

Award Accounts

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Molecular Design of Synthetic Receptors with Dynamic, Imprinting, and Allosteric Functions

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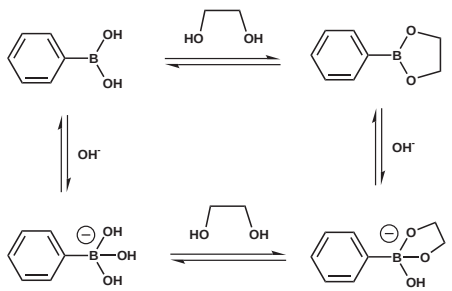
Sugar recognition in an aqueous system has been achieved using a boronic acid–diol interaction. Combination with an intramolecular amino group has enabled us to read out the binding process as a change in the fluorescence intensity. This novel sugar-sensing method has been combined with a concept of "molecular machinery", providing a new guest-binding mode with allosteric functions. When this method is combined with a concept of "molecular imprinting", it becomes possible to design sugar-selective receptors created by a combinatorial method. The sugar recognition event is useful as a trigger to control molecular assemblies such as micelles, membranes, vesicles, and gels.

The molecular design of artificial receptors, which show high affinity and high selectivity comparable with natural systems, has recently become a very active area of endeavor. Among them, we are particularly interested in sugar recognition with consequent detection of the molecular recognition processes.[1,2] An overview of past research teaches us that hydrogen-bonding interactions have been widely used for recognition of guest molecules, but the effect is limited to the events occurring in aprotic organic solvents. Hence, although hydrogen-bonding interactions are useful for sugar recognition in several systems,[3–6] they are practically useless for sugar recognition in water. This is because to "*touch*" sugars dissolved in water, the binding process must overcome the strong solvation energy operating between the sugar molecule and water molecules. A natural system solves this problem by constructing a hydrophobic pocket from which water molecules are mostly squeezed out and utilizing a multi-point hydrogen-bonding interaction. As an attempt to solve this dilemma in an artificial system, we and Czarnik et al. have proposed to use a boronic acid group that reversibly forms covalent-bonds with a variety of sugar molecules in water (Scheme 1).[7–12] Since this process is much faster than the human time-scale, one can treat this process in a similar manner to the noncovalent interactions frequently used for molecular recognition. Although this strategy is quite different from that employed by nature (using multiple hydrogen-bonding interactions in a hydrophobic pocket),[1–5] this is undoubtedly a more practical (and probably the sole) way to "*touch*" sugars in water. In this context, it is noteworthy to mention that Wulff et al. already in 1977 prepared a polymeric material from 4-vinylphenylboronic acid ester of phenyl-α-D-mannopyranoside to recognize sugars using affinity chromatography.[13]



Scheme 1. Boronate ester formation between a boronic acid and a diol in water.

1. Introduction of the Concept of PET (Photoinduced Electron Transfer) Sensors

Photoinduced electron transfer (PET) has been wielded as a tool of choice in fluorescent sensor design for protons and metal ions, but the design of fluorescent sensors for neutral organic species presents a harsher challenge due to the lack of electronic changes upon guest binding.[14,15] The design of a fluorescent sensor based on the boronic acid–saccharide interaction has been difficult due to the lack of sufficient electronic changes found in either the boronic acid moiety or in the saccharide moiety. Furthermore, facile boronic acid–saccharide complexation occurs only at the high pH conditions required to create a boronate anion. It is known, however, that saccharide complexation changes the pK_a of the boronic acid moiety, as is the case for 2- and 9-anthrylboronic acids, which display enhanced acidity upon binding to saccharides[11,16] and consequent fluorescent suppression via a PET mechanism. However, the photoinduced electron transfer from the boronate anion

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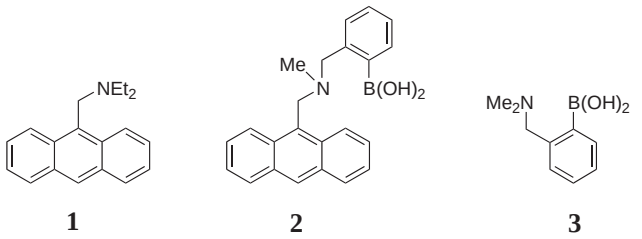
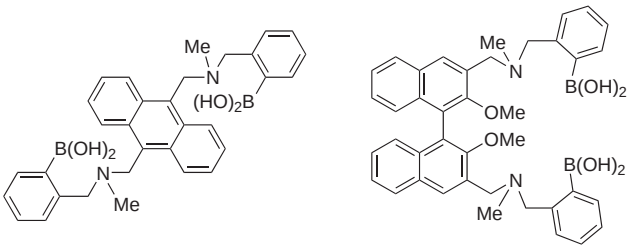


1 **2** **3**

Chart 1.



4 **5**

Chart 2.

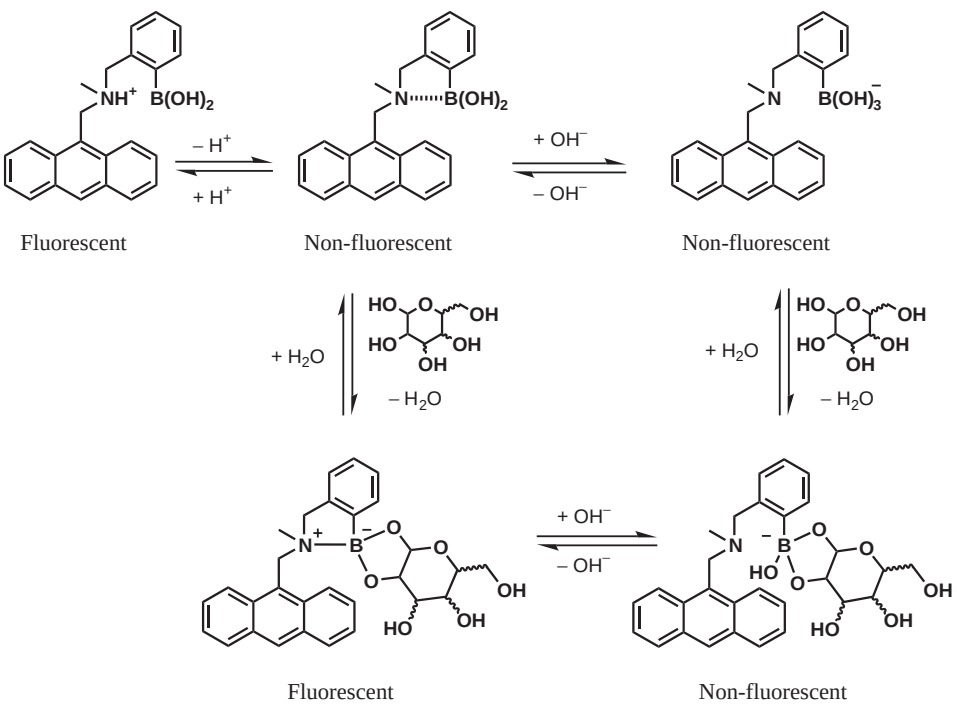
was not efficient despite the fact that it is directly bound to the chromophore.[11,16]

In order to overcome the above-mentioned disadvantages of boronic acid–saccharide interactions, we have modified the boronic acid binding site to create a better electron center around the boronic acid moiety.[17] In compound **2**, the basic skeleton of a known PET sensor, **1**, has been preserved with the addition of the improved binding site with a tertiary amine as in **3**[15] (Chart 1). The amine can interact intramolecularly with the boronic acid, creating a boronate anion-containing five-membered ring. The large shift of the pK_a is due to the interaction found between the boronic acid moiety and the amine group, but this does not inhibit the photoinduced electron transfer quenching process in the complex (Scheme 2).[17] Complete separation of the amine and the boronic acid moiety at the very high pH conditions further quenched the anthracene fluorescence, but the fluorescence decrease is insufficient for the calculation of the pK_a of this process. We have confirmed that the introduction of saccharides (D-glucose and D-fructose) strongly changes the fluorescence of **2** over a large pH range; Scheme 2 is suggestive of the most important species involved in the fluorescence changes. Saccharide binding increases the acidity of the boronic acid group, thus intensifying the B···N interaction, and this consequently inhibits the electron transfer process, giving rise to the greater fluorescence intensity.

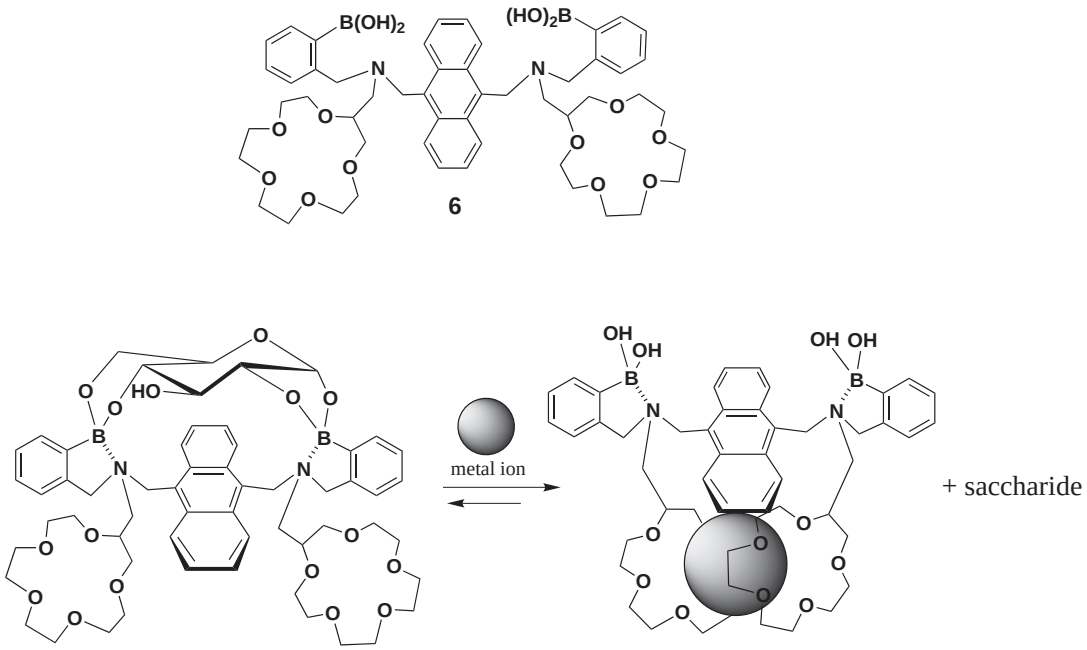
2. A Glucose Sensor and an Enantioselective Sensor

By successful combination of the concept of selective saccharide bindings with that of PET sensors, as outlined above, it should be possible to design a monosaccharide selective sensor; a suitable design strategy for this is exemplified by **4**[17–20] (Chart 2).

Because both binding sites must be occupied in order to prevent fluorescence quenching, non-cyclic 1:1 bound species could not be detected by fluorescence spectroscopy. In principle, both the 1:1 cyclic and 1:2 noncyclic complexes can give signals with the "switch-on" factor (ratio of maximum to minimum fluorescence intensity) for **4**. In fact, the K for the 1:1 cyclic complex is much greater than that for the 1:2 noncyclic complex, so that one can sense the saccharide that is selectively bound as a chelate-like complex to the diboronic-acid-based cleft. This is the first example that a saccharide is sensed "selectively" by a fluorescence method.



Scheme 2. Species and equilibria involved in the action of a PET sensor for saccharides.



Scheme 3.

Enantioselective recognition of saccharides by **5** utilizes both steric and electronic factors[21] (Chart 2). The asymmetric immobilization of the amine groups, relative to the chiral binaphthyl moiety, upon 1:1 complexation of saccharides by D- or L-isomers creates a difference in PET and this difference is manifested in the maximum fluorescence intensity of the complex. Steric factors arising from the chiral binaphthyl building blocks are chiefly represented by the stability constant of the complex; however, the interdependency of electronic and steric factors upon each other is not excluded. This molecular cleft, with a longer spacer unit compared to the anthracene-based diboronic acid **4**, gave the best recognition for the D-fructose that was best bound by (*R*)-**5** and gave a large fluorescence increase. In this system, steric factors and electronic factors bimodally discriminate between enantiomers, while competitive studies with D- and L-monosaccharides show the possibility of enantioselective detection of saccharides. Furthermore, the availability of both (*R*)- and (*S*)-isomers of this molecular sensor is an important advantage, since complementary detection using either form is possible.

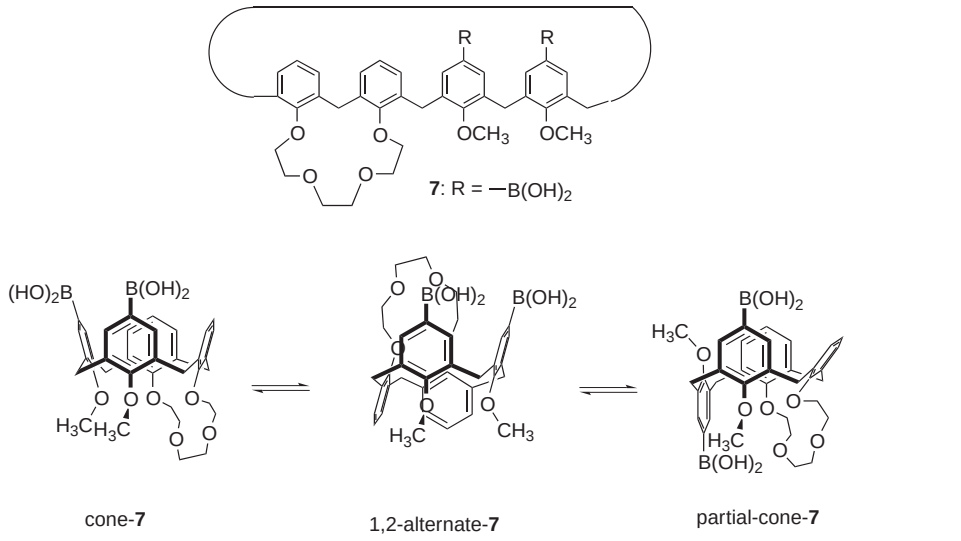
3. Molecular Design of Dynamic Sugar Binding Systems Featuring Allosteric Effects

The biomimetic design of allosteric systems is of great significance, because they are readily applicable to the efficient regulation of capture and release of analytes, catalytic reactions, information transduction to the remote site, etc. Basically, allosterism is classified into four different categories: that is, they may be negative heterotropic, positive heterotropic, negative homotropic, or positive homotropic.[22,23] Here, we introduce some typical examples that are associated with saccharide binding properties.

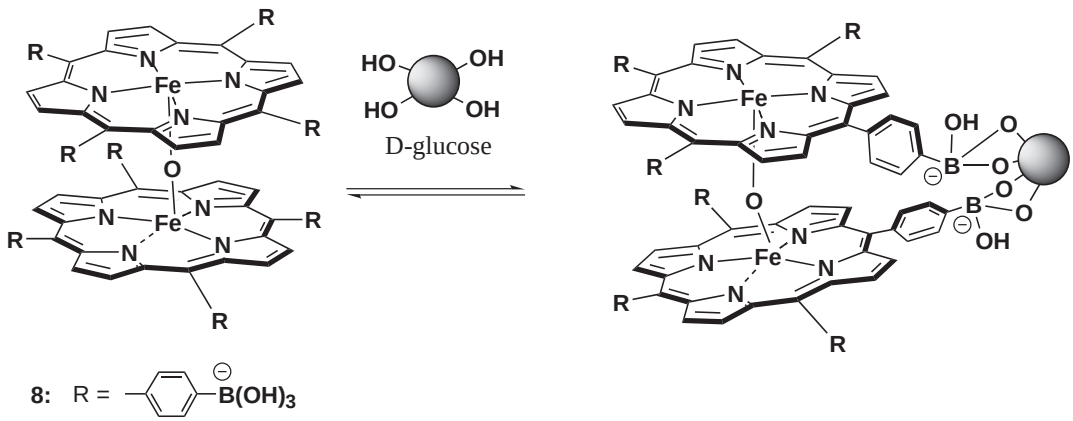
An example for the negative heterotropic action was demonstrated by compound **6**, which has both a saccharide-binding site and a metal-binding biscrown site within a molecule.[24] The saccharide-binding site constructed by two boronic acid groups can form a stable complex with D-glucose. Only when large alkali or alkaline earth metal cations are added, does it release the bound D-glucose because of a conformational charge induced by formation of a 1:2 metal/crown complexs (Scheme 3). One may propose, therefore, that the two different sites communicate "negatively" with each other.

In the positive heterotropic system, the binding of guest A enhances the binding of guest B to another site. In other words, two different sites communicate "positively" with each other. This relatively rare example was demonstrated by a calixcrown (**7**) bearing two boronic acid groups.[25] When a small Li^+ or Na^+ ion is added, this calix[4]arene adopts a "cone" conformation due to the predominant metal–oxygen interactions. In this interaction, the two boronic-acid-appended phenyl groups are too inclined into the ring to form a D-glucose complex (Scheme 4), so that the D-glucose binding to the diboronic site is suppressed by the binding of these metal cations to the calixcrown site: that is, metal cation and D-glucose communicate "negatively" with each other. In contrast, when a large Rb^+ or Cs^+ ion is added, this calix[4]arene adopts a "1,2-alternate" conformation due to the predominant cation–π interactions. In this conformation, the two boronic acid groups are arranged at the separation suitable for the D-glucose binding: that is, the metal binding enhances the binding ability of the boronic acid site for D-glucose.[25]

To arrange two boronic-acid-appended porphyrins in an appropriate spatial position, a μ-oxo dimer of porphinatoiron(III), **8**,[26] would have great potential: the μ-oxo dimer is formed stably in basic aqueous solution where the boronic acid–saccharide complex is also formed stably. Examination using CD spectroscopy established that only glucose and galactose can give the strong CD band in Soret band region, among many monosaccharides tested.[26] To obtain quantitative insights into the binding mode, we estimated the stoichiometry



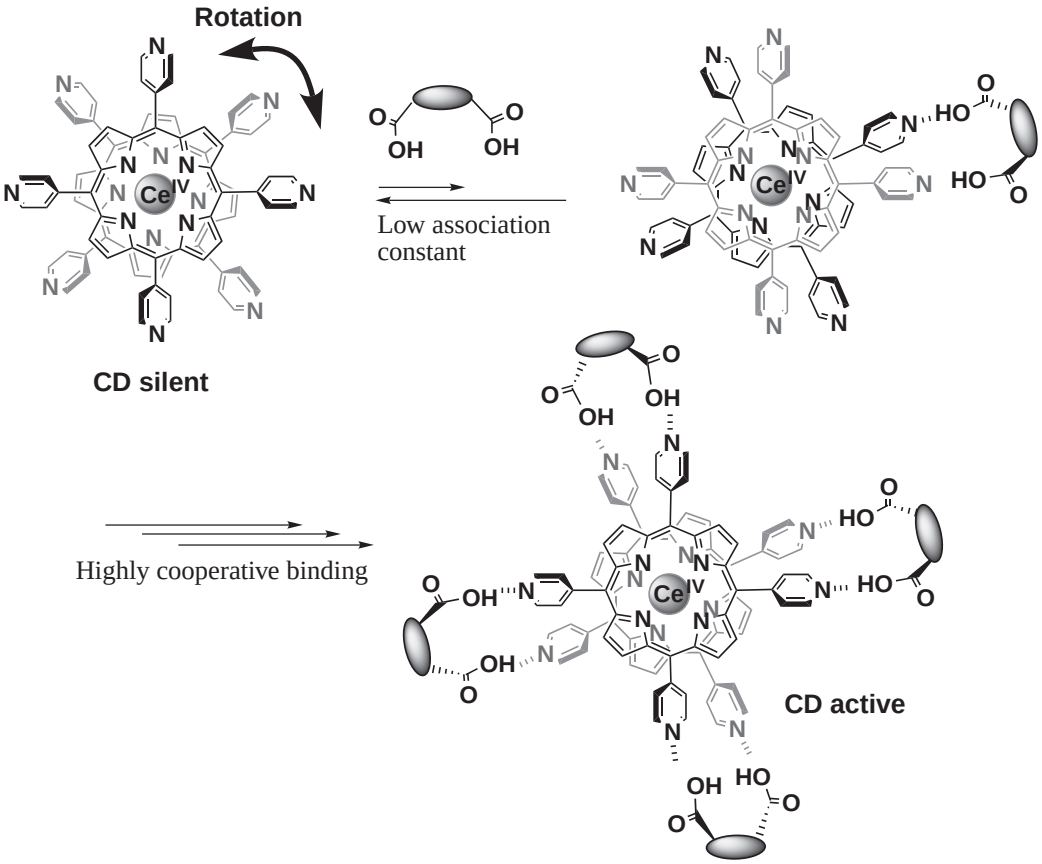
Scheme 4.



Scheme 5.

of the complexes by a continuous variation plot of CD intensity. Very surprisingly, a sharp maximum in the plots of CD intensity versus [**8**]/([**8**] + [D-glucose]) appeared at 0.5. The results indicate that, even though **8** has eight boronic acids, only one pair of boronic acids is used to form the 1:1 **8**·saccharide complexes. Examination utilizing computational simulation reveals that when two boronic acids react with four saccharide OH groups in these saccharides, they must get close to each other and the Fe–O–Fe bond angel is tilted to 150° from the regular 180° bond angle. As a result, the distances between the two boronic acids in the remaining three pairs become too long to complex saccharides intramolecularly (Scheme 5). Hence, this binding mode is classified as negative homotropic allosterism (or noncooperativity). From plots of CD intensity (θ at 380 nm) versus [saccharide], we estimated the association constants (K) to be 1.51×10^5 M^{-1} for glucose and 2.43×10^4 M^{-1} for galactose.[26] These values are the largest for artificial saccharide receptors working in aqueous solution and 1–2 orders of magnitude greater than those achieved so far.

Among four different modes of allosterism, positive homotropic allosterism is considerably more difficult to achieve because the initial binding of a guest species must have an positive effect on the subsequent guest binding events.[27] It is known, however, that it is very useful in amplifying and converting weak chemical or physical signals into other signals in a nonlinear responsing fashion.[22] We found that double-decker porphyrins act as a very useful scaffold for molecular design of such dynamic systems, particularly that of positive homotropic systems: that is, the binding of the first guest species suppresses the rotational freedom of two porphyrin planes and arranges the residual three binding sites in exactly the same geometry as that of the first binding site (Scheme 6). We observed a sigmoidal guest response, a typical feature of positive homotropic allosterism for the guest species such as dicarboxylic acids,[28] dianions,[29] sugars,[30] and sialyl Lewis oligosaccharides (Scheme 7).[31] It was shown that positive homotropic allosterism not only features the nonlinear guest binding but also enhances the affinity and selectivity due to the entropy-driven multi-site interaction. Among these guests, most interesting and most significant effect is the cooperative binding of sialyl Lewis oligosaccharides known as cancer-related sugars.[31] So far, there is no example of their recognition with artificial receptors. It became possible for the first time with a double decker porphyrin modified with boronic acid groups.[31] One may consider, therefore, that the binding is achieved by a synerges-

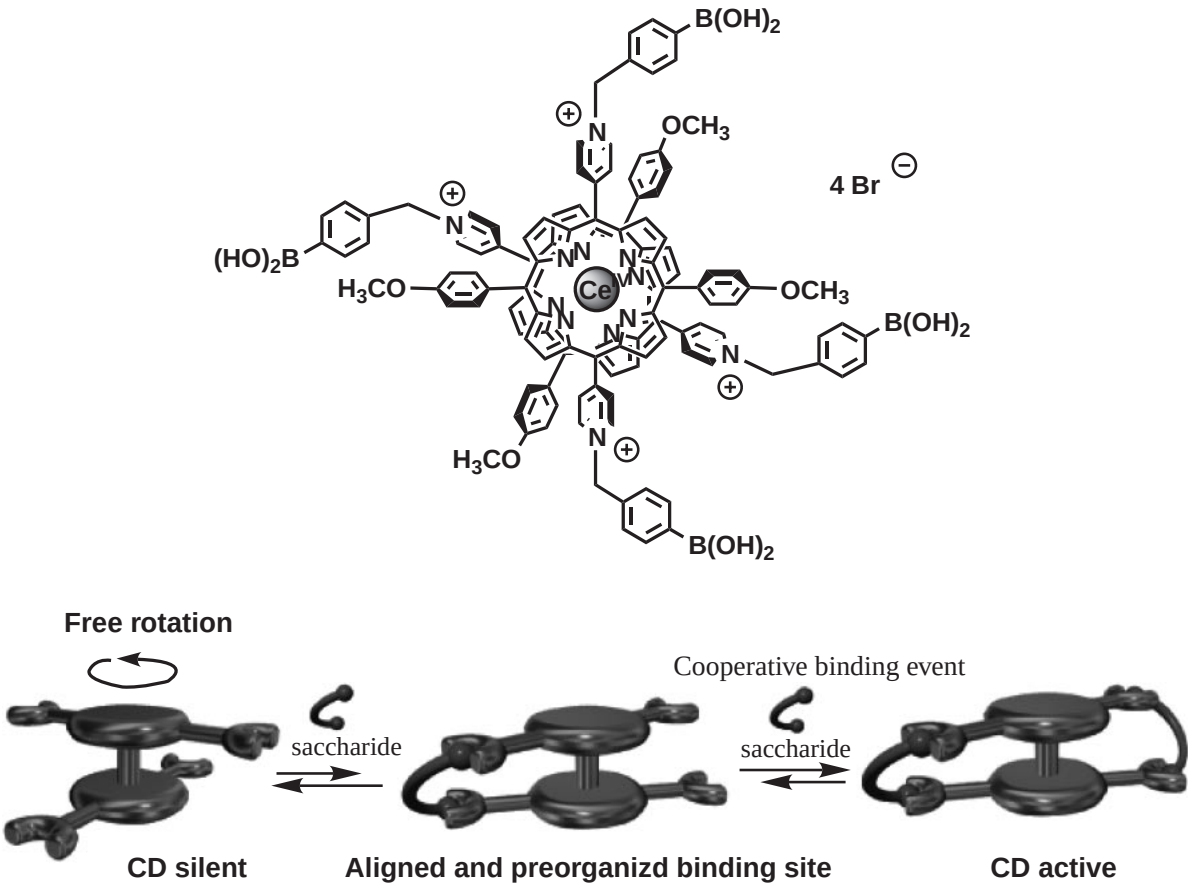


Scheme 6. Conceptual scheme of allosteric Boc-L-Asp complexation.

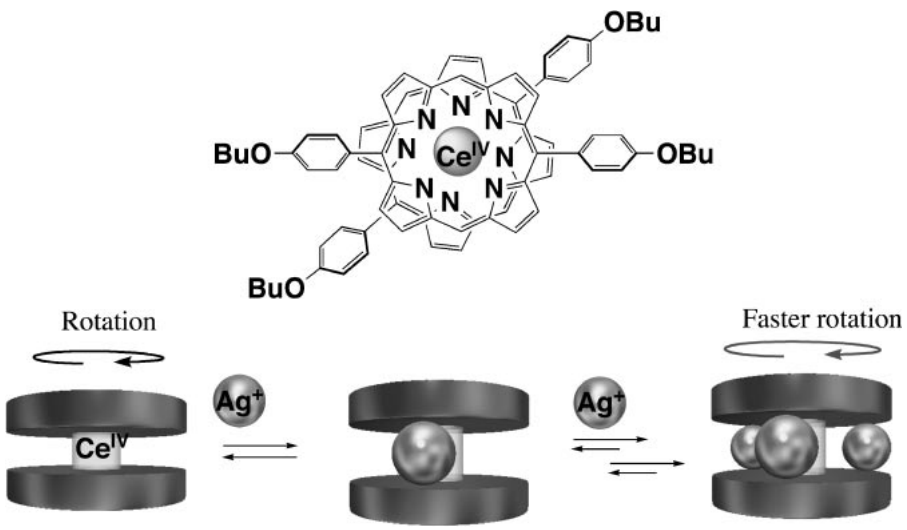
tic effect of the multi-point interaction and the positive allosterism. In the diagnostic detection of sialyl Lewis oligosaccharides, it is desired that the receptor will not respond under the critical concentration, while it will bind them efficiently above this concentration. Because of the sigmoidal concentration dependence, this requirement is well satisfied: that is, the host does not respond at the "safe" low concentration region but sensitively responds at the "risky" high concentration region.

A very peculiar guest binding property was observed for Ag^+ ion.[32] Ag^+ ions are inserted between two porphyrin planes, probably due to the cation–π interaction. The Ag^+ binding proceeds according to positive homotropic allosterism, indicating that the first Ag^+ binding facilitates the subsequent Ag^+ binding. Very strangely, the resultant complex has a 1:3 (but not 1:4) double decker/Ag^+ stoichiometry. Furthermore, the rate of the porphyrin ring rotation, as estimated by temperature-variable ^{1}H NMR, becomes faster upon the Ag^+ binding. These results suggest that the Ag^+ binding mode is totally different from those observed for other positive homotropic systems.[22] The spectroscopic analyses suggest that the distance between the two porphyrin planes is too narrow to accept an Ag^+ ion but is lengthened by the first Ag^+ binding.[32] This process is energetically less favorable and the association constant is relatively small. On the other hand, once the space is lengthened, the subsequent Ag^+ binding occurs cooperatively (Scheme 8). This binding mode results in an allosteric response to the Ag^+ concentration. Then, why does this complex have the 1:3 stoichiometry? We consider that this trick is also rationalized in terms of the dynamic complexation behavior: that is, in the 1:3 stoichiometry reserving the fourth binding site open, Ag^+ ion can enjoy a migration from one site to the residual open site. This type of movement becomes impossible in the 1:4 stoichiometry. In other words, the 1:4 complex is entropically much more unfavorable than the 1:3 complex. To reduce the entropy penalty to the minimum value, the fourth Ag^+ binding should be very difficult.

The developmental investigation of the novel application of dendrimers and dendric compounds has been of recent concern. Dendrimers as host molecules have attracted a great deal of attention because of their unique topology, well-defined structures, and unusual guest-binding behaviors compared to general polymers. For the crystal state, several articles have shown that porphyrin derivatives cocrystallize with C_{60} because of an attractive force between C_{60} and a porphyrin-ring center.[33] In organic solvents, Aida and co-workers[34] and Reed and co-workers[35] have shown that the porphyrin dimers have exceptionally high affinity with C_{60}. We thus designed rigid star-shaped D_3-symmetric receptors **9** bearing six porphyrin moieties linked with one another through phenylacetylene units.[36] The dendritic receptor **9** has three rotational axes which affect the spatial arrangement of the porphyrins and the shape of the three clefts, each of which consists of two porphyrin planes (Scheme 9). As shown in Scheme 9, when two porphyrins sandwich one C_{60} molecule, the complexion site successively suppresses the rotational freedom of the remaining porphyrin tweezers. This "domino" effect is expected to



Scheme 7. Molecular design of a sugar sensing system with an allosteric function.

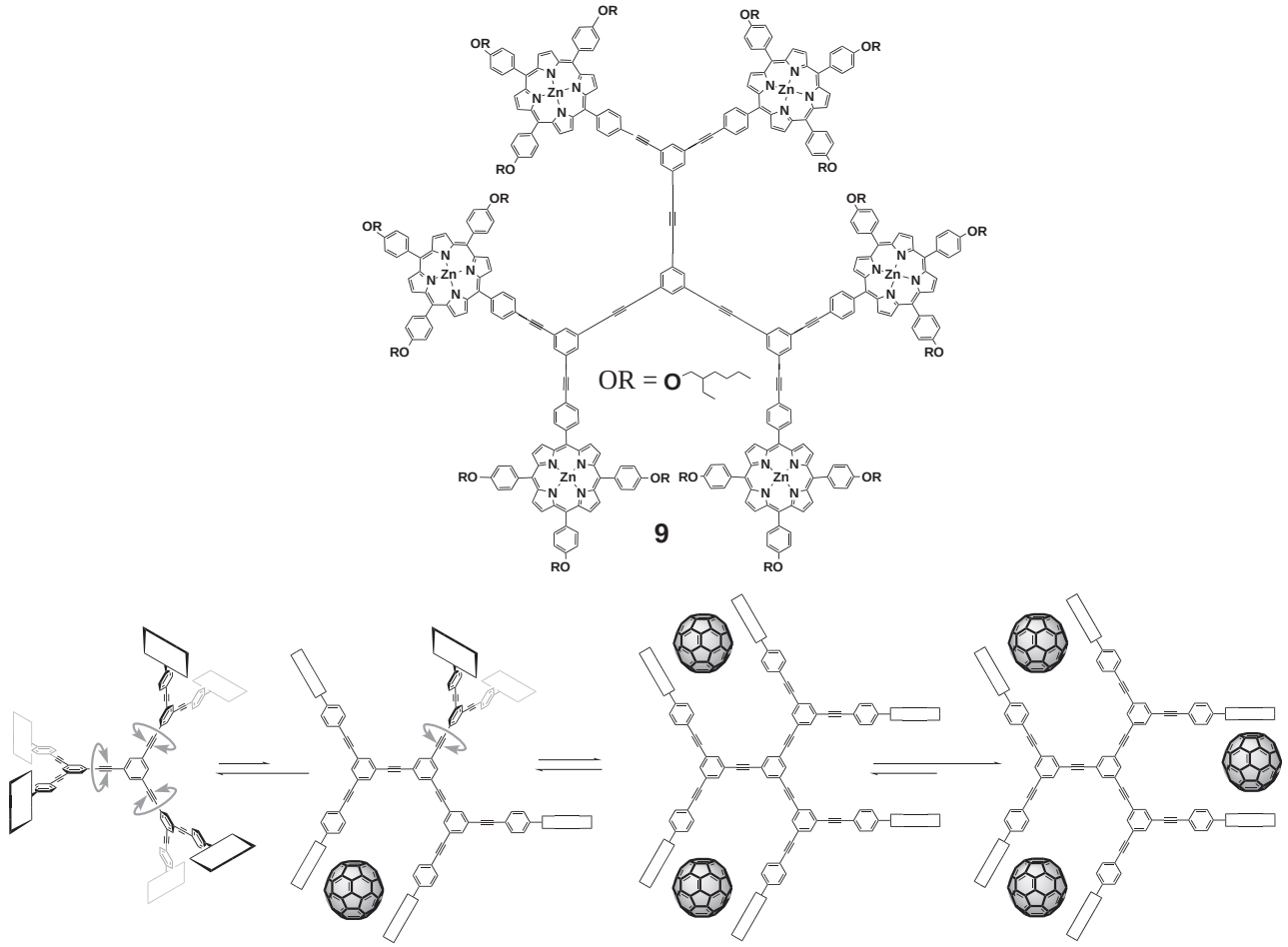


Scheme 8.

be effective for the binding of three equivalents of C_{60} in an allosteric manner to attain high C_{60} affinity.[36] It was found that **9** can bind C_{60} according to a sigmoidal curvature to form the 1:3 **9**/C_{60} complex. The association constant estimated in toluene at 25 °C was 1.4×10^8 M^{-3} and Hill's coefficient $n = 2.8$.[36] These analytical results support the view that in this system the "domino" effect is realized in relation to successive suppression of the rotational freedom.

4. Combination with the Concept of Molecular Imprinting

One of the early examples of molecular imprinting was shown by Wulff in 1977, where a successful example was demonstrated by using boronic acid as a receptor and sugars as target molecules.[13,37,38] We considered that this type of molecular imprinting might be executed more successfully and more conveniently in lower dimension systems than the 3-D



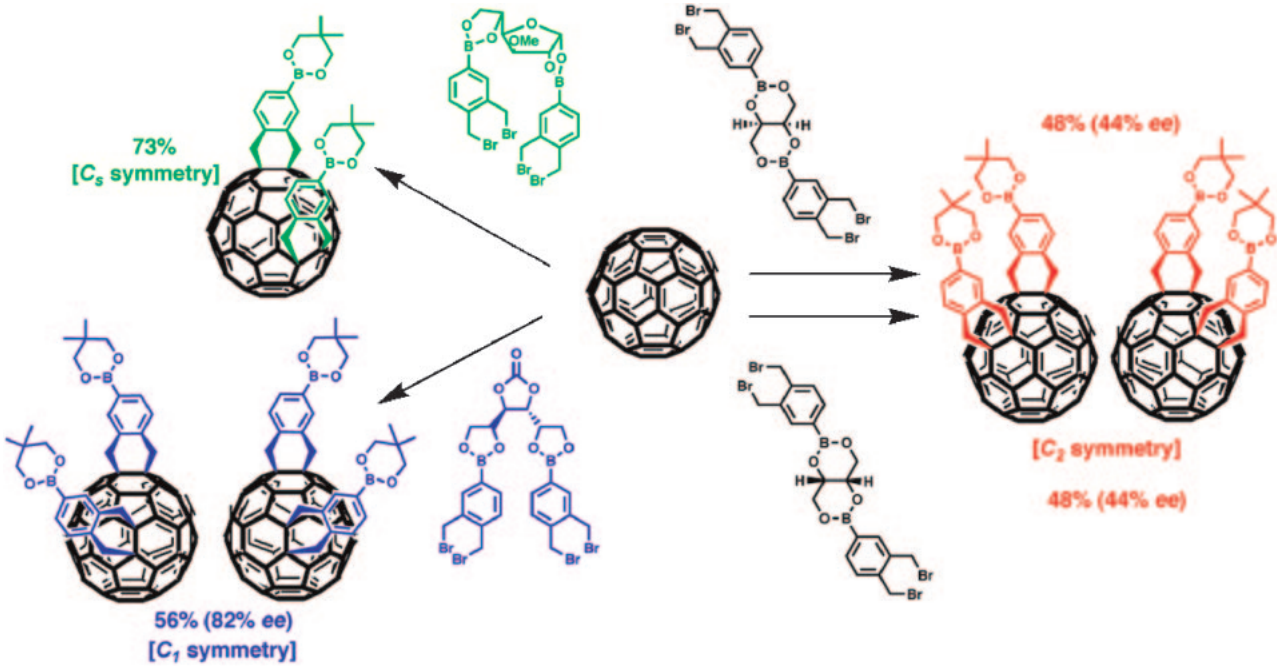
Scheme 9.

system (i.e., resin) used so far. We thus applied this concept to the 0-D system in the homogeneous solution, the 1-D system in the linear polymer, and the 2-D system in the interface. These lower dimension systems have made the imprinting procedure simpler and the analysis of the imprinting efficiency much easier.

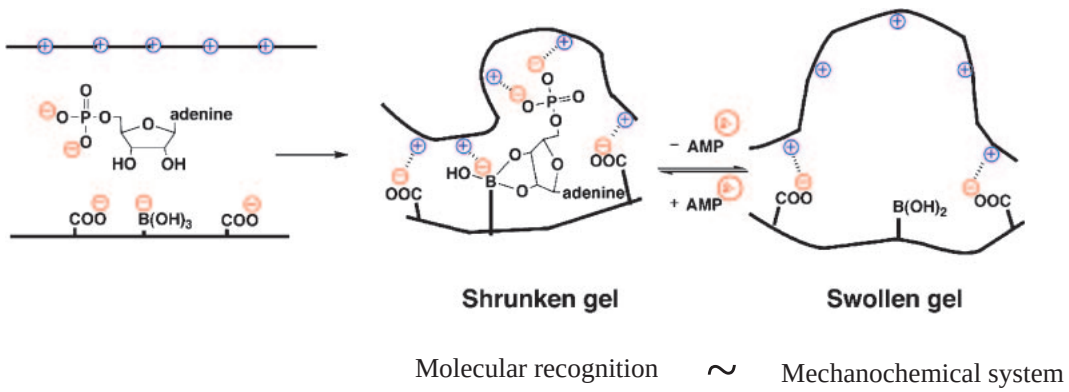
It seems nearly impossible or very difficult to store the memory in a homogeneous solution system. However, we considered that, when such a scaffold that has multi-point reaction sites is used as an imprinting base, the memory would be stored through selection of the reaction sites. The candidates having such potentials are fullerenes, dendrimers, etc. In the 0-D imprinting of our system, [60]fullerene was used as an imprinting base. Thus, two moles of a boronic acid of 1,2-bis(bromomethyl)benzene form a complex with one mole of sugar and the resultant 2:1 complex was allowed to react with [60]fullerene in a homogeneous solution (Scheme 10). In this system, therefore, the absolute configuration of the bound saccharide governs the choice of the reaction with C=C double bonds in [60]fullerene. The chiroselectivities attained in this method were very high (44–82% e.e.).[39] The diboronic acid/[60]fullerene receptors thus obtained showed a good memory for the templated sugars (44–48% d.e.).[40] The results indicate that the molecular imprinting is possible even in the homogeneous solution, utilizing [60]fullerene bearing many reactive C=C double bonds.

In the 1-D imprinting, the formation of polyion complex from anionic polymer and cationic polymer was utilized. It always consists of equimolar amounts of cationic and anionic charges. A polyanion containing boronic acid units can sustain AMP by a boronic acid–diol interaction. When this polyanion forms a polyion complex with a polycation according to 1:1 anion–cation stoichiometry, the phosphate anionic charges introduced into the polyanion by the AMP complexation are also counted (Scheme 11). Thus, after removal of AMP from the precipitated polyion complex, a "cleft" which has the memory for the AMP template is created.[41] It was proved that this cleft shows high affinity with AMP and the precipitate (gel) shows the reversible swelling–shrinking transformation in response to the AMP binding. One may conclude, therefore, that in this system an artificial-muscle-like exercise is conjugated with molecular recognition. When this gel is deposited on a QCM resonator, it responds to a slight change in the AMP concentration.[42] The results imply that one can design an AMP sensor by this molecular imprinting procedure.

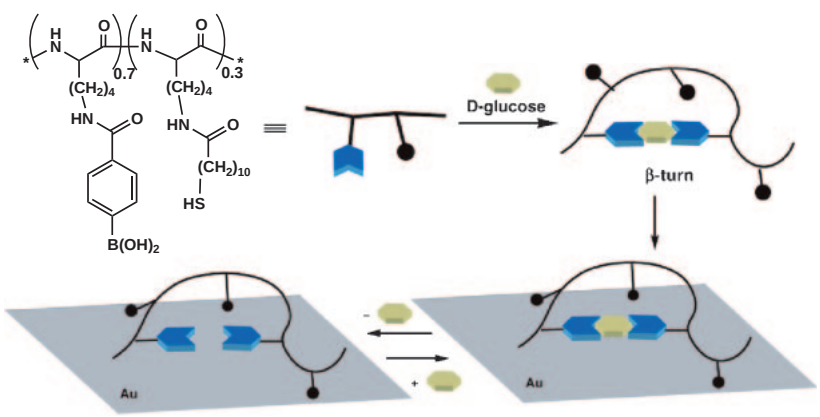
In the 2-D imprinting, a QCM resonator coated with Au was used (Scheme 12). The conformational transitions of poly(L-lysine) are related to very subtle changes in secondary forces, such as hydrogen-bonding interactions, electrostatic effects, and hydrophobicity. We previously found that the addition of monosaccharides to boronic-acid-appended poly(L-lysine) affects the α-helix content of the polypeptide chain and that



Scheme 10. Regio- and chiro-selective introduction of two boronic acid groups into [60]fullerene.



Scheme 11. AMP-imprinted polyion complex.



Scheme 12. Memory creation by molecular imprinting on the Au surface.

the pH at which the maximum α-helix content is observed is specific to the added monosaccharide.[43,44] To take advantage of such sugar-induced conformational changes, we synthesized a poly(L-lysine) derivative, appending 70 mol% of the $B(OH)_2$ group and 30 mol% of the SH group. After induction of the conformational change by the sugar–boronic acid interaction,

the polymeric complex was extended on Au. Thus, one can expect that the sugar-induced conformation is immobilized on the Au surface by the Au–SH group interaction, which keeps a memory for the templated sugar (Scheme 12). We obtained evidence for the occurrence of the positive imprinting effect using an Au-coated QCM resonator.[45] In particular, when D-glucose is used as a template sugar, the polypeptide backbone tends to adopt a unique β-turn structure. This situation has allowed us to design a D-glucose-selective QCM resonator by a simple imprinting method.[45]

More recently, it was shown that the molecular imprinting is achieved when one utilizes the reprecipitation process of functionalized "soluble" polymers[46–48] and the gel formation process of low molecular-weight gelators.[49] These new trends suggest the generality of the molecular imprinting concept: that is, the formation of 3-D cross-linked resins is not the sole way toward the molecular imprinting.

5. Beyond the 1:1 Complexation: Communication with Molecular Assembly Systems

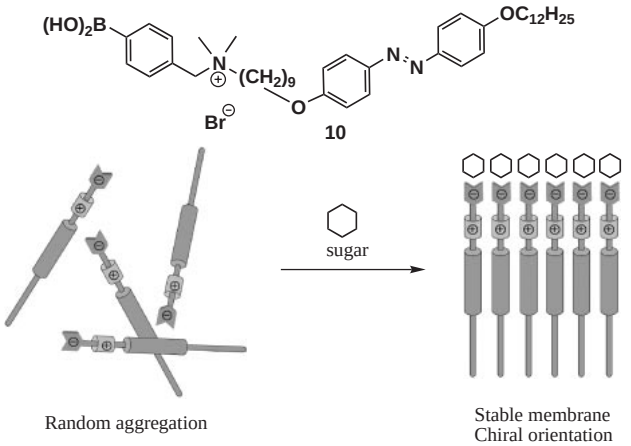
Originally, the sugar–boronic acid interaction was investigated for exploitation of sugar sensors useful in an aqueous system. Later, it was found that this interaction is useful as a communication point between carbohydrates and molecular assemblies. One may regard that this connection separates into two different ways: firstly, one can sense sugars by utilizing some changes in the physical properties of molecular assembly systems and secondly, one can control the superstructure of molecular assemblies by utilizing sugars as a trigger. Such studies should mimic saccharide recognition events on the cell surface, which lead to subsequent changes in the membrane morphology and the membrane potential.

Organogels and hydrogels are formed, mainly, by 1-D aggregation of amphiphilic molecules. Thus, a variety of superstructures are constructed in the gel system, reflecting the molecular shape of unit gelator molecules. When boronic-acid-appended amphiphiles are dispersed into solution, the superstructure of the resultant aggregates is strongly affected by the sugars added.[50–52] For example, the sol–gel phase-transition temperature is changed by the addition of sugars and, in some cases, the chirally twisted fibrils appear in the gel phase from achiral amphiphiles. When boronic-acid-appended cholesterol is used as a gelator, the gel can discriminate between D- and L-saccharides through a difference in the sol–gel phase-transition temperature.[53]

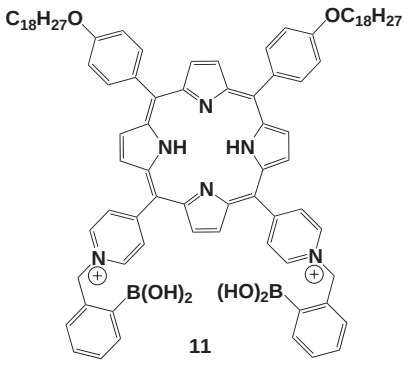
A similar sugar-triggered change in the physical properties is also observed in the 2-D systems. In 1991, we already noticed that the monolayer of boronic-acid-appended amphiphiles formed at the air–water interface selectively responds to saccharides, changing their π–A isotherms.[54] In this study, however, the correlation between the saccharide structure and the change in the π–A isotherms was not clarified yet. This information was elaborated to molecular design of an amphiphilic diboronic acid.[55,56] The change in the π–A isotherms is closely correlated with the binding ability of the diboronic acid in aqueous solution. The response becomes very sensitive when the diboronic acid is located in a cationic environment provided by a water-soluble quaternized polymeric amine.[55,56] In a few sophisticated cases, selective recognition and chiral recognition of sugars become possible by using diboronic acid amphiphiles and cholesterol-based boronic acids, respectively.[57,58]

The concept can also be applied to the structure control of ordered molecular assemblies formed in an aqueous system. For example, compound **10** (Scheme 13) bearing a boronic acid group and a chromophoric azobenzene group forms a micelle-like, orderless aggregate in aqueous solution. When a sugar which is recognized by the boronic acid group is added, it is transfigured into the well-ordered stable 2-D membrane.[59] The CD spectrum arising from the azobenzene chromophore suggests that this membrane has a chiral factor which changes in response to the absolute configuration of the added sugar. A similar system was also realized in a porphyrin-containing amphiphile **11**.[60] In this system, the arrangement of the porphyrin moiety in the molecular assemblies can be finely tuned by the added sugars (Scheme 14).

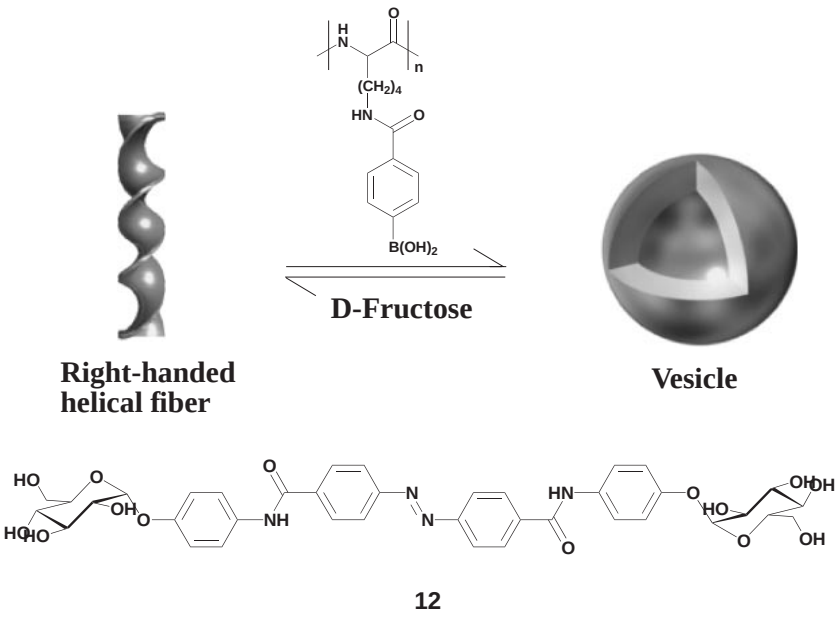
It was demonstrated that this kind of idea is also effective in a liquid crystal system. It is known that, in some cholesteric liquid crystals, the change in the helical pitch is reflected by the color change. We found that cholesterylboronic acid complexes of monosaccharides alter the color of a composite chiral cholesteric liquid crystal membrane.[10] Interestingly, the direction and the magnitude of the color change are indicative of the absolute configuration of the monosaccharide. This finding has allowed us to predict the name and the absolute configuration of the deposited monosaccharide just by a "color change".



Scheme 13. Ordering of a boronic-acid-appended amphiphileby the sugar binding.



Scheme 14. Sugar-controllable amphiphilic porphyrin.



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Scheme 15. Fiber–vesicle interconversion.

More recently, it was found that sugar-based amphiphiles can enjoy a fiber–vesicle structural interconversion in the presence of boronic-acid-appended poly(L-lysine).[61,62] The research objects of these papers were to design bolaamphiphilic gelators utilizing a sugar family as a source of solvophilic groups and an azobenzene segment as a solvophobic group and to monitor the aggregation mode utilizing the spectroscopic properties of the azobenzene chromophore. The results indicated that the bolaamphiphiles act, although only for specific DMSO–water mixtures, as gelators and form a unique supramolecular helical structure in the gel phase. The UV–vis and CD spectra showed that the azobenzene segments adopt H-type face-to-face orientation and that the dipole moments are arranged in the right-handed (*R*)-helicity. Since the fibrils as observed by electron microscope possess the right-handed helical structure, one may consider that the microscopic azobenzene–azobenzene orientation is reflected by the macroscopic supramolecular structure. Thus, one can consider that this 1-D aggregate is stabilized by the π–π and hydrophobic interactions among azobenzene segments and the sugar–sugar hydrogen-bonding interactions. When boronic acid-appended poly(L-lysine) was added, the gel phase of gelator **12** was changed into the sol phase in the macroscopic level and the fibrous aggregate was changed into the vesicular aggregate in the microscopic level. These changes, which are usually induced by a temperature change, are due to the specific boronic acid–sugar interaction occurring at the constant temperature. Interestingly, when D-fructose, which shows high affinity with the boronic acid group, was added, the sol phase and the vesicular aggregate were changed back to the gel phase and the fibrous aggregate, respectively (Scheme 15). As D-fructose has high affinity with the boronic acid group, the polymer-aggregate interaction is suppressed and the original sugar–sugar stabilization effect is regained. These behaviors show that the phase and morphological changes in the sugar-integrated bolaamphiphiles can be controlled reversibly.

6. Conclusion

In Nature, saccharides are captured by the hydrogen-bonding interaction in a hyrdorophobic protein pocket. This strategy is not applicable straightforwardly to the saccharide binding in water. However, it has now become possible to selectively capture saccharide utilizing the specific boronic acid–saccharide interaction and to sensitively read out the event utilizing the PET mechanism, although this is an unnatural approach. Again in Nature, the binding constants for saccharide–protein complexation, which is based on the hydrogen-bonding interaction, are relatively small. This is because the interaction must inevitably compete with solvation by water molecules. This drawback is compensated by a so-called "cluster effect", a sort of multi-point interaction. Again, in our artificial system, it is also possible to enhance the binding constants by a so-called "allosteric effect": e.g., even sialyl Lewis oligosaccharides can be captured, the binding of which is still very difficult by other methods. In addition, it has been demonstrated that the sugar–boronic acid interaction is also effective to control the superstructures formed by molecular assemblies. We now believe that combination of dynamic molecular recognition, multi-point interaction, and electron transfer will be useful to create various sugar-based functional systems.

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References

1 J. Rebek, Jr., *Angew. Chem., Int. Ed. Engl.*, **29**, 245 (1990).
2 S. K. Chang, D. Vanengen, E. Fan, and A. D. Hamilton, *J. Am. Chem. Soc.*, **113**, 7640 (1991).

3 Y. Aoyama, Y. Tanaka, H. Toi, and H. Ogoshi, *J. Am. Chem. Soc.*, **110**, 634 (1988).

4 K. Kano, K. Yoshiyasu, and S. Hashimoto, *Chem. Commun.*, **1998**, 801.

5 Y. Kikuchi, K. Kobayashi, and Y. Aoyama, *J. Am. Chem. Soc.*, **114**, 1351 (1992).

6 G. Lecollinet, A. P. Dominey, T. Valasco, and A. P. Davis, *Angew. Chem., Int. Ed.*, **41**, 4093 (2002).

7 S. Shinkai, K. Tsukagoshi, Y. Ishikawa, and T. Kunitake, *J. Chem. Soc., Chem. Commun.*, **1991**, 1039.

8 K. Tsukagoshi and S. Shinkai, *J. Org. Chem.*, **56**, 4089 (1991).

9 K. Kondo, Y. Shiomi, M. Saisho, T. Harada, and S. Shinkai, *Tetrahedron*, **48**, 8239 (1992).

10 T. D. James, T. Harada, and S. Shinkai, *J. Chem. Soc., Chem. Commun.*, **1993**, 857.

11 L. K. Mohler and A. W. Czarnik, *J. Am. Chem. Soc.*, **115**, 2998 (1993).

12 Y. Shiomi, M. Saisho, K. Tsukagoshi, and S. Shinkai, *J. Chem. Soc., Perkin Trans. 1*, **1993**, 2111.

13 G. Wulff, W. Vesper, R. Grobe-Einsler, and A. Sarhan, *Makromol. Chem.*, **178**, 2799 (1977).

14 R. A. Bissell, A. P. DeSilva, H. Q. N. Gunaratne, P. L. M. Lynch, G. E. M. Maguire, and K. R. A. S. Sandanayake, *Chem. Soc. Rev.*, **21**, 187 (1992).

15 A. J. Bryan, A. P. Desilva, S. A. Desilva, R. A. D. D. Rupasinghe, and K. R. A. S. Sandanayake, *Biosensors*, **4**, 169 (1989).

16 H. Suenaga, M. Mikami, K. R. A. S. Sandanayake, and S. Shinkai, *Tetrahedron Lett.*, **36**, 4825 (1995).

17 T. D. James, K. R. A. S. Sandanayake, and S. Shinkai, *J. Chem. Soc., Chem. Commun.*, **1994**, 477.

18 T. D. James, K. R. A. S. Sandanayake, and S. Shinkai, *Angew. Chem., Int. Ed. Engl.*, **33**, 2207 (1995).

19 T. D. James, K. R. A. S. Sandanayake, and S. Shinkai, *Nature*, **374**, 345 (1995).

20 M. Bielecki, H. Eggert, and J. C. Norrild, *J. Chem. Soc., Perkin Trans. 2*, **1999**, 449.

21 T. D. James, K. R. A. S. Sandanayake, R. Iguchi, and S. Shinkai, *J. Am. Chem. Soc.*, **117**, 8982 (1995).

22 S. Shinkai, M. Ikeda, A. Sugasaki, and M. Takeuchi, *Acc. Chem. Res.*, **34**, 494 (2001).

23 a) T. Nabeshima, T. Saiki, and S. Akine, *J. Synth. Org. Chem., Jpn.*, **60**, 184 (2002). b) T. Nabeshima, *Coord. Chem. Rev.*, **148**, 151 (1996).

24 T. D. James and S. Shinkai, *J. Chem. Soc., Chem. Commun.*, **1995**, 1483.

25 F. Ohseto, H. Yamamoto, H. Matsumoto, and S. Shinkai, *Tetrahedron Lett.*, **36**, 6911 (1995).

26 M. Takeuchi, T. Ikeda, and S. Shinkai, *J. Am. Chem. Soc.*, **118**, 10658 (2001).

27 M. Takeuchi, M. Ikeda, A. Sugasaki, and S. Shinkai, *Acc. Chem. Res.*, **34**, 865 (2001).

28 M. Takeuchi, T. Imada, and S. Shinkai, *Angew. Chem., Int. Ed.*, **37**, 15, 2096 (1998).

29 M. Yamamoto, A. Sugasaki, M. Ikeda, M. Takeuchi, K. Frimat, T. D. James, and S. Shinkai, *Chem. Lett.*, **2001**, 520.

30 A. Sugasaki, M. Ikeda, M. Takeuchi, and S. Shinkai, *Angew. Chem., Int. Ed.*, **39**, 3839 (2000).

31 A. Sugasaki, K. Sugiyasu, M. Ikeda, M. Takeuchi, and S. Shinkai, *J. Am. Chem. Soc.*, **123**, 10239 (2001).

32 a) M. Ikeda, T. Tanida, M. Takeuchi, and S. Shinkai, *Org. Lett.*, **2**, 1803 (2000). b) M. Ikeda, M. Takeuchi, S. Shinkai, F. Tani, Y. Naruta, S. Sakamoto, and K. Yamaguchi, *Chem.—Eur. J.*, **8**, 5542 (2002).

33 a) P. D. W. Boyd, M. C. Hodgson, C. E. F. Rickard, A. G. Oliver, L. Chaker, P. J. Brothers, R. D. Bolskar, F. S. Tham, and C. A. Reed, *J. Am. Chem. Soc.*, **121**, 10487 (1999). b) M. M. Olmstead, D. A. Costa, K. Maitra, B. C. Noll, S. L. Phillips, P. M. V. Calcar, and A. L. Balch, *J. Am. Chem. Soc.*, **121**, 7090 (1999).

34 a) K. Tashiro, T. Aida, J.-Y. Zheng, K. Kinbara, K. Saigo, S. Sakamoto, and K. Yamaguchi, *J. Am. Chem. Soc.*, **121**, 9477 (1999). b) T. Nishioka, K. Tashiro, T. Aida, J.-Y. Zheng, K. Kinbara, K. Saigo, S. Sakamoto, and K. Yamaguchi, *Macromolecules*, **33**, 9182 (2000). c) J.-Y. Zheng, K. Tashiro, Y. Hirabayashi, K. Kinbara, K. Saigo, T. Aida, S. Sakamoto, and K. Yamaguchi, *Angew. Chem., Int. Ed.*, **40**, 1858 (2001).

35 D. Sun, F. S. Tham, C. A. Reed, L. Chaker, M. Burgess, and P. D. W. Boyd, *J. Am. Chem. Soc.*, **122**, 10704 (2000).

36 M. Ayabe, A. Ikeda, Y. Kubo, M. Takeuchi, and S. Shinkai, *Angew. Chem., Int. Ed.*, **41**, 2790 (2002).

37 "Molecularly Imprinted Polymers," ed by B. Sellergren, Elsevier, New York (2001).

38 G. Wulff, *Nanoporous Mater. III*, **141**, 35 (2002).

39 T. Ishi-i, K. Nakashima, S. Shinkai, and A. Ikeda, *J. Org. Chem.*, **64**, 984 (1999).

40 T. Ishi-i, R. Iguchi, and S. Shinkai, *Tetrahedron*, **55**, 3883 (1999).

41 Y. Kanekiyo, Y. Ono, K. Inoue, M. Sano, and S. Shinkai, *J. Chem. Soc., Perkin Trans. 2*, **1999**, 557.

42 Y. Kanekiyo, M. Sano, R. Iguchi, and S. Shinkai, *J. Polym. Sci., Part A: Polym. Chem.*, **38**, 1302 (2000).

43 T. Kimura, S. Arimori, M. Takeuchi, T. Nagasaki, and S. Shinkai, *J. Chem. Soc., Perkin Trans. 2*, **1995**, 1889.

44 H. Kobayashi, K. Nakashima, E. Ohsima, Y. Hisaeda, I. Hamachi, and S. Shinkai, *J. Chem. Soc., Perkin Trans. 2*, **2000**, 997.

45 A. Friggeri, H. Kobayashi, S. Shinkai, and D. A. Reinhoudt, *Angew. Chem., Int. Ed.*, **40**, 4729 (2001).

46 K. Dabulis and A. M. Klibanov, *Biotechnol. Bioeng.*, **39**, 176 (1992).

47 H. Y. Wang, T. Kobayashi, T. Fukaya, and N. Fujii, *Langmuir*, **13**, 5396 (1997).

48 Y. Kanekiyo, M. Sano, Y. Ono, K. Inoue, and S. Shinkai, *J. Chem. Soc., Perkin Trans. 2*, **1998**, 2005.

49 K. Inoue, Y. Ono, Y. Kanekiyo, T. Ishi-i, K. Yoshihara, and S. Shinkai, *Tetrahedron Lett.*, **39**, 2981 (1998).

50 K. Koumoto, T. Yamashita, T. Kimura, R. Luboradzki, and S. Shinkai, *Nanotechnology*, **12**, 25 (2001).

51 T. Kimura and S. Shinkai, *Chem. Lett.*, **1998**, 1035.

52 T. Kimura, T. Yamashita, K. Koumoto, and S. Shinkai, *Tetrahedron Lett.*, **40**, 6631 (1999).

53 T. D. James, K. Murata, T. Harada, K. Ueda, and S. Shinkai, *Chem. Lett.*, **1994**, 273.

54 S. Shinkai, K. Tsukagoshi, Y. Ishikawa, and T. Kunitake, *J. Chem. Soc., Chem. Commun.*, **1991**, 1039.

55 R. Ludwig, K. Ariga, and S. Shinkai, *Chem. Lett.*, **1993**, 1413.

56 R. Ludwig, Y. Shiomi, and S. Shinkai, *Langmuir*, **10**, 3195 (1994).

57 R. Ludwig, T. Harada, K. Ueda, T. D. James, and S. Shinkai, *J. Chem. Soc., Perkin Trans. 2*, **1994**, 697.

58 C. Dusemund, M. Mikami, and S. Shinkai, *Chem. Lett.*,

1995, 157.
59 T. Kimura, M. Takeuchi, and S. Shinkai, *Bull. Chem. Soc. Jpn.*, **71**, 2197 (1998).
60 S. Arimori, M. Takeuchi, and S. Shinkai, *J. Am. Chem. Soc.*, **118**, 245 (1996).
61 H. Kobayashi, M. Amaike, J. H. Jung, A. Friggeri, and S. Shinkai, *Chem. Commun.*, **2001**, 1038.
62 H. Kobayashi, K. Koumoto, J. H. Jung, and S. Shinkai, *J. Chem. Soc., Perkin Trans. 2*, **2002**, 1930.

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