

Enhancement of Saponification Rates in Aqueous Dipolar Solvents. Hydroxide Ion Solvation vs. Transition State Solvation

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Abstract: The cause of the decrease in activation enthalpy associated with the greatly enhanced rates of base-catalyzed ester hydrolyses in aqueous dipolar aprotic solvents has been examined. Calorimetric determination of the relative enthalpies of the reactants in aqueous dipolar aprotic solvents vs. aqueous polar protic solvents reveals that the lower enthalpy of activation in the dipolar solvent is not caused by a correspondingly greater enthalpy of solvation of the reactants in the protic solvent. The enthalpy of transfer of the reactants from the dipolar solvent to the protic solvent was found to be about three times as great as the differences in the ΔH^\ddagger values in the two kinds of solvents. The reason for this, as well as the use to which these data can be put in evaluating the structures of the transition states in ester hydrolysis reactions, is discussed.

The discovery¹ that ester saponification rates, just like S_N2 and S_NAr reaction rates,² are subject to large rate accelerations on going from protic to dipolar aprotic solvents has led to two general explanations for this phenomenon. The first explanation^{1a,b} attributes the very large rate enhancement to desolvation of the hydroxide ion in the dipolar aprotic solvent relative to the protic solvent. Another explanation^{1c,g} attributes this effect to the superior ability of the dipolar aprotic solvent to solvate the transition state. The distinction between these two possibilities is an important one. While there is a considerably body of knowledge concerning the solvation of small ions in various solvents,³ very little direct information is available concerning the solvation of transition states for any reaction.⁴ In particular, although ester hydrolysis and related reactions have been thoroughly studied from various mechanistic points of view,⁵ no direct information is available about the nature of the solvation of the transition state leading to the tetrahedral intermediate in this reaction. Considering the importance of this process to a variety of biochemical transformations⁶ as well as to physical organic chemistry,⁷ such direct data would be of considerable value.

The rate enhancements observed for saponification in dipolar solvents are generally accompanied (and indeed determined^{1c}) by large decreases in the enthalpy of activation in the dipolar aprotic solvent relative to

the polar protic solvent. The above two explanations for this phenomenon can therefore be subjected to an experimental test. The difference in the enthalpies of the reactants in the two kinds of solvents can be determined calorimetrically. If the first explanation applied then the difference in the enthalpy of the reactants in the two kinds of solvents, $\delta\Delta H_s^\ddagger$, should be equal to the difference in the enthalpies of activation, $\delta\Delta H^\ddagger$, in the two solvents.

In the case of some S_N2 and S_NAr reactions we were able to demonstrate⁸ by this method that the dipolar aprotic solvent effect was caused mainly by enhanced solvation of the transition state in the dipolar aprotic solvent, although the other factor, desolvation of the nucleophile in the dipolar aprotic solvent, does contribute to the total effect in the case of a more basic nucleophile. The purpose of the present work was to determine the cause of the dipolar aprotic solvent effect for the saponification reaction.

On changing the solvent composition in mixtures of dipolar solvent and water the ΔH^\ddagger and $T\Delta S^\ddagger$ parameters for the saponification reaction frequently pass through a minimum even though the ΔG^\ddagger increases steadily with increasing water content of the solvent.^{1a,b} This clearly involves the detailed structures of these aqueous solvents and the changes in the structures of the solvation shells of the reactants and of transition states with changes in solvent composition. To avoid this complication at first, we can ask the question: what causes the dipolar solvent effect in the saponification reaction when comparing an aqueous solvent mixture containing a dipolar solvent as the organic component with an aqueous solvent mixture containing no dipolar aprotic solvent as the organic component? With this in mind we selected for examination the first four reactions shown in Table I. In addition, because of its great intrinsic interest, we wish to examine an effect involving only a fractional change in the composition of an aqueous dipolar solvent mixture which illustrates a remarkable change in sensitivity to a solvent effect on going from an isopropyl ester to a *tert*-butyl ester.

(8) (a) P. Haberfield, A. Nudelman, A. Bloom, R. Romm, H. Ginsberg, and P. Steinberg, *Chem. Commun.*, 194 (1968); (b) P. Haberfield, L. Clayman, and J. S. Cooper, *J. Amer. Chem. Soc.*, **91**, 787 (1969); (c) P. Haberfield, A. Nudelman, A. Bloom, R. Romm, and H. Ginsberg, *J. Org. Chem.*, **36**, 1792 (1971).

(1) (a) E. Tommila and M.-L. Murto, *Acta Chem. Scand.*, **17**, 1947 (1963); (b) E. Tommila and I. Palenius, *ibid.*, **17**, 1980 (1963); (c) D. D. Roberts, *J. Org. Chem.*, **29**, 2039 (1964); (d) *ibid.*, **29**, 2716 (1964); (e) *ibid.*, **30**, 3516 (1965); (f) W. Roberts and M. C. Whiting, *J. Chem. Soc.*, 1290 (1965); (g) D. D. Roberts, *J. Org. Chem.*, **31**, 4037 (1966); (h) M. Hojo, M. Utaka, and Z. Yoshida, *Tetrahedron Lett.*, No. 1, 19 (1966); N. Venkatasubramanian and G. Venkoba Rao, *ibid.*, No. 52, 5275 (1967).

(2) A. J. Parker, *Chem. Rev.*, **69**, 1 (1969).

(3) *E.g.*, see G. Choux and R. L. Benoit, *J. Amer. Chem. Soc.*, **91**, 622 (1969), and references cited therein.

(4) E. M. Arnett, W. G. Bentrude, J. J. Burke, and P. McC. Duggleby, *ibid.*, **87**, 1541 (1965).

(5) M. L. Bender, *Chem. Rev.*, **60**, 53 (1960); S. L. Johnson, *Advan. Phys. Org. Chem.*, **5**, 237 (1967).

(6) (a) T. C. Bruce and S. J. Benkovic, "Bioorganic Mechanisms," Vol. 1, W. A. Benjamin, New York, N. Y., 1966; (b) W. P. Jencks, "Catalysis in Chemistry and Enzymology," McGraw-Hill, New York, N. Y., 1969, pp 463-554.

(7) *E.g.*, C. K. Ingold, "Structure and Mechanism in Organic Chemistry," 2nd ed, Cornell University Press, Ithaca, N. Y., 1969, Chapter XV.

Table I. Enthalpies of Activation for the Alkaline Hydrolysis of Esters in Aqueous Dimethyl Sulfoxide and in Aqueous Ethanol

Ester	Solvent ^a	ΔH^\ddagger , kcal/mol	$\delta\Delta H^\ddagger$, kcal/mol
Ethyl acetate	0.60 aq DMSO	10.9 ^b	4.0
Ethyl acetate	0.60 aq ethanol	14.9 ^c	
Ethyl benzoate	0.60 aq DMSO	12.3 ^b	6.1
Ethyl benzoate	0.85 aq ethanol	18.4 ^d	
Isopropyl benzoate	0.70 aq DMSO	11.7 ^e	0.8
Isopropyl benzoate	0.60 aq DMSO	12.5 ^e	
<i>tert</i> -Butyl benzoate	0.70 aq DMSO	7.2 ^e	6.5
<i>tert</i> -Butyl benzoate	0.60 aq DMSO	13.7 ^e	

^a Composition of solvent indicated as mole fraction of organic component. ^b Data from ref 1e. ^c Data from ref 1d. ^d Data from ref 1c. ^e Data from ref 1g.

Results

To obtain the enthalpies of transfer of the esters from one solvent to the other, we measured their heats of solution in the four solvents of interest. The results are listed in Table II. To obtain the enthalpy of trans-

Table II. Heats of Solution^a

Solute	Solvent ^b	ΔH_s , kcal/mol
Ethyl acetate	0.60 aq DMSO	0.87 ± 0.04
Ethyl acetate	0.60 aq ethanol	1.10 ± 0.06
Ethyl benzoate	0.60 aq DMSO	1.94 ± 0.05
Ethyl benzoate	0.85 aq ethanol	1.41 ± 0.02
Isopropyl benzoate	0.70 aq DMSO	1.95 ± 0.07
Isopropyl benzoate	0.60 aq DMSO	2.29 ± 0.05
<i>tert</i> -Butyl benzoate	0.70 aq DMSO	2.20 ± 0.10
<i>tert</i> -Butyl benzoate	0.60 aq DMSO	2.55 ± 0.08
(<i>n</i> -C ₄ H ₉) ₄ NB(<i>n</i> -C ₄ H ₉) ₄	0.70 aq DMSO	13.18 ± 0.78
(<i>n</i> -C ₄ H ₉) ₄ NB(<i>n</i> -C ₄ H ₉) ₄	0.60 aq DMSO	13.97 ± 0.28
(<i>n</i> -C ₄ H ₉) ₄ NB(<i>n</i> -C ₄ H ₉) ₄	0.85 aq ethanol	10.52 ± 0.50
(<i>n</i> -C ₄ H ₉) ₄ NB(<i>n</i> -C ₄ H ₉) ₄	0.60 aq ethanol	10.95 ± 0.86
(<i>n</i> -C ₄ H ₉) ₄ NOH · 130.9 H ₂ O	0.732 aq DMSO	-156.62 ± 1.49
(<i>n</i> -C ₄ H ₉) ₄ NOH · 130.9 H ₂ O	0.622 aq DMSO	-143.08 ± 0.43
(<i>n</i> -C ₄ H ₉) ₄ NOH · 130.9 H ₂ O	0.633 aq ethanol	-18.11 ± 0.27
(<i>n</i> -C ₄ H ₉) ₄ NOH · 130.9 H ₂ O	Ethanol	-36.28 ± 0.14
H ₂ O	0.732 aq DMSO	-1.329 ± 0.014 ^c
H ₂ O	0.622 aq DMSO	-1.256 ± 0.022 ^d
H ₂ O	0.633 aq ethanol	-0.181 ± 0.001 ^e
H ₂ O	Ethanol	-0.300 ± 0.002 ^f

^a At concentrations as close as possible to those in the kinetic experiments used to measure the ΔH^\ddagger values (0.05 M) except for the heats of solution of H₂O. ^b Composition of solvent indicated as mole fraction of organic component. ^c Enthalpy of dilution (in kcal/mol of H₂O added) of aq DMSO from 0.732 aq DMSO to 0.700 aq DMSO [lit. value 1.313: J. Kurttämaa and J. J. Lindberg, *Suom. Kemistilehti*, **B**, **33**, 32 (1960)]. ^d Enthalpy of dilution from 0.622 aq DMSO to 0.600 aq DMSO (lit. value 1.296: Kurttämaa and Lindberg, footnote c). ^e Enthalpy of dilution of aq ethanol from 0.633 aq ethanol to 0.600 aq ethanol [lit. value 0.172: R. F. Lama and B. C. Y. Lu, *J. Chem. Eng. Data*, **10**, 216 (1965)]. ^f Enthalpy of dilution of ethanol to 0.85 aq ethanol (lit. value 0.279: Lama and Lu, footnote e).

fer of hydroxide ion, we used the extrathermodynamic assumption that the enthalpy of transfer of (*n*-C₄H₉)₄N⁺ is equal to the enthalpy of transfer of (*n*-C₄H₉)₄B⁻.^{3,8b,9}

(9) (a) E. Grunwald, G. Baughman, and G. Kohnstam *J. Amer. Chem. Soc.*, **82**, 5801 (1960); (b) E. M. Arnett and D. R. McKelvie, *ibid.*, **88**,

To obtain the heats of transfer of OH⁻ by this method one requires the heats of solution in the four solvents of (*n*-C₄H₉)₄NB(*n*-C₄H₉) and of (*n*-C₄H₉)₄NOH. As (*n*-C₄H₉)₄NOH cannot be obtained free of water,¹⁰ its enthalpy of transfer from one solvent to another was calculated as shown in Chart I, where $\delta\Delta H_s$ is the enthalpy of transfer of (*n*-C₄H₉)₄NOH from 0.60 aqueous DMSO to 0.60 aqueous ethanol.¹¹ The enthalpies of transfer of (*n*-C₄H₉)₄NOH for the other solvent pairs were calculated in an analogous manner and are listed in Table III, along with the single ion enthalpy of transfer of

Table III. Enthalpies of Solvent Transfer, $\delta\Delta H_s$, of Compounds and Ions (kcal mol)

	$\delta\Delta H_s^a$		
	0.60 aq DMSO → 0.60 aq ethanol	0.60 aq DMSO → 0.85 aq ethanol	0.70 aq DMSO → 0.60 aq DMSO
(<i>n</i> -C ₄ H ₉) ₄ NB(<i>n</i> -C ₄ H ₉) ₄	-3.02	-3.45	0.79
(<i>n</i> -C ₄ H ₉) ₄ N ⁺	-1.51	-1.73	0.40
(<i>n</i> -C ₄ H ₉) ₄ NOH	-15.75	-18.34	3.98
OH ⁻	-14.24	-16.61	3.50
Ethyl acetate	0.29		
Ethyl benzoate		-0.53	
Isopropyl benzoate			0.34
<i>tert</i> -Butyl benzoate			0.35

^a Composition of solvent indicated as mole fraction of organic component.

OH⁻ using the (*n*-C₄H₉)₄NB(*n*-C₄H₉)₄ extrathermodynamic assumption.

Discussion

As can be seen by comparing the enthalpy of transfer of OH⁻ from aqueous DMSO to aqueous ethanol (Table III) with the corresponding differences in ΔH^\ddagger for the saponification reaction (Table I) in these two kinds of solvents, the solvent effects on the enthalpies of activation are dwarfed by the even larger effects on the enthalpies of transfer of OH⁻. Thus for the saponification of ethyl acetate in 0.60 aqueous DMSO and in 0.60 aqueous ethanol a $\delta\Delta H^\ddagger$ value of 4.0 kcal/mol favoring the dipolar solvent is to be compared to a desolvation of OH⁻ in the dipolar solvent amounting to 14.24 kcal/mol. For the saponification of ethyl benzoate in 0.60 aqueous DMSO and in 0.85 aqueous ethanol, where a still larger solvent effect on the ΔH^\ddagger is observed ($\delta\Delta H^\ddagger = 6.1$ kcal/mol), the desolvation of OH⁻ in the dipolar solvent is 16.61 kcal/mol. In all cases, as might be expected, the enthalpies of transfer of the esters do not contribute significantly to the differences in the enthalpies of the reactants in these solvents. It thus appears that if the desolvation of the base were the only factor causing a solvent effect on rate and on ΔH^\ddagger in this reaction, then a far larger effect would be expected than is actually observed.

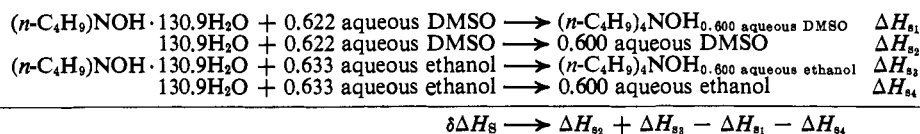
If we assume that the enthalpy of activation for the hydrolysis reaction is approximately equal to the activation enthalpy for the first step in this reaction, *i.e.*,

2598 (1966); (c) O. Popovych, *Anal. Chem.*, **38**, 558 (1966); (d) R. Fuchs, J. L. Bear, and R. F. Rodewald, *J. Amer. Chem. Soc.*, **91**, 5797 (1969).

(10) D. L. Fowler, W. V. Loebenstein, D. B. Pall, and C. A. Kraus, *ibid.*, **62**, 1141 (1940).

(11) Composition of solvent indicated as mole fraction of organic component.

Chart I



the formation of the tetrahedral intermediate,¹² then we can calculate the enthalpy of transfer of the transition state for this step from one solvent to another. For a single step, for which we have the activation enthalpy in two solvents, we can calculate the enthalpy of solvent transfer for the transition state in this step using the equation

$$\delta H^{\ddagger} = \delta\Delta H_s^{\ddagger} + \delta\Delta H^{\ddagger}$$

where δH^{\ddagger} is the enthalpy of solvent transfer of the transition state, $\delta\Delta H_s^{\ddagger}$ is the enthalpy of transfer of the reactants, and $\delta\Delta H^{\ddagger}$ is the difference in the activation enthalpies for the reaction in the two solvents. The assumption that the ΔH^{\ddagger} for the saponification reaction is equal to the activation enthalpy for the first step is not exact, although the available evidence¹² suggests that the deviation is of a smaller order of magnitude than the effects which we are considering here. The risk inherent in such an approximation is outweighed by the advantage of being able to compare the enthalpies of solvent transfer of the reactants with those of the transition states leading to the tetrahedral intermediate. As can be seen in Table IV such a com-

Table IV. Enthalpies of Solvent Transfer of Reactants, $\delta\Delta H_s^{\ddagger}$, and Transition States, δH^{\ddagger} (kcal/mol)

Reaction	Solvents ^b	$\delta\Delta H_s^{\ddagger}$	δH^{\ddagger}
Ethyl acetate + OH ⁻	0.60 aq DMSO → 0.60 aq ethanol	-13.95	-10.0
Ethyl benzoate + OH ⁻	0.60 aq DMSO → 0.85 aq ethanol	-17.14	-11.0
Isopropyl benzoate + OH ⁻	0.70 aq DMSO → 0.60 aq DMSO	3.84	4.6
tert-Butyl benzoate + OH ⁻	0.70 aq DMSO → 0.60 aq DMSO	3.85	10.4

^a The transition state in the first step of the reaction, going from reactants to the tetrahedral intermediate; assuming that the activation enthalpy for the hydrolysis reaction is equal to the activation enthalpy for the first step. ^b Composition of solvent indicated as mole fraction of organic component.

parison shows that the enormous desolvation of the reactants (due entirely to the effect on the OH⁻) in the dipolar solvent is diminished but still substantially present in the transition state (Figure 1). The solvent effect on the ΔH^{\ddagger} is caused by this decrease in the enthalpy of transfer of the transition state (δH^{\ddagger}) relative to that of the reactants ($\delta\Delta H_s^{\ddagger}$). The principal difference between these two kinds of solvents seems to be the ability of the aqueous ethanol to solvate small negative ions by hydrogen bonding. The superior ability of dipolar solvents to solvate dipolar molecules, large ions, and other extended charged entities such as transition states⁸ does not seem to determine the sign and

(12) This is a fairly reasonable assumption. M. L. Bender, R. D. Ginger, and J. P. Unik [*J. Amer. Chem. Soc.*, **80**, 1044 (1958)] found from the hydrolysis and carbonyl oxygen exchange rates in the base-catalyzed hydrolysis of ethyl benzoate in 33% dioxane-H₂O that the energy of activation for the hydrolysis reaction, $E_a^{\ddagger} = 12.9$ kcal/mol; and the activation energy for the first step in the reaction, $E_1^{\ddagger} = 13.2$ kcal/mol.

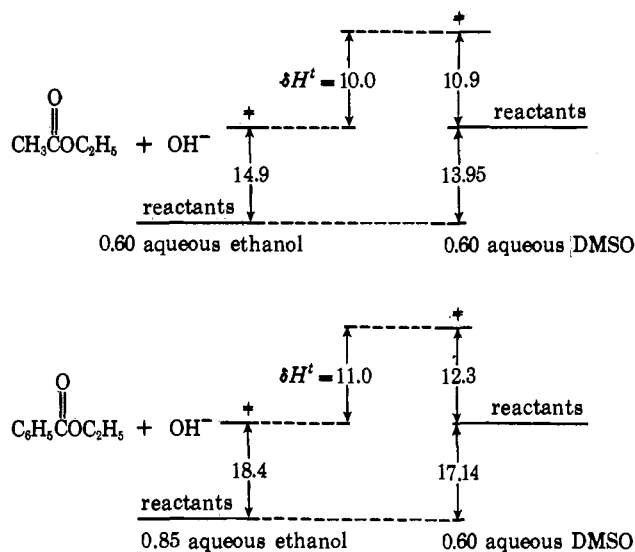


Figure 1. Relative enthalpies (kcal/mol) of reactants and transition states for the saponification of ethyl acetate and ethyl benzoate in aqueous ethanol and in aqueous DMSO.

magnitude of the transfer enthalpies in this system. The fact that the δH^{\ddagger} , though smaller than the $\delta\Delta H_s^{\ddagger}$, is still quite large suggests that there is considerable localization of charge in the transition states, *i.e.*, that they resemble products (the tetrahedral intermediate).¹³ In view of this it would be instructive to compare the enthalpy of transfer of the transition state with that of the tetrahedral intermediate as well as with that of the reactants to see the exact degree of similarity between the transition state and the tetrahedral intermediate.¹⁴ Calorimetric measurements of the heats of solution of such a transient intermediate are of course impossible, although such measurements might be performed on a model compound such as a suitably constituted alkoxide ion. The data presented here allow the following comparison: the enthalpy of transfer from aqueous DMSO to aqueous ethanol of a strongly hydrogen bonded anion (OH⁻) is -14 to -17 kcal/mol; that of an anion having no hydrogen bonding interactions with the solvent [(*n*-C₄H₉)₄B⁻] is less than -2 kcal/mol and that of the transition state is -10 to -11 kcal/mol. This suggests that the transition state resembles a species such as an alkoxide ion much more than a more delocalized anion having weaker hydrogen bonding interactions with the solvent. If there were more charge delocalization in this transition state, as is the case for the transition states in S_N2 and S_NAr reactions,^{8b} then the δH^{\ddagger} values would be much smaller and the solvent effect on ΔH^{\ddagger} would be very much larger than is actually the case.

It is worthwhile at this point to compare these results with those obtained in the very thorough and numerous studies of enzyme-catalyzed ester hydrolysis. In terms

(13) This is what would be expected from Hammond's postulate: G. S. Hammond, *J. Amer. Chem. Soc.*, **77**, 334 (1955).

(14) P. Haberfield, *ibid.*, **93**, 2091 (1971).

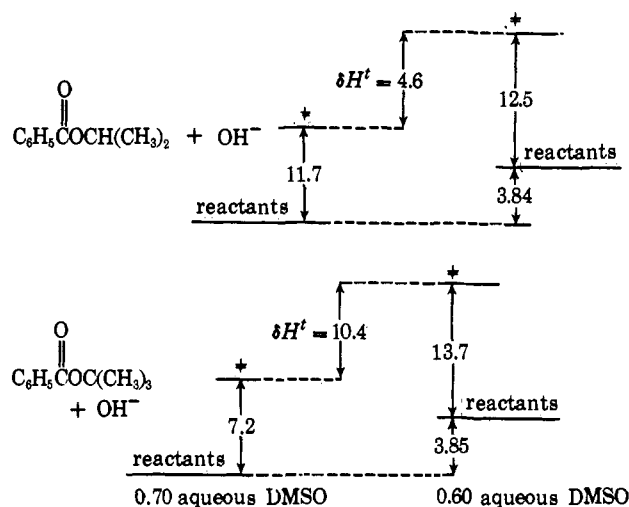


Figure 2. Relative enthalpies (kcal/mol) of reactants and transition states for the saponification of isopropyl benzoate and *tert*-butyl benzoate in 0.70 aqueous DMSO and 0.60 aqueous DMSO.

of the above concepts the mechanisms for the rate enhancement in the enzymatic process can be divided into two categories. Category 1 consists of cases where a raising of the energy of the substrate is postulated, as in Eyring's¹⁵ "rack effect." Category 2 consists of proposals¹⁶ in which the proximity of various groups is invoked which interact with the groups comprising the transition state, thus stabilizing the transition state, and again diminishing the energy gap between reactants and transition state. It is doubtful whether the DMSO enhanced saponification reaction bears much resemblance to any enzyme-catalyzed ester hydrolyses, although such a comparison is tempting in view of the same order of magnitude of the ΔH^\ddagger lowering effect in both cases. As far as the solvent effect is concerned, it is clear that raising the energy of the reactants brings about an inevitable raising of the transition state energy. To the extent that this is the consequence of the unavoidable similarities between the transition state and the reactants, this conclusion may be equally valid for the enzymatic processes. This similarity would then create a built-in limiting factor on any rate enhancing catalysis of ester hydrolysis and would have to be taken into account when considering enzymatic mechanisms as well.

An interesting effect involving only a small change in the composition of the aqueous dimethyl sulfoxide solvent is illustrated by the large solvent effect on the ΔH^\ddagger for the saponification of *tert*-butyl benzoate on going from 0.60 aqueous DMSO to 0.70 aqueous DMSO ($\delta\Delta H^\ddagger = 6.5$ kcal/mol) compared to the small solvent effect for the saponification of isopropyl benzoate ($\delta\Delta H^\ddagger = 0.8$ kcal/mol) for the same solvent change (Table I). The relevant enthalpies of reactants and transition states (Table IV) are illustrated in Figure 2. The most significant difference between the previous comparison (aqueous DMSO *vs.* aqueous ethanol) and this one is that here the solvent which better solvates the reactants (0.70 aqueous DMSO) is also the one for which a smaller ΔH^\ddagger value is observed. The reason

for this is the fact that the superior solvent properties of 0.70 aqueous DMSO *vs.* 0.60 aqueous DMSO seem to play a greater role in transition state solvation than in the solvation of the reactants. Thus the endothermic enthalpy of transfer of the reactants (0.70 aqueous DMSO \rightarrow 0.60 aqueous DMSO) is outweighed by the still greater endothermic enthalpy of transfer of the transition state producing a net decrease in the ΔH^\ddagger on going from 0.60 aqueous DMSO to 0.70 aqueous DMSO. This is a large effect ($\delta H^t = 10.4$) for the case of *tert*-butyl benzoate and a smaller effect ($\delta H^t = 4.6$) for the case of the isopropyl benzoate. The net result is that enhanced reactant solvation and enhanced transition state solvation being nearly the same for the isopropyl ester, they almost cancel and yield only a small effect on ΔH^\ddagger . For the *tert*-butyl ester the enhanced transition state solvation is unusually great and therefore no such cancellation takes place. The difference in sensitivity to solvent effect of the two esters is therefore entirely a matter of greatly enhanced solvation of the *tert*-butyl benzoate transition state in the more DMSO-rich solvent. Whatever the detailed reason for this may be, it certainly indicates a radical change in transition state structure on going from the isopropyl to the *tert*-butyl ester.

The endothermic enthalpy of transfer of OH^- into a more water-rich solvent (Table III) in the comparison of 0.70 aqueous DMSO with 0.60 aqueous DMSO is certainly very curious. The reason may be that the most stable DMSO- H_2O mixture being 1:2,¹⁷ the very DMSO-rich mixtures employed here should consist of $\text{DMSO}(\text{H}_2\text{O})_2$ complexes plus a large surplus of DMSO. In such a medium the unavailability of H_2O molecules for hydrogen bonding with OH^- may be so pronounced that the principal mechanism for OH^- solvation may not involve H_2O at all. If the principal mechanism for OH^- solvation in such a water-poor medium involves "free" DMSO molecules, then the best solvent would be that one which has the larger surplus of DMSO, *i.e.*, 0.70 aqueous DMSO.

Conclusions

Solvation of OH^- in aqueous ethanol is indeed very much greater than in aqueous DMSO. Explanation of the rate enhancing effect of DMSO on the saponification reaction in terms of a more highly solvated transition state in DMSO is not exactly correct since the enthalpy of transfer of the transition state (δH^t) from aqueous DMSO to aqueous ethanol is in fact exothermic. However, the smaller value of this transfer enthalpy (δH^t) relative to the transfer enthalpy of the reactants ($\delta\Delta H_s^r$) can be seen as the cause of the solvent effect on rate and on ΔH^\ddagger . This decrease in the δH^t relative to the $\delta\Delta H_s^r$ is certainly attributable to the ability of DMSO to solvate large polarizable anions. The difference in the transfer enthalpy of OH^- and of the transition state can also be taken as a measure of the degree of charge localization in the transition state. The degree of charge localization in the transition state of the first step of the saponification reaction was found to be very high, unlike the highly delocalized transition states of $\text{S}_\text{N}2$ and $\text{S}_\text{N}\text{Ar}$ reactions.

(15) H. Eyring, R. Lumry, and J. D. Spikes, "The Mechanism of Enzyme Action," W. D. McElroy and B. Glass, Ed., Johns Hopkins Press, Baltimore, Md., 1954, p 123.

(16) For a discussion and references see ref 6a, pp 242-258.

(17) J. M. G. Cowie and P. M. Toporowski, *Can. J. Chem.*, **39**, 2240 (1961).

Experimental Section

Materials. Dimethyl sulfoxide was dried over CaH_2 and distilled at 2 mm. Tetra-*n*-butylammonium hydroxide, 10% aqueous (Eastman), was titrated with HCl and found to have the composition $(n\text{-C}_4\text{H}_9)\text{NOH} \cdot 130.9\text{H}_2\text{O}$. Tetra-*n*-butylammonium tetra-*n*-butylboride (Alfa Inorganics), mp 99–103°, was recrystallized from isopropyl ether, mp 111–112° (lit.^{9d} mp 110.6–112.0°).

Heats of Solution. The calorimeter and the procedure employed have been described previously.^{8b}

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On the Possibility of Like-Charged Ion Pairing in Solution

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Contribution from the Department of Chemistry, Rutgers University, Newark, New Jersey 07102. Received July 9, 1971

Abstract: Previous experimental work provides evidence for strong cation–cation interactions in water. Using a kinetic approach it has been shown that for large ions there is a reasonable probability of forming stable cation pairs despite the repulsive potential. The lifetime of such dimers is comparable to the lifetime of usual ion pairs.

In recent years much attention has been given to the study of tetraalkylammonium salts in water and other solvents. Atkinson has stated that the $\text{R}_4\text{N}^+\text{X}^-$ salts exhibit some of the most complex electrolyte behavior seen to date.¹ There is no doubt that, in water, much of the observed behavior is due to ion–solvent interactions.² Nevertheless, a multitude of experimental findings indicate that strong cation–cation interactions occur. The techniques used in these investigations include emf measurements,³ ultrasonic absorption studies,¹ nmr studies,^{4,5} and measurements of volume changes upon mixing.⁶ The possibility of cation pairing has been considered in a few cases.^{1,5,7,8} While the concept of a stable cation pair is somewhat difficult to accept without invoking some type of attractive forces between the cations, no such forces are necessary. The simple sphere in a continuum model can qualitatively predict that such species might exist.

We must define ion pairs as any pair of ions which are in contact, without regard for the duration of such contact, and without intervening solvent molecules. This definition is the one adopted by Fuoss for the calculation of association constants between ions of unlike charge.⁹ The equilibrium constant for association can be calculated by taking the ratio of the rate constant for the formation of ion pairs (which we will take to be the rate at which ions collide) to the rate constant for the dissociation. If the interionic forces are purely electrostatic, it is reasonable to assume that the rate constant for the formation of the pair is equal to the diffusion-controlled rate constant, k_D , calculated by Debye¹⁰

$$k_D = C(D_A + D_B) \frac{afN}{1000} \quad (1)$$

with D_A , D_B the diffusion coefficients of species A and B, respectively, a the ion size parameter, N Avogadro's number, and C a constant equal to 4π for distinct species A and B, equal to 2π for a dimerization.¹¹

The factor f is given by

$$f = \left[a \int_a^\infty e^{u/kT} \frac{dr}{r^2} \right]^{-1} \quad (2)$$

where u is the potential energy of interaction between the ions. u is taken to be the coulombic potential

$$u = \frac{Z_A Z_B e_0^2}{r D k T} \quad (3)$$

with Z_A , Z_B , the charges of the ions with their algebraic signs, e_0 the charge on the electron, r the distance between ions, and D the dielectric constant; other symbols have their usual significance.

Using this value for u , f becomes

$$f = \frac{Z_A Z_B e_0^2}{D k T} \left[\exp\left(\frac{Z_A Z_B e_0^2}{a D k T}\right) - 1 \right]^{-1} \quad (4)$$

Combining eq 4 with eq 1 yields the Debye equation for ionic combination reactions. This equation has been tested for both like-charged^{12,13} and unlike-charged¹⁴ ion combination reactions and found to give reasonable approximations to the experimental rate constants.

The rate constant for the reverse reaction, k_{-D} , can be calculated by means of the treatment derived by Eigen.¹⁵ Using the same approximations as for the forward rate constant gives

$$k_{-D} = \frac{3Z_A Z_B e_0^2}{D k T a^3} (D_A + D_B) \left[1 - \exp\left(\frac{-u(a)}{kT}\right) \right]^{-1} \quad (5)$$

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