

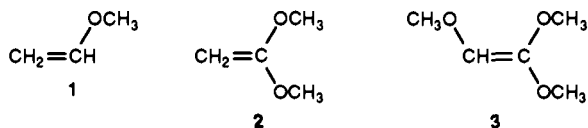
Kinetics and Mechanism of the Acid-Catalyzed Hydrolysis of 1,1-Dimethoxyethene (Ketene Dimethyl Acetal) and Trimethoxyethene in Aqueous Solution

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Abstract: Rates of acid-catalyzed hydrolysis of 1,1-dimethoxyethene and trimethoxyethene were measured in wholly aqueous solutions of perchloric acid, sodium hydroxide, and a series of carboxylic acid buffer solutions at 25 °C. The reactions show general acid catalysis and give substantial solvent isotope effects in the normal direction ($k_H/k_D > 1$). This indicates that hydrolysis occurs via proton transfer from catalyst to substrate followed by hydration of the dialkoxy cation so formed and subsequent decomposition of the hydrogen ortho ester hydration product; deuterium incorporation experiments show that the initial proton transfer is not reversible, even in sodium hydroxide solutions. Comparison of Bronsted exponents for these and other ketene acetal hydrolysis reactions with Bronsted exponents for vinyl ether hydrolysis suggests that ketene acetal hydrolysis is the intrinsically slower reaction, despite the fact that the presently available examples show it to be occurring more rapidly.

The acid-catalyzed hydrolysis of vinyl ethers such as methoxyethene (1), is a prototypical proton-transfer reaction that has been used extensively by us and by others to obtain detailed information about acid–base catalysis and reaction mechanisms.¹



A useful extension of this work to more rapidly reacting systems would be provided by the hydrolysis of ketene acetals such as 1,1-dimethoxyethene (2), but realization of this goal has proved to be difficult because of the great reactivity of ketene acetals. Some studies have been performed on substrates whose rates of hydrolysis are slowed by electronic or steric effects, and interesting information has been obtained.² Prior to the present investigation, however, no kinetic study of the hydrolysis of the parent substance, 2, had been reported, and the next higher homologue, ketene diethyl acetal, had been examined in aqueous solution only at high pH and low temperatures or in water/dioxane mixtures.³

We have found that by using stopped-flow spectroscopic methods we have been able to measure rates of acid-catalyzed hydrolysis of ketene dimethyl acetal at 25 °C in wholly aqueous solution across the entire pH range. Our results provide new information about the mechanism of this multistep process, and comparison with vinyl ether hydrolysis gives insight into how the structures of the transition states of these reactions respond to changes in reactivity.

We have included with this work a companion study of the acid-catalyzed hydrolysis of trimethoxyethene (3). This, together with our recent examination of *cis*- and *trans*-1,2-dimethoxyethene⁴ and tetramethoxyethene⁵ plus an earlier report on methoxyethene,⁶ now furnishes information on the hydrolytic reactivities of all of the possible methoxy-substituted ethenes.

Experimental Section

Materials. 1,1-Dimethoxyethene was obtained commercially (Wiley Organics), and trimethoxyethene was prepared by eliminating methanol from 1,1,1,2-tetramethoxyethane, which itself was synthesized from

methoxyacetonitrile (Aldrich).⁷ The ¹H NMR spectrum of trimethoxyethene, which had not been reported before, is consistent with its structure: δ /ppm (CDCl₃) 5.22 (s, 1 H), 3.61 (s, 3 H), 3.43 (s, 6 H). All other materials were the best available commercial grades. Solutions were prepared from deionized water, purified further by distillation, or from D₂O (Merck Sharp and Dohme, 99.8 atom % deuterium) as received.

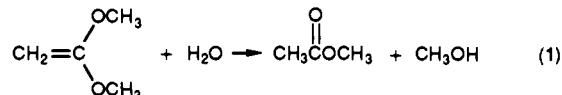
Kinetics. Rates of reaction were determined spectrophotometrically by monitoring the decrease in strong carbon–carbon double bond absorption of the substrates at $\lambda = 205$ – 225 nm. Measurements were made either with Cary 118 and 2220 spectrometers, whose cell compartments were thermostated at 25.0 ± 0.1 °C, or with a Hi-Tech SF-S1 stopped-flow spectrometer, also operating at 25.0 ± 0.1 °C.

For the stopped-flow experiments, substrates were supplied to the driving syringe as aqueous sodium hydroxide solutions, rather than dissolved in neutral water, in order to limit their hydrogen ion-catalyzed decomposition. In the case of 1,1-dimethoxyethene, there was also a rapid water-catalyzed decomposition ($t_{1/2} = 12$ s) even in these sodium hydroxide solutions, and the substrate was therefore added to aqueous sodium hydroxide already contained in one syringe of the instrument after the latter had come to 25.0 °C. It was found that in this way several kinetic runs could be performed before substrate concentrations dropped to nonuseful levels. Final concentrations of acid or buffer in these stopped-flow reaction mixtures were calculated from the known compositions of the mixed solutions and the mixing ratio (1:1).

The slower runs monitored by conventional spectrophotometry were initiated as usual by injecting the appropriate small quantities of substrate directly into thermally equilibrated acids or buffers contained in 3-mL cuvettes. All of the kinetic data conformed to the first-order rate law well, and observed rate constants were evaluated by least-squares fitting to an exponential function.

Results

Product Study. The products of hydrolysis of 1,1-dimethoxyethene were examined in order to determine whether or not the hydron transfer from catalyzing acid to substrate that must occur in this reaction was reversible. Our study showed that the process gives only methyl acetate and methanol products, as expected according to eq 1. This was apparent from the proton NMR



spectrum of a reaction mixture taken after hydrolysis was complete. This spectrum consisted only of signals at δ /ppm 3.51 and 1.90, which could be attributed to the alcohol and acyl methyl groups of methyl acetate, plus another signal at δ /ppm 3.18 due to methanol; these assignments were confirmed by the addition of authentic samples of methyl acetate and methanol. When the hydrolysis was conducted in 0.10 M DCl/D₂O or 0.010 M

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Table I. Catalytic Coefficients for the Hydrolysis of 1,1-Dimethoxyethene and Trimethoxyethene in Aqueous (H₂O) Solution at 25 °C^a

catalyst	pK _a	$k_{HA}/10^2 \text{ M}^{-1} \text{ s}^{-1}$	
		CH ₂ =C(OCH ₃) ₂	CH(OCH ₃)=C(OCH ₃) ₂
H ₃ O ⁺		7210	20.9
CH ₂ CNCO ₂ H	2.47		6.77
CH ₂ ClCO ₂ H	2.87	1340	5.00
CH ₃ OCH ₂ CO ₂ H	3.57	533	2.48
HCO ₂ H	3.75	400	1.37
CH ₂ OHCO ₂ H	3.83	466	1.64
CH ₃ CO ₂ H	4.76	149	0.605, 0.591
C ₂ H ₅ CO ₂ H	4.87	143	
H ₂ O		1.07×10^{-5}	8.92×10^{-8}

^a Ionic strength = 0.10 M.**Table II.** Solvent Isotope Effects on the Hydrolysis of 1,1-Dimethoxyethene and Trimethoxyethene in Aqueous Solution at 25 °C^a

catalyst	k_H/k_D	
	CH ₂ =C(OCH ₃) ₂	CH(OCH ₃)=C(OCH ₃) ₂
hydronium ion	2.71 ± 0.07	2.52 ± 0.12
water	6.61 ± 0.05	7.86 ± 0.13

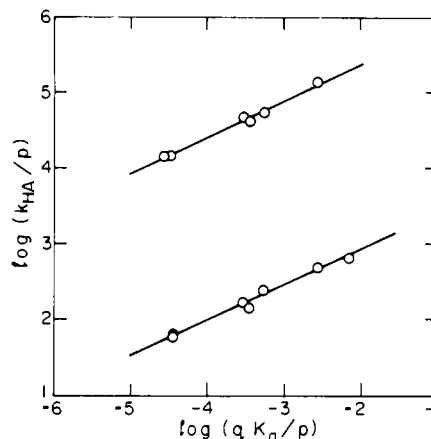
^a Ionic strength = 0.10 M.

NaOD/D₂O, the signal at δ/ppm 1.90 was reduced to two-thirds of the intensity of the other two signals and became a triplet with no evidence of further fine structure. Such a triplet is of course the signal expected from the protons in a CH₂D group split by the single deuterium, and this result thus shows that only one deuterium becomes incorporated in the substrate; hydron transfer from the catalyst to the substrate is thus not reversible.

Kinetics. Rates of hydrolysis of 1,1-dimethoxyethene and trimethoxyethene were measured in dilute H₂O and D₂O solutions of perchloric acid. Acid concentrations were varied by factors of 10–25 while ionic strength was held constant at 0.10 M. In each case, observed first-order rate constants were found to be directly proportional to acid concentration, and second-order hydrogen ion catalytic coefficients, k_{H^+} , were evaluated by linear least-squares analysis. The data are summarized in Tables S1 and S2 of the supplementary material,⁸ and the catalytic coefficients and isotope effects they provide are listed in Tables I and II.

Specific rates of hydrolysis of 1,1-dimethoxyethene and trimethoxyethene catalyzed by water serving as the hydron donor were evaluated in H₂O and D₂O solutions to which sodium hydroxide had been added to suppress catalysis by hydrogen ions. The sodium hydroxide concentration was varied while ionic strength was maintained constant at 0.10 M. In each case, only random variations in observed first-order rate constants with changes in sodium hydroxide concentration were found, and best values of water-catalyzed specific rates were therefore obtained as simple averages. These data are summarized in Tables S3 and S4 of the supplementary material,⁸ and the catalytic coefficients and isotope effects they provide are listed in Tables I and II. The rate constant obtained here for 1,1-dimethoxyethene at 25 °C, $k = 5.9 \times 10^{-2} \text{ s}^{-1}$, is consistent with $k = 8.9 \times 10^{-2} \text{ s}^{-1}$ estimated for 1,1-diethoxyethene from measurements made at lower temperatures³ when allowance is made for the fact that ethoxyethenes undergo hydrolysis somewhat more rapidly than methoxyethenes.⁹

Rates of hydrolysis of 1,1-dimethoxyethene and trimethoxyethene were also measured in H₂O solutions of carboxylic acid buffers; the data are summarized in Tables S5 and S6 of the supplementary material.⁸ Series of buffer solutions of constant buffer ratio and constant ionic strength (0.10 M) but varying buffer concentration were used, and buffer dilution plots were constructed. Marked buffer catalysis was observed, and a series

**Figure 1.** Bronsted relations for the hydrolysis of 1,1-dimethoxyethene (upper line) and trimethoxyethene (lower line) catalyzed by carboxylic acids in aqueous solution at 25 °C.

of kinetic runs performed with the same buffer but at different buffer ratios showed the catalysis to be of the general acid type. The data were therefore analyzed according to eq 2. Observed

$$k_{\text{obsd}} = k_{H^+}[H^+] + k_{HA}[HA] \quad (2)$$

rate constants were adjusted for buffer failure¹⁰ wherever necessary, and general acid catalytic coefficients, k_{HA} , were evaluated by linear least-squares analysis; the results are listed in Table I.¹¹

The intercepts of these buffer dilution plots, $k_{H^+}[H]$, provided hydrogen ion catalytic coefficients which were consistent with values determined directly in perchloric acid solutions: for 1,1-dimethoxyethene, six buffer solution series gave the average $k_{H^+} = (7.96 \pm 0.33) \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$ vs $k_{H^+} = (7.21 \pm 0.15) \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$ for perchloric acid, and for trimethoxyethene, seven buffer solution series gave the average $k_{H^+} = (2.38 \pm 0.15) \times 10^3 \text{ M}^{-1} \text{ s}^{-1}$ vs $k_{H^+} = (2.09 \pm 0.10) \times 10^3 \text{ M}^{-1} \text{ s}^{-1}$ for perchloric acid.

Bronsted relations constructed with the carboxylic acid coefficients obtained from these measurements are shown in Figure 1. Linear least-squares analysis gave the correlation lines $\log(k_{HA}/p) = (6.33 \pm 0.10) + (0.48 \pm 0.03) \log(qk_{HA}/p)$ for 1,1-dimethoxyethene and $\log(k_{HA}/p) = (3.88 \pm 0.10) + (0.47 \pm 0.03) \log(qk_{HA}/p)$ for trimethoxyethene; the statistical factors $p = 1$ and $q = 2$ were employed.

These Bronsted relations show systematic deviations characteristic of individual catalysts similar to those noted before for other ketene acetal and vinyl ether hydrolysis reactions;^{2c} these are especially prominent in the case of formic acid, whose catalytic coefficient falls consistently below the line defined by other catalysts.

Discussion

Reaction Mechanism. We have found that the hydrolysis of the prototype ketene acetal, 1,1-dimethoxyethene (2), is a general acid-catalyzed reaction with large kinetic hydrogen isotope effects: $k_{H^+}/k_{D^+} = 2.7$ and $k_{H_2O}/k_{D_2O} = 6.6$. This is classic evidence for rate-determining proton transfer¹⁰ and serves to corroborate the generally accepted mechanism for this reaction: protonation of the substrate on the β -carbon, eq 3, followed by hydration of the dialkoxy cation thus formed, eq 4, and subsequent decomposition of the hydrogen ortho ester hydration product, eq 5. Perhaps the strongest additional evidence for this reaction mechanism is the observation of hydrogen ortho ester intermediates during the hydrolysis of some ketene acetals.¹³

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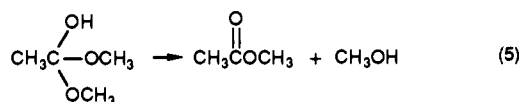
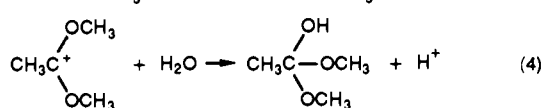
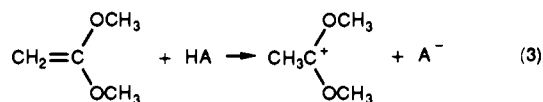
(11) Hydrogen ion and buffer acid concentrations needed for this analysis were obtained by calculation using literature pK_a's and activity coefficients recommended by Bates.¹²

(12) Bates, R. G. *Determination of pH. Theory and Practice*; Wiley: New York, 1973; p 49.

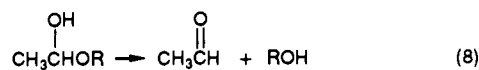
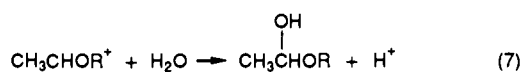
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(8) Supplementary material; see the paragraph at the end of this paper regarding availability.

(9) Chiang, Y.; Chwang, W. K.; Kresge, A. J.; Szilagy, S. *Can. J. Chem.* **1980**, *58*, 124–129.



This reaction mechanism is the exact analogue of the generally accepted and widely documented¹ reaction scheme for vinyl ether hydrolysis: rate-determining proton transfer from catalyst to substrate, eq 6, followed by hydration of the monoalkoxy cation thus formed, eq 7, and decomposition of the hemiacetal hydration product, eq 8. Ketene acetal hydrolysis and vinyl ether hydrolysis



are thus fundamentally similar reactions in a mechanistic sense. The greater reactivity of ketene acetals, moreover, follows naturally from this similarity, inasmuch as the dialkoxy cation intermediates formed in the ketene acetal reaction will be more stable than their monoalkoxy counterparts formed in vinyl ether hydrolysis.

It has been suggested that the proton transfer which occurs in the first step of this reaction scheme for ketene acetal hydrolysis, eq 3, might be reversible.¹⁴ This, however, is inconsistent with our observation that only one deuterium becomes incorporated in the ester product when the reaction is conducted in D₂O solution, even in the presence of sodium hydroxide where reversibility would be most expected.

Although this proton transfer is not reversible, it need not be the slowest step of the overall sequence; either one of the subsequent steps could be slower, and in that case an intermediate would build up in concentration during the course of the reaction. Such a buildup would not have been detected by the spectroscopic method we used to monitor the reaction, for both of the intermediates that could have accumulated, the dialkoxy cation and the hydrogen ortho ester, would have been transparent at the wavelength employed; i.e., the analytical method used was sensitive only to changes in concentration of the starting material. The starting material would of course have continued to decay in a first-order manner whether or not an accumulation of intermediate occurred.

Some further insight into this matter may be obtained from a recent study of the hydration of alkoxy cations in aqueous solution.¹⁵ That investigation reported a rate constant of $k = 1.3 \times 10^5 \text{ s}^{-1}$ for reaction of the dimethoxyethyl cation with water (eq 4), which makes the rate of this reaction equal to that of the preceding substrate protonation step at $[\text{H}^+] = 0.2 \text{ M}$. All of the measurements in the present study were performed at acidities much less than this, and substrate protonation was therefore always the slower reaction by a wide margin; the dialkoxy cation intermediate thus never accumulated to a significant extent. In strongly acidic solutions, however, substrate protonation would become faster than cation hydration, and the dimethoxyethyl cation might then be observed in such media if a suitable method of detection were available.

Table III. Reactivities of Methoxyethenes to Acid-Catalyzed Hydrolysis in Aqueous Solution at 25 °C^a

substrate	$k_{\text{H}^+}/\text{M}^{-1} \text{ s}^{-1}$	$\delta\Delta G^\ddagger/\text{kcal mol}^{-1}$ ^b	ref
	0.760	0.0	6
	720 000	-8.2	this work
	0.000 116	5.6	4
	0.000 039 8	6.2	4
	2090	-4.7	this work
	0.454	0.7	5

^a Ionic strength = 0.10 M. ^b Corrected for symmetry in the case of substrates with two equivalent protonation positions.

Less is known about the velocity of the last step of the ketene acetal hydrolysis reaction, decomposition of the hydrogen ortho ester, but a lower limit is available for the hydrogen ion catalytic coefficient of this reaction in the case of hydrogen dimethyl orthoacetate (eq 5): $k_{\text{H}^+} \geq 6.6 \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$.¹⁶ Since both this and the substrate protonation step are acid-catalyzed, their relative rates will be independent of acidity as long as only acid catalysis operates, and the ratio of the two rate constants then suggests that hydrogen ortho ester decomposition could be the slower reaction by as much as 1 order of magnitude. That, however, would be the case only in the more acidic solutions used in the present study, for whereas substrate protonation is catalyzed only by acids, hydrogen ortho ester decomposition is catalyzed by both acids and bases, and the base catalysis is strong enough to become dominant even at fairly low pH.¹⁷ It seems unlikely, therefore, that hydrogen ortho ester decomposition could have been slower than substrate protonation under most of the conditions of the present investigation.

Reactivity. The present measurements, together with results obtained in some of our previous studies, now provide a set of hydrogen ion catalytic coefficients for the hydrolysis of all possible methoxy-substituted ethenes. Since the process to which the rates refer in each of these reactions is proton transfer to the ethene double bond, these rate constants reflect the effect of methoxy substitution on carbon-carbon double-bond protonation. The relevant data are summarized in Table III.

It can be seen that the addition of a second methoxy group to the same carbon atom as the first, converting a vinyl ether to a ketene acetal, accelerates protonation markedly: 1,1-dimethoxyethene is 6 orders of magnitude more reactive than methoxyethene. Large as it is, however, this effect is much smaller than that of the first methoxy group introduced in going from ethene itself to methoxyethene. Ethene is so unreactive that its rate of protonation can be measured conveniently only in very concentrated acid solutions, and extrapolation of such data down to dilute acid is difficult. An estimate of the dilute-solution rate constant has nevertheless been reported, $k_{\text{H}^+} = 1.5 \times 10^{-15} \text{ M}^{-1} \text{ s}^{-1}$,¹⁸ and that makes ethene 15 orders of magnitude less reactive than methoxyethene; this corresponds to a difference in free energy of activation of $\delta\Delta G^\ddagger = 20 \text{ kcal mol}^{-1}$. The methoxy group can thus be seen to have a very strong activating effect on carbon-carbon double-bond protonation, as expected from its ability to stabilize the cationic product of the protonation reaction through conjugative charge delocalization, 4. The diminished effect of

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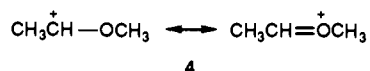
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a second methoxy group is consistent with the expected reduced selectivity of a more reactive substrate.



Introduction of a second methoxy group at the other carbon atom of the double-bond system, on the other hand, produces a decrease in reactivity. This, again, is as expected, for now the second methoxy group is in a position from which it cannot stabilize the protonation product through conjugative interaction with its cationic center. This second methoxy group can, however, lower the free energy of the reaction's initial state through its well-known carbon-carbon double-bond-stabilizing effect,¹⁹ and it will also destabilize the cationic product through its electron-withdrawing polar effect; both of these influences will increase the free energy difference between initial state and transition state and thus slow the rate of reaction.

The magnitude of this effect of a β -methoxy group also depends upon the reactivity of the system. The average of the two deactivating effects for *cis*- and *trans*-1,2-dimethoxyethene, each compared to methoxyethene, is $\delta\Delta G^\ddagger = 5.9 \text{ kcal mol}^{-1}$, whereas the deactivating effect of the third methoxy group in the more reactive trimethoxyethene, compared to 1,1-dimethoxyethene, is only $\delta\Delta G^\ddagger = 3.5 \text{ kcal mol}^{-1}$. This dependence of selectivity upon reactivity is continued in the pair tetramethoxyethene and trimethoxyethene, where $\delta\Delta G^\ddagger = 5.4 \text{ kcal mol}^{-1}$ is intermediate between the two other values of $\delta\Delta G^\ddagger$ cited above, just as the reactivity of the present pair is between that of the other two. It is likely, however, that steric effects in the highly congested tetramethoxyethene also contribute to its reduced reactivity through inhibition of conjugative stabilization of the cation intermediate.^{2c}

Transition-State Structure. Bronsted exponents are commonly believed to be indicators of transition-state structure and are often used to judge the extent of proton transfer at the transition states of proton-transfer reactions. Since more reactive systems are expected to have earlier transition states with less proton transfer²⁰ and ketene acetals are more reactive than vinyl ethers, Bronsted exponents for ketene acetal hydrolysis should then be smaller than those for vinyl ether hydrolysis. This expectation is borne out by the available data. Bronsted relations based upon homogeneous sets of carboxylic acid catalytic coefficients have now been constructed for the hydrolysis of nine ketene acetals; they are summarized in Table IV. These relations have the average exponent $\alpha = 0.44 \pm 0.08$, whereas similar relations for the hydrolysis of eight vinyl ethers²¹ provide the significantly larger average exponent $\alpha = 0.67 \pm 0.08$.²²

The substrates in each of these sets of Bronsted relations themselves cover a fairly large range of reactivity, and a systematic change in α with reactivity might therefore be expected to exist within each set. This is in fact the case for vinyl ether hydrolysis, where α was found to be a statistically significant function of reactivity as measured by R , the catalytic coefficient for a hypothetical carboxylic acid of $\text{p}K_a$ 4.00;²³ least-squares analysis gave the coefficient $d\alpha/d \log R = -0.036 \pm 0.010$.^{21a} Similar analysis of the data for ketene acetal hydrolysis given in Table IV, on the other hand, gives no statistically valid relationship: $d\alpha/d \log R = 0.009 \pm 0.017$. This is so despite the fact that the range of R is similar for both sets of data, which indicates that α changes less rapidly with reactivity for ketene acetal hydrolysis than for vinyl ether hydrolysis.

This analysis suggests that the extent of proton transfer at the transition state for protonation of ketene acetals is less sensitive

Table IV. Bronsted Exponents for the Hydrolysis of Ketene Acetals Catalyzed by Carboxylic Acids in Aqueous Solution at 25 °C

substrate	α	$\log R^a$	ref
	0.47	4.55	this work
	0.48	2.13	this work
	0.41	1.27	2c
	0.36	0.91	2c
	0.49	0.60	2a
	0.62	0.00	2a
	0.37	-0.54	2c
	0.39	-0.60	2c
	0.41	-1.58 ^b	this work

^a R = catalytic coefficient of a hypothetical carboxylic acid with $\text{p}K_a = 4.00$. ^b Corrected for symmetry because of two equivalent reaction positions.

to changes in reactivity than is that for protonation of vinyl ethers. This might seem unreasonable, inasmuch as ketene acetal hydrolysis is the faster reaction and transition states of faster reactions are believed to be more responsive to changes in reactivity than those of slower reactions; this is implicit, for example, in Marcus rate theory through the relationship between α and intrinsic barriers.²⁴

It is likely, however, that ketene acetal hydrolysis is an intrinsically slower reaction than vinyl ether hydrolysis despite the fact that the examples which have been examined put the difference the other way around. A similar paradox has been demonstrated for the protonation of simple olefins and vinyl ethers.^{24b} The simple olefin reaction has the lower intrinsic barrier but is slower because it is very strongly uphill; it is slowed by this endoergicity rather than by an intrinsic unreactivity. The greater intrinsic barrier for the vinyl ether reaction is attributed to the charge delocalization into the alkoxy group that accompanies this process but is absent from simple olefin protonation. Charge delocalization is well known to slow proton transfer; it is, for example, one of the principle factors responsible for the difference between slowly reacting pseudoacids and rapidly reacting normal acids.²⁵ Since the protonation of ketene acetals involves charge delocalization into yet a second alkoxy group, it is likely that this paradox extends to this system as well and that the protonation of these substances is intrinsically slower than the protonation of vinyl ethers.

Acknowledgment. We are grateful to the Natural Sciences and Engineering Research Council of Canada and the donors of the Petroleum Research Fund, administered by the American Chemical Society, for financial support of this work.

Supplementary Material Available: Tables S1–S6 containing rate data (12 pages). Ordering information is given on any current masthead page.

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(22) The error limits given are standard deviations of the populations.

(23) This corresponds approximately to the midpoint of each correlation.

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