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Liquid membrane transport using boronic acid carriers‡

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This review summarizes the recent research on a new application with boronic acids, namely their ability to act as transport carriers in bulk, liquid organic membranes. To date, boronic acids have been shown to facilitate the transport of reducing monosaccharides, ribonucleosides, aryl glycosides, catecholamines, α-amino acids, and riboflavin. The transport can either be passive (down a solute concentration gradient) or active (against a solute concentration gradient). The various chemical mechanisms for boronic acid mediated transport are described, as well as the chemical and physical factors that control transport rates.

INTRODUCTION

It has been known for more than forty years that boronic acids can form covalent complexes with a range of bidentate compounds.[1] This reversible interaction has been exploited extensively as a diol protecting group strategy in organic synthesis,[2] and is the basis of a chromatographic method to separate polyols.[3] The purpose of this review is to summarize the recent research on a new application with boronic acids, namely their ability to act as transport carriers in liquid organic membranes. Over the last twenty-five years, a large number of artificial carriers have been developed for membrane transport.[4] Most have been ionophores that are selective for cations;[5] however, more recently there has been increased emphasis on carriers for anions and neutral hydrophilic solutes.[6] There are a variety of potential applications for such carriers including small and large scale separations, electrode sensing, drug delivery, and controlled-release technology.[4]

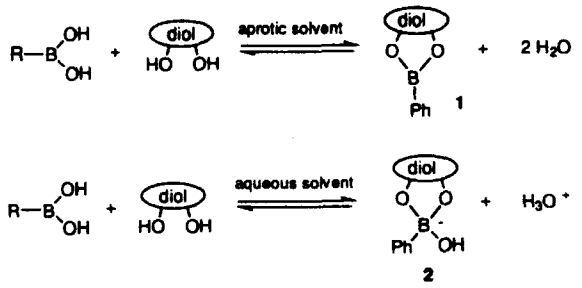
To date, boronic acids have been shown to facilitate the transport of reducing monosaccharides,[7] ribonucleosides,[8] aryl glycosides,[9] catecholamines,[10] α-amino acids,[11] and riboflavin.[12] The transport can either be passive (down a solute concentration gradient) or active (against a solute concentration gradient). Described below are the various chemical mechanisms for boronic acid mediated transport, as well as the chemical and physical factors that control transport rates. Boronic acids are also being studied in other areas of molecular recognition, particularly in chemosensing;[13] however, those efforts will not be discussed here.

Essentially all the transport experiments described here have used Bulk Liquid Membranes (BLMs) in a standard U tube apparatus.[4,5] In this configuration an aqueous departure phase is separated from an aqueous receiving phase by a dense organic solvent (*e.g.*, dichloroethane). The organic phase is stirred using a magnetic stir bar and in some cases the aqueous layers are also stirred. The main advantages of BLMs, compared to other membrane systems, are the ease of operation, low cost, and the less stringent requirement for the carriers to be highly lipophilic.[14] Disadvantages include the need for large amounts of carrier, the relatively low transport fluxes, and the poor reproducibility. This latter point is due to the difficulty in reproducing BLM permeability which is sensitive to a variety of factors such as stirring rate, temperature, U tube hydrodynamics, solvent viscosity, etc. Because of these uncertainties, BLMs are not practical on the industrial scale. BLMs are best used as an initial screen of transport ability for carrier candidates. For industrial applications, Supported Liquid Membranes (SLMs), where the organic layer is immobilized within the pores of a thin (~100 μm) polymer support, or Emulsion Liquid Membranes (ELMs) are considered to be more attractive, although the design requirements are significantly more complicated.[4,14,15] If the goal of the separation is to reclaim the transported material, the use of SLMs in a hollow fiber geometry is probably the membrane system of commercial choice.[4,5,14,15]

Transport of diol-containing compounds

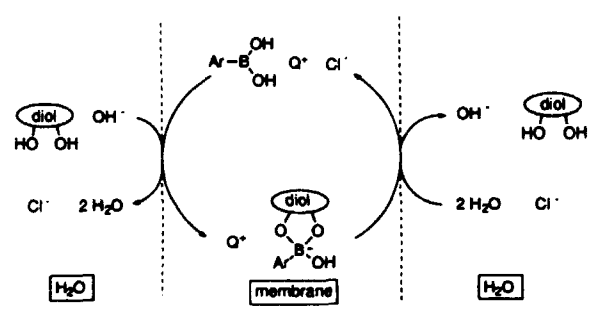
In anhydrous aprotic solvents, boronic acids readily condense with diol-containing compounds to form trigonal boronate esters, **1**. In aqueous solution, the trigonal boronates are unstable and either hydrolyze back to starting compounds or ionize to form anionic tetrahedral boronates, **2**. Since a boronate ester is more acidic than its parent boronic acid, the predominant complexation

product between an arylboronic acid, such as phenylboronic acid (pKa = 8.9), and a diol at pH 7 is boronate **2**. A salient point is that although covalent bonds are formed, the associated activation energy is low, so the process is rapid and reversible.



In 1986, Shinbo and co-workers reported that a mixture of phenylboronic acid (PBA) and trimethyloctylammonium (TOMA) chloride could extract reducing monosaccharides from aqueous solution and transport them through BLMs.[7] Transport was observed to be pH sensitive, in that active saccharide transport could be achieved from a basic departure phase into an acidic receiving phase. The mechanistic transport scheme invoked to explain these observations is described in Scheme 1.

Subsequent studies by Czarnik,[8a,b] and our group,[8c,9] showed that other hydrophilic diol-containing compounds, namely nucleosides and aryl glycosides, could be transported by this ion-pair process. Under low extraction conditions the order of transport enhancements reflected the known order of boronic acid affinities for cyclic diols which is cis-α,β-diol > cis-α,γ-diol > trans-α,γ-diol >> trans-α,β-diol. Thus, the order of transport enhancements for nucleosides was ribonucleosides >> 2'-deoxyribonucleosides, and for glycopyranosides, galactoside > mannoside > glucoside > xyloside. In the case of monosaccharides, the transport enhancement order was fructose ~ mannose > galactose > glucose.[7] In this series, however, the order of sugar selectivity is more difficult to rationalize because reducing sugars are known to isomerize in the presence of boronic acids making the identity of the sugar/boronate complex less certain.[9b] In particular, there is a strong bias towards complexation of hexoses as their furanose isomers.[16]

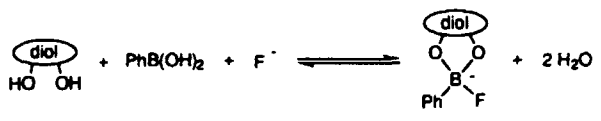


Scheme 1 Diol transport mediated by tetrahedral boronate formation. pH < boronic acid pKa. Q^+ = quaternary ammonium cation such as trioctylmethylammonium (TOMA).

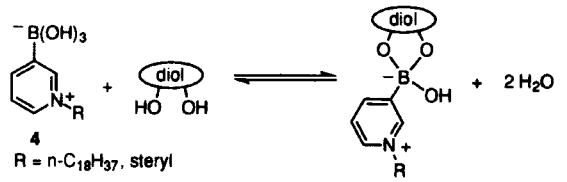
As already stated, the ion-pair transport pathway shown in Scheme 1 is pH sensitive; diol extraction increases significantly if the aqueous phase pH becomes more basic than the boronic acid pK_a. Since the ability of F^- to form dative bonds with trigonal boron acids is similar to that of OH^-, we wondered if F^- ions could be used as a substitute for OH^-. In otherwords, could F^- ions promote formation of the anionic tetrahedral fluoroboronate **3** (Scheme 2) and induce transport via an ion-pair mechanism analogous to that described in Scheme 1? This was indeed the case.[8c] Addition of KF (0.5 M) to a departure phase buffered at pH 7 was found to increase the passive nucleoside transport ability of a PBA-TOMA carrier admixture by a factor of three. Moreover, active nucleoside transport was achieved in the direction of a F^- concentration gradient. Control experiments showed that KCl and KBr had no effect on transport.

Czarnik devised an elegant improvement on PBA-TOMA as a carrier admixture by synthesizing the lipophilic alkylated pyridylboronic acids, **4**.[8b] Functioning as covalent versions of PBA-TOMA, carriers **4** were found to transport nucleosides up to eight-fold better (*e.g.*, 0.5 mM of carrier **4** enhanced uridine transport over 100 times the rate of background diffusion). At pH 7, compounds **4** exist as zwitterions, thus the principal binding equilibrium is that shown in Scheme 3.

Our research group has extended this ion-pair transport mechanism in an alternative direction. We reasoned that another way of producing a lipophilic cation to ion-pair with the diol-boronate anion would be to complex a metal cation inside a lipophilic ionophore. Our first attempt using a PBA-[2.2.2]cryptand admixture produced a modest transport enhancement of glucoside transport.[9a] The design was improved by covalently linking the boronic acid and the ionophore together. The first example was compound **5**, where an arylboronic acid and a benzo-15-crown-5 were fixed together in a preorganized cleft arrangement. Compound **5** was found to act as a functionally biomimetic sodium-saccharide cotransporter.[9d] A liquid membrane containing 1 mM of **5** transported an

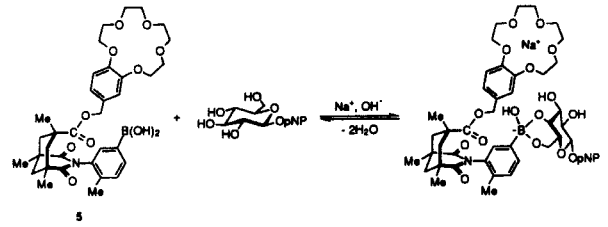


Scheme 2



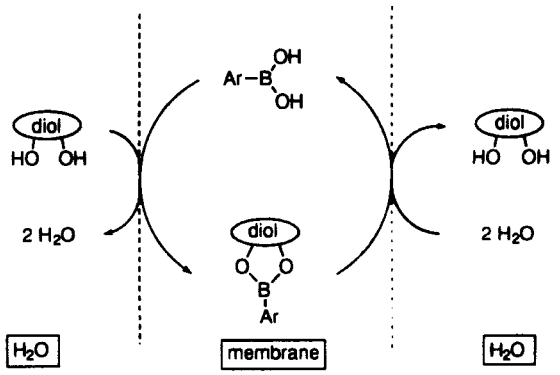
Scheme 3

aryl glucoside five times faster than the background rate, whereas an equimolar mixture of PBA and benzo-15-crown-5 produced negligible transport enhancement. Carrier **5**, however, was less than half as effective at glucoside transport as PBA-TOMA, reflecting among other things the inherent difficulty for a heterotopic receptor like **5** to simultaneously bind and cotransport two different solutes (Scheme 4). Consideration of the binding equilibrium in Scheme 4 indicated that glycoside transport should be sensitive to Na^+ ion concentrations in the aqueous phases. Moreover, active transport in the direction of a Na^+ ion gradient was predicted to occur and subsequently found to be the case. Carrier **5** represents the first artificial sodium-saccharide cotransporter to mimic, at least functionally, the way nature uses the ubiquitous inward-directed Na^+ gradient to actively transport sugars into cells.[9a,d]



Scheme 4 Simultaneous binding of Na^+ and aryl glycoside by carrier **5**.

In certain cases, significant transport has been achieved using boronic acids alone. We found that boronic acids can mediate glycopyranoside transport by forming a reversible trigonal boronate ester with a glycopyranoside diol (Scheme 5).[9b] The order of diol selectivity for this trigonal boronate transport pathway was observed to be cis-α,γ-diol > cis-α,β-diol ≈ trans-α,γ-diol >> trans-α,β-diol, which differs slightly from the selectivity of the tetrahedral boronate pathway. As noted above, trigonal boronate esters are usually unstable in an aqueous environment and thus a minor presence. However, at an aqueous / organic interface a lipophilic boronate ester is able to partition into the organic phase where it is protected from hydrolysis. Other factors that strongly effect the trigonal boronate transport pathway are the lipophilicity of the boronic acid carrier and aqueous phase pH. Shinkai and coworkers reported that highly lipophilic boronic acids are able to efficiently extract reducing monosaccharides into an organic



Scheme 5 Diol transport mediated by transient trigonal boronate ester formation.

layer.[17] Although liquid membrane transport was not the goal of their work, it seems likely that it would have occurred. The effect of pH on the trigonal boronate pathway is varied. We have found that PBA alone is unable to transport ribonucleosides at neutral pH, while significant transport is observed at pH 4.[18] On the other hand, galactopyranoside transport mediated by PBA was a maximum at pH 7. Most recently, Rotello has reported that 3 mM of PBA at pH 7 is able to enhance riboflavin transport over two hundred times the background rate.[12] There is little doubt that the trigonal boronate transport mechanism is operating here, although the stoichiometry and regiochemistry of binding is still to be established.

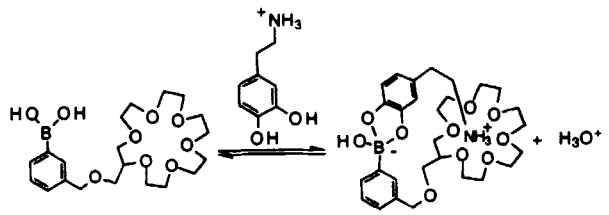
Dopamine transport

The crowned boronic acid **6** was designed as a selective carrier for dopamine transport.[10] A liquid membrane containing 1 mM of **6** transported dopamine 160 times faster than background diffusion (Table 1). An interesting design feature with carrier **6** is illustrated in Scheme 6.

Table 1 Transport rates for catecholamines, glycosides, and uridine in the presence and absence of carrier **6**.

entry	*transported compound*[a]	*no carrier (± 15%)*[f]	*carrier* **6** *(± 15%)*[f]	*rate enhancement*[g]
1	dopamine[b]	2.2	356	160
2	norepinephrine[b]	2	120	60
3	epinephrine[b]	3.4	6.8	2
4	tyramine[b]	70	70	1
5	*p*-nitrophenyl β-glucoside[c,d]	1.3	3.9	3
6	*p*-nitrophenyl β-mannoside[c,d]	1.6	5.3	2
7	uridine[c,d]	0.2	0.2	1

[a]Departure phase: sodium phosphate buffer (100 mM, pH 7.4), sodium dithionite (10 mM): Organic phase: carrier **6** (1 mM) in chloroform: Receiving phase: sodium phosphate buffer (100 mM, pH 7.4), sodium dithionite (10 mM). [b]Departure side initially contained 41 mM of catecholamine. [c]The starting concentration of transported species was adjusted to give a similar rate of background diffusion. [d]Departure side initially contained 1.36 mM of glycoside. [e]Departure side initially contained 20 mM of uridine. [f]Rate (10^{-8} M min^{-1}) that transported solute initially appeared in receiving phase. [g]Transport rate in the presence of carrier **6** divided by the rate in the absence of carrier.

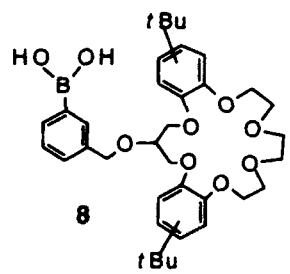


6 7

Scheme 6

Not only is it dopamine shape-selective, but the resulting complex **7** is charge balanced and does not need an accompanying counter ion for transport. This provided carrier **6** with a novel selectivity mechanism for dopamine transport which is reflected by the data shown in Table 1. Since the association of dopamine and carrier **6** was an acid-producing equilibrium, it was possible to use a pH gradient to actively drive the dopamine into an acidic receiving phase.

The goal of this ongoing project is to develop a dopamine carrier that will purify and concentrate body-fluid samples for clinical dopamine analysis.[10,19] The most likely membrane system for such an application is a SLM, which means the carrier has to be highly lipophilic. In an attempt to satisfy this requirement, carrier **8** was synthesized and its BLM transport ability determined. Unfortunately carrier **8** transported dopamine fifteen times more poorly than the prototype **6**.[20] It appears that although the carrier lipophilicity was greatly improved, the four phenolic oxygens in **8** are less able to form hydrogens bond with the dopamine ammonium group.[21] Transport studies with SLMs are currently underway.

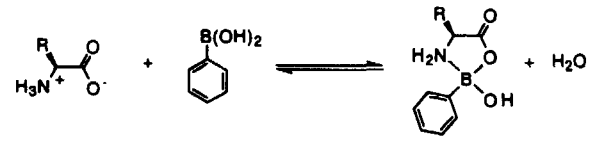


8

Amino acid transport

Boronic acids have also been reported to transport α-amino acids. Czarnik found that a liquid membrane containing 2 mM of PBA-TOMA enhanced phenylalanine transport about one hundred times over background.[11a] NMR studies of PBA mixed with amino acids in organic solvents suggested the formation of the chelated complex **9** as shown in Scheme 7.

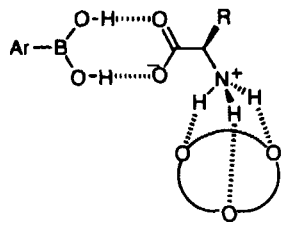
In a subsequent study, Reetz discovered that mixtures of arylboronic acids and crown ethers were even better at



9

Scheme 7

amino acid transport.[11b] For example, an admixture of PBA and 18-crown-6 transported phenylalanine forty eight times better than PBA-TOMA. Control experiments indicated that Czarnik's chelate mechanism was not the major transport pathway in this case. An X-ray analysis of crystals obtained upon mixing PBA, 18-crown-6, and phenylalanine, uncovered a remarkable three-component complex held together by hydrogen bonds. A schematic representation of the complex is shown in Scheme 8.



Scheme 8

Chemical and physical factors that control transport rate

In an attempt to fully understand the BLM transport process, we undertook a detailed study of the factors that control glycopyranoside transport rates.[9c] We found that transport was dependent on the extraction ability of the boronic acid carrier. An extraction constant, K_{ex}, was calculated using the following expression:

$$\underset{(aq)}{G} + \underset{(org)}{B} \overset{K_{ex}}{\rightleftharpoons} \underset{(org)}{GB}$$

where: G = uncomplexed glycoside
B = uncomplexed boronic acid
GB = glycoside-boronate complex

A plot of Transport Rate versus log K_{ex} exhibited an approximate bell-shaped curve with maximal transport occurring when the carrier had an extraction constant, $K_{ex(max)} \sim 2.2$ (Figure 1).

We were able to show that of the various transport models that can explain this bell-shaped relationship, a diffusion-controlled process was the most likely.[9c] The diffusion-controlled model, which is often seen in ionophore-mediated transport, assumes the kinetics of carrier complexation are rapid, and that the rate-determining step is diffusion of the solutes through the

unstirred layers (Nernst layers) of the three-phase system.[5a] Transport flux through the unstirred layers is in turn determined by the carrier extraction equilibrium constant, K_{ex}. The observed bell-shaped correlation is rationalized in the following way.[2] Transport is a multi-step process involving extraction of the solute from the departure phase, movement of the carrier/solute complex through the organic layer, and subsequent stripping of the complex into the receiving phase. Under conditions of weak extraction, transport is slow due to the low amounts of solute moving from the departure phase into the organic layer. Under conditions of high extraction, it is the low solute concentrations moving from the organic layer into the receiving phase that is the rate-determining step. Although the diffusion-controlled mechanism has only been proven in the case of glycopyranoside transport, it is likely the other boronic acid transport systems listed above are also diffusion-controlled. A corrollary of the diffusion-controlled process is that K_{ex} is the critical variable determining transport rate.[5a] Therefore, an analysis of the factors that control transport can be reduced to an analysis of the factors that change K_{ex} relative to $K_{ex(max)}$. In the case of glycopyranoside transport, the chemical and environmental factors that effect K_{ex} have been described in detail.[9c]

The bell-shaped relationship between transport rate and K_{ex} must be borne in mind if these transport systems are used in a separations application. If maximum rate is the desired result then the transport system should be adjusted either structurally or environmentally to achieve $K_{ex(max)}$. If the desired result is to maximize the difference in rate between two solutes, then a more sophisticated analysis is required. Consider, with the aid of Figure 2, the hypothetical stereoselective separation of isomer A from isomer B. Assume the carrier involved always extracts A better than B. Under low extraction conditions, where both $K_{ex}(A)$ and $K_{ex}(B) < K_{ex(max)}$, isomer A is transported more rapidly, but if the system is changed to high extraction conditions, where both $K_{ex}(A)$ and $K_{ex}(B) > K_{ex(max)}$, then A is transported more

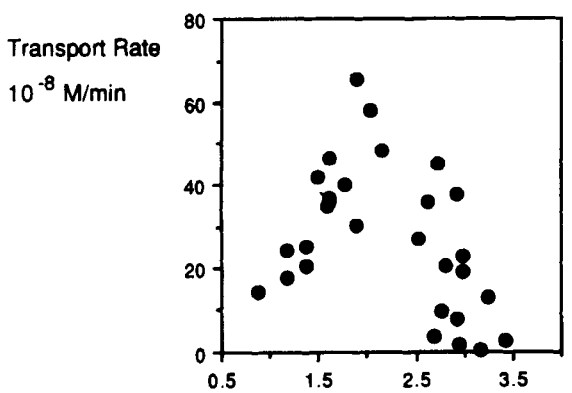


Figure 1 Plot of Glycoside Transport Rates versus log K_{ex}.

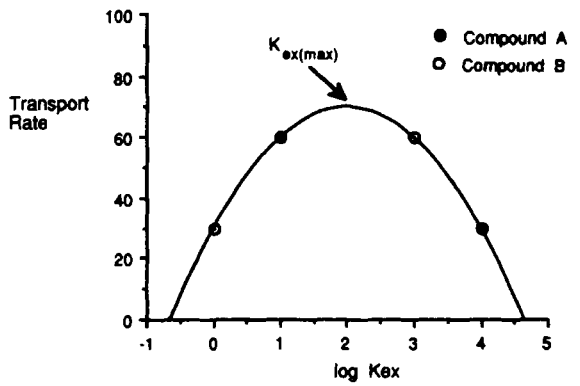


Figure 2 Hypothetical Plot of Transport Rate (arbitrary units) versus log K_{ex}.

slowly. It is possible that at the midpoint, where $K_{ex}(A) < K_{ex(max)} < K_{ex}(B)$, both rates of transport will be identical. This exercise highlights the important point that unless $K_{ex(max)}$ is known, competitive transport selectivities cannot be predicted from values of K_{ex} obtained under non-competitive conditions.[5a] Moreover, if one or more of the solutes in a competitive transport experiment has a $K_{ex} > K_{ex(max)}$ then transport selectivities will change rapidly with the extent of transport.[5a]

In conclusion, boronic acids have been shown to facilitate the transport of a range of hydrophilic organic compounds through BLMs. The results suggest that boronic acids have promise as transport carriers for practical applications ranging from separations to drug delivery. Their use in large-scale separations will require moving to more practical membrane systems such as SLMs with hollow fiber geometries. This in turn means the carriers will have to be redesigned to meet the constraints of the membrane system (in the case of SLMs, an important requirement is very high carrier lipophilicity). With regard to an application in drug delivery, the demands are even greater. A potential drug carrier must not only transport efficiently and selectively, but the issue of carrier toxicity must be addressed. Recently, we initiated the first steps in the drug delivery direction by showing that boronic acids can facilitate the transport of various monosaccharides, nucleosides, and α-hydroxy acids through lipid bilayers.[22] A noteworthy point uncovered by these preliminary studies is that certain solute/carrier systems that failed to transport through BLMs (*e.g.*, glucose transported by PBA alone) were eminently successful in achieving bilayer transport.

ACKNOWLEDGMENTS

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