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Which Is Reactive in Alkaline Solution, Boronate Ion or Boronic Acid? Kinetic Evidence for Reactive Trigonal Boronic Acid in an Alkaline Solution

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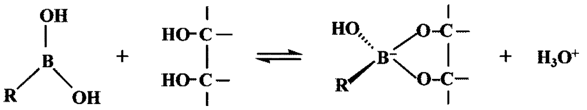
That boronic acid is a reactive species toward a diol moiety even in an alkaline solution and that the boronate ion is not very reactive were demonstrated by the estimated upper limit of the rate constants for the reactions of some boronic acids with 2,2′-biphenol and 2,3-dihydroxynaphthalene in a neutral-alkaline solution, which will correct a common misunderstanding in boron chemistry and would renew the idea of effective boronic acid sensor design for carbohydrates.

Almost all of the researchers working in the field of boron chemistry believe that a tetrahedral boronate ion [$RB(OH)_3^-$] is the reactive species in the alkaline solution of trigonal boronic acid [$RB(OH)_2$; $pK_a = 6.4-10.7$][1] because the reactions of boronic acid with bidentate ligands such as 1,2-diol occur in a substantially alkaline solution in which the boronate ion exists overwhelmingly. For example, it is believed in the area of molecular design of boronic acid sensors for carbohydrates that the boronate ion reacts with carbohydrates because the sensors are operative almost only in an alkaline solution.[2−6] However, no one has ever specified the reactive species in an alkaline solution, despite the fact that many kinetic studies have been carried out for the complex formation reactions of boric and boronic acids with bidentate ligands (H_2L) (eq 1).[1,7−21]



(1)

There are some difficulties in detailed kinetic analyses for the boronic acid/boronate ion complexation reactions. The main problem is that most of the reactions of boronic acids with bidentate ligands are generally accompanied with no explicit spectral change in the UV−vis region during the reaction, so that kinetic studies have been carried out only in an acidic aqueous solution by a relaxation method with the aid of a pH indicator for monitoring H_3O^+ in eq 1, as reported by Pizer et al.[7,8,11−16] Their kinetic results can provide only the upper limit of the rate constant for the

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Table 1. Rate Constants for the Reactions of $RB(OH)_2$ with 2,2′-Biphenol and 2,3-Dihydroxynaphthalene in a Neutral-Alkaline Solution[a]

		$RB(OH)_2$		$RB(OH)_3^-$
$RB(OH)_2$	pK_a[b]	$k_1/M^{-1}\ s^{-1}$	$k_2/M^{-1}\ s^{-1}$[c]	$k_3/M^{-1}\ s^{-1}$[c]
		2,2′-Biphenol		
		H_2L	HL^-	H_2L
$2,4\text{-}F_2PhB(OH)_2$	7.12	1100 ± 100	480 ± 40	160 ± 20
$3\text{-}CF_3PhB(OH)_2$	7.87	590 ± 30	170 ± 10	390 ± 30
$PhB(OH)_2$	8.72	130 ± 10	29 ± 1	850 ± 20
		2,3-Dihydroxynaphthalene		
		H_2L	HL^-	H_2L
$2,4\text{-}F_2PhB(OH)_2$	7.12	3600 ± 100	$(3.8 \pm 0.1) \times 10^5$	7800 ± 100
		4-Isopropyltropolone[d]		
		HL	L^-	HL
$m\text{-}NO_2PhB(OH)_2$	7.04	790	170	150

[a] $I = 0.10$ M and $T = 25$ °C. [b] Reference 1. [c] Upper limit estimated. [d] Reference 10.

reaction of the boronate ion because of so-called "proton ambiguity".[10,22] This ambiguity mainly comes from the opposite trend in the reactivity of H_2L toward boronic acids ($H_2L > HL^- > L^{2-}$) to that toward metal ions, which is explained by effective intramolecular hydrogen bondings in the *mono*coordinated intermediate, as reported previously.[10] Therefore, in the case of boronic acid reactions, it is very hard to perform a kinetic study on the systems without proton ambiguity.

Recently, we have obtained an interesting result for the reaction of 3-nitrophenylboronic acid [m-$NO_2PhB(OH)_2$] with 4-isopropyltropolone in a neutral solution; i.e., m-$NO_2PhB(OH)_3^-$ was at least 5 times less reactive than m-$NO_2PhB(OH)_2$ (Table 1),[10] which suggests that the upper limit of the rate constant for the $RB(OH)_3^-$ reaction varies largely depending on both of the acidities of H_2L and $RB(OH)_2$. Further, more recently, it is reported that diol functional groups react with boric acid rather than the borate ion.[23,24] In this situation, specifying the reactive species in an alkaline solution is essential. No directly accessible technique is available for specifying the reactive species except for kinetics, though there are some difficulties to overcome even in kinetics. Therefore, at present, the second best way to estimate the reactivity of $RB(OH)_3^-$ must be to lower the upper limit of the rate constant of $RB(OH)_3^-$, making use of suitable reaction systems with proton ambiguity.

In this study, we adopt the following reaction systems for the present purpose: the reactions of 2,4-difluorophenylboronic acid [$2,4\text{-}F_2PhB(OH)_2$, $pK_a = 7.12$], 3-(trifluoromethyl)phenylboronic acid [$3\text{-}CF_3PhB(OH)_2$, $pK_a = 7.87$], and phenylboronic acid [$PhB(OH)_2$, $pK_a = 8.72$] with 2,2′-biphenol having high pK_{a1} ($pK_{a1} = 7.6$; $pK_{a2} = 13.7$)[25] and the reaction of $2,4\text{-}F_2PhB(OH)_2$ with 2,3-dihydroxynaphthalene having higher pK_{a1} ($pK_{a1} = 8.81$; $pK_{a2} = 12.6$),[26] in a self-buffered solution (pH = 6.5−9.0).

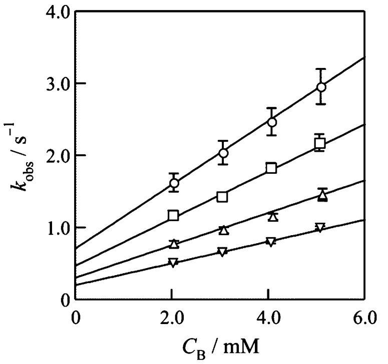
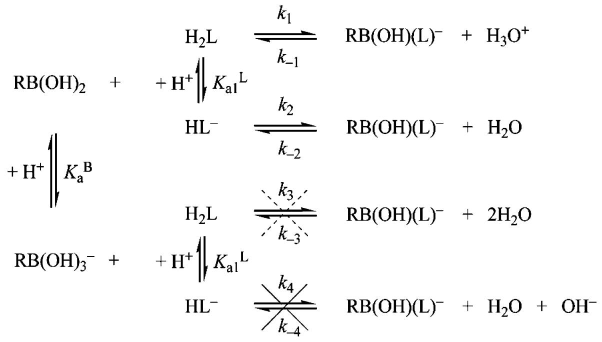


Figure 1. Dependence of k_{obs} on C_B for the reaction of $2,4\text{-}F_2PhB(OH)_2$ with 2,2′-biphenol (1×10^{-5} M) in an alkaline solution at $I = 0.10$ M and $T = 25$ °C: $[H^+]/M = 6.76 \times 10^{-8}$ (circle), 4.47×10^{-8} (square), 2.88×10^{-8} (triangle), 1.91×10^{-8} (upside down triangle).

Scheme 1. Possible Reaction Pathways for the Present Systems



The rate constants for the reaction systems were measured with a stopped-flow spectrophotometer under the pseudo-first-order conditions of $C_B \gg C_L$, 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 reactions were exactly first-order with respect to the total concentration of free ligand [L′] ($d[RB(OH)(L)^-]/dt = k_{obs}[L']$, where $[L'] = [H_2L] + [HL^-]$ in the present conditions). The rate constants obtained (k_{obs}) were dependent on both C_B and $[H^+]$ for all of the systems (e.g., see Figure 1). Therefore, k_{obs} is expressed by eq 2 at a given $[H^+]$. There are four possible parallel reaction pathways under the present conditions, as shown in Scheme 1. For Scheme 1, k_{obs} is given by eq 3, where $K_a^B = [RB(OH)_3^-][H^+][RB(OH)_2]^{-1}$, $K_{a1}^L = [HL^-][H^+][H_2L]^{-1}$, $K^* = (K_{a1}^L[H^+]^{-1} + 1)(K_a^B[H^+]^{-1} + 1)$, and K_W is the ion product of water. A comparison between eqs 2 and 3 gives eqs 4 and 5. Linearity in the plots of k_fK^* vs $[H^+]^{-1}$ and k_d vs $[H^+]$ (Figure 2) indicates negligible participation of the k_4 (k_{-4}) path as well as participation of the k_1 (k_{-1}), k_2 (k_{-2}), and/or k_3 (k_{-3}) path(s). The rate constants in eq 3 were determined by applying a nonlinear least-squares fit to the k_{obs} vs C_B plot (Table S1 in the Supporting Information). Obviously, the k_2 and k_3 (k_{-2} and k_{-3}) paths are indistinguishable kinetically (proton ambiguity), so that the upper

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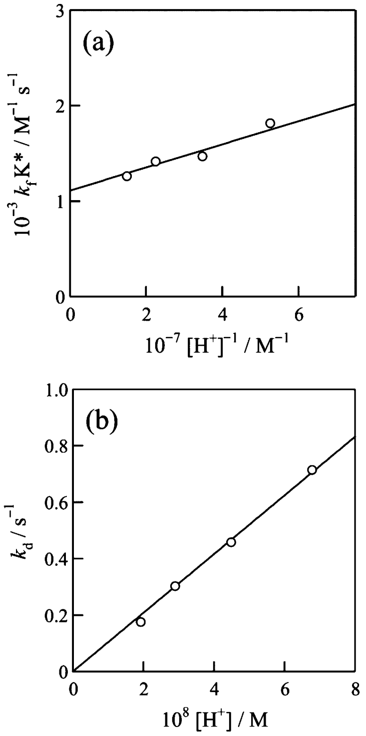

Figure 2. Plots of $k_f K^*$ against $[H^+]^{-1}$ (a) and k_d against $[H^+]$ (b) for the reaction of 2,4-$F_2PhB(OH)_2$ with 2,2′-biphenol at $I = 0.10$ M and $T = 25$ °C.

limits of k_2 and k_3 were calculated, assuming that only one of the two paths is relevant to the reaction.[10] The upper limits of the rate constants (k_2 and k_3) estimated from the results of nonlinear least-squares analyses (Table S1 in the Supporting Information) are tabulated in Table 1 together with the k_1 value. It is obvious from Table 1 that the reactivity of

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

$$k_{obs} = (k_1 + k_2 K_{a1}^{\ L}[H^+]^{-1} + k_3 K_a^{\ B}[H^+]^{-1} + k_4 K_{a1}^{\ L} K_a^{\ B}[H^+]^{-2}) K^{*-1} C_B + k_{-1}[H^+] + k_{-2} + k_{-3} + k_{-4} K_W [H^+]^{-1} \tag{3}$$

$$k_f K^* = k_1 + (k_2 K_{a1}^{\ L} + k_3 K_a^{\ B})[H^+]^{-1} + k_4 K_{a1}^{\ L} K_a^{\ B}[H^+]^{-2} \tag{4}$$

$$k_d = k_{-1}[H^+] + k_{-2} + k_{-3} + k_{-4} K_W [H^+]^{-1} \tag{5}$$

tetrahedral $RB(OH)_3^-$ for the reaction of $RB(OH)_2$ with 2,2′-biphenol is much lower than the values previously reported,[7,8,14,15] and the upper limit of the k_3 value decreases with decreasing pK_a of $RB(OH)_2$. It is worth noting that for all of the 2,2′-biphenol systems the slopes of the k_{obs} vs C_B plots (Figures 1 and S1 and S3 in the Supporting Information) increase with decreasing pH, whereas those for the 2,3-dihydroxynaphthalene system increase with increasing pH (Figure 3), indicating that the boronate ion also must be reactive in the latter system.[27] These results lead to an important conclusion that *trigonal boronic acid is always a reactive species irrespective of the pH of the solution*, because the k_1 path took part in all of the reactions studied, and *the reactivity of the tetrahedral boronate ion is comparable with or less than that of boronic acid*, which affects profoundly the future sensor design for carbohydrates.

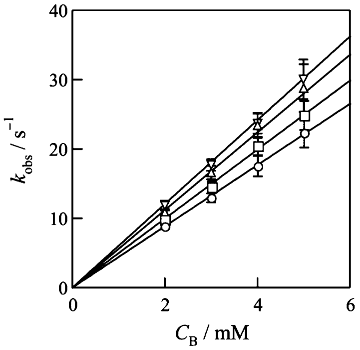

Figure 3. Dependence of k_{obs} on C_B for the reaction of 2,4-$F_2PhB(OH)_2$ with 2,3-dihydroxynaphthalene (1×10^{-5} M) in a neutral-alkaline solution at $I = 0.10$ M and $T = 25$ °C: $[H^+]$/M = 3.02×10^{-7} (circle), 1.48×10^{-7} (square), 7.59×10^{-8} (triangle), 4.57×10^{-8} (upside down triangle).

Whether the reaction of $RB(OH)_2$ with H_2L occurs or not simply depends on the conditional formation constant for the following reaction at a given condition because trigonal boronic acid is reactive even in an alkaline solution (cf. Scheme 1):

$$B' + L' \rightleftharpoons RB(OH)(L)^- \tag{6}$$

where $[B'] = [RB(OH)_2] + [RB(OH)_3^-]$ and $[L'] = [H_2L] + [HL^-]$. That is, the amount of $[RB(OH)(L)^-]$ depends on the acidity of the solution and the formation constant (K_1) for eq 1. For systems with small K_1 such as the reactions with aliphatic diols, higher pH is necessary in order to shift the formation equilibrium to the right, but excessive pH enhancement results in a decrease of the product due to a decrease in the concentration of reactive $RB(OH)_2$. This is the reason why the reaction proceeds only in an alkaline solution and the concentration of the product changes with a maximum as the pH increases.

In the present kinetic study, we evaluated for the first time the reactivity of the boronate ion toward diols to be low and showed that boronic acid is reactive even in an alkaline solution, which will alter a common misunderstanding in boron chemistry.

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Supporting Information Available: Experimental details, the rate constants obtained by nonlinear least-squares analyses (Table S1), and the kinetic data for the reactions of 2,4-$F_2PhB(OH)_2$, 3-CF_3-$PhB(OH)_2$, and $PhB(OH)_2$ with 2,2′-biphenol (Table S2 and Figures S1−S4) and for the reaction of 2,4-$F_2PhB(OH)_2$ with 2,3-dihydroxynaphthalene (Table S3 and Figure S5). This material is available free of charge via the Internet at http://pubs.acs.org.

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(27) Although the order of the estimated rate constants for the 2,3-dihydroxynaphthalene system are k_2 (upper limit) $\gg$ k_3 (upper limit) $>$ k_1, we believe that the reactivity of $RB(OH)_3^-$ toward H_2L would be comparable with that of $RB(OH)_2$ on the basis of our previous studies (see ref 1).