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Cavitand Boronic Acids Mediate Highly Selective Fructose Transport

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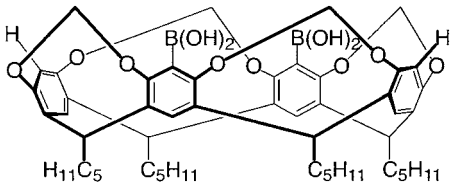
ABSTRACT



The synthesis sugar-transport properties of a family of five cavitand rim-appended boronic acids are reported. These conformationally rigid compounds are not observed to leach out of lipophilic membranes, and they exhibit unprecedented fructose to glucose transport selectivities and give higher fluxes than other neutral boronic acids. These properties make the cavitand boronic acids the best artificial fructose transporters described thus far.

Boronic acids that are able to selectively transport carbohydrates across lipophilic membranes have potential applications in drug delivery[1,2] and in environmentally benign industrial sugar production.[2c,3] Since fructose is the sweetest of all naturally occurring carbohydrates,[4] we have been developing carriers that select for fructose over glucose and sucrose.[5] Sucrose is poorly transported by boronic acid carriers,[3,5] so our emphasis has been on the improvement of the fructose to glucose flux ratio. We recently reported[6] the enhanced fructose selectivity shown by a diboronic acid (**1**), built on a pentaerythritol core, which is able to form a 2:1 diboronate ester with fructose (Figure 1). On the basis of this result, it seemed likely that even higher fructose selectivities—and higher fluxes—could be obtained with carriers that bear greater than two boronic acid groups, so long as the $B(OH)_2$ residues in these receptors are precluded

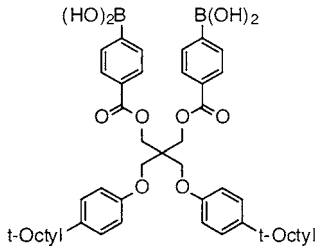


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Figure 1. Pentaerythritol-based diboronic acid **1**, which can form a 2:1 diboronate ester with fructose.[6]

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(2) (a) Takeuchi, M.; Koumoto, K.; Goto, M.; Shinkai, S. *Tetrahedron* **1996**, *52*, 12931−12940. (b) Smith, B. D. *Supramol. Chem.* **1996**, *7*, 55−60. (c) Smith, B. D.; Gardiner, S. J. *Adv. Supramol. Chem.* **1999**, *5*, 157−202 and references therein.
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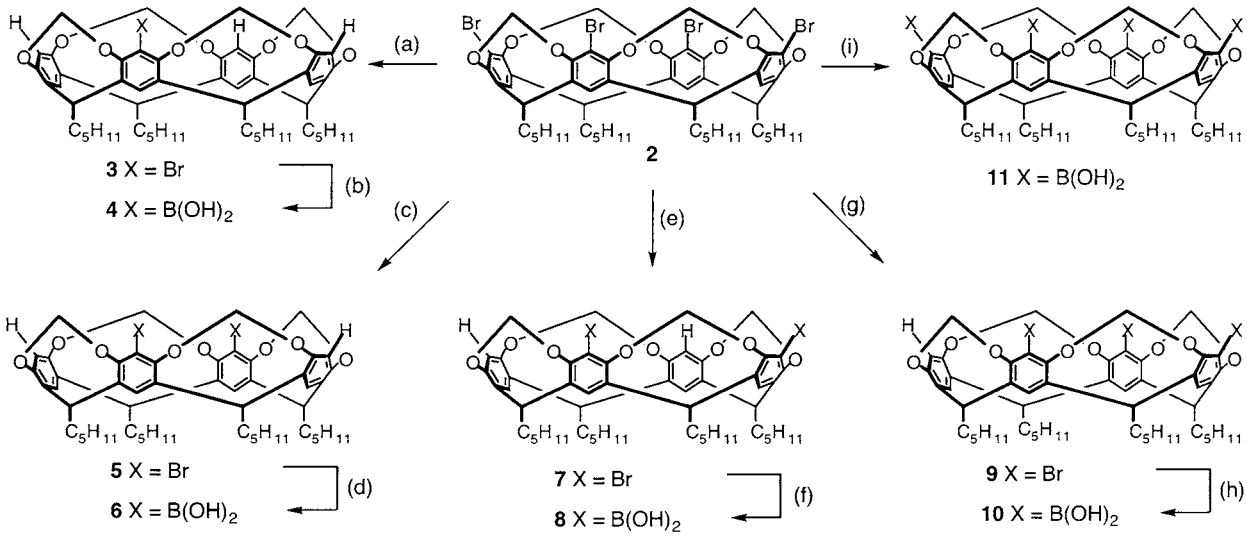
Scheme 1. Synthesis of Cavitand Bowl Boronic Acids **4**, **6**, **8**, **10**, and **11**[a]



[a] (a) (1) *n*-BuLi (1.1 equiv), THF, −78 °C, 20 min; (2) *i*-PrOH (1.1 equiv) −78 °C, 5 min; (3) *n*-BuLi (1.1 equiv), THF, −78 °C, 20 min; (4) *i*-PrOH (1.1 equiv), THF, −78 °C, 5 min; (5) *n*-BuLi (1.1 equiv), THF, −78 °C, 20 min; (6) MeOH (excess), −78 °C to rt, 37%; (b) (1) *n*-BuLi (1.1 equiv), THF, −78 °C, 20 min; (2) $B(OMe)_3$ (1.5 equiv), −78 °C to rt, 1 h; (3) 1 M aq HCl, rt, 45 min, 76%; (c) see ref 17; (d) (1) *n*-BuLi (2.1 equiv), THF, −78 °C, 20 min; (2) $B(OMe)_3$ (3.0 equiv), −78 °C to rt, 1 h; (3) 1 M aq HCl, rt, 45 min, 52%; (e) (1) *n*-BuLi (1.1 equiv), THF, −78 °C, 20 min; (2) *i*-PrOH (1.1 equiv) −78 °C, 5 min; (3) *n*-BuLi (1.1 equiv), THF, −78 °C, 20 min; (40 MeOH (excess), −78 °C to rt, 35%; (f) as described for (d), 30%; (g) (1) *n*-BuLi (1.1 equiv), THF, −78 °C, 20 min; (2) MeOH (excess), −78 °C to rt, 78%; (h) (1) *n*-BuLi (3.3 equiv), THF, −78 °C, 20 min; (2) $B(OMe)_3$ (6.0 equiv), −78 °C to rt, 1 h; (3) 1 M aq HCl, rt, 45 min, 28%; (i) (10 *n*-BuLi (4.4 equiv), THF, −78 °C, 20 min; (20 $B(OMe)_3$ (8.0 equiv), −78 °C to rt, 1 h; (3) 1 M aq HCl, rt, 45 min, 18%.

from cooperative sugar binding. Insolubility problems associated with the triboronic acid in the pentaerythritol series led us to search for an alternative scaffold on which to attach multiple boronic acids. We report here a series of membrane-soluble, cavitand boronic acids that show excellent sugar transport properties, both in terms of fructose selectivity and flux.

The results obtained with **1** suggested that fructose transport would be enhanced with a carrier in which several boronic acid groups could project from the same side of the chosen scaffold. Many conformationally flexible receptors carrying boronic acid groups have been reported.[7,8] The cavitand bowl platform[9] was attractive to us because of its structural rigidity: substituents appended to the rim of these molecules are in well-defined locations, and the fact that they are constrained to project from the same side of the bowl should facilitate fructose transport.[10] Furthermore, such a study would complement the landmark investigations by Aoyama et al.[11] into carbohydrate binding by resorcinarenes, the first synthetic receptors shown to exhibit such behavior.[12]

Cavitands have four sterically hindered bowl rim positions for substitution. With only $B(OH)_2$ groups and hydrogens present at the bowl rim, five different cavitand boronic acids can be envisaged: a monoboronic acid (**4**), A,C- and A,B-diboronic acids (**6** and **8**, respectively), a triboronic acid (**10**), and a tetraboronic acid (**11**). These compounds were prepared as shown in Scheme 1. Readily available pentyl-footed tetrabromocavitand **2**[13] was converted into each of the partially brominated analogues **3**, **5**, **7**, and **9** by procedures recently described for the undecyl-footed cavitand series.[14] The five rim-brominated cavitands were then converted into the boronic acids by lithium−bromine exchange, boronate formation, and hydrolysis with aqueous acid.[15] Isolated yields ranged from 78% for the monoboronic acid to 18% for the tetraboronic acid, with yields generally decreasing as the number of $B(OH)_2$ residues in the host increased. We ascribe this result to isolation difficulties, since in every case the

(7) James, T. D.; Shinkai, S. *Top. Curr. Chem.* **2002**, *218*, 159−200.

(8) Resorcinarenes with lower rim-appended phenylboronic acids have been used for the colorimetric detection of sugars. The active chromophore in these studies was recently found to be not a resorcinarene, but instead ring opened/oxidized compounds: He, M.; Johnson, R. J.; Escobedo, J. O.; Beck, P. A.; Kim, K. K.; St. Luce, N. N.; Davis, C. J.; Lewis, P. T.; Fronczek, F. R.; Melancon, B. J.; Mrse, A. A.; Treleaven, W. D.; Strongin, R. M. *J. Am. Chem. Soc.* **2002**, *124*, 5000−5009 and references therein.

(9) (a) Cram, D. J. *Science* **1983**, *219*, 1177−1183. (b) Cram, D. J.; Cram, J. M. Container Molecules and their Guests, *Monographs in Supramolecular Chemistry*; Stoddart, J. F., Ed.; Royal Society of Chemistry: Cambridge, 1994; Vol. 4. (c) Verboom, W. In *Calixarenes 2001*; Asfari, Z., Bohmer, V., Harrowfield, J., Vicens, J., Eds.; Kluwer: Dordrecht, 2001; pp 181−198.

(10) No cavitand-based boronic acids have been reported previously. An uncharacterized tetraboronic ester has been described: von dem Bussche-Huennefeld, C.; Helgeson, R. C.; Buehring, D.; Knobler, C. B.; Cram, D. J. *Croat. Chem. Acta* **1996**, *69*, 447−458. More conformationally flexible receptors bearing boronic acids, including calixarene-boronic acids[7] and resorcinarene-boronic acids,[8] have been prepared.

(11) Aoyama, Y.; Tanaka, Y.; Sugihara, S. *J. Am. Chem. Soc.* **1989**, *111*, 5397. Resorcinarenes bind carbohydrates through hydrogen bonds, although the precise mode of bonding is not known. See ref 12 for a discussion.

(12) Davis, A. P.; Wareham, R. S. *Angew. Chem., Int. Ed.* **1999**, *38*, 2979−2996.

(13) Byrant, J. A.; Blanda, M. T.; Vincenti, M.; Cram, D. J. *J. Am. Chem. Soc.* **1991**, *113*, 2167−2172.

(14) Irwin, J. L.; Sherburn, M. S. *J. Org. Chem.*, **2000**, *65*, 602−605.

(15) For related work leading to cavitands carrying phenol groups at the rim, see: Irwin, J. L.; Sherburn, M. S. *J. Org. Chem.*, **2000**, *65*, 5846−5848.

mass balance after aqueous workup was high and the crude products were rich in the target compounds. The boronic acids were purified by chromatography on silica, a step that led to a significant loss in material.[16] Efforts are underway to improve these isolated yields.

The fluxes of fructose and glucose through *o*-nitrophenyloctyl ether (NPOE) supported on porous polypropylene Accurel,[5,6] promoted by the cavitand boronic acids and Aliquat 336, are shown in Table 1. Plots of receiving phase sugar concentration versus time were always observed to be linear when the cavitand boronic acids were used as carriers, even after several days, indicating that no leaching of the carriers from the membrane had occurred.

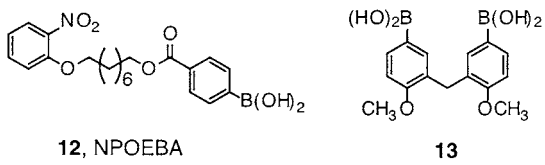
Table 1. Sugar Fluxes through a Supported Liquid Membrane[a]

		flux (10^{-8} mol m^{-2} s^{-1})		
entry	boronic acid	fructose	glucose	ratio of fluxes
1[b]	**12**	28.4	6.7	4.2
2[b]	**1**	26.1	3.4	7.6
3	**4**	18.3	2.8	6.5
4	**6**	24.4	2.3	10.6
5	**8**	34.3	8.2	4.2
6	**10**	105	18.4	5.7
7	**11**	67.2	10.5	6.4
8[b]	**13**	29.5	8.6	3.4

[a] The fluxes shown are averages of 2−3 runs. $T = 298$ K; flux uncertainty for fructose, ±10%; for glucose, ±25%. See Supporting Information for experimental details. [b] Data obtained in a previous study under similar conditions.[6]

Cavitand monoboronic acid **4** exhibits sugar transport properties similar to those witnessed previously for the monoboronic acid in the pentaerythritol series,[6] a compound with comparable molecular weight and solubility properties. This is important because it demonstrates that sterically hindered boronic acids can serve as effective sugar transport agents.

As anticipated, incorporation of a second boronic acid group at the cavitand rim results in enhanced fructose flux. The A,C- and A,B-diboronic acids exhibit quite different carrier properties, however, with the former showing a much higher fructose to glucose selectivity and the latter showing significantly higher fluxes of both monosaccharides. In fact, *the A,C-diboronic acid exhibits the highest fructose to glucose selectivity reported thus far* (10.6:1), easily surpassing the previous best (7.6:1) shown by **1**. The triboronic acid promotes remarkably high fluxes of both fructose and glucose: although the selectivity for fructose is not as high as other carriers, *flux rates for **10** are almost four times higher than those of the previous best neutral carrier*, (**12**).[5,6,18,19] Interestingly, the tetraboronic acid (**11**) exhibits fluxes lower than those of the triboronic acid (**10**), seemingly at odds with the rest of the transport data. We suspect that the anomalous behavior of the tetraboronic acid (**11**) relates to the physical properties of this compound and may indicate a limitation to the multi-boronic acid approach to better fructose transporters.



12, NPOEBA **13**

Figure 2. Benchmark fructose-transporting boronic acid (**12**) and Shinkai's glucose diboronic acid receptor (**13**).

The low selectivities shown by **8**, **10**, and **11** result from an enhanced glucose flux, the triboronic acid (**10**) being particularly impressive in this regard. A similar effect has been observed previously with Shinkai's diboronic acid (**13**),[6] which is known to form stable cyclic diboronate esters with glucofuranose.[20] It is likely that a related phenomenon, in which glucofuranose forms a bridging diester with adjacent boronic acids, is operating with compounds **8**, **10**, and **11**. The different sugar transport properties of the A,C-diboronic acid (**6**) probably arise from the wider separation of the boronic acid residues (cavitand rim diameter = ca. 9 Å), which cannot be bridged by a single glucose.

In summary, we have synthesized a new class of multidentate boronic acids and shown them to have outstanding monosaccharide transport properties. We have demonstrated that the judicious placement of boronic acid residues about a rigid scaffold can lead to carriers with unprecedented fluxes and fructose/glucose selectivities, findings which have implications in the development of chemosensors for sugars.[7] Investigations into the use of these carriers for large scale sugar separations are underway.

Acknowledgment. We thank the Australian Research Council, The University of Sydney, and Monash University for funding.

Supporting Information Available: Full details of synthetic procedures, transport experiments, and copies of ^{1}H and ^{13}C NMR spectra of **4**, **6**, **8**, **10**, and **11**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) 2,6-Dimethoxyphenylboronic acid is known to suffer much more facile proto-deboronylation than phenylboronic acid: Kuivila, H. G.; Reuwer, J. F.; Mangravite, J. A. *J. Am. Chem. Soc.* **1964**, *86*, 2666−2670.

(17) Barrett, E. S.; Irwin, J. L.; Turner, P.; Sherburn, M. S. *J. Org. Chem.* **2001**, *66*, 8227−8229.

(18) Paugam, M.-F.; Riggs, J.; Smith, B. D. *Chem. Commun.* **1996**, 2539−2540.

(19) A conjugated boronic acid-quaternary ammonium salt produces significantly higher saccharide fluxes than **12**. Unfortunately, this charged carrier leaches out of the membrane, precluding its use for practical separations.[5]

(20) (a) Tsukagoshi, K.; Shinkai, S., *J. Org. Chem.* **1991**, *56*, 4089−4091. (b) Norrild, J. C.; Eggert, H. *J. Am. Chem. Soc.* **1995**, *117*, 1479−1484.