Contribution

Molecular Capsules :
Container Compounds with an Isolated Nanoscale Cavity

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1. Introduction

Life activities are maintained by consuming energy supplied through a series of processes: food intake from the environment, its breakdown, and metabolism inside the body. Throughout these processes the biological membrane becomes a key locale. The biological membrane is formed by self-assembly of lipids driven by hydrophobic interaction, and defines boundaries between the inside and the outside of a cell. It protects the cell from foreign bodies and at the same time mediates energy exchange, substance transport and signal transmission as necessary. The plasma membrane also establishes specialized enzymatic reaction and energy conversion in response to the specific environment. Meanwhile, such a system can be experimentally constructed in an artificial system. One way is to create a micelle or a biomolecular membrane, which is used to solubilize insoluble substances or provide a space for various reactions. Nano particles developed recently are one of its wide-ranging applications. This brings us to a question as to if it is possible to create such a specific environment on a smaller scale to create an isolated cavity for inclusion of a single molecule or a few. Then, the interesting compounds, carcerands, created by host-guest and supramolecular chemistry draw attention.[1] Carcerands, or molecular capsules, are the synthetic host molecules with enclosed interiors, which are designed three dimensionally to ensure strong and precise molecular recognition. Due to their complex structures, enclosed guest molecules reside in the environment isolated from the outside. As a consequence, physical properties and chemical reactions specific to the environment can be identified. Such characteristics are similar to those of the biological membrane mentioned above, and it is not too much emphasis to say that the molecular capsule is the smallest experimental model that alternates the biological membrane. Ingenious use of non-covalent bond recently enabled facile synthesis of molecular capsules, and a variety of reports on molecular designing and functionality have started to emerge.

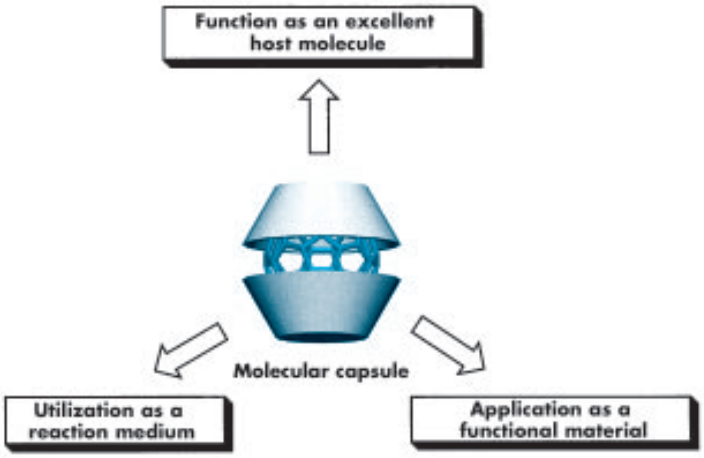


Figure 1.

Based on these facts, the research in our laboratory has been centered on facile synthesis of the molecular capsule by using non-covalent bond and hemispherical compounds as well as the application of synthesized host-guest complex to functional materials. In this paper, we will focus on the molecular capsules based on porphyrins and calixarenes including recent advancements in our research.

2. Molecular capsule using calixarene skeleton

Calixarene has rapidly become the focus of attention as a host molecule since Gutsche *et al.* established its single-step synthesis.[2] Its structure made of phenol units permits function as an excellent ionophore like crown ethers as well as accommodation of various functional groups, and a number of versatile derivatives have been reported.[3] Among many conformational isomers which calixarenes (mainly tetramers and homooxacalix[3]arenes are discussed in this section) are known to adopt, the cone conformation is preferentially exploited as a structural unit, because it carries a hemispherical cavity (Figure 2).[4]

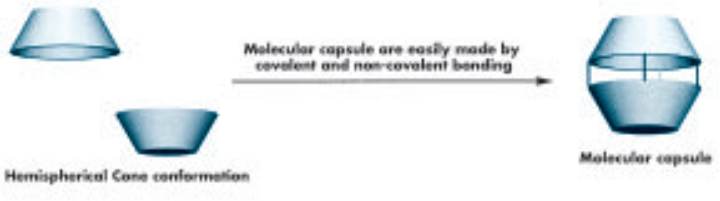


Figure 2.

In this section, self-assembling calixarene capsules are described.

2.1 Calixarene capsules formed by hydrogen bonding

Hydrogen bonding is known as the important interaction for the formation of DNA double helices and the maintenance of higher order protein structure. It is also essential in terms of molecular recognition and functional design of synthetic receptors and gel matrices. We previously reported that the capsule molecules self-assemble by hydrogen bonding built between carboxylic groups and pyridines (Figure 3).[5] This was the first report of calixarene capsules formed by the driving force of hydrogen bonding.

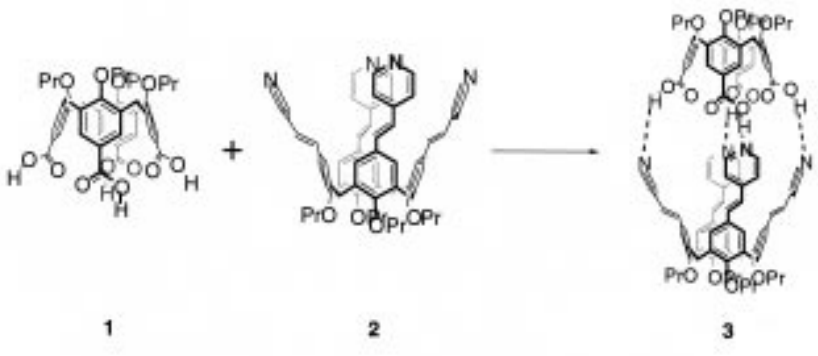


Figure 3.

Since then, many researchers have documented self-assembling capsules formed by hydrogen bonding.[6] Among them, the calixarene capsule reported by Rebek *et al.* has been of great interest. They introduced urea groups at the upper rim of calix[4]arene and found that their complementary interaction also made a capsule (Figure 4). [7] Moreover, the synergic effect between substituents (X and Y) placed in the urea group and the guest molecule built a capsule with a heteromeric structure. For example, **6a** preferentially formed a capsule with **6b**. Based on these results, they reported that a pair of pigments capable for energy and electron transfer (one as a donor and the other as an acceptor) could be developed into a molecular sensor using a technology such as FRET (Fluorescence Resonance Energy Transfer) [8].

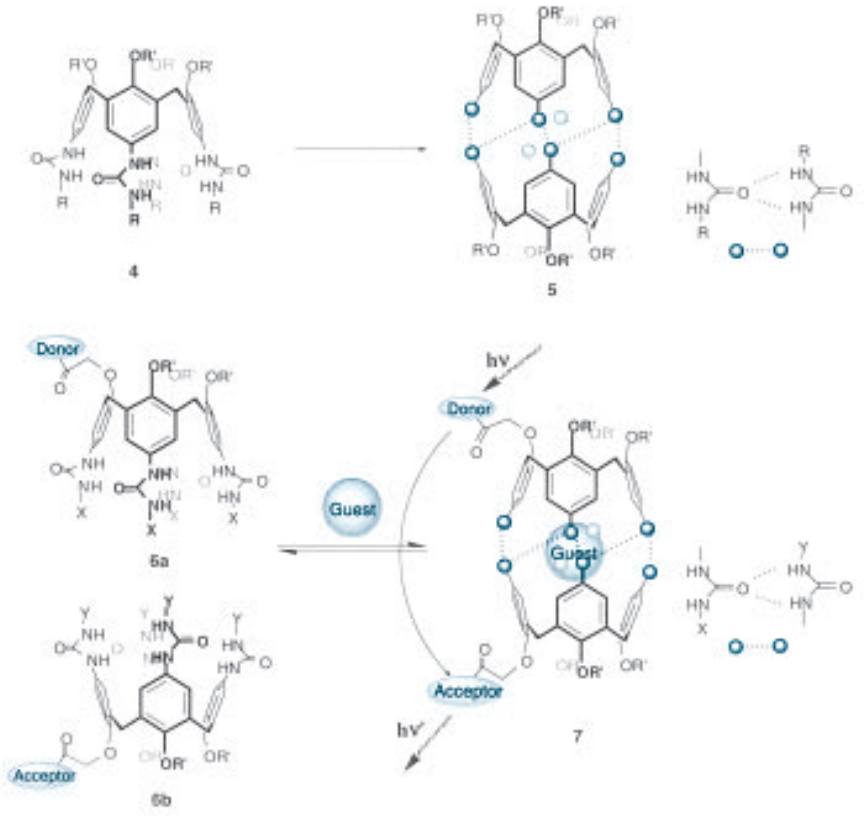


Figure 4.

2.2 Calixarene capsules using coordinate bonding

Coordinate bonding, along with hydrogen bonding, is one of the important interactions for the formation of molecular assemblies. Coordinate bonding to Pd(II) or Pt(II) complexes has mostly been employed to construct the desired capsule in recent years. The methods extensively studied by Fujita *et al.* and Stang *et al.* have been thoroughly discussed (see details in reference 9).

As shown in Figure 5, the fixed cis configuration in Pd(II) and Pt(II) complexes is very useful in the capsule formation, and the desired capsule can be readily obtained by adding the appropriate molecular equivalents.[10]

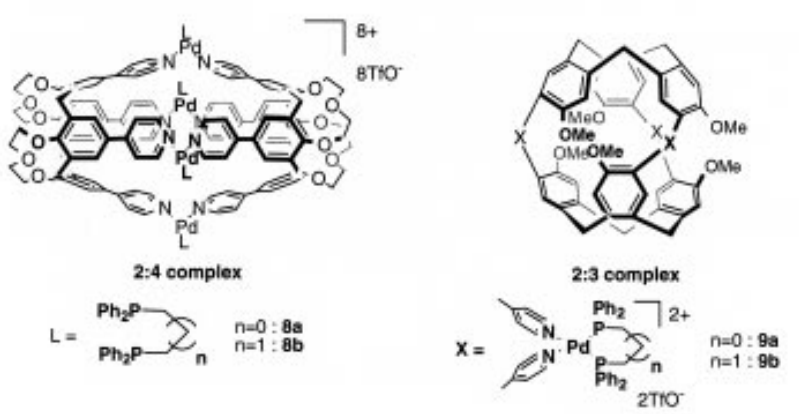


Figure 5. Capsule molecules based on coordinate bonding

We have reported that when homooxacalix[3]arene **10** and *cis*-Pd(II) complex **11** are mixed at the molar ratio of 2 : 3, highly symmetric capsule molecule **12** can be obtained (Figure 6).[11]

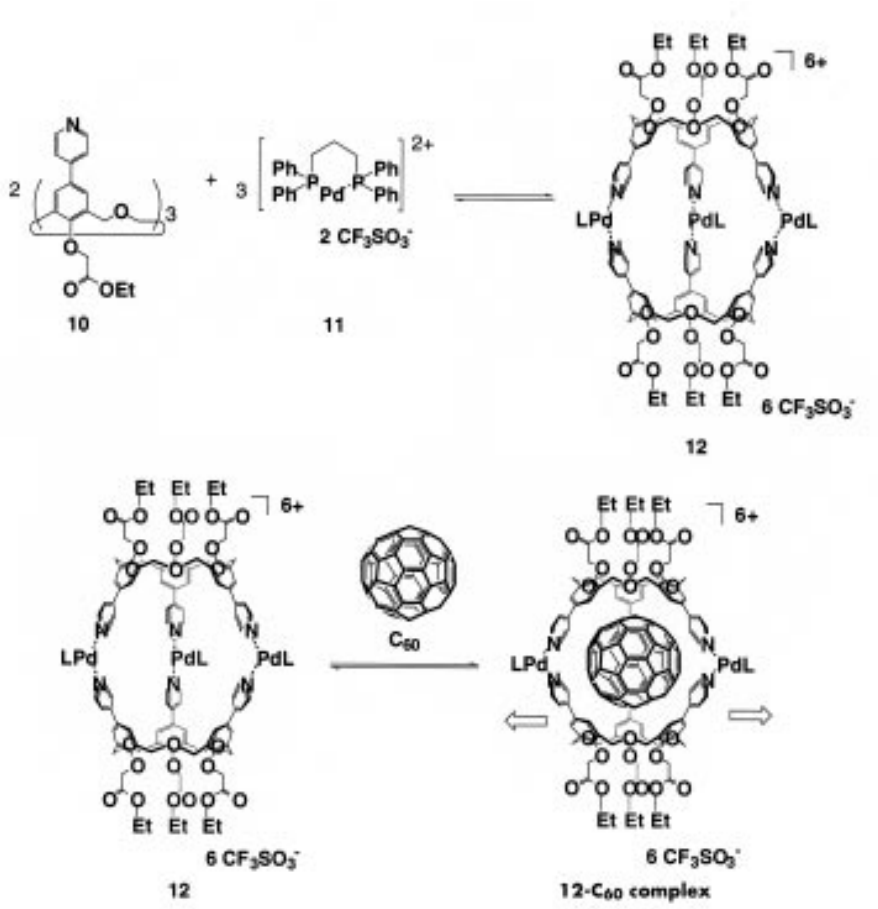


Figure 6.

This carcerand **12** is capable of inclusion of C_{60}, and the interconversion rate between complex and non-complex state is slower than the NMR time scale at room temperature.[12] Interestingly, it does not encapsulate a larger guest molecule, C_{70}. Since unmodified homooxacalix[3]arene monomers having two-dimensional cavities, shows little selectivity for C_{60} and C_{70} (C_{60}/C_{70} = 0.99), it is suggested that the three-dimensionality of the carcerand **12** cavity contributes to the strict C_{60}/C_{70} recognition. Also, addition of Li^+ ion preliminarily arranges **12** into the conformation suitable for the inclusion of C_{60}. When the associatin constant of **12**(Li^+) and C_{60} is actually measured in the presence of Li^+ ions, it is 50 times greater than that without Li^+ ions. When the Na^+ ions are added to this system, however, the capsule forms a complex with Na^+ ions due to its higher affinity than Li^+ ions. The resulting carceplex **12** (Na^+) is structurally unfavorable, and, therefore, C_{60} is released from the cavity.[13] This steric distortion is attributable to the larger radius of Na^+ than Li^+, which makes the capsule cavity more elongated than the size of C_{60} at the formation of the complex. This indicates that an external stimulus such as alkali metal ions is able to control the rate of inclusion and release of C_{60} by changing the capsule structure (Figure 7).

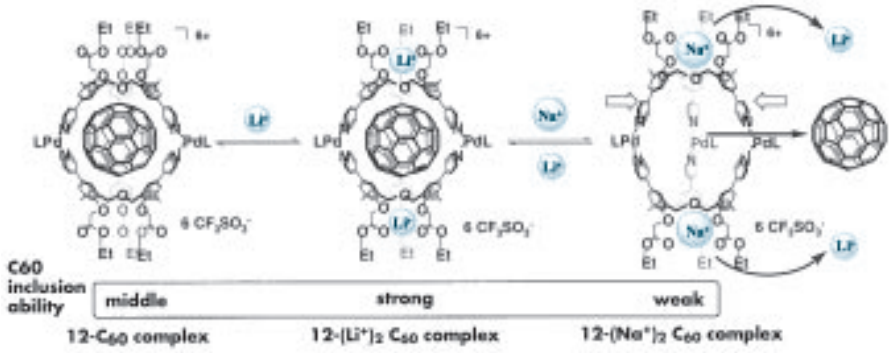
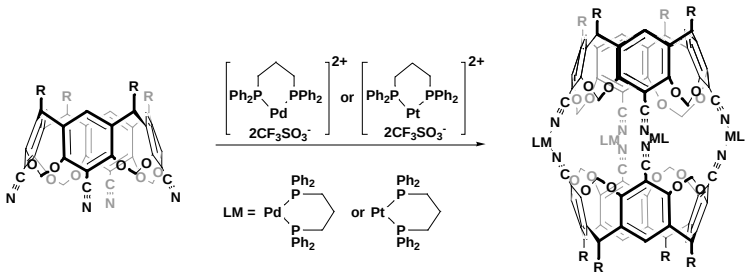


Figure 7.

Resorcinarene made up with resorcinol skeletons is a calixarene-like cyclic oligomer and one of the compounds which can be exploited as a constituting unit of molecular capsules.[14] Introduction of two cyano groups into a resorcinarene tetramer followed by coordinate bonding to Pd(II) or Pt(II) complexes also forms a capsule molecule **14** as reported by Dalcanale et al. (Figure 8).[15]



13 **14**

Figure 8.

This carcerand shows unique characteristics. It takes in a counteranion, a trifluorate molecule, at the capsule formation, as well as it forms only homomeric capsules by distinguishing a slight conformational difference.[16] Their study also includes the process of the capsule formation using AFM (Atomic Force Microscope) by arranging the capsule molecules on a grid (Figure 9).[17] If we can construct capsule molecules on a grid as their system, the application to membrane sensors will be feasible based on such unique inclusion ability.

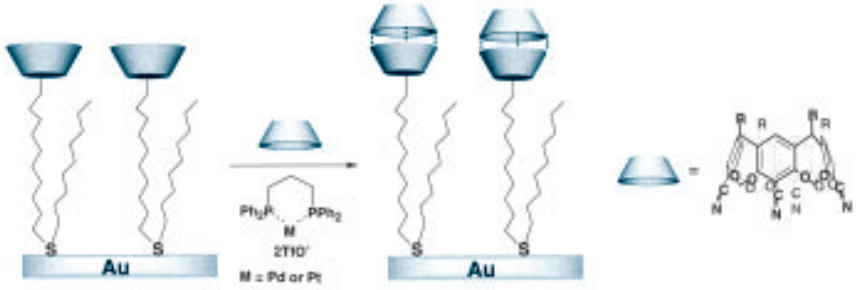


Figure 9. Construction of capsule molecules on a grid

2.3 Capsule molecule enclosing [C_{60}] fullerenes

C_{60} is one of the few excellent sensitizers, that satisfy criteria such as a broad absorption range within the visible light spectrum, almost 100% yield for inter-system crossing, high reducing potential energy, and characteristic absorption at excited triplet state and radicals. These characteristics are very interesting from a viewpoint of organic chemistry as well as inorganic chemistry and biochemistry. However, its low solubility has been hindering its use and especially the study of its physical properties in solution.

As described above, homooxacalix[3]arene molecules have high affinity and selectivity for C_{60}. We have successfully solubilized C_{60} in water by using the capsule structure of homooxacalix[3]arenes (Figure 10).[18] This host-guest complex is built by skillful use of hydrophobic and π-π interactions, and C_{60} is included both as a guest molecule and as a part of capsule constituents. As a result, a C_{60} molecule is able to act independently in solution without interacting with each other, and thereby allows a novel function to take place.

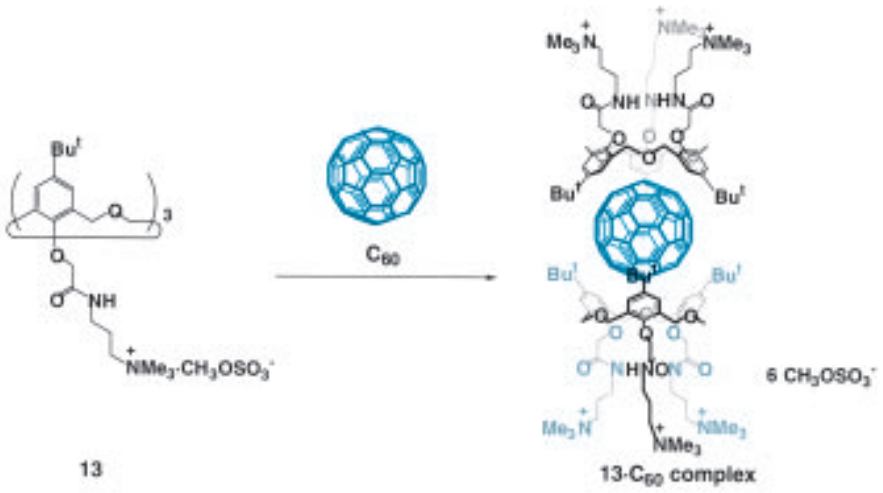


Figure 10.

We have obtained interesting results using this complex.

1) Light-induced cleavage of DNA

This carceplex binds to DNA molecules by electrostatic force derived from cationic hydrophilic groups within the complex. At the binding, adjacent DNA strands are cleaved by light irradiation to C_{60} (Figure 11).[19]

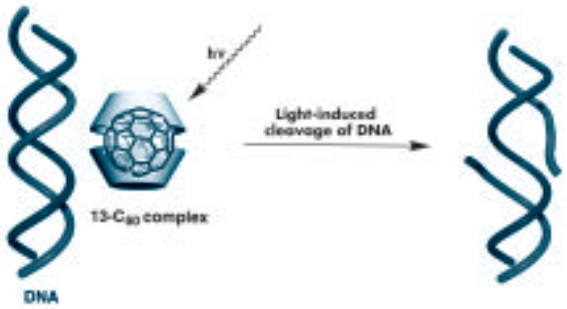


Figure 11. Light-induced cleavage of DNA

On the other hand, C_{60} solubilized by polyvinyl pyrrolidone (PVP) is known to show very low efficiency for DNA cleavage by irradiation. The difference in the cleavage rate is considered due to the facts that 1) PVP does not interact with DNA, and 2) C_{60} interacts with each other inside the PVP cavity. Compared to this, the **13**-C_{60} carceplex is an excellent chemical that induces DNA damage.

2) Application to organic photoelectric conversion elements

The C_{60} inclusion capsule described above can be easily developed to organic photoelectric conversion devices using the alternative layer-by-layer adsorption method, and to date, organic photoelectric conversion elements with dyad and triad are successfully constructed (Figure 12).[20] Especially in the triad system, its photo-electric conversion rate has reached 21%, proving the efficiency of the device derived from the C_{60} carceplexes.[21]

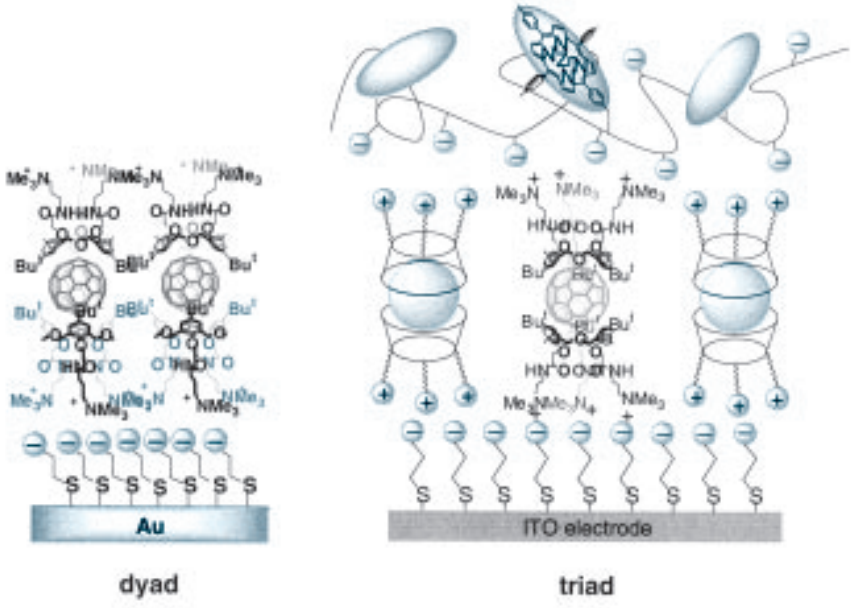


Figure 12.

3. Self-assembling carcerands based on porphyrins

Due to its electrochemical and optical activity, porphyrin has also been used as materials for electron and energy transfer.[22] Recently, it has been applied to fullerene recognition based on its ability as a donor[23] and a constituting unit of gel matrices,[24] and the range of application seems unbounded.

Previously Lehn *et al.* and Stang *et al.* have shown that, when various porphyrins with pyridyl units are mixed with Pd(II) or Pt(II) complexes with a fixed *cis* configuration at an appropriate ratio, porphyrins self-assemble into dimer and tetramer complexes.[25] Based on this result, we designed a self-assembling porphyrin capsule using interaction between Pd(II) and pyridines. Figure 13 shows a porphyrin capsule which self-assembles by coordinate bonding built between the Pd(II) complexes and pyridines placed in the porphyrin molecules.[26] The cavity of porphyrin **16b** is capable for inclusion of a bipyridine guest molecule which has a suitable dimension. The most interesting feature of this inclusion is that the pyridine of the guest molecule is encapsulated without forming a complex with Pd(II). In other words, the guest molecule stably resides in the cavity without disrupting the capsule structure. This is considered due to the stability of the carcerand and its high selectivity and inclusion ability for the guest molecule.

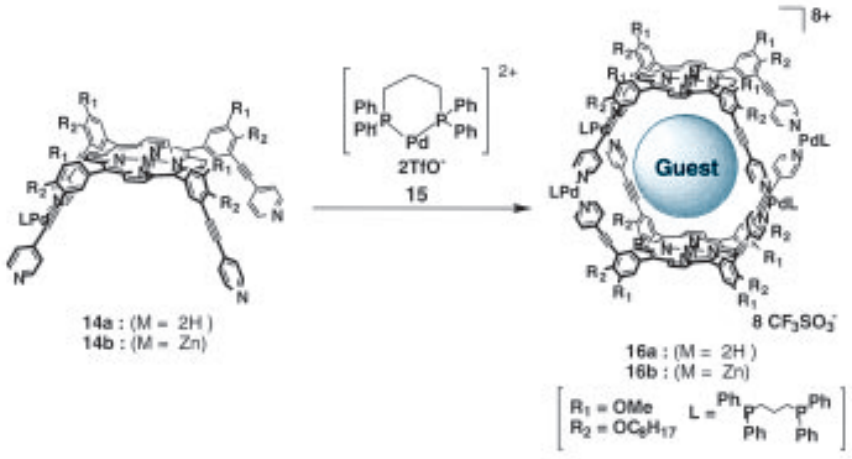


Figure 13.

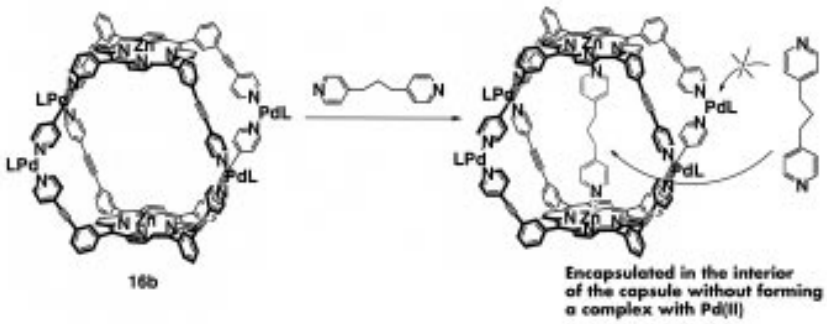


Figure 14.

We also reported the primary alignment (polymerization) of porphyrin capsules. Like the formation of a porphyrin capsule mentioned above, the porphyrin capsules self-assemble into a polymer as illustrated in Figure 15.[27] The main chain of the polymer takes a structure as though porphyrin capsules are linearly aligned. Thus, the porphyrin polymer retains the inclusion ability. In fact, it is possible to capture a guest molecule **1**, 3-dipyridylpropane, in the polymer cavities.

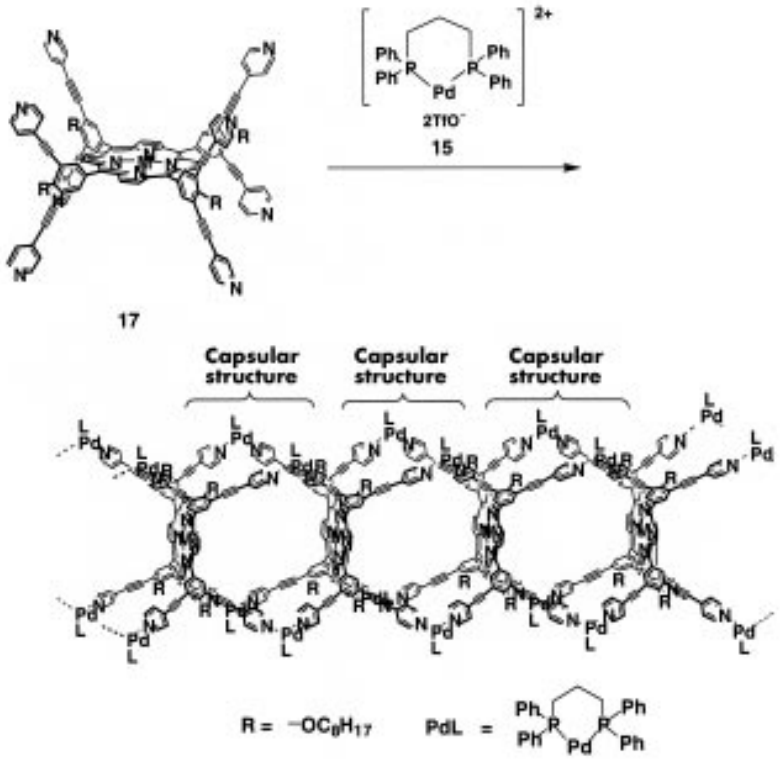


Figure 15.

3.1 Linked porphyrin-calixarene molecular capsules

There are a variety of constitutive units in carcerands, and a combination of them sometimes produces interesting results. Especially a heteromeric capsule comprising calixarenes and porphyrins often shows greater functionality than each species functioning by itself.

Osa and his colleagues synthesized calix[4]arenes capped with Fe(II)-porphyrins, and reported that this capsule functions as a model for oxygen carriers (Figure 16).[28] Although Fe(II)-porphyrin itself is able to bind oxygen, the complex is not very stable. However, when linked to calix[4]arenes having specialized cavities, the complex increases its stability at the inclusion of oxygen. Thus, the cavity of calixarenes may improve the function of porphyrins.

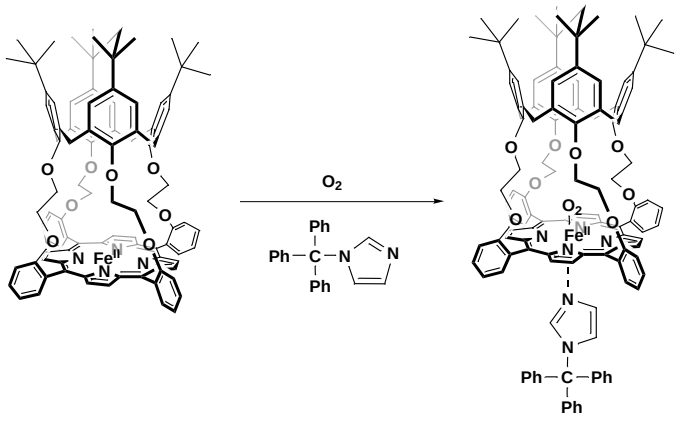


Figure 16.

We have synthesized calixarene-porphyrin capsules with a spacer substituent having high affinity with alkali metal cations, and found that they show specific inclusion activities of the linked capsules (Figure 17).[29] The container molecule **20** can capture alkali metal cations by four sets of carbonyl groups, and moreover, when NaI or KI is added, the counteranion I^- is also encapsulated. Detailed analysis has shown that I^- ions are taken up by coordination to Zn at the center of porphyrins and by the electrostatic interaction with alkali metal cations. In addition, this unique inclusion is observed most significantly when KI is added (KI has the most preferred size for the cavity of capsule **20**). This indicates that the carcerand **20** has high selectivity and recognition ability not only for the alkali metal ions, but also for their counteranions, and, therefore, it can be used as an excellent sensing material with an entirely new system not found in other ion sensors.

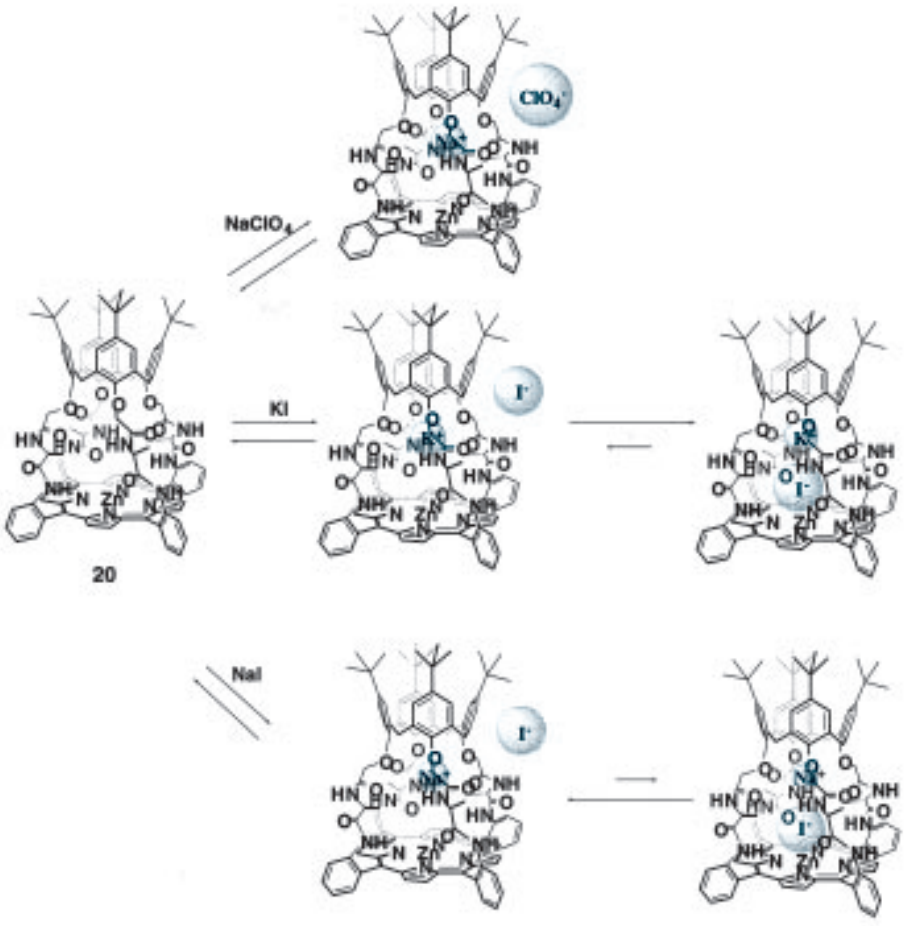


Figure 17.

As suggested by the two systems described above, a combination of porphyrins and calix[4]arenes with C4 symmetry is very favorable in terms of the number and orientation of bonds. This makes possible to construct a heteromeric capsule that self-assembles by non-covalent bonding. In fact, Reinhoudt *et al.* have introduced a cationic substituent in porphyrins, and showed a self-assembly of a heteromeric capsule **23** driven by the electrostatic force (Figure 18).[30]

Separately, we have found that homooxacalix[3]arenes with a pyridyl units placed at the upper rim and Zn(II)-porphyrin trimers form a heteromeric capsule **26** by coordination between Zn ions and pyridines (Figure 19).[31] It is also found that its cavity specifically includes acceptor molecules such as C_{60}.

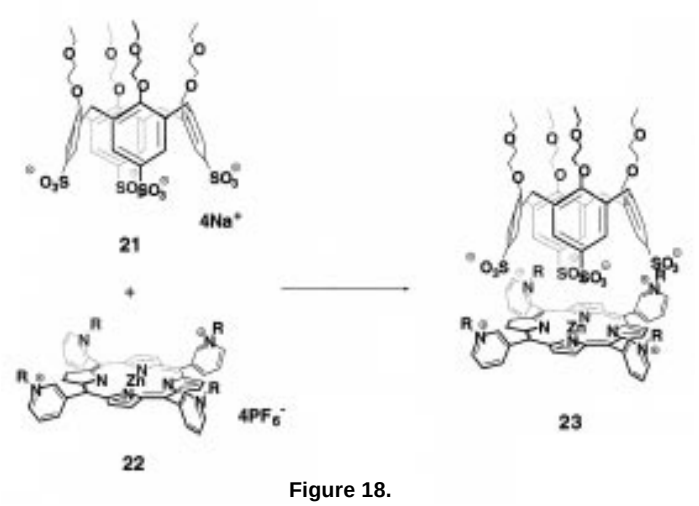


Figure 18.

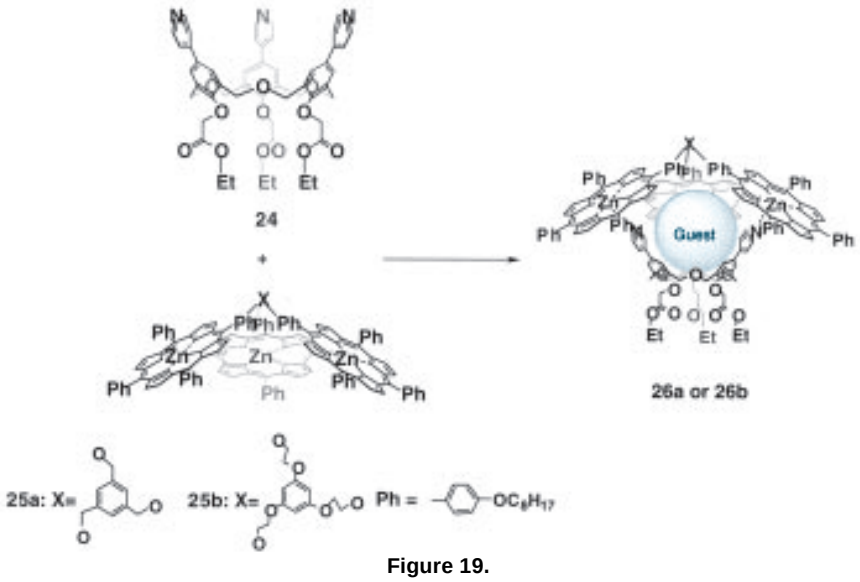


Figure 19.

4. Conclusion

In this article, we discussed mainly the specific inclusion activities of capsule molecules and applications of the host-guest complexes obtained. In the age when researchers around the world are engaged in fierce competition with nanotechnology and nanochemistry, the carcerands with nanoscale cavities may create a stir in forthcoming research. We look forward to the further development in this research in the future.

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