

## ORGANIC REACTIONS IN HIGHLY AQUEOUS BINARIES

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**Abstract** - In many cases peculiar kinetic solvent effects are observed for organic reactions in highly aqueous binary solvent systems. Often, but not always, these effects find their origin in hydrophobic interactions. Several examples are briefly reviewed. The main part of this lecture is devoted to a more detailed discussion of the water-catalyzed hydrolysis of aryl dichloroacetates and 2,2-dichloropropionates in *t*-BuOH-H<sub>2</sub>O and 2-*n*-butoxyethanol (2-BE)-H<sub>2</sub>O. A pseudothermodynamic approach is adopted in which an attempt is made to rationalize solvent effects on thermodynamic parameters of the initial and transition state. It is shown that the observed extrema in  $\Delta H_p^\ddagger$  and  $\Delta S_p^\ddagger$  reflect dominant hydrophobic interactions between the initial state and the organic cosolvent. The large and positive  $\Delta C_p^\ddagger$  values for hydrolysis in 2-BE-H<sub>2</sub>O at  $n_{H_2O} = 0.98$  are explained in terms of a pseudophase separation model. Finally it is demonstrated that solvent effects on the isobaric (constant pressure) and isochoric (constant volume) activation parameters differ dramatically for hydrolysis in water-rich *t*-BuOH-H<sub>2</sub>O. This difference is interpreted by considering the strong electrostriction occurring during the activation process and which leads to strongly negative volumes of activation.

## INTRODUCTION

Binary mixtures of water with organic solvents are among the most popular solvent systems for mechanistic studies in physical organic chemistry. The reasons are partially practical and often connected with solubility constraints. Most important for our discussion, however, kinetic studies in these media reveal the often overwhelming influence of solvation changes during the activation process (1,2). Particularly in the highly aqueous region of these binaries, the results of these studies shed light on the unique and exciting solvent properties of water which are also, of course, of such paramount importance in biochemistry (3-5).

In this lecture, largely devoted to some of our recent work in this area, I will outline several aspects of the interpretation of kinetic solvent effects on simple organic reactions in mixed aqueous solvent systems. At the outset it is appropriate to introduce briefly two fundamental concepts. The first, *hydrophobic hydration*, can be illustrated by considering the thermodynamic parameters (at 25°C) for solution of methane, as the archetype of an apolar organic compound, in cyclohexane (an apolar solvent) and in water (Table 1) (6). The

TABLE 1. Thermodynamic parameters of solution of gaseous methane at 25°C (6).

Solvent	$\Delta G_s^\ominus$ kcal.mol <sup>-1</sup>	$\Delta H_s^\ominus$ kcal.mol <sup>-1</sup>	$\Delta S_s^\ominus$ e.u.
H <sub>2</sub> O	6.3	-3.3	-32
Cyclohexane	3.4	-0.6	-13

unfavorable Gibbs free energy ( $\Delta G_s^\ominus$ ) for solution in water is the result of a strongly negative entropy of solution ( $\Delta S_s^\ominus$ ) which prevails over the favorable enthalpic contribution ( $\Delta H_s^\ominus$ ). This  $\Delta H_s^\ominus$  term is clearly too large to be attributed only to the difference between the Van der Waals interaction energy of methane with cyclohexane and with water. In fact, water is only capable of weak Van der Waals interactions as indicated, for example, by its low internal pressure [ $P_i = (\delta U / \delta V)_T$ ] (7). Therefore, the negative enthalpy and entropy of transfer of methane from cyclohexane to water have been interpreted in terms of an increased degree of water-water hydrogen bonding in the cybotactic region around the apolar solute molecule. This phenomenon has been called "hydrophobic hydration" (8). The strengthening of the hydrogen bond regime is accompanied by a large, positive heat capacity. Both the translational and rotational diffusion modes of water are influenced by the presence of the apolar solute as borne out by a narrowing of the water-water pair distribution function. Further support for the effect is found in theoretical (computer simulation) studies (9,10) and in

light scattering (11), ultrasonic absorption (12) and NMR investigations (13). It is likely that the hydrophobic hydration shell around the apolar solute molecule resembles a clathrate framework, implying interstitial solution of the solute in the three-dimensional hydrogen-bond network.

In aqueous solution, hydrophobically hydrated groups tend to associate either by contact interactions or by longer-range ("solvent-separated") interactions. This process, known as *hydrophobic interaction* (14), is responsible, for example, for the maintenance of the structure of many biological macromolecules, enzyme-substrate interactions, and the association of amphiphiles to form micelles or vesicles. The subject has been reviewed several times, emphasizing thermodynamic (15) and statistical-thermodynamic analyses (16). The concentration dependence of thermodynamic quantities of solutes has often been employed to characterize hydrophobic interactions. It is found that the association process is entropy driven. Fig. 1 shows the enthalpy ( $\Delta H_{tr}^{\theta}$ ) and entropy ( $\Delta S_{tr}^{\theta}$ ) for transfer of the hydrophobic sulfonate 1 from water to *t*-BuOH-H<sub>2</sub>O mixtures (up to 20 mol % of *t*-BuOH) as determined from solubility

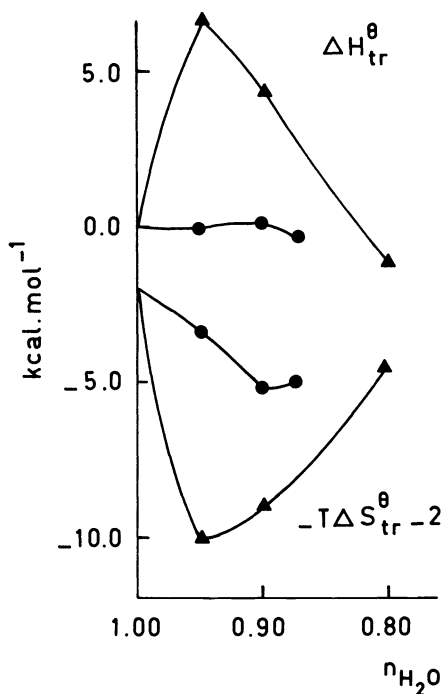
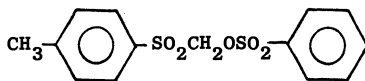


Fig. 1. Plots of  $\Delta H_{tr}^{\theta}$  and  $-T\Delta S_{tr}^{\theta}$  vs.  $n_{H_2O}$  for transfer of 1 from water to *t*-BuOH-H<sub>2</sub>O (▲) and 1,4-dioxane-H<sub>2</sub>O (●) at 25°C.

measurements (17). The transfer is an exergonic process. In the highly aqueous region the



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strongly positive changes in entropy clearly overcompensate the unfavorable enthalpic contributions. Mutually disrupting overlap of the hydrophobic hydration sheaths of 1 and *t*-BuOH can account for these results (18). Thus it is the contribution of the solvent to the interaction between the apolar compounds 1 and *t*-BuOH which should be designated as hydrophobic interaction (16). This interpretation is supported by the observation that  $\Delta H_{tr}^{\theta}$  and  $\Delta S_{tr}^{\theta}$  pass through extrema at a mole fraction of water ( $n_{H_2O}$ ) of about 0.95, which is the solvent composition at which the formation of hydrophobic hydration shells reaches a maximum in the *t*-BuOH-H<sub>2</sub>O solvent system. Although this type of behavior is quite general for apolar solutes in mixtures of water with an apolar cosolvent (*vide infra*), the exact location and

magnitude of the extrema in  $\Delta H_{tr}^{\ominus}$  and  $\Delta S_{tr}^{\ominus}$  depend on the balance of hydrophobic hydration and specific solvation effects (19). This balance is, in turn, determined by the ratio of non-polar and polar groups present in the solute and, of course, by the nature of the nonaqueous solvent component. If the organic cosolvent is rather hydrophilic as, for example, 1,4-dioxane, the changes in  $\Delta G_{tr}^{\ominus}$  are not very different from those in  $t\text{-BuOH-H}_2\text{O}$  but now only very modest variations in  $\Delta H_{tr}^{\ominus}$  and  $\Delta S_{tr}^{\ominus}$  are involved (Fig.1).

Franks (8) has introduced a very useful distinction between two types of aqueous binaries, depending on whether the solution properties of the organic cosolvent are dominated by the apolar part of the molecule or by the hydrogen bonding sites in the polar part (Table 2).

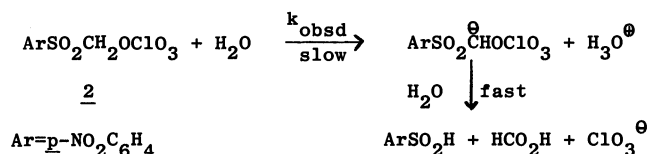
TABLE 2. Mixed aqueous solutions

Typically Aqueous Solutions: Organic Component	Typically Nonaqueous Solutions: Organic Component
Alkanes	Hydrogen peroxide
Aromatic Hydrocarbons	Acetonitrile
Alcohols (monofunctional)	Urea
Ethers	Dimethyl sulfoxide
Diethers	Carbohydrates
Ketones	Polyalcohols
Amines (monofunctional)	Sulfolane
	1,3- and 1,4-Dioxane

In the typically aqueous (TA) solutions, hydrophobic hydration of the organic component predominates and reaches a maximum in the water-rich region (at the "magic mole fraction" of water). Thermodynamically, these solutions often show large deviations from ideal behavior. At lower water content the structuring decreases until finally the solvent properties resemble those of nonaqueous mixtures of polar compounds.

In typically nonaqueous (TNA) solutions, the organic component is capable of participating in significant hydrogen-bonding interactions with water molecules. Now specific and orientation-dependent interactions between these polar sites and water primarily determine the solvent properties. There is no tendency for increased water structuring and, in fact, TNA solvents reduce the possibility of forming hydrophobic hydration shells around apolar solutes.

Before I will discuss kinetic solvent effects on one type of ester hydrolysis in some detail, a few selected examples may illustrate the peculiar solvation behavior that can be found for organic reactions in TA solutions and sometimes also in TNA solutions. The first example involves the general base catalyzed hydrolysis of covalent [(*p*-nitrophenyl)sulfonyl]methyl perchlorate (**2**) in TNA mixtures of water with 1,4- and 1,3-dioxane (17,20,21). In the presence of ca.  $10^{-3}$  M HCl, hydrolysis occurs via rate-determining deprotonation at the  $\alpha$ -sulfonyl



Scheme I

carbon atom by water (Scheme I) (22).

In the anhydrous dioxanes, solvolysis of **2** is extremely slow. However, upon addition of small amounts of the dioxanes to water, there is an appreciable increase of the pseudo-first-order rate constant ( $k_{\text{obsd}}$ ) until a maximum is reached at about  $n_{\text{H}_2\text{O}} = 0.80$  (Fig. 2). The initial increase of the kinetic basicity of the aqueous binaries is unexpected in view of the decreased concentration of the active general base ( $\text{H}_2\text{O}$ ) and the fall of the solvent polarity. Interestingly, the ethanolysis of **2** is actually retarded by 1,4-dioxane at all concentrations (Fig. 2) (17). The peculiar kinetic behavior in the highly aqueous dioxane- $\text{H}_2\text{O}$  mixtures is not related to cosolvent-induced changes in the three-dimensional hydrogen-bond regime (at least at  $n_{\text{H}_2\text{O}} < 0.95$ ). In our view the solvent effects reflect specific dioxane- $\text{H}_2\text{O}$  hydrogen-bond interactions which lead to an enhanced kinetic basicity of the complexed water (21). However, the data have also been discussed in terms of a rather different approach (*vide infra*).

An unusual solvent cage effect was observed by Nodelman and Martin (23) in their thorough study of the photolysis of azomethane (**3**) in  $t\text{-BuOH-H}_2\text{O}$  (Scheme II). Cage recombination of methyl radicals (rate constant  $k_c$ ) yields ethane, whereas diffusional separation of radical pairs from the cage (rate constant  $k_d$ ) provides methyl radicals which subsequently scavenge

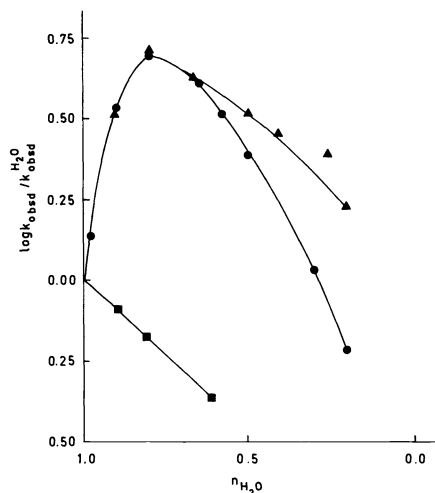
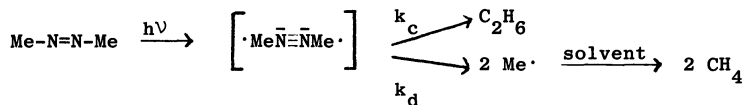


Fig. 2. Plots of  $\log k_{\text{obsd}}/k_{\text{obsd}}^{\text{H}_2\text{O}}$  vs.  $n_{\text{H}_2\text{O}}$  for the hydrolysis of 2 in 1,4-dioxane- $\text{H}_2\text{O}$  (●) and in 1,3-dioxane- $\text{H}_2\text{O}$  (▲) and a plot of  $\log k_{\text{obsd}}/k_{\text{obsd}}^{\text{EtOH}}$  vs.  $n_{\text{EtOH}}$  for the ethanolsis of 2 in 1,4-dioxane-EtOH (■).



Scheme II

hydrogen atoms from the solvent to give methane. The magnitude of the cage effect is set equal to the ratio  $[\text{CH}_4]/2[\text{C}_2\text{H}_6]$  ( $=k_d/k_c$ ) and measures the rate of diffusion of methyl radicals from the cage relative to recombination within the cage. Diffusion from the cage will be retarded upon increasing viscosity ( $\eta$ ) of the solvent. In fact, for photolysis of 3 in a series of organic solvents there is a linear relationship between  $k_d/k_c$  and the fluidity ( $1/\eta$ ) of the solvent (24). Surprisingly, Nodelman and Martin (23) find that in t-BuOH- $\text{H}_2\text{O}$  in the region  $n_{\text{H}_2\text{O}} = 0.9$  to 0.6 diffusional separation of methyl radicals from the cage increases with increasing macroscopic viscosity (Fig. 3). A minimum in  $k_d/k_c$  was found at  $n_{\text{H}_2\text{O}} = 0.90$ , a sol-

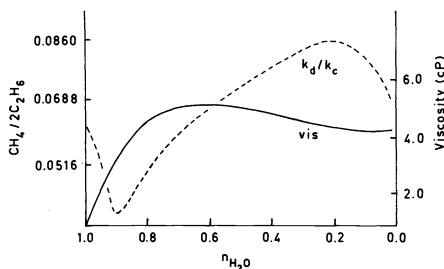
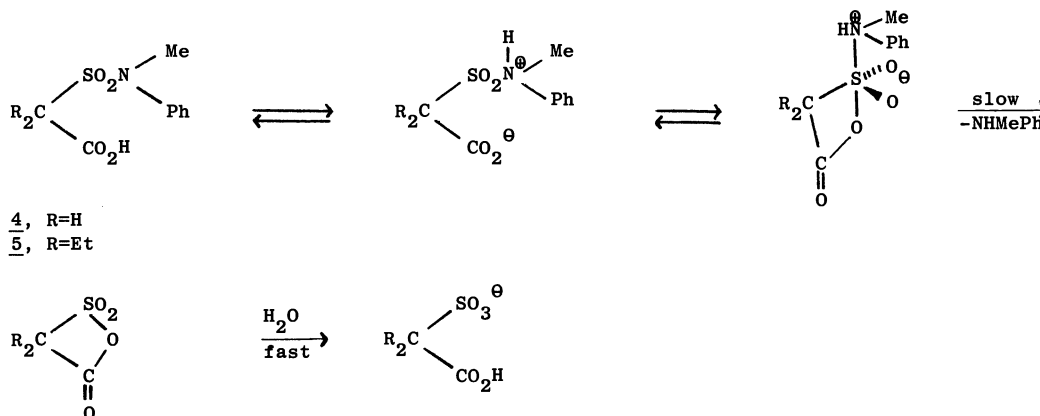


Fig. 3. Plots of  $k_d/k_c$  (---) for photolysis of azomethane and viscosity (—) vs.  $n_{\text{H}_2\text{O}}$  in t-BuOH- $\text{H}_2\text{O}$  at 25°C.23

vent composition very different from that where the viscosity passes through a maximum ( $n_{\text{H}_2\text{O}}$  ca. 0.60). The minimum in  $k_d/k_c$  was ascribed to a reduction in the effective free vol-

ume of the liquid resulting from an increased stiffness of the fluctuating network of hydrogen bonds as induced by the hydrophobic cosolvent. Using a phenomenological model, the authors (23) could derive a semiempirical diffusion equation which allows a successful correlation of  $k_d/k_c$  for a series of organic solvents as well as TA mixtures like  $t$ -BuOH-H<sub>2</sub>O.

The complexity of kinetic solvent effects on organic reactions in water-rich TA solutions is further demonstrated by the fact that changes in rate constants (and thus, in  $\Delta G_p^\ddagger$ ) often conceal (1) much more drastic and sometimes even capricious variations of  $\Delta H_p^\ddagger$  and  $\Delta S_p^\ddagger$ . Any theory aiming at an interpretation of the medium effects within the framework of transition state theory should endeavor to provide a link between these (semi)thermodynamic quantities and a microscopic picture of the interactions of the initial state and transition state with the solvent. The behavior of the thermodynamic activation parameters for the intramolecular carboxyl-catalyzed hydrolysis of the sulfonamides 4 and 5 in EtOH-H<sub>2</sub>O constitutes an interesting illustration (Table 3). This reaction proceeds via the formation of a pentacoordinate sulfur intermediate (of trigonal-bipyramidal geometry) which decomposes in the rate-determining step to afford the mixed cyclic anhydride (Scheme III) (25,26).



Scheme III

The data in Table 3 reveal that the rate of hydrolysis of 4 and 5 is reduced with increasing concentration of the cosolvent (27). However there is a striking difference between both

TABLE 3. Intramolecular carboxyl-catalyzed hydrolysis of sulfonamides

Solvent	$\Delta G_p^\ddagger$ kcal.mol <sup>-1</sup>		$\Delta H_p^\ddagger$ kcal.mol <sup>-1</sup>		$\Delta S_p^\ddagger$ e. u.	
	R=H	R=Et	R=H	R=Et	R=H	R=Et
H <sub>2</sub> O	28.9	25.2	27.0	24.6	- 6	- 2
EtOH-H <sub>2</sub> O, n <sub>H<sub>2</sub>O</sub> = 0.764	29.4	25.9	29.0	24.0	- 1	- 7
EtOH-H <sub>2</sub> O, n <sub>H<sub>2</sub>O</sub> = 0.264	30.2	26.5	34.5	22.1	+14	-15

All data at 25 °C; the p subscripts refer to isobaric (constant pressure) parameters

hydrolytic processes. For 4, the increase in  $\Delta G_p^\ddagger$  is the result of a large increase in  $\Delta H_p^\ddagger$  which is partly offset by an increase in  $\Delta S_p^\ddagger$ . By contrast, for 5 the increase in  $\Delta G_p^\ddagger$  is the result of a decrease in  $\Delta H_p^\ddagger$  which is overcompensated by a decrease in  $\Delta S_p^\ddagger$ . This situation implies that the temperature dependence of the solvent effect will be very different for the two sulfonamides and complicates a comparison of their relative reactivities. Evidence has been presented that the different behavior of 4 and 5 primarily stems from the large difference in hydrophobicity between both substrates (27).

The latter example also demonstrates the inherent limitations in attempts to rationalize kinetic solvent effects in terms of (linear) correlations between rate constants and solvent

parameters. Apart from all possible "practical" advantages of this type of approach, no differentiation can be made between solvent effects on the initial and transition state. Nevertheless, medium effects on rate constants have been correlated with a large number of solvent parameters, including empirical parameters of solvent polarity (28). In highly aqueous binaries, simple relationships are only rarely found and if so, their physical significance is far from clear. Two parameters which particularly pertain to these media are "water structure" and the number of "free" OH groups and "free" lone pairs in the hydrogen-bond network of water. The structure of water has been defined by Ben-Naim (16) starting from the function

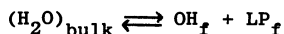
$$\psi_1(X^N) = \sum_{\substack{j=1 \\ j \neq 1}}^N G(X_i, X_j)$$

Herein is  $N$  the number of water molecules and the function  $G(X_i, X_j)$  a geometrical stipulation on the relative configuration of the pair of water molecules. By definition  $G(X_i, X_j)=1$  if the water molecules  $i$  and  $j$  are in a configuration favorable for formation of a hydrogen bond and  $G(X_i, X_j)=0$  for all other configurations. Thus  $\psi_1$  measures the number of hydrogen bonds in which the  $i$ th molecule participates when the system is at configuration  $X^N$ . In principle,  $\psi_1$  may attain the integral values 0 (gas phase), 1, 2, 3, and 4 (ice). If the average value of  $\psi_1(X^N)$  is  $\langle \psi \rangle_0$ , then the average number of hydrogen bonds in the system can be set equal to the structure of water (SOW):

$$\text{SOW} = \langle G \rangle_0 = \frac{N}{2} \langle \psi \rangle_0$$

Variation of SOW directly affects the strength of hydrophobic interactions which in turn affects kinetic solvent effects in water-rich media. Numerical values of SOW may be obtained experimentally or by simulation techniques, but we emphasize that these values will depend critically on the criterion involved in the definition of a hydrogen bond. As yet, no quantitative correlation with kinetic parameters seems to have been made.

Recently, Symons (29) made an interesting attempt to relate water structure with reactivity by considering the equilibrium



in which  $\text{OH}_f$  refers to non-hydrogen bonded ("free") OH groups and  $\text{LP}_f$  to non-hydrogen bonded lone pairs (in waters still forming three hydrogen bonds). Estimates of  $[\text{OH}_f]$  were made on the basis of infrared measurements in the  $2\nu_{\text{OH}}$  region for HOD in  $\text{D}_2\text{O}$ . At present there is no method for directly detecting  $\text{LP}_f$  groups, but in the absence of additives  $[\text{OH}_f] = [\text{LP}_f]$ . For hydrolysis reactions it was assumed that (1) fully hydrogen-bonded water molecules are inert and that (2) reactions involving attack by OH groups only occur via  $\text{OH}_f$  groups and reactions requiring attack by lone pairs only involve  $\text{LP}_f$  groups. Trends in solvent and salt effects on some hydrolytic processes (including the hydrolysis of arylsulfonylethyl perchlorates, *vide supra*) could be reproduced, but tests for numerical prediction must await further refinement of the theory. Of course, the treatment only hinges on reactant ( $\text{OH}_f$ ,  $\text{LP}_f$ ) concentration effects and completely ignores differences in the solvation of the initial and transition state.

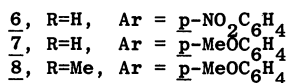
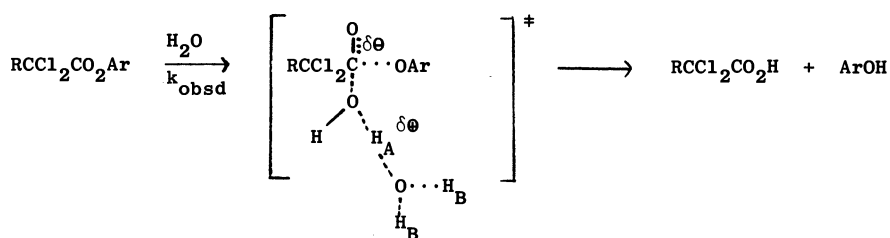
At present we prefer a pseudothermodynamic analysis of kinetic solvent effects (1). Herein, solvent effects on activation parameters ( $\Delta G_p^\ddagger$ ,  $\Delta H_p^\ddagger$ ,  $\Delta S_p^\ddagger$ ,  $\Delta V^\ddagger$ ,  $\Delta C_p^\ddagger$  etc.) are combined with the corresponding transfer (tr) parameters for the initial state (R) to give the thermodynamic quantities of transfer for the transition state (TS). For example, if  $\delta_m \Delta G_p$  is the change in  $\Delta G_p^\ddagger$  going from solvent  $S_1$  to solvent  $S_2$ , then it follows that

$$\delta_m \Delta G_p^\ddagger = \Delta G_{p, S_2}^\ddagger - \Delta G_{p, S_1}^\ddagger = \Delta G_{\text{tr}}^\ominus(\text{TS}) - \Delta G_{\text{tr}}^\ominus(\text{R})$$

Care should be taken that the proper solution standard states are employed (30). Now the analysis of kinetic solvent effects is reduced to an interpretation of  $\Delta G_{\text{tr}}^\ominus(\text{TS})$  and  $\Delta G_{\text{tr}}^\ominus(\text{R})$  in terms of changes in the molecular interactions of the transition state and the reactants with the solvent. This implies a detailed knowledge about the microscopic structure of the solvation shells as well as of the mechanistic pathway of the reaction. Furthermore it is assumed that simple transition-state theory is an adequate vehicle for the analysis of rate processes (31).

#### SOLVENT EFFECTS ON THE NEUTRAL HYDROLYSIS OF ACYL-ACTIVATED ESTERS IN TYPICALLY AQUEOUS SOLUTIONS

In the remaining part of this lecture we will see how this method works for one type of model reaction, the water-catalyzed hydrolysis of the acyl-activated esters 6-8 in TA solutions. The mechanism of the neutral hydrolysis involves water-catalyzed nucleophilic attack of water



on the ester carbonyl group and is characterized by substantial kinetic deuterium isotope effects ( $k_{\text{H}_2\text{O}}/k_{\text{D}_2\text{O}} \sim 3$ ) and strongly negative entropies of activation ( $\Delta S_p^\ddagger$  ca. -35 e.u.) (32). Proton inventory studies indicate that three protons ( $\text{H}_A$ ,  $\text{H}_B$ 's) contribute to the overall isotope effect (33). Rates and isobaric activation parameters (Fig. 4) have been determined for the neutral hydrolysis of 6 in *t*-BuOH-H<sub>2</sub>O and *t*-BuOD-D<sub>2</sub>O at 25°C (34). The rates pertain

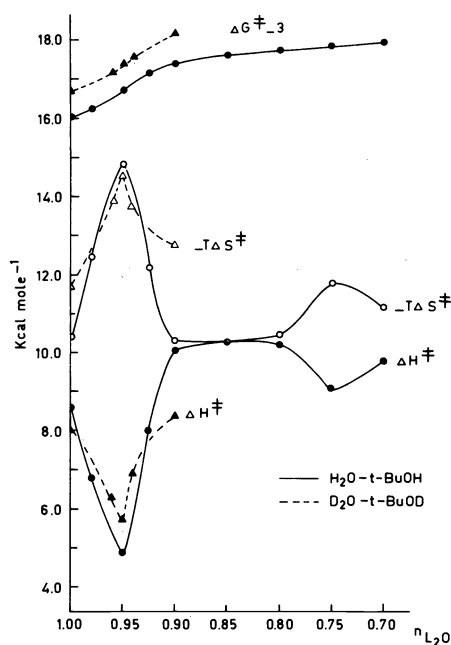


Fig. 4. Plots of  $\Delta G_p^\ddagger$ ,  $\Delta H_p^\ddagger$ , and  $-T\Delta S_p^\ddagger$  vs.  $n_{\text{H}_2\text{O}}$  (or  $n_{\text{D}_2\text{O}}$ ) for the neutral hydrolysis of 6 in *t*-BuOH-H<sub>2</sub>O and *t*-BuOD-D<sub>2</sub>O at 25°C.

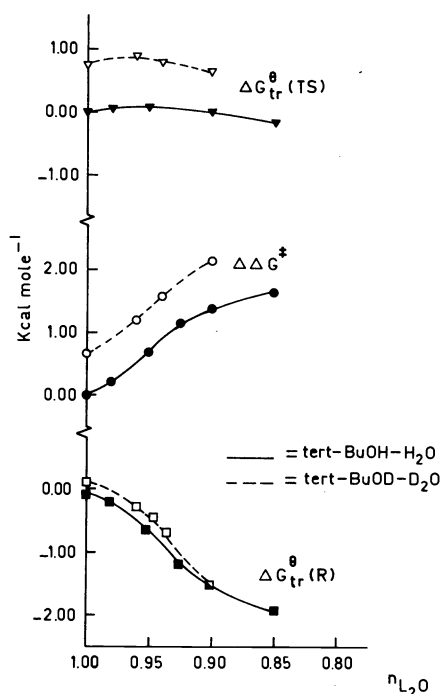


Fig. 5. Dissection of  $\Delta\Delta G_p^\ddagger$  for the neutral hydrolysis of 6 in *t*-BuOH-H<sub>2</sub>O and *t*-BuOD-D<sub>2</sub>O into initial state and transition state solvation effects.

to water reactions because solvolysis of 6 in *t*-BuOH is very slow. The pseudo-first-order rate constants ( $k_{\text{obsd}}$ ) decrease continuously with increasing alcohol content but do not show a simple relation with solvent parameters like dielectric constant ( $\epsilon$ ),  $(\epsilon-1)/(2\epsilon+1)$ , or solvatochromism scales.

Using *p*-nitrophenyl acetate (9) as a model for 6, the changes in the activation parameters were dissected into thermodynamic transfer parameters for the reactants (R) and transition state (TS) (1). The results for the free energies (Fig. 5) reveal that the rate retardation induced by the alcohol is primarily due to reactant stabilization and is not caused by destabilization of the polar transition state with decreasing solvent polarity. Interestingly,  $\Delta H_p^\ddagger$  and  $\Delta S_p^\ddagger$  display much more drastic variations than  $\Delta G_p^\ddagger$  and shed more light on the origin of the solvent effects. These parameters show mirror-image behavior for both solvent systems and pass through extrema at  $n_{\text{H}_2\text{O}} \sim 0.95$ , the solvent composition at which hydrophobic hydration of the cosolvent is at a maximum. The enthalpy changes for the initial and transition state are depicted graphically in Fig. 6. Upon the addition of the first 5 mole percent of

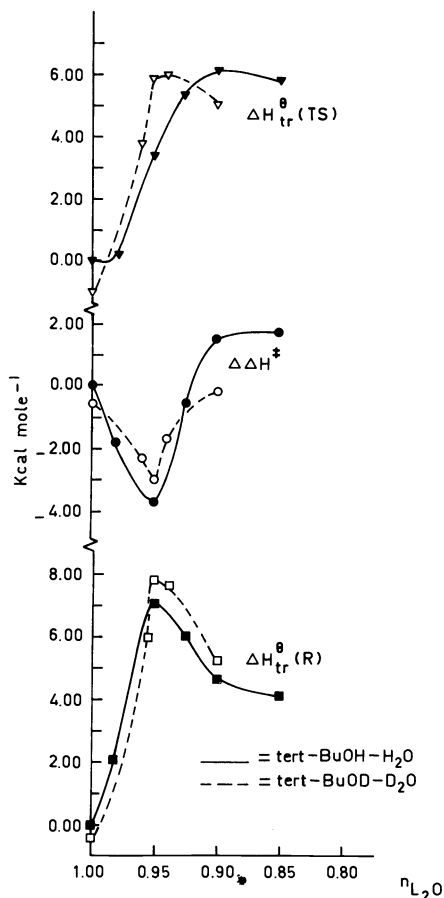


Fig. 6. Dissection of  $\Delta\Delta H_p^\ddagger$  for the neutral hydrolysis of **6** in *t*-BuOH-H<sub>2</sub>O and *t*-BuOD-D<sub>2</sub>O into initial state and transition state solvation effects.

alcohol,  $\Delta H_{tr}^\ominus(R)$  increases by no less than 7.1 kcal.mol<sup>-1</sup>, the increase being even somewhat larger in the deuterated solvent system. This behavior is clearly indicative of hydrophobic interactions between the ester and the organic cosolvent which are most pronounced at about  $n_{H_2O} = 0.95$ . Fig. 6 shows that a rather similar effect is observed for the transition state, but, as expected for a polar species, hydrophobic interactions are diminished. The increase in enthalpy is less than that for the apolar initial state and the maximum in  $\Delta H_{tr}^\ominus(TS)$  is reached at lower water concentration (35). Essentially the same conclusions can be drawn from the solvent effects on  $\Delta S_{tr}^\ominus(R)$  and  $\Delta S_{tr}^\ominus(TS)$ . In fact, the term  $-T\Delta S_{tr}^\ominus(R)$  overcompensates  $\Delta H_{tr}^\ominus(R)$ , leading to the decrease in  $\Delta G_{tr}^\ominus(R)$ . The domination of entropy effects is often found for chemical processes in water and in water-rich TA solutions (1,2). If hydrophobic interactions do indeed dominate the  $\Delta H_p^\ddagger/\Delta S_p^\ddagger$  compensation, then one would expect that the magnitude of the changes in these activation parameters would increase with increasing hydrophobicity of the substrate. The data for **7** and **8** (Fig. 7) show that this expectation is borne out in practice. The relation has also been verified for the neutral hydrolysis of 1-acyl-1,2,4-triazoles (1).

In TNA solutions (for example, MeCN-H<sub>2</sub>O) the rates of hydrolysis of **6** are also reduced. But now specific solvation effects play a major role and the changes in  $\Delta H_p^\ddagger$  and  $\Delta S_p^\ddagger$  are much less than in *t*-BuOH-H<sub>2</sub>O (32c, 34). Medium effects on the water-catalyzed hydrolysis of 1-acyl-1,2,4-triazoles in TNA 1,4-dioxane-H<sub>2</sub>O solutions have been compared with those experienced by the same substrates in the Stern layer of micelles (36).

So far the interpretations seem relatively straightforward. However, more recent results obtained using 2-*n*-butoxyethanol (2-BE) as the cosolvent demonstrate that the picture may be more complex. The 2-BE-H<sub>2</sub>O system was chosen because it exhibits extreme typically aqueous behavior. Thermodynamic data (37) indicate that large structural changes take place in the solvent near  $n_{H_2O} = 0.98$  and that at this mole fraction the effect of temperature on the hydrogen-bond network is larger than for *t*-BuOH-H<sub>2</sub>O.

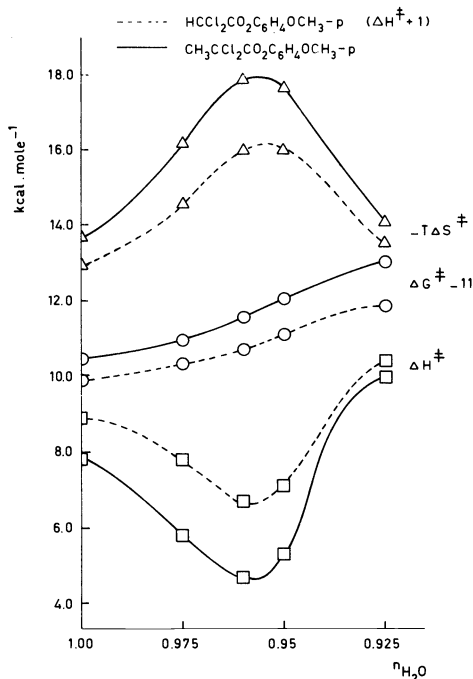


Fig. 7. Plots of  $\Delta G_p^\ddagger$ ,  $\Delta H_p^\ddagger$ , and  $-T\Delta S_p^\ddagger$  for the neutral hydrolysis of **7** and **8** in *t*-BuOH-H<sub>2</sub>O at 25°C.



TABLE 4. Pseudo-first-order-rate constants and thermodynamic activation parameters for the neutral hydrolysis of p-methoxyphenyl dichloroacetate (7) and 2,2-dichloropropionate (8) in 2-BE-H<sub>2</sub>O (25°C).<sup>a</sup>

Compd.	n <sub>H<sub>2</sub>O</sub>	k <sub>obsd</sub> · 10 <sup>5</sup>	ΔG <sub>p</sub> <sup>‡</sup> kcal.mol <sup>-1</sup>	ΔH <sub>p</sub> <sup>‡</sup> kcal.mol <sup>-1</sup>	ΔS <sub>p</sub> <sup>‡</sup> e.u.
<u>8</u>	1.000	307	20.88	7.9	-44
	0.995	235	21.04	7.6 <sub>b</sub>	-45
	0.980	36.2	22.15	2.2	-67 <sup>b</sup>
	0.950	4.67	23.36	10.4	-44
	0.900	2.63	23.70	10.4	-45
<u>9</u>	1.000	115	21.46	7.8	-46
	0.995	84.6	21.65	7.2	-48
	0.980	6.19	23.20	0.8 <sup>c</sup>	-75 <sup>c</sup>
	0.950 <sup>d</sup>	0.65	24.53	9.5	-50

<sup>a</sup>Containing (6.0-10.0) · 10<sup>-3</sup> mol.Kg<sup>-1</sup> HCl. <sup>b</sup>ΔC<sub>p</sub><sup>‡</sup> = 224 + 51 cal.mol<sup>-1</sup> K<sup>-1</sup>; 20-48°C. <sup>c</sup>ΔC<sub>p</sub><sup>‡</sup> = 342 ± 51 cal.mol<sup>-1</sup> K<sup>-1</sup>; 20-48°C. <sup>d</sup>No HCl added.

Pseudo-first-order rate constants and isobaric activation parameters for hydrolysis of 7 and 8 in 2-BE-H<sub>2</sub>O are listed in Table 4 (38). These data pertain to hydrolysis since alcoholysis in pure 2-BE is exceedingly slow. Again, the continuous increase of ΔG<sub>p</sub><sup>‡</sup> with increasing concentration of 2-BE conceals large and mutually compensating changes in ΔH<sub>p</sub><sup>‡</sup> and -TΔS<sub>p</sub><sup>‡</sup>. Extrema in the apparent ΔH<sub>p</sub><sup>‡</sup> and ΔS<sub>p</sub><sup>‡</sup> are located at n<sub>H<sub>2</sub>O</sub> = 0.980. However, hydrolysis at this mole fraction displays another rather surprising kind of behavior. Whereas excellent straight Eyring plots are obtained at n<sub>H<sub>2</sub>O</sub> = 1.000 and 0.950, the plots for n<sub>H<sub>2</sub>O</sub> = 0.980 show strong curvature. For hydrolysis of 8, this plot is shown in Fig. 8. Fitting of the observed rate constants to the Valentiner equation (39) [eq. 1; A = -ΔH<sub>oR</sub><sup>‡</sup>,

$$\ln k_{\text{obsd}} = AT^{-1} + B \ln T + C \quad (1)$$

B = ΔC<sub>p</sub><sup>‡</sup>R<sup>-1</sup> + 1, and C = (ΔS<sub>o</sub><sup>‡</sup> - ΔC<sub>p</sub><sup>‡</sup>)R<sup>-1</sup> + ln R(Nh)<sup>-1</sup>] by the method of least squares gives large and positive apparent heat capacities of activation for hydrolysis of 7 (ΔC<sub>p</sub><sup>‡</sup> = 224 + 51 cal.mol<sup>-1</sup> K<sup>-1</sup>) and 8 (ΔC<sub>p</sub><sup>‡</sup> = 342 ± 51 cal.mol<sup>-1</sup> K<sup>-1</sup>). These results contrast sharply with the negative ΔC<sub>p</sub><sup>‡</sup> values (between -30 and -150 cal.mol<sup>-1</sup> K<sup>-1</sup>) found previously for hydrolysis reactions of the S<sub>N</sub><sup>-</sup> type in TA solutions (39-41). One rather trivial origin for the positive ΔC<sub>p</sub><sup>‡</sup> values could be the occurrence of mixed kinetics (42). But this possibility can reasonably be discarded since it would imply an unrealistic difference between the ΔH<sub>p</sub><sup>‡</sup> values for the two

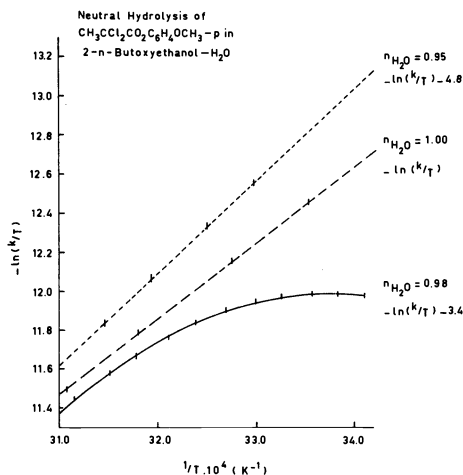


Fig. 8. Plots of  $-\ln(k/T)$  vs.  $(1/T)$  for the neutral hydrolysis of 8 in 2-BE-H<sub>2</sub>O. The experimental error in  $\ln(k/T)$  is indicated by the lengths of the vertical stripes.

reaction paths ( $\geq 13$  kcal.mol<sup>-1</sup> for 7 and  $\geq 15$  kcal.mol<sup>-1</sup> for 8). In addition, it is difficult to understand why mixed kinetics would only be significant at n<sub>H<sub>2</sub>O</sub> = 0.98. To shed more light on the origin of the positive ΔC<sub>p</sub><sup>‡</sup> values, thermodynamic transfer parameters were determined using p-nitrophenyl acetate (9) and propionate (10) as model substrates. Both solutes clear-

ly show positive heat capacities for transfer from water to 2-BE-H<sub>2</sub>O, n<sub>H<sub>2</sub>O</sub> = 0.98. As shown in Table 5, the greater temperature dependence of  $\Delta H_{tr}^{\theta}$  is found for the more hydrophobic

TABLE 5. Gibbs free energies, enthalpies, and entropies of transfer of p-nitrophenyl acetate (9) and propionate (10) from H<sub>2</sub>O to 2-BE-H<sub>2</sub>O<sup>a</sup> at 25°C.

Compd.	n <sub>H<sub>2</sub>O</sub>	$\Delta G_{tr}^{\theta}$ kcal.mol <sup>-1</sup>	$\Delta H_{tr}^{\theta}$ kcal.mol <sup>-1</sup>	$\Delta S_{tr}^{\theta}$ e.u.
9	1.00	0.0	0.0	0.0
	0.98	-0.66	+6.5 <sup>b</sup>	+24 <sup>b</sup>
10	1.00	0.0	0.0	0.0
	0.98	-0.84	+8.9 <sup>c</sup>	+33 <sup>c</sup>
	0.95	-2.11	+5.1	+24

<sup>a</sup>Containing 10<sup>-3</sup> mol.kg<sup>-1</sup> HCl. <sup>b</sup> $\Delta C_{p,tr}^{\theta} = 56 \text{ cal.mol}^{-1} \text{ K}^{-1}$ . <sup>c</sup> $\Delta C_{p,tr}^{\theta} = 134 \text{ cal.mol}^{-1} \text{ K}^{-1}$ .

propionate 10. These new data invalidate an earlier suggestion (38) that the  $\Delta C_p^{\ddagger}$  values should be rationalized in terms of strong hydrophobic interaction between the initial state and 2-BE. If this were the case, negative  $\Delta C_{p,tr}^{\ddagger}$  values for the model substrates would be expected.

A new tentative explanation for the  $\Delta C_p^{\ddagger}$  and  $\Delta C_{p,tr}^{\theta}$  values hinges on a consideration of the strong microheterogeneity proposed for the water-rich 2-BE-H<sub>2</sub>O mixture. Apart from Desnoyers' thermodynamic studies (37), evidence for pseudophase separation comes from NMR studies of spin-lattice relaxation times (43), ultrasonic absorption measurements (44), and Rayleigh scattering measurements (45). All these studies point to the formation of water-rich (WR) and cosolvent-rich (CR) microphases (also called "microdomains", "pseudophases", or "moving units"), the properties of the latter resembling those of micelles formed from nonionic amphiphiles. These microphases start to be formed at about n<sub>H<sub>2</sub>O</sub> = 0.98 and, upon comparison with nonionic amphiphiles (46), this solvent composition indeed corresponds with a reasonable "cmc" for 2-BE at 25°C. The apolar substrates 7 and 8 as well as the model substrates 9 and 10 will preferentially bind to the 2-BE-rich (CR) microphase and their solubility in this microphase will increase more strongly with temperature than the solubility of these solutes in the water-rich microphase [ $\Delta H_{sol}^{\theta}(\text{CR}) > \Delta H_{sol}^{\theta}(\text{WR})$ ] (6a). Since the fraction of the CR microphase will increase with temperature (47), there will be a concomitant faster increase of the solubility of 9 and 10 with temperature leading to an apparent *positive* heat capacity for transfer from water to 2-BE-H<sub>2</sub>O (n<sub>H<sub>2</sub>O</sub> = 0.98). Space does not permit a discussion of the complete kinetic analysis in terms of the pseudophase separation model (48). But assuming that at n<sub>H<sub>2</sub>O</sub> > 0.98 (almost) no CR microphase is formed and that at n<sub>H<sub>2</sub>O</sub> < 0.98 the initial state is (almost) completely bound to the CR microphase, it is possible to account for the effect of the temperature on  $k_{obsd}$  at n<sub>H<sub>2</sub>O</sub> = 0.98 and thus for the observed *positive*  $\Delta C_p^{\ddagger}$  values. This theory reasonably explains why these  $\Delta C_p^{\ddagger}$  values are only observed near n<sub>H<sub>2</sub>O</sub> = 0.98 and why the magnitude of the  $\Delta C_p^{\ddagger}$  values is related to substrate hydrophobicity.

In the foregoing discussion, it was habitually assumed that *isobaric* (constant pressure) activation parameters ( $\Delta G_p^{\ddagger}$ ,  $\Delta H_p^{\ddagger}$ ,  $\Delta S_p^{\ddagger}$ ) lend themselves to interpretations of kinetic solvent effects. This, in fact, implied that the consequences of volume changes during the activation process (reflected in the volume of activation,  $\Delta V^{\ddagger}$ ) are ignored. In the past, some attention was drawn to this problem (49,50). In the final part of this lecture, I will briefly examine the differences between the trends in the isobaric ( $\Delta H_p^{\ddagger}$ ,  $\Delta S_p^{\ddagger}$ ) and isochoric (constant volume) activation parameters ( $\Delta U_v^{\ddagger}$ ,  $\Delta S_v^{\ddagger}$ ) for hydrolysis of p-methoxyphenyl 2,2-dichloropropionate (8) in t-BuOH-H<sub>2</sub>O in the solvent composition range n<sub>H<sub>2</sub>O</sub> = 1.000-0.925. Isochoric activation parameters are not easily measured, but they can be obtained from the equations (51):

$$\Delta U_v^{\ddagger} = \Delta H_p^{\ddagger} - T\alpha\Delta V^{\ddagger}/\beta$$

$$\Delta S_v^{\ddagger} = \Delta S_p^{\ddagger} - \alpha\Delta V^{\ddagger}/\beta$$

in which  $\alpha$  is the isobaric thermal expansivity and  $\beta$  the isothermal compressibility of the solvent. Since  $\alpha$  is unusually low for pure water, large variations occur in  $\alpha/\beta$  (and thus, in the internal pressure  $P_i$ ) (7) in TA solutions of high water content. This implies that if  $|\Delta V^{\ddagger}|$  is not too low, there is a substantial difference between the solvent effects on the sets ( $\Delta H_p^{\ddagger}$ ,  $\Delta S_p^{\ddagger}$ ) and ( $\Delta U_v^{\ddagger}$ ,  $\Delta S_v^{\ddagger}$ ) as the sole result of changes in the (macroscopic) solvent parameters  $\alpha$  and  $\beta$ . This conclusion holds even if  $\Delta V^{\ddagger}$  is invariant with solvent composition.

Table 6 records  $\Delta V^{\ddagger}$  values (52) for the neutral hydrolysis of 8 in highly aqueous t-BuOH-H<sub>2</sub>O and the changes in the isobaric and isochoric activation parameters. We presume that the large contraction upon formation of the transition state in water reflects electrostriction involved in the formation of the zwitterionic structure (53). The further drastic decrease

TABLE 6. Isobaric and isochoric activation parameters for the neutral hydrolysis of *p*-methoxyphenyl 2,2-dichloropropionate in *t*-BuOH-H<sub>2</sub>O at 25°C.

Medium	$\Delta H_p^\ddagger$ kcal.mol <sup>-1</sup>	$\Delta S_p^\ddagger$ e.u.	$\Delta V_p^\ddagger$ cm <sup>3</sup> .mol <sup>-1</sup>	$\alpha.10^6$ K <sup>-1</sup>	$\beta.10^6$ bar <sup>-1</sup>	$\Delta U_v^\ddagger$ kcal.mol <sup>-1</sup>	$\Delta S_v^\ddagger$ e.u.
H <sub>2</sub> O	7.8	-46	-32	257	44.6	9.1	-41
<i>t</i> -BuOH-H <sub>2</sub> O	5.3	-59	-63	560	42.7	11.2	-40
<i>n</i> H <sub>2</sub> O = 0.950							
<i>t</i> -BuOH-H <sub>2</sub> O	10.0	-47	-69	703	45.6	17.6	-22
<i>n</i> H <sub>2</sub> O = 0.925							

of  $\Delta V^\ddagger$  upon addition of *t*-BuOH is most likely caused by a negative volume contribution due to increased hydrogen bond formation and by zwitterion-dipole forces. The changes are apparently too large to be explained in terms of the pressure dependence of hydrophobic interactions (16).

The data in Table 6 show the huge difference in the solvent dependence of the isobaric and isochoric activation parameters. Going from *n*H<sub>2</sub>O = 1.000 to *n*H<sub>2</sub>O = 0.950,  $\Delta H_p^\ddagger$  and  $\Delta U_v^\ddagger$  even vary in opposite direction! Comparison of  $\Delta H_p^\ddagger$  and  $\Delta U_v^\ddagger$  at *n*H<sub>2</sub>O = 1.000 and *n*H<sub>2</sub>O = 0.925 shows that the increase in  $\Delta U_v^\ddagger$  amounts to 8.5 kcal.mol<sup>-1</sup> whereas the increase in  $\Delta H_p^\ddagger$  is only 2.2 kcal.mol<sup>-1</sup>. It is obvious that both sets of activation parameters contain fundamental information about the solvation changes determining the kinetic solvent effects. But it should be remembered that the influence of the variation in  $\alpha/\beta$  on the difference between the sets is completely independent of the reaction under study.

An interpretation of the trends in  $\Delta H_p^\ddagger$  and  $\Delta S_p^\ddagger$  as a function of *n*H<sub>2</sub>O has already been given. At constant volume the temperature dependence of the rate constants is larger than at constant pressure ( $\Delta U_v^\ddagger > \Delta H_p^\ddagger$ ; Table 6). We assume that this is primarily caused by the fact that the solvent volume in regions far from the transition state must be expanded in order to compensate the decrease in volume during the activation process as a result of electrostriction. Upon addition of *t*-BuOH, the attractive non-hydrogen bond interactions will increase (reflected in an increase of  $P_i$ ) (7,54) leading to a rise of  $\Delta U_v^\ddagger$ . At constant volume this effect apparently outweighs the energy changes associated with hydrophobic interaction between *s* and *t*-BuOH. It is evident that further more detailed studies of pressure effects on hydrolysis reactions showing different patterns of  $\Delta H_p^\ddagger/\Delta S_p^\ddagger$  compensation in aqueous binaries may be highly rewarding.

In conclusion we note that further development of detailed theories for the nature of water and mixed aqueous solvents is a prerequisite for a thorough understanding of kinetic solvent effects in these peculiar reaction media. Apart from recent experimental advances, much has been learned from theoretical calculations (55).

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