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Highly Fructose Selective Transport Promoted by Boronic Acids Based on a Pentaerythritol Core

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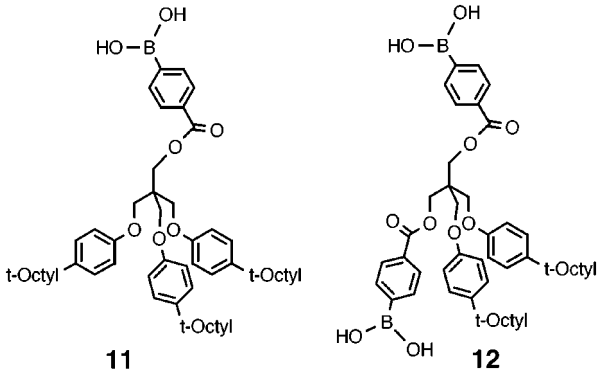
ABSTRACT



We have designed and synthesized a highly lipophilic boronic acid (11) with a molecular shape that makes it much more effective at carrying sugars through organic membranes than a previously used steroidal boronic acid. The corresponding diboronic acid (12) was also found to transport fructose ahead of glucose with a very high selectivity (7.6:1.0). Modeling suggests that 12 is able to carry two fructose molecules at once in a complex stabilized through hydrogen bonding and ion pairing.

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.[2,3] With the latter application in mind, we have been investigating the inherent selectivity for fructose transport exhibited by aryl boronic acids, with the aim of developing a new method for the production of high fructose syrup.

Figure 1 shows how the transport of a sugar out of an alkaline aqueous departure phase, through a lipophilic membrane, and into a slightly acidic aqueous receiving phase can be promoted by a boronic acid. This transport process is thought to be diffusion-controlled,[2] with the formation of the boronate esters at the interface being rapid and reversible. Since, in this mechanism, every sugar molecule is co-transported with a hydroxide ion, sugar transport can be driven uphill via the application of a pH gradient across the membrane.[3]

Membrane stability and ease of preparation of carriers are of prime importance if this process is to become industrially feasible. In our early experiments with bulk liquid membranes (BLM's),[3] we tried to address these issues through the use of a boronic acid derived from cholesterol, PBCC (**1**, Figure 2).[4] This highly lipophilic boronic acid, which is expected to be resistant to leaching, unfortunately possesses very poor transport properties in a BLM, with virtually no sugar transport being observed under standard conditions.

(1) Riggs, J. A.; Hossler, K. A.; Smith, B. D.; Karpa, M. J.; Griffin, G.; Duggan, P. J. *Tetrahedron Lett.* **1996**, *37*, 6303−6306.

(2) Smith, B. D.; Gardiner, S. J. *Adv. Supramol. Chem.* **1999**, *5*, 157−202 and references sited therein.

(3) Karpa, M. J.; Duggan, P. J.; Griffin, G. J.; Freudigmann, S. J. *Tetrahedron* **1997**, *53*, 3669−3678.

(4) James, T. D.; Harada, T.; Shinkai, S. *J. Chem. Soc., Chem. Commun.* **1993**, 857−858.

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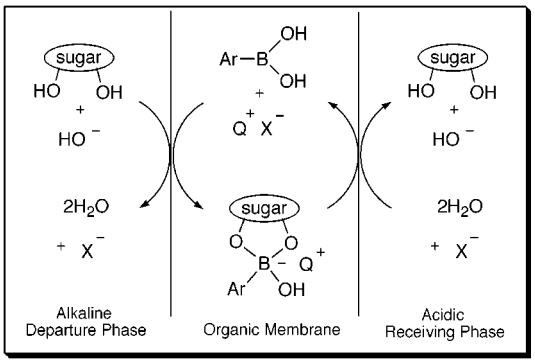


Figure 1. Accepted mechanism for boronic acid mediated pH driven sugar transport through an organic membrane (Q^+ = quaternary ammonium cation).[3]

We suggested that steroidal boronic acids of this type probably self-assemble at the membrane interface, inhibiting transport.[3]

More recently, we have been studying sugar transport through supported liquid membranes (SLM's) because these membranes are more likely to be industrially useful than BLM's, and they require much lower quantities of carrier.[5] We have now found that the poor transport properties of PBCC, particularly for fructose, are not confined to the BLM experiment (Table 1). The fructose flux promoted by PBCC through an SLM does not compare well with that induced by NPOEBA (**2**), the standard reference monoboronic acid used in SLM transport experiments.[5,6]

To circumvent the apparent interfacial problems presented by PBCC, we have designed and synthesized a lipophilic boronic acid (**11**) with an overall conical shape, through a combination of a pentaerythritol core and the cheap, readily available *p-tert*-octylphenol. The use of the pentaerythrityl core also allowed us to prepare two closely related boronic acids (**12** and **13**) with the purpose of comparing the effect

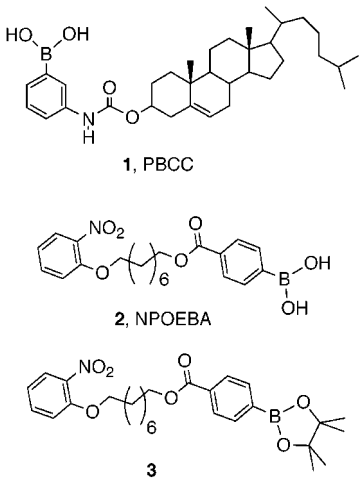


Figure 2.

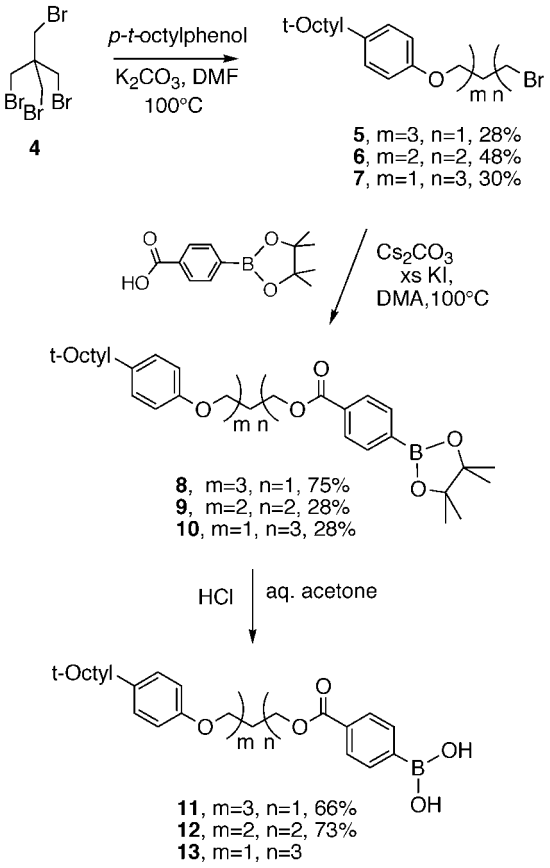
Table 1. Sugar Fluxes through a Supported Liquid Membrane[a]

		flux (10^{-8} mol m^{-2} s^{-1})		
entry	boronic acid/ester	fructose	glucose	ratio of fluxes
1	1	7.6	4.1	1.9
2	2	28.4	6.7	4.2
3	3	28.9	7.2	4.0
4	8	17.1	3.4	5.1
5	11	17.9	3.5	5.1
6	12	26.1	3.4	7.6
7	14	31.8	9.3	3.4
8[6]	15	21	3.4	6.1

[a] Carrier dissolved in 2-nitrophenyl octyl ether (50 mM) with 1 equiv of Aliquat 336 and supported on Accurel type 1E (12.6 cm^2). Departure phase (34 mL) contained 0.3 M fructose and glucose and was buffered at pH 11.3 with 0.5 M Na_2CO_3. Receiving phase (34 mL) was buffered at pH 6.0 with 0.1 M Na_2HCO_3. Both phases were stirred with a magnetic stirring bar at 250 rpm. Aliquots were removed at hourly intervals and analyzed in triplicate for glucose with a coupled hexokinase-glucose-6-phosphate dehydrogenase assay and fructose with the addition of phosphoglucose isomerase, as previously described.[5] Fluxes were determined from slopes of plots of [total NADPH abs (340 nm)] vs time over periods of at least 5 h and the results averaged over two runs. T = 298 K, flux uncertainty ± 10%. [b] Data obtained in a previous study under slightly different conditions.[5]

of incorporating one, two, and three boronic acids into carriers of similar shape and size. Scheme 1 shows the route used to synthesize these boronic acids. The mono-, di-, and tribromides (**5**−**7**) were readily prepared from pentaerythrityl

Scheme 1. Synthesis of Carriers with a Pentaerythritol Core



tetrabromide by treatment with *p-tert*-octylphenol and potassium carbonate in DMF. By variation in the ratio of bromide to phenol, and the application of careful flash chromatography, all three bromides could be produced in pure form. NPOEBA and related carboxylate esters had previously been synthesized through the direct alkylation of *p*-carboxyphenyl boronic acid;[5,6] however, the boronic acid products produced in these reactions are usually difficult to isolate from the often complex reaction mixtures. We have optimized the preparation of such esters by first protecting the boronic acid of *p*-carboxyphenyl boronic acid with the stable pinacol protecting group, which appears to minimize side reactions and make the products easier to isolate. Yields of the highly hindered protected boronic acids (**8**−**10**) were also enhanced by the use of $CsCO_3$, an excess of KI, and the use of DMA as the solvent. Deprotection to the boronic acids (**11**−**13**) was achieved through a simple treatment with HCl in aqueous acetone.

The fluxes of fructose and glucose through *o*-nitrophenyloctyl ether (NPOE) supported on porous polypropylene Accurel,[5] promoted by the pentaerythrityl boronic acids and esters, are shown in Table 1. No leaching of carriers from the membrane was observed during these transport experiments. Interestingly, we have found that for monoboronic acids such as NPOEBA and **11** it is not necessary to cleave the pinacol boronate ester prior to incorporation in the membrane. Deprotection apparently occurs very rapidly at the start of the transport experiment, with the results obtained with NPOEBA (**2**) and pinacol-protected NPOEBA (**3**) (Table 1, entries 2 and 3) and **8** and **11** (Table 1, entries 4 and 5), each within experimental error. We saw this as a potentially attractive solution to the solubility problems encountered with triboronic acids such as **13**, which are not usually soluble in NPOE. Unfortunately, the apparent rapid deprotection observed with the monoboronic acids did not occur with the di- and triboronic acids (**12** and **13**). The dipinacol ester (**9**) gave significantly reduced fluxes of fructose and glucose when compared with **12**, and the tripinacol ester (**10**) did not appear to promote sugar transport at all. The low solubility of the triboronic acid (**13**) in NPOE has prevented us from performing transport experiments with this compound.

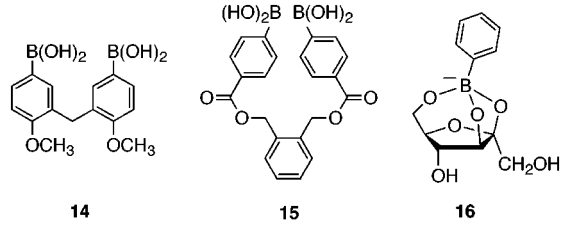
In terms of improving sugar flux by adjusting the molecular shape of the carrier, it is gratifying to find that moving from the steroidal structure of PBCC to the overall conical shaped carrier based on a pentaerythritol core significantly improves carrier performance. The monoboronic acid (**11**), despite having a considerably higher molecular weight than PBCC, promotes a fructose flux 2.2 times greater than that produced by PBCC. We have therefore achieved the principal aim of this investigation, which was to produce a highly lipophilic boronic acid by a simple synthetic route with a molecular shape that does not inhibit sugar transport.

(5) Gardiner, S. J.; Smith, B. D.; Duggan, P. J.; Karpa, M. J.; Griffin, G. J. *Tetrahedron* **1999**, *55*, 2857−2864.

(6) (a) Paugam, M.-F.; Riggs, J. A.; Smith, B. D. *J. Chem. Soc., Chem. Commun.* **1996**, 2539−2540. (b) Paugam, M.-F.; Bien, J. T.; Smith, B. D.; Chrisstoffels, L. A. J.; de Jong, F.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1996**, *118*, 9820−9825.

Given the importance of fructose to the food and beverage industry,[6a] another long-term aim of our research is to develop sugar carriers that are highly selective for fructose. As demonstrated by the NPOEBA transport results (Table 1, entry 1), monoboronic acids naturally show a strong preference to transport fructose ahead of glucose, despite *extracting* fructose with a much lower selectivity.[3,5] We originally rationalized this transport preference through a realization that the most stable boronate esters of glucose are formed with its furanose form.[7] This form is not readily available in aqueous solution, and under the kinetically controlled transport experiment, we felt that this lack of availability of the furanose form of glucose is enough to retard glucose flux relative to fructose. This theory appears to be supported by the transport results obtained with Shinkai's diboronic acid (**14**),[8] shown in Table 1. This diboronic acid is known to bind strongly to the furanose form of glucose,[7] and in fact, we have now found that in extraction experiments performed at pH 11, a combination of **14** and Aliquat 336 extracts glucose into 1,2-dichloroethane ahead of fructose in a ratio of 1.8:1.0. This preference for glucose extraction exhibited by **14** is the highest we have observed, yet **14** still selects for fructose in the transport experiment (Table 1, entry 7), despite promoting a relatively high glucose flux.

We have previously tried to improve fructose selectivity by making a series of diboronic acids with a variable linker,[5] and observed an improvement in selectivity (6.1:1.0), with the diboronic acid (**15**) that molecular modeling suggested was most capable of bonding to the pyranose form of fructose in two places (Figure 3).[5] Similar modeling with **12** shows



14 **15** **16**

Figure 3.

that the bite angle and size for this compound is inappropriate for it to readily bond to the pyranose form of fructose in two places. We were therefore surprised to find that the fructose selectivity exhibited by **12** (Table 1, entry 6) is significantly better than that of **15** and is *the highest ever recorded*.

Fructose is also able to form very stable monoboronate esters in its furanose form, an example of which is **16**.[9] Glucose is incapable of forming similarly stable monoboronate esters, so it is possible that much of the observed

(7) Norrild, J. C.; Eggert, H. *J. Am. Chem. Soc.* **1995**, *117*, 1479−1484.

(8) Tsukagoshi, K.; Shinkai, S. *J. Org. Chem.* **1991**, *56*, 4089−4091.

(9) Norrild, J. C.; Eggert, H. *J. Chem. Soc., Perkin Trans. 2* **1996**, 2583−2588.

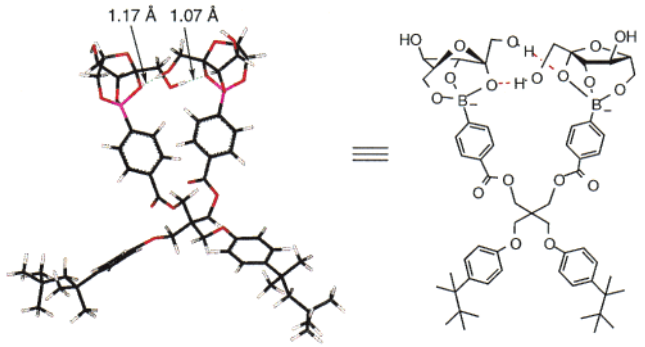


Figure 4. Molecular mechanics[10] structure of diboronate ester formed between **12** and two molecules of fructose in the furanose form.

boronic acid promoted fructose flux results from transport of monoboronate esters of its furanose form. Given that these esters have a lower molecular weight than the diboronates formed with glucose, and that the effect of size on diffusion rates will be magnified when the large ammonium counterions are taken into account, the ability to bind fructose as a monoboronate ester may be an important contributing factor in the demonstrated preference for boronic acids to selectively transport fructose. These considerations have led us to model the diboronate ester formed between one molecule of **12** and two fructose molecules in the furanose form (Figure 4).[10] These calculations have shown that two stabilizing hydrogen bonds (1.17 and 1.07 Å) can be formed between the two fructose fragments in this diester[11] and that this structure nicely accommodates the quaternary ammonium counterions (omitted for clarity) into an overall charge-neutral package. Modeling of similar esters formed with **14** and **15** shows that these diboronic esters cannot place the fructose fragments in suitable positions to take advantage of such stabilizing effects. The diester of **14** is unlikely to form for steric reasons, and the diester formed with **15** cannot bring the fructose fragments close enough together, with modeling predicting the formation of a single, 1.91 Å hydrogen bond.

In summary, we have designed and synthesized two new lipophilic boronic acids (**11** and **12**) that have an overall conical shape, which promote facile and highly selective transport of fructose through an SLM. The high selectivity for fructose shown by the diboronic acid **12** *may* indicate that it is able to transport two molecules of fructose at the same time as a part of a complex stabilized by hydrogen bonds and ion pairing. This prediction is difficult to confirm experimentally, but we have initiated a careful investigation of the structures of the boronate esters involved in transport, the results of which will be reported in due course. Interestingly, Shinkai's diboronic acid (**14**) also selectively transports fructose over glucose, despite being able to form very stable esters with glucose and being able to extract glucose into organic solvents more readily than it can fructose.

Acknowledgment. We thank Dr. Jens Norrild, University of Copenhagen, for the generous gift of **14**, Tim Altamore for preparing **3**, and Dr. Peter Nichols for assistance with molecular modeling. We gratefully acknowledge financial support from the Australian Research Council and Monash University.

Supporting Information Available: Synthetic details and characterization data for compounds **3** and **5**−**12** along with the experimental procedure used for transport experiments and associated absorbance vs time plots. This material is available free of charge via the Internet at http://pubs.acs.org.

OL015560X

(10) Insight II, Discover Minimisation Module, MSI, San Diego, CA.

(11) Shinkai and co-workers have recently suggested that a similar type of H-bonding might occur in difructose boronate diesters appended to poly(L-lysine); Kobayashi, H.; Nakashima, K.; Ohshima, E.; Hisaeda, Y.; Hamachi, I.; Shinkai, S. *J. Chem. Soc., Perkin Trans. 2* **2000**, 997−1002.