Positive Allosteric Systems Designed on Dynamic Supramolecular Scaffolds: Toward Switching and Amplification of Guest Affinity and Selectivity†

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ABSTRACT

Positive homotropic allosterism appears in important information transduction processes where chemical and physical signals are efficiently amplified. The phenomena are ubiquitous in nature, but the general methodology for the design of such allosteric systems is not yet established in an artificial system. This account reviews such artificial receptors that can bind guest ions and molecules in a positive allosteric manner and discusses what kinds of factors are indispensable as scaffolds in the design of this novel class of allosteric systems and what common factors are needed to realize the cooperativity. It has been shown that the scaffolds are mostly dynamic and are skillfully combined with the molecular recognition systems so that the subsequent guest binding can occur more favorably than the first guest binding. In addition, it has been suggested that positive homotropic allosterism can be utilized as a new strategy to attain high guest selectivity and guest affinity which cannot be attained by conventional 1:1-type guest binding.

Introduction

Positive or negative allosterisms are ubiquitous in nature where biological events must be efficiently regulated in response to chemical or physical signals from the outside world. Typical examples are observed for cooperative dioxygen binding to hemoglobin,[1] hexamerization of arginine repressor,[2] a cooperative effect with respect to the concentration of arachidonate-containing phospholipids in cytosolic phospholipase A_2,[3] etc.[4] Allosteric systems provide a means of obtaining chemical feedback, which is a necessary step toward achieving total control over molecular-scale chemical processes. These systems are characterized by nonlinear binding, which is quite different from conventional linear binding. Nonlinear binding, by definition, requires that the initial binding of a guest has an effect that is different from that of subsequent enzyme−substrate or host−guest interactions. Undoubtedly, the natural systems which have some allosteric contrivance must be very dynamic, like "molecular machines". The biomimetic design of such allosteric systems is of great significance in regulating the complexation ability or the catalytic activity of artificial receptors according to the nonlinear dependence.[5−14] The simplest mode of allosteric action takes the form of heterotropic allosterism, where the binding of one chemical species influences the binding of a second, different chemical species. Homotropic allosterism, however, is considerably more difficult to achieve because the initial binding of a guest species must have an effect that is different from that of the subsequent interactions with the same guest species. Inevitably, therefore, the system must have dynamic multipoint binding sites. It is clear, however, that positive homotropic allosterism is very useful in amplifying and converting weak chemical or physical signals into other signals which are convenient for us to read and record. In conventional binding, for example, the input signal is "linearly" transmitted to the output signal, followed by saturation in the high-input region (Figure 1A). This linearity, useful as a calibration curve, is an important factor in conventional sensing events. In positive homotropic allosterism, on the other hand, a small change in the input signal is amplified into a large change in the output signal in the steep transition region (Figure 1B). In addition, it can be seen that the region below this transition is an "off" state, whereas the region above this transition is an "on" state. Conversely, when the input signal is viewed from the output signal axis, it can be seen that this system possesses a sort of buffer function. This kind of cooperative guest-binding process can be analyzed according to the Hill equation:[15] $\log(y/(1 - y)) = n \log [\text{guest}] + \log K$, where K and n are the association constant and Hill coefficient, respectively, and $y = K/([\text{guest}]^{-n} + K)$. From the slope and the intercept of the linear plots, one can estimate K (association constant) and n (Hill coefficient), which are useful as measures of the cooperativity.

In this Account, we will consider how one can design such intriguing positive allosteric systems in relation to

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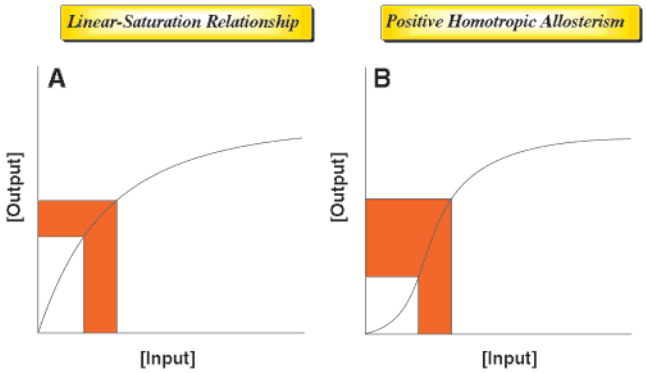


FIGURE 1. Input−output correlation in linear and nonlinear bindings.

molecular recognition for small molecules, metal ions, natural products, etc. Inevitably, the molecular design concept of positive allosteric systems is profoundly associated with that of "molecular machines".

Supramolecular and Molecular Assembly Systems

In polymeric and molecular assembly systems, it is not unusual to come across positive allosteric phenomena. For example, Piszkiewicz proposed that the well-known micelle formation event at the critical micelle concentration (cmc) can be analyzed according to the positive homotropic interaction.[16] In the interaction between polymers and low-molecular-weight compounds, the binding of surfactants and related compounds to water-soluble polymers takes place according to positive allosterism: the binding of one surfactant molecule facilitates the subsequent binding owing to the (mainly) hydrophobic interaction among bound surfactant molecules.[17,18] In polymer−polymer interactions, one can consider the double-strand formation in DNA and RNA. It is worth mentioning that in these cooperative processes the interaction is supported mainly by entropy-driven factors. However, as the main focus of this account is not the positive allosterism in the molecular assembly and polymeric systems but that in the unimolecular "molecular machine" systems, we here concentrate on the supramolecular systems related to molecular recognition.

Mono-6-(hexadecylamino)-β-cyclodextrins and mono-6-(octylamino)-β-cyclodextrins (m = 16 and 8, respectively, in **1**, Chart 1) were titrated against organic guests in aqueous solution.[9] It was found that the plots of complex vs guest concentration give sigmoidal binding isotherms with, for example, $K = 3700\ M^{-1}$ (assuming the formation of 1:1 complex) and $n = 2.2$ for the $\mathbf{1}_{m=16}$ + 4-nitrophenol.[9] The results clearly indicate that initial binding events render subsequent binding events more favorable. The cooperativity in this system is discussed in terms of the aggregation properties of the amphiphilic hosts in the cmc region. Traylor et al.[19] found that the CN^- adduct formation with a protoporphyrin IX derivative **2** (Chart 1) occurs according to two-state cooperative bindings. In this compound, the side chain is too short for the pyridyl group to bind internally to form the chelated heme. Thus, the reaction system consists of a monomer (T-state)−dimer (R-state) equilibrium of **2** and a CN^- adduct formation equilibrium with the monomer and the dimer. Here, the positive allosterism can appear if the CN^- affinity of $\mathbf{2}_2\cdot(CN^-)$ is higher than that of $\mathbf{2}_2$ or $\mathbf{2}\cdot(CN^-)$.

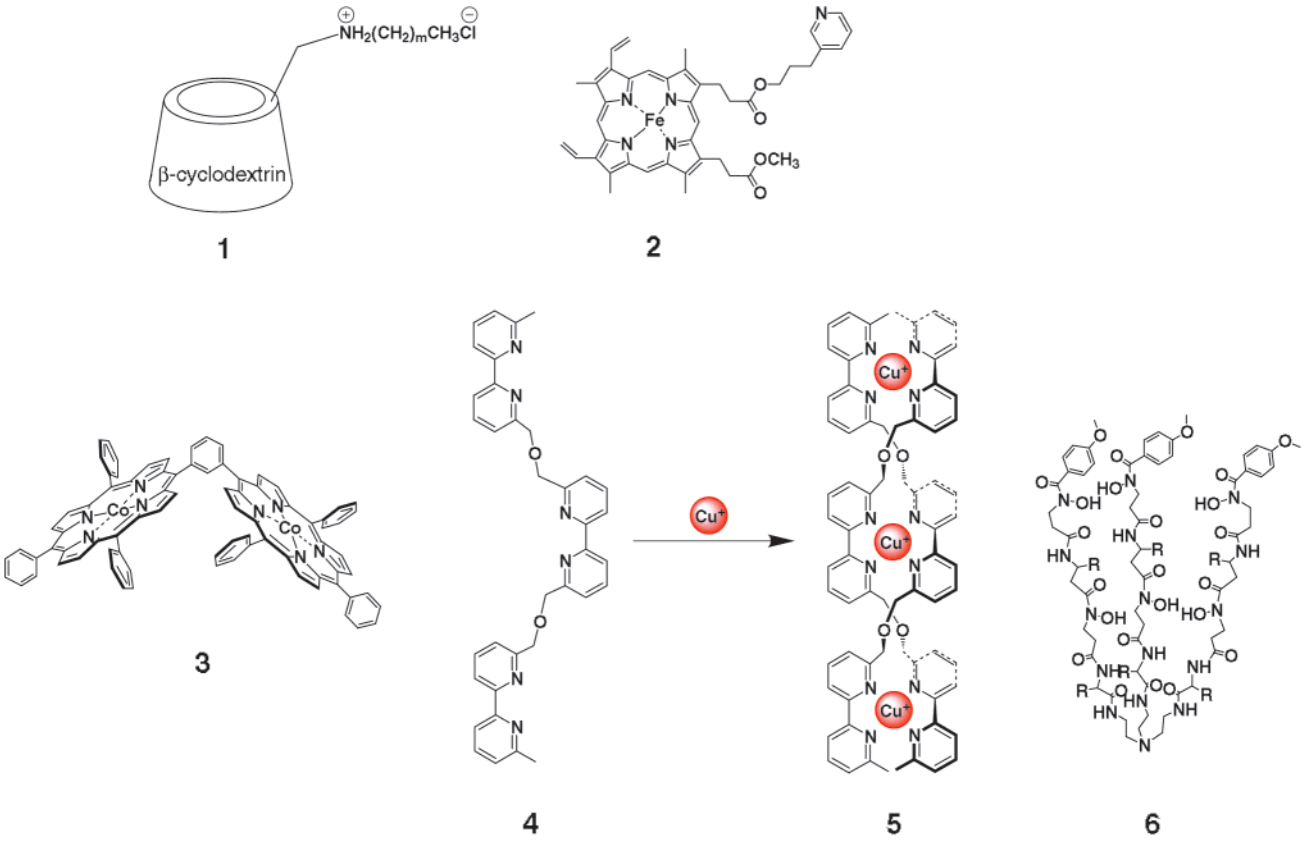
The similar positive allosterism arising from the association−dissociation equilibrium of hosts is reported for tetrakis(crown ether)-appended porphyrins[20] and phthalocyanines.[21] The unique behavior is explained by the formation of a metal/crown 1:2 sandwich complex which preorganizes residual crown rings that are suitable for subsequent metal binding. Despite these intriguing examples, however, it seems to us that the positive allosterism accompanying the molecular assembling is somewhat complicated and unsuitable for a clear demonstration of the essence of the positive allosterism. For example, the binding process in **1** should be fairly complicated but actually is analyzed assuming the formation of a 1:1 complex for the sake of simplicity, although this is an "allosteric" process accompanying the aggregation.

Allosteric Binding of Small Molecules and Metal Ions

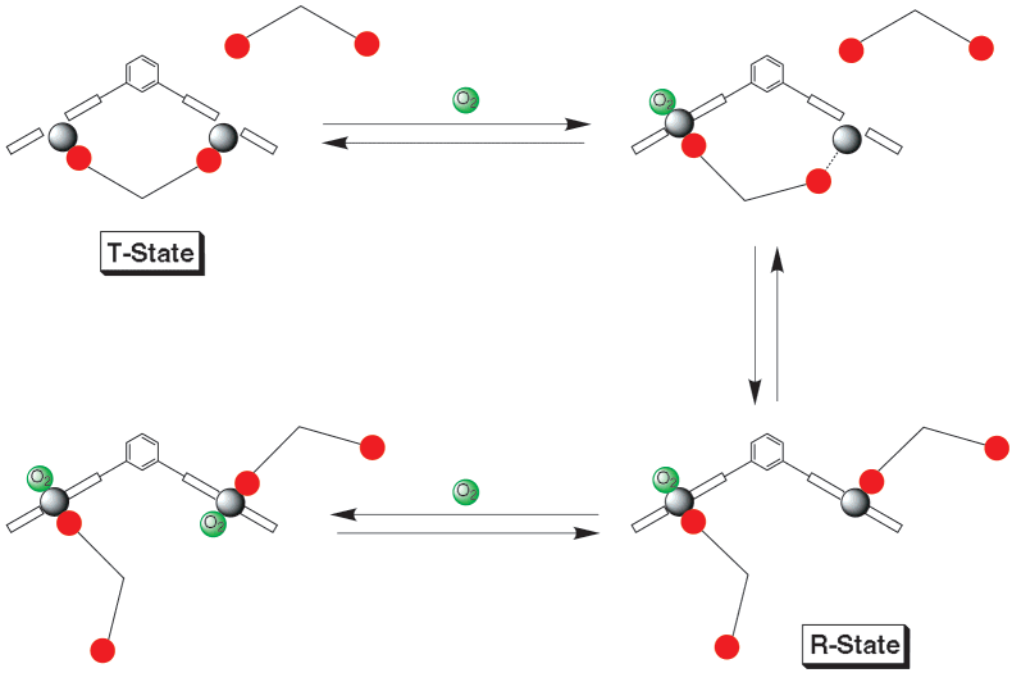
The basic concept included in Traylor's system[19] is more clearly demonstrated by Tabushi et al.[7] in cooperative dioxygen binding with a dimeric metalloporphyrin **3** (Chart 1). When they used *N*,*N*′-diimidazolylmethane as a ligand and carried out O_2 binding, the plot of P_{O_2} vs $\mathbf{3}\cdot O_2$ complex showed clear cooperativity with $n = 1.5$. As shown in Scheme 1, when the first O_2 binds to the deoxy T-state, Co(II) prefers to take a planar coordination. This results in the strain increase in the ligand−Co(II) bond and eventually the monooxy R-state. Thus, the second O_2 binding can occur more easily than the first O_2 binding. One may regard the function of this gable porphyrin as an example of a dynamic structural change information transmission mechanism.

A similar structural change that favors subsequent guest binding can be also induced by metal ions. Lehn et al.[22] found that treatment of oligobipyridine ligands with Ag(I) or Cu(I) yields metal helicates which have a double strand, a structural characteristic of RNA and DNA. The analysis of the Cu(I) binding to **4** indicated that the assembly of **1** with Cu(I) to give the trihelicate **5** (Chart 1) is a self-organization process displaying positive allosterism.[23] This finding implies that the first $Cu(I)(bpy)_2$ helicate formation preorganizes the residual bpy units, which facilitates the subsequent binding of Cu(I) to open helicate units in the double-strand structure. The n values estimated on the basis of the Hill equation were 1.72−1.75. A more simplified metal binding system was reported by Shanzer et al.[24] They examined the Fe(III) coordination properties of tripodal ligands (e.g., **6**, Chart 1) possessing hydroxamate coordination cavities by various methods. The association constants for each Fe(III) binding step, determined by spectrophotometric titration, were $\log K_1 = 5.7-5.9$, $\log K_2 = 12.1-12.2$, and $\log K_3 = 16.8$. One may consider, therefore, that the binding of the first Fe(III)

Chart 1



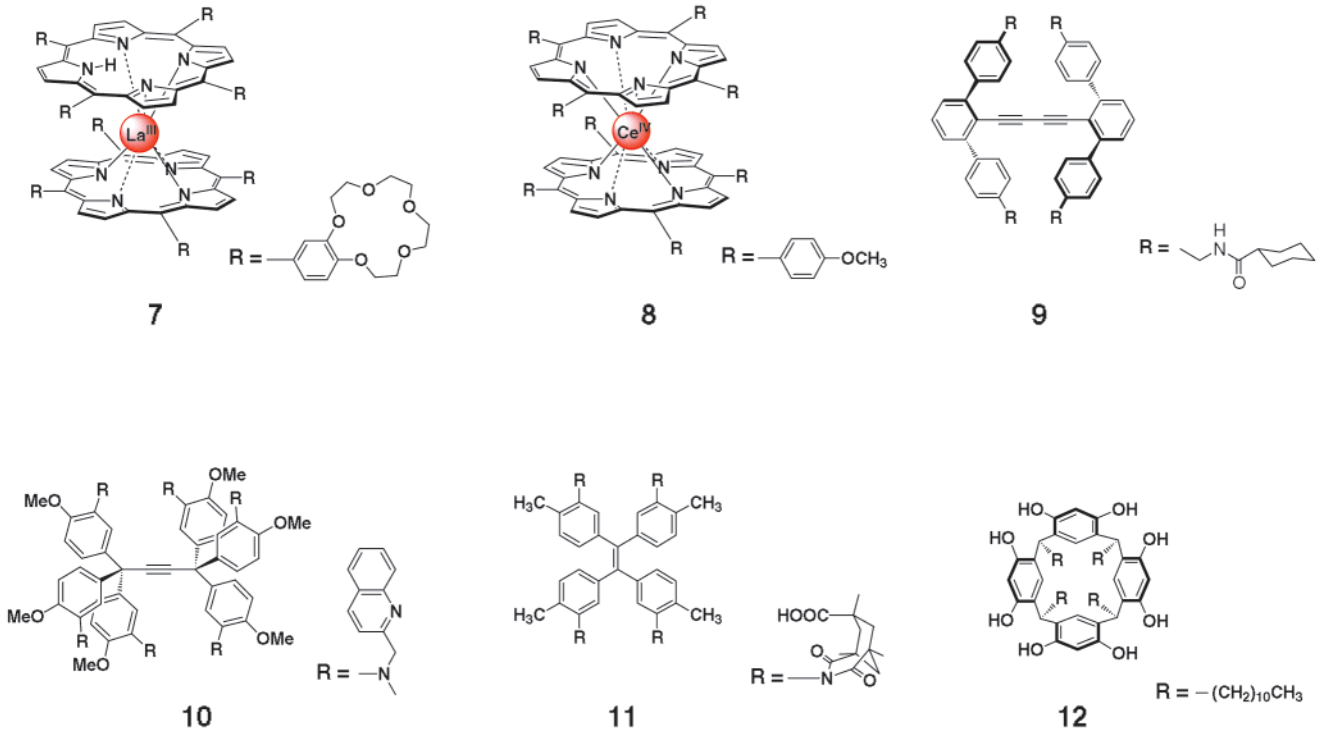
Scheme 1



enforces the orientation of three hydroxamate chains to create the two additional coordination cavities which possess Fe(III) affinity higher than that of the first one. This system, forming a host/guest 1:3 complex, offers a very convenient way to quantitatively estimate the degree of positive allosterism, because the ultimate *n* value in this allosteric system should be very close to 3.0. In the reported work,[24] however, the data were not obtained under conditions suitable for analysis by the Hill equation (i.e., low host concentration and high guest concentration).

The positive allosterism observed for tetrakis(crown ether)-appended porphyrins[20] and phthalocyanines[21] stems from the formation of metal/crown 1:2 sandwich com-

Chart 2

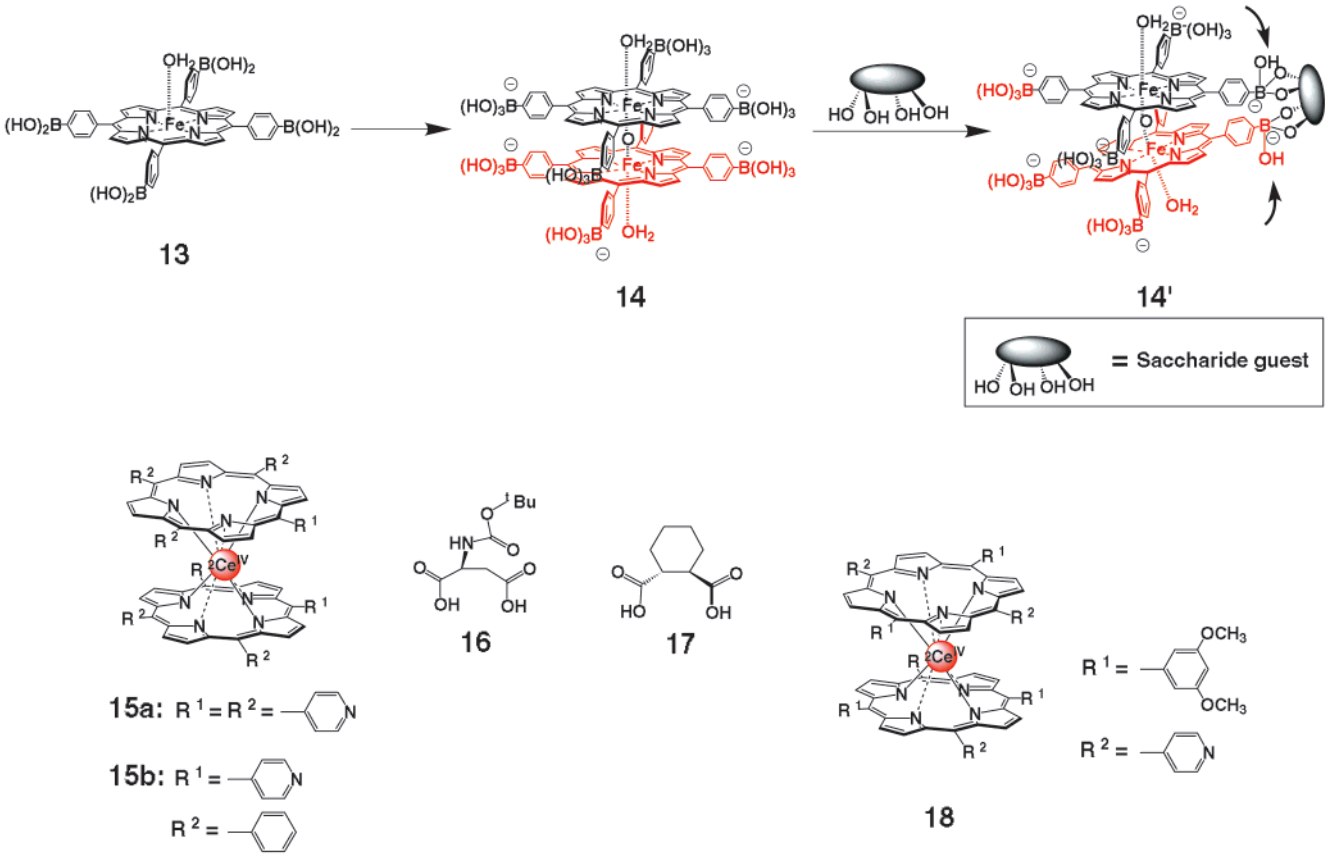


plexes, which results in dimeric or oligomeric π-stacking aggregates. This phenomenon directed us to a new, more simplified idea: that the positive allosterism would be more clearly demonstrated by using a rationally designed "dimeric" porphyrin scaffold. The structure of metal bis(porphyrinate) double deckers, the syntheses of which have been studied exensively by Buchler et al.,[25] seems to satisfy this steric requirement. They have a rotational speed that is a little slower than the NMR time scale, unless the meso positions have particularly bulky substituents.[25−27] These findings suggest that, if the first guest binding can suppress the rotation of the two porphyrin rings, the subsequent guest bindings will occur cooperatively because of their lessened entropy penalty processes.

With this in mind, we designed the tetrakis(benzocrown)-appended lanthanum(III) porphyrin double decker **7** (Chart 2);[28] one may regard **7** as a simplified system of the aggregates formed from tetrakis(crown ether)-appended porphyrins[20] and phathalocyanines.[21] Being different from the preceding aggregation systems, however, this system is very suitable for the demonstration of positive allosterism according to the Hill equation. It was found that this compound is capable of binding K^+ in a cooperative, allosteric fashion to form a 1:4 complex.[28] Analysis of this system by means of the Hill equation gave an overall binding constant (K) of 1.0×10^{14} M^{-4} and a Hill coefficient of 4.0. This same system, however, binds Na^+ in a conventional, linear fashion to form 1:1 Na^+/crown complexes. These results clearly indicate that the novel positive allosteric binding occurs as the result of 1:2 sandwich complex formation between K^+ and appended crown ether moieties of the two joined porphyrins. A similar positive allosterism can be created for Ag^+ with a cerium(IV) double-decker porphyrin without tetrakis(crown ether) groups (**8**, Chart 2).[29] This is due to the specific nature of Ag^+, which enjoys the cation$-\pi$ interaction. Since the significant absorption spectral change in the Soret band is induced, one may notice that Ag^+ ions directly interact with the porphyrin π-systems, forming Ag^+/porphyrin sandwich complexes.[29] Both the Hill plot (log $K = 11.2$ and $n = 2.2$) and the Job plot indicate that **8** forms the **8**/Ag^+ 1:3 complex according to the positive allosteric binding mode.[29] Thus, binding of the first Ag^+ ion to the peripheral π cleft of **8** provides entropically favorable conditions for subsequent Ag^+ binding. It is not yet clear, however, why the stoichiometry of **8**/Ag^+ is 1:3 and not 1:4.

When double-decker porphyrins such as **7** and **8** are viewed from the top of the porphyrin ring, they are regarded as two overlapped wheels rotating around a molecular axle. This view has enabled us to design compound **9** (Chart 2), in which two-bladed wheels rotate around an acetylenic axle.[30] Since the molecular system is fully π-conjugated, the suppression of the rotational speed by guest binding is readily detectable by the increase in the fluorescence intensity. The preliminary study showed that two pairs of amide groups introduced into the blade moieties bind anionic guests (e.g., carbonate and phosphate) in a positive allosteric manner.[30] The positive allosterism concept, in which the first guest binding suppresses the rotational freedom of the axle-wheel-type host, is also demonstrated by using bistritylacetylenes **10** (Chart 2).[31] From Hill analysis of Ag^+ binding, $K = 7.94 \times 10^{16}$ M^{-3} and $n = 2.9$ are obtained.[31] It is proposed that the interaction of the first Ag^+ ion with the two quinolinylmethylamino groups suppresses the rotation of three-bladed wheels.

Chart 3



Positive Allosteric Systems Induced by Molecular Recognition

Molecular recognition of neutral and ionic species by synthetic receptors has fascinated many chemists for the past few decades. In many reported synthetic receptors, hydrogen-bonding interactions play a central role.[32] This type of guest molecule binding based on the hydrogen-bonding interaction can induce positive homotropic allosterism. Ebmeyer and Rebek[33] synthesized compound **11** (Chart 2) utilizing Kemp's triacid as a building block. They observed positive cooperativity for hydrazine and ethylenediamine and negative cooperativity for DABCO and 2-aminopyrimidine. In the binding of the former two guests, chelation of one diamine molecule by nonadjacent acid groups of **11** forces the remaining acid groups to the other side of the ethylene planes in a conformation where they are preorganized for chelation of a second diamine. This enforced conformational change is the origin of the cooperativity in the present system. Aoyama's system, reported for saccharide binding, is somewhat different from others in the mechanistic viewpoint.[34] The resorcinol tetramer **12** (Chart 2) binds methyl and *n*-octyl glucopyranosides via hydrogen-bonding using the phenolic OH groups in apolar media. Methyl glucopyranoside forms a 2:1 host/guest complex with remarkable β/α anomer selectivity. On the other hand, *n*-octyl glucopyranoside is bound to **12** to give a 1:4 host/guest complex with only low anomer selectivity.[34] The four guest molecules are bound at the four resorcinolic hydrogen-bonding sites of **12** with high positive cooperativity ($n = 4$). The fact that **12** does not have any rotational freedom in the preceding examples is important. Thus, this positive allosterism should arise from intracomplex guest−guest hydrogen-bonding interactions between adjacent glucoside molecules. When the four guests are bound, the circular hydrogen-bonded loop is completed. It can be seen, therefore, that this is a hydrogen-bond-dependent, cyclic version of the polymer−surfactant interactions mentioned above.[17]

The foregoing hydrogen-bond-dependent molecular recognition systems were achieved in apolar media where the hydrogen bonds can play a central role. It is shown, however, that they are less effective for recognition of guests that are soluble only in aqueous media. We are currently investigating the recognition of various saccharides which are exactly classified into such water-soluble guest molecules. As an alternate force to bind saccharides in aqueous media, we and others have proposed the use of a boronic acid function which can self-associatively form covalent complexes with a variety of saccharides.[35] We previously synthesized a porphyrinatoiron(III) complex bearing four boronic acid groups (**13**, Chart 3).[14] The μ-oxo dimer **14** is formed from **13** in the slightly alkaline pH region and shows extraordinarily high affinity and selectivity for glucose and galactose. Surprisingly, only one pair of boronic acid groups is used to form 1:1 complexes with the saccharides, and the remaining three pairs of boronic acid groups do not bind them at all.[14] The strong

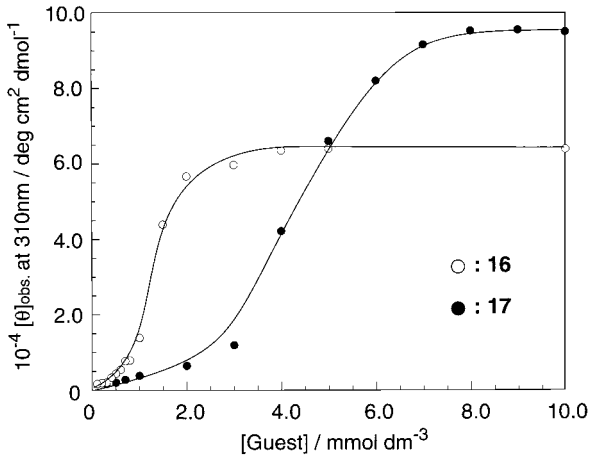


FIGURE 2. Cooperative binding of **16** and **17** to **15a** using the hydrogen-bonding interaction.[37]

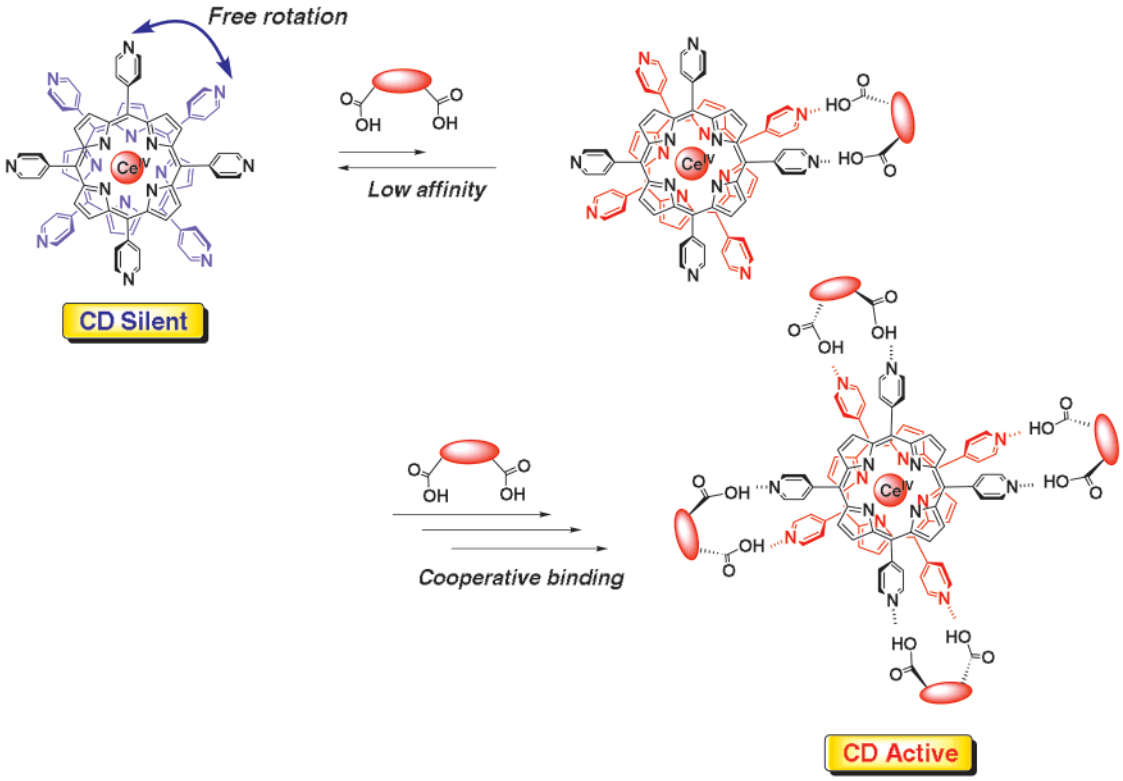
negative allosterism observed here was attributed to an inclination of two porphyrin planes, which was induced by the binding of the first saccharide guest to the first pair of boronic acid groups (as in **14′**, Chart 3). This finding implies that if the first guest can suppress the rotation of the two porphyrin planes without inducing the inclination, the system will exhibit positive allosterism.

To construct such a porphyrin-based positively allosteric system, we chose a cerium(IV) bis(porphyrinate) double decker,[36,37] namely, the tetrakis(4-pyridyl)porphyrin derivative **15a** (Chart 3). This molecule is expected to satisfy our requirements: first, slow rotation of the two porphyrin planes with respect to one another should be possible at room temperature, in analogy to similar cerium(IV) bis(diarylporphyrin) and bis(tetraarylporphyrin) complexes studied by Aida et al.;[26] second, tilting of the two porphyrin planes is more difficult than that in **14**; and third, the four pairs of 4-pyridyl groups are available as hydrogen-bond-acceptor sites for diols, hydroxycarboxylic acids, and dicarboxylic acids. Compound **15b**, which has only one pair of 4-pyridyl groups, was used as a reference. Compound **15a** has a sharp positive allosteric effect with $n = 4.0$ and shows high selectivity for the enantiomers of BOC-aspartic acid (**16**; BOC = *tert*-butoxycarbonyl) and of 1,2-cyclohexanedicarboxylic acid (**17**) (Chart 3, Figure 2). In this system, the binding of these chiral guests can be conveniently monitored by observing CD spectral changes arising from the induced chirality in **15a**. Quantitative demonstration of such strong allosteric effects is very rare in artificial systems. The origin of the cooperative guest binding is attributable to the successive suppression of the rotation of the porphyrin planes without deformation of the basic structure of the cerium(IV) double decker (Scheme 2).[36,37] Thus, the present system should be readily applicable to the regulation of association processes and catalytic activities: for example, **15a** is useful for the efficient release or capture of **16** and **17** in solution, and the catalytic activity of porphyrins can be regulated by means of **16** or **17**. When moderately bulky substituents are introduced into the meso phenyl groups, they cause steric hindrance to suppress the porphyrin ring rotation. In compound **18**, for example (Chart 2), the 3,5-dimethoxyphenyl groups make the porphyrin ring rotation very slow.[38] Hence, chirality of the guest can be "imprinted" into **18**, whereas it can be erased by heat treatment in the presence of pyridine (Scheme 3).[38] After the erasing treatment, the chiral memory can be stored at low temperature, as estimated by the half-life, for 3 days at 0 °C, one year at −37 °C, and 1.9×10^6 years at −100 °C.[38]

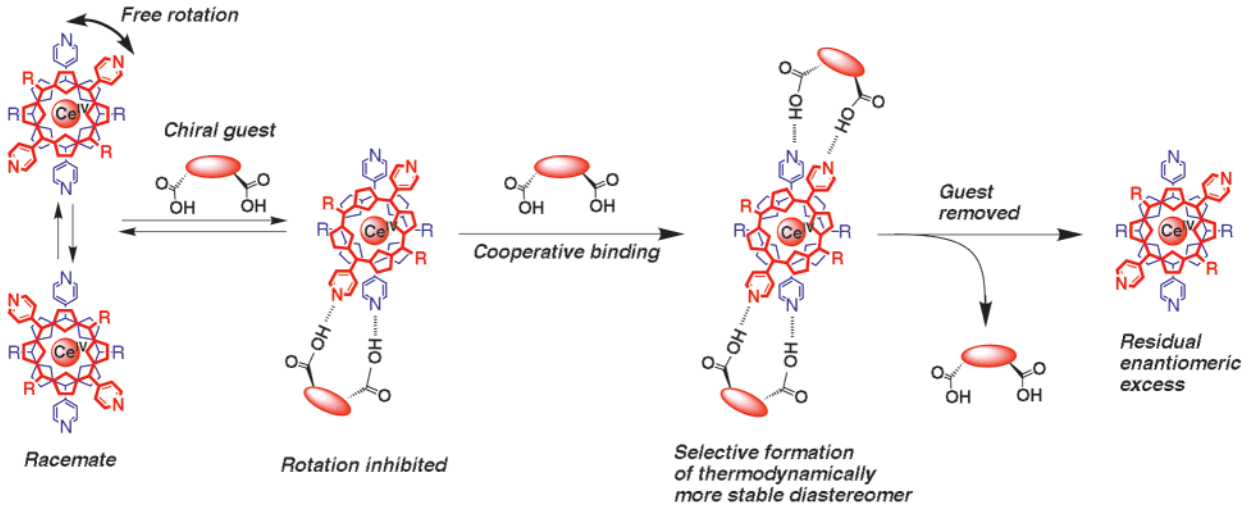
We extended the concept discussed above to saccharide recognition in aqueous solutions. We attempted to introduce eight boronic acid groups into **15a** by quaternization, but isolation of the product bearing eight cationic charges was very difficult. Thus, we compromised by using **19a** (Chart 4) bearing two saccharide binding sites comprised of two pairs of boronic acid groups.[39,40] Compound **19b**, bearing only one pair of boronic acid groups, was used as a reference.[40] As expected, the first example of a positive, homotropic system in aqueous saccharide binding has been achieved using **19a**.[40] In this system, binding of the first guest (1:2 saccharide/boronic acid complex) suppresses the rotational freedom of the two porphyrin planes, which facilitates binding of the second guest (Scheme 4). As a result, two pairs of boronic acid groups in **19a** can cooperatively bind these guests and yield the CD-active species. The analyses of CD intensity−guest concentration plots according to the Hill equation resulted in $K = 3.7 \times 10^4$ M^{-2} and $n = 2.0$ for D-fructose and $K = 9.6 \times 10^5$ M^{-2} and $n = 1.6$ for D-glucose. Thus, the present system, which is in action even in aqueous media, is widely applicable, as a source of "molecular machines", to allosteric control of drug release and catalytic reaction, information transduction, etc. of saccharide-containing guest molecules.

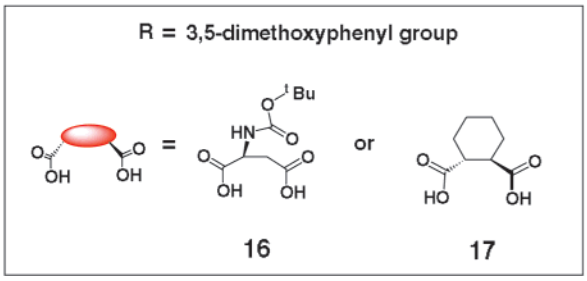
Very surprisingly, it was found that **19a** can bind even oligosaccharides such as maltooligosaccharides ($\mathbf{M}_m$) and laminarioligosaccharides ($\mathbf{L}_m$).[40] To the best of our knowledge, this is the first artificial receptor which has *K* values similar to those for monosaccharides.[40] Utilizing the CD spectral changes, the *K* and *n* values were determined from Hill plots, and the stoichiometries were determined from Job plots for $\mathbf{M}_m$. The results are summarized in Table 1. It can be seen from Table 1 that **19a** forms 1:2 **19a**/$\mathbf{M}_m$ complexes with $\mathbf{M_1}$ (D-glucose)−$\mathbf{M_5}$ (maltopentaose), but $\mathbf{M_6}$ and $\mathbf{M_7}$ seem to be too flexible to give the CD-active complex species. Judging from the Hill parameters, high cooperativity is observed for $\mathbf{M_2}$ and $\mathbf{M_3}$ with $n = 2.0$, and high affinity is observed for $\mathbf{M_2}$ and $\mathbf{M_5}$ with $K = 2.9 \times 10^6$ M^{-2}. In contrast, **18b**, bearing only one saccharide binding site (comprised of two boronic acid groups) to form 1:1 complexes, gives $K = 154$ M^{-1} for $\mathbf{M_2}$.[40] Although the dimension of the *K* values is different, one can safely conclude that, at millimolar oligosaccharide concentrations, the oligosaccharide affinity of **19a** with the positive allosteric effect is incomparably higher than that of **19b** without it. It is very attractive to propose that the unusually high affinity of **19a** for oligosaccharides is due to positive homotropic allosterism; however, this proposal must be proven more carefully on the basis of

Scheme 2



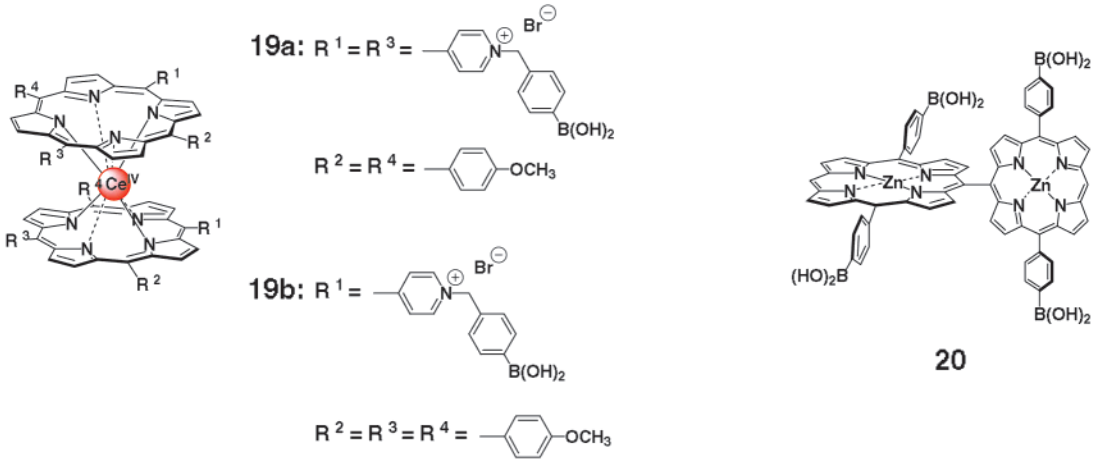
Scheme 3





the thermodynamic method in future. The findings consistently indicate that the binding of the first saccharide guest suppressed the rotational freedom of the two porphyrin planes, and the remote second binding site is

Chart 4



Scheme 4

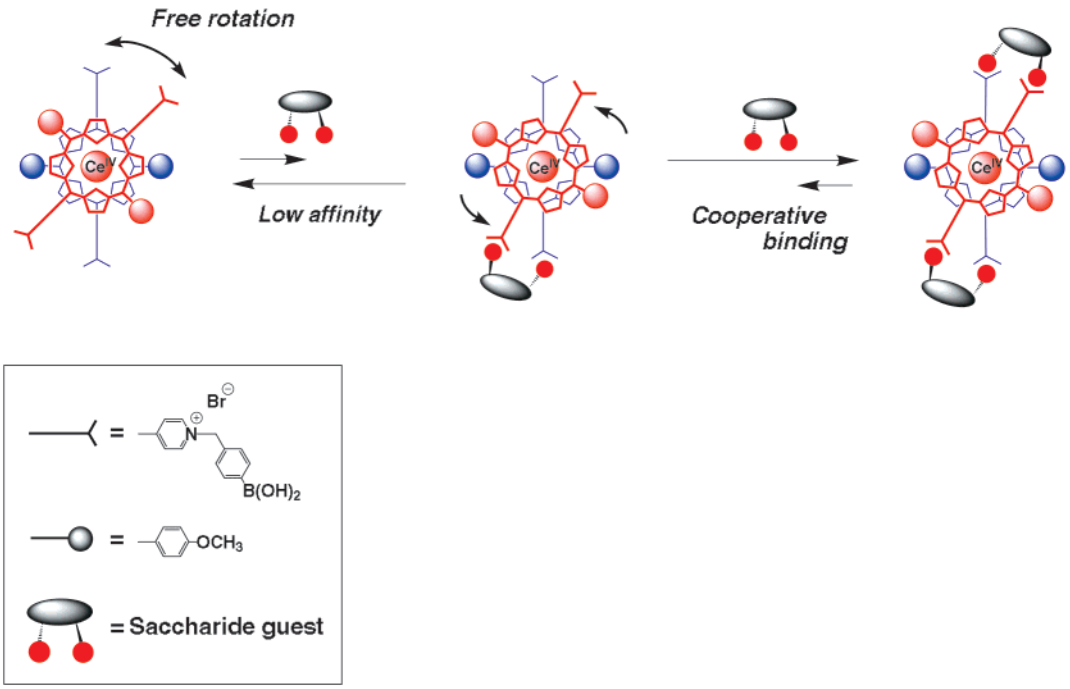


Table 1. Binding Parameters Obtained from Hill Plots and Job Plots

$\mathbf{M}_m$	K/M^{-2}	n	stoichiometry
$\mathbf{M_1}$ (D-glucose)	9.6×10^5	1.6	1:2
$\mathbf{M_2}$	2.9×10^6	2.0	1:2
$\mathbf{M_3}$	1.5×10^6	2.0	1:2
$\mathbf{M_4}$	5.7×10^5	1.8	1:2
$\mathbf{M_5}$	2.9×10^6	1.8	1:2
$\mathbf{M_6}$	*a*	*a*	*a*
$\mathbf{M_7}$	*a*	*a*	*a*

[a] CD spectral changes were too small for K and n to be determined.

aligned for highly cooperative binding of the second guest. As a result, two pairs of boronic acid groups in **19a** can cooperatively bind the oligosaccharide guest molecules with high association constants and give CD-active species. The binding of the saccharide is conceptually illustrated in Scheme 4. The saturated CD_{max} values at 405 nm plotted against $\boldsymbol{m}$ reveal that (a) in the $\mathbf{M}_m$ series, maltose ($\mathbf{M_2}$) and maltopentaose ($\mathbf{M_5}$) give a particularly strong peak at 405 nm, whereas D-glucose ($\mathbf{M_1}$) and other maltooligosaccharides give a relatively weak peak at 405 nm; (b) the complexes with $\mathbf{M_1}$ and $\mathbf{M_5}$–$\mathbf{M_7}$ give a positive peak at 405 nm, whereas $\mathbf{M_2}$–$\mathbf{M_4}$ all give a negative peak at 405 nm; and (c) in an $\mathbf{L}_m$ series, $\mathbf{L_1}$–$\mathbf{L_7}$ all give a positive peak at 405 nm (Figure 3). The results suggest that (1) $\mathbf{M_2}$ and $\mathbf{M_5}$ can form stable complexes with **19a** and **(**2) two porphyrin planes are oriented in opposite directions in the $\mathbf{L}_m$, $\mathbf{M_1}$, and $\mathbf{M_5}$–$\mathbf{M_7}$ complexes compared to their orientation in other complexes. In addition, *n*-dodecyl-*β*-maltoside and *p*-nitrophenyl-α-maltopentaoside, which have only one available diol moiety for binding to boronic acid, do not yield any perceptible CD band.[39] These findings support the view that two diol moieties in the two terminal glucose units of saccharides are bound to two boronic acid groups in **19a** and bridge two porphyrin

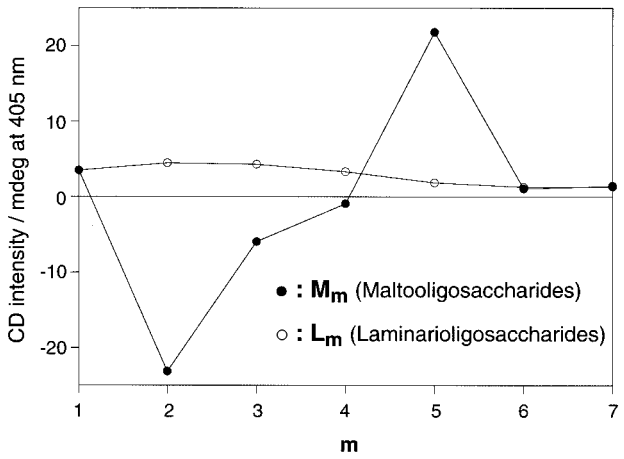


FIGURE 3. Maximum CD intensity at 405 nm plotted against ***m*** in maltooligosaccharides and laminarioligosaccharides.

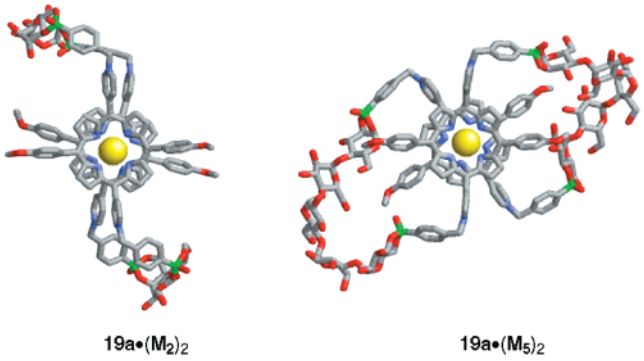


FIGURE 4. Energy-minimized structures of **19a**·$(\mathbf{M_2})_2$ and **19a**·$(\mathbf{M_5})_2$ complexes. Note that the two porphyrin planes are twisted in opposite directions.

planes. This bridging effect suppresses the rotation of the two porphyrin planes and is regarded to be the origin of the strong CD band.[39] The most stable conformations of the **19a**·$(\mathbf{M_2})_2$ and **19a**·$(\mathbf{M_5})_2$ complexes as calculated by computational methods (Discover 3/Insight II 98.0) are shown in Figure 4.[40] It can be seen from Figure 4 that the **19a**·$(\mathbf{M_2})_2$ complex with a short disaccharide chain has a right-handed helical twist, whereas the **19a**·$(\mathbf{M_5})_2$ complex with a longer pentasaccharide chain has a left-handed helical twist. The result undoubtedly shows that the difference in the length of the oligosacharide chain is the origin of the opposite CD signs observed for the two complexes. There are many biologically important oligosaccharides to which this receptor may be applied. In a preliminary experiment, we have already found that Sialyl Lewis^X, which is a trigger saccharide for cell adhesion, can be also bound to **19a** as a result of positive homotropic allosterism ($K = 3.2 \times 10^6$ M^{-2}, $n = 2.0$).[41]

A meso-meso-linked porphyrin dimer **20** (Chart 4), bearing four boronic acid groups, also shows the oligosaccharide affinity (particularly, high affinity with $\mathbf{M_4}$) to form 1:2 **20**/oligosaccharide complexes with $K = 2.0 \times 10^3$ M^{-2} (for $\mathbf{M_7}$)−6.3×10^5 M^{-2} (for $\mathbf{M_4}$) and $n = 1.5$−1.8.[42] This finding suggests again that positive allosterism may play an indispensable role in the binding of oligosaccharides.

Conclusions

In this account, we have evaluated how positive homotropic allosterism appears in artificial receptor systems. In most systems, it is due to entropy-driven factors, although there are a few enthalpy-driven factors which make subsequent bindings easier than the first binding. The molecular scaffolds useful in the design of such contrivances are double-decker porphyrins, tripodal chelates, rotational molecules with a central axis, etc. One should note that these potential scaffolds are all "dynamic"; that is, positive homotropic allosterism can appear only when molecular recognition is coupled with dynamic factors in the molecular system. As mentioned in the Introduction and also ubiquitously demonstrated by Mother Nature, the most well-known advantage inherent to the positive homotropic system is its ability to amplify (or buffer) chemical information. As a result of the present review process, we have noticed that this phenomenon can be utilized as a new strategy to realize for guest molecules high selectivity and high affinity which cannot be attained by simple 1:1-type complexation. We believe that the concepts and the systems introduced in this account will be widely applied in the future, for example, to sensing a trace amount of biologically important species, regulating the function of drugs and membranes, monitoring enzyme activities, etc.

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