place the oxidized enzyme at a potential (real or effective) too negative to permit reduction to Mo(IV) under physiological circumstances, either by two single-electron transfers in the return leg of cycle 17 or by oxo abstraction in the substrate reaction step of cycle 18. Here the role of two or more thiolate ligands in modulating the reducibility of a $Mo(VI)O_2$ or Mo(VI)OS coordination unit to a physiologically attainable condition may be crucial to catalysis. A further aspect relates to the role of the pterin portion of the minimal Mo-co structure **3**. Our current view is that it may constitute part of the electron-transfer circuit in and out of the catalytic site. Thus, we have demonstrated in analogue reaction systems the reduction of dihydropterin by thiol to tetrahydropterin (consistent with earlier results[43]), and reduction of $MoO_2(L\text{–}NS_2)$ by the latter. This allows tentative inclusion of the H_2pterin/H_4pterin couple in the C_{ox}/C_{red} apparatus of cycle 17. The reverse process, oxidation of the Mo(IV)O state as in cycle 18, remains to be demonstrated.

Concluding Remarks

The results, interpretations, and speculations offered here and elsewhere[11,12,18–21] represent our initial endeavors directed toward reducing the mechanism(s) of action of the Mo-oxo transferases to a molecular description founded on proven chemistry. Much remains to be done in the immediate future before this goal can be achieved. Outstanding among required investigations are additional isotope labeling work designed to probe the operation of enzymatic oxo-transfer pathways, synthesis and characterization of Mo(VI)OS and Mo(IV)S species as pertinent to xanthine and aldehyde oxidases, further elucidation of the role of pterin in reactivity, and development of additional analogue reaction systems capable of, e.g., oxidizing sulfite, aldehydes, and xanthine and other heterocyclic substrates, and cleanly reducing nitrate to nitrite.

Another significant goal is the attainment of models that closely simulate the EPR spectra of enzymic Mo(V) states.[7a,44] Under the oxo-transfer hypothesis, these states appear mainly as intermediates in redox reactions returning the enzyme to its E_{ox} or E_{red} form. An example is thiol reduction of E_{ox} to E_{red} in cycle 16, via a Mo(V) intermediate (not shown). Encouraging results have recently been obtained with a Mo(V)O(OH) complex.[45] A variety of Mo(V) species $[MoO(L\text{–}NS_2)L']^{0,1+}$ are accessible by oxidation of $MoO(L\text{–}NS_2)(DMF)$.[12] It is probable that reductions of sulfoxides and *N*-oxides are not only among the first oxo transferase reactions to be achieved but are also the simplest of substrate transformations to perform in analogue systems. Nonetheless, these results provide a suitable beginning to the attainment of oxo transferase analogue reaction systems and a description of enzymatic action.

In a more general context, progress on systems mimicking the action of metalloenzymes such as carboxypeptidase A,[46] carbonic anhydrase,[47] urease,[48] tyrosinase,[49] catechol dioxygenases,[50] and cytochrome P-450[5] further sustain the proposition that functional models of enzymatic sites are viable objectives that ultimately will be contributory to elucidation of catalytic mechanisms.

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Registry No. Mo, 7439-98-7; hydroxylase, 9046-59-7.

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Mechanism of Acid-Catalyzed Hydrolysis of Ketene Dithioacetals: Reversibility of the Carbon Protonation

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It is generally accepted that acid-catalyzed hydration of olefins occurs through the initial rate-determining protonation of the carbon–carbon double bond to give carbocation intermediates.[1] The reaction of simple

$$>C{=}C< + H_3O^+ \xrightarrow{\text{slow}} R^+ + H_2O \rightarrow ROH + H^+ \quad (1)$$

alkenes is slow, and the rates are measured conveniently only in strong acids. The olefinic linkage activated by electron-releasing substituents, such as alkoxy groups,

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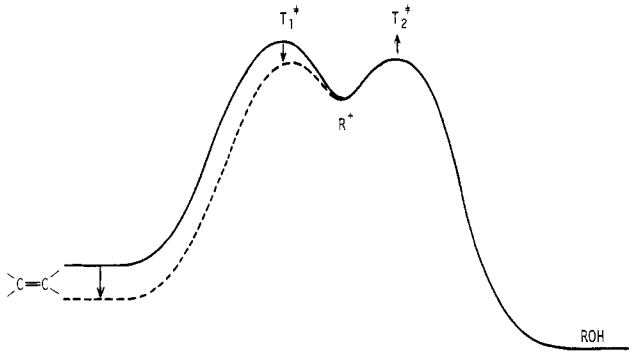
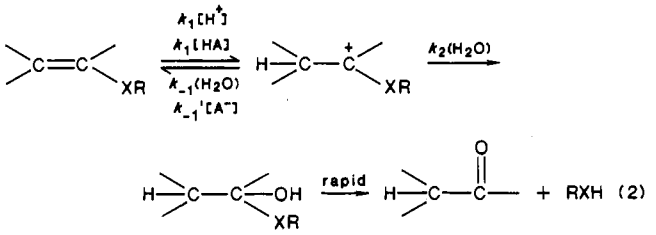


Figure 1. An energy profile of the hydration of olefin. Arrows show possible energy changes to induce a change in the rate-determining step.

are so reactive that their hydration can easily be followed in dilute acids where interpretation of the kinetic data is more straightforward. In these cases, the hydrates undergo further rapid reaction to lead to the carbonyl compounds; the overall reaction is hydrolysis (eq 2). The acid-catalyzed hydrolysis of vinyl ethers



(X = O) has therefore been extensively studied to establish the detailed reaction mechanism.[2] Investigations have been extended to the hydrolysis of vinyl sulfides (X = S)[3] and ketene acetals.[4] All these reactions were found to proceed through rate-determining protonation of the double bond ($k_{-1} \ll k_2$).

Hydrolysis of a cyclic vinyl ether, 9-methoxyoxacyclonon-2-ene (1), was, however, reported to occur through reversible protonation in acetate buffers where acetate ion accelerates the deprotonation from the carbocation intermediate.[5] This was not completely unexpected since the difference between k_{-1} and k_2 should not be very large. In the acid-catalyzed hydration of simple alkenes such as isobutene, for example, the carbocation intermediates hydrate (k_2) only 1–2 orders of magnitude more rapidly than they revert to the starting substrate (k_{-1}), as evaluated from the dehydration and ^{18}O exchange of tertiary alcohols.[6]

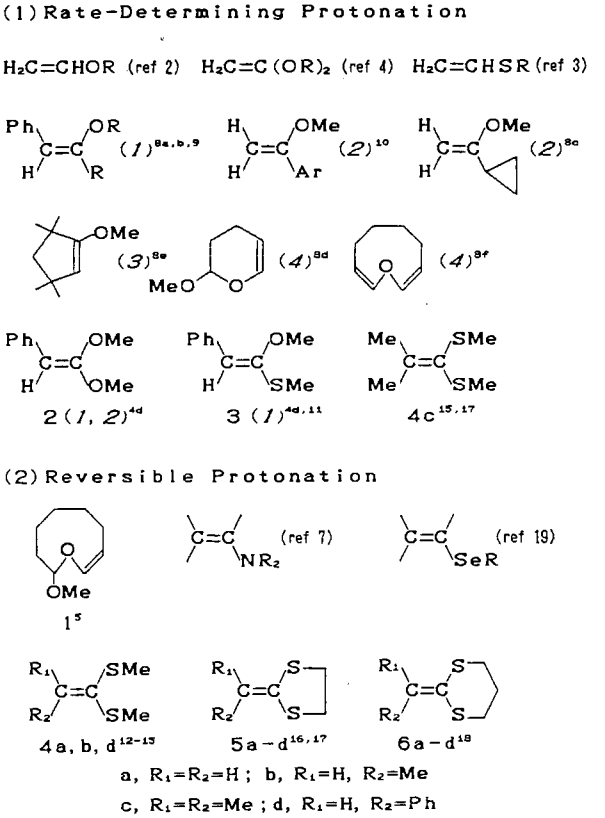


Figure 2. Vinyl ethers and related olefins examined for the mechanism of hydrolysis. Numbers in parentheses refer to conceivable categories of structural modification to affect the mechanism (see text).

Moreover, enamines undergo hydrolysis with reversible carbon protonation in acid solutions where iminium ions are built up.[7] The rate constant k_2 was estimated to be only about 7 times greater than k_{-1} for the hydrolysis of 1-piperidino-1-phenylpropene.[7c]

Kresge and his co-workers[8] thus believed that rather minor structural modification of vinyl ethers might induce a change in the rate-determining step of the hydrolysis, and tried to find some examples of vinyl ethers which undergo reversible carbon protonation during the hydrolysis. Their strategies are classified into four categories:

(1) The olefinic bond is stabilized by conjugation with a β substituent and thereby the barrier against deprotonation ($T_1^{\ddagger}$ of Figure 1) is lowered without affecting the energetics of the ensuing step ($T_2^{\ddagger}$).[8a,b]

(2) General bases accelerate the deprotonation (lowering of $T_1^{\ddagger}$)[8c] and this is examined with very reactive

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substrates and stronger bases in a higher pH region.

(3) The I strain of the substrate, which is enhanced by the hybridization change $sp^2 \rightarrow sp^3$ of the α carbon, retards the hydration of the carbocation (raise of $T_2^{\ddagger}$) but little affects the deprotonation ($T_1^{\ddagger}$).[8e]

(4) Structural analogy to the exceptional example (**1**).[8d,f]

However, all their examinations revealed that vinyl ethers are hydrolyzed through rate-determining carbon protonation. The first exceptional example (**1**) seems to need careful reexaminations.[5b] Structures of vinyl ethers and related olefins which have been examined for the hydrolysis mechanism are summarized in Figure 2. They are divided into two groups: one undergoes hydrolysis through rate-determining protonation and the other through reversible protonation. A possible structural characteristic which affects the reaction mechanism is also given by the number of the above categories.

We previously found that the reactivity of alkyl vinyl sulfides CH_2=CHSR decreases in the order R = CH_3 > C_2H_5 > $(CH_3)_2CH$ > $(CH_3)_3C$ in acid-catalyzed hydrolysis, which is just opposite to that of vinyl ethers CH_2=CHOR.[3a] This difference might have arisen from the difference in rate-determining step of hydrolysis of these two groups of substrates because vinyl sulfides could gain an extra stabilization from the electron-accepting conjugation involving the 3d orbitals of the sulfur (category 1). However, this was proved not to be the case.[3] The rate-determining step is the carbon protonation in both cases.

Schmir and his co-workers[11] on the other hand observed a slightly curved buffer dependence of the rate of hydrolysis of some ketene *O,S*-acetals and suggested that a change in rate-determining step was occurring. We reexamined carefully their results by using clearer criteria of the rate-determining step[4d] and at the same time examined the behavior of ketene *S,S*-acetals (dithioacetals) in acidic media.[12] It was concluded that hydrolysis of the *O,S*-acetals as well as *O,O*-acetals occurs through rate-determining protonation while that of the *S,S*-acetals proceeds with (partially) reversible carbon protonation.

The present account explains how this mechanistic change was detected and how the structural modification affects the rate constant of each step of the overall reaction to look into reasons for the change.

Criteria for a Change in Rate-Determining Step. A change in the rate-determining step of the hydrolysis can be probed according to the following experimental criteria.

(1) *Curved buffer dependence* is observed when the carbon protonation is rate determining at low buffer concentration $[B]_t$ and is taken over by the ensuing step with increasing $[B]_t$. This occurs because the first step is accelerated by buffer while the second step is less so. The pseudo-first-order rate constant k_{obsd} for disappearance of the substrate in the reactions shown in eq 2 is described by eq 3.[20] In buffer solutions where $[H^+]$

$$k_{obsd} = (k_1[H^+] + k_1'[HA])k_2/(k_{-1} + k_{-1}'[A^-] + k_2) \quad (3)$$

is constant and both [HA] and $[A^-]$ are proportional to the total buffer concentration $[B]_t$, the dependence of k_{obsd} on $[B]_t$ follows a saturation curve. Limiting rate constants k_0 and k_{max} at zero and infinite concentrations of the buffer are given by eq 4 and 5, respectively. The

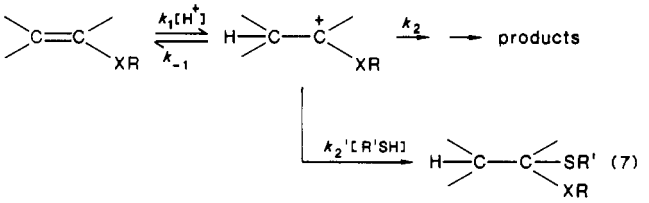
$$k_0 = k_1k_2[H^+]/(k_{-1} + k_2) \quad (4)$$

$$k_{max} = k_1k_2[H^+]/k_{-1} \quad (5)$$

rate constant k_{max} corresponds to that when the protonation becomes completely reversible ($k_{-1} + k_{-1}'[A^-] \gg k_2$). The ratio k_2/k_{-1} is then calculated by eq 6.

$$k_2/k_{-1} = (k_{max} - k_0)/k_0 \quad (6)$$

(2) *Nucleophilic trapping* of the carbocation intermediate by added thiol is observed even in acidic aqueous media. Although most of the nucleophiles are basic and cannot act as such in acidic media, thiols are very weakly basic and satisfactorily nucleophilic in acids to compete with solvent water. When thiol, R'SH, is added to the reaction system of eq 2, the carbocation intermediate is trapped by R'SH (eq 7). If the decay



(7)

$$k_{obsd} = k_1(k_2 + k_2'[R'SH])[H^+]/(k_{-1} + k_2 + k_2'[R'SH]) \quad (8)$$

of the intermediate (k_2) is involved in the rate-determining steps, the apparent rate constant k_{obsd} for disappearance of the substrate increases with increasing [R'SH], following the saturation curve of eq 8. The limiting rate constant $k_{max'}$ at the infinite [R'SH] is given by eq 9, where the protonation is completely rate

$$k_{max'} = k_1[H^+] \quad (9)$$

$$k_2/k_{-1} = k_0/(k_{max'} - k_0) \quad (10)$$

determining ($k_{-1} \ll k_2 + k_2'[R'SH]$). The ratio k_2/k_{-1} is thus expressed by eq 10.

(3) *Isotope exchange* of the β hydrogen of the substrate occurs in deuterium media when the protonation

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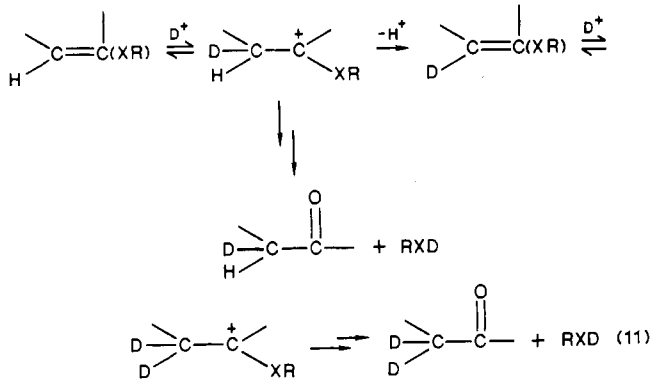
(20) (a) Hydration of a carbocation may be subject to general base catalysis,[20b-d] but the detection of catalysis by weak bases is often very hard.[20c,d] In the present treatments, a possible term $k_2'[A^-]$ is neglected since k_{max} for **4d** was found to be constant in carboxylate buffers (Figure 3).[13] Equation 3 is obtained by using the steady-state approximation. (b) Young, P. R.; Jencks, W. P. *J. Am. Chem. Soc.* **1977**, *99*, 8238–8248. (c) Bunton, C. A.; Davoudazedeh, F.; Watts, W. E. *Ibid.* **1981**, *103*, 3855–3858. (d) Gandler, J. R. *Ibid.* **1985**, *107*, 8218–8223.

is reversible (eq 11). If the hydrolysis is stopped before



completion, the recovered substrate is deuterated. The product contains more than one deuterium atom. We can observe directly by ^1H NMR spectroscopy rapid loss of the signal of the β hydrogen while the other signals due to the reactant still remain. In addition, deuteration of the substrate is also reflected on the kinetics. Since the deuterated substrate is hydrolyzed more rapidly than the original protium one owing to secondary kinetic isotope effects, the reaction is accelerated in deuterium media as reaction proceeds; i.e., the first-order plots curve to reach a slope for the deuterated substrate.

(4) *Geometrical isomerization* can be observed when the protonation of an isomerizable olefin is reversible.

(5) *Kinetic solvent isotope effects* are normal ($k_{H^+} > k_{D^+}$) for the reaction involving rate-determining protonation, and become smaller as the protonation becomes reversible. In the latter case, the isotope exchange of the β hydrogen is accompanied.

All these criteria were used to examine the mechanism of hydrolysis of ketene dithioacetals.[12-18] Isotope exchange and geometrical isomerization were also observed during the hydrolysis of vinyl selenides.[19]

Phenylketene Acetals.[4d,12,13] Among three acetals of phenylketene (**2**, **3**, and **4d**), only the *S,S*-acetal (**4d**) undergoes reversible protonation, while hydrolysis of the others, *O,O*- (**2**) and *O,S*-acetals (**3**), sets in by the rate-determining protonation of the double bond.

The product ester obtained from hydrolysis of **2** and **3** in acidic deuterium media contained only one deuterium atom, PhCHDCOOMe, but the thiolester produced from **4d** was almost completely deuterated at the α carbon, $PhCD_2COSMe$. The time-dependent change of the ^1H NMR spectrum of the reaction mixture of **4d** in CD_3CN–D_2O showed that the signal of the β hydrogen disappeared rapidly with a corresponding increase in the intensity of solvent protons (HOD), leaving a slower change of the signals of the methylthio groups. Quantitative evaluations of the intensities allow calculations of rate constants k_{ex} for the isotope exchange as well as those for the hydrolysis k_h. For a typical example, $k_{ex}/k_h = 3.0$ in 80 vol % CD_3CN–D_2O containing 0.05 M of DCl at about 30 °C.

Curvatures of the pseudo-first-order plots for the reaction of **4d** in D_2O (DCl) and for the reaction of the deuterated substrate **4d**-d_1 in H_2O (HCl) were observed in the opposite directions, reflecting H → D and D → H isotope exchanges, respectively. That is, the former reaction is accelerated while the latter is decelerated as reaction proceeds: **4d**-d_1 was 1.38 times as reactive as **4d**.

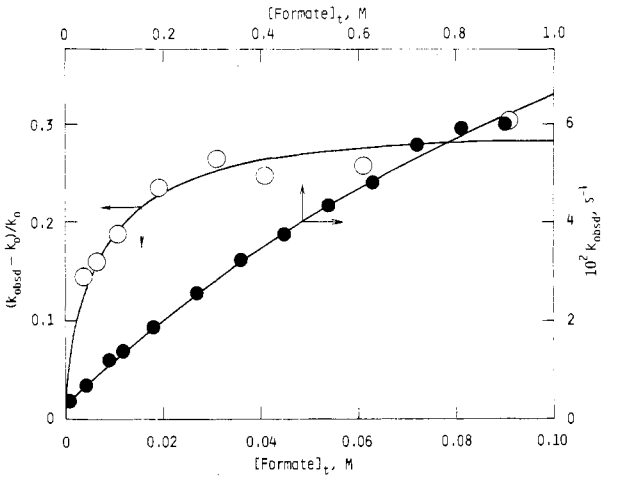


Figure 3. Effects of the formate buffer concentration on the rate of hydrolysis of **4d** (○) at pH 3.1[13] and **3** (●) at pH 3.7[4d] in 10 vol % CH_3CN–H_2O (μ = 0.45 M) at 30 °C.

Table I.
Rate Constants for the Hydrolysis of Dimethylketene Dithioacetals[a]

substrate	k_{H^+}, M^{-1} s^{-1}	k_1, M^{-1} s^{-1}	k_2/k_{-1}	k_{H^+}/k_{D^+}
4a	33.4	35.6	3.13	3.7
4b	1.28	1.9	2.0	3.4
4c	5.3×10^{-5} [b]		large	
4d	9.39×10^{-2}	0.35	0.36	2.0

[a] In 10 vol % CH_3CN–H_2O (μ = 0.45 M) at 30 °C. [b] Extrapolated by using the Cox–Yates X_0 function treatments[21b] of the data obtained in $HClO_4$ solutions.

Addition of 2-hydroxyethanethiol increased the rate of reaction of **4d**. The rate was almost linear to [R′SH], gradually reaching saturation as [R′SH] increased. By contrast, the rate of reaction of **2** or **3** was not affected by added thiol.

Buffer dependences of the rate of hydrolysis of **4d** strongly curved at relatively small concentrations of the buffer as shown in Figure 3, while those of **2** and **3** were linear in the same range of $[B]_t$. At high concentrations of carboxylate buffers, however, k_{obsd}–$[B]_t$ plots curved slightly for the hydrolysis of **3** (Figure 3).[4d,11] Nonetheless, added thiol (up to 0.5 M) had essentially no effects on the rate of reaction of **3** in a formate buffer at 0.9 M. The weak curvature for **3** may be ascribed to some solvent effect due to carboxylic acid but not to the mechanistic change. Rates of this ionic reaction sharply decrease with an increasing fraction of organic component of the solvent. Analysis of the curvatures for the rates of reaction of **4d** gave the value k_2/k_{-1} = 0.36.

This was also substantiated by using the isolated salts of cation **7d** (eq 12).[21] A rapid introduction of a stock

$$\underset{\textbf{7d}}{PhCH_2C^+(SMe)_2} + H_2O \rightarrow \underset{\textbf{4d}}{PhCH{=}C(SMe)_2} + PhCH_2COSMe \quad (12)$$

solution of **7d** in acetonitrile into a weakly acidic solution (e.g., 10^{-3} M HCl) resulted in formation of **4d** and the thiolester in a ratio of 4.9/1, the value corresponding to k_{-1}/k_2, while quenching in carboxylate buffers afforded mostly **4d**.

(21) The perchlorate of **7d** was obtained by treatments of **4d** or $PhCH_2C(SMe)_3$ with 70% perchloric acid in acetic anhydride.

Table II.
Kinetic Parameters for the Reactions of 5 at 25 °C[a]

	5a	5b	5c	5d
$k_{H^+}/M^{-1}\ s^{-1}$	130	3.93	0.148	0.0451
k_2/k_{-1}	7.24	1.33	0.68	1.02
$k_1/M^{-1}\ s^{-1}$	148	6.90	0.367	0.0893
k_{-1}/s^{-1}	2.9	24	36	38
k_2/s^{-1}	21	32	24	39
$k_{-2}/M^{-1}\ s^{-1}$	39	62	120	20
$k_3^a/M^{-1}\ s^{-1}$	0.28	0.18	0.22	0.05
$10^{-11}k_3^b/M^{-1}\ s^{-1}$	1.4	1.8	2.2	2.0
K_1/M^{-1}	51	0.29	1.03×10^{-2}	2.36×10^{-3}
K_2/M	0.54	0.52	0.20	2.0
$1/K_1K_2$	0.036	6.63	490	212

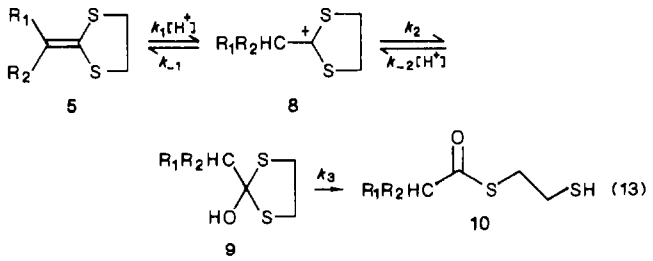
[a] Ionic strength, 0.50 M (KCl). Taken from ref 16 and 17.

Ketene Dimethyl *S,S*-Acetals.[14,15] Hydrolyses of the parent dithioacetal and the methyl derivatives (**4a**, **4b**, and **4c**) were also examined in the same way. Kinetic results are summarized in Table I along with those for the phenyl derivative **4d**. The rate constant ratios k_2/k_{-1} obtained from the buffer and thiol curvatures show that the hydrolysis of the unsubstituted substrate **4a** occurs mostly at rate-determining protonation but the reversibility is enhanced by the β mono-substitution. Effects of the phenyl group are greater than those of the methyl group. This trend is that expected in terms of the olefin stabilization (category 1). Solvent isotope effects decrease as the reversibility increases.

In accord with the kinetic results, the thiolester product obtained from reaction of **4a** in 80% CH_3CN–D_2O was only 25% deuterated at the α carbon in 0.01 M DCl while almost completely in a formate buffer (buffer ratio = 1.0, $[B]_t$ = 0.2 M).

The dimethyl substitution (**4c**) greatly reduces the reactivity of **4a** and inhibits the reversibility of the protonation. Steric effects against protonation may greatly raise the reaction barrier ($T_1^{\ddagger}$) and overwhelm the effects of olefin stabilization to result in the inhibition of the reversibility. This behavior is much different from that observed for the cyclic acetals (see below).

2-Alkylidene-1,3-dithiolanes.[16,17] Cyclic dithioacetals **5** undergo hydrolysis similarly through a three-stage mechanism (eq 13). The three-step process



(13)

can be observed directly by UV spectroscopy. Although disappearance of **5** occurred with simultaneous formation of the product **10** at pH > 3, instantaneous formation of the cation **8** (λ_{max} 330 nm) was observed in strong acids (H_0 < 0) and slower decay of **8** followed. In an intermediate pH region (~2), disappearance of the unsubstituted substrate **5a** was much faster than the formation of **10a** without any appreciable development of absorption attributable to the cation **8a** as followed by conventional UV spectroscopy. This implies the existence of another intermediate which does not absorb UV light. A triphasic absorbance change can be observed at pH 0–1 by stopped-flow spectrophotometry: there is a rapid increase followed by a biphasic decrease in the absorbance at 330 nm. The analysis of triphasic traces of the absorbance change coupled with that of the buffer-dependence curvatures above pH 3 allowed us to evaluate all the rate constants of the individual steps of eq 13 (Table II). With the β-substituted derivatives **5b–d**, however, buildup of the tetrahedral intermediate **9** was not observed. Disappearance of **5** was accompanied by a short induction period in the pH range 0–3. This is attributed to the fact that the third step is rate determining, with the preequilibrium established in favor of **5**.

The initial absorbances A_{330}^0 of the cation **8** at 330 nm extrapolated on a conventional UV spectrometer in strong acids follow a sigmoid curve against the appropriate acidity function[22] to give the equilibrium constants. The initial absorbances A_{304}^0 of **5d** (at 304 nm) also follow the sigmoid curve of the same midpoint as that for A_{330}^0, and the extrapolation of A_{304}^0 to the lower acidity limit showed that essentially the whole fraction is present in the form of **5d** there. That is, the equilibrium observed is mostly due to the first step in this case.

The constants summarized in Table II show that the relative equilibrium concentrations [**5**]/[**9**] (= $1/K_1K_2$) are much greater than unity except for **5a**. This is responsible for the relative importance of steps 1 and 2 in the equilibrium and shows that the olefinic linkage is greatly stabilized by the β substituent. The magnitude of the stabilization conforms to thermochemical data.[23] The kinetic reversibility (k_2/k_{-1}) of the protonation is increased by β substitution, consistent with the equilibrium observations (category 1). The value of $1/K_1K_2$ may be taken as the equilibrium reversibility and is reflected in the H–D isotope exchange in strong acids. The isotope exchange of **5d** in 80% CD_3CN–D_2O at 0.1 M of DCl was 10^3 times as rapid as the hydrolysis ($k_{ex}/k_h = 10^3$). A similar value for the acyclic analogue **4d** was 3. This difference arises from the fact that the reversible reaction of the former involves the tetrahedral intermediate but the latter reverts only from the carbocation intermediate in this acidity region.

It is also worth noting here that **5c** is not extremely unreactive and the protonation is reversible in contrast to the acyclic analogue **4c**. Dithiane derivatives **6** showed behavior similar to **5**.[18]

Behavior observed with isolated salts of carbocations **8**[24] conforms to the kinetic results. When the perchlorate of **8a** was quenched in weakly acidic solution, the UV absorption immediately disappeared (owing to the formation of **9a**), and slower formation of **10a** followed. By contrast, the initial rapid breakdown of the other cations **8b–d** resulted mainly in the formation of **5** under similar conditions.

(22) (a) The H_R[22b] and H_C[22c] acidity functions are used for **5a** and the others **5b–d**, since K_2 and K_1 mainly contribute to the equilibrium, respectively. By definition, $h_X = 10^{-H_X}$, which becomes equal to $[H^+]$ in dilute acid solutions. (b) Kresge, A. J.; Chen, H. J.; Capen, G. L.; Powell, M. F. *Can. J. Chem.* **1983**, *61*, 249–256. (c) Reagan, M. T. *J. Am. Chem. Soc.* **1969**, *91*, 5506–5510.

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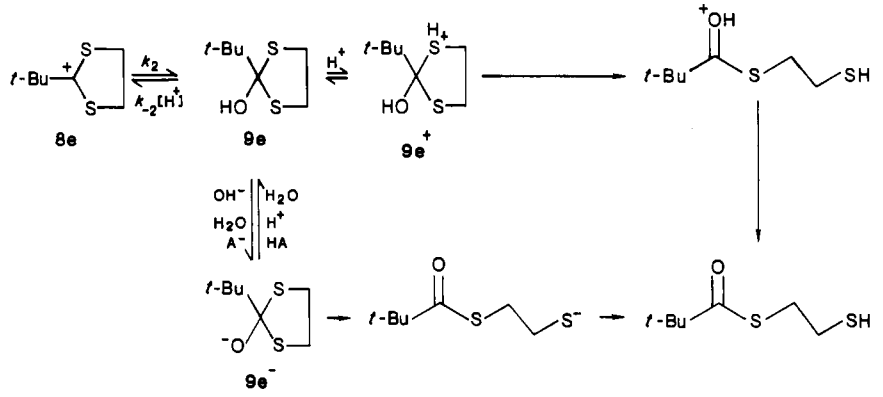

(16)

Decay of Carbocation Intermediate. The decay of dithio carbocations occurs at least in two steps. For the cyclic derivatives **8**, the hydration of **8** is rate determining at pH > 3, but the breakdown of **9** becomes the slow step below pH 2–3 ($k_{-2}[H^+] \gg k_3$). A similar change in the rate-determining step seems to take place at a much higher acidity of $H_0 = 0$ to −1 for the acyclic analogues, bis(methylthio) carbocations. The C–S bond involved in the cyclic structure is less readily cleaved.

The observation that the hydration of dithio cations is rate determining at lower acidities is in contrast to the previous findings that the breakdown of a hydrogen ortho ester intermediate is the slow step of the overall reaction of dioxo carbocations in the wide range of pH (even near neutral pH)[25] and similar suggestions for the selenium derivatives.[19]

The change in rate-determining step of decay of thio carbocations corresponds to the change in relative ease in releasing hydroxy (k_{-2}) and alkylthio groups (k_3) from the tetrahedral intermediate. The protonated intermediate loses H_2O more readily than RSH in strong acids while the neutral or anionic one gives away RS^- more rapidly, in accord with the previous observations with *O,S*-acetals.[11,26]

Breakdown of the Tetrahedral Intermediate. Since the breakdown of **9** is rate determining of the hydrolysis of the dithiolane derivatives **5** at higher acidities, the k_3 values can be calculated in a certain range of acidity by eq 14, where h_X is an appropriate acidity function.[22] The pH–k_3 profiles show that the

$$k_3 = k_0(1/K_1 + K_2 + h_X)/K_2 \qquad (14)$$

breakdown of **9** is catalyzed both by acid and base, but the water-catalyzed (uncatalyzed) reaction was hardly observed (Figure 4).[16,17] The magnitudes of k_3 are little influenced by the structure. The acid-catalyzed breakdown follows the acidity function H_S defined for sulfur protonation ($H_S = 1.3H_0 + 0.3 \log [H^+]$).[16,17,27]

$$k_3 = k_3^a h_S + k_3^b[OH^-] \qquad (15)$$

The base-catalyzed reaction can be measured only in a very limited range of pH because of the slow reaction of **5**. With an isolated cation **8e** which has no β hydrogen capable of deprotonation (eq 16), k_3 can be determined up to pH 3.5 as shown in Figure 4.[27] The slope of the high-pH portion of the pH–log k_3 profile is not simple, reflecting a change in the rate-determining step of the base-catalyzed breakdown of the tetrahedral intermediate **9e**. In accord with this observation, the rate was strongly buffer-dependent, but the rate increase leveled off at higher $[B]_t$. The logarithms of the limiting rate constants k_3^{max} at the infinite $[B]_t$ increase with pH with a slope of unity. These results are consistent with the reaction mechanism of eq 16 where a diffusion-controlled proton transfer from **9e** to OH^- is mostly rate determining at high pHs at limiting zero buffer concentration, but hydronium ion and general acids accelerate the reverse of this step and the ring-opening decay of the anionic intermediate **9e**$^-$ becomes rate determining at low pHs or high $[B]_t$ (k_3^{max}).

This was substantiated further by the solvent kinetic isotope effects as well as the Eigen curvature[28] in the

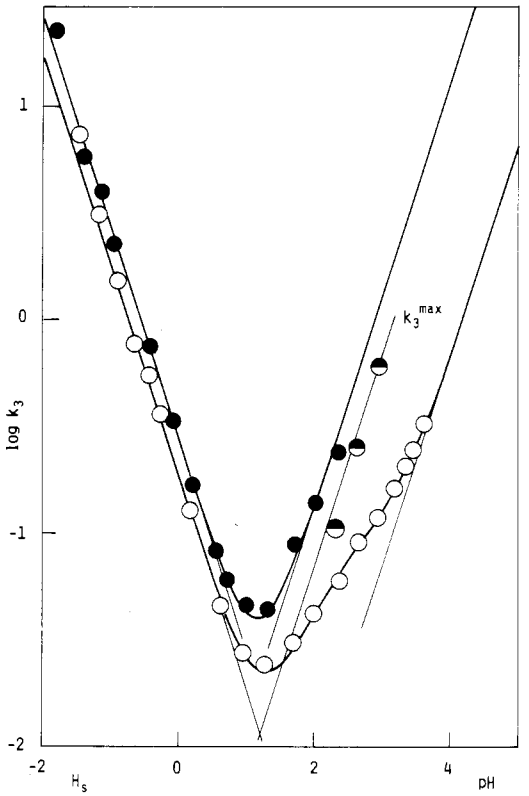

Figure 4. Acidity–k_3 profiles for the breakdown of the tetrahedral intermediates **9a** (●)[16] and **9e** (○)[27] (25 °C, μ = 0.50 M). Half-filled points (◓) show k_3^{max} obtained from the buffer dependencies of k_3 for **9e**.

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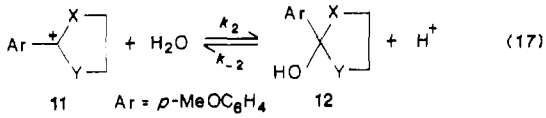
Table III.
Rate Constants for Reaction 17

cation	pK_2	k_2, s^{-1}	k_{-2}, M^{-1} s^{-1}	reaction conditions
11a	4.1	6.1×10^{-2}	7.8×10^{2}	30 °C, μ = 0.45[a]
11b[b]	1.8	4.6×10	2.9×10^{3}	25 °C, μ = 1.0
11c[c]	1.1 (1.8)[d]	1.2×10^{3}	1.5×10^{4}	25 °C, μ = 0.1

[a] 10 vol % CH_3CN–H_2O. [b] Reference 25. [c] Reference 24. [d] μ = 1.0.

correlation of the general-base-catalytic constants with the pK_a of the catalysts. A similar change in the rate-determining step was recently found to occur in the base-catalyzed decay of an oxygen analogue, 2-hydroxy-2-phenyl-1,3-dioxolane.[29]

Comparison with Oxygen Analogues. Reactions of a very stable salt of **11a** in aqueous media (eq 17)



(17)

11 Ar = *p*-MeOC$_6$H$_4$ 12

(a); X = Y = S
(b); X = S, Y = O
(c); X = Y = O

were examined[30] and compared with those of the oxygen analogues.[25,26] Rate and equilibrium constants are given in Table III. Although reaction conditions for kinetic measurements are somewhat different for each cation, a comparison of the data shows clearly the following trends. Relative stabilities of 11 (compared with the corresponding hydroxy derivatives **12**) increase in the order X,Y = O,O < S,O < S,S. *Both* rate constants for hydration (k_2) and dehydration (k_{-2}) decrease in the same order. The sulfur-substituted cation is *more stable but less readily generated* from **12** than the oxygen cation is. This unusual reactivity may have some connection with the special stability of ortho-ester-type compounds owing to "negative hyperconjugation".[31]

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The marked stability of the dithio carbocations must be due to the remarkably slow rate of hydration. The rate-determining step of breakdown of these cations is the hydration in dilute acid solutions for the same reason although the oxygen analogues break down through this step as a rapid equilibrium.[25] Reversibility of the protonation of ketene dithioacetals is also ascribed to slowness of hydration (k_2) rather than rapidity of deprotonation (k_{-1}).

Conclusion. Ketene dithioacetals are a distinct class of polar olefins which undergo hydration through partially reversible carbon protonation. Hydration of selenium olefins seems to proceed similarly, but oxygen analogues and monothio derivatives are subject to irreversible rate-determining protonation. The reversibility of protonation of ketene dithioacetals is ascribed to slowness of hydration of the intermediate dithio carbocation but not to rapidity of the reverse deprotonation. The reversibility is enhanced by the β substitution through the double-bond stabilization. Breakdown of the carbocation involves another change in the rate-determining step from the hydration (at high pHs) to decay of the tetrahedral intermediate (at low pHs). Base-catalyzed decay of the latter is accompanied by a further change in the rate-determining step involving an anionic tetrahedral intermediate.

These results are closely related to other topics of recent interest, the reactivity–selectivity principle,[32] the relative effects of adjacent sulfur and oxygen on the stability of carbocations,[33] and the tetrahedral intermediates of acyl-transfer reactions,[34] as well as alkene hydration.

I thank Professors T. Fueno, A. J. Kresge, and S. Oae for stimulating discussions and valuable suggestions.

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CORRESPONDENCE

Self-Citation and Ethical Transgression

I have just read the "Ethical Guidlines to Publication of Chemical Research."[1]

I am extremely disappointed to find these guidelines clearly lacking as to one of the most crucial unethical aspects of present-day chemical publications: self-citation. The subject is not approached in the "Obligations to Authors" (see B.4, which keeps to vague generalities, and C.8, which warns reviewers, but reviewers alone, not to be self-serving!). Yet self-citation is certainly one of the most damaging, unethical characteristics of a significant fraction of the contemporary literature published in chemical journals.

I will give one example of self-citation which speaks for itself. In 1984, a leading ACS journal published a single-author article with 69 references. Of these, 29 referred to the author's own work. One of these references, in addition, carried a detailed list of exactly 50 previous papers published by the author!

(1) Editors of Am. Chem. Soc. Journals, *Acc. Chem. Res.* **1985**, *18*, 355.

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