Acid-Catalyzed Hydrolysis of a (γ-Hydroxyalkyl)ketene Dithioacetal. A Cyclic Intermediate and Product Distribution

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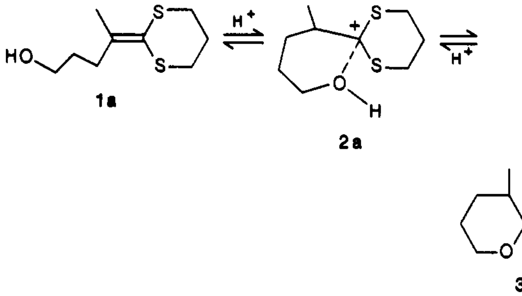
2-(Hydroxyalkylidene)-1,3-dithiane **1a** undergoes acid-catalyzed hydrolysis. Disappearance of **1a** is faster than formation of the products thio ester **5a** and lactone **5a′**. The product distribution changes with pH in a similar way to that of hydrolysis of the cyclic intermediate **3a**. Hydrolysis of **1a** must proceed mostly through **3a**, accompanying its accumulation. In comparison with the reference substrate **1b**, anchimeric assistance by the internal hydroxyl group was not observed in wholly aqueous solution, but it becomes apparent in aqueous acetonitrile solutions at high organic concentration. Neighboring hydroxyl participation is considered to occur by internal solvation, and the carbocation **2a** can exist as a discrete intermediate of the hydrolysis.

Acid-catalyzed cyclization of (hydroxyalkyl)ketene dithioacetal has been used for one of the steps of macrolide syntheses.[1-3] The cyclization is a consequence of neighboring participation of the internal hydroxyl group in an electrophilic addition to the double bond. Anchimeric assistance (rate acceleration) can also be observed in such systems.[4] It was found in our previous paper[5] that the acid-catalyzed reaction of the (hydroxyalkyl)ketene dithioacetal **1a** is much faster than that of 2-isopropylidene-1,3-dithiane **1b** in organic solutions. It was concluded that the neighboring group participation is of an internal solvation-type, but the protonation and the C–O bond formation are not concerted. The carbocation **2a** does exist as a discrete intermediate in the cyclization of **1a** (eq 1).[5]



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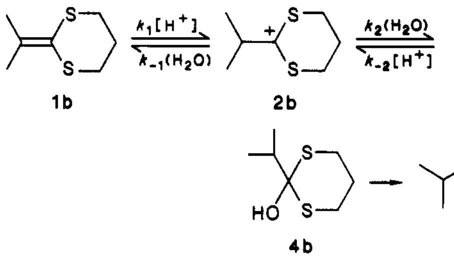
On the other hand, the anchimeric assistance was not clearly observed in the reaction of **1a** in wholly aqueous solution, and this reaction is examined in more detail in the present investigation in order to elucidate the nature of the hydroxyl participation in this medium. The reactions involved are shown in Scheme I. The cyclization leading to **3a**, if any, may be followed by further hydrolysis to give the lactone **5a′** as well as the thio ester **5a**.

It has recently been demonstrated that the acid-catalyzed hydrolysis of simple ketene dithioacetals proceeds through reversible protonation:[6] deprotonation of the carbocation **2b** is faster than the hydration to give **4b** (eq 2).[7] If **2a** is trapped internally to give **3a** in competition with the hydration in the hydrolysis of **1a**, reversibility of the protonation will be inhibited. This was found to be the case and the cyclization does occur to form a substantial amount of the lactone **5a′** as a hydrolysis product.



(2)

Results

When the stock solution of **1a** was added to strong acids ([HCl] > 1 M), absorption due to the carbocation **2a** developed immediately at 312 nm and disappeared to form absorption of thio ester at 234 nm. In 70% perchloric acid, the absorption of **2a** was stable. The UV spectra of the substrates and the products are compared in Table I. Ketene dithioacetals **1a** and **1b** and carbocations formed therefrom, **2a** and **2b**, show closely similar spectra, both in wavelength and extinction coefficient. The thio ortho lactone **3a** showed spectral behavior similar to that of **1a** in strong acids.

In dilute acid, the absorption of **1a** at 252 nm disappeared without development of absorption of **2a** and *delayed* formation of **5a** followed. The absorbance at 234 nm increased gradually owing to the formation of **5a** in the later stage of reaction after the initial rapid decrease due to the disappearance of **1a**. At the same acidity, weak absorption of **3a** at 245 nm changed into the stronger absorption of **5a** as reaction proceeded. The strength of absorbance of the final product mixture decreased with decreasing acid concentration. A similar change in the product absorbance with acidity was also observed for the hydrolysis of **1a**. Apparent extinction coefficients of the product solutions at 234 nm, which were calculated by dividing the observed absorbances by the initial substrate concentration, are plotted against pH in Figure 1. Fractions of **5a** in the hydrolysis products obtained from **1a** and **3a**, respectively, decrease sigmoidally with increasing pH according to eq 3, where ϵ_1 and ϵ_2 are the

$$\epsilon = (\epsilon_1[\mathrm{H}^+] + \epsilon_2 K')/([\mathrm{H}^+] + K') \tag{3}$$

limiting extinction coefficients at higher and lower acidities, respectively, and pK' ($-\log K'$) is the midpoint of the sigmoid curve. Values obtained for **1a** and **3a** are as follows: **1a**, $\epsilon_1 = 4630 \pm 70$, $\epsilon_2 = 2150 \pm 70$, p$K' = 1.076 \pm 0.015$; **3a**, $\epsilon_1 = 4410 \pm 70$, $\epsilon_2 = 2150 \pm 70$, p$K' = 1.054 \pm 0.038$.

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[1] Corey, E. J.; Beames, D. J. *J. Am. Chem. Soc.* **1973**, *95*, 5829–5831.

[2] Suzuki, K.; Tomooka, K.; Katayama, E.; Matsumoto, T.; Tsuchihashi, G. *J. Am. Chem. Soc.* **1986**, *108*, 5221–5229.

[3] Suzuki, K.; Masuda, T.; Fukazawa, Y.; Tsuchihashi, G. *Tetrahedron Lett.* **1986**, *27*, 3661–3664.

[4] de la Mare, P. B. D.; Bolton, R. *Electrophilic Additions to Unsaturated System*, 2nd ed.; Elsevier: Amsterdam, 1982.

[5] Okuyama, T.; Fueno, T. *Proceedings of 8th IUPAC Conference on Physical Organic Chemistry*, Tokyo, August, 1986; Elsevier: Amsterdam, 1987.

[6] Okuyama, T. *Acc. Chem. Res.* **1986**, *19*, 370–376.

[7] Okuyama, T.; Inaoka, T.; Fueno, T. *J. Org. Chem.* **1986**, *51*, 4988–4990.

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Scheme I

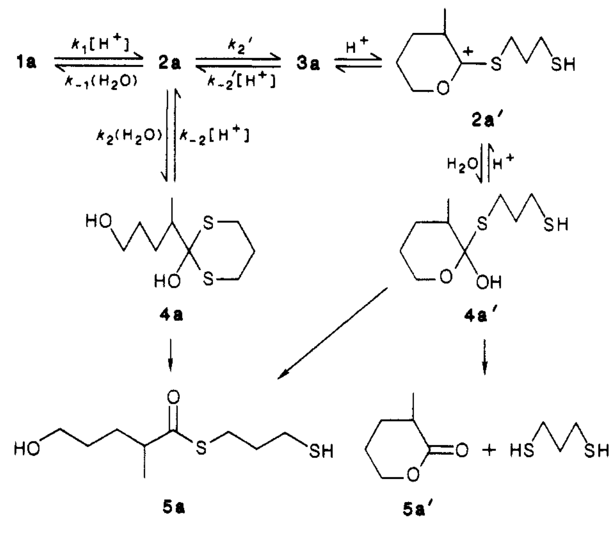

Table I. UV Absorption Spectra[a]

solvent	1a	3a	1b
CH_3CN	255 (8560)		254 (7660)
H_2O	252 (8250)	245 (830)	251 (7260)
70% $HClO_4$[b]	312 (12200)	312 (12500)	311 (12200)
0.2 M HCl			234 (4900)[c]

[a] Maximum wavelengths are given in nm with extinction coefficients in parentheses. [b] Spectra of carbocations. [c] Spectrum of the product **5b**.

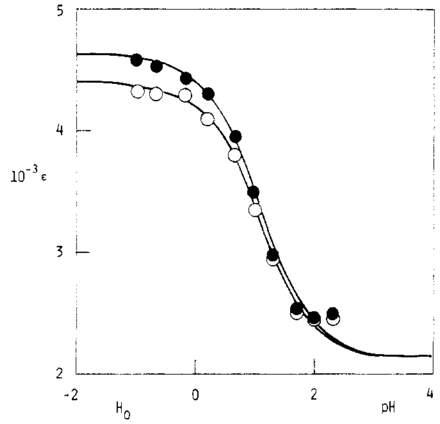

Figure 1. Absorbances of product mixtures of hydrolyses of **1a** (●) and **3a** (○) at 234 nm.

Rate constants for the hydrolysis were evaluated from time-dependent absorbance changes. Pseudo-first-order plots for disappearance of **1a** followed at 252 nm were not excellent because of slowly changing reading at the infinite time. First-order rate constants k_{obsd} were calculated by the modified Guggenheim method.[8] Observed rate constants k_{obsd} are proportional to acid concentration below [HCl] = 0.05 M with $k_{H^+} = 3.70 \times 10^{-2}$ M^{-1} s^{-1} (Figure 2). Rate constants were also evaluated from the increasing absorbance at 234 nm in the later part of the reaction of **1a** and are plotted against pH in Figure 2. Pseudo-first-order plots for appearance of **5a** (234 nm) in the reaction of **3a** were linear over 4 half-times and gave k_{obsd} close to those obtained from appearance of **5a** from **1a** (Figure 2). The pH–log k_{obsd} profile for **3a** seems to have a break around pH 1.

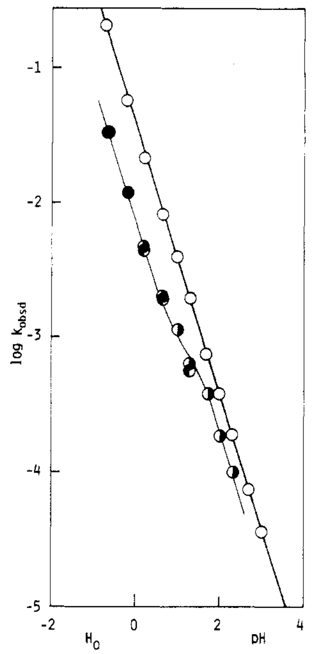

Figure 2. Rate constants for disappearance of **1a** (○) and for formation of the products from **1a** (◐) and **3a** (◑) measured at 25 °C and 0.50 M ionic strength.

Table II. Effects of Buffer and Thiol on the Rate Constants for Disappearance of 1a at 25 °C

	Formate Buffer (pH 3.24)[a]				
$[B]_t$, M	0.1	0.2	0.3	0.4	0.5
10^5k_{obsd}, s^{-1}	3.61	5.08	6.36	7.63	8.96
	2-Hydroxyethanethiol[b]				
[RSH], M	0	0.113	0.226	0.452	
10^3k_{obsd}, s^{-1}	2.78	2.74	2.73	2.81	

[a] Measured at 0.50 M ionic strength. [b] Measured at 0.10 HCl and 0.45 M ionic strength. Organic phase was kept constant at 10 vol % with CH_3CN.

Table III. Rate Constants for Disappearance of 1a and 1b in Aqueous Acetonitrile Solutions[a]

	10^4k_{obsd}, s^{-1}		rel rate
vol % CH_3CN	1a	1b	1a/1b
1.0	2.61	2.63	1.0
10	1.90	1.79	1.1
20	1.21	1.00	1.2
40	0.434	0.270	1.6
60	0.250	0.113	2.2
80	0.448	0.127	3.5
90	4.25	0.217	20
95	73.4	0.776	95
100	17000[b]		

[a] Measured at 0.01 M HCl and 25 °C without any added salt. [b] Evaluated from data obtained at [HCl] = 10^{-4}–10^{-3} M.[5]

Rate constants for the disappearance of **1a** were also measured in formate buffer solutions at pH 3.24 (Table II). The observed rate constants k_{obsd} are linearly dependent on buffer concentrations $[B]_t$, least-squares analysis giving the relationship $10^5k_{obsd} = (13.3 \pm 0.2)[B]_t + (2.35 \pm 0.05)$. The intercept at $[B]_t = 0$ coincides with that calculated from k_{H^+}, 2.13×10^{-5} s^{-1}.

Effects of added thiol on the rate of disappearance of **1a** were examined at [HCl] = 0.10 and 0.45 M ionic strength using 2-hydroxyethanethiol. The volume fraction of organic phase of the reaction solution was kept constant at 10% with added acetonitrile. The observed rate constants k_{obsd} are constant within experimental errors up to [RSH] = 0.45 M as listed in Table II.

Rate constants for disappearance of **1a** and **1b** were measured at 0.01 M of HCl in aqueous acetonitrile solu-

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(8) Swinbourne, E. S. *J. Chem. Soc.* **1960**, 2371.

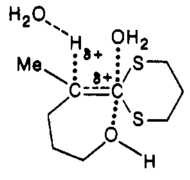
tions of varying composition. Results summarized in Table III show that the rates are essentially the same in mostly aqueous solutions, but **1a** is much more reactive in solutions of high acetonitrile composition.

Discussion

Disappearance of 1a. Formation of products is slower than disappearance of the substrate **1a** in the hydrolysis, and the rate-determining step of the overall reaction must be a later step of the multistep reaction (Scheme I). Disappearance of **1a** is catalyzed by acid. The observed rates are linearly dependent on buffer concentrations but independent of thiol concentrations. These results indicate that the protonation is rate determining for the disappearance of **1a**. If the ensuing nucleophilic reactions on **2a** were (partially) rate determining, the buffer dependence would have curved owing to the change in rate-determining step and added thiol accelerated the reaction, as observed for simple ketene dithioacetals.[6] The reference substrate **1b** undergoes partially reversible protonation in the hydrolysis. The buffer dependence was curved and the ratio k_2/k_{-1} was found to be 3.5.[7]

In the reaction of **1a**, the ensuing reaction is rapid owing to the additional intramolecular attack by the hydroxyl group (k_2') leading to cyclization. The total rate constant for the ensuing reactions is estimated to be at least 50-fold greater than that for the deprotonation (k_{-1}) as a limit that the curvature of buffer dependence could not be detected:[9] $(k_2 + k_2')/k_{-1} > 50$. Since there is no reason that k_2/k_{-1} for **1a** is much different from that for **1b**, the ratio k_2'/k_2 is evaluated to be greater than 13. That is, the intramolecular reaction of the hydroxyl group of **2a** is more than one order of magnitude faster than bimolecular attack by water. In accord with this evaluation, the product analysis shows that the hydrolysis proceeds mainly through the cyclyzed intermediate **3a** (see below).

The rate of disappearance of **1a** is essentially the same as that of **1b** in mostly aqueous solutions, but the former becomes greater than the latter as the acetonitrile content of the solution increases (Table III). In 95 vol % acetonitrile, **1a** is nearly 100-fold more reactive than **1b**. These results suggest that the participation of the internal hydroxyl group accelerates the reaction of **1a** in organic aqueous solutions as was found in methanol solution.[5] This participation could have directly resulted in cyclization; that is, the cyclization was concerted with protonation and the carbocation **2a** was not a discrete intermediate. The cation **2a** could have been the intermediate only in the wholly aqueous solution where the anchimeric assistance (acceleration) was not observed. However, in acidic acetonitrile solution (which does not contain any water), the equilibrium formation of **2a** can be observed at [HCl] > 0.05 M. Stopped-flow measurements of the rates of appearance of the carbocations from **1a** and **1b** at [HCl] = 0.1 M showed that the formation of **2a** was found to be accelerated by the internal hydroxyl group by more than two orders of magnitude.[5] The anchimeric assistance does occur in the formation of **2a** in the wholly acetonitrile solution. In the same manner, the internal hydroxyl participation may occur at the transition state of the protonation in aqueous acetonitrile solutions. The hydroxyl group may internally solvate the developing positive center in competition with water molecules as shown in structure **6**. The resulting carbocation **2a** is internally solvated as shown in eq 1, and there is another energy barrier against the C–O bond formation upon going from **2a** to the cyclized intermediate **3a**. In the wholly aqueous solution, the internal solvation may be less effective since the nucleophilicity of the hydroxyl group may be reduced by hydrogen bonding with water. As a result, the internal solvation may only substitute one molecule of solvated water but may not be more effective. The anchimeric assistance is thus not apparent but the cyclization does occur extensively in the ensuing step.



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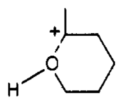
Similar observations have been made in the hydration of simple alkenols in strong acid: anchimeric assistance was not observed but the main products were cyclic ethers.[10] Contrary to these observations, it was suggested that a significant fraction of the assisted reaction gave the normal (bimolecular) addition products in bromination of alkenols.[11] Such a suggestion was also made in solvolysis reactions.[12] All these observations and suggestions can be rationalized by the intermediate formation of an internally solvated carbocation like **7** rather than an O-protonated cyclic ether like **8**. A bimolecular product will be formed if the external nucleophile is strong enough, while the cyclized product will predominate owing to entropic preference if the nucleophile is similar to the internal hydroxyl group.



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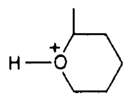

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Formation of Products. Rate constants for the formation of the product **5a** determined from the later stage of the reaction of **1a** coincide well with those obtained for the hydrolysis of the isolated **3a**. Precise values of k_{obsd} for the reaction of **1a** could not be obtained because of weaker absorbance of the product at higher pH, but k_{obsd} obtained with **3a** show a break in the pH–rate profile (Figure 2) around pH 1. This may reflect some change in rate-determining step of the reaction.

On the other hand, the absorbance of the product mixture at 234 nm changes with pH owing to the change in product composition, **5a** and **5a′**. The changes are very similar for both reactions of **1a** and **3a**. Let us consider first about the results on the reaction of **3a**. The limiting extinction coefficients ϵ_1 and ϵ_2 at high and low acidities are 4410 and 2150, respectively. In order to calculate the product composition from the apparent extinction coefficients, we have to know the molar extinction coefficients ϵ of pure **5a** and **5a′**. The lactone **5a′** hardly absorbs light at 234 nm, and the observed absorption is essentially due to **5a**. The thio ester **5b** obtained from **1b** has ϵ of 4900 (Table I), and similar thio esters of 1,2-ethanedithiol have ϵ values between 4800 and 5100. We can safely assume ϵ for **5a** to be 4900 (for the sake of comparison, fractions of **5a** calculated on the basis of $\epsilon = 5000$ are also given in parentheses below). Thus, the fraction of **5a** changes from

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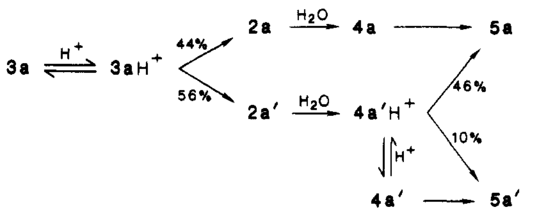
(9) Okuyama, T.; Kawao, S.; Fujiwara, W.; Fueno, T. *J. Org. Chem.* **1984**, *49*, 89–93.

(10) Herlihy, K. P.; Sagatys, D. *Abstracts 7th IUPAC Conference on Physical Organic Chemistry*, Auckland, New Zealand, Aug 1984; p 28.

(11) Hooley, S. R.; Williams, D. L. H. *J. Chem. Soc., Perkin Trans. 2* **1975**, 503–506.

(12) Blandamer, M. J. B.; Golonkin, H. S.; Robertson, R. E. *J. Am. Chem. Soc.* **1969**, *91*, 2678–2683.

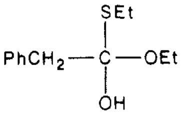
Scheme II



90% (88%) at higher acidity to 44% (43%) at pH about 3 and follows a sigmoid curve of the midpoint pK' = 1.05.

The product composition is determined by the partitioning of **3a** (to **2a** and **2a′**) and that of **4a′** (to **5a** and **5a′**) as shown in Scheme I. The change in partitioning ratio with pH reflects the different partitioning in acid-catalyzed and uncatalyzed breakdowns of the tetrahedral intermediate. It was found that hydrogen thio ortho esters derived from ketene O,S-acetals and from mixed thio ortho esters underwent such a change at pK' between −0.55 and 1.66, as summarized by Santry and McClleland.[13] However, a similar change in the hydrolysis of mixed thio ortho ester itself occurs at much higher pH; the uncatalyzed reaction becomes important only at high pH.[14] The change in partitioning ratio observed in a pH range 0–2 must be due to **4a′** but not to **3a**. The acid-catalyzed breakdown of **4a′** gives mainly **5a** while the uncatalyzed reaction may lead mostly to **5a′**, as usually the case for hydrogen thio ortho esters.[13] The fraction of **5a** formed as the limit around pH 3 must arise from **2a**, which is in turn formed by the acid-catalyzed reaction of **3a**. The change in partitioning ratio of **3a** must occur at higher pH. In summary, the acid-catalyzed reaction of **3a** results in 44% (43%) C–O bond fission to give **2a** and 56% (57%) C–S bond cleavage to **2a′**, and the acid-catalyzed reaction of **4a′** gives rise to 82% (46/56) C–O bond cleavage to **5a** and 18% (10/56) C–S bond cleavage to **5a′** as shown in Scheme II. (Protonated intermediates **3aH$^+$** and **4a′H$^+$** are considered here in the acid-catalyzed breakdown, but this is not conclusive.[13,15])

The acid-catalyzed partitioning of 4a′ is comparable to that found for a tetrahedral intermediate **9**, which leads



$$PhCH_2-\overset{SEt}{\underset{OH}{C}}-OEt$$

9

to 79% of C–O bond cleavage with pK' = 1.66.[15] The partitioning of **3aH$^+$** is corrected for the two C–S bonds involved to be 61/39 as the relative C–O/C–S bond cleavage. The acid-catalyzed reaction of **3a** also leads preferably to C–O bond cleavage. This may be ascribed to greater basicity of the ether oxygen than of the sulfide sulfur atoms.[16]

The sigmoid curve of the absorbances of the product mixtures from the reaction of **1a** gives essentially the same midpoint and the same limiting value of ϵ_2 around pH 3 as that from the reaction of **3a**, but the limiting value of ϵ_1 at higher acidity is slightly greater than that of **3a** and corresponds to 94% (93%) of **5a**. A larger amount of **5a** formed from **1a** suggests that some fraction of the reaction of **1a** may lead to **5a** directly from the incipient intermediate **2a** in strong acid without passing through **3a**. In any case, hydrolysis of **1a** must take place mainly through intermediate formation of **3a** and accumulation of **3a** seems to occur during the hydrolysis.

The break of the pH–log k_{obsd} profile for the hydrolysis of **3a** occurs at nearly the same pH as the change of the partitioning of **4a′** takes place. This strongly suggests that the breakdown of the tetrahedral intermediate **4a′** is mostly rate determining, if not solely, in the hydrolysis of **3a**. A similar break of the pH–rate profile was previously interpreted in terms of the partitioning of tetrahedral intermediates.[17] A similar kinetic analysis may be applicable to the present reaction, but the reaction appears too complex to make precise analysis.

Even in the wholly aqueous solution, the hydrolysis of 1a takes place mainly through the cyclized intermediate 3a although the anchimeric assistance was not observed.

Experimental Section

Materials. 2-(4-Hydroxy-1-methylbutylidene)-1,3-dithiane (**1a**) and the ortho lactone **3a** were provided by Dr. K. Suzuki and Professor G. Tsuchihashi (Keio University).[2,3] 2-Isopropylidene-1,3-dithiane (**1b**) was obtained as described previously.[7,18] 2-Hydroxyethanethiol was distilled just before use. Acetonitrile was distilled from calcium hydride. Other chemicals were used as received.

UV Spectra. The spectra were recorded in a 1-cm quartz cuvette on a Shimadzu UV 200 spectrophotometer. Spectra of the product mixtures were obtained after 6 half-times at 25 °C. Reactions were started by introducing 30 μL of an appropriate stock solution of the substrate from a microsyringe into 3.0 mL of the acid solution.

Kinetic Measurements. Rates were measured spectrophotometrically at 25.0 ± 0.1 °C as described previously.[7,9] Aqueous acetonitrile solutions were prepared in a volumetric flask by diluting the necessary amounts of hydrochloric acid and acetonitrile (or water) with water (or acetonitrile) to the mark at 25 °C when the acetonitrile (or water) content is less than 50 vol %.

Acknowledgment. We are grateful to Dr. K. Suzuki and Professor G. Tsuchihashi for providing samples of the substrates **1a** and **3a** and for useful comments.

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[13] Santry, L. J.; McClleland, R. A. *J. Am. Chem. Soc.* **1983**, *105*, 3167–3172.

[14] Okuyama, T.; Kitano, M.; Fueno, T. *Abstracts 8th IUPAC Conference on Physical Organic Chemistry*, Tokyo, August, 1986; p 286.

[15] Hershfield, R.; Schmir, G. L. *J. Am. Chem. Soc.* **1972**, *94*, 1263–1270.

[16] Bonvicini, P.; Levi, A.; Lucchini, V.; Modena, G.; Scorrano, G. *J. Am. Chem. Soc.* **1973**, *95*, 5960–5964. Perdoncin, G.; Scorrano, G. *Ibid.* 1977, *99*, 6983–6986.

[17] Schmir, G. L. *J. Am. Chem. Soc.* **1968**, *90*, 3478–3486. Hershfield, R.; Schmir, G. L. *Ibid.* **1973**, *95*, 7359–7369.

[18] Okuyama, T.; Fujiwara, W.; Fueno, T. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 453–456.