Mechanism of Enolization of Ketones in Sulfuric Acid[1-3]
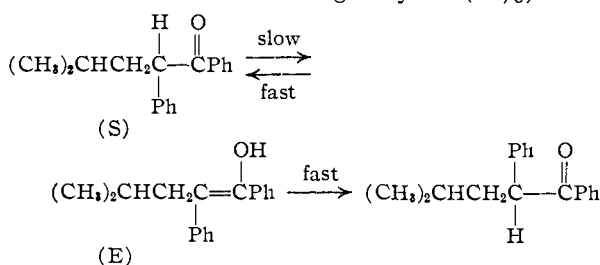
By C. Gardner Swain and Arthur S. Rosenberg

A nucleophile is required, and water is about a hundred times more reactive than bisulfate ion as a nucleophile, in t racemization of D-α-phenylisocaprophenone in 85 to 94% sulfuric acid solutions at 25°. A fast equilibrium protonatic of the ketone precedes the rate-determining step in which the nucleophile attacks. The interpretation of deviations fro h_0-dependence for reactions in more dilute strong acid and the use of isotope effects to determine the position of the ، hydrogen at the transition state also are discussed.

D-α-Phenylisocaprophenone (S) racemizes at a convenient rate in aqueous solutions containing 85–94% sulfuric acid by weight at 25°. The DL-ketone was recovered in good yield (87%) after

$$(CH_3)_2CHCH_2\overset{\overset{\displaystyle H}{|}}{C}\overset{\overset{\displaystyle O}{\|}}{—}CPh \underset{\text{fast}}{\overset{\text{slow}}{\rightleftharpoons}}$$

(S)

$$(CH_3)_2CHCH_2\overset{\overset{\displaystyle OH}{|}}{C}=\overset{\overset{\displaystyle }{|}}{C}Ph \xrightarrow{\text{fast}} (CH_3)_2CHCH_2\overset{\overset{\displaystyle }{|}}{C}\overset{\overset{\displaystyle O}{\|}}{——}CPh$$

Ph   H

(E)

ten half-lives in 93% acid. The first-order rate constant for racemization is ten times *larger* in 85% acid than in 94% acid. Table I gives first-order rate constants observed at different

Table I

RACEMIZATION OF D-α-PHENYLISOCAPROPHENONE IN AQUEOUS SULFURIC ACID AT 25°

H_2SO_4, %	$k_1 \times 10$, sec.$^{-1}$	$\dfrac{[SH^+]}{[S]+[SH^+]}$ [a]	$[H_2O]$, M	$[HSO_4^-]$, M	H_0 [b]
85.0	37.9	0.650	1.59	13.2	−7.66
86.4	27.9	.729	0.956	12.5	−7.82
87.9	19.5	.799	.583	11.5	−7.99
89.3	14.7	.858	.357	10.4	−8.17
91.0	8.48	.907	.194	8.82	−8.38
92.3	5.87	.933	.125	7.70	−8.53
93.8	3.96	.965	.0683	6.20	−8.83

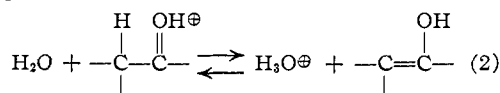[a] Ratio of protonated ketone to stoichiometric (free plus protonated) ketone, calculated from $h_0/(K_{SH^+} + h_0)$; $pK_{SH^+} = -7.39$. [b] Hammett acidity function $H_0 = -\log h_0$.[4]

$$k_1 = \frac{[SH^+]}{[S] + [SH^+]}(3.46 \times 10^{-4}[H_2O] + 3.3 \times 10^{-6}[HSO_4^-]) \quad (1)$$

acid concentrations; they fit eq. 1. Justification for treating 85–94% sulfuric acid as an ideal solution is given in the section entitled "Activity Coefficients in 83–100% Sulfuric Acid."

Equation 1 shows that a nucleophile (H_2O or HSO_4^-) is required and that water has a rate con-

stant about a hundred times larger than that (bisulfate ion. A fast equilibrium protonation (the ketone must precede this step in which th nucleophile attacks because Reitz found the bromination of acetone catalyzed by a strong aci is 2.1 times faster in D_2O than in H_2O.[5] There fore the principal mechanism has the rate-determining step

$$H_2O + \overset{\overset{\displaystyle H}{|}}{—}\overset{\overset{\displaystyle OH^\oplus}{\|}}{C}\overset{\overset{\displaystyle }{|}}{—}C— \underset{\longleftarrow}{\overset{\longrightarrow}{}} H_3O^\oplus + \overset{\overset{\displaystyle OH}{|}}{—}C=\overset{\overset{\displaystyle }{|}}{C}— \quad (2)$$

This mechanism has been called the A-2 mecha nism[6] in the forward direction and the A-S$_E$2 mech anism[7] in the reverse direction.

Previous Studies of the Effect of Acidity o Rates of Enolization.—Experiments by Lapworth Bartlett and others cited in a previous paper demonstrate that enolization is ordinarily rate determining for both halogenation and racemiza tion. Piperitone (1-*p*-menthen-3-one) racemize more rapidly in sulfurous acid at 100° than in 90% sulfuric acid at 30–40°.[9] Zucker and Hammet found that the first-order rate constant for iodina tion of acetophenone in 0.2–3.6 M perchloric acic solutions is more closely proportional to $[H_3O^+]$ than to h_0, although it appears to rise more rapidly than calculated from $[H_3O^+]$ above 1.4 M per chloric acid and so is actually intermediate betweer the two.[10] Hammett interpreted the failure tc follow h_0 as due to involvement of water in the rate-determining step.

It has been suggested[7] that the A-S$_E$2 mech anism (of which eq. 2 in the reverse direction is an example) might show the same dependence of k_1 on h_0 as the A-1 mechanism (which does not involve the elements of water in the transition state). This suggestion was based on the assumption that there is no specific structural role to be as signed to a molecule solvating a proton; *i.e.*,

(1) Supported in part by the Atomic Energy Commission, the National Institutes of Health and the National Science Foundation.

(2) Cf. C. G. Swain, A. J. Di Milo and J. P. Cordner, *J. Am. Chem. Soc.*, **80**, 5983 (1958).

(3) For complete experimental details, cf. A. S. Rosenberg, S. M. Thesis in Organic Chemistry, M.I.T., January, 1959, pp. 15–38.

(4) L. P. Hammett and A. J. Deyrup, *J. Am. Chem. Soc.*, **54**, 2721 (1932); M. A. Paul and F. A. Long, *Chem. Revs.*, **57**, 1 (1957). R. P. Bell, "The Proton in Chemistry," Cornell Univ. Press., Ithaca, N. Y., 1959, p. 75.

(5) O. Reitz, *Z. physik. Chem.*, **A179**, 119 (1937); O. Reitz and J. Kopp, *ibid.*, **A184**, 429 (1939). We use "nucleophilic" to refer to attack (by an electron pair) on carbon, hydrogen or other nucleus in a rate-determining step, but "basic" (or "acidic") to refer to a prior-equilibrium step or to any equilibrium not involving a transition state. The rate-determining step of a reaction is the one with the slowest rate; this need not be the one with the smallest rate constant.

(6) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell Univ. Press, Ithaca, N. Y., 1953, p. 753.

(7) F. A. Long and M. A. Paul, *Chem. Revs.*, **57**, 943 (1957).

(8) C. G. Swain, E. C. Stivers, J. F. Reuwer, Jr., and L. J. Schaad, *J. Am. Chem. Soc.*, **80**, 5885 (1958).

(9) J. Read and H. G. Smith, *J. Chem. Soc.*, **123**, 2271 (1923).

(10) L. Zucker and L. P. Hammett, *J. Am. Chem. Soc.*, **61**, 2791 (1939); L. P. Hammett, "Physical Organic Chemistry," McGraw–Hill Book Co., Inc., New York, N. Y., 1940, pp. 275–276.

that such a molecule would not be kinetically significant and would not appear in the rate expression. Kresge and Satchell pointed out that this suggestion cannot be correct as applied to ketonization of enols if it is proved that water is kinetically significant in enolization of ketones catalyzed by strong acid, because both reactions have the same transition state, and the activity coefficients of unchanged ketone and enol should change similarly with acidity.[11] Our experiments now prove that water is in fact kinetically significant in enolization of a ketone catalyzed by a strong acid, and therefore the reverse reaction also should show a less sharp dependence on acidity than $h_0/(K_a + h_0)$. For the reverse reaction, K_a is the acid dissociation constant of EH^+, the enol conjugate acid.

Thus a nucleophile (water or bisulfate ion) is required even in 94% sulfuric acid. Isotope effects discussed in the final section below show that water is involved in the transition state in dilute acid also.

Confusion can easily arise about the extent of involvement of water in dilute acid because the activity of water decreases only 20% from 1 to 25% sulfuric acid while molarity changes 30-fold (0.1 to 3.0) and h_0 230-fold (0.1 to 23). In this intermediate range of acidity, therefore, the dependence on acidity is determined more by the way in which the activity coefficient of the transition state changes than by the number of water molecules involved as reactants. This is discussed more fully below in the section on "Dilute Strong Acid Solutions."[12]

Activity Coefficients in 83–100% Sulfuric Acid.— Deno and Taft showed that values of H_0 calculated from

$$H_0 = -6.78 - \log([H_3O^+]/[H_2O])$$

and an equilibrium constant of 50 for
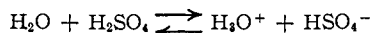
$$H_2O + H_2SO_4 \rightleftharpoons H_3O^+ + HSO_4^-$$

are in good agreement with experimental values of H_0 from 83 to 99.8% sulfuric acid.[13] This implies that the activity coefficient ratio $\gamma_{H_3O^+} \cdot \gamma_{HSO_4^-}/\gamma_{H_2O}\gamma_{H_2SO_4}$ is constant over this region. Since these activity coefficients correspond to species which vary widely in structure and charge type, it suggests that these individual activity coefficients also remain nearly constant. In fact, the activity coefficient for water alone calculated from vapor pressure data for 83–95% sulfuric acid[14] is constant in this range. Therefore we will assume in the following section that the activity coefficient ratios $\gamma_{SH^+}\gamma_{H_2O}/\gamma^*_{H_2O}$ and $\gamma_{SH^+}\gamma_{HSO_4^-}/\gamma^*_{HSO_4^-}$ are constant from 85 to 94% sulfuric acid

where γ_{SH^+} is the activity coefficient of protonated ketone and γ^* activity coefficients refer to transition states involving the subscript nucleophiles. The concentrations of water and bisulfate ion in Table I were calculated from this equilibrium constant of 50.

Kinetics of Reaction of Protonated Substrates with Nucleophiles in 83–100% Sulfuric Acid.— The observed over-all first-order rate constant for nucleophiles (N_i) with a substrate (S) which is protonated (to SH^+) in a prior rapidly reversible equilibrium step is

$$k_1 = \frac{[SH^+]}{[S] + [SH^+]} \sum_i k_1 \frac{\gamma_{SH^+}\gamma_{Ni}}{\gamma_i^*} [N_i] \qquad (3)$$

where k_1 is the rate constant associated with N_i and γ_i^* is the activity coefficient of the i-th transition state. Using the assumption supported in the previous section that the activity coefficient ratios are constant in 83–100% sulfuric acid, eq. 3 reduces to the form of eq. 1 for these conditions. In 83–100% sulfuric acid at 25°, interpretations of the effect of acidity are relatively simple because it is usually possible to assume constant activity coefficient ratios in this region.

Kinetics of Reaction of Protonated Substrates with Nucleophiles in More Dilute Strong Acid Solutions.—Other reactions beside enolization which have first-order rate constants k_1 which increase more slowly than in proportion to h_0 include acid-catalyzed hydrolysis of ethyl acetate (0.5–10.2 M HCl and 1.4–6.8 M H$_2$SO$_4$),[15] hydrolysis of γ-butyrolactone (0.5–3.9 M HCl and 0.4–3.3 M HClO$_4$),[16] hydrolysis of ethylidene diacetate (0.3–8.9 M HCl),[17] hydrolysis of benzamides,[18] and hydration of α,β-unsaturated carbonyl compounds.[19] There is supporting evidence of other kinds that these reactions do have water involved in their transition states. For example, the acid-catalyzed hydrolysis of methyl acetate in acetone-water solutions is kinetically first order in water concentration.[20,21] The rate of hydrolysis of benzamide decreases above 3.5 M sulfuric acid.[18] Hydration of α,β-unsaturated carbonyl compounds has a very negative activation entropy (due to binding a water molecule) compared to the h_0-dependent hydration of olefins lacking carbonyl or other electron-withdrawing substituents.[22] Many of these reactions which have both H^+ and water firmly bound at the transition state do show significant deviations above 3 MH$_3$O$^+$ from simple proportionality between k_1 and [H$_3$O$^+$] or from any simple kinetic expression.[10,15,17,18] Their acid dependence is often intermediate between h_0-

(11) A. J. Kresge and D. P. N. Satchell, *Chemistry & Industry*, 1328 (1958).

(12) For further discussion and additional references especially concerned with h_0-dependent reactions, *cf.* C. G. Swain and R. E. T. Spalding, *J. Am. Chem. Soc.*, **82**, 6104 (1960).

(13) N. C. Deno and R. W. Taft, Jr., *ibid.*, **76**, 244 (1954). Their −6.66 is changed to −6.78 to correspond to a small correction in the H_0 scale.[4] For an alternative treatment, *cf.* P. A. H. Wyatt, *Disc. Faraday Soc.*, **24**, 162 (1957).

(14) Vapor pressure data cited in ref. 13. *Cf.* also C. H. Greenewalt, *Ind. and Eng. Chem.*, **17**, 522 (1925); L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., New York, N. Y., 1940, p. 278; C. D. Coryell and R. C. Fix, *J. Inorg. and Nuclear Chem.*, **1**, 119 (1955).

(15) R. P. Bell, A. L. Dowding and J. A. Noble, *J. Chem. Soc.*, 3106 (1955).

(16) F. A. Long, F. B. Dunkle and W. F. McDevit, *J. Phys. Colloid Chem.*, **55**, 829 (1951).

(17) R. P. Bell and B. Lukianenko, *J. Chem. Soc.*, 1686 (1957).

(18) J. T. Edward and S. C. R. Meacock, *ibid.*, 2000 (1957).

(19) S. Winstein and H. J. Lucas, *J. Am. Chem. Soc.*, **59**, 1461 (1947); H. J. Lucas, W. T. Stewart and D. P. Pressman, *ibid.*, **66**, 1818 (1944).

(20) H. B. Friedman and G. V. Elmore, *ibid.*, **63**, 864 (1941).

(21) However, A. I. Talvik and V. A. Palm, *Zhur. Fiz. Khim.*, **33**, 1214 (1959), conclude that acid hydrolysis of ethyl acetate involves no water in the transition state, the failure of rate to follow h_0 being due to practically complete protonation of the substrate beyond 4 M sulfuric acid.

(22) R. W. Taft, Jr., *J. Am. Chem. Soc.*, **74**, 5372 (1952).

dependence and H_3O^+-dependence between 3 M and 13 M H_3O^+.

To explain why these deviations from proportionality between k_1 and $[H_3O^+]$ below 83% H_2SO_4 occur, it is helpful to re-examine the assumptions which led to an expectation of H_3O^+-dependence. The water term in eq. 3 is CD, where

$$C = \frac{[SH^+]}{[S] + [SH^+]} = \frac{h_0}{K_{SH^+} + h_0}$$

$$D = \frac{k_{H_2O}\gamma_{SH^+}\gamma_{H_2O}[H_2O]}{\gamma^*_{H_2O}} = \frac{k'_{H_2O}\gamma_S\gamma_{H_3O^+}[H_3O^+]}{h_0\gamma^*_{H_2O}}$$

It would follow that the rate should be proportional to H_3O^+ concentration rather than h_0 if six assumptions were valid: (1) that $h_0 \ll K_{SH^+}$; (2) that SH^+ behaves as an acid like the Hammett indicator acids; (3) that water is the only important nucleophile; (4) that only one more water molecule is involved in the transition state than in solvating a Hammett indicator acid (anilinium ion); and that $\gamma_S\gamma_{H_3O^+}/\gamma^*_{H_2O}$ is a constant independent both of acidity (5) and of the exact structure of the transition state (6). Unfortunately, these assumptions may all be false. (1) The h_0 may become comparable to K_{SH^+}, and a leveling-off of the effect of increasing acidity is inevitable in this region of h_0.[21] (2) Most of the Hammett indicators are anilinium ions; it would be valuable to redetermine h_0 using (a) only anilinium ions, (b) only dimethylanilinium ions and (c) only acids with positive charges distributed by resonance, to see if different scales are obtained. (3) Chloride ion, sulfate ion or other nucleophiles may compete with water for SH^+ (4) Two water molecules may become involved in some reactions in solutions below 83% H_2SO_4, where the water concentration is very high. (5) Only in the region above 83% sulfuric acid is there evidence that such ratios of activity coefficients are independent of acidity. (6) There is considerable evidence that activity coefficients for ions vary in quite different ways with acidity depending on the exact structure of the ions. Points 4, 5 and 6 will be considered in more detail in the three paragraphs which follow.

An attempt might be made to attribute all of the deviations from an h_0 dependence for reactions studied in 10–83% sulfuric acid on the variation from one reaction to another in the number of water molecules in the transition state in excess of those associated with the other reactants in their normal ground states in solution. If this number were zero, the rate would depend on h_0; if it were one or more, the rate would change more slowly with % acid. Thus a plot of log k − log$[h_0/(K_{SH^+} + h_0)]$ vs. log a_{H_2O} might seem more appropriate than a plot of log k vs. log $[H_3O^+]$. The slope of the new plot might then be taken as the average number of extra water molecules involved. Such a plot for the data[10] in 0.5–46% sulfuric has a slope of 4 and is linear. However the slope for the data[10] in 2–30% perchloric acid is 7. The large magnitude of the number from perchloric acid solutions makes this approach also appear unpromising except as a quantitative empirical description of the acid dependence.[23]

The failure of this attempt to attribute all deviations to variations in the number and activity of extra water molecules required to form the transition state is not without precedent. The extent of ionization of a triarylmethanol to a triarylcarbonium ion increases with acidity much more sharply than does the extent of conversion of an ordinary Hammett indicator base to its conjugate acid at equilibrium. Measurements on the triarylcarbonium ion equilibria define an acidity function called h_R, j_0 or c_0, which increases approximately as the square of h_0. An early attempt was made to predict h_R from h_0 by the relation $h_R = h_0/a_{H_2O}$ because the two equilibria might be expected to differ by only one water molecule if it could be assumed that the activity coefficient of a triarylcarbonium ion changes with acidity in the same manner as the activity coefficient of an ordinary Hammett indicator acid.[24] That relation failed experimentally (by five powers of ten) over the range from 0.5 to 83% sulfuric acid.[25] The relation $h_R = h_0/a^n_{H_2O}$ works best for $n \cong 4$ (corresponding to the assumption that Hammett indicator acids are solvated by 3 water molecules and carbonium ions by none), but even this gives calculated h_R values deviating from those observed by about two powers of ten (on both sides) over the range 0.5 to 83% sulfuric acid. This inability to ascribe all differences to differing numbers of free water molecules among the reactants demonstrates that activity coefficients of ions can vary with acidity in widely different ways (due to differences in hydrogen bonding with solvent) depending on the structure of the ion and the particular section of this 0.5–83% range of acidity. Even activity coefficients of neutral reactants may vary by an amount too large to ignore. The equilibrium constant between γ-butyrolactone and γ-hydroxybutyric acid decreases by a factor of two from 0.025 to 2.0 M perchloric acid or from 0.05 to 3.5 M hydrochloric acid.[26] Such changes are not negligible and invalidate any simple analysis for the number of excess water molecules in the transition state from the slope of a plot log k_1 − log$[h_0/(K_{SH^+} + h_0)]$ vs. log a_{H_2O}.

A more profitable approach to the interpretation of different kinds of acidity dependence (h_R, h_0 or H_3O^+) in 10–83% sulfuric acid or other comparable acid solutions may involve determining the acidity dependence of activity coefficients of all reactants by independent studies of vapor pressure, solubilities, distribution coefficients, reaction equilibrium constants, etc., then combining such data with

idea are the evidence for multimolecular solvation by water in uncatalyzed hydrolysis of alkyl halides discussed by D. N. Glew and E. A. Moelwyn-Hughes, *Disc. Faraday Soc.*, **15**, 150 (1953), E. A. Moelwyn-Hughes, *Proc. Roy. Soc. (London)*, **A164**, 295 (1938), J. Steigman and L. P. Hammett, *J. Am. Chem. Soc.*, **59**, 2536 (1937) and N. T. Farinacci and L. P. Hammett, *ibid.*, **59**, 2542 (1937). However, it seems less likely that the transition state would be more strongly solvated than the reactants in an acid-catalyzed process where the reactants include H_3O^+ with its concentrated positive charge. Water molecules already associated with the reactants should certainly not appear in the rate expression.

(24) V. Gold and B. W. V. Hawes, *J. Chem. Soc.*, 2102 (1951).

(25) N. C. Deno, J. J. Jaruzelski and A. Schriesheim, *J. Am. Chem. Soc.*, **77**, 3044 (1955); *cf.* also R. W. Taft, *ibid.*, **82**, 2965 (1960).

(26) F. A. Long, W. F. McDevit and F. B. Dunkle, *J. Phys. Colloid Chem.*, **55**, 813 (1951).

(23) J. F. Bunnett, *J. Am. Chem. Soc.*, **82**, 499 (1960) has proposed independently that data be analyzed in this way. The roots of the

the kinetic data to calculate the acidity dependence of the activity coefficient for the *transition state*. It has been suggested[27] that transition states can be classified as ones not forming hydrogen bonds (*e.g.*, carbonium-or NO^+-like), SH^+-like or H_3O^+-like, according to whether h_R, h_0 or H_3O^+ dependence fits best in this region of acidity. The acidity dependence of the activity coefficients of many types of uncharged reactants has already been found to be small.[28] A major difficulty is in knowing how many water molecules to include; *i.e.*, what power to use of the water activity. However, most data are at the dilute acid end of the 10–83% sulfuric acid range, where the water activity does not vary much. Its common logarithm drops only by 0.08 from 0.1 to 3.0 M (1 to 25%) sulfuric acid (−1.00 to +1.37 for log h_0). Therefore here it makes relatively little difference whether one assumes zero, one or two waters.[29] Higher values than this seem unrealistic. Much further work is needed to confirm or disprove these tentative classifications of transition states in this intermediate range of acidity, but the approach is promising.

Position of the α-Hydrogen at the Transition State.—Variations in the location of the α-hydrogen atom at the transition state with changing experimental conditions must be measured and understood before one can claim to have a good picture of the mechanism of enolization of ketones. Fortunately these can now be determined from solvent isotope effects in light and heavy water, by comparing them with calculated isotope effects for conversion of $LO^-(L = H$ or $D)$ to $LO^{\delta-}$ or of L_2O to $L_2O^{\delta+}$ to determine the magnitude of the partial charge on the oxygen of the nucleophile at the transition state.[30] Application of this new tool shows that the α-hydrogen is nearly symmetrically

(27) N. C. Deno, H. E. Berkheimer, W. L. Evans and H. J. Peterson, *J. Am. Chem. Soc.*, **81**, 2344 (1959).

(28) N. C. Deno and C. Perizzolo, *ibid.*, **79**, 1345 (1957).

(29) It has been suggested that the Hammett–Zucker hypothesis[10] is invalidated as a criterion of mechanism by the observation that olefin hydration and alcohol dehydration rates closely follow h_0 in 0–4 M sulfuric acid (R. W. Taft, Jr., N. C. Deno and P. S. Skell, *Ann. Rev. Phys. Chem.*, **9**, 306 (1958)). It was concluded that the hypothesis violates the principle of microscopic reversibility by ascribing two different compositions (olefin plus a proton or alcohol plus a proton) to the same transition state. However, we do not agree with these inferences. The hypothesis says merely that the *transition state* behaves like a Hammett anilinium ion (as it should if it were close to an oxonium ion ROH_2^+ in structure), but not like the reactants (substrate and H_3O^+). Non-correlation with h_R shows that it is also not like a carbonium ion. Nothing is said or implied about the number of water molecules among the *reactants* because the water activity is nearly constant in 0–4 M sulfuric acid and therefore does not appear in the rate law.

One might attempt to determine the number of water molecules among the *reactants* from kinetics in 80–100% sulfuric acid as was done for enolization in the present paper, but this would be complicated for olefin or alcohol reactions by inconveniently high rates and by side reactions forming ether, esters and polymers.

Similarly the observation that the rate of inversion and O^{18} exchange of *sec*-butyl alcohol is proportional to h_0 in 0–4 M perchloric acid (C. A. Bunton and D. R. Llewellyn, *J. Chem. Soc.*, 3402 (1957)) is neither evidence against water in the transition state nor for a carbonium ion, but is quite consistent with a transition state close to ROH_2^+.

(30) C. G. Swain and R. F. W. Bader, *Tetrahedron*, **10**, 182 (1960); C. G. Swain, R. F. W. Bader and E. R. Thornton, *ibid.*, **10**, 200 (1960); C. G. Swain and R. F. W. Bader, *J. Am. Chem. Soc.*, **81**, 2353 (1959); C. G. Swain and E. R. Thornton, two papers submitted for publication.

placed between O and C in enolizations catalyzed by hydroxide ion or hydronium ion but much closer to O as in the products (H_3O^+ + enolate) in uncatalyzed reactions with water as the nucleophile.

With hydroxide ion as the nucleophile, k_{D_2O}/k_{H_2O} values expected at 25° if the change in charge from that in hydroxide ion to that in water is zero, half complete or complete at the transition state are 1.0, $(1.79)^{1/2} = 1.34$, and 1.79, respectively.[30] The observed k_{D_2O}/k_{H_2O} value is 1.2 for acetone at 25°,[31] showing that the α-hydrogen is slightly closer to C (ketone) than to O (enolate) at the transition state. It is 1.4 for nitromethane at 0–5°,[32] corresponding to a transition state slightly closer to products than the symmetrical one.

With water as the nucleophile, calculated k_{H_2O}/k_{D_2O} values are 1.00 for zero transfer, $(2)^{1/2} = 1.41$ for half transfer or 2 for complete transfer at 25°, calculated from the relative basicities of H_2O and D_2O for zero, half or all of the change in charge from that in water to that in hydronium ion.[30] Observed values are 1.37 for 3-methyl-2,4-pentanedione at 25°,[33] 1.7 for nitromethane at 70°,[34] and 2.2 for ethyl 2-oxocyclopentanecarboxylate at 25°[35] Evidently with 3-methyl-2,4-pentanedione the transition state is close to symmetrical, but with nitromethane and ethyl 2-oxocyclopentanecarboxylate the transition state is close to hydronium ion and anion. The exponent in the Brönsted catalysis law, which measures discrimination between different bases, increases from nitromethane[34] to β-ketoesters to simple ketones.[36] Therefore simple ketones like acetone or α-phenylisocaprophenone (S) would be expected to have transition states relatively still closer to enolate in their uncatalyzed reactions with water. All of this is in accord with the Hammond postulate.[37] The α-CH/CD isotope effects are also generally consistent with this interpretation. For example, with nitromethane the values with different nucleophiles fall from 6.53 for CH_3COO^- to 4.28 for $ClCH_2COO^-$ to 3.78 for H_2O^{34} as the transition state increasingly resembles the product.

With H_3O^+ catalysis, the transition state for simple ketones should be shifted back from close to enol to nearly symmetrical again, because the conjugate acid of the ketone must be much more reactive and less discriminating than the free ketone. The CH/CD isotope effect bears this out, since it is high (7.7) for acetone.[5,38] Unfortunately β-ketoesters, nitroalkanes and β-diketones do not show acid catalysis. If they did, the CH isotope effect for the H_3O^+ term might well fall again, corresponding to a transition state closer to reactants.

Thus the observed isotope effects seem to correspond to transition states ranging from close to

(31) Unpublished measurements by R. P. Bell and M. H. Ford-Smith, quoted by R. P. Bell, "The Proton in Chemistry," Cornell Univ. Press, Ithaca, N. Y., 1959, p. 199.

(32) S. H. Maron and V. K. LaMer, *J. Am. Chem. Soc.*, **60**, 2588 (1938).

(33) F. A. Long and D. Watson, *J. Chem. Soc.*, 2019 (1958).

(34) O. Reitz, *Z. physik. Chem.*, **A176**, 363 (1936).

(35) R. P. Bell, J. A. Fendley and J. R. Hulett, *Proc. Roy. Soc. (London)*, **A235**, 453 (1956).

(36) R. P. Bell, ref. 31, p. 172.

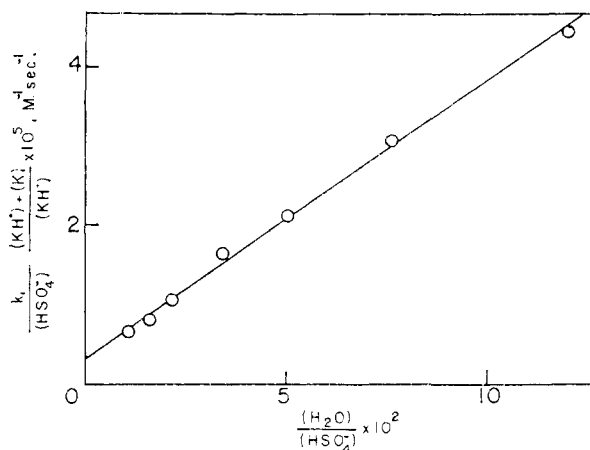(37) G. S. Hammond, *J. Am. Chem. Soc.*, **77**, 334 (1955).

(38) Reference 36, p. 201.

Fig. 1.—Rate constants for enolization of D-α-phenyl-isocaprophenone in 85 to 94% sulfuric acid at 25° plotted according to eq. 1.

symmetrical with strong catalysts or reactive substrates to ones close to the products (enolate ion or enol) without catalysis or with less reactive substrates.

This interpretation is significantly different from one which we suggested earlier[39] before the solvent isotope effect was developed[30] into an unambiguous tool for deciding whether decreasing α-hydrogen isotope effects correspond to a hydrogen closer to C (ketone) or O (enol) at the transition state. However, the conclusions of the previous work[39] concerning the identity of the attacking nucleophile in the enolization of ketones catalyzed by acetic acid are unchanged in spite of this change in the detailed correlation of α-hydrogen isotope effects with the position of hydrogen at the transition state. A rule for predicting the effect of structural changes in reactants on the structure of transition states[40] is consistent with these conclusions because the bond between acetate ion and the α-hydrogen should be longer at the transition state with hydrogen-ion catalysis ($k_H/k_T = 11.4$) than without ($k_H/k_T = 10.2$).

Experimental

Materials.—D-α-Phenylisocaprophenone was prepared as described previously.[8] Although this ketone is strongly dextrorotatory in most solvents, its conjugate acid is strongly levorotatory, $[\alpha]^{25}D \cong -200°$ in 98% sulfuric acid. Initial rotations in a 4-dm. tube were $-4.39°$ (0.0303 M) in 89.27% sulfuric acid, $-5.09°$ (0.0306 M) in 91.04% acid, $-5.25°$ (0.0302 M) in 92.25% acid, $-5.77°$ (0.0314 M) in 93.81% acid, -6.05 (0.0300 M) in 98.51% acid.

Sulfuric acid concentrations are given as % by weight. Solutions below 95% were prepared by dilution of du Pont

(39) Reference 8, p. 5887.

(40) C. G. Swain and E. R. Thornton, *Tetrahedron Letters*, in press.

reagent grade acid with distilled water and analyzed by determining density in a 28-ml. pycnometer at 24.9°, interpolating between measurements reported at 17.9 and 28.1°.[41] For more concentrated solutions, reagent grade fuming acid and analyses by melting point[3,42] were used.

Recovery of Starting Material.—D-α-Phenylisocaprophenone (0.9713 g.) dissolved in 50 ml. of 93.2% sulfuric acid was held at 25° for more than ten half-lives for racemization, then diluted with water and neutralized with potassium hydroxide. The slurry was extracted thrice with ethyl ether and the extracts were washed with water, dried over Drierite and evaporated to dryness, yielding 0.8415 g. (87%), m.p. 75.0–75.8°, infrared spectrum[3] (10% solution in CCl₄, Perkin–Elmer model 21) identical to that of the original ketone. One recrystallization from absolute ethanol gave m.p. 77.2–77.6° (lit.[8] 77.6–77.8°, 77.5–77.7°).

Anal. Calcd. for $C_{18}H_{20}O$: C, 85.67; H, 7.99. Found: C, 85.91; H, 7.99.

In 98% sulfuric acid some destruction of the ketone was evident. After 4 hours at 25° only 76%, m.p. 50–67°, same infrared spectrum, was recovered by the above procedure; after 9 hours only 36%, m.p. 75.8–76.4°, same infrared spectrum.[3] Ketone dissolved in 100% acid for a short time yielded only water-soluble material, presumably sulfonated ketone.[43]

Determination of pK_{SH^+} for α-Phenylisocaprophenonium Ion.—A yellow color in solutions of α-phenylisocaprophenone in 85% or stronger sulfuric acid was attributed to the protonated ketone. A 0.037 M solution of the ketone in ethanol showed no absorption from 320 to 430 mμ in a Beckman DU spectrophotometer fitted with tungsten lamp. Transmittance values were determined at five wave lengths from 395 to 425 mμ for two 10-ml. 0.00162 M solutions, one in 99% sulfuric acid, the other in 90.6% acid.[3] With the assumption that the ketone was all protonated in 99% acid, the values of [SH⁺]/[S] were calculated from log (I/I_0) 90.6%/log(I/I_0)99% and averaged. From the H_0 value of -8.33 for 90.6% acid and the equation $pK_{SH^+} = \log$ ([SH⁺]/[S]) $+ H_0$, pK_{SH^+} is -7.39 ± 0.04.

Kinetic Procedure.—A weighed sample of ketone was dissolved in the acid solution in a thermostated 100-ml. volumetric flask. The resulting solution was then transferred to a water-jacketed all-glass 35-ml. 4-dm. polarimeter tube and measurements of time and rotation begun. Water at 25.0° from a constant temperature bath was circulated through the jacket. Readings were taken with a Schmidt and Haensch polarimeter and a sodium vapor lamp. In all runs after at least ten half-lives, the readings were within 0.02° of the reading without the tube in place. Readings were reproducible to ±0.02°. The first-order rate constant k_1 was determined from $0.693/t^{1/2}$, where $t^{1/2}$ is the difference in time between 0 and 50% reaction taken from the straight line of a semi-logarithmic plot of fraction unreacted, $(\alpha - \alpha_\infty)/(\alpha_0 - \alpha_\infty)$, vs. t, where α is the observed rotation at time t, α_0 at zero time and α_∞ at infinite time.

Excellent straight first-order plots were obtained in 85.0–93.8% acid. In 96.4 and 98.5% acid the plots were no longer linear, the rate constant increasing with time.

For calculating k_{H_2O} and $k_{HSO_4^-}$, eq. 1 was rearranged to

$$\frac{k_1([SH^+] + [S])}{[HSO_4^-][SH^+]} = k_{H_2O}\frac{[H_2O]}{[HSO_4^-]} + k_{HSO_4^-}$$

which is of the form $y = ax + b$ and is plotted in Fig. 1. The least-squares values of k_{H_2O} and $k_{HSO_4^-}$ are given in eq. 1.

(41) S. U. Pickering, *J. Chem. Soc.*, **57**, 64 (1890).

(42) C. M. Gable, H. F. Betz and S. H. Maron, *J. Am. Chem. Soc.*, **72**, 1445 (1950).

(43) R. J. Gillespie and J. A. Leisten, *J. Chem. Soc.*, 1, 7 (1954).