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Influence of Boric Acid on the Hydrolysis Rate of a Hydroxy Schiff Base

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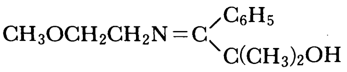
Effects of boric acid on the rate of hydrolysis of a Schiff base derived from α-hydroxyisobutyrophenone and 2-methoxyethylamine were examined in the pH range 4.2—10.4 at 30 °C. The rate increased above pH 7 but decreased below pH 7 with increasing borate concentration following a saturation curve. This is consistent with a reaction sequence involving a preequilibrium formation of a borate-substrate complex followed by its rate-determining decay to the hydrolysis products. The formation constant of the complex showed a bell-shaped change with pH but the rate constant for the complex decay was constant above pH 7, a small change being observed at lower pH. A mechanism involving an intramolecular transfer of the boron-coordinated hydroxide ion to the imine carbon within the complex is presented. Hydrazone formation from the hydroxy ketone was also examined in the presence of boric acid.

Hydrolyses of some hydroxy esters[1,2] and imines[3,4] have been found to be accelerated remarkably by boric acid in aqueous solutions. The reactions undoubtedly proceed through a borate-substrate complex similar to the one formed from diol and boric acid.[5,6] Although detailed mechanisms of the catalytic actions of boric acid are yet to be solved, they are of great interest in view of their similarity to the enzyme catalysis.[2,7]

We previously studied the borate-catalyzed hydrolysis of a hydroxy thiocarboxylic *S*-ester[2] and demonstrated that the catalysis occurs through a mechanism involving an intramolecular transfer of a boron-coordinated hydroxide ion within a borate-substrate complex. In the present investigation are examined effects of added boric acid on the rate of hydrolysis of a Schiff base derived from α-hydroxyisobutyrophenone **1**. It has been found that the hydrolysis is accelerated above pH 7 but the reaction is contrastingly decelerated below pH 7 by boric acid. A mechanism of the borate action on the hydrolysis is proposed.



$\mathrm{CH_3OCH_2CH_2N{=}C}\begin{array}{l}\nearrow\mathrm{C_6H_5}\\ \searrow\mathrm{C(CH_3)_2OH}\end{array}$

1

Results

Hydrolysis of the hydroxy Schiff base **1** was studied in aqueous solutions of ionic strength of 0.5 (KCl) at 30 °C. The reaction was monitored by following spectrophotometrically the formation of the product ketone at 245 nm. The rates were first measured without any added boric acid in usual buffer solutions of carboxylates, phosphate, tertiary and secondary amines, carbonate, and 2,2,2-trifluoroethanol as well as in HCl solutions in the pH range 0—12. Buffer effects were observed below pH 9.3 but not examined in detail here. The logarithms of the observed rate constants k_0 extrapolated to zero buffer concentration are plotted against pH in Fig. 1.

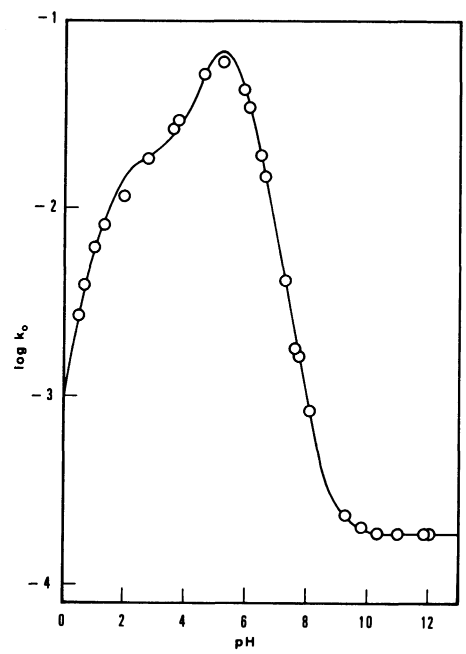
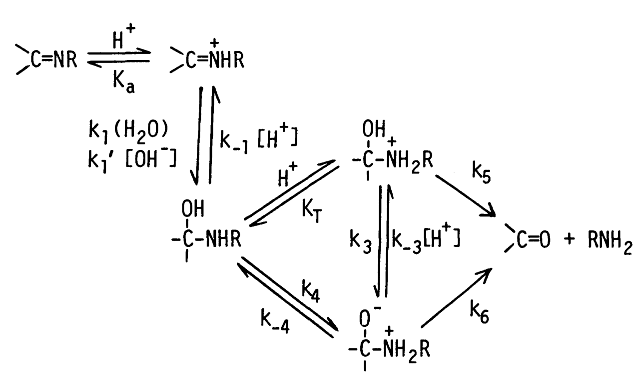


Fig. 1. pH-rate profile for the hydrolysis of the Schiff base **1** at 30 °C. The curve was calculated according to Scheme 1 and parameters given in Table 1.



Scheme 1.

The pH rate profile is quite similar to that observed for a benzophenone Schiff base[8a] and may be interpreted in the same way (Scheme 1). This mechanism is analogous to that proposed by Kayser and Pollack;[8b] it involves changes in the rate-determining step of the decay of a carbinolamine (α-amino alcohol) intermediate in a low pH region in addition to the changeover of the slow step from the formation (pH>6) to the decay of the carbinolamine (pH<6). Kinetic parameters (defined in Scheme 1) are summarized in Table 1. The value of pK_a for the protonated Schiff base $1H^+$ was estimated also from the bell-shaped correlation of pH

Table 1. Kinetic parameters for the hydrolysis of the Schiff Base **1**[a)]

pK_a	5.75
k_1/s^{-1}	1.22×10^{-1}
$k_1'/M^{-1}\ s^{-1}$	2.30×10^{4}
$(K_1k_3/K_T)/s^{-1}$	2.2×10^{-2}
$K_1k_4/M^{-1}\ s^{-1}$	2×10^{-6}
$K_1K_4k_6/M^{-1}\ s^{-1}$	9.0×10^{-4}
K_c/M^{-1}	4.35×10^{2}
$(k_7/K_3)/M^{-1}\ s^{-1}$	$\approx10^{3}$
k_8/s^{-1}	9.9×10^{-3}
$k_8'/M^{-1}\ s^{-1}$	$<10^{2}$

a) 30 °C, μ=0.50 (KCl).

with the equilibrium constant K_{app} for the borate complexation (see below). A solid curve of Fig. 1 is a theoretical one based on the parameters given in Table 1.

When a small amount of boric acid was added to the reaction mixture, the hydrolysis was markedly accelerated at high pH but inhibited at low pH. The spectra of the product solutions were the same as those found in the absence of boric acid. Induction periods were not observed in any kinetic runs.

The dependence of hydrolysis rate on boric acid concentrations was examined at constant pH maintained with a second buffer. The rate increased at pH>7 while it decreased at pH<7 with increasing total borate concentration $[B]_t$, following the saturation curve expressed by Eq. 1 (Fig. 2).

$$k_{obsd} = (k_{obsd}{}^0 + k_\infty K_{app}[B]_t)/(1+K_{app}[B]_t) \quad (1)$$

where $k_{obsd}{}^0$ is the rate constant observed in the absence of boric acid. Borate is known to associate by itself at higher concentrations especially in the pH range 8—9;[5,9)] this may diminish the activity of boric acid. To avoid this effect borate concentrations were kept low

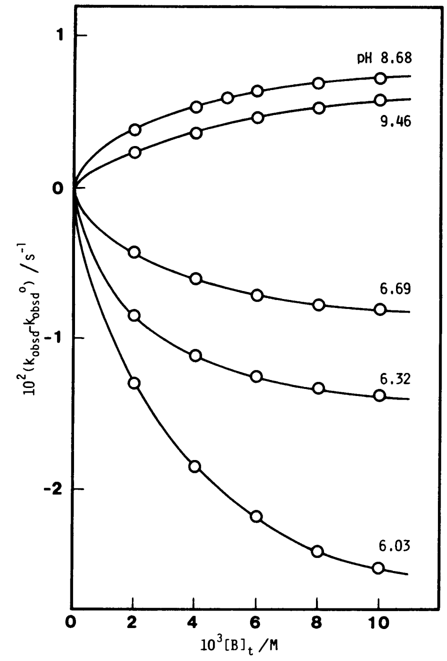


Fig. 2. Dependence of the hydrolysis rate of **1** on the borate concentration at pH indicated (30 °C, μ=0.50).

Table 2. Kinetic parameters for the hydrolysis of the Schiff base **1** in the presence of boric acid[a)]

pH[b)]	Added buffer (concn/M)	K_{app}/M^{-1}	$10^3k_\infty/s^{-1}$
4.21	Acetate (0.10)	12.2±0.5	8.6±2.4
4.62	Acetate (0.10)	23.7±0.7	8.60±1.08
4.90	Acetate (0.10)	40.9±0.4	9.76±0.34
5.20	Acetate (0.10)	82.2±1.3	10.19±0.49
5.24	Acetate (0.08)	90.0±3.2	9.91±0.29
5.45	Acetate (0.10)	149±2	10.60±0.48
5.65	Phosphate (0.10)	195±8	11.40±1.23
5.79	Phosphate (0.10)	235±13	10.31±1.60
5.86	Phosphate (0.10)	263±11	11.56±1.56
6.03	Phosphate (0.10)	321±7	12.1±0.3
6.04	Phosphate (0.08)	301±7	9.77±0.75
6.16	Phosphate (0.10)	332±24	10.51±2.13
6.32	Phosphate (0.10)	345±19	9.73±1.42
6.58	Phosphate (0.10)	366±28	9.32±2.23
7.27	Phosphate (0.05)	422±20	9.76±0.78
7.40	*N*-Methylmorph. (0.08)	412±9	9.83±0.35
7.70	*N*-Methylmorph. (0.10)	416±11	9.73±0.42
8.05	*N*-Methylmorph. (0.10)	405±12	9.88±0.48
8.30	*N*-Methylmorph. (0.10)	384±10	9.50±0.40
8.52	Morpholine (0.10)	365±26	9.48±1.07
8.68	Morpholine (0.10)	346±13	9.72±0.58
8.97	Morpholine (0.10)	269±4	9.89±0.36
9.08	Morpholine (0.10)	243±5	9.86±0.30
9.30	Carbonate (0.10)	213±4	9.92±0.29
9.46	Carbonate (0.10)	148±5	10.06±0.46
9.88	Carbonate (0.10)	65.7±2.8	10.18±0.63
10.40[c)]	Carbonate (0.05)	26.7±1.8	9.05±0.92

a) 30 °C, μ=0.50 (KCl). b) Deviations are greater than ±0.02 unless stated otherwise. c) ±0.05.

enough ($[B]_t < 0.01$ M (mol dm^{-3}) at pH 6.5—9.5 and < 0.2 M at other pH); so the observed curvatures are not affected by the association.

The curved rate dependence of Eq. 1 is consistent with the reaction sequence involving an equilibrium formation of a borate–substrate complex followed by its breakdown to give the hydrolysis products (Eq. 2), where K_{app} and k_∞ stand for the equilibrium constant for the complexation and the rate constant for the decay of the complex, respectively. Constants K_{app} and k_∞ were calculated by a least-squares treatment of the data according to Eq. 4 which is derived from Eq. 1.

$$\mathbf{1} + \text{borate} \xrightleftharpoons{K_{app}} \text{complex} \xrightarrow{k_\infty} \text{products} \tag{2}$$

$$K_{app} = [\text{complex}]/[\mathbf{1}][B]_t \tag{3}$$

$$(k_{obsd} - k_{obsd}{}^0)/[B]_t = K_{app}k_\infty - K_{app}k_{obsd} \tag{4}$$

Since the substrate concentration ($[\mathbf{1}] \simeq 10^{-4}$ M) is significantly smaller than $[B]_t$ ($> 10^{-3}$ M), initial borate concentrations were used for $[B]_t$. The constants K_{app} and k_∞ in various buffer solutions are summarized in Table 2 and plotted against pH in Fig. 3.

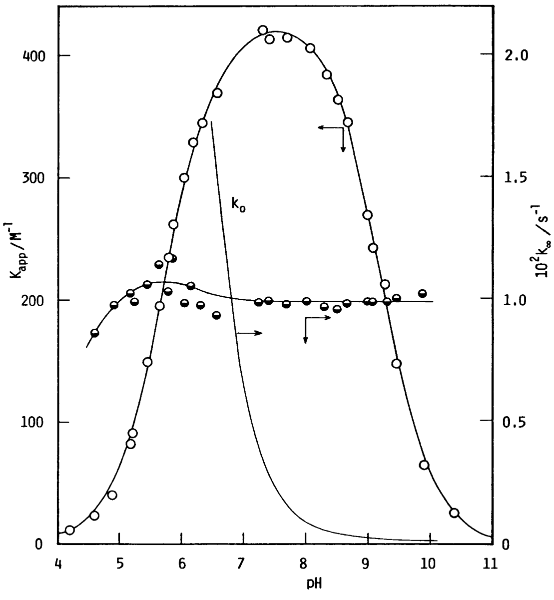


Fig. 3. Correlations of K_{app} (○) and k_∞ (◓) with pH. The curves are theoretical (Eq. 8 and 10). Hydrolysis rate k_0 is partly shown.

Possible buffer effects have to be taken into account in two ways. Although borate definitely exerts specific effects on the hydrolysis rate of **1**, potential general base catalytic acceleration must be subtracted, if any, from the observed effects of borate in order to evaluate quantitatively its specific effects. The catalytic constant for such catalysis by borate can be estimated to be $k_B \simeq 5$ M^{-1} s^{-1} from k_1 (for H_2O) and approximate k_B values for phosphate and N-methylmorpholine (1 and 1.5 M^{-1} s^{-1}, respectively). The apparent catalytic constant k_{Bt}, referring to total borate concentration, is proportional to both conjugate base fraction of borate and acid fraction of the substrate $1H^+$ (Eq. 5), and the k_{Bt} value is at its maximum at pH$\simeq$7.5, where $k_{Bt} \simeq 1.8 \times 10^{-3}$ M^{-1} s^{-1}.

$$k_{Bt} = k_B\left(\frac{[H^+]}{K_a + [H^+]}\right)\left(\frac{K_{BH}}{K_{BH} + [H^+]}\right) \tag{5}$$

Table 3. Effects of added buffers on the borate-assisted hydrolysis of the Schiff base **1** at 30 °C

[Buffer]/M	K_{app}/M^{-1}	10^3k_∞/s^{-1}
Acetate pH 5.24±0.02		
0$^{a)}$	91.1±0.9	9.81±0.41
0.02	91.9±2.8	9.76±1.03
0.04	90.0±1.1	10.10±0.51
0.06	93.0±2.7	10.16±1.04
0.08	90.0±3.2	9.41±0.29
Phosphate pH 6.03±0.02		
0$^{a)}$	312±13	8.94±1.01
0.02	309±12	9.19±0.94
0.04	308±9	9.48±0.57
0.06	294±7	9.66±0.66
0.08	301±7	9.77±0.75
0.10	321±7	12.1±0.3
N-Methylmorpholine pH 7.40±0.02		
0$^{a)}$	413±9	9.85±0.30
0.08	412±9	9.83±0.35
0.12	437±16	9.68±0.32
0.16	431±12	9.63±0.44
0.20	415±8	9.76±0.40

a) Calculated from k_{obsd} extrapolated to zero buffer concentration.

From these evaluations, a general-base catalytic contribution is less than $1/10^3$ of the observed effects of borate over the whole pH range examined.

Secondly, the borate reaction which is responsible for the specific effects may be subject to the general catalysis by a second buffer added to keep pH constant. Buffer effects were, however, not detected in morpholine (pH 8.1) nor in carbonate buffers (pH 9.3) at borate concentration of 0.01 M. Detailed analyses according to Eq. 1 were carried out at varying concentrations of 3 typical buffers and the results are given in Table 3. Both K_{app} and k_∞ are independent of buffer concentrations of acetate (pH 5.24) and N-methylmorpholine (pH 7.4) within experimental uncertainties, but k_∞ slightly increases with buffer concentration in phosphate buffer solutions of pH 6.0.

A kinetic investigation of hydrazinolysis of the Schiff base **1** was also attempted to know if boric acid influences the rate, but the attempts were unsuccessful because of a very small spectral change due to the reaction.

The effects of added boric acid on the hydrazone formation from α-hydroxyisobutyrophenone (**2**) were examined briefly as a reverse reaction of the Schiff base hydrolysis. Reactions were carried out in hydrazine buffers (pH 8—9) with or without added boric acid. For runs at pH 7.1 and above pH 9.3, low concentrations of phosphate and carbonate buffers were used to maintain constant pH. A possible initial drop of ketone absorption due to carbinolamine formation was not observed in the absence nor in the presence of boric acid. Observed pseudo-first-order rate constants k_{obsd}' were obtained from the decrease in the ketone absorption (245 nm) and divided by concentrations of neutral hydrazine [Hy] to give rate constants for the hydrazone formation.[10] The rate was linearly increased with

$$k_{obsd}' = k_{Hy}[Hy] \tag{6}$$

$$k_{Hy} = k_{Hy}{}^0 + k_{Hy}{}^B[B]_t \tag{7}$$

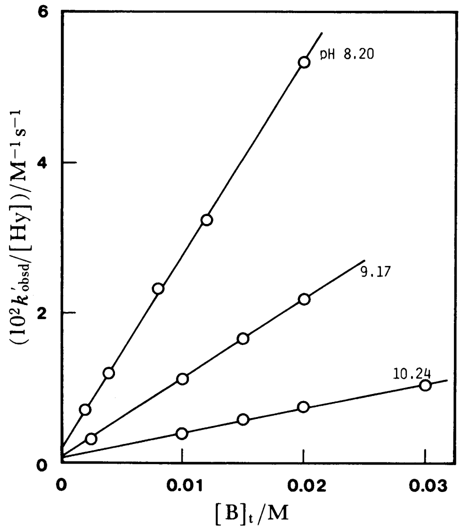


Fig. 4. Dependence of rate for the hydrazone formation from **2** on the borate concentration at pH indicated (30 °C, μ=0.50).

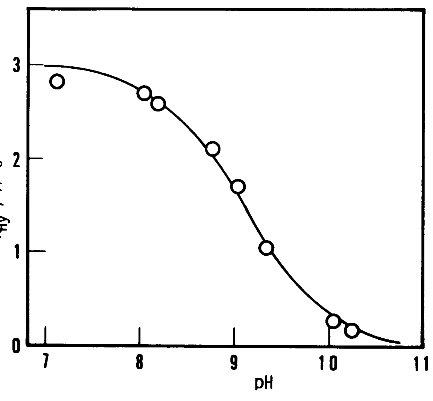


Fig. 5. Plot of k_{Hy}^B against pH.

increasing concentration of boric acid $[B]_t$ as shown in Fig. 4. The slopes k_{Hy}^B are much greater than those expected for the general catalysis.[11] General catalysis by hydrazine (second-order terms) and borate may be small enough to be neglected under the reaction conditions employed ($[Hy]_t \leq 0.125$ M, $[B]_t \leq 0.03$ M). Plots of the catalytic constants k_{Hy}^B *vs.* pH fit a sigmoid curve with $pK_a = 9.2$ (Fig. 5). Boric acid involved in the catalysis is its acid form, a limiting value of the catalytic constant k_{Hy}^B at lower pH being 2.9 M^{-2} s^{-1}.

Discussion

Hydrolysis of the Schiff base **1** derived from the α-hydroxy ketone 2 takes place in a usual way in well-behaved buffer solutions, exhibiting a pH-rate profile typical of the hydrolysis (Fig. 1).[8] On the other hand, borate buffer has never shown any unusual effects on the hydrolysis of Schiff bases except for those derived from *o*-hydroxybenzaldehyde.[3,4]

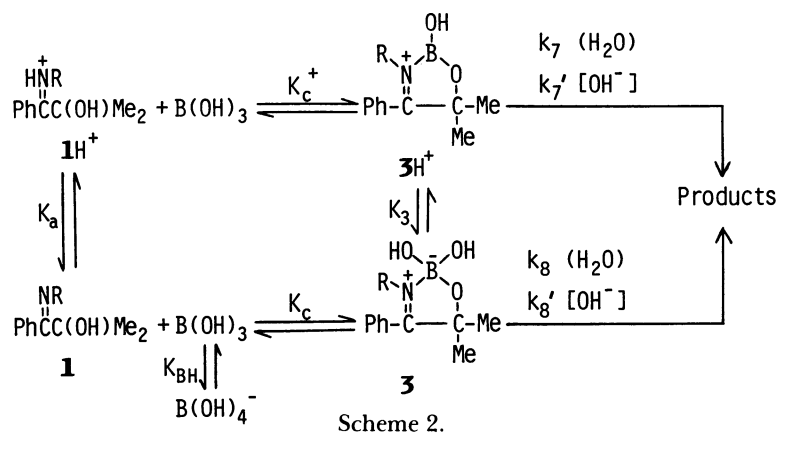
The specific effects of boric acid observed here must arise from the interaction of the hydroxyl group of **1** with boric acid and the associated borate function may facilitate the hydrolysis. In fact the observed rate constants change with borate concentration according to Eq. 1 which is based on the mechanism involving equilibrium formation of a borate-substrate complex. The complex formation must be very rapid as compared with its decay because no induction period was observed in spite of a large extent of complexation during the borate reaction.

The apparent equilibrium constants K_{app} for the complexation show a bell-shaped change with pH as seen in Fig. 3. The bell-shaped pH-K_{app} curve fits well Eq. 8, where $K_c = 435$ M^{-1}, $pK_a = 5.75$, and $pK_{BH} = 9.2$.

$$K_{app} = K_c\left(\frac{K_a}{K_a+[H^+]}\right)\left(\frac{[H^+]}{K_{BH}+[H^+]}\right) \tag{8}$$

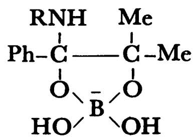
$$K_c = [\mathbf{3}]/[\mathbf{1}][B(OH)_3] \tag{9}$$

The parameters are defined in Scheme 2 which presents possible reaction sequences. A main form of the complex present must consist of the neutral form of the substrate **1** and boric acid (acid form), and the formation constant K_c is as great as 435 M^{-1}; a probable structure **3** is presented in Scheme 2. In this complex **3** a borate group associated with the α-hydroxyl group coordinates on the imine nitrogen in a Lewis acid-base fashion forming a five-membered ring. Salicylaldehyde oxime was reported to form a stable complex with boric acid, the formation constant being about 300 M^{-1} (pH 9.2).[12] Salicylamide was also found to form a borate complex of six-membered ring involving nitrogen.[5] On the other hand, well-known complexations between boric acid and 1,2-diols usually give formation constants of 1—10 M^{-1}.[6] The formation constant K_c observed here is too large to be ascribed to a diol complex, carbinolamine-borate complex like **4**.



Scheme 2.

Furthermore, formation of the carbinolamine intermediate is not always rapid enough. The complex **4** is unlikely and the structure **3** is most probable. The complex **3** may equilibrate with a cationic form **3**H$^+$ at low pH but its contribution to the kinetics is small even at pH 4; the acid dissociation constant of **3**H$^+$ is thus estimated to be greater than 10^{-4} (pK_3<4).



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The limiting rate constant k_∞ extrapolated to the infinite concentration of borate refers to the breakdown of the complex to give the hydrolysis products. The k_∞ value does not change greatly over the pH range 5—10, showing only a slight increase at pH about 6 and a tendency to decrease below pH 5. The Schiff base hydrolysis takes place through a nucleophilic reaction of water with the protonated substrate. The borate complexes with Lewis acid-type boron coordination at the imine nitrogen (**3** and **3**H$^+$) are structurally similar to the protonated Schiff base and may be subject to the nucleophilic attack by water and hydroxide ion.

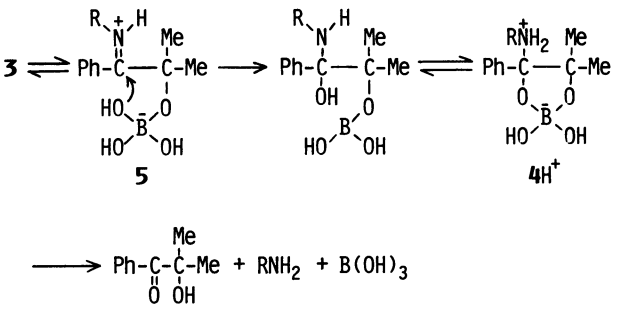
In analogy to the usual mechanism of the Schiff base hydrolysis (Scheme 1), the decrease in k_∞ at low pH (<5) must be due to the changeover of the rate-determining step from the formation to the breakdown of the (complexed) carbinolamine intermediate.

Above pH 5 nucleophilic attacks by water and hydroxide ion on the complexes **3** and **3**H$^+$ to form carbinolamine species would be rate determining and k_∞ is described by Eq. 10 using rate constants given in Scheme 2.

$$k_\infty = (k_7/K_3)[\mathrm{H}^+] + k_7'K_w/K_3 + k_8 + k_8'[\mathrm{OH}^-] \qquad (10)$$

Since the k_∞ value is constant over pH 7—10, the hydroxide-ion catalysis is negligible ($k_8'<10^2\ \mathrm{M}^{-1}\ \mathrm{s}^{-1}$). The uncatalyzed term consists of two terms due to the hydroxide ion reaction of **3**H$^+$ and the water reaction of **3** ($k_7'K_W/K_3+k_8=9.9\times10^{-3}\ \mathrm{s}^{-1}$). If the former term mainly contributed to k_∞, $k_7'>10^8\ \mathrm{M}^{-1}\ \mathrm{s}^{-1}$: This value is too large as compared to the rate constant for the hydroxide reaction of **1**H$^+$ ($k_1'=2.30\times10^4\ \mathrm{M}^{-1}\ \mathrm{s}^{-1}$). Thus the main reaction here must be the water reaction of **3**: $k_8=9.9\times10^{-3}\ \mathrm{s}^{-1}$, which is about 1/10 of k_1 for **1**H$^+$. If the water reaction of **3** were mechanistically similar to that of **1**H$^+$, *i. e.* a simple nucleophilic reaction, the reactivity difference between **3** and **1**H$^+$ would allow to estimate the rate constant for the hydroxide reaction k_8' from k_1'. Since the reactivity difference is usually smaller toward hydroxide ion than toward water,[8] k_8' must be greater than $10^3\ \mathrm{M}^{-1}\ \mathrm{s}^{-1}$. This is too large as compared with the observed value ($<10^2\ \mathrm{M}^{-1}\ \mathrm{s}^{-1}$). That is, a simple water reaction of **3** is unlikely. Observed lack of general base catalysis of the k_∞ reaction in this pH region is also incompatible with the rate-determining water attack on **3**.

An alternative mechanism kinetically equivalent to this process may involve the rearrangement of **3** to an open-type complex like **5** followed by an intramolecular transfer of a hydroxide ion coordinated to the boron atom (Scheme 3). This process does not require any general catalysis and may be more effective than the hydroxide reaction k_8' up to pH 10. Furthermore, this mechanism closely resembles that proposed for the borate catalysis of hydrolysis of a hydroxy thiocarboxylic *S*-ester.[2]



Scheme 3.

In the pH region near **6**, scattering of plots of k_∞ is rather large because of experimental limitations due to a small rate change caused by boric acid but a small increase in k_∞ seems to be real. This may be attributed to the water reaction of **3**H$^+$; $k_7/k_3\simeq10^3\ \mathrm{M}^{-1}\ \mathrm{s}^{-1}$ and $k_7>10^{-1}\ \mathrm{s}^{-1}$. The k_7 value is near or greater than k_1, which may not be unreasonable. In accord with the mechanism, general catalysis of the k_∞ process was observed at pH 6.0.

The apparent effect of added boric acid was acceleration of the hydrolysis up to 50-fold at high pH while the deceleration below pH 7. This arises from the smaller reactivity of the complexed substrate **3** than the protonated Schiff base **1**H$^+$ and the large formation constant K_c of the complex **3**. At higher pH equilibrium concentration of **3** is much greater than that of **1**H$^+$, which results in acceleration. At lower pH, where the concentration of **1**H$^+$ is large enough for the hydrolysis to be rapid, added boric acid converts **1**H$^+$ into less reactive complex **3** to inhibit the hydrolysis. Similar effects of boric acid on the Schiff base hydrolysis were previously examined with *N*-salicylideneaniline.[3] It was noted that the hydrolysis rate increased linearly with boric acid concentration, suggesting that the formation constant of the complex is small in this case. Deceleration has never been observed. The proposed mechanism involving a reaction of a cationic complex (similar to **3**H$^+$) with hydroxide ion[3] is however very unlikely in view of the present observations.

Hydrazone formation from the hydroxy ketone **2**, a reverse of the hydrolysis, was found to be accelerated by boric acid in the pH range 7—10. The rate increased linearly with borate concentration. A mechanism for the borate catalysis in this pH region is considered, as a microscopic reverse of the hydrolysis, to involve rate-determining formation of a stable borate-hydrazone complex from a borate–carbinolamine adduct. The formation constant for the borate-carbinolamine adduct (similar to **4**) must be small to allow linear dependence of the rate on borate concentration as observed. The key step of the reaction may be an intramolecular hydroxide transfer from the carbon to the boron atom in accord with the mechanism of the borate-assisted hydrolysis.

Experimental

Materials. α-Hydroxyisobutyrophenone **2** was prepared from α-bromoisobutyrophenone[13] according to the literature.[14] The Schiff base **1** was prepared from **2** and 2-methoxyethylamine in a usual way[15] and recrystallized from ligroine, mp 53.8—54.4 °C. Found: C, 70.26; H, 8.59; N, 6.37%. Calcd for $C_{13}H_{19}NO_2$: C, 70.56; H, 8.65; N, 6.33%.

Other chemicals were obtained as before.[2,7] Glass-distilled water was used throughout.

Kinetic Measurements. All the aqueous solution containing appropriate amounts of boric acid, hydrazine, and other buffers were prepared in a volumetric flask at room temperature and adjusted to ionic strength of 0.5 with KCl. Stock solutions of the substrates were obtained as an acetonitrile solution of about 10^{-2} M. Reactions were started by adding 0.03 cm^3 of the substrate stock solution from a microsyringe into a 3-cm^3 buffer solution equilibrated at 30.0±0.1 °C in a stoppered quartz cuvette inserted in a water-jacketed cell holder. The reaction was followed by the increase (hydrolysis) or the decrease (hydrazone formation) in the absorption of the ketone **2** at 245 nm on a Shimadzu UV 200 or UV 140 spectrophotometer. Pseudo-first-order rate constants were calculated by a modified Guggenheim method.[16] Infinity absorbances calculated coinside well with those observed. pH of buffer and reaction solutions were measured by a Hitachi-Horiba F7 pH meter.

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