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# Competitive Transport of Reducing Sugars Through a Lipophilic Membrane Facilitated by Aryl Boron Acids

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***Abstract:*** The extraction and competitive transport of fructose, glucose and sucrose through dichloroethane facilitated by combinations of aryl boron acids and tetraalkyl ammonium salts is described. Although extraction abilities of the boron acids are comparable, there are distinct differences in their sugar transport properties. The aqueous solubility of the aryl boron acid is apparently a critical controlling factor of sugar flux. A combination of PBA and aliquat® 336 in the membrane effectively separates fructose from an equimolar mixture of fructose, glucose and sucrose, despite extraction experiments displaying comparable extraction of glucose and fructose.


The transport of hydrophilic diols through organic membranes, facilitated by boron acids, has been the focus of much attention in recent years.[1-5] Largely, this work was prompted by a preliminary study of Shinbo *et al,*[1] who observed that phenylboronic acid (PBA), in combination with trioctylmethylammonium chloride, facilitated the transport of fructose, mannose, galactose and glucose through dichloroethane. The investigation of boronic acid facilitated transport of other diol containing species, such as *p*-nitrophenyl glycosides,[2,3] nucleosides[4] and catecholamines,[5] has followed. These latter studies has been thorough, particularly in the case of the glycosides, but they have not involved a detailed examination of the factors governing the transport of reducing sugars and disaccharides. Herewith, we describe the results of our work in this area.

The two main transport processes identified by previous workers in the field are shown in Figure 1. In the trigonal mechanism, the diol is transported as a neutral trigonal boronate ester, whereas in the tetrahedral mechanism, the diol is transported as an anionic tetrahedral boronate salt, ion paired with a lipophilic quaternary ammonium cation. It is relevant to the current study to note that Shinbo's results suggested that the trigonal transport mechanism is ineffective at transporting reducing sugars through a bulk organic membrane.

*Results and Discussion*

The majority of the work described here has involved the transport of sugars from an alkaline departure phase to a slightly acidic receiving phase. The reasons for this are two-fold: Firstly, in the tetrahedral mechanism, hydroxide ions are co-transported with the sugar, hence sugar transport can be driven by a pH gradient.[1] Secondly, the use of a pH gradient avoids the types of complications encountered by Smith in the transport of *p*-nitrophenyl glycosides.[3a] In that study, it was found that when the pH of the departure and receiving phases were equal, a careful balance between good extraction into the membrane and effective sugar release into the receiving phase was required for efficient sugar transport to occur.

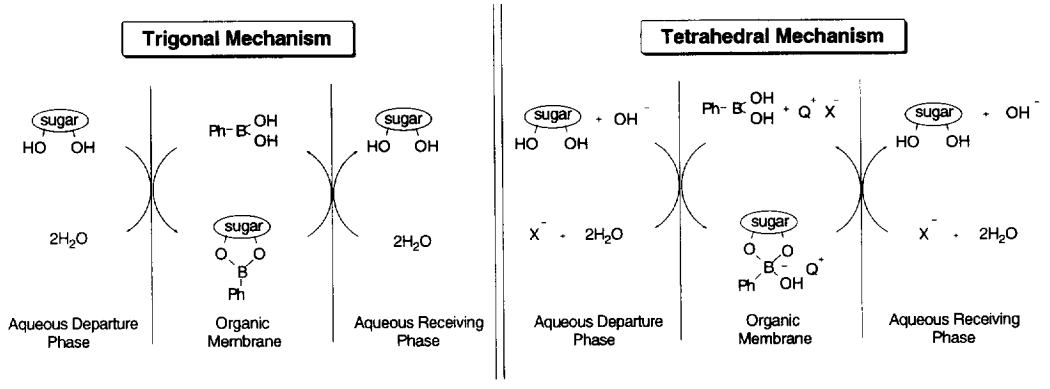


Figure 1. $Q^+$ = quaternary ammonium cation.

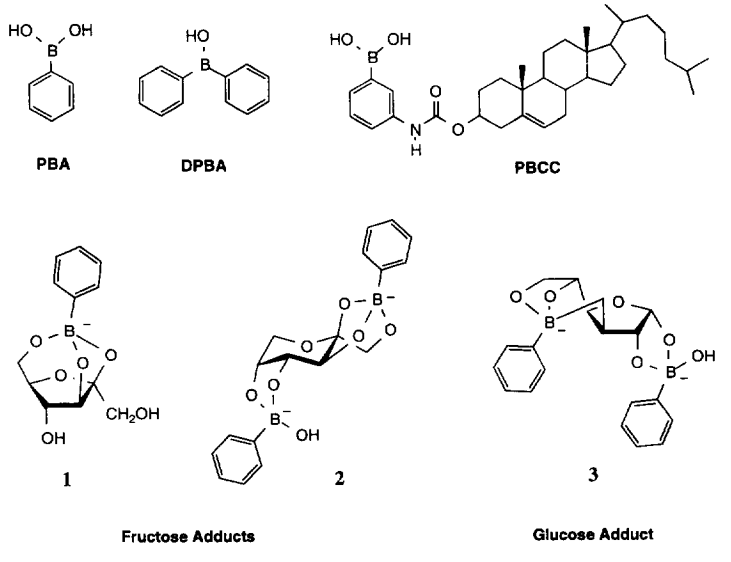


Figure 2

The present study focuses on the three sugars of primary concern to the local sugar industry, glucose, fructose and sucrose, and examines the influence of the lipophilicity of the boron acid and the quaternary ammonium salt on extraction and membrane transport of these sugars. The ability of the boron acids DPBA and PBCC (Figure 2) to transport reducing sugars or disaccharides had not been previously studied, and were chosen for their lipophilic properties, which were expected to minimise their leakage into the aqueous phases. Aliquat® 336, which predominantly consists of trioctylmethylammonium chloride, and tetrabutyl ammonium chloride (TBA) were employed as sources of lipophilic cations.

*Extraction Studies.* To find the optimum conditions for pH driven transport, a series of extraction experiments were carried out in which sugars were extracted from buffered aqueous solutions into 1,2-dichloroethane containing extractants. These extractions were performed such that an equilibrium distribution of sugars between the two phases was established. Sugar concentrations in the aqueous phase were determined by means of an enzyme assay, and the results are shown in Table 1.

Table 1. pH[a] Dependence of Percentage Extraction[b] of Sugars into 1,2-Dichloroethane Containing Extractant.

| entry | extractant[c] | fructose | | | | glucose | | | | sucrose | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | pH 6 | pH 7 | pH 8 | pH 11 | pH 6 | pH 7 | pH 8 | pH 11 | pH 6 | pH 7 | pH 8 | pH 11 |
| 1 | aliquat | 1.3 | 0.7 | 0.0 | 1.2 | 0.0 | 0.0 | 0.0 | 3.4 | 0.0 | 1.2 | 0.3 | 2.6 |
| 2 | PBA | 0.0 | 0.0 | 0.8 | 1.7 | 2.1 | 3.4 | 3.7 | 1.6 | 0.0 | 0.0 | 0.0 | 0.0 |
| 3 | PBA/TBA | 0.0 | 0.0 | 0.0 | 5.3 | 0.0 | 0.0 | 0.0 | 8.2 | 0.0 | 0.0 | 0.0 | 0.0 |
| 4 | PBA/aliquat | 0.0 | 3.2 | 0.5 | 38.2 | 0.3 | 6.4 | 0.3 | 44.0 | 0.0 | 0.3 | 0.0 | 7.5 |
| 5 | DPBA/aliquat | 43.0 | 47.3 | 47.9 | 24.9 | 26.1 | 29.8 | 31.8 | 19.8 | 2.1 | 7.0 | 0.0 | 2.3 |
| 6 | PBCC | 2.9 | 3.6 | 7.2 | 32.6 | 1.7 | 2.7 | 8.0 | 17.4 | 0.0 | 0.0 | 4.4 | -[d] |
| 7 | PBCC/aliquat | 2.5 | 1.2 | 9.4 | 59.2 | 0.0 | 0.7 | 2.1 | 46.6 | 3.0 | 0.0 | 7.1 | 2.9 |

*Footnotes:* a; pH's are of aqueous phase prior to extraction. For entries 2-4 and 7, the initial pH of 11 dropped to 10.3-10.5 after extraction. In all other cases, pH's of aqueous phases before and after extraction were identical. b; Errors: ±3.0(%). c; Boron acids and quaternary ammonium salts 10 mM, sugars 6 mM, 0.1 M phosphate buffer. No extraction into pure dichloroethane was observed at any pH for any sugar. d; Measurement not possible due to formation of permanent emulsion/gel in aqueous phase.

Controls showed that dichloroethane and aliquat in dichloroethane extracted little or no sugar from the aqueous phases at all pH's examined (Table 1, footnote c and entry 1). In the presence of boron acids, however, the pH of the aqueous phase was found to have a marked influence on the extent of sugar extracted. The observed trends in Table 1 can be explained by consideration of the $pK_a$ of the trigonal boronate esters involved: When the pH is below the $pK_a$ of the trigonal boronate ester (slightly less than 8.8 for PBA and PBCC esters and ~6.2 for DPBA esters),[3a] extraction occurs mainly *via* the trigonal esters. When the pH is above the $pK_a$ of the trigonal boronate ester, extraction *via* the tetrahedral boronate/ammonium ion pair can dominate. Examination of Table 1, entries 2, 4, 6 and 7, reveals that under conditions that essentially only allow

trigonal extraction by PBA, PBA/aliquat, PBCC and PBCC/aliquat (ie pH 6-8), minimal sugar extraction occurred indicating that for these systems, extraction as the trigonal esters is not particularly effective. In contrast, the results at pH 11 show that extraction as the tetrahedral boronate/ammonium ion pair is much more favourable. Presumably this is because the trigonal boronate esters of these sugars are not lipophilic enough to be highly soluble in the organic phase, but the addition of the lipophilicity of the ammonium cation, in the form of a tetrahedral boronate/ammonium ion pair, enhances the organic solubility of the boronate esters appreciably. Changing from PBA/aliquat to PBA/TBA results in a significant drop in sugar extraction (Table 1, entries 3 and 4), indicating that the lipophilicity of the tetrabutyl ammonium cation is not sufficient to allow high sugar extraction.

The greater lipophilicity of PBCC makes it a somewhat better extractant at pH 11, when combined with aliquat, than the other systems (Table 1, entry 7). Even in the absence of an ammonium salt, PBCC is quite effective at extracting fructose and glucose at pH 11 (Table 1, entry 6). Presumably in the latter cases, the counter ion for the tetrahedral boronate anion is $K^+$. At lower pH's (pH 6-8) the DPBA/aliquat system shows strong fructose and glucose extraction (Table 1, entry 5), but at pH 11, sugar extraction is suppressed. This is apparently a result of a competition between hydroxide and sugar for DPBA, with hydroxide competing more effectively at higher pH's.[3a]

Where high extractions were observed, they were generally in the order fructose ≥ glucose >> sucrose, which is consistent with previous conclusions that *cis*-1,2 diols and convergent triols form the more stable boronate esters.[3-7] Sucrose lacks such diol arrangements and has the additional impediment of having a larger hydrophilic surface than either fructose or glucose. Hence it is not surprising that minimal sucrose extraction was observed under all conditions. The structures of the boronate adducts of fructose and glucose with PBA in alkaline aqueous solution are thought to resemble those shown in Figure 2.[6,7]

*Transport Studies.* The ability of a range of carrier combinations to transport fructose, glucose and sucrose was examined. Table 1 shows that the maximum differential in extraction occurs between pH 6 and 11 for PBA/aliquat and PBCC/aliquat (entries 4 and 7) and pH 6 and 8 for DPBA/aliquat (entry 5). It was therefore expected that optimal transport would occur when those pH's were used for the receiving and departure phases respectively. The enzyme assay procedure employed to measure sugar concentrations allows the determination of individual sugar concentrations in a mixture, hence the majority of the sugar fluxes described here are competitive transport rates. This contrasts with previous sugar transport studies, where only uncompetitive fluxes were measured.[1-3] Sugar fluxes into the receiving phase, determined in this study, are shown in Table 2.

PBA mediated transport, particularly the PBA/aliquat system (Table 2, entry 3), gave the highest fluxes and so will be discussed first. PBA alone gave poor sugar transport (Table 2, entry 1), as did a combination of neutral departure and receiving phases in the PBA/aliquat system (Table 2, footnote a). These results,

consistent with Shinbo's findings,[1] indicate that the tetrahedral pathway with PBA is the most effective transport mechanism for reducing sugars.

Table 2. Competitive Sugar Fluxes.

| entry | Carrier system[a] | flux receiving phase[b] ($10^{-7}$ mol $s^{-1}$ $m^{-2}$) | | |
|---|---|---|---|---|
| | | fructose | glucose | sucrose |
| 1 | PBA | 0.2 | 0.0 | 0.0 |
| 2 | PBA/TBA | 0.6 | 0.0 | 0.0 |
| 3 | PBA/aliquat | 18.2 | 2.8 | 0.4 |
| 4 | DPBA/aliquat | 2.8 | 2.3 | 0.8 |
| 5 | PBCC | 1.6 | 1.1 | 1.3 |
| 6 | PBCC/aliquat | 0.5 | 0.0 | 0.4 |

a; Phosphate buffer was used in all cases shown. Entries 1-3, 5 and 6; pH 11 departure and pH 6 receiving phases; entry 4; pH 8 departure and pH 6 receiving phases. Solvent was 1,2-dichloroethane. No sugar transport was observed for the cases where (i) no carrier was present, (ii) when the carrier system was DPBA/TBA, (iii) when both aqueous phases were neutral or (iv) when the solvent contained aliquat alone. b; In each case, fluxes shown are averages from at least two transport experiments. Errors: $\pm 2 \times 10^{-7}$ mol $s^{-1}$ $m^{-2}$

It is evident from Table 2 and Figures 3-6 that the observed sugar fluxes are sensitive to a number of factors. The critical nature of the lipophilicity of the counter ion is highlighted by the flux differentials between the PBA/aliquat with PBA/TBA systems (Table 2, entries 2 and 3). Maintenance of the departure phase pH above the $pK_a$ of trigonal boronate ester, thus ensuring continued tetrahedral boronate transport throughout the experiment, is also crucial, as demonstrated in Figures 3 and 4: A pH drop in the departure phase was observed as the transport experiment proceeded, if the departure phase pH was out of the effective buffering range of the buffer. This is because hydroxide ions are transported by PBA/aliquat with (or without) sugars (see Figure 1). Such a pH drop was observed when the departure phase contained potassium phosphate (Figure 3), and translated into a significant fall off in transport rate once the pH of the departure phase had dropped below ~8.8 (Figure 4). When carbonate buffer was used in the departure phase however, its pH was maintained well above 8.8 for the entire experiment (Figure 3), and the transport rate did not drop off until the majority of the fructose had been transported into the receiving phase (Figure 4). It should be noted from Figure 4 that for the first ~5 hours of the experiment, the fructose transport out of phosphate and carbonate buffers occurred at essentially identical rates.

The importance of maintaining the receiving phase pH below the $pK_a$ of the trigonal boronate ester is demonstrated in Figure 5. In this experiment, both aqueous phase pH's were set at 11. Initially the fructose flux out of the departure phase was high, but an induction period of approximately 2 hours occurred before fructose began to appear in the receiving phase. Soon after, both fluxes subsided. In contrast to all other

experiments, there was also considerable build up of fructose in the membrane, and fructose concentration in departure and receiving phases became equivalent after 24 hours. These results mirror the observations of Smith in the transport of aryl glycosides.[3a]

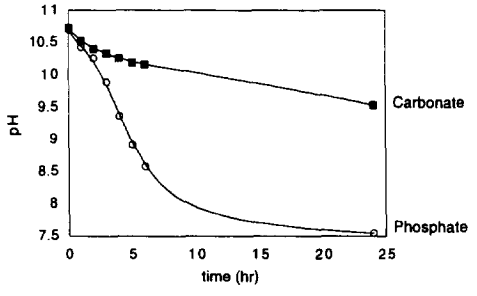


Figure 3

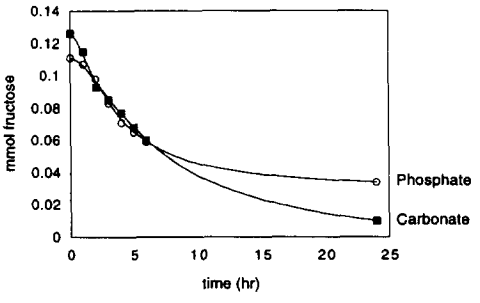


Figure 4

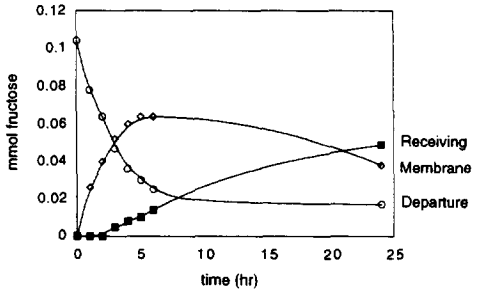


Figure 5

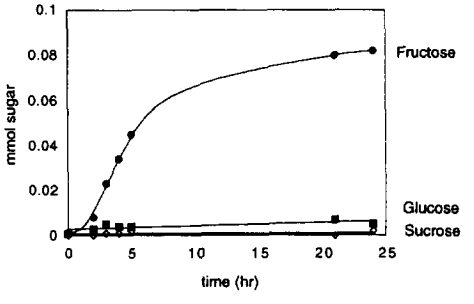


Figure 6

*Footnotes:* All curves represent lines of best fit. Data for Figures 3 and 4 come from same experiment.

*Figure 3:* Plot showing pH of departure phase as a function of time for phosphate (0.1 M) and carbonate buffers (0.1 M). PBA/aliquat carrier system, departure phase initially contained 6 mM fructose, glucose and sucrose, receiving phases buffered at pH 6 with potassium phosphate (0.1M). *Figure 4:* Amount of fructose in departure phase as a function of time with phosphate and carbonate used to buffer the departure phase. *Figure 5:* Transport experiment in which both aqueous phases contained potassium phosphate (0.1M) at pH 11. PBA/aliquat carrier system, fructose (6 mM) was the only sugar present. Membrane sugar concentration was determined by difference. Volume receiving phase was three times volume of departure phase, hence final sugar concentrations in both phases were identical, within experimental error. *Figure 6:* Amounts of sugars in receiving phase as a function of time. PBA/aliquat carrier system, departure and receiving phases initially buffered with potassium phosphate (0.1 M) at pH 11 and 6 respectively. Departure phase initially contained fructose, glucose and sucrose at 6 mM.

Transport mediated by PBCC and DPBA will now be considered: Given the large extraction differential between pH 6 and 11 for the PBCC/aliquat system (Table 1, entry 7), it was somewhat surprising to find that this system gave minimal sugar transport (Table 2, entry 6). In attempting to understand this apparent dichotomy, it should be kept in mind that the extraction data represent final equilibria, whereas sugar fluxes are also governed by the kinetics of diffusion, particularly in interfacial regions. In addition, it is assumed that the

formation and hydrolysis of the sugar boronate esters is not rate limiting.[3a] Importantly, no significant build-up of sugars in the membrane was observed in any of the experiments referred to in Table 2. This indicates that in all of those cases, the release of sugar from the membrane is not rate limiting, even with the more lipophilic boron acids. This result is of particular note for the DPBA/aliquat system, which displays only negligible difference in extraction between departure and receiving phase pH's (pH 6 and 8, Table 1, entry 5), and hence could be expected to give high sugar build-up in the membrane during the transport experiment. The lack of such a build-up for this system clearly indicates that its poor transport properties (Table 2, entry 4) are predominantly a result of the DPBA being unable to extract the sugars from the aqueous phase in a kinetically competent manner. This should be contrasted with the PBA/aliquat system that employed pH 11 departure and receiving phases, in which substantial sugar build-up in the membrane occurred (Figure 5).

We propose that the reason PBA/aliquat succeeds where DPBA/aliquat and PBCC/aliquat fail relates to the fact that PBA is much more soluble in the aqueous departure phase than the other boron acids. Thus PBA is able to diffuse from the organic membrane into the aqueous phase, react with sugars to form a tetrahedral boronate, ion pair with aliquat at the interface and move back into the membrane.[3b] The low water solubility of DPBA and PBCC means that, in contrast to PBA, they are unable to readily move into the aqueous departure phase, and sugar transport is negligible. Reducing the lipophilicity of the quaternary ammonium cation, by changing to DPBA/TBA, made no improvement on the transport by DPBA (Table 2, footnote a),[8] indicating that it is the lipophilicity of DPBA alone, not that of the overall boronate anion-cation pair that hinders sugar transport in that system. The poor transport promoted by PBCC is also likely to be due to aggregation behaviour at the aqueous-organic interface. These results suggest that, in general, reducing sugar fluxes through bulk liquid membranes mediated by highly lipophilic boron acids are likely to be low, and have highlighted an important aspect of boron acid promoted sugar transport that has only recently been considered.[3b]

Another striking feature of the transport results, when compared to the extraction data, is the change to a high selectivity for fructose, when the three sugars are in direct competition for boron acid carrier.[9] Figure 6 shows how effective the PBA/aliquat system is at separating fructose from an equimolar mixture of fructose, glucose and sucrose. In fact, it was found that after 24 hours, approximately 70% of the fructose was transported out of the departure phase, compared to <4% for glucose and sucrose. As in the extraction experiments, the poor sucrose flux probably results from its greater hydrophilic surface and lack of suitably arranged alcohol groups. The highly selective transport for fructose over glucose, given that the extractions were virtually equivalent (Table 1), is less easy to rationalise. To do so, one must consider the structures of the most stable tetrahedral PBA boronate esters of fructose and glucose formed under alkaline conditions, thought[6,7] to resemble those shown in Figure 2. PBA apparently reacts with both the pyranose and furanose forms of fructose to form stable tetrahedral boronate esters (**1** and **2**). Since both forms of fructose are relatively abundant in aqueous solution,[7] formation of these adducts is rapid and so is transport. Glucose exists almost exclusively in the pyranose form in aqueous solution,[7] but it is the reaction between PBA and the furanose form

that produces the stable complex shown as **3**. Isomerisation of glucose to the furanose form, and its subsequent extraction as **3**, can readily occur under the equilibrium conditions of the extraction experiments, and hence fructose and glucose are extracted to similar extents. However, in the kinetically controlled transport experiment, glucose transport is minimal presumably because the concentration of its furanose form in aqueous solution is very low.

*Conclusions*

Consistent with a previous study,[1] it has been found that the tetrahedral mechanism for the boronic acid mediated transport of reducing sugars through a chlorinated solvent is far more important than the trigonal mechanism. Changing the lipophilicity of the boron acid has shown that pH driven sugar transport rates are controlled by the ability of the carrier combination to extract the sugar into the membrane, *in a kinetically competent manner*. For high sugar fluxes, intermediate lipophilicity of the boronic acid is required, so that a balance between extraction ability and aqueous solubility[3b] is achieved. This is a new perspective on the factors controlling sugar transport through a lipophilic membrane.

It has also been shown that PBA/aliquat, although able to extract fructose and glucose into an organic solvent equally well, can readily separate fructose from an equimolar mixture of fructose, glucose and sucrose, by the highly selective transport of fructose through a bulk organic membrane. This effect most likely reflects the low concentration of the furanose form of glucose in aqueous solution.

The results described here show that one should be very cautious about using extraction data to directly predict transport rates.

*Experimental*

*General.* Phenylboronic acid (PBA), Aliquat® 336 and tetrabutyl ammonium chloride were obtained from Aldrich Chemical Company and used without further purification. Diphenylborinic acid was prepared by deprotection of diphenylborinic acid ethanolamine ester according to the method of Coates and Livingstone.[10] ATP (disodium salt), Glucose-6-phosphate dehydrogenase, phosphoglucose isomerase and invertase were obtained from Sigma. Hexokinase, $NAD^+$ (free acid) and bovine serum albumin were obtained from Boehringer Manheim. Sugar concentrations were determined according to the procedure described by Boehringer Manheim.[11]

*Cholest-5-en-3-ol (3β)-, (3-boronophenyl)carbamate (PBCC)* Cholesterol chloroformate (2.4 g, 5.4 mmol) and 3-aminophenylboronic acid (1.0 g, 5.4 mmol) where dissolved in dry distilled diethyl ether under nitrogen. N-methylimidazole (0.9g, 11 mmol) was then added with stirring. The resulting cloudy solution was stirred at room temperature for 24 hours and the reaction monitored by TLC. The mixture was then diluted with diethyl ether (150 mL) and washed with water (4x). The ether layer was dried over $MgSO_4$ and the solvent removed by rotary evaporation. Pure PBCC was obtained as a white powder (1.0 g, ~35%) by recrystallisation from

hexane/ethyl acetate (2:1). mp 255 - 258°C [lit[12] mp 220°C (decomp.)] A proton nmr spectrum ($CDCl_3$) of this product suggested that it consisted of a mixture of free boronic acid and the corresponding trimeric anhydride. The spectrum simplified to that of a monomer on addition of a few drops of $D_2O$ or $CD_3OD$. The addition of a few drops of water also enhanced the solubility of PBCC in chlorinated solvents. $^1H$ NMR (300 MHz, $CDCl_3/D_2O$ ~90:10) δ 0.6-2.6 (m, 43H), 4.5-4.7 (m., 1H), 5.41 (d, *J*=3.3 Hz, 1H), 6.69 (s, 1H), 7.35 (m, 2H), 7.48 (d, *J*=5.5 Hz, 1H), 7.83 (s, 1H). IR (Nujol) ν $cm^{-1}$: 3309 (br.), 1741, 1683, 1566, 1232, 1130, 1036, 694.

*Extraction Studies.* A solution of the appropriate carrier (0.5 mL, 10 mM boron acid and/or ammonium salt) in 1,2-dichloroethane was added to a 1.5 mL eppendorf tube. A solution of the sugar (0.5 mL, 6 mM) buffered to the appropriate pH with 0.1 M potassium phosphate, was then added and the resultant mixture vigorously shaken on a Griffin mechanical shaker for 10 min. The mixture was then clarified by centrifugation. Sugar concentrations in the aqueous phase were determined in duplicate before and after exposure to the extractant by means of enzyme assay. The whole process was repeated four more times for each carrier combination. Thus, each value in Table 1 is an average of ten individual determinations. Shaking for longer periods resulted in no further change in aqueous phase sugar concentration.

*Transport Studies.* Transport cells were modified from a design by Lamb.[13] They consisted of two concentric glass cylinders, 28 mm and 55 mm in diameter. The outer cylinder was 100 mm high and sealed flat at the bottom. The inner cylinder was 67 mm high and mounted 9 mm from the bottom. This arrangement ensured that the departure and receiving phases never came in direct contact with each other. The apparatus was maintained at 22°C by means of a water jacket and a Thermoline Unistat II heater/circulator and water bath. The organic phase was stirred with a single paddle (22 mm x 5 mm) attached to a Janke and Krunkel RW10R mechanical stirrer operating at 230 ± 10 rpm, as determined by an Emtek DT 2234 digital tachometer.

Transport experiments were performed as follows: A solution of the appropriate carrier(s) (60 mL) in 1,2-dichloroethane was shaken in a separatory funnel with an equal volume of potassium phosphate solution (0.1 M) buffered to the pH of the departure phase. After the layers separated, 60 mL of the organic phase was placed in the bottom of the transport cell. The receiving phase were then carefully added, followed by the departure phase. In all but one case, the receiving phase consisted of potassium phosphate solution (60 mL, 0.1 M, pH 6). The exception was when the pH of the receiving phase was initially set to 11. The results from that experiment are displayed in Figure 5. The PBA and PBCC experiments employed potassium phosphate or potassium carbonate solution (20 mL, 0.1 M, pH 11) as the departure phase whereas the DPBA experiments used potassium phosphate solution (20 mL, 0.1 M, pH 8). Sugars were initially in equimolar concentrations in the departure phase (6 mM each). Carrier concentrations were 10 mM for both boron acid and ammonium salt.

Immediately after the addition of the aqueous phases to the transport apparatus, aliquots (2 x 20 μL) were taken from departure and receiving phases, and analysed for sugar content by enzyme assay. The average of these values was taken as the sugar concentrations in both aqueous phases at t = 0. The process was

repeated at one hour intervals for the first 5 - 6 hours, and again at t = 20 and/or 24 hours (see figures 4 - 6 for representative examples). The data shown in Table 2 are receiving phase sugar fluxes, averaged over the first 5 - 6 hours of the experiment. The surface area used in the flux calculation was the area of the interface between the two phases only, i.e. for flux out of the departure phase, the interface was a disc 28 mm in diameter, whereas for the receiving phase it was the area of a disc 56 mm in diameter minus the area of a disc 28 mm in diameter. The values are averages from at least two transport experiments. The pH of the aqueous phases was monitored with a Hanna Instruments 8521 pH meter using a HI 1230 electrode.

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8 This contrasts with Smith's observations of aryl glycoside transport facilitated by DPBA.[3a] In those experiments, both receiving and departure phases were set at pH = 7.4.

9 Uncompetitive fluxes were found to be of the same order of magnitude as those shown in Table 2.

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