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Kinetic Evidence for High Reactivity of 3-Nitrophenylboronic Acid Compared to Its Conjugate Boronate Ion in Reactions with Ethylene and Propylene Glycols

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The rate constants for a boronate ion were determined for the first time using the reaction systems of 3-nitrophenylboronic acid ($3\text{-NO}_2\text{PhB(OH)}_2$) with ethylene glycol (EG) and propylene glycol (PG) in an alkaline solution: the rate constants (25 °C, $I = 0.10$ M) for the reactions of $3\text{-NO}_2\text{PhB(OH)}_3^-$ are 1.2 $M^{-1}\ s^{-1}$ (EG) and 1.5 $M^{-1}\ s^{-1}$ (PG), which are at least 10^3 times smaller than those for the reactions of $3\text{-NO}_2\text{PhB(OH)}_2$ [1.0×10^4 $M^{-1}\ s^{-1}$ (EG) and 5.8×10^3 $M^{-1}\ s^{-1}$ (PG)].

Much attention has been paid to the reactions of boric and boronic acids with aliphatic dihydric alcohols including sugars in various fields of chemistry and biochemistry,[1] e.g., in the areas of molecular design of boronic acid chemosensors[2] and saccharide recognizations.[3] In these areas, it has been presumed that only a boronate ion [RB(OH)_3^-] reacts with carbohydrates because the sensors are mainly operative only in an alkaline solution.[4,5] Many kinetic studies on the complex formation reactions of boric and boronic acids with bidentate ligands (eq 1)[6–21] have been carried out to date, and it has been concluded on the basis of the estimated upper limit of the rate constants of boronate ions that a boronate ion is at least several orders of magnitude more reactive than its conjugate boronic acid.[6] However, the reactive species have not been specifically identified, except in our recent work,[22] and the rate constant for a boronate ion has not been directly measured so far.

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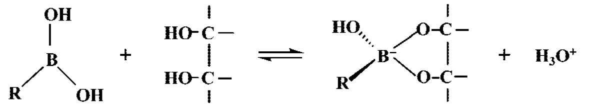


(1)

Mainly because most reactions of boronic acids are accompanied with no explicit UV–vis spectral change and the reactivities of bidentate ligands (H_2L) toward boronic acids decrease with increasing deprotonation of H_2L ($H_2L > HL^- > L^{2-}$),[10] setting up reaction systems without "proton ambiguity"[10,23] is very difficult. For example, we performed a kinetic study on the reaction of boric acid [$B(OH)_3$, p$K_a = 8.98$] with a reagent for the determination of boron, chromotropic acid (H_2cht^{2-}, p$K_{a3} = 5.35$, p$K_{a4} = 13.0$), in the pH range of 8.2–9.2,[10] where only two reaction pathways, $B(OH)_3 + Hcht^{3-}$ and $B(OH)_4^- + Hcht^{3-}$, were expected; i.e., no proton ambiguity would exist. However, unfortunately, this approach failed to succeed because of an unexpected proton ambiguity arising from the much higher reactivity of H_2cht^{2-} than $Hcht^{3-}$.

Recently, we have positively made use of proton ambiguity to correct the widespread misunderstanding of the reactivity of a boronate ion and succeeded in lowering the upper limit of the rate constant of a boronate ion,[22] which has led to important conclusions, that *trigonal boronic acid is always a reactive species irrespective of the pH of the solution* and *the reactivity of its conjugate tetrahedral boronate ion is comparable with or less than that of the boronic acid.*

In this study, we set up the following reaction systems to avoid proton ambiguity: the reactions of 3-nitrophenylboronic acid ($3\text{-}NO_2PhB(OH)_2$, pK_a = 7.04)[7] with ethylene glycol (EG) and propylene glycol (PG) having high pK_{a1} [pK_{a1} = 15.4 ± 0.2 (EG)[24,25]] in buffered solution [pH = 10.3−10.8, 0.10 M CAPS (*N*-cyclohexyl-3-aminopropanesulfonic acid)].

The rate constants were measured with a stopped-flow spectrophotometer under pseudo-first-order conditions of $C_B << C_L$, where C_B and C_L denote the total concentrations of boronic acid ($RB(OH)_2$) and the ligand (H_2L), respectively (experimental details are given in the Supporting Information). The reaction gave an excellent fit to first-order kinetics with respect to the total concentration of uncomplexed boronic acid and boronate ion [B′] ($d[RB(OH)(L)^-]/dt = k_{obs}[B']$, where $[B'] = [RB(OH)_2] + [RB(OH)_3^-]$ in the present conditions). The rate constants obtained (k_{obs}) were dependent on both C_L and $[H^+]$ for both systems, as shown in Figure 1. Therefore, k_{obs} is expressed by eq 2 at a given $[H^+]$. There are two possible parallel reaction pathways under the present conditions, as shown in Scheme 1, because the reactivity of HL^- is lower than that of H_2L and $[HL^-] << [H_2L]$.[10]

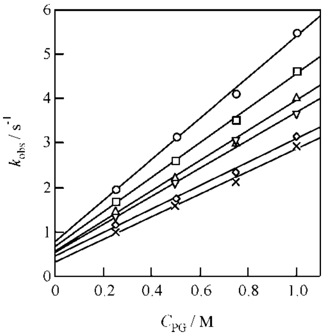
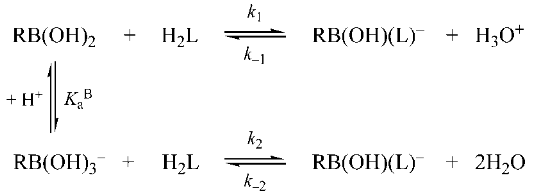


Figure 1. Dependence of k_{obs} on C_{PG} for the reaction of $3\text{-}NO_2PhB(OH)_2$ (6.0×10^{-4} M) with PG in an alkaline solution at $I = 0.10$ M and $T = 25$ °C. CAPS buffer (0.10 M) was used. $[H^+]/M = 5.01 \times 10^{-11}$ (circle), 3.98×10^{-11} (square), 3.16×10^{-11} (triangle), 2.51×10^{-11} (wedge), 2.00×10^{-11} (diamond), 1.58×10^{-11} (cross). The straight lines were drawn by applying a linear least-squares fitting of eq 2 to the experimental data.

Scheme 1. Plausible Reaction Pathways



For Scheme 1, k_{obs} is given by eq 3, where $K_a^B = [RB(OH)_3^-][H^+][RB(OH)_2]^{-1}$ and $K^* = K_a^B[H^+]^{-1} + 1$. A comparison between eqs 2 and 3 gives eqs 4 and 5.

$$k_{obs} = k_f C_L + k_d \tag{2}$$

$$k_{obs} = (k_1 + k_2 K_a^B [H^+]^{-1}) K^{*-1} C_L + k_{-1}[H^+] + k_{-2} \tag{3}$$

$$k_f K^* = k_1 + k_2 K_a^B [H^+]^{-1} \tag{4}$$

$$k_d = k_{-1}[H^+] + k_{-2} \tag{5}$$

The linear plots of $k_f K^*$ vs $[H^+]^{-1}$ and k_d vs $[H^+]$ (Figure S1 in the Supporting Information) indicate participation of the k_1 (k_{-1}) and k_2 (k_{-2}) paths. It was confirmed for both the EG and PG systems that the relationship $K_1 = K_2 K_a^B$ (Scheme 1) held within experimental uncertainties, where K_1 and K_2 were calculated from the relationships $K_1 = k_1/k_{-1}$ and $K_2 = k_2/k_{-2}$. So, the rate constants were refined by applying a nonlinear least-squares fitting of eq 3 to the kinetic data (Figure 1) and are tabulated in Table 1.

It is obvious from Table 1 that the reactivities of trigonal $3\text{-}NO_2PhB(OH)_2$ toward both EG and PG are at least several thousand times higher than that of tetrahedral $3\text{-}NO_2PhB(OH)_3^-$, which is consistent with the previous findings for the reactions of some boronic acids with aromatic diols.[22] This is the reason why $3\text{-}NO_2PhB(OH)_2$ is still reactive even in a strongly alkaline solution in which a trace of trigonal boronic acid exists. It is calculated from Table 1 that the reaction of $3\text{-}NO_2PhB(OH)_2$ with PG proceeds through both the k_1 path ($k_1 C_L/K^* + k_{-1}[H^+]$) and the k_2 path ($k_2 K_a^B C_L [H^+]^{-1}/K^* + k_{-2}$) with a ratio of 21:79 at 25 °C, $C_B = 2.0 \times 10^{-4}$ M, $C_L = 0.20$ M, and pH = 11.2, which is the thermodynamically optimum pH [(pK_a^B + pK_a^L)/2 = 11.2] for the system. In conclusion, trigonal boronic acid is always a reactive species irrespective of pH

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Table 1. Rate Constants for the Reactions of $3\text{-}NO_2PhB(OH)_2$ with EG and PG in an Alkaline Solution[a]

	$3\text{-}NO_2PhB(OH)_2$			$3\text{-}NO_2PhB(OH)_3^-$		
H_2L	$k_1/M^{-1}\ s^{-1}$	$k_{-1}/10^{10}\ M^{-1}\ s^{-1}$	$K_1{}^b/10^{-7}$	$k_2/M^{-1}\ s^{-1}$	k_{-2}/s^{-1}	$K_2{}^b/M^{-1}$
EG	10100 ± 200	4.30 ± 0.16	2.3	1.18 ± 0.04	0.460 ± 0.052	2.6
PG	5770 ± 100	1.04 ± 0.05	5.5	1.47 ± 0.03	0.242 ± 0.021	6.1

[a] $I = 0.10$ M (0.10 M CAPS buffer) and $T = 25$ °C. [b] Calculated from the relationships $K_1 = k_1/k_{-1}$ and $K_2 = k_2/k_{-2}$.

of the solution, whereas its conjugate tetrahedral boronate ion is reactive in solutions having a pH substantially higher than $pK_a{}^B$ of its conjugate acid, in which a boronate ion exists overwhelmingly. It is of note that the k_{-1} values for both systems are close to those for the diffusion-controlled protonation of acids, which means that the activated complex for the k_{-1} path would be similar to the protonated reaction product, RB(OH)(L)(H).

As described in the previous reports,[22,26] the present system is expressed by eq 6, where $[B'] = [RB(OH)_2] + [RB(OH)_3^-] = [RB(OH)_2](1 + K_a{}^B/[H^+])$.

$$B' + H_2L \xrightleftharpoons{K'} RB(OH)(L)^- \qquad (6)$$

Then, the conditional formation constant K' depending on $[H^+]$ is given by eq 7.

$$K' = \frac{[RB(OH)(L)^-]}{[B'][H_2L]} = \frac{K_1}{K^*[H^+]} = \frac{K_1}{[H^+] + K_a^B} \qquad (7)$$

Equation 7 indicates that K' decreases to zero at pH values lower than 5 because K_1 is very small (Table 1); that is, no reaction substantially proceeds.

In the present kinetic study, we obtained for the first time the reaction rate constants of a boronate ion with aliphatic diols and showed explicitly that they are much smaller than those of boronic acid, which breaks down the fixed idea that a boronate ion reacts much faster than its conjugate boronic acid.

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Supporting Information Available: Experimental details, kinetic data, etc., for the reactions of $3\text{-}NO_2PhB(OH)_2$ with ethylene glycol and propylene glycol (Tables S1 and S2 and Figures S1−S6). This material is available free of charge via the Internet at http://pubs.acs.org.

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