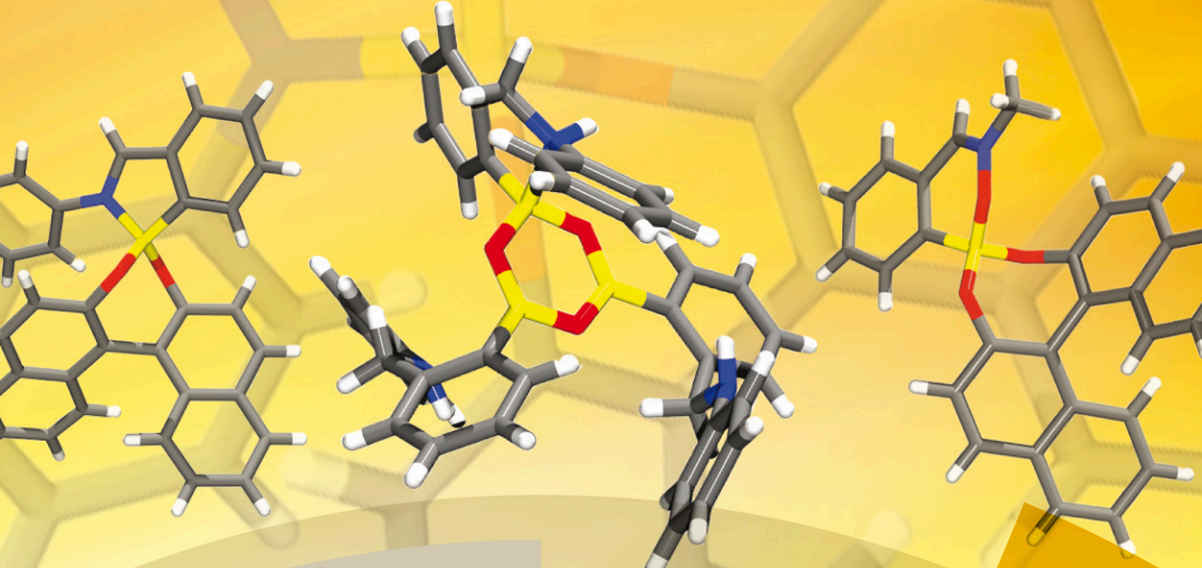

Monographs in Supramolecular Chemistry

Boron

Sensing, Synthesis and Supramolecular Self-Assembly

Edited by Meng Li, John S. Fossey,
and Tony D. James

ROYAL SOCIETY OF CHEMISTRY

Boron

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Monographs in Supramolecular Chemistry No. 16

Print ISBN: 978-1-84973-674-9
PDF eISBN: 978-1-78262-212-3
ISSN: 1368-8642

A catalogue record for this book is available from the British Library

Published by The Royal Society of Chemistry,
Thomas Graham House, Science Park, Milton Road,
Cambridge CB4 0WF, UK

Registered Charity Number 207890

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Preface

Welcome to Fabulous Boron

This book, entitled *Boron: Sensing, Synthesis and Supramolecular Self-Assembly*, is part of the Monographs in Supramolecular Chemistry series edited by Philip Gale and Jonathan Steed and follows in the footsteps of *Boronic Acids in Saccharide Recognition* released in 2006 as part of the same series and edited by Sir J. Fraser Stoddart.[1] This present book extends the scope in that it covers all aspects of the supramolecular chemistry of boron and also includes many interesting developments in the use of boron-based synthetic building blocks.

The editorial team of James, Fossey and Li have assembled a diverse collection of chapters from world leading experts involved in the chemistry of boron from diverse areas of expertise, including synthetic, material and biological aspects of boron based systems. The chapters take us on a journey from molecules to polymers and from covalent to supramolecular bond forming reactions and interactions.

Whether you are visiting for the first time or as a regular visitor, we are delighted to welcome you to Fabulous Boron, we hope you enjoy your stay (Figure 1).

Importance of Boron

Boron is found in many everyday applications, from cleaning materials to glass, and its utility in the world of chemical synthesis and sensing has never been more important. Boron-containing materials are found in nature as minerals and have been well studied in this regard. Boron, in the eyes of the target reader of this book, may be more readily recognised in the chemical sciences for its utility and versatility in synthesis; boron is an important

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Figure 1 Welcome to Fabulous Boron – Please enjoy your visit. Main image ©trekandshoot and http://www.ShutterStock.com.

component in reducing agents, *e.g.* sodium borohydride and borane. Indeed it plays dual roles as both hydride source (BH_3) and a Lewis acid when one employs the CBS catalyst to asymmetrically reduce ketones, for example. It is the empty p-orbital of boron that bestows a Lewis acid character on the atom and one may also be familiar with boron's use as a Lewis acid catalyst (*e.g.* boron trifluoride). It is as boronic acids or boronic esters that boron might be most revered by the synthetic chemistry community. These oxygen and carbon appended boron-containing species are key organic building blocks, as cross-coupling partners in palladium catalysed Suzuki–Miyaura reactions. They are vital to the world of small molecule synthesis for pharmaceuticals, agrochemicals and veterinary science. Readers are pointed to Chapters 3 and 13 of this book that pay particular attention to synthetic strategies exploiting boron.

In recent years the interplay between boronic acids and boronic esters has underpinned an explosion of self-assembly and supramolecular chemistry, which is also well covered by chapters within this book. Furthermore, the reversible binding of diols with boronic acids to form boronic esters has been exploited in the development of new chemical sensors or *chemosensors* for carbohydrates, including new sensing regimes for glucose. The fact boron is capable of functioning as a sensor for anions through conversion into a boronate emphasises the importance of this atom to the sensing community.

Sensing systems using boronic acids are of particular interest to the editors of this book,[2–6] who have established a track record in the area over a number of years. The editors, often in collaboration with authors of chapters in this book, have reported on boron-containing anion sensors,[7–9] carbohydrate sensors,[10–13] glycation recognition,[14,15] reactive oxygen species detection[16,17] and enantiodiscrimination sensors;[18–24] and mechanisms of sensing

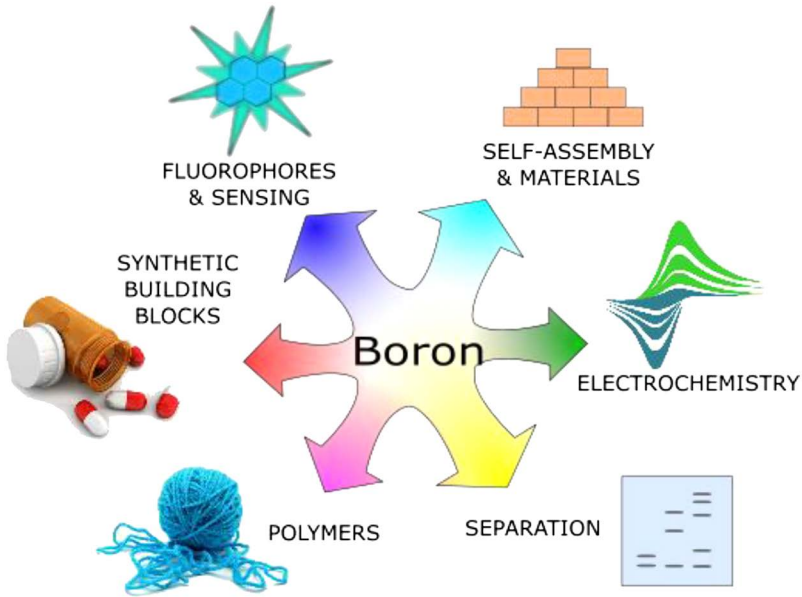

Figure 2 Some of the potential applications of "fabulous" boron contained within the chapters of this book. Karel Lacina is acknowledged for supplying the graphic design used in the figure, the Marken Group is thanked for the cyclic voltammogram, the red medical pills are ©Sashazamarasha and http://www.Dreamstime.com, and the blue wool ball photo is ©Dulsita and http://www.Dreamstime.com.

have included fluorescence, NMR spectroscopy, self-assembly, electrochemical responses and colorimetric assays (Figure 2).[25–28]

Summary of Contents

Chapter 1

Shinkai and Kanekiyo discuss the development of boronic acid-based supramolecular systems. Supramolecular systems discussed include sugar-responsive gels, porphyrin–boronic acid, systems that exhibit guest-induced spectroscopic changes, two-dimensional self-assembly at the air–water interface, boronic acid-functionalized metal nanoparticles and boronic acid-appended polymers.

Chapter 2

Anslyn and co-author's provide a comprehensive description for the investigation of boron containing species by NMR spectroscopy. Indeed this chapter will be of broad interest in the field and provides both a handy first port of call and more in-depth analysis of issues pertaining to boron in NMR spectroscopy.

Chapter 3

Blandin and Chavant discuss the use of boronic esters, other than pinacol, for use in cross-coupling reactions. They have identified an interesting alternative to the typical approaches that use hexyleneglycol, resulting in significant advantages that are discussed in detail in their chapter.

Chapter 4

Yoon and Guo describe boronic acid systems that can bind to nucleophilic species, 1,2-diols, and arylboronates that are converted into the corresponding phenols by treatment with hydrogen peroxide. Resulting in fluorescent chemosensors for carbohydrates, dopamine, fluoride, metal ions and hydrogen peroxide.

Chapter 5

Singaram and co-authors survey the development of boronic acids towards optical, continuous, sensing of saccharides. Since this group has made seminal contributions to the area it is pleasing to see the authors taking this opportunity to discuss their progress, the underpinning fundamental science and setting their contribution in context lets readers experience the full, impressive, story.

Chapter 6

Zhao and co-workers describe boronic acid based systems for enantioselective fluorescent recognition. The scaffold used for the chiral sensors employs a fluorophore, arylboronic acid binding sites (two are best) and a linker (of appropriate size for the guest) between the two receptors.

Chapter 7

The current understanding of synthesis and photophysical properties of 4,4-difluoro-4-bora-3*a*,4*a*-diaza-*s*-indacene derivatives (BODIPY dyes) and their important applications for molecular sensors are described by Zhu and Zhao. The often complicated synthetic routes required for the preparation of BODIPY derivatives has restricted their use as fluorescent reagents. However, Chapter 7 describes up-to-date methods for the preparation of many BODIPY derivatives. In addition, recent advances of using BODIPYs as signaling units for fluorescent probes selective towards different analytes are presented.

Chapter 8

The latest developments in boronic acid chemistry for applications to electroanalysis are discussed by Marken. Boron and its derivatives used as Lewis acidic units have many applications for a range of nucleophilic targets in

analytical electrochemistry. Chapter 8 reports recent progress in boronic acid-based electrochemical sensors both in solution processes and surface processes (on surfaces, in films, and in composites) for the detection of general biological analytes.

Chapter 9

Boronic acids can be incorporated into polymers in order to improve polymer-polymer interactions and develop polymer based materials. The incorporation of specific boronic acid–diol interactions, dramatically improves the polymer properties. Such that, structural changes caused by the complexation are amplified and readily detected. Details of polymer–polymer interactions prompted by the boronic acid–diol interaction are reviewed in this chapter by Numata.

Chapter 10

Guan and Zhang take a detailed look at boron-containing hydrogels with a view to their use as medical diagnostic tools. Their chapter comprehensively evaluates different assembly and application approaches across a diverse range of platforms.

Chapter 11

Boronate affinity materials, such as macroporous monoliths, magnetic nanoparticles, mesoporous nanoparticles and molecularly imprinted polymers, for *cis*-diol-containing biomolecules' recognition and separation has attracted significant attention over recent years. Liu and Li describe useful strategies for reducing the binding pH and enhancing the binding strength of the boronate affinity materials and also illustrate in detail their applications in recognition and separation of *cis*-diol-containing biomolecules including nucleosides, intact proteins and glycoproteins.

Chapter 12

Kubo and Nishiyabu describe the use of reversible boronate esterification to build well-ordered microparticles through supramolecular polymerisation of benzene-1,4-diboronic acid with tetraols. When pentaerythritol is used as the tetraol component for self-assembly, thermodynamically stable flower-like microparticles are produced. Surface functionalisation enables formation of nanometal-deposited heterogeneous catalysts and white-light-emissive chemosensors.

Chapter 13

Buckley's chapter makes an impressive overview of the use of boron as a cross-coupling partner. The Suzuki–Miyaura reaction is one of the most versatile and important reactions in modern day organic synthesis and this

chapter details some important recent cases in the area. Readers are taken through some of the principles of this chemistry and brought up-to-date with intriguing cases from the recent literature.

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Published by the Royal Society of Chemistry, www.rsc.org

About the Editors

Figure 1 Editors left to right: John S. Fossey, Tony D. James and Meng Li pictured together at the University of Birmingham. Daniel Payne is acknowledged for taking the photograph.

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Tony D. James

Tony D. James is Professor of chemistry at the University of Bath and is a Fellow of the Royal Society of Chemistry. In 1986 he obtained a BSc degree from the University of East Anglia, in 1991 was awarded a PhD by the University of Victoria, and from 1991 to 1995 was a Postdoctoral Researcher working with Seiji Shinkai in Kyushu, Japan. After this he became a University Royal Society Research Fellow based initially at the University of Birmingham before relocating to the University of Bath in 2000. He was a visiting professor at Kyushu, Osaka and Tsukuba Universities, an AMADEus invited professor at the University of Bordeaux and is a guest Professor at Xiamen University, Shandong Normal University, East China University of Science and Technology, Nanjing University and is a Hai-Tian (Sea-Sky) Scholar at Dalian University of Technology. In 2013 he was part of a team awarded a Daiwa Adrian Prize and in 2015 received the Inaugural Catalysis and Sensing for our Environment (CASE) Prize. His supramolecular chemistry interests include molecular recognition, self-assembly and chemosensor design. His groups fundamental research findings into glucose sensing and recognition are being translated by long-term collaborators at *Glysure Ltd.* into point-of-care sensing devices for use in hospitals.

John S. Fossey

John S. Fossey is a senior lecturer in synthetic chemistry at the University of Birmingham and is presently a Royal Society Industry Fellow, working closely with *Syngenta*. In 2000 he obtained an MChem degree from Cardiff University, and in early 2004 was awarded a PhD degree by Queen Mary University London. He then became a JSPS postdoctoral research fellow at the University of Tokyo, working with Professor Shū Kobayashi on asymmetric catalysis. After this, he became a research and teaching fellow at the University of Bath and in 2008 moved to the University of Birmingham to begin his first permanent academic position. He was visiting Professor at Henan Normal University and is guest Professor at East China University of Science and Technology. In 2013 he was part of a team awarded a Daiwa Adrian Prize. His research interests are underpinned by the theme of *Catalysis and Recognition for Health and Sustainability*, and he enjoys unravelling and exploiting inter- and intramolecular interactions.

Meng Li

Meng Li is a PhD student at the University of Bath. She obtained her BSc in 2011 from the East China University of Science and Technology, and joined Professor Weihong Zhu's group at ECUST and now works with Professor Tony D. James as a PhD student at the University of Bath. She has been a visiting student for two months at Ewha Womans University in South Korea (with Professor Juyoung Yoon). Her research interests consist of many aspects of supramolecular chemistry and electrochemistry, including molecular recognition, sensor design and electrochemical sensing.

Acknowledgements

The editors of this book are grateful to members of the CASE Network (Catalysis and Sensing for our Environment) for vibrant and productive discussions and exchanges at our regular symposium series. The editors thank the following organisations and institutions for past and present support: the University of Birmingham, the University of Bath, East China University of Science and Technology, the Great Britain Sasakawa Foundation, the Daiwa Anglo-Japanese Foundation, the Engineering and Physical Sciences Research Council (EPSRC), the Japan Society for the Promotion of Science (JSPS), the Leverhulme Trust, the China Scholarship Council, the Nuffield Foundation, the Royal Society and the Royal Society of Chemistry.

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CHAPTER 1

Supramolecular Chemistry of Boronic Acids

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1.1 Boronic Acid-Based Organogels

1.1.1 Low Molecular Weight Gelators

Various organic solvents are gelatinized by low molecular weight gelators. These phenomena are interesting in that the fibrous aggregates formed by non-covalent interactions between gelators are responsible for the gelation. In particular, cholesterol-based gelators show excellent gelation ability towards various organic solvents at sufficiently low concentrations. The resulting gels display chirally oriented structures that are imparted from the cholesterol skeleton having chiral centers.

James *et al.* synthesized a new gelator by combining a boronic acid moiety with the cholesterol skeleton (cholesterylphenylboronic acid **1**).[1,2] It was found that saccharide complexes of **1** efficiently gelatinize several organic solvents. The gelation properties such as the sol–gel phase transition

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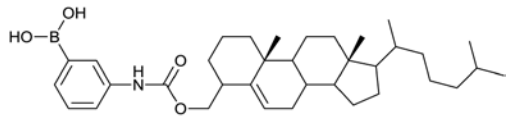
temperature, xerogel fiber structure, gel stability difference between the D- *versus* L-complexes, *etc.* are changeable by a slight difference in the saccharide structure (Figure 1.1).



1

Inoue *et al.* utilized the xerogel fibers prepared from **1** to host matrixes exhibiting binding ability towards saccharides.[3] The process consists of three stages. In the initial stage, benzene is gelatinized by the 1 : 2 complex between xylose and **1**, and then the gel is freeze-dried. In the next stage, the resulting xerogel is washed with aqueous acetic acid solution and a water/methanol mixture to remove xylose from the xerogel. In the final stage, the xylose-removed xerogel is dispersed in aqueous xylose solutions, and the amount of re-bound xylose is determined after stirring for 40 h. Interestingly, the xerogel prepared with L-xylose as a template exhibits four-times higher re-binding ability for L-xylose than for D-xylose. This chiral discrimination ability indicates that the "memory" for the originally imprinted saccharide is retained in the xerogel.

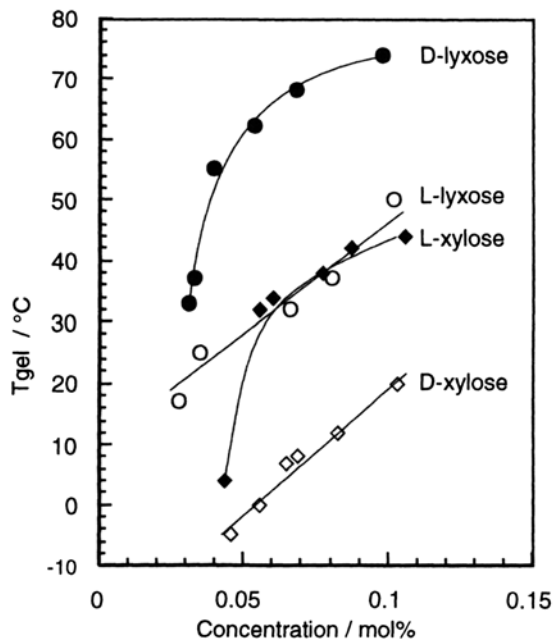
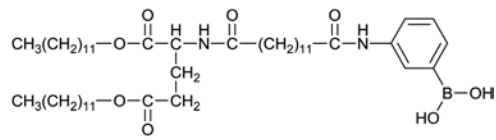


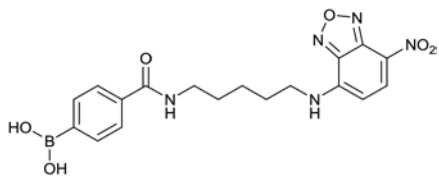
Figure 1.1 Gel–solution phase transition temperature (T_{gel}) in chloroform *versus* the mol.% of complex. Reproduced from ref. 1 with permission from The Chemical Society of Japan.

Kimura *et al.* prepared another type of boronic acid-appended gelator **2** consisting of long alkyl chains and L-glutamate segment.[4] Aqueous solutions containing **2** were gelatinized in the presence of various saccharides, and the aggregation structures of the gelator were observed by TEM measurements. It was revealed that various types of higher-order structures are developed depending on the saccharide used.



2

A gel-based fluorocolorimetric sensor for polyols was reported by Ikeda *et al.*[5] A boronic acid-appended receptor bearing 7-nitrobenzoxal[1,2,5]diazole (NBD) (**3**) is incorporated into self-assembled nanofibers consisting of gelator **4** and hydrophobic coumarin dye **5**. In the absence of polyols, FRET (fluorescence resonance energy transfer) from the NBD moiety of **3** to the coumarin unit in **5** is observed. With increasing polyol concentration, the spectral change appeared due to cancellation of FRET. This is attributed to the migration of **3** from the hydrophobic nanofiber phase to the hydrophilic aqueous phase upon binding of polyols (Scheme 1.1). The authors demonstrated that the gel-based sensor is capable of detecting polyols such as catechol, dopamine, and catechin under dry conditions by integrating the gel-based sensor into a filter paper.



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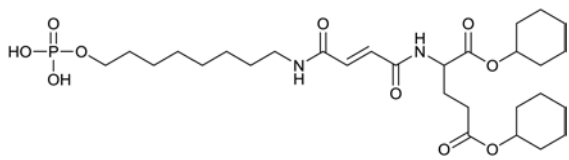

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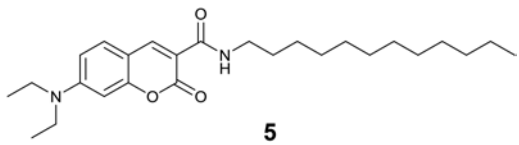
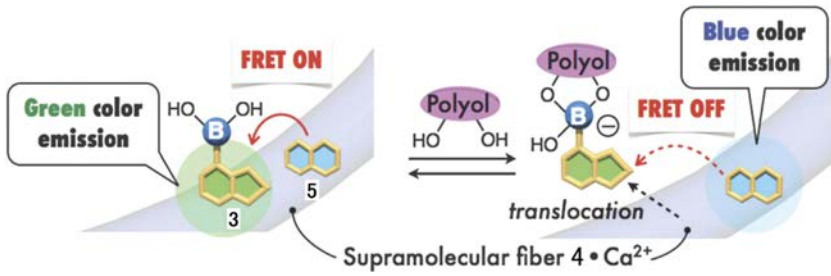


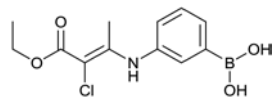
5

Zhou *et al.* developed a new boronic acid-based gelator **6** that can gelate several organic solvents by self-assembling to form a nanofiber network.[6] The driving force for the aggregation is attributed to the hydrogen bonding



Scheme 1.1 Schematic representation of translocation of receptor **3** upon the binding of a polyol from hydrophobic interior of the nanofiber **4**·Ca^{2+} containing FRET donor **5** to aqueous phase, which leads to the change in FRET efficiency. Reproduced from ref. 5 with permission from The Royal Society of Chemistry.

and the π–π stacking between the gelators. It was found that the addition of glucose induces a gel–sol transition, due to the formation of a gelator–glucose complex. This gel exhibits excellent sensitivity towards glucose among six saccharides (mannitol, galactose, lactose, maltose, sucrose, and fructose). The gelator is reusable by dissociating the complex with an acidic solution and then extracting with an organic solvent.

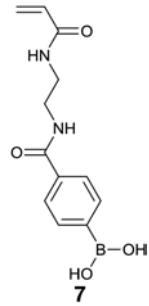


6

1.1.2 Polymeric Hydrogels

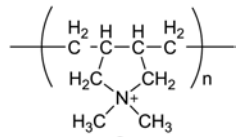
Stimuli-responsive polymer gels have attracted much attention due to their potential application for the design of self-regulated materials and systems. So far, many attempts have been made to design of glucose-regulated insulin delivery systems using stimuli-responsive hydrogels. Usually, two different types of approaches have been utilized for endowing hydrogels with glucose-responsiveness: (1) enzymatic reactions between glucose oxidase and glucose and (2) complementary binding of lectin (concanavalin A) to glucose. The boronic acid-based system is a third candidate.

Matsumoto *et al.* developed boronic acid-based hydrogels showing glucose responsiveness.[7] They were synthesized by copolymerizing boronic acid monomer **7**, *N*-isopropylmethacrylamide, and 2-carboxyisopropylacrylamide with a crosslinker (*N*,*N*′-methylene-bis-acrylamide). The hydrogels tend to shrink with increasing temperature due to the thermo-responsive nature of the main chain [poly(*N*-isopropylmethacrylamide)]. The gel prepared under the optimal monomer composition is shrunken in the absence of glucose, whereas the gel volume increases with increasing glucose concentration. The observed glucose responsiveness is derived from the formation of anionic boronate esters that make the polymer chain more hydrophilic. This totally-synthetic material is potentially applicable to insulin-delivery diabetes-devices that can tolerate long-term use and storage.



7

It is known that polycations and polyanions form charge-neutralized polyion complexes in aqueous solutions. By using polyion complex formation reactions, Kanekiyo *et al.* invented a novel molecular imprinting method for nucleotides as templates.[8] Firstly, a polycation (**8**) was mixed with a boronic acid-containing polyanion (**9**) in the presence of AMP (adenosine monophosphate). Then, the obtained polyion complex containing AMP was washed with an acidic solution to remove the template AMP. Finally, the resultant "cleft" polyion complex was tested for the re-binding ability towards nucleotides. It was proven that the "cleft" polyion complex shows high affinity and selectivity towards AMP. This means that the memory for AMP is retained in the polyion complex matrix. Interestingly, the removal and re-binding processes for AMP coincide with the swelling and shrinking of the polyion complex (Scheme 1.2): without AMP, it is swollen due to existence of excess cationic charges, which create electrostatic repulsion within the polyion complex matrix, whereas the re-binding of AMP neutralized the excess cationic charges resulting in the shrinkage of the polyion complex. This stimuli-responsive polyion complex was subsequently applied as a sensing element in a QCM (quartz crystal microbalance) system.[9] For this purpose, the polyions were alternatingly adsorbed onto a QCM resonator surface in the presence of AMP (Scheme 1.3). After removal of AMP from the surface polyion complex, a swollen gel layer with excess cationic charges resulted. It was confirmed that this QCM system selectively responds to AMP among various adenosine derivatives. The responsiveness is derived from the mass decrease induced by the shrinkage of the surface.



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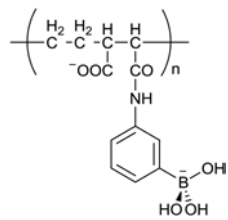

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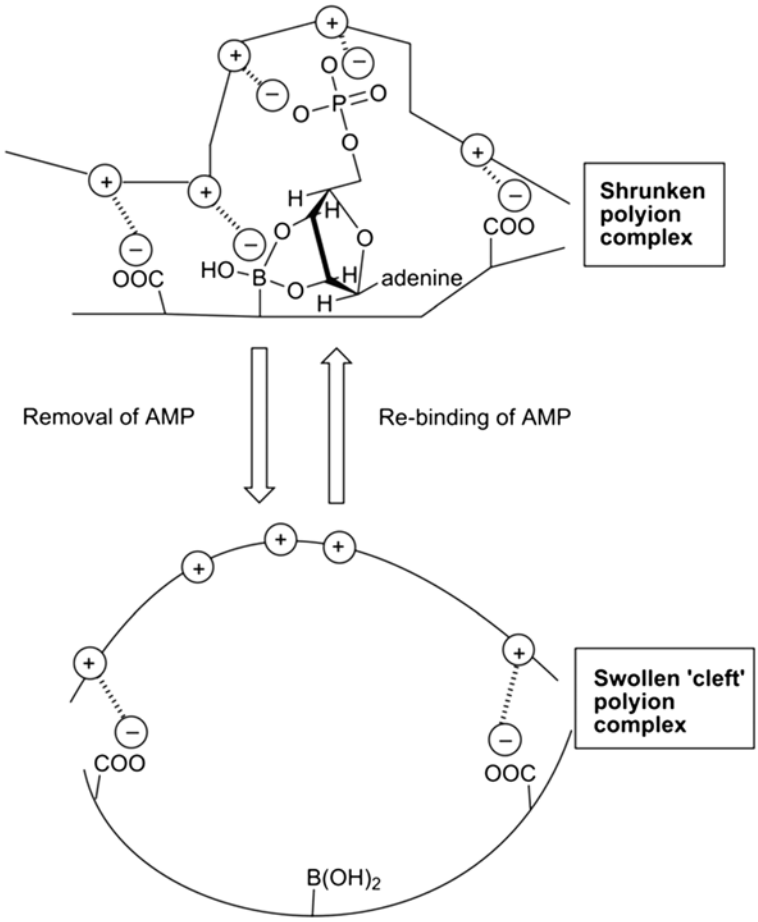
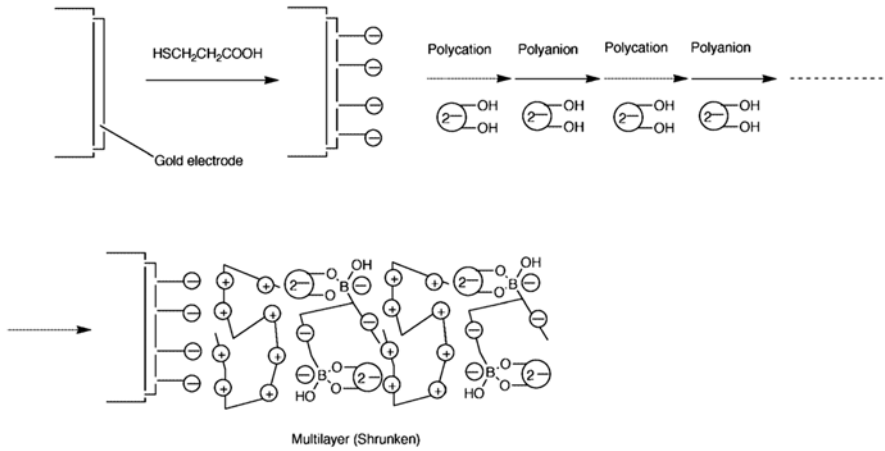
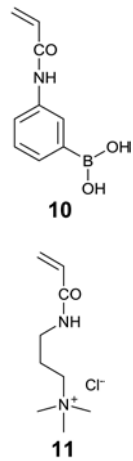


Scheme 1.2 AMP-responsive swelling and shrinkage of a polyion complex. Reproduced from ref. 8 with permission from The Royal Society of Chemistry.

Kanekiyo *et al.* also developed nucleotide-responsive hydrogels by copolymerizing boronic acid monomer **10** and cation monomer **11** with a cross-linker (*N*,*N*′-methylene-bis-acrylamide).[10] The hydrogels efficiently bind nucleotides such as AMP and ATP (adenosine triphosphate) by a cooperative action of the boronate ester formation and the electrostatic interaction between the cationic units and the phosphate group. The binding process coincides with the swelling and shrinking behavior of these hydrogels. For the hydrogel with the specific monomer composition, a unique "charge inversion" is observable: with increasing nucleotide concentrations, the cation-rich hydrogel is gradually shrunken due to charge neutralization, then it is swelled again because of the introduction of excess anionic charges (Scheme 1.4). These nucleotide-induced swelling and shrinking phenomena are applicable to nucleotide sensors by reproducing the gels on the surface of a QCM resonator.



Scheme 1.3 Alternating adsorption of polycation **8** and polyanion **9** on a gold-coated quartz crystal microbalance (QCM) resonator. Reproduced from ref. 9 with permission from The Royal Society of Chemistry.

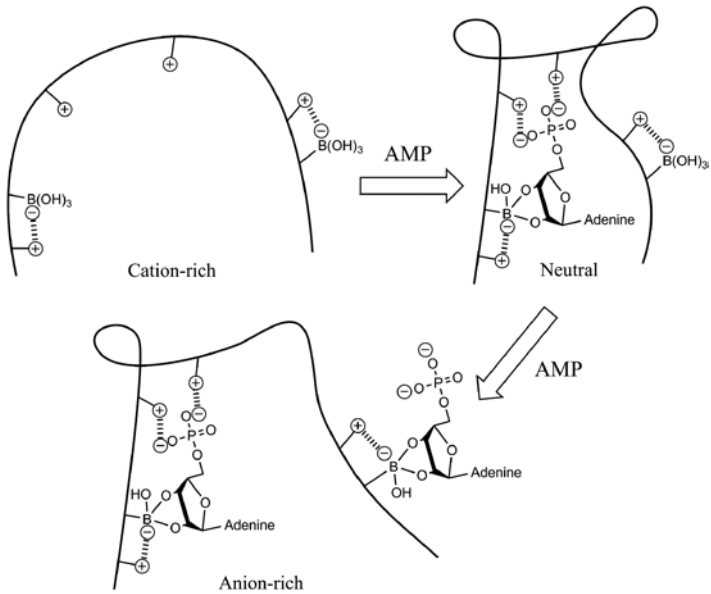


1.2 Boronic Acid-Appended Porphyrins

1.2.1 Monomeric Porphyrins

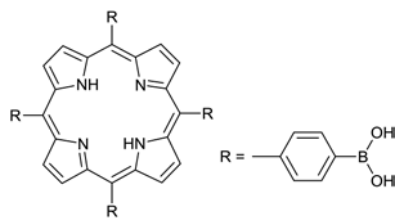
Porphyrin is a useful scaffold for developing molecular recognition elements, since it shows highly sensitive UV-vis absorption and fluorescence emission. By combining porphyrin and boronic acid, one can construct supramolecular systems that exhibit unique guest-induced spectroscopic changes.

Imada *et al.* synthesized a porphyrin derivative bearing four boronic acid moieties (**12**).[11] It was confirmed that **12** forms a one-dimensionally stacked aggregate in water/DMSO mixture at pH 6.9. After adding saccharides to the solution, CD (circular dichroism) spectra were measured. In the presence of saccharides (except fructose), the solutions of **12** become CD-active



Scheme 1.4 Binding of AMP to the hydrogel bearing boronic acid and cationic units, which induces "charge inversion" *via* a neutral stage.

and the sign of the exciton-coupling band (ECB) changes depending on the added saccharides. These results demonstrate that the absolute configuration of saccharides is predictable by CD measurements. Subsequently, a further sophisticated procedure was reported by Takeuchi *et al.*[12] A porphyrin derivative bearing only one boronic acid moiety (**13**) was synthesized, and 1 : 2 sugar–boronic acid complexes were prepared. Then, the photochemical properties of the 1 : 2 complexes were studied by UV, fluorescence, and CD spectroscopy. It was confirmed that the extinction coefficients and fluorescence intensities are linearly correlated with the theoretically calculated dihedral angles between the two porphyrin moieties in the 1 : 2 complexes. In addition, the CD signs are explained by the absolute configurations of saccharides. These results establish that the dihedral angle between the two porphyrins plays a decisive role in electronic properties of the 1 : 2 complexes, and the saccharide structure can be conveniently determined by CD measurements.



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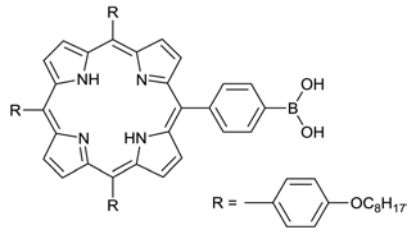
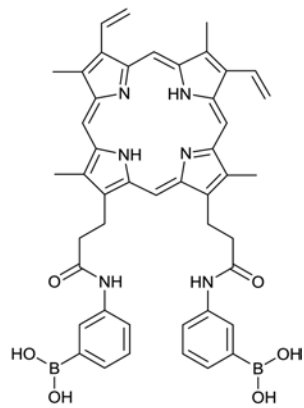


13

The sugar sensing utilizing aggregation properties of boronic acid-appended porphyrin **14** were investigated by Murakami *et al.*[13,14] In the absence of saccharides, **14** forms aggregates that are non-fluorescent. The aggregates are dissociated by the addition of saccharides, resulting in strong fluorescence. Among four monosaccharides tested, the spectral change occurs in the order D-fructose > D-arabinose > D-mannose > D-glucose. Sugar-controlled aggregate formation of **15** was studied by Arimori *et al.*[15] It was demonstrated that the morphology of oriented aggregates in aqueous media can be controlled by adding saccharides. Well-developed fibrous aggregates were obtained in the presence of D-fructose and D-glucose, whereas less-developed coagulated fibrous aggregates were obtained in the presence of D-ribose and D-fucose.



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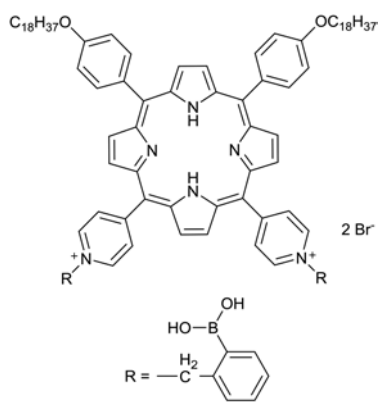
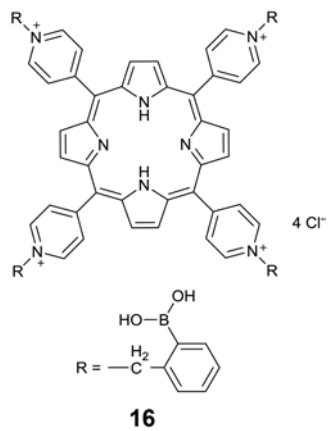


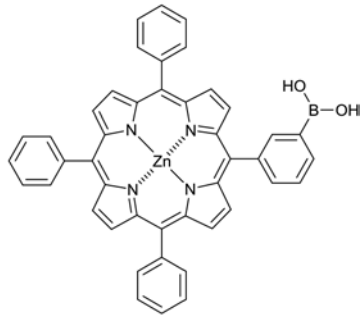
15

Arimori *et al.* succeeded in controlling photo-induced electron transfer process of porphyrins by saccharides.[16] For this purpose, positively-charged porphyrins bearing boronic acids (**16**) were synthesized. When anionic fluorophores such as naphthalenedisulfonate and anthraquinonedisulfonate are mixed with **16** in aqueous solutions, fluorescence emission from these fluorophores is largely quenched. This change is attributed to the formation of electrostatically associated complexes between cationic **16** and the anionic fluorophores in which photo-induced electron transfer between the two components can efficiently take place. Addition of fructose dissociates the complexes because the positive charges on **16** are neutralized by the anionic charges on the boronate groups. As a result, the fluorescence intensity increases with fructose concentration since the quenching efficiency is sufficiently lowered by the dissociation of the complexes. An interaction between **16** and DNA was investigated by Suenaga *et al.*[17] At pH 8.01, **16** is strongly bound to DNA. Comparison of the absorption spectra and the CD spectra established that poly(dGdC)·poly(dGdC) double strand intercalates **16**, whereas poly(dAdT)·poly(dAdT) double strand binds **16** to the outside of the main chain. When D-fructose is added, **16** is dissociated from DNA through complexation with D-fructose. These results show that one can conveniently control the association–dissociation equilibrium between **16** and DNA by saccharides.



16

The cooperative action of two boronic acids is indispensable to the selective binding of saccharides in aqueous solution. However, it is not so easy to synthesize porphyrin derivatives bearing two appropriately arranged boronic acid groups within a molecule. To overcome this difficulty, Takeuchi *et al.* designed a boronic acid-based porphyrin receptor utilizing the metal coordination property in a metalloporphyrin with an axial ligand.[18] For example, a boronic acid-appended Zn(II) porphyrin (**17**) was synthesized and mixed with 3-pyridylboronic acid to create a self-organized diboronic acid system. When saccharides are added to this system, characteristic CD patterns inherent to the absolute configurations of saccharides are observed. Imada *et al.* utilized **17** for selective binding of glucose-6-phosphate and 3,4-dihydroxyphenylalanine (DOPA).[19,20] It was shown that **17** can bind these guest molecules in a two-point interaction manner: one between the diol and the boronic acid and the other between the phosphate or amino group and Zn(II) in the metalloporphyrin moiety.



17

Hirata *et al.* designed porphyrin derivatives bearing a pair of boronic acid groups (**18**, **18-Zn**, and **18-Cu**).[21] These compounds have a diethynyl porphyrin axis, which act as a saccharide-binding modulator. Saccharide binding studies were conducted in water–methanol (1 : 1, v/v) mixed solvent by UV-vis, fluorescence, and CD spectroscopies. It was found that **18-Zn** can bind mono- and oligo-saccharides to produce 1 : 1 host–saccharide complexes with association constants (log *K*) of 2–3. The CD spectra indicate that the two boronic acid groups of **18-Zn** are cooperatively used to bind one saccharide. The porphyrin unit efficiently works as a read-out functional moiety for the saccharide-binding

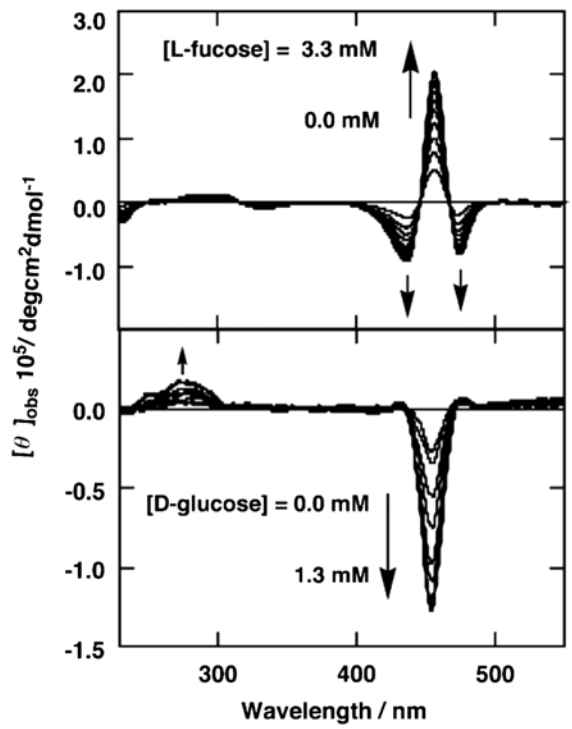
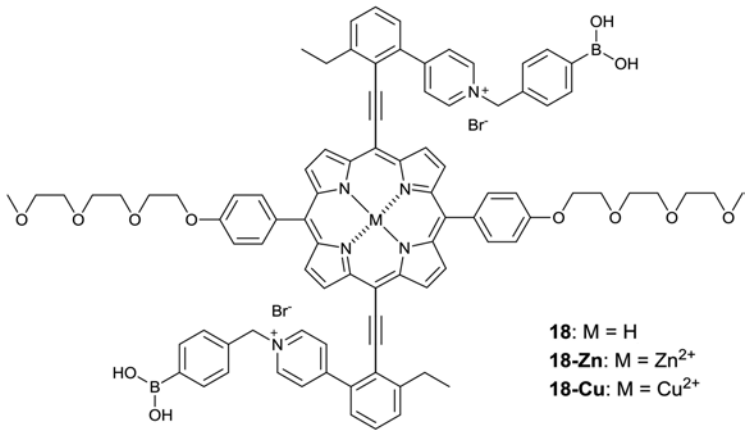
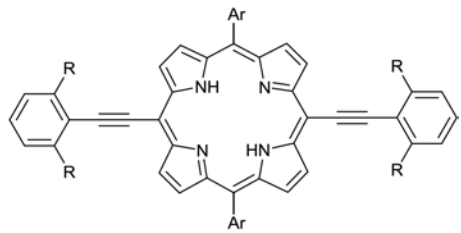
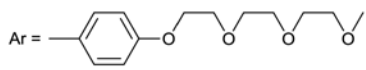


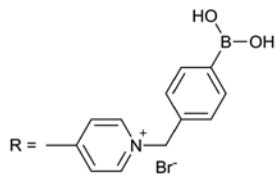
Figure 1.2 Change in the CD spectra of **18**·Zn (5.0 μM) by the addition of L-fucose (0–3.3 mM) or D-glucose (0–1.3 mM); 25 °C; water (pH 10.5 with 50 mM carbonate buffer)/MeOH = 1 : 1 (v/v) mixture; cell length = 1.0 cm. Reprinted from ref. 21, Copyright 2004, with permission from Elsevier.

information to give sharp spectral changes (Figure 1.2). The binding signal can be finely turned by metalation of the porphyrin unit. Following this study, Hirata *et al.* designed porphyrin derivatives bearing two pairs of boronic acid groups **19** to construct an allosteric saccharide-sensing system.[22] The conditions utilized for saccharide-binding studies are identical to those used for **18**. The stepwise binding constants (log K_1 and log K_2) were, respectively, evaluated to be 3.58 and 3.48 for L-fucose and 3.95 and 3.69 for D-xylose. These K_2 values are significantly larger than those that are statistically expected ($K_1 = 4K_2$). Therefore, the obtained data imply that once a pair of boronic acids in **19** binds the first guest saccharide, another pair of boronic acids enhances its affinity toward the second guest saccharide. Binding of the first guest saccharide is entropically disfavored since the host molecule has to lose its rotational freedom, whereas the second guest binding is entropically favored due to preorganization and alignment of the second binding site (Scheme 1.5). Thus, **19** can behave as a saccharide receptor exhibiting a positive allosteric effect.

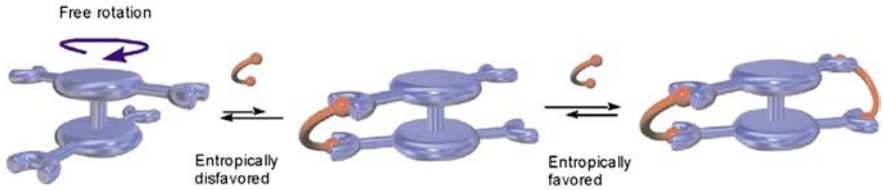






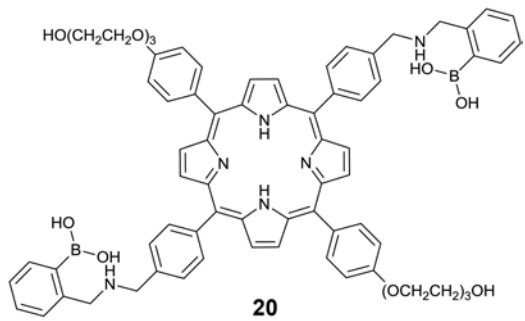


19



Scheme 1.5 Allosteric binding of saccharides by **19**. Reprinted from ref. 22, Copyright 2002, with permission from Elsevier.

Hargrove *et al.* synthesized another porphyrin derivative (**20**) bearing a pair of boronic acid groups.[23] This receptor was used for sensing ginsenoside derivatives such as **21** through fluorescence spectroscopy. The fluorescence intensity is decreased with increasing ginsenosides concentrations, and the obtained quenching curves are used to estimate the 1 : 1 binding constants. The results support a view that the sugar units in the ginsenosides are bound to the boronic acid groups, while the steroid core and porphyrin ring participate in hydrophobic interactions.



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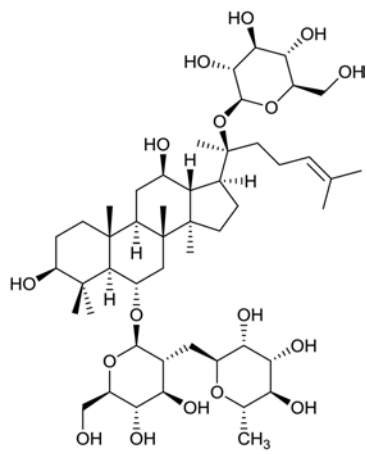
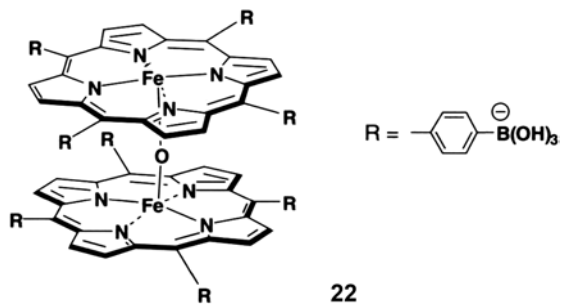


21

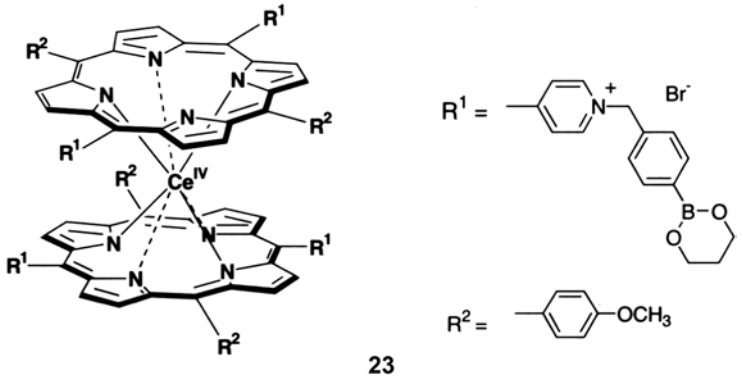
1.2.2 Dimeric Porphyrins

To achieve successful two-point binding of a specific saccharide, it is important to manipulate two boronic acid moieties in an appropriate special position. In the previous section, porphyrins bearing two or more boronic acid groups display specific saccharide selectivity and the resultant complexes become CD-active only when two boronic acid groups are intramolecularly bridged by a saccharide molecule. To arrange two molecules of boronic acid-appended porphyrins in an appropriate special position, Takeuchi *et al.* utilized a μ-oxo dimer of a metalloporphyrin (**22**) to manufacture "sugar tweezers'".[24,25] The μ-oxo dimer is stably formed in basic aqueous solutions where complexes between boronic acids and saccharides are also formed. The saccharide binding process of **22** can be conveniently monitored by CD spectroscopy, and the association constants (log *K*) for glucose and galactose were determined to be 5.18 and 4.39, respectively. In contrast, other monosaccharides are CD-silent. The origin of the CD activity is attributed to the formation of 1 : 1 μ-oxo dimer/saccharide complexes, in which two porphyrin rings are chirally bridged by one saccharide molecule.



22

The first example of positive allosterism in an aqueous saccharide-binding system was achieved by Sugasaki *et al.* using a Ce(IV) bis(porphyrinate) double decker scaffold bearing two pairs of boronic acid groups (**23**).[26] In this system, the binding of the first guest saccharide suppresses the rotational freedom of the two porphyrin planes, which facilitates the binding of the second guest saccharide. As a result, two pairs of boronic acid groups in **23** can auto-acceleratively bind two saccharide molecules and yield CD-active species. The 1 : 2 association constants of **23** for saccharides were determined by analysis of the CD intensity–guest concentration plots: log *K* = 4.57 for D-fructose, 5.98 for D-glucose. Compound **23** was also used for oligosaccharide binding.[27,28] Oligosaccharides such as malto-oligosaccharides, laminari-oligosaccharides, and Lewis oligosaccharides are bound by **23** in aqueous media through the boronic acid–diol interaction with association constants (log *K*) of 5–6. Characteristic sigmoidal binding isotherms are observed (Figure 1.3), indicating that the binding of two equivalents of oligosaccharides to **23** occurs cooperatively.



23

A meso–meso-linked porphyrin dimer bearing four boronic acid groups (**24**) was reported by Ikeda *et al.*[29] A strong CD band is observed when maltotetraose is added to the solution containing **24**, while virtually no CD band is observed when glucose is added. The results indicate that maltotetraose bridges two boronic acid groups in **24**, whereas glucose is too small to bridge the two boronic acid groups. The CD intensity measured as a function of maltotetraose concentration provides a sigmoidal curve indicating that the 1:2 complex is

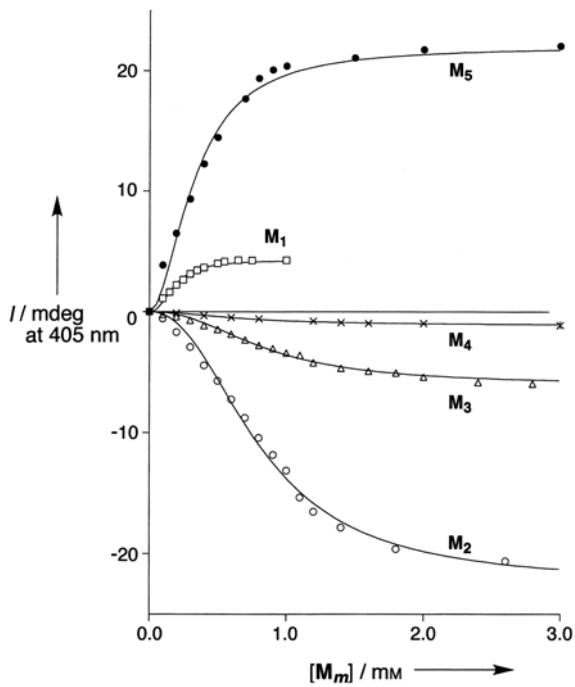
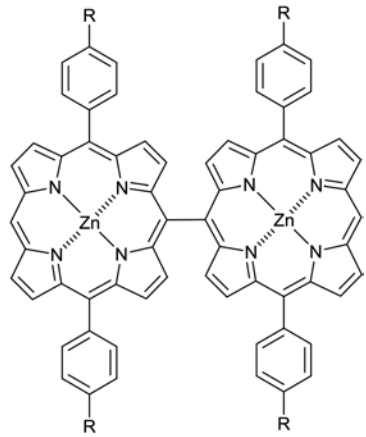


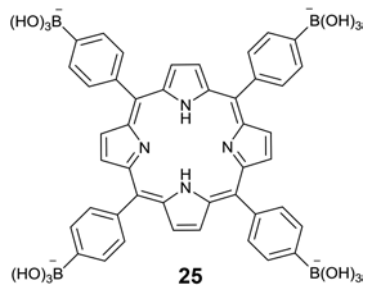
Figure 1.3 Plots of the CD intensity of **23** (1.00×10^{-5} M) at 405 nm *versus* [$\mathbf{M_m}$]. The solid lines represent the theoretical curves for the formation of the [**23**·($\mathbf{M_m}$)$_2$] complex. $\mathbf{M_1}$: glucose, $\mathbf{M_2}$: maltose, $\mathbf{M_3}$: maltotriose, $\mathbf{M_4}$: maltotetraose, $\mathbf{M_5}$: maltopentaose. Reproduced with permission from ref. 27. © 2000 John Wiley & Sons.

formed in a cooperative manner. The obtained association constant (log K) for maltotetraose is 5.78. A computational study predicts that the distance between the two boronic acid groups is comparable with that between 1,2-diol and 4,6-diol in the two terminal glucose units of maltotetraose.



24

Arimori *et al.* utilized the electrostatic interaction to generate dimeric boronic acid-appended porphyrins.[30] Anionic porphyrin **25** and cationic porphyrins **16** form **1 : 1** complexes, which give the specific exciton-coupling bands in CD spectroscopy only in the presence of glucose and xylose. The CD sign is characteristic for the absolute configuration of the saccharides. Structural examination established that only these monosaccharides can bridge two porphyrins by ester formation with boronic acid and twist them asymmetrically.



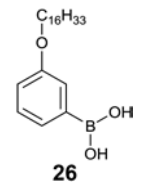
25

1.3 Interfacial Molecular Recognition by Boronic Acid-Appended Amphiphiles

The air–water interface has interesting features as a medium for molecular recognition. For example, (1) a molecularly flat environment is formed at the interface, (2) a boundary region is facing the two phases with different dielectric constants, (3) macroscopically dynamic changes can be taken place

within the plane of the interface, and (4) an access point between hydrophilic and hydrophobic compounds is provided. By utilizing these features, one can construct fascinating supramolecular systems exhibiting unique molecular recognition behaviors.

Shinkai *et al.* investigated the molecular recognition ability of amphiphilic boronic acids **26** towards mono- and di-saccharides at the air–water interface.[31] Compound **26** forms a stable monolayer at the interface, and the surface pressure–molecular area (π–*A*) isotherms are affected by the addition of saccharides in the water subphase. Ludwig *et al.* conducted more detailed examinations and found that the detection of saccharides by the monolayers of **26** at the air–water interface becomes more sensitive by adding a polycation in the subphase.[32] Figure 1.4 depicts typical π–*A* isotherms of **26** at pH 10.0 when the subphase contains D-fructose and a polycation [quaternized poly(4-vinylpyridine)]. The molecular area and compressibility increase with saccharide concentration, and 0.05 mM of D-fructose or 0.1 mM of D-glucose are unequivocally detected. The effect of polycation is explained by the fact that the polycation facilitates hydrolysis of boronic acid group to form anionic boronate [$-B(OH)_3^-$], which makes the formation of boronate ester with saccharide thermodynamically favorable. Amphiphilic diboronic acids **27**–**31** were also synthesized and used for sugar recognition at the air–water interface. Mono- and di-saccharides are selectively detected because of the fixed distance between the boronic acid moieties in the amphiphilic molecule and the organized structure of the monolayer.[33,34]



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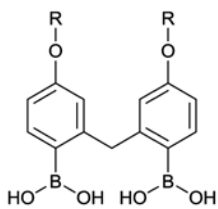
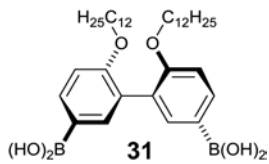


27: R = Methyl
28: R = 2-Octyldodecyl
29: R = 4-tert-Butylbenzyl
30: R = Geranyl



31

Ludwig *et al.* demonstrated that cholesterol-substituted phenylboronic acid **1** can be utilized for chiral discrimination of monosaccharide at the

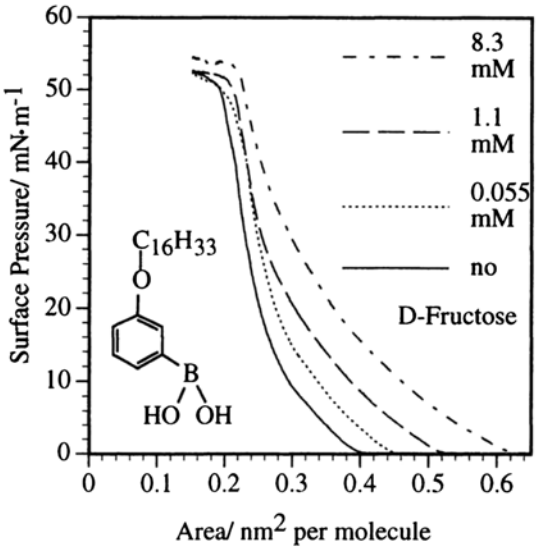
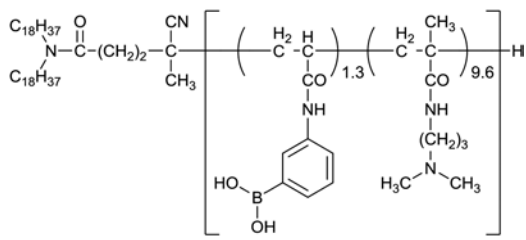


Figure 1.4 Typical pressure–area isotherms of monoboronic acid **26** at pH 10.0 and 293 K on a subphase containing 0.01 wt% PVI and D-fructose. Reproduced from ref. 32 with permission from The Chemical Society of Japan.

air–water interface.[35] Langmuir–Blodgett (LB) films were prepared with **1**, and π–*A* isotherms were recorded in the presence of monosaccharide in the water subphase. It was found that the phase transition pressures of the monolayers are correlated with the Ph–Ph dihedral angle of the 1 : 2 saccharide–**1** complexes (Figure 1.5). The monolayer exhibits chiral discrimination towards optical isomers of monosaccharides.

Polymeric amphiphile **32** carrying boronic acid groups in its polar head regions was prepared by Kitano *et al.*[36] The amphiphile forms a stable monolayer and the π–*A* profile is changeable by the addition of sugars in the subphase. The limiting molecular area of **32** at pH 11 is in the following order: lactose > mannose > no sugar ≈ fructose ≈ galactose > glucose. Notably, glucose decreases the molecular area, which is attributed to shrinkage of the boronic acid-containing head group by the formation of inter- and intramolecular crosslinks consisting of 1 : 2 glucose–boronate complexes. The polymeric amphiphile **32** was also used for the recognition of sugar proteins. By the addition of ovalbumin, which has a sugar chain consisting of two *N*-acetylglucosamine residues and seven mannose residues, the surface area of monolayer of **32** is greatly increased.



32

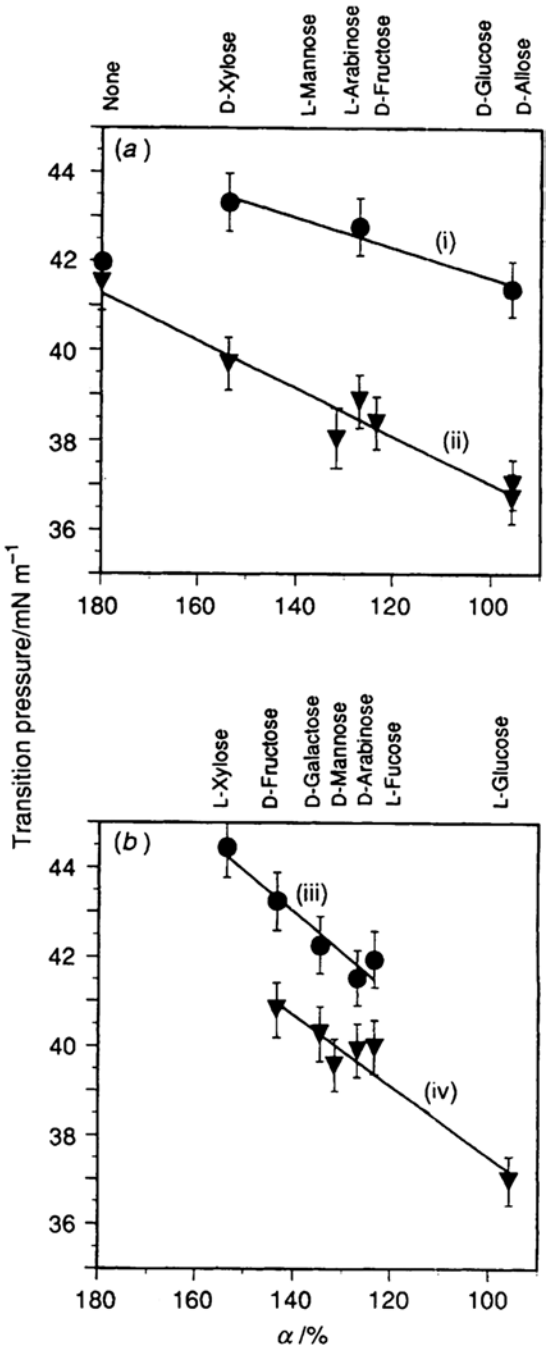
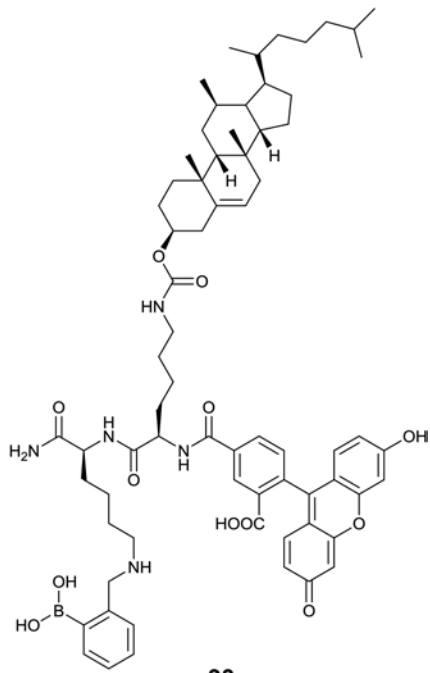


Figure 1.5 Plots of surface pressure of monolayers of complexed **1** at phase transition *versus* the water-facing angle (α) at which the complexes destabilize (a) or stabilize the cholesteric liquid crystals (b). The points are the average of two to three experiments: (●) 293 and (▼) 303 K; R = (i) 0.96, (ii) 0.9, (iii) 0.93, and (iv) 0.9. Reproduced from ref. 35 with permission from The Royal Society of Chemistry.

Recently, a mechanically controlled molecular recognition at the air–water interface was applied to the indicator displacement assay (IDA) by Sakakibara *et al.*[37] For that purpose, the amphiphilic molecule **33** consisting of phenylboronic acid, cholesterol, and fluorescein was synthesized. The cholesterol unit provides a hydrophobic functionality, and the carboxyfluorescein was chosen as a fluorescent probe because it can serve as an acceptor of fluorescence resonance energy transfer (FRET) for coumarin-based indicators such as 4-methylesculetin (ML). Firstly, a monolayer of **33** was formed at the interface in the presence of ML, then fluorescence spectra of the monolayer were measured at different surface pressures (π). At a π of 10 mN m^{-1}, excitation at 373 nm produces a blue emission at around 450 nm. As the surface pressure increases to 20 mN m^{-1}, a new green emission appears at around 530 nm. These phenomena indicate that compression of the monolayer can switch the energy transfer between excited ML and ground state fluorescein. Next, the effect of glucose on the fluorescence behavior was evaluated. With increasing glucose concentration in the water subphase, the energy transfer gradually turned off in a ratiometric fashion (Figure 1.6). This result indicates the displacement of indicator (ML) from **33** by glucose.



33

1.4 Boronic Acid-Functionalized Metal Nanoparticles

Metal nanoparticles (NPs) have been widely investigated for nanoscale optical devices because of their unique properties. Organic monolayer-protected metal NPs are particularly attractive for their photostability,