Acid-Catalyzed Hydrolysis of a Phenylketene Dithioacetal. Reversible Protonation of the Carbon-Carbon Double Bond[1]

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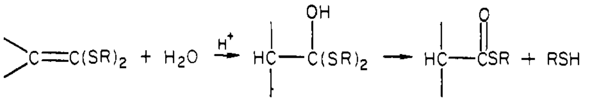
Abstract: Reactions of 1,1-bis(methylthio)-2-phenylethene (**1**) were followed in acidic CD_3CN-D_2O (50–90 vol %) solutions by ^1H NMR spectroscopy. The H-D isotope exchange at the 2-position (to give 2-deuterio derivative **1**-*d*) occurs concurrently with hydrolysis, which gives *S*-methyl phenylthioacetate. Relative rates of the isotope exchange to the hydrolysis increase from 1.0 to 13.4 on going from 50 to 90 vol % content of CD_3CN. Rates of the hydrolysis were also measured by UV spectroscopy in 10 vol % CH_3CN-H_2O (D_2O) at 30 °C. Pseudo-first-order plots for the reaction of **1** in CH_3CN-D_2O curved as expected from the concurrent isotope exchange, the relative rate of exchange to hydrolysis being 2.1 in this medium. The deuterated substrate **1**-*d* is about 1.4 times as reactive as **1**; this large apparent secondary kinetic isotope effect is ascribed mainly to the reduced reversibility of protonation of **1**-*d* rather than to true secondary effects. The hydrolysis rate increases rapidly with increasing buffer concentration to reach a constant maximum value at about 30% increase. Added 2-mercaptoethanol accelerates the disappearance of **1**. All the results are accommodated by a mechanism involving a largely reversible protonation of the double bond and a mostly rate-determining hydration of the carbocation intermediate.

Ketene dithioacetals undergo acid-catalyzed hydrolysis to give thiol esters[1-6] similarly to ketene acetals.[5,7]



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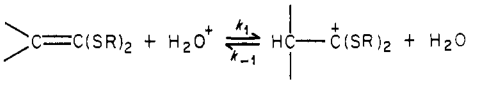
Hydration of the double bond is the primary reaction, which proceeds through carbon protonation (eq 2) and the ensuing water attack on the intermediate carbocation (eq 3). We have recently



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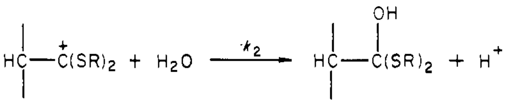

(3)

found that the initial protonation is not fully rate determining in the hydrolysis of ketene dithioacetals,[1,6] in contrast to the hydrolysis of ketene acetals,[5,8-12] vinyl sulfides,[13-15] and vinyl ethers.[16-25]

Table I. Rate Constants[a] for the Hydrolysis of **1** and **1**-*d*[b]

substrate	CH_3CN-H_2O	CH_3CN-D_2O	k_{H^+}/k_{D^+}
1	4.68	2.26[c] (3.15)[d]	2.07
1-*d*	6.46[c]	3.16	2.04
$k(1)/k(1\text{-}d)$	1.38	1.40	

[a] $10^3 k_{obsd}$, s^{-1}. [b] In 10% CH_3CN-H_2O (D_2O) [HCl (DCl)] = 0.05 M, ionic strength of 0.45 (KCl), and 30 °C. [c] Obtained from the initial slope. [d] Obtained from the ultimate slope.

The present paper describes full accounts of the acid-catalyzed hydrolysis of 1,1-bis(methylthio)-2-phenylethene (**1**), the protonation of which is largely reversible and is followed by slow hydration of a resultant carbocation.[1] The results are compared with those for 1,1-bis(methylthio)ethene (**2**).[6]

Results

Acid-catalyzed hydrolysis of phenylketene dithioacetal **1** gives *S*-methyl phenylthioacetate (**3**) as a product (eq 4), as demon-

$$PhCH{=}C(SMe)_2 + H_2O \xrightarrow{H^+} PhCH_2COSMe + MeSH \qquad (4)$$

strated by ^1H NMR and UV spectra. Rates of hydrolysis of **1** were measured spectrophotometrically in 10% aqueous acetonitrile at 30 °C. The ionic strength was maintained at 0.45 by adding KCl. Other salts like KNO_3, KBr, NaCl, $NaClO_4$, and $LiClO_4$ had no specific effects. The reaction obeyed pseudo-first-order kinetics in aqueous hydrochloric acid (Figure 1, line a), and first-order rate constants k_{obsd} were proportional to acid concentration, [HCl] = 0.005–0.1 M: $k_{H^+} = 9.39 \times 10^{-2}\ M^{-1}\ s^{-1}$. Data are given in Table S1 (supplementary material).

Pseudo-first-order plots for the hydrolysis of **1** in deuterium media (10% CH_3CN-D_2O), however, curved significantly as illustrated in Figure 1 (line b). This observation was attributed to the H-D isotope exchange at the 2-position of **1**, which was directly observed in solutions of higher acetonitrile content by ^1H NMR spectroscopy[1] (see below). The ultimate slope of the first-order plots agrees perfectly with the slope of the plots for

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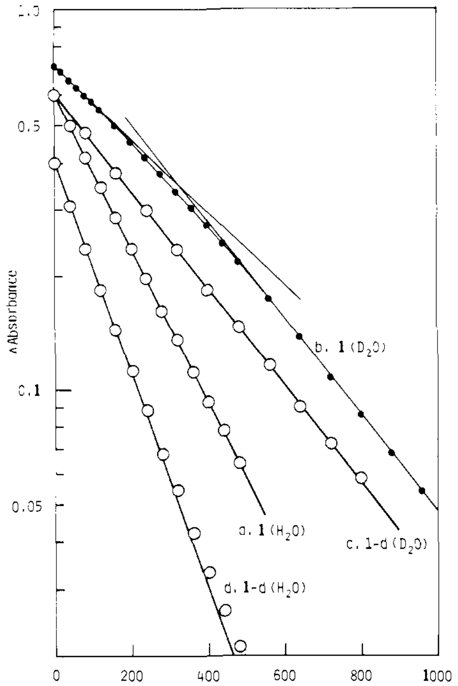

Figure 1. Pseudo-first-order plots for the hydrolysis of **1** in 10% CH_3CN-H_2O (line a) and in 10% CH_3CN-D_2O (line b) and for the hydrolysis of **1**-*d* in 10% CH_3CN-D_2O (line c) and in 10% CH_3CN-H_2O (line d) at [HCl (DCl)] = 0.05 M and 30 °C. The ionic strength was maintained at 0.45 by adding KCl.

the deuterated substrate **1**-*d* in the same deuterium media (Figure 1, line c). In contrast, the hydrolysis of the deuterated substrate **1**-*d* in protium media (10% CH_3CN-H_2O) was slightly decelerated at the later stage of the reaction, as seen in Figure 1 (line d). This must be due to a partial D-H exchange ($\mathbf{1}\text{-}d \rightarrow \mathbf{1}$), which is much slower than the isotope exchange in the opposite direction ($\mathbf{1} \rightarrow \mathbf{1}\text{-}d$). The rate constants obtained at an acid concentration of 0.05 M are summarized in Table I. The deuterated substrate **1**-*d* is more reactive than **1** ($k_D/k_H = 1.38$), and the reaction in deuterium media is slower than in protium solutions ($k_{H^+}/k_{D^+} = 2.04$).

The hydrolysis of **1** was carried out in 90 vol % CH_3CN-D_2O containing 0.1 M DCl in a preparative scale, and the isolated products were analyzed by ^1H NMR spectroscopy. Singlets found at 2.16 and 1.95 ppm are assigned to *S*-methyl groups of the thiol ester **3** and trimethyl ortho thio ester $PhCH_2C(SMe)_3$, respectively. The latter must have arisen from the reaction of the intermediate carbocation with methanethiol liberated on formation of **3**. Although phenyl and *S*-methyl resonances of these products were clearly observed, signals for the methylene groups (3-4 ppm) of the products were recognized in only ca. 6% of their expected intensities. That is, the hydrogen atoms of the methylene groups must be displaced extensively by deuterium atoms during the reaction. A control experiment showed that **3** does not undergo any detectable H-D exchange under the same reaction conditions. The deuterated substrate **1**-*d* was obtained in satisfactory purity under similar conditions but in a shorter reaction time.

The reactions of **1** in acidic CD_3CN-D_2O solutions were directly monitored by ^1H NMR spectroscopy. NMR spectral changes of the reaction mixtures clearly showed that the H-D isotope exchange at the 2-position of **1** precedes hydrolysis, as presented in a preliminary communication.[1] The resonance of the 2-hydrogen (6.69 ppm) of **1** disappeared rapidly, while the SCH_3 signals from **1** at 2.32 and 2.39 ppm remained substantially. These signals disappeared slowly with the accompanying formation of the signal at 2.23 ppm, which is due to the SCH_3 group for **3**.[26] The methylene resonance (3.84 ppm) for **3** was hardly perceived.

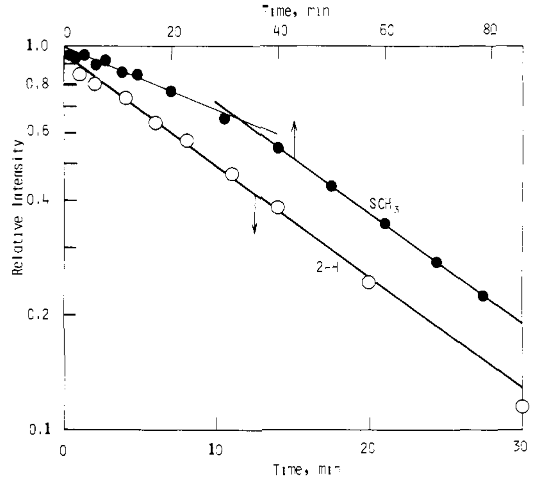

Figure 2. Time-dependent changes in NMR intensities of the signals for the olefinic hydrogen (○, lower abscissa) and *S*-methyl group (●, upper abscissa) of **1** during the reaction in 80% CD_3CN-D_2O at [DCl] = 0.05 M.

Table II. Rates of the Isotope Exchange and Hydrolysis of **1** in Aqueous Acetonitrile[a]

acetonitrile, vol %	$(k_{ex} + k_h)/k_h'$ [b]	k_{ex}/k_h	$10^4 k_h'$,[c] s^{-1}
10	2.25[d]	2.1[d]	22.0
50	1.48	1.0	2.02
70	1.80	1.5	2.04
80	2.89	3.0	3.27
90	10.4[e]	13.4[e]	6.03

[a] [DCl] = 0.05 M. [b] Obtained by NMR spectroscopy in CD_3CN-D_2O at 31 ± 2 °C. [c] Obtained by UV spectroscopy in CH_3CN-D_2O at 30 °C. [d] Evaluated from the curved first-order plots of the UV kinetics (eq 5). [e] [DCl] = 0.025 M.

Furthermore, the intensity of the signal of HOD (~3 ppm) contaminated from the solvent increased by the intensity corresponding to one atom of the substrate proton during the reaction.

The rates of H-D exchange and hydrolysis were estimated from the integral curves of the spectra obtained at appropriate time intervals. The decreasing intensities of the olefinic hydrogen resonance, measured in reference to the total phenyl intensity, gave linear pseudo-first-order plots (Figure 2), the slope of which provides the sum of the rate constants for isotope exchange, k_{ex}, and for hydrolysis of **1**, k_h. The disappearance of the SCH_3 signals for **1** gave curved first-order plots as was found in UV kinetics in deuterium media. The ultimate slope corresponds to the rate constant k_h' for the hydrolysis of **1**-*d*. No reliable value of the initial slope (k_h) was obtained.

The results obtained at several solvent compositions are given in Table II. Because we failed to accurately define the temperature of the NMR sample compartment (31 ± 2 °C),[27] the results are given as relative values $(k_{ex} + k_h)/k_h'$. The accurate values at 30 °C of k_h' were independently measured by UV spectrophotometry in appropriate CH_3CN-D_2O media and given in Table II. If we extend the quality $k_h/k_h' = 0.7$ obtained in 10% CH_3CN-D_2O to all the solvent systems used here, the values k_{ex}/k_h are easily calculated, changing from 1.0 to 13.4 with increasing organic components of the solvent (50 → 90%).

The kinetic parameters for 10% CH_3CN-D_2O can be evaluated from the curved first-order plots of Figure 1, obtained by the UV method. According to Scheme I, the curved plots are described by eq 5, where x is total concentration of **1** and **1**-*d*, and the initial

$$x/x_0 = \frac{k_{ex}\exp(-k_h't) + (k_h - k_h')\exp[-(k_{ex} + k_h)t]}{k_{ex} + k_h - k_h'} \quad (5)$$

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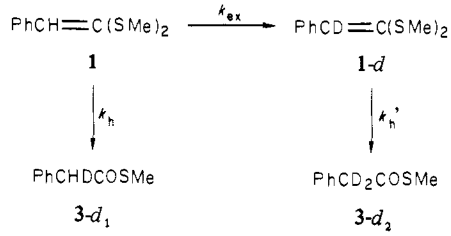
[26] Formation of a minor product, $PhCD_2C(SMe)_3$, was also observed during the NMR monitoring.

[27] The constancy of the temperature during each measurement was satisfactory.

Scheme I



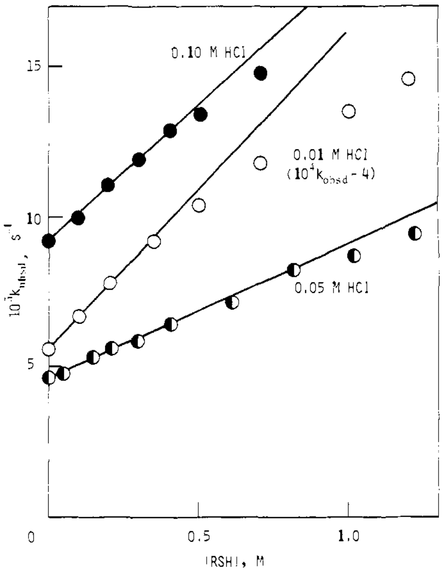


Figure 3. Dependences of the rate of disappearance of **1** on the concentration of 2-mercaptoethanol at [HCl] = 0.01 (○), 0.05 (◐), and 0.10 M (●). Total organic components ($HOCH_2CH_2SH + CH_3CN$) of the solutions were kept constant at 10% by volume.

concentrations of **1** and **1**-*d* are x_0 and 0, respectively. Fitting experimental data to the theoretical curve has been done on a trial-and-error basis by using known k_h and k_h' values (Figure 1), and an approximate value of k_{ex}/k_h obtained is given in Table II.

Rates of disappearance of **1** (295 nm) were measured in aqueous hydrochloric acid in the presence of 2-mercaptoethanol while the total organic components ($CH_3CN + HOCH_2CH_2SH$) of the solution were kept constant at 10 vol % (Table S2). The rate increased linearly with increasing thiol concentration [RSH], accompanying small downward deviations at higher [RSH] (Figure 3). Slopes of the linear parts of the plots were 1.02×10^{-3}, 4.34×10^{-3}, and 9.28×10^{-3} M^{-1} s^{-1} at [HCl] = 0.01, 0.05, and 0.10 M, respectively. Relative rate constants of the thiol reaction to the hydrolysis are essentially constant (1.0 M^{-1}).

Hydrolysis rates of **1** were also examined in buffer solutions of cyanoacetate, chloroacetate, formate, and glycolate. The rate increased sharply with buffer concentration $[B]_t$ but leveled off rapidly to reach the almost constant rate at the value of about 30% increase (Table S3). Because of rather strong acidities of the buffers used, pH as well as buffer ratio changed with $[B]_t$ even though the ratio of added acid to carboxylate was kept constant. Therefore, analysis of the results is not simple and will be presented under Discussion. The deuterated substrate **1**-*d* showed rather mild curvature in protium buffer solutions and essentially linear dependence in deuterium buffers.

Discussion

Isotope Exchange. The NMR spectra of the reaction mixtures as well as the products from the hydrolysis of **1** in acidic acetonitrile–D_2O solutions showed clearly that the olefinic hydrogen of **1** is exchanged by the solvent deuterium more rapidly than **1** is hydrolyzed. This isotope exchange is no doubt due to the reversible protonation (deuteration) of the carbon–carbon double bond.

$$\underset{\mathbf{1}}{\mathrm{PhCH{=}C(SMe)_2}} \xrightleftharpoons{D_3O^+} \underset{\mathbf{4}\text{-}d_1}{\mathrm{PhCDHC^+(SMe)_2}} \xrightarrow{-H^+}$$
$$\underset{\mathbf{1}\text{-}d_1}{\mathrm{PhCD{=}C(SMe)_2}} \xrightleftharpoons{D_3O^+} \underset{\mathbf{4}\text{-}d_2}{\mathrm{PhCD_2C^+(SMe)_2}} \xrightarrow{D_2O}$$
$$\mathrm{PhCD_2COSMe + MeSD} \quad (6)$$

A monodeuterated carbocation intermediate (**4**-d_1) formed by the deuteration of **1** releases a proton to give the deuterated substrate **1**-*d* more easily than it gives away a deuteron to revert to **1**, and **4** eventually takes D_2O to lead to hydrolysis. This is one of the first definite examples of the reversible protonation of carbon–carbon double bonds observed during their hydration.[1] A similar isotope exchange has recently been found during the hydrolysis of some vinyl selenides.[28,29]

$$\mathrm{RCH{=}C(R')(SeMe) + H^+ \rightleftharpoons RCH_2C^+(R')(SeMe)} \xrightarrow{H_2O}$$
$$\mathrm{RCH_2COR' + MeSeH} \quad (7)$$

The relative rates of the exchange to hydrolysis k_{ex}/k_h were determined from time-dependent NMR spectral changes. The curved first-order plots observed by means of the UV method for the hydrolysis of **1** in 10% CH_3CN–D_2O were ascribed to the isotope exchange and the curvature was reasonably analyzed by the reaction scheme involving the exchange and the hydrolysis (Scheme I). Data summarized in Table II show that the relative rate k_{ex}/k_h, i.e., the reversibility of the protonation, is greatly dependent on the solvent composition. The exchange is markedly accelerated by going from 80% to 90% content of acetonitrile; k_{ex} and k_h show 8- and 2-fold increases, respectively. The transition state for the deprotonation (protonation) seems to be influenced more greatly by a solvent composition than that for the hydration. The former state may be more polar than the latter.

Effect of Thiol. Since the protonation was found to be reversible during the hydrolysis of **1**, the rate-determining step must involve a water attack at the positive carbon of the carbocation **4**. Thus added thiol should accelerate the disappearance of the substrate **1** as it can compete in the nucleophilic reaction with water in aqueous solutions.

$$\underset{\mathbf{4}}{\mathrm{PhCH_2C^+(SMe)_2}} + \mathrm{RSH} \rightarrow \mathrm{PhCH_2C(SMe)_2(SR)} \quad (8)$$

This was in fact observed by using 2-mercaptoethanol as a thiol as shown in Figure 3. Relative rate constant of the thiol reaction to the hydrolysis was about 1.0 M^{-1}, as is reasonable for a reaction involving rate-determining trapping of a carbocation by nucleophiles (2-mercaptoethanol vs. water).[30]

A reactive species of the thiol is a neutral one in the present pH region (1–2), while it was found to be mostly a thiolate ion in the higher pH range of 3.6–5.4 for the reaction of the ketene thioacetal **2**.[6] The relative nucleophilicity of the thiolate ion to the thiol can be estimated to be about 5×10^6 and both species may equally contribute a nucleophilic reaction at about pH 3 since pK_a of the thiol is 9.7.

Buffer Effect. Curved dependences of the rate on buffer concentration may be accommodated by a mechanism given in eq 9 as found for the simple ketene dithioacetal **2**.[6,31]

$$\mathbf{1} \xrightleftharpoons[\substack{k_{-1}(H_2O) \\ k_{-1}'[B]}]{\substack{k_1[H^+] \\ k_1'[BH^+]}} \underset{\mathbf{4}}{\mathrm{PhCH_2C^+(SMe)_2}} \xrightarrow{k_2(H_2O)}$$
$$\underset{\mathbf{5}}{\mathrm{PhCH_2C(OH)(SMe)_2}} \xrightarrow{\text{rapid}} \underset{\mathbf{3}}{\mathrm{PhCH_2COSMe}} \quad (9)$$

The rate-determining step of the decay of the carbocation **4** is considered to be the hydration of **4** to form the hydrogen ortho

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(31) The buffer effects observed were incorrectly suggested to be ascribed to a general-base catalysis of the hydration of **4**.[1]

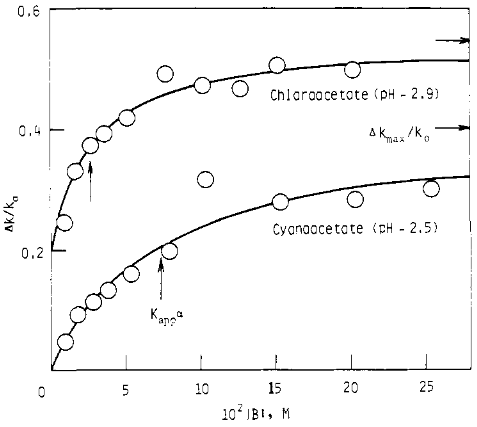

Figure 4. Dependences of the hydrolysis rate of **1** on the conjugate base concentrations of cyanoacetate (lower line) and chloroacetate buffers (upper line). Plots for the latter buffers are moved upward by 0.2 unit. Curves are theoretical ones based on eq 14 and parameters given in Table III. Horizontal and vertical arrows show $\Delta k_{max}/k_0$ and $K_{app}\alpha$, respectively.

thio ester **5** rather than the decomposition of the latter. The nucleophilicity of the thiol calculated on this basis is reasonable, as described above. Furthermore, a similar carbocation, $CH_3C^+(SMe)_2$, derived from **2** was found to decompose through the rate-determining hydration at least in the pH range 3–5.[6] Similar reactions O,O-stabilized carbocations (intermediates of ortho ester hydrolysis) were however found to proceed differently, decomposition of the hydrogen ortho esters being rate determining.[32] This difference between S,S and O,O cations may largely arise from *slow* hydration of S,S cations as was found in the reactions of isolated cations.[33]

According to eq 9 the curvature of the buffer dependence is described by eq 10, where $\Delta k = k_{obsd} - k_0$ and $\Delta k_{max} = k_{max} - k_0$.

$$\Delta k = \frac{\Delta k_{max}[B]_t}{K_{app} + [B]_t} \qquad (10)$$

The limiting rate constants k_0 and k_{max} at the zero and infinite buffer concentrations and the parameter K_{app} are described by eq 11–13, where α stands for the base fraction of the buffers.

$$k_0 = k_{H^+}[H^+] = k_1k_2[H^+]/(k_{-1} + k_2) \qquad (11)$$

$$k_{max} = k_1'k_2(1 - \alpha)/k_{-1}'\alpha = k_1k_2[H^+]/k_{-1} \qquad (12)$$

$$K_{app} = (k_{-1} + k_2)/k_{-1}'\alpha \qquad (13)$$

Buffer solutions used in the present work are of relatively high acidity, and both pH and buffer ratio change with buffer concentration owing to the dissociation of acid. Since parameters in eq 10 are dependent on pH ([H$^+$]) and buffer ratio (or base fraction α), eq 10 was modified to eq 14 by dividing by k_0. Now,

$$\Delta k/k_0 = \frac{(\Delta k_{max}/k_0)[B]_t}{K_{app} + [B]_t} = \frac{(\Delta k_{max}/k_0)[B]}{K_{app}\alpha + [B]} \qquad (14)$$

values $\Delta k_{max}/k_0$ and $K_{app}\alpha$ are independent of both pH and α.

$$\Delta k_{max}/k_0 = k_2/k_{-1} \qquad (15)$$

$$K_{app}\alpha = (k_{-1} + k_2)/k_{-1}' \qquad (16)$$

To get values of $\Delta k/k_0$, k_0 values were calculated from k_{H^+} obtained in HCl solutions and the pH of the buffer solutions.

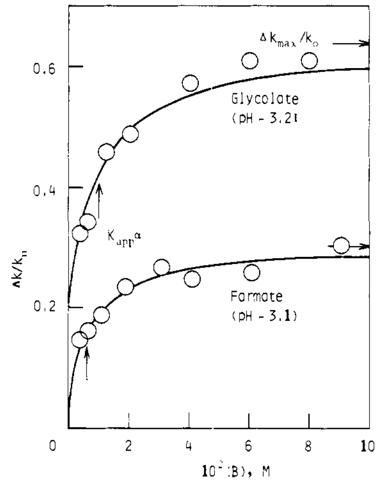

Figure 5. Dependences of the hydrolysis rate of **1** on the conjugate base concentrations of formate (lower line) and glycolate buffers (upper line). Plots for the latter buffers are moved upward by 0.2 unit. Curves are based on eq 14 and parameters given in Table III. Horizontal and vertical arrows show $\Delta k_{max}/k_0$ and $K_{app}\alpha$, respectively.

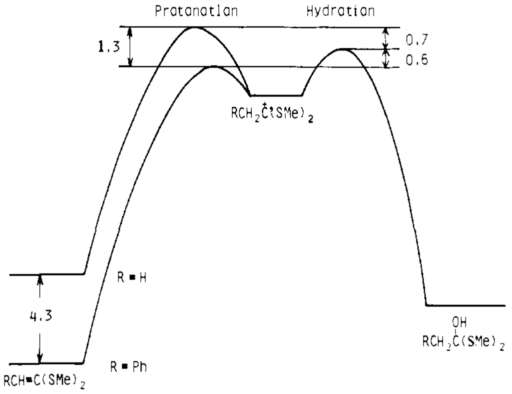

Figure 6. Free energy profiles for the hydrolysis of ketene dithioacetals $RCH{=}C(SCH_3)_2$, where R = C_6H_5 for **1** and R = H for **2**. Energy differences are given in kilocalories/mole.

Table III. Kinetic Parameters for the Buffer Dependence of Hydrolysis Rate of **1**[a]

buffer	pH range	k_{-1}/k_2	$10^2K_{app}\alpha$, M	k_{-1}'/k_{-1}, M^{-1}
cyanoacetate	2.47–2.69	2.44 ± 0.35	7.28 ± 1.39	19.4
chloroacetate	2.85–2.96	2.90 ± 0.13	2.67 ± 0.27	50.5
formate	3.01–3.19	3.33 ± 0.14	0.60 ± 0.09	218
glycolate	3.18–3.28	2.28 ± 0.34	1.01 ± 0.27	143

[a] In 10% CH_3CN–H_2O at the ionic strength of 0.45 (KCl) and 30 °C.

Carboxylate concentrations [B] were evaluated from the pH and concentrations of added carboxylate ion and acid.

Figures 4 and 5 show dependences of $\Delta k/k_0$ values on concentrations of carboxylate ions [B]. Curves are based on eq 14 and parameters given in Table III. The kinetic parameters were calculated by the least-squares treatment of $k_0/\Delta k$ vs. 1/[B]. Values of k_{-1}/k_2 range from 2.3 to 3.3, the average being 2.74. That is, deprotonation of the carbocation **4** is about 3 times as fast as the hydration of **4** at zero buffer concentration.

The value of k_{-1}/k_2 for the unsubstituted substrate **2** was found to be 0.32.[6] The β-phenyl substitution of the ketene dithioacetal **2** enhances the reversibility of the protonation by about 9 times. On the other hand, the rate of protonation (k_1) of **2** is 126 times as great as that of **1**.[6] This situation may be presented by free energy profiles of Figure 6, both in reference to the individual carbocations. So that the profiles may be constructed, it is assumed that the β-phenyl group does not affect energetics of the

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right half of the profiles (hydration of the carbocation). This may be admitted if we consider that the phenyl group affects the relative energies of the species involved largely by π conjugation. Free energy differences between two transition states for the protonation and hydration are calculated to be about 0.6 and 0.7 kcal/mol for **1** and **2**, respectively, from the values of k_{-1}/k_2. The transition state for the protonation of **1** is thus estimated to be lower by 1.3 kcal/mol in energy than that for **2**. A difference of free energy between **1** and **2** is in turn evaluated to be 4.3 kcal/mol from the relative rate of the protonation. This energy of 4.3 kcal/mol corresponds to double-bond stabilizing energy for a phenyl group, which is in accord with the values estimated previously (4.77[34] and 4.9[35] kcal/mol). These estimations indicate that the stabilization of the olefinic linkage by the phenyl conjugation in fact lowers the activation barrier against deprotonation.[19]

The phenyl conjugation reduces the rate of protonation of the ketene dithioacetal **2** 126 times,[6] while it reduces the reactivity of the vinyl ether 300–1000 times depending on the geometrical structure (cis or trans).[23,37] The greater effects of the β-phenyl substitution on vinyl ether may not necessarily mean a difference of transition-state structure. This may simply be accommodated by the reactivity–selectivity principle, since **2** is about 50 times as reactive as methyl vinyl ether,[36] or ascribed to some steric factors.

Kinetic Isotope Effect. Data given in Table I show that the deuterated substrate (**1**-*d*) is hydrolyzed about 1.4 times as easily as the undeuterated one (**1**) and the hydrolysis proceeds twice more rapidly in H_2O than in D_2O. The former result at first seemed to be ascribed to the secondary isotope effects from the 2-deuterium; hybridization of the carbon atom carrying the isotopic hydrogen changes fully from sp^2 to sp^3 on going from the reactant to transition state since the rate-determining step is largely the hydration of the intermediate carbocation. The value is, however, still too large to ascribe simply to the full hybridization change sp^2 → sp^3. The fractionation factor for an olefinic hydrogen was evaluated to be 1.194 for the change.[38]

(17)

Furthermore, hyperconjugative effects from the hydrogen isotope may diminish the value, for the transition state should have a substantial carbonium ion character.

The isotope effects observed here cannot simply be ascribed to the single step of the reaction sequence. Both first and second steps of the reaction 9 are responsible for the observed effects and the deuterium substitution alters the relative importance of these steps. Thus the observed effects may be accounted for as follows.

For the sake of simplicity let us neglect the true secondary isotope effects arising from the isotopes at the 2-position, which might be less than 10%. The reactions of the substrate **1** in H_2O, **1**-*d* in H_2O, **1** in D_2O, and **1**-*d* in D_2O are respectively described by eq 18–21, where rate constants $k_{-1}{}^{\mathrm{d}}$, $k_1{}^{\mathrm{d}}$, $k_{-1}{}^{\mathrm{s}}$, $k_{-1}{}^{\mathrm{ds}}$, and $k_2{}^{\mathrm{s}}$ refer to those for dedeuteration by H_2O, deuteration, deprotonation by D_2O, dedeuteration by D_2O, and hydration by D_2O, respectively. The intermediate **4**-d_1 carries both H and D atoms at the 2-position and releases either of them at the rate of $0.5k_{-1}$ or $0.5k_{-1}{}^{\mathrm{d}}$ to regenerate the substrate.[39] The factor 0.5 here corresponds to a statistical factor. Under the steady-state assumptions for the carbocation intermediate **4**, the following kinetic equations can be obtained for reactions 18–21.[39]

$$\mathbf{1} + \mathrm{H}^+ \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathbf{4} \xrightarrow{k_2} \mathrm{P} \tag{18}$$

$$\mathbf{1}\text{-}d + \mathrm{H}^+ \underset{0.5k_{-1} + 0.5k_{-1}{}^{\mathrm{d}}}{\overset{k_1}{\rightleftharpoons}} \mathbf{4}\text{-}d_1 \xrightarrow{k_2} \mathrm{P} \tag{19}$$

$$\mathbf{1} + \mathrm{D}^+ \underset{0.5k_{-1}{}^{\mathrm{s}} + 0.5k_{-1}{}^{\mathrm{ds}}}{\overset{k_1{}^{\mathrm{d}}}{\rightleftharpoons}} \mathbf{4}\text{-}d_1 \xrightarrow{k_2{}^{\mathrm{s}}} \mathrm{P} \tag{20}$$

$$\mathbf{1}\text{-}d + \mathrm{D}^+ \underset{k_{-1}{}^{\mathrm{ds}}}{\overset{k_1{}^{\mathrm{d}}}{\rightleftharpoons}} \mathbf{4}\text{-}d_2 \xrightarrow{k_2{}^{\mathrm{s}}} \mathrm{P} \tag{21}$$

$$k_{18} = k_1k_2/(k_{-1} + k_2) \tag{22}$$

$$k_{19} = k_1k_2/(0.5k_{-1} + 0.5k_{-1}{}^{\mathrm{d}} + k_2) \tag{23}$$

$$k_{20} = k_1{}^{\mathrm{d}}k_2{}^{\mathrm{s}}/(0.5k_{-1}{}^{\mathrm{s}} + 0.5k_{-1}{}^{\mathrm{ds}} + k_2{}^{\mathrm{s}}) \tag{24}$$

$$k_{21} = k_1{}^{\mathrm{d}}k_2{}^{\mathrm{s}}/(k_{-1}{}^{\mathrm{ds}} + k_2{}^{\mathrm{s}}) \tag{25}$$

Now, we have the value $k_{-1}/k_2 = 2.74$. The value $k_1/k_1{}^{\mathrm{d}}$, primary effects on protonation, may be estimated on the basis of the correlation found between the isotope effects $k_{\mathrm{H}^+}/k_{\mathrm{D}^+}$ and reactivity of vinyl ethers in their acid-catalyzed hydrolysis:[36] $k_1/k_1{}^{\mathrm{d}} = 2.4$. This estimation should be reasonable since $k_{\mathrm{H}^+}/k_{\mathrm{D}^+}$ for the hydrolysis of 1,1-bis(methylthio)ethene was found to fit the correlation.[6] The value of $k_2/k_2{}^{\mathrm{s}}$, secondary solvent isotope effects on hydration of a carbocation, can be evaluated to be 1.6 based on the solvent isotope effects $k_{\mathrm{H_2O}}/k_{\mathrm{D_2O}} = 0.56$ obtained for the reverse process of a similar reaction (eq 26).[40] Secondary solvent isotope effects are conveniently described in terms of fractionation factors.[41] We can calculate the fractionation factor for the transition state of reaction 26 by using the fractionation factor of 0.69 for hydronium ion and the above $k_{\mathrm{H_2O}}/k_{\mathrm{D_2O}}$. This in turn gives $k_2/k_2{}^{\mathrm{s}} = 1.6$. Similar solvent isotope effects on deprotonation of $k_{-1}/k_{-1}{}^{\mathrm{s}}$ are assumed to be 1.5, since the fractionation factors predict the equilibrium isotope effects $k_{\mathrm{H_2O}}/k_{\mathrm{D_2O}} \simeq 3$[41] and the deprotonation may proceed about halfway at its transition state. Finally, we might assign a value of 3 to the primary isotope effects on the deprotonation, $k_{-1}/k_{-1}{}^{\mathrm{d}}$ and $k_{-1}{}^{\mathrm{s}}/k_{-1}{}^{\mathrm{ds}}$.

$$\mathrm{ROH} + \mathrm{H_3O^+} \rightarrow \mathrm{R^+} + \mathrm{H_2O} \tag{26}$$

$$\mathrm{R} = \text{diferrocenylphenylmethyl}$$

These estimated values for the isotope effects on individual rate constants allow calculations of the following isotope effects for comparison with the observed values given in Table I.

$$\frac{k_{19}}{k_{18}} = \frac{k_{-1} + k_2}{0.5k_{-1} + 0.5k_{-1}{}^{\mathrm{d}} + k_2} = 1.32$$

$$\frac{k_{21}}{k_{20}} = \frac{0.5k_{-1}{}^{\mathrm{s}} + 0.5k_{-1}{}^{\mathrm{ds}} + k_2{}^{\mathrm{s}}}{k_{-1}{}^{\mathrm{ds}} + k_2{}^{\mathrm{s}}} = 1.70$$

$$\frac{k_{18}}{k_{20}} = \frac{k_1k_2}{k_1{}^{\mathrm{d}}k_2{}^{\mathrm{s}}}\left(\frac{0.5k_{-1}{}^{\mathrm{s}} + 0.5k_{-1}{}^{\mathrm{ds}} + k_2{}^{\mathrm{s}}}{k_{-1} + k_2}\right) = 1.89$$

$$\frac{k_{19}}{k_{21}} = \frac{k_1k_2}{k_1{}^{\mathrm{d}}k_2{}^{\mathrm{s}}}\left(\frac{k_{-1}{}^{\mathrm{ds}} + k_2{}^{\mathrm{s}}}{0.5k_{-1} + 0.5k_{-1}{}^{\mathrm{d}} + k_2}\right) = 1.68$$

The first and the second values correspond to the relative hydrolysis rates of **1**-*d* to **1** in H_2O and D_2O, respectively, and are compared with the observed values 1.38 and 1.40. The third and the fourth values refer to the solvent isotope effects on the hydrolysis rates of **1** and **1**-*d*, respectively, and are compared with the values of 2.07 and 2.04. The comparisons are not unsatisfactory in spite of very crude assumptions made to obtain the calculated values.

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[39] Strictly speaking, the k_{-1} and $k_{-1}{}^{\mathrm{d}}$ reactions give **1**-*d* and **1**, respectively, but eq 19 and 20, and consequently eq 23 and 24, are approximately valid in terms of kinetics at least in the initial stage of the reaction, since UV spectroscopy cannot differentiate between **1** and **1**-*d*.

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The calculations predict different relative hydrolysis rates of **1**-*d* to **1** in H_2O and D_2O and different solvent isotope effects on the rates for **1** and **1**-*d*. The experimental results are, however, essentially the same for these values. The initial slope for the first-order plots in the hydrolysis of **1** in D_2O may be too large since the curvature was downward. If we take a smaller value for the hydrolysis rate of **1** in D_2O (k_{20}), the values corresponding to k_{21}/k_{20} and k_{18}/k_{20} become greater. This make the results resemble more closely the predictions, although the predictions for the solvent isotope effects are still somewhat too small.

Reaction 20 allows us to describe the rate constant for the isotope exchange in the early stage of the reaction (eq 27). The

$$k_{ex} = k_1^d k_{-1}^s/(k_{-1}^s + k_{-1}^{ds}) \qquad (27)$$

relative rate k_{ex}/k_h can be calculated by using the estimated values for the relative rate constants:

$$\frac{k_{ex}}{k_h} = \frac{k_{-1}^s}{k_2^s}\left(\frac{0.5k_{-1}^s + 0.5k_{-1}^{ds} + k_2^s}{k_{-1}^s + k_{-1}^{ds}}\right) = 2.21$$

The value 2.21 agrees well with the observed one, 2.1 (Table III).

The observed kinetic isotope effects are thus rationalized by reactions 18–21. Since the reversibility of the initial protonation is delicately balanced by the relative magnitude of k_{-1} and k_2, the isotopic substitution of **1** easily affects the reversibility through the relative value of k_{-1}/k_2. In other words, the isotopic substitution as well as the change in solvent (composition of mixed organic aqueous solvents and H_2O–D_2O) influences the mechanism of the hydrolysis of the ketene dithioacetals.

Experimental Section

Materials. 1,1-Bis(methylthio)-2-phenylethene (**1**) was prepared from 1,1,1-tris(methylthio)-2-phenylethane, which was in turn obtained from phenylacetyl chloride and methanethiol:[42] bp 144–145 °C (5 mmHg) [lit.[3] bp 94–96 °C (0.25 mmHg)]; NMR (CCl_4) δ 2.26 (s, 3 H), 2.30 (s, 3 H), 6.66 (s, 1 H), 7–7.5 (m, 5 H).

2-Deuterio-1,1-bis(methylthio)-2-phenylethene (**1**-*d*) was obtained by the reaction of **1** in 9:1 CH_3CN–D_2O (v/v). In 100 mL of CH_3CN–D_2O containing 0.002 M DCl was dissolved 1 g of **1** at 30 °C. After 80 min of reaction with occasional shaking the reaction was quenched by the addition of 1 mL of 1 M NaOH. The reaction mixture was extracted with ether, washed with water 3 times, and dried over $MgSO_4$. After evaporation of ether the product was distilled. The NMR spectrum showed that the isotopic purity was about 94%.

S-Methyl phenylthioacetate (**3**) was prepared from phenylacetyl chloride and methanethiol:[43] bp 115 °C (5 mmHg) [lit.[43] bp 112–112.2 °C (4 mmHg)]; NMR (CCl_4) δ 2.18 (s, 3 H), 3.68 (s, 2 H), 7.15 (s, 5 H).

Other materials were obtained as described previously[6] or of the best grade commercially available.

Kinetic measurements were made in the same way as before.[6] The reaction was carried out in 10 vol % aqueous acetonitrile at the ionic strength of 0.45 (KCl) and 30 °C and monitored by the decrease in absorbance at 295 nm on a Shimadzu UV 200 spectrophotometer. The pH values of 10% CH_3CN–H_2O solutions were measured on a Hitachi-Horiba F-7 pH meter calibrated with aqueous buffers and corrected by subtracting 0.06 from the pH meter readings.

Products of the Reaction of 1 in CH_3CN–D_2O. A sample of 1 g of **1** was dissolved in 50 mL of 9:1 CH_3CN–D_2O (v/v) containing 0.1 M DCl. After standing for 5 h with occasional shaking at room temperature, the mixture was concentrated to about 10 mL by vacuum evaporation and extracted with ether. The extract was washed 3 times with water and dried over $MgSO_4$. The ether was completely removed under reduced pressure. The residues were dissolved in CCl_4 and the NMR spectrum was recorded on a JNM-4H-100 spectrometer. Three strong singlets are observed at 1.95, 2.16, and 7.16 ppm in relative intensities of about 3:1.3:5.7. Small broad singlets are also perceived at 3.65 and 3.12 ppm, their intensities being roughly 0.06 and 0.01, respectively.

Treatments of **3** with acidic CH_3CN–D_2O in the same way as above did not change its NMR spectrum at all.

NMR Kinetics of Isotope Exchange. Mixed solvents of 50 and 80% CD_3CN–D_2O containing 0.05 M DCl were prepared respectively by bringing 1.0 mL of 0.10 M DCl in D_2O to 2.0 mL and 1.0 mL of 0.25 M DCl in D_2O to 5.0 mL with added CD_3CN in volumetric flasks. Combination of 1.0 mL of the 50% solvent and 2.0 mL of the 80% solvent gave a 70% CD_3CN–D_2O solvent. A 90% solvent containing 0.025 M DCl was obtained by mixing 1.0 mL of the 80% solvent with 1.0 mL of CD_3CN. Reaction was started by adding an appropriate amount (2–10 μL) of **1** from a microsyringe to 0.4 mL of the acidic CD_3CN–D_2O solvent in an NMR sample tube. ^1H NMR spectra were recorded on a JNM-FX-100 spectrometer at appropriate time intervals (>1 min) starting 1 min after the addition of the substrate. The temperature of the sample compartment was found to be 29–33 °C depending on the ambient temperature. Rate constants were evaluated from the integral curves and estimated to be accurate to within ±10%.

Acknowledgment. We are grateful to H. Okuda for recording NMR spectra and to S. Kawao and A. Oshio for technical assistance.

Registry No. 1, 14063-69-5; hydrogen, 1333-74-0; deuterium, 7782-39-0; 2-mercaptoethanol, 60-24-2.

Supplementary Material Available: Tables of observed rate constants for the hydrolysis of **1** (Tables S1–S3) (4 pages). Ordering information is given on any current masthead page.

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