[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CALIFORNIA]

Carbonyl Reactions. VI. Evidence for Alternate Mechanisms for the Dehydration of β-Hydroxy Ketones[1]

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The rates of dehydration of 4-(*p*-methoxyphenyl)-4-hydroxy-2-butanone (I), 4-phenyl-4-hydroxy-2-butanone (II) and 4-(*p*-nitrophenyl)-4-hydroxy-2-butanone (III) have been studied in aqueous acid. The rates of dehydration of I, II and III are all comparable in 1 molar sulfuric acid; II and III show non-linear dependence upon H_0, while I shows a linear correlation with H_0. It is concluded that II and III undergo dehydration by rate-determining enolization; I undergoes dehydration through a carbonium ion intermediate.

Introduction

In preceding papers[2-5] we have pointed out the important kinetic role of β-hydroxyketones in the acid-catalyzed aldol condensation. It is the purpose of the present report to examine more closely the effects of a variety of structural changes upon the dehydration process.

Dehydration of alcohols has received a good deal of attention kinetically in recent years. Taft has studied the rate of dehydration of *t*-butyl alcohol[6] and *t*-amyl alcohol.[7] Recently Taft has also reported that the dehydration of *t*-butyl alcohol follows Hammett's acidity function H_0.[8] Dostrovsky and Klein have also reported rate data for the dehydration of *t*-butyl alcohol and find that it is slower than the O^{18} exchange rate.[9]

Lucas and co-workers have reported rates of dehydration for aldol,[10] β-hydroxyisovaleraldehyde,[11] diacetone alcohol,[12] β-hydroxybutyric acid[13] and β-hydroxyisovaleric acid.[14] From the limited range of acidity covered in the studies of Lucas, it appears that the rate of dehydration of the ketone and the aldehydes more closely parallels the molar concentration of the catalyzing acid, rather than H_0. Taft comments upon the differences in entropy of activation for these substances, in comparison with the *t*-butyl alcohol–isobutylene system.

Ease of dehydration is well known to be strongly dependent upon structure. This may also be seen, if the data of the above authors are extrapolated to common conditions. There is a rate difference of 10^5 between the most rapid and the slowest of the compounds above.

The previously reported correlation[5] of the rate of dehydration of 4-(*p*-methoxyphenyl)-4-hydroxy-3-methyl-2-butanone with H_0 in both aqueous sulfuric acid and in sulfuric acid in acetic acid solution made it seem highly desirable to carry out a more extensive study of the rate of dehydration of β-hydroxyketones. Accordingly a representative series of β-hydroxyketones have been prepared from substituted benzaldehydes and acetone. 4-(*p*-Methoxyphenyl)-4-hydroxy-2-butanone (I), 4-phenyl-4-hydroxy-2-butanone (II) and 4-*p*-nitrophenyl-4-hydroxy-2-butanone (III) have been prepared as crystalline solids by condensation in dilute alkali. Compound II has been reported by Schopf and Thierfelder[15] from decarboxylative condensation of acetoacetic acid and benzaldehyde; III has been obtained previously by alkaline condensation by Baeyer and Becker.[16] We have carried out studies of the rates of dehydration in aqueous acid as a function of the nature of the catalyzing acid, dependence upon acid concentration and temperature. It has thus been possible to draw quite detailed conclusions regarding the mechanisms operating with these substances.

Experimental[17]

Preparation of 4-(*p*-Methoxyphenyl)-4-hydroxy-2-butanone (I).—A mixture of 50 g. (0.368 mole) of anisaldehyde and 200 g. (3.4 moles) of acetone was cooled to 0° and added rapidly to a precooled solution of 600 ml. of 0.03 *N* sodium hydroxide. The reaction was maintained at 0° in an ice-bath and stirred for 25 minutes, after which it was neutralized with 20 ml. of 1 *M* sulfuric acid and the solution extracted with ether. The ether extracts were dried with anhydrous magnesium sulfate and distilled at 6 mm. pressure to remove the excess anisaldehyde. The residue was dissolved in ether and cooled to yield a pale yellow solid, m.p. 30–35°. Some of the product was distilled at 91–93° (6 mm.). Recrystallization of the pale yellow solid from 95% ethanol yielded a white crystalline solid, m.p. 40°. The recovery from ethanol was poor but afforded analytical material.

Anal. Calcd. for $C_{11}H_{14}O_3$: C, 68.02; H, 7.26. Found: C, 68.27; H, 7.43.

Preparation of 4-Phenyl-4-hydroxy-2-butanone (II).—Similarly, benzaldehyde and acetone afforded II, b.p. 131–137° (6 mm.). Extensive manipulation afforded crystals, m.p. 32–34°, which were recrystallized from carbon tetrachloride. In this manner there was obtained 2.2 g. of II, m.p. 34–36° (lit.[15] 38°).

The 3,5-dinitrobenzoate was prepared by the method of Brewster and Ciotti,[18] m.p. 128–129°.

Anal. Calcd. for $C_{17}H_{14}N_2O_7$: C, 56.98; H, 3.94; N, 7.82. Found: C, 57.64; H, 3.94; N, 8.25.

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[1] Presented in part at the XVI International Congress of Pure and Applied Chemistry, Paris, July, 1957, and at the 133rd Meeting of the American Chemical Society, San Francisco, Calif., April, 1958.

[2] D. S. Noyce and W. A. Pryor, THIS JOURNAL, **77**, 1397 (1955).

[3] D. S. Noyce, W. A. Pryor and A. T. Bottini, *ibid.*, **77**, 1402 (1955).

[4] D. S. Noyce and L. R. Snyder, *ibid.*, **80**, 4033 (1958).

[5] D. S. Noyce and L. R. Snyder, *ibid.*, **80**, 4324 (1958).

[6] R. W. Taft and P. Reisz, *ibid.*, **77**, 902 (1955).

[7] E. L. Purlee, R. W. Taft and C. A. De Fazio, *ibid.*, **77**, 838 (1955).

[8] R. H. Boyd, R. W. Taft, A. P. Wolf and D. Christman, Abstracts 132nd Meeting, A.C.S., New York, N. Y., September, 1957, pp. 76P.

[9] I. Dostrovsky and F. S. Klein, *J. Chem. Soc.*, 791 (1955).

[10] S. Winstein and H. J. Lucas, THIS JOURNAL, **59**, 1461 (1937).

[11] H. J. Lucas, W. T. Stewart and D. Pressman, *ibid.*, **66**, 1818 (1944).

[12] D. Pressman, H. J. Lucas and L. Brewer, *ibid.*, **64**, 1122 (1942).

[13] D. Pressman and H. J. Lucas, *ibid.*, **61**, 2271 (1939).

[14] D. Pressman and H. J. Lucas, *ibid.*, **62**, 2060 (1940).

[15] C. Schopf and K. Thierfelder, *Ann.*, **518**, 127 (1935).

[16] A. Baeyer and P. Becker, *Ber.*, **16**, 1968 (1883).

[17] Analyses are by the Microanalytical Laboratory, University of California.

[18] J. H. Brewster and C. J. Ciotti, THIS JOURNAL, **77**, 6214 (1955).

4-(p-Nitrophenyl)-4-hydroxy-2-butanone (III) was prepared by the method of Baeyer and Becker[16] using more dilute sodium hydroxide, m.p. 60–62° (lit.[16] 61°). **4-Phenyl-3-buten-2-one** (V) **and 4-(p-methoxyphenyl)-3-buten-2-one** (IV) were prepared by the method of reference 19. 4-(p-Nitrophenyl)-3-buten-2-one (VI) was prepared by nitration of V following the procedure of Burckhalter and Johnson.[20]

Kinetic Procedures.—The rate of dehydration of the ketol was followed by observing the formation of product as the increase in absorption in the ultraviolet spectrum. The absorption spectra of the aldehyde, acetone, ketol and α,β-unsaturated ketone are sufficiently different to make this type of analysis possible. The optical density of the solution read from a Beckman model DU spectrophotometer at a selected wave length was used to calculate the percentage reaction. All kinetic determinations were allowed to proceed to 10 half-lives to determine the optical density of the solution at complete reaction. The optical density of the corresponding α,β-unsaturated ketone was determined at the selected wave length in each acid solution used to determine that the dehydration of the ketol went only to product. The spectrum of the final solution was recorded from 240 to 340 mμ. In all cases the observed optical density corresponded to complete reaction.

For reactions with relatively long half-lives a sample of solution was withdrawn from the flask in the constant temperature bath for each reading. In the case of fast reactions the cell compartment of the spectrophotometer was fitted with a cell block which was connected to the constant temperature bath and all readings were made on one sample.

The acidity of the reaction solution was determined after each kinetic run by titration of an aliquot with standard 1 M sodium hydroxide solution using brom thymol blue indicator. The rate constants were determined by both graphical and analytical methods. Least squares calculations were carried out on typical results, indicating that the precision of the data was of the order of 3%.

Product Isolation from the Dehydration of the Ketols Under Kinetic Conditions.—A solution of 110 mg. of I in 500 ml. of 1 M sulfuric acid was heated at 45° for a period of time calculated to be 10 half-lives. The reaction mixture was neutralized with 6 M sodium hydroxide and extracted with ether on a continuous liquid extractor. The ethereal solution was concentrated and dried by azeotropic distillation of the water with benzene. The material obtained was sublimed to yield 77 mg. of IV (77.2% yield), m.p. 68–71°. The infrared spectrum of the product obtained was identical with that of IV.

Compound II, 593 mg., dissolved in 500 ml. of 1 M sulfuric acid, was heated at 45° for a period of time calculated to be 10 half-lives. The solution was neutralized with 167 ml. of 6 M sodium hydroxide solution and extracted with ether on a continuous liquid extractor. The ether solution was concentrated until a pale yellow solid separated and then 40 ml. of benzene was added and distilled to remove any water. A yield of 515 mg. of a light yellow oily solid was obtained (97.5%) which had the same infrared absorption spectrum in carbon tetrachloride as a sample of the product V.

Compound III, 418 mg., was dissolved in 1 liter of approximately 3 M sulfuric acid and allowed to react at 45° for a period of time calculated to be 10 half-lives. The solution was not neutralized as the nitro compound is sensitive to base. The ethereal extract of the solution was dried over anhydrous potassium carbonate. Evaporation of the ether afforded pale yellow crystals which were recrystallized from aqueous ethanol. In this manner there was obtained 329 mg. of VI, m.p. 107–109° (86.1% yield). The infrared spectrum of the product obtained was identical with that of VI.

Results

The results obtained are presented in Tables I–III.

TABLE I

RATE OF DEHYDRATION OF 4-(p-METHOXYPHENYL)-4-HYDROXY-2-BUTANONE (I)

Concentration of ketol = 2.87 × 10^{-5} M, T = 25.00°

H_2SO_4, molar	H_0[21]	$k_{obs} \times 10^6$, sec.$^{-1}$	log $k_{obs} + H_0$	$k_0 \times 10^6$, sec.$^{-1a}$	log $k_0 + H_0$
1.04	−0.29	36.0 ± 0.5	−4.73	18.5	−5.02
		327 ± 4^b			
1.82	−0.74	108	−4.71	69	−4.90
2.59	−1.17	308	−4.68	244	−4.78
3.47	−1.61	937	−4.64	830	−4.69
3.94	−1.83	1635	−4.62	1530	−4.65
$HClO_4$, molar					
3.36	−1.39	552	−4.65	510	−4.68

^{a} Derived by subtracting the appropriate interpolated values from Table II. ^{b} At 45.01°.

TABLE II

RATE OF DEHYDRATION OF 4-PHENYL-4-HYDROXY-2-BUTANONE (II)

Concentration of ketol 3.18 × 19^{-5} M, T = 25.00°

H_2SO_4, molar	H_0	$k \times 10^6$, sec.$^{-1}$	log $k + H_0$
0.48	+0.10	6.25	−5.10
1.00	−0.26	16.32 ± 0.29	−5.05
		115 ± 4^a	
2.54	−1.14	62.1	−5.35
3.40	−1.57	103	−5.56
5.09	−2.32	228	−5.96
7.66	−3.68	807	−6.77
$HClO_4$, molar			
3.00	−1.23	32.2	−5.72
7.32	−3.84	286	−7.38
9.30	−5.28	2450	−7.89

^{a} At 44.97°

TABLE III

RATE OF DEHYDRATION OF 4-(p-NITROPHENYL)-4-HYDROXY-2-BUTANONE (III)

Concentration of ketol 5 × 10^{-6} M, T = 25.00°, 10-cm. cells

H_2SO_4, molar	H_0	$k \times 10^6$, sec.$^{-1}$	log $k + H_0$
1.02	−0.27	15.8 ± 0.1	−5.07
		106 ± 1^a	
2.59	−1.17	60.2	−5.39
3.75	−1.73	122	−5.64
5.61	−2.55	285	−6.10
7.30	−3.46	578	−6.70

^{a} At 44.81°.

The results which have been obtained are striking from the following points of view: (1) The rates obtained show very little variation with the substituent in 1 molar sulfuric acid; (2) the correlations with the acidity function differ for the three compounds; (3) the effect of using sulfuric acid or perchloric acid differs for I and II; (4) the activation parameters show no monotonic change with the electron-withdrawing ability of the substituent. It is perhaps profitable to discuss the kinetic results, which are presented in Tables I, II and III from the point of view of the above general observations.

Effect of Structure Upon Rate.—The rates of dehydration of *sec*-butyl alcohol and t-butyl alcohol differ by about 10^4, the rates of dehydration of β-hydroxybutyric acid and β-hydroxyisovaleric acid

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(19) "Organic Syntheses," Coll. Vol. I, 2nd ed., John Wiley and Sons, Inc., New York, N. Y., 1941, p. 77.

(20) J. H. Burckhalter and S. H. Johnson, THIS JOURNAL, **73**, 4835 (1951).

(21) Values from F. A. Long and M. A. Paul, *Chem. Revs.*, **57**, 1 (1957).

differ by 20, while β-hydroxybutyraldehyde and β-hydroxyisovaleraldehyde differ by only 25%. In the present instance the change from *p*-methoxyl to *p*-nitro in the aromatic ring causes only a threefold change in rate. Were the rate-controlling step of the dehydration process for all three compounds to involve the formation of the substituted benzyl carbonium ion, one would expect a rate change of the type observed for the benzyl tosylates.[22,23] Further, the rates of dehydration of a series of β-aryl-β-hydroxypropionic acids[24] show strong structural effects, with β-(*p*-methoxyphenyl)-β-hydroxypropionic acid undergoing dehydration at nearly 10^7 times the rate of β-(*p*-nitrophenyl)-β-hydroxypropionic acid. The rate of dehydration of β-(*p*-methoxyphenyl)-β-hydroxypropionic acid is similar to the rate of dehydration of I.

These considerations suggest that the rate-determining process takes place insulated from the benzene ring and any substituent effect. Such a process is rate-determining enolization. In 1 molar sulfuric acid the rate of halogenation of acetophenone[25] (rate of enolization) is about 1.5 times the rate of dehydration observed for II. A variety of structural changes slow enolization. Though it is difficult to assess these sufficiently to provide a basis for accurate prediction of the rate of enolization of II, it is sufficient to point out that the enolization process (taking place two to three atoms removed from the ring) would not be expected to show any substituent effect.

The preceding argument makes plausible a mechanism in which acid-catalyzed enolization of the β-hydroxyketone is rate determining (equations 1 and 2). The subsequent dehydration of the enolic form is reasonably expected to be rapid. Acid-catalyzed loss of the benzylic (and allylic) hydroxyl group leads directly to the protonic salt of the unsaturated ketone (equations 3 and 4).

We conclude then that the dehydration of II and III proceeds *via* enolization.

Correlation with the Acidity Function, H_0.—An enolization process should not follow the acidity function.[25] Such is the case for 4-phenyl-4-hydroxy-2-butanone and 4-(*p*-nitrophenyl)-4-hydroxy-2-butanone. Figure 1 shows the results of Table II plotted against H_0. When the rate of dehydration of II is compared with Zucker and Hammett's data for the enolization of acetophenone good correlation is observed (Fig. 2).

In contrast the experimentally measured rate of dehydration of I parallels the acidity function very closely with a slope of 1.07 ± 0.007. Noyce and Snyder[5] have suggested that the similar dehydration of 4-(*p*-methoxyphenyl)-4-hydroxy-3-methyl-2-butanone proceeds *via* a carbonium ion intermediate. We feel that such is also the case with I (equations 6–8).

Consideration of the enolization mechanism suggests that a variable fraction of the observed dehydration of I is also proceeding *via* an enolization

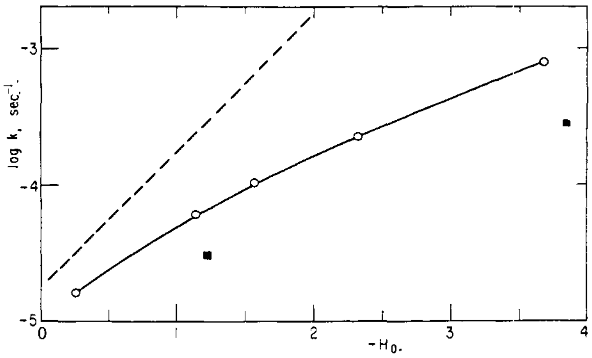


Fig. 1.—Rate of dehydration of $C_6H_5CHOHCH_2COCH_3$: O—O, sulfuric acid; ■, perchloric acid; -------, predicted slope for linear correlation with H_0.

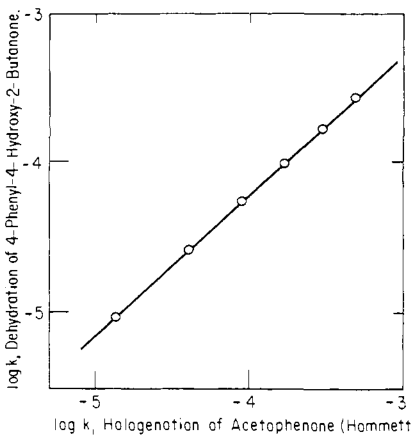
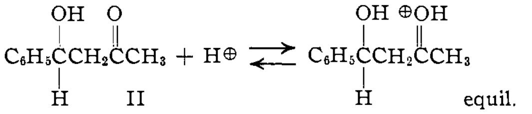


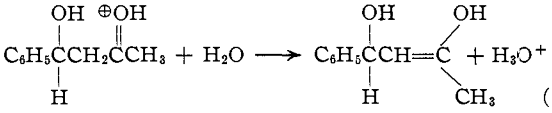
Fig. 2.—Points are interpolated from Table II and Reference 25.

mechanism, but that the *major* portion of the reaction is taking place by another pathway. The derived rate constants, k_c for the alternate pathway are given in Table I. When plotted against H_0, these derived rate constants k_c show linear correlation with H_0, with a slope of 1.24 ±

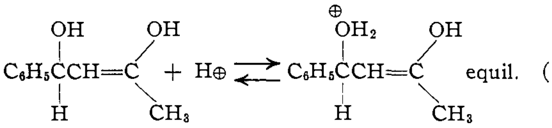


$$C_6H_5\underset{H}{\overset{OH}{C}}CH_2\overset{O}{\overset{\|}{C}}CH_3 + H^{\oplus} \rightleftarrows C_6H_5\underset{H}{\overset{OH}{C}}CH_2\overset{\oplus OH}{\overset{\|}{C}}CH_3 \qquad \text{equil.} \quad (1)$$

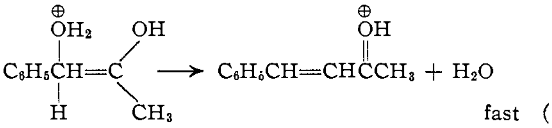
II



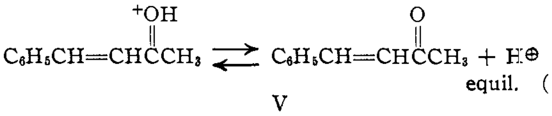
$$C_6H_5\underset{H}{\overset{OH}{C}}CH_2\overset{\oplus OH}{\overset{\|}{C}}CH_3 + H_2O \longrightarrow C_6H_5\underset{H}{\overset{OH}{C}}CH{=}C\begin{matrix}OH\\CH_3\end{matrix} + H_3O^+ \text{ slow} \quad (2)$$



$$C_6H_5\underset{H}{\overset{OH}{C}}CH{=}C\begin{matrix}OH\\CH_3\end{matrix} + H^{\oplus} \rightleftarrows C_6H_5\underset{H}{\overset{\overset{\oplus}{OH_2}}{C}}CH{=}C\begin{matrix}OH\\CH_3\end{matrix} \qquad \text{equil.} \quad (3)$$



$$C_6H_5\underset{H}{\overset{\overset{\oplus}{OH_2}}{C}}H{=}C\begin{matrix}OH\\CH_3\end{matrix} \longrightarrow C_6H_5CH{=}CH\overset{\overset{\oplus}{OH}}{\overset{\|}{C}}CH_3 + H_2O \qquad \text{fast} \quad (4)$$



$$C_6H_5CH{=}CH\overset{^+OH}{\overset{\|}{C}}CH_3 \rightleftarrows C_6H_5CH{=}CH\overset{O}{\overset{\|}{C}}CH_3 + H^{\oplus} \qquad \text{equil.} \quad (5)$$

V

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[22] J. K. Kochi and G. S. Hammond, THIS JOURNAL, **75**, 3445 (1953).

[23] F. T. Fang, J. K. Kochi and G. S. Hammond, *ibid.*, **80**, 563 (1958).

[24] D. S. Noyce and P. A. King, to be published.

[25] L. Zucker and L. P. Hammett, THIS JOURNAL, **61**, 2791 (1939).

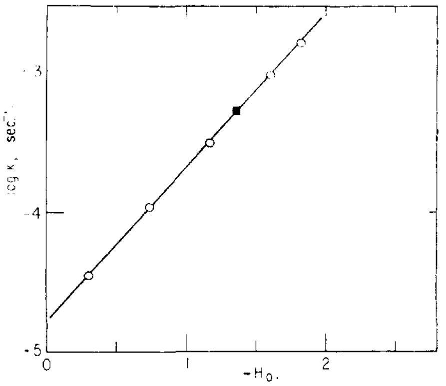
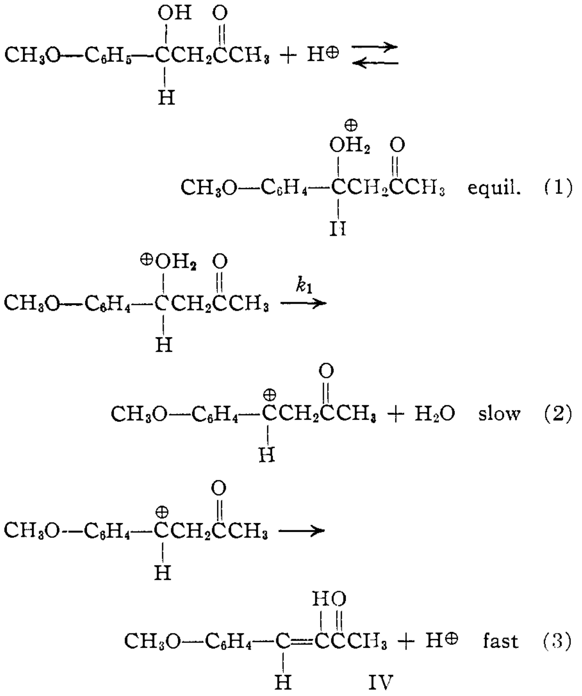


Fig. 3.—Rate of dehydration of $CH_3OC_6H_4CHOHCH_2COCH_3$: O—O, sulfuric acid; ■, perchloric acid.

0.01. We conclude that k_c represents dehydration by a carbonium ion process (representing 51% of the reaction at 1 molar sulfuric acid, and 93% of the total reaction of I at 3.94 molar sulfuric acid).



$$\mathrm{CH_3O{-}C_6H_5{-}\underset{H}{\overset{OH}{C}}CH_2\overset{O}{\overset{\|}{C}}CH_3 + H^{\oplus} \rightleftharpoons CH_3O{-}C_6H_4{-}\underset{H}{\overset{\overset{\oplus}{OH_2}}{C}}CH_2\overset{O}{\overset{\|}{C}}CH_3} \quad \text{equil.} \quad (1)$$

$$\mathrm{CH_3O{-}C_6H_4{-}\underset{H}{\overset{\oplus OH_2}{C}}CH_2\overset{O}{\overset{\|}{C}}CH_3 \xrightarrow{k_1} CH_3O{-}C_6H_4{-}\underset{H}{\overset{\oplus}{C}}CH_2\overset{O}{\overset{\|}{C}}CH_3 + H_2O} \quad \text{slow} \quad (2)$$

$$\mathrm{CH_3O{-}C_6H_4{-}\underset{H}{\overset{\oplus}{C}}CH_2\overset{O}{\overset{\|}{C}}CH_3 \longrightarrow CH_3O{-}C_6H_4{-}\underset{H}{C}{=}\overset{HO}{C}\overset{O}{\overset{\|}{C}}CH_3 + H^{\oplus}} \quad \text{fast} \quad (3)$$

IV

The recent work of Taft[8] showing that the rate of dehydration of *t*-butyl alcohol may be correlated with H_0 and the work of Dostrovsky and Klein,[9] of Grunwald, Heller and Klein,[26] and of Bunton and Llewellyn[27] on other dehydrations and carbonium ion reactions suggest that acid-catalyzed reactions of alcohols proceeding through carbonium ion intermediates may be expected to show correlation with H_0.[28]

Correlation with the C_0 function of Deno is not satisfactory; the slope is definitely less than unity and a plot of the data reveals a distinct downward curvature.

Effect of the Nature of the Catalyzing Acid.—One conclusion from the H_0 treatment of acid catalyzed reaction rates is that the correlation should be independent of the particular acid used. For I, one kinetic experiment carried out at $H_0 = -1.39$ using perchloric acid, gives a rate of reaction indistinguishable from that predicted from the data obtained in sulfuric acid. On the other hand, II shows a marked decrease in rate of reaction using perchloric acid as does the halogenation of acetophenone.[25] These experiments serve to support the classification into two distinct reaction pathways and in particular are consistent with the mechanisms outlined.

TABLE IV

ACTIVATION PARAMETERS

Compound	$\Delta F^{\ddagger}$, kcal./mole	$\Delta H^{\ddagger}$, kcal./mole	$\Delta S^{\ddagger}$, e.u.
I[a]	23.5	20.2	−10.9 ± 0.6
I[b]	23.9	22.4	− 5.2 ± 2.0
II	24.0	18.1	−19.6 ± 1.6
III	24.0	17.5	−21.9 ± 0.3

[a] For directly observed rates. [b] For k_c calculated.

Activation Parameters.—In 1 molar sulfuric acid the heats and entropies of activation for II and III are essentially identical (Table IV). For I the entropy of activation is a good deal less negative, corresponding to less constraint in the activated complex. If one adopts the Zucker–Hammett hypothesis without further discussion, one might expect a difference of 15–20 entropy units (corresponding to the entropy of freezing of a molecule of water in the transition state). Taft has used such an argument in support of the difference for the hydration of crotonaldehyde and isobutene.

The data presented all support the proposed alternative mechanisms, one involving a carbonium ion pathway, the other involving enolization as the rate-determining step.

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(26) E. Grunwald, A. Heller, and F. S. Klein, *J. Chem. Soc.*, 2604 (1957).

(27) C. A. Bunton and D. R. Llewellyn, *ibid.*, 3402 (1957).

(28) The slope of such correlations may appreciably exceed unity, depending upon the rate of ionization and the rate of subsequent steps. For the acid-catalyzed racemization of 1-phenylethanol,[26] the slope is about 1.2 in dilute perchloric acid solution, thus falling between the expected results for H_0 or C_0. Deno[29] has suggested that correlation with C_0 may be observed if the carbonium ion represents a prior equilibrium step. However, experimental demonstration of such a dependency has not been observed with only moderate concentrations of acid. For the sake of expediency, we shall adopt the point of view that correlation with H_0, with a slope of uuity or greater is consistent with a carbonium ion mechanism, without suggesting a more detailed interpretation.

(29) N. C. Deno and C. Perizzolo, THIS JOURNAL, **79**, 1348 (1957).