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Boronate derivatives of bioactive amines: potential neutral receptors for anionic oligosaccharides

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Abstract—Oligomeric δ-aminoboronates were synthesized via reductive amination of *o*-formylbenzene boronic acid with several polymines. The process entails the direct addition of *o*-formylbenzene boronic acid to the polyamine in methanol at room temperature followed by reduction of the resulting imine with $NaBH_4$. Di-, tri-, and tetrameric δ-aminoboronates have been prepared in this manner and these are anticipated to have enhanced affinities for certain oligosaccharides. A novel templating method for the synthesis of these compounds is also described. © 2003 Elsevier Science Ltd. All rights reserved.

The property of reversible, covalent binding to 1,2- and 1,3-diols has made boronic acids useful components in the design of artificial carbohydrate receptors.[1] The interaction of boronic acids with polyols has been studied in detail over a number of years.[2] Binding of diols by boronates becomes much more facile at physiologic pH if the boron is involved in an intramolecular Lewis acid–base complex with an amine.[3] This structural feature also creates a strong dipole moment and an overall charge neutral system that attracts charged species.[4] Such a component is expected to enhance the affinity of the amino boronate toward anionic carbohydrates—a common element of cell surfaces (step 1, Fig. 1). Alternatively, addition of a divalent ligand, might create a charge balanced system capable of binding DNA or RNA and the neutral nature of this species should make it more membrane permeable (step 2, Fig. 1).[5]

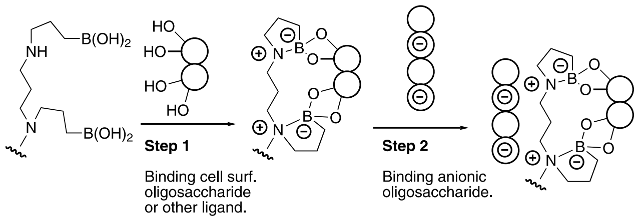

Figure 1. Two possible oligosaccharide binding modes.

Smith's group has recently demonstrated that liposomes armed with boronic acids on the surface show stronger binding of erythrocyte cells than in the absence of these boronates,[6] and Wang has reported a bisboronate sensor for cell surface tetrasaccharide sialyl Lewis X.[1i] Bertozzi has pioneered a broad ranging approach to modify cell surfaces by utilizing a lenient step in sialic acid biosynthesis to incorporate reactive functional groups at the nonreducing termini of membrane oligosaccharides.[7,8]

The cell surface oligosaccharides that are attractive targets for oligomeric boronates include those with a high percentage of mannose and/or galactose residues whose *cis*-vicinal diols are unsubstituted. These include the lipoarabinomannan[9] (LAM) of *Mycobacterium tuberculosis* and the lipophosphoglycan[10] (LPG) of *Leishmania* protozoa. Both play important roles in the infection cycle of their respective organisms, the causative agents of tuberculosis and leishmaniasis. Previous work by Shinkai on the affinity of diboronic acids for oligosaccharides has focused on carbohydrate systems that lack internal *cis*-diols. High affinities and selectivities are observed for oligosaccharides of proper length to bind both the reducing (through the 1- and 2-OH's) and non-reducing termini (through the 4- and 6-OH's).[11] Even higher affinities might be expected for multiple boronic acid–carbohydrate interactions in a single oligosaccharide chain.

Initially, we required a method for the rapid incorporation of multiple δ-aminoboronic acids into a single molecule. There are a number of methods for the

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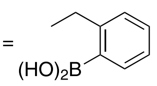
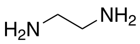
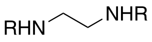
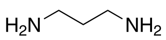
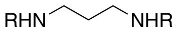
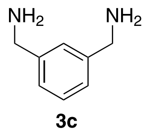
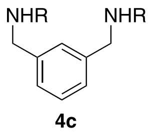
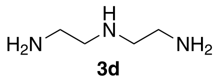
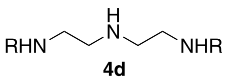
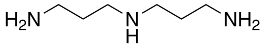
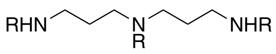
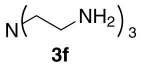
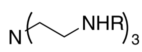
Table 1.

R = 

Polyamine	Product *	Yield
 **3a**	 **4a**	74%
 **3b**	 **4b**	70%
 **3c**	 **4c**	82%
 **3d**	 **4d**	78%
 **3e**	 **4e**	63%
 **3f**	 **4f**	80%
$NH_2(CH_2)_2NH(CH_2)_2NH(CH_2)_2NH_2$ **3g**	$NHR(CH_2)_2NR(CH_2)_2NH(CH_2)_2NHR$ **4g**	49%
$NH_2(CH_2)_3NH(CH_2)_4NH(CH_2)_3NH_2$ **3h**	$NHR(CH_2)_3NR(CH_2)_4NR(CH_2)_3NHR$ **4h**	36%

* Di- , tri-, and tetrameric products **4b**, **4e**, and **4h** were analyzed by HR FAB-MS. This data is outlined below. Masses represent the most abundant isotope.

4b. 439.2436 $[M+H]^+$ (HR FAB-MS, glycerol)
Δ.00047 of the calculated

4e. 702.3957 $[M+H]^+$ (HR FAB-MS, glycerol)
Δ.0034 of the calculated

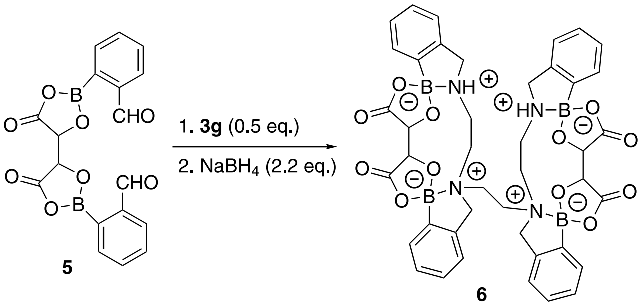
4h. 963.5418 $[M+H]^+$ (HR FAB-MS, glycerol)
Δ.0038 of the calculated

synthesis of this particular functional group array: (1) hydroboration of *N*-protected allylamines [e.g. -*N*-sulfonyl, *N*,*N*-bis(trimethylsilyl)] followed by deprotection,[12] (2) azide displacement of haloboronic esters followed by reduction and ester hydrolysis,[13] (3) *N*-alkylation of amines with bromoboronic acids,[14] or (4) directed *ortho*-metallation of benzylamine derivatives followed by quenching with trimethylborate.[15] While the *N*-alkylation method is the most direct, it is low yielding (ca. 25–40%) and carrying out multiple alkylations on oligomeric amines did not seem feasible. We sought a more direct and efficient route for the modification of oligomeric amines with boronic acids. Anslyn's group has recently demonstrated that trimeric *meta*-aminomethylbenzene boronates can be synthesized through reductive amination of *m*-formylphenylboronic acid.[1d] This method is preferred by ourselves[16] and others[1g] for installation of *o*-phenylboronic acids onto amines.[17]

We turned our attention to our primary goal—utilizing this method for functionalizing multiple amines in a single molecule. These results are shown in Table 1. Diboronates **4a**–**c** were synthesized in good yields (70–82%) and relative reaction rates for these molecules were noticeably faster than for higher oligomers, **4d**, **4e**, **4g**, and **4h**, due to the fact that they possess primary amines exclusively. Yields for the higher oligomers were lower (36–63%) which may be due to the presence of less reactive secondary amines in their structures. It should be noted that for trimeric and tetrameric compounds, **4d** and **4g**, with two-carbon linkers separating the amines, only their respective diboronate and triboronate products were observed. This is possibly due to steric difficulties encountered during imine formation.

All compounds were isolated using the following procedure. After slow addition of $NaBH_4$ in small portions, the mixtures were concentrated in vacuo. Next, the residue was redissolved in methylene chloride to leave borohydride as a white powder. The mixture was vacuum filtered and the filtrate was collected and once again concentrated. The oligomeric mixture was then redissolved in a small amount of methylene chloride and hexane was added dropwise until precipitate was observed. The precipitate was collected via vacuum filtration and determined by ^{1}H and ^{13}C NMR, and HRMS (FAB) to be the desired δ-aminoboronate products.[18] Product **4c** precipitated from the methanol solution upon addition of $NaBH_4$. The precipitate was collected by vacuum filtration and analyzed using the aforementioned techniques.

To circumvent the low yields encountered during the reaction of tetraamines, the divalent ligand L-tartrate was used as a template to order the formylphenylboronates into pairs (**5**). Based on the high affinity of bis(boronates) for tartrate,[16a] it was reasoned formation of **5** would facilitate reaction of the internal secondary amines by relegating imine formation at these sites to an intramolecular reaction. Indeed, it became possible to install four boronates onto **3g** whereas only the trimer **4g** was obtained when the reaction was performed without the template. The mono- and ditartrate (**6**) adducts were both observable by electrospray ionization MS, and this was confirmed by lithium doping to displace the sodium adducts. Following standard work-up, a 44% yield of total tetraboronate (both mono- and ditartrate adducts) was obtained.[19] Such a method should prove useful in molding aminoboronate receptors around a particular target as has been demonstrated by Wulff in polymeric materials.[20] The chiral nature of the boron centers in **6** means that a number of stereoisomers might exist in equilibrium. Importantly, the template is readily available as either enantiomer and it is certain that these antipodal complexes, particularly **4h**–ditartrate, will have differing affinities for a number of biomolecules.



In conclusion, reductive aminations of *o*-formylbenzene boronic acid provide access to oligomeric δ-aminoboronate derivatives in reasonable yield. More importantly for our goals, it allows for the rapid synthesis of an array of these functional groups on a single molecule. Binding of oligosaccharides by oligoboronates should not only enhance the modest affinity of boronates for individual saccharides, but should also amplify the small selectivity differences among monosaccharides.[21] Work is underway to study the binding properties of these multivalent compounds with important cell-surface oligosaccharides and oligonucleotides.

Acknowledgements

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17. For an early example of the same chemistry using LAH, see: Dunn, H. E.; Catlin, J. C.; Snyder, H. R. *J. Org. Chem.* **1968**, *33*, 4483.
18. *Supporting data for representative compounds* ***4a*** *and* ***4h***: **4a**: ^{1}H NMR (300 MHz, CD$_3$OD) δ 3.23 (s, 4H), 4.11 (s, 4H), 7.20 (m, 6H), 7.43 (m, 2H) ppm; ^{13}C NMR (300 MHz, CD$_3$OD) δ 44.9, 54.0, 122.6, 126.4, 127.3, 130.2, 141.5 ppm; FAB MS (positive-ion mode, diglycerol adduct) m/z 441.1.
    4h: ^{1}H NMR (300 MHz, CD$_3$OD) δ 1.84 (m, 4H), 2.07 br m, 4H), 2.72 (t, $J=7.1$ Hz, 4H), 2.87 (br m, 8H), 4.00 (br s, 8H), 7.15 (m, 12H), 7.48 (m, 4H) ppm. For MS data see Table 1.
19. The *o*-formylphenylboronic acid (1.33 mmol) and L-tartaric acid (0.666 mmol) were added to 15 mL MeOH and stirred for 5 min. The tetraamine **3g** (0.336 mmol) was added dropwise causing a precipitate to form. This mixture was stirred for an additional 2 h before NaBH$_4$ (1.45 mmol) was added causing the solution to clarify. The solution was then stirred for an additional 6 h before standard work-up provided 238 mg pale yellow solid as predominantly the monotartrate adduct (ca. 9:1 monotartrate: ditartrate[**6**]). EI MS (positive-ion mode, monotartrate adduct+Li$^+$) m/z 785.4.
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