Transition State Enthalpies of Transfer in Aqueous Dimethyl Sulphoxide Solutions. The Hydroxide-catalysed Racemisation of D-α-Methyl-α-phenylacetophenone

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Enthalpies of solution of D-α-methyl-α-phenylacetophenone in a series of dimethyl sulphoxide–water mixtures have been measured. Taken in conjunction with the enthalpies of transfer of the hydroxide ion from a 27.8 mol % dimethyl sulphoxide–water mixture to solutions of higher dimethyl sulphoxide concentrations, and the previously published enthalpies of activation for the racemisation of the ketone, transition state enthalpies of transfer have been calculated. The results show that the increase in rate accompanying the increase in dimethyl sulphoxide concentration can be mainly accounted for by desolvation of the hydroxide ion but that desolvation of the transition state makes the increase less than it would otherwise be.

THE role of the solvent in reaction kinetics has recently been the subject of much attention.[1,2] This interest has come about partly as a result of the observation that many rates can be dramatically increased by a change from a protic solvent to a dipolar aprotic solvent. The lowering of the enthalpy of activation which usually accompanies this rate acceleration results from either decreased solvation of the reactants or enhanced solvation of the transition state. Alternatively, a combination of both effects may be operative. By measuring the enthalpies of solution of the reactants as well as the enthalpies of activation for the particular reaction in different media several workers[2-4] have shown which of the two contributions is the more important. Amongst the reactions studied in this way have been the Menshutkin reaction,[5] base-catalysed ester hydrolyses,[3,4] and several S_N2 and S_NAr type reactions.[6] One important kind of reaction, the hydroxide-catalysed ionisation of carbon acids, has however not been the subject of such an analysis. The present study reports on such a case.

The basicity of an aqueous hydroxide ion solution can be greatly increased by the addition of increasing amounts of dimethyl sulphoxide, and several studies[7,8] on carbon acids bear witness to the very large rate increases that ensue when the reactions are studied in these highly basic solutions. Only in a few cases however are enthalpies of activation available, *e.g.* the ethoxide-catalysed detritiation of fluorene[9] in dimethyl sulphoxide–ethanol mixtures shows that changes in $\Delta H^\ddagger$ are more important than changes in $\Delta S^\ddagger$. A similar finding[10] has been reported in the detritiation of various di- and tri-arylmethanes in methanolic sodium methoxide solutions. In the hydroxide-catalysed detritiation of chloroform[11] in dimethyl sulphoxide–water mixtures (0—23.8 mol % DMSO) the enthalpy of activation decreases by 6.7 kcal mol^{-1} and $\Delta S^\ddagger$ by nearly 10 cal mol^{-1} K^{-1}. The most detailed study[12] refers to the hydroxide-catalysed racemisation and detritiation of D-α-methyl-α-phenylacetophenone in dimethyl sulphoxide–water mixtures and it is on these data that the present investigation is based. The study provides

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information on the solvation of transition states in proton transfer reactions and has a bearing on the validity of the Brönsted rate–equilibrium relationship.

EXPERIMENTAL

Materials.—Details of the preparation of D-α-methyl-α-phenylacetophenone[12] and the purification of dimethyl sulphoxide[13] have been given.

Calorimetry.—The procedure employed was the same as that outlined previously.[13] The low solubility and slow solubilisation of the ketone in the more aqueous mixtures restricted measurements to media of DMSO content no lower than 27.8 mol %. For this solution as well as the 36.8 mol % mixture the accuracy of the ΔH_s measurements is within the range 0.2—0.3 kcal mol^{-1}. For the higher mol % DMSO solutions the ΔH_s values can be quoted to within 0.1 kcal mol^{-1}. The aqueous DMSO solutions were prepared by weight. Using finely divided ketone samples solution was effected within 10 min in the most highly aqueous media, and more rapidly in the other solvents.

RESULTS AND DISCUSSION

The measured enthalpies of solution (ΔH_s) in the various water–dimethyl sulphoxide mixtures are listed in Table 1. From the extrathermodynamic assumption[13] $\Delta\Delta H_s(\mathrm{Ph_4P^+}) = \Delta\Delta H_s(\mathrm{Ph_4B^-})$ single ion enthalpies of transfer for the hydroxide ion have been calculated, it being assumed that in these polar media the values are independent of the cation ($\mathrm{Na^+}$ or $\mathrm{Me_4N^+}$). The enthalpies of transfer ($\Delta\Delta H_s$) for the reactants from 27.8 mol % dimethyl sulphoxide to the other mixtures, together with the previously measured enthalpy of activation data[12] for the racemisation of D-α-methyl-α-phenylacetophenone, were then used to calculate the transition state enthalpies of transfer (Table 2) using the relationship $\Delta\Delta H_s^{\ddagger} = \Sigma\Delta\Delta H_s(\mathrm{react}) + \Delta\Delta H^{\ddagger}$.

TABLE 1

Enthalpies of solution[a] for D-α-methyl-α-phenylacetophenone in aqueous dimethyl sulphoxide at 25°

DMSO (mol %)	27.8	36.8	43.3	49.2	51.6
ΔH_s	+8.0	+7.7	+6.2	+6.3	+6.2

[a] Values of ΔH_s in kcal mol^{-1} are averages of 2—6 determinations in the concentration range of 5—50 × 10^{-4}M. No effect of concentration on ΔH_s was observed.

Over the composition range 27.8—51.6 mol % dimethyl sulphoxide the rate of racemisation increases by a factor of *ca.* 15. This rate increase is accompanied by a decrease in the enthalpy of activation until a minimum is reached at a mol % composition of 43.3; changes in the entropy of activation $\Delta S^{\ddagger}$ follow a similar pattern. That these changes are related to the transition state structure can be seen from the variation in the primary hydrogen isotope effect[12] $k^{\mathrm{H}}/k^{\mathrm{T}}$ and from the fact that for the tritium labelled compound $\Delta H^{\ddagger}$ decreases in a more regular manner whilst $\Delta S^{\ddagger}$ remains virtually unchanged over the same composition range. If therefore the results can be interpreted purely in terms of enthalpy changes the data in Tables 1 and 2 show that in so far as the effect of increasing dimethyl sulphoxide concentration on the reactants is concerned it is the hydroxide ion which is affected most, being desolvated to the extent of 6.4 kcal mol^{-1}. There is a trend toward desolvation of the transition state over the whole composition range, but there is a local desolvation maximum at 36.8 mol % dimethyl sulphoxide, which is close in composition to the mixture (33%) in which water–dimethyl sulphoxide interactions are believed to be at their most powerful.[14,15] This would seem reasonable in view of the fact that the transition state resembles a rather large ion (or ion pair) of limited polar ability with the developing negative charge residing partially on the ketonic oxygen atom. Furthermore it is interesting to note that the solvation of the transition state follows the same trends in solvation as does the transition state for ethyl acetate saponification.[4] However, the latter case more nearly resembles hydroxide ion, which would be expected for an ion in which charge is localized on a single (oxygen) atom.

TABLE 2

Enthalpies of transfer[a,b] of reactants and transition state in the ionisation of D-α-methyl-α-phenylacetophenone

DMSO (mol %)	$\Delta H^{\ddagger}$ [c,d]	$\Delta\Delta H^{\ddagger}$ [d]	$\Delta\Delta H_s$ ($\mathrm{OH^-}$) [e]	$\Sigma\Delta\Delta H_s$ (reactants)	$\Delta\Delta H_s$ [d]
27.8	13.7	0	6.1	0	0
	(14.8)	(0)			(0.0)
36.8	12.4	−1.3	10.1	3.7	2.4
	(13.9)	(−0.9)			(2.8)
43.3	11.9	−1.8	10.8	2.9	1.1
	(13.8)	(−1.0)			(1.9)
49.2	12.9	−0.8	11.9	4.1	3.3
	(13.7)	(−1.1)			(2.9)
51.6	12.7	−1.0	12.5	4.6	3.6
	(13.2)	(−1.6)			(3.0)

[a] From 27.8 mol % DMSO to aqueous DMSO mixtures at 25°. [b] In kcal mol^{-1}. [c] Ref. 12. [d] Values in parentheses refer to the tritiated ketone. [e] Ref. 4. Single ion enthalpies of transfer from water to indicated solvent.

Isotope substitution of the ionizable hydrogen of the ketone by deuterium (or tritium) should not lead to large changes in the enthalpies of solution. Measurements have been made of the heats of solution of chloroform,[16] acetone,[16] and cyclohexane,[17] and the deuteriated derivatives in a variety of solvents. In no case did isotopic substitution lead to differences as large as 0.2 kcal mol^{-1}; in most instances the differences amounted to only 0.01—0.04 kcal mol^{-1}. By assuming therefore that the ΔH_s and $\Delta\Delta H_s$ values for a given solvent composition are the same for the hydrogen and tritium forms of the ketone it is possible to calculate

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transfer values for the tritium transition state, and these are given in the final column of Table 2. In all cases but two (49.2 and 51.6 mol % DMSO) the values are higher than those obtained for the hydrogen compound. Unfortunately the differences, with the possible exception of the results for the 43.3 mol % DMSO mixture, are of the same order of magnitude as the combined experimental errors in the ΔH_s and $\Delta H^\ddagger$ values. Whether differential solvation (H *versus* T) of the transition states is a contributory factor in the observed variation of primary hydrogen isotope effects must therefore await further study.

Studies[7,8] of the hydroxide-catalysed rates of detritiation of other carbon acids in dimethyl sulphoxide–water mixtures show that the weaker the acid the more receptive it is to changes in basicity (the greater the log k–H_- slope) and this has been interpreted in terms of increasing asymmetry of the transition state. If the relative changes in $\Delta\Delta H_s$ and $\Delta\Delta H_s^\ddagger$ follow a similar pattern to that shown by the present ketone such an approach would seem justified. However if this were not generally true it could lead to erroneous conclusions being drawn.

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