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Boron-Carbohydrate Interactions

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1. Introduction

Boron-polyol interactions are of fundamental importance to human health [1], plant growth [2] and quorum sensing among certain bacteria [3]. Such diversity is perhaps not surprising when one considers boron is one of the ten most abundant elements in sea water and carbohydrates make up the planet's most abundant class of biomass. Several boronic acids matrices are commercially available for the purification of glycoproteins by affinity chromatography [4], and boronic acids are also useful carbohydrate protecting groups.[5,6] Recently, complexes between boron and sugars have become a lynchpin for the development of synthetic carbohydrate receptors.[7] These complexes involve covalent interactions that are reversible in aqueous solution. This chapter reviews current understanding of these processes, provides a historical perspective on their discovery, identifies methods for studying these complexes and classifies these interactions by carbohydrate type. Such information is key to the design and synthesis of synthetic lectins, also termed "boronlectins" when containing boron [7].

The very nature of the reversible binding between boron acids and alcohols has been exploited in many different ways. The use of boronic acid carbohydrate recognition molecules could provide an avenue for the selective detection of specific sugars for future use in early diagnostics. By targeting cell-surface sugars, a boron-based probe could recognize particular characteristic epitopes for the identification of diseases leading to earlier treatments. In this chapter we not only review some of the fundamental aspects of boron-carbohydrate interactions but also discuss how this translates into the design of synthetic carbohydrate receptors.

2. Boron-carbohydrate interactions

2.1. Discovery of boron-sugar interactions

The first hint of the marriage between boron and polyols was detected by Biot in his seminal studies on optical rotation. In 1832 he noted that the rotation of tartaric acid

changed in the presence of boric acid.[8] It would be a century later before interaction of boron acids (boric, boronic and borinic) and monosaccharides was studied in detail. In 1913, Böeseken first noted that glucose increased the acidity of boric acid solutions.[9] It was nearly another half century before Lorand and Edwards published work quantifying the affinity of boric and phenylboronic acids for simple diols (e.g.-ethylene glycol, catechol) and common monosaccharides (i.e.-glucose, fructose, mannose, galactose).[10] The covalent product between a boronic acid and a diol is termed a boronate ester, analogous to a carboxylate ester. These interactions are favoured at basic pH ranges where the tetrahedral boronate ester is formed (Figure 1). The interchange between boron acids and divalent ligands in aqueous solution can be complex and varied depending on pH.

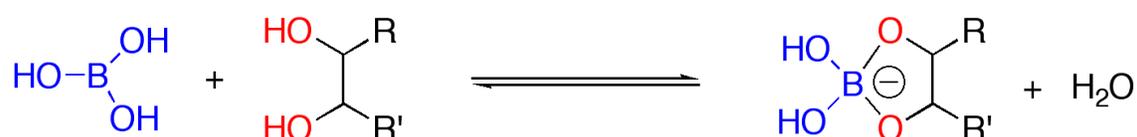


Figure 1. Boric acid interactions with vicinal diol of sugar.

2.2. Fundamentals of boron-diol exchange

There are two general organoboron families of boric acid descent that can form esters with diols through loss of water. These are boronic acids--where one hydroxy group of the parent boric acid is substituted by carbon--and borinic acids, where two hydroxy groups are substituted by carbon-based substituents.

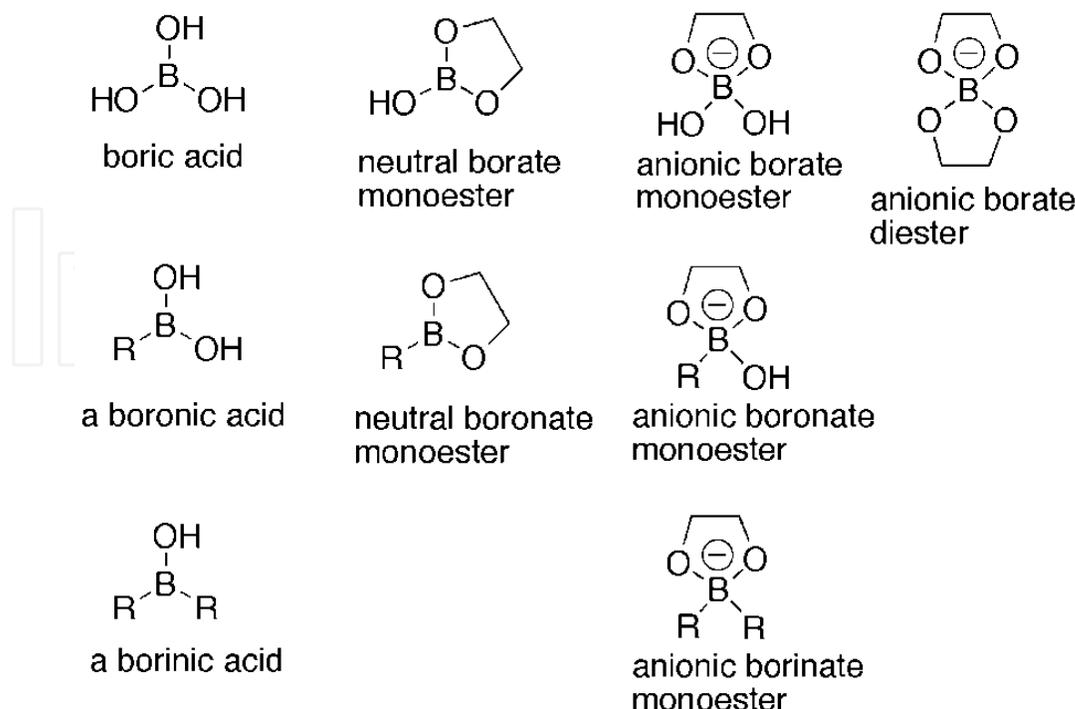


Figure 2. Boron acids and possible esters with ethylene glycol.

Boric and boronic acids can form either neutral or anionic esters depending on the pH. Diol binding by boron acids is favoured at basic pH, while esterification of boron by hydroxycarboxylic acids is favoured in acidic pH ranges. Boronic acids can only form anionic borinate esters upon dehydrative condensation with a diol or divalent ligand. Boric acid can also form an anionic, tetrahedral diester with diols and related divalent ligands (Figure 2). While boronates can form neutral esters in non-polar solvents, they tend to form anionic boronate esters in water (Figure 3). Boronate ester formation is not favoured near physiologic pH and is completely cleaved under strongly acidic conditions.

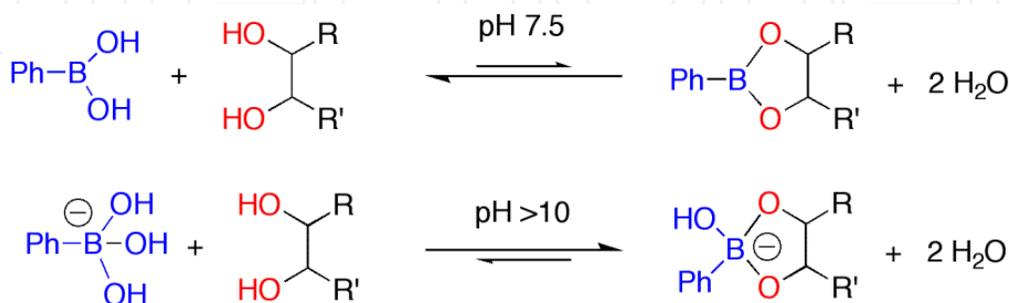


Figure 3. Diol exchange with phenylboronic acid at varied pH.

This is because the neutral boronate ester is generally more Lewis acidic than the parent boronic acid—i.e. $pK_a(\text{acid}) > pK_a(\text{ester})$, (Scheme 1).[11] Thus, boronate ester formation is favoured at higher pH where elevated hydroxide concentrations ensure the boronate ester is “trapped” in its more stable tetrahedral form. However, depending on the specific monosaccharide, its boronate esters are not always more Lewis acidic than the free boronic acid.[12] Rate constants for esterification of simple boronates by diols fall in the range of 10^2 – $10^3 \text{ M}^{-1}\text{s}^{-1}$. [13] Ishihara uncovered evidence it is the trigonal boronic acid that exchanges most rapidly with diols irregardless of pH.[14] The relative affinity of boronates for diols in most carbohydrates is of the order: *cis*-1,2-diol $>$ 1,3-diol \gg *trans*-1,2-diol. Thus, certain monosaccharides have an intrinsically higher affinity for boron acids.

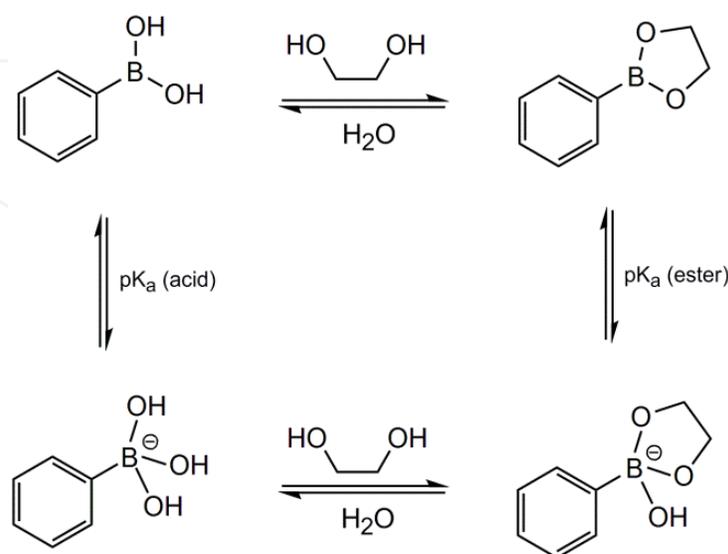


Figure 4. Multiple equilibria involved in diol exchange with phenylboronic acid.

2.3. Detection and elucidation of boron-sugar complexes

Methods for identifying boron-polyol interactions include the following, listed in roughly chronological order of the introduction of their use in this area:

- a. Optical rotation/ORD: 1832 [8,15,16]
- b. pH change/titration: 1913 [9]
- c. Conductivity: 1928
- d. Temperature jump: 1969 [17]
- e. X-ray crystallography: 1973 [18,19]
- f. ^{11}B -NMR: 1973 [19-22]
- g. Fluorescence/CD: 1990's [23-25]
- h. ESI/MALDI Mass Spectrometry: 1990's [26-28]

The second half of the list defines techniques that are most frequently used today in the study of boron-carbohydrate interactions. Obviously, X-ray crystallography provides the least ambiguous information about the structure of the boronate ester of interest. However, these boronate-sugar adducts are often amphiphilic in nature and do not lend themselves to the production of suitable crystals. The relatively slow exchange between boron acids and diols on the NMR time scale often makes it difficult to study by proton NMR. However, ^{11}B -NMR can be quite useful due to the dramatic shift of the boron resonance when it is converted from its neutral, trigonal form as a boronic acid to its anionic, tetrahedral form as a boronate ester. [20-22]

Optical methods such as fluorescence and circular dichroism (CD) are powerful tools for detecting boron-carbohydrate binding interactions. Yoon and Czarnik reported the first fluorescent boronate designed to detect binding to monosaccharides.[23] James, Shinkai and co-workers reported the first fluorescent boronates to function by photoinduced electron transfer (PET) to generate an increased fluorescence output upon carbohydrate binding.[24] This type of "turn-on" system tends to be most useful in a biological setting where background fluorescence quenching can be a problem for fluorophores that respond by fluorescence quenching ("turn-off") to ligand binding. A more complete understanding of the aminoboronate PET fluorescence mechanism has been developed by the groups of Wang [29] and Anslyn [30]. They have demonstrated that solvent insertion disrupting any dative boron-nitrogen interaction is responsible for the increased fluorescence output upon ligand binding. The Shinkai group has also designed a number of CD-active boronate receptors for oligosaccharides and have used this method to detect binding of target substrates.[25]

Advances in mass spectrometry (MS) over the past few decades, particularly electrospray ionization (ESI) and matrix-assisted laser desorption/ionization (MALDI), have revolutionized the application of this instrumental method to the study of host-guest and protein-ligand interactions. Certainly, the field of boron-based carbohydrate receptors has also benefited from the substantial improvement and refinement of these and other MS techniques. However, the tendency of boronates to dehydrate and/or oligomerize to

varying degrees depending on their solvation can complicate MS analysis of boronate-carbohydrate esters. We have found that use of a glycerol matrix for fast atom bombardment (FAB) ionization is particularly useful for mass spectrometric characterization of diboronate species.[31] While other techniques are used in the study of boron-polyol complexes, those mentioned here are among the most common routinely used in the field today.

3. Boron-based carbohydrate receptors

3.1. Boron-based monosaccharide receptors

The 1992 work of Yoon and Czarnik first demonstrated the potential of boronic acids as fluorescent carbohydrate receptors for sensing applications.[23] In the past 20 years, a great deal of research has focused on the development of boron-based glucose receptors for incorporation as sensors in blood sugar monitors for diabetics.[7, 32] This has led to the commercial development of contact lenses that can signal when circulating glucose levels drop by changing the colour of the lense to alert the wearer.[33] The affinity of mono-boronates for glucose is low at physiologic pH, but bis-boronates offer a substantial improvement in binding affinity. A landmark study from the Shinkai group involved development of a chiral glucose sensor capable of discriminating between enantiomers of glucose.[34] This utilized aminoboronates as PET sensors around a chiral binaphthol core (Figure 5). The Singaram group has developed bis-boronate bipyridinium salts (viologens) that can be tuned for selective binding of glucose (Figure 6).[35] These compounds coupled with anionic dyes are also in commercial development as blood glucose sensors.

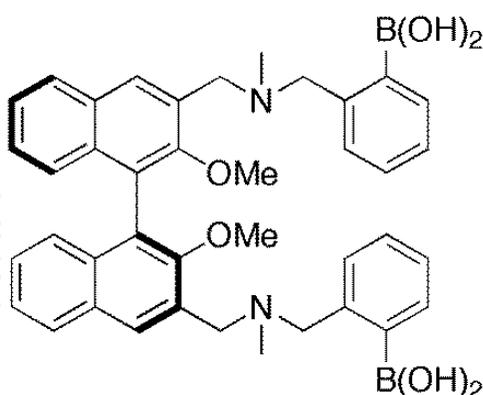


Figure 5. Shinkai's chiral binaphthol glucose sensor.

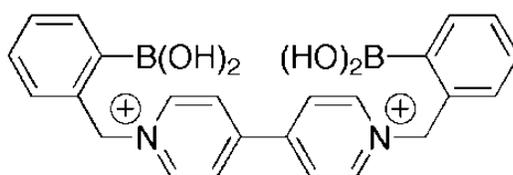


Figure 6. One isomer of Singaram's family of glucose sensors.

It was initially presumed that two boronates could bind to the C-1/C-2 diol and the C-4/C-6 diol of glucose in its hexopyranoside form.[5] However, it has been shown that boronic acids have a much higher affinity for the furanoside form of free hexoses.[36] In fact, boronates have virtually no affinity for methyl glycosides locked in their pyranoside form at physiologic pH. This means that boronates would not be useful components in synthetic carbohydrate receptors for many cell surface carbohydrates. Mammalian cell-surface glycoconjugates, in particular, are dominated by hexopyranoside structures. The Hall group has provided an important solution to this problem when they showed that benzoboroxoles can bind methyl hexopyranosides in water at pH 7.5.[37] For glucopyranosides, the only significant binding site is the C-4/C-6 diol as all vicinal diols in this system are of a *trans* relationship. In galactopyranosides, there is an additional possible binding site: the C-3/C-4 *cis*-diol (Figure 7):

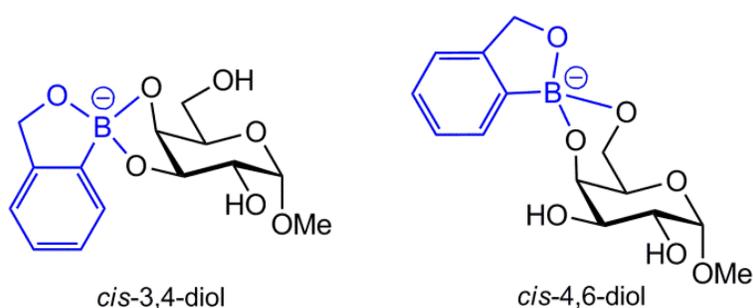


Figure 7. Potential binding modes between benzoboroxole (blue) and methyl-galactoside.

While a significant amount of research has been dedicated to the study of boronate-monosaccharide interactions, very little has been invested in borinate-monosaccharide exchange. Taylor has recently reported that borinic acids have substantial affinity for catechols and α -hydroxycarboxylates,[38] greater than that of 2-fluoro-5-nitrophenylboronic acid,[39] a boronate that is able to bind sugars at neutral pH. The affinity of this boronate for monosaccharides is greater than the affinity of a borinic acid for the same sugars, but this affinity in the latter case is still significant. Whether borinates can effectively bind to hexopyranosides under the same conditions still needs to be defined.

3.2. Boron-based sugar acid receptors

Boron-tartaric acid interactions were studied throughout the 20th century beginning with a report in 1911 on the ability of tartrate to increase the solubility of boric acid.[40] The design of sophisticated boron based receptors for tartrate did not arise until near the end of the century when Anslyn reported the first in 1999.[41] This receptor (Figure 8) also binds citrate with what is perhaps the highest association constant reported for a small molecule with a boron-based receptor ($K_a = 2 \times 10^5$).[42] In 2002, we showed that Shinkai's binaphthol glucose receptor (Figure 5) has a high affinity for tartrate as well.[43] Bis-boronates such as this can bind simultaneously to both α -hydroxycarboxylates. James further showed that chiral discrimination between tartrate enantiomers can also be obtained with this receptor as was the case with monosaccharide enantiomers.[44] While the history of study surrounding

boron-tartaric acid interactions is long and varied, study of the interaction of boron with sugar acid monosaccharides such as sialic acid and glucuronic acid has arisen much more recently. Fundamental to the understanding of these complexes is the fact that, unlike esterification with diols, boronate esterification by α -hydroxycarboxylic acids is favoured below pH 7.[44] We have recently provided a short review on the subject of boron: α -hydroxycarboxylate interactions used in sensing and catalysis.[45]

Shinkai first reported a boron-based sugar acid receptor containing a metal chelate that has significant affinity for glucuronic acid ($\log K_a = 3.4$) and galacturonic acid ($\log K_a = 3.1$) while the affinity for sialic acid was an order of magnitude lower ($\log K_a = 2.3$).[46] Presumably the carboxylate of the sugar acid can coordinate to the chelated zinc while the boron binds to a vicinal diol on the monosaccharide. Smith and Taylor used a combination of electrostatic interaction and a boronate anchor within a polymeric system to bind to sialic acid selectively.[47] In 2004, Strongin identified a boronate that offered a colorimetric response to the presence of sialic acid.[48]

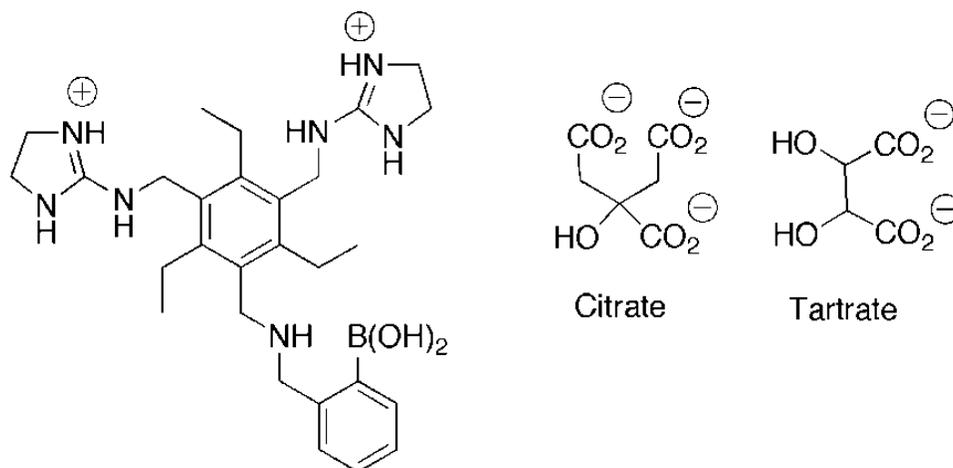


Figure 8. Anslyn's guanidino-boronate receptor and high affinity ligands.

We have recently communicated the development of a bis-boronate that can bind to sialic acid at both its α -hydroxycarboxylate-type group at the anomeric centre and its glycerol tail (Figure 9).[49] Elevated levels of free sialic acid in the blood can be indicative of the presence of certain cancers. This system uses a unique combination of boronates whose esterification has an opposing affect on the overall fluorescence output of the receptor. This diminishes signals from competing ligands such as glucose that are present at much higher concentration in the blood but cannot span both binding site to strongly quench fluorescence.

As discussed in the following sections, several groups have taken advantage of the affinity of boronates for the glycerol tail of sialic acid to target glycoconjugates on cell surfaces. Several of these synthetic compounds display lectin-like biological characteristics that offer promise of the future development of bioactive boron-based molecules.

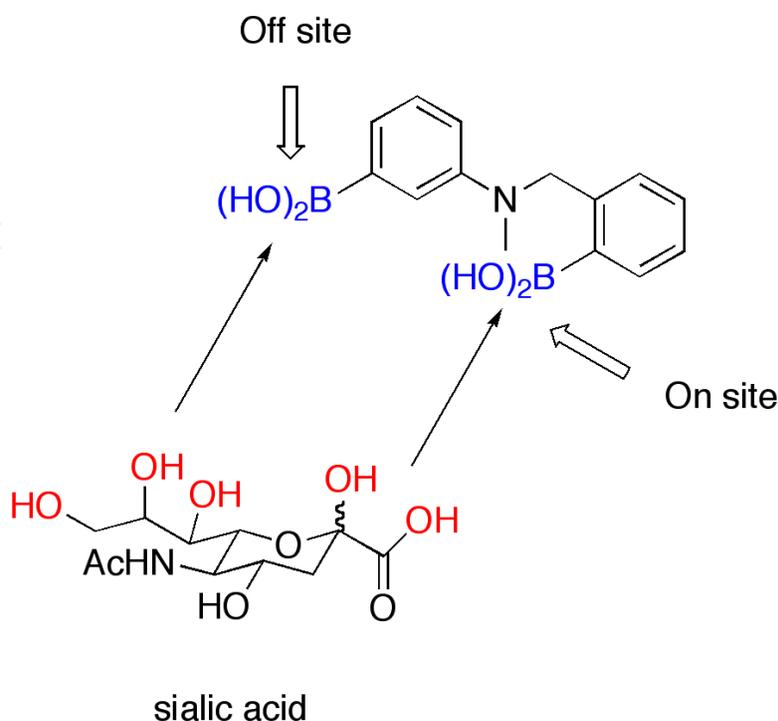


Figure 9. Our divergent response fluorescent receptor for sialic acid.

3.3. Boron-based oligosaccharide receptors

Creating receptors for oligosaccharides offers additional levels of complexity relative to monosaccharides. An obvious difference is the increased degrees of freedom available to oligosaccharides, particularly those that contain 1,6-linkages. In 2000, Shinkai reported development of a meso-meso-linked porphyrin scaffold where distance between two boronates was tuned to selectively bind to a tetrasaccharide of maltose (maltotetraose) over other oligomers containing from two to seven glucose units (Figure 10).[50] Binding of the two boronates must take place at both the reducing and non-reducing termini of the oligosaccharide. This is due to the fact that the C-1/C-2 diol at the reducing end and the C-4/C-6 at the non-reducing end are the only potential binding sites with an appreciable affinity for boronates. The ability to bind the tetramer selectively stems from the rigidly defined distance between the two boronates, i.e.-the tetrasaccharide offers the optimal fit to bridge these two boronates. The Shinkai group has also reported a similar strategy to bind to the important cell-surface trisaccharide, Lewis X.[51] In this case interaction is not with a reducing sugar but presumably with diols on both the galactose and fucose residues.

Heparin is a natural polysaccharide used clinically for its anti-coagulant properties. In 2002, Anslyn communicated a colorimetric sensing ensemble for detection of heparin.[52] As heparin has a high anionic charge density, the receptor was designed with a number

of complementary cationic amino groups alongside boronic acids. This group has further reported success in sensing heparin within serum using a second generation receptor.[53] Schrader has recently developed a fluorescent polymeric heparin sensor that can quantify this polysaccharide with unprecedented sensitivity (30 nM).[54] Coupling of boron-carbohydrate interactions with electrostatic attraction in a multivalent manner is responsible for the high affinity of this receptor for its substrate. In spite of this avidity, the interaction can be controlled in a biologically relevant manner. Binding of the polymer to heparin can be reversed by the addition of protamine, similar to reversal of the complex between heparin and its natural target, anti-thrombin III. Other examples of biological mimicry by boron-based systems are delineated below and in the next section.

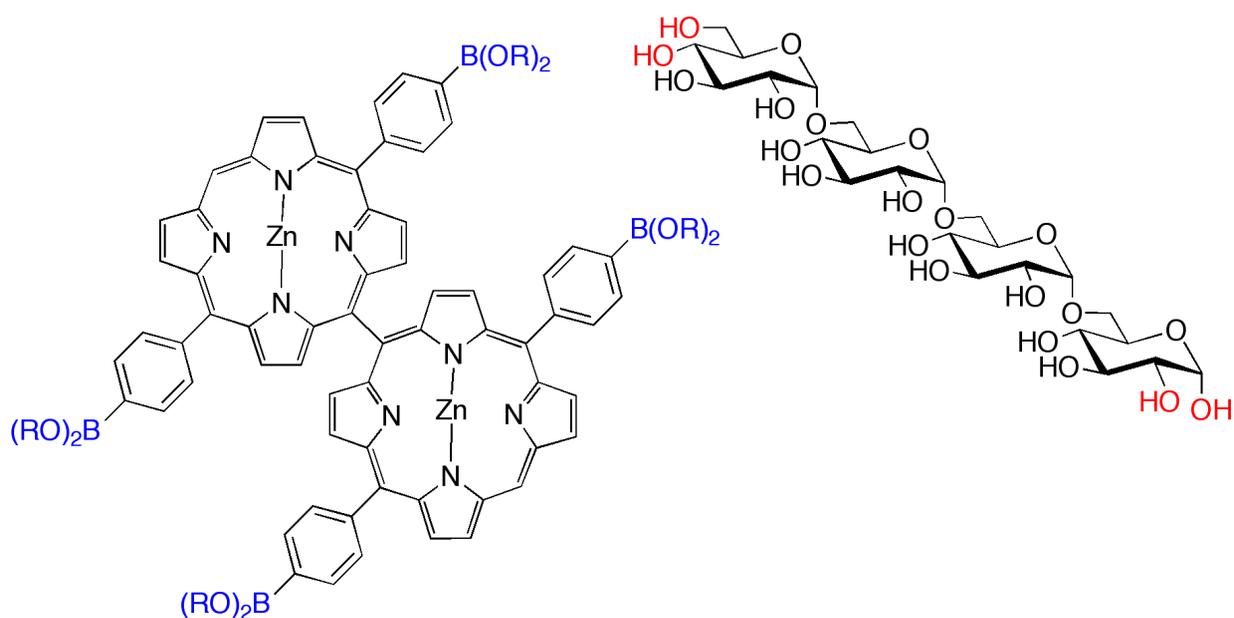


Figure 10. Shinkai's oligosaccharide receptor and maltotetraose.

The demonstrated affinity of benzoboroxoles for hexopyranosides makes these boron derivatives attractive components of receptors designed to target mammalian oligosaccharides. In 2010, Hall reported development of a bis-benzoboroxole receptor for the Thomsen-Friedenreich (TF) antigen, a tumor marker composed of consecutive galactose-based residues Figure 11.[55] This receptor was optimized within a combinatorial library constructed to add additional H-bonding and hydrophobic interactions between host and its oligosaccharide guest. A natural lectin receptor for this disaccharide, peanut agglutinin lectin (PNA), binds the TF antigen quite strongly relative to other protein-carbohydrate interactions ($K_d = 10^7$). However, the synthetic bis-benzoboroxole inhibits binding of PNA to TF-antigen labelled protein at low micromolar concentrations. The bis-benzoboroxole has a higher affinity for the disaccharide than the

corresponding bis-boronate although the latter still has significant affinity highlighting the importance of the additional H-bonding and hydrophobic interactions in this system. This work indicates it should be possible to target multiple hexopyranoside structures with other oligomeric benzoboroxole systems.

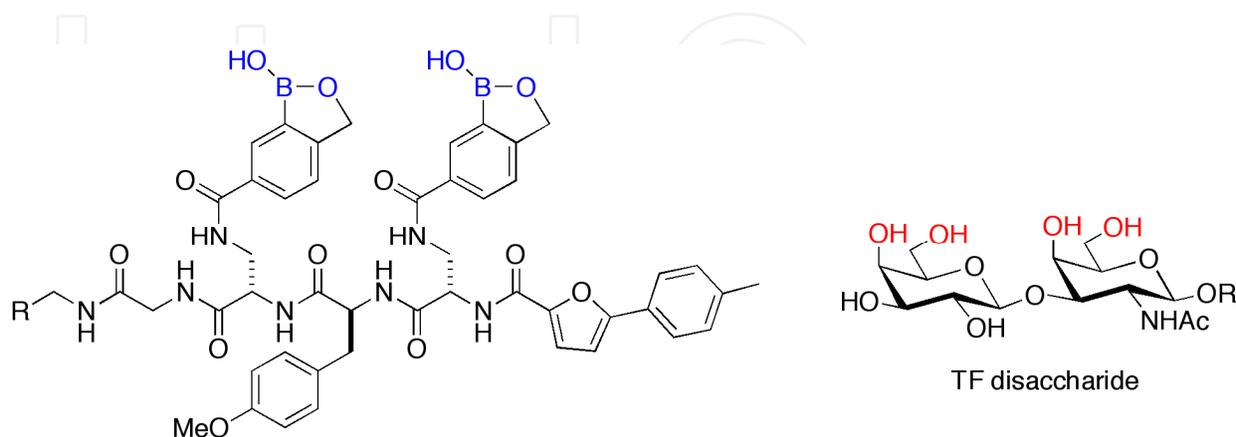


Figure 11. Hall's bis-benzoboroxole receptor for the TF antigen.

4. Boron-cell surface interactions

One ultimate goal of research into synthetic carbohydrate receptors is the development of compounds that can bind directly to cell surface glycoconjugates. Such synthetic lectins may serve as diagnostics to monitor changes in cell surface structure associated with disease progression such as cancer. Additionally, they may be used as drug-targeting agents to deliver chemotherapeutic agents to specific cell types. An early and initially underappreciated demonstration of the targeting of cell-surface structures was the work of Hageman with fluorescent dansyl boronates shown to associate with *Bacillus subtilis*.^[56] They were also able to show a diboronate could display other lectin like properties such as promoting the agglutination of erythrocytes. Not long after that, Gallop developed a method he defined as "boradaption" using boronates to transfer lipophilic dyes and probes into cells.^[57] Although the precise mechanism was not delineated, some boronates were shown to alter the latter stages of *N*-linked glycoprotein processing.^[58] A great deal of work has also gone into the development of lipophilic boronic acids as membrane transport agents for hydrophilic molecules such as sialic acid and its derivatives.^[59] There is commercial interest in such artificial transporters for the extraction of monosaccharides, such as glucose and fructose, and disaccharides like lactose from natural sources.^[28]

In 2002, Weston and Wang reported the ability to target a specific oligosaccharide epitope of a cell surface glycoconjugate.^[60, 61] Use of a fluorescent bis-boronate to label the cancer-related antigen sialyl Lewis X on hepatocellular carcinoma cells was an important

achievement. They used a combinatorial approach to optimize a bis-boronate in targeting the sialic acid and fucose residues on the tetrasaccharide. The receptor did not label cells that contained Lewis Y antigens lacking sialic acids, or were treated with fucosidase, to remove fucose from the cell surface. This indicates that both components are necessary for interaction with the synthetic receptor. The study marked the first time, as far as we are aware, that two different monosaccharide types had been targeted by design with a boronolactin on a cell surface (Figure 12).

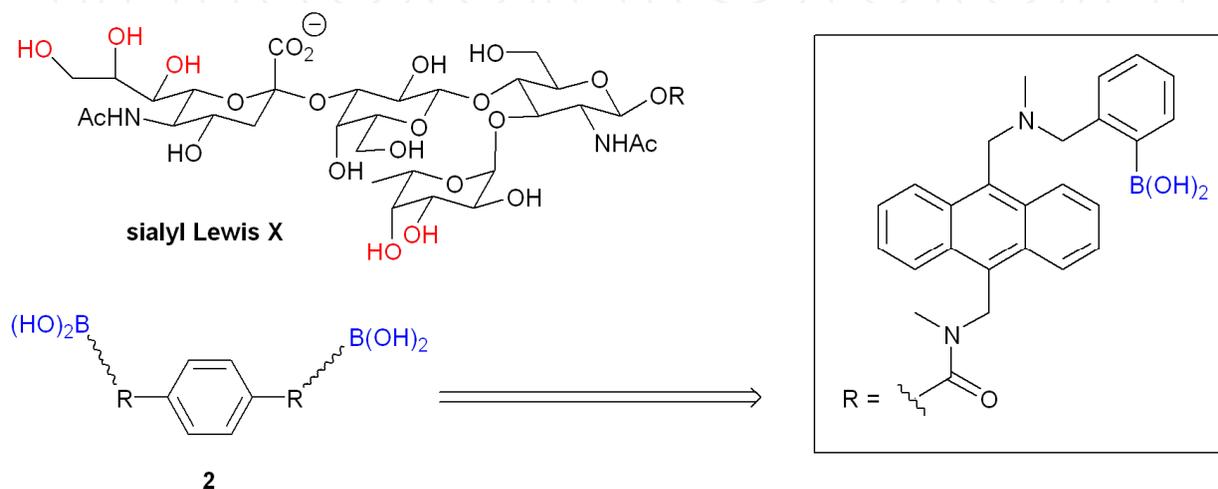


Figure 12. Wang's sialyl Lewis X receptor. Reprinted with permission. John Wiley & Sons, ©2010.

The Kataoka group has used boronic acids on a number of platforms to target cell surface sialic acids to engender a biological or analytical response. They have shown that polymeric boronates can cause the induction of lymphocytes in the same way as natural lectins do.[62] In addition these polyboronates can out-compete natural sialic acid-specific lectins for a cell surface. In collaboration with Miyahara, a powerful method for the direct determination of cell-surface sialic acid levels has been developed.[63, 64] Use of a self-assembled monolayer on a gold electrode allows a coating of boronates to be applied. Potentiometric measurements in the presence of cell suspensions containing either 0, 15, 30, or 100% metastatic cells are readily distinguishable (Figure 13).[64]

The study, application and manipulation of boron-carbohydrate interactions continues to expand into its third century. The properties of oligomeric and polymeric boronic acids in a cellular setting demonstrate that the terms "boronolactin" and/or synthetic lectin are appropriate. What remains for the field to advance are more examples targeting cell-surface carbohydrate structures beyond those containing sialic acid. The Hall group's receptor for the TF antigen marks a seminal step in this direction.[54] For a more comprehensive review of boron-based carbohydrate receptors in the context of other synthetic and biologic sugar binding systems, readers are directed to the recent publication of Wang.[7]

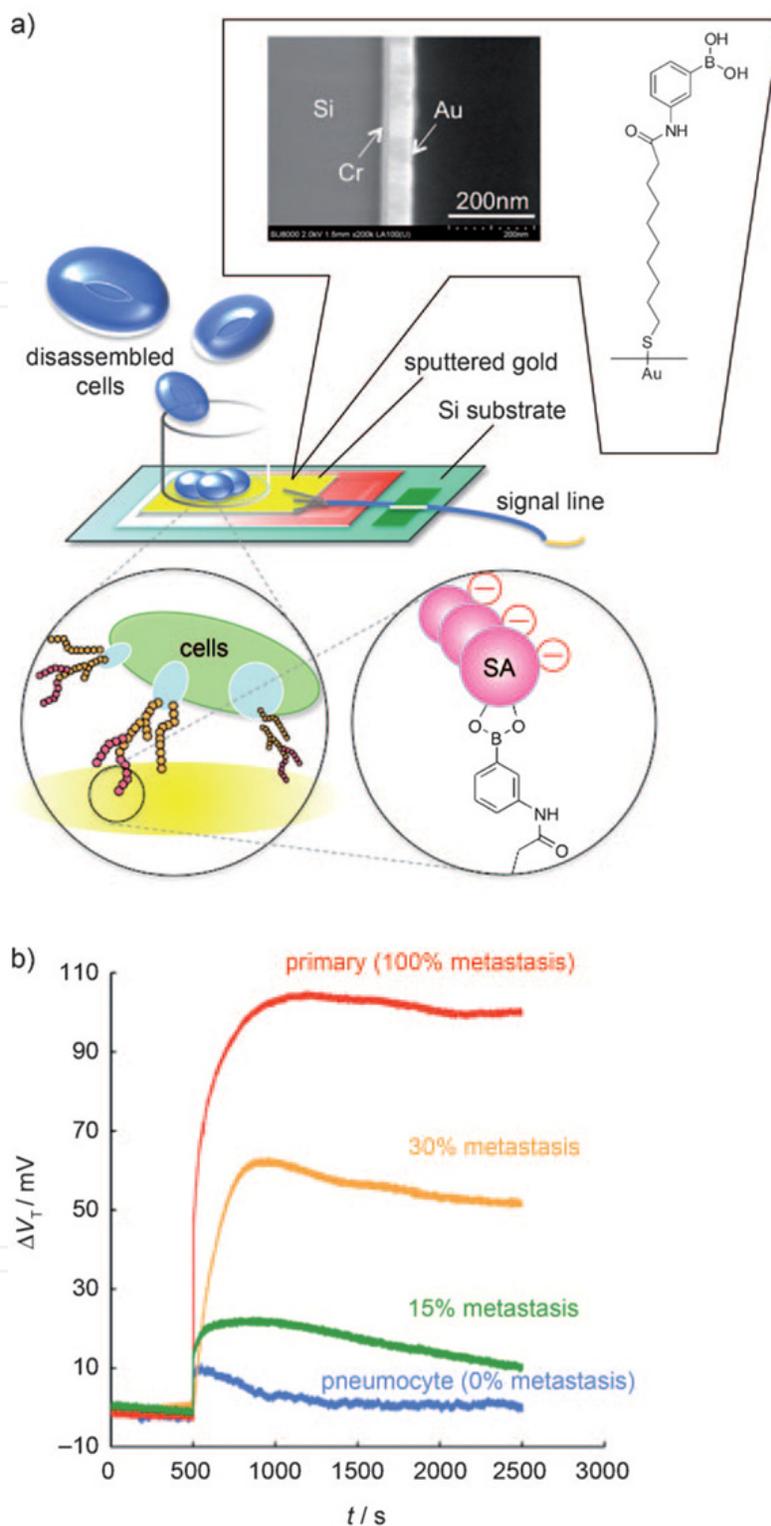


Figure 13. a) Schematic representation of potentiometric SA detection with a PBA-modified gold electrode. An SEM image of a cross-section of the electrode is shown at the top next to the chemical structure of the PBA-modified self-assembled monolayer introduced onto the electrode surface. b) Change in the threshold voltage (V_T) of the PBA-modified FET as a function of time upon the addition of cell suspensions (10^6 cells/mL) with various degrees of metastasis. [64] Reprinted with permission. John Wiley & Sons, ©2010.

5. Conclusions

In spite of its long and rich history, understanding of boron acid interactions with carbohydrates continues to increase into the 21st century. In the past 20 years, much fundamental knowledge has been gained, principally from the development of boronate-based glucose receptors for application toward blood sugar monitoring in diabetics. Currently, however, significant effort is being dedicated to the development of boron-based receptors for more complex oligosaccharides. This challenge is being undertaken by an increasing number of research groups throughout the world. These designer receptors may find application in diagnostics for cancer or infectious diseases, in drug targeting, or in providing a more fundamental understanding of the biochemical roles of cell-surface carbohydrates. The ability of boron acids to distinguish between closely related polyols either stereoselectively or chemoselectively makes them an obvious choice for anchoring synthetic carbohydrate receptors.[65] Engineering these interactions to target specific oligosaccharides is currently a difficult challenge as witnessed by the limited number of boron-based oligosaccharide receptors that have been developed at this stage. However, coupling boron-carbohydrate interactions with several additional non-covalent interactions—electrostatic, H-bonding, hydrophobic—offers the best chance of success. Future endeavours will determine the scope and limitations of boron-based carbohydrate receptors and sensors.

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