Rate Enhancement of Ester Saponification in Aqueous Dimethyl Sulphoxide: a Case for the Importance of Transition State Solvation

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On the basis of kinetic data for the alkaline hydrolysis of a number of acetate esters, glycol di- and mono-esters, and αβ-unsaturated esters and lactones in aqueous dimethyl sulphoxide (DMSO) and aqueous ethanol, an assessment of the relative importance of the two factors generally associated with rate enhancement in aqueous DMSO, the existence of a desolvated and more reactive hydroxide ion and the remarkable ability of DMSO to solvate the transition state, is attempted. A qualitative discussion of the data in the light of an equation connecting the rate increase in a dipolar aprotic solvent with the solvent activity coefficients of the ester molecule, hydroxide ion, and the transition state anion in the two solvent systems is made. It is shown that hydroxide ion desolvation is not the exclusive factor causing rate accelerations in DMSO. Spectral evidence shows that solvation of the ester molecule in the two solvent systems plays a negligible role. The results fit well with the concept of 'loose' and 'tight' transition states and the influence of the dipolar aprotic and the protic solvent systems on these types of transition states is analysed.

ALTHOUGH it is well established that ester saponification is subject to rate acceleration on changing the solvent from ethanol or methanol to dimethyl sulphoxide (DMSO), the exact role of DMSO in such enhancement has not been unequivocally settled. The two factors that are generally recognised in this context are the superior ability of DMSO to solvate effectively the transition state for ester saponification and the presence of a poorly solvated and consequently highly active hydroxide ion in DMSO–water mixtures. A recent attempt[1] sought to evaluate the relative importance of the two factors on the basis of calorimetric studies. This was, however, confined only to a few alkyl benzoates.

With this end in view, we have made a detailed investigation of the rate of ester saponification in aqueous DMSO and in aqueous ethanol employing a variety of esters under varying conditions of solvent composition and temperature. The study, the results of which are presented in this paper, includes the alkaline hydrolysis of a number of alkyl acetates, aliphatic and aromatic γ-lactones, aliphatic and aromatic αβ-unsaturated esters, and glycol mono- and di-esters.

TABLE 1

Rate data for the alkaline hydrolysis of acetate esters at 30°

	10^3k/l mol^{-1} s^{-1}	
Ester	70% EtOH(v/v)	70% DMSO(v/v)
Methyl acetate	32·5	714
Ethyl acetate	21·1	325
Isopropyl acetate	6·08	48·0
t-Butyl acetate	0·313	2·84
n-Butyl acetate	21·6	251
Cyclohexyl acetate	6·55	62·3
Cyclopentyl acetate	8·59	101
Isoamyl acetate	16·7	180
Allyl acetate	33·7	609
2-Methoxyethyl acetate	37·3	907
2-Ethoxyethyl acetate	32·9	776
Benzyl acetate	35·5	1090

RESULTS AND DISCUSSION

A comparative picture of the rate coefficients for the saponification of the esters studied is presented in Tables 1—5.*

TABLE 2

Alkaline hydrolysis of αβ-unsaturated esters and their saturated analogues at 30°

	10^2k/l mol^{-1} s^{-1}	
Ester	70% DMSO(v/v)	70% EtOH(v/v)
Ethyl acrylate	21·4	1·43
Methyl acrylate	76·7	1·90
Methyl methacrylate	27·7	0·646
Ethyl propionate	20·3	1·29
Ethyl crotonate *	2·42	0·240
Ethyl butyrate *	8·88	0·771
Ethyl cinnamate *	7·63	0·492

* In 60% DMSO–EtOH (v/v).

TABLE 3

Rate data for the alkaline hydrolysis of glycol dibenzoates at 30°

	10^3k/l mol^{-1} s^{-1}		
	80% DMSO (v/v)	80% EtOH (v/v)	k^s
Ethylene glycol dibenzoate	2030	6·31	320
Propane-1,3-diol dibenzoate	867	7·57	115
2,2-Dimethylpropane-1,3-diol dibenzoate	437	4·83	92
Butane-1,4-diol dibenzoate	383	4·20	91
3,6-Dioxaoctane-1,8-diol dibenzoate	830	5·28	160

$k^s = k_{DMSO}/k_{EtOH}$.

TABLE 4

Rate data for the alkaline hydrolysis of glycol monobenzoates at 30°

	10^3k/l mol^{-1} s^{-1}		
	80% DMSO (v/v)	80% EtOH (v/v)	k^s
Ethylene glycol monobenzoate	626	0·625	1000
Propane-1,3-diol monobenzoate	192	1·08	177
2,2-Dimethylpropane-1,3-diol monobenzoate	219	0·986	220
Butane-1,4-diol monobenzoate	124	1·12	112
3,6-Dioxaoctane-1,8-diol monobenzoate	401	0·800	500
Ethyl benzoate	173	1·47	118

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* A detailed discussion of the structural effects in each group of esters will be given elsewhere. However, the comparative rate data for all the esters studied have been presented to demonstrate that not only different groups of closely related esters, but also members of the same group show varying sensitivity to DMSO-induced rate acceleration.

[1] P. Haberfield, J. Friedman, and M. F. Pinkston, *J. Amer. Chem. Soc.*, 1972, **94**, 71.

TABLE 5

Saponification of lactones and their open chain analogues at 30°

	10^2k/l mol^{-1} s^{-1}		
	70% DMSO(v/v)	70% EtOH(v/v)	k^s
γ-Butyrolactone	236	31·7	7·5
γ-Valerolactone	106	19·7	5·4
Phthalide	66·0	7·10	9·4
Ethyl acetate	32·5	2·11	15·4
Isopropyl acetate	4·80	0·608	8
Methyl benzoate	13·7	0·383	36

The rate constants for the alkaline hydrolysis of an ester (RX) in the two solvent systems, k^o for aqueous ethanol and k^s for aqueous DMSO, can be correlated by equation (1) [2] where the γ values represent the solvent

$$\log k^s/k^o = \log {}^o\gamma^s{}_{Y^-} + \log {}^o\gamma^s{}_{RX} - \log {}^o\gamma^s{}_{YRX^{-\ddagger}} \quad (1)$$

activity coefficients of the anion Y^- (*i.e.* OH^-), the ester (RX), and the anionic transition state $YRX^{-\ddagger}$. From equation (1), it is obvious that rate enhancement in the aprotic solvent, as represented by higher k^s/k^o values, will be greater if (i) both the reactants, the hydroxide ion and the ester, are desolvated by the aprotic solvent relative to the protic solvent, which will make the respective activity coefficient values more positive and (ii) if the transition state is solvated to a greater extent by the aprotic solvent which will lead to a higher negative value for the corresponding activity coefficient term and consequently to a larger overall k^s/k^o value. Our results are examined on the basis of equation (1) so that, at least qualitatively, one can gauge the relative importance of the two factors causing rate enhancement in the dipolar aprotic solvent.

Solvation of Initial States.—A perusal of the rate data shows that the rate enhancement in aqueous DMSO over aqueous ethanol depends on the substrate employed, the aromatic esters showing greater rate acceleration than the corresponding aliphatic esters, an unusually high acceleration of 1000 times being observed with ethylene glycol monobenzoate.

From equation (1) it is evident that such varying degrees of rate enhancement cannot arise from the hydroxide ion desolvation factor alone, which was considered as the exclusive cause for rate enhancements in aqueous DMSO by Tommila.[3] For all the esters, under constant conditions of solvent composition and temperature, the first term $\log {}^o\gamma^s{}_{Y^-}$ will have the same value so that any change in the value of $\log k^s/k^o$ will have to be traced to changes in the ${}^o\gamma^s$ value of the neutral molecule RX (ester) and the anionic transition state $YRX^{-\ddagger}$.

From a perusal of the data obtained previously,[2] it is clear that the solvation of the non-electrolyte (ester molecule) is not of major importance in causing rate enhancement in aprotic solvents. In most cases, the value of $\log {}^o\gamma^s{}_{RX}$ tends to be close to zero. Thus one can say that significant changes in the value of k_{DMSO}/k_{EtOH} are not due to changes in the solvation of the ester molecule.

Roberts [4] who first observed a greater k^s value in the case of aromatic esters attributed this to DMSO *stabilising* the carbonyl polarisation of the aromatic esters to a greater extent. It is appropriate here to refer to Kingsbury's work [5] on the reaction of benzylamine with aryl halides. On the basis of a rate increase of 80 times for only one reaction of benzylamine which was transferred from methanol to 80% DMSO–methanol, he concluded that 'catalysis' by DMSO and related solvents is independent of the charge on the nucleophile. He made the further suggestion that the mechanism of DMSO catalysis in DMSO–methanol mixtures involves the polarisation of aromatic substrates by random DMSO molecules followed by rapid nucleophilic attack upon the species. Similar explanations for increased reaction rates in dipolar aprotic solvents based on some ground state interaction between the polar substrate and the solvent followed by nucleophilic attack on the 'active' species have been made recently.[6] These, however, have been rejected by Parker.[7] It may be that DMSO molecules which solvate the transition state for a reaction lower the free energy of the transition state relative to that for a reaction in pure methanol. This would lead to faster reactions in mixed solvents. An interaction of this type is mechanistically quite a different proposition from the polarisation of the substrate prior to the reaction with the nucleophile.

That the polarisability of a neutral molecule is not significantly affected by changeover to a dipolar aprotic solvent may be established by examining the effect of solvent on spectra. The i.r. spectra of ethyl cinnamate, benzyl cinnamate, diethyl isophthalate, diethyl terephthalate, ethylene glycol dibenzoate, 3,6-dioxaoctane-1,8-diol dibenzoate, 2,2-dimethylpropane-1,3-diol dibenzoate, and butane-1,4-diol dibenzoate in $CHCl_3$ and DMSO were obtained. The spectra in the region 1900—1600 cm^{-1} for any particular compound in the two solvents are completely superimposable. If DMSO affects the carbonyl carbon polarisability in the case of aromatic esters, this should have resulted in a shift in the carbonyl frequency. This coupled with the fact that in the case of acetophenone, $\Delta\bar{\nu}_{C=O}$ in DMSO was found to be only 8 cm^{-1} (the reference solvent being benzene) [8] shows that the polarisability of a keto-group attached to an aromatic ring is not very much affected by DMSO. The superimposability of the n.m.r. spectra of ethylene glycol dibenzoate in $CDCl_3$ and $[^2H_6]$DMSO is also consistent with this.

It is well established that DMSO is transparent above 300 nm. We have, therefore, studied the u.v. spectrum of *p*-nitroaniline both in aqueous ethanol and aqueous

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[2] A. J. Parker, *Chem. Rev.*, 1969, **69**, 1.

[3] E. Tommila and M. L. Murto, *Acta Chem. Scand.*, 1963, **17**, 1947.

[4] D. D. Roberts, *J. Org. Chem.*, 1964, **29**, 2039; 1966, **31**, 4037.

[5] E. A. Kingsbury, *J. Org. Chem.*, 1964, **29**, 3262.

[6] S. Yoneda, J. Monshima, K. Fukin, and Z. Yoshida, *Kogyo Kagaku Zasshi*, 1965, **68**, 1077.

[7] A. J. Parker, *Adv. Phys. Org. Chem.*, 1967, **5**, 173.

[8] M. J. R. Dack, *Chem. in Brit.*, 1970, **6**, 347.

DMSO and the results are presented in Table 6. The negligible shift in $\lambda_{max.}$ clearly proves that the polarisability of even a highly polarisable neutral molecule is not very much affected by DMSO. If the polarisability had been enhanced by DMSO, a pronounced red shift (*ca.* 50 nm) similar to that in the case of *p*-nitrothiophenoxide [9] should have been observed.

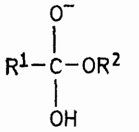
TABLE 6

Solvent effects on the u.v. spectra of *p*-nitroaniline

Solvent (v/v)	$\lambda_{max.}$/nm	ε/cm^3 mol^{-1}
95% EtOH	381	13,500
50% DMSO	386	13,900
99% DMSO	388	14,500

It thus emerges that any significant increase of k^s value in the case of aromatic esters is not due to changes in the ground state solvation of the ester molecules. An extension of this inference to aliphatic systems exhibiting varying sensitivity to DMSO ' catalysis ' appears logical.

Solvation of the Transition State.—Substitutions at aryl, vinyl, and carbonyl carbon atoms (ester hydrolysis) are reactions in which the bond formation precedes bond breaking.[2] They are, in fact, two-step reactions, comprising an addition to give high energy adducts and then an elimination of the leaving group. The structure and charge distribution in the transition states for the formation or decomposition of these high energy intermediates have led them to be considered as ' tight ' transition states.[10] The data in the literature as well as our own investigations show that most ester saponifications are very much less sensitive to the influence of dipolar aprotic solvents. This is because the negative charge localised on the carbonyl oxygen atom in the transition state (I) makes it a good hydrogen bond acceptor and hence better solvated by a protic solvent. This picture of the transition state has been further supported by a recent report [1] on the calorimetric determination of the relative enthalpies of reactants and transition states in both aqueous dipolar aprotic and aqueous protic solvents. The conclusion is that the transition state resembles a species such as an alkoxide ion much more than a delocalised anion having weak hydrogen bonding interactions with the solvent.



$$R^1-\overset{\overset{\displaystyle O^-}{|}}{\underset{\underset{\displaystyle OH}{|}}{C}}-OR^2$$

(I)

However, as the transition state anion is appreciably larger than the hydroxide ion, the dispersion force interaction between it and DMSO should be larger than that between the hydroxide ion and DMSO. As a result, the $B_{AC}2$ transition state should be stabilised relative to hydroxide ion. The greater the polarisability, the greater will be the stabilisation by DMSO. It is well known that aprotic solvents like DMSO stabilise charged structures such as polarisable transition state anions.[2]

The transition state anion in the case of an aromatic ester will be much more polarisable than that for an aliphatic ester. Further, the phenyl ring attached to the carbonyl group acts as an electron sink and thus lowers the electron density around the carbonyl group, thereby decreasing the localisation of negative charge on the carbonyl oxygen atom with concurrent decrease in the hydrogen bond acceptor capacity of the transition state. This will lead to a less positive value for the solvent activity coefficients for the transition state, resulting in an increase of the k_{DMSO}/k_{EtOH} value. This is evident from Table 7 which contains the k^s values for various benzoates. It is seen that ethyl *p*-nitrobenzoate has a much higher k^s value compared to ethyl *p*-methoxybenzoate or ethyl benzoate.

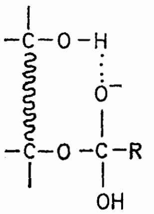
TABLE 7

Rates of alkaline hydrolysis of *para*-substituted ethyl benzoates at 25° *

	10^2k/l mol^{-1} s^{-1}		
Substituent	0·69M-DMSO	0·69M-EtOH	k^s
p-NO_2	4467	7·7	580
H	28	0·07	400
p-Cl	131	0·301	439
p-OMe	4·37	0·015	290

* From M. Hojo, M. Utaka, and Z. Yoshida, *Tetrahedron Letters*, 1966, 25.

The transition state for the alkaline hydrolysis of the glycol monoester can be represented as (II).[11] A similar transition state was proposed for the alkaline hydrolysis of a number of cyclopenta- and norborna-diol monoacetates.[12] The rate-enhancing influence of a hydroxy-group in these systems was more than could be explained on the basis of an inductive effect. The results of i.r. studies demonstrated that the influence of a vicinal hydroxy-group is not greatly dependent on the types of possible internal hydrogen bonding in the ground state.[12]



(II)

In the transition state (II), the negative charge on the carbonyl oxygen atom is decreased by diffusion through intramolecular hydrogen bonding. The transition state thus acquires a charge distribution similar to that for an S_N2 reaction, unlike the case of the hydrolysis of normal esters in which there is localisation of the negative charge on the carbonyl oxygen atom. It is well documented that bimolecular reactions involving anions and passing through such transition states are considerably accelerated by a changeover from a protic to a dipolar aprotic solvent. This accounts for the huge k^s value of 1000 for the saponification of ethylene glycol mono-

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[9] A. J. Parker, *Acta Chem. Scand.*, 1962, **16**, 855.

[10] G. S. Hammond, *J. Amer. Chem. Soc.*, 1955, **77**, 334.

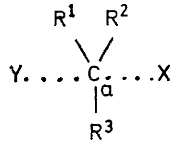
[11] M. Balakrishnan, G. Venkoba Rao, and N. Venkatasubramanian, *Tetrahedron Letters*, 1972, 4617.

[12] T. C. Bruice and T. H. Fife, *J. Amer. Chem. Soc.*, 1962, **84**, 1973.

benzoate. If the data are extrapolated to 90% organic solvent (from the linear log k against mole fraction DMSO plot), the k^s value is as high as 8000. This dramatic increase in rate bears ample testimony to the effect of DMSO on the stabilisation of such transition states. In this case it is quite probable that the solvent activity coefficient of the transition state will have a negative value, thereby leading to a very high k^s value. The reversal in the reactivity pattern among the various glycol monobenzoates on solvent transfer,[11] the progressive decrease in the solvent effects with increasing chain length in the glycol monobenzoates, and the absence of such specific solvent effects in the hydrolysis of the dibenzoates are all consistent with this situation. It is obvious that these observations cannot be accounted for by the explanation which attributes saponification rate acceleration in DMSO exclusively to the presence of a desolvated hydroxide ion.

The exceptionally good agreement between our rate data and the concept of ' loose ' and ' tight ' transition states and the influence of the two types of solvents on these transition states, also confirms our contention that transition state solvation plays an important part in rate enhancement of ester saponification in aqueous DMSO.

From a consideration of the results obtained in S_N2, E_2C, and E_2Hal reactions, Parker and Ko[13] arrived at the following generalisations. (i) Steric interactions of the attacking nucleophile Y and the leaving group X with increasing bulky groups at C_α increase the ' looseness ' of the transition state (III). (ii) Substituents which stabilise the carbonium ion in C_α increase the ' looseness ' of the transition state. This is because of the increasing localisation of negative charge on small anions Y and X which are strongly solvated by protic solvents. (iii) Electron-attracting substituents increase the ' tightness ' of the transition state while electron-releasing substituents increase its ' looseness '. (iv) A ' tight ' transition state is stabilised by an aprotic solvent while a ' loose ' one is favoured by a protic solvent.



(III)

If one examines the results of the alkaline hydrolysis of alkyl acetates in aqueous DMSO and aqueous ethanol, it is seen that with increasing bulk of the alkyl group the rate enhancement in DMSO drops. With increasing alkylation, the corresponding transition state would become ' looser ', a situation favoured by a protic solvent like aqueous ethanol. With an electron-attracting substituent, as in benzyl acetate and allyl acetate, a ' tighter ' transition state results, leading to a concurrent increase of rate enhancement in aqueous DMSO. The greater rate enhancement in aqueous DMSO of ethyl cinnamate compared to ethyl crotonate presents a parallel situation, the electron-attracting phenyl group in the former contributing to a ' tighter ' transition state.

The rate data obtained for the hydrolysis of lactones and their corresponding open chain analogues are also compatible with the above postulate. The ring strain and the greater polarity of the lactone carbonyl atom tend to make the transition state for lactone, hydrolysis ' looser ' compared with that for the corresponding open chain ester. Thus the lactones are not susceptible to DMSO-enhanced hydrolytic rates as much as their open chain counterparts. Hence the lower k^s values for the lactones and also the smaller $k_{\text{lactone}}/k_{\text{ester}}$ values in aqueous DMSO.

The most compelling evidence for the operation of differential solvent effects on these types of transition states comes from the study of the hydrolysis of the glycol monoesters. The charge dispersed transition state structure (II) for ethylene glycol monobenzoate constitutes a typical ' tight ' transition state and thus experiences a highly pronounced dipolar aprotic solvent influence.

The data in Table 8 reveal that substitution of DMSO for ethanol in the aqueous solvent mixtures leads, in general, to both reduced entropy and enthalpy of activation, an observation consistent with the presence of a highly stabilised transition state in aqueous DMSO.

TABLE 8

Activation parameters for ester hydrolysis[a]

	$\Delta H^\ddagger$/kcal mol^{-1}		$\Delta S^\ddagger$/cal mol^{-1} K^{-1} [b]	
Ester	70% DMSO (v/v)	70% EtOH (v/v)	70% DMSO (v/v)	70% EtOH (v/v)
Ethylene glycol monobenzoate	10·8	15·9	−24	−18
Ethyl acetate	7·64	17·5	−34	−6·5
Methyl methacrylate	7·98	15·0	−33	−17
γ-Butyrolactone	9·20	13·1	−25	−16
Phthalide	4·34	15·4	−43	−11
Cyclopentyl acetate	8·74	12·0	−32	−26
2-Methoxyethyl acetate	7·83	13·2	−31	−20

[a] Rate measurements were taken at three temperatures between 25 and 40°. [b] At 30°.

The present studies, therefore, demonstrate the importance of the transition state solvation factor in rate enhancement of ester saponification in aqueous DMSO. Though the desolvation of the hydroxide ion in these solvent systems has a definite role to play, it is not the major factor, especially in the case of esters (*i.e.* aromatic and glycol monoesters) where structural features contribute to the diminution of the localisation of the negative charge on the carbonyl oxygen atom in the transition state. In these instances, the remarkable ability of DMSO to solvate the transition state appears to make a much more significant contribution towards rate enhancement.

EXPERIMENTAL

Most of the esters were commercial samples (Fluka AG, BDH, Merck, or Schuchardt) and were purified by distillation or by crystallisation from a suitable solvent before use.

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[13] A. J. Parker and E. C. F. Ko, *J. Amer. Chem. Soc.*, 1968, **90**, 6447.

Cyclopentyl acetate was prepared by the method described by Bruice and Fife.[13] The dibenzoates of ethylene glycol, propane-1,3-diol, and butane-1,4-diol were prepared by benzoylation of the diol with benzoyl chloride in the presence of pyridine.[14] The physical data for the esters employed are in agreement with the literature data. The organic solvents (BDH, Riedel, or Crown Zellerbach) were purified by standard procedures.

The solutions were thermostatted on a water-bath to ±0·01° for at least 3 h before performing the kinetic run. The reactions were followed by previously described titrimetric procedures.[15] For the glycol diesters, the second-order rate constants for the two steps of hydrolysis, the diester giving the monoester and the hydrolysis of the latter, were evaluated from a single kinetic run by the method of Frost and Schwemer.[16] The velocity constants for the rest of the esters were calculated from integrated second-order rate equations. The rate constants reported here are accurate to ±3% and are the average of at least three runs. The rate measurements were made at three different temperatures in the range 25—40° and the activation parameters were evaluated from the slopes of least-square Arrhenius plots. The data for a representative selection of esters are collected in Table 8.

I.r. spectra were obtained with a Perkin-Elmer 700 spectrophotometer (AgBr cells for DMSO; NaCl cells for $CHCl_3$). U.v. spectra were taken with a Unicam SP 700 spectrophotometer and n.m.r. spectra with a Varian HA 100 spectrophotometer.

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[3/1398 *Received, 5th July,* 1973]

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[14] H. C. Hein and C. F. Poe, *J. Org. Chem.*, 1944, **9**, 299.

[15] G. Venkoba Rao and N. Venkatasubramanian, *Tetrahedron Letters*, 1967, 5275.

[16] A. A. Frost and W. C. Schwemer, *J. Amer. Chem. Soc.*, 1952, **74**, 1268.