

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA AND THE COLLEGE OF CHEMISTRY AND PHYSICS, THE PENNSYLVANIA STATE UNIVERSITY]

Steric and Ring-size Effects on Ketal Hydrolysis Rates^{1a}

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Rates of acid-catalyzed hydrolysis in 50% dioxane–50% water have been measured for cyclic and for bulky ketals. The rates are all consistent with the hypothesis that the hydrolysis transition state has made substantial progress toward a carbonium ion geometry.

In an earlier paper² the rates of a large number of acetal and ketal hydrolyses were correlated by a consideration of Baker–Nathan effects and inductive effects on reactivity. The ketal of 4,4-dimethyl-2-pentanone did not fit this relation, being somewhat more than a power of ten too fast. Since the starting state for the hydrolysis has a saturated, tetrahedral, central carbon atom, and there is independent evidence of very considerable carbonium ion character in the transition state,^{2–4} it was suggested that the formation of the hydrolysis transition state is accompanied by an enlargement of the angles made with the central carbon atom by the bonds to those groups which are not leaving. The accelerated hydrolysis for the ketal of 4,4-dimethyl-2-pentanone is, then, attributed to a release of strain accompanying the activation process and should be general for ketals having bulky substituents.⁵ The effect of ring size on the rate also can be predicted qualitatively.⁶ The present paper reports the hydrolysis rates for the ketals of 3,3-dimethyl-2-butanone and a series of cyclic ketals. These rates are in complete accord with the predictions made on the basis of a carbonium ion-like transition state.

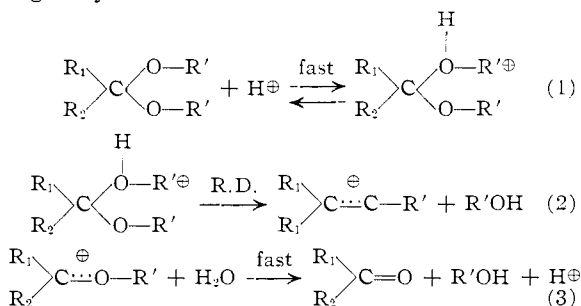
Results

Acid-catalyzed hydrolysis rates at 25° were determined spectrophotometrically in the manner already described.^{2,7} The solvent contained 50.4% water and 49.6% dioxane by weight and was made up as before.⁷ All of the rates showed a precise linear dependence on the hydronium ion concentration and on the substrate concentration. Table I lists the observed second-order rate constants along with several previously-measured rate constants for comparison. In all the reactions except those of the cyclobutanone ketal, the hydronium ion concentration was governed by acetic acid-

acetate buffers. Hydronium ion concentrations were obtained from the acid dissociation constant of acetic acid in this medium and the activity coefficients given by the Debye–Hückel theory in the manner previously described.² In no case was any dependence of rate on the molecular acetic acid concentration detected.

Discussion

The mechanism of acetal and ketal hydrolysis shown in eq. 1–3 was first postulated by O'Gorman and Lucas and now is supported by a very convincing body of evidence.^{3,4,7,8}



If eq. 3 represents the rate-determining step, and especially if, as has been suggested,⁴ the transition state resembles $\text{R}_1\text{R}_2\text{C}^\oplus\text{---OR}'$, it is plain that the angle R_1CR_2 is larger in the transition state than in the starting state. If R_1 and R_2 are bulky enough so that they repel each other significantly in the starting state, there will be a release of strain on going to the transition state.⁵ If R_1 and R_2 are part of a carbocyclic ring of less than five members, the activation process will be accompanied by an increase in strain due to the added deformation of the preferred bond angles.⁶

The suggested model for the transition state predicts no gross abnormalities for the five-, six- or seven-membered carbocyclic ketals. For the five-membered ring, a decrease in torsional-strain energy accompanying the activation process is predicted,^{6c,9} but there will also be an increase in bond-angle strain.⁹ In the six-membered carbocyclic ketal there will be a small uncompensated increase in torsional-strain energy accompanying the activation process due to the tendency of the $\text{---OR}'$ group to eclipse two adjacent hydrogen atoms.^{6c,10} No careful conformational analysis

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(2) M. M. Kreevoy and R. W. Taft, Jr., *THIS JOURNAL*, **77**, 5390 (1955).

(3) M. M. Kreevoy and R. W. Taft, Jr., *ibid.*, **79**, 4016 (1957).

(4) M. M. Kreevoy, *Tetrahedron*, **5**, 233 (1959).

(5) (a) H. C. Brown, *Science*, **103**, 385 (1946); (b) H. C. Brown and R. S. Fletcher, *THIS JOURNAL*, **72**, 1223 (1950); (c) P. D. Bartlett, *Bull. soc. chim. France*, C100 (1951).

(6) (a) A. Baeyer, *Ber.*, **18**, 2269 (1885); (b) A. Baeyer, *ibid.*, **18**, 2277 (1885); (c) H. C. Brown and K. Ichikawa, *Tetrahedron*, **1**, 221 (1957); (d) H. C. Brown, R. S. Fletcher and R. B. Johannesen, *THIS JOURNAL*, **73**, 212 (1951); (e) P. Riesz, R. W. Taft, Jr., and R. H. Boyd, *ibid.*, **79**, 3724 (1957).

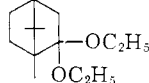
(7) M. M. Kreevoy and R. W. Taft, Jr., *ibid.*, **77**, 3146 (1955).

(8) (a) J. M. O'Gorman and H. J. Lucas, *ibid.*, **72**, 5489 (1950); (b) F. A. Long and M. A. Paul, *Chem. Revs.*, **57**, 935 (1957); other references may be found in this paper and in ref. 2.

(9) K. S. Pitzer and W. E. Donath, *THIS JOURNAL*, **81**, 3213 (1959).

(10) W. G. Dauben and K. S. Pitzer in M. S. Newman, "Steric Effects in Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., p. 40.

TABLE I
 KETAL HYDROLYSIS RATES

Ketal	$k_2, \text{l. mole}^{-1} \text{sec}^{-1}$			$\log (k_{\text{obs}}/k_{\text{calc}})$
$(\text{CH}_3)_2\text{C}(\text{OC}_2\text{H}_5)_2$	7.52×10^{2d}			
$(\text{CH}_3)_3\text{CCH}_2\text{C}(\text{OC}_2\text{H}_5)_2\text{CH}_3$	9.2×10^{2d}	+1.12	+0.96	
$(\text{CH}_3)_3\text{CC}(\text{OC}_2\text{H}_5)_2\text{CH}_3$	8.2×10^4	+2.52	+2.04	
$\text{CH}_2(\text{CH}_2)_2\text{C}(\text{OC}_2\text{H}_5)_2$	1.37	-2.02	-2.34	$\text{CH}_3, \text{C}_2\text{H}_5$
$\text{CH}_2(\text{CH}_2)_3\text{C}(\text{OC}_2\text{H}_5)_2$	3.27×10^2	0.00	-0.32	$\text{C}_2\text{H}_5, \text{C}_2\text{H}_5$
$\text{CH}_2(\text{CH}_2)_4\text{C}(\text{OC}_2\text{H}_5)_2$	96	-0.59	-.91	$n\text{-C}_3\text{H}_7, \text{C}_2\text{H}_5$
$\text{CH}_2(\text{CH}_2)_5\text{C}(\text{OC}_2\text{H}_5)_2$	2.92×10^3	+0.84	+.52	$n\text{-C}_3\text{H}_7, n\text{-C}_3\text{H}_7$
	4.22×10^2	+0.43	-.05	$s\text{-C}_4\text{H}_9, i\text{-C}_4\text{H}_9$

^a Calcd. from eq. 4. ^b Calcd. from eq. 5. ^c Substituents by which $\Sigma\sigma^*$ for cyclic ketals was estimated. ^d Taken from ref. 3.

of seven-membered carbocyclic compounds seems to be available at the moment but it seems likely that the saturated compounds are overcrowded, resulting in torsional and/or angle strain, and that this is partially relieved by introducing a trigonal carbon.¹¹ It is, therefore, predicted that the ketal of cyclobutanone will have an "abnormally" small rate constant, the ketals of 4,4-dimethyl-2-pentanone and 3,3-dimethyl-2-butanone may well have "abnormally" large rate constants, and the ketals of cyclopentanone, cyclohexanone and cycloheptanone should have rates close to "normal," with the five- and seven-membered ring compounds having larger rate constants than the six-

The "normal" rate constants can be estimated either by means of eq. 4 or eq. 5, both of which correlate hydrolysis rate constants for the acetals and ketals of a large number of fairly simple, non-conjugated aldehydes and ketones.^{2,12} In these equations σ^* is a constant measuring the electron-withdrawing power of a substituent and derived by

$$\log (k/k_0) = \rho^*\Sigma\sigma^* + h(n - n_0) \quad (4)$$

$$\log (k/k_0) = \rho^*\Sigma(\sigma^* - 0.49) + n_{\text{H}}h_{\text{H}} + n_{\text{C}}h_{\text{C}} \quad (5)$$

Taft from ester hydrolysis rates,¹³ and ρ^* (3.600) is a constant characteristic of the reaction and measuring its susceptibility to polar effects. In eq. 4, n is the number of α -hydrogen atoms in the general acetal or ketal and n_0 is the number in a standard compound; h (0.54) is the Baker-Nathan effect per α -hydrogen atom.¹⁴ The standard substituent, for which σ^* is defined as zero, is the methyl group, so the standard ketal is that of acetone and n_0 is 6. The parameters ρ^* and h were originally determined empirically from rate data,² but the latter also has been estimated independently from theory.¹⁵ The term $\rho^*\Sigma\sigma^*$ is a measure of polar effects on rate constants, while the term $h(n - n_0)$ is a measure of Baker-Nathan effects. In eq. 5, the standard substituent is the

(11) Reference 10, p. 42.

(12) R. W. Taft, Jr., and I. C. Lewis, *Tetrahedron*, **5**, 211 (1959).

(13) (a) R. W. Taft, Jr., *THIS JOURNAL*, **75**, 4231 (1953); (b) ref. 10, Chap. 31.

(14) The term "Baker-Nathan effect" is used here to mean an effect of α -hydrogen atoms on reactivity.

(15) M. M. Kreevoy and H. Eyring, *THIS JOURNAL*, **79**, 5121 (1957).

hydrogen atom, which necessitates the subtraction of 0.49, σ^* for the hydrogen atom, from each substituent σ^* before they are summed. In eq. 5, n_{H} is the number of α -hydrogen atoms, n_{C} is the number of α -carbon atoms, h_{H} is the Baker-Nathan effect per α -hydrogen, and h_{C} has the corresponding significance for α -carbon atoms. Significant deviations from the rates predicted by eq. 4 and 5 are thought to represent the contribution to relative reactivity of factors other than polar and Baker-Nathan effects; *i.e.*, steric effects, resonance effects due to conjugation.³ Table I lists these deviations for the present hydrolysis rates. Qualitatively eq. 4 and 5 give about the same sort of results.

The differences between observed and "normal" rate constants are fully in accord with the predictions made above and provide additional support for the accepted mechanism.

Figure 1 compares the trend in rate constants for the present reaction with those for methylcycloalkyl chloride solvolysis¹⁶ and borohydride reduction of ketones^{6c} as one proceeds from four- through seven-membered cyclic compounds. It is plain that there are similarities (inverted in the case of the borohydride reductions) but no exact correlation. This is in accord with the view that similar factors govern rates in all three series but they are of varying relative importance. Brown and Ichikawa^{6c} have presented a substantial body of similar comparisons and suggested that the borohydride reduction could be used *quantitatively* as a model for other reactions of cyclic systems. This seems to be an oversimplification.

Camphor is essentially a five-membered cyclic ketone and the hydrolysis rate of its ketal is about what would be expected of such a compound. It shows no sign of important neighboring-group effects. This can be contrasted with the solvolysis rates of the corresponding isobornyl compounds which have been estimated to show a neighboring-group effect of about five powers of ten.¹⁷ In the ketal, one of the ethoxy groups must occupy the favored, *exo*, position. Since the cleavage of the first carbon-oxygen bond is rate determining, it must be concluded that resonance of the type I

(16) A. Streitwieser, Jr., *Chem. Revs.*, **56**, 667 (1956).

(17) S. Winstein, *Bull. soc. chim. France*, C59 (1951).

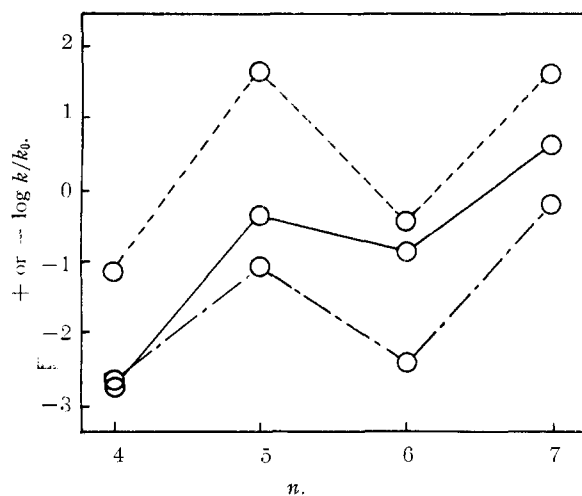
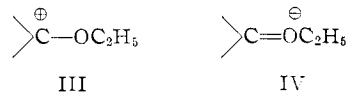


Fig. 1.—A plot of $\log(k/k_0)$ (or $-\log k/k_0$) vs. n for reactions of cyclic compounds. In each case, k is the rate constant for a reaction of a cyclic compound and n indicates the number of carbon atoms in the ring. For ketal hydrolysis, k_0 is the corresponding rate constant for acetone, and for chloride solvolysis it is the corresponding rate constant for *t*-butyl chloride. For the borohydride reductions, $-\log(k/k_0)$ is used and k_0 is the corresponding rate constant (obtained by extrapolation) for δ -undecanone: — is ketal hydrolysis; ---- is borohydride reduction; - - - is chloride solvolysis.

\longleftrightarrow II is much less important in the ketal hydrolysis transition state than in the solvolysis transition state. The difference may be due to resonance



of the type III \longleftrightarrow IV, although the latter does not prevent stabilization of the ketal hydrolysis

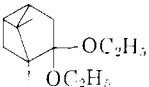


transition state by α,β -unsaturated groups.²⁻⁴ The ketal hydrolysis transition state may also be less carbonium ion-like than the solvolysis transition state.

Experimental¹⁸

All the ketals except that from cyclobutanone were prepared as previously described² from ethanol, ethyl orthoformate, and the corresponding ketone using a trace of mineral acid as a catalyst. The ketal of cyclobutanone has a b.p. very close to that of ethyl orthoformate so it was prepared from ethanol and the ketal of cyclopentanone in a similar fashion. Yields ranged from fair to good, and no attempt was made to maximize them. Table II lists the

TABLE II

Ketal	B.p., °C.	Ref.
$(\text{CH}_3)_3\text{CC}(\text{OC}_2\text{H}_5)_2\text{CH}_3$	157-158	
$\text{CH}_2(\text{CH}_2)_2\text{C}(\text{OC}_2\text{H}_5)_2$	138-141	
$\text{CH}_2(\text{CH}_2)_3\text{C}(\text{OC}_2\text{H}_5)_2$	165-166	^d
$\text{CH}_2(\text{CH}_2)_4\text{C}(\text{OC}_2\text{H}_5)_2$	74-76 ^a	^d
$\text{CH}_2(\text{CH}_2)_5\text{C}(\text{OC}_2\text{H}_5)_2$	108.5 ^b	
	119-120 ^c	

^a 15 mm. ^b 29 mm. ^c 16.5 mm. ^d J. Böeseken and F. Tellegen, *Rec. trav. chim.*, **57**, 133 (1938). ^e A. Arbusow, *J. Russ. Phys. Chem. Soc.*, **40**, 647 (1908); *Chem. Centr.*, **79**, II, 1340 (1908).

boiling points of all the ketals and literature references for those which were previously known compounds. The ketal of cycloheptanone was analyzed.

Anal. Calcd. for $\text{C}_{11}\text{H}_{22}\text{O}_2$: C, 70.92; H, 11.91. Found¹⁹: C, 70.81; H, 11.97.

The ketal of methyl *t*-butyl ketone was analyzed.

Anal. Calcd. for $\text{C}_{11}\text{H}_{22}\text{O}_2$: C, 68.97; H, 12.64. Found²⁰: C, 68.58; H, 12.53.

The ketal of cyclobutanone was analyzed.

Anal. Calcd. for $\text{C}_8\text{H}_{16}\text{O}_2$: C, 66.63; H, 11.18. Found²⁰: C, 66.92; H, 10.73.

All the starting ketones were the best quality commercially available. They were redistilled before use and had boiling points in reasonable accord with those recorded in the literature.

Kinetic procedures and the method of making up the solvent have been reported^{2,7} previously and no special difficulties were encountered in the present work.

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(18) All boiling points are uncorrected.

(19) Microanalysis performed by Mrs. Olga Hammerston of the University of Minnesota microanalytical laboratory.

(20) Microanalysis performed by Clark Microanalytical Laboratory of Urbana, Illinois.