

Kinetics of Hydrolysis of Acetaldehyde Ethyl Hemiacetal in Aqueous Solution

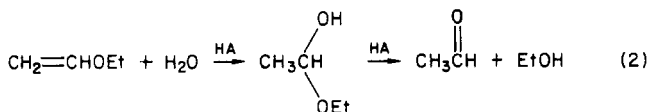
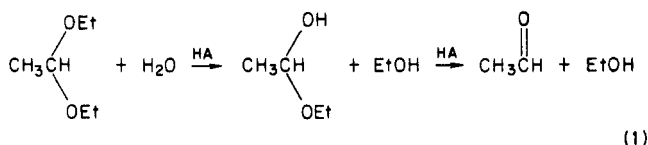
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Rates of hydrolysis of acetaldehyde ethyl hemiacetal were measured in aqueous buffer solutions of acetic and formic acids and semicarbazide hydrochloride at 25 °C. The catalytic coefficients so obtained are all greater than the corresponding rate constants for acetaldehyde diethyl acetal and ethyl vinyl ether hydrolysis, thus supporting the commonly held belief that hemiacetal formation is slow and its subsequent decomposition is fast in these two reactions. A correlation of rate constants for hydrolysis of acetals and the corresponding hemiacetals indicates, however, that the difference between the rates of these reactions decreases with increasing reactivity and that hemiacetal or hemiketal hydrolysis will become the rate-determining step in the hydrolysis of sufficiently reactive vinyl ethers, acetals, and ketals.

Acetaldehyde ethyl hemiacetal is an intermediate in the acid-catalyzed hydrolysis of acetaldehyde diethyl acetal, eq 1,¹ and also in the acid-catalyzed hydrolysis of ethyl



vinyl ether, eq 2.² It is generally believed that formation of the hemiacetal in these reactions is rate-determining and that its subsequent decomposition is fast. Examples of acetal hydrolysis are known, however, in which decomposition of the hemiacetal intermediate is either slower than its formation³ or where the two steps occur at comparable rates.⁴ In order to learn about the relative velocities of the two steps in the reactions of eq 1 and 2, we have measured the rate of acetaldehyde hemiacetal hydrolysis in dilute aqueous acid solutions.

Experimental Section

Materials. Acetaldehyde ethyl hemiacetal was generated in ethanol solution by adding acetaldehyde (freshly distilled under argon) to absolute ethanol and allowing the resulting mixture to stand for 2–3 h. These stock solutions, which remained stable for several days, were then used directly for the kinetic measurements. The formation of hemiacetal in ethanol could be speeded up by adding a small amount of sodium hydroxide, but this also reduced the stability of the solutions. Semicarbazide

Table I. Summary of Rate Data for the Hydrolysis of Acetaldehyde Ethyl Hemiacetal in Aqueous Buffer Solutions at 25 °C^a

buffer	buffer ratio ^b	10 ⁴ [H ⁺], ^c M	10 ³ k _o , s ⁻¹	10 ² k _{cat} , M ⁻¹ s ⁻¹
acetic acid	0.52	0.141	2.70	4.07
	0.68	0.185	3.11	4.21
	0.85	0.231	3.03	4.91
	1.30	0.354	4.94	5.22
	2.06	0.560	7.51	4.77
	4.05	1.10	13.5	5.09
formic acid	0.44	1.24	15.4	4.57
semicarbazide hydrochloride	0.71	1.52	17.7	1.18
	1.03	2.20	26.0	1.41
	1.52	3.23	37.0	2.26
	2.06	4.36	48.5	1.45

^aIonic strength = 0.10 M. ^bBuffer ratio = [acid]/[base]. ^cCalculated values obtained by using pK_a = 4.76,⁶ 3.75,⁸ and 3.65⁷ for acetic acid, formic acid, and semicarbazide hydrochloride, resp., plus the ionic activity coeffs. *f* = 0.83 for H⁺,⁸ *f* = 0.76 for RCO₂⁻,⁸ and *f* = 0.80 for BH⁺.⁹

hydrochloride was recrystallized before use; all other materials were best available commercial grades. Solutions were made with deionized water purified further by distillation.

Kinetics. Rates of acetaldehyde ethyl hemiacetal hydrolysis were measured spectroscopically, either by monitoring the appearance of the acetaldehyde absorption band at λ 280 nm directly or by semicarbazide scavenging using the much stronger absorbance of acetaldehyde semicarbazone at λ 230 nm. Absorbance measurements were made with a Cary 210 spectrometer whose cell compartment was thermostated at 25.0 ± 0.05 °C. Kinetic runs were carried out by allowing ca. 3-mL volumes of wholly aqueous buffer solutions, contained in spectrometer cuvettes, to come to temperature equilibrium with the cell compartment and then adding a few microliters of ethanolic hemiacetal stock solution to initiate reaction. The concentration of ethanol in the final reaction solutions was never more than 0.5%, and the concentrations of hemiacetal substrate were ca. 1 × 10⁻² M for runs based on acetaldehyde appearance and 2–3 × 10⁻⁵ M for those using semicarbazide scavenging. The kinetic data conformed to the first-order rate law well, and observed first-order rate constants were evaluated by linear least-squares analysis of the relationship between ln(A_∞ - A) and time.

Results

Rates of hemiacetal hydrolysis were measured by the acetaldehyde appearance method in acetic and formic acid buffer solutions and by semicarbazide scavenging in semicarbazide buffers. The kinetic data are summarized in Table S1.⁵

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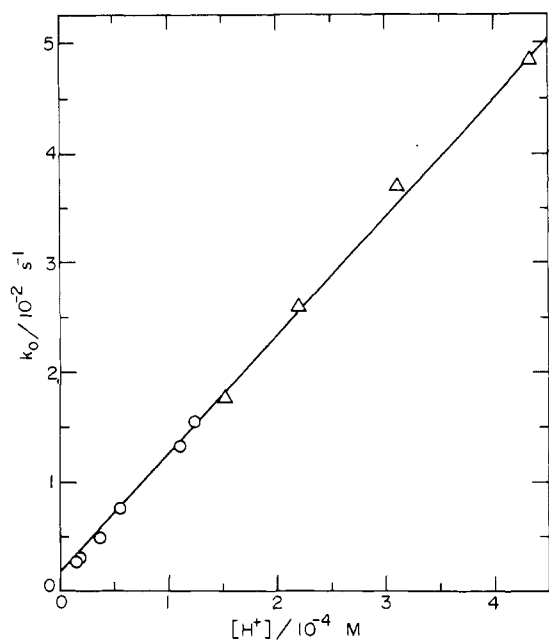


Figure 1. Relationship between buffer-independent rate constants for acetaldehyde ethyl hemiacetal hydrolysis and hydrogen ion concentration in aqueous solution at 25 °C; (O) measurements made in carboxylic acid buffers by the aldehyde appearance method; (Δ) measurements made in semicarbazide buffers by semicarbazide scavenging.

Marked catalysis of the hydrolysis reaction by buffer constituents was found in the carboxylic acid buffer solutions. Rate measurements were therefore made in series of buffers at constant buffer ratio but varying buffer concentration and the observed first-order rate constants so obtained were fitted by least-squares methods to the linear expression in total buffer concentration shown in eq 3; the results are summarized in Table I. In the ex-

$$k_{\text{obsd}} = k_o + k_{\text{catal}}[\text{buffer}] \quad (3)$$

pression of eq 3, k_o refers to reaction through solvent-derived species, i.e., H^+ and H_2O at the acidities used, and k_{catal} represents catalysis by the buffer acid and buffer base. The rate constant k_{catal} is therefore a function of the general acid and general base catalytic coefficients, k_{HA} and k_{A} (eq 4), and it can be separated into its constituent parts

$$k_{\text{catal}} = k_{\text{HA}}f_{\text{HA}} + k_{\text{A}}(1 - f_{\text{HA}}) \quad (4)$$

by analyzing its dependence on f_{HA} , the fraction of buffer present in acid form. The data for acetic acid buffers give $k_{\text{HOAc}} = (5.62 \pm 0.45) \times 10^{-2} \text{ M}^{-1} \text{ s}^{-1}$ and $k_{\text{OAc}^-} = (3.64 \pm 0.52) \times 10^{-2} \text{ M}^{-1} \text{ s}^{-1}$. Kinetic measurements in formic acid buffers were made at only one buffer ratio, and individual general acid and general base catalytic coefficients could in this case therefore not be evaluated.

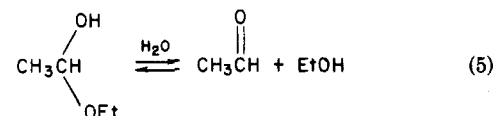
Buffer catalysis in the semicarbazide solutions, on the other hand, was very weak at the concentrations we were obliged to use by our desire to keep ionic strength constant at 0.10 M. Values of k_{catal} could therefore not be determined accurately, and there is consequently considerable uncertainty in the general acid and general base catalytic coefficients obtained here: $k_{\text{BH}^+} = (2.54 \pm 1.18) \times 10^{-2} \text{ M}^{-1}$

s^{-1} and $k_{\text{B}} = (0.41 \pm 1.43) \times 10^{-2} \text{ M}^{-1} \text{ s}^{-1}$.

The experiments in semicarbazide buffers nevertheless provided good values of k_o . As Figure 1 shows, these plus those from the carboxylic acid buffers were accurately proportional to hydrogen ion concentration. Least-squares analysis gave the results $k_{\text{H}^+} = (1.10 \pm 0.01) \times 10^2 \text{ M}^{-1} \text{ s}^{-1}$ and $k_{\text{H}_2\text{O}} = (1.19 \pm 0.20) \times 10^{-3} \text{ s}^{-1}$.

Discussion

The hydrolysis of acetaldehyde ethyl hemiacetal is a reversible process, eq 5. However, on the reasonable



assumption that the equilibrium constant for this reaction is similar to that measured for the hydrolysis of acetaldehyde methyl hemiacetal,¹⁰ it may be estimated that reversal will occur only to the extent of 0.8% at the highest substrate concentration used in the present study (0.01 M), and at lower substrate concentrations, the amount of reversal will be even less. Acetaldehyde is also hydrated to the extent of about 50% in dilute aqueous solution.¹¹ The hydration equilibrium, however, is achieved an order of magnitude more rapidly than hemiacetal hydrolysis occurs,^{11b,12} and it will therefore not disturb rate measurements based on aldehyde appearance. Further indication that these potential difficulties had little influence on the present experiments comes from the fact that rate constants determined by the semicarbazide scavenging method, which avoids complications due to reversibility and hydration, are in good agreement with those measured by aldehyde appearance (see Figure 1).

The hydrogen ion catalytic coefficient for acetaldehyde hemiacetal hydrolysis determined here, $k_{\text{H}^+} = 110 \text{ M}^{-1} \text{ s}^{-1}$, is greater, by a factor of 67, than the rate constant for hydrolysis of acetaldehyde diethyl acetal catalyzed by the same species, $k_{\text{H}^+} = 1.64 \text{ M}^{-1} \text{ s}^{-1}$.¹³ This rate difference, which applies to these two reactions conducted in dilute mineral acid solutions, will be augmented somewhat in acidic buffers because hydrolysis of the hemiacetal is catalyzed by general acids whereas hydrolysis of the acetal shows only catalysis by hydrogen ions.¹ In basic buffers the rate difference will be increased even more, for hemiacetal hydrolysis is catalyzed by bases but acetal hydrolysis is not;¹ this base catalysis, moreover, is quite strong and becomes important at relatively low pH. It seems clear, therefore, that in the hydrolysis of acetaldehyde diethyl acetal in aqueous solution at 25 °C the first stage of the process, generation of the hemiacetal intermediate, is slower than the second by sizeable margins and is therefore rate-controlling.

This rate constant for hemiacetal hydrolysis, $k_{\text{H}^+} = 110 \text{ M}^{-1} \text{ s}^{-1}$, is also greater than the values $k_{\text{H}^+} = 1.71$,^{2a} 1.75,^{2b} 1.89,^{2a} and 1.95¹³ reported for the hydrolysis of ethyl vinyl ether. The factor of ca. 60 provided by these rate constants will apply to these reactions in dilute mineral acid solution. In acidic buffers, this difference will be diminished somewhat, for both reactions are general acid catalyzed and the ratios of general acid catalyzed coefficients are

(5) Supplementary material; see paragraph at the end of this paper.
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Table II. Hydrogen Ion Catalytic Coefficients for Acetal and Hemiacetal Hydrolysis in Aqueous Solution at 25 °C

substrate	$k_{H^+}, M^{-1} s^{-1}$	
	acetal (k_1)	hemiacetal (k_2)
HCH(OEt) ₂	0.00015 ^a	0.74 ^b
3-NO ₂ C ₆ H ₄ CH(OEt) ₂	0.95 ^c	26 ^d
CH ₃ CH(OEt) ₂	1.63 ^e	110 ^f
C ₆ H ₅ CH(OEt) ₂	160 ^g	1000 ^g
C ₆ H ₅ CH(O- <i>t</i> -Bu) ₂	25 000 ^g	2600 ^g

^aReference 16. ^bReference 14. ^cReference 4b. ^dCalculated by using rate factor $k_1/k_2 = 0.036$ of ref 4a and rate constant $k_1 = 0.95 M^{-1} s^{-1}$ of ref 4b. ^eReference 13. ^fThis work. ^gReference 3b.

probably less than 60. For example, the acetic acid rate constant determined here for hemiacetal hydrolysis, $k_{HOAc} = 5.6 \times 10^{-2} M^{-1} s^{-1}$, is 41 times that measured for ethyl vinyl ether hydrolysis, $k_{HOAc} = 1.38 \times 10^{-3} M^{-1} s^{-1}$,^{2c} and the ratio is likely to be reduced for stronger carboxylic acids inasmuch as Brønsted exponents for hemiacetal hydrolysis¹⁴ appear to be smaller than those for vinyl ether hydrolysis.^{2c} This diminution, however, will be compensated for by the fact that in the more acidic buffers less reaction will take place through catalysis by the general acids and more through catalysis by the hydrogen ion.¹⁵ Calculations using what appear to be reasonable values of catalytic coefficients show that the vinyl ether hydrolysis reaction will be some 40 to 50 times slower than hemiacetal hydrolysis in buffer solutions of carboxylic acids of $pK_a \approx 4-5$ and that the rate difference is unlikely to drop below 30 even in buffers of acids with $pK_a = 2$. Vinyl ether hydrolysis is not catalyzed by bases,² and these rate differences will therefore increase markedly when the strong base catalysis of hemiacetal hydrolysis begins to exert its influence at pHs above about 5. It seems clear, therefore, that acetaldehyde ethyl hemiacetal formation is the rate-determining stage in the hydrolysis of ethyl vinyl ether by moderate margins in acidic solutions and by increasingly greater factors in basic solutions.

It is likely, however, that this situation will not persist for more reactive examples of these reactions. The data for the still rather small number of systems in which rate constants have been measured for both acetal and the corresponding hemiacetal hydrolysis (Table II) show a decided trend for the difference between the two rates to decrease with increasing substrate reactivity. As Figure 2 indicates, hydrogen ion catalytic coefficients for hemiacetal hydrolysis (k_2) correlate reasonably well with hydrogen ion catalytic coefficients for acetal hydrolysis (k_1). For the less reactive systems, k_2 is greater than k_1 by several orders of magnitude; this may be seen in Figure 2 as the difference between the correlation line and the (broken) line of unit slope for which $k_2 = k_1$. As reactivity increases, however, the difference between the two lines diminishes, and they eventually cross at $k_2 = k_1 \approx 10^3 M^{-1} s^{-1}$; above this point k_2 is less than k_1 , and hemiacetal hydrolysis is rate-determining. Hydrogen ion catalytic

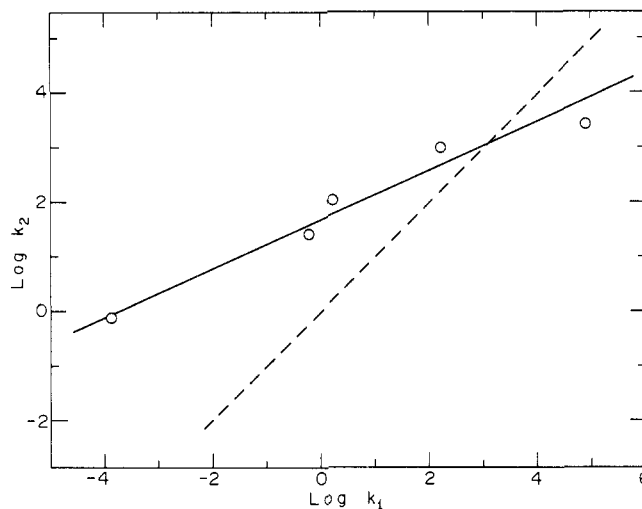


Figure 2. Relationship between hydrogen ion catalytic coefficients for hydrolysis of acetals (k_1) and the corresponding hemiacetals (k_2) in aqueous solution at 25 °C. The broken line of unit slope is the locus of points for which $k_1 = k_2$; points lying above this line represent systems in which acetal hydrolysis is rate determining, and points lying below this line represent systems in which hemiacetal hydrolysis is rate determining.

coefficients for the hydrolysis of acetone ketals lie in the region $k_{H^+} = 1-2 \times 10^3 M^{-1} s^{-1}$,¹⁷ and this implies that hemiketal hydrolysis may be partly rate-determining in these reactions. We have experiments underway designed to determine whether or not this is so.

The correlation of Figure 2 also implies that the hemiacetal or hemiketal hydrolysis step may be at least partly rate-determining in the hydrolysis of some of the more reactive vinyl ethers which have been studied, such as alkyl isopropenyl^{2a,c} or alkyl α -cyclopropylvinyl¹⁸ ethers. Rates of vinyl ether hydrolysis, however, are usually determined by measuring the decrease in vinyl ether concentration, as monitored by the disappearance of the strong vinyl ether UV absorption band; this technique will produce rate constants for the first stage of this reaction, i.e., for conversion of vinyl ether to hemiacetal or hemiketal, regardless of whether or not hydrolysis of these intermediates is faster than their formation.

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Registry No. Acetaldehyde ethyl hemiacetal, 7518-70-9.

Supplementary Material Available: Table S1 of rate data (4 pages). Ordering information is given on any current masthead page.

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