Cutting-Edge Science of Cyclodextrin

Review

Development of Supramolecular Saccharide Sensors Based on Cyclodextrin Complexes and Self-assembling Systems

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Cyclodextrins (CDs) are water-soluble host compounds having nano-size hydrophobic cavities that enable them to incorporate organic molecules in water. Optically inert CDs can be efficiently combined with various types of chromoionophores and fluoroionophores. In this study, using diverse combinations of phenylboronic acid fluorescent sensors and azoprobes with CDs, the unique saccharide recognition functions of CD, chemically modified CD, and CD gel complexes based on their synergistic function are clarified, thereby confirming their use as supramolecular saccharide sensors. To realize novel supramolecular chirality, the twisted structure of two ditopic azoprobes inside the γ -CD chiral cavity is controlled by multi-point recognition of guest ions in water. As different types of supramolecular saccharide sensors, phenylboronic acid-based self-assembling systems are also reviewed.

Key words cyclodextrin (CD); saccharide recognition; phenylboronic acid; supramolecular sensor; supramolecular chirality; self-assembling system

1. Introduction

Saccharides play numerous significant roles in living organisms because of their diverse structures.^{1,2)} In biological systems, lectins, which are saccharide-binding proteins, selectively recognize saccharides.^{3,4)} Lectins bind saccharides *via* the formation of hydrogen bonds with the saccharide hydroxyl groups, van der Waals forces, or hydrophobic interactions. However, lectins are easily denatured by environmental factors, such as heat or pH changes, thereby losing their function.⁵⁾ In addition, lectins are expensive because of their limited availability. Therefore the development of more stable, non-lectin-dependent saccharide sensors is highly anticipated.^{6,7)} Synthetic chemical receptors are robust to environmental changes and can be readily modified to enhance activity and cell permeability. Signal transduction groups, such as fluorophores or azo moieties, can be easily incorporated into synthetic chemical receptors, resulting in higher sensitivity than protein or biological receptors, including lectins. In this regard, synthetic chemical receptors have attracted much attention for possible analytical and therapeutic applications.^{8,9)}

Phenylboronic acids are known to form reversible covalent bonds with *cis*-1,2- and *cis*-1,3-diol-containing biomolecules,^{10,11)} such as saccharides and glycoproteins, forming five- and six-membered cyclic boronic esters, respectively, that are stable in alkaline aqueous solution and dissociate at acidic pH¹²⁾ (Fig. 1). Because of this unique property, phenylboronic acids have been used in the development of saccharide receptors and sensing systems as a synthetic mimic of lectins.^{13–18)} The binding affinity of phenylboronic acids for monosaccharides follows the order of fructose > galactose > mannose > glucose.¹⁹⁾ In general, simple phenylboronic acid sensors have

weak affinity and low selectivity for saccharides. To improve the binding affinity and selectivity, the versatile design strategy of synthetic phenylboronic acid receptors based on supramolecular chemistry is an attractive approach.

Supramolecular chemistry is concerned with an assembly of molecules bound by multiple weak non-covalent forces such as hydrogen bonds, aromatic π -stacking, and van der Waals interactions.²⁰⁾ These supramolecular structures are expected to provide novel functions that differ from those found in simple molecules. Cyclodextrins (CDs) are water-soluble host molecules having nano-size hydrophobic cavities that enable them to incorporate various organic compounds in water. In addition, optically inert CDs can be combined with various types of chromoionophores and fluoroionophores. In recent years, our group has been advancing studies on saccharide recognition and guest-induced supramolecular chirality in water with the objective of designing new supramolecular CD complex sensors and self-assembling systems. In this review, we will introduce the novel functions and properties of supramolecular CD complex sensors and phenylboronic acid-based self-assembling systems by focusing on selective saccharide recognition in water.

Fig. 1. Reaction of Diol with Tetrahedral Phenylboronate Anion to Form Anionic Ester

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2. Saccharide Recognition with Supramolecular CD Complex Sensors

2.1. Supramolecular CD Complex Sensors CDs are widely used as host compounds capable of incorporating organic molecules matching their cavity size, thereby rendering the organic molecules soluble in water (Fig. 2). The CD cavity can be used as a nanospace in which various reactions take place.^{21–24} We have developed supramolecular complexes (inclusion complexes) of γ -CD and various compounds that can be incorporated into the γ -CD cavity, such as crown-ether-containing fluorescent probes and azoprobes, which has led to high-sensitivity for alkali metal ion sensing in water.^{25,26} Pyrene-based fluorescent probes incorporating benzo-15-crown-5 into their recognition sites showed selectivity for Na^+ ions that match the size of the crown ether ring in organic solvent. In water, however, the addition of K^+ ions in the presence of γ -CD caused quenching of pyrene monomer emission and the appearance of a new, broad pyrene dimer emission band in the long wavelength region (Fig. 3). These findings suggest that the formation of γ -CD and probe molecule complexes promotes selective complex formation between the crown ether moiety and alkali metal ions, thereby exhibiting supramolecular function. By replacing the binding sites from crown ether moiety to phenylboronic acid, novel functions for saccharide recognition are expected as a supramolecular CD complex sensor.

2.2. Saccharide Recognition with Supramolecular CD Complex Sensors We have designed boronic acid fluorescent probes **Cn-CPB** ($n=1, 4$) and **C1-APB**^{27,28} (Fig. 4) in which the pyrene fluorophore is linked to phenylboronic acid via an appropriate alkyl chain, with the aim of developing supramolecular CD complexes with a saccharide recognition function. Although **Cn-CPB** and **C1-APB** aggregate in water and thus emit almost no fluorescence, when β -CD is added, **Cn-CPB** and **C1-APB** become water-soluble and exhibit a strong pyrene monomer emission. Typical changes in the fluorescence emission spectra and the pH profile of **C1-APB**/ β -CD complex are shown in Fig. 5. Whereas the $\text{p}K_a$ is 8.04 in the absence of saccharide, the apparent $\text{p}K_a$ shifts to 6.03 in the presence of 30.0 mM fructose. Thus when fructose is added to **Cn-CPB**/ β -CD and **C1-APB**/ β -CD complexes, fluorescence emission response is observed under neutral pH.²⁹ The response of boronic acid fluorescent probe/ β -CD complexes has been shown to be mediated by a new mechanism that is based on inhibition of photoinduced electron transfer (PET) from pyrene (donor) to phenylboronic acid (acceptor) by anionic complex formation between saccharide and boronic acid (Fig. 4). The selectivity for saccharides follows the order of fructose>arabinose>galactose>glucose, which is consistent with the general binding order of phenylboronic acid for saccharides. The $\text{p}K_a$ changes for fructose, the binding constants, and the fluorescence emission recovery rates for the β -CD complex sensors of **Cn-CPB** and **C1-APB** are summarized in Table 1. Based on this PET mechanism, it is evident that the response efficiency is higher with **C1-CPB**, which has a shorter spacer, than with **C4-CPB**.

The effect of CD species on glucose recognition has been examined using **C1-APB**, which exhibits excellent fluorescence response (Table 2). For example, we investigated the glucose recognition function of **C1-APB**/ NH_2 -CD complexes for both β -CD and γ -CD, which differ in their cavity size,

Fig. 2. Structure of Cyclodextrins and Their Cavity Diameters

Fig. 3. Dimer Formation of **15C5-C3Py** inside γ -CD Induced K^+ Binding

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Fig. 4. Sugar Recognition Function of Supramolecular CD Complexes

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using 6- NH_2 -CD (amino-substituted CD at primary hydroxyl sites) and 3- NH_2 -CD (amino-substituted CD at the secondary hydroxyl sites). As for 3- NH_2 -CD, we found that the inclusion function of **C1-APB** is lost when it is combined with 3- NH_2 - β -CD. On the other hand, the **C1-APB**/3- NH_2 - γ -CD complex shows high binding ability for glucose.³⁰ It is suggested that multipoint recognition, including electrostatic interactions, is facilitated in the **C1-APB**/3- NH_2 - γ -CD complex (Fig. 6a). These findings demonstrate that the saccharide recognition function may also vary to a great extent depending on the type of CDs to combine. Similarly, we have reported that a receptor incorporating phenylboronic acid, which is introduced to the secondary hydroxyl group side of γ -CD, exhibits glucose selectivity in water when complexed with **C1-APB**³¹ (Fig. 6b). Thus given the diversity of the combina-

Fig. 5. (a) Fluorescence Spectra and (b) I_{377} as a Function of pH for **C1-APB**/ β -CD

[**C1-APB**]=1.0 μ M containing 5.0 mM β -CD, pH was adjusted with 0.01 M phosphate buffer, $I=0.1$ M with NaCl, $\lambda_{\text{ex}}=328$ nm, (1) [fructose]=0 mM and (2) [fructose]=30 mM. Reprinted with permission from Ozawa R. *et al.*, *Anal. Sci.*, **24**, 207–212. Copyright (2008) The Japan Society for Analytical Chemistry (JSAC).

Table 1. Comparison of Fructose Recognition Ability for Boronic Acid Probe/ β -CD Complexes^{a)}

Probe	pK_a^{app}	ΔpK_a	$K_{\text{LS}}/\text{M}^{-1}$	$\phi_{\text{L}}/\phi_{\text{HL}}$
C1-CPB	6.30	1.96	2800	57.4
C4-CPB	6.06	1.89	2500	15.2
C1-APB	6.03	2.01	3900	34.5

a) Apparent pK_a (pK_a^{app}) was obtained in the presence of 30.0 mM fructose. ΔpK_a is the difference of pK_a in the absence and presence of 30.0 mM fructose. K_{LS} is binding constant of probe/ β -CD complex for fructose. $\phi_{\text{L}}/\phi_{\text{HL}}$ is ratio of quantum yields of L- and HL-forms.

Table 2. Comparison of Glucose Recognition Ability for **C1-APB**/CD Complexes^{a)}

CD	pK_a^{app}	ΔpK_a	$K_{\text{LS}}/\text{M}^{-1}$	$\phi_{\text{L}}/\phi_{\text{HL}}$
β -CD	7.60	0.58	93	34.9
6-NH ₂ - β -CD	7.54	0.53	80	19.3
3-NH ₂ - β -CD	7.50	0.61	1.0×10^2	27.3
γ -CD	7.36	0.49	70	30.9
6-NH ₂ - γ -CD	6.91	-0.37	ND	8.1
3-NH ₂ - γ -CD	6.95	1.07	3.6×10^2	30.8

a) Apparent pK_a (pK_a^{app}) was obtained in the presence of 30.0 mM glucose. ΔpK_a is the difference of pK_a in the absence and presence of 30.0 mM glucose. K_{LS} is binding constant of **C1-APB**/CD complexes for glucose. $\phi_{\text{L}}/\phi_{\text{HL}}$ is ratio of quantum yields of L- and HL-forms.

Fig. 6. Glucose Recognition by (a) **C1-APB**/3-NH₂- γ -CD Complex and (b) **C1-APB**/Phenylboronic Acid-Modified γ -CD Complex

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tion of supramolecular CD complexes, novel responses that have not been observed with single fluorescent sensors are expected. This is one of the distinctive appeals of supramolecules.^{32–34)}

Fig. 7. Structure of **B-Azo-C8** and **B-Azo-C8**/ γ -CD Gel

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2.3. Saccharide Recognition with Supramolecular CD Complex Gel Taking advantage of the supramolecular properties, we have designed CD gels that provide hydrophobic nano-size inclusion cavities. By introducing water-insoluble molecular recognition ligands, we have developed a supramolecular separation system with a dynamic separation function.³⁵⁾ Molecular recognition ligands immobilized by non-covalent interactions undergo dynamic rearrangement in response to the separation target substrate inside the hydrophobic nano-size inclusion cavity. It is expected that separation functional materials that differ from conventional separation materials in terms of the ability to identify substrates with highly complex structures could be developed. Moreover, the concept of soft molecular template can be introduced. This represents a completely new supramolecular separation system that, similar to biological functions, demonstrates self-learning ability to change the recognition structure in accordance with the substrate form, or if the recognition site is disrupted, it can spontaneously recover its function by self-repairing the disrupted site.

We synthesized phenylboronic acid azoprobe possessing long alkyl chain (**B-Azo-C8**) and introduced it into a γ -CD to

Fig. 8. Adsorption Behavior of Glucose, Fructose, and Galactose in Water by **B-Azo-C8**/ γ -CD Gel of (a) without Glucose-Template, and (b) with Glucose-Template

[NaCl]=0.1 M, [Na₂CO₃]=10 mM. Reproduced with permission from Hashimoto T. *et al.*, *Chem. Lett.*, **43**, 228–230. Copyright (2014) The Chemical Society of Japan.

form a gel using ethylene glycol diglycidyl ether (EGDE) in the presence or absence of glucose. The template glucose was completely removed by washing with HCl solution at pH 3, to avoid the influence of glucose residues (Fig. 7). Figure 8 shows the adsorption behavior of saccharides for **B-Azo-C8**/ γ -CD gels. The glucose-template gel could selectively adsorb glucose through analysis of the adsorption isotherm of the supramolecular CD gel with the glucose template and that with no molecular template. This is due to the forward orientation at the time of gelation with respect to glucose, which provides an arrangement that facilitates easy binding between boronic acid and glucose in the ratio of 2:1, whereas the amount of galactose adsorption is reduced due to the difference in the binding position. Fructose, which binds in the ratio of 1:1, cannot readily bind to boronic acid because of electrostatic repulsion and steric hindrance. The template-free gel shows high adsorption selectivity for galactose. This is likely due to the similarity in binding mode between the **B-Azo-C8**/ γ -CD complex and the **B-Azo-C8**/ γ -CD-galactose complex.

2.4. Supramolecular Chirality Exhibited by Supramolecular CD Complexes Studies of chirality control with a supramolecular assembly and spiral-shaped polymers have drawn attention in recent years due to the need separately to create right-handed and left-handed molecules for use in chirality recognition within an organism and display light sources.^{36–40)} Furthermore, in the research of new chemical sensors, systems that exhibit improved selectivity only when different elements are all present, due to strong intermolecular interactions, have entered the spotlight. Ditopic sensors demonstrate recognition function only when two types of guest molecules are present, which promote supramolecular complex formation. In a recent study, we designed a ditopic probe having two moieties—a crown ether moiety and a dipicolylamine moiety, which has been incorporated into γ -CD in water, in an attempt to develop a novel molecular recognition system (Fig. 9). By allowing ditopic azoprobes to be incorporated into γ -CD in water, we have revealed the response behavior of the supramolecular complex in the presence of each cationic and anionic species by measuring induced circular dichroism (ICD) spectra and UV-visible (Vis) absorption spectra. We have examined the alkali metal ion selectivity, the heavy metal ion selectivity, and the anion selectivity of this complex and confirmed that only when K⁺, Zn²⁺, and CO₃²⁻ are all

Fig. 9. Guest-Induced Supramolecular Chirality in **15C5-Azo-dpa**/ γ -CD Complex

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present, a large split-type Cotton effect appears in the measured ICD spectra and a significant short-wavelength shift occurs in the measured UV-Vis spectra (Fig. 10). Zn²⁺ forms a 1:1 complex with the dipicolylamine moiety, and CO₃²⁻ forms a 1:1 complex with K-**15C5-Azo-dpa**-Zn/ γ -CD. These results clearly demonstrate that the **15C5-Azo-dpa**/ γ -CD complex in water can exhibit supramolecular chirality due to the twisted structure of the azoprobe dimer inside the γ -CD cavity, only when it recognizes K⁺ or Zn²⁺ in the presence of CO₃²⁻.^{2–41)}

By replacing the binding site from crown ether moiety to phenylboronic acid, a large split-type Cotton effect was induced for **BA-Azo-dpa**/ γ -CD complex in the presence of both glucose and Zn²⁺ at pH 11. Interestingly, we found that the anticlockwise twisted structure of glucose-**BA-Azo-dpa**-Zn²⁺/ γ -CD complex is reversed by addition of phosphate anions (Fig. 11). This behavior was only noted for glucose complex among other monosaccharides.⁴²⁾

3. Saccharides Recognition with Self-assembling Supramolecular Sensors

3.1. Ion Recognition with Self-assembling Supramolec-

Fig. 10. (a) ICD and (b) UV-Vis Spectra of **15C5-Azo-dpa**/γ-CD Complex

[**15C5-Azo-dpa**]=40 μM, [γ-CD]=5 mM, (1) 0.1 M K⁺, (2) 40 μM Zn²⁺, (3) 0.1 M K⁺+40 μM Zn²⁺, (4) 0.1 M K⁺+40 μM Zn²⁺+3.0 mM triphosphate, pH 11 at 25°C. Reprinted with permission from Nonaka K. *et al.*, *Chem. Commun.*, **50**, 10059–10061. Copyright (2014) Royal Society of Chemistry.

Fig. 11. Guest-Induced Supramolecular Chirality in **BA-Azo-dpa**/γ-CD Complex

ular Sensors Typical supramolecular functions include self-assembly of amphiphilic molecules. Amphiphilic molecules (*e.g.*, surfactants) form self-assembled structures, such as micelles, at concentrations exceeding the critical micelle concentration (CMC), which can then present much more functions than a single amphiphilic molecule. The hydrophilic–lipophilic balance (HLB) of amphiphilic molecules greatly affects their self-assembly behaviors.²⁶⁾ If there is a way to alter HLB by means of external stimuli, it will offer the prospect of controlling amphiphile self-assembly in water.⁴³⁾

We have developed amphiphilic crown ether azoprobes that interact with metal ions, thereby allowing control of HLB, as shown in Fig. 12.^{44–46)} The hydrophilic portion contains a quaternary ammonium group whereas the optical information conversion unit consists of an azobenzene chromophore attached *via* an alkyl spacer to a terminal crown ether backbone, which serves as an alkali metal ion recognition site. UV irradiation causes a large decrease in absorption at around 350 nm due to π–π* transition of the azobenzene backbone. In the dark, a short-wavelength shift with the formation of *H* aggregates and a long-wavelength shift with the formation of *J* aggregates have been observed based on exciton interaction among azobenzene backbones on molecular assembly.^{47,48)}

Fig. 12. Structures of Amphiphilic Crown Ether Azoprobes

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B-Azo-Cn ($n = 4, 8, 12$)

Fig. 13. TEM Images of the **B-Azo-C8** (0.02 mM) in 1% MeOH–99% Water (v/v) in the Absence (a) and in the Presence of 20 mM Glucose (b), 10 mM Na₂CO₃ (pH 11.0)

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Spectral changes associated with this assembly process can be extracted as optical information and changes in the assembly state can be captured in the form of UV-Vis spectral information.

Using **15C5-Azo-Cn**, a probe containing the benzo-15-crown-5 (B15C5) moiety in its recognition unit, we observed changes in the absorbance ratio (A_{370}/A_{420}) on the addition of alkali metal ions.⁴⁵⁾ When K⁺ ions, which readily form sandwich complexes with the crown ether moieties, were added, an ion-selective short-wavelength shift was observed in the absorption spectrum. This primarily demonstrates the promotion of aggregate formation, likely dimer formation. We found that this response was dependent on the length of the alkyl spacer, and that the probe achieved excellent K⁺ ion selectivity when $n=6$. Using **18C6-Azo-Cn**, which has a larger crown ether ring, we noted the emergence of selectivity for Cs⁺ ions in water. The recognition of alkali metal ions in water by molecular recognition reagents based on a simple crown ether backbone has been viewed as a challenge until recently. However, by taking advantage of the ability of these molecules to self-assemble on ion recognition (*i.e.*, supramo-

Fig. 14. Effect of Saccharide Concentration on Absorbance at 352 nm of **B-Azo-Cn** [(a) $n=4$, (b) $n=8$, (c) $n=12$] in 1% MeOH Aqueous Solution (v/v) [**B-Azo-Cn**]=0.02 mM, $[\text{Na}_2\text{CO}_3]$ =10 mM (pH 11.0). Reprinted with permission from Tsuchido Y. *et al.*, *Langmuir*, **32**, 10761–10766. Copyright (2016) American Chemical Society.

Fig. 15. Structures of **1-BAzo-NP** and PAMAM Dendrimer

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lecular assembly), it is possible to obtain a novel molecular recognition function as described in this section.

3.2. Saccharide Recognition with Amphiphilic Phenylboronic Acids Figure 13 shows the amphiphilic azoprobes (**B-Azo-Cn**), which have a boronic acid group introduced as the hydrophilic component, to be used as a self-assembling supramolecular sensor. We examined a new saccharide recognition function that takes advantage of the self-assembling ability of this molecule. As an amphiphilic molecule, **B-Azo-C8** has both hydrophilic and hydrophobic components on the same molecule. When added to water, **B-Azo-C8** self-assembles to form an aggregate in such a way that its hydrophobic component is positioned away from the surrounding water molecules. When hydrophilic saccharide is added, the aggregate binds saccharide, thereby changing its assembly state as the balance between hydrophilicity and hydrophobicity (*i.e.*, HLB) is disrupted. Then, using several monosaccharides, we investigated whether this change is affected by the type of saccharide. In this study, the assessment was carried out under basic conditions in 1% methanol solution where **B-Azo-C8** was in its aggregate state. Determining the size of the aggregate by dynamic light scattering (DLS) measurement, we confirmed that aggregate formation took place in the absence

of saccharide (126 ± 43 nm) as well as in solution to which glucose was added (329 ± 9 nm). On the other hand, the aggregate disappeared in solution to which fructose was added. These results suggest that only when fructose was added did **B-Azo-C8** change from the aggregate state to the dispersed state. Then, to observe differences in aggregate state between solution containing no saccharide and that containing glucose, we performed transmission electron microscopy (TEM) measurement (Fig. 13). TEM images revealed the state of disordered assembly in the solution containing no saccharide, as opposed to the formation of string-like assembly structures in the solution containing glucose. These results demonstrate that when glucose was added to the solution, a different aggregate state was established through morphological changes, as compared with the solution containing no saccharide. These morphological changes could be captured, as reflected by changes in the UV-Vis absorption spectra, thereby making it possible to distinguish between glucose and fructose based on absorption spectral changes. Thereafter, the effect of alkyl chain length on saccharide recognition was examined (Fig. 14). The observation that **B-Azo-C4** and **B-Azo-C12** did not respond to saccharides demonstrated that an appropriate alkyl chain length was required for recognizing saccharides. These

Fig. 16. Saccharide Recognition by **1-BAzo-NP** and Various Generations of the PAMAM Dendrimer ((a) Generation-4, (b) Generation-5)

[**1-BAzo-NP**]=0.02 mM, [saccharide]=30, 1.0 mM phosphate buffer (pH 7.0). Reprinted with permission from Tsuchido Y. *et al.*, *New J. Chem.*, **39**, 2620–2625. Copyright (2015) Royal Society of Chemistry.

Fig. 17. TEM Images of the **1-BAzo-NP**/PAMAM₆₄ Complex in the Presence of (a) Fructose and (b) Glucose

[**1-BAzo-NP**]=0.02 mM, [PAMAM₆₄]=0.41 mM, [saccharide]=30, 1.0 mM phosphate buffer (pH 7.0). Reprinted with permission from Tsuchido Y. *et al.*, *New J. Chem.*, **39**, 2620–2625. Copyright (2015) Royal Society of Chemistry.

results signify that the control of HLB was a key factor for the saccharide recognition based on micelle formation and dissociation.⁴⁹⁾

3.3. Saccharide Recognition with Phenylboronic Acid Azoprobe/Polyamidoamine Dendrimer Complexes Dendritic macromolecules, or dendrimers, are unique in that the number of surface functional groups can be strictly controlled. Therefore we focused on polyamidoamine dendrimers (PAMAMs), which have surface functional groups containing amines. Under neutral conditions, PAMAMs carry a positive surface charge that enables them electrostatically to accumulate **1-BAzo-NP**, a probe containing a terminal sulfo group. Furthermore, depending on the dendrimer generation, the density of amine surface functional groups can be varied; therefore it is possible to design **1-BAzo-NP**/PAMAM complexes in which the distance between probes is controlled (Fig. 15). We examined changes in turbidity when PAMAMs of different generations were added to a solution of **1-BAzo-NP** containing various saccharides at fixed concentrations, and found that the addition of PAMAMs increased the turbidity until the probes became densely accumulated on the PAMAM surface (Fig. 16). Another interesting finding was that saccharide selectivity varied depending on the dendrimer generation; prominent responses were exhibited by generation 4 (PAMAM₆₄) to glucose (Fig. 16a), and by generation 5 (PAMAM₁₂₈) to galactose (Fig. 16b). As such, it became clear that different saccharide recognition selectivities could be attained by controlling the density of **1-BAzo-NP** that accu-

mulated on the surface of PAMAMs depending on the dendrimer generation. To confirm this response mechanism, TEM observation was carried out; the results are shown in Fig. 17. In PAMAM₆₄ complexes, no aggregates were observed in the presence of fructose, which can only interact with **1-BAzo-NP** in the ratio of 1:1. On the other hand, 100–200-nm aggregates were formed in the presence of glucose. This observation was confirmed by DLS measurements. Therefore we demonstrated that this specific response is mediated by aggregate formation among dendrimers, which is based on the recognition of glucose and galactose at two points on the surfaces of dendrimers by **1-BAzo-NP**.⁵⁰⁾

4. Conclusion

In this review, the supramolecular functions of CD complexes and phenylboronic acid-based self-assembling systems were used for the design of supramolecular saccharide sensors. Using various combinations of CDs with phenylboronic acid fluorescent probes and azoprobes, selective saccharide recognition was achieved in water by means of CD complexes, chemically modified CD complexes, and CD gel complexes based on their synergistic functions. We have shown that the 2:1 inclusion complex of ditopic azoprobes with γ -CD realized a novel supramolecular chirality in response with multi-point binding of guest ions. For the other type of supramolecular saccharide sensors, we have designed amphiphilic phenylboronic acid azoprobes. Guest-induced changes in aggregate structures were successfully used for saccharide recognition. Similarly, anionic phenylboronic acid probes were self-assembled on the surface of various generations of polyamidoamine dendrimers for specific saccharide recognition in water.

It is expected that the concept of supramolecular chemistry will contribute to key technology development of next-generation sensors from various aspects. Studies on host-guest chemistry, in which reactions take place on the basis of the recognition of guest molecules by host molecules in a 1:1 interaction, and molecular recognition chemistry have progressed considerably. By skillfully applying appropriate combinations of these interactions, new reaction fields for multicomponent and macromolecular systems having highly advanced molecular recognition function for the identification of complex substrates are being created. We hope that these

studies will pave the way toward the development of next-generation supramolecular sensors.

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Conflict of Interest The authors declare no conflict of interest.

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