Mechanism of Hydrolysis of 1,3-Dithiane Derivatives. Breakdown of the Tetrahedral Intermediate

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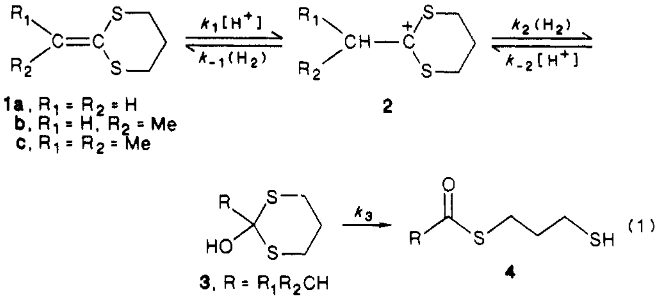
Acid-catalyzed hydrolysis of 2-methylene-1,3-dithiane (**1a**) was reinvestigated at 25 °C, and the equilibrium constants for the first two steps of the three-step reaction were determined to afford rate constants for the third step, breakdown of the tetrahedral intermediate (**3**). The pH–rate profiles show that the acid-catalyzed breakdown occurs through an S-protonated intermediate without any change in the rate-determining step. The base-catalyzed breakdown of **3** was examined with the *tert*-butyl derivative **3d′** and found to undergo a change in the rate-determining step with pH. The β,β-dimethyl derivative of **1a** was 1/600 as reactive as **1a** and undergoes partially reversible protonation in contrast to the acyclic derivative.

We have previously reported on the hydrolysis of some 2-alkylidene-1,3-dithianes **1** (eq 1).[1] The hydrolysis proceeds through a three-stage mechanism involving a dithio carbocation **2** and a hydrogen ortho thio ester **3** as intermediates. Breakdown of the tetrahedral intermediate **3** was found to be rate-determining at low pH, and the rate constant k_3 could be calculated by using the equilibrium constants for stages 1 and 2 (K_1 and K_2). The breakdown is catalyzed by both acid and base.[2] In the previous paper[1] we considered that acid-catalyzed breakdown of the tetrahedral intermediate **3a** derived from 2-methylene-1,3-dithiane (**1a**) underwent an unusual change in the rate-determining step. This was deduced from a break in a pH–rate constant (k_3) profile that was calculated on the basis of an assumed equilibrium constant K_2. The break is now proved to be an artifact that arose from a wrong value of K_2 for **1a**, and we would like to correct the previous discussion.



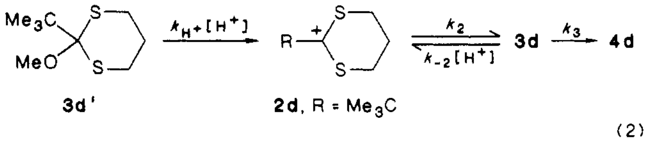
1a, R1 = R2 = H
b, R1 = H, R2 = Me
c, R1 = R2 = Me

2

3, R = R1R2CH

4

On the other hand, the base-catalyzed breakdown of the tetrahedral intermediate derived from 2-*tert*-butyl-2-methoxy-1,3-dithiolane undoubtedly involves a change in the rate-determining step, and diffusion-controlled proton transfer from the neutral intermediate to hydroxide ion becomes rate-determining at higher pH.[3] In order to look into the generality of this change in the rate-determining step, hydrolysis of the dithiane derivative **3d′** was examined (eq 2), and results are presented herein.

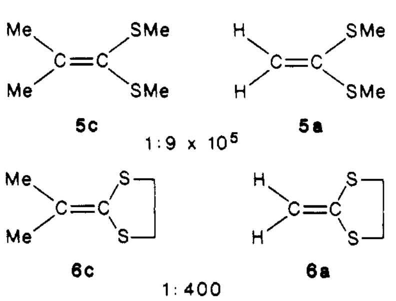


3d′

2d, R = Me3C

(2)

Furthermore, hydrolysis of 2-isobutylidene-1,3-dithiane (**1c**) was also investigated for comparison with the unusual reactivities observed previously with acyclic analogues (**5c**).[4] The β,β-dimethyl substitution retards enormously the hydrolysis of the ketene dithioacetal **5a** (1/9 × 10⁵) while similar retardation is much less (1/400) in the five-membered cyclic derivatives **6a** and **6c**.[5,6] We wished to determine the magnitude of this effect on the six-membered cyclic derivatives **1a** and **1c**.



5c **5a**

6c **6a**

Results

Hydrolysis of 2-Alkylidene-1,3-dithianes 1. Rates of hydrolysis of **1a–c** were measured in aqueous solution (at 0.50 M ionic strength and 25 °C) in the same way as before,[1] although the reaction conditions are somewhat different. Results are illustrated in Figure 1.

The hydronium-ion catalytic constanstss k_{H^+} were calculated from the data obtained in dilute HCl solutions in the pH range 3–4, where the first and second steps of eq 1 are both partially rate-determining (eq 3). Rate constants are given in Table I.

$$k_{H^+} = k_1k_2[H^+]/(k_{-1} + k_2) \tag{3}$$

Curved buffer dependencies (eq 4) were examined for **1c** to evaluate the rate constant ratio k_2/k_{-1} (eq 5)[2] where

$$\Delta k = \Delta k_{max}[B]_t/(K_{app} + [B]_t) \tag{4}$$

Δk (= $k_{obsd} - k_{H^+}[H^+]$) is a rate increase induced by the buffer at total concentation $[B]_t$. The parameters were

$$k_2/k_{-1} = \Delta k_{max}/k_{H^+}[H^+] \tag{5}$$

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[1] Okuyama, T.; Kawao, S.; Fujiwara, W.; Fueno, T. *J. Org. Chem.* **1984**, *49*, 89–93.

[2] Okuyama, T. *Acc. Chem. Res.*, in press.

[3] Okuyama, T.; Fueno, T. *J. Am. Chem. Soc.* **1985**, *107*, 4224–4229.

[4] Okuyama, T.; Kawao, S.; Fueno, T. *J. Am. Chem. Soc.* **1983**, *105*, 3320–3326; *J. Org. Chem.* **1984**, *49*, 85–88.

[5] Okuyama, T. *J. Am. Chem. Soc.* **1984**, *106*, 7134–7139.

[6] Okuyama, T.; Toyoda, M.; Fueno, T. *Can. J. Chem.* **1986**, *64*, 1116–1123.

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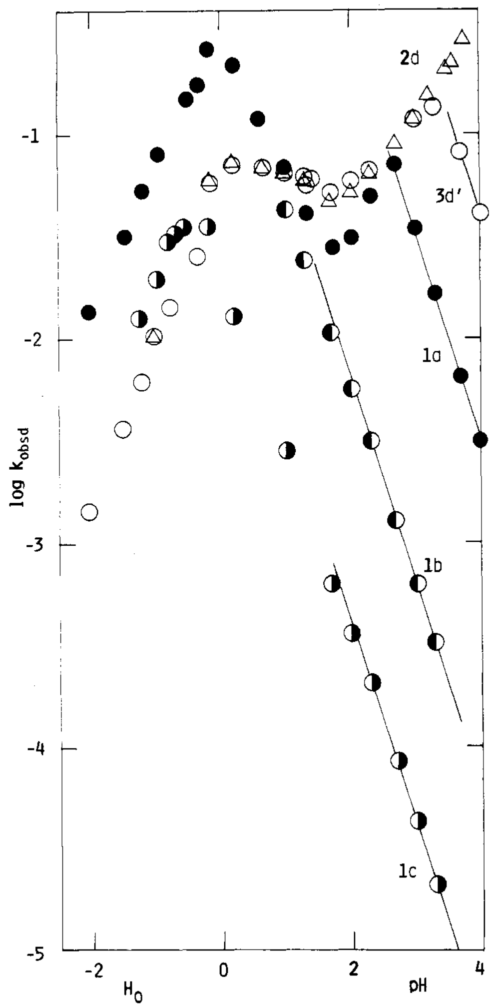

Figure 1. Acidity dependence of rate constants for the hydrolysis of dithiane derivatives, **1a** (●), **1b** (◐), **1c** (◑), **2d** (△), and **3d′** (○).

Table I. Rate Constants for the Hydrolysis of Dithiane Derivatives[a]

substrate	$k_{H^+}[H^+]$, M^{-1} s^{-1}	k_2/k_{-1}	k_1, s^{-1}	pK_R[b]
1a	33.2	45[c]	34	0.103 (0.092)
1b	0.654	12[c]	0.71	
1c	0.0428	3.5	0.055	
3d′	417			1.503 (0.086)

[a] In aqueous solution of 0.50 M ionic strength containing 1 vol % of CH_3CN at 25 °C. [b] Standard deviations are given in parentheses. [c] Values obtained in 10 vol % CH_3CN-H_2O at 0.45 M ionic strength and 30 °C.[1]

Table II. Buffer Effects on the Rate of Hydrolysis of 1c

buffer (pH)[a]	range of buffer concn, M	$\Delta k_{max}/k_{H^+}[H^+]$[b]	K_{app},[b] M
chloroacetate (2.64)	0.1–0.5	3.70 (0.35)	0.90 (0.10)
formate (3.24)	0.1–0.6	3.24 (0.10)	0.43 (0.02)

[a] Constant to ±0.02. [b] Standard deviations are given in parentheses.

Table III. Buffer Effects on the Rate of Formation of 4d from 2d

buffer (pK_a)[a]	pH	$10^2\Delta k_{max}$,[b] s^{-1}	$10^2 k_{max}$, s^{-1}	K_{app},[b] M	k_B, M^{-1} s^{-1}
cyanoacetate (2.43)	2.63	5.61 (0.02)	14.2	0.252 (0.005)	0.149
methoxyacetate (3.53)	2.84	12.1 (0.3)	22.6	0.134 (0.005)	2.48
	3.02	16.0 (0.6)	28.3	0.101 (0.008)	2.52
formate (3.77)	2.98	16.7 (0.5)	28.5	0.087 (0.006)	8.95

[a] Taken from: Sober, H. A., Ed. *CRC Handbook of Biochemistry*; CRC Press: Cleveland, OH, 1968. [b] Standard deviations are given in parentheses.

calculated by linear least-squares analysis of the correlations of $k_{H^+}[H^+]/\Delta k$ against $1/[B]_t$[7] and are given in Table II. Values of k_2/k_{-1} were used to calculate k_1 (Table I).

The β,β-dimethyl substitution does not extremely deactivate **1a** (a relative value of k_1 for **1a**/**1c** being about 600), and the protonation of **1c** is partially reversible. This behavior is similar to that of the dithiolane dervatives[5-7] but is in marked contrast to that of the acyclic ketene dithioacetals (the relative reactivity of **5a**/**5c** is about 10^6 and the protonation of **5c** is irreversible).[4]

In strong acid, absorption of the dithio carbocation **2** was observed at about 310 nm. In moderately strong acids, a very rapid increase followed by a slow decrease in the absorbance at 310 nm was observed when the stock solution of **1a** was rapidly mixed with acid in a stopped-flow spectrophotometer. The later part of the decrease, which fits the pseudo-first-order kinetics, was extrapolated to zero time to give "initial" absorbances. The initial absorbances so obtained follow a sigmoid curve against the H_R acidity function ($pK_R = 0.103 \pm 0.092$). The absorbances must correspond approximately to equilibrium concentrations of **2a** in the first two steps and $K_R = (1/K_1) + K_2$, since the third step is slow in the acidity range concerned.

Hydrolysis of 2-*tert*-Butyl-1,3-dithianylium Ion (2d). The reaction of **2d** was followed by starting with the isolated salt of **2d** or the 2-methoxy derivative **3d′**. In the reaction of **2d** above pH 2, disappearance of its absorption (313 nm) was instantaneous but formation of the thio ester **4d** (232 nm) was slow. Below pH 1.5, both disappearance of **2d** and formation of **4d** could be monitored to give the same rate constants k_{obsd}. In the intermediate pH region (2–3), an induction period for the formation of **4d** was observed, and k_{obsd} was calculated from the later part of the reaction.

Effects of buffer concentrations on the rate of formation of **4d** from **2d** were examined in some carboxylate buffer solutions in the pH range 2.6–3. The reaction in buffer solutions did not show any induction period. Plots of k_{obsd} against $[B]_t$ strongly curved approaching a constant limiting rate k_{max} with increasing $[B]_t$ as observed previously with the dithiolane derivative.[3] The curvature followed eq 4, although the kinetic significance of the parameters is different.[3] Least-squares analysis of the reciprocal correlations of Δk vs. $[B]_t$ gave parameters listed in Table III.

The reaction of **3d′** showed the same behavior as isolated **2d** at higher acidities, where the formation of **2d** is very rapid (eq 2). At higher pH (>4), on the other hand, the slow acid-catalyzed formation of **4d** was observed; the formation of **2d** is rate-determining here. The pH–rate profiles are shown in Figure 1.

The "initial" absorbances at 313 nm were measured by starting with **2d** or **3d′** and extrapolating the absorbance to the time of mixing on a conventional UV spectrometer. Plots of the absorbances against the H_R function gave a sigmoid curve ($pK_R = pK_2 = 1.503 \pm 0.086$).

Discussion

The complicated pH–rate profiles of Figure 1 and other kinetic behavior of **1** observed are well accommodated by the mechanism of eq 1, where both the first and second

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(7) Okuyama, T.; Fueno, T. *J. Am. Chem. Soc.* **1983**, *105*, 4390–4395.

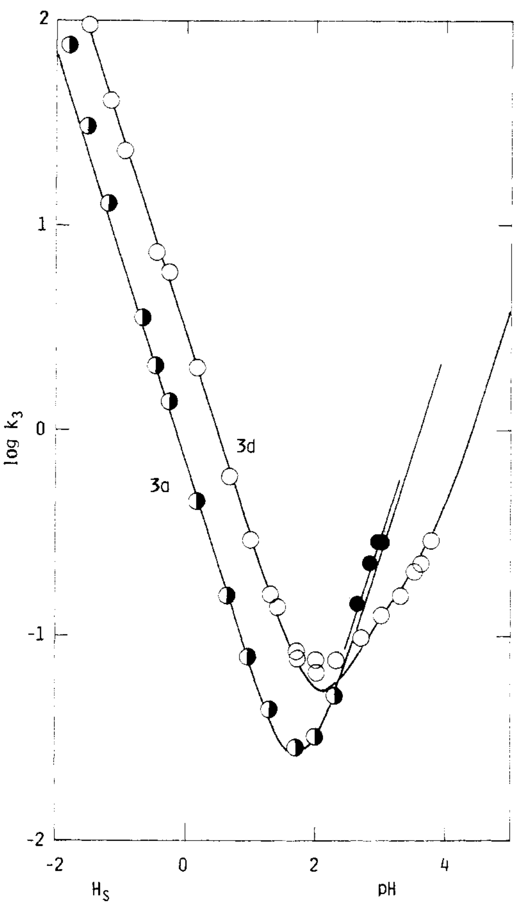


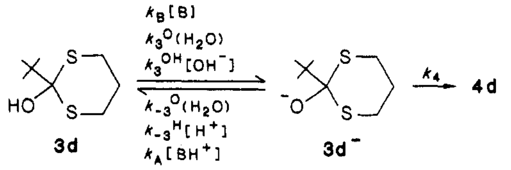
Figure 2. Acidity–k_3 profiles for the decay of **3a** (◑) and **3d** (○). Closed circles are k_{max} for **3d**.

steps are partially rate-determining at higher pH and the third step becomes rate-determining with increasing acidity.[2] The rate constants k_3 for the third step can be calculated in the latter acidity range by eq 6.[8] The k_3

$$k_3 = (K_R + h_S)k_{obsd}/K_2 \qquad (6)$$

values for **1a** are logarithmically plotted against pH or the acidity function h_S (defined for sulfur protonation)[3,5] in Figure 2. The profile shows that both acid and base catalyses are operating in this reaction. The acid-catalyzed reaction is simple, contrary to the previous suggestion[1] that was made on the basis of an assumed value of K_2. Since that assumed value of K_2 is found to be too large, the suggestion was simply wrong. The rate constants k_3^a and k_3^b are 0.70 M^{-1} s^{-1} and about 2.5 × 10^{10} M^{-1} s^{-1}, respectively, where $k_3 = k_3^a[H^+] + k_3^b[OH^-]$.

In the case of the *tert*-butyl derivative **2d**, similar calculation of k_3 gave the acidity–k_3 profile shown in Figure 2. The acid-catalyzed reaction is also simple, giving k_3^a = 2.9 M^{-1} s^{-1}. However, the slope of the base-catalyzed portion of the profile is smaller than unity, suggesting some mechanistic complexity. In some carboxylate buffers, the observed rate constants for the appearance of **4d** from **2d**, which are close to k_3 in this pH range, showed a strongly curved dependence on buffer concentration. The limiting rate constants k_{max} of the buffer curve fall on a line of a unit slope defined by k_3^b = 3.1 × 10^{10} M^{-1} s^{-1}. These observations conform to a mechanism similar to that given for the dithiolane derivative, which involves a change in the rate-determining step of the base-catalyzed decay of **3d** (eq 7).[3] At higher pH and limiting zero buffer concentration, diffusion-controlled proton transfer from **3d** to OH^- (k_3^{OH} being about 4 × 10^9 M^{-1} s^{-1} as obtained from the profile) to form the anionic intermediate **3d⁻** is mostly rate-determining, while the unimolecular ring opening of **3d⁻** becomes rate-determining as hydronium ion and acids accelerate the reverse proton transfer at higher acid concentrations: a limiting rate constant is k_3^b. Attempts to examine this mechanistic change with other 2-alkyl derivatives of **2** and dithiolanylium ion were unsuccessful owing to an accompanying side reaction to form deprotonated products like **1**.



(7)

In conclusion, the breakdown of the tetrahedral intermediates like **3** occurs through two paths involving the *S*-protonated and the anionic intermediates. The base-catalyzed reaction through the latter intermediate undergoes a change in the rate-determining step, but the acid-catalyzed reaction does not involve such a change.

Experimental Section

Materials. 2-Alkylidene-1,3-dithianes **1a–c** were prepared from the corresponding perchlorates of carbocations **2**.[10,11] 2-*tert*-Butyl-1,3-dithianylium (**2d**) perchlorate was obtained in the same way as described previously;[3,11] UV ($HClO_4$), λ_{max} 313 nm (ε 11 300). Treatment of **2d** with methanol in the presence of triethylamine in the same way as the dithiolane derivative[3] and Kugelrohr distillation at oven temperature of 120 °C and 2 mmHg gave 2-*tert*-butyl-2-methoxy-1,3-dithiane (**3d′**). Anal. Calcd for $C_9H_{18}OS_2$: C, 52.38; H, 8.79; S, 31.07. Found: C, 52.08; H, 8.64; S, 31.69. ^1H NMR (CCl_4): δ 1.09 (s, 9 H), 1.7–2.0 (m, 2 H), 2.7–2.9 (m, 4 H), 3.45 (s, 3 H).

Kinetic and equilibrium measurements were carried out in the same way as before[1,3] in aqueous solution containing 0.5–1 vol % of CH_3CN at 0.50 M ionic strength (except for strong acids) and 25 ± 0.1 °C on a Shimadzu UV 200 spectrometer or a Union RA 1100 stopped-flow apparatus. Values of pK_R were calculated according to literature procedures.[12]

Registry No. **1a**, 21777-31-1; **1b**, 51102-62-6; **1c**, 36998-38-6; **3d′**, 105064-91-3.

Supplementary Material Available: Tables of rate constants and absorbances (3 pages). Ordering information is given on any current masthead page.

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(8) K_2 = 0.78 and K_R = 0.79 were used.

(9) The solid curve for **3d** in Figure 2 is a theoretical one according to eq 10 of ref 3 with k_3^O = 0.15 s^{-1}, k_3^O/k_4 = 0.13, and k_{-3}^H/k_4 = 480 M^{-1}.

(10) Okuyama, T. *Tetrahedron Lett.* **1982**, *23*, 2665–2666.

(11) Okuyama, T.; Fujiwara, W.; Fueno, T. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 453–456.

(12) Albert, A.; Sergeant, E. P. *Ionization Constants of Acids and Bases. A Laboratory Manual*; Methuen: London, 1962; Chapter 4.