[CONTRIBUTION FROM THE DEPARTMENTS OF CHEMISTRY OF THE OHIO STATE UNIVERSITY, COLUMBUS, O., AND THE UNIVERSITY OF CINCINNATI, CINCINNATI, O.]

The Effects of Ring Size on the Rates of Acid- and Base-catalyzed Enolization of Homologous Cycloalkanones and Cycloalkyl Phenyl Ketones

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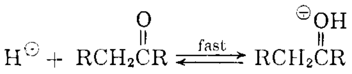
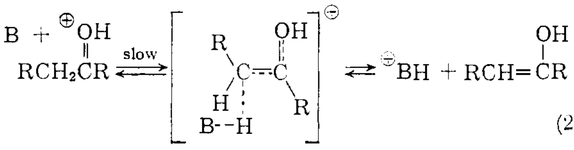
The reactivity for enolization of cycloalkanones in hydrochloric acid–90% acetic acid as a function of ring size is $6 > 8 > 5 > 7 > 4$; that for enolization by deuteroxide in dimethylformamide–deuterium oxide is $4 > 5 > 6 > 7$. The reactivity order for acid-catalyzed enolization of cycloalkanones is interpreted primarily on the basis of differences in steric requirements in conversion of the ketones to transition states having endocyclic unsaturated character which is highly developed; that for base-catalyzed enolization is based on the s-character of the carbon orbital directed toward enolizable hydrogen as a function of ring size. The reactivity for acid-catalyzed enolization of cycloalkyl phenyl ketones with respect to ring size of the cycloalkyl group is $5 > 4 > 6 > 3$; for base-catalyzed enolization: $3 \geqq 4 > 5 > 6$. The relative rates of enolization of the cycloalkyl phenyl ketones by acid are generally correlated by the steric and hybridization requirements for conversion of a tetragonal atom to near trigonal in saturated monocyclic systems. The sequence for cycloalkyl phenyl ketones in the presence of bases is attributed to factors similar to that considered for base-catalyzed enolization of cycloalkanones.

The present study is concerned with the effects of ring size on the rates, kinetic parameters and mechanisms of enolization of homologous cycloalkanones and cycloalkyl phenyl ketones in acids and in bases. Model dialkyl ketones and alkyl phenyl ketones have also been investigated for purposes of comparison with related cyclic derivatives.

Acids and bases catalyze enolization of ketones by similar mechanisms. In the presence of strong acids, a ketone is converted reversibly to its conjugate acid (eq. 1); loss of an alpha proton occurs by reaction with a nucleophile in the rate-determining step to give the corresponding enol (equation 2).[2] Enolization by strong bases[2,3] involves reaction of a base and a ketone with assistance of the weak electrophiles present to yield the enolate ion (eq. 3). The transition states for enolization in the presence of acids (I) and bases (II) differ with respect to charge, charge distribution and to the strengths of bonds developed by the nucleophiles and electrophiles.

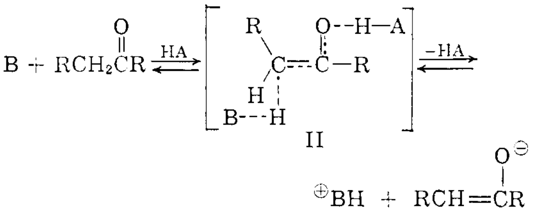


$$H^{\oplus} + RCH_2\overset{O}{\overset{\|}{C}}R \overset{fast}{\rightleftharpoons} RCH_2\overset{\oplus OH}{\overset{\|}{C}}R \qquad (1)$$



(2)

I



II

(3)

The over-all rates of acid- and base-catalyzed enolization may be determined using methods which involve halogenation to give α-haloketones, isotopic exchange of α-hydrogen or racemization of enolizable asymmetric centers.[4] As a result of isotope effects on rates of enolization,[2b,c,5a] the stereochemistry of ketonization of enols[5b] and correlations of reaction rates and equilibria on the basis that an enol is a high energy intermediate relative to ketone,[5c] it is apparent that the transition state I for acid-catalyzed enolization is very close to enol in geometry. Related data and logic also indicate that the structure of the transition state II for base-catalyzed enolization has certain enolate character.[5a]

Enolization of acetophenones in the presence of acids is accelerated by electron-donating and retarded by electron-withdrawing substituents in *m*- or *p*-positions.[6a] The effects of electron-donating and electron-withdrawing groups on the rates of base-catalyzed enolization of acetophenones[6b] are opposite to that for the acid-catalyzed reactions. Halogenation of alkyl methyl ketones and cycloalkyl methyl ketones in acidic media generally occurs in alkyl and cycloalkyl rather than in methyl groups[7a,b]; base-catalyzed halogenation

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(1) (a) The study of acid-catalyzed enolization was effected by authors 1a with support from the Graduate School of The Ohio State University, E. I. du Pont de Nemours and Co., and the Office of Ordnance Research (Contract No. DA-33-019-ORD-3218). (b) The investigations of base-catalyzed enolization were conducted by authors 1b with support by the Petroleum Research Fund (PRF-417A). (c) Petroleum Research Fund Predoctoral Fellow, 1959–1961.

(2) (a) Catalysis of enolization of α-phenylisocaprophenone by acetic acid[2b,c] does not involve simultaneous addition of the acid to the carbonyl group and nucleophilic attack at the α-position during the rate-determining step, but rather a proton transfer in a rapid equilibrium process and subsequent nucleophilic reaction by acetate ion; (b) C. G. Swain, A. J. DiMilo and J. P. Cordner, *J. Am. Chem. Soc.*, **80**, 5983 (1958); (c) C. G. Swain, E. C. Stivers, J. F. Reuwer, Jr., and L. J. Schaad, *ibid.*, **80**, 5885 (1958).

(3) A. Lapworth, *J. Chem. Soc.*, **85**, 30 (1904).

(4) H. M. Dawson and M. S. Leslie, *ibid.*, **95**, 1860 (1909); P. D. Bartlett, *J. Am. Chem. Soc.*, **56**, 967 (1934); C. K. Ingold and C. L. Wilson, *J. Chem. Soc.*, 773 (1934); C. K. Ingold, S. K. Hsu and C. L. Wilson, *ibid.*, 78 (1938); W. D. Walters and K. F. Bonhoeffer, *Z. physik. Chem.*, **A182**, 265 (1938).

(5) (a) W. D. Emmons and M. F. Hawthorne, *J. Am. Chem. Soc.*, **78**, 5593 (1956); (b) H. E. Zimmerman, *ibid.*, **78**, 1168 (1956); (c) G. S. Hammond, *ibid.*, **77**, 334 (1955).

(6) (a) D. P. Evans, V. G. Morgan and H. B. Watson, *J. Chem. Soc.*, 1167 (1935); (b) V. G. Morgan and H. B. Watson, *ibid.*, 1173 (1935).

(7) (a) H. M. E. Cardwell and A. E. H. Kilner, *ibid.*, 2430 (1951); (b) enolization of such derivatives is of the Saytzeff type in that the more substituted enol is formed the more rapidly; (c) H. M. E. Cardwell, *ibid.*, 2442 (1951); (d) the position of attack of alkyl methyl

of such ketones takes place preferentially in the methyl groups.[7c,d] Such information along with limited kinetic data[8] have led to the conclusion that acid-catalyzed enolization of ketones is significantly controlled by hyperconjugative factors,[7a] whereas the base-catalyzed process depends primarily on inductive effects.[7c,e] Recently it has been suggested that steric factors are important in acid- and base-catalyzed enolization of cyclopentyl phenyl ketone and cyclohexyl phenyl ketone[5a] and in acid-catalyzed enolization[9] of cyclopentanone and cyclohexanone.

Experimental

Acid-Catalyzed Bromination. Reagents.—Cyclobutanone (Aldrich Chemical Co.) was purified by precision rectification; its purity was attested by vapor phase chromatography. Cyclopentanone, cycloöctanone and di-*n*-propyl ketone were obtained *via* decomposition of their highly purified semicarbazones with aqueous oxalic acid, steam distillation and fractionation. Cyclohexanone and cycloöctanone were purified by decomposition of their bisulfite addition compounds followed by fractional distillation. The cycloalkyl phenyl ketones were prepared by described methods[10] and purified by rectification. Initial purification of cyclopropyl phenyl ketone was effected through its semicarbazone; cyclohexyl phenyl ketone was obtained in highest purity by recrystallization from petroleum ether at −70° and subsequent vacuum sublimation. The acetic acid used throughout the acid-catalyzed enolizations was refluxed over excess chromium trioxide, distilled, and rectified in a bubble-plate column.

Acid-catalyzed Bromination Rates.—The rates of acid-catalyzed bromination of the various ketones were determined upon adaptation of the method of Evans.[8] In general the rates of bromination were determined under pseudo-first order conditions at 14, 20 and 29.9°; bromination of acetone, di-*n*-propyl ketone and cyclobutanone were investigated as pseudo-zero order processes (the ketone was used in 20-fold excess).[11] The extent to which a reaction was followed depended on the ketone and the temperature. In general, reaction was followed much nearer to completion with the more reactive ketones. Thus, at 30° cyclopentyl phenyl ketone was followed until 75% of the ketone had reacted; bromination of cyclohexyl phenyl ketone was followed only to 30% completion.

Bromination of the cycloalkanones is complicated by the facts that their rates of enolization are considerably greater than that of the cycloalkyl phenyl ketones, and the cycloalkanones have more than one enolizable hydrogen. The catalyst concentration (0.0502 *M* HCl) used for the cycloalkanones was thus considerably smaller than that for the cycloalkyl phenyl ketones (0.53 *M* HCl); autocatalysis of bromination of the cycloalkanones by hydrogen bromide formed during reaction was found important under certain conditions. Thus when the concentration of cyclopentanone was 0.07 *M*, the reaction obeyed a first-order rate law over the entire period studied (39% mono-enolization); when the concentration of the ketone was 0.125 *M*, the reaction only followed a first-order rate law until monobromination was 25% complete. In general mono-enolization of cycloalkanones was followed up to 30–50% completion.

The rate of bromination of a ketone is first order with respect to ketone but independent of bromine concentration. The rate constant was evaluated on use of eq. 4 in which $[\text{ketone}]_0$ and $[\text{ketone}]_t$ refer to concentrations of ketone at $t = 0$ and time t, respectively. The rate constant was determined graphically from the slope of the line (multiplied by 2.303) obtained upon plotting $\log_{10} [\text{ketone}]_0/[\text{ketone}]_t$ against time. Under pseudo-zero order conditions the ketone

$$k = \frac{2.303}{t} \log_{10} \frac{[\text{ketone}]_0}{[\text{ketone}]_t} \qquad (4)$$

concentration remains sensibly constant and the rate of absorption of bromine decreases linearly with time. The zero-order rate constant was evaluated by plotting the concentration of bromine *versus* time; the zero-order rate constant is the slope divided by the ketone concentration.

Important details of the experimental procedure are described as follows. A solution of hydrochloric acid (1.06 *M*) in 90% acetic acid was prepared for bromination of cycloalkyl phenyl ketones; 0.1004 *M* hydrochloric acid in 90% acetic acid was used for bromination of the cycloalkanones. Bromine was added to the stronger hydrogen chloride solution and aliquots withdrawn over a period of 3 days. The bromine was determined iodometrically; there was no measurable reaction of bromine with the solvent during this period.

A weighed quantity of the ketone was dissolved in glacial acetic acid. Water (5 ml.) was added to the solution and the mixture then diluted to 50 ml. at the kinetic temperature with glacial acetic acid. The ketone solution was mixed with a solution (50 ml.) of bromine in the hydrochloric–acetic acid catalyst mixture (for the pseudo-first-order runs the concentrations of the bromine and the ketone were approximately the same). Aliquots (5 ml.) of the reaction mixture were withdrawn at various times and added to excess potassium iodide in water. The iodine liberated was titrated with sodium thiosulfate using starch as the indicator.

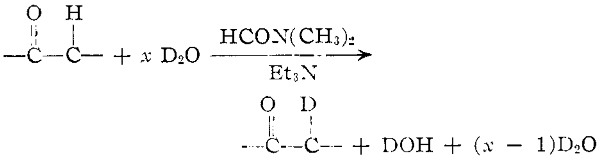
Acid-catalyzed Bromination of Cyclobutyl Phenyl Ketone.—A solution of cyclobutyl phenyl ketone (1.002 g., 0.00624 mole) in 90% acetic acid was mixed with a solution (150 ml.) of bromine (0.00666 mole) in hydrogen chloride (0.014 mole) in 90% acetic acid at 30°. The mixture was left overnight, then poured on ice and shaken with a small amount of dilute aqueous sodium thiosulfate. Upon vacuum evaporation of the mixture, a red-brown solid remained. The aqueous acetic acid which had been removed was extracted with petroleum ether (30–60°); the extract was washed with 2 *N* sodium hydroxide and then with water. Upon removal of the petroleum ether, a white solid was obtained whose infrared spectrum was identical with that of the previous red-brown solid. The yield of crude α-bromocyclobutyl phenyl ketone was 95.1%. The product upon sublimation was obtained as a white solid, m.p. 59.0–59.5° (uncor.), lit.[12] m.p. 61°. Identification of the product was confirmed by its nuclear magnetic resonance.

Base-catalyzed Enolization. Reagents.—All of the solvent materials were prepared in the previously described manner.[13]

The cycloalkanones were purchased commercially, except for cyclobutanone, which was prepared according to the method described by Hurd.[14] The cycloalkyl phenyl ketones were as described in the previous section.

All of the ketones were distilled shortly before use, and sealed in glass ampoules under nitrogen.

Base-catalyzed Enolization Rates.—The rates of exchange of deuterium for the active hydrogen of the ketones in the



$$-\overset{\overset{\displaystyle O}{\|}}{C}-\overset{\overset{\displaystyle H}{|}}{C}- + x\,D_2O \xrightarrow[Et_3N]{HCON(CH_3)_2} -\overset{\overset{\displaystyle O}{\|}}{C}-\overset{\overset{\displaystyle D}{|}}{C}- + DOH + (x-1)D_2O$$

system were measured spectrophotometrically by following the absorption due to the DOH species which result from the D/H exchange using the method described by Dessy.[13]

Results and Discussion

Acid-catalyzed Enolization.—The first-order rate constants and the kinetic parameters for bromina-

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ketones by bases is analogous to that in Hofmann elimination of quaternary ammonium compounds; (e) D. P. Evans and J. J. Gordon, *J. Chem. Soc.*, 1434 (1938).

[8] D. P. Evans, *ibid.*, 785 (1936).

[9] O. H. Wheeler and J. L. Mateos, *J. Org. Chem.*, **22**, 1153 (1957).

[10] R. P. Mariella and R. R. Raube, *J. Am. Chem. Soc.*, **74**, 521 (1952); C. H. Tilford and M. G. Van Campen, Jr., *ibid.*, **76**, 2431 (1954).

[11] The acid-catalyzed bromination of acetone has been previously studied under pseudo-zero order conditions by E. D. Hughes, H. B. Watson and E. D. Yates, *J. Chem. Soc.*, 3318 (1931).

[12] T. A. Favorskaya and I. P. Yakovlev, *J. Gen. Chem. U.S.S.R.*, **22**, 113 (1952); (b) the present sample also gave the proper analysis: Calcd. for $C_{10}H_{11}OBr$: C, 55.25; H, 4.64; Br, 33.42. Found: C, 55.27; H, 4.79; Br, 33.41.

[13] R. E. Dessy, Y. Okuzumi and A. Chen, *J. Am. Chem. Soc.*, **84**, 2899 (1962).

[14] J. W. Williams and C. D. Hurd, *J. Org. Chem.*, **59**, 1235 (1940).

TABLE I

ACID-CATALYZED BROMINATION OF CYCLOALKANONES AND CYCLOALKYL PHENYL KETONES IN 90% ACETIC ACID

Ketone	HCl, M^a	$k_1^{14°} \times 10^{7\,b,c}$	$k_1^{20°} \times 10^7$	$k_1^{29.9°} \times 10^7$	Rel. rates 29.9°	ΔH^*, kcal. mole^{-1}	ΔS^*, e.u.
Cyclobutanone	0.0502			5.23	1		
Cyclopentanone	.0502	114 ± 2	251 ± 2	786 ± 0.1	150	20.4 ± 0.2	−10.1 ± 0.7
Cyclohexanone	.0502	617 ± 3	1350 ± 30	4140 ± 60	793	20.1 ± .2	− 7.8 ± .8
Cycloheptanone	.0502	80.2 ± 0.9	169 ± 3	531 ± 6	101	20.2 ± .2	−11.6 ± .9
Cycloöctanone	.0502		1001 ± 14	3150 ± 60	603		
Acetone	.0502		86.2 ± 1.8				
Dipropyl ketone	.0502		93.5 ± 0.2				
Cyclopentyl phenyl ketone	.0502	13.8 ± 0.3					
Cyclopropyl phenyl ketone	.53			68.5 ± 1^d	1		
Cyclobutyl phenyl ketone	.53	299 ± 5	660 ± 10	2140 ± 10	31.2	20.7 ± 0.3	− 7.2 ± 1.2
Cyclopentyl phenyl ketone	.53	740 ± 6	1410 ± 20	4080 ± 30	60.5	17.9 ± .1	−14.8 ± 0.7
Cyclohexyl phenyl ketone	.53	32.7 ± 0.3	78.6 ± 1.2	293 ± 7	4.28	23.2 ± .4	2.7 ± 1.3

^{a} Reaction was catalyzed by hydrochloric acid of concentration indicated. ^{b} First-order rate constants in sec.$^{-1}$. ^{c} The rate constants *were not* corrected on the basis of the number of enolizable α-hydrogens. ^{d} The rate constant is a maximum value; see Results and Discussion.

tion of the homologous C_4-through C_8-cycloalkanones in 90% acetic acid as catalyzed by 0.05 *M* hydrochloric acid are summarized in Table I. Over the temperature range investigated the relative ordering of rates of enolization of the cycloalkanones as a function of ring size is 6 > 8 > 5 > 7 > 4. The rates of enolization of C_5- through C_8-cycloalkanones are considerably greater than those for acetone and dipropyl ketone. Where comparisons are possible, the present results are in general agreement with previous kinetic investigations[15]; there is limited correlation between the rates of acid-catalyzed enolization of the cycloalkanones and the enol contents of the ketones at equilibrium as recently reported.[16]

The greater rates of acid-catalyzed enolization of cyclic ketones than of comparable dialkyl ketones and the irregular order of reactivity of the cycloalkanones with respect to ring size indicate that these processes are controlled by steric, entropy and possibly solvation factors.[17] Such interpretation is consistent with the differences in structural requirements of solvated cyclic ketone and a near-enolic (endocyclic) transition state (I) as derived by attack of the nucleophile on α-hydrogen in axial positions. Enolization of cyclobutanone is apparently retarded with respect to its homologs because of strain effects upon near-introduction of the second trigonal atom; strain increase resulting from bond angle deformations in the small-ring transition state thus appears to be of greater significance than any effects such as removal of eclipsing,[18] solvation or entropy factors which may lower the energy of the transition state. The greater rate of acid-catalyzed enolization of cyclohexanone than cyclopentanone parallels their enol contents in water[16b] and is of theoretical significance in that in this system a 6-membered ring accepts a double bond more readily than does its 5-membered homolog.[19] The specific ordering of enolization of cycloheptanone and cycloöctanone presumably is related to the differences in conformational and solvation requirements of these exocyclic derivatives and their rate-controlling endocyclic transition states.

It is of interest to compare the present rates of enolization of the C_{4-8}-cycloalkanones in 90% acetic acid and the equilibria for enolization of cyclopentanone and cyclohexanone in water[16b] with thermodynamic data for the equilibria between methylenecycloalkanes and 1-methylcycloalkenes in glacial acetic acid at 25° (Table II).[20]

TABLE II

EQUILIBRIA BETWEEN METHYLENECYCLOALKANES AND 1-METHYLCYCLOALKENES IN ACETIC ACID AT 25°[22]

Ring size	$K_{endo/exo}$	$\Delta F°^a$	$\Delta H°^a$	$\Delta S°^b$
4	5.66	−1.05	−0.95	0.0
5	1144	−4.17	−3.9	+0.9
6	240	−3.24	−2.4	+2.8
7	74.4	−2.55	−2.3	+0.8
8	598	−3.79		

^{a} Kcal./mole ^{b} Cal./mole. °K.

Since there is a correlation between the rates of enolization of the C_4-, C_7- and C_8-cycloalkanones and the free energies of isomerization of the corresponding methylenecycloalkanes in similar sol-

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(15) First-order rate constants reported for enolization of cyclopentanone and cyclohexanone in 90% acetic acid as catalyzed by 0.0617 *M* hydrogen chloride at 25° are 4.61×10^{-5} and 1.34×10^{-3} sec.$^{-1}$, respectively.[9]

(16) In water the percentage of enol from cyclohexanone (20×10^{-3}) is greater than that from cyclopentanone (4.8×10^{-3}).[16b] For pure ketones in the absence of an external solvent, the percentage enol as a function of ring size is C_4, 0.55; C_5, 0.09; C_6, 1.18; C_7, 0.56; and C_8, 9.3; the order with respect to enol content under these conditions is $C_8 > C_6 > C_4 \geqq C_7 > C_5$.[16c] It is not necessary that the rates of acid-catalyzed enolization of cycloalkanones parallel their keto–enol equilibria. It has also been found that the enol content of a ketone is markedly dependent on the solvent environment.[16d] The present kinetic results in a single solvent are thus not strictly comparable to the equilibrium data for enolization of the pure cycloalkanones since in the latter system each ketone functions as its own internal solvent, and thus the polar and steric environment for enolization of each pure ketone is different. (b) G. Schwarzenbach and C. Wittmer, *Helv. Chim. Acta*, **30**, 656, 669 (1947). (c) A. Gero, *J. Org. Chem.*, **26**, 3156 (1961). (d) A. Gero, *ibid.*, **19**, 1960 (1954).

(17) The relative rates of enolization of the C_5 through C_8 cycloalkanones primarily reflect differences in the entropies of activation.

(18) Development of the transition state may allow removal of as much as a pair of non-bonded interactions.

(19) (a) H. C. Brown, J. H. Brewster and H. Shechter, *J. Am. Chem. Soc.*, **76**, 467 (1954); (b) H. C. Brown, *J. Org. Chem.*, **22**, 439 (1957).

(20) (a) A. C. Cope, D. Ambros, E. Ciganek, C. F. Howell and Z. Jacura, *J. Am. Chem. Soc.*, **82**, 1750 (1960); (b) E. Gil-Av and J. Herling, *Tetrahedron Letters*, **1**, 27 (1961); (c) R. B. Turner in "Kekulé Symposium on Theoretical Organic Chemistry," Butterworth Scientific Publications, London, 1959, p. 79.

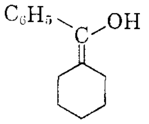
vents, it appears that the dominant structural features involved in enolization of these ketones and isomerization of these methylenecycloalkanes are similar.

Neither the equilibria nor the rates of enolization of cyclopentanone and cyclohexanone are of the same relative order ($C_6 > C_5$), however, as the equilibria for isomerization of methylenecyclopentane and methylenecyclohexane to their corresponding 1-methylcycloalkenes (Table II, $C_5 > C_6$).[20a,21] Since cyclopentanone and cyclohexanone served in part as the models for the generalization[19] that conversion of an *exo*-unsaturated 6-membered ring to its endocyclic isomer is favored when compared with corresponding 5-membered homologs, the lack of correlation with the *exo–endo* equilibria of methylenecyclopentane and methylenecyclohexane is of interest.[22,23]

Prediction of the abilities of methylenecyclohexane and methylenecyclopentane to undergo *endo* isomerization was based primarily on enolization data and thermochemical (enthalpy) correlations for cyclohexanone and cyclopentanone.[19] In extrapolating the conclusions with respect to the cyclic ketones to methylenecyclohexane and methylenecyclopentane it was presumed that because of eclipsing introduced between the exo-methylene hydrogens and the two equatorial hydrogen atoms in the α-positions of the cyclohexane ring there should be even greater relative tendency for the 6-membered ring becoming endocyclic. The reasons for the relative equilibria of isomerization of methylenecyclopentane and methylenecyclohexane and the lack of correlation with the enolization of cyclopentanone and cyclohexanone are not yet understood.[24] It is possible that the failure in correlation of abilities of these 5- and 6-membered derivatives to accommodate double bonds[25] stems primarily from the greater difference in solvation energies for isomerization of the cycloalkanones than for the methylenecycloalkanes,[26] or indeed that the non-bonded electrons on carbonyl oxygen have greater steric effects than previously envisioned.

The kinetics of bromination of homologous cycloalkyl phenyl ketones have been determined in 90% acetic acid–0.53 M hydrochloric acid. The first-order rate constants and the kinetic parameters for these reactions are included in Table I. The reactivity order with respect to ring size of the cycloalkyl groups in enolization of these ketones is 5 > 4 > 6 > 3.[27] The greater rates of reaction of cyclopentyl phenyl ketone than of cyclohexyl phenyl ketone indicate the importance of steric factors in these enolizations. The results are in agreement with previous correlations of steric effects in that 5-membered alicyclic rings have greater abilities for accepting trigonal atoms than do their 6-membered homologs.[28] The data also support the postulate that the structure of the rate-controlling transition state in the reactions is close to that of enol (III and IV).[5a,c]

The result of particular interest is that the rates of acid-catalyzed enolization of cyclobutyl phenyl ketone are considerably greater than those of cyclohexyl phenyl ketone and only slightly less than that of cyclopentyl phenyl ketone. It is to be expected that because of angle strain a 4-membered ring which is tetragonally substituted will resist conversion to its trigonally related enol, V.[28a] The relatively rapid rate of enolization of cyclobutyl phenyl ketone may result from the smaller *cis* steric effects in the transition state related to V than in those related to III and IV, and thus there is relatively large conjugative interaction of the benzal and cyclobutylidene groups with the developing carbon–carbon double bond. Additional features which may be expressed in the reactivity of cyclobutyl phenyl ketone are removal of 1,2-non-bonded interactions on enolization and



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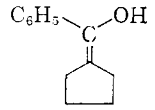

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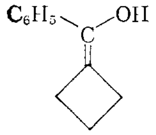
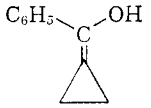


V



VI

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[21] The differences in free energy ($\Delta\Delta F°$) for enolization of cyclohexanone and cyclopentanone at 25° in the absence of an external solvent and in water are −1.52 and −0.85 kcal./mole; that for isomerization of methylenecyclohexane to 1-methylcyclohexene and of methylenecyclopentane to 1-methylcyclopentene at 25° is 0.93 kcal./mole.

[22] R. B. Turner, *J. Am. Chem. Soc.*, **80**, 1424 (1958).

[23] E. Gil-Av and J. Shabtai, *Chemistry & Industry*, 1630 (1959) have shown that the *exo-endo* equilibria for ethylidenecyclopentane and ethylidenecyclohexane, respectively, agree with the previous generalization concerning the abilities of 5- and 6-membered rings in accepting unsaturation.[19]

[24] (a) The fact that substituted 6-membered rings accept *endo* double bonds more readily than do analogous 5-membered systems appears to result primarily from greater *cis* steric interaction of the alkylidene substituents and α,α'-methylene hydrogen atoms in the rings of 6- than of 5-membered derivatives.[22,23,34b] (b) H. Shechter, D. E. Ley and E. B. Robertson, Jr., *J. Am. Chem. Soc.*, **78**, 4984 (1956).

[25] It has been previously proposed[22] that the correlation failure stems from differences in abilities of carbonyl and methylene groups to accept angle distortion in 5-membered rings or that cyclopentanone is relatively stabilized by hyperconjugation since its geometry is presumably more favorable for such hybridization than is cyclohexanone and the electrical demand of the carbonyl function is greater than that of the methylene group.

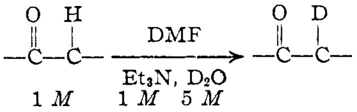
[26] Methylenecyclopentane, methylenecyclohexane and their corresponding 1-methylcycloalkenes are much less polar and thus less subject to solvation in polar media than are the 5- and 6-membered ketones and their corresponding enols. On the supposition that the interactions of a solvent are greater for the ketones than for the enols whereas those for the methylenecycloalkanes and 1-methylcycloalkenes are more similar, it is possible that cyclopentanone will be solvent stabilized relative to cyclohexanone because of its greater dipole moment, rigidity and more favorable stereochemistry. The relatively greater ground state energy of cyclohexanone than of cyclopentanone in such an environment may thus be expressed in the enolization equilibria and the rates of enolization.

[27] First-order rate constants reported for bromination of cyclopentyl phenyl ketone and cyclohexyl phenyl ketone in aqueous acetic acid–hydrochloric acid (0.0722 M) at 26.7° are 1.3×10^{-6} and 9.0×10^{-7} sec.$^{-1}$, respectively.[5a] These results are consistent with those of the present study.

[28] (a) H. C. Brown, R. S. Fletcher and R. B. Johannesen, *J. Am. Chem. Soc.*, **73**, 212 (1951); H. C. Brown and M. Borkowski, *ibid.*, **74**, 1894 (1952); (b) G. S. Hammond in M. S. Newman, "Steric Effects in Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1956, p. 444.

TABLE III

BASE-CATALYZED DEUTERIUM EXCHANGE RATES OF CYCLOALKANONES AND CYCLOALKYL PHENYL KETONES IN DMF



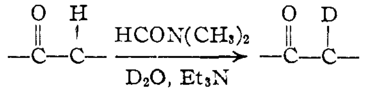
$$-\overset{\overset{O}{\|}}{C}-\overset{\overset{H}{|}}{\underset{1\,M}{C}}- \xrightarrow[\substack{Et_3N,\ D_2O \\ 1\,M\quad 5\,M}]{DMF} -\overset{\overset{O}{\|}}{C}-\overset{\overset{D}{|}}{C}-$$

Ketone	$k_1^{10°} \times 10^7$ [a,b]	$k_1^{30°} \times 10^7$	$k_1^{40°} \times 10^7$	$k_1^{50°} \times 10^7$	$k_1^{60°} \times 10^7$	$k_1^{80°} \times 10^7$	Rel. rates 40°	Ea, kcal. mole^{-1}	ΔS^*, e.u.
Cyclobutanone	140		2300				290	12.3	−31
Cyclopentanone	35	300	680				85	15.9	−26
Cyclohexanone			100	170	320		12	12.2	−42
Cycloheptanone			19	37	77		2.4	14.6	−37
Dipropyl ketone			8		38	138	1.0	15.5	−36
Diisopropyl ketone			0.6						
Cyclopropyl phenyl ketone			10		49		20	15.7	−38
Cyclobutyl phenyl ketone			8.4	19	31	165	17	16.8	−35
Cyclopentyl phenyl ketone			2.9	5.9	9.9	44	5.7	13.1	−48
Cyclohexyl phenyl ketone			0.5	1.2	3.0	14	1.0	17.0	−39
Isobutyrophenone			0.7		2.8	9.5	1.4	14.2	−49
Propiophenone			490	1700				13.1	−42
Acetophenone			2200					11.4	−39

[a] First-order rate constants in sec.$^{-1}$. [b] The rate constants *were* corrected for the statistical factor where necessary.

the relatively minimal steric restriction to solvation during reaction.[29] The relative inability of cyclopropyl phenyl ketone to undergo enolization is interpretable in terms of the large strain and rehybridizational energies involved in formation of a transition state similar to that of enol VI in which a double bond is attached to a 3-membered ring.[30,31]

Base-catalyzed Enolization.—Table III summarizes the first-order rate constants and the kinetic parameters for base-catalyzed isotopic exchange of α-hydrogen in the series of homologous cycloalkanones and cycloalkyl phenyl ketones (eq. 5) in deuterium oxide–triethylamine–dimethylformamide. It has been shown that in the system

 (5)

$$-\overset{\overset{O}{\|}}{C}-\overset{\overset{H}{|}}{C}- \xrightarrow[D_2O,\ Et_3N]{HCON(CH_3)_2} -\overset{\overset{O}{\|}}{C}-\overset{\overset{D}{|}}{C}- \qquad (5)$$

triethylamine–deuterium oxide the actual base involved in proton abstraction is deuteroxide ion (OD^-)[32]; thus steric factors involving the base are kept low in the transition state for enolization. The following correlations and conclusions may be drawn: (a) in cyclic ketones the rate of exchange decreases as the ring size increases ($4 > 5 > 6 > 7$) approaching as an approximate limit the open-chain analog dipropyl ketone; (b) in cycloalkyl phenyl ketones the rate of exchange decreases as the ring size increases ($3 > 4 > 5 > 6$) approaching as an approximate limit the open-chain analog isobutyrophenone[33]; and therefore (c) the order of reactivity with respect to ring size for base-catalyzed enolization of cyclic ketones and cycloalkyl phenyl ketones is decidedly different from that for the acid-catalyzed processes.

The ratios of rate constants k_4/k_5 and k_5/k_6 (where k_n refers to the rate constant for the n carbon ring size) are about the same in both series of ketones and suggest a common origin. With respect to base-catalyzed enolization,[2c] Swain, *et al.*, have more clearly delineated the details of the structure of the transition state II and concluded that there is little bond making between B and H in the transition state, but that the bond between H and C is nearly broken. Particularly for hydroxide ion catalysis, as in the present cases, "distances are long in the transition state," and "hydroxide ion supplies more driving force through coulombic and Pauli repulsions against the electron pair in the old bond than through covalent bond formation with hydrogen." This would also seem to suggest that the sequences of enoli-

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[29] First-order rate constants (sec.$^{-1}$) reported[8] for bromination of the following ketones in 75% acetic acid–0.5 *M* hydrochloric acid at 25° are: acetophenone, 0.241; propiophenone, 0.104; butyrophenone, 0.0721; valerophenone, 0.0851; isobutyrophenone, 0.0213; and isovalerophenone, 0.0325. Present interpretation of these results indicates that steric effects (*cis* and solvation) in enolization are of importance along with possible hyperconjugative and inductive factors previously described.[7a,8]

[30] The authors wish here to emphasize that the rate constant presently reported for acid-catalyzed bromination of cyclopropyl phenyl ketone is a *maximum* value. The reaction product isolated contained more than one equivalent of bromine and the structures of the various components have not been determined.

[31] Acid-catalyzed bromination of 7-ketocholestane yields 6-bromo-7-ketocholestane rather than 8-bromo-7-ketocholestane. The reaction is of interest in that the 6,7-enol which leads to product is derived by enolization of secondary rather than tertiary hydrogen and thus is of the Hofmann rather than the Saytzeff type. The result has been discussed previously[9] on the basis that an equilibrium exists between the two enols which favors the Δ^7-isomer; however, attack of bromine on the once-formed Δ^7-enol is impeded by the angular methyl groups on C-10 and C-13 and hence the ultimate reaction involves the 6,7-enol. The authors wish here to suggest a more conventional[3,4] alternate mechanism in which, because of steric factors, the 6,7-enol is formed much more rapidly than the Δ^7-isomer; bromination of the 6,7-enol in a step which is not rate-determining gives 6-bromo-7-ketocholestane. Decision as to the possible mechanism of acid-catalyzed bromination of 7-ketocholestane can be made upon determining the rates of deuteration and bromination of the ketone under identical conditions.

[32] Evidence for this conclusion is the fact that E_a-values for NaOD and "Et$_3$N" catalysis in the ketone series are identical, and no steric effect is observable in $k^{NaOD}/k^{''Et_3N''}$ ratios for a series of ketones with increasing steric requirements. Rough calculations of the catalytic constants for Et$_3$N and OD^- species support this; *cf.* ref. 13.

[33] Ultraviolet and gas chromatographic analysis of the exchange mixtures indicated that there were no products derived by dehydration of possible intermediates obtained by aldol condensation. Because the kinetic plots were well-behaved, formation of protium oxide by any process competitive with deuterium exchange could not have been appreciable, *e.g.*, non-dehydrated aldol condensation.

zation rates for cyclic and cycloalkyl phenyl ketones found in the present study are not a reflection of steric hindrance involving the base.

Application of the concepts involved in the stabilities of *exo* and *endo* double bonds in cyclic systems[19] and the factors involved in the ability of a carbocyclic ring to have one of its members undergo a coördination number change of four to three fail to correlate the present data.

One possible explanation that seems to agree with the experimental results centers around the position of the transition state along the reaction coördinate, and is concerned with the effect of hybridization of the ring carbons on the acidity of the hydrogens attached.

Cardwell and Kilner[7c] suggest that much more unsaturation develops, through partial carbonium ion formation, in the transition state for acid-catalyzed enolization than in the base-catalyzed reaction. It is therefore suggested that the transition state for base-catalyzed enolization occurs *early* in the process, and has its energy determined to a large extent by factors affecting the ketone, unlike that for acid-catalyzed enolization, which occurs much later and has its energy determined to a larger extent by steric and hybridization factors in the enol.

Coulson and Moffitt[34] have calculated the hybridization coefficients for a series of cycloalkanes, acetylene and ethane, with the results: cyclo-C_3H_6, 1.51; cyclo-C_4H_8, 1.67; cyclo-C_5H_{10}, 1.73; C_2H_6, 1.73; C_2H_4, 1.41; C_2H_2, 1.36. This coefficient reflects the s-character of the carbon orbital directed toward hydrogen and thus in part expresses the ionic character of the C–H bond.

This effect is, of course, evident in the carbonyl stretching frequencies for cycloalkanones which increase as one goes from cyclohexanone to cyclobutanone.[35] The effect is also reflected in the basicities of these ketones as measured by hydrogen bonding[36a] or by ultraviolet spectral shifts,[36b] $7 > 6 > 5 > 4$.

If one assumes a transition state that resembles factors (ketones) more than the product (enol), or one in which the α-carbon atom is predominantly sp^3-hybridized, one would conclude, combining Swain's postulated mechanism for enolization which involves long distances, and Pauli repulsion at the α-C–H unit, and the relative acidities of hydrogens attached to succeedingly smaller carbocyclic rings, that a sequence of exchange rates $(3) > 4 > 5 > 6 > (7)$ is consistent.

It is interesting that the cycloalkanones exchange more rapidly than the cycloalkyl phenyl ketones.

It is to be noted that in the changes in E_a and $\Delta S^{\ddagger}$, a facet other than just "acidity" of the α-hydrogen is to be detected. Presumably the fluctuations are to be attributed to solvation and steric effects. However, since strict compartmentalizing of solvent and steric effects into the energy parameter does not occur, it is at present not profitable to dissect the data further.

The reported equivalent acidity of cyclopropyl phenyl sulfone[37] and isopropyl phenyl sulfone is not relevant here since the comparison was made on an equilibrium (thermodynamic) basis rather than a kinetic one. Cyclopentyl phenyl sulfone and cyclohexyl phenyl sulfone exchange their α-H's for D at more nearly equal rates[38]; $k_5/k_6 \cong 1.5$. In the analogous ketones $k_5/k_6 = 6$.

Work in the sulfone area, which is currently in process, we hope will shed some light on the differences in α-H activation by carbonyl and sulfone groupings. The recent work by Cram,[39] indicating the markedly different steric courses followed by these substrates in D/H exchange reactions, suggests a distinct difference.

Acknowledgments.—R.E.D. wishes to thank Professors H. H. Jaffé and H. Zimmerman for several valuable discussions.

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[CONTRIBUTION NO. 165 FROM THE GRADUATE DEPARTMENT OF BIOCHEMISTRY, BRANDEIS UNIVERSITY, WALTHAM 54, MASS.]

The Nucleophilic Reactivity of Alcoholate Anions Toward *p*-Nitrophenyl Acetate

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The nucleophilic reactivity of a series of alcoholate anions toward the ester, *p*-nitrophenyl acetate, has been determined by measurement of reaction rates in dilute, buffered solutions or by measurement of product ratios after base-catalyzed solvolysis of the ester in alcohol–water mixtures. Strongly basic oxygen anions show only a slight increase in reactivity with increasing basicity, and thus deviate from the Brønsted relationship of slope 0.76–0.80 observed with less basic oxygen anions.

It was shown recently that, near neutral *p*H, the base-catalyzed reaction of *p*-nitrophenyl acetate with the hydroxyl group of N-acetylserinamide is much faster than the base-catalyzed hydrolysis or ethanolysis of this ester.[1] Bruice, *et al.*, found that the pK_a of N-acetylserinamide is 13.6 and that the reactivity of its anion toward *p*-nitrophenyl acetate does not deviate signifi-

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