Instances of Non-electrolyte Solvation leading to Less Pronounced Rate Enhancements of Ester Hydrolyses in Dipolar Aprotic Solvents: the Possibility of Hydrolysis *via* Conjugate Base Formation in the Case of Ethyl Indole-2-carboxylate and Methyl 4-Pyridylacetate

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The kinetics of alkaline hydrolysis of various heterocyclic esters (I)—(X), ethyl benzoate (XI), and ethyl phenylacetate (XII) have been investigated in binary solvent mixtures of dimethyl sulphoxide (DMSO)–water and ethanol–water. The rate data for esters (I) and (II) indicate the possibility of an $E1cb$ route for their hydrolysis. The hydrolysis of heterocyclic esters constitute a unique case in which the rate enhancements of ester saponifications on transfer from protic to dipolar aprotic solvents are governed by the solvation of the non-electrolyte (ester) molecule by DMSO, a factor hitherto relegated to the background.

It is a well documented fact that ester saponifications and other bimolecular reactions involving anions such as S_N2 substitutions, $E2$ eliminations, and S_NAr reactions are considerably accelerated on transfer from a protic to a dipolar aprotic solvent such as dimethyl sulphoxide (DMSO).[1] The two factors that are generally recognised in this context are the superior ability of DMSO to solvate effectively the transition states for these reactions and the presence of a poorly solvated and consequently active anion, OH^- in the present instance. Our earlier studies with a number of esters and lactones[2-7] had shown that the solvation of the non-electrolyte (ester molecule) is not of major importance in governing the rate enhancements of saponifications in aprotic solvents. This has been found to be the case with most of the other bimolecular reactions involving anions.

In the present paper we report on a unique case of a group of esters where the solvation of the ester significantly affects the rate enhancements of saponification in DMSO.

RESULTS AND DISCUSSION

In this study we have investigated the kinetics of the alkaline hydrolysis of the following esters in DMSO–water and ethanol–water mixtures: ethyl indole-2-carboxylate (I), methyl 4-pyridylacetate (II), ethyl pyridine-2-carboxylate (III), ethyl pyridine-3-carboxylate (IV), ethyl pyridine-4-carboxylate (V), ethyl pyrazinecarboxylate (VI), ethyl furan-2-carboxylate (VII), ethyl thiophen-2-carboxylate (VIII), ethyl 2-pyridylacetate (IX), ethyl 3-pyridylacetate (X), ethyl benzoate (XI), and ethyl phenylacetate (XII). The rate data for the alkaline hydrolysis of esters (III)—(XII) are collected in Table 1. Tables 2 and 3 provide the rate constants for the hydrolysis of (I) and (II) respectively.

In our preliminary studies on the saponification of isomeric pyridinecarboxylates, we had reported that these three esters are less susceptible to dipolar aprotic solvent accelerations than is the corresponding non-heterocyclic analogue, ethyl benzoate.[8] This was at-

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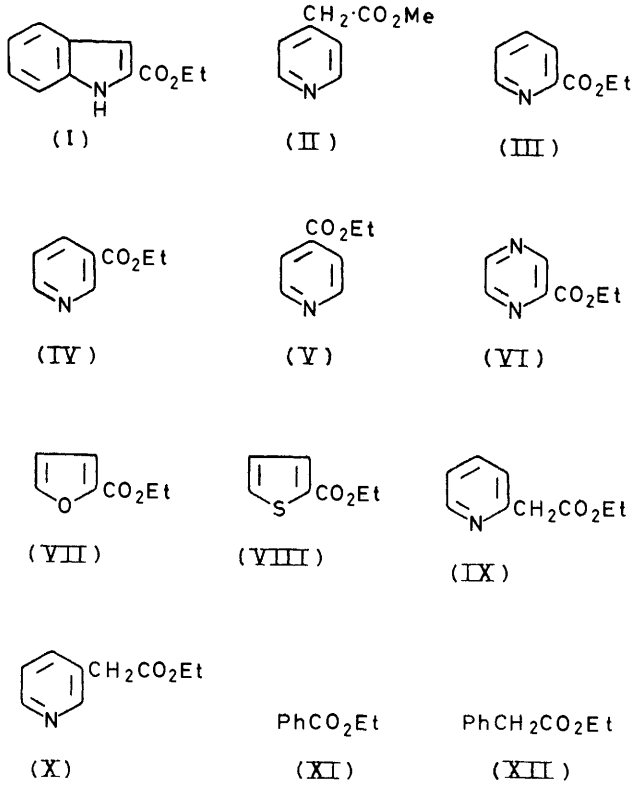
tributed by us to the increased solvation of the pyridine esters by DMSO as a result of the interaction between the



positive end of the sulphoxide dipole in DMSO and the lone pair on the ring nitrogen. The n.m.r. data of pyridine and related esters in DMSO, chloroform, and CCl_4 the two solvent systems, ethanol (E) and DMSO (D), to the solvent activity coefficients (γ) for OH^-, the ester molecule and the transition state for the saponification, the effect of the aforesaid stabilisation of the ester molecule is to make the γ_{ester} term in the equation negative or less positive.

$$\log k^D/k^E = \log {}^E\gamma^D{}_{OH^-} + \log {}^E\gamma^D{}_{ester} - \log {}^E\gamma^D{}_{t.s.} \quad (1)$$

The replacement of ethanol by DMSO in the solvent system in such a situation would bring about a less pronounced rate acceleration. It would be pertinent here to refer to our earlier observations on the saponification of other esters wherein we had noticed no change in the spectral properties on solvent transfer from ethanol to DMSO.[6] Presumably, in these cases, as in most other cases, the solvent activity coefficient for the ester has a very low or zero value.

The n.m.r. studies further pointed out that consequent upon this interaction, there was a development of a positive charge on various carbon atoms of the pyridine moiety as evidenced by the differential downfield shifts of ring protons on solvent changeover. The development of positive charge on the three carbon atoms of the pyridine nucleus, on the basis of n.m.r. data, is in the order $\gamma > \beta > \alpha$. Interestingly enough, the k_s ($= k_{DMSO}/k_{EtOH}$) values for the three pyridine esters and ethyl benzoate are found to be in the order ethyl benzoate > ethyl pyridine-4-carboxylate > ethyl pyridine-3-carboxylate > ethyl pyridine-2-carboxylate.

The near equivalence of k_s values of ethyl benzoate and ethyl pyridine-4-carboxylate in spite of the high ground state stabilisation is to be traced to the changes in the third term of equation (1), the changes in the solvation

TABLE 1

Rate coefficients for the alkaline hydrolysis of esters (III)—(XII) at 30 °C ($10\ k_2$/l mol^{-1} s^{-1})

Solvent (v/v)	(III)	(IV)	(V)	(VI)	(VII)	(VIII)	(IX)	(X)	(XI)	(XII)
50% DMSO	11.4	9.36	39.0	95.9	1.97	0.519	3.39	12.0		
60% DMSO	15.9	14.3	88.5	199	2.52	0.850	5.68	14.8		3.78
70% DMSO	22.6	20.7	156		4.00	1.38	7.88	20.7	0.70	5.09
80% DMSO		70.6			5.46	2.51	22.5	30.0	1.73	7.34
90% DMSO					7.29	6.22	26.2	99.1	5.61	
50% EtOH	1.79	1.19	4.74		0.224	0.048	1.25	1.70		
60% EtOH	1.42	0.854	4.48	12.4	0.164	0.041	1.02	1.51		0.300
70% EtOH	1.36	0.799	4.06	10.2	0.135	0.032	0.807	1.40	0.019	0.265
80% EtOH	1.15	0.708		8.86	0.107	0.025	0.628	1.14	0.015	0.206
90% EtOH					0.085	0.019	0.467	0.934	0.012	
k *	17	26	38	20 †	30	43	10	15	36	19

* $k_s = k_{70\%\ DMSO}/k_{70\%\ EtOH}$. † $k_{60\%\ DMSO}/k_{70\%\ EtOH}$.

have proved beyond doubt the existence of such an interaction and the resulting ground state stabilisation of the ester molecule. Considered in the light of Parker's equation (1) correlating the ratio of the rate constants in

TABLE 2

Rate data for the hydrolysis of ethyl indole-2-carboxylate (I) at 30 °C

Solvent (v/v)	10^5k_1/s^{-1}	Solvent (v/v)	10^5k_1/s^{-1}
50% EtOH	6.25	50% DMSO	34.5
60% EtOH	5.16	60% DMSO	31.9
70% EtOH	4.18	70% DMSO	23.4
80% EtOH	3.84	80% DMSO	5.19
90% EtOH	3.74	90% DMSO	1.05

TABLE 3

Rate data for the hydrolysis of methyl 4-pyridylacetate (II) at 20 °C

Solvent (v/v)	10^4k_1/s^{-1}
90% EtOH	11.0
70% DMSO	240
80% DMSO	104
90% DMSO	14.1
96% DMSO	0.910

requirements for the transition state. The greater development of positive charge at C-4 would decrease the localisation of the negative charge in the carbonyl oxygen in the transition state which would, in turn, lead to

its increased solvation by the diplar aprotic DMSO. We must recall here the fact that ester saponifications are less susceptible to dipolar aprotic solvent accelerations than are the S_N2 and S_NAr reactions because of the localisation of negative charge on the carbonyl oxygen of the ester in the transition state [1,6] and any reduction in such localisation, as in glycol esters for instance,[4] would increase the k_s value. The two effects, rate-enhancing transition state solvation and rate-retarding ground state solvation of the ester, largely cancel out each other in the pyridine-4-carboxylate, while in the other two isomeric esters, presumably, the second effect is predominant causing an overall reduction in their k_s values relative to that of ethyl benzoate.

The ethyl esters of pyridylacetic acid (IX) and (X) and their non-heterocyclic analogue, ethyl phenylacetate (XII) exhibit a similar reactivity pattern towards solvent transfer, their k_s values being in the order (XII) > (X) > (IX). Their reduced susceptibility to ' DMSO catalysis ' compared with the pyridinecarboxylates is an obvious consequence of the extra methylene group in the sense that the reduction in the negative charge on the carbonyl oxygen in the transition state will be less efficient than in (III) and (IV) because of the intervening methylene group.

The results of the present studies with heterocyclic esters other than those with nitrogen as the heteroatom are also in conformity with expectations. The interaction between the sulphoxide dipole and the lone pair of electrons on the ring heteroatom which seems to govern the overall rate depends on the electronegativity of the heteroatom, the electron pair donor. N.m.r. data presented elsewhere [9] indicate that this interaction is less efficient in ethyl furan-2-carboxylate than in the corresponding thiophen ester. A less efficient interaction would mean lower ground state stabilisation of the ester and also reduced development of positive charge on the ring carbon atoms (to which ethoxycarbonyl groups are attached) leading to diminished transition state stabilisation. The k_s values in solvent mixtures of 90% organic content for (VII) and (VIII) are 85 and 322 respectively, a trend which underlines the importance of transition state solvation as a factor in rate enhancements of ester saponifications in aqueous DMSO. The corresponding value of 470 for ethyl benzoate is again revealing.

Thus, these heterocyclic esters appear to constitute a rather uncommon example in which non-electrolyte solvation, a factor hitherto relegated to the background, assumes importance in determining rate enhancements in dipolar aprotic solvents. The overall rate accelerations, as measured by the k_s values, are governed by the delicate balance of two factors, (i) the ground state stabilisation of the ester molecule through the interaction between the sulphoxide dipole in DMSO and the lone pair on the ring heteroatom which results in the development of fractional positive charges on various ring carbon atoms and (ii) the consequent increased transition state solvation arising out of this development of positive charge.

The other two heterocyclic esters (I) and (II) present a different picture altogether. In fact, we notice a marked *decrease* in the hydrolytic rate constants on increasing the DMSO content of the solvent mixture, a behaviour which is in direct contrast to that of the other esters whose hydrolytic rates increase with increasing percentages of DMSO. A comparison of the rate data of (II) with those for ethyl phenylacetate, its non-hetero-analogue and with those for (IX) and (X) is revealing. It appears that (I) and (II) are not hydrolysed exclusively by the conventional $B_{AC}2$ pathway. Having in view the fact that the hydrolysis of β-keto-esters is also characterised by similar solvent effects,[10] we propose the operation of a concurrent $E1cb$ mechanism for the hydrolysis of (I) and (II). While the possible existence of a few percent of the un-ionised ester and unchanged OH^- at equilibrium, through which a $B_{AC}2$ reaction could contribute, is to be recognised, the basis for the formation of the ester anion and the consequent operation of an $E1cb$ mechanism is considered below in detail.

In our studies we have investigated the spontaneous decomposition of the conjugate base of these esters. Equal concentrations of the ester and NaOH were mixed and the rate of spontaneous decomposition of the conjugate base formed immediately was followed by titrimetric estimation of unchanged base. We confirmed the immediate formation of the conjugate base on addition of NaOH to the ester by means of i.r. spectroscopy. While the pure esters in DMSO and ethanol exhibit a peak for the carbonyl absorption in the region 1 700—1 730 cm^{-1}, on addition of NaOH, a new peak is formed immediately at 1 650 cm^{-1}, characteristic of a carbonyl group adjacent to a carbanion and the area covered by the peak is exactly proportional to the concentration of NaOH added. When the concentrations are equal, the peak in the region 1 730—1 700 cm^{-1} disappears and instead a single peak at 1 650 cm^{-1} appears.

The dipolar aprotic solvent effects, as in the case of β-keto-esters, suggest that the hydrolysis of (I) and (II) occurs *via* conjugate base formation. Since the rate-determining step involves the decomposition of the conjugate base to give the products, any stabilisation of the conjugate base by DMSO should result in the retardation of rate. The basis for such a conclusion can be summarised as follows. (i) Large anions which are polarisable, but are poor hydrogen bond acceptors and fit poorly into the hydrogen bonded solvent structure (*e.g.* picrate, phenoxide) are *ca.* 10—10^3 times more solvated by the dipolar aprotic solvents than by protic solvents.[1] (ii) *p*-Nitrophenoxide ion (and its sulphur and selenium analogues) exhibits a large bathochromic shift

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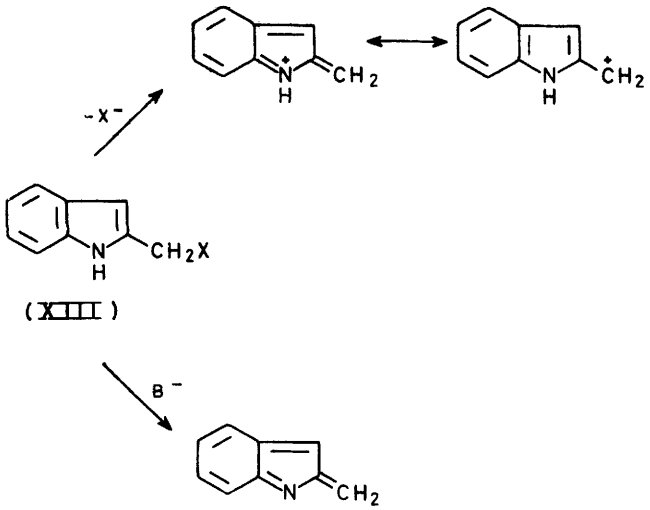
on solvent change over from ethanol to dipolar aprotic dimethylformamide [11] and DMSO.[12]

It is obvious from the foregoing discussion that the conjugate bases of (I) and (II) can be stabilised more by the aprotic DMSO than by the protic ethanol and water and such a stabilisation would result in an inhibition of the overall hydrolysis of (I) and (II). The i.r. data discussed earlier are also in consonance with the proposal of the formation of the conjugate bases.



SCHEME

The relative acidity of the methylene proton in (II) and indolyl proton in (I) is evident from a perusal of the n.m.r. data of these compounds in various solvents.[9] Further, there is evidence in the literature to show that indoles are relatively acidic varying in pK_a from 12 for indole-3-carbaldehyde to 18 for tryptamine and they are readily converted into the corresponding anions by treatment with base.[13] The fact that the mass spectrum of of ethyl indole-2-carboxylate has a base peak at $M - 46$, indicating the loss of ethanol in a primary process, is also relevant in this context. Mass spectral fragmentation patterns with certain other benzindole and dihydrobenzindole esters also reveal the easy formation of the corresponding keten.[14] Further, the ' *o*-quinonoid ' nature of the intermediate is also well identified for reactions with bases for compounds of type (XIII) (Scheme).[15]

The evidence thus indicates that in the case of (I) and (II) the anion is formed in a fast pre-equilibrium step followed in succession, as in earlier instances,[16] by a slow rate-determining decomposition of the anion to give a keten and rapid reaction of the latter with water.

In direct contrast to the behaviour of (II), the structurally related esters (IX) and (X) do not give carbanions on addition of NaOH as seen from i.r. studies and exhibit normal DMSO solvent effects on hydrolysis, the rate constants increasing with increasing percentages of DMSO. The unusual dipolar aprotic–protic solvent effects observed thus in esters susceptible to *E*1cb hydrolysis, in our opinion, merit detailed attention so that their efficacy as a kinetic probe for this hydrolytic route can be established.

EXPERIMENTAL

All esters used in this work were commercially available. They were purified by standard methods and the purity was checked by chromatographic techniques. The kinetic methods used were those detailed previously.[2-7] I.r. studies were carried out with a Perkin-Elmer 257 spectrophotometer. For spectra of DMSO and ethanolic solutions, AgBr cells were used. NaCl cells were used for Nujol mulls. 0.025M Solutions of ester and NaOH in the respective solvents were used for i.r. studies. For n.m.r. 10% solution samples were analysed on a Varian HA-100 instrument. The mass spectra of (I) was recorded by the courtesy of Dr. A. J. Kirby, Cambridge University.

We thank Messrs Crown Zellerbach Corporation, U.S.A. for a generous gift of DMSO. We are also grateful to Dr. A. J. Kirby, University Chemical Laboratories, Cambridge, for his help with the mass spectra and to the Government of India for the award of a fellowship to one of us (P. V. S.).

[6/1927 *Received*, 14*th October*, 1976]

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