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Ketonization of Acetophenone Enol in Aqueous Buffer Solutions. Rate–Equilibrium Relations and Mechanism of the "Uncatalyzed" Reaction

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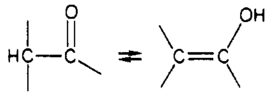
Contribution from the Department of Chemistry, University of Toronto, Toronto, Ontario M5S 1A1, Canada, and Institut für Physikalische Chemie, Universität Basel, CH-4056 Basel, Switzerland. Received January 15, 1988

Abstract: Rates of ketonization of acetophenone enol, generated by photohydration of phenylacetylene and Norrish type II photoelimination of γ-hydroxybutyrophenone, were measured at 25 °C in aqueous buffer solutions of six carboxylic acids, six phosphonic acid monoanions, phosphoric acid, and dihydrogen phosphate. Analysis of the carboxylic acid data produced catalytic coefficients from which linear Brønsted correlations were constructed, with $\alpha = 0.50$ for ketonization of the enol and $\alpha = 0.32$ for the more rapid ketonization of the enolate ion. A more extended, curved Brønsted correlation for ketonization of the enolate ion was constructed by combining the carboxylic acid results with catalytic coefficients for the phosphonic acid monoanions, and analysis of this by Marcus theory gave the intrinsic barrier $\Delta G_0^{\ddagger} = 12$ kcal mol^{-1} and the work terms $w^r = 2$ kcal mol^{-1} and $w^p = 4$ kcal mol^{-1}. These results differ from the much smaller intrinsic barrier and strongly disparate work terms obtained previously in a similar study of isobutyrophenone enol, and an explanation of the difference in terms of a looser transition state (Kreevoy $\tau = 0.30$) for the isobutyrophenone system is offered. Evidence is also supplied which indicates that the so-called "uncatalyzed" ketonization reaction occurs by a stepwise route rather than by a cyclic single-step mechanism.

With the recent development of techniques for generating simple enols in aqueous solution in greater than equilibrium amounts,[1] it has become possible to study enolization, eq 1, a prototype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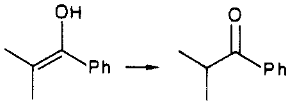
proton-transfer reaction, from the reverse direction. This has certain advantages. For example, enolization is frequently a slow process, and its rate is consequently often measured over only the first few percent reaction, using initial rate methods; ketonization, on the other hand, is generally much faster, and ketonization reactions can usually be followed conveniently over their entire course, thus avoiding difficulties inherent in initial rate methods. Rates of enolization, moreover, are commonly determined indirectly, by monitoring the concentration of a halogen scavenger used to react with the enol as it forms. This requires conditions under which the halogenation step is sufficiently fast to make enolization fully rate-determining, a requirement that has not always been fulfilled even for so much investigated a substance as acetone.[2] Ketonization, on the other hand, can be followed directly by monitoring the optical absorption of the enol.

We have already conducted a detailed investigation of the ketonization of the enol of isobutyrophenone, eq 2, catalyzed by a number of different acids.[3] This study generated a body of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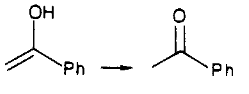
rate and equilibrium data, which, when analyzed by Marcus[4] or Lewis–More O'Ferrall[5] rate theories, gave unexpected results. In order to probe this matter further, we have now made a similar investigation of a somewhat simpler system, the ketonization of acetophenone enol, eq 3. Our new results conform to the expectations of these simple rate theories much better, and they also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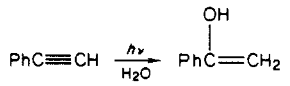
offer insight into the different behavior of isobutyrophenone enol.

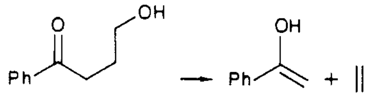
The present study, in addition, provides a much more reliable value of the rate constant for the so-called "uncatalyzed" ketonization of acetophenone enol than we were able to supply before,[6] and this, taken together with other data from the literature, leads to a decision about the mechanism of this reaction.

We generated acetophenone enol in the present study for the most part by photohydration of phenylacetylene, eq 4;[7] in a few



$$\mathrm{PhC{\equiv}CH} \xrightarrow[\mathrm{H_2O}]{h\nu} \mathrm{Ph}\overset{\mathrm{OH}}{\overset{|}{\mathrm{C}}}{=}\mathrm{CH_2} \qquad (4)$$

cases, however, we used Norrish type II cleavage of γ-hydroxybutyrophenone, eq 5.[6,8]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Experimental Section

Materials. Phenylacetylene (Aldrich Chemical Co.) was purified by fractional distillation. γ-Hydroxybutyrophenone was a sample that had been prepared before,[6] and phosphonic acids were made and purified as described.[9] All other materials were best available commercial grades and were used as received. Solutions were prepared from deionized water purified further by distillation.

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[§] Universität Basel.

(1) Kresge, A. J. *CHEMTECH* **1986**, *16*, 250–254. Capon, B; Guo, B.; Kwok, F. C.; Siddhanta, A.; Zucco, C. *Acc. Chem. Res.* **1988**, *21*, 135–140. Keeffe, J. R.; Kresge, A. J.; Schepp, N. P. *J. Am. Chem. Soc.* **1988**, *110*, 1993–1995.

(2) Chiang, Y.; Kresge, A. J.; Tang, Y. S.; Wirz, J. *J. Am. Chem. Soc.* **1984**, *106*, 460–462.

(3) Pruszynski, P.; Chiang, Y.; Kresge, A. J.; Schepp, N. P.; Walsh, P. A. *J. Phys. Chem.* **1986**, *90*, 3760–3766.

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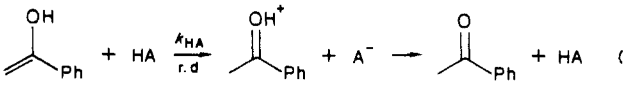
Kinetics. Rates were measured spectrophotometrically with flash photolysis apparatus which has already been described.[6,10] Reactions were monitored at λ = 260 nm by using solutions with an initial concentration of phenylacetylene of 2 × 10^{-4} M or γ-hydroxybutyrophenone of 1 × 10^{-4} M. Ionic strength was maintained at 0.10 M by adding sodium chloride as required, and reaction temperature was kept at 25.0 ± 0.1 °C by using a jacketed cell with water circulating from an external constant temperature bath.

Results

Rates of ketonization of acetophenone enol were measured in buffer solutions of six carboxylic acids, six phosphonic acid monoanions, phosphoric acid, and phosphoric acid monoanion. Series of buffer solutions of constant buffer ratio but varying (fivefold) buffer concentration were used; from two to eight such series were employed for each buffer system. These data are summarized in Table S1.[11]

The ketonization reaction showed both general-acid and general-base catalysis. This is the expected behavior, inasmuch as ketonization can occur either through direct proton transfer from an acid to the enol, eq 6 (r.d., rate-determining), or by prior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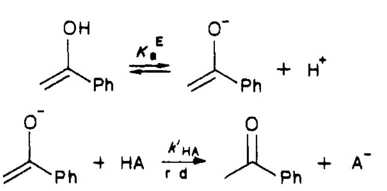
ionization of the enol to enolate followed by proton transfer from the acid to that species, eq 7; the first of these mechanisms will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produce general-acid catalysis, and the second will give specific hydroxide ion catalysis plus general-acid catalysis, which is operationally equivalent to general-base catalysis.

The rate law that applies to this situation is given by eq 8. It denotes reactions of the enol with unprimed symbols and reactions

$$k_{\mathrm{obsd}} = (k_0 + k_{\mathrm{H^+}}[\mathrm{H^+}] + k_{\mathrm{HA}}[\mathrm{HA}])[\mathrm{H^+}]/([\mathrm{H^+}] + K_a^{\mathrm{E}}) + (k'_0 + k'_{\mathrm{H^+}}[\mathrm{H^+}] + k'_{\mathrm{HA}}[\mathrm{HA}])K_a^{\mathrm{E}}/([\mathrm{H^+}] + K_a^{\mathrm{E}}) \quad (8)$$

of the enolate ion with primed symbols, and it allows for proton transfer from water (k_0, k'_0) and the solvated hydrogen ion ($k_{\mathrm{H^+}}$, $k'_{\mathrm{H^+}}$) in addition to proton transfer from undissociated buffer acids (k_{HA}, k'_{HA}); K_a^{E} is the acid dissociation constant of the enol, and the fractions $[\mathrm{H^+}]/([\mathrm{H^+}] + K_a^{\mathrm{E}})$ and $K_a^{\mathrm{E}}/([\mathrm{H^+}] + K_a^{\mathrm{E}})$ express the portions of substrate present in enol and enolate form, respectively. Since $K_a^{\mathrm{E}} = 4.6 \times 10^{-11}$ M[8] and [H$^+$] in the present buffer solutions was never less than 2.5 × 10^{-9} M, this rate law may be simplified by eliminating K_a^{E} from the denominator of these fractions. The gradient of k_{obsd} upon [HA] at constant [H$^+$] is then given by eq 9.

$$(\Delta k_{\mathrm{obsd}}/\Delta[\mathrm{HA}])_{[\mathrm{H^+}]} = k_{\mathrm{HA}} + k'_{\mathrm{HA}}K_a^{\mathrm{E}}/[\mathrm{H^+}] \quad (9)$$

This relationship was used to analyze most of the rate data. Values of $(\Delta k_{\mathrm{obsd}}/\Delta[\mathrm{HA}])_{[\mathrm{H^+}]}$ were obtained as slopes of buffer dilution plots by least-squares analysis of the relationship between k_{obsd} and [HA] for series of solutions at constant buffer ratio (and thus constant [H$^+$]), and the data so obtained were then fitted to eq 9, also by least-squares methods. Values of [H$^+$] needed for this purpose were obtained by calculation using thermodynamic dissociation constants for the buffer acids from the literature and activity coefficients either recommended by Bates[12] or evaluated in the course of the acidity constant determinations.[9] The data adhered to this rate law well.

Table I. Catalytic Coefficients for the Ketonization of Acetophenone Enol and Enolate Ion in Aqueous Solution at 25 °C (Ionic Strength, 0.10 M)

catalyst	pK_a	$k_{\mathrm{HA}}{}^a/\mathrm{M^{-1}\,s^{-1}}$	$k'_{\mathrm{HA}}{}^b/10^6\,\mathrm{M^{-1}\,s^{-1}}$
$CNCH_2CO_2H$	2.47	90.1	234
$ClCH_2CO_2H$	2.87	77.7	214
$CH_3OCH_2CO_2H$	3.57	25.0	91.9
HCO_2H	3.75	18.8	109
CH_3CO_2H	4.76	4.53	46.2
$C_2H_5CO_2H$	4.88	9.84	40.9
$Cl_3CPO_3H^-$	4.93		42.8
$Cl_2CHPO_3H^-$	5.60		34.7
$ClCH_2PO_3H^-$	6.59		23.4
$HOCH_2PO_3H^-$	7.36		10.2
$CH_3PO_3H^-$	8.00		7.09
$(CH_3)_3CPO_3H^-$	8.71		2.42
H_3PO_4	2.15	462	4240
$H_2PO_4^-$	7.20		18.1

[a] Enol. [b] Enolate ion.

In buffer solutions of the stronger acids employed ($CNCH_2CO_2H$, $ClCH_2CO_2H$, $CH_3OCH_2CO_2H$, HCO_2H, and H_3PO_4), buffer failure[13] caused hydrogen ion concentrations to change systematically with changing buffer concentration along series of solutions of constant (stoichiometric) buffer ratio, and $(\Delta k_{\mathrm{obsd}}/\Delta[\mathrm{HA}])_{[\mathrm{H^+}]}$ could not be evaluated as described above. The data were therefore fitted to a version of eq 8, eq 10, which

$$k_{\mathrm{obsd}} - (1.25 \times 10^3)[\mathrm{H^+}] - 0.18 = k_{\mathrm{HA}}[\mathrm{HA}] + k'_{\mathrm{HA}}[\mathrm{HA}]/[\mathrm{H^+}] \quad (10)$$

treated both [H$^+$] and [HA] as independent variables and had known values of $k_{\mathrm{H^+}}$ (1.25 × 10^3 $\mathrm{M^{-1}\,s^{-1}}$)[6] and $(k_0 + k'_{\mathrm{H^+}}K_a^{\mathrm{E}})$ (=0.18 $\mathrm{s^{-1}}$, vide infra) supplied. This method produced well-defined values of k_{HA} for all of the acids involved and also of k'_{HA} for $CH_3OCH_2CO_2H$ and HCO_2H. In the case of $CNCH_2CO_2H$, $ClCH_2CO_2H$, and H_3PO_4, however, too little reaction occurred through the enolate to allow k'_{HA} to be determined in this way.

This difficulty was overcome and values of k'_{HA} for $CNCH_2CO_2H$ and $ClCH_2CO_2H$ were obtained by making rate measurements in unbuffered solutions of the conjugate bases of these acids at higher pH. These data, summarized in Table S2,[11] were fitted to eq 11, which may be derived from eq 10 by making the

$$k_{\mathrm{obsd}} - (1.25 \times 10^3)[\mathrm{H^+}] - 0.18 = k_{\mathrm{HA}}[\mathrm{A^-}][\mathrm{H^+}]/Q_a + k'_{\mathrm{HA}}K_a^{\mathrm{E}}[\mathrm{A^-}]/Q_a \quad (11)$$

substitution $[\mathrm{HA}] = [\mathrm{A^-}][\mathrm{H^+}]/Q_a$, where Q_a is the acid dissociation constant (concentration quotient) of the acid being used at the ionic strength employed (0.10 M). Solutions of pH 5–6 were employed in order to minimize rate contributions from solvent-related species, and values of [H$^+$] were calculated from pH readings (Beckman Model 1019 research pH meter) with $\gamma = 0.83$ as the activity coefficient of H$^+$.[12] Values of k_{HA}, known from the rate measurements made in buffered solutions, were also supplied, and the only parameter determined from the least-squares fits to eq 11 was therefore $k'_{\mathrm{HA}}K_a^{\mathrm{E}}/Q_a$, from which k'_{HA} could be calculated since K_a^{E} and Q_a were also known.

All of the general-acid catalytic coefficients determined by these methods are listed in Table I.

The specific rate of the "uncatalyzed" ketonization of acetophenone enol, k_{uc}, was obtained from the intercepts of the acetic and propionic acid buffer dilution plots. These intercepts were corrected for minor contributions from catalysis by hydronium and hydroxide ions, using the known rate constants for these reactions,[6,8] and the remainders were averaged; this gave $k_{\mathrm{uc}} = 0.175 \pm 0.044$ $\mathrm{s^{-1}}$. This result is an order of magnitude smaller than our previous estimate of this rate constant,[6] but that value was obtained from measurements performed in hydrochloric acid solutions, where k_{uc} makes only a very small contribution to

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(11) Supplementary material; see paragraph at the end of this paper.

(12) Bates, R. G. *Determination of pH. Theory and Practise*; Wiley: New York, 1973; p 49.

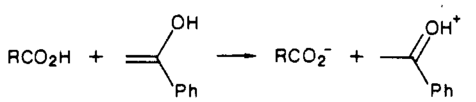
(13) Keeffe, J. R.; Kresge, A. J. *Techniques of Chemistry, Investigations of Rates and Mechanisms of Reactions*; Bernasconi, C. F., Ed.; Wiley: New York, 1986; Vol. 6, Part 1, Chapter XI.

observed rates and its accurate determination is therefore difficult.

Discussion

Brønsted Exponents. The carboxylic acid catalytic coefficients determined here give a Brønsted relation with the exponent $\alpha = 0.50 \pm 0.07$ for the ketonization of acetophenone enol and another with $\alpha = 0.32 \pm 0.03$ for the ketonization of acetophenone enolate ion. Each of these exponents is less than the value obtained for the corresponding, considerably slower, reaction of isobutyrophenone enol ($\alpha = 0.58$) or enolate ion ($\alpha = 0.37$);[3] this is consistent with the idea that α measures the extent of proton transfer at the transition state[14] coupled with the expectation that the present system, because of its greater reactivity, will have an earlier transition state.[15]

Simple rate-equilibrium relationships such as Marcus[4] and Lewis-More O'Ferrall[5] rate theories predict that Brønsted exponents will have values of one-half when proton transfer is ergoneutral. It is of interest to determine whether the present ketonization of acetophenone enol, with $\alpha = 0.50$, conforms to this expectation. This can be done by estimating the free energy change of the rate-determining step of this reaction, eq 12, by summing up the free energy changes for the processes shown in eq 13-15. The free energy change for the process of eq 13 may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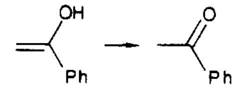
$$RCO_2H \rightarrow RCO_2^- + H^+ \qquad (13)$$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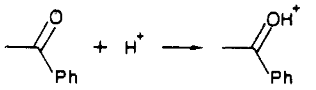
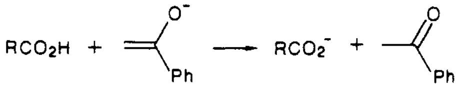

(15)

be taken as $\Delta G = 5.0$ kcal mol^{-1}, from $pK_a = 3.68$ for a catalyst lying at the midpoint of the present correlation. The keto-enol equilibrium constant of acetophenone ($pK_E = 7.96$)[16] then gives $\Delta G = -10.9$ kcal mol^{-1} for the reaction of eq 14, and the acid dissociation constant of oxygen-protonated acetophenone ($pK_a = -4.16$)[17] gives $\Delta G = 5.7$ kcal mol^{-1} for the reaction of eq 15. The sum of these three values is $\Delta G = -0.2$ kcal mol^{-1}, which is essentially zero and thus in remarkably good agreement with expectation.

These rate theories also require α to be less than one-half for exoergic proton transfers. Once again the present results, this time for the ketonization of acetophenone enolate ion, eq 16,


(16)

support this idea: combination of $\Delta G = 5.0$ kcal mol^{-1} for the ionization of RCO_2H with $\Delta G = -25.0$ kcal mol^{-1} for carbon protonation of the enolate ion, based on $pK_a^K = 18.31$ for the ionization of acetophenone as a carbon acid,[16] gives $\Delta G = -20.0$ kcal mol^{-1} for the reaction of eq 16. This proton transfer with $\alpha = 0.32$ is thus indeed an appreciably exoergic process.

A further analysis of the present results on the basis of simple rate theory may be made using the Marcus expression shown in eq 17, which relates the rate of change of α with respect to ΔG,

$$d\alpha/d\Delta G = \tfrac{1}{8}\Delta G_0^{\ddagger} \qquad (17)$$

$d\alpha/d\Delta G$, to the intrinsic barrier for the system, $\Delta G_0^{\ddagger}$. Setting $d\alpha$ equal to the difference in α values for the enol and enolate correlations and $d\Delta G$ equal to the difference in estimated free energy changes then leads to $\Delta G_0^{\ddagger} = 14$ kcal mol^{-1}. This calculation assumes that the enol and enolate reactions belong to a single reaction series and have a common intrinsic barrier; support for this assumption comes from the fact that the result obtained on this basis is consistent with $\Delta G_0^{\ddagger} = 12$ kcal mol^{-1} derived from the curvature of a more extended Brønsted correlation constructed with data for the enolate reaction alone, as described in the next section.

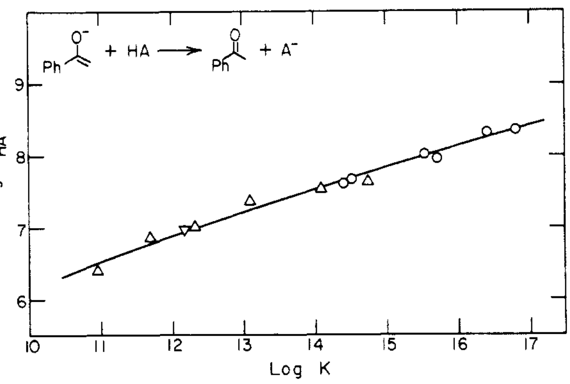


Figure 1. Rate-equilibrium relation for the ketonization of acetophenone enolate ion in aqueous solution at 25 °C catalyzed by RCO_2H (○) and RPO_3H^- (including $HOPO_3H^-$) (△). The points represent "chemical" rate and equilibrium constants with symmetry-induced contributions removed by using the following statistical factors: $p = 1$, $q = 2$ for RCO_2H; $p = 1$, $q = 3$ for RPO_3H^-; $p = 2$, $q = 3$ for $H_2PO_4^-$; $p = 3$, $q = 1$ for $PhCOCH_3$.

Table II. Rate Theory Parameters for Ketonization of Acetophenone Enolate Ion in Aqueous Solution at 25 °C

parameter, kcal mol^{-1}	Marcus	Lewis-More O'Ferrall
$\Delta G_0^{\ddagger}$	12 ± 14	24 ± 28
w^r	2 ± 19	-9 ± 31
w^p	4	-8

Rate Theories. Most rate theories require rate-equilibrium relationships such as Brønsted correlations to be curved. The curvature expected for proton transfer to carbon, however, is generally small and cannot be detected with a group of catalysts covering a limited pK_a range such as the carboxylic acids discussed above. We overcame this difficulty in the case of isobutyrophenone enolate ion by constructing a more extended Brønsted correlation based upon a combination of carboxylic acid and phosphonate anion data; the result was decidedly curved.[3]

A similar correlation for the ketonization of acetophenone enolate ion catalyzed by carboxylic acids, phosphonate anions (RPO_3H^-), and dihydrogen phosphate ($H_2PO_4^-$) is shown in Figure 1. Curvature is just barely detectable, and the question can be raised whether it is legitimate to fit the data to a curved (quadratic) expression, as was done, rather than to a straight line. Perhaps the best justification for using a curved fit is that it is required by theory.

The two kinds of catalyst used in this correlation differ in charge type. The data, however, as was also the case for isobutyrophenone enolate ion,[3] do not disperse into two separate sets, presumably because the electrostatic interaction between catalyst and substrate is repulsive and will therefore be minimized by maximum separation of the charge centers.

The parameters obtained from least-squares fitting of the data to a quadratic expression were translated into intrinsic barriers, $\Delta G_0^{\ddagger}$, and work terms for assembling reaction complexes from reactants, w^r, and products, w^p, through the use of Marcus[4] and Lewis-More O'Ferrall[5] rate theories. The results are listed in Table II. It may be seen that application of Lewis-More O'Ferrall theory did not give sensible results: because $\Delta G_0^{\ddagger}$ is so large, w^r and w^p have negative values. Marcus theory, on the other hand, does well, giving reasonable values of all three parameters. This is unlike the situation for ketonization of isobutyrophenone

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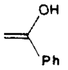
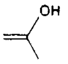
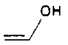
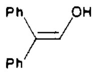
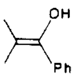
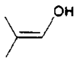
[14] Kresge, A. J. In *Proton Transfer Reactions*; Caldin, E. F., Gold, V., Eds.; Chapman and Hall: London, 1975; Chapter 7.

[15] Leffler, J. E. *Science (Washington, D.C.)* **1953**, *117*, 340-341. Hammond, G. S. *J. Am. Chem. Soc.* **1955**, *77*, 334-338.

[16] Keeffe, J. R.; Kresge, A. J.; Toullec, J. *Can. J. Chem.* **1986**, *64*, 1224-1227.

[17] Cox, R. A.; Smith, C. R.; Yates, K. *Can. J. Chem.* **1979**, *57*, 2952-2959.

Table III. Specific Rates of Ketonization and Enol Acidity Constants for Some Simple Enols in Aqueous Solution at 25 °C (Ionic Strength, 0.10 M)

enol	k_{uc}/s^{-1}	$k_{H^+}/M^{-1}\ s^{-1}$	pK_a^E	$k'_{H^+}/10^6$ $M^{-1}\ s^{-1}$
	0.18	1250^a	10.34^a	3800
	0.077^b	5380^c	10.94^d	6700
	0.040^c	33.0^c	10.50^c	1260
	0.00079^e	0.0021^e	9.40^e	1.97
	0.00050^f	2.14^f	11.78^f	303
	0.00039^g	0.585^g	11.63^g	170

[a] Reference 6. [b] Calculated from $k = 8.33 \times 10^{-12}\ M^{-1}\ s^{-1}$ for uncatalyzed enolization (given by Stewart, R.; Srinivasan, R. *Can. J. Chem.* **1981**, *59*, 957–963) using $K_E = 6.0 \times 10^{-9}$ from ref 2. [c] Reference 10. [d] Reference 2. [e] Chiang, Y.; Kresge, A. J.; Krogh, E. T. *J. Am. Chem. Soc.* **1988**, *110*, 2600–2607. [f] Reference 3. [g] Chiang, Y.; Kresge, A. J.; Walsh, P. A. *J. Am. Chem. Soc.* **1986**, *108*, 6314–6320.

enolate ion, where Lewis–More O'Ferrall theory appeared to perform better then Marcus theory.[3]

In the case of isobutyrophenone, however, both theories gave widely disparate values of w^r and w^p, with w^p exceeding w^r by 14–17 kcal mol^{-1}. A rationalization of this difference involving differential desolvation of reactant and product forms of the catalysts was advanced, but this now seems improbable in view of the fact that the same catalysts were used in the present study but the disparity is gone. The cause, therefore, would seem to lie in some property of the substrates, and an explanation can be advanced on the basis of a looser transition state in the isobutyrophenone reaction produced by a steric effect of the β,β-dimethyl groups.

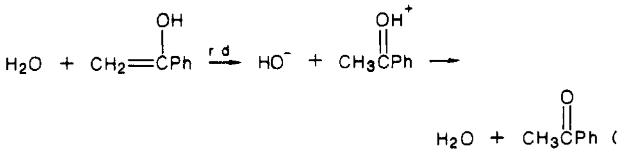
An elaboration of Marcus theory suggested by Kreevoy[18] is useful for this purpose. Kreevoy's modification leads to an expression for α, which is given by eq 18 for systems of the kind

$$\alpha = 0.5(1 + \Delta G/4\Delta G_0^{*}) + 0.5(1 - \tau) \qquad (18)$$

under discussion here. The first term on the right side of the equation is the usual Marcus theory expression for α, and τ is a tightness parameter defined as the sum of the orders of the reacting bonds to the proton undergoing transfer. When bond order is conserved, $\tau = 1$ and simple unmodified Marcus theory is obeyed. This apparently is the case for ketonization of acetophenone enolate ion, for application of the simple theory leads to sensible results with $\alpha = {}^1/_2$ at $\Delta G \cong 0$ as predicted by the first term of eq 18. In the case of isobutyrophenone, however, α has the much higher value 0.85 at $\Delta G = 0$, and the second term of eq 18 is thus making a significant contribution. Use of $\alpha = 0.85$ and the requirement that the first term of eq 18 make a contribution of 0.5 at $\Delta G = 0$ leads to $\tau = 0.30$. This implies a loose transition state with bond orders of 0.15 to the proton being transferred, which is consistent with a steric effect hindering close approach of catalyst to substrate.

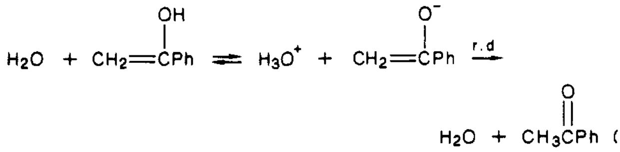
How forcing a system to conform to simple Marcus or Lewis–More O'Ferrall theory when a more elaborate formalism is required can lead to disparate work terms may be seen from the following argument. The empirical rate–equilibrium correlations for isobutyrophenone give $\alpha = {}^1/_2$ when $\Delta G = -14$ or -17 kcal mol^{-1}.[19] These are overall free energy changes, i.e. free energy changes for proton transfer within the reaction complex, ΔG_R, plus contributions from the two work terms: $\Delta G = w^r + \Delta G_R - w^p$. The simple theories require ΔG_R to be zero when $\alpha = {}^1/_2$, and at this point ΔG must therefore be equal to $w^r - w^p$, which for isobutyrophenone has the appreciable value -14 or -17 kcal mol^{-1}. Use of the Kreevoy modification removes the restriction that ΔG_R be zero when $\alpha = {}^1/_2$, and that allows a more sensible situation with w^r and w^p having comparable values.

Mechanism of the "Uncatalyzed" Reaction. The "uncatalyzed" ketonization of acetophenone enol, for which the rate constant $k_{uc} = 0.18\ s^{-1}$ was determined here, could in principle occur by analogues of either of the two mechanisms given above in eq 6 and 7. In the mechanism analogous to eq 6, shown as eq 19, water



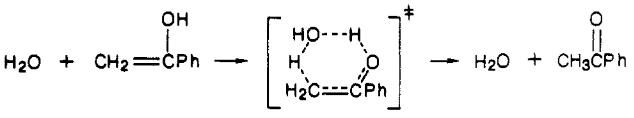
$$H_2O + CH_2{=}\overset{OH}{\overset{|}{C}}Ph \xrightarrow{r.d} HO^- + CH_3\overset{OH^+}{\overset{\|}{C}}Ph \longrightarrow H_2O + CH_3\overset{O}{\overset{\|}{C}}Ph \qquad (19)$$

would serve as the proton donor in a rate-determining carbon protonation step, and this would then be followed by rapid proton loss from the ketone conjugate acid so formed. In the mechanism analogous to eq 7, eq 20, ionization of the enol to enolate would



$$H_2O + CH_2{=}\overset{OH}{\overset{|}{C}}Ph \rightleftharpoons H_3O^+ + CH_2{=}\overset{O^-}{\overset{|}{C}}Ph \xrightarrow{r.d} H_2O + CH_3\overset{O}{\overset{\|}{C}}Ph \qquad (20)$$

be followed by rate-determining protonation of enolate on carbon by a hydronium ion; in this process the hydronium ion first produced is later used up, and the overall reaction would therefore be independent of hydronium ion concentration. There is, in addition, still another possible reaction path, a mechanism in which proton transfer from oxygen to carbon occurs in a single step through proton jumps down an intervening solvent bridge, as shown in eq 21 for the case where the solvent bridge consists of one water molecule; evidence for a cyclic mechanism of this kind was recently supplied for a somewhat different system.[20]



(21)

In the first of these mechanisms, water is functioning as a general acid, and an estimate of the rate constant for reaction by this pathway may be made from the Brønsted relation constructed here for general-acid-catalyzed ketonization of acetophenone enol. This leads to the prediction $k = 2.3 \times 10^{-5}\ s^{-1}$, which is 4 orders of magnitude less than the rate constant observed, $k_{uc} = 0.18\ s^{-1}$. This mechanism can therefore be ruled out. Such a conclusion is warranted, even though water seldom falls directly on a Brønsted plot determined by carboxylic acid catalytic coefficients, because a deviation of 10^4 would be unexpected; for example, in the hydrolysis of methyl α-cyclopropylvinyl ether, water deviates from a Brønsted relation based upon carboxylic acids by a factor of 14,[21] and for aromatic hydrogen exchange in 1,3,5-trimethoxybenzene, the deviation amounts to a factor of only 5.[22]

This leaves two mechanisms, the stepwise route of eq 20 and the cyclic pathway of eq 21. A decision between these alternatives

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(18) Kreevoy, M. M; Lee, I.-S. H. *J. Am. Chem. Soc.* **1984**, *106*, 2550–2553.

(19) Two correlations were made, one with data for all 13 catalysts (as here for acetophenone), which gave $\Delta G_{\alpha={}^1/_2} = -17$ kcal mol^{-1}, and another leaving out the possibly deviant *tert*-butylphosphonate anion, which gave $\Delta G_{\alpha={}^1/_2} = -14$ kcal mol^{-1}.

(20) Bernasconi, C. F.; Fairchild, D. E.; Murray, C. J. *J. Am. Chem. Soc.* **1987**, *109*, 3409–3415. See also: Kasha, M. *J. Chem. Soc., Faraday Trans. 2* **1986**, *82*, 2379–2392.

(21) Kresge, A. J.; Chwang, W. K. *J. Am. Chem. Soc.* **1978**, *100*, 1249–1253.

(22) Kresge, A. J.; Slae, S.; Taylor, D. W. *J. Am. Chem. Soc.* **1970**, *92*, 6309–6314.

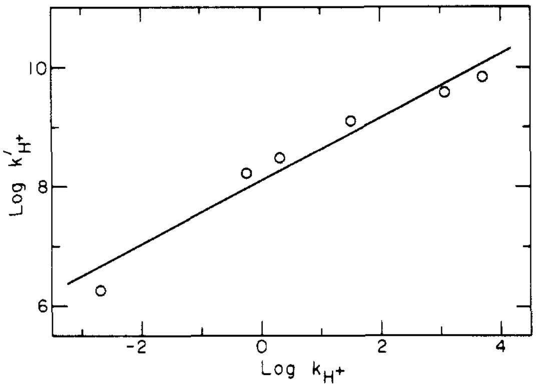
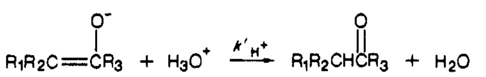


Figure 2. Relationship expected for a stepwise mechanism for the "uncatalyzed" pathway of enol ketonization.

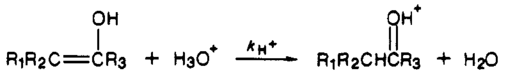
may be made on the basis of different structure–reactivity relationships that may be predicted for them. Testing these different relationships requires data for more than one enol, and the necessary information is now available for six systems; this is listed in Table III.

The rate-determining step of the stepwise mechanism is shown, in generalized form for different substrates, as eq 22. Rate



$$R_1R_2C{=}C(O^-)R_3 + H_3O^+ \xrightarrow{k'_{H^+}} R_1R_2CHC({=}O)R_3 + H_2O \quad (22)$$

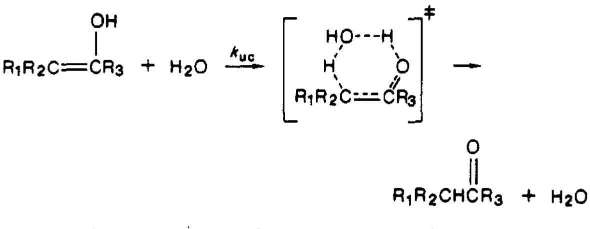
constants for this process, k'_{H^+}, will depend upon the structures of R_1–R_3 in much the same way as do rate constants, k_{H^+}, for the first step of the hydronium ion catalyzed ketonization of the corresponding enols, eq 23, because the acid catalyst is the same



$$R_1R_2C{=}C(OH)R_3 + H_3O^+ \xrightarrow{k_{H^+}} R_1R_2CHC({=}OH^+)R_3 + H_2O \quad (23)$$

in the two reactions and the substrates differ only by the presence or absence of a proton. Therefore, if this stepwise mechanism is operative, there should be a good correlation between k_{H^+} and values of k'_{H^+} calculated according to the requirements of this pathway: $k'_{H^+} = k_{uc}/K_a^E$.

Rate constants, k_{uc}, for the cyclic mechanism, shown in generalized form as eq 24, will also depend upon the structures of



$$R_1R_2C{=}C(OH)R_3 + H_2O \xrightarrow{k_{uc}} \left[\begin{matrix} HO{\cdots}H \\ H\quad O \\ R_1R_2C{\cdots}CR_3 \end{matrix}\right]^{\ddagger} \longrightarrow R_1R_2CHC({=}O)R_3 + H_2O \quad (24)$$

R_1–R_3; k_{uc} should therefore vary with substrate structure in a manner similar to k_{H^+}. In this case, however, there is an additional factor governing reactivity, for here the proton donor is the enol whose acid strength also changes with enol structure; values of k_{uc} should therefore also correlate with values of the enol acidity constant, K_a^E. Since changes in R_1–R^3 will affect k_{uc} and k_{H^+} in the same way, the influence of this variable may be removed by taking the ratio k_{uc}/k_{H^+}. This then leads to the expectation of a correlation between the quantity k_{uc}/k_{H^+} and K_a^E if the cyclic mechanism is operating.

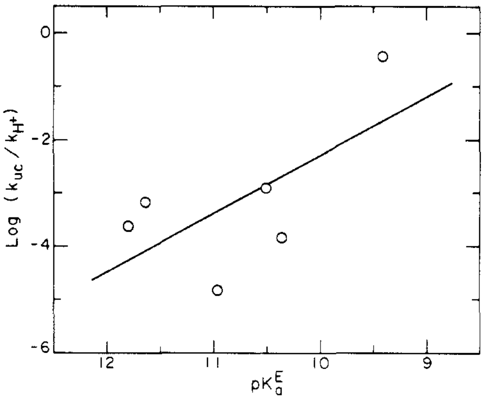


Figure 3. Relationship expected for a concerted mechanism for the "uncatalyzed" pathway of enol ketonization.

Data for the six systems listed in Table III correlated according to the first of these relationships are shown in Figure 2, and according to the second, in Figure 3. The first correlation is clearly better than the second: least-squares analysis gives a good correlation coefficient, $r = 0.977$, for the former but only $r = 0.653$ for the latter. This indicates that "uncatalyzed" ketonization occurs by the stepwise mechanism of eq 20 rather than by the cyclic route of eq 21.

Values of the rate constant k'_{H^+} for carbon protonation of enolate ions calculated on the basis of this mechanism are shown in the last column of Table III. Although these rate constants are large, none is as great as the value $k'_{H^+} = 4 \times 10^{10}$ M^{-1} s^{-1} estimated previously[3] for the ketonization of acetophenone enolate ion on the basis of a preliminary, and unfortunately inaccurate, value of k_{uc}. It appears unnecessary, therefore, to suggest, as was done before,[3] that this reaction is facilitated by a Grotthus chain mechanism similar to that which makes proton transfer between nitrogen and oxygen acids and bases so rapid in aqueous solution.

It is of interest that the slope of the enolate–enol correlation shown in Figure 2 is significantly less than 1: 0.53 ± 0.06. This indicates that carbon protonation of the enolate ions, which is 10^6–10^9 faster than carbon protonation of the enols, is the less selective process, in keeping with the reactivity–selectivity principle.

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Registry No. $(CH_3)_2C{=}C(OH)Ph$, 4383-10-2; $CH_2{=}C(OH)Ph$, 4383-15-7; PhC≡CH, 536-74-3; $PhC(O)(CH_2)_3OH$, 39755-03-8; acetophenone enolate ion, 34438-71-6.

Supplementary Material Available: Tables S1 and S2 of rate data (17 pages). Ordering information is given on any current masthead page.