Rate-Equilibrium Relationship for General Acid-Catalyzed and Uncatalyzed Hydrolyses of Acetaldehyde Methyl Phenyl Acetals

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Rates of hydrolysis of some 1-methoxy-1-phenoxyethanes (acetaldehyde methyl phenyl acetals) with electron withdrawing substituents on the phenoxy group were measured in aqueous acid, base and buffer solutions. General acid catalysis was observed in buffer solutions and spontaneous uncatalyzed hydrolysis in dilute bases. The possibility of introducing both of these into a single rate-equilibrium relationship is discussed.

The hydrolysis of acetals has been reported to occur by acid-catalyzed and uncatalyzed pathways.[1,2] The acid catalysis may be either by specific oxonium ion or general acid catalysis. Low basicity and easy heterolysis of the carbon-oxygen bond are those factors which affect the change in the mechanism from the former to the latter.[2,3] Of these features, the ease of C-O bond cleavage is regarded as more important.[2] The uncatalyzed hydrolysis of acetals has been presented as proceeding by a spontaneous unimolecular mechanism without proton transfer from water to the substrate.[4,5] The same factor, ease of C-O bond cleavage, that is regarded as important for detecting general acid catalysis is also operative in this reaction. Thus a rate of the uncatalyzed hydrolysis might be a critical factor in determining whether the catalyzed reaction occurs by concerted general acid catalysis or stepwise specific oxonium ion catalysis.

We here report kinetic data on the hydrolysis of acetaldehyde methyl phenyl acetals where the C-O bond cleavage is facilitated by substituents on the phenoxy group which tend to withdraw electrons by resonance. For this series, three different types of rate coefficients were measured: for oxonium ion-catalyzed; general acid-cata-

lyzed; and uncatalyzed hydrolysis. A method to introduce these in a common rate-equilibrium relationship is suggested.

Experimental

Materials. The studied methyl phenyl acetals of acetaldehyde were prepared by acid-catalyzed addition of phenol to the double bond of methyl vinyl ether.[6]

1-(4-Acetylphenoxy)-1-methoxyethane had t(vap) = 92–93 °C at p = 2 mmHg and 1-(4-cyanophenoxy)-1-methoxyethane had t(vap) = 86.5–87.0 °C at p = 2–3 mmHg. 1-(4-Nitrophenoxy)-1-methoxyethane was obtained as a solid residue after evaporation of ether and was recrystallized from ether/light petroleum (t(vap) = 80–95 °C). The product had t(fus.) = 33 °C. Under preparation, the reaction mixture was protected from light.

The ^{1}H NMR spectra of the prepared compounds were consistent with their structures.

Reaction solutions. Perchloric acid (E. Merck, *p.a.*) was diluted with carbon dioxide-free distilled water. Sodium chloride (E. Merck, *p.a.*) was added to make the ionic strength 0.100 mol dm^{-3}. Buffer solutions were prepared by dissolving a weighed amount of carboxylic acid in water.

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This solution was partially neutralized with standard sodium hydroxide solution. When necessary, sodium chloride was added to obtain an ionic strength of 0.100 mol dm^{-3}.

Kinetics. Rates of hydrolysis were measured spectrophotometrically by following the increase in the absorbance of the product, phenol in acid solutions and phenoxide ion in base solutions. The measurements were performed with a Unicam 1700 spectrophotometer, where the temperature of the cell housing was kept constant with water circulating from a Lauda thermostat and controlled by a calibrated thermistor. Silica cells with path length 10 mm and equipped with teflon stoppers were used throughout. The reaction was initiated by injecting the substrate from a Hamilton syringe into the reaction medium which had been prethermostated in the cell. A freshly prepared solution with 0.1 volume fraction of substrate in dioxane was used. The volumes injected were $0.5–5.0$ mm^3 to obtain an appropriate concentration of substrate in the reaction solution. The absorbance readings were recorded at suitable intervals.

The first-order rate constants were calculated

from about 20 absorbance readings corresponding to about 10–80 % change. Their constancy proved that first-order kinetics were obeyed throughout. The rate constants of slow reactions were calculated by the method of Guggenheim.

Results

The rates of hydrolysis of *para* substituted phenyl methyl acetals of acetaldehyde were measured in dilute aqueous perchloric acid solutions. The second-order rate coefficients for the oxonium ion-catalyzed hydrolysis were obtained by dividing the observed first-order rate constant by the acid concentration. They remained constant in all the acid solutions used ($c(HClO_4)$ = 10^{-3}–10^{-2} mol dm^{-3}) indicating that the contribution of uncatalyzed hydrolysis in the observed rate coefficient was negligible. The results are presented in Table 1.

The rate coefficients of the water-induced or uncatalyzed reaction, $k(H_2O)$, could be measured separately. Dilute aqueous base solutions were used to prevent the presence of any acid species. The obtained first-order rate coefficients were independent of the base concentration. The results of these experiments are summarized in Table 1.

To determine carboxylic acid catalytic coefficients, rates of hydrolysis were measured in series of carboxylic acid/sodium carboxylate buffer solutions with constant buffer ratio and ionic strength, but changing the total buffer concentration. Observed rate constants are presented in Table 2. In all cases, carboxylic acids were moderately strong and the oxonium ion concentration in a series of solutions decreased with decreasing buffer concentration. Such buffer failure could be compensated for by adjusting the observed rate constant within a given series of buffer solutions to a common oxonium ion concentration as described in detail by Gold and Waterman.[7] Another procedure which is described for carbonate buffer solutions with changing hydroxide ion concentration[8] could also be used in the present case. Both corrections were based on oxonium ion concentrations calculated from the acidity constants and mean ionic activity coefficients determined by Debye-Hückel equation, with ion size parameter 0.60 nm for formic acid and 0.70 nm

Table 1. Summary of catalytic coefficients for the hydrolysis of substituted phenyl methyl acetals of acetaldehyde in aqueous solutions at 25 °C. Ionic strength adjusted to 0.100 mol dm^{-3} with sodium chloride.

Catalyst	Substituent		
	4-COCH₃	4-CN	4-NO₂
	$k(HA)/(10^{-2}$ dm^3 mol^{-1} $s^{-1})$		
H_3O^{+} [a]	107(1)	75.5(1)	60.8(4)
$Cl_2CHCOOH$	7.1(14)	7.5(11)	5.1(6)
$ClCH_2COOH$	0.254(45)	0.472(33)	0.426(26)
HCOOH	0.122(4)	0.129(6)	0.142(6)
α [c]	0.58(7)	0.52(7)	0.50(5)
	$k(H_2O)/(10^{-6}$ $s^{-1})$ [b]		
	4.29(7)	7.22(33)	49.1(4)

[a] In solutions, where $c(HClO_4)$ = 10^{-2}–10^{-3} mol dm^{-3}. [b] In sodium hydroxide solutions, $c(NaOH)$ = 0.100 mol dm^{-3}. [c] Coefficient of the Brönsted relation.

for chloro and dichloroacetic acid. Both treatments gave the values of carboxylic acid catalytic coefficients which are presented in Table 1. The oxonium ion catalytic coefficients obtained by calculation from the results in buffer solutions were in good agreement with those obtained by measurements in perchloric acid solutions. This attests to the validity of the applied treatments.

Discussion

The observation of general acid catalysis in the hydrolysis of acetaldehyde methyl phenyl acetals indicates that the mechanism of the reaction involves the presence of the conjugate base of the catalyst in the transition state of the reaction. The proposed mechanism for the general acid-catalyzed hydrolysis of acetals is proton transfer from the catalyst to the substrate concerted with the cleavage of the carbon-oxygen bond.

The catalytic power of different acids in general acid catalysis is usually analyzed by a linear Gibbs energy relationship, which correlates the catalytic coefficients, $k(HA)$, for a given reaction with the acidity constants of the catalysts, $K_a(HA)$, and is known as the Brønsted relation (1). The rate and acidity constants used in the correlation should be "chemical" constants corrected for symmetry properties by the method presented by Benson.[9]

$$\log k(HA) = \log G + \alpha \log K_a(HA) \qquad (1)$$

The conventional treatment of the oxonium ion is to use the acidity constant $K_a(H_3O^+) = 55.5$ mol dm^{-3} from the stoichiometric concentration of solvent water. Fair linear correlations are obtained for the Brønsted relation for the hydrolysis of the studied compounds catalyzed by three carboxylic acids and the oxonium ion. The slope representing the Brønsted α coefficient shows a tendency to decrease as the phenolic substituent becomes more electronegative (Table 1). Similar behaviour is reported in the hydrolysis of various acetals derived from benzaldehyde.[10–12]

It has been recognized that solvent-derived catalytic species, the oxonium ion in acid catalysis in water, exhibit anomalous behaviour in many cases.[13] There is difficulty in assigning the exact acid strength of the oxonium ion because it is itself the species formed in the dissociation of all other acids in aqueous solutions. To introduce these reactions into the Brønsted relation, a somewhat different form of this rate-equilibrium

Table 2. Observed rate constants for the hydrolysis of substituted phenyl methyl acetals of acetaldehyde in aqueous buffer solutions of carboxylic acids at 25 °C. Ionic strength adjusted to 0.100 mol dm^{-3} with sodium chloride.

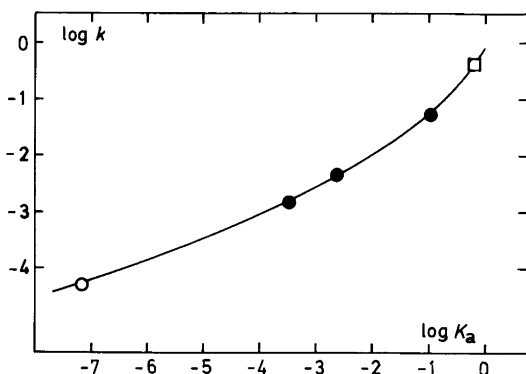| HA	$\dfrac{c(HA)}{c(A^-)}$	[HA]/ mol dm^{-3}	Substituent 4-COCH$_3$	4-CN	4-NO$_2$
			k(obs)/(10^{-3} s^{-1})		
Cl$_2$CHCOOH	1.00	0.050	29.5	21.7	17.4
		0.0400		18.6	15.1
		0.0333	22.6		
		0.0300		15.2	12.2
		0.0250	18.2		
		0.0200	15.3	11.2	9.10
ClCH$_2$COOH	4.93	0.493	11.69	10.01	7.97
		0.370	10.98	9.33	7.06
		0.246	10.13	8.25	6.37
		0.123	8.77	6.91	5.23
HCOOH	9.92	0.992	4.18	3.39	3.13
		0.744	3.85	3.01	2.74
		0.496	3.47	2.66	2.37
		0.248	3.07	2.28	1.94

Fig. 1. The Brönsted relation for the hydrolysis of acetaldehyde methyl 4-nitrophenyl acetal at 25 °C catalyzed by carboxylic acids (●) and the oxonium ion (□). The uncatalyzed hydrolysis introduced into the relationship by the pK_a of 4-nitrophenol (○).

relationship is adopted. Kresge et al.[14] presented this form for a general proton transfer process. In the present case, the rate limiting step for the reaction is assumed to be proton transfer from the catalyst to the oxygen atom of the substrate, S, concerted with the C-O bond cleavage. In the hydrolysis of mixed acetals, protonation and the subsequent heterolysis take place via the less basic oxygen atom.[15] Thus, in this step in the hydrolysis of the studied acetals, phenol, PhOH, and oxo-carbenium ion, I[+], are formed. The Brönsted relation for this reaction is presented in eqn. (1).

$$S + HA \xrightarrow{\text{rate lim.}} I^+ + PhOH + A^- \xrightarrow{\text{fast}} \text{products} \tag{2}$$

The equilibrium constant for the first step of reaction (2) may be written as a product of the acidity constant of the catalyst acid and an equilibrium constant, K, which is not dependent on the catalyst (3).

$$K(HA) = \frac{a(I^+)a(PhOH)a(A^-)}{a(S)a(HA)}$$

$$= \frac{a(I^+)a(PhOH)}{a(H_3O^+)a(S)} \cdot \frac{a(H_3O^+)a(A^-)}{a(HA)} = K K_a(HA) \tag{3}$$

Application of the Brönsted relation and the above result to two different catalysts, HA_1 and HA_2, leads to eqn. (4). This expression shows that the Brönsted relation also includes a correlation of the rate constants of the concerted proton transfer reaction with equilibrium constants of that reaction step.

$$\log \frac{k(HA_1)}{k(HA_2)} = \alpha \log \frac{K(HA_1)}{K(HA_2)} \tag{4}$$

The equilibrium constant for the rate limiting step in the oxonium ion-catalyzed hydrolysis is presented in eqn. (5).

$$K(H_3O^+) = \frac{a(I^+)a(PhOH)a(H_2O)}{a(S)a(H_3O^+)} \tag{5}$$

The ratio of equilibrium constants, $K(HA)$ and $K(H_3O^+)$, reduces to the form (6), because the substrate and the intermediate oxo-carbenium ion are the same for both reactions.

$$\frac{K(HA)}{K(H_3O^+)} = \frac{a(H_3O^+)a(A^-)}{a(HA)a(H_2O)} = \frac{K_a(HA)}{a(H_2O)} \tag{6}$$

The expression includes the activity of solvent water, $a(H_2O)$. The acidity constant, $K_a(HA)$, is represented by activities of the solute species on the concentration scale ($c^{\ominus} = 1$ mol dm^{-3}). For the solvent, however, the mole fraction scale activity is always used by convention. In dilute aqueous solutions, the activity of water, $a(H_2O) = f(H_2O)x(H_2O)$, is usually approximated as unity. Replacement in eqn. (4) leads to a Brönsted relation where the value of the constant G is the rate constant for the oxonium ion-catalyzed hydrolysis (7). This implies that the acidity constant for the oxonium ion, $K_a(H_3O^+)$, should be unity when compared with other acids in the Brönsted relation. This is against the usual practice of regarding the conventional acidity constant of the oxonium ion, $K_a(H_3O^+) = 55.5$ mol dm^{-3}, as consistent with that of other acids.

$$\log k(HA) = \log k(H_3O^+) + \alpha \log K_a(HA) \tag{7}$$

The hydrolysis of acetals in solutions where

solvent water is the only acidic species shows very high sensitivity to the basicity of the leaving group.[4,5,12,16] This indicates that the reaction takes place as a spontaneous unimolecular process without water acting as a proton transfer agent in the transition state. Therefore, the observed rate constants are used in the subsequent discussion without dividing them by the stoichiometric concentration of water as done in another context.[12] The uncatalyzed hydrolysis can be presented as occurring according to eqn. (8) and the equilibrium constant for the rate limiting step is given by eqn. (9). The ratio of this constant and that for the oxonium ion-catalyzed hydrolysis reduces to form (10), where $K_a(PhOH)$ is the acidity constant of the phenol forming the leaving group in the reaction.

$$S \xrightarrow{\text{rate lim.}} I^+ + PhO^- \xrightarrow[\text{H}_2\text{O}]{\text{fast}} \text{products} \quad (8)$$
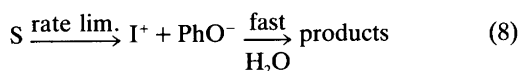
$$K(H_2O) = \frac{a(I^+)a(PhO^-)}{a(S)} \quad (9)$$

$$\frac{K(H_2O)}{K(H_3O^+)} = \frac{K_a(PhOH)}{a(H_2O)} \quad (10)$$

The activity of solvent water is again replaced by unity and combination of this ratio and eqn. (4) gives an expression for the rate coefficient of the uncatalyzed reaction (eqn. 11). Comparison of this equation with eqn. (7) shows that the uncatalyzed hydrolysis may be introduced into the Brönsted relation through the acidity constant of the phenol forming the leaving group in the reaction.

$$\log k(H_2O) = \log k(H_3O^+) + \alpha \log K_a(PhOH) \quad (11)$$

When the kinetic data observed for the hydrolysis of acetaldehyde methyl 4-nitrophenyl acetal are presented in the suggested way as a Brönsted relation, a slightly upward concave plot is obtained (Fig. 1). This suggests that the α coefficients might depend on the acid strength of the catalyst.

The possibility of presenting both general acid-catalyzed and uncatalyzed hydrolyses for the studied acetals in a common rate-equilibrium relationship attests to the validity of the suggested treatment and the proposed mechanisms for the hydrolyses.

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