The Influence of the Solvent on Reaction Velocity

XXIV. The Acid Hydrolysis of Ethyl Acetate in Dimethyl Sulphoxide-Water Mixtures

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The first-order rate constant k_1 of the acid hydrolysis of ethyl acetate in dimethyl sulphoxide-water mixtures first increases with increasing proportion of dimethyl sulphoxide, passes through a maximum when the water concentration is 650—750 ml/l, and then decreases rapidly. On the other hand, $k' = k_2/[H_2O]$ increases continuously with increasing DMSO concentration. The behaviour of k' is in accordance with electrostatic theories and suggests that the transition state probably is not highly polar. The structure of the transition state which best conforms to the experimental observations is discussed. The solvent effect is discussed in terms of the reaction mechanism and changes in the solvation of the reacting system. The results are compared with those previously obtained for the acid hydrolysis of ethyl acetate in acetone-water mixtures.

In contrast to what is the case in general in hydrolysis reactions in aqueous mixed solvents, the rate of the alkaline hydrolysis of ethyl acetate in aqueous dimethyl sulphoxide (DMSO) increases with increasing concentration of the organic component, the enhancement being particularly marked at high DMSO concentrations.[1] In continuation of our studies of solvent effects, we have investigated also the acid hydrolysis of ethyl acetate in various DMSO-water mixtures. It was furthermore of interest to compare the results with those obtained by Tommila and Hella [2] for the reaction in acetone-water mixtures.

EXPERIMENTAL

Ethyl acetate and dimethyl sulphoxide were the same chemicals as in the previous work.[1] Tenth-normal solutions of the ester and hydrogen chloride in a series of DMSO-water mixtures were prepared. The reactions were carried out in sealed 5-ml ampoules of Pyrex glass into which 2 ml of ester and acid solutions had been measured by means of a pipette. The initial concentrations of ester and hydrogen chloride were hence 0.05 mole/litre. In other particulars the procedure was similar to that used by Tommila and Hella.[2] In the experiments with high hydrogen chloride concentrations, the method

Table 1. The acid hydrolysis of ethyl acetate in DMSO-water mixtures. The initial concentrations of ester and HCl were 0.05 mole/l.

Water in the solvent			$10^5 k_2$ l mole^{-1} sec^{-1}				E cal	log A	ΔS^* E.U.	ΔG^* cal
ml	mole/l	x_w	15.00°	25.00°	40.00°	50.00°				
1000	55.5	1.000	4.04	10.7	41.8	95.8	16 760	8.316	−22.5	22 805
900	50.0	0.972	4.59	12.0	44.8	102	16 370	8.076	−23.6	22 803
800	44.5	0.938	5.05	13.2	46.8	101	15 830	7.718	−25.2	22 750
600	33.3	0.850	5.51	13.5	46.1	98.3	15 230	7.293	−27.1	22 730
400	22.2	0.716	4.32	10.3	35.8	74.9	15 120	7.101	−28.0	22 880
200	11.1	0.490	2.22	5.70	19.6	43.5	15 670	7.234	−27.4	23 250
100	5.55	0.302	1.38	3.53	12.0	25.3	15 330	6.775	−29.5	23 540
50	2.77	0.171	0.859	2.09	6.73	14.3	14 680	6.062	−32.8	23 860
10	0.55	0.045	0.179	0.427	1.21	2.40	13 630	4.587	−39.5	24 850

differed from the above only in that after removing samples at suitable reaction times a volume of 0.1 N sodium hydroxide equivalent to the hydrogen chloride was quickly added and the acetic acid formed in the reaction was titrated with a 0.02 N baryta solution. Cresol red was used as indicator.

Good agreement with the first-order rate law was observed in all cases. Second-order constants k_2 were obtained by dividing the first-order constants k_1 by the concentration of the mineral acid.

RESULTS

The results of the kinetic runs are summarized in Table 1. The rate constants satisfy the Arrhenius equation within the experimental error. The values of E, log A (A expressed in l mole^{-1}sec^{-1}), ΔH^*, ΔS^* (for 25°) and ΔG^* were calculated as in the previous paper. Some experiments were conducted to study the influence of the hydrogen chloride concentration and sodium chloride. The results are shown in Table 2.

The following points should be noted:

(1) The rate of the reaction is directly proportional to the hydrogen chloride concentration (Table 2). The influence of added sodium chloride is very weak.

(2) The rate constants k_1 and k_2 first increase with increasing proportion of DMSO in the solvent, the relative enhancement being the greater the lower the temperature. Above a certain DMSO content the rate constant decreases with decreasing water concentration. In Fig. 1 the ratio k/k_w (k_w is the rate

Table 2. The influence of the concentration of HCl and NaCl. Solvent: DMSO-water containing water 600 ml/l. a is the initial concentration of ethyl acetate. Temperature 25.00°.

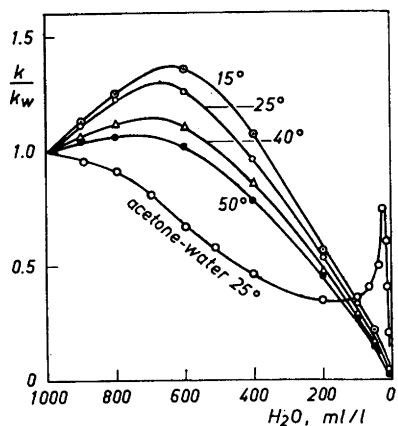| a, mole/l	0.050	0.0486	0.100	0.100	0.100	0.100	0.100
HCl, mole/l	0.050	0.0503	0.050	0.100	0.250	0.500	1.000
NaCl, mole/l	—	0.200	—	—	—	—	—
$10^5 k_1$, sec^{-1}	0.6752	0.7191	0.7508	1.488	3.962	8.275	15.78
$10^5 k_1$/[HCl]	13.5	14.3	15.0	14.9	15.8	16.5	15.8

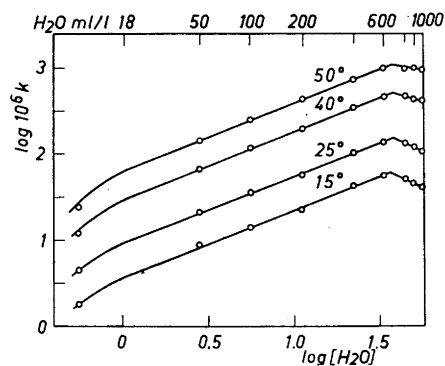*Fig. 1.* Variation of k/k_w with solvent composition.

Fig. 2. Plot of log k against log [H_2O].

constant in pure water) is plotted as a function of the composition of the solvent. The curves pass through a maximum when the water concentration is 650— 750 ml per litre; the water concentration for this maximum increases with temperature. For the sake of comparison, a corresponding curve for acetone-water mixtures [2] is also given.

(3) Over the range from the water content where the rate is a maximum to a water content of about 20 ml/l, the plot of log k against log [H_2O] is a straight line of slope 0.80 (Fig. 2).
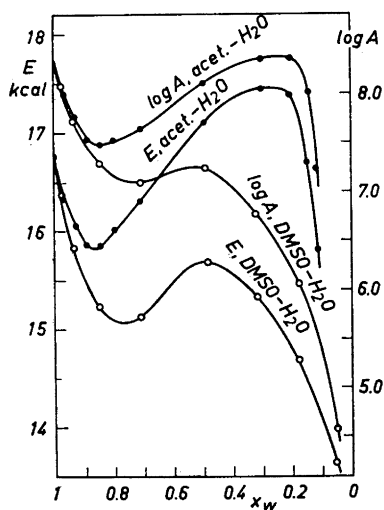

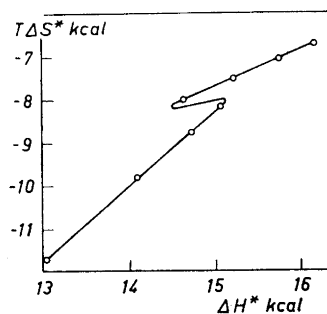*Fig. 3.* Variation of E and log A with solvent composition.

Fig. 4. Plot of $T\varDelta S^*$ against $\varDelta H^*$.

(4) As in the alkaline hydrolysis,[1] E and log A pass through a minimum when the proportion of DMSO in the solvent is gradually increased (Fig. 3). After a maximum at $x_{DMSO} = 0.5$, the curves fall steeply, whereas the curves for the alkaline hydrolysis rise continuously.[1] In contrast to what is the case for the alkaline hydrolysis, the curves for the acid hydrolysis in acetone-water mixtures [2] run above those for the reaction in DMSO-water mixtures.

(5) Corresponding to the changes in E and log A, the activation enthalpy and entropy, ΔH^* and $\Delta S,^*$ are greatly affected by changes in the composition of the solvent, but, as in general, the variations in their values compensate each other, so that the free enthalpy of activation, ΔG^*, varies much less.

(6) The plot of $T\Delta S^*$ against ΔH^* (or log A against E) comprises two linear parts, one in the region where the water content is greater than 600 ml/l, and the other in the region where the water content is less than 200 ml/l (Fig. 4).

<center>DISCUSSION</center>

The view is now generally accepted that the acid-catalysed hydrolysis of carboxylic esters involves a fast proton transfer pre-equilibrium
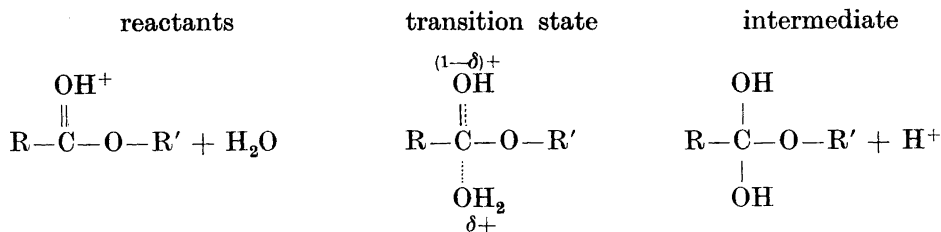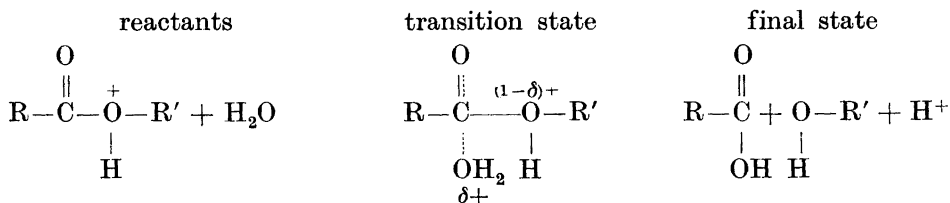
$$RCOOR' + SH^+ \xrightleftharpoons[k_I'']{k_I'} RCOOR'H^+ + S \qquad (I)$$

where SH^+ is the solvated proton. This is followed by a slow reaction with water:

$$RCOOR'H^+ + H_2O \xrightarrow{k_{II}} RCOOH + R'OH + H^+ \qquad (II)$$
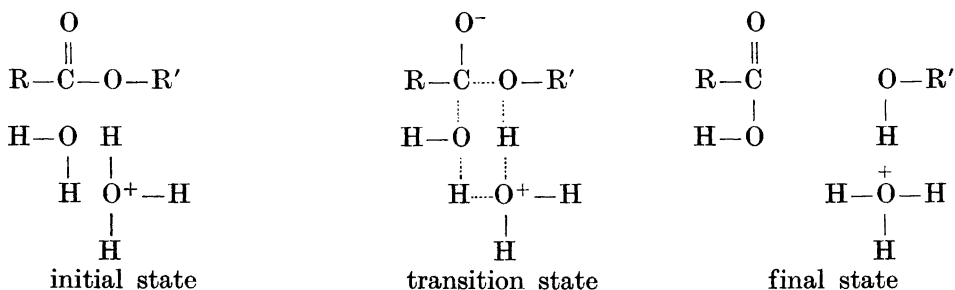
The existence of the pre-equilibrium is supported by the different rates of reaction in water and heavy water [3] and other observations.[4] The assumption of a rapid pre-equilibrium seems quite natural when atoms with lone and not too tightly held electron pairs are involved in the reaction, e.g. oxygen and nitrogen[5]. There has been much controversy about whether the proton in the conjugate acid of the ester is on the ether oxygen or on the carbonyl oxygen, and different locations are possible in different cases.
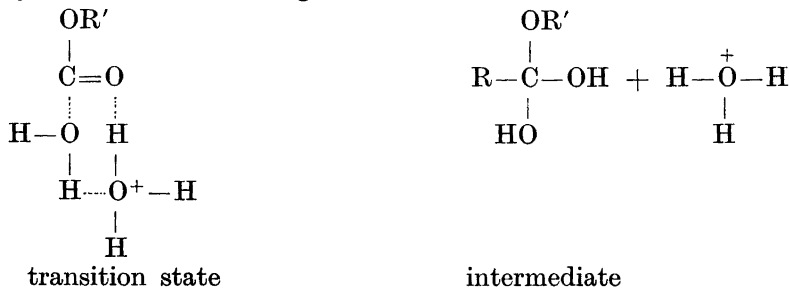
The attack of the water molecule can take place as an addition to the carbonyl carbon or as a nucleophilic substitution (Ref.[6], p. 770). In the former case a tetrahedral intermediate is formed, and the exchange of oxygen-18 between ester and solvent studied by Bender et al.[7] suggests that the intermediate has a lifetime long enough to allow appreciable exchange with solvent. Whalley [8] has concluded on the basis of the pressure effect that if the transition state is not very polar, then either the proton is on the carbonyl and the water molecule adds or the proton is on the ether oxygen and the water molecule substitutes. According to Osborn and Whalley,[9] the pressure effect shows that the transition state of the acid-catalysed hydrolysis of ethyl acetate and other simple esters is not highly polar and in particular that the carbonyl group is not appreciably ionized in the transition state. The transition states proposed by Whalley [8] are:

Addition mechanism:

reactants	transition state	intermediate

$$\underset{\text{R}-\overset{\displaystyle \text{OH}^+}{\overset{\|}{\text{C}}}-\text{O}-\text{R}' + \text{H}_2\text{O}}{}$$

transition state: $\overset{(1-\delta)+}{\text{OH}}$, R—C—O—R', $\underset{\delta+}{\text{OH}_2}$

intermediate: $\text{R}-\overset{\text{OH}}{\underset{\text{OH}}{\text{C}}}-\text{O}-\text{R}' + \text{H}^+$

Substitution mechanism:

reactants	transition state	final state

reactants: $\text{R}-\overset{\displaystyle \overset{\text{O}}{\|}}{\underset{\text{H}}{\text{C}}}-\overset{+}{\text{O}}-\text{R}' + \text{H}_2\text{O}$

transition state: $\text{R}-\overset{\displaystyle \overset{\text{O}}{\|}}{\underset{\underset{\delta+}{\text{OH}_2}}{\text{C}}}\!-\!-\!-\overset{(1-\delta)+}{\underset{\text{H}}{\text{O}}}-\text{R}'$

final state: $\text{R}-\overset{\displaystyle \overset{\text{O}}{\|}}{\underset{\text{OH}}{\text{C}}} + \underset{\text{H}}{\text{O}}-\text{R}' + \text{H}^+$

A different mechanism, a simultaneous attack of a hydronium ion on the ether oxygen and a water molecule on the carbonyl carbon with the formation of a cyclic transition state, has been proposed by Laidler and Landskroener[10]:

initial state	transition state	final state

initial state:

$$\text{R}-\overset{\displaystyle \overset{\text{O}}{\|}}{\text{C}}-\text{O}-\text{R}'$$
$$\overset{\text{H}-\text{O}}{\underset{\text{H}}{|}}\;\overset{\text{H}}{\underset{\text{O}^+-\text{H}}{|}}$$
$$\underset{\text{H}}{|}$$

transition state:

$$\text{R}-\overset{\displaystyle \overset{\text{O}^-}{|}}{\text{C}}\!-\!-\!\text{O}-\text{R}'$$
$$\text{H}-\text{O}\quad \text{H}$$
$$\text{H}\!-\!-\!\text{O}^+-\text{H}$$
$$\underset{\text{H}}{|}$$

final state:

$$\text{R}-\overset{\displaystyle \overset{\text{O}}{\|}}{\text{C}}\qquad \text{O}-\text{R}'$$
$$\text{H}-\text{O}\qquad \text{H}$$
$$\text{H}-\overset{+}{\text{O}}-\text{H}$$
$$\underset{\text{H}}{|}$$

In their formulation the transition state is highly polar, the carbonyl group being ionized. The formation of a rigid cyclic transition state would result in a great increase of order in the reacting system and would thus explain in a simple manner the low frequency factors found for the ester hydrolysis. The above cyclic transition state ignores the formation of a tetrahedral addition

transition state:

$$\overset{\displaystyle \text{OR}'}{\underset{\displaystyle \text{C}=\text{O}}{|}}$$
$$\overset{\text{H}-\text{O}}{|}\quad \overset{\text{H}}{|}$$
$$\text{H}\!-\!-\!\overset{\text{O}^+-\text{H}}{}$$
$$\underset{\text{H}}{|}$$

intermediate:

$$\text{R}-\overset{\displaystyle \overset{\text{OR}'}{|}}{\underset{\text{HO}}{\text{C}}}-\text{OH} + \text{H}-\overset{+}{\underset{\text{H}}{\text{O}}}-\text{H}$$

intermediate which according to Bender [7],[11] occurs in the first step of the process, but this objection can be met by modifying the transition state in a relatively minor way, as shown by Syrkin and Moiseew: [12]

Syrkin and Moiseev have critisized the intermediacy of the protonated species on the assumption that substrates such as esters are not sufficiently basic to form appreciable concentrations of kinetically important protonated species in dilute solution. Bender,[11] however, opposes the exclusion of protonated substrates as intermediates in acid-catalyzed reactions. While there is no question that the concentrations of certain protonated species are extremely low, this fact, in his opinion, in no way excludes their participation in kinetic processes. Martin [13] assumes that the equilibrium constant of the equilibrium (I) for carboxylic esters is of the order 10^{-7}, and thus at pH 3 where the acid catalysis sets in, $[RCOOR'H^+]$ is about 10^{-10} M, and he says that this concentration may not be too low for a reactive species like $RCOOR'H^+$. At any rate, it must be taken as confirmed that water is involved in the transition state of the slow step.[14],[15]

If stage (II) is the slow step, the overall reaction rate will be given by

$$\text{rate} = k_{II}\ [RCOOR'H^+]\ [H_2O] \tag{1}$$

or by

$$\text{rate} = k_{II}K[RCOOR']\ [H^+]\ [H_2O] \tag{2}$$

where K is the thermodynamic equilibrium constant of equilibrium (I).
The experimental rate constant k_2 of Table 1 is calculated from the equation

$$\text{rate} = k_2\ [RCOOR']\ [H^+] \tag{3}$$

hence

$$k_{II}K = k' = k_2/[H_2O] \tag{4}$$

According to the theory of absolute reaction rates,

$$\text{rate} = k_o'\ [E]\ [H^+]\ [H_2O]\ \frac{f_E\,f_{H^+}\,f_{H_2O}}{f_{X*}} \tag{5}$$

where k_o' is the rate constant in very dilute solution where the substances behave ideally. E is the ester, X* is the transition complex and the f's are activity coefficients. The experimental rate constant k_2 is thus given also by

$$k_2 = k_o'\ [H_2O]\ \frac{f_E\,f_{H^+}\,f_{H_2O}}{f_{X*}} \tag{6}$$

A trimolecular reaction would also lead to eqn. (5).

Friedman and Elmore [16] observed that the rate of acid-catalysed hydrolysis of methyl acetate is proportional to the water concentration in acetone-water mixtures. Hockersmith and Amis [17] found that in the range from pure water to a water concentration of about 400 ml per litre, k' for the acid-catalyzed hydrolysis of methyl propionate increases with decreasing water concentration, in accordance with the theory proposed by Amis [18] for reactions between positive ions and dipoles as expressed by the equation

$$\ln k = \ln k_{\varepsilon=\infty} + \frac{z\,e\,\mu}{k\,T r_*^2 \varepsilon} \tag{7}$$

Table 3. The values of $10^6 k_2/[H_2O] = k'$ (l^2 mole^{-2} sec^{-1}) at 25.00°. [H_2O] is the water concentration in the reaction mixture. The dielectric constants ε of the solvents are taken from Ref.[20]

H_2O, mole/l	55.5	49.5	44.0	33.0	22.0	11.0	5.50	2.77	0.55
$10^6 k'$	1.95	2.42	3.00	4.09	4.68	5.17	6.42	7.55	7.77
log A'	6.58	6.38	6.07	5.77	5.76	6.19	6.04	5.62	4.85
$\Delta S^{*\prime}$	−30.4	−31.3	−32.7	−34.1	−34.2	−32.2	−32.9	−34.8	−38.3
$\Delta G^{*\prime}$, kcal	25.23	25.11	24.98	24.80	24.72	24.68	24.54	24.46	24.45
ε	78.5	78.2	77.7	76.0	72.1	63.8	56.2	52.2	48.0

In this equation k and $k_{\varepsilon=\infty}$ are the rate constants when the dielectric constant is ε and when it is infinity, respectively, z is the valence of the ion, e the electronic charge, μ the dipole moment of the molecule, r_* the distance of closest approach of the ion and dipole (*i.e.* the radius of the transition complex), and k the Boltzmann constant. According to this equation, a plot of log k *vs.* $1/\varepsilon$ should yield a straight line with a slope that is positive for a positive ionic reactant and negative for a negative ionic reactant. The magnitude of the slope should be equal to $ze\mu/kTr_*^2$ and from it r_* can be calculated. In accordance with the theory, Hockersmith and Amis obtained a linear plot in the region mentioned above and from its slope they obtained the values of $r_* = 3.43$ Å at 25° and 3.01 Å at 45.48°. Much greater values were found for ethyl acetate in dioxan-water and acetone-water mixtures.[19]

Tommila and Hella [2] found that $k_2/[H_2O]$ for ethyl formate, ethyl acetate, ethyl propionate, methyl acetate and propyl acetate in acetone-water mixtures increases when the water concentration decreases from 1000 ml to about 800 ml per litre, and remains thereafter practically constant until at high acetone concentrations it rises again with decreasing water concentration. In all of these cases the catalyst was hydrogen chloride.

The values of $k_2/[H_2O]$ or k' for the acid hydrolysis of ethyl acetate in DMSO-water mixtures increase continuously with decreasing water concentration (Table 3). When the values of the water concentrations were calculated,
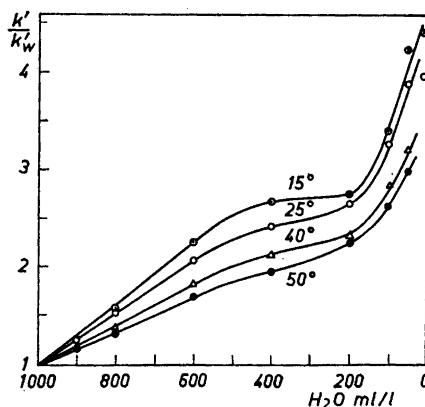

Fig. 5. Plot of k'/k'_w against solvent composition.

the volume occupied by the ester and the thermal expansion of water were taken into account. The variation of k'/k_w' (k_w' is the values of k' for the reaction in pure water) is seen from Fig. 5. In contrast to curves of Fig. 1, these curves rise continuously. Division of k_2 by $[H_2O]$ leads to no appreciable change in the activation energies, but the frequency factors will be divided by $[H_2O]$. Also the values of $\log (A/[H_2O]) = \log A'$ are given in Table 3.

The dielectric constants of DMSO-water mixtures have been measured only at 25°.[20] The plot of $\log k'$ against $1/\varepsilon$ for this temperature is given in Fig. 6. The slope of the curve has the sign predicted by eqn. (7) for a reaction
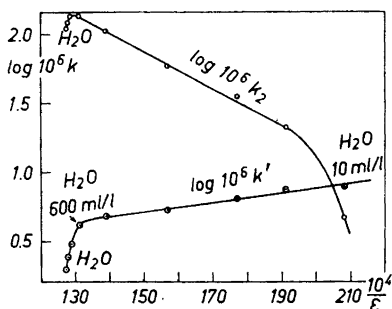

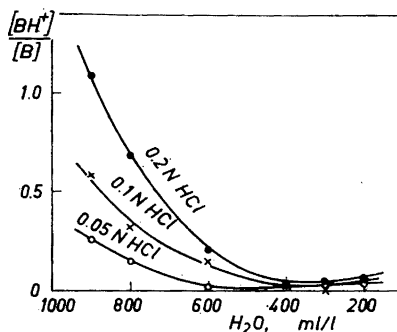Fig. 6. Plot of $\log k$ against $1/\varepsilon$. Temperature 25°.

Fig. 7. The ratio $[BH^+]/[B]$ as a function of the solvent composition. Temperature 25°.

between a positive ion and a dipole. The curve rises initially very rapidly, but is linear within the limits of experimental error in the range where the water concentration is less than 600 ml/l. Hockersmith and Amis assumed that the rate-determining step is the reaction between the hydronium ion and the ester molecule. However, if the existence of the pre-equilibrium (I) is accepted, the reaction in question is the step (II), the ion being the protonated ester and the dipole the water molecule. In the following the problem is treated on this basis. Equating the slope, $s = 35$, of the long linear part of the curve in Fig. 6 to $e\mu/kTr_*^2$ and using for water the value $\mu = 1.9$ Debye units, one obtains the value 1.7 Å for r_*. This is considerably lower than the values found by Amis et al. and by Laidler [10,21] (4.0 Å) for acetone-water mixtures, but is at least of the same order of magnitude.

According to the theory propounded by Laidler,[21] the relation between the rate constant and the dielectric constant of the solvent for an ion-dipole reaction is given by the equation

$$\frac{\mathrm{d}\ln k}{\mathrm{d}(1/\varepsilon)} = \frac{1}{kT}\left[\frac{z_A^2 e^2}{2}\left(\frac{1}{r_A} - \frac{1}{r_*}\right) + \frac{3}{4}\left(\frac{\mu_A^2}{r_A^3} + \frac{\mu_B^2}{r_B^3} - \frac{\mu_*^2}{r_*^3}\right)\right] \qquad (8)$$

The radius of the transition state, r_*, will always be greater than that of the ion, r_A, and thus if the term involving z^2e^2 predominates the slope should be positive. Laidler has applied the equation to the rate constants k_2 of the acid hydrolysis of esters, amides and anilides and he explains the observed decrease

of k_2 with decreasing dielectric constant by assuming a large value of μ_*^2/r_*^3, i.e. a high polarity of the transition complex. Also k_2 for the acid hydrolysis of ethyl acetate in DMSO-water mixtures increases with increasing dielectric constant, the plot of log k_2 against $1/\varepsilon$ being linear when the water concentration varies from 600 ml to 50 ml/l (Fig. 6). However, when the equation is applied to $k' = k_2/[H_2O]$, the slope is positive, as we have seen (Fig. 6). This can be the case only if μ_*^2/r_*^3 is not large, i.e. if the transition state is not highly polar, a result which is in agreement with the view of Osborn and Whalley.[9]

The values of the molecular radii derived from the molar refraction,[22,23] from the viscosity,[24] and from the constant b of van der Waals equation are, respectively, 2.1, 2.1, and 2.4 Å for ethyl acetate, and 1.14, 1.15, and 1.45 Å for water.[25] Considerably greater values, 3.0 Å for the ester and 1.7 Å for water, are computed from the formula given by Moelwyn-Hughes.[26] As an approximation one can assume that the radius and dipole moment (cf. Ref.[21], Appendix) of the protonated ester (A) do not seriously differ from those of the ester. In every case, owing to the large value of r_A, the effect of μ_A^2/r_A^3 is small. From Fig. 6 we obtain d log $k'/d(1/\varepsilon) = 35$ for the linear part of the plot. Using the values of 1.9 and 1.82 D for the dipole moments of water (B) and the protonated ester and 1.30 and 2.40 Å for the radii, and assuming that the dipole moment of the transition complex is so small that the term μ_*^2/r_*^3 can be neglected, we obtain from eqn. (8) the value $r_* = 4.0$ Å for the radius of the transition state. This is same value as Laidler[21] obtained for the acid hydrolysis of ethyl acetate in acetone-water mixtures. For dioxan-water mixtures Laidler obtained $r_* = 4.6$ Å. The value of 1.40 Å for the radius of the water molecule would give $r_* = 4.3$ Å. The values $\mu_A = 4$ D, $r_A = 2.4$ Å, and $r_B = 1.3$ Å would give $r_* = 3.7$ Å. These results show that the term μ_*^2/r_*^3 is very small in aqueous DMSO when water concentration is less than 600 ml/l.

According to the results of Tommila and Hella[2] the plots of log k' vs. $1/\varepsilon$ for the reaction in acetone-water mixtures are straight lines with positive slopes in the region from pure water to a water concentration of about 800 ml/l. For ethyl acetate the slope is 30, which by eqn. (8) gives $r_* = 3.7$ Å for the radius of the transition state. For methyl acetate (slope 16, $\mu_A = 1.7$ D, $r_A = 2.2$ Å)[25] the value $r_* = 2.4$ Å is obtained (Laidler 4.2 Å).

It deserves attention that the linear part of the plot is in the range of low water concentrations in DMSO-water mixtures, whereas it is in the range of high water concentrations in acetone-water mixtures. However, we must remember that the above treatment is pertinent only when electrostatic influence upon reactants in solution predominate over specific effects such as those arising from the solvent due to solvation and other causes. The dimethyl sulphoxide molecule is pyramidal,[27] whereas the acetone molecule is planar, and in addition the dimethyl sulphoxide molecule is much more polar ($\mu = 3.9$ D)[28] than the acetone molecule ($\mu = 2.7$ D). The dimethyl sulphoxide molecule has a lone electron pair, on the sulphur atom, whereas the acetone molecule has none. Thus it is not surprising that the variation of the rate is different in the two series of solvent mixtures.

The fact that log k_2 also varies linearly with the reciprocal of the dielectric constant (Fig. 6) is easily understood. From the relationship $k' = k_2/[H_2O]$ it follows that log $k_2/(1/\varepsilon) = \log k'/(1/\varepsilon) + \log [H_2O]/(1/\varepsilon)$. For water concentra-

tions from 600 ml to 50 ml per litre in DMSO-water mixtures, $\log [H_2O]/(1/\varepsilon)$ is constant and equal to -175.[20] As we have seen, $\log k'/(1/\varepsilon) = 35$; thus $\log k_2/(1/\varepsilon) = -140$, which is just the observed value.

Concerning the frequency factor the following points may be noted. The number of binary collisions between the protonated ester molecules and water molecules in water can be estimated to be of the order of 2×10^{13} $(mole/l)^{-1}$ $sec.^{-1}$ (Ref.[26], chapters I and VIII). If every activated collision were to lead to reaction, the frequency factor for reaction (II) would be about 2×10^{13}. The rate constant $k_{II} = k'/K = k_2/K[H_2O]$. If the frequency factor relating to k_2 is A and that relating to k_{II} is $A_{,I}$, we get $A_{II} = A/K[H_2O] = A'/K = 2 \times 10^{13}$, or since $A = 2 \times 10^8$ (Table 1), $K = 2 \times 10^8/(55 \times 2 \times 10^{13})$ or about 10^{-7}. According to Martin,[13] the equilibrium constant K is of the order of 10^{-7}. If the rate of proton release from the protonated ester is diffusion controlled,[13] $k_I'' = 10^{10}$ sec^{-1}, the rate constant for the protonation of the ester is $k_I' = K \times 10^{10}$ or about 10^3 l $mole^{-1}$ sec^{-1}, and is much higher than the hydrolysis rate constant of about 10^{-4} l $mole^{-1}$ sec^{-1}. Thus the establishment of the pre-equilibrium (I) is very rapid compared with the rate of step (II).

We see that the above treatment conforms to all known facts for the acid-catalysed hydrolysis of ethyl acetate in DMSO-water mixtures, *viz.* to the prediction of theory concerning the relation between the rate and the dielectric constant, to the predictions based on the pressure effect, and to the value of the frequency factor. The structure of the transition state which best conforms to our results and to the theory of Bender (see also Refs.[11,29,30]) is clearly that proposed by Whalley for the addition mechanism and given above. The applicability of the above treatment also to the reactions in acetone-water mixtures in the region of high dielectric constant witnesses that it might have a more general validity in the interpretation of the acid-catalysed hydrolysis of carboxylic esters.

The energy of activation is about four to five thousand calories higher for the acid hydrolysis than for the alkaline hydrolysis. In alkaline hydrolysis the negatively charged hydroxide ion attacks the carbonyl carbon, whereas in the acid hydrolysis it is the uncharged water molecule that attacks this carbon atom. The repulsion is undoubtedly greater in the latter than in the former case, and should lead to a higher activation energy. In general, a water molecule can approach the carbonyl carbon atom in the formation of the transition complex only if the carbonyl carbon atom is made positive enough by a prior addition of a proton to the ester.

It may be pointed out that the relation between the rate and the dielectric constant in the acid-catalysed hydrolysis can be satisfactorily interpreted in terms of a cyclic transition state and eventually of a trimolecular process only if the transition state is highly polar, which, however, is in contradiction to the observed pressure effect. The transition state proposed by Whalley for the substitution mechanism would be in agreement with the above conclusions, but it does not conform to the formation of the tetrahedral intermediate. In fact it is the transition state of the theory of Lowry.[31] Possibly both mechanisms are operating simultaneously, *cf.*[32]

One could expect that the rate constant $k' = Kk_{II}$ (eqn. 4) follows the changes in K, *i.e.*, in the concentration of $RCOOR'H^+$. In general, k' depends

on the activity coefficient term in eqn. (5), which is a function of the solvent composition. However, the values of the activity coefficients in different solvents, except that of water,[33] are not known. The concentration of the proton adduct $RCOOR'H^+$ is dependent on the basicity of the ester and on the ability of the solvent to donate protons to a Hammett base. Recent investigations have shown that hydrochloric acid is completely ionized in DMSO and that the basicity of DMSO is comparable to that of water,[28] or probably that in a mixture of DMSO and water the proton of hydrogen chloride is more attracted to DMSO than to water.[34] Thus it is less probable that the ability of the solvent to donate protons increases with the DMSO concentration. This is in accordance with the preliminary experiments we have carried out using p-nitroaniline as indicator. These experiments showed that $[BH^+]/[B]$ first decreases with increasing proportion of DMSO to a minimum in the about 60 vol. % mixture after which it possibly increases slowly (Fig. 7). However, it must be pointed out that the behaviour of bases may vary greatly with solvent composition, and that nitroaniline differs as a base from an ester. However, it can be deduced also from the values of A' (Table 3) that $K = A'/A_{II}$ probably is a minimum in the about 60 vol. % mixture. It is interesting to note that A' is relatively little affected by changes in the composition of the solvent. Summing up, the increase of k' with decreasing water concentration is caused rather by changes in the value of the term containing the activity coefficients than by a greater ability of the solvent to donate protons to the ester or by an increase in the concentration of the protonated species.

Attention was already drawn to the fact that in acid hydrolysis as in alkaline hydrolysis the curves plotting ΔH^* and $T\Delta S^*$ as functions of the composition of the solvent pass through a minimum and that thereafter the curves for the alkaline hydrolysis rise continuously, whereas those for the acid hydrolysis have a maximum when x_w is about 0.5, after which they sink again. The variations of ΔH^*, $\Delta S^{*'}$ and $\Delta G^{*'}$ are seen from Fig. 8. It is very interesting to note that the curves for the acid ester hydrolysis resemble those for the solvolyses of ethyl bromide [35] and benzyl chloride [36] in acetone-water mixtures and those for the solvolysis of alkyl benzenesulphonates in ethanol-acetone and ethanol-benzene mixtures,[37] but do *not* resemble the curves for the solvolyses of *tert.*-butyl chloride and bromide[35] which are S_N1 reactions (Fig. 9). This resemblance gives support to the view that the rate-governing step of the acid-catalysed hydrolysis is a bimolecular reaction between the protonated ester and a water molecule. However, it must be pointed out that here the substrate is a charged species, whereas in the other reactions mentioned the substrates are neutral molecules.

The changes in the enthalpies and entropies of activation arise chiefly from changes in the solvation of reactants and especially from changes in the solvation of the transition complex, the water molecules having a specific attraction for the hydrophilic groups and the organic molecules for alkyl or other groups.[28,39] The solvation phenomena and changes in the values of ΔH^* and ΔS^* are also closely connected with changes in the internal structure of the solvent that occur when the relative amounts of the solvent components are varied.[2,39]
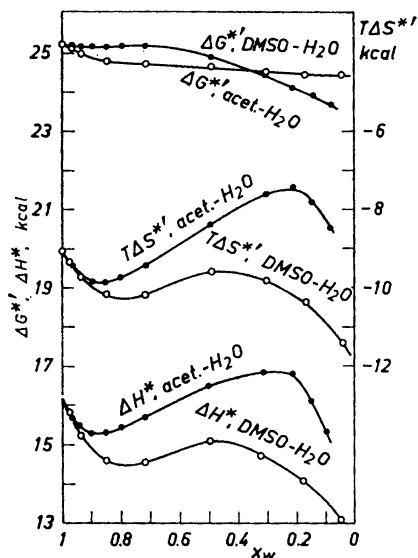
Fig. 8. Variation of ΔH^*, $\Delta S^{*\prime}$ and $\Delta G^{*\prime}$ with solvent composition.
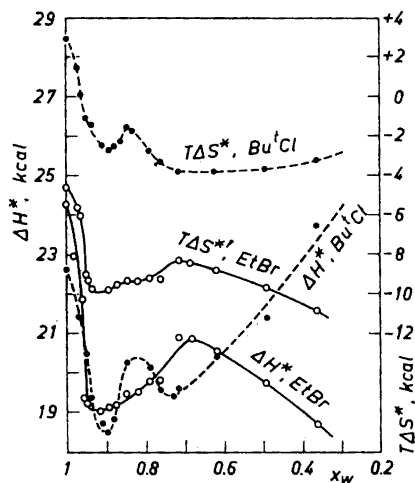
Fig. 9. Solvolysis of ethyl bromide and tert.-butyl chloride in acetone-water mixtures (Ref.[35]). Variation of ΔH^* and $\Delta S^{*\prime}$ with solvent composition.

The origin of the minima can be understood as presented previously.[1,2,38] The drop in the values of ΔH^* and ΔS^* at higher DMSO contents is more difficult to explain. Perhaps the following suggestion is applicable. The number of "free" water molecules decreases with increasing content of DMSO; already at the mole fraction $x_w = 0.7$ of water the water molecules are largely bound to DMSO molecules as 2:1 complexes (cf. Ref.[1]), and at mole fractions $x_w = 0.5$ or less the number of free water molecules is very small and rapidly decreasing. Since the hydrogen bonds between water molecules and DMSO molecules are stronger than the hydrogen bond between two water molecules (cf. Ref.[1]), the complex $Me_2SO.....H-O-H$ and not a free water molecule is here the attacking reagent:

$$
\begin{array}{cc}
\overset{(1-\delta)+}{\overset{OH}{\underset{\parallel}{}}} & \overset{OH}{\underset{\mid}{}} \\
R-\overset{\shortmid}{\underset{\vdots}{C}}-OR' \longrightarrow & R-\overset{\mid}{\underset{\mid}{C}}-OR' + Me_2SOH^+ \\
Me_2SO\cdots H-OH & OH \\
\overset{\delta+}{} &
\end{array}
$$

$$\text{transition state} \qquad\qquad \text{intermediate}$$
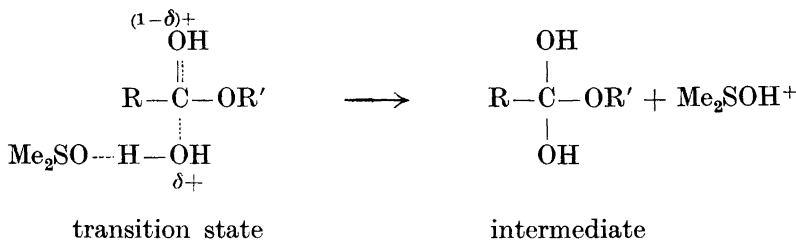
If the attached proton is on the ether oxygen, we may write

$$\underset{\substack{\text{Me}_2\text{SO} \cdots \text{H} - \overset{\displaystyle |}{\text{OH}} \\ \delta+ \\ \text{transition state}}}{\overset{\displaystyle \text{O}}{\underset{\displaystyle \text{H}}{\overset{\displaystyle \|}{\text{R} - \overset{(1-\delta)+}{\text{C}} - \text{O} - \text{R}'}}}} \longrightarrow \underset{\displaystyle \text{products}}{\overset{\displaystyle \text{O}}{\underset{\displaystyle \text{OH}}{\overset{\displaystyle \|}{\text{R} - \text{C}}}} + \text{R}'\text{OH} + \text{Me}_2\text{SOH}^+}$$
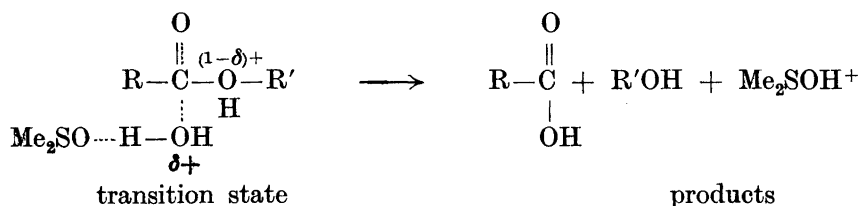
It is not impossible that both processes occur side by side. Owing to the strong hydrogen bond the oxygen atom of water in the DMSO-water complex is more negative than in pure water. This weakens the repulsion between it and the carbonyl carbon and lowers the enthalpy of activation. The attachment of the complex to the protonated ester in the transition state brings about a greater increase of order than in the case of pure water and, accordingly, makes the entropy of activation more negative. A further lowering of the enthalpy and entropy of activation is caused by solvation of the transition state either by single solvent molecules or by DMSO-water complexes. The hydrogen bonds between acetone and water are much weaker than those between DMSO and water, as can be concluded from the heats of mixing (*cf.* Ref.[1]), and thus the repulsion of the carbonyl carbon atom is greater for acetone-water complexes than for DMSO-water complexes. This explains why the enthalpies of activation are lower in DMSO-water mixtures than in acetone-water mixtures. The activation entropies show that the increase in order in the formation of the transition state is greater in DMSO-water than in acetone-water mixtures.

Over the whole range of mixtures, the changes in ΔH^* and $\Delta S^{*\prime}$ counteract each other, and hence $\Delta G^{*\prime}$ and the rate constant k' are very little affected by solvation.

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