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Cyclodextrin-Based Molecular Machines†

AKIRA HARADA
Department of Macromolecular Science, Graduate School of Science, Osaka University, Toyonaka, Osaka 560-0043, Japan

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ABSTRACT
Cyclodextrins have been used as a cyclic component in the construction of supramolecular architectures. Recently they have been studied as a component in the construction of rotaxanes and catenanes. A cyclodextrin ring can translocate in some rotaxane and catenane structures. Therefore, much attention has been given to cyclodextrins as a component of molecular shuttles, motors, and machines. Attempts to design and synthesize molecular-level machines using cyclodextrins as a cyclic component are described.

Introduction

A machine is defined as "an assembly of parts that transmit and modify forces, motion, and energy one to another in a predetermined manner". When the word "parts" is replaced by "molecules", a machine turns into a molecular or supramolecular machine. Therefore, a molecular machine is defined as an assembly of a distinct number of molecular components designed to perform machine-like movements in response to an appropriate external stimulus.[1] In addition, a molecular machine has features characteristic of the molecules. In biological systems, there are many molecular and/or supramolecular machines, such as enzymes, antibodies, and viruses.

Recently, much attention has been paid to constructing machine-like supramolecules starting from molecular components. Mechanically interlocked molecules, such as rotaxanes[2] and catenanes,[3] are suitable candidates for the construction of molecular machines, and they are now studied as a type of molecular motors and machines. Many kinds of molecular components can be used to construct molecular-level machines. Crown ethers,[4] cyclophanes,[5] and calixarenes[6] have been extensively used as cyclic components in the construction of the supramolecular structures.

We chose cyclodextrin as a cyclic component of such supramolecular assemblies, because cyclodextrin has a rigid, well-defined ring structure and an ability to bind various low-molecular-weight compounds.[7] Recently, cyclodextrins have been found to form supramolecular complexes not only with small molecules but also with large polymeric molecules.[8] They thread onto a polymer chain from the end groups of the polymer chain. We can observe the threading process by ^{1}H NMR spectrum in real time using cationic polymers.[9] On the basis of these observations, we have decided to prepare a molecular shuttle[10] in which a cyclodextrin ring moves back and forth along a polymer chain. In this Account, various attempts, mainly from our laboratory and others, to design and synthesize molecular-level machines using cyclodextrin as a cyclic component are presented.

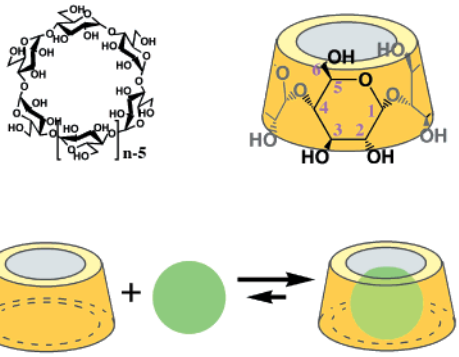

FIGURE 1. Cyclodextrins: α-cyclodextrin (n = 6), β-cyclodextrin (n = 7), and γ-cyclodextrin (n = 8). Formation of the inclusion complex of cyclodextrin with a small guest molecule.

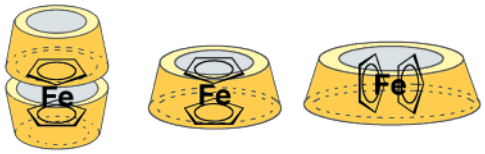

FIGURE 2. Structures of inclusion complexes of ferrocene with cyclodextrins: the complexes with α-cyclodextrin (left), with β-cyclodextrin (middle), and γ-cyclodextrin (right).[12]

Cyclodextrins

Cyclodextrins are cyclic compounds consisting of six to eight glucose units. They are called α-, β-, and γ-cyclodextrin, respectively (Figure 1). They are known to form inclusion complexes with various low-molecular-weight compounds, ranging from nonpolar aliphatic molecules to polar amines and acids.[7] Recently, they attracted renewed interest because they can be used as cyclic components in the construction of various supramolecular architectures.[11] We consider these cyclodextrin molecules as promising molecular components for the construction of molecular-based machines, because they are able to be threaded onto a long axle and to slide along a chain or to rotate around an axle.

Cyclodextrins form inclusion complexes with metallocenes such as ferrocene, cobaltocene, and nickelocene to form crystalline compounds.[12] The structures of the complexes are dependent on the sizes of cyclodextrins (Figure 2). Although ferrocene and its derivatives are strongly bound in uncharged states, when they are oxidized, the complexes dissociate. Dendrimers containing ferrocene units at the ends of the molecule have been

Akira Harada received his Ph.D. in chemistry from Osaka University in 1977. From 1979 to 1980, he worked for IBM Research, San Jose, CA, as a visiting scientist. From 1980 to 1981, he was a Postdoctoral Fellow at Colorado State University. Prior to joining the faculty of Science at Osaka University, he was a member of faculty at the Institute of Scientific and Industrial Research, Osaka University. In 1990, he was a visiting scientist at the Scripps Institute. He is now Professor in the Graduate School of Science, Osaka University. His research interests include supramolecular science, polymer synthesis, and biorelated polymers.

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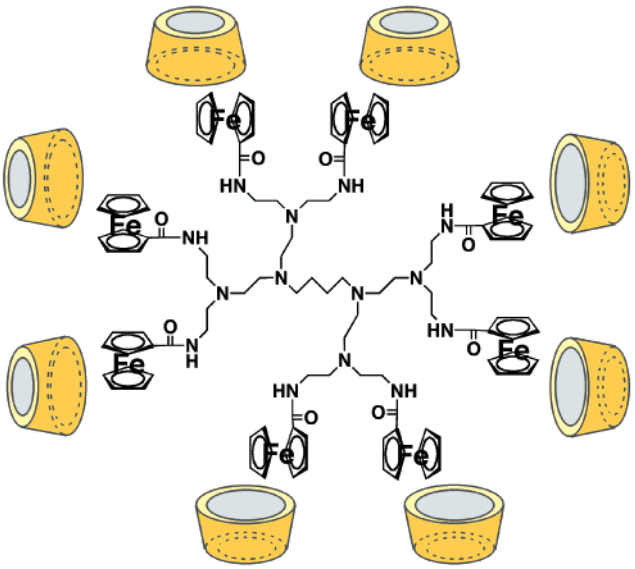


FIGURE 3. Dendrimer containing ferrocenes at the ends of the molecule and cyclodextrin.[13]

prepared (Figure 3). The dendrimers form large supramolecular structures that can be broken apart or assembled on oxidation of the ferrocene units.[13] The opposite behavior has been found in the complex of cyclodextrins with cobaltocene. Cobaltocenium derivatives do not form inclusion complexes with cyclodextrins. However, they form complexes with β-cyclodextrin upon one-electron reduction to give the neutral cobaltocene.[14] The dendrimers containing cobaltocenium units in the ends of the molecule do not form complexes with cyclodextrins, but upon reduction of the cobaltocenium units the dendrimers give large complexes with cyclodextrins. Although compounds containing bipyridinium in the dicationic forms are not included in the β-cyclodextrin cavity, they form weak complexes with β-cyclodextrin when they are reduced to their monocationic forms, and they form stable pseudorotaxane with β-cyclodextrin when they are fully reduced to their uncharged forms.[15] These systems are examples of electrochemically driven molecular complexes.

Cyclodextrin Derivatives

Reversible cis/trans photoisomerization of the azobenzene group has been used to control the configuration of the host molecules. The azobenzene-capped β-cyclodextrin has been prepared (Figure 4). The azobenzene-capped β-cyclodextrin does not bind 4,4′-bipyridine when the azobenzene group is in the trans form. However, upon irradiation with UV light, the compounds change from trans to cis conformation, and then the host includes 4,4′-bipyridine in its cavity.[16] When the compound goes back to the trans isomer, the guest compound is ejected from the cavity of β-cyclodextrin.

Methylated cyclodextrins have been frequently used as host molecules, because they are soluble not only in water but also in some organic solvents. Methylated cyclodextrins form even more stable complexes than cyclodextrins

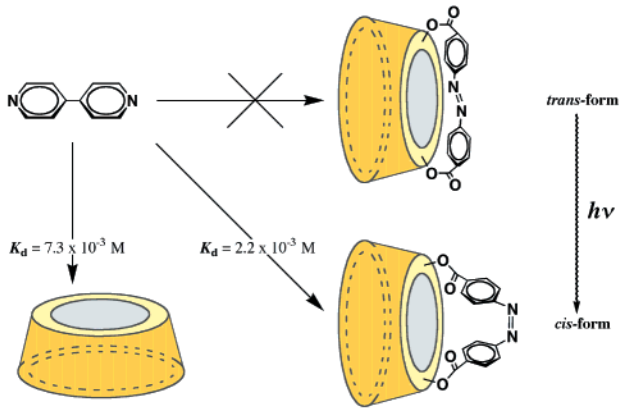


FIGURE 4. Azobenzene-capped β-cyclodextrin: regulation of inclusion complex formation by photoisomerization of the azobenzene group.[16]

with some guest molecules such as ferrocene and its derivatives and can be used as machine-like hosts for the redox-active guests.

Rotaxanes

Rotaxanes are considered to be a typical prototype of molecular machines, because they have a rotor and an axle in the molecule. α-Cyclodextrin was first used as a rotor of rotaxane by Ogino and Ohta in 1978.[17] They used metal complexes as stoppers. Since then, some rotaxanes containing cyclodextrins have been reported (Figure 5).[18−22] Most of those rotaxanes used metal complexes as stopper groups. However, metal coordination bonds are so labile that cyclodextrin rings may escape from the bond. All the rotaxanes reported are ionic and thus soluble in water. One example in which all the components are nonionic and soluble in organic solvents[23] was reported. In such a case there are some interactions between a cyclodextrin ring and stopper groups. In all cases, there is no clear evidence for the rotatory motion of cyclodextrins around an axle. The dynamic behavior of the rotaxanes is a subject that remains to be explored.

Polyrotaxanes

Cyclodextrins were found to form inclusion complexes with various polymers with high selectivity.[2] For example, α-cyclodextrin forms complexes with poly(ethylene glycol) (PEG) to give crystalline compounds in high yields, although β-cyclodextrin does not give crystalline complexes with PEG. However, β-cyclodextrin forms complexes with poly(propylene glycol) (PPG), which has methyl groups on a PEG main chain, although α-cyclodextrin does not give any complexes with PPG. γ-Cyclodextrin forms complexes with poly(methyl vinyl ether), although α- and β-cyclodextrins do not give complexes with this polymer. There is a good correlation between the sizes of the cyclodextrin cavities and the cross-sectional area of the polymers.

Recently, we found that cyclodextrins form complexes not only with hydrophilic polymers, but also with hydrophobic polymers. α-Cyclodextrin gives complexes with

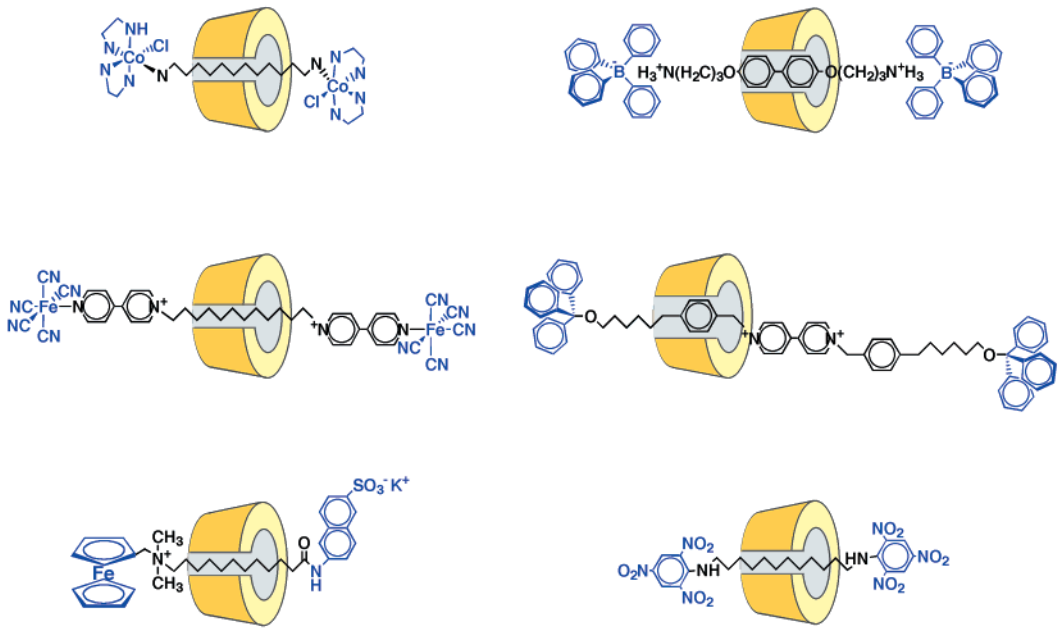


FIGURE 5. [2]Rotaxane containing cyclodextrin.[17−22]

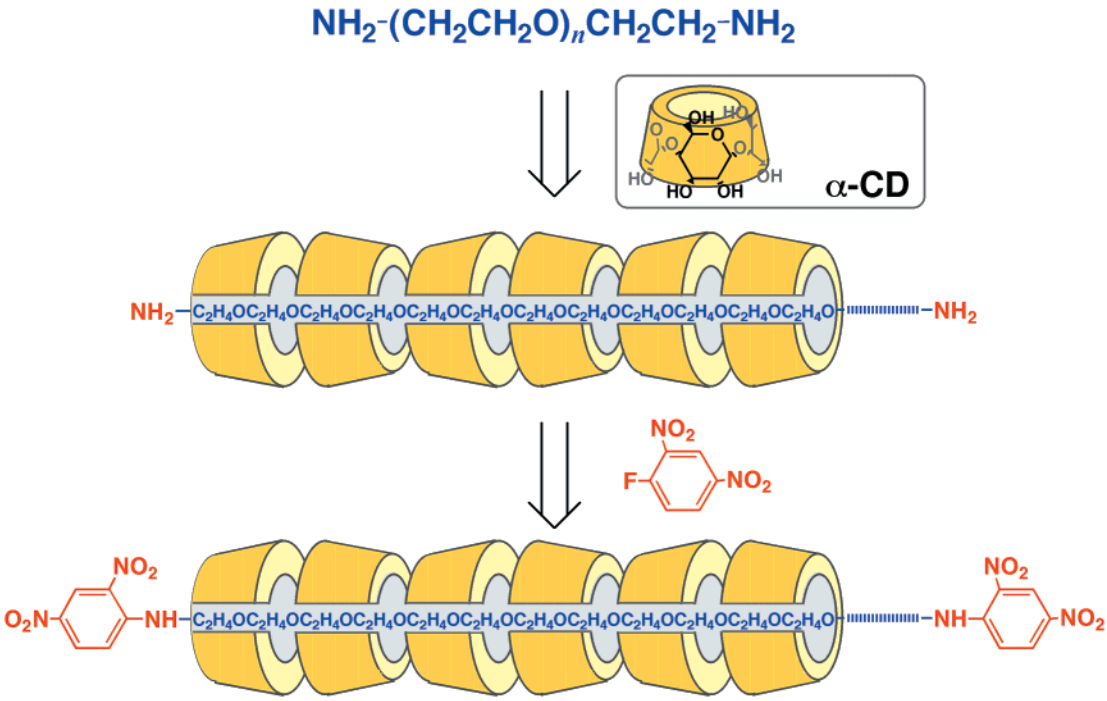


FIGURE 6. Polyrotaxane containing α-cyclodextrins (molecular necklace).

polyethylene of molecular weight less than 1000, β-cyclodextrin with polypropylene, and γ-cyclodextrtin with polyisobutylene. Again, there is a good correlation between the sizes of the cyclodextrin cavities and the thickness of the polymers.

In the case of complex formation of cyclodextrins with nonionic polymers, the complexes are formed as crystalline solids. Since the complexes are sparingly soluble in water, it is difficult to observe the behavior of the complexes in the aqueous phase.

Polyrotaxanes in which many cyclodextrins are threaded onto a polymer chain have been prepared, starting from poly(ethylene glycol) and α-cyclodextrins, by capping the chain ends with bulky stoppers (dinitrophenyl groups) (Figure 6).[24] We have obtained many kinds of polyrotaxanes starting from PEG of various molecular weights. The polyrotaxanes are insoluble in water, although both α-cyclodextrin and poly(ethylene glycol) are soluble in water. However, the polyrotaxanes are soluble in a basic solution (0.1 N NaOH). Hydrogen bonds between cyclodextrins may be destroyed by addition of a base capable of deprotonating OH groups of CD. However, the hydrogen bonds can be restored by the addition of an acid that is capable of reprotonation of the OH function. Cyclodextrin

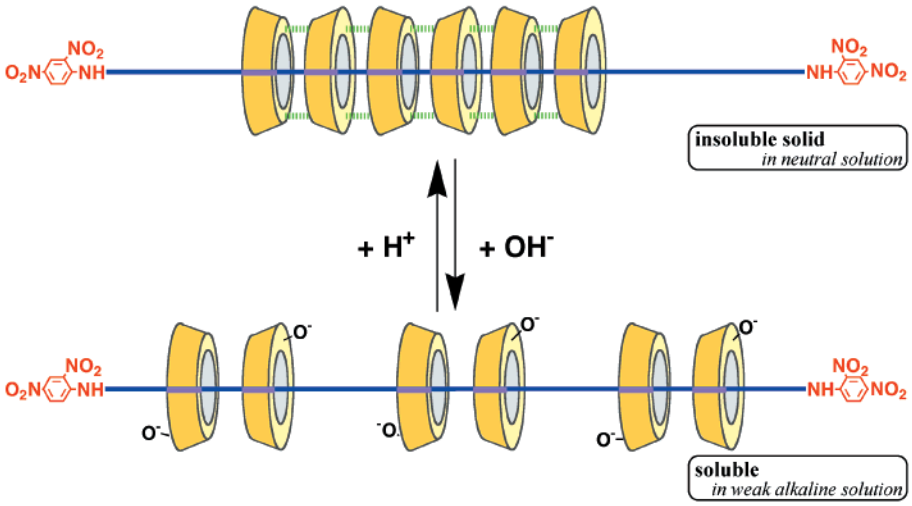


FIGURE 7. Molecular abacus 1. Cyclodextrin beads can be manipulated along a polymer chain by means of chemical (acid/base) stimulation.

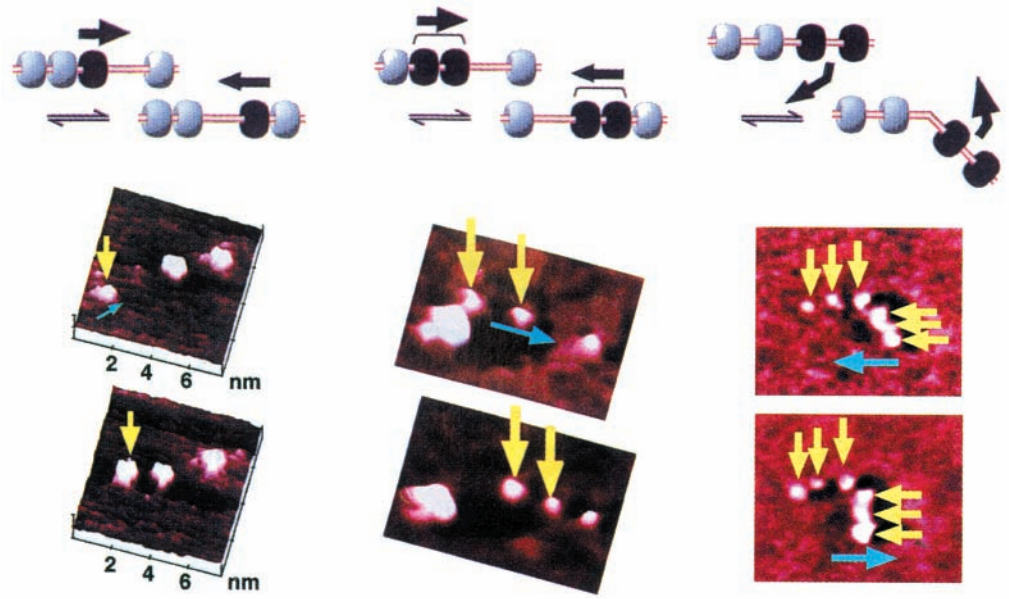


FIGURE 8. Molecular abacus 2. A cyclodextrin bead (or two) can be manipulated along a polymer chain by means of scanning tunneling microscopy.

rings move away from each other along a polymer chain with a base due to repulsive interactions between ionized hydroxyl groups and move back toward each other upon neutralization to form a hydrogen bond network ("go-wasan" in Japanese, to clear an abacus) (Figure 7). Thus, in the supramolecular polymer complexes based on hydrogen-bonding interactions, mechanical motions can be driven by means of chemical (acid/base) stimulation.

Recently, it has been found that a cyclodextrin ring or two in a polyrotaxane can be manipulated by using the tip of a scanning tunneling microscope.[25] Figure 8 shows an STM image of a polyrotaxane composed of α-cyclodextrin and PEG. One of the cyclodextrins in the molecular necklace was mechanically pushed by the STM tip along the main chain of PEG. Upon moving the tip in the reverse direction, the α-cyclodextrin retraced its path and returned to its original position. Thus, the shuttling of one α-cyclodextrin could be repeated. It was also possible to move a pair of cyclodextrins simultaneously. Although all the cyclic components move in solution thermally or photochemically, in this system only a single cyclodextrin ring can be moved along a polymer chain.

More recently, we found that cyclodextrins form complexes not only with nonionic polymers but also with ionic polymers (Figure 9) such as linear polymers consisting of bipyridinium (viologen) bridged by polymethylene chians. Although these polymers do not give crystalline complexes with any cyclodextrins at all, cyclodextrins form complexes with these polymers in the aqueous phase, because polymethylene units are favorable for complex formation with cyclodextrins.[9] The ^{1}H NMR spectra of this polymer in the presence of cyclodextrins proved their structures (Figure 10).

We found that the methylene peaks split in two upon addition of α-cyclodextrin, although these peaks did not change upon addition of γ-cyclodextrin. These peaks are

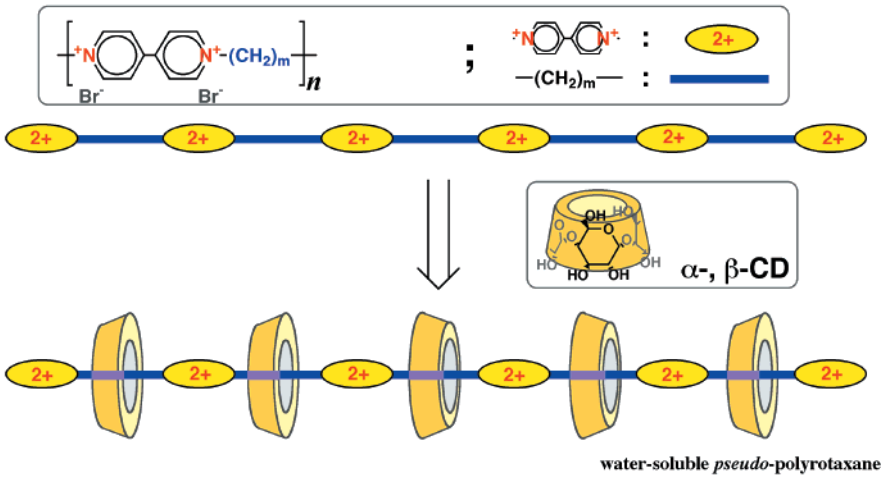


FIGURE 9. Complex formation of cyclodextrin with cationic polymers in an aqueous solution.

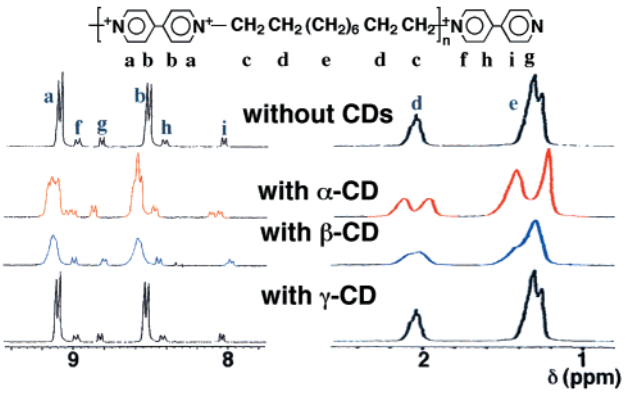


FIGURE 10. ^{1}H NMR specrtra of viologen polymers in the absence and in the presence of cyclodextrins (α-CD stands for α-cyclodextrin, β-CD for β-cyclodextrin, and γ-CD for γ-cyclodextrin).

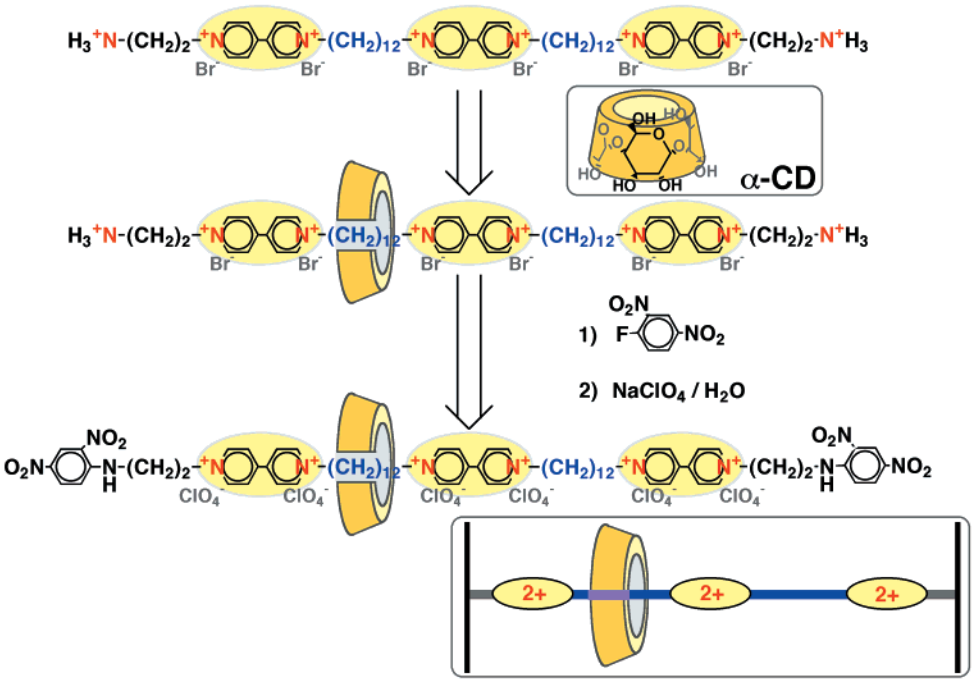
broadened upon addition of β-cyclodextrin. These results indicate that α-cyclodextrin stays at one of the methylene chains on the ^{1}H NMR time scale, and β-cyclodextrin moves along the polymer chain faster than the ^{1}H NMR time scale.

On the basis of these observations, we have decided to make a molecular shuttle in which a cyclodextrin moves back and forth along a chain.

Molecular Shuttles

We have designed a molecular shuttle as follows: α-cyclodextrin as a ring, two polymethylene chains as stations, 4,4′-bipyridinium units as linkers, and dinitrophenyl groups as stoppers. The molecular shuttles have been prepared as shown in Scheme 1. We prepared an axle first, and then the axle was treated with an aqueous solution of α-cyclodextrin. A molecular shuttle containing dodecamethylene units, 4,4′-bipyridinium units, and α-cyclodextrin has been obtained by closing the end groups of the

Scheme 1



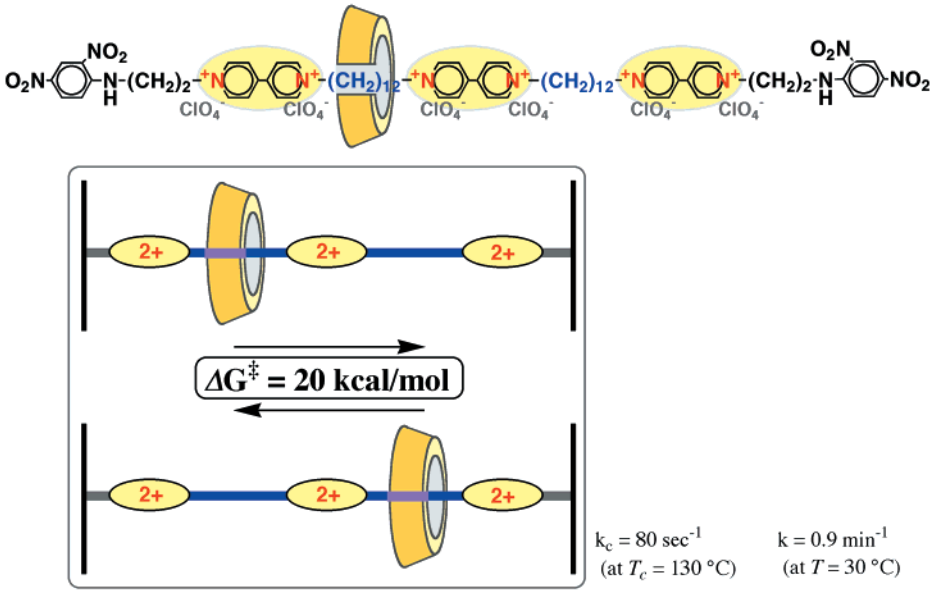


FIGURE 11. Molecular shuttle containing α-cyclodextrin.[10]

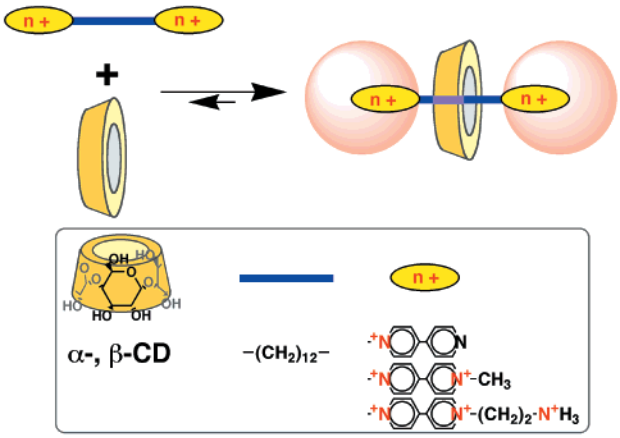


FIGURE 12. An electric trap: cationic groups stabilize a rotaxane structure.[26]

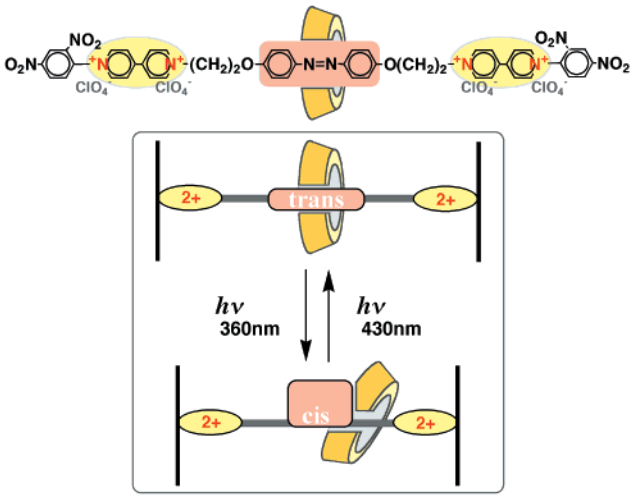


FIGURE 13. Molecular shuttle containing α-cyclodextrin and an azobenzene group: a cyclodextrin ring moves along the chain with photoisomerization.[27]

chain by using dinitrofluorobenzene.[10] Shuttling behavior of the molecular shuttle is solvent- and temperature-sensitive and could be controlled by double interactions: hydrophobic interaction between a cyclodextrin ring and a station and a repulsive interaction between a cyclodextrin ring and a linker. This is a new method to control the mobility of a bead in a molecular shuttle (Figure 11).

While we were preparing a molecular shuttle, we found that cationic groups serve as a potential surface for the translocation of a cyclodextrin ring on a polymer chain. Therefore, we studied the interactions between cyclodextrins and some dodecamethylene derivatives with different numbers of cationic groups (Figure 12). We found that a cyclodextrin ring did not escape from a dodecamethylene derivative with three cationic groups at the chain ends. Multiple cationic groups stabilize a rotaxane structure by inhibiting a cyclodextrin ring from coming off.[26] A rotaxane containing an azobenzene group in its axle and α-cyclodextrin has been prepared (Figure 13).[27] The cyclodextrin ring stays around the *trans*-azobenzene site. When the rotaxane is exposed to light, the azobenzene unit isomerizes from trans to cis and moves the α-cyclodextrin group away to encircle one of the ethylene glycol chains. Upon irradiation with visible light, the azobenzene unit isomerizes from cis back to trans. The cyclodextrin ring is shuttling along the chain in this photoisomerization.

Catenanes

Catenanes containing cyclodextrins have been prepared by Stoddart et al. (Figure 14).[28] One or two cyclodextrins are incorporated in a catenane structure. These compounds are important as "a molecular train" in which a small ring can slide along a large circle as though they are trains on a molecular scale. We have prepared cyclodextrin-containing catenanes starting from the complexes of cyclodextrin with polymethylene derivatives using a poly(ethylene glycol) spacer. In this case, a cyclodextrin ring may move along the polymer chain if the solvents

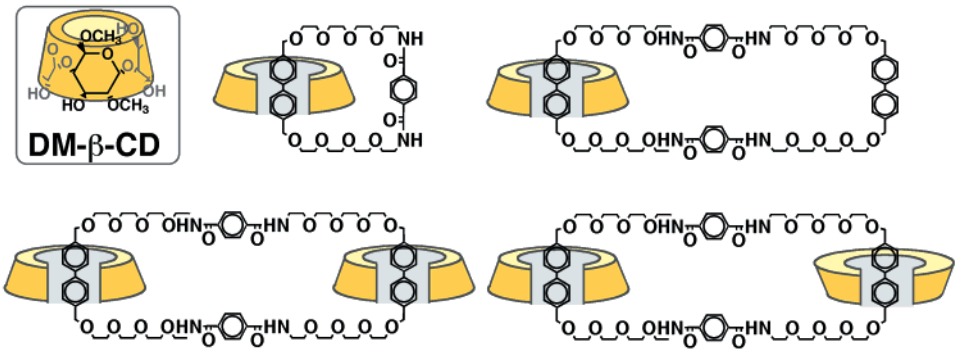


FIGURE 14. Catenanes containing cyclodextrin.[28]

are changed from hydrophilic to hydrophobic ones. We also prepared polycatenanes in which many cyclodextrin rings are imprisoned in a large circle composed of PEG and anthracene stoppers by photodimerization of the precursor of polyrotaxanes containing cyclodextrins.[29] This polycatenane can go back to a polyrotaxane by irradiation with UV light or heating through decomposition of the photodimer.

Daisy Chains

When a guest group is covalently attached to a cyclic host, the molecule may form an intramolecular complex or intermolecular complexes to give supramolecular polymers. When supramolecular polymers are treated with bulky stopper groups, they may form poly[2]rotaxane "daisy chains". We have found that a cyclodextrin derivative which has a cinnamoyl group as a guest at the 6-position forms an oligomeric supramolecular structure in aqueous solutions and that the supramolecular structure could be stabilized by attaching bulky stoppers to give daisy chains.[30] Poly[2]rotaxanes are unique polymers, because the polymers can expand and shrink in response to external conditions. The behavior of the polymers reminds us of those of muscle fibrils (actins and myosins).

Cyclic Daisy Chains

Cyclic tri[2]rotaxanes (daisy chain necklace) containing cyclodextrins have been prepared by closing a tri[2]-rotaxane containing α-cyclodextrin and 6-(4-aminocinnamate) with 2,4,6-trinitrobenzenesulfonic acid sodium salt[30] (Figure 15). If the molecule changes its conformation (or co-conformation[1]), the cycle may expand or shrink in response to external conditions (temperature, solvents, photochemically, electrochemically). These compounds are important because the cycle can be used as a chemical valve, as can be seen in ion channels in biological membranes.

Monolayer Electrode

If a signal is put in to and read out from interlocked molecular systems, the interlocked compounds should be immobilized on an electrode surface. A *β*-cyclodextrin monolayer was prepared on a Au electrode. The monolayer acts as an active interface for the electrochemical

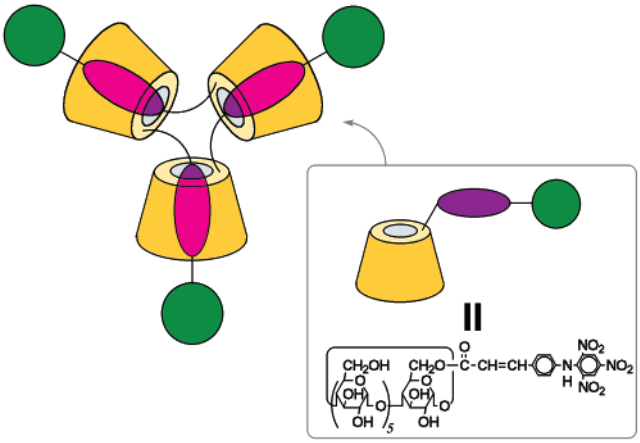


FIGURE 15. Daisy chain necklace: cyclic tri[2]rotaxane containing α-cyclodextrin.[30]

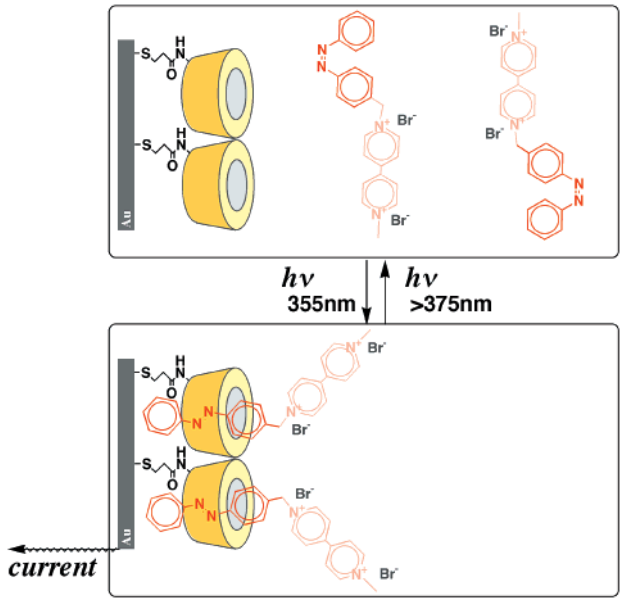


FIGURE 16.

and microgravimetric transduction of optical signals recorded by a bipyridinium−azobenzene diad (Figure 16).[31−33]

Very recently, a light-driven molecular shuttle has been organized on a gold electrode surface.[34] The ferrocene-functionalized *β*-CD resides on the *trans*-azobenzene, and photoisomerization (to the cis form) occurs at the trans locations of the ring to the alkyl chain part of the thread.

The signal is electronically transduced by chronoamperometry. The assembly functions as a molecular optoelectronic system that records optical information and transduces it by an electronic signal.

Perspective

Recently, much attention has been paid to the construction of molecular machines, molecular motors, and molecular devices as alternatives for VLSI produced by classical lithography. Many successful attempts have been made in the construction of mechanically interlocked molecular assemblies. In the future, communication with these molecular assemblies—how to stimulate each molecule and how to read its information—will be important. Addressing each molecule will also be important. Scanning probe micrography should be used as a tool to access each molecule. For this purpose, it is important that the interlocked molecules are immobilized on the surface of the solid base-like electrode. Alternatively, the classical lithography (top-down procedure) and the bottom-up procedure should be combined, so that the molecule is used as a conducting wire in VLSI. Polyacetylene (found by Prof. Shirakawa), polythiophene, and polyaniline can be used for this purpose.

In any case, in biological systems many molecular machines, such as enzymes, antibodies, receptors, and other moving molecular assemblies, play important roles to maintain their lives. Artificial molecular machines are going to be able to aid, substitute, and/or expand our five senses in the future.

Conclusion

Cyclodextrins are considered to be promising candidates for the construction of molecular-based machines, because they have not only rigid, well-defined ring structure but also rotational symmetry with an asymmetric environment. Therefore, rotational motion will accompany unidirectional motion, and sliding motion will accompany asymmetric motion. The movement will be monitored (read out) by attaching a chromophore on cyclodextrin, because cyclodextrin is basically photochemically and electrochemically inactive.

When we compare the cyclodextrins with other cyclic molecules, cyclodextrins are produced from amylose and made of glucose, so they are water-soluble and nontoxic. Therefore, they can be used in the human body, for example, as drug delivery systems.

Other cyclodextrin derivatives, such as tubular polymers and double-strand inclusion complexes, will be used as components of molecular-size devices.[35−37]

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