General Acid-Catalyzed and Uncatalyzed Hydrolyses of Acetone Methyl Phenyl Ketals

Markku Lahti* and Erkki Kovero

Department of Chemistry, University of Turku, SF-20500 Turku, Finland

Lahti, M. and Kovero, E., 1988. General Acid-Catalyzed and Uncatalyzed Hydrolyses of Acetone Methyl Phenyl Ketals. – Acta Chem. Scand., Ser. A 42: 124–129.

Rates of hydrolysis of some methyl substituted-phenyl ketals of acetone (2-methoxy-2-phenoxypropanes) were measured in dilute aqueous base solutions. A spontaneous unimolecular mechanism is suggested for this hydrolysis on the basis of structural and solvent deuterium isotope effects. General acid catalysis was observed in aqueous buffer solutions. Catalytic coefficients for the oxonium ion were estimated from the measurements in buffer solutions. These were used, together with the rate constants for the uncatalyzed hydrolysis, to express the acidity of the transition state. Comparison of this acidity with that of the phenol corresponding to the leaving group in the reaction is suggested to lead to a Brønsted-like coefficient which may be used for transition state characterization.

General acid catalysis in the hydrolysis of acetals has been reported in numerous cases.[1-6] The factors leading to the observation of general acid catalysis are low basicity of the substrate oxygen atom and easy cleavage of the bond between that oxygen and the pro-acyl carbon atom.[1,2] Of these features, the ease of C–O bond cleavage is regarded as the more important.[2] The stability of the intermediate oxo-carbenium ion is a structural feature responsible for easy bond-breaking.

The replacement of the acetal hydrogen by an alkyl group in simple ketals leads to stabilization of the oxo-carbenium ion. This makes ketals more reactive than corresponding acetals.[1] General acid catalysis has not been observed in the hydrolysis of simple ketals. In the hydrolysis of tropone diethyl ketal, where a tropylium ion intermediate has extreme stability, general acid catalysis was observed.[7]

Phenolates are better leaving groups than aliphatic alcoholates, and pronounced general acid catalysis has often been observed in the hydrolysis of acetals with phenolic leaving groups.[4-6,8-10]

It has been predicted[11] that the hemiketal hydrolysis step in the hydrolysis of reactive ketals might, at least partly, be rate-determining. For this step, marked catalysis by buffer constituents has been found in carboxylic acid buffer solutions,[11] and this might confuse the conclusions concerning the catalytic nature of the preceding step, i.e. generation of oxo-carbenium ion. Rates of hydrolysis of acetals and ketals with phenolic leaving groups, however, are usually determined by measuring the increase in phenol concentration as monitored by the appearance of the phenol UV-absorption band. This technique will produce rate constants for the first stage of the reaction, i.e. conversion of acetal or ketal to oxo-carbenium ion.

The uncatalyzed hydrolysis has been reported to take place in aqueous base solutions for acetals and ortho-esters with phenolic leaving groups.[5,6,9,12-14] The rate of uncatalyzed reaction has been proposed to be a critical factor in determining whether the catalyzed reaction is subject to general acid catalysis or specific oxonium ion catalysis.[6]

To gain information on the effect of a good leaving group on the catalytic nature of ketal hydrolysis, the rates of hydrolysis of some substituted phenyl methyl ketals of acetone (2-methoxy-2-phenoxypropanes) were measured in aqueous buffer and base solutions.

---

*To whom correspondence should be addressed.

Experimental

Materials. The studied acetone methyl phenyl ketals were prepared by acid-catalyzed addition of phenol to the double bond of 2-methoxypropene.[15] 2-Methoxypropene was prepared from 2,2-dimethoxypropane, which was cleaved to 2-methoxypropene and methanol by heating with 4-toluenesulfonic acid as catalyst. The mixture was distilled slowly through a 50 cm high column filled with glass helices. The fraction boiling between 35 °C and 60 °C was redistilled from potassium carbonate. The fraction with boiling point 35 °C was shown by ^{1}H NMR spectrum to be pure enough for subsequent syntheses.

The phenol was dissolved in 2-methoxypropene and a small amount of 4-toluenesulfonic acid was added. The reaction took place instantaneously with evolution of heat. The reaction mixture was dissolved in ether and the solution was washed with 10 per cent sodium hydroxide solution. The ethereal solution was dried with potassium carbonate. The ether was evaporated and the R-substituted phenyl methyl ketal was purified by distillation under reduced pressure: R = H, t(vap) = 47 °C at p = 2 mmHg (270 Pa); R = 4-OCH$_3$, t(vap) = 78–80 °C at p = 2 mmHg (270 Pa); R = 4-CH$_3$, t(vap) = 50–52 °C at p = 2 mmHg (270 Pa); R = 3-CH$_3$, t(vap) = 58–59 °C at p = 2–3 mmHg (270–400 Pa); R = 4-Cl, t(vap) = 65–67 °C at p = 2–3 mmHg (270–400 Pa); R = 3-Cl, t(vap) = 60 °C at p = 2 mmHg (270 Pa).

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

Reaction solutions. Sodium hydroxide solutions were prepared by dilution of a standard solution with carbon dioxide-free distilled water. Sodium chloride was added to the solutions to maintain the ionic strength at 0.100 mol dm^{-3}. Corresponding solutions in D$_2$O were prepared by D$_2$O-dilution of a stock solution of NaOD, which was made by dissolving metallic sodium in deuterium oxide under toluene in a separatory funnel. Deuterium oxide was supplied by NEN Chemicals GmbH. The product had an isotopic purity of 99.7 % according to the supplier.

Buffer solutions were prepared by dissolving weighed amounts of acid and corresponding salt in water, or by partially neutralizing the acid solution with sodium hydroxide solution or the salt solution with hydrochloric acid. When necessary, sodium chloride was added to obtain an ionic strength of 0.100 mol dm^{-3}.

Kinetics. Kinetic measurements were carried out as described earlier.[6]

Results

The rate constants for the water-induced or uncatalyzed reaction, $k(H_2O)$, were measured in dilute aqueous base solutions to eliminate the presence of any acid species. The first-order rate constants obtained were independent of the base concentration. The results of these experiments are summarized in Table 1.

To determine general acid catalytic coefficients, rates of hydrolysis were measured in series of buffer solutions with constant buffer ratio and ionic strength but varying total buffer concentra-

Table 1. Rate constants for the uncatalyzed hydrolysis of acetone methyl subst.-phenyl ketals in aqueous base solutions at 25 °C. Ionic strength was adjusted to 0.100 mol dm^{-3} with sodium chloride.

Substituent	$k(H_2O)/10^{-4}$ s^{-1} [a]	$k(D_2O)/10^{-4}$ s^{-1} [b]	$k(H_2O)/k(D_2O)$
4-OCH$_3$	1.30	–	–
4-CH$_3$	2.08	–	–
3-CH$_3$	5.10	3.36	1.52
H	7.52	4.68	1.61
4-Cl	76.8	52.7	1.46
3-Cl	91.3	58.0	1.57

[a] In sodium hydroxide solutions; c(NaOH) = 0.100–0.001 mol dm^{-3}. [b] In sodium deuteroxide solutions; c(NaOD) = 0.010 mol dm^{-3}.

Table 2. Observed rate constants for the hydrolysis of acetone methyl subst.-phenyl ketals in aqueous buffer solutions at 25 °C. Ionic strength was adjusted to 0.100 mol dm^{-3} with sodium chloride.

HA	$\dfrac{c(HA)}{c(A^-)}$	$c(HA)/$ 10^{-3} mol dm^{-3}	$k(obs)/10^{-3}$ s^{-1} [a]		
			Substituent		
			H	4-CH$_3$	4-OCH$_3$
CH$_3$COOH	0.1	10.00	6.73	6.25	6.64
		7.50	6.44	5.80	6.26
		5.00	5.87	5.28	5.78
		2.50	5.42	–	5.28
COOH(CH$_2$)$_2$COO$^-$	1	25.00	11.2	9.10	
		18.75	10.7	8.50	
		12.50	10.0	8.29	
		6.25	9.27	7.46	
H$_2$AsO$_4^-$	2	28.6	2.53	1.81	1.52
		21.4	2.26	1.66	1.36
		14.3	1.98	1.45	1.20
		7.14	1.70	1.22	1.04
H$_2$PO$_4^-$	1	25.00	1.99	1.04	
		18.75	1.75	0.898	
		12.50	1.49	0.802	
		6.25	1.24	0.667	
HCO$_3^-$	1	25.00	0.799		
		18.75	0.799		
		12.50	0.794		
		6.25	0.819		
HCO$_3^-$	10	76.9	0.809		
		57.7	0.809		
		38.5	0.811		
		19.2	0.817		

[a]Mean value for 2–3 runs.

tion. The relevant data are summarized in Table 2. The observed first-order rate constants were fitted using a least-squares method with the linear expression in buffer acid concentration in eqn. 1.

$$k(obs) = k(H_2O) + k(H_3O^+) \cdot c(H_3O^+) + k(HA) \cdot c(HA) \tag{1}$$

The analysis gave values of the slope, corresponding to catalysis by the undissociated acid (Table 3), and of the intercept, referring to reaction through solvent-derived species, i.e. the oxonium ion and water molecule.

The hydrolysis of the studied ketals was too fast to be followed by conventional methods in aqueous mineral acid solutions. The oxonium ion

catalytic coefficients were estimated using the data obtained with buffer solutions. The differences between the intercepts from the linear least-squares analysis and the rate constants for uncatalyzed hydrolysis were divided by the oxonium ion concentrations of the buffer solutions determined either kinetically or by calculation.

To determine kinetically the oxonium ion concentrations of the buffer solutions, the rates of hydrolysis of acetone dimethylketal (2,2-dimethoxypropane) were measured in the solutions concerned. The hydrolysis of this ketal is specifically oxonium ion-catalyzed. The hydrolysis rate in buffer solutions is dependent on the oxonium ion concentration only, which can be calculated using the second-order rate coefficients deter-

Table 3. Summary of catalytic coefficients for the acid-catalyzed hydrolysis of acetone methyl subst.-phenyl ketals at 25 °C.

HA	$k(HA)/10^{-2}$ dm^3 mol^{-1} s^{-1}		
	Substituent		
	H	4-CH$_3$	4-OCH$_3$
CH$_3$COOH	18.0(11)	19.4(25)	18.2(8)
COOH(CH)$_2$COO$^-$	11.2(16)	8.24(13)	–
H$_2$AsO$_4$$^-$	3.87(5)	2.76(15)	2.24(4)
H$_2$PO$_4$$^-$	3.98(13)	1.93(75)	–
H$_3$O$^+$ [a]	161000	180000	180000
α [b]	0.39(2)	0.49(2)	0.52

[a]Estimated from the measurements in buffer solutions. [b]Coefficient of the Brønsted relation without oxonium ion catalyzed reaction.

mined in acid solutions $[k(H_3O^+) = 989.0$ dm^3 mol^{-1} s^{-1} at 25 °C].[16]

The oxonium ion concentrations were also calculated from stoichiometric buffer compositions, thermodynamic acidity constants and estimated activity coefficients. For acetate buffer solutions, a value $c(H_3O^+) = 2.73 \cdot 10^{-6}$ mol dm^{-3} was obtained by using p$K_a = 4.756$[17] and ionic activity coefficients recommended by Bates.[18] This is in excellent agreement with the kinetically deter-
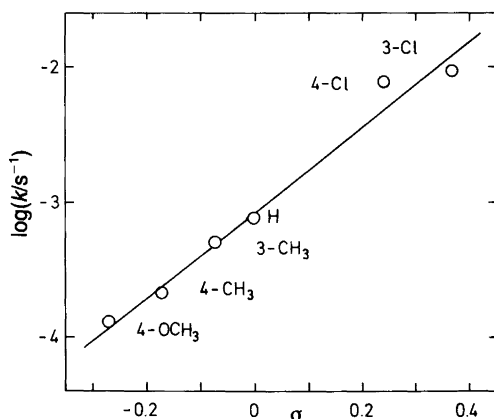

Fig. 1. Structural effects on the rate of water-induced hydrolysis of methyl subst.-phenyl ketals of acetone at 25 °C, presented as the Hammett relationship.

mined value $(2.74 \cdot 10^{-6}$ mol dm$^{-3})$. For phosphate buffers, the calculated oxonium ion concentration was $1.66 \cdot 10^{-7}$ mol dm^{-3} using p$K_a = 7.200$,[19] and the kinetically determined value was $1.57 \cdot 10^{-7}$ mol dm^{-3}.

The values for the oxonium ion catalytic coefficients for the hydrolysis of acetone methyl subst.-phenyl ketals, which are used in further discussion (Table 3), are averages of those obtained as the results of measurements in different buffer solutions with kinetically determined oxonium ion concentrations.

Discussion

Structural effects on the rate of water-induced or uncatalyzed hydrolysis of methyl substituted-phenyl ketals of acetone are illustrated by the Hammett plot in Fig. 1. A straight-line relationship with satisfactory correlation between log (k/s^{-1}) and the substituent constant σ is obtained. The slope of this line, the Hammett reaction constant, has a value of 3.16(24). The high positive value indicates development of negative charge on the atom adjacent to the aromatic ring on passing from initial to transition state. This observation supports a mechanism for the reaction which involves an uncatalyzed unimolecular decomposition of the substrate without a water molecule acting as a proton-transfer agent in the transition state. On similar grounds, a spontaneous unimolecular mechanism has been suggested for the water-induced hydrolysis of some acetals[12,14] and ortho-esters.[13]

Solvent deuterium isotope effects on the rate of the uncatalyzed hydrolysis have been used to distinguish the spontaneous unimolecular from a general acid-catalysis mechanism in which the proton is transferred from the water molecule to the oxygen atom of the substrate.[9,10,20] According to this distinction, the value $k(H_2O)/k(D_2O) \approx 1.5$ obtained for the uncatalyzed hydrolysis of acetone methyl phenyl ketals would not be consistent with the spontaneous mechanism. For the uncatalyzed hydrolysis of phenyl dimethyl ortho-formates,[13] it was shown by examination of the possible magnitude of the Gibbs energy of transfer for the anionic part of the activated complex, and the fractionation factors for the hydrogens of the water molecules solvating the activated complex, that values larger than unity are possible for the spontaneous hydrolysis.
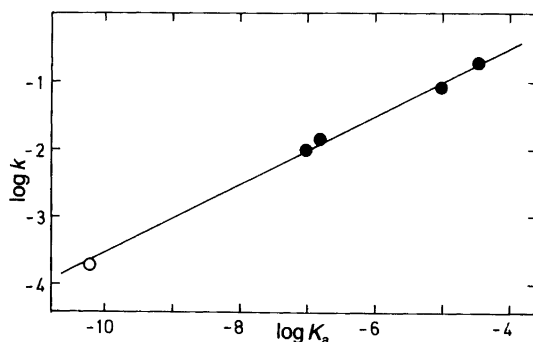
Fig. 2. The Brønsted relation for the hydrolysis of acetone methyl 4-methylphenyl ketal at 25 °C. The uncatalyzed hydrolysis is introduced into the relationship by the K_a of 4-methylphenol (O).

The same factor, ease of C–O bond cleavage, that is operative in uncatalyzed hydrolysis, is important for detecting general acid catalysis. This is demonstrated by the observation of general acid catalysis for the studied ketals in buffer solutions (Table 2). The slope of a plot according to the Brønsted relation, the α-coefficient, shows a tendency to increase as the phenolic substituent becomes less electronegative (Table 3). Similar behaviour has been observed in the hydrolysis of acetals derived from acetaldehyde[6] and benzaldehyde.[3,5,8]

It has been suggested that uncatalyzed hydrolysis may be incorporated in the Brønsted relation, in the form of the acidity constant for the phenol corresponding to the leaving group in the reaction.[6] In all the cases studied, the rate constant for the uncatalyzed hydrolysis, $k(H_2O)$, can be

Table 4. Transition state acidities in the hydrolysis of methyl subst.-phenyl ketals of acetone and acetals of acetaldehyde at 25 °C.

Compound	Substituent	$pK_a(\ddagger)$	α^a
Ketal	4-OCH$_3$	7.15	0.70
	4-CH$_3$	6.94	0.68
	H	6.33	0.63
Acetal^b	4-COCH$_3$	5.40	0.67
	4-CN	5.02	0.63
	4-NO$_2$	4.09	0.57

^{a}Brønsted-like coefficient of eqn. 3. ^{b}Calculated from the data of Ref. 6.

introduced using the acidity constant for the corresponding phenol into a common rate-equilibrium relationship with general acid catalysis. An example is presented in Fig. 2.

The suggested treatment also implies that catalysis by an acid weaker than the phenol formed in the hydrolysis cannot be observed. To test this assumption, measurements were performed in hydrogen carbonate buffer solutions. The acidity of the hydrogen carbonate ion is of the same magnitude as that of phenol. The rate constants in two buffer solutions with buffer ratios differing by a factor of ten (Table 2) reveal that no catalysis by hydrogen carbonate ion is observed. This gives support to the concept that the driving force for general acid catalysis arises from the thermodynamically more favourable position of the proton in the reacting substrate than in the catalyst.

The catalytic coefficients estimated for the oxonium ion fit these linear Brønsted relations less well. The deviation from the Brønsted line is about two orders of magnitude.

When both acid-catalyzed and uncatalyzed rate constants for a reaction are known, the transition state can be characterised by the $pK_a(\ddagger)$ approach of Kurz.[21,22] The virtual equilibrium constant for dissociation of the catalyst from the activated complex is obtained by the simple relationship of eqn. (2):

$$pK_a(\ddagger) = \log \frac{k(H_3O^+)}{k(H_2O)} \, . \tag{2}$$

The calculated transition state acidities for the hydrolysis of the studied ketals of acetone and some acetals of acetaldehyde studied earlier[6] are presented in Table 4. The values differ for the two groups of compounds. This could refer to differences in the character of the transition state. An alternative approach to transition state acidities is presented for hydrolysis in which the catalytic proton transfer is concerted with C–O bond cleavage.

The decrease in the Gibbs energy level of the transition state brought about by the catalyst, i.e. the difference between catalyzed and uncatalyzed reactions, here represented by $pK_a(\ddagger)$, is assumed to arise ultimately from the thermodynamically favourable proton transfer ("libido rule").[23] In the hydrolysis of the acetals and ketals with a phenolic leaving group, the basicity of the oxygen atom accepting the proton increases

while the cleavage of the C–O bond is taking place. The maximum difference, which is attained when the bond is totally broken, is represented by the acidity of the phenol, pK_a(PhOH). The fraction of that maximum difference that is achieved in the transition state describes the extent to which the transition state resembles the products, and may be represented by a Brønsted-like coefficient, α (3):

$$\alpha = \frac{pK_a(\ddagger)}{pK_a(\text{PhOH})} \cdot \tag{3}$$

The calculated α-values presented in Table 4 show that no difference between the transition state characters of acetals and ketals actually exists. The values are larger than those obtained for the slope of the Brønsted relation for different acids.

The transition state characterization presented suggests that the mechanism of hydrolysis of the studied ketals containing phenolic leaving groups is similar to that of corresponding acetals. The treatment will be applied to different acetals and ortho-esters in further work to test the validity of the information obtained.

References

1. Cordes, E. H. and Bull, H. G. *Chem. Rev. 74* (1974) 581.
2. Fife, T. H. *Acc. Chem. Res. 5* (1972) 264 and references therein.
3. Jensen, J. L., Herold, L. R., Lenz, P. A., Trusty, S., Sergi, V., Bell, K. and Rogers, P. *J. Am. Chem. Soc. 101* (1979) 4672.
4. Jensen, J. L. and Wuhrman, W. B. *J. Org. Chem. 48* (1983) 4686.
5. Lamaty, G. and Menut, C. *Recl. Trav. Chim. Pays-Bas 103* (1984) 54.
6. Lahti, M. and Kauppi, K. *Acta Chem. Scand., Ser. A 40* (1986) 533.
7. Anderson, E. and Fife, T. H. *J. Am. Chem. Soc. 91* (1969) 7163.
8. Capon, B. and Nimmo, K. *J. Chem. Soc., Perkin Trans. 2* (1975) 1113.
9. Fife, T. H. and Brod, L. H. *J. Am. Chem. Soc. 92* (1970) 1681.
10. Fife, T. H. and Jao, L. K. *J. Am. Chem. Soc. 90* (1968) 4081.
11. Chiang, Y. and Kresge, A. J. *J. Org. Chem. 50* (1985) 5038.
12. Graze, G.-A. and Kirby, A. J. *J. Chem. Soc., Perkin Trans. 2* (1978) 354.
13. Lahti, M. *Acta Chem. Scand., Ser. A 41* (1987) 93.
14. Lönnberg, H. and Pohjola, V. *Acta Chem. Scand., Ser. A 30* (1976) 669.
15. Müller, E. In: Houben-Weyl, *Methoden der Organischen Chemie,* Thieme, Stuttgart 1965, Vol. VI/3, p. 229.
16. *Unpublished results.*
17. Harned, H. S. and Ehlers, R. W. *J. Am. Chem. Soc. 55* (1933) 652.
18. Bates, R. G. *Determination of pH,* 2nd ed., Wiley, New York 1973, p. 49.
19. Grzybowski, A. K. *J. Phys. Chem. 62* (1958) 555.
20. Capon, B. and Page, M. I. *J. Chem. Soc., Perkin Trans. 2* (1972) 522.
21. Kurz, J. L. *J. Am. Chem. Soc. 85* (1963) 987.
22. Kurz, J. L. *Acc. Chem. Res. 5* (1972) 1.
23. Jencks, W. P. *J. Am. Chem. Soc. 94* (1972) 4731.