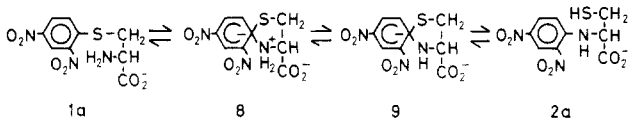
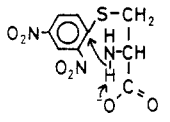
Scheme I



1a 8 9 2a

might be due to the fact that the mechanism is different from that of **1a**, because the reaction mechanism is dependent much on the nature of a migrating aromatic ring.[2] It is, however, conceivable that a complex was not detected because of an unfit choice of solvent. We believe that the reaction mechanism of the Smiles rearrangement could be better understood, at least partly, by a suitable choice of solvents.

In summary, the mechanism of the present Smiles rearrangement may be illustrated as in Scheme I. Formula **9** is assigned to the anionic σ complex observed in DMF, since it should be more stable than 8 under alkaline conditions.[15] As shown in the Results section the carboxylate group of **1a** plays an essential role in the formation of the σ complex and its replacement by the carboxamide made the substrate unreactive. Since there is not a large difference in both the electronic effect and the steric bulkiness between the two groups, the observed difference in the reactivity may be explained in terms of the neighboring participation of the carboxylate in the reaction through space. This is accomplished presumably by intramolecular proton abstraction from **1a** to form the key intermediate **9** as shown in **10**. The positive effect of added bases is



10

consistent with this hypothesis. Although intramolecular catalysis is well documented in many organic reactions,[16] this is the first explicit example of such catalysis in Smiles rearrangements.

Registry No. 1a, 23815-63-6; **1b**, 76466-52-9; **2a**, 35749-09-8; **2b**, 76466-53-0; **3a**, 23067-16-5; **3b**, 76479-86-2; L-cysteinamide, 758-90-7; 2,4-dinitrofluorobenzene, 70-34-8.

(15) C. F. Bernasconi, C. L. Gehriger, and R. H. de Rossi, *J. Am. Chem. Soc.*, 98, 8451 (1976).

(16) W. P. Jencks, "Catalysis in Chemistry and Enzymology", Chapter 1, McGraw-Hill, New York, 1969.

Mechanism of Hydrolysis of Hydroxy Thiolesters in the Presence of Boric Acid

Tadashi Okuyama,* Hiroaki Nagamatsu, and Takayuki Fueno

Department of Chemistry, Faculty of Engineering Science, Osaka University, Toyonaka, Osaka 560, Japan

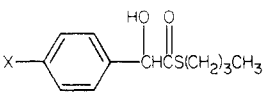
Received November 13, 1980

The catalytic effect of boric acid on the hydrolysis of *S*-butyl 2-hydroxy-2-phenylthioacetate (thiomandelate, **1**) and 3-hydroxy-3-phenylthiopropionate (**2**) has been investigated in aqueous solution. The catalytic constants increased sigmoidally with increasing pH, the pK_a of the curve being 9.2 for both **1** and **2**. Approximate Hammett ρ values were 1.2 and 0.6 for the alkaline and borate-catalyzed hydrolyses of ring-substituted derivatives of **1**, respectively. Boric acid did not show any specific influence on the hydrazinolysis of **1**. These results lead to the conclusion that the borate catalysis occurs through an intramolecular transfer of the boron-coordinated hydroxide ion to the carbonyl carbon within a borate–substrate complex.

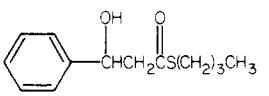
It has long been known that boric acid easily forms chelate complexes with polyols[1,2] and α-hydroxy carboxylic acids.[3,4] These complexes equilibrate very rapidly in aqueous solution as temperature-jump experiments demonstrated.[5-7]

Capon and Ghosh[8] on the other hand found that hydrolysis of phenyl salicylate is accelerated in borate buffers and considered that the acceleration was due to the transient formation of a borate complex with the substrate. Similar observations were made during the hydrolysis of salicylideneaniline.[9] However, the speculative mechanism presented for the borate catalysis was later criticized by Tanner and Bruice,[10] who investigated kinetically the formation and hydrolysis of boric acid esters of salicylamides.

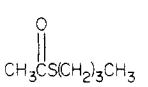
In this paper we describe an investigation of the mechanism of boric acid catalysis of the hydrolysis of thiolesters of α- and β-hydroxy carboxylic acids. The substrates examined include *S*-butyl 2-hydroxy-2-phenylthioacetates (thiomandelates, **1a–c**), 3-hydroxy-3-phenylthiopropionate (**2**), and thioacetate (**3**).



1a, X = H
b, X = CH_3
c, X = Cl



2



3

(1) Böeseken, J. *Adv. Carbohydr. Chem.* **1949**, *4*, 189-210.
(2) Lappert, M. F. *Chem. Rev.* **1956**, *56*, 959-1064.
(3) Vermaas, N. *Recl. Trav. Chim. Pays-Bas* **1932**, *51*, 955-963.
(4) Larsson, R.; Nunziata, G. *Acta Chem. Scand.* **1970**, *24*, 2156-2168.
(5) Anderson, J. L.; Eyring, E. M.; Whittaker, M. P. *J. Phys. Chem.* **1964**, *68*, 1128-1132.
(6) Kustin, K.; Pizer, R. *J. Am. Chem. Soc.* **1969**, *91*, 317-322.
(7) Kajimoto, O.; Saeki, T.; Nagaoka, Y.; Fueno, T. *J. Phys. Chem.* **1977**, *81*, 1712-1716.
(8) Capon, B.; Ghosh, B. Ch. *J. Chem. Soc. B* **1966**, 472-478.
(9) Hoffmann, J.; Štěrba, V. *Collect. Czech. Chem. Commun.* **1972**, *37*, 2043-2051.

(10) Tanner, D. W.; Bruice, T. C. *J. Am. Chem. Soc.* **1967**, *89*, 6954-6971.

0022-3263/81/1946-1336$01.25/0

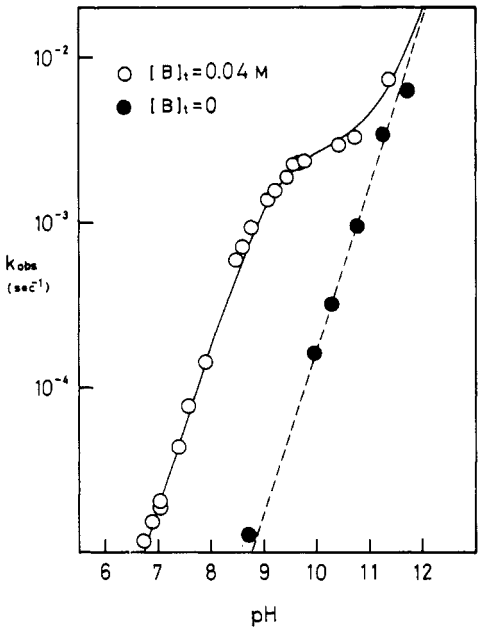


Figure 1. pH–rate profiles for the hydrolysis of **1a** in the absence (●) and in the presence of borate buffer (○).

Table I. Rate Constants for the Hydrolysis of Thiolesters

substrate	pH range	no. of pH values	k_{OH}, M^{-1} s^{-1}	k_{obsd},[a] s^{-1}
1a	9-12	6	1.12	1.37×10^{-3}
1b	10.3	1	0.74	1.14×10^{-3}
1c	10.3	1	2.16	1.95×10^{-3}
2	10-13	4	0.151	4.55×10^{-5}
3	12-13	4	0.0804	

[a] k_{obsd} in a borate buffer; $[B]_t$ = 0.04 M, [BH]/[B⁻] = 1, pH 9.05.

Results

All the reactions were carried out at 30 °C in aqueous solution of constant ionic strength of 0.2 M. The rates were determined spectrophotometrically by following the disappearance of the thiolester absorption. Pseudo-first-order plots were usually linear over four half-lives. The final spectra of reaction mixtures coincide well with those of expected hydrolysis products (acid + thiol) except for cases where a nucleophile-like hydrazine was used.[11-13] At higher pH (>10), oxidation of thiol formed became significant to affect the infinite absorbance readings; therefore, a modified Guggenheim treatment[14] of data was employed.

Hydrolysis rates of hydroxy thiolesters **1** and **2**, as well as a simple thiolester **3**, increased linearly with [OH⁻] at pH >9 and showed little buffer dependence in tertiary amine and carbonate buffers (not shown). However, the reactions of **1a** were markedly accelerated in borate buffers. The hydrolysis rate of **1a** in a dilute borate buffer, whose total concentration $[B]_t$ = 0.04 M, buffer ratio = 1, and pH 9.05, is 78 times greater than that in the absence of borate buffer at the same pH. Figure 1 shows pH–rate profiles of **1a** in the absence and presence of borate buffer. Similar accelerations were found also for the other hydroxy thiolesters, **1b**, **1c**, and **2**, but not for a simple thiolester, **3**. The kinetic results are summarized in Table I.

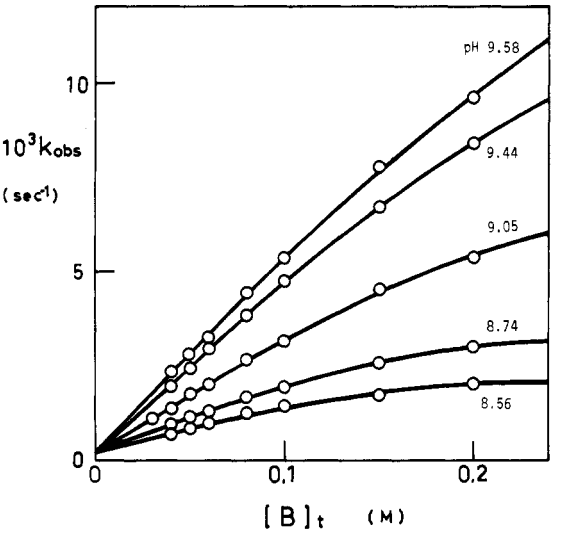


Figure 2. Dependence of the hydrolysis rate on the borate concentration at various pH's indicated.

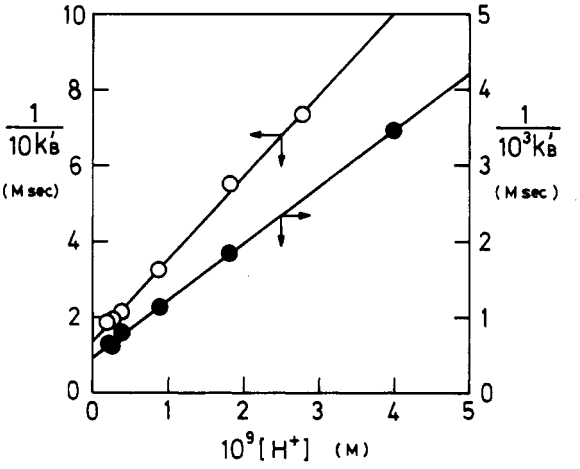


Figure 3. Plots of $1/k_B'$ vs. hydronium ion concentration for **1a** (○) and **2** (●).

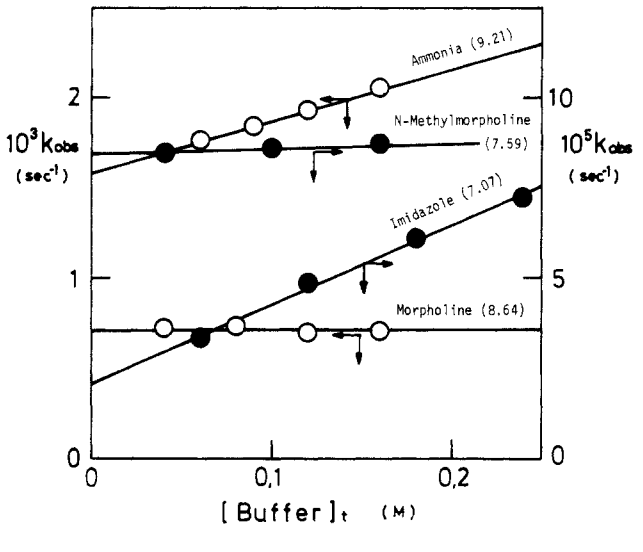
Table II. Effects of Borate Buffer on Hydrolysis of 1a and 2

pH	1a, $10^2 k_B'$, M^{-1} s^{-1}	2, $10^4 k_B'$, M^{-1} s^{-1}
8.40		2.90
8.56	1.37	
8.74	1.81	5.40
9.05	3.10	8.92
9.44	4.70	12.5
9.58	5.24	16.2
9.68	5.31	15.9
K_a	6.50×10^{-10}	6.29×10^{-10}
pK_a	9.19	9.20
k_{max}, s^{-1}	4.76×10^{-11}	1.34×10^{-12}
k_B, M^{-1} s^{-1}	7.32×10^{-2}	2.13×10^{-3}

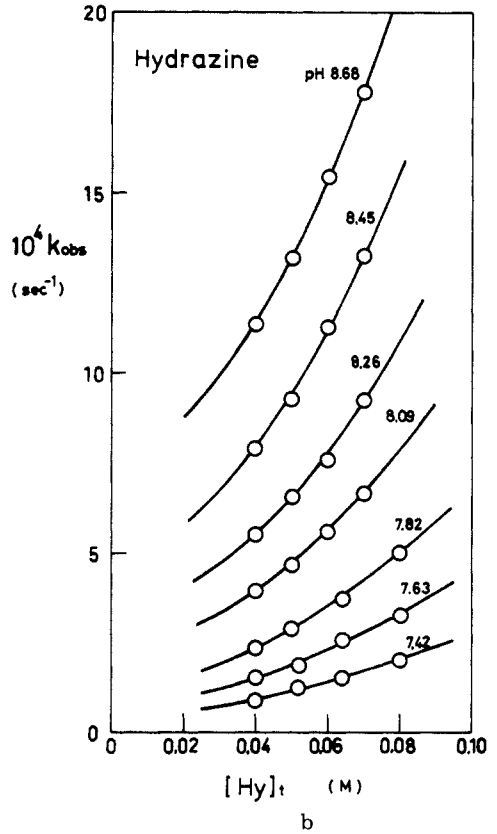
The observed rate constants, k_{obsd}, increased linearly with total borate concentration, $[B]_t([B(OH)_3] + [B(OH)_4^-])$, up to $[B]_t \simeq 0.1$ M (Figure 2). At higher borate concentrations $[B]_t > 0.1$ M, the slopes of the lines decreased, probably because of the association of borate ions.[5,15,16] Apparent catalytic constants k_B' (eq 1) were

$$k_{obsd} = k_{OH}[OH^-] + k_B'[B]_t \quad (1)$$

(11) Bruice, T. C.; Bruno, J. J.; Chou, W.-S. *J. Am. Chem. Soc.* **1963**, *85*, 1659–1669.
(12) Fedor, L. R.; Bruice, T. C. *J. Am. Chem. Soc.* **1964**, *86*, 4117–4123.
(13) Bruice, T. C.; Benkovic, S. "Bioorganic Mechanisms"; Benjamin: New York, 1966; Chapter 3.
(14) Swinbourne, E. S. *J. Chem. Soc.* **1960**, 2371–2372.
(15) Ingri, N.; Lagerstrom, G.; Frydman, M.; Sillén, L. G. *Acta Chem. Scand.* **1957**, *11*, 1034–1058. Ingri, N. *Ibid.* **1962**, *16*, 439–448; **1963**, *17*, 573–580, 581–589.
(16) Momii, R. K.; Nachtrieb, N. H. *Inorg. Chem.* **1967**, *6*, 1189–1192.



a



b

Figure 4. Dependence of k_{obsd} on the concentration of second buffers in the presence of constant concentration ($[B]_t$ = 0.04 M) of borate buffer. The second buffer used and pH are indicated.

determined from the slope of initial linear part of the plots. The k_B' values for **1a** and **2** obtained at various pH's are listed in Table II. They increase sigmoidally with increasing pH according to eq 2.

$$k_B' = \frac{k_{max}}{K_a + [H^+]} \tag{2}$$

Transformation of eq 2 gives eq 3. Linearities between

$$\frac{1}{k_B'} = \frac{K_a}{k_{max}} + \frac{[H^+]}{k_{max}} \tag{3}$$

$1/k_B'$ and $[H^+]$ are shown in Figure 3. From these linearities (eq 3), the kinetic parameters, k_{max} and K_a, were

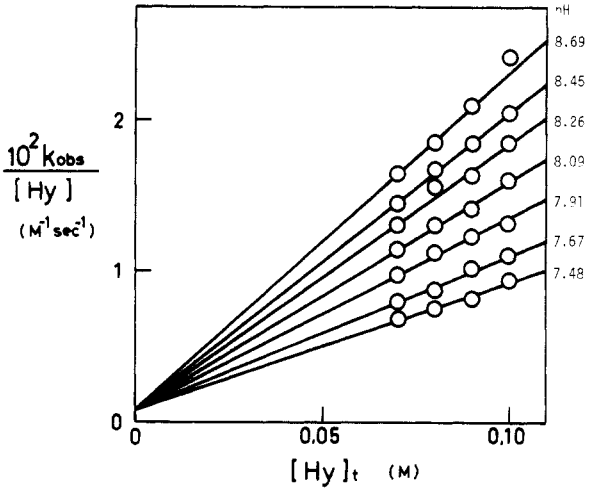


Figure 5. Dependence of the hydrazinolysis rate of **1a** on the hydrazine concentration at various pH's indicated.

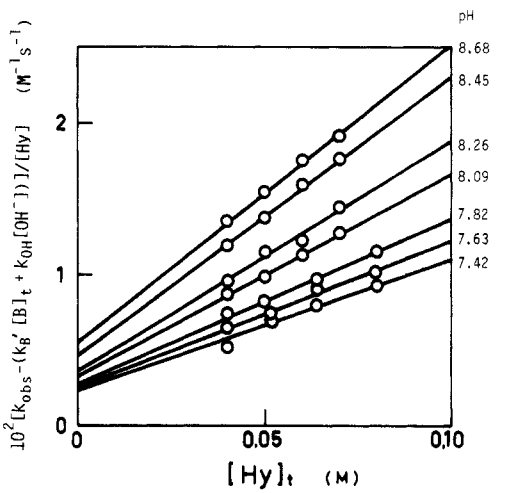


Figure 6. Correlations between k_{obsd} and hydrazine concentration in the presence of borate buffer, $[B]_t$ = 0.04 M, at the pH's indicated.

calculated and are given in Table II.

To examine catalytic effects of boric acid in lower pH region, a second buffer was used to attain constant pH while keeping $[B]_t$ = 0.04 M. Among the second buffers added, morpholine and *N*-methylmorpholine showed little buffer effect, whereas hydrazine, imidazole, and ammonia exhibited significant effects (Figure 4). The rate constants k_{obsd} extrapolated to zero added buffer concentration while keeping $[B]_t$ = 0.04 M are plotted against pH for **1a** in Figure 1. The solid curve of Figure 1 is a theoretical one calculated with the parameters k_{max} and K_a obtained above.

In order to characterize the effects of a second buffer found in the borate-catalyzed hydrolysis of **1a**, the effect of hydrazine was examined in detail. The rates increased sharply with hydrazine concentration (Figure 4b) as found previously for the hydrazinolysis of thiolacetates and thiolactones.[11-13] Without added borate, eq 4 holds, as

$$k_{obsd}/[Hy] = k_{Hy}'[Hy]_t + k_{hy} \tag{4}$$

illustrated in Figure 5, where $[Hy]_t = [Hy] + [HyH^+]$ and Hy and HyH^+ stand for neutral and protonated hydrazine, respectively. The linear plots merge into one point at the ordinate in Figure 5 ($k_{hy} = 8.36 \times 10^{-4}$ M^{-1} s^{-1}). Similar plots obtained in the presence of constant concentrations of borate ($[B]_t$ = 0.04 M) are shown in Figure 6. Here, calculated values of the hydrazine-independent terms, $k_B'[B]_t + k_{OH}[OH^-]$, are negated from k_{obsd} (eq 5). The

$$\frac{k_{obsd} - (k_B'[B]_t + k_{OH}[OH^-])}{[Hy]} = k_{Hy}'[Hy]_t + k_{hyB}'[B]_t + k_{hy} \quad (5)$$

ordinate intercepts are dependent on pH. The rate constants k_{Hy}' obtained from the slopes are plotted against the fraction of neutral hydrazine in Figure 7. The values obtained without added borate (open circles) show excellent linearity ($r = 0.9994$), while the points obtained in the presence of borate buffer (closed circles) reasonably fall on the same line. The values of k_{Hy} and k_{HyH} are calculated from the data obtained in the absence of borate (eq 6).

$$k_{Hy}'[Hy]_t = k_{Hy}[Hy] + k_{HyH}[HyH^+] \quad (6)$$

The data obtained with the constant concentration of hydrazine ($[Hy]_t = 0.04$ M) and varying $[B]_t$ also follow eq 5. Figure 8 shows such a relationship at several pH's. The calculated values ($k_{Hy}[Hy] + k_{HyH}[HyH^+] + k_{hy}$) are used for the points at $[B]_t = 0$. The pH-dependent values of k_{hyB}' obtained from the slopes are now plotted vs. the base fraction of borate buffer in Figure 9. Although the range of the base fraction examined is limited and scattering of the points is rather great because of accumulated experimental errors, the least-squares treatment gives the kinetic parameters, k_{hyB} and k_{hyBH}, as listed in Table III.

$$k_{hyB}'[B]_t = k_{hyB}[B^-] + k_{hyBH}[BH] \quad (7)$$

As a whole, the kinetic equation for the reaction of **1a** in the presence of both borate buffer and hydrazine becomes as shown in eq 8, where $k_B = k_{max}/K_a$. All the

$$k_{obsd} = k_{Hy}[Hy]^2 + k_{HyH}[Hy][HyH^+] + k_{hy}[Hy] + k_{hyB}[Hy][B^-] + k_{hyBH}[Hy][BH] + k_B[B^-] + k_{OH}[OH^-] \quad (8)$$

kinetic parameters were summarized in Table III.

Discussion

Hydrolysis of thiolesters in alkaline solutions is catalyzed by hydroxide ion as a typical nucleophilic reaction.[13] An α-hydroxy thiolester **1a** is hydrolyzed 14 times more rapidly than the thioacetate **3** and the β-hydroxy thiolester **2** is about 2 times more reactive than **3**. This is reasonably understood from the electron-withdrawing character of hydroxy and phenyl groups.[17] The hydroxy group does not seem to show any specific effects on the rate of alkaline hydrolysis.

The rate was little affected by added buffers like tertiary amines and carbonate. However, the reaction was found to be markedly accelerated in borate buffers. A borate buffer of $[B]_t = 0.04$ M accelerates the hydrolysis of **1a** and **2** by a factor of about 80 and 20 at pH 9, respectively. Spectral change during the reaction is not different from that found in the absence of borate buffer, indicating neither change in products nor accumulation of any intermediate.

Plots of the apparent catalytic constants k_B' vs. pH gave a sigmoid curve with pK_a close to that of boric acid (Figure 3). That is, the rate is dependent only on borate ion but not on boric acid concentration. The catalytic constants k_B are only $^1/_{15}$ and $^1/_{71}$ of k_{OH} for **1a** and **2**, respectively, in spite of large difference (10^6) in K_a between borate and hydroxide ion. Simple thiolesters did not undergo any appreciable reaction with borate.[11] Since the Brönsted slope for a nucleophilic reaction is usually large and near to 1, the acceleration by borate may reach the factor of 10^4 when compared with a hypothetical nucleophile of the same pK_a. This large acceleration must have resulted from

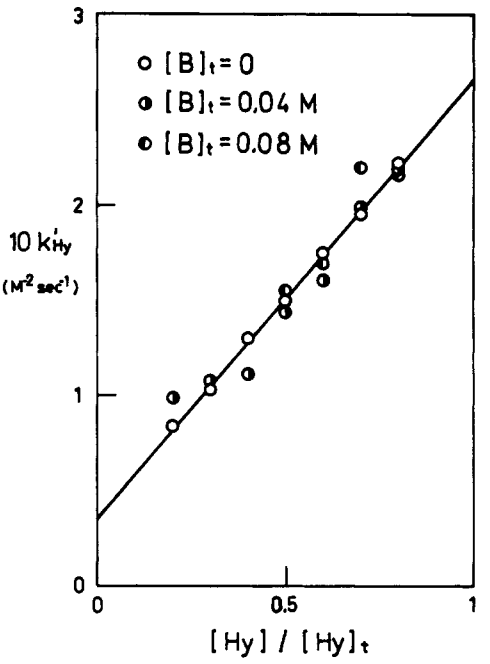


Figure 7. Plot of the apparent third-order rate constants k_{Hy}' for the hydrazinolysis of **1a** against the molar fraction of neutral hydrazine.

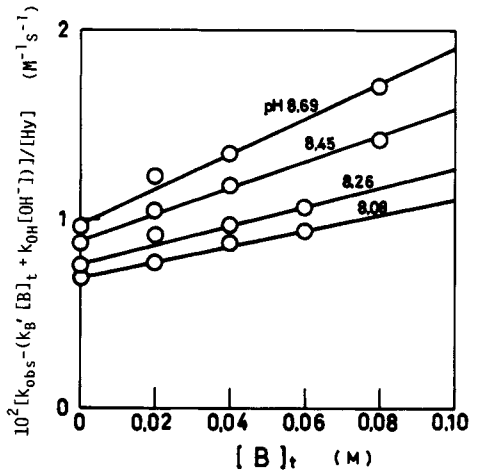


Figure 8. Correlations between k_{obsd} and borate concentration in the presence of hydrazine, $[Hy]_t = 0.04$ M, at the pH's indicated.

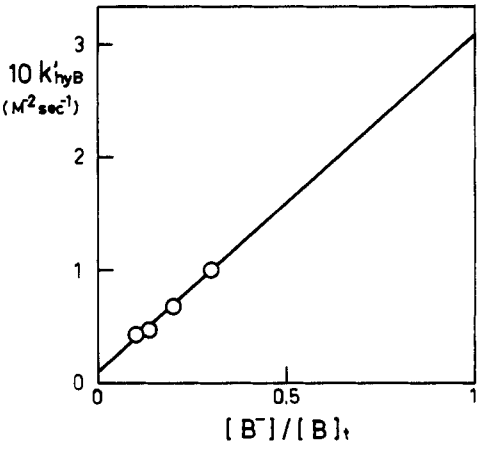


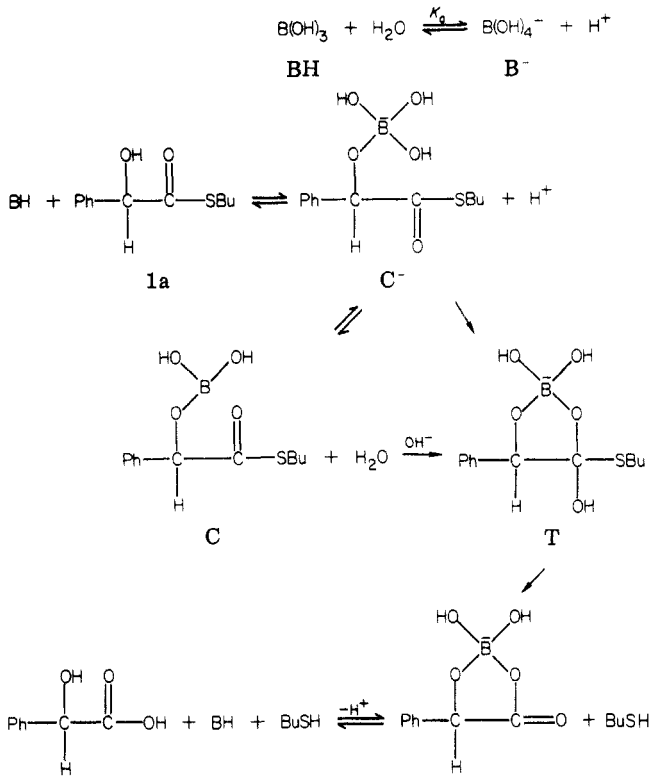
Figure 9. Plot of the apparent rate constants k_{hyB}' against the base fraction of borate buffers.

(17) Taft, R. W., Jr. In "Steric Effects in Organic Chemistry"; Newman, M., Ed.; John Wiley: New York, 1956; Chapter 13. E.g., if $\rho^* = 2.48$ for ester hydrolysis, $\sigma^* = 0.765$, and $E_s \simeq -1$ for the PhCHOH group, then **1a** will be 8 times more reactive than **3**.

Table III. Rate Constants for Reaction of 1a in the Presence of Hydrazine and Borate Buffers

k_{Hy}, M^{-2} s^{-1}	2.66×10^{-1}
k_{HyH}, M^{-2} s^{-1}	3.64×10^{-2}
k_{hy}, M^{-1} s^{-1}	8.36×10^{-4}
k_{hyB}, M^{-2} s^{-1}	3.1×10^{-1}
k_{hyBH}, M^{-2} s^{-1}	8.7×10^{-3}
k_B, M^{-1} s^{-1}	7.32×10^{-2}
k_{OH}, M^{-1} s^{-1}	1.12

Scheme I



some interaction between the hydroxy group of the substrate and boric acid. Furthermore, the activation complex for the rate-determining step must involve borate ion (or its kinetic equivalent, boric acid and hydroxide ion) as well as the substrate.

A possible reaction mechanism which agrees with such requirements is given in Scheme I. The first step may be the reaction of boric acid (electrophile) with the hydroxy group as a nucleophile. This step cannot be rate determining. The rate-determining transition state must be anionic as mentioned above. Formation or breakdown of the chelate tetrahedral intermediate T would be a rate-determining step. In these steps, the borate group of the complex must effectively operate intramolecularly to accomplish a catalytic role. The formation of T may take place either by an intramolecular nucleophilic reaction within an anionic complex C^- or by an intramolecular "Lewis acid"-type assistance of hydroxide ion attack on a neutral adduct C.

Figure 10 shows the Hammett plots for the alkaline and borate-catalyzed hydrolysis of 1, approximate ρ values being 1.2 and 0.6, respectively. The ρ value of 1.2 for the alkaline hydrolysis is reasonable as compared with the values of about 1.0 for the alkaline hydrolysis of ethyl phenylacetates,[18,19] 2.5 for that of ethyl benzoates,[19] and

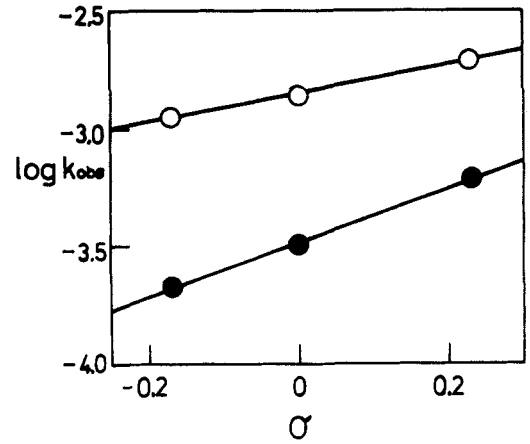
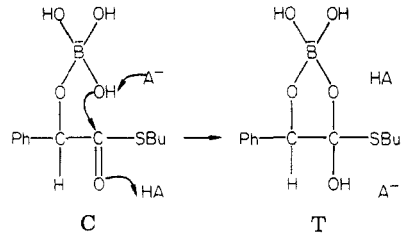


Figure 10. Hammett plots for the hydrolysis of **1a–c**: (●) triethylamine buffer, $[buffer]_t = 0.04$ M, pH 10.3; (○) borate buffer, $[B]_t = 0.04$ M, pH 9.05.

2.0 for that of acyl-substituted phenyl benzoates.[20] The ρ value of 0.6 found for the borate-catalyzed hydrolysis seems to be incompatible with the mechanism involving the rate-determining breakdown of the borate complex T. The ρ value for the formation of T may well be negative in view of an electrophilic role of boric acid as discussed by Tanner and Bruice.[10] Elimination of thiol from T would barely be influenced by the ring substituents ($\rho \simeq 0$). If the breakdown of T were rate determining, a negative overall ρ value would have resulted as a sum of the two individual ρ values.

In the presence of hydrazine, **1a** preferentially undergoes hydrazinolysis. Hydrolysis hardly competes with hydrazinolysis in the present pH region. The results on the hydrazinolysis found here are very similar to those reported by Bruice et al.[11-13] for simple thiolesters and thiolactones. Nucleophilic attack by hydrazine is assisted by both general acids and bases; terms second-order in hydrazine (k_{Hy} and k_{HyH}) were observed. In the presence of both hydrazine and borate buffer, hydrolysis competes well with hydrazinolysis. The rate constant k_B is nearly 10^2 times greater than k_{hy} for **1a**. The mixed third-order terms, k_{hyB} and k_{hyBH}, are comparable with the values k_{Hy} and k_{HyH}. The value k_{hyB} is slightly greater than k_{Hy} while k_{hyBH} is smaller than k_{HyH}. These seem to reflect the greater pK_a (9.2) of boric acid over that of hydrazine (8.1). Borate ion and boric acid might operate simply as a general base and acid to assist hydrazinolysis, respectively. Intramolecular-type catalytic effects within a borate–substrate complex (C or C^-) do not seem to be influential on the hydrazinolysis. From these results, a mechanism involving the rate-determining intramolecular "Lewis acid"-type catalysis by the boronic acid group of the adduct C must be ruled out. If this were the case, the nucleophilic attack by hydrazine (hydrazinolysis) would have also been catalyzed effectively by borate buffer.

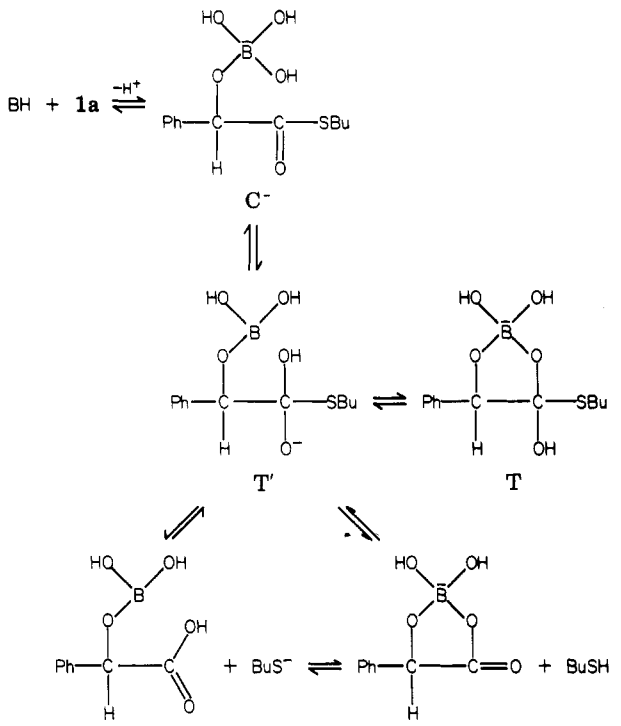
Now let us consider the step $C^- \rightarrow T$ as a possible



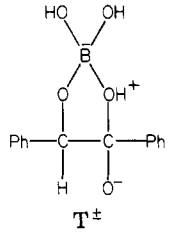
(9)

(18) Bowden, K. *Can. J. Chem.* **1963**, *41*, 2781–2793.
(19) Kirby, A. J. In "Comprehensive Chemical Kinetics"; Bamford, C. H., Tipper, C. F. H., Eds.; Elsevier: Amsterdam, 1972; Vol. 10, Chapter 2.
(20) Kirsch, J. F.; Clewell, W.; Simon, A. *J. Org. Chem.* **1968**, *33*, 127–132.

Scheme II

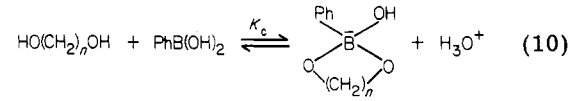


rate-determining step. The direct formation of T from C^- requires proton transfer and must be subject to concurrent general acid–base catalysis, which was not observed in practice. Without this catalysis an intermediate $T^{\pm}$, which



seems to be too unstable to exist, should have resulted. The most probable pathway must involve the intramolecular transfer of the boron-coordinated hydroxide ion to the carbonyl carbon to form T′, followed by the rapid chelation to result in the formation of T as illustrated in Scheme II. The chelate intermediate T must be more stable than T′, and they may equilibrate very rapidly. This mechanism seems to conform to all the above kinetic results. Furthermore, it closely resembles the mechanism of metal ion catalysis of ester hydrolysis, where a metal-coordinated hydroxide ion or water often operates as a nucleophile.[21-24]

In terms of this mechanism, relative catalytic effects of borate on the hydrolysis of **1a** and **2** must be closely related with the relative ease of chelate formation which is probably governed largely by the size of the chelate ring. Comparison of k_B/k_{OH} values indicates that the borate catalysis is 4.6 times more effective in the hydrolysis of **1a** than in that of **2**. This is not unreasonable in view of the relative ease of complex formation between diols and benzeneboronic acid.[25] The equilibrium constant K_c for



the five-membered chelate formation (n = 2) is 3.1 times greater than that for the six-membered one (n = 3).[25]

Although the breakdown of T is considered to be rapid, the reasonable pathway is presented for the sake of completeness. The direct elimination of thiol from T must involve proton transfer and may hardly take place. The decay from an alternate intermediate T′ seems to be more likely and may occur either stepwise or concertedly with chelation as shown in Scheme II.

In conclusion, the borate-catalyzed hydrolysis of hydroxy thiolesters proceeds through the equilibrium formation of a borate–substrate complex C^-, followed by the rate-determining intramolecular transfer of the boron-coordinated OH^- to the carbonyl carbon to form T′, which is rapidly equilibrated with a chelate complex T and at the same time decays to borate–carboxylic acid and thiol. The intramolecular Lewis acid assistance by the boron within a boric acid–substrate adduct C is firmly excluded by the lack of catalytic ability of boric acid on the hydrazinolysis. Reaction mechanisms of this kind previously assigned to the borate-catalyzed hydrolysis of salicylic acid derivatives[8-10] are doubtful, and a mechanism similar to the one given in Scheme II would reasonably explain the previous results.

Experimental Section

Materials. *S*-Butyl 2-hydroxy-2-phenylthioacetate **1a** and its ring-substituted derivatives, **1b** and **1c**, were prepared from the corresponding phenylglyoxals[26] which were obtained by the oxidation of acetophenones.[27] **1a**: bp 150–151 °C (2 mmHg); NMR (CCl_4) δ 0.88 (t), 1.2–1.6 (m), 2.80 (t), 4.16 (s), 5.03 (s), 7.2–7.4 (m), relative intensities 3:4:2:1:1:5. Anal. ($C_{12}H_{16}SO_2$) C, H. **1b**: bp 143–144 °C (0.5 mmHg); NMR (CCl_4) δ 0.86 (t), 1.1–1.6 (m), 2.27 (s), 2.72 (t), 4.38 (s), 4.98 (s), 6.9–7.3 (m), relative intensities 3:4:3:2:1:1:4. Anal. ($C_{13}H_{18}SO_2$) C, H. **1c**: bp 159–160 °C (0.5 mmHg); NMR (CCl_4) δ 0.86 (t), 1.1–1.6 (m), 2.79 (t), 4.80 (s), 5.13 (s), 7.2–7.4 (m), relative intensities 3:4:2:1:1:4. Anal. ($C_{12}H_{15}SO_2Cl$) C, H.

S-Butyl 3-hydroxy-3-phenylthiopropionate (**2**) was prepared from **3** and benzaldehyde according to the literature:[28] bp 137–140 °C (0.5 mmHg); NMR (CCl_4) δ 0.85 (t), 1.1–1.6 (m), 2.6–2.9 (m), 3.92 (s), 5.00 (dd), 7.1–7.3 (m), relative intensities 3:4:4:1:1:5. Anal. ($C_{13}H_{18}SO_2$) C, H.

S-Butyl thioacetate (**3**) was prepared by the reaction of acetyl chloride and butanethiol:[12,29] bp 163–165 °C (lit.[29] 163.4 °C); NMR (CCl_4) δ 0.92 (t), 1.2–1.7 (m), 2.27 (s), 2.83 (t), relative intensities 3:4:3:2.

Boric acid, borax, hydrazine hydrochloride, ammonium chloride, and potassium chloride were reagent grade and used without purification. Morpholine and *N*-methylmorpholine were distilled immediately before use. Imidazole was recrystallized from benzene. Glass-distilled water was used for all aqueous solutions.

Kinetic Measurements. All the aqueous solutions containing appropriate amounts of boric acid, hydrazine, and other buffers were prepared at room temperature by using a volumetric flask and adjusted to ionic strength of 0.20 with added KCl. Stock solutions of thiolesters were obtained by dissolving an appropriate amount of the substrate in acetonitrile (usually about 3×10^{-2}

(21) Breslow, R.; McClure, D. E.; Brown, R. S.; Eisenach, J. *J. Am. Chem. Soc.* **1975**, *97*, 194–195.
(22) Buckingham, D. A.; Foster, D. M.; Sargeson, A. M. *J. Am. Chem. Soc.* **1969**, *91*, 4102–4112. Boreham, C. J.; Buckingham, D. A.; Keene, F. R. *Ibid.* **1979**, *101*, 1409–1421.
(23) Wells, M. A.; Bruice, T. C. *J. Am. Chem. Soc.* **1977**, *99*, 5341–5356.
(24) Fife, T. H.; Przystas, T. J.; Squillacote, V. L. *J. Am. Chem. Soc.* **1979**, *101*, 3017–3025.
(25) Lorand, J. P.; Edwards, J. O. *J. Org. Chem.* **1959**, *24*, 769–774.
(26) Franzen, V. *Chem. Ber.* **1955**, *88*, 1361–1367.
(27) Riley, H. A.; Gray, A. R. "Organic Syntheses"; Wiley: New York, 1943; Collect. Vol. 2, pp 509–511.
(28) Wemple, J. *Tetrahedron Lett.* **1975**, 3255–3258.
(29) Wenzell, F. W., Jr.; Reid, E. E. *J. Am. Chem. Soc.* **1937**, *59*, 1089–1090.

M). Reaction was started by adding 10 μL of the substrate stock solution with use of a microsyringe into a 3-mL buffer solution equilibrated at 30 ± 0.1 °C in a stoppered quartz cuvette inserted in a water-jacketed cell holder. The reaction was followed by the decrease in the absorption at about 237 nm or the increase in that at 226 nm (at pH >10), using a Shimadzu UV 200 spectrophotometer. The values of pH of buffer and reaction solutions were determined by a Hitachi-Horiba CTE F-5 pH meter.

Acknowledgment. We thank S. Kawao for his assistance in some kinetic measurements.

Registry No. **1a**, 63860-13-9; **1b**, 76334-32-2; **1c**, 76334-33-3; **2**, 35468-63-4; **3**, 928-47-2; $B(OH)_3$, 10043-35-3.

Imidoyl Azide to Tetrazole Cyclization Limited by Internal Hydrogen Bonding and Imine Isomerization

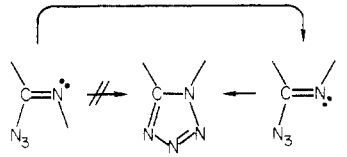
Anthony F. Hegarty*[1] and Edward P. Ahern

Chemistry Department, University College, Cork, Ireland

Received September 18, 1980

The rates of cyclization of the 2-azido-3-benzoyl enamine **6** to the corresponding tetrazole **9** have been measured in D_2O as a function of pD at 25 °C. A complex pD–rate profile is observed with a maximum rate at a pD of ca. 2.0. The observed rate constants are reduced (typically 7-fold) in D_2O in those regions where proton transfer to the enamine is rate determining; however, the actual rate of isomerization about the iminium ion intermediate ($C{=}N^+$) remains unchanged in D_2O, indicating that the solvent most likely does not add reversibly in the slow step for isomerization. The imidoyl azide **15** is stabilized in the open-chain azido form by internal hydrogen bonding to the *o*-OH group. Both the neutral (**15**) and anionic (**16**) forms cyclize to the tetrazole **18**, the latter 35-fold more rapidly. The protonated species **17** does not cyclize to the tetrazole and is inert to hydrolysis.

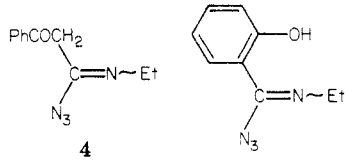
In the previous papers in this series[2,3] we have shown that those imidoyl azides which have been isolated as such, rather than as the isomeric tetrazole **2**, are stabilized in the azido form due to stereochemical factors: the azido group is trans to the lone pair on the adjacent nitrogen (**1**).



1 **2** **3**

Only the *E* isomer **3** is able to cyclize directly to the tetrazole **2**, so that the slow step is $Z \rightarrow E$ (**1** → **3**) isomerization. Reflecting this, most of those imidoyl azides reported in the literature have substitutents which would specifically be expected to slow this nitrogen inversion.

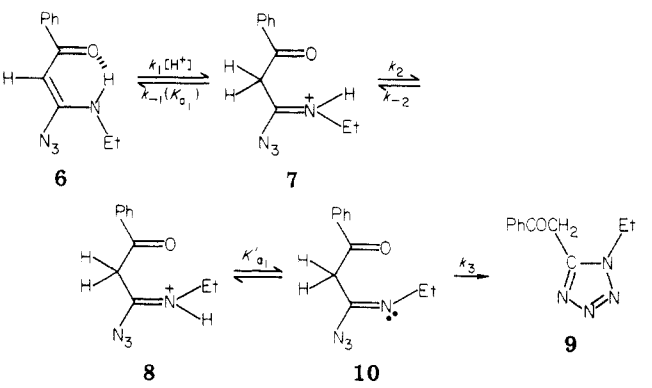
The azide **4** reported by Woodard and co-workers[4] was



4 **5**

an apparent exception to this since, in the absence of other factors, nitrogen inversion should be rapid in this case. We have shown, however,[2] that this group of azides actually has the hydrogen-bonded enamine structure **6**. Cyclization of **6** to the tetrazole **9** occurs only subsequent to proton transfer to carbon (to give **7**) and $Z \rightarrow E$ isomerization of the protonated substrate, which yields an imidoyl azide, **10**, correctly oriented for cyclization to **9** (Scheme I). Either of the precyclization steps (proton transfer, **6** → **7**, or iminium ion isomerization, **7** → **8**) can be rate determining (dependent on pH) but not the cyclization step (**10** → **9**) itself.

Scheme I



6 **7** **8** **10** **9**

However, important questions have remained unanswered. At low pH, or in the presence of an "infinite" concentration of general-acid catalysts, the rate-determining step for the conversion of **6** to **9** is the isomerization about the $C{=}N^+$ bond (**7** → **8**).[2] This could occur either as a spontaneous process or via an addition–elimination (involving the solvent or other nucleophilic species). In related iminium salts there is support (sometimes conflicting) for both processes in the literature,[5-8] while the

(1) Present address: Chemistry Department, University College, Belfield, Dublin 4, Ireland.

(2) P. Ahern, K. J. Dignam, and A. F. Hegarty, *J. Org. Chem.*, **45**, 4302 (1980).

(3) (a) A. F. Hegarty, K. Brady, and M. Mullane, *J. Chem. Soc., Perkin Trans. 2*, 535 (1980); (b) A. F. Hegarty, K. Brady, and M. Mullane, *J. Chem. Soc., Chem. Commun.*, 871 (1978).

(4) R. B. Woodward and R. A. Olofson, *J. Am. Chem. Soc.*, **83**, 4671 (1961).

(5) W. B. Jennings, S. Al-Showiman, M. S. Tolley, and D. R. Boyd, *J. Chem. Soc., Perkin Trans. 2*, 1535 (1975).

(6) J. M. Lehn, *Fortschr. Chem. Forsch.*, **15** 311 (1970).

0022-3263/81/1946-1342$01.25/0