Kinetics and Mechanism of the Hydrolysis of 2-Phenyl-1,3,2-benzodiazaborole

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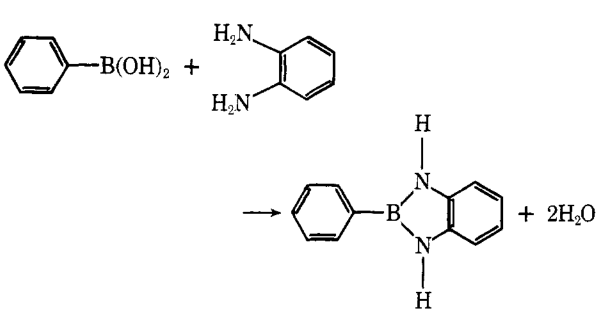
Rates of hydrolysis of 2-phenyl-1,3,2-benzodiazaborole and its substituted derivatives have been measured in 25% aqueous acetonitrile in the pH range of 4–11. The reaction was catalyzed by both general acids and bases. The kinetic solvent isotope effects $k_H/k_D > 1$ were obtained except for hydronium-ion catalysis ($k_{H_3O^+}/k_{D_3O^+} = 0.55$). The Hammett ρ values for various catalytic constants were found to be positive in sign (0.81–1.76) again with the single exception of the H_3O^+ catalysis ($\rho = -0.68$). A possible reaction mechanism has been presented.

Boronic acids as well as boric acid easily form complexes or adducts with bifunctional oxygen or nitrogen compounds.[1] Among many other examples, benzeneboronic acid and *o*-phenylenediamine react to give a stable heterocyclic adduct, 2-phenyl-1,3,2-benzodiazaborole, under appropriate conditions.[2] Dewar et al.[3] showed that the stability of this adduct arises from its heteroaromaticity and noted its reluctance in hydrolysis. On the other hand, this type of boron compounds attract the interest of medicinal chemists for their possible use in cancer therapy.[2,4] Hydrolytic properties at the physiological pH are essential for this use.[4]


(1)

However, detailed investigations on the hydrolysis of this type of compounds are scanty. The only report on such studies is concerned with in situ formation and hydrolysis of cyclic esters of boric acid and salicylamide and related compounds.[5] Semiquantitative hydrolysis rates were measured with boric acid esters[6,7] and aminoboranes.[8]

In the present investigation, hydrolysis of 2-phenyl-1,3,2-benzodiazaborole (**1a**) and its substituted derivatives (**1b–1g**) to the corresponding benzeneboronic acid and *o*-phenylenediamine has kinetically been studied in the pH range of 4–11.

Experimental Section

Materials. 2-Phenyl-1,3,2-benzodiazaborole **1a** and its derivatives **1b–1g** were prepared according to the literature[2] by the condensation of an appropriate areneboronic acid[9] with an ortho-aromatic diamine in xylene or toluene. The crude products were recrystallized twice from toluene: mp **1a**, 207–208 °C (lit.[9] 212–214 °C); **1b**, 245–246 °C (lit.[9] 242–243 °C); **1c**, 235–237 °C; **1d**, 222–223.5 °C (lit.[9] 219–221 °C); **1e**, 157–159 °C; **1f**, 221–223 °C (lit.[9] 224–225 °C); **1g**, 182–184 °C (lit.[9] 183–184 °C). Elemental analyses of all the substrates showed satisfactory results.

Acetonitrile was distilled from P_2O_5. Inorganic salts of reagent grade were used without further purification. Organic buffers were distilled or recrystallized before use. Freshly boiled, glass-distilled water was used for all rate determinations.

Kinetics. All measurements were carried out at 30 ± 0.1 °C in 25% aqueous acetonitrile (v/v), ionic strength being maintained at 0.10 by the addition of KCl. To prepare buffer solutions, necessary amounts of a buffer and KCl (to bring the ionic strength to 0.10) were placed in a volumetric flask, to which 0.24 part of acetonitrile was added. Then, water was added to fill the flask at room temperature. Three milliliters of the buffer solution was equilibrated at constant temperature in a stoppered quartz cuvette inserted in a water-jacketed cell holder. Into the buffer solution was injected 30 μL of a stock solution of **1** in anhydrous acetonitrile with the use of a microsyringe. After thorough mixing, the reaction was monitored by the decrease of the absorption of the substrate (~295 nm), using a Shimadzu spectrophotometer UV-200 with an automatic cell-positioner assembly. Pseudo-first-order plots were linear up to more than 90% reaction over the entire pH range studied.

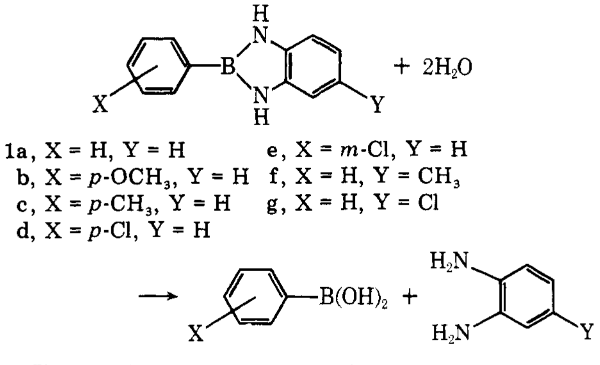
Rates of the fast reactions in hydrochloric acid were determined with a stopped-flow spectrophotometer, Union RA-1100. The stock solution of **1a** in this case was an unbuffered 25% aqueous THF solution, in which the half-time of **1a** was no shorter than 30 min.

The pH values of buffer solutions and reaction mixtures were determined with a Hitachi-Horiba pH meter CTE F-5 calibrated with aqueous standard buffers[10] supplied by the Nakarai Chemicals, Inc.

Solvent Isotope Effects. Deuterium oxide (99.75%) as well as DCl and NaOD solutions in D_2O (99%) was supplied by E. Merck, Darmstadt. Anhydrous K_2CO_3 and CH_3COONa were used for buffer preparations. The pD values are given as approximate values with use of the glass electrode correction formula of Fife and Bruice.[12]

Results

For slow reactions of the unsubstitued substrate **1a**, scannings of the ultraviolet spectra of the reaction mixture were carried out at appropriate time intervals. Absorbance decreased in the whole wavelength region scanned, 230–320 nm, to result in a final spectrum which completely agreed with that of the equimolar mixture of benzeneboronic acid and *o*-phenylenediamine. Undoubtedly, the overall reaction proceeds according to eq 2.


1a, X = H, Y = H
b, X = *p*-OCH$_3$, Y = H
c, X = *p*-CH$_3$, Y = H
d, X = *p*-Cl, Y = H
e, X = *m*-Cl, Y = H
f, X = H, Y = CH$_3$
g, X = H, Y = Cl

(2)

The reaction was then followed spectrophotometrically at the wavelength of maximum absorbance change (~295 nm). First-order plots were linear over 90% conversions for all the runs studied. Rate constants were determined at 30 °C with varying buffer concentrations in aqueous solution containing 25% (v/v) acetonitrile at a constant ionic strength of 0.10. Observed rate constants k_{obsd} were linearly dependent on the total buffer concentrations [B];

$$k_{obsd} = k_0 + k_B[B] \qquad (3)$$

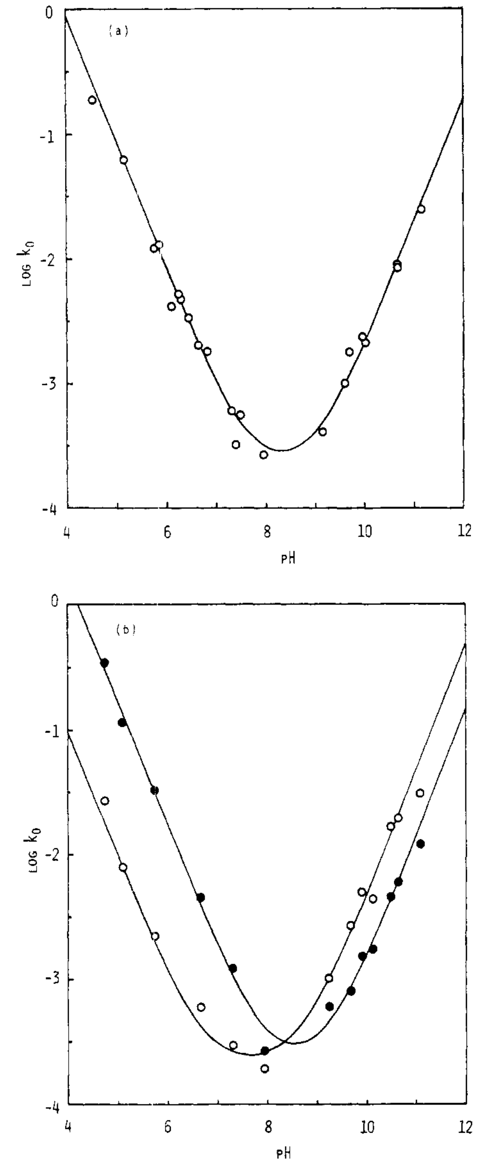


Figure 1. pH–rate profiles for the hydrolysis of diazaboroles: (a) **1a**, (b) **1f** (○) and **1g** (●).

where k_0 is the first-order rate constant extrapolated to zero buffer concentration.

The intrinsic rate constants k_0 showed a pH dependence of the inverse bell shape; both the acid catalysis from acidic to neutral pH and the base catalysis at alkaline pH were observed. Examples of the pH–rate profiles are shown in Figure 1.

$$\begin{aligned} k_0 &= k_{H_3O^+}[H_3O^+] + K_w k_{OH^-}/[H_3O^+] + k_{H_2O} \\ &= k_{H_3O^+}[H_3O^+] + k_{OH^-}[OH^-] + k_{H_2O} \end{aligned} \tag{4}$$

Rate constants obtained are given in Table I. The rate constant k_{OH^-} was calculated from the $K_w k_{OH^-}$ value obtained from the pH–rate profile. The ionic product K_w of the medium was estimated by the comparison of k_{OH^-} determined separately for **1a** in NaOH solution with the $K_w k_{OH^-}$ value: $K_w = 0.47 \times 10^{-14}$. The K_w value estimated here is reasonable for 25% aqueous acetonitrile at 30 °C. A mixed organic aqueous solvent would have a K_w value considerably smaller than that for pure water.[13] The water-catalysis term was necessary to reproduce the pH–rate profile of a shallow bottom. The k_{H_2O} value was essentially the same for all the substrates studied here: $k_{H_2O} = 2 \times 10^{-4}\ s^{-1}$.

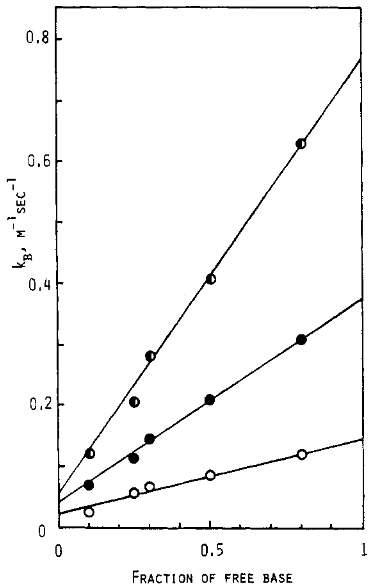


Figure 2. Buffer-dependent rate constants in imidazole buffers for the hydrolysis of **1a** (○), **1d** (●), and **1e** (◐).

Table I. Rate Constants for the Hydrolysis of Diazaboroles at 30 °C

Diazaborole	$10^{-3} k_{H_3O^+}$, $M^{-1} s^{-1}$	k_{OH^-},[a] $M^{-1} s^{-1}$
1a	8.85[b]	42.7[c]
1b	10.7	23.8
1c	10.1	26.5
1d	5.31	66.7
1e	4.04	102
1f	17.5	29.3
1g	0.99	97.5
ρ[c]	−0.68 ± 0.08	0.99 ± 0.05

[a] Calculated with $K_w = 0.471 \times 10^{-14}\ M^2$ except for **1a.** [b] $k_{H_3O^+} = (8.65 \pm 0.32) \times 10^3\ M^{-1} s^{-1}$ at [HCl] = 0.005 M. [c] Obtained from the hydrolysis in NaOH solutions ([NaOH] = 0.001–0.004 M). Standard deviation = ±0.2 $M^{-1} s^{-1}$. [d] The Hammett ρ constant obtained from the rate constants for **1a–1e.**

Buffer-dependent rate constants k_B were partitioned into the acid and base catalytic constants, k_{HA} and k_{A^-}, by their plots against the fraction of conjugate base of the buffer, as shown in Figure 2.

$$k_B = (k_{HA}[HA] + k_{A^-}[A^-])/([HA] + [A^-]) \tag{5}$$

For most buffers the k_{HA} and k_{A^-} terms were negligible respectively in the higher and lower pH regions. Only near the neutral pH (phosphate and imidazole buffers) both k_{HA} and k_{A^-} terms were observed. Catalytic constants obtained are summarized in Table II.

The correlation of base catalytic constants with the pK_a of the conjugate acid is shown in Figure 3 for **1a.** These Bronsted plots show a considerable scatter from the line (the slope β = 0.3). But we find no systematic deviations which imply the operation of possible nucleophilic catalysis. The scatter may have arisen simply because of the variety of catalyst structures.

The substituent effects on the catalytic constants were analyzed by the Hammett $\rho\sigma$ relationship for substrates **1a–1e.** Linearities of the relationship are shown in Figure 4, as examples, for (a) the hydronium and hydroxide ion catalyses and (b) the imidazole buffer catalyses. The reaction

Table II. Catalytic Constants, k_{HA} and k_{A^-} (M^{-1} s^{-1}), for the Hydrolysis of Diazaboroles at 30 °C

Registry no.	Acid or base	1a[b]	1b[b]	1c[b]	1d[b]	1e[b]	1f[b]	1g[b]	ρ[a]
75-04-7	$EtNH_2$	2.58							
109-89-7	Et_2NH	3.31							
121-44-8	Et_3N	1.57							
3812-32-6	CO_3^{2-}	1.09	0.497	0.593	1.82	3.02	0.562	2.89	1.22 ± 0.06
920-66-1	$(CF_3)_2CHOH$	1.92	1.02	1.20	4.79	8.08	1.45	8.18	1.45 ± 0.09
15390-83-7	$B(OH)_4^-$	0.0916	0.0418	0.0552	0.177	0.259			1.24 ± 0.01
280-57-9		3.78							
110-91-8		1.09	0.509	0.622	2.34	3.54			1.35 ± 0.04
77-86-1	Tris	0.172	0.0735	0.0912	0.361	0.634			1.48 ± 0.04
14066-19-4	HPO_4^-	0.0844	0.0412	0.0467	0.185	0.301	0.0752	0.222	1.40 ± 0.07
288-32-4	Imidazole	0.148	0.0590	0.0750	0.375	0.770			1.76 ± 0.07
7803-49-8	NH_2OH	0.0998							
14066-20-7	$H_2PO_4^-$	0.0447	0.0254	0.0278	0.0732	0.108	0.0233	0.0592	1.01 ± 0.06
17009-90-4	Imidazolium	0.0240	0.0182	0.0198	0.0427	0.0580			0.81 ± 0.08
64-19-7	CH_3CO_2H	0.19							

[a] The Hammett ρ constant obtained from the catalytic constants for 1a–1e. [b] Registry no.: 1a, 2479-64-3; 1b, 24341-80-8; 1c, 63181-66-8; 1d, 5747-25-1; 1e, 5785-83-1; 1f, 28249-53-8; 1g, 63181-67-9.

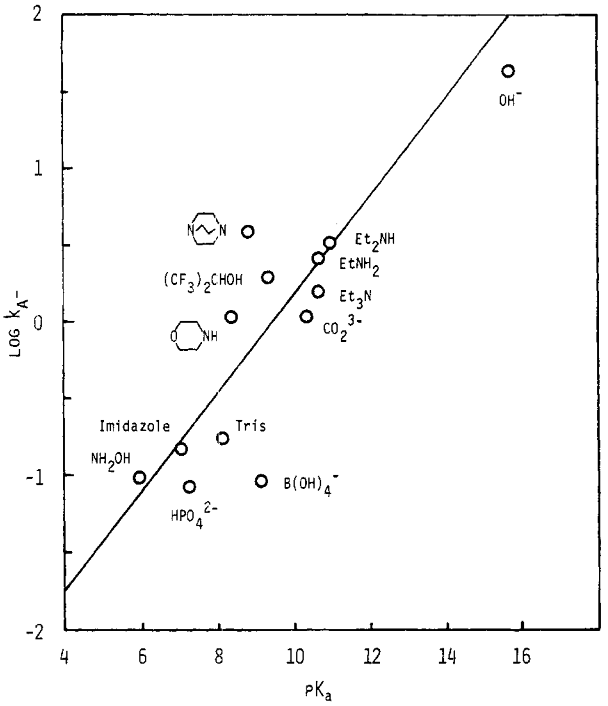


Figure 3. The Bronsted plots for general base catalysis in the hydrolysis of **1a.**

constants ρ are summarized in Tables I and II. The ρ values are positive (0.81–1.76) in sign except for the hydronium-ion catalysis ($\rho = -0.68$).

The effects of a 5 substituent can be seen in the results with **1a, 1f,** and **1g.** They are positive in the sense of the Hammet ρ value (reactivity increasing with the increasing electron attraction of a 5 substituent) except for H_3O^+ catalysis. Because of the structural complexity and a small number of substituents examined, the effects cannot be treated quantitatively.

Solvent kinetic isotope effects in the hydrolysis of 1a were examined at both acid and alkaline pH. The kinetic results in deuterium media are given in Table III. The results in hydrochloric acid and sodium hydroxide solutions give the isotope effects,

$$k_{H_3O^+}/k_{D_3O^+} = 0.55 \pm 0.05$$

and

$$k_{OH^-}/k_{OD^-} = 1.40 \pm 0.02$$

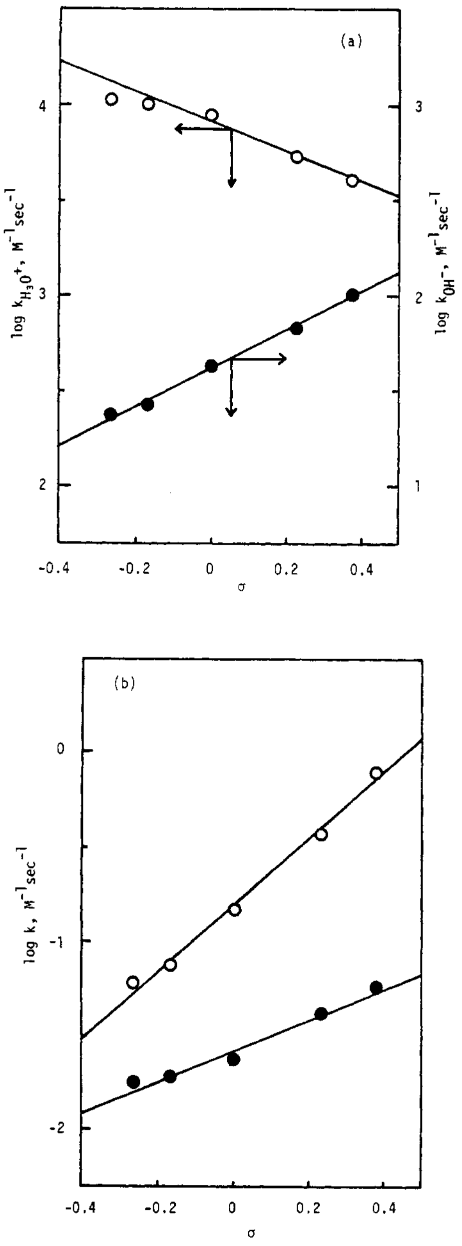


Figure 4. Hammett's $\rho\sigma$ relations: (a) $k_{H_3O^+}$ (○) and k_{OH^-} (●), (b) k_{A^-} (○) and k_{HA} (●) in imidazole buffers.

Table III. Kinetic Data for the Hydrolysis of 1a in D_2O

Buffer	DA/A$^-$	pD	[Buffer], M	k_0, s^{-1}	k_B, M^{-1} s^{-1}
Acetate	1.104	5.58 ± 0.02	0.02–0.10	$(3.99 \pm 0.02) \times 10^{-2}$	$(4.57 \pm 0.38) \times 10^{-2}$
Carbonate	1.669	11.07 ± 0.03	0.008–0.042	$(3.06 \pm 0.21) \times 10^{-3}$	$(2.21 \pm 0.08) \times 10^{-1}$
DCl			0.005		$(1.56 \pm 0.09) \times 10^{4}$
NaOD			0.002–0.004		$(3.04 \pm 0.02) \times 10^{1}$

Since in the acetate and carbonate buffers the base and acid catalyses are respectively negligible,

$$k_{\mathrm{AcOD}} = 8.7 \times 10^{-2}\ \mathrm{M}^{-1}\,\mathrm{s}^{-1}$$

and

$$(k_{\mathrm{CO_3^{2-}}})^{\mathrm{D}} = 0.59\ \mathrm{M}^{-1}\,\mathrm{s}^{-1}$$

That is, the isotope effects on buffer catalyses are

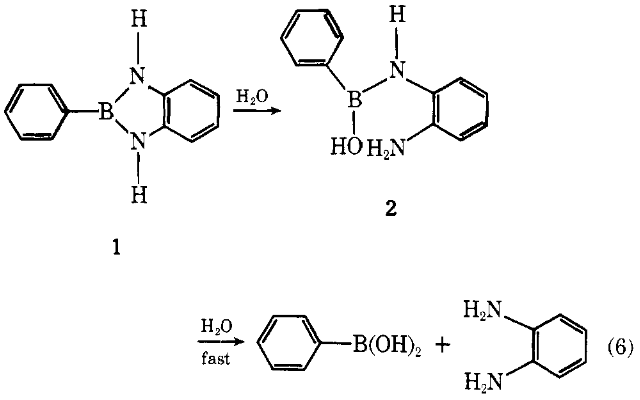
$$k_{\mathrm{AcOH}}/k_{\mathrm{AcOD}} = 2.2$$

and

$$(k_{\mathrm{CO_3^{2-}}})^{\mathrm{H}}/(k_{\mathrm{CO_3^{2-}}})^{\mathrm{D}} = 1.85$$

Although the pD values given for the deuterium buffer solutions are only approximate,[12] the k_0 values obtained are reasonable in view of the close agreement with those estimated from the $k_{\mathrm{H_3O^+}}$ and $k_{\mathrm{OD^-}}$ values.

Discussion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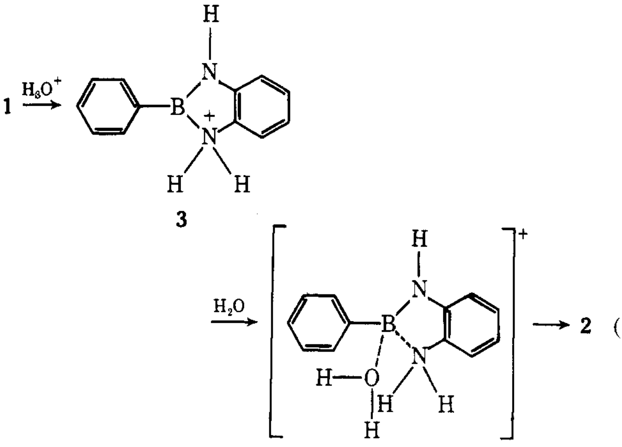
(6)

Hydrolysis of 1 must proceed in a stepwise manner through an intermediate formation of the acyclic aminoborinic acid 2. The intermediate 2 must be hydrolyzed much more easily than the starting diazaborole 1 of cyclic structure.[3,8] We observed no sign of accumulation of such an intermediate. Thus, in discussing the reaction mechanism in kinetic terms, we have only to consider the first step of eq 6.

Kinetics of the hydrolysis is relatively simple with acid catalysis at lower pH and base catalysis at higher pH. Acidic and basic centers of the diazaborole are a priori boron and nitrogen atoms, respectively. The acid and base catalyses should correspondingly operate at the nitrogen and boron atoms of the diazaborole. A mechanism involving nucleophilic catalysis may be excluded as mentioned above.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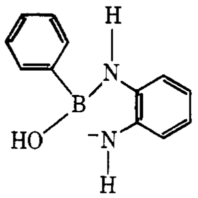
(7)

Hydronium-Ion Catalysis. Hydronium-ion catalyzed hydrolysis with $k_{\mathrm{H_3O^+}}/k_{\mathrm{D_3O^+}} < 1$ must take place through preequilibrium protonation.[14] A mechanism involving the rate-determining proton transfer would have resulted in $k_{\mathrm{H_3O^+}}/k_{\mathrm{D_3O^+}} > 1$. The observed substituent effects must be composites of those on the first protonation equilibrium and those on the rate-determining attack of H_2O toward the protonated diazaborole, 3. The negative ρ value observed indicates that the effect on the preequilibrium step is the greater. The transition state (4) of the second step must be structurally nearer to its initial state (3).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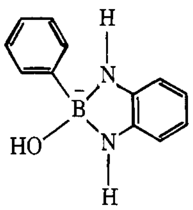
Base Catalysis. Base-catalyzed hydrolysis takes place with normal isotope effects of $(k_{\mathrm{A^-}})^{\mathrm{H}}/(k_{\mathrm{A^-}})^{\mathrm{D}} > 1$. A mechanism involving simultaneous B–O bond formation and B–N bond cleavage is unlikely because of the instability of the nitrogen anion intermediate 5.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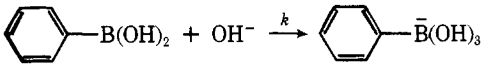
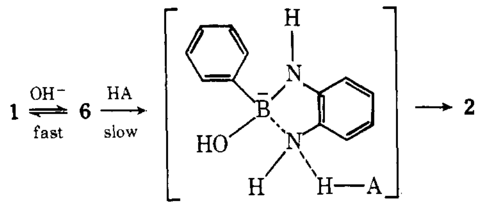

(8)

The intermediacy of a tetrahedral anion like 6 is more likely. The tetrahedral intermediate of type 6 is similar to the conjugate base form of boric[15] and boronic acids.[16] The rate of the hydroxide addition (eq 8) was measured for benzeneboronic acid by the temperature-jump technique; $k = 4.75 \times 10^7\ \mathrm{M}^{-1}\,\mathrm{s}^{-1}$ in 0.10 M aqueous KCl at 35 °C.[17] The rate constant for the reaction of 1 with OH^- to form 6 would also be of the order of $10^7\ \mathrm{M}^{-1}\,\mathrm{s}^{-1}$. At least, it would never be as small as the $k_{\mathrm{OH^-}}$ value (42.7 $\mathrm{M}^{-1}\,\mathrm{s}^{-1}$) observed here. Furthermore, the solvent isotope effects on rate-determining "hydroxide-destroying" reactions are usually ranged from 0.6 to 0.8.[18] Our present results (k_{OH^-}/k_{OD^-} = 1.4) evidently fall outside this isotope-effect range. Thus, the rate-determining step is likely to be the decay of the tetrahedral intermediate **6** (eq 9). The rate-determining step involves proton transfer to give rise to the isotope effects $(k_{A^-})^H/(k_{A^-})^D > 1$. A buffer conjugate acid (HA) operates as a general acid. In the hydroxide-ion catalysis, HA should be H_2O.



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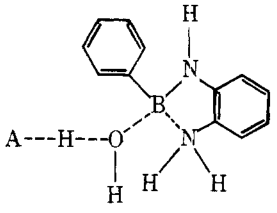
(9)

The ρ values observed (0.99–1.76) are reasonable as the sums of those for the first equilibrium (ρ_1) and those for the rate-determining step (ρ_2). The ρ_1 values would not be much different from the value observed for the equilibrium of benzeneboronic acid (ρ_1 = 2.00[17]), while the ρ_2 values would no doubt be negative in sign.

General Acid Catalysis. The mechanism of general acid-catalyzed hydrolysis, where $k_H/k_D > 1$ and $\rho > 0$, seems not to be straightforward. The mechanism must be an extraporation of that of either hydronium ion or base catalysis. In eq 7 the rate-determining water attack may be facilitated by a general base A^- or in eq 9 the intermediate **6** may be in an O-protonated form. That is, the transition state structurally resembles **8** or **9**. The isotope effects observed (k_{AcOH}/k_{AcOD} = 2.2) seem to be compatible with both these mechanisms. The substituent effects would be close to those for eq 7 and 9; $\rho < 0$ and $\rho > 0$, respectively. Thus, the mechanism similar to eq 9, where **6** is protonated at the O atom and the transition state resembles **9**, seems to be more probable for the general acid-catalyzed hydrolysis.



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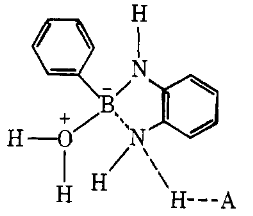

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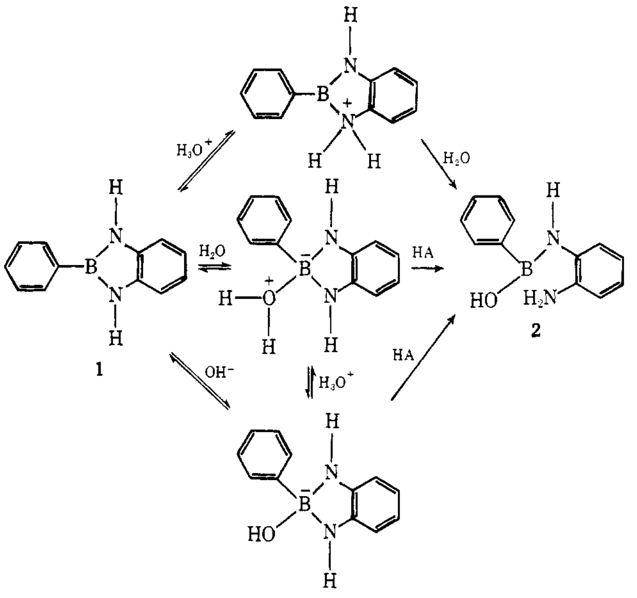
In conclusion, the mechanism of the hydrolysis is summarized below. The acid and base catalyses occur cooperatively, but not concertedly, and the hydrolysis undergo easily in the whole pH range in aqueous solutions.



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