over magnesium sulfate, and filtered. The solvent was removed and the product analyzed by glpc.[42] The product ratio obtained by integration of the peaks was 48% *cis*- and 52% *trans*-4-*t*-butylcyclohexanol.

Camphorpinacol. Reduction of 5.0 g of camphor by 12.5 g of lithium was carried out in the manner described as method B. The crude reaction product was heated at 40° (0.1 mm) for 24 hr to remove the monomeric material. The residue, 2.5 g, was chromatographed on 100 g of neutral alumina and elution with benzene afforded 0.87 g (17%) of yellow semisolid material. The nmr spectrum showed no proton adjacent to hydroxyl in the region δ 3.2–4.2 and the infrared spectrum was consistent with the structure of camphorpinacol. Although this material was homogeneous to tlc, it could not be crystallized and is probably a mixture of diastereomers. Oxidation of 0.060 g of this material with 0.50 g of lead tetraacetate gave 0.050 g of yellow oil which contained 8% camphor (glpc) and showed carbonyl absorption at 5.75 μ.[43]

Norcamphorpinacol. The reduction of 5.0 g of norcamphor by method B described above for the preparation of camphorpinacol gave 4.0 g of yellow oil. This material was taken up in benzene and chromatographed on 240 g of Bio-Rad neutral alumina. Elution with methylene chloride–2% methanol gave 2.7 g of a mixture of norborneols and pinacol. Rechromatography of this mixture on 100 g of neutral alumina and elution with methylene chloride–0.5% isopropyl alcohol gave 1.4 g (28%) of crystalline material, the infrared and nmr spectra of which were consistent with the structure of norcamphorpinacol. Four recrystallizations from hexane gave the analytical sample, mp 144° (sublimes).

Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.72; H, 9.98. Found: C, 75.44; H, 9.78.

Cleavage of Norcamphorpinacol. Impure norcamphorpinacol, 0.11 g, containing about 50% of the norborneols, was mixed with 1.0 g of lead tetraacetate and 15 ml of glacial acetic acid and stirred 3 hr at room temperature. Saturated sodium chloride solution was added and the mixture extracted with ether. The extracts were washed with 5% aqueous sodium carbonate, then with water, and dried; the solvent was removed through a Vigreux column, giving 0.40 g of a yellow semicrystalline material, 20% norcamphor by glpc. The infrared spectrum showed carbonyl absorption at 5.78 μ. The 2,4-dinitrophenylhydrazone was prepared, mp 126–129° (lit.[44] mp 131.5–132°), mmp 125–127° with an authentic sample.

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(43) R. Criegee, E. Buckner, and W. Walther [*Chem. Ber.*, 73, 571 (1940)] have pointed out that camphorpinacol is extremely resistant to cleavage by lead tetraacetate.

(44) R. L. Bixler and C. Niemann, *J. Org. Chem.*, 23, 742 (1958).

The Possibility of a Cyclic Mechanism for Acid-Catalyzed Ester Hydrolysis

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Abstract: The rates of hydrolysis of protonated ethyl benzoate and ethyl acetate in 12–79% sulfuric acid and the carbonyl oxygen-18 exchange of ethyl acetate have been found to be linearly dependent on the square of the activity of water. The observed kinetic dependence for hydrolysis and exchange was rationalized by hydrogen-bonded cyclic transition states consisting of protonated ester and two water molecules. The rates of hydrolysis of protonated ester were calculated from the observed concentration of protonated ester and ordinary rates of hydrolysis.

Acid-catalyzed ester hydrolysis is known to be first order in acid and ester.[1] The order in water was not known before our preliminary communication[2] because of the paucity of good water activity data[3] and the perturbing influence[4] of prior protonation equilibrium. We now wish to report complete results for the hydrolysis of two simple esters in sulfuric acid solutions. The concentration of protonated ester was determined in solutions with measurable rates of hydrolysis thereby allowing us to calculate the rate of hydrolysis of protonated ester. This rate was linearly dependent on the square of the activity of water.[5]

Hydrolysis and Carbonyl Oxygen-18 Exchange Data

Table I. Hydrolysis of Ethyl Acetate at 25.0°

% H_2SO_4	$-H_0$	k_{obsd}, sec^{-1}	$[BH^+]/[B]$	k_{BH^+}[b] × 10^2 sec^{-1}	a_{H_2O}
12.2[a]	0.46	1.88×10^{-4}	6.76×10^{-5}	278	0.942
16.4[a]	0.76	3.09×10^{-4}	1.05×10^{-4}	294	0.914
23.9[a]	1.29	5.61×10^{-4}	2.32×10^{-4}	242	0.836
25.5[a]	1.41	6.55×10^{-4}	2.76×10^{-4}	237	0.816
29.4[a]	1.68	7.97×10^{-4}	4.14×10^{-4}	193	0.761
33.43[a]	1.96	1.04×10^{-3}	6.24×10^{-4}	167	0.694
36.67[a]	2.18	1.28×10^{-3}	8.71×10^{-4}	147	0.633
43.56[a]	2.72	1.66×10^{-3}	1.96×10^{-3}	84.8	0.490
47.00	3.06	1.785×10^{-3}	3.18×10^{-3}	56.3	0.415
48.00[a]	3.17	1.92×10^{-3}	3.76×10^{-3}	51.2	0.393
51.55	3.55	1.86×10^{-3}	6.61×10^{-3}	28.3	0.317
55.60	3.98	1.97×10^{-3}	1.24×10^{-2}	16.1	0.238
56.25	4.05	1.84×10^{-3}	1.39×10^{-2}	13.4	0.225
59.18	4.37	1.84×10^{-3}	2.21×10^{-2}	8.49	0.176
59.88	4.45	1.83×10^{-3}	2.51×10^{-2}	7.48	0.164
66.32	5.25	1.21×10^{-3}	8.26×10^{-2}	1.58	0.078
68.97	5.64	9.03×10^{-4}	1.47×10^{-1}	0.704	0.054
69.88	5.79	9.03×10^{-4}	1.83×10^{-1}	0.584	0.047
73.55	6.33	4.44×10^{-4}	4.16×10^{-1}	0.151	0.0241
78.80	7.16	9.18×10^{-5}	1.41×10^{0}	0.0157	0.00769

[a] R. P. Bell, A. L. Dowding, and J. A. Noble, *J. Chem. Soc.*, 3106 (1955). [b] Hydrolysis.

The rate of hydrolysis of ethyl acetate in sulfuric acid solutions has been followed by titration, dilatometry, and changes in absorption at 200 mμ. These data are summarized in Table I and shows a rate

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(1) M. L. Bender, *Chem. Rev.*, 60, 53 (1960).

(2) C. A. Lane, *J. Am. Chem. Soc.*, 86, 2521 (1964).

(3) J. Koskillalio, *Suomen Kemistilehti, B.*, 35, 62 (1962).

(4) E. M. Arnett and G. W. Mach, *J. Am. Chem. Soc.*, 88, 1177 (1966).

(5) The water activity is precisely known from the results of W. F. Giauque, E. W. Hornung, J. E. Kunzler, and T. R. Rubin, *ibid.*, 82, 62 (1960).

Table II. Carbonyl Oxygen-18 Exchange of Ethyl Acetate at 25.0°

% H_2SO_4	$-H_0$	k_{obsd}, sec^{-1}	$[BH^+]/[B]$	$k_{BH^+}{}^a \times 10^2\ sec^{-1}$	a_{H_2O}
11.46	0.41	2.05×10^{-5}	6.23×10^{-5}	32.9	0.945
59.18	4.37	3.81×10^{-4}	2.23×10^{-2}	1.74	0.176
73.55	6.33	1.27×10^{-4}	4.10×10^{-1}	0.0437	0.0241

[a] Exchange.

maximum at 56% sulfuric acid. Table II includes carbonyl oxygen-18 exchange data for ethyl acetate which also shows a maximum in the 56% region. The hydrolysis of methyl benzoate is 140 times slower than ethyl acetate and shows a maximum at 60% acid (Table III).

Table III. Hydrolysis of Methyl Benzoate at 25.0°

% H_2SO_4	$-H_0$	k_{obsd}, sec^{-1}	$[BH^+]/[B]$	$k_{BH^+}{}^a \times 10^2\ sec^{-1}$	a_{H_2O}
42.04	2.57	5.68×10^{-6}	1.82×10^{-5}	31.4	0.522
52.93	3.69	1.17×10^{-5}	1.60×10^{-4}	7.30	0.290
59.32	4.39	1.39×10^{-5}	6.26×10^{-4}	2.22	0.174
65.20	5.09	1.33×10^{-5}	2.45×10^{-3}	0.545	0.091
69.76	5.77	1.15×10^{-5}	9.20×10^{-3}	0.126	0.049
73.75	6.37	7.47×10^{-6}	2.96×10^{-2}	0.0260	0.024
75.12	6.58	6.32×10^{-6}	4.47×10^{-2}	0.01476	0.018

[a] Hydrolysis.

Protonation Equilibrium

Protonation prior to hydrolysis is strongly suggested by greater rates of hydrolysis in deuterated solvents,[6] kinetic acid dependence,[1] and the observation of the C=OH+ proton signal in the nuclear magnetic resonance spectrum of ethyl acetate in fluorosulfuric acid.[7]

Protonation causes a flat shoulder to appear at 300 mμ in the ultraviolet spectrum of methyl benzoate. The solvent shifts that occur before protonation do not produce absorption at 300 mμ and any shifts after complete protonation are minimized by the flat absorption curve. Forty-five observations of the optical density at 300 mμ at various sulfuric acid concentrations gave a good nonlinear least-squares fit to the equation[8]

$$\log([BH^+]/[B]) = 0.846(8.18 - H_0) \qquad (1)$$

The nonlinear confidence limits were 0.772–0.928 for the slope and 8.13–8.22 for the pK_a.

The extent of protonation of ethyl acetate was obtained independently by optical density increases at 190 mμ and by downfield shifts of the acetyl proton resonance. The two methods are described in the Experimental Section, and the data from each agreed very well. Twenty-eight observations of [BH+]/[B] gave a satisfactory graphical fit to[8]

$$\log([BH^+]/[B]) = 0.645(-6.93 - H_0) \qquad (2)$$

Kinetic Order in Water

The simplest mechanism satisfying prior protonation and water dependence is

$$E + H^+ \overset{K}{\rightleftharpoons} EH^+ \qquad (3)$$

$$EH^+ + nH_2O \xrightarrow{k_2} \text{products} \qquad (4)$$

Since the observed rate is dependent on the total ester concentration we write[9]

$$k_{obsd}[E + EH^+] = k_2[EH^+]a_{H_2O}{}^n \qquad (5)$$

The ratio $[EH^+]/[E] = \alpha$ is known from protonation studies, then

$$\log k_{obsd}[(1 + \alpha)/\alpha] = \log k_2 + n \log a_{H_2O} \qquad (6)$$

Thus a plot of $\log k_{obsd}[(1 + \alpha)/\alpha]$ *vs.* $\log a_{H_2O}$ gives the order in water provided the ratio of the activity coefficients for protonated ester and transition state remains constant. Figure 1 shows such a plot for ethyl acetate hydrolysis, methyl benzoate hydrolysis, and ethyl acetate carbonyl oxygen-18 exchange. The respective plots are linear with slopes of 2.00, 2.25, and 1.87. Since the slopes are all nearly two we conclude that if differences in activity coefficient behavior[10,11] are small, the order in water is two.

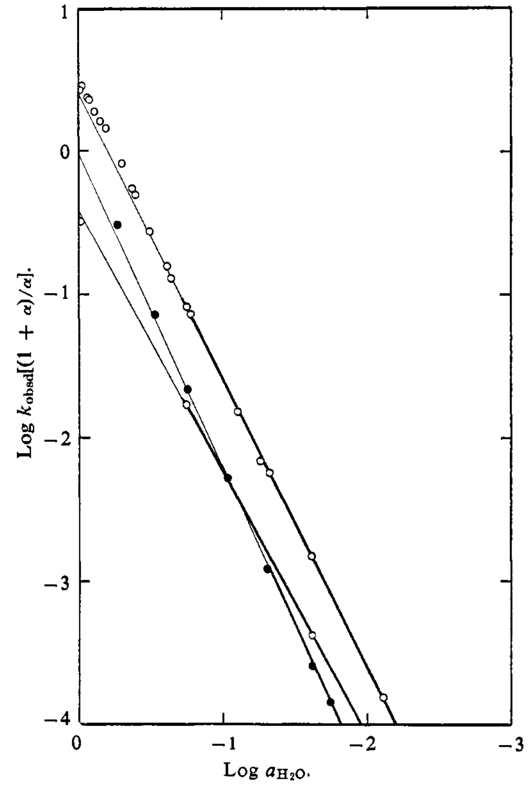

Figure 1. Rate of reaction of protonated ethyl acetate (open circles) and methyl benzoate (closed circles) *vs.* activity of water. The upper ethyl acetate plot is for hydrolysis and the lower plot is for carbonyl ^{18}O exchange. The heavy lines indicate the region where the concentration of protonated ester was measured.

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(6) P. Salomaa, L. L. Schlaeger, and F. A. Long, *J. Am. Chem. Soc.*, **86**, 1 (1964).

(7) T. Birchall and R. J. Gillespie, *Can. J. Chem.*, **43**, 1045 (1965).

(8) H_0 is the acidity function based on the protonation of substituted anilines. We have used the H_0 values of M. J. Jorgenson and D. R. Hartter, *J. Am. Chem. Soc.*, **85**, 878 (1963).

(9) If k_2 in eq 5 is interpreted in terms of transition-state theory, $k_2 = k_2{}^0(f_{EH^+}/f^\ddagger)$ where $k_2{}^0$ is the rate constant in a dilute aqueous solution. f_{EH^+} and $f^\ddagger$ are the activity coefficients of the protonated ester and the transition state, respectively.

(10) The activity coefficients of cations in sulfuric acid solutions are nearly the same for the same type of cation, such as substituted anilinium ions, but differ between types: R. H. Boyd, *J. Am. Chem. Soc.*, **85**, 1555 (1963); L. A. Sweeting and K. Yeates, *Can. J. Chem.*, **44**, 2395 (1966).

(11) (a) It has been suggested[11b] that London forces between solute and solvent will vary with solvent composition. Apparently this is not a serious concern in moderately concentrated sulfuric acid as methyl benzoate with its extensive charge delocalization has the same behavior as ethyl acetate. (b) E. Grunwald and E. Price, *J. Am. Chem. Soc.*, **86**, 4517 (1964).

Approximate pK_a's from the Hydrolysis Data

We now wish to describe a technique which could be used to obtain an estimate of a substrate's pK_a from hydrolysis data. It should be used with caution since the aniline bases used for H_0 are different from the substrates employed in hydrolysis studies. If the hydrolysis reaction is dependent on two water molecules and some function of H_0, it might be possible to derive the pK_a from the rate data. Equation 5 was modified for this purpose by setting $n = 2$ and using the exponential form of the Hammett equation

$$\alpha = 10 \exp(\text{slope}(pK_a - H_0)) \tag{7}$$

$$k_{\text{obsd}} = k_2 a_{H_2O}{}^2 \alpha/(1 + \alpha) \tag{8}$$

The known terms are a_{H_2O}, k_{obsd}, and H_0. Nonlinear least-squares fit to the known terms gave the best values of pK_a, slope, and k_2. The ethyl acetate hydrolysis data yielded $pK_a = -7.66$, slope $= 0.594$, $k_2 = 5.25$ sec^{-1}. The values from the spectroscopic determinations were $pK_a = -6.93$ and slope $= 0.745$. The best fit of the methyl benzoate hydrolysis data gave $pK_a = -8.29$, slope $= 0.745$, $k_2 = 0.379$ sec^{-1}. The spectroscopic values were $pK_a = -8.18$ and slope $= 0.846$.

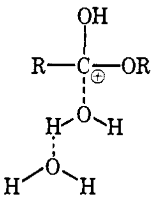
Since the slopes of eq 1, 2, and 7 must increase to unity in the pH region the equations must fail in dilute acid. We, therefore, rest our conclusions on data from the region where we can observe the concentration of protonated ester, this is indicated by the heavy lines in Figure 1. The remaining plot depends on the validity of the protonation equations and is indicated by the thinner lines in Figure 1.

Discussion

Swain and Rosenberg have used the same approach to water dependence in their study of the enolization of 1,2-diphenyl-4-methyl-1-pentanone in sulfuric acid solutions.[12] They found dependence on water and bisulfate, but their water activity was calculated from a theoretical relationship. We have replotted their data using Giauque's water activity data and their protonation ratios.[13] The plot similar to Figure 1 is linearly dependent on water with a slope of 0.86. This strongly suggests that a water molecule is required to remove the α-hydrogen from the protonated ketone.

Yates has recently reported that the hydrolysis of most acetates is dependent on two water molecules, especially in dilute sulfuric acid. Their approach is similar to ours, except that the protonation behavior is assumed to be the same for all of the acetates.[14]

The function of the second water molecule can be explained by two transition states. Transition state I leads either to hydrolysis or exchange after further proton transfers to the OR or OH, respectively. Transition state II accomplishes all of the proton transfers in one step through the cyclic hydrogen bonds. Carbonyl oxygen-18 exchanges may occur by exchanging the positions of the OH and OR.



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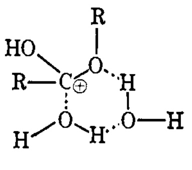

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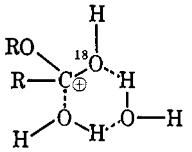

Experimental Section

Carbonyl Oxygen-18 Exchange. Ethyl acetate containing 33.13% carbonyl oxygen-18 was prepared from ethyl acetimidate and 30% oxygen-18 water. Solutions of the enriched ethyl acetate in sulfuric acid were thermostated at 25.0° and aliquots were immediately neutralized in disodium phosphate solutions at 0°. The ethyl acetate was distilled from solution and gas chromatographed and the mass spectrum determined. The isotopic ratio of oxygen-18 to oxygen-16 was calculated from the equation

$$i = \frac{P_{90} - 0.04545P_{89} + 0.00206P_{88} - 0.000093P_{87}}{P_{88} - 0.04442P_{87}}$$

which corrects for isotopic contributions to the peak heights, *P*. The isotopic ratio was converted to per cent oxygen-18, 0.40% subtracted for natural abundance, yielding excellent first-order plots.

Hydrolysis of Ethyl Acetate. The hydrolysis was followed by dilatometry of 1% ethyl acetate in 47–69% sulfuric acid solutions at 25.0° (variation ±0.001°). In the more concentrated runs the volume changes were complicated by formation of ethyl hydrogen sulfate,[15] and the rate constant for hydrolysis was obtained by nonlinear least-squares analysis of the consecutive reactions.

The region 59–79% sulfuric was studied by decreases in optical density at 200 mμ. This wavelength is necessary because of a solvent-induced blue shift of the 204-mμ $n \rightarrow \pi^*$ absorption. Thus, we are in good agreement with the independent work of Jaques,[16] but not with that of Talvik and Palm[17] at 220 mμ.

Hydrolysis of Methyl Benzoate. The hydrolysis was followed by the increase in optical density at the wavelength having maximum per cent change in optical density. These wavelengths were near 290 mμ for dilute acid and increased to 312 mμ for the more concentrated acid solutions. Very satisfactory first-order kinetic plots were obtained.

Protonation of Ethyl Acetate. The extent of protonation of ethyl acetate was followed at 190 mμ in an Applied Physics Corp. Cary 15 spectrophotometer with a nitrogen atmosphere. The optical density was measured three times and extrapolated to the time of mixing. The extinction coefficient changed linearly from 60 to 82 in the 0–0.18-mol fraction region of H_2SO_4. The extinction coefficient then rapidly increased to 363 by mol fraction 0.70 and remained constant to mol fraction 0.89. In this region ethyl acetate has an *i* factor of 1.93[18] indicating monoprotonation. The extinction coefficient of unprotonated ester (ϵ_B) at any mol fraction was estimated by extrapolation of the linear changes up to 0.18. The extinction coefficient of protonated ester was 363 and therefore

$$[BH^+]/[B] = \frac{\epsilon - \epsilon_B}{363 - \epsilon}$$

Independent data were obtained by determining the difference in proton chemical shift of the acyl and alkyl methyl in sulfuric acid solutions. The difference initially increased linearly with mol fractions of sulfuric acid to δ 0.045, then rapidly to a constant δ 0.325. The indicator ratios were obtained as before and agreed very well with the ultraviolet data.

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[12] C. G. Swain and A. R. Rosenberg, *J. Am. Chem. Soc.*, **83**, 2154 (1961).

[13] The protonation ratio was only measured at 90.6% sulfuric but this introduces little error since the ketone is extensively protonated in all kinetic solutions employed.

[14] K. Yates and R. A. McClelland, *J. Am. Chem. Soc.*, **89**, 2686 (1967).

[15] D. J. Clark and G. Williams, *J. Chem. Soc.*, 4218 (1957).

[16] D. Jaques, *ibid.*, 3874 (1965).

[17] A. I. Talvik and V. A. Palm, *Zh. Fiz. Khim.*, **33**, 1214 (1959).

[18] L. P. Kuhn and A. H. Corwin, *J. Am. Chem. Soc.*, **79**, 3370 (1948).