The Kinetics of Simultaneous Hydrolysis and Alcoholysis of Esters in Aqueous Alcohol Solutions[1]

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The kinetics of simultaneous basic hydrolysis and alcoholysis of esters in aqueous alcohol solutions was determined by following the disappearance of total base, which is a measure of the hydrolysis reaction and the change during the reaction of the specific activity of esters labeled with carbon-14 in the alcoholic moiety, which is a measure of the alcoholysis reaction. These two pieces of information, together with data on the equilibria between hydroxide ion and alkoxide ion, resulted in a complete kinetic analysis of the following systems: (1) the hydrolysis and methanolysis of acetyl-L-phenylalanine methyl ester in methanol–water mixtures; (2) the hydrolysis and ethanolysis of acetyl-L-phenylalanine ethyl ester in ethanol–water mixtures; and (3) the hydrolysis and phenolysis of phenyl acetate in aqueous solution. For phenyl acetate, the ratio k_{OH^-}/k_{OPh^-} was found to be 0.020 ± 0.003. It was found that both methanolysis and ethanolysis occurred faster than hydrolysis in a number of alcohol–water mixtures. Increasing the water content of the mixture increased the rate of both alcoholysis and hydrolysis reactions. However, 40–85% of the total solvent effect in the alcohol–water solutions was due to changes in the alkoxide–hydroxide equilibria. It was further shown that the remaining kinetic solvent effect could not be wholly accounted for in terms of dielectric effects. By extrapolation of the data on methanolysis and ethanolysis to pure water, it was calculated that the relative rates of attack on an ester by hydroxide ion, methoxide ion and ethoxide ion are in the ratio $1:1.59:4.17$. This order of nucleophilicities does not parallel the relative basicities of these substances but does parallel the relative nucleophilicities calculated by the Edwards equation.[39]

Introduction

The base-catalyzed alcoholysis of an ester can be characterized by the equation

$$RCO_2R' + R''O^- \rightleftharpoons RCO_2R'' + R'O^-$$

while the base-catalyzed hydrolysis of an ester is represented as

$$RCO_2R' + HO^- \longrightarrow RCO_2^- + R'OH$$

These two reactions are formally similar and, indeed, there is strong experimental evidence that the similarity can be extended to the mechanisms of these reactions. The mechanism of the base-catalyzed hydrolysis of a normal ester[3] consists of addition of hydroxide ion to the carbonyl carbon atom of the ester in a rate-determining step, to form a tetrahedral intermediate which can then break down into products (or reactants) in a fast step. The mechanistic similarity between hydrolysis and alcoholysis in basic solution has been demonstrated[4] in the study of the methoxide ion-catalyzed methanolysis of o-, m- and p-substituted l-menthyl benzoates in methanol. Second-order kinetics (first order with respect to methoxide ion and ester), acyl–oxygen fission and acceleration and retardation of the rate of reaction by electron withdrawing and electron donating substituents, respectively, were observed. The reaction was found to follow the Hammett relation for m- and p-substituents with ρ equal to $+2.530$, whereas ρ equals $+2.498$ for the alkaline hydrolysis of ethyl benzoate in 88% ethanol–water solution.[33] On the basis of the above evidence, the mechanism of the base-catalyzed alcoholysis of a normal ester, in basic solution, may be written as

$$\underset{R}{\overset{O}{\underset{\diagdown}{\overset{\|}{C}}}}\overset{R'}{\underset{O}{\diagup}} + R''O^- \rightleftharpoons$$

(1) This research was supported by Contract At(11-1)-295 of the U. S. Atomic Energy Commission.

(2) From the Ph.D. thesis of W.A.G.

(3) M. L. Bender, This Journal, 73, 1626 (1951).

(4) R. W. Taft, Jr., M. S. Newman and F. H. Verhoek, ibid., 72, 4511 (1950).

$$\left[\underset{R}{\overset{O^-}{\underset{\diagdown}{\underset{|}{\overset{|}{\underset{O}{\overset{C}{\diagup}}}}}}}\overset{R'}{\underset{\underset{R''}{|}}{\overset{}{\diagup}}}\overset{}{\underset{O}{}}\right] \rightleftharpoons \underset{R}{\overset{O}{\underset{\diagdown}{\overset{\|}{C}}}}\overset{R''}{\underset{O}{\diagup}} + R'O^-$$

Up to the present there have been no quantitative kinetic studies on the alkoxide ion-catalyzed alcoholysis of esters in aqueous alcohol solutions. Qualitative observations on the alcoholysis and hydrolysis of benzoyl-L-phenylalanine ethyl ester in alkaline 50% methanol–water solution[6] indicated that complete alcoholysis had occurred after 80% hydrolysis. Infrared analysis of the remaining ester was used as the basis for the above conclusion.

The problem of analyzing the kinetics of simultaneous alcoholysis and hydrolysis is threefold: (a) the kinetics of alcoholysis must be followed; (b) the kinetics of hydrolysis must be followed; (c) the acid–base equilibria of the solvent system in question must be known. In the present study, the use of carbon-14 as tracer has been used for following the kinetics of alcoholysis. There are two possible tracer techniques: (1) the alcohol is labeled and the increase in the specific activity of the ester, isolated after a given time, is determined; (2) the alcohol moiety of the ester is labeled and the decrease in the specific activity of the ester, isolated after a given time, is determined.

When using the labeled alcohol technique (1), representations (1), (2) and (3) are applicable for the hydrolysis and alcoholysis reactions

$$E + OH^- \xrightarrow{k_{OH}} \text{products} \qquad (1)$$

$$E^* + OH^- \xrightarrow{k_{OH}} \text{products} \qquad (2)$$

$$E + OR^{-*} \underset{}{\overset{k_{OR}}{\rightleftharpoons}} E^* + OR^- \qquad (3)$$

where E denotes the ester, the asterisk signifies a labeled species, and k_{OR} and k_{OH} are the observed rate constants for alcoholysis and hydrolysis, respectively. By assuming pseudo first-order processes for hydrolysis and alcoholysis and by using

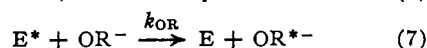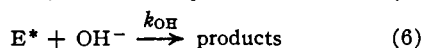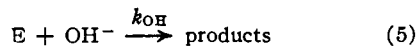(5) M. L. Bender and K. C. Kemp, ibid., 79, 111 (1957).

the following definitions of the specific activity of the ester at time t, and the alcohol at time zero

$$S_t = (E^*)/(E); \quad S_0 = (OR^{*-})/(OR)$$

it is possible[6] to show that

$$-\ln(1 - S_t/S_0) = k_{OR}(OR^-)t \quad (4)$$

When the labeled ester technique 2 is used, the following reaction equations are applicable

$$E + OH^- \xrightarrow{k_{OH}} products \quad (5)$$

$$E^* + OH^- \xrightarrow{k_{OH}} products \quad (6)$$

$$E^* + OR^- \xrightarrow{k_{OR}} E + OR^{*-} \quad (7)$$

where the alcoholysis reaction is irreversible with a large excess of alcohol. Equation (8) can be shown[6] to be applicable to this case assuming that $(OR^-)/(OH^-)$ is constant.

$$\ln \frac{S_t}{S_0} = \frac{k_{OR}(OR^-)}{k_{OH}(OH^-)} \ln (1 - f_{OH}) \quad (8)$$

In this equation S_t and S_0 are the specific activities of the ester at time t and time zero, and f_{OH} is the fraction of the hydrolysis reaction.

In the present investigation, the kinetics of simultaneous hydrolysis and alcoholysis in alkaline solution were determined for the following systems: (1) phenoxide ion and phenyl acetate in water, (2) methoxide ion and acetyl-L-phenylalanine methyl ester in methanol–water solutions and (3) ethoxide ion and acetyl-L-phenylalanine ethyl ester in ethanol–water solutions.

As is apparent from the rate equations, a knowledge of the acid–base equilibria of the solvent systems is necessary in order to evaluate k_{OR} and k_{OH}. In system 1 no problem is encountered since the ionization constant of phenol, in water, is well known.[7] The corresponding data for the ionization of methanol in methanol–water and the ionization of ethanol in ethanol–water solutions are known but the accuracy of these data is only semi-quantitative. Using a spectrophotometric method, apparent equilibrium constants for the reaction between ethoxide ion and water in ethanol–water solutions have been determined.[8] The apparent constants are defined as

$$K' = \frac{OH^-}{OEt^-} \times \frac{a_{EtOH}}{a_{H_2O}} = Kf_{OEt^-}/f_{OH^-} \quad (9)$$

where a and f denote the activity and the activity coefficient, and K' and K denote the apparent and true thermodynamic equilibrium constants. It is readily seen that a knowledge of K' and the activities of ethanol and water will allow calculation of the desired ratio OEt^-/OH^-. The values of K' reported by these authors are considered accurate to $\pm 15\%$ and thus this is considered the limit of accuracy in determining the value of the above ratio.

Recently, an estimate has been made of the true thermodynamic equilibrium constant for the reaction of methoxide ion with water on the basis of potentiometric measurements of the apparent ion-

product of methanol–water mixtures.[9] The equation for the experimentally determined ion product is given as

$$K_{exp} = \frac{K_1}{f_{H_2O} \cdot f_{OH^-}} \left(1 + \frac{1}{K} \times \frac{f_{CH_3OH}}{f_{H_2O}} \times \frac{m_{CH_3OH}}{m_{H_2O}}\right) \quad (10)$$

where K_1 is the ion product of water, in pure water as the standard state, K_3 is the true thermodynamic equilibrium constant for the reaction of methoxide ion with water, and m denotes molality. The first term on the right-hand side of the equation is termed K_1' and is the apparent ion product of water in the methanol–water mixtures studied. The value of K_3 was estimated from the known variation in K_{exp} with solvent composition and the assumption that the variation in K_1', with solvent composition, could be taken equal to the variation in the ionization constant of acetic acid, with varying methanol–water compositions. The value obtained, in this way, is 0.13 ± 0.02. This value is probably good to $\pm 15\%$. The data of Hine[10] can be used to calculate the value of K_3, assuming no significant effect on changing the solvent from isopropyl alcohol to methanol, and this value is 0.14.

One further point must be considered in order to evaluate completely the kinetic data on hydrolysis and alcoholysis in mixed alcohol–water solvents. This point, the necessary correction for the decrease in hydroxide ion concentration due to the equilibrium with alkoxide ion, has been treated by Tommila.[11]

Given the equilibrium

$$ROH + OH^- \rightleftharpoons H_2O + RO^- \quad (11)$$
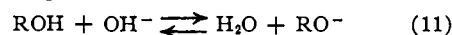
then the concentration of hydroxide ion is given by

$$(OH^-) = b\alpha \quad (12)$$

where b is the stoichiometric concentration of hydroxide ion $((OR^-)+(OH^-))$ and α is the fraction of the total base added which is hydroxide ion. Therefore the observed rate constant for hydrolysis is given by

$$k_{obsd} = k\alpha \quad (13)$$

Experimental

Materials.—Phenol-1-^{14}C (100 μc., Tracerlab, Inc.) was diluted with 75 g. of unlabeled phenol (Baker and Adamson) and the solid was distilled at 30 mm.; m.p. 37–38°, lit.[12] m.p. 41°. Aqueous phenol solutions were standardized by treating an aliquot with freshly prepared saturated bromine–water, extracting any bromine and brominated phenol with carbon tetrachloride, and titrating the liberated hydrobromic acid in the aqueous solution with alkali, using methyl red as the indicator.[13] Phenyl acetate was an Eastman White Label product; residual phenol and acetic acid were removed by dissolving in pentane, shaking with a 0.5 M aqueous sodium carbonate, drying over sodium sulfate, and distillation, b.p. 45° (1.0 mm.), lit. b.p. 78° (10 mm.); n^{22}D, 1.5039, lit. n^{27}D, 1.503).

Acetyl-L-phenylalanine was prepared from acetic anhydride and L-phenylalanine (Mann Research Lab., Inc.) according to the method of du Vigneaud[14] and Sealock. The

(6) W. A. Glasson, Ph.D. Thesis, Illinois Institute of Technology, 1959.

(7) H. Zollinger, W. Büchler and C. Wittwer, Helv. Chim. Acta, 36, 1711 (1953).

(8) E. F. Caldin and G. Long, J. Chem. Soc., 3737 (1954).

(9) J. Koskikallio, Suomen Kemistilehti, 30B, 111 (1957).

(10) J. Hine and M. Hine, THIS JOURNAL, 74, 5266 (1952).

(11) E. Tommila, A. Koivisto, J. Lyyra, K. Antell and S. Heimo, Ann. Acad. Sci. Fennicae, 47A, 1 (1952).

(12) The depression of the melting point could be accounted for by less than 1% water, which was assumed to be the major impurity.

(13) I. Kolthoff and V. Stenger, "Volumetric Analysis," Vol. II, Interscience Publishers, Inc., New York, N. Y., 1947, p. 216.

(14) V. du Vigneaud and R. Sealock, J. Biol. Chem., 96, 511 (1932).

crude product was recrystallized from 20% methanol–water, yielding colorless flat platelets (m.p. 174–175°, lit.[15] m.p. 170–171°). Acetyl-L-phenylalanine methyl ester was prepared by refluxing acetyl-L-phenylalanine with excess methanol using sulfuric acid as catalyst. On cooling the solution, the sulfuric acid was neutralized with 0.5 M aqueous sodium carbonate and the solution diluted with water. The methanol was then removed *in vacuo* until precipitation of the ester occurred and the resulting mixture was extracted with methylene chloride. The methylene chloride solution was washed with 0.5 M aqueous sodium carbonate, followed by washing with water, and drying over sodium sulfate. The methylene chloride was allowed to evaporate, and the resulting solid was recrystallized from petroleum ether (b.p. 65–110°), yielding colorless needles (m.p. 91–92°, lit.[16] m.p. 90–91°). Acetyl-L-phenylalanine ethyl ester was prepared from acetyl-L-phenylalanine and ethanol (Commercial Solvents Corp.) in the manner described above for the methyl ester. Recrystallization from petroleum ether yielded colorless needles (m.p. 88–89°, lit.[17] m.p. 69–70°). Acetyl-L-phenylalanine ethyl-^{14}C ester and acetyl-L-phenylalanine methyl-^{14}C ester were prepared from acetyl-L-phenylalanine and the respective labeled alcohols (Tracerlab, Inc.) in the manner described above for the unlabeled compounds.

Kinetic Methods.—The kinetics of the hydroxide ion-catalyzed hydrolysis of phenyl acetate were determined spectrophotometrically by following the production of phenoxide ion at 236 mμ on a Beckman DK-2 ratio recording spectrophotometer. The reaction was run under pseudo first-order conditions with the concentration of hydroxide ion being more than one hundred times that of phenyl acetate. Under these conditions the reaction is quite rapid[18] and, as a result, special means were required to initiate the reaction. A plunger mechanism was devised which allowed for addition of substrate and thorough mixing in a matter of seconds.

The pK_a of phenol was determined under the conditions under which the phenolysis reactions were studied. From the known concentrations of the species present and the pH,[19] one can calculate the value of pK_a for phenol. The value obtained in this manner was 9.92 at 25° at an ionic strength of 0.094 molar. This value compares favorably with that given in the literature[7] for the conditions used in this investigation.

The kinetics of the hydroxide ion-catalyzed hydrolysis of acetyl-L-phenylalanine methyl and ethyl esters in various methanol–water and ethanol–water solutions, respectively, were measured by the usual titration techniques.

The alcoholysis reactions were followed by allowing the reaction to proceed for a given amount of time, noting the time of quenching, isolating and purifying the remaining ester, and measuring the specific activity of this ester. For the most part, identical conditions were used in the hydrolysis and the corresponding alcoholysis experiments.

The specific procedure used in the phenolysis experiments consisted of quenching the reaction with sufficient aqueous potassium dihydrogen phosphate solution to give a final pH of seven, after which the ester was extracted with ligroin (Eastman Kodak, b.p. 35–60°) and any phenol or acetic acid removed by extraction with 0.5 M aqueous sodium carbonate solution. The resulting ligroin solution then was dried over anhydrous sodium sulfate and the solvent removed by distillation *in vacuo*. The ester was purified by vacuum distillation in a semi-micro apparatus[20] and samples for radioassay were sealed off in capillary tubes equipped with break tips.

The same procedure was used in the alcoholysis experiments involving acetyl-L-phenylalanine methyl and ethyl

esters. Quenching was accomplished by pouring the reaction mixture into sufficient hydrochloric acid to give a final pH of five. The ester then was extracted with methylene chloride and the organic layer washed with 0.5 M aqueous sodium carbonate solution. The resulting solution was dried over anhydrous sodium sulfate and the solvent allowed to evaporate. The solid material remaining was recrystallized a minimum of five times from petroleum ether and the crystals collected and dried in a vacuum desiccator. In certain cases where the alcohol content of the reaction solution was high, it was necessary to remove alcohol by vacuum distillation at room temperature before extraction was feasible.

It has been suggested that rate-determining proton removal from the amide nitrogen atom in acetyl-L-phenylalanine methyl and ethyl esters to yield an azlactone intermediate would create uncertainty in the results presented here. A consequence of such a reaction would be racemization of the ester and this fact was used to investigate the possibility of this side reaction. Using reaction conditions identical to those given previously, the base-catalyzed hydrolysis of acetyl-L-phenylalanine methyl ester was carried out in 15% methanol–water and the reaction quenched after 20% hydrolysis occurred. The ester was isolated and purified and its optical rotation compared with that of the unreacted ester. The two samples had identical molecular rotations and hence the possible intermediacy of an azlactone is not a significant factor in the reactions studied, under the conditions of the kinetic experiments.

Radioassay Method.—The samples of ^{14}C-esters were quantitatively converted to carbon dioxide by combustion with copper and cupric oxide at 640° for 10 hours[21] in Pyrex 172 glass combustion tubing. A pressure blank was determined for any carbon in the oxidizing mixture. The amount of ester used was determined by measuring the pressure of carbon dioxide, at a given temperature, in a calibrated constant volume manometer. The samples were flushed into ionization chambers with tank carbon dioxide giving a final total pressure of approximately one atmosphere. The specific activities of the samples were measured with a vibrating reed electrometer (Applied Physics Corp., model 30) by the rate of charge method. The carbon dioxide from each combustion was divided into three aliquots, each of which was measured manometrically and the specific activity determined. Measurements for specific activity of each aliquot were repeated five to ten times, depending on the magnitude of the current produced. The specific activity of the aliquot was then taken as the average of the total number of measurements and the specific activity of the ester was taken as the average of the three aliquots. In general, the values of the aliquot specific activities determined in this way, were within 1% of one another.

Results

Phenyl Acetate.—In the pseudo first-order reaction of hydroxide ion with phenyl acetate, the rate constant was evaluated by the method of Guggenheim.[22] The value obtained at 24.6° in water was 1.25 l. mole⁻¹ sec.⁻¹ and compares favorably with the value obtained by Skrabal,[23] 1.36 l. mole⁻¹ sec.⁻¹. Duplicate runs were made and identical rate constants were obtained.

The results of the study of the phenolysis of phenyl acetate are given in Table I and graphically represented in Fig. 1.

The rather large experimental error (13%) was due to the difficulties incurred in the purification of phenyl acetate on a semi-micro scale.[24]

The results of the investigation of the hydroxide ion-catalyzed hydrolysis of acetyl-L-phenylalanine methyl and ethyl esters in various methanol–

(15) W. Schuller and C. Niemann, THIS JOURNAL, **73**, 1644 (1951).

(16) H. T. Huang, R. J. Foster and C. Niemann, *ibid.*, **74**, 105 (1952).

(17) L. Berlinguet, *Can. J. Chem.*, **32**, 31 (1954). The compound in question was prepared by half-saponification of diethyl α-phenyl-α-acetamidomalonate, followed by acidification and subsequent thermal decarboxylation. The mode of preparation suggests that the compound isolated was the D,L-form, and the difference in m.p. with the L-form is then not unexpected.

(18) The half-life of this reaction was 25 seconds.

(19) The pH was checked against a standard pH 10 buffer prepared according to V. E. Bower and R. G. Bates, *J. Res. Natl. Bur. Standards*, **55**, 197 (1955).

(20) M. Babcock, *Anal. Chem.*, **21**, 632 (1949).

(21) K. Wilzbach and W. Sykes, *Science*, **120**, 494 (1954).

(22) E. Guggenheim, *Phil. Mag.*, **2**, 538 (1926).

(23) A. Skrabal and M. Hugetz, *Monatsh.*, **47**, 23 (1926).

(24) For a thorough discussion of the problem of the purification of ^{14}C labelled compounds see G. Ropp, *J. Chem. Ed.*, **34**, 60 (1957).

TABLE I

THE KINETICS OF THE PHENOLYSIS OF PHENYL ACETATE[a]

(S_t/S_0), corr.[b,d]	Phenoxide $\times 10^3$, M	Time, sec.	$k_{OPh} \times 10^{1a}$, l./mole sec.
0.145	1.75	400	2.25
.303	1.96	718	2.58
.470	1.75	1240	2.92
.790	1.96	1550	..
.921	1.90	3900	3.42
			2.79 ± 0.37[e]

[a] In aqueous solution at 25.0 ± 0.1°. The concentration of phenyl acetate in all runs was 8.8×10^{-4} M, the pH was 10.02, as calculated from the experimental pK of phenol, and the total hydroxide ion added, and the ionic strength was 0.094 M. [b] An empirical correction term was determined by plotting the original S_t/S_0 values vs. time and the intercept of this straight line subtracted from all values of S_t/S_0 to yield values of (S_t/S_0) corr. The source of this "blank reaction" is considered to be the phosphate-catalyzed phenolysis of phenyl acetate by analogy with the phosphate-catalyzed hydrolysis of p-nitrophenyl acetate.[2b] The correction was 0.055. [c] Run four was not included in calculating the average value of k_{OPh}. [d] The initial specific activity of the phenol-^{14}C was measured on the benzoate ester due to the difficulty in handling pure phenol in air. [e] The values were calculated from equation 4.

water and ethanol–water mixtures, respectively, are given in Table II.

The results of the methoxide ion-catalyzed methanolysis of acetyl-L-phenylalanine methyl ester in methanol–water and the ethoxide ion-

Fig. 2.—The methoxide ion-catalyzed methanolysis of acetyl-L-phenylalanine methyl ester in methanol–water mixtures at 25.0 ± 0.1°; volume per cent. methanol in mixture: A, 15%; B, 30%; C, 50%; and D, 80%.

Fig. 1.—The phenoxide ion-catalyzed phenolysis of phenyl acetate in water at 25.0 ± 0.1°.

catalyzed ethanolysis of acetyl-L-phenylalanine ethyl ester in ethanol–water are given in Table III and graphically presented in Figs. 2 and 3.

(25) T. C. Bruice and G. L. Schmir, THIS JOURNAL, 80, 148 (1958); M. C. Neveu, Illinois Institute of Technology, Ph.D. thesis, 1959.
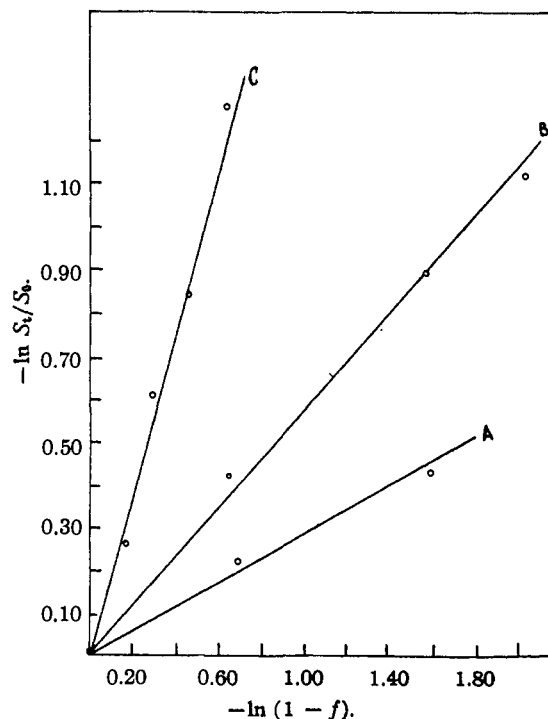
Fig. 3.—The ethoxide ion-catalyzed ethanolysis of acetyl-L-phenylalanine ethyl ester in ethanol–water mixtures at 25.0 ± 0.1°; volume per cent. ethanol in mixture: A, 30%; B, 50%; and C, 80%.

Discussion

Phenyl Acetate.—For phenyl acetate, the ratio k_{OPh}/k_{OH} has been found to be 0.020 ± 0.003, while

TABLE II

THE HYDROXIDE ION-CATALYZED HYDROLYSIS OF ACETYL-L-PHENYLALANINE METHYL AND ETHYL ESTERS IN METHANOL–WATER AND ETHANOL–WATER SOLUTIONS[a,b]

Volume % alcohol	Mole fraction alcohol	Ester × 10³ M	Hydroxide ion × 10³ M	α	$k_{obsd.}$ hydrolysis × 10³, l./mole sec.	k_{OH} × 10³,[c] l./mole sec.	k_{OR} × 10³,[c] l./mole sec.
Acetyl-L-phenylalanine methyl ester in methanol–water mixtures							
15	0.072	0.47	0.47	0.53	83.7	158	276
30	.156	1.17	1.18	.33	41.2	125	200
50	.294	1.17	1.18	.21	11.7	55.7	124
80	.625	1.18	1.18	.086	2.10	24.4	60
Acetyl-L-phenylalanine ethyl ester in ethanol–water mixtures							
30	0.113	0.94	0.94	0.93	20.3	21.8	84.8
50	.223	1.92	1.90	.87	10.8	12.4	48.6
80	.517	1.42	1.42	.59	5.38	9.13	24.5

[a] The temperature was 25.0 ± 0.1°. [b] Aqueous sodium chloride solution was added to maintain constant ionic strength in all runs of a given set. In methanol–water, μ = 0.0959 M and in ethanol–water μ = 0.0690 M. [c] The experimental error in these values is ±16%. The error in k_{obsd} is ±5% and the error in α is ±15%; see ref. 29 for the method of calculation of the total error.

TABLE III

THE KINETICS OF THE METHOXIDE ION-CATALYZED METHANOLYSIS OF ACETYL-L-PHENYLALANINE METHYL ESTER IN METHANOL–WATER MIXTURES AND THE ETHOXIDE ION-CATALYZED ETHANOLYSIS OF ACETYL-L-PHENYLALANINE ETHYL ESTER IN ETHANOL–WATER MIXTURES[a]

Volume% alcohol	$\frac{S_t}{amp./mmole}$ × 10¹⁴,[b]	$(1 - f_{OH})$	k_{OR},[c] l./mole sec.	k_{OR} (av.)[d] l./mole sec.
Acetyl-L-phenylalanine methyl ester in methanol–water mixtures[e]				
15.0	258	0.810	2.97	
15.0	164	.585	2.67	2.76 ± 0.44
15.0	115	.458	2.65	
30.0	250	.897	2.16	
30.0	161	.781	2.05	2.00 ± 0.32
30.0	118	.671	1.75	
30.0	60.6	.577	2.02	
30.0	34.6	.491	2.04	
50.0	232	.950	1.33	
50.0	141	.895	1.28	
50.0	91.7	.852	1.28	
50.0	39.2	.760	1.21	1.24 ± 0.20
50.0	18.3	.690	1.19	
50.0	8.63	.623	1.17	
50.0	1.65	.515	1.21	
80.0	307	.994	0.685	
80.0	236	.982	.566	0.600 ± 0.096
80.0	108	.950	.552	
80.0	4.9	.846	.598	
Acetyl-L-phenylalanine ethyl ester in ethanol–water mixtures[f]				
30.0	175	0.500	0.780	
30.0	142	.203	.916	0.848 ± 0.136
50.0	144	.522	.532	
50.0	89.8	.208	.470	0.486 ± 0.078
50.0	71.5	.131	.456	
80.0	169	.847	.199	
80.0	119	.740	.265	0.245 ± 0.039
80.0	94.0	.629	.246	
80.0	60.7	.528	.270	

[a] All runs were carried out at 25.0 ± 0.1°. [b] S_0 values for acetyl-L-phenylalanine methyl and ethyl esters were 367 and 218, respectively. [c] The values were calculated from equation 8. The activities of alcohol and water, in various mixtures of methanol–water and ethanol–water used, were obtained from the data of Butler[26] and Caldin,[5] respectively.

The densities of the various mixtures, necessary to convert volume % alcohol to weight % and mole fraction alcohol were obtained from the data of Dittmar and Fawsitt[27] for methanol–water mixtures, and the National Bureau of Standards[28] for ethanol–water mixtures. [d] The arithmetic mean of all values is given in each set. The deviations given are estimated experimental errors.[29] [e] The initial concentrations of the ester and the total base were equal to 4.71 × 10⁻³ M in all runs except the sixth run in which the initial concentration of ester and total base were 1.88 × 10⁻³ M, and except the last run, in which the initial concentration of ester was 1.10 × 10⁻² M and that of the total base was 2.37 × 10⁻² M. In all runs the ionic strength was maintained at a value of 0.0959 through addition of aqueous sodium chloride solution. [f] The initial concentrations of the ester and the total base were 1.44 × 10⁻² M in all runs except the sixth run in which the initial concentration of the ester was 9.88 × 10⁻³ M and that of the total base was 1.90 × 10⁻² M and the last three runs in which the initial concentration of the ester was 1.00 × 10⁻² M and that of the total base was 1.90 × 10⁻² M. The ionic strength was maintained at 0.0690 M in all runs through the addition of aqueous sodium chloride solution.

for p-nitrophenyl acetate this ratio has been found to be 0.019 ± 0.003 in 28.5 volume per cent. ethanol–water solutions.[30] Within experimental error these values are identical assuming the solvent effect on the ratio to be negligible.[31] Using these values and taking the value of ρ for the hydroxide ion-catalyzed hydrolysis of m- and p-substituted phenyl acetates in 60% acetone–water to be 1.00[32] and σ for p-nitrophenols to be 1.27,[33] the value of ρ for the reaction of phenoxide ion with substituted phenyl acetates has been calculated to be 1.0 ± 0.2. An attempt has been made[32] to explain the relative values of ρ for imidazole- and hydroxide ion-catalyzed hydrolysis of m- and p-substituted

(26) J. Butler, D. Thompson and W. MacLennan. J. Chem. Soc., 674 (1933).

(27) "International Critical Tables," Vol. III. 1928, p. 115.

(28) Ibid., Vol. III, 1928, p. 116.

(29) As seen from equation 8, k_{OR} was calculated at time t, from the product of the slope (between $t = t$ and $t = 0$), the observed rate constant for hydrolysis, and $(1 - \alpha)$. The experimental error in the latter is approximately 15% while that in the former two is about 6% each. The error obtained in calculating k_{OR} can be calculated by the method of A. A. Benedetti-Pichler. Ind. Eng. Chem., Anal. Ed., 8, 376 (1936).

(30) T. C. Bruice and R. Lapinski, THIS JOURNAL, 80, 2265 (1958).

(31) The ratios k_{OR}/k_{OH}, for acetyl-L-phenylalanine ethyl ester in fifty and thirty volume per cent. ethanol–water solutions are identical within experimental error.

(32) T. Bruice and G. Schmir, THIS JOURNAL, 79, 1663 (1957).

(33) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, p. 188.

phenyl acetates of 1.90 and 1.00, respectively. It was concluded that the effect of the m- and p-substituent was maximal in the case where there was a strong competition between X and Y, in the partitioning of the tetrahedral intermediate

$$R-\overset{\displaystyle O^-}{\underset{\displaystyle Y}{\overset{|}{\underset{|}{C}}}}-X$$

between reactants and products. The competition would then be dependent on the relative stabilities of X and Y and the relative magnitudes of ρ, given above, are in accord with such ideas. In the case of phenolysis, however, one would expect a much larger ρ-value than that obtained, due to the symmetrical nature of the reaction. Since the ρ-value was obtained on the basis of just two points, any conclusions reached must be only of a tentative nature.

Methyl and Ethyl Esters.—As noted previously, k_{obsd} for hydrolysis must be corrected for the equilibrium between alkoxide ion and hydroxide ion according to eq. 13. Table II lists the uncorrected and corrected values (k_{obsd} hydrolysis and k_{OH}) along with the corresponding values of α, the composition of the solution in terms of the mole fraction of alcohol and the corresponding values of k_{OR}.

The logarithms of k_{OH} and k_{OR} are plotted $vs.$ the mole fraction of alcohol in the solvent mixture in Fig. 4. In all cases the rate constant increases with increasing water content of the solvent mixture. Generally this type of behavior is found for the alkaline hydrolysis of esters. The effect of the solvent on the rate of the alkaline hydrolysis of esters in alcohol–water solutions is the summation of two separate effects: (a) the effect of the solvent on the equilibrium between alkoxide ion and hydroxide ion and (b) the effect of the solvent on the true kinetic constant for the reaction in question.

It can be seen from Table II that there is a 40-fold decrease in k_{obsd} (hydrolysis) in changing the solvent from 15 to 80 volume per cent. methanol–water, whereas there is only a 6.5-fold change in k_{OH} due to this solvent change; similarly for ethanol–water, changing from 30 to 80 volume per cent. results in a 3.8-fold change in k_{obsd} (hydrolysis) but only a 2.4-fold change in k_{OH}. Therefore 85% of the total solvent effect in the ethanol–water solutions is due to changes in this equilibrium. The degree to which the equilibrium solvent effect takes part is a function of the acidity of the alcohol, which is seen readily from Table II since the acidity scale is $CH_3OH > H_2O > C_2H_5OH$. Thus methanol exerts a powerful equilibrium effect over the entire solvent range studied; ethanol, on the other hand, exerts very little effect until the region of eighty volume per cent. ethanol is reached.

It is of interest to compare the solvent effect (excluding the alkoxide–hydroxide equilibrium) on k_{OH} and k_{OR} since k_{OR} is a pure kinetic constant and k_{OH} is a complex constant.[34] The slopes (d ln k_i/d N_A) for the hydrolysis and alcoholysis (k_{OH} and k_{OR}) in methanol– and ethanol–water solutions

(34) For the kinetic scheme $RCO_3R' + OH^- \overset{1}{\underset{2}{\rightleftarrows}} [I^-] \overset{3}{\rightarrow}$ products
it can be shown that $k_{OH} = k_1 k_3/(k_1 + k_3)$. Since $k_2 = k_3$ for symmetrical alcoholysis, $k_{OR} = k_1/2$.

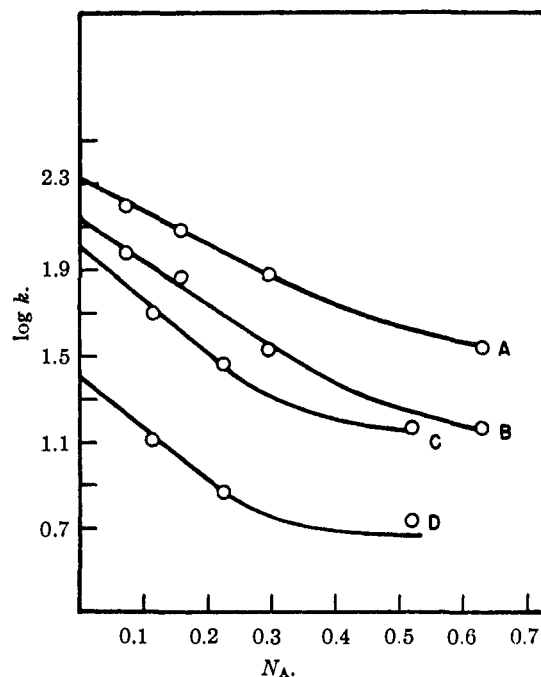Fig. 4.—log k_{OH} and log k_{OR} as a function of the mole fraction of alcohol, N_A, in the aqueous mixture, at 25.0 ± 0.1°: A, k_{OCH_3}, and B, k_{OH}, reactions of acetyl-L-phenylalanine methyl ester in methanol–water mixtures; C, $k_{OC_2H_5}$, and D, k_{OH}, reactions of acetyl-L-phenylalanine ethyl ester in ethanol–water mixtures.

are −3.8 and −2.9 and −5.0 and −4.8, respectively. It is verified readily that in the case of k_{OH} the slope is equal to a difference in slopes, $i.e.$

$$\text{d ln } k_{OH}/dN_A = \text{d ln } k_1/dN_A - \text{d ln } (k_2/k_3)/dN_A$$

Since the slopes for k_{OH} and k_{OR}, for a given substrate, are of comparable value it can be concluded that the solvent effect measured is predominantly that due to k_1 for hydrolysis.[35] This result is not totally unexpected since qualitatively one would predict similar dependencies of k_2 and k_3 on solvent composition.

The slopes (d ln k_i/dN_A) given above yield a value for the total kinetic solvent effect (dielectric effects and solvation effects). The data of Tommila[11] were used to calculate the slopes corresponding to the alkaline hydrolysis of ethyl acetate in aqueous dioxane, acetone, methanol, ethanol and isopropyl alcohol solutions, and the values obtained were −3.2, −3.9, −4.4, −4.8 and −5.7, respectively. It is readily apparent that there is fair agreement between the two sets of kinetic solvent effect data covering a wide range in solvents. However, it must be pointed out that these values are only applicable to solutions of approximately 0–50 volume per cent. of the organic component; in solutions which are predominantly non-aqueous other effects come into play as evidenced by non-linearity in the plots.

Assuming that the total kinetic solvent effect (d ln k_{OH}/dN_A) due to an organic component in aqueous solution, can be represented as being

(35) This conclusion is confirmed by studies on the effect of solvent on oxygen exchange during hydrolysis; unpublished results of R. D. Ginger.

entirely due to a dielectric effect, then one can calculate the slope d ln k_{OH}/d (1/D) from d ln k_{OH}/dN_A and the known dependence of D on mole fraction of organic solvent in the solvent mixture. The calculation was carried out for the alkaline hydrolysis of ethyl acetate in methanol–water and ethanol–water solutions with the calculated slope for both being approximately -6.6×10^2. The experimental slopes of plots of ln k_{OH} vs. 1/D gave reasonable linearity over the range of 15–80 volume per cent. methanol and 30–50 volume per cent. ethanol with curvature occurring in the range from 50–80 volume per cent. ethanol. The experimental slopes were found to be approximately equal to -2.2×10^2. Thus there is a factor of three difference between these slopes and the calculated slopes which implies effects other than pure dielectric effects are operative in these reactions. The theoretical treatments[36,37] of the dependence of the rate constant for the reaction of an ion with an uncharged molecule on the dielectric constant of the solvent system are therefore not completely valid in these systems.

Ingold[38] has discussed the effect of the solvent in the SN2 reaction of isopropyl bromide with hydroxide ion in aqueous ethanol–water mixtures, involving solutions consisting of more than 60% ethanol. He has concluded that since the transition state is less polar than the ground state, the transition state will be stabilized less than the ground state by increasing the polarity of the solvent medium. This will result in a higher energy of activation and thus a lower rate of reaction. The solvation difference between the transition state and ground state is moderate and thus a relatively small decrease in rate is expected as the solvent polarity is increased. On the basis of this argument one would expect that the rate of base-catalyzed ester hydrolysis would also decrease as the polarity of the solvent is increased. Since this change is not found to be the case in this investigation and in many other investigations of ester hydrolysis, it is implied that the transition state is more polar than the ground state. This can be reconciled qualitatively as follows: (1) assume that the solvation of the hydroxide ion is unchanged from zero to thirty mole per cent. organic component; (2) then the differences in change of solvation (stabilization) between the transition state (ester-hydroxide ion) and ground state (ester and hydroxide ion) as the polarity of solvent is increased will depend only on the relative change in stabilization of the ester and the transition-state, and (3) the ester will be stabilized by a decrease in solvent polarity while the polar transition state will be destabilized by a decrease in solvent polarity.

Edwards[39] has proposed an equation which relates polarizability and basicity with the nucleophilic character of a given species. Since rate data exist for methoxide ion-catalyzed methanolysis, ethoxide ion-catalyzed ethanolysis and hydroxide

ion-catalyzed hydrolysis of similar substrates in the same solvent, water, it was felt that application of this equation to the data might throw some light on the relative nucleophilicities of these species compared to their relative basicities. The values of En and H, the relative nucleophilicities and basicities, respectively, of the various anions are shown in Table IV.[40,41] It is seen that the calculated relative nucleophilicities follow the order ethoxide ion > methoxide ion > hydroxide ion. The rates k_{OR}/k_{OH} extrapolated to pure water are 4.2 and 1.6 for ethoxide ion and methoxide ion, respectively, relative to hydroxide ion. If we assume no drastic change in k_{OR}/k_{OH} on going from the ethyl ester to the methyl ester, the order of efficiency in attacking a carbonyl carbon atom is the same as that for the calculated relative nucleophilicities of the species in question. Bunnett[42] has investigated the relative reactivities of methoxide ion and hydroxide ion with 2,4-dinitrochlorobenzene and found the order methoxide ion > hydroxide ion, although the values listed are not corrected for the solvent effect obtained on changing the solvent from pure methanol to 62% dioxane–water.

TABLE IV

POLARIZABILITIES, BASICITIES AND NUCLEOPHILICITIES OF SOME OXYGEN BASES

Donor	pK_a	H	R_∞	P	En (calcd.)	Nucleophilicity to C=O[f]
H_2O	-1.74[39]	0.00	3.67	0.00	0.00	..
HO^-	15.8[39]	17.5	5.1[40]	.143	1.60	1.0
CH_3O^-	15.0[a]	16.7[b]	10.9[c]	.473[d]	2.74[e]	1.6
$C_2H_5O^-$	16.6[a]	18.3[b]	14.4[c]	.594[d]	3.28[e]	4.2

[a] Obtained by extrapolation of plots of log vs. mole fraction of alcohol for methanol–water[9] and ethanol–water[8] solutions to pure water as solvent. [b] Calculated from H = pK_a +1.74.[39] [c] Calculated from the atomic refraction constants of Eisenlohr,[41] assuming additivity. [d] Calculated from $P = \log (R_\infty/R_{H_2O})$.[39] [e] Calculated from $En = aP + bH$.[42] [f] Calculated from the ratio k_{OR}/k_{OH} for the two substrates used in the investigation.

It was desired to ascertain why the relative basicities of hydroxide ion, methoxide ion and ethoxide ion did not parallel their relative nucleophilicities. Calculations were therefore made to determine what percentage of the relative rates of reaction of the esters with the various nucleophiles was due to the relative basicities of the species and what percentage was due to the relative nucleophilicities as defined in Table IV, using the equation log k/k_0 = AP + BH. Assuming a value of 9.4 for the logarithm of the ratio of the rate constants for the hydroxide ion-catalyzed and water catalyzed hydrolysis of the esters[43] and using rates of hydrolysis and alcoholysis extrapolated to pure water, it is possible to calculate the fractional contribution of the basicity term (BH) to the total relative rate.

(36) K. J. Laidler and H. Eyring, *Ann. New York Acad. Sci.*, **39**, 303 (1940).

(37) E. S. Amis and G. Jaffe, *J. Chem. Phys.*, **10**, 598 (1942).

(38) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, p. 345.

(39) J. O. Edwards, THIS JOURNAL, **78**, 1819 (1956).

(40) Landolt-Börnstein, "Zahlenwerte und Funktionen," Verlag-Springer, Berlin, 1950, 6. Aufgabe, I. Band, I. Teil, p. 399.

(41) F. Eisenlohr, *Z. physik. Chem.*, **75**, 585 (1910); **79**, 129 (1912).

(42) J. F. Bunnett and G. T. Davis, THIS JOURNAL, **76**, 3011 (1954).

(43) Bruice,[30] and M. L. Bender and B. W. Turnquest, *ibid.*, **79**, 1652 (1957), have reported 8.81 and 8.71, respectively, for this ratio in the hydrolysis of *p*-nitrophenyl acetate. A. Skrabal and A. Zahorka, *Monatsh.*, **53**, 562 (1929), reported 10.4 for this ratio in the hydrolysis of ethyl acetate.

The fractional contributions of the basicity term for the attack of hydroxide ion on the esters is 0.97–0.99; that for the attack of methoxide ion is 0.91; and that for the attack of ethoxide ion is 0.98.

In all cases, the contribution of basicity to the rate of the reaction is very large, indicating that the basicity of the attacking species is the controlling factor in the relative reactivity of such species toward the carbonyl carbon atom of esters. Evidence has been given recently for nucleophilic catalysis in the hydrolysis of esters, by Bender[44]

(44) See ref. 45 and M. L. Bender and B. W. Turnquest, THIS JOURNAL, **79**, 1656 (1957).

and Bruice.[45] The catalysts studied by these workers showed good correlation with the Brönsted equation and hence basicity of the nucleophile. Basicity again is the controlling factor for reactivity as shown in this investigation, with the exception of the methoxide ion. Apparently the greater polarizability of the methoxide ion is sufficient to reverse the order expected from basicity alone.

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(45) See refs. 26, 32, 34 and G. L. Schmir and T. C. Bruice, *ibid.*, **80**, 1173 (1958).

CHICAGO 16, ILL.

Anionic Copolymerization of Isoprene and Styrene. I[1]

BY DONALD J. KELLEY AND ARTHUR V. TOBOLSKY

Lithium, n-butyllithium and sodium were used to catalyze the polymerization of equimolar mixtures of isoprene and styrene in various solvents. The compositions of the copolymers initially formed were studied, since this illuminates the nature of the propagation step. Under otherwise similar conditions, the copolymers produced by lithium and by n-butyllithium were identical. This is because the propagating species is the ion pair (polymer$^-$Li$^+$) in both cases. In benzene or in undiluted monomers, these catalysts gave copolymers containing somewhat less than 20 weight % styrene. In triethylamine, diethyl ether, and tetrahydrofuran the initial copolymers contained 60, 68 and 80% styrene, respectively. Sodium produces copolymers of 66 weight % styrene in hydrocarbons and from 75 to 80% styrene in ionizing solvents. We deduce that the composition of the copolymers depends mainly on the ionic character of the propagating ($\sim$C$^-$M$^+$) ion pair. A nearly completely free anion gives a copolymer containing 80% styrene. Repressing the ionic character of the complex, by using Li$^+$ rather than Na$^+$ and by using non-ionizing solvents lowers the styrene content. Other factors which might contribute to the observed effect also are discussed.

Introduction

Lithium and alkyllithium-catalyzed polymerizations of isoprene differ markedly from sodium polymerizations in that a stereospecific polymer containing more than 90% of the *cis*-1,4-isomer is produced in bulk and in hydrocarbon solvents.[2–4] In diethyl ether and tetrahydrofuran (THF) stereospecificity vanishes, and polymer containing a mixture of 1,2-, 3,4- and *trans*-1,4-structures is obtained.[4,5] Since the nature of the polymerization medium exerts a strong influence on the stereochemistry of the propagation step, the composition of the copolymer initially formed from an equimolar mixture of isoprene and styrene should also depend on the solvent.

In a previous publication,[6] it was shown that, in a particular solvent, the structures of isoprene polymers produced by organometallic initiators like n-butyllithium, amyllithium and phenyllithium are not affected by the negatively charged organic fragment of the initiator. This implies that this fragment starts the chain, but that the propagation step is the addition of ($\sim$isoprene$^-$M$^+$) to a monomer double bond. Under otherwise similar conditions the isoprene polymers produced by

lithium and by n-butyllithium are identical.[3] We believe that metallic lithium first forms a mono- or dialkenyl or an alkyl with the monomer or solvent, which initiates isoprene polymerization in the same manner as does n-butyllithium. The propagating species, with both catalysts, is the growing ion pair ($\sim$isoprene$^-$M$^+$). The same is true for sodium and organosodium compounds.

According to the Q–e scheme of copolymerization reactivity ratios, the polarity constants (e) for butadiene and styrene are both -0.8.[7] Also the reactivities of these two monomers with carbanions are the same.[8] Unfortunately, the e-value for isoprene is not published. However, the electron-donating power of the methyl group in isoprene would be expected to produce a lower "e-value" than for butadiene and hence also below that of styrene. Thus, an isoprene–styrene copolymer formed by a truly anionic propagation should contain an excess of styrene.

Experimental

Materials.—Phillips Polymerization Grade isoprene, benzene and diethyl ether were refluxed over sodium wire for two hours and fractionally distilled under dry nitrogen just prior to use. Styrene monomer was fractionally distilled under nitrogen at reduced pressure. THF was refluxed over lithium wire and triethylamine (Et$_3$N), over potassium hydroxide before distillation.

n-Butyllithium was prepared in benzene and in diethyl ether in dry helium atmospheres by the methods of Ziegler[9]

(1) This article is based upon a dissertation submitted by Donald J. Kelley in partial fulfillment of the requirements for the degree of Doctor of Philosophy at Princeton University.

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(8) G. E. Ham, *ibid.*, **14**, 483 (1954).

(9) K. Ziegler and H. Colonius, *Ann.*, **479**, 135 (1930).