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# Diffusion NMR Studies of Diol-boronates: Implications for Membrane Transport Carrier Design

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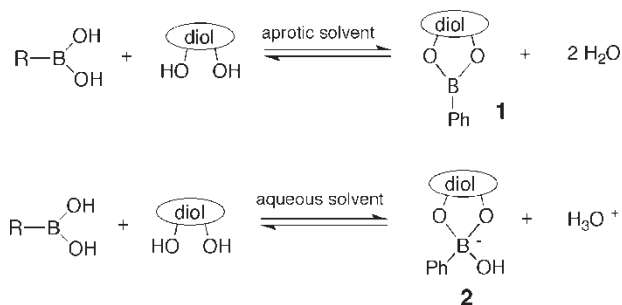
Diffusion coefficients for various neutral trigonal and anionic tetrahedral cyclic diol-boronate esters in chloroform and acetonitrile were measured using PFG-NMR. As expected, bulk diffusion of neutral trigonal boronate decreases with molecular weight. However, diffusion of tetrahedral boronate anion is affected by the structure of the tetralkylammonium counter-cation,  $Q^+$ , and the polarity of the solvent. In weakly polar chloroform, the slow rates of  $Q^+$ /boronate diffusion indicate tight ion-pairing and ion-pair aggregation. In the more polar solvent acetonitrile, the diffusion rates depend on the structure of  $Q^+$ . When  $Q^+$  is tetrabutylammonium, the boronate diffusion coefficient is low suggesting that there is strong ion-pairing, but when  $Q^+$  is tetraoctylammonium the boronate diffusion is remarkably high suggesting that there is very little ion-pairing. The results have relevance to the boronic acid mediated transport of sugars through liquid organic membranes, a process that is known to be controlled by diffusion of the transient sugar-boronate esters. The diffusion data show how the design of boronate transport carriers can be fine-tuned to produce higher membrane transport fluxes.

**Keywords:** Membrane transport; Diffusion NMR; Ion-pairing; Boronic acid

## INTRODUCTION

Although known for nearly 50 years, the interaction of boronic acids with polyols remains the subject of considerable research activity. At present, boronic acids are being investigated for use as biochemical sensors, antibody mimics, affinity ligands, drug delivery agents, protecting groups,

and catalysts for organic synthesis [1–10]. 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 hydrolyse back to starting compounds or ionize to form anionic tetrahedral boronates, **2**. The amount of **2** increases with pH, however, the equilibrium position depends strongly on the structure of the boronic acid and the diol. In the case of polyols, the situation is potentially more complicated because the boronates can exist as structural isomers.



Although covalent bonds are formed, the reactions that produce **1** and **2** are reversible, which means that boronic acids can be employed as membrane transport agents. Indeed, lipophilic boronic acids are known to promote the transport of hydrophilic monosaccharides, such as fructose and glucose, across bilayer and liquid organic membranes [5–9]. Depending on conditions,

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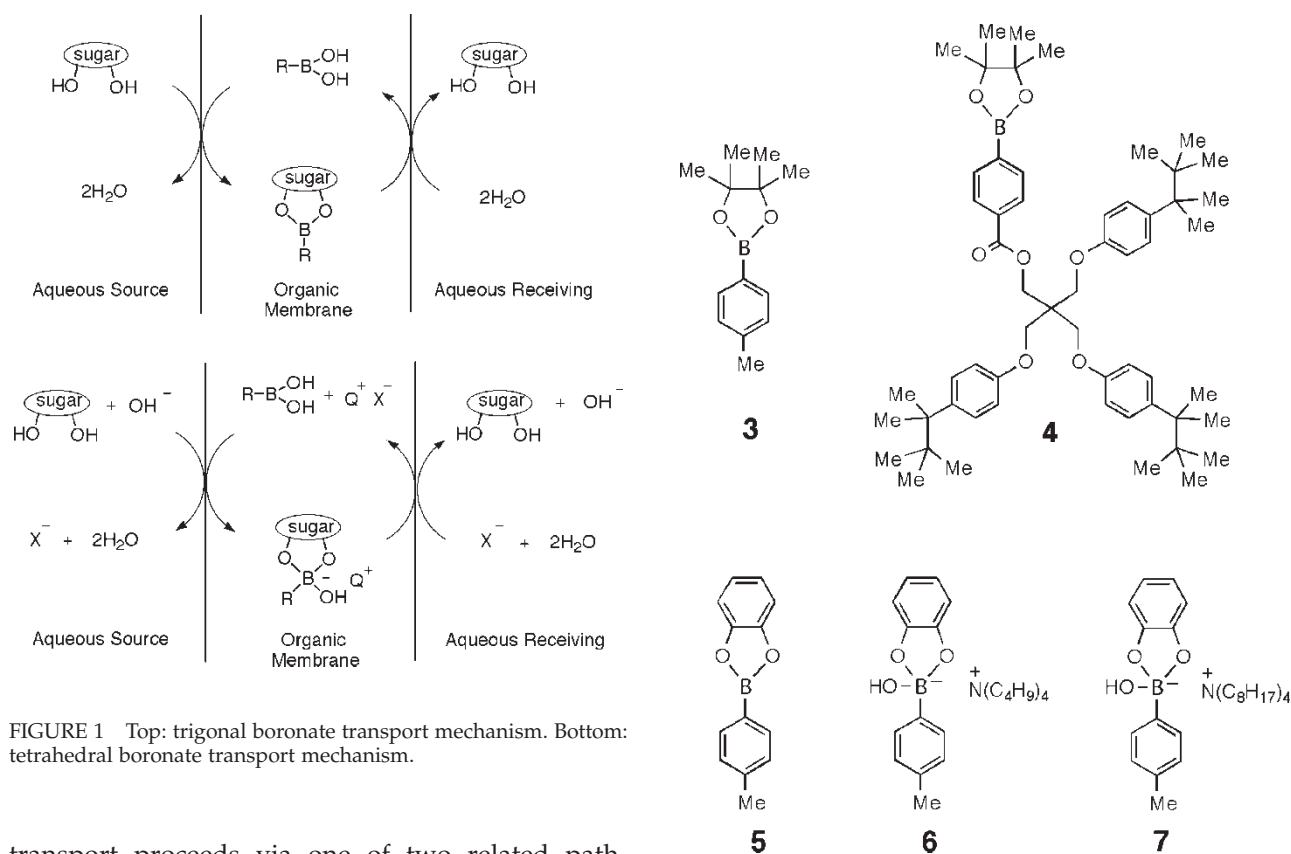


FIGURE 1 Top: trigonal boronate transport mechanism. Bottom: tetrahedral boronate transport mechanism.

transport proceeds via one of two related pathways. At neutral pH, a trigonal boronate mechanism can operate (Fig. 1); whereas, the tetrahedral boronate pathway dominates when the pH of the departure phase is above the  $pK_a$  of the boronic acid (e.g.  $pK_a$  of phenylboronic acid is 8.8). Since the tetrahedral boronate is anionic, a lipophilic tetralkylammonium cation ( $Q^+$ ) is included in the membrane so that the transported species is a membrane-soluble ion-pair. Boronate complexation is relatively rapid compared to the transport timescale, and it is diffusion of the boronates through the membrane that is the transport rate-limiting step [11]. According to Fick's first law, transport flux is proportional to the rate of diffusion through the stagnant layers associated with the membrane [12,13]. Thus, attempts to fine-tune the design of membrane transport carriers to produce higher fluxes must consider the structural factors that govern the rates of carrier diffusion. In this present study, Pulsed-Field-Gradient NMR (PFG-NMR) is used to measure the diffusion coefficients of trigonal and tetrahedral boronates, 3–7, and the data are correlated with boronate and  $Q^+$  structure. The results provide supramolecular insight that can be used to develop improved membrane transport carriers for sugar separation processes.

## RESULTS AND DISCUSSION

To simplify the interpretation of results we decided to examine boronate esters of catechol and pinacol. With these simple 1,2-diols, the unambiguous nature of the boronate structure facilitates rationalization of the data. The trigonal boronates 3–5 were prepared by condensing 4-tolueneboronic acid with either catechol or pinacol.<sup>†</sup> This was achieved by dissolving the two components in toluene and removing the solvent with heating on a rotary evaporator. The tetrahedral boronates 6 and 7 were prepared by treating 5 with one mole equivalent of the appropriate tetralkylammonium hydroxide in methanol, followed by evaporation. This initially produced a mixture of hydroxy and methoxy boronate adducts. Successive treatments with wet toluene followed by rotary evaporation led eventually to samples of hydroxy boronates 6 and 7 that were >95% pure as judged by <sup>1</sup>H NMR.

Although PFG-NMR has been known for more than thirty years, it is only recently that the technique

<sup>†</sup>Trigonal boronate 4 was available from a previous study [7].

TABLE I Molecular weights (Da) and diffusion coefficients,  $D$  ( $10^{-9} \text{m}^2 \text{s}^{-1}$ )

	3	4	5	6	7
MW	218	889	210	469	694
$D$ ( $\text{CDCl}_3$ )*	$1.41 \pm 0.04$	$0.53 \pm 0.02$	$1.59 \pm 0.04$	$0.82 \pm 0.02$	$0.57 \pm 0.02$
$D$ ( $\text{CD}_3\text{CN}$ )*	–	–	$2.41 \pm 0.06$	$1.65 \pm 0.04$	$2.89 \pm 0.06^\ddagger$
					$1.38 \pm 0.04^\ddagger$

\*Average of the  $D$  values for all measurable  $^1\text{H}$  NMR signals over three experiments. Solutions are 50 mM and 25°C.  $^\ddagger D$  for boronate signals.  
 $^\ddagger D$  for tetraoctylammonium signals.

has gained popularity with supramolecular chemists [14–16]. The diffusion coefficient for a small molecule in solution is measured using a simple pulse sequence [14]. Typically, two field-gradient pulses are inserted either side of the central  $180^\circ$  pulse of a standard spin echo sequence. The first gradient pulse disorders the phase, whereas the second gradient pulse reorders the phase. If the molecules do not diffuse during the intervening time, then the signal intensity will be the same as that observed using a normal spin echo sequence. However, diffusion due to Brownian motion means that the second gradient pulse cannot completely eliminate the phase differences induced by the first, so the amplitude of the echo signal is attenuated. Plotting the change in signal intensity as a function of gradient pulse strength allows the diffusion coefficient,  $D$ , to be extracted via standard curve fitting procedures.

The diffusion NMR data were acquired using a Bruker Avance 400 MHz instrument equipped with a 5 mL inverse geometry  $z$ -gradient probe. A PFG-LED pulse sequence was employed (more specifically the Bruker sequence, ledgs2s) because it minimizes eddy current effects [17]. Each experiment measured signal intensity at sixteen pulse gradient strengths ranging from 6.5 to 62  $\text{G cm}^{-1}$ . The data were analysed with Bruker XWINNMR software (version 2.6) and each diffusion experiment was conducted independently three times. The diffusion coefficients listed in Table I are the average for all measurable  $^1\text{H}$  NMR signals.

Diffusion data are often interpreted in terms of the Stokes-Einstein equation ( $D \sim kT/6\pi\eta r$ ), a quantitative relationship that relates the diffusion coefficient,  $D$ , to temperature,  $T$ , viscosity,  $\eta$  and effective hydrodynamic radius,  $r$  [18]. Furthermore, it has been shown that  $D$  is often proportional to the cube-root of the molecular weight [16]. However, this relationship is only expected to hold for spherical molecules and will break down under non-ideal conditions.

Initially, we examined the diffusion of neutral trigonal boronate esters **3** and **4** in  $\text{CDCl}_3$ . As anticipated,  $D$  is lower with the larger compound; however, the decrease was more than

predicted by the cube-root of mass relationship (i.e.  $D_4/D_3 < (m_3/m_4)^{0.33}$ ), suggesting that **4** does not diffuse like a rigid sphere. It appears that its relatively long arms inhibit diffusion.

We next measured the diffusion of trigonal boronate **5** and related tetrahedral boronate salts **6** and **7**, in two solvents,  $\text{CDCl}_3$  and the more polar but less viscous  $\text{CD}_3\text{CN}$ . As predicted by the Stokes-Einstein equation, the observed ratio,  $D(\text{CH}_3\text{CN})/D(\text{CDCl}_3) = 1.52$  for neutral **5** is very close to the inverse ratio of solvent viscosities. $^\ddagger$  For salt **6** in  $\text{CD}_3\text{CN}$ , there are two pieces of evidence suggesting that the two counter-ions diffuse primarily as a single unit. First, the individual NMR signals for both counter-ions all give essentially the same  $D$  value of  $1.65 \times 10^{-9} \text{m}^2 \text{s}^{-1}$ . Second, the ratio  $D_6/D_5 = 0.69$  is in reasonable agreement with the cube-root of mass relationship [ $(m_5/m_6)^{0.33} = 0.76$ ]. When **6** is in the less polar  $\text{CDCl}_3$  the value of  $D$  ( $0.82 \times 10^{-9} \text{m}^2 \text{s}^{-1}$ ) is about 75% of the value expected from the increase in viscosity suggesting that **6** exists in  $\text{CDCl}_3$  as an aggregate of ion-pairs. A similar conclusion is inferred from the low  $D$  value for **7** in  $\text{CDCl}_3$ . In the more polar but less viscous  $\text{CD}_3\text{CN}$ , it appears that **7** exists as predominantly dissociated free ions. The primary evidence for this is that the NMR signals for the boronate anion in **7** have  $D = 2.89 \times 10^{-9} \text{m}^2 \text{s}^{-1}$ , whereas the signals for the tetraoctylammonium cation have  $D = 1.38 \times 10^{-9} \text{m}^2 \text{s}^{-1}$ . Thus, it seems that in the more polar  $\text{CD}_3\text{CN}$ , strong ion-pairing of **7** does not occur owing to the steric bulk of the tetraoctylammonium cation.

## IMPLICATIONS FOR THE DESIGN OF BORONATE MEMBRANE TRANSPORT CARRIERS

The major technical difficulty with facilitated membrane transport through liquid organic membranes is long-term membrane instability, which is generally caused by leaching of the transport carrier from the membrane [5,12]. The most obvious way to reduce membrane leaching is to use a larger, more lipophilic carrier but this, of course, leads to slower

$^\ddagger$ At 25°C the viscosities of chloroform and acetonitrile are 0.5648 and 0.354 cP (centipoise), respectively.

diffusion. For example, on the basis of the values of  $D$  for trigonal boronates **3** and **4**, the larger compound **4** is expected to have a transport flux that is almost three times slower than that of **3** (all other factors being equal).

In the case of the tetrahedral boronate transport pathway, a  $Q^+$ /tetrahedral boronate ion-pair is larger than a trigonal boronate and, thus, is expected to have a slower diffusion coefficient if there is significant ion-pair association. This problem of slow diffusion due to ion-pairing is likely to be amplified in non-polar solvents, which promote further aggregation. However, ion-pairing is diminished if a more polar solvent or a very large, sterically bulky  $Q^+$  is used, leading to higher diffusion rates for the anionic tetrahedral boronate. This produces effects that are, at first glance, counter-intuitive. For example, changing from salt **6** to the *larger* salt **7** in  $CD_3CN$  leads to an *increase* in the boronate diffusion coefficient. In the extreme case, the use of a very large and bulky  $Q^+$  that inhibits ion-pairing in a liquid organic membrane should produce a transport mechanism that is reminiscent of fixed-site jumping [19–21]. That is, the positions of the large immobile  $Q^+$  cations are essentially fixed and the relatively mobile anionic boronates move quickly through the membrane by jumping from  $Q^+$  to  $Q^+$ .

In summary, the boronic acid mediated transport of sugars through liquid organic membranes is known to be controlled by diffusion of the transient sugar-boronate esters. The boronate diffusion data reported in this paper show how the design of boronic acid carriers can be fine-tuned to produce higher transport fluxes. Larger boronate carriers may reduce the problem of carrier leaching from the membrane, but they also lead to slower transport fluxes. Similarly,  $Q^+$ /boronate ion-pairing and ion-pair aggregation will also lead to slower transport fluxes. From a more general perspective, ion-pairing effects within a liquid organic membrane should

always be considered when developing carrier-mediated transport systems.

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