that demonstrate sophisticated functionality.

The superiority of biological supermolecules is typified by the highly sophisticated protein assemblies of the bacterial flagellar motor. A bacterium, such as a colon bacillus, swims by rotating its flagella at high speed. These flagella are rotated by a protein motor. This interesting object has been intensively researched, and it has been shown that this motor is composed of various proteins built up through supramolecular assembly in a sophisticated way. The flagellar motor has a diameter of ~ 30 nm, can rotate at 1500 rpm, and can change its direction of rotation within one millisecond. Its size and functionality are way beyond those of any man-made ultrasmall machines.

Figure 6.1 shows the structure of the flagellar motor in a simple illustration that reminds us of artificial machines. This machine-like motor is constructed through the self-assembly of proteins. The superior functionality and complexity of biological supermolecules is quite apparent from this example. The energy for the rotation of the motor is provided by a proton flow from the outside to the inside of the bacteria. When an electrical potential difference is applied between the outside and the inside of the bacteria by immobilizing the bacterial cell on micropipette, the rotation speed can be controlled by al-

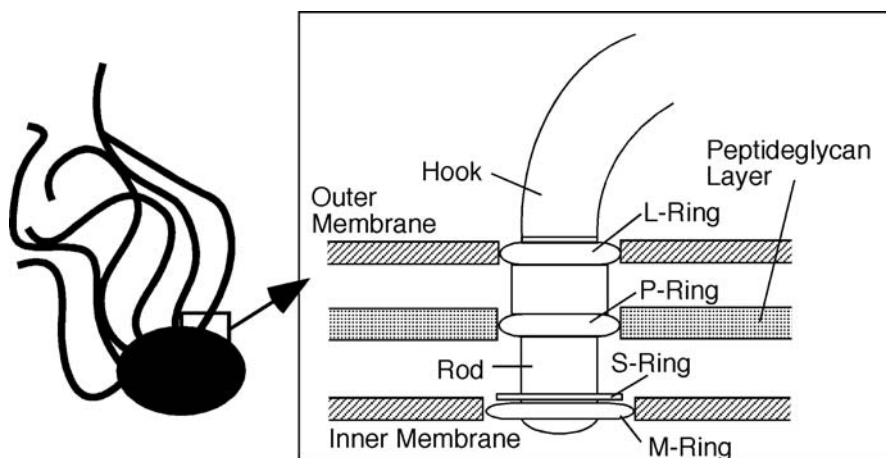


Figure 6.1. Bacterial flagellar motor

tering the magnitude of the applied potential difference. This can therefore be regarded as an electrically driven ultrasmall rotator.

The second example of a biological supermolecule is a cell membrane. As described in Chap. 4, a cell membrane consists mainly of a fluidic lipid bilayer containing proteins (Fig. 6.2). The lipids are self-assembled into the bilayer structure and the proteins float within the lipid bilayer. The whole structure is formed through self-assembly processes.

The membrane protein is stably buried in the lipid bilayer due to the amphiphilic nature of the membrane protein. The surfaces of some parts of the protein have mainly hydrophobic amino acid residues, and hydrophilic residues are located on the other surfaces. The former parts are accommodated in the hydrophobic lipid bilayer and the latter protein regions are exposed to the surface of the water. Membrane proteins work as receptors, channels and so on. Specific interactions between these proteins lead to complex functions such as signal transduction and energy conversion. Many of the functions expressed by the cell membrane can be attributed to the functionality of the membrane proteins.

The amounts and species of proteins in the cell membrane depend on the functions of the particular cell. The protein weight content of the myelin-forming protein that covers nerve cells is only 25%. The inner membrane of a mitochondrion, which performs energy conversion, contains 75% by weight of proteins.

The arrangement of the proteins buried in the lipid bilayer allows them to respond dynamically to external stimuli. These characteristics of the membrane proteins are related to their various functions. In the following sections, the excellent functions expressed by these membrane proteins are explained and their artificial mimics are introduced.

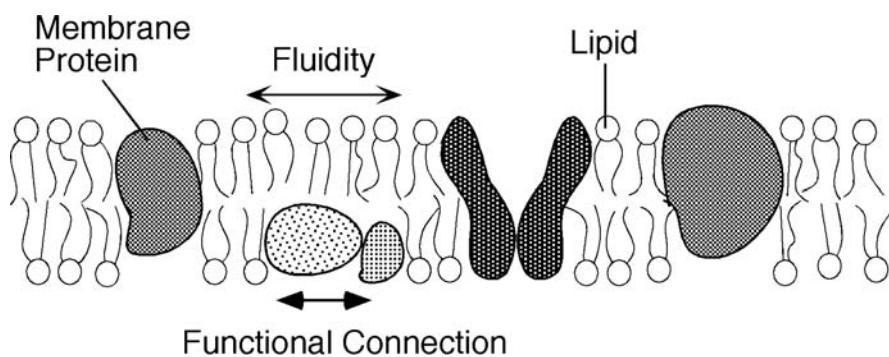


Figure 6.2. Schematic illustration of a cell membrane (cross-section)

6.2 Controlling Material Transport – Ion Channels

The ion composition outside a cell is not usually the same as the ion composition inside it. For example, in the case of mammalian cells, the Na^+ concentrations outside and inside a cell are 145 mM and 5–15 mM, respectively. The concentrations of K^+ are also different: the K^+ concentration inside a cell (140 mM) is higher than that outside it (5 mM). Cells can store energy in this ion concentration gradient. This energy is then used in electrical signal transduction, ATP production and the transport of various materials through the membrane.

These unbalanced ion concentrations are generated by via the cell membrane's selective ion transport mechanism. Figure 6.3 shows selective exchange between K^+ and Na^+ by Na^+/K^+ -ATPase. In this exchange mechanism, the transportation of ions against the ion concentration gradient requires energy. This mechanism is achieved by changing the affinity of the channel protein to the corresponding ion. The protein must be in a state of high affinity to the ion for efficient binding to occur at a low-concentration site. In contrast, the protein must be in a conformation that has a low ion affinity for efficient release to occur at a high-concentration site. This conformational change in the channel protein is caused by phosphorylation of the protein upon ATP consumption.

The exchange transport mechanism for Na^+ and K^+ can be briefly explained as follows. When three Na^+ ions bind to the protein, phosphorylation occurs,

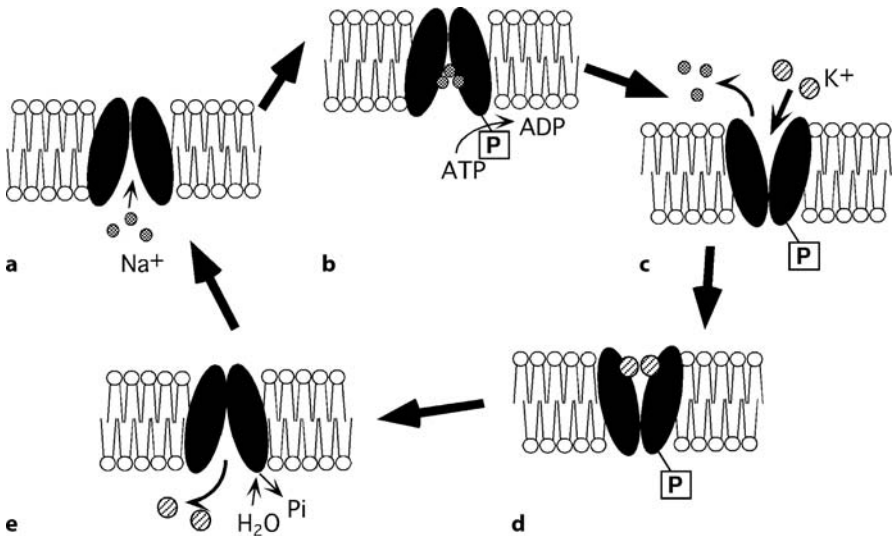


Figure 6.3. Na^+/K^+ -ATPase

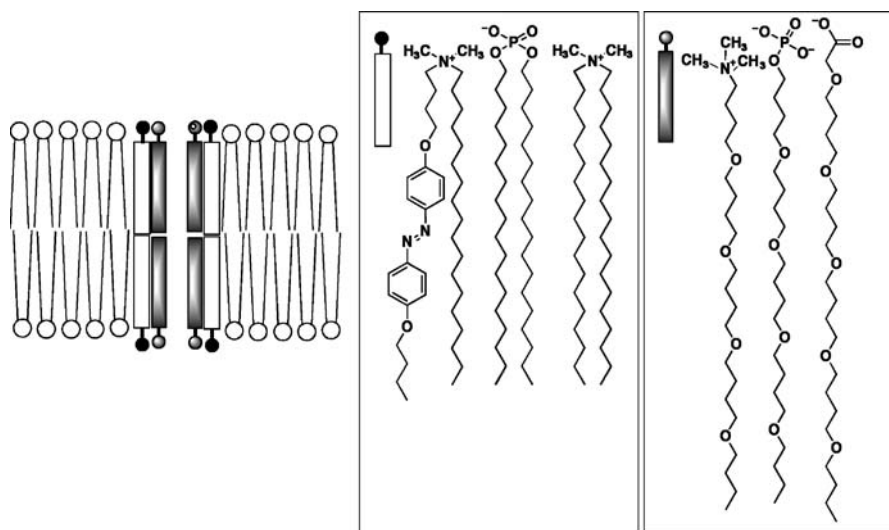


Figure 6.4. Artificial ion channel with a supramolecular assembly

inducing a conformational change in the protein (a, b). This change lowers its affinity to Na^+ , resulting in the release of Na^+ to the extracellular site (c). Binding two K^+ ions to the protein induces dephosphorylation, which leads to the release of K^+ into the cell (d, e). In total, the hydrolysis of one ATP molecule triggers the release of three Na^+ ions and the uptake of two K^+ ions. This exchange process is an active transport mechanism that proceeds against the pre-existing ion gradient. Therefore, this process requires energy for the ATP hydrolysis to occur.

When a nerve system is excited, Na^+ flows into the cell from inside and K^+ flows out of the cell through ion channels. These flows obey ion gradients. Active transport occurs upon ATP consumption in order to compensate for these flows and maintain an unbalanced ion distribution between the inside and the outside of the cell.

As described above, ion channels play an important role in biological activity and they can be mimicked using a supramolecular approach. In this area of research, stable pore structures are formed from artificial molecules that are buried in a lipid bilayer membrane. For example, artificial channel structures have been prepared using specifically designed oligopeptides.

Some natural ion channels are believed to form amphiphilic α -helix bundles in hydrophobic lipid membranes, where the α -helices assemble with their hydrophilic parts facing each other, resulting in a hydrophilic channel. If artificial peptides that had appropriate combinations of both hydrophobic amino acid residues and hydrophobic amino acid sequences were used, the peptides would self-assemble to form a hydrophilic pathway in the lipid membrane.

Modifying amino acid side chains is therefore a useful way of controlling ionic permeation.

α -Helix bundles aside, piling cyclic compounds on top of each other can result in a channel structure. One example of this has already been shown in Fig. 4.53. The stacking structures of hydrogen-bonded cyclic peptides or crown ethers satisfy this strategy.

Assembling rather simple compounds to form a channel structure is an attractive approach in supramolecular chemistry. Figure 6.4 shows a channel formed from simple long-chain compounds. An amphiphilic ion complex formed between hydrophobic dialkyl compounds and hydrophilic oligoethylene compounds assembles into a form that mimics a transmembrane channel. The preparation of an ion channel based on the assembly of simple compounds was also achieved by assembling resorcinol tetramers with long chains. Interestingly, in the latter case, the permeability of K^+ was three times larger than that observed for Na^+ .

6.3 Information Conversion and Amplification – Signal Transduction

Individual cells in the bodies of multicellular creatures communicate with each other by exchanging information, resulting in synchronized functions. Information is delivered across the body by chemical substances such as hormones. Such chemicals are specifically recognized by receptors on the cell surface, and information is transmitted and amplified by enzymatic actions.

Some external chemicals are misrecognized by the receptors, and this bad signal input can trigger undesirable changes in the body. Some of these substances are known as endocrine disrupters. Only a small number of wrong signals can result in serious consequences due to the high sensitivities of living systems.

Signal transduction and amplification systems are useful specimens to study when designing molecular devices because they are based on supramolecular interactions between substances. G-proteins play an important role in bio-

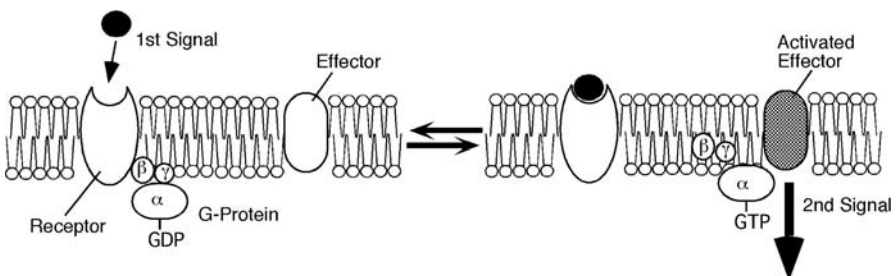


Figure 6.5. Signal transduction mediated by G-protein

logical signal transduction, and the mechanism of G-protein-mediated signal transduction is briefly summarized in Fig. 6.5. Note the presence of receptors and effectors on the cell membrane. A receptor takes in an external signal from outside of the cell, while the effector transmits such signals into the cell. These two functions are connected by the G-protein (GTP-binding protein). The G-protein consists of three subunits (α , β and γ) with GTP (or GDP). In its inactive form, the G-protein exists as a trimer, with GDP bound to the α subunit. When a signal molecule (the first signal; such as a hormone) binds to the receptor, the G-protein binds to the receptor–signal complex, which activates the G-protein. The guanyl–nucleotide binding site on the α subunit is altered when GTP is allowed to bind in place of GDP. The binding of GTP is thought to dissociate the α subunit from the β and γ subunits. The dissociated α subunit tightly binds to the effector enzyme (adenylate cyclase), which is then triggered to produce cyclic AMP (the second signal). Within less than a minute, the α subunit hydrolyzes its bound GTP to GDP, causing the α subunit to dissociate from the enzyme. The α , β and γ subunits then reform the inactive form of the G-protein. Since hydrolysis of GTP at the α subunit is a relatively slow process, the receptor–signal complex can activate many G-proteins. The cascade-like enzymatic reaction linked to the effector reaction significantly enhances the amount of signal. As a result, one signal molecule binding to a receptor produces a huge signal in the cell.

If we were able to mimic biological signal transduction systems using artificial molecular systems, it would lead to the development of highly efficient information conversion devices. Such an artificial system, could use combinations of receptors, effector enzymes and signal amplification systems that would be targeted at whichever chemical we were interested in detecting, resulting in highly efficient sensing systems.

Figure 6.6 shows a mimic of the biological signal transduction system, where an artificial receptor and a naturally occurring enzyme coexist on a lipid bilayer membrane. The binding of a chemical signal to an artificially designed receptor activates a specific enzymatic reaction. In the example system shown, a steroidal-amine-type receptor and lactate dehydrogenase (LDH, the effector) were immobilized on a bilayer vesicle. In its initial state (the OFF state), the

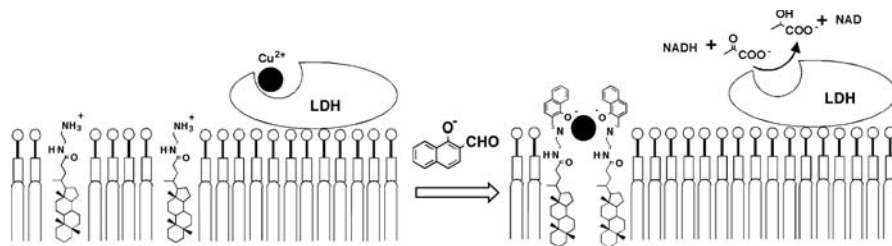


Figure 6.6. Artificial signal transduction

activity of LDH was inhibited by Cu^{2+} , which is a mimic of G-protein. When a suitable signal molecule (hydroxynaphthaldehyde) is added to the system, a signal–receptor complex called a Schiff base is formed in a reaction between the receptor amine and the signal aldehyde. Because the signal–receptor complex has a higher affinity for the metal ion than the enzyme, the metal ion is removed from the enzyme in an activated state (the ON state). In the ON state, the system catalytically produces lactate and NAD. This system is driven by the difference in binding affinity to the metal ion between the enzyme, the uncomplexed receptor and the signal–receptor complex.

The advantage of this artificial system is the freedom that we have when designing the combination of receptors and enzymes. The membrane system has another merit: the wide array of substances that it can be immobilized on. The system can be coated onto various devices, such as electrodes and optical fibers, leading to easy readout of the output signals as electrical and/or optical responses. For example, highly sensitive devices for detecting toxic chemicals such as endocrine disrupters can be prepared using this concept. Systems that release drugs upon sensing the presence of toxins are also possible.

6.4

Energy Conversion – Photosynthesis

The process of photosynthesis is crucial to the continued existence of life on Earth: it is the process that converts solar energy into chemical energy. The way that dyes and proteins are arranged in a photosynthetic system is one of the most elegant examples of functional arrays seen in biological systems. It is an excellent example of a well-designed supramolecular system. As shown in the schematic of a bacterial reaction center (Fig. 6.7), several dyes and proteins are systematically organized in a lipid bilayer membrane. The absorption of photonic energy by a bacteriochlorophyll special pair (BC–BC) induces electron transfer to a quinone (Q_a) via a bacteriopheophytin (BP). Another quinone (Q_b) accepts two electrons from the reaction center and two protons from the inner cell and converts into a hydroquinone ($Q_b\text{H}_2$). The trapped electrons and protons are carried to the outside of the cell by cytochrome b/c_1 . The electrons are returned to the BC–BC special pair by cytochrome c_2 . In this cycle, the protons are transported from the inside to the outside of the cell using energy from light. ATP can be synthesized by ATPase using the proton gradient as a driving force. The controlled array of functional molecules seen in this system is necessary for cooperative function.

This controlled dye array can be mimicked using thin film preparation techniques. The LB method is the technique most suited to layering various dye molecules in a desired sequence and at desired distances. Figure 6.8 shows hetero-type LB films that can mimic the dye array in the photosynthetic system of a cyanobacterium. Detailed time-resolved fluorescence spectra upon

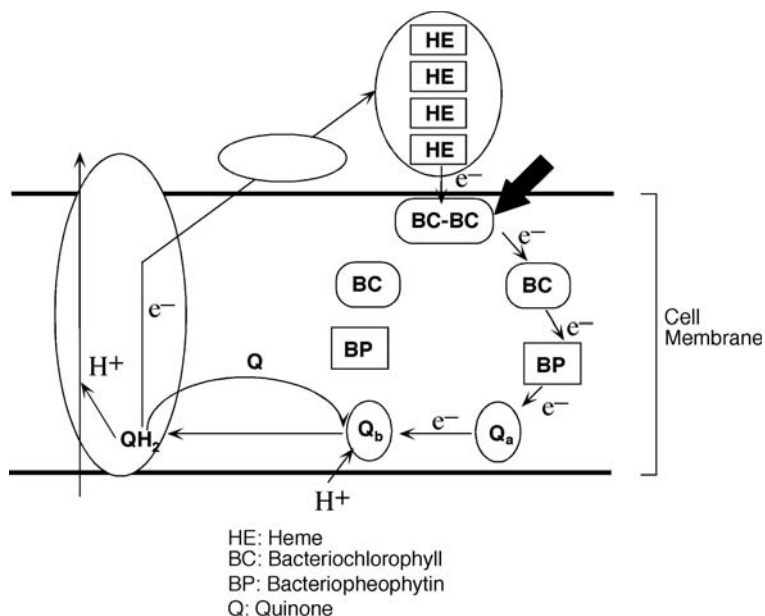


Figure 6.7. Schematic illustration of a bacterial reaction center

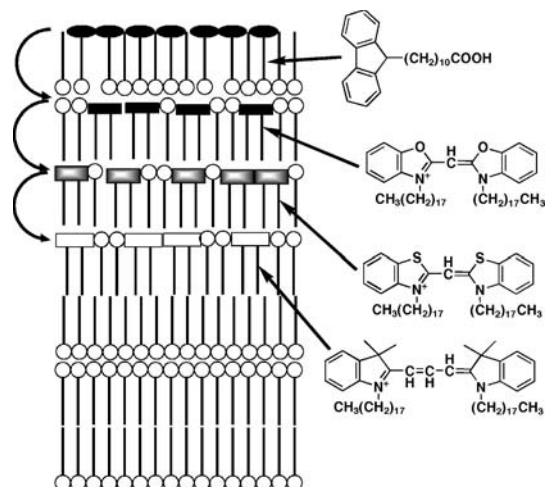


Figure 6.8. LB film as a mimic of the dye array in the photosynthetic system of a cyanobacterium

photoexcitation of the outermost layer have demonstrated that energy is transferred from the upper layer to the lower layer.

In a more realistic model, photoenergetically driven ATP synthesis was mimicked by the system described in Fig. 6.9. The triad carotene–porphyrin–

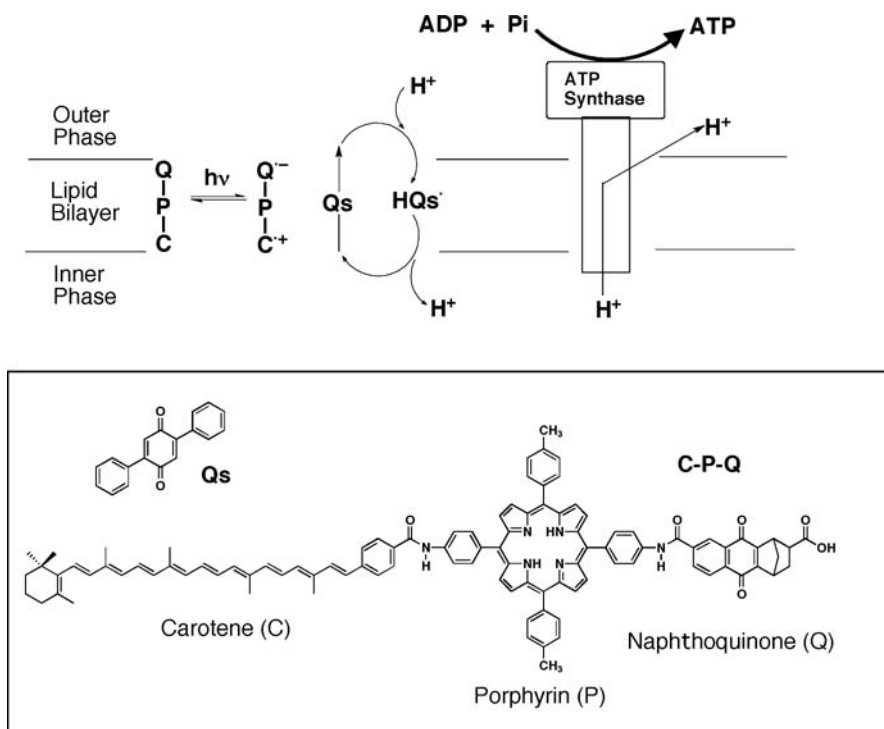


Figure 6.9. Mimic of photoinduced ATP synthesis

quinone (C–P–Q) molecule was buried in a lipid bilayer membrane. Visible light irradiation induced charge separation in the triad (the carotene and quinone became cation and anion radicals, respectively). Another hydrophobic quinone (Q_s) located in the membrane accepted an electron from the triad quinone and a proton from the outside, resulting in semiquinone (HQ_s^{\bullet}) formation. The semiquinone diffused inside the membrane, where it donated the electron to the carotene and released a proton inside the bilayer membrane. The ATPase immobilized in the lipid bilayer then converted ADP to ATP using the resulting proton gradient.

6.5

Material Conversion – Natural and Artificial Enzymes

Biological processes are highly sophisticated but are not driven by unknown and mysterious powers. They occur due to complicated combinations of known chemical reactions. These chemical reactions are conducted by enzymes (biological catalysts), which encourage desirable reactions to occur with high selectivity and efficiency. The application of naturally occurring enzymes to

artificial systems has resulted in many beneficial technologies. However, not all of the reactions we desire are catalyzed by enzymes. A limited range of conditions are needed for enzymes to function, and these conditions are often far from those required for engineering processes. Also, the amount of enzyme that occurs naturally is usually limited, and the enzyme extraction process can be expensive and time-consuming. Therefore, it is important to develop enzyme mimics (artificial enzymes) that can overcome these disadvantages. Artificial enzymes would be useful when performing information conversion in molecular devices. The application of artificial enzymes to biological systems would also benefit biotechnology.

Before we look at artificial enzymes, we will first outline the features of naturally occurring enzymes using the example (carboxypeptidase A) shown in Fig. 6.10. This enzyme sequentially performs C-terminal protein hydrolysis. In the active site of the enzyme, the Zn(II) coordinated with His 196, His 69, and Glu 72 coordinates with the amide carbonyl of the substrate. The hydroxyl group of the neighboring Tyr 248 forms a hydrogen bond with an amide N–H. These interactions lead to a significant decrease in electron density at the substrate amide linkage. Nucleophilic attack by Glu 270 via a water molecule therefore results in the hydrolysis of the amide linkage. The enzyme's Arg 145 recognizes the C-terminal of the substrate protein. A pocket accommodating the hydrophobic side chain of the substrate exists near this reaction site. The reaction is activated more when the substrate C-terminal has a more hydrophilic side chain.

As seen in the above-mentioned example, the high efficiency and high selectivity of this enzymatic reaction results from several features, such as the spatial organization of the catalytic site, the cooperative interaction between

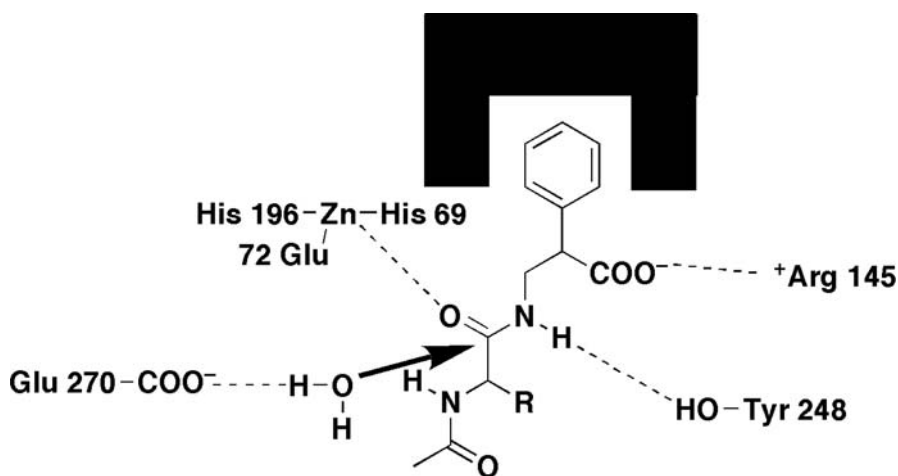


Figure 6.10. Catalytic mechanism of carboxypeptidase A

multiple amino acid residues, and the presence of a microenvironment that is favorable to the reaction. These features are accomplished via supramolecular concepts. Therefore, mimicking enzymes using supramolecular chemistry is a highly attractive area of research. For example, excellent designs for artificial enzymes have been reported based on modified cyclodextrin. Generally speaking, mimicking all of the features of naturally occurring enzymes is a pretty difficult task. However, separately mimicking just one a few features of enzymes is definitely possible. For example, it is reasonably easy to supply an enzyme-like hydrophobic microenvironment.

Water-insoluble materials such as hydrophobic polymers can supply hydrophobic interfacial environments. However, molecular assemblies such as micelles and lipid bilayer vesicles are more advantageous, because they supply large surface areas that are in contact with a water phase and more flexible organization. These characteristics are advantageous for substrate incorporation and product release. As explained in Chap. 4, a lipid bilayer provides a more stable hydrophobic environment, while micelles provide more dynamic and less stable assemblies. Structural and orientational control between the

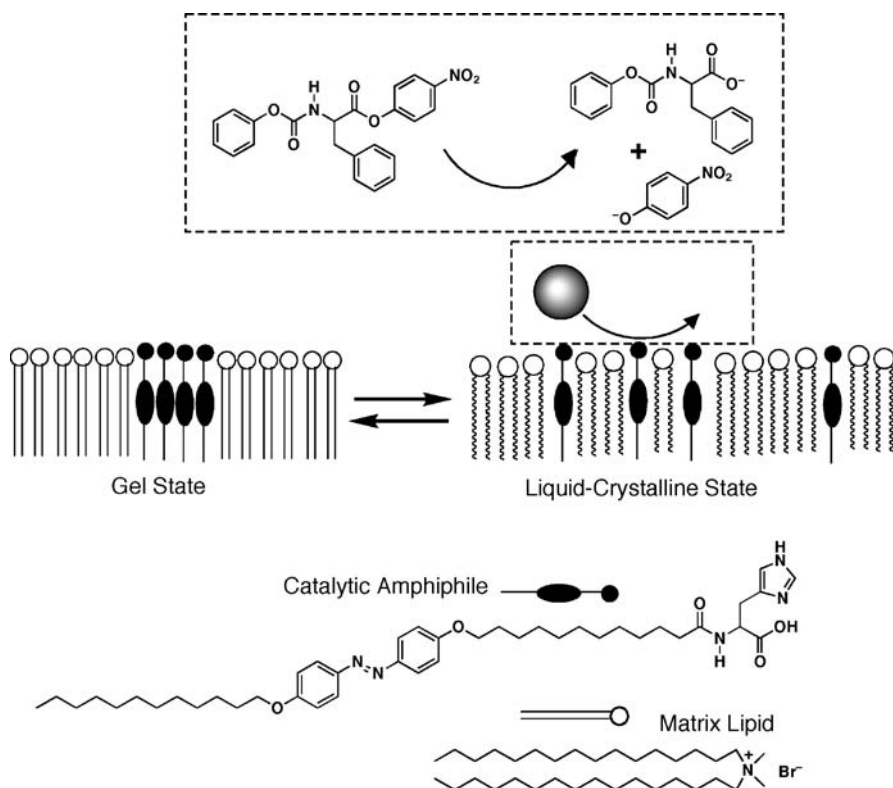


Figure 6.11. Controlling the activity of an artificial enzyme in a lipid bilayer

substrate and the catalytic site can be achieved more efficiently in the lipid bilayer membrane. Immobilizing catalytic sites with functions such as coenzyme activity in lipid bilayers sometimes leads to enzyme-like functions featuring hydrophobic microenvironments and controlled geometries.

Figure 6.11 shows the activity of an artificial enzyme can be controlled based on the phase behavior of a lipid bilayer. The catalytic site for hydrolysis was supplied by a monoalkyl azobenzene compound with a histidine residue which was buried in the hydrophobic environment of a lipid bilayer matrix formed using a dialkyl ammonium salt. Azobenzene compound association depended on the state of the matrix bilayer. The azobenzene catalyst aggregated into clusters when the bilayer matrix was in a gel state. In contrast, the azobenzene derivative can be dispersed into the liquid crystalline phase of the bilayer matrix above its phase transition temperature. This bilayer-type artificial enzyme catalyzed the hydrolysis of a *Z*-phenylalanine *p*-nitrophenyl ester. The activation energy for this reaction in the gel state is twice as large as that observed in the liquid crystalline state. The clustering of the catalysts upon phase separation suppress their catalytic activity, probably due to the disadvantageous electrostatic environment around the catalysts and the suppressed substrate diffusion. This activity control is unique to such molecular assemblies.

6.6

Cleaving Genes – Restriction Enzymes

Genetic engineering can be used to modify fundamental information related to life processes, and it is expected to result in significant improvements to our quality of life in years to come. Restriction enzymes, which can cut DNA at specific sequences, are an indispensable tool in the genetic sciences. The restriction enzyme recognizes a specific sequence in DNA and RNA. However, if the recognized sequence is not long enough, the DNA will be cut at many positions, and even in undesirable ways. As an example, let's consider the case for a sequences consisting of six nucleotide bases. In this case, the number of possible base sequences is $4^6 = 4096$. Therefore, the same sequence should exist at two or more positions when the DNA or RNA contains more than 4096 base pairs. Human DNA is known to contain 3×10^9 base pairs, and so a simple calculation suggests that DNA contains the same six-base sequence at over 700 000 positions. Therefore, if a restriction enzyme that recognized this six-base sequence was applied to human DNA, the DNA would be cut into countless pieces. This means that restriction enzymes that recognize long and desirable base sequences are far more advantageous in genetic engineering. However, it is not easy to find such restriction enzymes in nature; they need to be developed as artificial enzymes.

Before we consider an artificial restriction enzyme, we will briefly explain the mechanism by which ribonuclease A hydrolyzes RNA (Fig. 6.12). In the

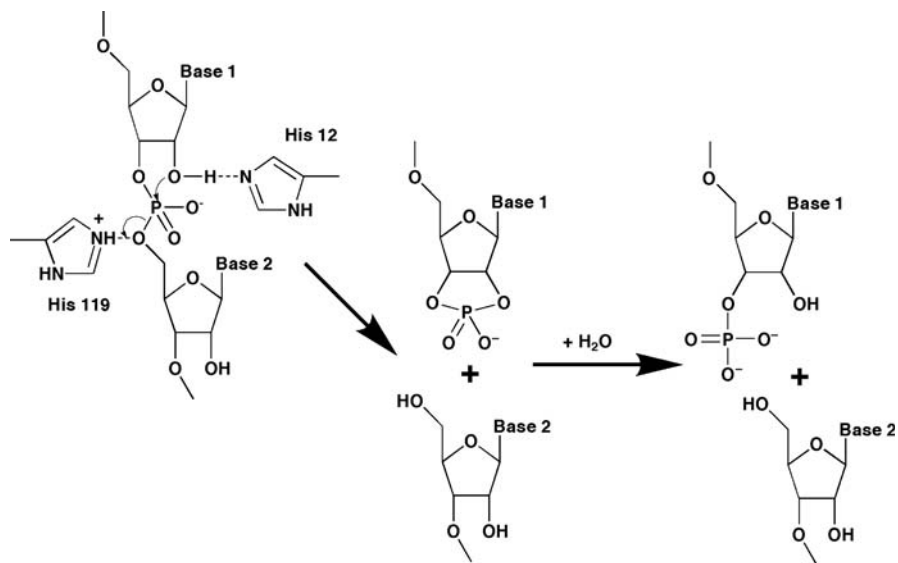


Figure 6.12. Catalytic mechanism of ribonuclease A

first step (step I), the 2'-OH group of the RNA is activated by the removal of the 2'-proton by histidine 12, and a P-O-C linkage is broken due to the nucleophilic attack of the phosphorus atom by the activated 2'-oxygen, resulting in a cyclic phosphodiester (base 1 side) and a ribose terminal (base 2 side). In this step, protonation of the phosphodiester by histidine 119 increases the electrophilicity of the phosphorus atom, aiding nucleophilic attack by the 2'-oxygen. The catalytic roles of the histidines' are reversed in step II. In this step, water is activated by the neutral histidine 119, and the activated water attacks the cyclic phosphodiester. Cleavage of the cyclic ester is encouraged by the protonation of the other histidine (12). Cooperation between the neutral and protonated histidines is crucial to these reaction steps.

The above-mentioned mechanism suggests that positioning the two histidines appropriately would lead to artificial ribonuclease under optimized pH conditions. Figure 6.13 shows an example of an artificial ribonuclease created in this way, which has a cyclodextrin core as the hydrophobic pocket and two histidine residues as catalytic sites. This artificial enzyme catalyzed the second step of the phosphodiester cleavage. The hydrophobic part of the cyclic phosphodiester (substrate) was accommodated into the core of the cyclodextrin and the phosphodiester was exposed between the two histidines. The water molecule was activated through proton removal (performed by the neutral histidine, left), and the activated water performed a nucleophilic attack on the phosphate atom. The protonated histidine (right) assisted this nucleophilic attack by protonating of the phosphodiester. Because of the cooperation between

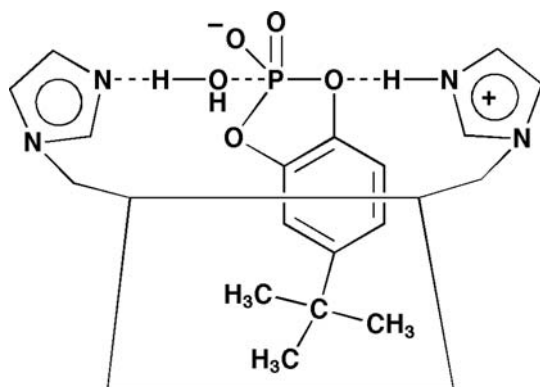


Figure 6.13. Hydrolysis of a phosphodiester by a functionalized cyclodextrin as a model of the second stage of the reaction shown in Fig. 6.12

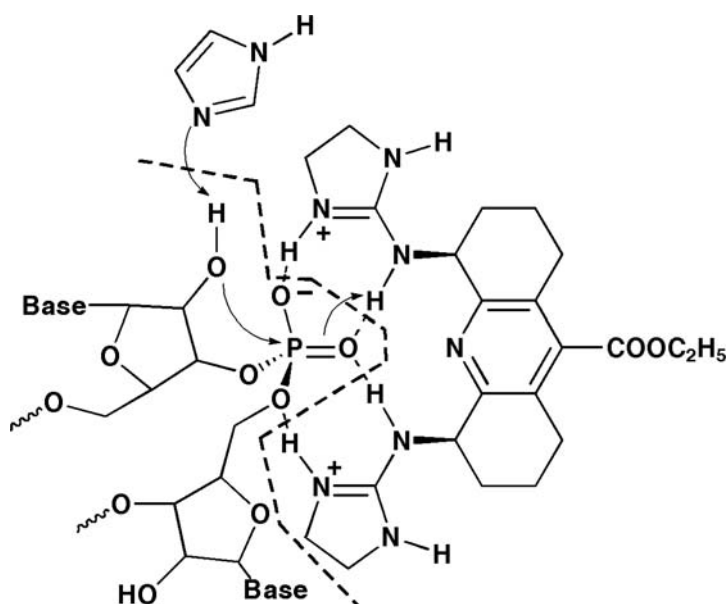


Figure 6.14. Hydrolysis of RNA by an artificial enzyme

the neutral and protonated histidines, the maximum activity of the artificial ribonuclease was obtained at around the pK_a of the histidines (approximately pH 7). However, this artificial enzyme cannot cleave actual RNA, because it only catalyzes the second step.

Actual RNA has been cleaved by the artificial enzyme shown in Fig. 6.14 which is a mimic of Staphylococcal nuclease. This is molecular-cleft-type artificial enzyme, where guanidinium residues connected to a rigid backbone

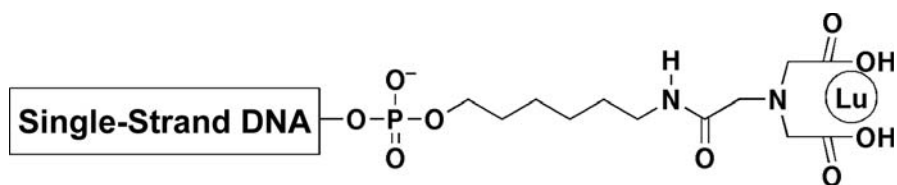


Figure 6.15. Artificial restriction enzyme

immobilize the RNA phosphodiester moiety. Imidazole present in the solution activated the 2'-OH and then nucleophilically attacked the phosphate. The transition state during the hydrolysis can be stabilized by hydrogen bonding with the guanidiniums. This stabilization increases the reaction rate of the RNA cleavage.

In order to develop an artificial restriction enzyme that can cleave a desired sequence, an oligonucleotide tag needs to be attached to the catalysis site. The artificial enzyme shown in Fig. 6.15 has an oligonucleotide tag (the rectangle) connected to a metal-chelate-type catalysis site (the circle). The catalytic site was fixed to a particular site on the substrate upon base pairing between the artificial enzyme and the substrate. When the Lu-chelate site was connected to single-stranded DNA, and the DNA moiety was hybridized to RNA with the complementary sequence, the RNA was hydrolyzed at the desired site. If the DNA sequence in the artificial enzyme is designed appropriately, RNA can be cleaved at any site desired.

DNA cleavage is much more difficult than RNA cleavage, but it is a more attractive target. Since the 2'-OH that plays an important role in RNA cleavage does not exist in DNA, DNA hydrolysis is much more difficult. Most living creatures store their genetic information in stable DNA. Catalytic sites that do not require substrate 2'-OH have to be used for DNA cleavage. Instead of an Ru-type artificial enzyme, a Ce-chelate artificial enzyme has been reported to possess DNA cleavage activity.

6.7

Tailor-Made Enzymes – Catalytic Antibodies

Actual enzymes have precisely constructed active sites consisting of finely designed sequences of amino acids. Highly sophisticated enzyme structures have been revealed by crystallographic techniques. Approaches to developing artificial enzymes are based on using organic chemistry and supramolecular chemistry to mimic the enzyme function. However, the construction of such a complicated structure by organic synthesis is an energy- and time-consuming task. Therefore, instead of designing a totally artificial system, partially utilizing a biological system might provide an easier approach. The catalytic antibodies described in this section satisfy this concept.

A biological immune system has outstanding ability to bind foreign substances (antigens). A specific antibody is created for each antigen. The antibody is frequently described as a Y-shaped protein, and the target antigen is specifically recognized at the top of the Y. The amino acid sequence at the recognition site of the antibody can be changed by modifying the genetic code, so antibodies that recognize various antigens can be produced biologically. This biological process is very useful when considering how to design proteins that can recognize a specific target molecule.

Various sites that mimic enzymes can be produced using a biological immune system, because the system can be triggered to produce an antibody corresponding to the transition state of the reaction of interest: in other words, the antigen would catalyze the reaction. This type of artificial enzyme is called a catalytic antibody. Because the transition state is usually unstable, an analog of the state is used to prepare the catalytic antibody. Figure 6.16 shows an example of a catalytic antibody used for ester hydrolysis. Carboxylic acid ester hydrolysis proceeds via a tetrahedral transition state which is produced by the nucleophilic attack of a hydroxide ion on a carbonyl carbon. Therefore, a phosphonic acid ester provides a good analog of the tetrahedral transition state. In this example, a dose of an albumin-bound phosphonic acid ester was given to animals, and an antibody recognizing the analog was then obtained immunologically. The obtained antibody was able to stabilize the transition state and enhance the rate of carboxylic acid ester hydrolysis. Various catalytic antibodies have been designed to catalyze a variety of reactions. These can be thought of as tailor-made enzymes.

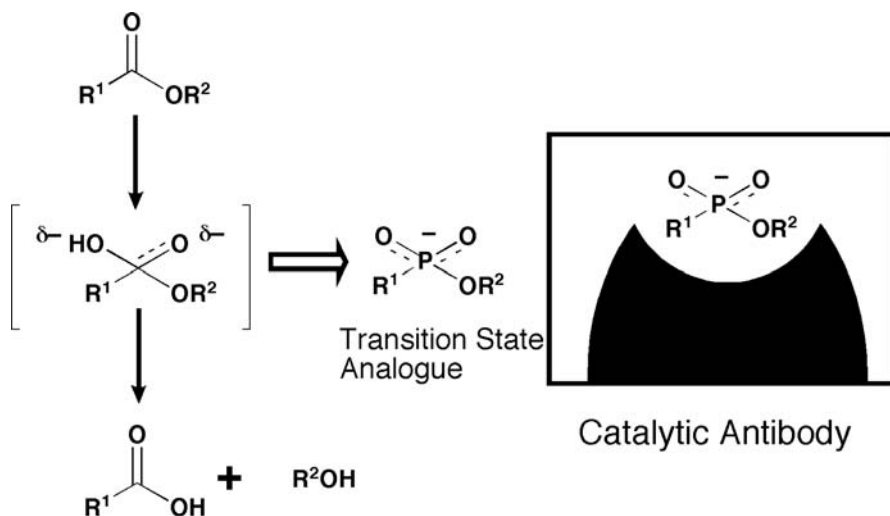


Figure 6.16. Performing ester hydrolysis with a catalytic antibody

6.8 Key to the Origin of Life – Ribozymes

In biological systems, proteins and nucleic acids perform two major roles: metabolism and conversion of materials and the storage and transmission of genetic information. Proteins are synthesized according to programs written in DNA, while nucleic acid replication and repair both require protein functionality. Proteins and nucleic acids need each other – they are interdependent.

Did this interdependency between proteins and nucleic acids exist during the origins of life? Or did one of them play the roles of both in the initial stages of life? These questions can be answered by investigating the protein-like functions of nucleic acids or the nucleic-acid-like functions of proteins. Indeed, nucleic acids are known to exhibit protein-like functions, and some RNA molecules show enzymatic activity. The first example found of this was the self-splicing ability of RNA. The reaction shown in Fig. 6.17 proceeds under protein-free conditions. RNA that can cleave another RNA molecule and RNA that can catalyze RNA polymerization have also been reported.

An RNA that exhibits enzyme-like activity is called a ribozyme. The discovery of ribozymes had a great impact on research into the origins of life. Identifying catalytic capabilities in RNA, an information molecule, led to a new theory: the *RNA world hypothesis*. This suggests that RNA was the first life form on Earth, and when it first evolved it performed both catalytic and enzymatic functions. The natural selection process associated with evolution eventually caused the RNA to evolve into the highly sophisticated supramolecular systems observed in the complex life forms present today.

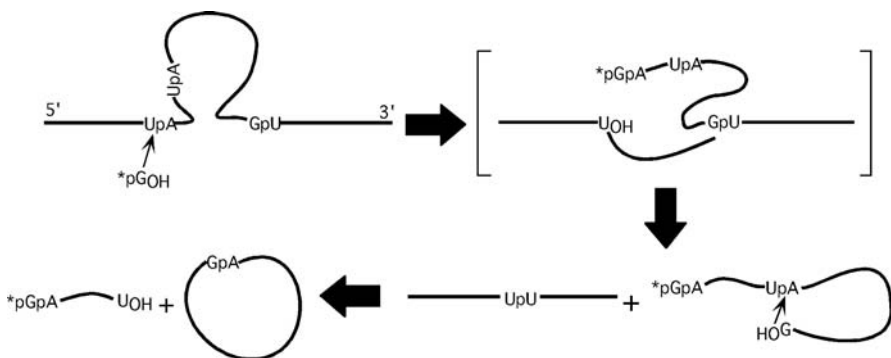


Figure 6.17. A self-splicing ribozyme

6.9

Combinatorial Chemistry and Evolutionary Molecular Engineering

In the usual approach to developing a new functional supramolecular system, the target molecule is first designed and then it is synthesized using organic chemistry techniques. The success of this approach significantly depends upon the effectiveness of the molecular design. The process of evolution that occurs in nature adopts a totally different methodology. Nature selects the best system to perform a particular task from a countless number of candidates, although this selection process requires a very long period of time! This type of approach can be more effective in some cases than the pin-point design methodology usually used. If the most suitable receptor is selected from numerous candidates using a rather simple procedure, the trial-and-error process often used when designing supermolecules can be eliminated.

Combinatorial chemistry is based on this concept. In this method, we synthesize a library – a group of many different candidates. When the library is prepared, a tag is sometimes attached to each candidate to identify each of them in a systematic way. Therefore, in the case of selecting a receptor for particular target guest, a library of receptor candidates is used. The responses of all of the receptor candidates in the library to a target guest are then examined, and the molecule that exhibits the greatest affinity to the guest molecule is selected and identified from the tag.

Various types of libraries, such as the peptide library, are widely used. Among them, the nucleic acid library is among the most interesting, because nucleic acids exhibit self-replication. Figure 6.18 shows an example where the oligo(nucleic acid) with the best affinity to thyroxine is selected from a random library. In this example, a PCR that multiplies nucleic acid was used.

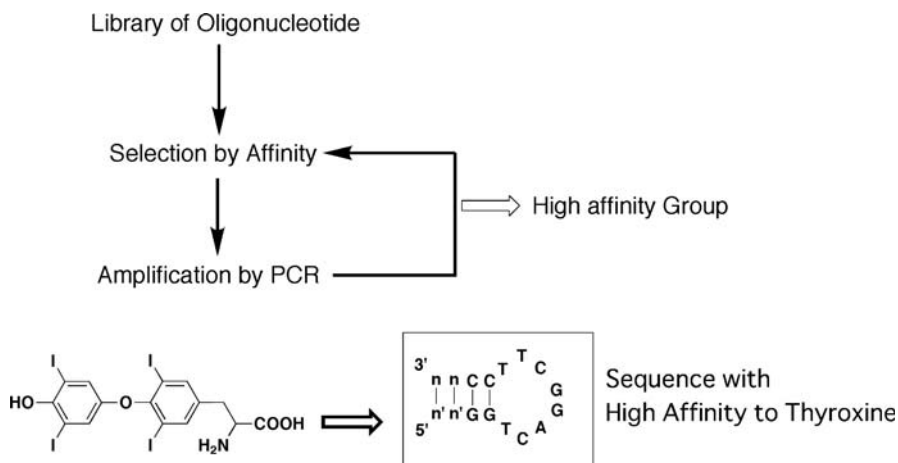


Figure 6.18. Selecting the best sequence for thyroxine binding

In the first selection, a group of nucleic acids with a high affinity to the target thyroxine was selected. The group was then multiplied using PCR treatment. The library obtained should have a higher affinity to the target than the initial

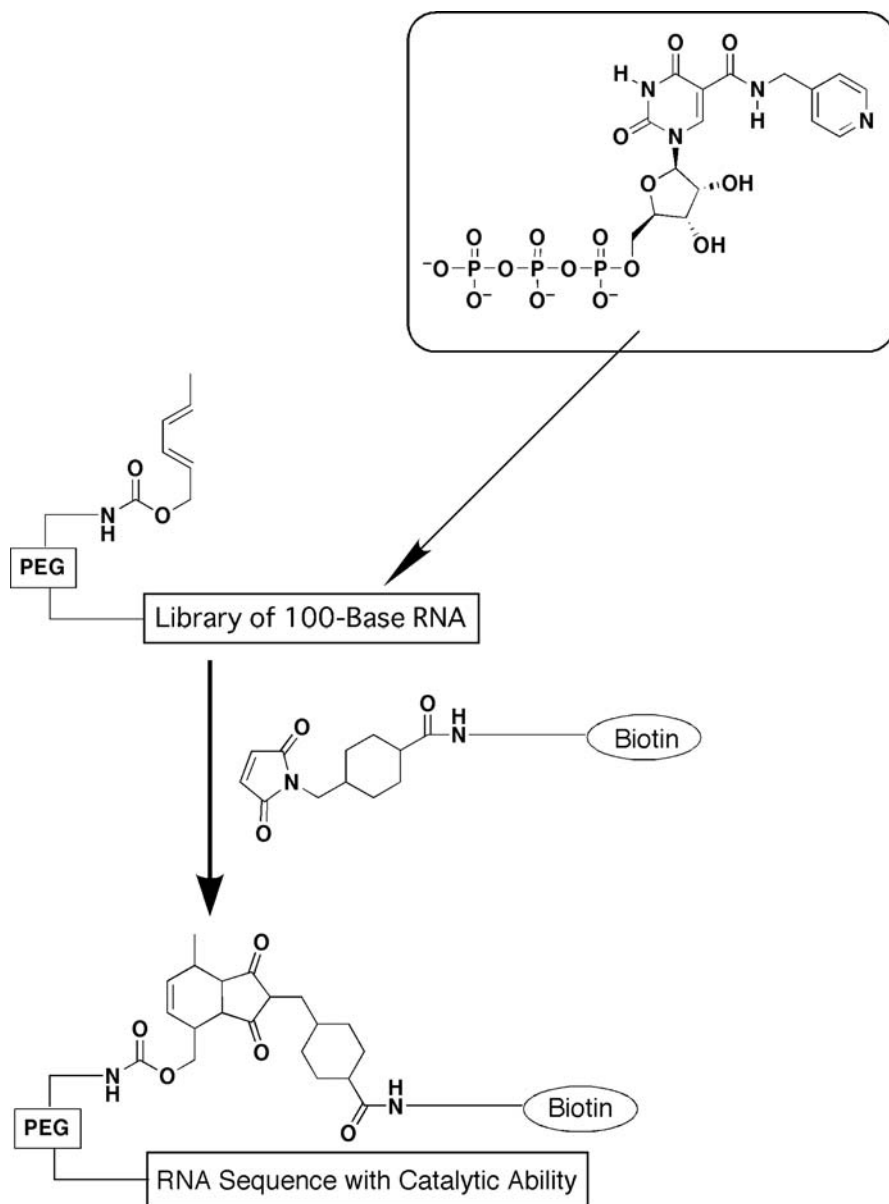


Figure 6.19. Catalyst selection by evolutionary molecular engineering

library. Repeating selection and multiplication processes eventually results in the selection of a few nucleic acids that strongly bind to thyroxine. Analyzing nucleic acids for common base sequences then reveals the important sequence for thyroxine binding.

This combination of selection and multiplication reminds us of natural selection. This methodology is called *evolutionary molecular engineering* or *in vitro selection*. It can be used to perform the selection processes within relatively short times, while the selection processes used in nature occur over very long periods.

Figure 6.19 shows an example of the application of this technique to select a catalytic site: an RNA sequence that catalyzes Diels–Alder reactions. A library containing random sequences of RNA was first prepared using a uridine derivative with a pyridyl moiety instead of the usual uridine. Each oligo-RNA chain in the library was connected to a diene part via a flexible poly(ethylene glycol) (PEG) chain.

A biotin-linked maleimide derivative was used as the reactive partner in the Diels–Alder reaction. These compounds were reacted in the presence of appropriate metal ions. The products of the Diels–Alder reaction contained both biotin and an RNA chain. The products with biotin attached were selected through specific binding with streptavidin. The RNA sequences of interest show catalytic activity towards the Diels–Alder reaction. These were transcribed into DNA form. The DNA sequences obtained were multiplied by PCR treatment, and a new RNA library was synthesized from these DNA sequences. Repeating the reaction / selection process and PCR treatment yielded RNA sequences that were optimized for catalyzing the Diels–Alder reaction.

This method of selecting catalytic sites significantly depends on spontaneous processes, in contrast to the development of artificial enzymes and catalytic antibodies. The selection process is based on self-assembly, self-organization and self-optimization. Therefore, this selection approach bears the characteristics of supramolecular chemistry. A similar concept is used in natural evolution processes, resulting in the complicated life forms we see around us today. Therefore, it is clear that we can design the self-organizational processes used in supramolecular chemistry to proceed according to the concepts followed by this natural evolutionary process.

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