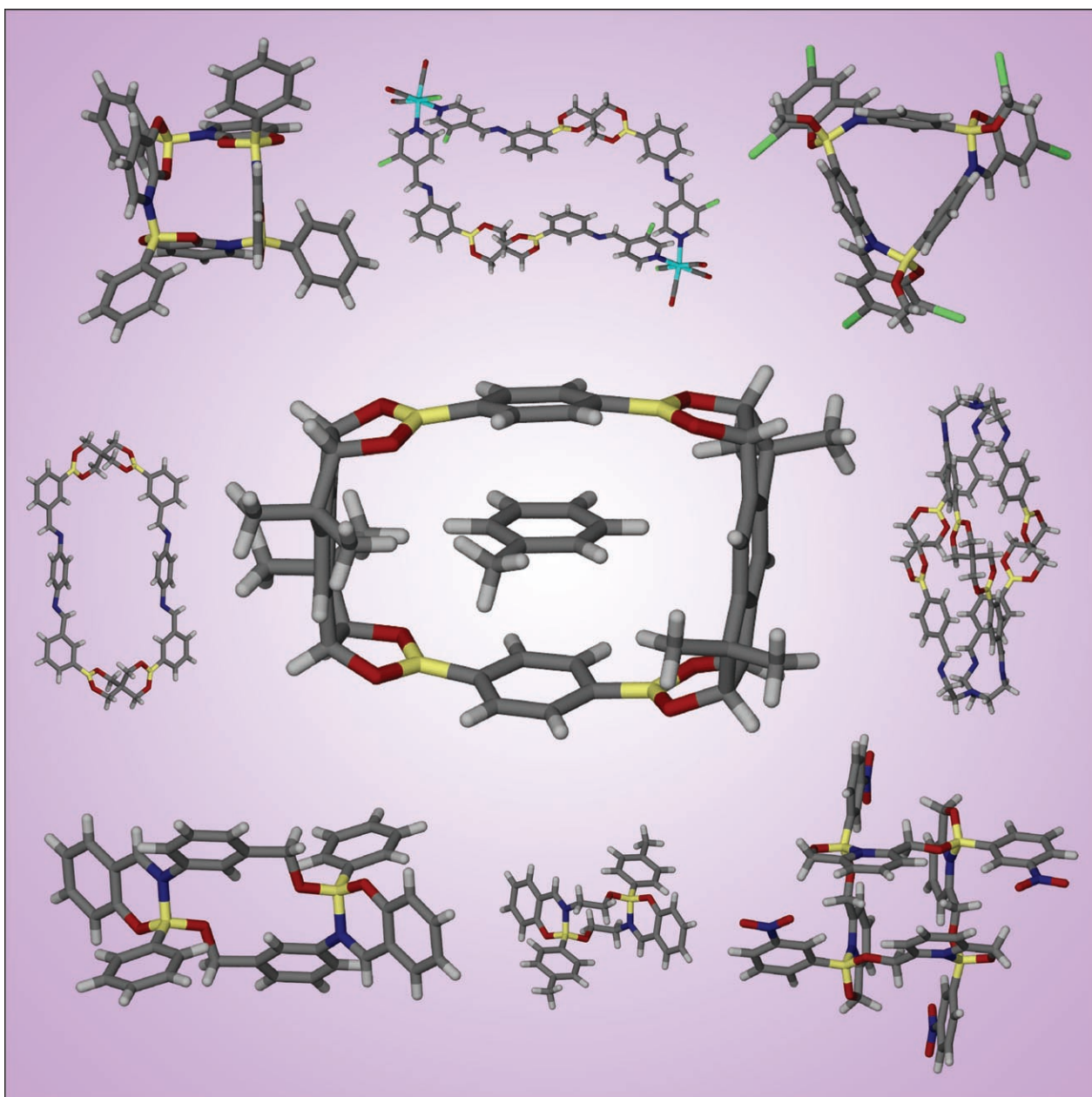


Boronic Acids in Molecular Self-Assembly

Norifumi Fujita,^[b] Seiji Shinkai,^[b] and Tony D. James*^[a]



Abstract: The reversibility of boronic acid and diol interaction makes it an ideal candidate for the design of self-assembled molecular structures. Reversibility is required to ensure that the thermodynamically most stable struc-

ture is formed. Reversibility also ensures that any errors produced during the assembly process are not permanent.

Keywords: boron • complexation • molecular recognition • self-assembly • supramolecular chemistry

Complexation of Boronic Acids

Introduction

Boronic acid chemistry has its roots in the work of Frankland, who in 1860 documented the preparation of ethylboronic acid, with the first synthetic publication on organoboron chemistry.^[1] In 1880 Michaelis and Becker reacted boron trichloride and diphenyl mercury to form dichlorophenylborane. This in turn was added to water and recrystallized as white needles in the first synthesis of phenylboronic acid.^[2,3] The route was refined by 1909 and the classical synthesis of boronic acids from Grignard reagents and trialkyl borates established.^[4]

The development of boronic acid based saccharide sensors has been the topic of a number of recent comprehensive reviews.^[5–9] With this focus review we will explore another important aspect of boronic acid chemistry—molecular self-assembly.

So, why is the boronic acid diol interaction an important force in molecular assembly? (a) The boronic acid–diol interaction is reversible. Self-assembled systems require reversibility to ensure that the thermodynamically most stable structure is formed. Reversibility ensures that any errors in the assembly process are removed and only the desired assembly is formed. (b) The boronic acid–diol interaction is a

covalent binding interaction and unlike non-covalent interactions, the interaction is directional. The strong directionality of the bonds makes it possible to control the final geometry of the assembly with a high level of precision. (c) The diol unit used for the assembly is ubiquitous in nature in the form of saccharides. The availability of a large chiral pool of building blocks for self-assembly permits the structural diversity of these systems.

However, before describing some of the complex structures assembled using boronic acid chemistry, it is important to introduce the boronic acid covalent binding motif in some detail. Knowledge relating to the factors affecting the binding constants and reversibility are vital to a chemist setting out to design a self-assembled system involving the boronic acid–diol interaction.


Boronic Acid–Diol Complexation

Given the significance of boric acid in the determination of saccharide configurations,^[10,11] it is perhaps surprising that the same properties were not observed in boronic acids until 1954.^[12] During a course of investigations into aromatic boronic acids, Kuivila and co-workers observed a new compound being formed on addition of phenylboronic acid to a solution of saturated mannitol, correctly postulating the formation of a cyclic boronic ester analogous to the one known to form between boric acid and polyols.

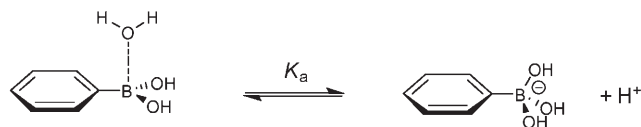
A number of publications followed examining the properties and synthesis of boronic acids,^[13–15] with the first quantitative investigation into the interactions between boronic acids and polyols in 1959.^[16] In a study to clarify the disputed structure of the phenylboronate anion, Lorand and Edwards added a range of polyols to solutions of phenylboronic acid. The pH of the solutions was adjusted such that there was an equal speciation of phenylboronic acid in its neutral and anionic forms; the pH matching the pK_a . As diol was added, the pH of the systems decreased, allowing binding constants to be determined through the technique of pH depression.

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From these experiments Lorand and Edwards concluded that the conjugate base of phenylboronic acid has a tetrahedral, rather than trigonal structure.^[16] The dissociation of a hydrogen ion from phenylboronic acid occurs from the interaction of the boron atom with a molecule of water. As the phenylboronic acid and water react, a hydrated proton is liberated, thereby defining the acidity constant K_a .^[17] This is depicted in Scheme 1 by considering an explicit water mole-



Scheme 1. The acid-conjugate base equilibrium for phenylboronic acid in water. The dissociation of the hydrogen ion from phenylboronic acid occurs from the interaction of the boron atom with a molecule of water. Here we consider an explicit water molecule associated with the Lewis acidic boron.^[17] As the phenylboronic acid and water react a solvated hydrogen ion is liberated, thereby defining the acidity constant K_a , where $pK_a = 8.70$ in water at 25 °C.^[24]

cule associated with the Lewis acidic boron. The reported pK_a s of phenylboronic acid fluctuate between ~8.7 and 8.9,^[18–23] with a recent in-depth potentiometric titration study refining this value to 8.70 in water at 25 °C.^[24]

Whilst one explicitly associated molecule is shown in a number of illustrative schemes, for clarity, water should be considered to be in rapid exchange on the Lewis acidic boron in much the same way that hydrated Lewis acidic metal ions exchange bound water. A pertinent comparison can be found with the ionisation of Zn^{2+} in water, the reaction $Zn-OH_2 \rightarrow Zn-OH + H^+$ having a pK_a of 8.8.^[25]

Boronic acids have been reported to rapidly and reversibly^[26] interact with dicarboxylic acids,^[27,28] α -hydroxy carboxylic acids^[22,28–30] and diols^[16] to form boronic esters in aqueous media.^[31] The most common interaction is with 1,2 and 1,3 diols to form five- and six-membered rings, respectively. Until recently it was believed that the kinetics of this interconversion was fastest in aqueous basic media where the boron is present in its tetrahedral anionic form.^[32] However a recent paper by Ishihara has reported that reaction rate constants of boronate ion with aliphatic diols are much smaller than those with boronic acid.^[33]

In considering these interactions, the equilibria in Scheme 2 can be readily expanded to form a thermodynamic cycle, as illustrated in Scheme 3.

Abstract in Japanese:

ボロン酸とジオールの可逆的な相互作用は、自己集積により分子構造を設計する目的に対しては理想的な条件を備えている。可逆性は熱力学的に最安定な構造を形成する上で必要な要素である。また、可逆性は分子の集積過程で生じるミスマッチを自己修復する上からも重要である。

Considering Scheme 3, we define the formation of the diol boronate anion complex as K_{tet} and the formation of the diol boronic acid complex as K_{trig} , where it is observed that $K_{tet} > K_{trig}$. For instance the logarithm of these constants for phenylboronic acid binding fructose in 0.5 M NaCl water is: $\log K_{tet} = 3.8$ whereas $\log K_{trig} < -1.4$. This difference in the value of the binding constant between K_{tet} and K_{trig} is typical, with differences of up to ~five orders of magnitude being commonplace.^[24] It is also known that the neutral boronic acid becomes more acidic upon diol complexation. The acidity constant of the bound complex is defined by K'_a , where it is observed that $pK'_a > pK_a$. For instance the pK'_a of phenylboronic acid = 9.0 in 0.1 M NaCl 1:2 (v/v) methanol/



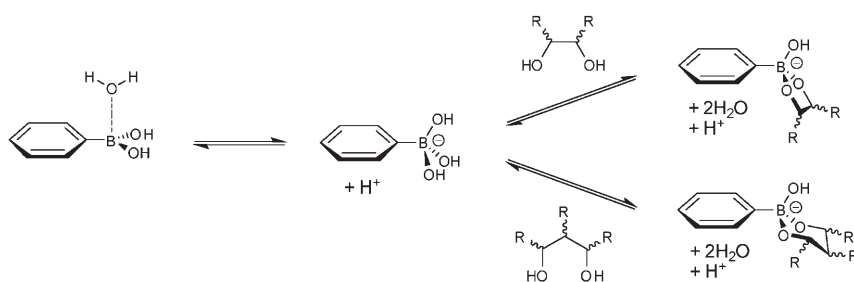
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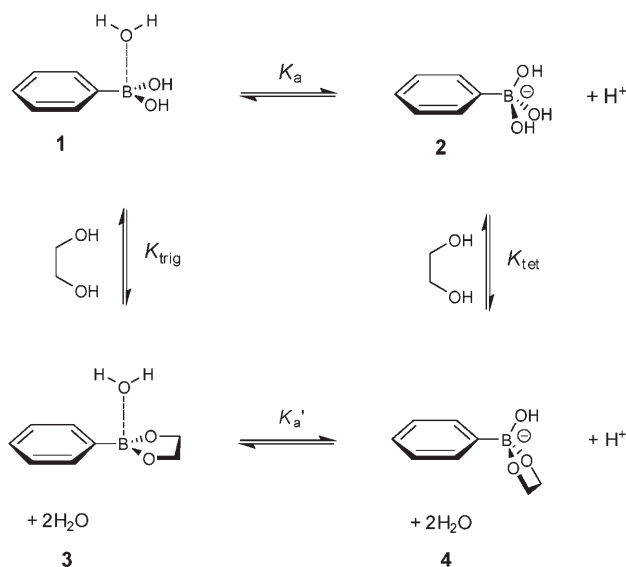
Seiji Shinkai is a professor at Kyushu University. He was born in 1944 in Fukuoka, Japan, and received his Ph.D. in 1972 from Kyushu University. After postdoctoral work at the University of California, Santa Barbara, he joined Kyushu University in 1975. He was director of the Shinkai Chemirecognics (1990–1995), Chemotransfiguration (1997–2001) and SORST (2002–2007) Projects. He led the COE Projects entitled “Design and Control of Advanced Molecular Assembly Systems” (1998–2002) and “Functional Innovation of Molecular Informatics” (2002–2007). His research interests include host-guest chemistry, molecular recognition, sugar sensing, allosteric functions, organogels, sol-gel transcription, and polysaccharide-polynucleotide interactions.



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Scheme 2. Interaction of the phenylboronate anion with 1,2 and 1,3 diols to form diol-phenylboronate complexes with five and six-membered rings, respectively.



Scheme 3. The equilibria for boronate ester formation couple to generate a thermodynamic cycle. The formation of the diol boronate anion complex is defined as K_{tet} and the formation of the diol boronic acid complex is defined as K_{trig} , where it is observed that $K_{tet} > K_{trig}$. The acidity constant of the unbound complex is defined as K_a and the acidity constant of the bound complex is defined as K_a' , where it is observed that $pK_a > pK_a'$.

water. Under the same conditions, the pK_a' of phenylboronic acid bound to fructose = 5.2; in other words the boronic ester is more acidic than the boronic acid.^[24]

The stability constants (K) between various polyols and boronic acids were first quantified by Lorand and Edwards (Table 1) and it is the case that the trends established now appear inherent in all monoboronic acids.^[16]

It is well known that boronic acids readily form five-membered rings with vicinal diols in basic aqueous media. It is also the case that six-membered rings can be formed with 1,3-diol groups, although the stability of these cyclic diesters is somewhat lower than their five-membered counterparts.^[32,34–37]

In response to the growing demand for an accurate interpretation of the complex multi-component equilibria involved in these systems, an extensive investigation was conducted using the potentiometric titration technique.^[24] The refined values for the acidity and binding constants dis-

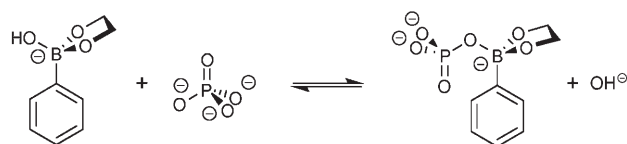
played a good match with previously published data. Nevertheless, it became clear from the results that the thermodynamic cycle in Scheme 3 is somewhat of a simplification. Stable complexes were found to form readily between boronic acids and Lewis bases. This represents a significant finding in sensor design as Lewis bases such as the conjugate bases of

Table 1. The binding constants calculated by Lorand and Edwards for phenylboronic acid in water at 25 °C.^[16] The four monosaccharides most routinely used in the evaluation of sensors for saccharides are in bold.

Polyol	K [mol^{-1}]
1,3-Propanediol	0.88
Ethylene glycol	2.80
Propylene glycol	3.80
3-Methoxy-1,2-propanediol	8.50
D-Glucose	110
D-Mannose	170
D-Galactose	280
Pentaerythritol	650
Mannitol	2300
D-Fructose	4400
Catechol	18000

phosphate, citrate and imidazole are commonly used to buffer the pH of solutions during the spectrophotometric evaluation of sensors, adding a new degree of sophistication to the understanding of the species present in solution.

It was shown that in buffered solutions binary (boronate–Lewis base) complexes as well as ternary (boronate–Lewis base–saccharide) complexes will be formed. Under acidic conditions these ternary complexes are significant and under certain stoichiometric conditions can become the dominant components in solution (Scheme 4).



Scheme 4. In addition to the pair-wise interaction of boronic acids with polyhydroxyl species, boronic acids also form stable complexes with buffer conjugate bases. These complexes can be formed between both the free boronate anion and Lewis bases as well as between saccharide boronate complexes and Lewis bases.

When conducting experiments in solutions buffered with a Lewis basic component, there is therefore a “medium dependence” related to the formation of Lewis base adducts.^[19] These complexes reduce the free boronate and boronic acid

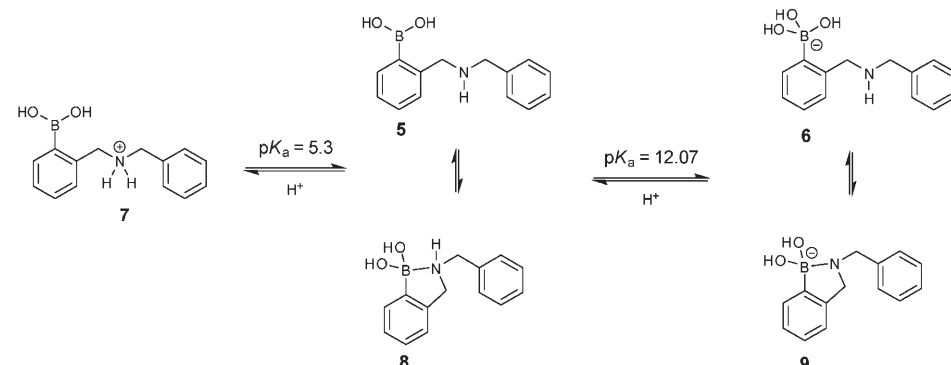
concentrations, diminishing the observed stability constants (K_{obs}).

Amine–Boron (N–B) Interactions

The so-called coordinative or dative, nitrogen to boron (N–B or alternatively N→B) bonds have been studied for more than 100 years. The strength of N–B bonds depends greatly on the substituents on both atoms; electron-withdrawing groups increase the Lewis acidity of boron, whilst electron-donating groups increase the Lewis basicity of nitrogen. In considering the bond strength, it is necessary to balance these electronic factors against the counteracting steric requirements of these same substituents. An investigation of 144 compounds with coordinative N–B bonds concluded that steric interactions as well as ring strain (in the case of cyclic diesters) weaken and elongate the N–B bond, which occurs with a concurrent reduction in the tetrahedral geometry of the boron center.^[38]

The *N*-methyl-*o*-(phenylboronic acid)-*N*-benzylamine **5** system has been investigated separately by Wulff, Anslyn and ourselves.^[24,39,40] Scheme 5 depicts a general model where, at one extreme, the acyclic forms (**5** and **6**) illustrate no N–B interaction, and at the other, the cyclic forms (**8** and **9**) illustrate a full N–B interaction; the species existing in equilibrium. Species **7** involves a protonated nitrogen, there-

fore the ammonium cation precludes any N–B interaction.



Scheme 5. The extent of the interaction between nitrogen and boron is illustrated within the upper and lower bounds of possible contact depicted as the cyclic and acyclic forms.^[24]

The approximate energy of the N–B interaction in these systems has been calculated from the stepwise formation constants of potentiometric titrations, based on the relative stabilities of ternary phosphate complexes (boronate + saccharide + phosphate) for boronic acids **1** and **5**. The stability of the phosphate complex with **1** is taken as the situation with no N–B interaction and is compared with the stability of **5** where an N–B interaction is present. From this analysis, it was calculated that the upper and lower limits of the N–B interaction must be bound between approximately 15 and 25 kJ mol⁻¹ in *N*-methyl-*o*-(phenylboronic acid)-*N*-benzylamine.^[24] This value is in good agreement with computational

data which estimated the N–B interaction to be 13 kJ mol⁻¹ or less in the absence of solvent.^[41] To qualify this in terms of familiar bonding motifs, the energy of the N–B interaction in these systems is approximately the same as that of a hydrogen bond.

Whilst speculative this structural interpretation of the interaction between boronic acid and the proximal tertiary amine through a bound protic solvent molecule (solvent insertion into the N–B bond) corresponds well with contemporary computational and potentiometric titration data, in which the formation of intramolecular seven-membered rings should not be ignored.^[19,24,42,43] The values for the bond length (from the X-ray crystal structure) and for the bond strength (from the potentiometric titrations) are those that would be expected for a hydrogen bonding interaction manifested through a bound solvent molecule at the boron center.

The idea postulated is by no means a new one. An infrared study into the interaction between nitrogen and boron in a similar system came to a similar “tentative conclusion” in 1964.^[44] The experimental rationale was based on comparing two emergent peaks in infrared spectra to similar peaks in known model systems (Figure 1). The results indicated that in carbon tetrachloride the interaction between the nitrogen and boron of 8-quinolineboronic acid could be modulated by either water or phenol bound to the boron center at oxygen.

Anslyn recently performed a detailed structural investigation of the N–B interaction in *o*-(*N,N*-dialkyl aminomethyl) arylboronate systems.^[45] From detailed ¹¹B NMR spectroscopy (and X-ray data) it was shown that in an aprotic solvent, the N–B dative bond is usually present. However, in a protic media, solvent insertion into the N–B occurs to afford a hydrogen-bonded zwitterionic species. Earlier work by Wang and co-workers had also suggested that

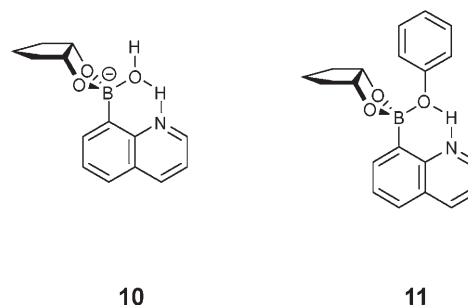
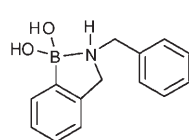
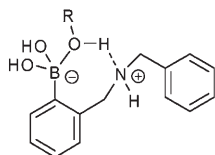


Figure 1. Morrison's proposed complexes of the cis-1,2-cyclopentanediol ester of 8-quinolineboronic acid with solvent water and phenol molecules bridging the nitrogen and boron centers.^[44]

solvolytic instead of N–B bond formation would occur upon sugar binding.^[41]

Thanks to the seminal publication from Anslyn^[45] and current work from a number of other groups,^[24,41,45,46] the N–B interaction in water can, in many cases, be ascribed to a hydrogen bonding interaction mediated through a bound solvent molecule. In other words the N–B interaction in protic media such as water or methanol should not be represented as the N–B form **8** but, rather the solvent inserted form **8** (Solvent).

**8****8** (Solvent)

R = H (water),
R = CH₃ (methanol),
R = CH₃CH₂ (ethanol) etc

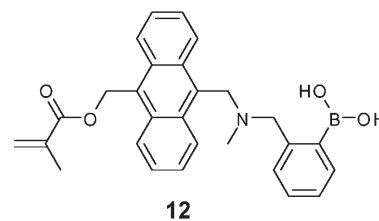
Although the N–B bond is not significant in protic media it is worth noting that the calculated and experimentally derived dative N–B bond energy ranges from 58 to 152 kJ mol⁻¹.^[47–49] Therefore, when designing self-assembling systems, the N–B interaction should be taken into consideration. This is particularly important for systems prepared using non-protic media or materials where no solvent is present.

Molecular Assembly

Molecular Imprinting

Molecular imprinting of saccharides using boronic acids was pioneered by Wulff in 1977.^[39,50–52] The approach employed by Wulff produces a 3-D polymer network. Shinkai has also applied the concept of molecular imprinting to homogeneous (0-D), linear polymers (1-D) and at interfaces (2-D). The analysis and preparation of these lower dimensional systems (0-,1-,2-D) is much simpler than the 3-D polymeric systems.

Wang and co-workers have prepared a D-fructose selective system based on molecular imprinting.^[53,54] The system is the first boronic acid based fluorescent saccharide sensor and was prepared by reacting monomer **12** with D-fructose in a dioxane pyridine mixture. The templated unit was then used then in the preparation of a polymer using 2-hydroxy-

**12**

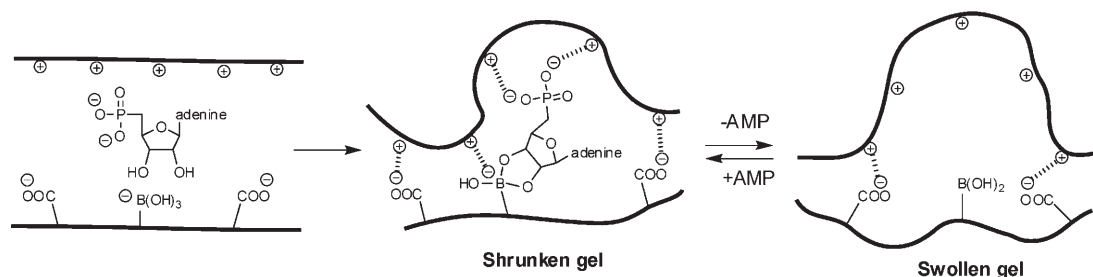
ethyl methacrylate as a comonomer and EGDM (ethylene-glycol dimethacrylate) as cross-linker.

Ishi-i has investigated homogeneous imprinting (0-D) where [60]fullerene was used as an imprinting base. Two moles of a boronic acid of 1,2-bis(bromomethyl)benzene formed a complex with one mole of sugar and the resultant 2:1 complex

was allowed to react with [60]fullerene in a homogeneous solution. The chiroselectivities attained in this method were very high (44–82% *ee*) for the C₂ symmetric fullerenes formed.^[55] The diboronic acid/[60]fullerene receptors thus obtained showed a good memory for the templated sugars (44–48% *de*).^[56] The results indicate that the molecular imprinting is possible even in the homogeneous solution, utilizing [60]fullerene containing numerous reactive C=C double bonds.

Kanekiyo explored linear polymer imprinting (1-D) where the formation of a 1:1 dimer between anionic polymers and cationic polymers was utilized. The polyanion fragment contains boronic acid units to complex with AMP (Scheme 6). On removal of AMP from the precipitated polyion complex, a “cleft”, which has the memory for the AMP template, is created.^[57] It was demonstrated that this cleft shows high affinity for AMP and the precipitate (gel) displays reversible swelling-shrinking in response to the binding of AMP. When this gel is deposited on a QCM resonator, it responds to small changes in the concentration of AMP.^[58]

Friggeri investigated imprinting at 2-D interfaces using a QCM resonator coated with Au.^[59] The conformational transitions of poly(L-lysine) are related to very subtle changes in secondary forces such as hydrogen-bonding interactions, electrostatic effects and hydrophobicity. Previously, it was discovered that the addition of monosaccharides to boronic-



Scheme 6. AMP-imprinted polyion complex.

acid-appended poly(L-lysine) affects the α -helix content of the polypeptide chain and the pH at which the maximum α -helix content is observed is specific to the added monosaccharide.^[60,61] To take advantage of such sugar-induced conformational changes, Friggeri synthesized a poly(L-lysine) derivative appending 70 mol% of the B(OH)₂ group and 30 mol% of the SH group. After induction of the conformational change by the sugar–boronic acid interaction, the polymeric complex was extended on Au. The sugar-induced conformation was then immobilized on the Au surface, which keeps a memory for the templated sugar. Evidence for the imprinting was obtained using an Au-coated QCM resonator.^[59] In particular, when D-glucose is used as a template sugar, the polypeptide backbone tends to adopt a unique β -turn structure. Therefore a D-glucose-selective QCM resonator was created by a simple imprinting method.^[59]

More recently, it has been shown that molecular imprinting can be achieved utilising the reprecipitation process of functionalized “soluble” polymers^[62–64] and the gel formation process of low molecular-weight gelators.^[65] These new trends suggest the generality of the molecular imprinting concept, that is the formation of 3-D cross-linked resins, is not the only way of employing molecular imprinting.

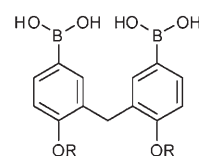
The Air–Water Interface

Molecular assemblies of monolayers and their properties have been well established.^[66] The unique characteristics of Langmuir and Langmuir–Blodgett (LB)^[67,68] films have drawn particular attention. The self-assembled Langmuir films developed at the air–water interface allow accurate placing of boronic acid receptors for saccharide recognition. The position of the receptors can be randomly dispersed or templated by guests in the subphase. Once formed, the Langmuir monolayers can then be transferred to a solid support using Langmuir–Blodgett (LB) techniques thus transferring the information from the monolayer to a surface. This attribute makes the monolayer environment one of the best for producing durable solid supported sensors.

The basic concept of the systems relies on the fact that the pressure of a Langmuir film is sensitive to the activity of its individual constituents. The boronic acids **13** and **14** were prepared by Shinkai in order to demonstrate the effect of saccharide binding at the air/water interface.^[34] The reactivity of the boronic acids was tested by solvent extraction

methods (solid–solvent, neutral solvent–solvent and basic solvent–solvent). Extractabilities of both compounds were found in the order D-fructose > D-glucose > D-maltose > D-saccharose. Monolayers formed by **13** were found to be unstable, based on both unreproducible pressure–area (*P–A*) isotherms and the crystalline nature of the monolayer. The *meta*-isomer, **14** featuring lower molecular symmetry, on the other hand, gave very reproducible results. The *P–A* isotherm of **14** was affected by the introduction of saccharide into the subphase at pH 10. The cholesterylboronic acid derivative **15** investigated by Ludwig behaved similarly.^[69] Arising from its chiral nature, **15** could selectively recognize enantiomers of fructose. The influence of quaternized amines on the saccharide binding has also been investigated by Ludwig.^[70] Quaternized amines added into the subphase facilitate the saccharide detection by the monolayer at neutral pH. Assistance of closely located ammonium cations in the formation of a boronate anion is believed to be the source of enhancement.

The cooperative binding of saccharides by the diboronic acid derivatives **16** on monolayers has also been investigated by Ludwig and found to be in agreement with its recogni-



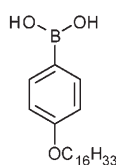
R = Me, 2-octyldodecyl, 4-*t*-butylbenzyl or Geranyl

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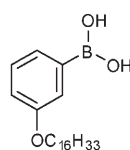
tion pattern in homogeneous solutions.^[71,72] Molecular recognition in this system has been studied by Dusemund and also seems to be facilitated by closely located ammonium cations.^[72]

Pietraszkiwicz has investigated the interaction of L-sorbose, D-glucose, D-galactose and D-cellobiose with Langmuir films of boron-containing cavitands derived from calix[4]resorcinarenes.^[73] Binding could be detected but they were unable to make any conclusions regarding the stereochemistry or stoichiometry of the complexes formed.

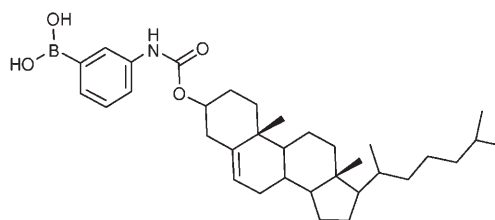
Recently Kurihara prepared electroconductive LB films for sugar recognition. A polymerized electroconductive boronic acid LB film was transferred onto a gold surface. The binding with an electroactive manoside (nitrobenzene) was monitored by cyclic voltammetry.^[74]



13



14

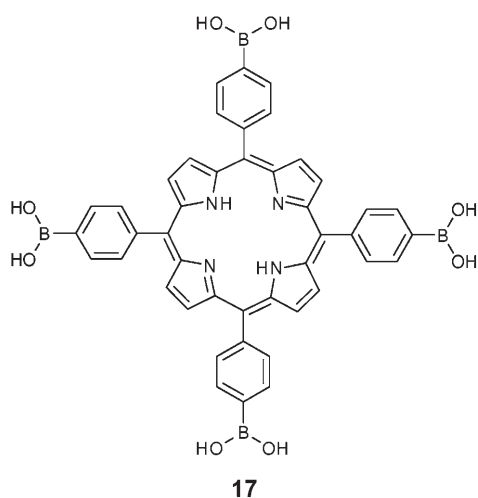


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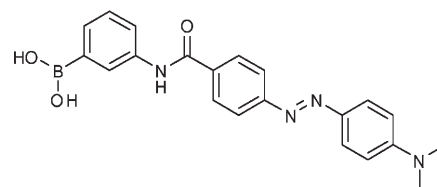
Heterogenous and Polymeric Systems

The saccharide–boronic acid interaction can be used to develop molecular assemblies. This can be achieved in two ways. Firstly, one can sense saccharides using changes in the physical properties of the molecular assembly and secondly, one can control the superstructure of molecular assembly using saccharides as a trigger.

Some chiral molecules are known to form chiral helical aggregates.^[75] Likewise, chirality can be induced in aggregates of nonchiral molecules by interactions with chiral species.^[76,77] Imada found that helical chiral aggregates are formed when aggregates of a nonchiral tetraboronic acid porphyrin **17** are treated with monosaccharides.^[78] Induced chir-



ality of the aggregate can be monitored by CD spectroscopy. Furthermore, the sign of the exciton coupling of the sugar complexed aggregate can be predicted by the structural orientation of the complex. The chromophoric boronic acid derivative **18** was also found to aggregate in mixed solvents (water/dimethyl formamide) and became CD active when saccharides were added.^[79,80] The use of CD to determine the configuration and conformation of saccharides has been

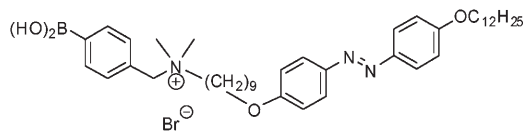
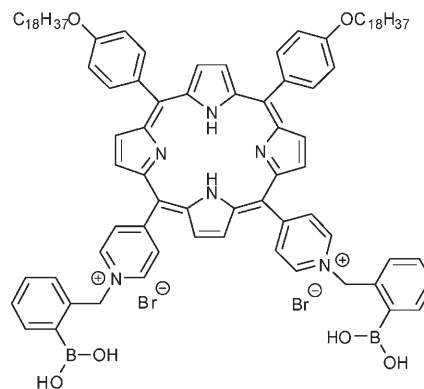
**18**

well established by Harada and Nakanishi who employed the perbenzoylation of the saccharide methyl glycoside.^[81]

Organogels and hydrogels are formed mainly by 1-D aggregation of amphiphilic molecules. Thus, a variety of superstructures are constructed in the gel system, reflecting the molecular shape of unit gelator molecules. When boronic acid-appended amphiphiles are dispersed into solution, the superstructure of the resultant aggregates is strongly affected by added sugars.^[82–84] For example, the sol-gel phase-transition temperature is changed by the addition of sugars and in some cases, the chirally twisted fibrils appear in the gel phase from achiral amphiphiles. When boronic acid-appended cholesterol is used as a gelator, the gel can discriminate between D- and L-saccharides through a difference in the sol-gel phase-transition temperature.^[77]

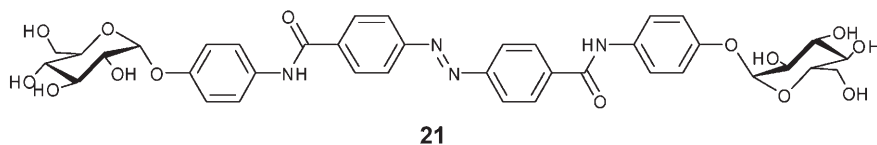
Kimura has applied the concept to the structure control of ordered molecular assemblies formed in an aqueous system. Compound **19** bearing a boronic acid group and a chromophoric azobenzene group forms a micelle-like, orderless aggregate in aqueous solution. When saccharides are added, a stable membrane is formed.^[85] The CD spectrum arising from the azobenzene chromophore suggests that this membrane changes in response to the absolute configuration of added sugars. Arimori developed a similar system using the porphyrin-containing amphiphile **20**.^[86,87] In this system, the arrangement of the porphyrin moiety in the molecular assemblies can be finely tuned by added saccharides.

James demonstrated that this idea is effective in a liquid crystal system. It is known that in some cholesteric liquid crystals, the change in the helical pitch is reflected by the color change. It was found that cholesterylboronic acid **15** complexes of monosaccharides alter the color of a compo-

**19****20**

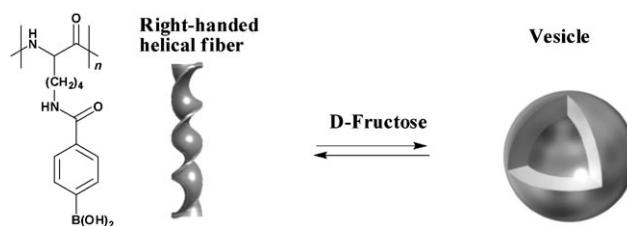
site chiral cholesteric liquid crystal membrane.^[88] Interestingly, the direction and the magnitude of the color change is indicative of the absolute configuration of the monosaccharide. This finding makes it possible to predict the absolute configuration of the monosaccharide by a simple “color change”.

Kobayashi found that sugar-based amphiphiles can enjoy a fiber-vesicle structural interconversion in the presence of boronic acid-appended poly(L-lysine).^[89,90] The research objectives of these papers were to design bolaamphiphilic gelators utilizing a sugar family as a source of solvophilic groups and an azobenzene segment as a solvophobic group, and to monitor the aggregation mode utilizing the spectroscopic properties of the azobenzene chromophore. The results indicated that the bolaamphiphiles act, although only for specific DMSO–water mixtures, as gelators and form a unique supramolecular helical structure in the gel phase. The UV/Vis and CD spectra showed that the azobenzene segments adopt H-type face-to-face orientation and the dipole moments are arranged in the right-handed helicity. Since the fibrils, as observed by electron microscope, possess the right-handed helical structure, one may consider that the microscopic azobenzene–azobenzene orientation is reflected by the macroscopic supramolecular structure. When boronic acid-appended poly(L-lysine) was added, the gel phase of gelator **21** was changed into the sol phase in the macroscopic



level and the fibrous aggregate was changed into the vesicular aggregate in the microscopic level. These changes, which are usually induced by a temperature change, arise from the specific boronic acid–saccharide interaction occurring at constant temperature. Interestingly, when D-fructose

which shows high affinity with the boronic acid group was added, the sol phase and the vesicular aggregate were changed back to the gel phase and the fibrous aggregate, respectively, as shown in Scheme 7.



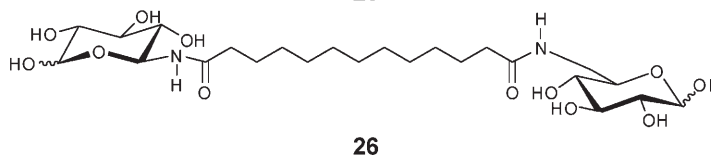
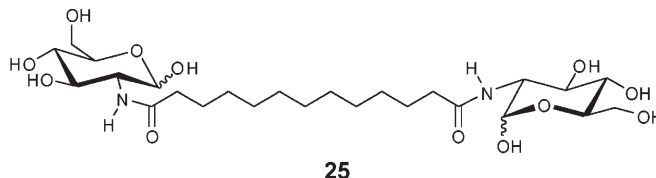
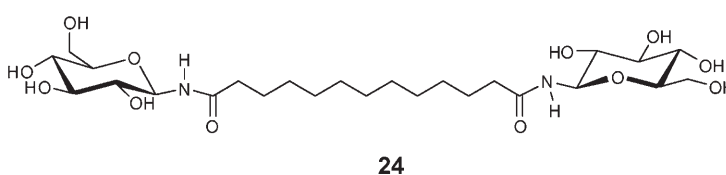
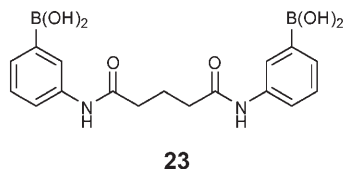
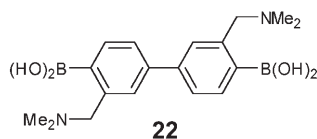
Scheme 7. Fiber-vesicle interconversion.

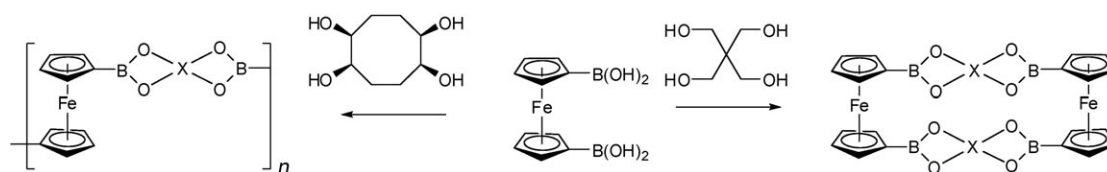
This means that the phase and morphological changes in the sugar-integrated bolaamphiphiles can be controlled reversibly.

Covalently derived polymeric materials can also be prepared using boronic acids. Mikami^[91] employed boronic acid **22** in the preparation of self-assembled sugar backbone polymers using D-fructose, L-fructose and D-glucose as the sugar units. The polymers formed were helical in nature with D- and L-fructose displaying mirrored CD spectra. The polymers formed had a molecular weight of 106kDa (L-fructose) and 40.0kDa (D-glucose).

Shimizu^[92] has also used boronic acid **23** in conjunction with glucuronamide bolaamphiphiles **24–26** to prepare self-assembled sugar backbone polymers.

The condensation of 1,1'-ferrocenediboronic acid with two different tetraols has been shown by Aldridge to result in two different self-assembled structures (Scheme 8). When 1,1'-ferrocenediboronic acid is reacted with pentaerythritol, a macrocycle is formed. However, if (1*R*,2*S*,5*R*,6*S*)-tetrahy-





Scheme 8. When pentaerythritol is condensed with 1,1'-ferrocenediboronic acid, a macrocycle is formed, but when (1*R*,2*S*,5*R*,6*S*)-tetrahydroxycyclooctane is used, a polymeric material is produced.

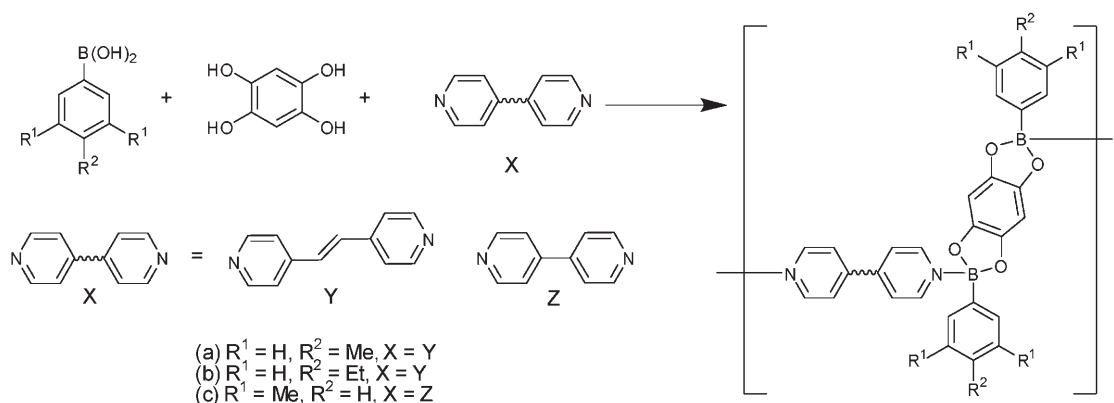
droxycyclooctane is used, a self-assembled polymer is obtained.^[93]

Severin^[94] has developed a novel three component self-assembled polymeric system using monoarylboronic acids, 1,2,4,5-tetrahydroxybenzene and 1,2-bis(4-pyridyl)ethylene or 4,4'-bipyridine. The system is interesting in that the polymeric backbone is held together by N–B bonds (Scheme 9). The resulting crystalline polymers are deeply colored arising from intrastrand charge-transfer transitions. However, because of the weak N–B interaction, the polymers are not stable in solution. It was noted that the reversible formation of the polymer backbone could, in itself, be interesting from a polymer processing point of view.

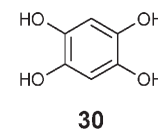
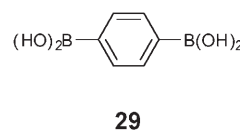
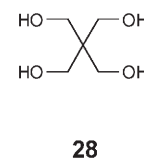
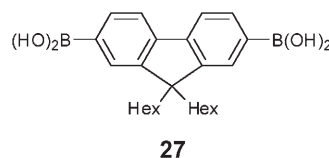
The reversible nature of boronate esterification has been exploited by Lavigne who used this property to create self-healing polymers.^[95] A polymer created between **27** and **28** can be formed under anhydrous conditions but when water is added, the monomers are reformed. If solvent is then removed from the monomers, a linear polymer is reformed. Using the same boronic acid **27** with 1,2,4,5-tetrahydroxybenzene **30** results in a conjugated polymer that exhibits blue emission.^[96] The emission wavelength of the polymer is significantly longer than the monomers or the emission wavelength of the nonconjugated polymer between **27** and **28**. Lavigne has also prepared polymers composed of **29** and **30**.^[97]

Wang has prepared a N–B dimer of 8-quinoline boronic acid and observed the hydrogen bond directed supramolecular assembly of the dimeric species in the solid state.^[98]

Several other interesting supramolecular systems based on the hydrogen bonding properties of boronic acid units^[99] have also been evaluated in the solid state.^[100–102]



Scheme 9. Three component self-assembled polymer with N–B backbone.



Organic Frameworks

The development of porous covalent organic frameworks (COFs) is an important area in which the boronic acid–diol interaction is beginning to play an important role. The potential applications of porous covalent organic materials include gas storage,^[103–107] catalysis,^[108] and separation.^[109] Recently, Yaghi has used both the formation of boronic acid, trimeric anhydrides, and diol esterification to generate a number of open organic frameworks.^[110–112]

The frameworks developed by Yaghi can be broken down into two main classes, being either planar layered or three dimensional honeycombed. The planar layered structures are derived from the trimeric anhydride formed when phenylboronic acid is dehydrated or a cyclic ester between phenyl boronic acid and hexahydroxy triphenylene **36**. These two units, the cyclic anhydride or hexahydroxy triphenylene **36**, are represented as trianglular building blocks, as shown in Figure 2a. The planar layered COFs were prepared

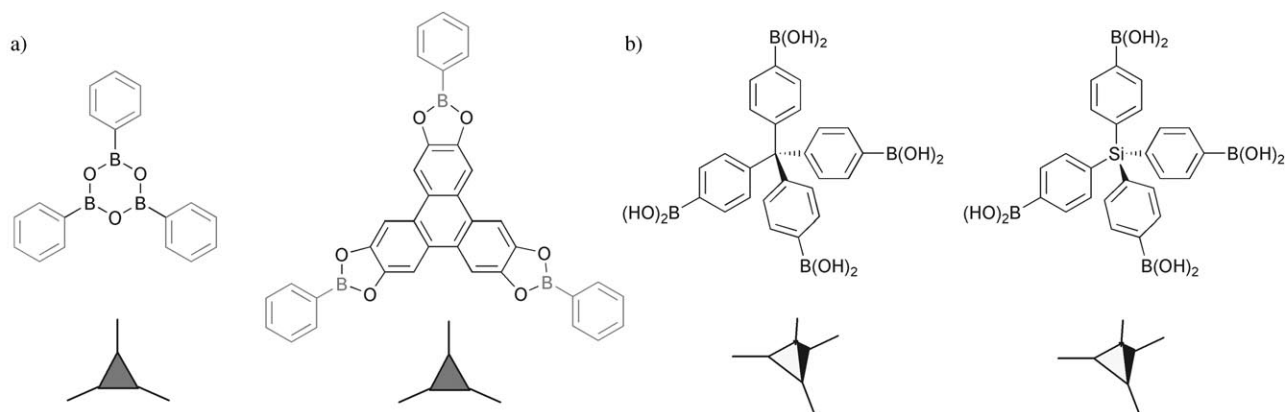


Figure 2. a) Triangular and b) tetrahedral building blocks employed by Yaghi in the preparation of COFs.

by heating boronic acid **29** either by itself or with hexahydroxy triphenylene **36** at 120 °C for 72 h under a mesitylene–dioxane solution in a sealed pyrex tube (Figure 3 a). The sparing solubility of the boronic acid in the solvent mix-

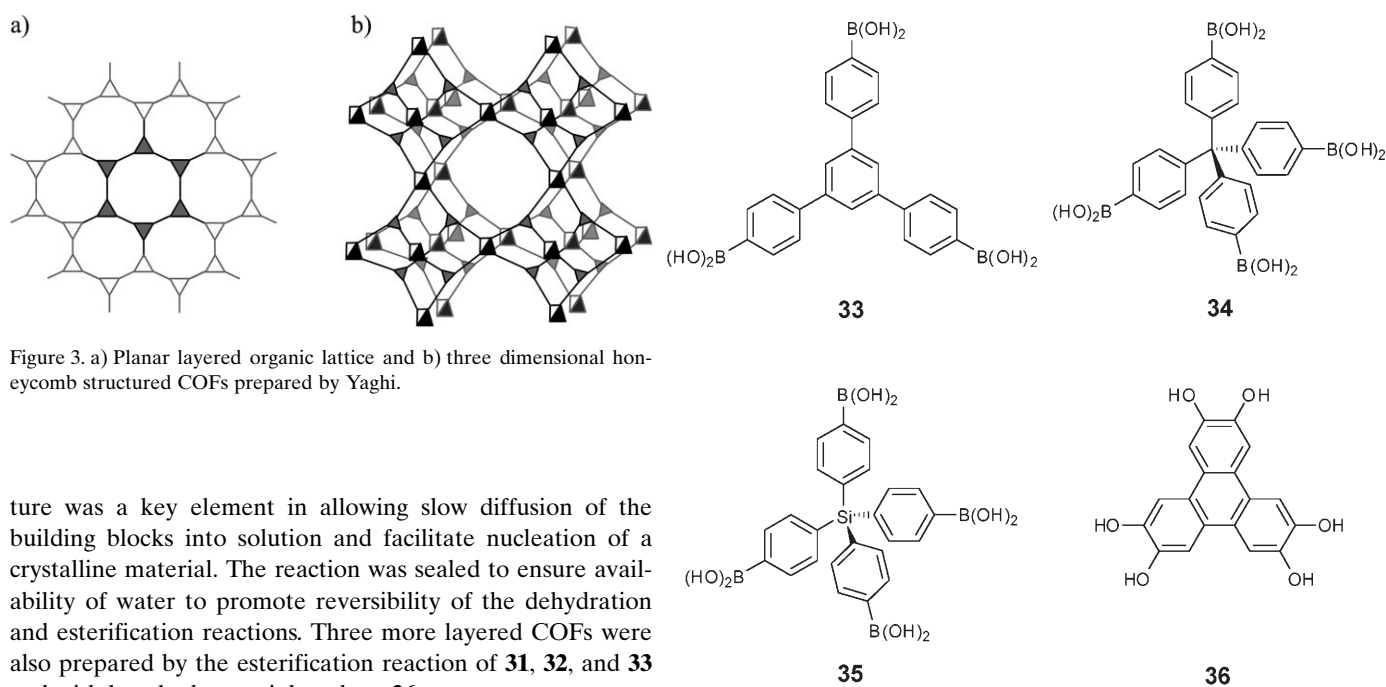


Figure 3. a) Planar layered organic lattice and b) three dimensional honeycomb structured COFs prepared by Yaghi.

ture was a key element in allowing slow diffusion of the building blocks into solution and facilitate nucleation of a crystalline material. The reaction was sealed to ensure availability of water to promote reversibility of the dehydration and esterification reactions. Three more layered COFs were also prepared by the esterification reaction of **31**, **32**, and **33** and with hexahydroxy triphenylene **36**.

The honeycombed structures are derived from boronic acids, such as **34** and **35**, and represented as tetrahedral building blocks (Figure 2b). In order to prepare honeycombed structures these tetrahedral boronic acids were dehydrated to form a cyclic anhydride or esterified using hexahydroxy triphenylene **36** to generate four honeycombed COFs (Figure 3b).

Lavigne has also employed a similar approach to prepare an open organic framework using **30** with trisboronic acid **32**.^[113]

Macrocycles and Cages

The boronic acid interaction with diols has also been used in the construction of discrete macrocycles and cages. The reversible nature of the boronic acid–diol interaction makes the interaction suitable in the self-assembly of multicomponent systems. With reversible systems, any errors in the assembly process can be removed since for a system in equi-

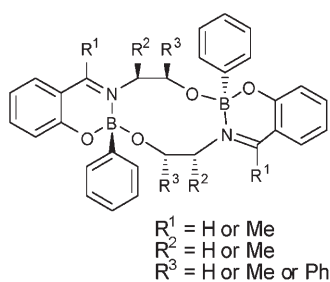
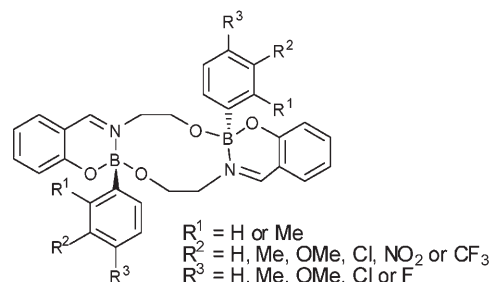
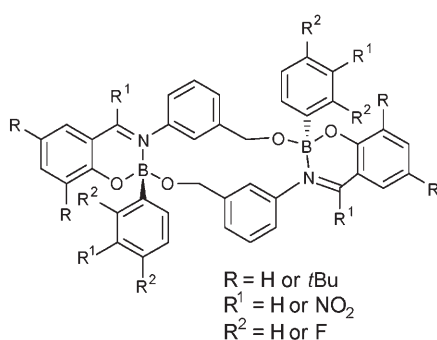
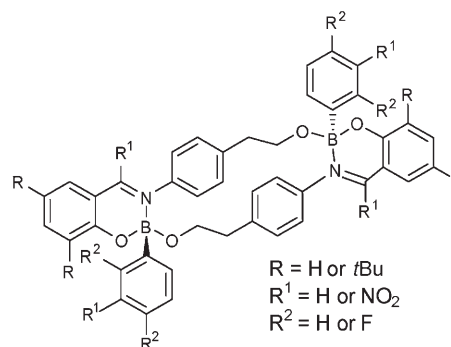
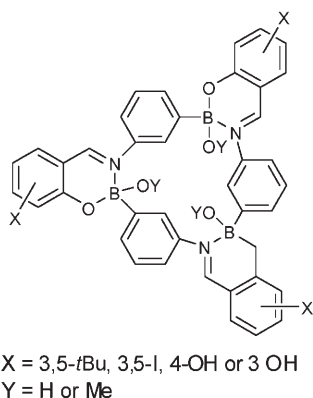
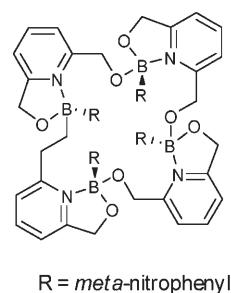
librium the final state is always the one with the lowest energy.

Pioneers in the development of boronic acid macrocycles are Hopfl, Farfan, and Barba. In particular, they have employed a combination of facile imine (Schiff Base) formation and boronic acid esterification in the development of multicomponent macrocycles. **37–42**.^[114–121]

Iwasawa has developed a novel templated dynamic self-assembly system employing a racemic tetraol **43** and 1,4-benzenediboronic acid **44**.^[122] When the two components are mixed in methanol a linear polymer is formed. However, when toluene is added to the solution, dynamic self-assembly occurs with formation of a 2:2 macrocycle (a crystal

structure of the complex was obtained). When the guest was switched to benzene, instead of the formation of a 2:2 macrocycle, a new 3:3 macrocycle was formed (Figure 4).

Severin has also prepared macrocycles using both formation of cyclic boronate esters and intermolecular N–B interactions.^[123] The 4:4 self-assembly of phenylboronic acids with 2,3-dihydroxy pyridine **47** was evidenced by X-ray crystallography. Severin has employed an analogous strategy for the preparation of dendritic nanostructures.^[124] More recently, the same group has prepared macrocycles and cages using three and four component systems. The three component systems employ a *meta* formylboronic acid, a *bis* primary amine, and pentaerythritol (tetraol) **48** or *para* formyl-

**37****38****39****40****41****42**

FOCUS REVIEWS

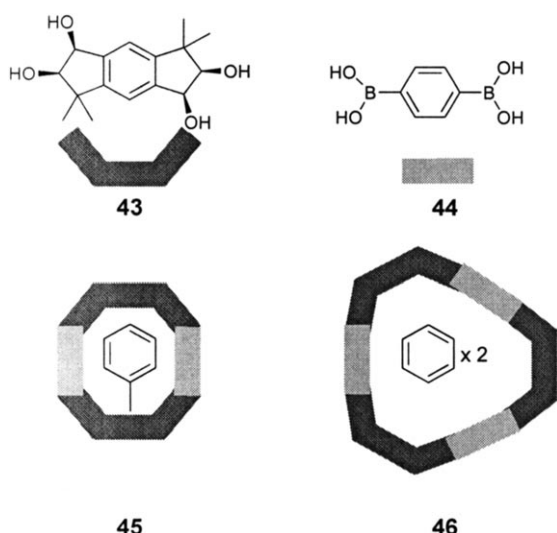


Figure 4. Self-assembled structures **45** and **46** formed from **43** and **44** in methanol with added toluene or benzene.

boronic acid, a *tris* primary amine, and pentaerythritol (tetraol) **49**. These three component systems are reminiscent of the three component assembly of *ortho* formylboronic with chiral amines and chiral diols used by Bull and James for the determination of the enantiomeric excess of chiral amines^[125,126] or chiral diols.^[127,128] The Severin group have recently extended their work to include four component systems. The system comprises of a *meta* formylboronic acid unit, primary amine, pentaerythritol (tetraol) and pyridine nitrogen for coordination to a metal **50**.^[129]

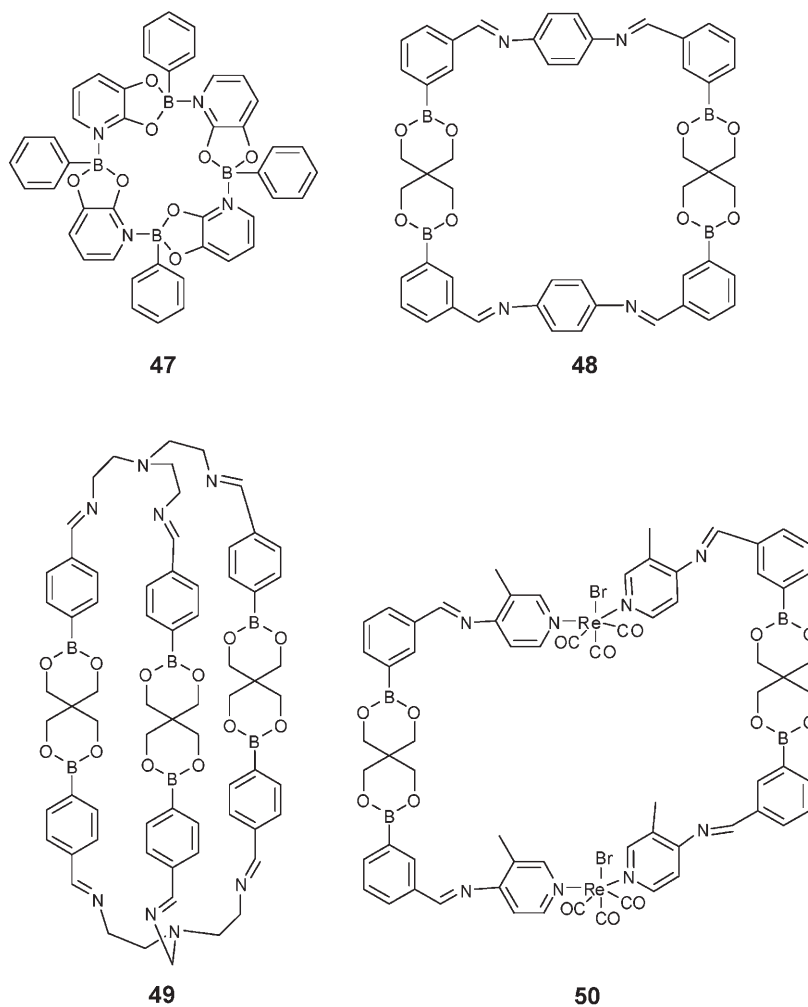
Barba^[130] has prepared two hemicarcerands by the N–B bond directed self-assembly of 3-aminophenylboronic acid with *bis-ortho-phenol* aldehyde and *bis-ortho-phenol* methylketone (Scheme 10). Nabeshima has prepared self-assembled cyclic boron–dipyrrin oligomers prepared by the reaction of catecholdipyrrin with boron trichloride.^[132]

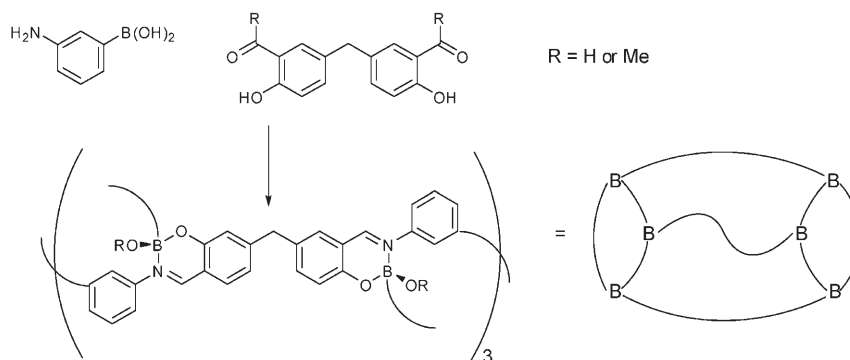
Kubo^[131] has designed an ion pair-driven heterodimeric capsule. The system consists of cyclotriatechylene and a boronic acid-appended hexahomotrioxalix[3]arene

(Scheme 11). The two components do not interact with each other until Et_4NAcO is added to the solution. On addition of Et_4NAcO , quantitative formation of the capsule by boronate esterification is observed. The self-assembly process is a direct result of anion directed boronate ester formation and the Et_4N^+ template. Reversible boronate esterification also allowed for selective control of capsule formation as a function of pH.

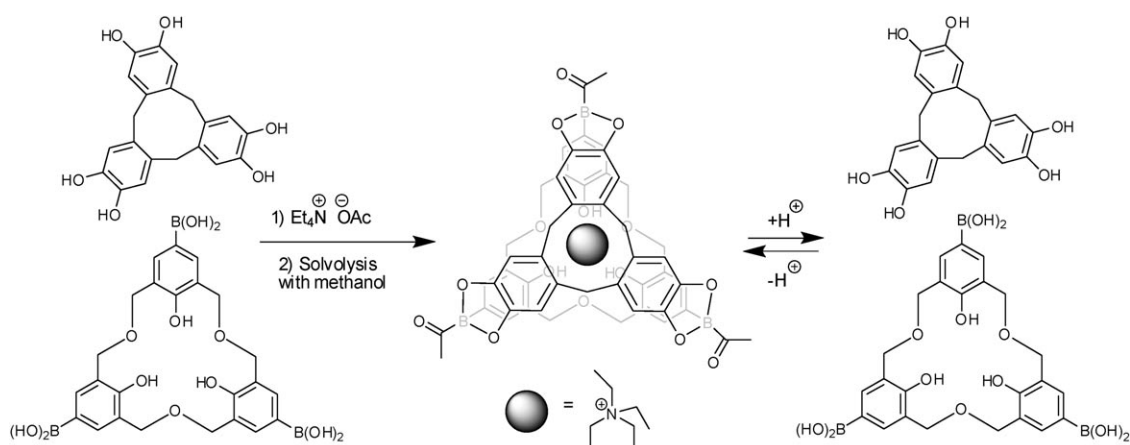
Conclusions and Future Prospects

In conclusion, over the past few years, the boronic acid–diol interaction has found its way into numerous self-assembly systems. In particular there has been growing interest in the development of porous molecular frameworks and molecular capsules and cages derived from the facile boronic acid–diol interaction. The frameworks will lead to the development of new materials with applications in gas storage, catalysis, and separation, while the capsules will be employed in receptor and sensor development, extraction, or for drug delivery.





Scheme 10. N–B bond driven hemicarcerand formation.



Scheme 11. Anion driven capsule formation.

Many of these systems take advantage of the fact that:

- The boronic acid–diol interaction is reversible.
- The boronic acid–diol interaction is directional.
- The boronic acid–diol interaction can take advantage of a cheap and diverse chiral pool of diols.

Future developments will include the development of materials and capsules with the ability to self-repair and assemble or disassemble when required, whether it be to deliver a drug or to encapsulate toxic waste—“The age of boronic acid based organic materials has arrived.”

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