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Selective Fructose Transport Mediated by Di-Boronic Acids Derived from Neopentyl Glycol

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Boronic acids that are able to selectively transport carbohydrates across lipophilic membranes have potential application in environmentally benign industrial sugar production.[1,2] The accepted mechanism by which boronic acids are able to facilitate the passage of sugars through organic membranes is shown in Figure 1. In this so-called 'tetrahedral mechanism',[1,2] a lipophilic quaternary ammonium salt plays a vital part in the transport process, mainly by improving the solubility of the boronate esters in the organic membrane.

With industrial applications in mind, we have been developing carriers that select for fructose over glucose and sucrose; fructose being the sweetest of the naturally occurring carbohydrates.[3] Sucrose is poorly transported through lipophilic membranes by boronic acid carriers,[2,4] so, apart from aiming for high fluxes and stable membranes, the main challenge in this work is the improvement of the ratio of fructose to glucose fluxes. We recently reported[5] the enhanced fructose selectivity (Table 1) of a diboronic acid (1) (Scheme 1), constructed on a pentaerythritol core. This di-boronic acid is thought to form, within the membrane, a 2 : 1 diboronate ester with fructose stabilized by intramolecular hydrogen bonds (2).

The favourable transport properties of (1) suggested to us that higher fructose selectivities and fluxes could be obtained with carriers that bear more than two boronic acid groups projecting from the same side of a given scaffold. Consistent with this prediction, the fructose transport promoted by a series of cavitand boronic acids was found to be highly selective and rapid compared with previously reported carriers.[6] Cavitand (3) in particular is impressive in this regard (Table 1).

With our intention to further this work through the development of polyvalent boronic acid based carriers, it became important for us to explore the properties of the different

Table 1. Sugar fluxes through supported liquid membrane

Boronic acid	Flux (10^{-8} mol m^{-2} s^{-1})[A]		Ratio of fluxes
	Fructose	Glucose	
(1)[B]	26.1 ± 2.6	3.4 ± 0.3	7.6 ± 1.1
(3)[C]	24.4 ± 2.4	2.3 ± 0.6	10.6 ± 2.9
(7)	24.7 ± 1.0	2.5 ± 0.7	9.9 ± 2.8
(11)	15.5 ± 1.1	3.8 ± 0.4	4.1 ± 0.5
(15)	42.3 ± 2.8	10.6 ± 1.0	4.0 ± 0.5

[A] Boronic acid concentration in membrane = 52 mM. Fluxes shown are averages of 2–3 runs. T = 298 K.
[B] Data from ref. [5].
[C] Data from ref. [6].

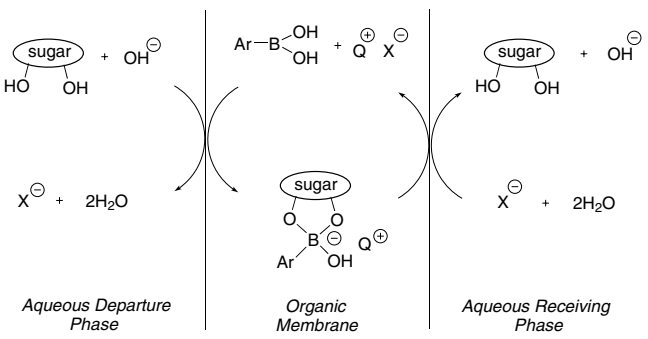
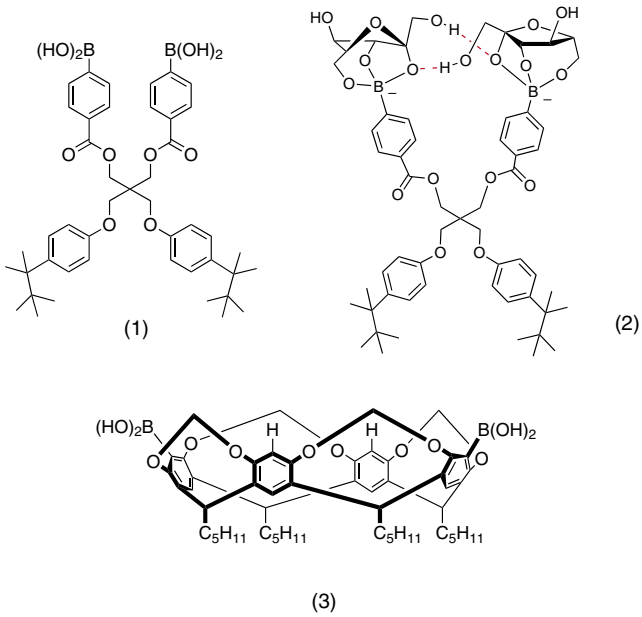


Fig. 1. Accepted 'tetrahedral' mechanism whereby boronic acids assist membrane passage. $Q^{\oplus}$ is a quaternary ammonium cation.



Scheme 1. Structures of di-boronic acids (1)–(3).

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linking groups through which aromatic boronic acids might be attached to a range of possible scaffolds. We report here the results of our first investigation of this sort, in which we have examined the transport properties of diboronic acids linked to a neopentylglycol core though ether and carboxylate ester links.

Results and Discussion

Design and Synthesis of Carriers

Molecular modelling performed on the pentaerythritol-derived di-boronic acid (1) and its fructose boronate esters suggested that the high fructose selectivity shown by this carrier results from the favourable placement of its boronic acids, such that stable diesters similar to (2) can readily form within the membrane. Thus, (2) is thought to transport two fructose molecules per molecule of boronic acid[5] for most of its passages across the membrane. We were interested to discover the role played by the carboxylate ester links in this arrangement, and if the analogous and potentially more stable benzyl ether links would give the same outcome. For ease of synthesis, we chose to use neopentyl glycol (5) as the core rather than the closely analogous pentaerythritol. We expected that the absence of the large lipophilic tails possessed by (1) may result in some leaching of the neopentyl glycol-derived boronic acids from the membrane during transport, but would present fewer synthetic challenges. Thus (7) and (11) were both prepared from neopentyl glycol as shown in Schemes 2 and 3.

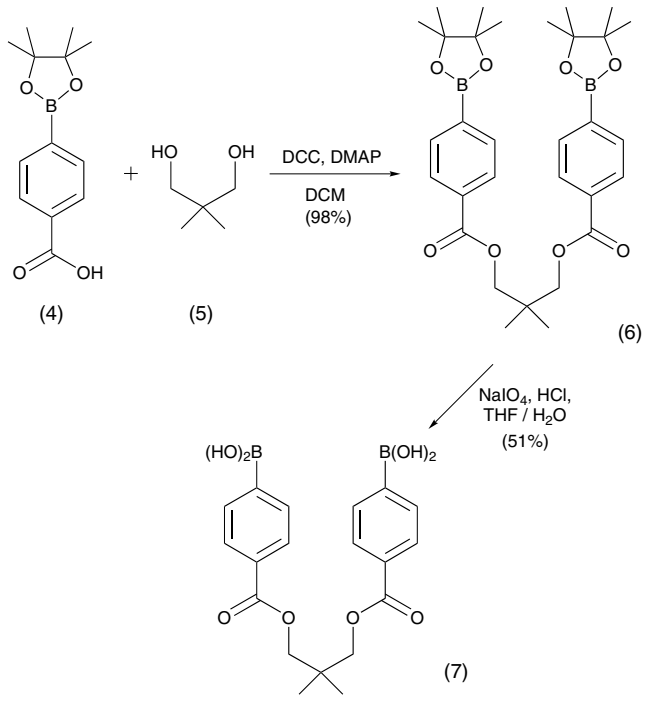
In the preparation of (7), Scheme 2, we first used a DCC/DMAP activating system to acylate neopentyl glycol (5) to produce the di-carboxylate ester (6) in excellent yield and purity. This is a significant improvement on the alkylation method used in the preparation of (1).[5] The pinacol protecting groups were removed by treatment with periodate[7] which, although not high yielding, provided the di-boronic acid (7) in a highly pure form.

Alkylation of neopentyl glycol (5) with *p*-bromobenzyl bromide (8), Scheme 3, afforded the di-bromide (9) in good yield. Palladium-catalyzed boronation of (9) with bis(pinacolato)diboron provided the di-boronate ester (10), which was deprotected to afford the di-benzyl ether linked di-boronic acid (11).

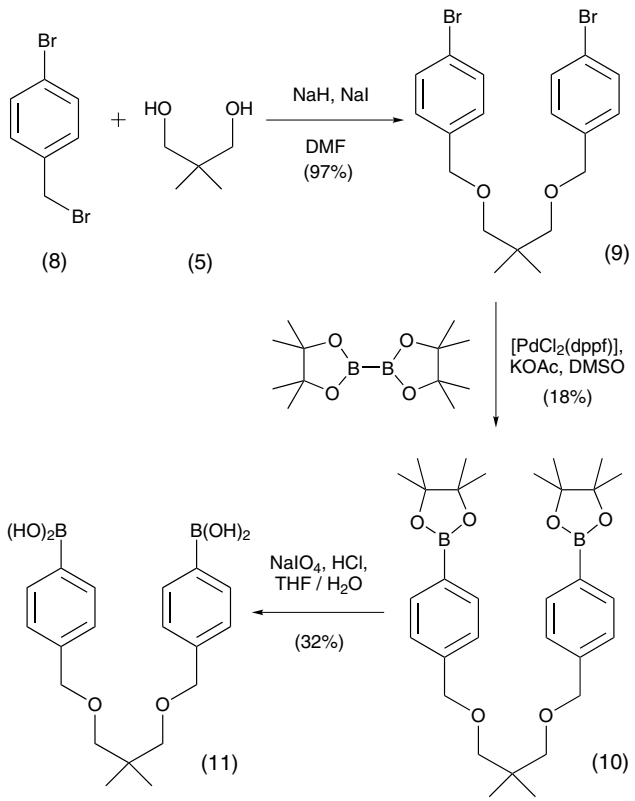
In order to find evidence for intramolecular cooperativity between boronic acids, it is important to compare the sugar-transport properties of di-boronic acids with an appropriate mono-boronic acid. Given that (7) and (11) are somewhat smaller than many of the boronic acid carriers we have used in the past, it seemed appropriate that a new mono-boronic acid, similar in structure to (7) and (11), be prepared and its transport properties used as a standard for the results obtained with (7) and (11). The nitro compound (15) was chosen for this purpose because it possesses a closely related substitution pattern to (7) and (11). In addition, the inclusion of a nitro substituent gives (15) physical properties more compatible with *ortho*-nitrophenyloctyl ether (NPOE), the commonly used lipophilic liquid membrane employed in transport experiments.[1,2,4–6] The monoboronic acid (15) was prepared in three steps, as shown in Scheme 4.

Transport Studies

An examination of Figure 1 reveals that sugar transport promoted by boronic acid can be driven with a pH gradient



Scheme 2. Preparation of di-boronic acid (7). DCC = 1,3-dicyclohexylcarbodiimide; DMAP = 4-(*N*,*N*-dimethyl-amino) pyridine.



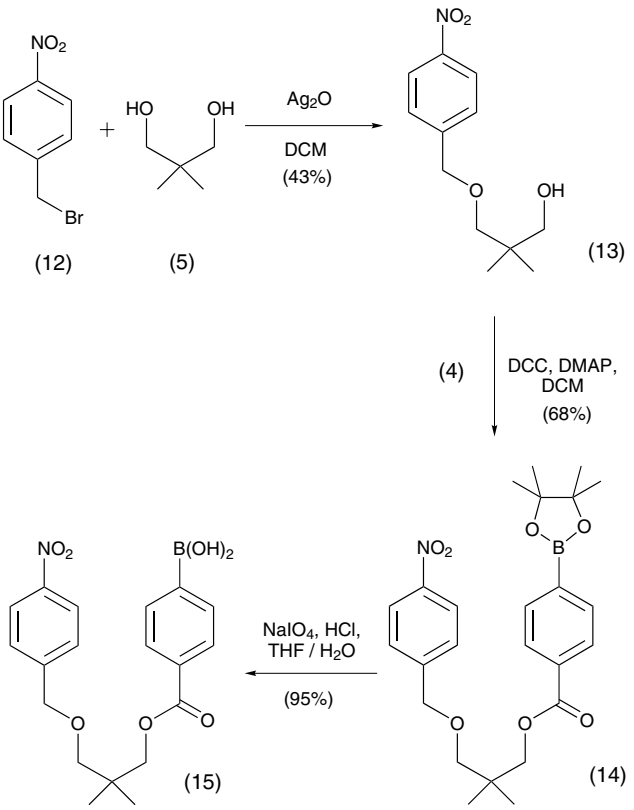
Scheme 3. Preparation of di-benzyl ether linked di-boronic acid (11).

because, as in the tetrahedral mechanism, one equivalent of hydroxide is transported through the membrane with each equivalent of sugar. Thus, in the present study and in accord with previous investigations,[4–6] the pH of the departure and receiving phases were buffered at 11.3 and 6.0, respectively. The fluxes of fructose and glucose through NPOE supported on the porous polypropylene Accurel,[4–6] promoted by the neopentylglycol-derived boronic acids (7), (11), and (15) and the lipophilic quaternary ammonium salt Aliquat 336 in the presence of the above-mentioned pH gradient, are shown in Table 1.

Despite our concerns regarding the leaching of these smaller, and potentially more water-soluble boronic acids, plots of receiving phase sugar concentration versus time over the 7 h transport experiments were observed to be linear. Only one carrier, (11), was studied for a longer period, 32 h, and the plot in that case still appeared to be linear.

In a broad sense, the sugar fluxes promoted by (7) and (11) are quite similar to those of previously studied di-boronic acids (Table 1), but the transport facilitated by the reference mono-boronic acid (15) is the highest of any mono-boronic acids studied thus far. One of the rate-limiting steps in the membrane-transport process has been shown to be diffusion of the sugar-boronate ester through the organic membrane,[1] so the enhanced sugar flux produced by (15) most likely relates to its compact nature.

The fructose to glucose transport selectivity shown by (15) is similar to that observed for other mono-boronic acids,[4–6] and reflects the inherent preference for fructose transport possessed by boronic acids. Importantly, the fructose preference



Scheme 4. Preparation of mono-boronic acid (15).

of almost 10 : 1 shown by the di-carboxylate (7) is actually superior to that previously observed for (1) and second only to the cavitand di-boronic acid (3). This result supports the idea that the di-boronic acid motif present in both (1) and (7) is particularly well suited to binding and transporting fructose. The ease of preparation of (7), combined with its impressive sugar transport properties, makes it an ideal candidate for use in future pilot-scale sugar-separation experiments.

The most striking result shown in Table 1, however, is the low fructose selectivity shown by the di-benzyl ether (11). The change from two carbonyl carbons to two methylene carbons in the linking groups, although seemingly minor, not only reduces the angle at which the boronic acids project from the neopentylglycol core but also introduces more degrees of freedom into the links. These two features are likely to work against the stabilizing effect identified for the di-fructose di-boronate (2) and expected to be present in similar fructose esters of (7).

Conclusions

Three new boronic acids based on a neopentyl glycol core have been prepared, a di-boronic acid linked through carboxylate esters (7), a di-boronic acid linked through ether links (11), and a reference mono-boronic acid (15). All three compounds were found to be good carriers for fructose and glucose through the lipophilic membrane NPOE, containing Aliquat 336, in the presence of a pH gradient. No evidence for carrier leaching was observed during the several-hour time frame of the transport experiments. Relative to the reference mono-boronic acid (15), the carboxylate-linked di-boronic acid (7) showed a remarkable fructose : glucose transport selectivity, almost 10 : 1, approaching the best thus far reported.[6] It is thought that (7), analogous to (1), is able to form stable di-fructose di-boronate esters similar to (2), and that this is how most of the fructose is transported through the NPOE by (7). In contrast, the ether linked di-boronic acid (11) gave the slowest fructose transport of the three carriers studied, and a fructose : glucose selectivity of 4 : 1, similar to that typically observed for mono-boronic acids. Apparently, the different angle at which the boronic acids project from the neopentyl glycol core in (11), and the added flexibility of its ether links, reduces the stability of its di-fructose di-boronate esters, resulting in lower rates of fructose transport.

Experimental

General Methods

All non-specialized starting materials were commercially available research-grade chemicals and used without further purification. THF was distilled from sodium wire / benzophenone and used directly. DMF and DMSO were stored over activated 4 Å molecular sieves for at least 24 h. Dry DCM was obtained by distillation from CaH_2 and used directly. All other solvents were used as purchased. Thin-layer chromatography was performed on silica-coated aluminium sheets (Merck, Silica gel 60 F_{254}) and viewed using ultraviolet (254 nm) light. Compounds containing boronic acids were visualized with the aid of diphenylcarbazone stain. Melting points were determined with a Reichert hot-stage melting point apparatus. Microanalyses were performed by Chemical and Micro Analytical Services (Belmont, Victoria). The majority of IR spectra were

recorded with a Perkin–Elmer 1600 series instrument. Samples were analysed as thin films (neat) or Nujol mulls mounted on NaCl plates. The IR spectrum of (15) was recorded on a Bruker IFS 55 spectrometer using a Specac single-reflection ATR system fitted with a single bounce diamond top-plate. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian 300 MHz spectrometer and referenced to the residual protonated solvent peak. Carbon atoms attached to boron were not observed due to band broadening. Low-resolution mass spectra of methanol solutions were recorded with a Micromass Platform II API QMS electrospray mass spectrometer operating in the positive ion mode. High resolution mass spectra were recorded on a Bruker BioApex 47e Fourier Transform mass spectrometer.

*2,2-Dimethyl–1,3-propanediyl bis[*p-*(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) benzoate] (6)*

Following a procedure adapted from that of Ward et al. for the synthesis of an alanine ester derivative,[8] *p*-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-benzoic acid (4)[5] (0.755 g, 3.25 mmol), neopentyl glycol (0.156 g, 1.49 mmol), and DMAP (0.081 g, 0.66 mmol) were dissolved in dry DCM (6.6 mL) at room temperature under N_2. The solution was cooled to 0°C and DCC (0.715 g, 3.47 mmol) added. The resulting mixture was stirred at 0°C for 1 h, then allowed to warm to room temperature and stirred for a further 20 h. Ethyl acetate (10 mL) was added, and the precipitated urea was removed by suction filtration and washed with more ethyl acetate (2 × 2 mL). The combined filtrate and washings were washed with 0.5 M citric acid (2 × 10 mL) and saturated $NaHCO_3$ (2 × 10 mL), then dried over Na_2SO_4 and filtered. The filtrate was concentrated in vacuum to give the crude product as an off-white solid (0.83 g, 98%). The *title compound* (6) was the only component in the crude reaction mixture detectable by ^{1}H NMR spectroscopy. A sample was further purified by recrystallization from EtOH / H_2O to give a white powder. M.p. 124–126°C. (Found: C, 65.85; H, 7.61. $C_{31}H_{42}B_2O_8$ requires C, 65.98; H, 7.50%). ν_{max} (Nujol)/cm^{-1} 1721 s, 1399 s, 1361 s, 1264 m, 1144 m, 1112 m, 1098 m, 1018 m, 857 m, 711 m; δ_H ($CDCl_3$) 8.01 (4 H, d, *J* 8.4, *o*-ArH), 7.86 (4 H, d, *J* 8.4, *m*-ArH), 4.25 (4 H, s, CH_2), 1.35 (24 H, s, $OC(CH_3)_2$), 1.16 (6 H, s, $(CH_2)_2C(CH_3)_2$); δ_C($CDCl_3$) 166.5, 134.8, 132.3, 128.6, 84.3, 70.0, 35.6, 25.1, 22.3; *m*/*z* 587.5 (100%, [M + Na$^+$]), 628.6 (60).

*2,2-Dimethyl–1,3-propanediyl bis(*p-*borono benzoate) (7)*

Following a procedure adapted from Falck et al.[7] $NaIO_4$ (1.25 g, 5.84 mmol) was added to a solution of (6) (0.505 g, 0.894 mmol) in THF / H_2O (6.7 mL / 1.6 mL) and stirred at room temperature until the reaction mixture was homogenous. HCl (2 M, 5.0 mL) was then added and the reaction mixture stirred for a further 20 min. Thereafter, the organic soluble material was extracted with ethyl acetate (2 × 15 mL). The combined organics were washed with water (2 × 10 mL) and brine (1 × 10 mL), dried over Na_2SO_4, then filtered. The filtrate was concentrated in vacuum to give an off-white coloured residue. This was dissolved in DCM (3 mL), and toluene (1 mL) was added. The DCM was removed in vacuum and cyclohexane (2 mL) added. Upon refrigeration of this solution a white precipitate formed which was filtered, washed with cyclohexane, and then dried under vacuum (~2 mmHg) to give the *title compound* (7) (0.18 g, 51%) as a white solid. M.p. 205–208°C. ν_{max} (Nujol)/cm^{-1} 3410 b, 1722 m, 1265 s, 1144 m, 1112 m 1098 m, 1018 m, 711 m; δ_H ([D$_6$]acetone) 8.01 (4 H, d, *J* 8.4, *o*-ArH), 7.96 (4 H, d, *J* 8.4, *m*-ArH), 4.27 (4 H, s, CH_2), 1.19 (6 H, s, CH_3); δ_C ([D$_6$]acetone) 166.5, 134.9, 132.4, 128.9, 70.3, 36.0, 22.2; δ_B ([D$_6$]acetone) 28.1; *m*/*z* 213.1 (70%), 225.2 (100), 249.2 (40), 437.4 (50, [monomethyl boronate + Na$^+$]), 451.4 (90, [dimethyl borate + Na$^+$]), 559.6 (30).

*1,1′-[(2,2-Dimethyl–1,3-propandiyl) bis(oxymethylene)]-bis(*p-*bromobenzene) (9)*

NaH (4.56 g, 114 mmol) was added to a solution of neopentyl glycol (2.02 g, 19.4 mmol) in dry DMF (240 mL) under an atmosphere of N_2 at 0°C. The mixture was allowed to warm to room temperature and then stirred for 30 min. Upon cooling to 0°C, NaI (5.48 g, 36.6 mmol) was added, followed by dropwise addition of 4-bromobenzyl bromide (8) (9.75 g, 39.0 mmol) in DMF (10 mL). The reaction mixture was then heated to 90°C for 24 h then allowed to cool to room temperature. Thereafter the mixture was diluted with water (70 mL) and extracted with DCM (3 × 40 mL). The organic layers were combined, washed with water (5 × 80 mL) and brine (1 × 50 mL), dried over Na_2SO_4, and filtered. The filtrate was concentrated in vacuum to give the crude product as a yellow oil (8.26 g, 97%). This compound was used for the next step without further purification. ν_{max} (neat)/cm^{-1} 3025 w, 2928 s, 2854 s, 1593 m, 1487 s, 1399 m, 1356 m, 1298 w, 1278 w, 1244 w, 1201 w, 1094 s, 1070 s, 1012 s, 828 m, 803 s, 734 m, 629 w; δ_H ($CHCl_3$) 7.45 (4 H, d, *J* 8.6, *m*-ArH), 7.18 (4 H, d, *J* 8.6, *o*-ArH), 4.44 (4 H, s, Ar-CH_2), 3.25 (4 H, s, CCH_2O), 0.95 (6 H, s, CH_3); δ_C ($CDCl_3$) 138.2, 131.6, 129.2, 121.4, 76.7, 72.7, 36.7, 22.2; *m*/*z* 463.0 (100%, [M + Na$^+$]).

*1,1′-[(2,2-Dimethyl–1,3-propandiyl) bis(oxymethylene)] bis[*p-*(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)] (10)*

The procedure for the synthesis of (10) was adapted from methodology used by Malan and Morin.[9] Potassium acetate (1.70 g, 17.3 mmol), (9) (0.53 g, 1.20 mmol), and 1,1-bis(pinacolato)diboron (1.08 g, 4.25 mmol) were combined in DMSO (13 mL) and stirred for 4 h at room temperature with a constant stream of Ar bubbling through the mixture. Thereafter, [$PdCl_2$(dppf)] (0.16 g, 0.20 mmol) was added and the reaction was stirred for a further 20 h at 100°C under Ar. Upon cooling, the mixture was diluted with ethyl acetate (100 mL) and washed with 1 M HCl (20 mL) and water (3 × 20 mL). The aqueous washings were extracted with ethyl acetate (1 × 30 mL) and the organic layers combined, dried over Na_2SO_4, and filtered. The filtrate was concentrated in vacuum to give a near-black oil. This was dissolved in acetonitrile (30 mL) and extracted with cyclohexane / *n*-hexane (2 / 1, 2 × 50 mL). The hexane layers were combined, washed with acetonitrile (2 × 20 mL), and then concentrated in vacuum to give a pale yellow oil which partially crystallized on standing (4°C). This partly crystalline mixture was triturated with acetonitrile, filtered, and washed again with acetonitrile, and the remaining white solid dried under high vacuum (~2 mmHg) overnight to give the *title compound* (10) as fine white crystals (0.82 g, 18%). M.p. 98–101°C. (Found: M + Na$^+$, 559.3445. $C_{31}H_{46}B_2O_6$.Na requires 559.3378). ν_{max} (Nujol)/cm^{-1} 1616 m, 1518 m, 1362 s, 1323 s, 1275 s, 1143 s, 1100 s, 1020 m, 860 m, 825 m, 660 m; δ_H ($CDCl_3$) 7.77 (4 H, d, *J* 8.1, *m*-ArH), 7.31 (4 H, d, *J* 8.1, *o*-ArH), 4.51 (4 H, s, ArCH_2), 3.25 (4 H, s, CCH_2O), 1.35 (24 H, s, $OC(CH_3)_2$), 0.92 (6 H, s, $(CH_2)_2C(CH_3)_2$); δ_C ($CDCl_3$) 142.3, 134.8, 126.6, 83.8, 76.6, 73.3, 35.6, 25.1, 22.6; δ_B $CDCl_3$) 31.1; *m*/*z* 559.6 (100%, [M + Na$^+$]).

*1,1′-[(2,2-Dimethyl–1,3-propandiyl) bis(oxymethylene)]-bis(*p-*borono benzene) (11)*

Compound (10) (0.100 g, 0.18 mmol) was deprotected using $NaIO_4$ (0.305 g, 1.42 mmol), THF (2.25 mL), water (0.40 mL), and HCl (2 M, 1.00 mL) according to a similar procedure to that used for the deprotection of (6). In this case, the reaction mixture was stirred for 2 h at room temperature and following workup, the crude product was obtained as an orange solid. This was purified using DCM (2 mL), toluene (1 mL), and cyclohexane (2 mL), as described for (7), to give *the title compound* (11) as a white solid (0.021 g, 32%). M.p. 188–190°C. ν_{max} (Nujol)/cm^{-1} 1613 m, 1408 s, 1340 s, 1304 s, 1133 m, 1084 m, 1021 m, 847 s, 728 m, 687 m; δ_H ($CDCl_3$) 7.78 (4 H, d, *J* 7.8, *m*-ArH), 7.17 (4 H, d, *J* 7.8, *o*-ArH), 4.51 (4 H, s, ArCH_2), 3.31 (4 H, s, CCH_2O), 0.98 (6 H, s, CH_3); δ_C ($CDCl_3$) 143.2, 135.4, 126.4, 74.3, 72.5, 36.2, 22.8; *m*/*z* 409.4 (15%, [monomethyl boronate + Na$^+$]), 423.5 (100, [dimethyl boronate + Na$^+$]).

*3-[(*p-*Nitrophenyl)methoxy]–2,2-dimethyl-1-propanol (13)*

Following the procedure of Bouzide and Suave for the mono-alkylation of diols,[10] Ag_2O (1.02 g, 4.32 mmol) was added, under an atmosphere of N_2 to a stirred solution of neopentyl glycol (0.30 g, 2.88 mmol) and *p*-nitrobenzyl bromide (12) (0.68 g, 3.17 mmol) in dry DCM (5 mL).

The resulting mixture was protected from light and stirred at room temperature for 24 h then filtered through a short silica plug. This was washed with DCM (200 mL) then ethyl acetate (200 mL). The ethyl acetate fraction was collected and washed with water (3 × 20 mL) and brine (1 × 20 mL), dried over Na_2SO_4, and filtered. The filtrate was concentrated in vacuum to give the desired product as a pale yellow oil (0.44 g, 43%). (Found: M + Na^+, 262.1046. $C_{12}H_{17}NO_4$.Na requires 262.1055). ν_{max} (neat)/cm^{-1} 3414 bs, 2960 s, 2871 s, 1605 m, 1522 s, 1495 w, 1477 m, 1403 w, 1347 s, 1201 w, 1175 w, 1105 s, 1050 s, 1016 m, 860 m, 843 m, 738 s; δ_H ($CDCl_3$) 8.21 (2 H, d, *J* 8.7, *m*-ArH), 7.48 (2 H, d, *J* 8.7, *o*-ArH), 4.61 (2 H, s, ArCH_2), 3.49 (2 H, s, CH_2OH), 3.36 (2 H, s, CH_2OCH_2), 1.61 (1 H, br, OH), 0.96 (6 H, s, CH_3); δ_C ($CDCl_3$) 147.4, 145.9, 127.6, 123.8, 79.4, 73.0, 71.6, 36.7, 22.0 (CH_3 signals overlapping); *m*/*z* 262.7 (100%, [M + Na^+]).

*3-[(*p*-Nitrophenyl)methoxy]–2,2-dimethyl-1-propanol-[*p*-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) benzoate] (14)*

The pinacol boronate (14) was prepared from the alcohol (13) (0.14 g, 0.59 mmol) using DMAP (0.01 g, 0.12 mmol), (4) (0.16 g, 0.64 mmol), DCC (0.15 g, 0.73 mmol), and dry DCM (2.1 mL) according the procedure used for the preparation of (6). Ethyl acetate (5 mL) was used to precipitate the DCU and, after workup, the crude product was obtained as a yellow oil. This was refrigerated (4°C) for 15 h, causing most of the oil to crystallize. The solid was collected and recrystallized from ethanol / H_2O. The resulting crystals were washed with MeOH to give the *title compound* (14) (0.19 g, 68%) as a white solid. M.p. 95–98°C. ν_{max} (Nujol)/cm^{-1} 1704 s, 1604 m, 1521 s, 1400 m, 1360 s, 1344 s, 1268 s, 1125 m, 1104 m; δ_H ($CDCl_3$) 8.10 (2 H, d, *J* 8.7, *m*-Ar*H*-*p*-NO_2), 7.95 (2 H, d, *J* 8.1, *m*-Ar*H*-*p*-BO_2), 7.84 (2 H, d, *J* 8.1, *o*-Ar*H*-*p*-BO_2), 7.43 (2 H, d, *J* 8.7, *o*-Ar*H*-*p*-NO_2), 4.58 (2 H, s, ArCH_2), 4.19 (2 H, s, CO_2CH_2), 3.36 (2 H, s, $ArCH_2OCH_2$), 1.37 (12 H, s, $OC(CH_3)_2$), 1.08 (6 H, s, $(CH_2)_2C(CH_3)_2$); δ_C ($CDCl_3$) 166.3, 147.1, 146.1, 134.6, 132.4, 128.4, 127.5, 123.5, 84.2, 76.6, 72.1, 70.1, 36.0, 25.0, 22.3 (CH_3 signals overlapping); *m*/*z* 492.4 (100%, [M + Na^+]).

*3-[(*p*-Nitrophenyl)methoxy]–2,2-dimethyl-1-propanol-(*p*-borono benzoate) (15)*

The pinacol-protected boronate (14) (36 mg, 0.08 mmol) was deprotected using $NaIO_4$ (60 mg, 0.28 mmol), THF (0.7 mL), water (0.14 mL), and HCl (2 M, 0.2 mL) according to the procedure used for the deprotection of (6). The reaction mixture was stirred for 3.5 h at room temperature and, following workup, the *title compound* (15) was obtained as a white solid (28 mg, 95%). M.p. 126–129°C. ν_{max} (ATR)/cm^{-1} 3493 br, 1708 s, 1606 m, 1518 s, 1402 m, 1340 s, 1264 s, 1125 m, 1101 s, 1019 m, 736 m; δ_H ([D_6]acetone/D_2O) 8.14 (2 H, d, *J* 8.6, *m*-Ar*H*-*p*-NO_2), 7.95 (4 H, br s, Ar*H*-*p*-BO_2), 7.43 (2 H, d, *J* 8.6, *o*-Ar*H*-*p*-NO_2), 4.67 (2 H, s, ArCH_2), 4.18 (2 H, s, CO_2CH_2), 3.44 (2 H, s, $ArCH_2OCH_2$), 1.08 (6 H, s, CH_3); δ_C ([D_6]acetone/D_2O) 66.6, 147.7, 146.4, 134.8, 132.2, 128.7, 127.5, 123.9, 76.8, 72.3, 70.4, 36.3, 22.3 (CH_3 signals overlapping); *m*/*z* 410.3 (32%, [M + Na^+]), 424.2 (100, [monomethyl boronate + Na^+]).

Transport Experiments

Transport Apparatus: Transport studies followed a procedure similar to one previously reported.[5] The transport apparatus consisted of two water-jacketed half-cells, clamped together and separated by a supported liquid membrane. The cells were maintained at 298 K. The half-cell volume (32.5–34.0 mL) was specific for each half-cell and measured independently for each transport study. Each half-cell was stirred by an internally mounted magnetic stirrer and paddle (200–210 rpm). The departure phase consisted of a freshly prepared solution of fructose (0.30 M) and glucose (0.30 M) in Na_2CO_3 (0.10 M, buffered at pH 11.3). The receiving phase consisted of a solution of NaH_2PO_4 (0.10 M, buffered at pH 6.0).

Membrane Preparation: The supported liquid membrane consisted of a polymer support (flat sheet of Accurel 1E membrane (thickness 0.1 mm, pore size 0.1 μm)) coated in a solution of the carrier, Aliquat 336, and 2-nitrophenyloctyl ether (NPOE). The membrane solution was generally prepared in duplicate by dissolving 25 μmol carrier and Aliquat 336 (1 equiv. per boronic acid) in a suitable solvent, dividing the solution into two equal parts, and then adding NPOE (0.25 g) to each. The solvent was removed in vacuum to give an oil, which was used to coat the polymer support. The membrane was then stored under vacuum (~2 mmHg) for 15 h.

Enzyme Assay: At 30 min intervals, aliquots were taken from the receiving phase and analyzed for sugar content. Fructose and glucose assays were undertaken following a procedure adapted from Kinksy.[11] An aliquot (initially 500 μL, but less as the sugar concentration in the receiving phase increased) of the sugar solution was transferred into a 1 mL cuvette. To this, hexokinase and glucose–6-phosphate dehydrogenase (2.5 units in 50 μL of NaH_2PO_4 (70 mM) and $MgCl_2$ (4 mM) at pH 7) and ATP (0.2 M, in 5 μL NaH_2PO_4 (70 mM), pH 7.5) were added. NADP (0.1 M, in 5 μL NaH_2PO_4 (70 mM), pH 7.5) and, subsequently, buffer (NaH_2PO_4 (0.10 M), pH 7.5) were added so that the combined volume of sugar solution and buffer was 890 μL. The absorbance of NADPH at 340 nm was monitored until a maximum was reached. The total change in absorbance was used to calculate glucose concentrations. Subsequent to stabilization of the absorbance curve, phosphoglucose isomerase (14.3 units in 50 μL of NaH_2PO_4 (70 mM) and $MgCl_2$ (4 mM) at pH 7) was added to the cuvette and the second absorbance change was used to calculate fructose concentrations.

Determination of Sugar Flux: Before each transport study, stock solutions of fructose and glucose were used to produce standard curves of fructose and glucose concentrations versus total change in absorbance resulting from the enzymatic reactions. This standard curve was then used to determine glucose and fructose concentrations in the subsequent transport experiments for that day. This approach was found to give more reliable data than simply using the literature extinction coefficient for NADPH to determine its and, hence, fructose and glucose concentrations in the receiving phase. Plots of fructose and glucose concentrations in the receiving phase versus time were used to determine sugar flux, according to Equation (*1*), where *F* is the sugar flux [mol m^{-2} s^{-1}], *S* the slope of the time-dependent concentration plot [M s^{-1}], *V* the volume in receiving phase [L], and *r* the radius of membrane exposed to the departure phase [m^2].

$$F = S \times V/\pi r^2 \qquad (1)$$

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