Nuclear Magnetic Resonance Studies of the Mechanism of Keto–Enol Tautomerism in 3-Hydroxy-2,4-dimethylcyclobutenone. II. Solvent and pH Effects

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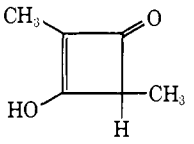
Abstract: An nmr method is applied to a study of prototropic shifts in a highly enolized system. The temperature-dependent nmr spectrum of 3-hydroxy-2,4-dimethylcyclobutenone (**1**) has been examined as a function of pH, and the nmr rates obtained were analyzed according to the general acid–base catalysis scheme. In the low pH limit investigated (pH ~0), the nmr rates are insensitive to the concentration of **1**. At higher pH, the rates become concentration dependent. Rates were found dependent on the water concentration. The pH–rate profile is explained on the basis of two competing reactions, both involving the enolate ion of **1** and proceeding by way of 2,4-dimethyl-1,3-cyclobutanedione. Activation parameters, E_a of 13.6 and 13.2 kcal/mol and ln A of 28.9 and 24.7 sec^{-1}, were calculated at pH 1.6 and 2.8, respectively, and a solvent deuterium isotope effect, k_{H_2O}/k_{D_2O}, of 5.0 ± 1.0 and 3.0 ± 1.0 was observed.

Enolization, and subsequently ketonization, comprises the most familiar form of prototropic tautomerism.[1] Numerous techniques that include halogen titrations, acidimetric methods, and spectrophotometric methods have been widely used to study equilibria in tautomeric systems.[2] Recently, nuclear magnetic resonance spectroscopy including ^{17}O studies[3] and double resonance,[4] relaxation methods,[5] and other studies[6] have also been applied to investigate this phenomenon. Often, however, unfavorable equilibrium constants limit the effectiveness of these techniques. A considerable number of cyclic systems, ranging from the aromatic tropolones[7] and phenols[8] to 1,2- and 1,3-diketones in small and medium size rings, favor one tautomer. Equilibrium constants and rates of protopropic shifts in these systems are not in general attainable by these methods. In fact, the kinetics of prototropic shifts have rarely been determined directly;[6] instead rates of racemization, isotope exchange, and other indirect methods have commonly been employed.[2]

Recently, we reported a study of enol–keto tautomerism employing a spin memory technique to obtain information concerning the mechanism of prototropy in an interesting and well-studied system,[9,10] 2,4-dimethyl-3-hydroxycyclobutenone (**1**). We report herein



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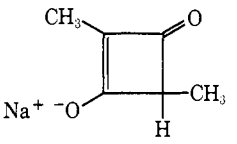

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how additional qualitative and quantitative information about the little studied ketonization of enols can be obtained. The technique, used frequently in the study of pyramidal inversion of amines,[11] takes advantage of the pH dependence of the dynamic nuclear magnetic resonance spectrum expected of tautomeric systems, when rates of prototropy are on the nmr time scale.

Results

As previously reported,[9] the room-temperature spectrum of **1** consists of a pair of doublets centered at τ 8.9 and 8.58 with methine methyl coupling constants of 7.0 and 2.5 Hz, respectively. In aqueous solutions at 115°, the methyl resonances appeared as a slightly broadened singlet with line shapes that were concentration independent as determined over a sixfold dilution. On the basis of the molecular weight measured in water (calcd 112, found 128), **1** appears to be monomeric in this medium.

When the pH of solutions of **1** was varied (at constant temperature 97°), significant changes in the rate of methyl group exchange ($rate_{exch}$) were observed. The

(1) L. N. Ferguson, "The Modern Structural Theory of Organic Chemistry," Prentice-Hall, Englewood Cliffs, N. J., 1964, pp 368–379; E. S. Gould, "Mechanism and Structure in Organic Chemistry," Holt, Rinehart and Winston, New York, N. Y., 1959, pp 376–384; G. S. Hammond in "Steric Effects in Organic Chemistry," M. S. Neuman, Ed., Wiley, London, 1956, pp 445–454.

(2) For a recent review of enolization, see S. Forsen and M. Nilsson in "The Chemistry of the Carbonyl Group," Vol. II, J. Zabicky, Ed., Interscience, New York, N. Y., 1970, pp 157–240.

(3) M. Gorodetsky, Z. Luz, and Y. Mazur, *J. Amer. Chem. Soc.*, **89**, 1183 (1967); A. Yogev and Y. Mazur, *J. Org. Chem.*, **32**, 2162 (1967).

(4) S. Forsen and R. Hoffmann, *J. Chem. Phys.*, **39**, 2892 (1963); S. Forsen, F. Merinyi, and M. Nilsson, *Acta Chem. Scand.*, **18**, 1208 (1964); **21**, 620 (1967).

(5) M. Eigen and L. de Maeyer in "Technique of Organic Chemistry," Vol. 8, Part 2, A. Weissberger, Ed., Interscience, New York, N. Y., 1963, p 895; M. Eigen, W. Kruse, G. Maass, and L. De Maeyer, *Progr. React. Kinetics*, **2**, 285 (1964).

(6) For two examples of direct observations of prototropic shifts in simple enols and ketones, see H. M. R. Hoffmann and E. A. Schmidt, *J. Amer. Chem. Soc.*, **94**, 1373 (1972); E. W. Garbisch, Jr., *ibid.*, **87**, 4971 (1965).

(7) D. Lloyd, "Carbocyclic Non-Benzenoid Aromatic Compounds," Elsevier, New York, N. Y., 1966, Chapter 6.

(8) G. W. Wheland, "Advanced Organic Chemistry," 3rd ed, Wiley, London, 1960, Chapter 14.

(9) J. S. Chickos, D. W. Larsen, and L. E. Legler, *J. Amer. Chem. Soc.*, **94**, 4266 (1972).

(10) D. G. Farnum, M. A. T. Heybey and B. Webster, *ibid.*, **86**, 673 (1964); D. G. Farnum, J. R. Johnson, R. E. Hess, and B. Webster, *ibid.*, **87**, 5191 (1965); D. G. Farnum, M. A. T. Heybey, and B. Webster, *Tetrahedron Lett.*, 307 (1963); R. B. Woodward and G. Small, Jr., *J. Amer. Chem. Soc.*, **72**, 1297 (1950).

(11) M. Saunders and F. Yamada, *J. Amer. Chem. Soc.*, **85**, 1882 (1963); W. R. Morgan and D. E. Leyden, *ibid.*, **92**, 4527 (1970); J. J. Delpuech, J. Ducom, and V. Michon, *Bull. Soc. Chim. Fr.*, 1848 (1971); J. L. Sudmeier and G. Occupati, *J. Amer. Chem. Soc.*, **90**, 154 (1968).

Table I. Dependence of $Rate_{exch}$ on pH and Concentration[a]

[HA][a]	[HA] + [A]	$P_A k_4[H_3O^+] + P_{HA}k_2[H_2O]$	$P_A k_6[HA]$	$Rate_{exch}$ Calcd[b]	$Rate_{exch}$ Obsd[c]	pH
0.44	0.44	19.1	0.1	19.2	15	−0.37[d]
0.48	0.48	18.8	2.5	21.3	18	1.0[e]
0.515	0.515	18.3	7.6	26.9	24	1.5[f]
0.463	0.463	18.0	8.5	26.5	20	1.6
0.275	0.275	17.7	6.3	24.0	22	1.7
0.093	0.093	16.7	3.5	20.2	23	2.0
0.393	0.449	16.7	16.7	33.4	31	2.0
0.396	0.494	15.3	26.8	42.1	46	2.2
0.368	0.485	14.5	30.4	44.9	54	2.3
0.297	0.507	11.2	41.9	53.1	62	2.6
0.388	0.653	11.3	53.6	64.9	69	2.6
0.175	0.348	9.6	29.6	39.2	40	2.8
0.306	0.608	9.6	51.7	61.3	59	2.8
0.356	0.711	9.6	60.6	70.2	68	2.8
0.361	0.728	9.5	62	71.5	72	2.8
0.388	0.898	8.3	75.1	83.4	82	2.9
0.213	0.512	7.9	42.4	50.3	53	3.0
0.378	1.16	6.2	86.9	93.1	80	3.1
0.174	0.495	6.7	38.4	45.1	50	3.1
0.073	0.488	2.9	21.2	24.1	26	3.6
0.065	0.525	2.4	19.4	21.8	19	3.7
	0.5			7×10^{-4}	$\sim 10^{-4}$	8.2

[a] Added HA (mol/l.), solvent: H_2O, estimated error in concentrations, 10%. [b] Calculated using values of 1.2×10^4 and 340.7 M^{-1} sec^{-1} for k_2 and k_4. [c] Average of three runs, average deviation: approximately 15% of $rate_{obsd}$. [d] In 2.5 *N* HCl. [e] In 0.1 *N* HCl. [f] In 0.01 *N* HCl. [g] At 97°.

Table II. Effect of the Water Concentration on $Rate_{exch}$

[1][a]	$Rate_{exch}$[b,c]	$[H_2O]$[a]	$Rate_{exch}$ *vs.* $[H_2O]$
In DMSO-d_6			
0.85	5.4	9	0.6
0.70	9.8	17.2	0.6
1.58	9.0	18.4	0.5
0.60	12.6	22.7	0.6
0.47	16.5	29.8	0.6
0.34	18.0	36.8	0.5
0.48	24.0	55.5	0.4
In DMF			
0.72	9.9	14.0	0.7
0.58	13.6	21.7	0.6
0.47	18.5	28.2	0.7
0.38	19.6	33.0	0.6
0.40	20.9	40.5	0.5
0.48	24.0	55.5	0.4

[a] Concentration in moles/liter (20°). [b] Rates of methyl group interconversion. [c] At 97°.

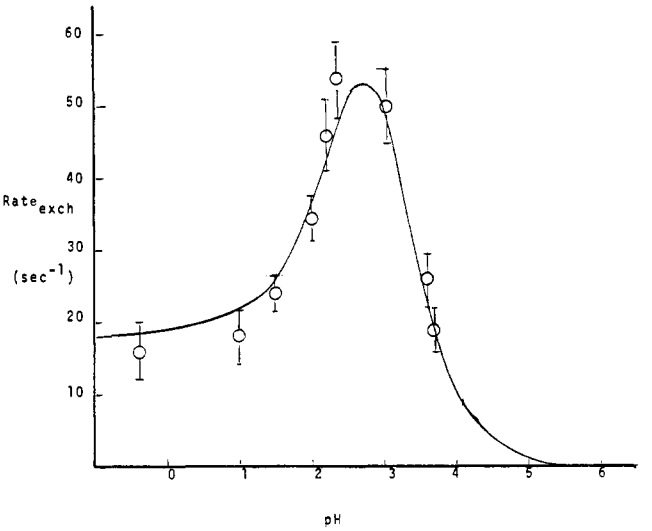


Figure 1. Variation in rate ($rate_{exch}$) with respect to a pH at a total concentration of approximately 0.5 *M* (**1** and **2**). Solid line: calculated rate from eq 5; estimated error in experimental points from three determinations.

pH–rate profile consisted of two regions, a pH and concentration insensitive region at low pH (pH 0–2) and a pH and concentration dependent region at medium pH (pH 3–5). A profile of the experimental rate ($rate_{exch}$) *vs.* pH is shown in Figure 1. Since this profile consists of both a concentration sensitive and insensitive region, the rates shown were obtained by keeping the sum of the total concentrations of **1** and the anion, **2**, constant. These and additional data from runs in which the concentrations were varied are shown in Table I. The maximum rate, corresponding to a concentration of $\mathbf{1} + \mathbf{2} \approx 0.5$ *M*, was obtained at a pH approximately equal to the pK_a of **1**. Further increases in pH drastically reduced the rate.

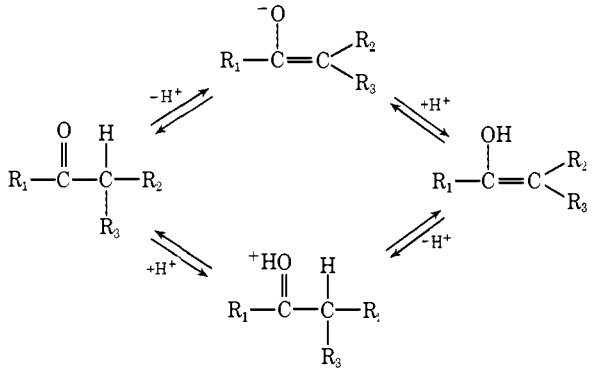
In addition to being pH dependent, the line shapes were also solvent dependent. Thus, when **1** was dissolved in dry dioxane, dimethylformamide (DMF), dimethyl-d_6 sulfoxide (DMSO-d_6), or acetic-d_3 acid, the pair of nmr doublets of **1** was clearly resolved at temperatures where complete collapse had occurred in aqueous solutions. In DMSO-d_6, for example, no line broadening was observed up to 126°. Above 126°, **1** rapidly decomposed. On the basis of the minimum rate constant which leads to a detectable amount of line broadening, methyl group interconversion must be occurring at least two orders of magnitude more slowly in DMSO-d_6 than in water. The failure to observe any line broadening in nonaqueous solvents prompted us to examine the line shapes as a function of the water concentration in both DMSO-d_6 and DMF. The results of these studies are shown in Table II. The rates as determined by line-shape analysis are clearly dependent upon the water concentration in both solvents. The ratio of the observed rate ($rate_{exch}$) to the water concentration, column 4 in Table II, is approximately a constant, essentially invariant with the water concentration

and independent of solvent. The importance of water in effecting the observed line shapes is further illustrated by the magnitude of the deuterium isotope effect. Values of k_{H_2O}/k_{D_2O} of 5.0 ± 1.0 and 3.0 ± 1.0 were obtained at a pH of 1.6 and 2.8, respectively.

Kinetics

Two main mechanisms have been proposed for keto–enol tautomerism.[2,12] The most generally applicable mechanism, recently demonstrated in the ketonization of the enol of cyclohexanone,[13] involves a series of consecutive reactions proceeding through cations and anions and subject to acid–base catalysis (Scheme I).

Scheme I



The other mechanism[14] appears to be of minor importance for reactions in aqueous solutions and will not be considered.[16]

The rate expression for tautomerism involving general acid and base catalyses (Scheme I) is given by[12]

$$\text{rate} = \Sigma k_i(A_iS) + \Sigma k_j(B_jS)$$

where k_i, k_j are the catalytic constants, A_i and B_j are the acids and bases present, and S is the substrate reacting. In this system the expanded rate expression takes the general form of eq 1 since both the acid HA (**1**) and its conjugate base (A, **2**) can be involved in the rate process. The equation contains 12 terms, half involving acid catalysis (k_1–k_6) and the remaining 6 involving base catalysis (k_7–k_{12}).

$$\begin{aligned}\text{rate}_{exch} = {} & k_1[HA][H_3O^+] + (k_2 + k_7)[HA][H_2O] + \\ & k_3[HA]^2 + k_4[A][H_3O^+] + (k_5 + k_{10})[A][H_2O] + \\ & (k_6 + k_8)[HA][A] + k_9[HA][OH^-] + \\ & k_{11}[A]^2 + k_{12}[A][OH^-] \quad (1)\end{aligned}$$

If base catalysis of this system (**1**) is important in the pH range under consideration, cyclobutadienoid intermediates should be generated. This possibility can be tested by the line-shape arguments previously presented,[9] since such would give rise to complete loss of spin memory at the methine position regardless of where proton capture occurs. In contrast, acid catalysis results in a loss of spin memory only if the methyl groups in **1** are interconverted. Consequently, the two processes give rise to different calculated line shapes. A comparison of the observed line shapes with those calculated for both acid and base catalysis as a function of pH and temperature has been carried out. The line shapes[17] clearly indicate that base catalysis in this system can be considered relatively unimportant. Therefore eq 1 reduces to six terms, k_1–k_6.

The rates (rate_{exch}) observed in this study are the sum of the reciprocal lifetimes of the species reacting; this includes both **1** (HA) and its conjugate base, **2** (A, eq 2). Since the process detected by nmr is a rate of

$$\text{Nmr rate}\left(\frac{1}{\tau}\right) = \frac{1}{\tau_{HA}} + \frac{1}{\tau_A} \quad (2)$$

equilibration (of methyl groups), the line shapes are independent of the concentration of the substrate equilibrating (eq 3). The mole fractions P_{HA} and P_A are

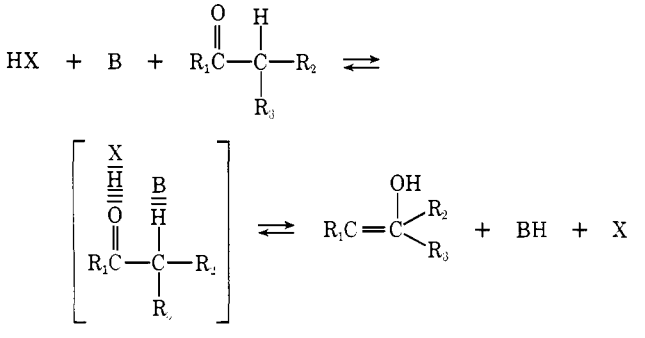
$$\text{Nmr rate}_{exch}\left(\frac{1}{\tau}\right) = P_{HA}\frac{d[HA]}{[HA]}\frac{1}{dt} + P_A\frac{d[A]}{[A]}\frac{1}{dt} \quad (3)$$

included in the rate process because the average lifetime of each species is pH dependent.[11,18] The nmr rate for a general acid catalyzed interconversion of methyl groups can thus be expressed as eq 4. As a

$$\begin{aligned}\text{Nmr rate}_{exch}\left(\frac{1}{\tau}\right) = {} & P_{HA}k_1[H_3O^+] + P_{HA}k_2[H_2O] + \\ & P_{HA}k_3[HA] + P_Ak_4[H_3O^+] + P_Ak_5[H_2O] + \\ & P_Ak_6[HA] \quad (4)\end{aligned}$$

$$\begin{aligned}\text{Nmr rate}_{exch}\left(\frac{1}{\tau}\right) = {} & P_{HA}k_2[H_2O] + P_Ak_4[H_3O^+] + \\ & P_Ak_6[HA] \quad (5)\end{aligned}$$

qualitative aid, a graphical representation of the variation of each of the six terms in eq 4 with respect to pH is shown in Figure 2. A comparison of the pH profile of these terms[19] with the observed pH–rate profile of **1**, Figure 1, suggests that several of these terms are not important in the pH region under consideration. A least-squares analysis of the data in Table I concurred with this interpretation. The terms containing k_2 and



(12) R. P. Bell, "The Proton in Chemistry," Cornell University Press, Ithaca, N. Y., 1959, p 140.

(13) G. Lienhard and T. C. Wang, *J. Amer. Chem. Soc.*, **91**, 1146 (1969).

(14) The so-called concerted process, also subject to acid–base catalysis, appears to be important only in special cases.[2,15] However, the kinetic expressions for the concerted process also fit the data. For a review of bifunctionally catalyzed reactions, see J. P. Li, *Aldrichimica Acta*, **5**, 5 (1972).

(15) R. P. Bell, "Acid Base Catalysis," Oxford University Press, London, 1941.

(16) Reference 12, p 154.

(17) The line shapes obtained in the pH region studied were comparable to those previously reported.[9] The interpretation thereof is subject to the same restrictions. Chemical shifts were solvent and pH dependent. The maximum difference in chemical shifts, however, was only about 1 Hz. No attempt was made to correct for this difference in chemical shift. Coupling constants were invariant to both solvent and pH.

(18) A rapid equilibrium between A (**2**) and HA (**1**) is assumed.

(19) The curve of rate_{exch} *vs.* pH (Figure 1) is a continuous function of pH only if the sum of the concentrations of **1** and **4** is kept constant. Equation 4 can thus be written with **1** or **4** as the only independent variable.

Table III. Contributions of the Terms for Acid Catalysis to the Rate[a]

Rate constant	k_{calcd},[b] M^{-1} sec^{-1}	Term	pH 1[c] $rate_{exch}$	pH 1.7[c] $rate_{exch}$	pH 2.8[c] $rate_{exch}$	pH 3.6[c] $rate_{exch}$	k_{calcd},[d] M^{-1} sec^{-1}
k_1	−1.7	$P_{HA}k_1[H_3O^+]$	−0.17	−0.031	0.001	−0.00004	0
k_2	0.43	$P_{HA}k_2[H_2O]$	23.3	22.0	12.0	3.0	0.35
k_3	−11.8	$P_{HA}k_3[HA]$	−5.2	−2.4	−0.10	−0.09	0
k_4	14,900	$P_Ak_4[H_3O^+]$	23.3	22.0	12.0	3.0	12,000
k_5	0.0052	$P_Ak_5[H_2O]$	0.004	0.022	0.14	0.25	0
k_6	337	$P_Ak_6[HA]$	2.6	5.8	29.6	19.4	341
	Experimental rate ($rate_{exch}$)		18	22	40	26	

[a] At 97°. [b] Calculated rate constants for methyl group interconversion by a least-squares treatment. [c] Maximum contribution of each respective term to the overall rate. [d] Rate constants calculated by least-squares treatment with k_1, k_3, and k_5 set equal to zero.

Table IV. Arrhenius Activation Parameters[a]

Rate constants[b]	E_a, kcal	ln A, sec^{-1}	$\Delta G^{\ddagger}$, kcal	$\Delta H^{\ddagger}$, kcal	$\Delta S^{\ddagger}$, kcal	Correl coeff	pH
k_{pseudo} (2 × $rate_{exch}$)[c]	13.6	22.4	18.9	12.8	−16	0.998	1.6
$k_{2(ke)}$ ($rate_{ke}/([H_2O]P_{HA})$)[c]	13.6	18.46	21.7	12.8	−24	0.998	1.6
$k_{4(ke)}$ ($rate_{ke}/([H_3O^+]P_A)$)[c]	13.6	28.9	14.1	12.8	−3.4	0.998	1.6
$k_{6(ke)}$ ($rate_{ke}/([HA]P_A)$)	13.2	24.7	16.6	12.5	−11.7	0.995	2.8

[a] Activation parameters were calculated by a least-squares treatment. [b] Rate constants for keto–enol tautomerism (2 × $rate_{exch}$). [c] Activation parameters for this process were calculated from the activation energy and frequency factor previously reported.[9]

k_4, in eq 4, although differing both in appearance and mechanistic implication, represent the same mathematical function. Thus, substituting the ionization expression for a weak acid for the hydronium ion concentration converts the term containing k_4 in eq 4 to a form ($p_{HA}k_4K_a[H_2O]$, where K_a is the acidity constant of **1**) indistinguishable from the term containing k_2. Thus only the sum of these two terms can be determined by kinetic methods. In an aqueous solution of **1** alone (pH 1.6), the sum of the k_2 and k_4 terms is the major contributor to the rate ($rate_{exch}$). At low pH, both terms are essentially independent of the concentration of **1** and insensitive to small changes in pH and concentration. This behavior is consistent with the insensitivity of the line shapes to changes in the concentration of **1** as cited above.

The expression containing k_6 is the term mainly responsible for the "bell-shape" variation in rate at intermediate pH and it is this term which is responsible for the observed concentration dependence. This dependence of the $rate_{exch}$ on concentration is also shown in Table I. Increasing the concentration of **1** while keeping the ratio of **1** to **2** constant at pH 2.8 resulted in an increase in the observed rate. This behavior is characteristic of general acid catalysis.[20]

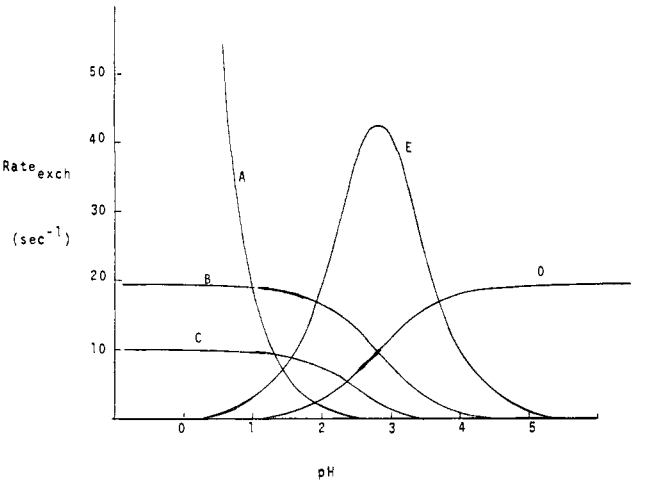


Figure 2. Rate *vs.* pH variation of each term in eq 4. A, $P_{HA}k_1[H_3O^+]$: concentration insensitive term; B, $P_{HA}k_2[H_2O]$: concentration insensitive term; B, $P_Ak_4[H_3O^+]$: concentration insensitive term; C, $P_{HA}k_3[HA]$: concentration dependent term; D, $P_Ak_5[H_2O]$: concentration insensitive term; E, $P_Ak_6[HA]$: concentration dependent term.

Calculations

Least-Squares Analysis. The results from the least-squares analysis are shown in Table III. The values for k_2 and k_4 shown in column 1 were obtained by assuming a value of zero for the other; thus they are maximum values. The contribution that each of these terms make at various pH ranges is shown in columns 4–7. The experimental rate is given in the last entry. Column 8 contains the rate constants recalculated with k_1, k_3, and k_5 set equal to zero. This simplifies eq 4 to eq 5.

Activation Parameters. Activation parameters were calculated at a pH of 1.6 and 2.8 on the basis of mechanism A. These two regions were chosen to best separate the contributions of the k_2 (and/or k_4) term from the k_6 term. It was not possible, however, to completely freeze out competing terms, successively, *e.g.*, the k_6 term at pH 1.6 and the k_2 and k_4 terms at pH 2.8 (see Table III); therefore the activation parameters shown in Table IV are subject to this error (see Experimental Section).

Activation parameters were calculated on the assumption that dimethylcyclobutenedione (**3**) is an intermediate in this process. The rates of keto–enol tautomerism differ from the rates of methyl group exchange by a statistical factor of 2 ($rate_{ke}$ = 2 × $rate_{exch}$). The first entry in Table IV lists the activation parameters previously calculated for keto–enol tautomerism assuming a pseudo-first-order process. The second and third entries list the activation parameters for the k_2 term (assuming k_4 = 0) and the k_4 term (assuming

(20) J. Hine, "Physical Organic Chemistry," 2nd ed, McGraw-Hill, New York, N. Y., 1962, Chapter 5.

Table V. Rates of Protolysis and Hydrolysis (at 25°)

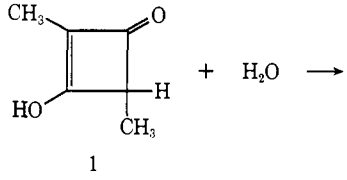
Compd	Reaction	k_p	k_h	Ref
Acetylacetone	$H_3O^+ + \text{enolate} \rightleftharpoons \text{enol} + H_2O$	3×10^{10}	1.7×10^2	*a,b*
	$H_3O^+ + \text{enolate} \rightleftharpoons \text{keto} + H_2O$	1.2×10^7	1.4×10^{-2}	*a,b*
Acetic acid	$H_3O^+ + CH_3CO_2^- \rightleftharpoons CH_3CO_2H + H_2O$	4.5×10^{10}	8×10^5	*a,c*
Water	$H^+ + OH^- \rightleftharpoons H_2O$	1.3×10^{11}	2.6×10^{-5}	*a,d*
1	$\mathbf{2} + H_3O^+ \rightleftharpoons \mathbf{3} + H_2O$	$\sim 3 \times 10^2$	$\geqslant 10^4$	

[a] Reference 2, pp 148, 150. [b] M. Eigen and W. Kruse, *Z. Naturforsch.*, **186**, 857 (1963). [c] M. Eigen and J. Schoen, *Z. Elektrochem.*, **59**, 483 (1955). [d] M. Eigen and L. de Maeyer, *ibid.*, **59**, 986 (1955).

$k_2 = 0$). The last entry contains the activation parameters calculated at a pH of 2.8 where the term containing k_6 is the major contributor to the rate.

Discussion

The general acid catalysis observed for the nmr line shapes of **1** clearly demonstrates the mechanistic similarity of tautomerization in enols to the more familiar prototropy observed in ketones. Two, possibly three, competing processes are consistent with the previous line-shape arguments and eq 5. The k_2 term can be represented mechanistically as a slow protonation of **1** at carbon by water to yield after rapid H^+ loss, 2,4-dimethylcyclobutane-1,3-dione (**3**). The k_4 and k_6



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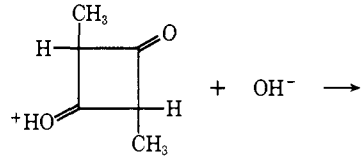

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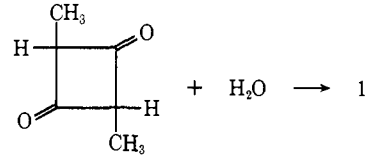
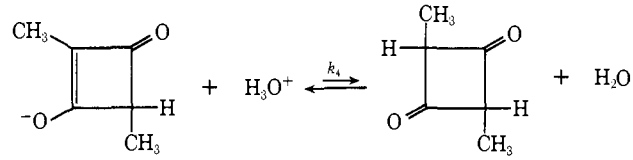


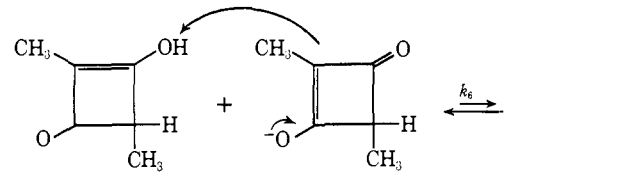
3

terms are representative of the alternative protonation pathways available to **3**. In view of the failure to observe acid catalysis of **1** in the region, $0.37 < \text{pH} < 1.6$ (see Figure 1), it can be safely concluded that any terms involving the protonation of **1** are relatively unimportant. Consistent with this interpretation are the solvent effects previously mentioned. The failure to observe line broadening in glacial acetic acid, a medium considerably better than water both for proton donation and for generating a weaker conjugate base, eliminates the k_2 term as a major contributor to the rate. The relative kinetic[21] and thermodynamic basicities[22] of carbon and oxygen of similar systems are also in agreement with this conclusion. Protonation of **1** would be expected to give "nmr inactive" **4** rather than **5** as the acid strength is increased.

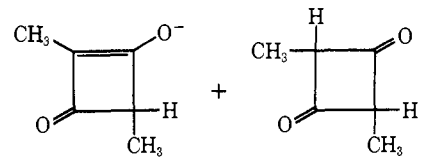
The observed rate dependence on the water concentration (Table II) is not inconsistent with this interpretation since ionization of **1** should be suppressed in nonaqueous solvents. The failure to observe line broadening in polar aprotic solvents such as acetonitrile and dimethyl sulfoxide is also consistent with a mechanism of catalysis of **2** rather than **1** and suggests that the barrier for the "pseudointramolecular" proton transfer mechanism[2,23] must be substantially higher by at least 3.5 kcal/mol.



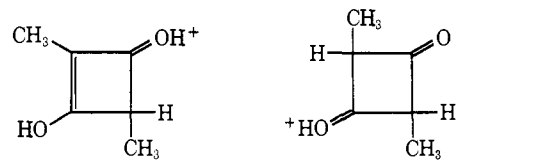
2 3



1 2



2 3



4 5

The remaining terms in the rate expression for this system, k_4 and k_6, suggest that the pathway to the cyclobutanedione intermediate, **3**, is through the enolate anion, a process general acid catalyzed. The magnitude of the solvent deuterium isotope effect at both pH 1.6 and 2.8 is also in agreement with proton transfer occurring in the rate determining step of the reaction.[25]

The rates of protolysis and hydrolysis of acetylacetone provide an interesting comparison (Table V) with the results of this study. A factor of 10^3 differentiates the rate of proton capture at carbon *vs.* capture at oxygen by the enolate anion of acetylacetone, the latter being

(21) I. Amdur and G. Hammes, "Chemical Kinetics," McGraw-Hill, New York, N. Y., 1966, p 152.
(22) G. Olah and M. Colin, *J. Amer. Chem. Soc.*, **90**, 4672 (1968).
(23) A purely intramolecular proton transfer in **1**[24] would be expected to give rise to two closely spaced doublets in the ratio of 2:1 in fast exchange limit.
(24) D. J. Cram, "Fundamentals of Carbanion Chemistry," Academic Press, New York, N. Y., 1965, p 175.
(25) Reference 20, p 120.

faster. Rates of hydrolysis of carbon acids vary considerably, depending on the nature of the bond broken. From our results, the rate of hydrolysis of **3** must be a minimum of 10^6 faster than the hydrolysis of acetylacetone (at carbon). In view of the fact that relative rates of proton capture by **2** to give **3** and the rate of hydrolysis of **3** are reversed, compared with other carbon acids, suggests that the transition state for protonation of **2** occurs late along the reaction coordinate. Thus the transition state must resemble dimethylcyclobutanedione (**3**). Most of the barrier to enol–keto tautomerism probably results from the difference in ground state enthalpies of **1** and **3**.

Conclusions

The nmr method, described in this and previous studies, affords an opportunity to examine dynamic prototropic processes under situations where only one tautomer can be observed. In addition to obtaining mechanistic information from pH effects and rate data, many alternative mechanisms can be eliminated on the basis of the line shapes themselves. It is expected that the combination of line shapes and pH effects would be of considerable utility in investigating prototropic shifts in other similar systems where one tautomer predominates. The only requirements of the method described are rates on the nmr time scale (often adjustable by pH) and some form of spin–spin coupling.

Experimental Section

Nuclear magnetic resonance spectral measurements were recorded with a Hitachi Perkin–Elmer R-20, 60-MHz spectrometer equipped with a variable-temperature probe. Temperature calibration was by ethylene glycol peak separation. Room-temperature spectra were also recorded with a Varian T-60 spectrometer.

Calculations were performed on an IBM 360/65 computer.

Hydrogen Ion Concentrations. The concentrations of both **1** and **2** used are specified in Table I. A pK_a value of 3.0 has recently been reported for **1**.[26] Measurement of the pH of an aqueous solution of **1** (0.236 *M*) at 70° gave a pK_a of 2.88. Consequently, a pK_a value of 2.8 was used for 97°. The hydrogen ion concentrations were calculated assuming a weak acid. The calculated rates were found to be insensitive to pK_a values after normalization of the rate constants to the limiting rates.

Activation Parameters. The rate constants used in the calculation of the activation parameters were the second-order rate constants for keto–enol tautomerism. The activation parameters calculated in the pH and concentration sensitive region (pH 2.8) are subject to considerably more error than the parameters previously reported because of the slow decomposition of **1** to diethyl ketone. In order to minimize this error, a stock solution of **1** and **2** in water was prepared and a fresh sample was used for every few measurements (**1**, 63 mg; **2**, 75 mg; H_2O, 1577 mg). All samples were allowed 5 min for temperature equilibration with the probe. The rate constants (rate/P_A[HA]) obtained as a function of temperature are listed as follows as $rate_{ke}$ (temp, °K): 78 (328), 104 (332), 122 (336), 136 (338), 202 (342), 261 (346), 321 (350), 381 (354), 486 (358), 523 (362), 641 (366), 742 (370).

To assess the error associated with the approximation that at a pH of 1.6 and 2.8 the only terms contributing to the rate were the k_4 and k_6 terms, respectively, the following correction was made. Using the Arrhenius equation and the activation parameters previously calculated at low pH, the observed rates in the concentration sensitive region were altered by subtracting out the concentration insensitive terms. A least-squares fit to this corrected data at a pH of 2.8 is shown in the third entry below. This compares with the ln A and E_a terms for the original data shown in the second entry. Since the magnitude of the activation parameters in both pH regions is comparable, the corrected parameters were not significantly altered. Furthermore, the estimated error associated with these values is larger than the corrections. No attempt was made to refine the data further.

pH	E_a	ln A	Correl coeff
1.6	13.6	28.9	0.998
2.8	13.2	24.7	0.995
2.8	13.1	24.4	0.992

2,4-Dimethyl-3-hydroxycyclobutenone Sodium Salt (2). The pH of the solutions was varied by varying the ratio of sodium salt (**2**) to acid (**1**). The sodium salt was prepared by neutralizing **1** with dilute sodium hydroxide (0.1 *N*) to a pH of 5, measured potentiometrically. Evaporation of the water afforded **2** as a white, stable solid. Acidification regenerated the acid.

Acknowledgments. We thank the Research Corporation for partial support, the University of Missouri-St. Louis Computer Center for a generous contribution of computer time, and Professor Robert A. Rouse for assistance with the least-squares calculations.

(26) R. H. Hasek and J. C. Martin, *J. Org. Chem.*, **27**, 3743 (1962).