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Reversible covalent interactions of β-aminoboronic acids with carbohydrate derivatives†

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β-Aminoalkylboronic acids are capable of binding to carbohydrate derivatives through reversible covalent interactions. An anthracene-bearing β-aminoboronic acid has been synthesized, enabling determinations of association constants for binding of sugars by fluorescence spectroscopy. The diol-binding properties of β-aminoboronic acids are also useful in catalysis: one such compound displays remarkably high activity for regioselective *O*-acylation of a pyranoside derivative.

Interactions between arylboronic acids and carbohydrates have been applied extensively in glycoscience,[1] including in the design of sensors,[2] imaging agents,[3] drug delivery systems[4] and affinity materials.[5] The strength of these reversible covalent interactions and their selectivity for particular diol motifs are key advantages that underlie this broad range of applications. The structures of the boronic acids employed in carbohydrate recognition are diverse, and include simple arylboronic acids,[6] heterocyclic derivatives,[7] *ortho*-aminomethyl-substituted boronates[8] and benzoxaboroles (Fig. 1, compounds **1**–**3**).[9] A feature that is common to each of these classes of receptors is the bonding of the boronic acid group to an sp^2-hybridized carbon atom. Alkylboronic acid derivatives have been essentially ignored as prospective carbohydrate receptors: their relatively high pK_a values should give rise to lower affinity for diols,[10] and their propensity towards oxidation is another potential limitation.[11] Herein, we describe the synthesis of a fluorescent β-aminoboronic acid derivative whose affinity for carbohydrates rivals those of the arylboronic acids that are currently employed for this purpose. We further show that the reversible covalent interactions of β-aminoboronic acids with diols can be exploited in catalysis, enabling the regioselective activation of sugar derivatives.

Reductive amination reactions of α-boryl aldehyde derivatives bearing the *N*-methyliminodiacetyl (MIDA) group have been developed in one of our laboratories as an efficient method to prepare structurally diverse β-aminoboronic acid derivatives from primary or secondary amines.[12,13] Given that the incorporation of an *ortho*-aminomethyl substituent has significant beneficial effects on the carbohydrate recognition behavior of arylboronic acids,[8,14] we sought to investigate the properties of the corresponding β-aminoalkylboronic acids as sugar receptors. In particular, we targeted anthracene-bearing β-aminoboronic acid **5** with the goal of using changes in emission to signal carbohydrate binding. As noted above, little is known about the interactions of alkylboronic acid derivatives with carbohydrates. Wang and co-workers' studies of fluorescent α-amidoboronic acid receptors (*e.g.*, boronic acid **4**, Fig. 1) constitute the closest precedent for this work.[15]

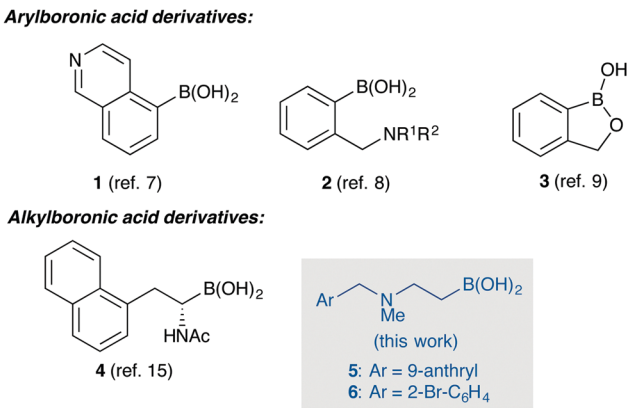

Fig. 1 Boronic acid derivatives that have been employed as carbohydrate receptors.

Compound **5** was synthesized from MIDA-protected α-borylacetaldehyde by reductive amination, followed by hydrolysis of the boronate under basic conditions (Scheme 1). The formate salt **5**·HCO_2H was isolated after purification by reverse-phase flash chromatography. Emission spectroscopy was used to determine the pK_a values of **5** in a 2 : 1 methanol : water mixture containing 50 mM sodium chloride (Fig. 2). A decrease

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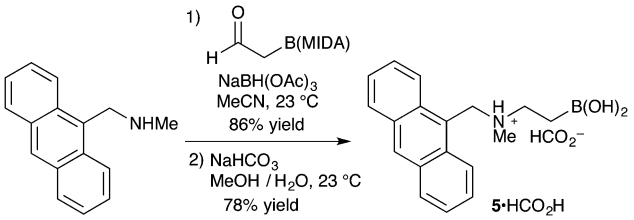


Scheme 1 Synthesis of β-aminoboronic acid receptor **5**.

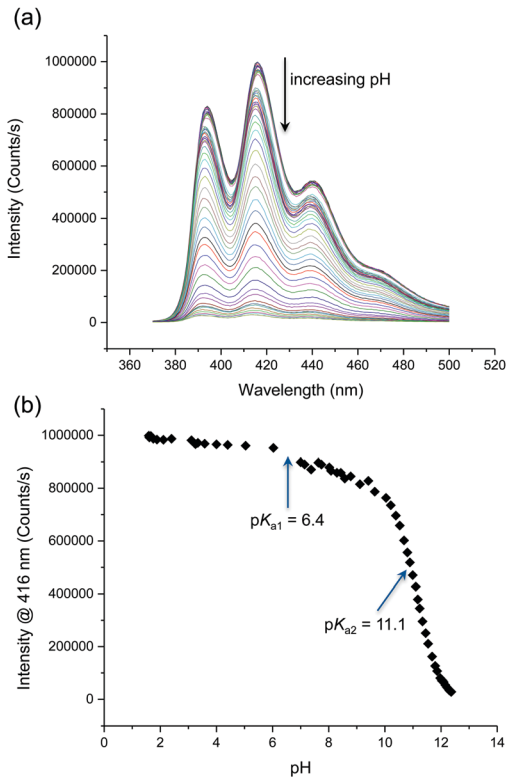
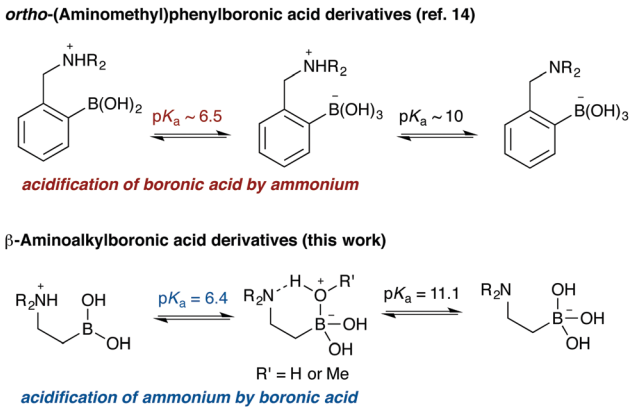


Fig. 2 (a) Effect of solution pH on emission spectrum of **5** (50 mM NaCl in 2 : 1 MeOH/H_2O, pH values ranging from 1.6 to 12.4, excitation wavelength 350 nm); (b) intensity of emission at 416 nm *versus* solution pH.

in emission was observed upon increasing pH, with two inflection points being evident. The first pK_a of 6.4 was associated with a relatively small change in emission intensity, whereas a larger change signalled the second pK_a of 11.1.

For *ortho*-aminomethyl-substituted arylboronic acids, the first pK_a (roughly 6.5) is proposed to involve the ionization of the boronic acid group while the second pK_a (roughly 10) is associated with protonation of the amine (Scheme 2).[14] We speculated that the situation could be different in the case of compound **5**, given that alkylboronic acids are less acidic than arylboronic acids. This proposal would require that the ammonium group of **5** have a pK_a of roughly 6.4, and thus be significantly more acidic than a typical trialkylammonium group. Stabilization of the amine, most likely by a solvent-mediated B–OH–N interaction, could give rise to this effect. Such an interaction is consistent with the relatively small decrease in emission intensity associated with the first deprotonation,

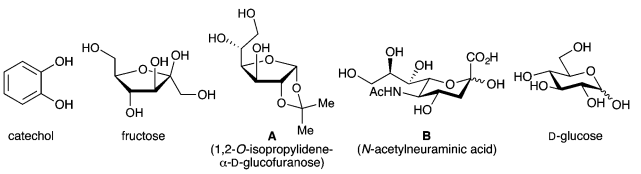


Scheme 2 Proposed acid–base equilibria for amine-functionalized arylboronic (top) and alkylboronic acids (bottom).

since photoinduced electron transfer (PET) from nitrogen-centered nonbonding electrons to the anthryl group would be suppressed in both the ammonium and the amine forms. The second pK_a (roughly 11) would then involve the formation of the tetracoordinate boronate ion, and be consistent with reported values for typical alkylboronic acids (*e.g.*, the pK_a of $MeB(OH)_2$ is 10.4).[16] A larger decrease in emission quantum yield would be expected, as quenching of the anthracene fluorescence by PET is possible in the conjugate base. This interpretation of the titration data is also consistent with the reported pH dependence of the ^{11}B NMR chemical shift of related β-aminoboronic acid **6** (Fig. 1, above: see the ESI† for details).[12] Thus, whereas the presence of an ammonium group acidifies the boronic acid moiety of *ortho*-(aminomethyl)-phenylboronic acids, it appears that the reverse is true for β-aminoalkylboronic acids, with the boronic acid causing an acidification of the ammonium group.

Emission spectroscopy was employed to determine association constants (K_a) for interactions of diol-containing compounds with β-aminoboronic acid **5** (Table 1). A 3 : 1 mixture of methanol and

Table 1 Association constants (K_a) of boronic acid **5** with carbohydrate derivatives and catechol



Guest	K_a[a] (3 : 1 MeOH/H_2O, pH 7.4)	K_a[a] (H_2O, pH 7.0)
Catechol	11500 ± 400 M^{-1}	4100 ± 200 M^{-1}
D-Fructose	4000 ± 500 M^{-1}	n.d.[b]
A	1040 ± 70 M^{-1}	n.d.[b]
B	115 ± 6 M^{-1}	n.d.[b]
D-Glucose	102 ± 6 M^{-1}	n.d.[b]

[a] K_a values were determined by fitting changes in emission intensity as a function of diol concentration to 1 : 1 binding isotherms. Each reported value is the average of at least three independent K_a determinations. The reported uncertainties reflect the standard deviation for each set of determinations. [b] Not determined.

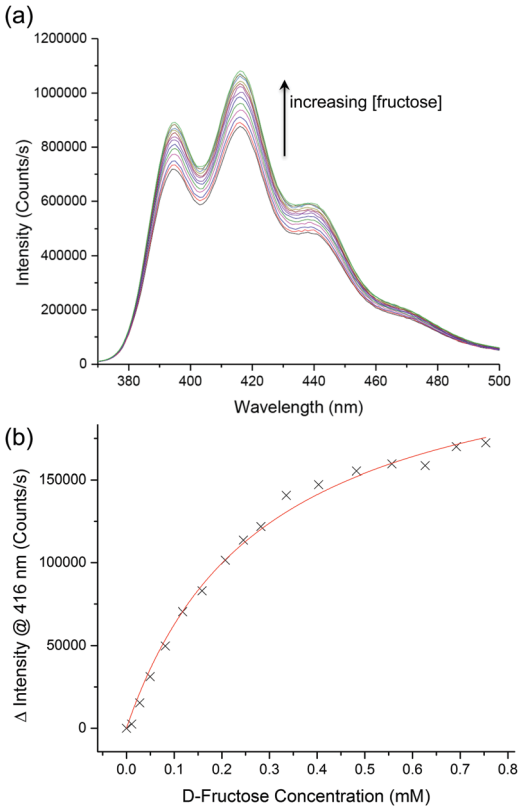


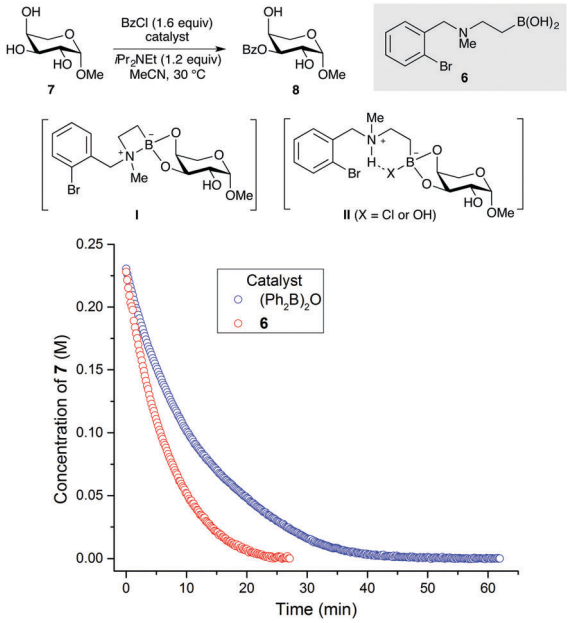
Fig. 3 (a) Changes in emission spectrum of **5** (6.5 μM in 3 : 1 MeOH/aqueous HEPES buffer (pH 7.4), excitation wavelength 350 nm) upon addition of fructose; (b) intensity of emission at 416 nm *versus* fructose concentration. Curve of best fit to a 1 : 1 binding isotherm is shown.

pH 7.4 aqueous 2-[4-(2-hydroxyethyl)piperazin-1-yl]ethanesulfonic acid (HEPES) buffer was used for these experiments. Upon addition of diol to a solution of the receptor, an increase in emission was generally observed (Fig. 3). The concentration dependence of this change in emission was fitted to a 1 : 1 binding isotherm to determine each association constant. Determinations were carried out in triplicate or quadruplicate, and the standard deviations of the results were used to estimate the uncertainties shown in the table. We also attempted to use an indicator displacement assay (IDA)[17] to determine association constants of diols with aminoboronic acid **6**, which lacks the emissive anthryl substituent (Fig. 1). Binding with the Alizarin Red S dye was evident in aqueous buffer and methanol/aqueous buffer mixtures, as judged by optical absorbance spectroscopy, but the high association constants prevented straightforward implementation of the IDA (see the ESI†).

Contrary to what might be expected based on the low acidities of alkylboronic acids, the affinity of **5** for fructose is roughly on par with those of the *ortho*-(aminomethyl)phenylboronic acid derivatives that have been employed extensively in carbohydrate recognition. For example, association constants of 308 M^{-1} and 1960 M^{-1} with fructose have been reported for *ortho*-(*N*,*N*-dimethylaminomethyl)phenylboronic acid and Shinkai's anthracenylmethyl-substituted fluorescent receptor **2** (4 : 1 CD_3OD/deuterated aqueous pD 7.4 phosphate buffer).[9] A direct comparison with α-amidoboronic acid **4** is not possible because the titrations were carried out under different conditions: compound **4** showed an association constant of 55 M^{-1} with fructose in pH 7.4 phosphate buffer.[15] The selectivity of **5** across the series of compounds tested largely parallels the observed trends for boronic acid receptors, with catechol and fructose being bound more favorably than glucose.[18] Carbohydrate derivatives having exocyclic diol moieties (glucofuranose **A** and *N*-acetylneuraminic acid **B**) also bind to compound **5**. This observation suggests that functionalization with a β-aminoboronic acid group may be a way to promote interactions with diol groups on cell-surface glycans.[4]

Having established that β-aminoboronic acids bind to carbohydrate derivatives through reversible covalent interactions, we evaluated them as catalysts for regioselective functionalization reactions of such compounds. We have previously shown that regioselective acylations, alkylations, sulfonylations and glycosylations of pyranoside and furanoside derivatives can be conducted using diarylborinic acids (Ar_2BOH) and their derivatives as catalysts.[19] Our mechanistic proposal involves complexation of diol groups by the borinic acid to generate tetracoordinate, anionic complexes that behave as activated nucleophiles. Accordingly, boronic acids generally display low catalytic activities in such reactions,[20] since complexation of a diol would lead to a tricoordinate complex in the absence of an additional Lewis base. When we have observed catalysis by boronic acids, it has been using electron-deficient aromatic derivatives that show relatively high Lewis acidity at boron. Given this background, it is remarkable that β-aminoalkylboronic acid **6**[12] showed superior activity to diphenylborinic acid for the catalytic, regioselective *O*-benzoylation of arabinopyranoside substrate **7** (Scheme 3). The data used to construct the concentration *versus* time plots were obtained by *in situ* reaction monitoring, using attenuated total reflection infrared (ATR-IR) spectroscopy. The selective formation of product **8** is consistent with catalyst binding to the *cis*-1,2-diol group and functionalization of the equatorial oxygen, following the general pattern of regioselectivity that we have observed for borinic acids.

The identification of a new structural motif capable of activating pyranosides towards regioselective functionalization is significant from the perspective of catalyst design, and is particularly relevant to the development of chiral variants. This observation also raises questions regarding the mode of activation of the diol. Based on our previous mechanistic studies, a tetracoordinate adduct derived from **6** is most likely involved, but the nature of the intermediate is unclear. A solvent-mediated B–N interaction of the type shown in Scheme 2 is unlikely, given that the reaction was conducted in acetonitrile. A direct B–N interaction is also improbable, as it would generate a four-membered ring (Scheme 3, complex **I**). No evidence of such an interaction could be found upon computational modelling of a β-aminoalkylboronic ester using density functional theory. Structure **II**, in which X is either an OH group (from the starting boronic acid) or chloride (which is generated as a product of the acylation reaction), may be more reasonable. In any case, the high activity of **6** relative to those of



Scheme 3 Selective monobenzoylation of arabinopyranoside **7** using $(Ph_2B)_2O$ (4.5 mol%, ○) and β-aminoboronic acid **6** (9 mol%, ○) as catalysts. Proposed modes of activation by catalyst **6** are depicted below the reaction scheme. Graphs of substrate concentration *versus* time are from data obtained by *in situ* reaction monitoring by ATR-IR spectroscopy.

unfunctionalized alkylboronic acids almost certainly points towards the involvement of the amino group in the mechanism of catalysis.[21]

The key finding of the present study—namely, that β-aminoalkylboronic acids show appreciable affinities for carbohydrate derivatives—suggests several directions for further research. Given that the carbohydrate-binding properties of fluorescent aminoboronic acid **5** are comparable to those of *ortho*-aminomethyl-substituted arylboronic acids that have been employed extensively in molecular recognition, it would be of interest to incorporate the β-aminoboronic acid functional group into more complex receptor architectures. As mentioned above, complexation of boronic acids with diol groups provides a way to promote the interactions of biological probes or prospective therapeutic agents with cell-surface glycans. Incorporation of aminoboronic acid groups could represent a new way to equip functional molecules of interest with carbohydrate-binding ability. Finally, β-aminoboronic acids represent the most active boronic acids identified to date for regioselective acylation of carbohydrate derivatives. Further explorations of catalyst structure–activity relationships, as well as the preparation of chiral derivatives, are of interest. For each of these types of applications, the ability to introduce the aminoboronic acid functional group at a late stage through a simple reductive amination/MIDA deprotection sequence is a key strategic advantage.

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