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Solvolysis of Arylsulfonylmethyl Perchlorates in Dioxane–Water, *tert*-Butyl Alcohol–Water, and Acetonitrile–Water. An Analysis of Solvent Effects on a Water-Catalyzed Process

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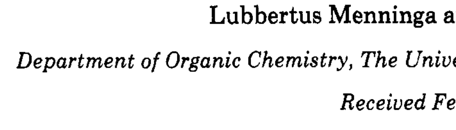
This paper presents a study of the water-catalyzed hydrolysis of two covalent arysulfonylmethyl perchlorates (involving rate-determining proton transfer to water) in dioxane–H_2O, t-BuOH–H_2O, and CH_3CN–H_2O. The characteristic kinetic behavior for each aqueous binary is discussed in terms of the variation of the activation parameters $\Delta G^{\ddagger}$, $\Delta H^{\ddagger}$, and $\Delta S^{\ddagger}$ as a function of the mole fraction of water (n_{H_2O}). Addition of the weak Bronsted bases dioxane and CH_3CN markedly increases the kinetic basicity of water. It is proposed that the magnitude of the effect is correlated with the amount of polarization of the water molecule as a result of hydrogen bonding to the organic cosolvent. Thermodynamic data for transfer of a model substrate **3** from H_2O to the aqueous mixtures support the idea that especially in t-BuOH–H_2O effects due to changes in "water structure" should be invoked to explain the remarkable extrema observed for $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ in the region of high water concentration. Possible biochemical implications are briefly indicated.

Few systematic studies have been made of the effect of solvent composition upon rates and activation parameters of hydrolysis reactions involving proton transfer to or from water in the rate-determining step.[1-4] Recently, we have reported that the neutral hydrolysis of covalent arylsulfonylmethyl perchlorates, which is subject to efficient general base catalysis by water[5] (Scheme I), may be a useful probe for such studies.[2,4]

Scheme I



$$\mathrm{ArSO_2CH_2OClO_3 + H_2O \xrightarrow{slow} [ArSO_2\bar{C}HOClO_3] + H_3O^+}$$

$$\downarrow{\scriptstyle H_2O\ fast}$$

$$\mathrm{ArSO_2H + HCOOH + ClO_3^-}$$

1, Ar = p-$NO_2C_6H_4$

2, Ar = p-$CH_3C_6H_4$

The hypothesis was advanced that the peculiar behavior of the kinetic parameters as a function of solvent composition can be rationalized by assuming that the diffusionally averaged "water structure"[6] is one of the factors determining $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ in mixed aqueous solvents of high water concentration.[2] It was also argued that the water-catalyzed process depicted in Scheme I is by no means a *general* probe for the kinetic basicity of mixed aqueous solutions.[4]

In this paper we report a more detailed analysis of the trends in $\Delta G^{\ddagger}$, $\Delta H^{\ddagger}$, and $\Delta S^{\ddagger}$ for hydrolysis of **1** and **2** as a function of solvent composition in dioxane–H_2O, t-BuOH–H_2O, and CH_3CN–H_2O using transition-state theory. The data provide a deeper insight into the propensity of water molecules to deprotonate pseudoacids like **1** and **2** under conditions of changing water–water hydrogen bonding interaction. In addition, the present results may possess relevance for our understanding of microenvironmental factors at the active sites of enzymes which catalyze C–H bond fission.[7,8]

Results

Hydrolysis of 1, 1a, and 2 in 1,4-Dioxane–H_2O Mixtures.[9] Pseudo-first-order rate constants (k_{obsd}), second-order rate constants ($k_2 = k_{obsd}\, c_{H_2O}^{-1}$), and activation parameters for hydrolysis of **1**, **1a** (p-$NO_2C_6H_4SO_2CD_2OClO_3$), and **2** in dioxane–H_2O mixtures of varying mole fraction of water (n_{H_2O}) are shown in Table I. Plots of log $k_{obsd}/k_{obsd}^{H_2O}$ and log $k_2/k_2^{H_2O}$ vs. n_{H_2O} are given for **1** in Figures 1 and 2, respectively, and $\Delta H^{\ddagger}$ and $-T\Delta S^{\ddagger}$ are plotted as a function of n_{H_2O} in Figure 3. These data all pertain to water-induced processes because the substrates are stable in anhydrous dioxane for a long time.[5] Since **1** and **2** exhibit closely similar trends in their data, the following discussion will be largely limited to **1**. Two observations are particularly noteworthy: firstly, the nearly constant value of $k_2/k_2^{H_2O}$ between n_{H_2O} = 0.2–0.8, and secondly, the extrema in $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ around n_{H_2O} = 0.7. Upon the first addition of dioxane to water, the rate enhancement is governed by a decrease of $\Delta H^{\ddagger}$ which is only partly compensated by a decrease of $\Delta S^{\ddagger}$. Below n_{H_2O} = 0.7 almost completely compensatory changes in $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ are observed. Between n_{H_2O} = 0.7 and 0.5 these changes in $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ are in opposite direction to those found in the region n_{H_2O} = 0.7–1.0. Hydrolysis of **1** and **2** in the region n_{H_2O} = 0.8–1.0 is associated with real isokinetic temperatures (**1**, T_c = 375 ± 10 K; **2**, T_c = 369 ± 10 K) as indicated by application of Petersen's criterium.[10]

The substantial changes of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ with n_{H_2O} for hydrolysis in dioxane–H_2O may be contrasted with the small changes of these quantities of activation for ethanolysis of **1** in dioxane–EtOH (Table II). In the latter solvent system there is no initial increase of k_{obsd}/k_{obsd}^{EtOH} upon the first addition of dioxane to ethanol (Figure 1). It should also be noted that k_{obsd} is only moderately sensitive to changes in the dielectric constant of the medium.[2b]

Solvolysis of 1 in t-BuOH–H_2O Mixtures.[9] The kinetic data for solvolysis of **1** in t-BuOH–H_2O are listed in Table III. A plot of log $k_{obsd}/k_{obsd}^{H_2O}$ vs. n_{H_2O} is shown in Figure 1. It should be emphasized that the k_{obsd} values for the t-BuOH–H_2O mixtures represent the sum of the rate constants for hydrolysis and alcoholysis, which are, in the respective pure solvents, of the same order of magnitude (Table III). Interestingly, k_{obsd} increases sharply upon the first addition of t-BuOH to H_2O until k_{obsd} reaches around n_{H_2O} = 0.9 a value well above that for solvolysis in either pure water or pure t-BuOH. Between n_{H_2O} = 0.9–0.2 k_{obsd} is nearly constant and then, below n_{H_2O} = 0.2, falls off rapidly to the value for alcoholysis in pure t-BuOH. A rather similar behavior of k_{obsd} as a function of n_{H_2O} has been observed for solvolysis in EtOH–H_2O and in glycol–H_2O although in these solvent systems the rate increase upon initial addition of the alcohol is appreciably smaller.[2]

The variation of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ as a function of solvent composition shows mirror image behavior, as for hydrolysis in dioxane–water, but now extrema are located at n_{H_2O} = 0.85 (Figure 4). Clearly the increase in rate between n_{H_2O} = 1.0 and 0.85 is the result of a decrease in $\Delta H^{\ddagger}$ which is incompletely compensated by a decrease in $\Delta S^{\ddagger}$. Almost perfect $\Delta H^{\ddagger}$–$\Delta S^{\ddagger}$ compensation occurs in the region n_{H_2O} = 0.9–0.1. Below n_{H_2O} = 0.1 the increase of $\Delta G^{\ddagger}$ is caused by an endothermic change in $\Delta H^{\ddagger}$.

Table I. Rate Constants and Activation Parameters for the Neutral Hydrolysis of 1, 1a, and 2 in Dioxane–H_2O[a] at 25 ± 0.04 °C

Compd	n_{H_2O}	$k_{obsd} \times 10^4$, s^{-1}[b]	$k_2 \times 10^6$, $M^{-1} s^{-1}$[c]	$\Delta H^{\ddagger}$, kcal mol^{-1}	$\Delta S^{\ddagger}$, eu	k_H/k_D[d]
1	1.00	32.5	58.6	18.4	−8	
1	0.98	44.7	88.7	17.9	−9	
1	0.90	111	306	15.6	−15	
1	0.80	164	645	14.0	−20	
1	0.75	166	770	13.3	−22	
1	0.70	148	804	13.0	−23	
1	0.65	135	864	13.0	−23	
1	0.58	106	859	13.8	−22	
1	0.50	79.4	811	14.3	−20	
1	0.30	35.2	788	14.0	−23	
1	0.20	19.9	736	12.5	−29	
1a	1.00	5.7	10.3	19.2	−9	5.6
1a	0.80	25.4	98.1	14.6	−22	6.4
1a	0.50	12.5	129	15.3	−21	6.4
1a	0.30	5.5	120	14.6	−24	6.2
1	1.00[e]	18.4	33.3	18.6	−9	1.7[f]
1	0.80	104	402	13.7	−22	1.6[f]
1	0.50	54.8	561	14.0	−22	1.5[f]
1	0.30	25.6	555	12.2	−29	1.6[f]
2	1.00	6.10	11.0	19.7	−7	6.2[g]
2	0.98	7.23	14.2	18.5	−11	
2	0.90	13.3	36.0	17.0	−15	
2	0.80	17.0	65.6	14.4	−23	7.7
2	0.75	15.2	69.4	15.0	−21	
2	0.65	11.0	69.2	15.3	−21	
2	0.50	6.92	71.3	15.7	−21	7.3
2	0.30	2.88	62.6			7.1
2	0.20	1.71	61.1	14.0	−29	

[a] Containing 10^{-3} M HCl. [b] Pseudo-first-order rate constant. [c] $k_2 = k_{obsd} C_{H_2O}^{-1}$. [d] Primary kinetic deuterium isotope effect. [e] n_{D_2O}. [f] Solvent deuterium isotope effect, k_{H_2O}/k_{D_2O}. [g] $k_{H_2O}/k_{D_2O} = 1.7$.

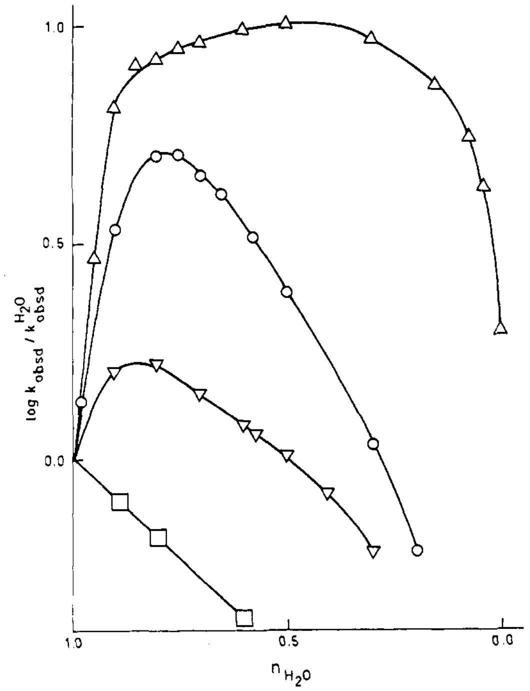
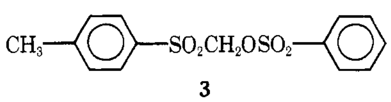


Figure 1. Plot of $\log k_{obsd}/k_{obsd}^{H_2O}$ vs. n_{H_2O} for the neutral hydrolysis of 1 in *t*-BuOH–H_2O (△), dioxane–H_2O (○), CH_3CN–H_2O (▽), and dioxane–EtOH (□). In the last case $\log k_{obsd}/k_{obsd}^{EtOH}$ is plotted as a function of n_{EtOH}.

Hydrolysis of 1 in CH_3CN–H_2O Mixtures. Kinetic data for hydrolysis of 1 in CH_3CN–H_2O mixtures are summarized in Table IV. The data comprise the region n_{H_2O} = 0.3–1.0; 1 is not solvolyzed in pure CH_3CN, as expected. As shown in Figure 1, there is a small increase of k_{obsd} upon going from pure water to n_{H_2O} ca. 0.8, further addition of CH_3CN then results in a smooth decrease. The modest increase of k_2 upon increasing concentration of CH_3CN is displayed in Figure 2. A striking difference with the results for solvolysis in dioxane–H_2O and *t*-BuOH–H_2O is the absence of extrema in $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ in the region of high water concentration (Figure 5) although again $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ vary as a function of n_{H_2O} in a compensating fashion.

Thermodynamic Parameters of Transfer for 3. Unfortunately the perchlorates 1 and 2 are too readily hydrolyzed to allow the determination of thermodynamic quantities for transfer from water to the aqueous mixtures employed in the kinetic studies. Therefore we have chosen the less reactive sulfonate 3[11] as a reasonable model compound for 1 and 2.



3

Justification for this choice is found in Cox's observation[12] that for such different substrates as ethyl acetate, acetone, benzene, and trimethyl phosphate the enthalpies ($\Delta H_{tr}°$) and entropies ($\Delta S_{tr}°$) for transfer from water to various aqueous mixtures show trends which are similar in their gross features.[13] The thermodynamic parameters $\Delta G_{tr}°$, $\Delta H_{tr}°$, and $\Delta S_{tr}°$ for transfer of 3 were obtained from solubility measurements and are tabulated in Table V. Figure 6 shows a plot of $\Delta H_{tr}°$ and $-T\Delta S_{tr}°$ as a function of n_{H_2O} for the three solvent systems. The plots clearly reveal mirror image behavior. Most noteworthy are the pronounced extrema in $\Delta H_{tr}°$ and $\Delta S_{tr}°$ at n_{H_2O} = 0.95 for *t*-BuOH–H_2O.

Discussion

Solvent Effects on $\Delta G^{\ddagger}$. Since the $\Delta G^{\ddagger}$ value for solvolysis

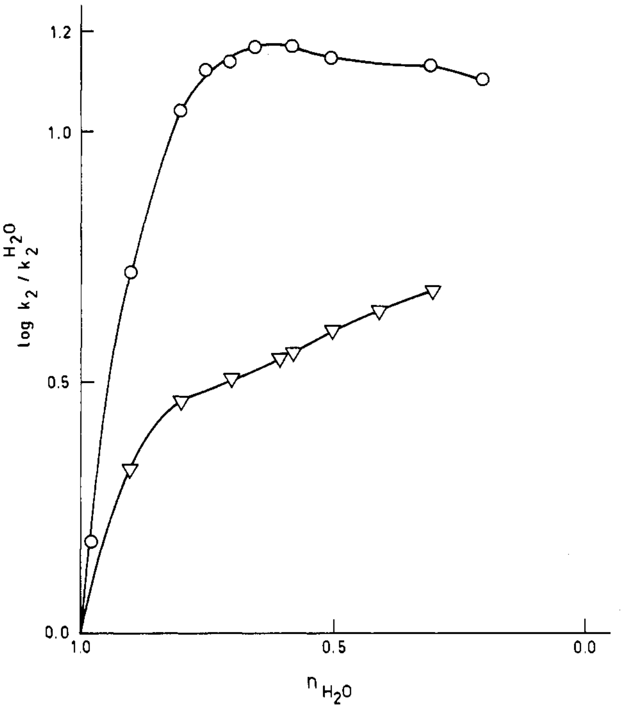


Figure 2. Plot of log $k_2/k_2^{H_2O}$ vs. n_{H_2O} for the neutral hydrolysis of 1 in dioxane–H_2O (○) and in CH_3CN–H_2O (▽).

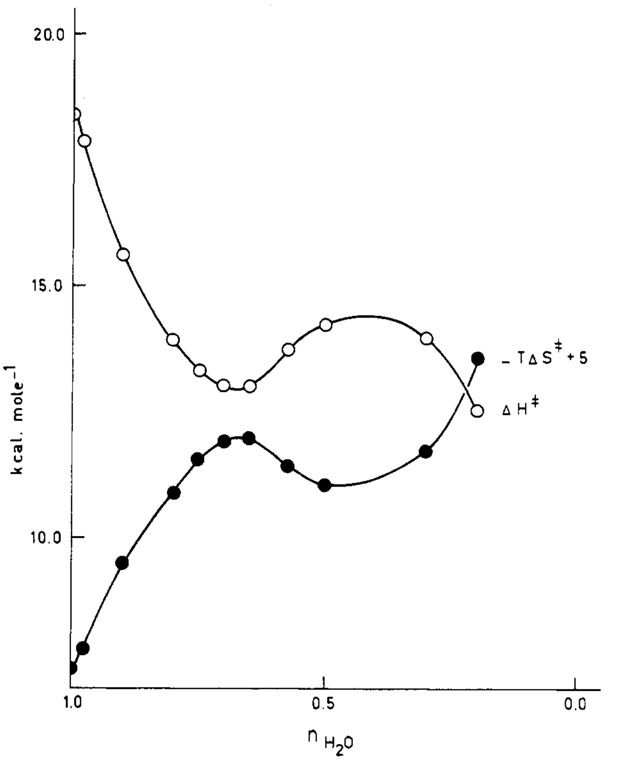


Figure 3. Plot of $\Delta H^{\ddagger}$ and $-T\Delta S^{\ddagger}$ vs. n_{H_2O} for the neutral hydrolysis of 1 in dioxane–H_2O.

Table II. Rate Constants and Activation Parameters for the Neutral Hydrolysis of 1 in Dioxane–EtOH[a] at 25 ± 0.04 °C

n_{EtOH}	$k_{obsd} \times 10^4$, s^{-1} [b]	$k_2 \times 10^6$, $M^{-1} s^{-1}$ [c]	$\Delta H^{\ddagger}$, kcal mol^{-1}	$\Delta S^{\ddagger}$, eu
1.00	45.1	207	15.8	−16
0.90	36.1	201	16.3	−15
0.80	30.3	206	16.3	−15
0.60	19.1	200	16.1	−17

[a] Containing 10^{-3} M HCl. [b] Pseudo-first-order rate constant. [c] $k_2 = k_{obsd} c_{EtOH}^{-1}$.

Table III. Pseudo-First-Order Rate Constants (k_{obsd}) and Activation Parameters for the Neutral Hydrolysis of 1 in t-BuOH–H_2O[a] at 25 ± 0.04 °C

n_{H_2O}	$k_{obsd} \times 10^4$, s^{-1}	$\Delta H^{\ddagger}$, kcal mol^{-1}	$\Delta S^{\ddagger}$, eu	k_H/k_D [b]
1.00	32.5	18.4	− 8	5.6
0.95	95.5	16.9	−11	
0.90	214	14.5	−18	
0.85	269	13.2	−22	
0.80	275	14.0	−19	
0.75	288	14.1	−18	
0.70	299	14.0	−19	
0.60	320	13.4	−21	
0.50	331	13.1	−21	
0.30	306	12.8	−23	6.1
0.15	240	12.6	−24	
0.075	180	12.7	−24	
0.040	138	12.9	−24	
0.0	64.6	14.6	−20	

[a] Containing 10^{-3} M HCl. [b] Primary kinetic deuterium isotope effect, k_{obsd} (1)/k_{obsd} (1a).

Table IV. Rate Constants and Activation Parameters for the Neutral Hydrolysis of 1 in CH_3CN–H_2O[a] at 25 ± 0.04 °C

n_{H_2O}	$k_{obsd} \times 10^4$, s^{-1} [b]	$k_2 \times 10^6$, $M^{-1} s^{-1}$ [c]	$\Delta H^{\ddagger}$, kcal mol^{-1}	$\Delta S^{\ddagger}$, eu
1.00	32.5	58.6	18.4	−8
0.90	51.9	124	17.1	−12
0.80	54.3[d]	169	16.2	−15
0.70	46.2	188	15.6	−17
0.60	39.0	207	15.5	−18
0.58	37.2	212	15.4	−18
0.50	33.1	234	14.6	−21
0.41	26.9	256	14.4	−22
0.30	19.8	278	14.0	−24

[a] Containing 10^{-3} M HCl. [b] Pseudo-first-order rate constant. [c] $k_2 = k_{obsd}\, C_{H_2O}^{-1}$. [d] $k_{H_2O}/k_{D_2O} = 1.9$, $k_H/k_D = 6.4$.

of 1 and 2 measures the "kinetic basicity" of the reaction medium,[14] it is remarkable that the first addition of the weak Bronsted bases dioxane and CH_3CN to water lead to enhanced reaction rates as expressed in the k_2 values (Figure 2). These results serve to indicate that the activation process is strongly affected by solvation factors.[15] From previous work it seems evident that proton transfer in the transition state is far from complete since the Bronsted β is ca. 0.5.[5] In addition, the rather small negative entropy of activation for hydrolysis in pure water (−8 eu) reveals that no drastic change in the solvation pattern is required to reach the transition state for proton transfer to water. Since 1 and 2 should be considered as "pseudoacids",[16] it is reasonable to assume that only one water molecule will be tightly bound in the transition state and that the rate of deprotonation will not be seriously affected by the necessity of substrate desolvation. The proposed transition state structure also implies that solvation of the dispersed negative charge at the α-sulfonyl carbon atom is relatively unimportant.[4] Because proton transfer from 1 and 2 in dioxane–H_2O and CH_3CN–H_2O occurs only to water molecules,[17] we suggest that the increase in the kinetic basicity of water in these solvents should be ascribed to water–organic

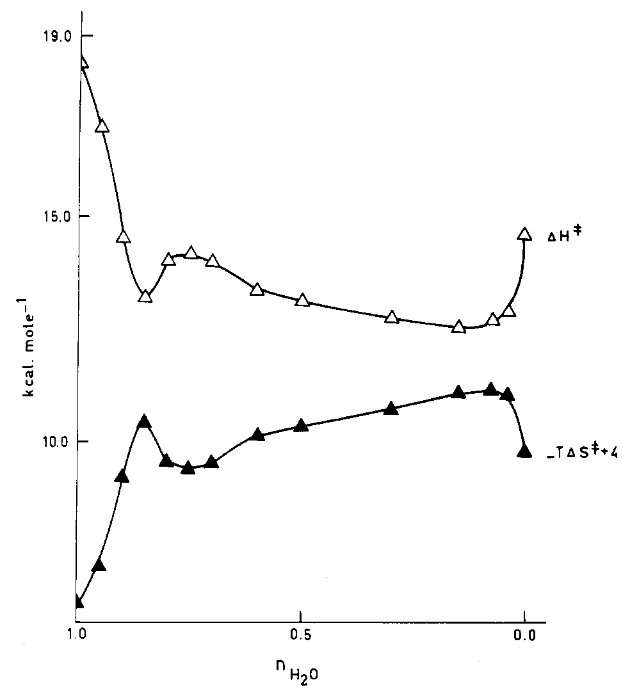


Figure 4. Plot of $\Delta H^{\ddagger}$ and $-T\Delta S^{\ddagger}$ vs. n_{H_2O} for the neutral hydrolysis of 1 in t-BuOH–H_2O.

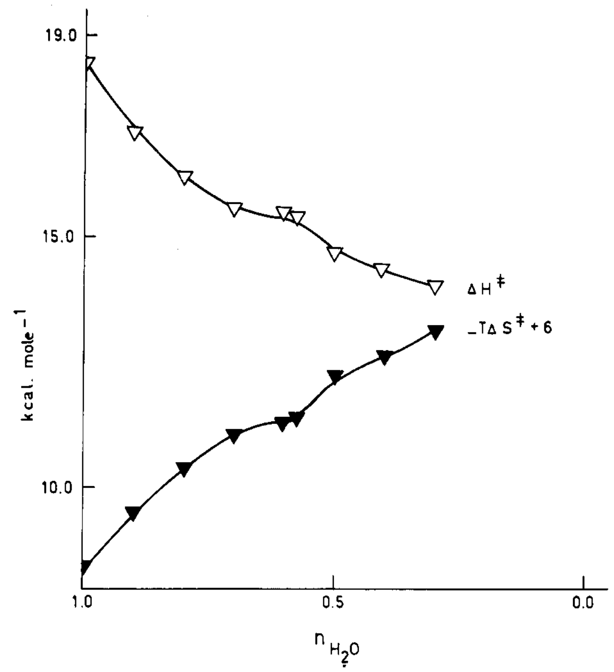
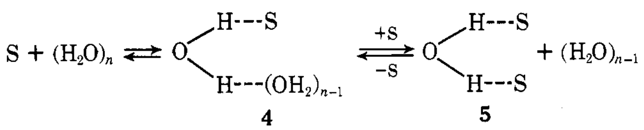


Figure 5. Plot of $\Delta H^{\ddagger}$ and $-T\Delta S^{\ddagger}$ vs. n_{H_2O} for the neutral hydrolysis of 1 in CH_3CN–H_2O.

solvent hydrogen bonding interactions in complexes of type 4 and 5. This type of association apparently results in an enhanced electron density at the water oxygen atom as compared with that in water–water hydrogen bond complexes. Experimental evidence for the intrinsic high hydrogen bonding capability (high proton affinity) of ether molecules like dioxane has been obtained from gas-phase ion equilibria.[18] In these studies it was shown that the interaction of H_3O^+ with three ether molecules is more favorable than with three water molecules. Acetonitrile has also a greater proton affinity than water. In the light of these data for the gas phase, it is interesting to see that the curves of k_2 as a function of n_{H_2O} for hydrolysis of 1 in dioxane–H_2O and CH_3CN–H_2O show a strong conformity (Figure 2), except for the size of the effect, which is smaller for CH_3CN. The low kinetic basicities of dioxane and CH_3CN molecules themselves, either in the pure liquid or in their aqueous solutions, find their explanation in their aprotic character which strongly discourages proton transfer to these molecules because of the associated highly unfavorable $\Delta S^{\ddagger}$ values. Our results therefore reinforce the idea[19] that the relatively high Bronsted basicity of water in aqueous solutions, despite its low gas-phase proton affinity, is largely due to the presence of extensive three-dimensional hydrogen bond networks and its associated low entropy. As a consequence, the loss of entropy associated with proton transfer to water will be less than for proton transfer to less associated solvent molecules although the latter may form hydrogen bonds of comparable enthalpy as water does. In addition to this effect, cooperative hydrogen bonding between water molecules will also enhance the hydrogen bond basicity of water in the enthalpic sense.[20] Support for the idea that the enhanced rates in the water-rich dioxane–H_2O and CH_3CN–H_2O mixtures are due to a predominating transition state effect, is found in the exothermic $\Delta G_{tr}°$ values for these solvent systems given in Table V.



4 5

S = dioxane, CH_3CN

An explanation for the rate–solvent composition profile for solvolysis of 1 in t-BuOH–H_2O[21] may be given along similar lines but now the situation is still more complex because the organic cosolvents also functions as an efficient Bronsted base. The rate enhancement in the region $n_{H_2O} = 1.0$–0.8 will be due to transition state stabilization as suggested by the $\Delta G_{tr}°$ data in Table V. Apparently, transition state solvation is promoted by the formation of water–t-BuOH hydrogen bond complexes at the expense of water–water interactions in the bulk solvent. Support for this conclusion is found in the strongly *reduced* rates of solvolysis of 1 in 2,2,2-trifluoroethanol (TFE)–H_2O mixtures ($n_{H_2O} = 0.827$, $k_{obsd} = 69.3 \times 10^{-5}\ s^{-1}$, $k_2 = 26.9 \times 10^{-6}\ M^{-1}\ s^{-1}$, $\Delta H^{\ddagger} = 17.6$ kcal mol^{-1}, $\Delta S^{\ddagger} = -14$ eu). Now the alcohol is only a weak hydrogen bond acceptor and formation of complexes like 4 and 5 (S = TFE) is much less favorable.

The nearly constant k_2 values and activation parameters for ethanolysis of 1 in dioxane–EtOH ($n_{EtOH} = 0.6$–1.0; Table II) are understandable in view of the relatively small differences in gas-phase proton affinities between EtOH and most cyclic ethers[18] and the absence of large three-dimensional hydrogen bond structures in liquid EtOH.[21,22] The minor role which solvent polarity plays in determining the rates of solvolysis is readily reconciled with a transition state occurring early on the reaction coordinate (vide supra).

Since the above discussion of the trends in the rates as a function of solvent composition is perforce qualitative, we cannot decide, at the moment, whether or not a secondary effect is imposed on $\Delta G^{\ddagger}$ by changes in the diffusionally averaged "water structure" induced by the organic cosolvent in the region of high water concentration.[23] In the following section it will be argued that the $\Delta H^{\ddagger}$–$\Delta S^{\ddagger}$ compensation phenomena observed in t-BuOH–H_2O and possibly in dioxane–H_2O, respond to "water structure" perturbation but the possibility remains that $\Delta G^{\ddagger}$ is (almost) insensitive to changes in solvent structural integrity. In this context it is significant to note that in t-BuOH–H_2O the maximum rate is reached at a higher n_{H_2O} than in EtOH–H_2O.[2] This correlates with the

Table V. Thermodynamic Quantities of Transfer for 3 from Water to Aqueous Solvent Mixtures (25 °C)

Solvent mixture	n_{H_2O}	$\Delta H_{tr}°$, kcal mol^{-1}	$\Delta S_{tr}°$, eu	$\Delta G_{tr}°$, kcal mol^{-1}
Dioxane–H_2O	0.95	−0.2	+5	−1.75
Dioxane–H_2O	0.90	+0.2	+11	−2.90
Dioxane–H_2O	0.875	−0.5	+10	−3.40
t-BuOH–H_2O	0.95	+6.5	+27	−1.43
t-BuOH–H_2O	0.90	+4.4	+23	−2.36
t-BuOH–H_2O	0.80	−1.2	+8	−3.48
CH_3CN–H_2O	0.95	+0.6	+6	−1.23
CH_3CN–H_2O	0.925	+1.3	+11	−1.87
CH_3CN–H_2O	0.875	−1.4	+8	−3.68

higher n_{H_2O} for the maximum in "water structure" in *t*-BuOH–H_2O in comparison with that in EtOH–H_2O.

Solvent Effect on $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$. The data shown for the three solvent systems in Tables I, III, and IV reveal that the first addition of organic cosolvent to water leads to smaller $\Delta H^{\ddagger}$ values. In the previous section it was proposed that these lower $\Delta H^{\ddagger}$ values manifest an enhanced kinetic basicity of water as a result of cosolvent-induced, stronger C–H···OH_2 interaction in the transition state. Invariably, this exothermic shift of $\Delta H^{\ddagger}$ is largely compensated by an endothermic shift of $\Delta S^{\ddagger}$. This is expected for stronger binding of water in the transition state resulting in more extensive solvent reorientation. Compensatory behavior of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ is characteristic for many chemical processes in aqueous solutions.[24,25] On the basis of this concept, one would expect that $\Delta H^{\ddagger}$ changes smoothly upon lowering n_{H_2O}. The change in $\Delta G^{\ddagger}$ is then dependent on whether the reaction is enthalpy or entropy controlled. This situation is encountered for hydrolysis of 1 in CH_3CN–H_2O (Figure 5). For this solvent system it is known that there is no initial "structure-making" effect by small amounts of CH_3CN.[26,27] In sharp contrast, the $\Delta H^{\ddagger}$–$\Delta S^{\ddagger}$ pattern for solvolysis in dioxane–H_2O and *t*-BuOH–H_2O shows marked extrema at n_{H_2O} = 0.7 and 0.85, respectively (Figures 3 and 4). We suggest that these minima may find a reasonable explanation by consideration of effects due to changes in the diffusionally averaged "water structure" induced by the organic addendum.[28] Before proceeding to a qualitative interpretation of the trends in $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$, we will first consider the thermodynamic quantities of transfer for the model substrate **3** (Table V). It appears that for *t*-BuOH–H_2O pronounced extrema occur in $\Delta H_{tr}°$ and $\Delta S_{tr}°$ at n_{H_2O} = 0.95 which nearly coincides with the n_{H_2O} of 0.92 for maximal "water structure" as indicated by studies employing such techniques as low angle x-ray scattering,[29] ultrasound absorption,[30] and measurements of molar excess functions.[21] Since water–water hydrogen bonding will be stronger than solute–water hydrogen bonding,[31] the large and positive $\Delta H_{tr}°$ for n_{H_2O} = 0.95 will reflect the increase in enthalpy necessary under conditions of enhanced "water structure" for forming a cavity in the solvent to accommodate the solute. Despite this large $\Delta H_{tr}°$, the transfer of **3** is exothermic ($\Delta G_{tr}°$ = −1.43 kcal mol^{-1} at n_{H_2O} = 0.95) because of a dominant and positive $\Delta S_{tr}°$. We contend that this is the result of a release of strongly hydrogen bonded water molecules consistent with the occurrence of hydrophobic contacts between **3** and *t*-BuOH. As expected,[23] this entropy effect will reach an extremum at the n_{H_2O} of maximum structural integrity of the solvent. Since highly "structured water" is present around the active sites of several enzymes (as revealed by x-ray diffraction studies[8,32,33]), one wonders how far a similar entropy effect also operates on the binding process of the substrate to the active site. For example, it is known that the strongly ordered water molecules present in the groovelike active site of papain[34] are displaced by the substrate upon formation of the Michaelis complex. Notwithstanding the limitations of the above theory for aqueous binaries,[35] we like to suggest that a loss of the amount of solvent "structure" may help to overcome the unfavorable entropy inherent in bringing the substrate to the binding site.

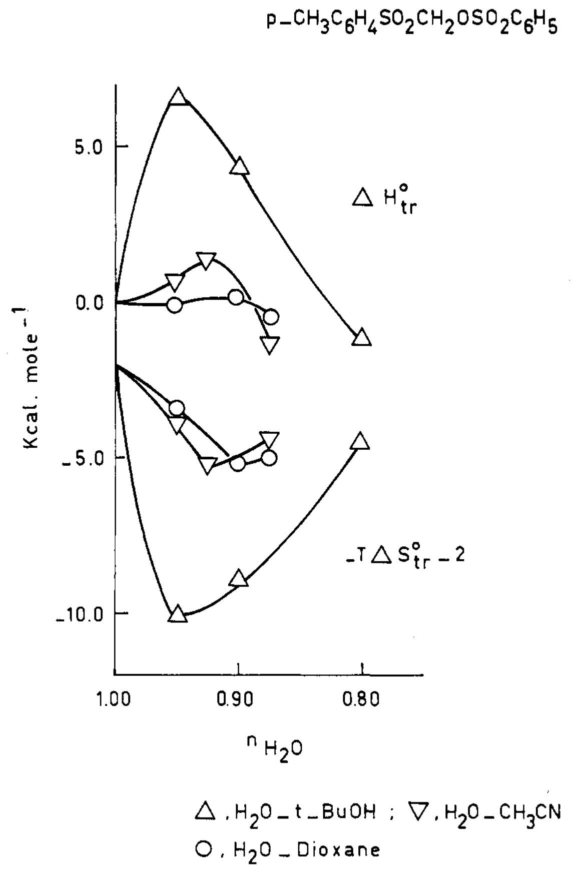


Figure 6. Plot of $\Delta H_{tr}°$ and $-T\Delta S_{tr}°$ vs. n_{H_2O} for transfer of **3** at 25 °C.

The extrema in $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ for solvolysis of 1 in *t*-BuOH–H_2O occur at a somewhat lower water concentration (n_{H_2O} = 0.85) than that of maximum water–water hydrogen bonding. Most likely, however, these extrema also reflect solvation effects originating from changes in "water structure".[36] We infer that the extrema arise because these "water structure" effects differ for the initial state and the transition state. This will be mainly due to the fact that for the transition state the loss of enthalpy as a result of cavity formation will be partly offset by strong CH···OH_2 interaction and which will increase with enhanced "water structure".[20] In view of the complex factors which affect the hydrolysis of 1 in *t*-BuOH–H_2O one would not expect, a priori, that the extrema in $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ and the maximum in "structuredness" of the solvent occur at exactly the same n_{H_2O}. In the hydrolysis of 1 and 2 "water structure" effects only modulate primary solvation changes induced by addition of the organic cosolvent and these effects should only be invoked to explain the extrema of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ in the water-rich region.

The sharp increase of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ in *t*-BuOH–H_2O below n_{H_2O} = 0.1 is remarkable. A similar behavior has been observed in a few other studies. According to Caldin and Bennetto,[37] and in agreement with Franks and Ives,[21] the addition of small quantities of water to alcohols leads to a stronger hydrogen bonded structure, build around water molecules, as compared with that in the unperturbed alcohol. It seems likely that the dramatic changes in $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ reflect this solvent structuring effect.

In the dioxane–H_2O system the compensatory changes in $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ between $n_{H_2O} = 0.2$ and 1.0 are qualitatively similar to those in t-BuOH–H_2O but now extrema are reached at $n_{H_2O} = 0.7$. Despite some controversy in the literature,[38] many authors agree that the presence of small amounts of dioxane enhances water–water interactions or, at least, does not break "water structure".[39,40] This is indicated by, for instance, dielectric relaxation times,[41,42] enthalpies of mixing,[43] ultrasound absorption,[44] and self-diffusion coefficients.[42] Consequently, the extrema in $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ may find their explanation in similar effects as proposed for t-BuOH–H_2O.[45] The $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ values for ethanolysis of **1** in dioxane–EtOH exhibit only small and smooth changes for $n_{EtOH} = 0.6$–1.0 and serve to indicate the much more pronounced role of solvation effects in dioxane–H_2O. However, there remains some ambiguity in the explanation of the kinetic data in dioxane–H_2O because of the less well characterized structural properties of this solvent and the possibility that the apolar dioxane molecules preferentially solvate **1** and/or the transition state to an unknown extent.[46]

Experimental Section

Materials. Compounds **1–3** were prepared by methods described previously.[5,11] The water used in all experiments was demineralized and distilled twice in an all-quartz distillation unit. Deuterium oxide (99.75% D_2O) was purchased from Merck AG (Uvasol quality) and was used as such. The organic solvents were of the highest grade available, usually obtained from Merck AG. 1,4-Dioxane was filtered through active, neutral alumina in a nitrogen atmosphere and was stored under nitrogen at 0 °C. The solvent mixtures were all made up by weight.

Kinetic Measurements. Pseudo-first-order rate constants (reproducible to within 2%) were obtained using the uv technique described previously.[2] Solvolysis was accurately first order for more than 3 half-lives. All hydrolyses were carried out in the presence of small amounts of HCl (Tables I–IV) in order to suppress catalysis by OH^-. The thermodynamic quantities of activation were calculated from k_{obsd} values at three to five temperatures between 25 and 45 °C. In all cases excellent Arrhenius plots were found. The accuracy of $\Delta H^{\ddagger}$ is usually ± 0.3 kcal mol^{-1} and of $\Delta S^{\ddagger}$ ± 1 eu. Since only trends in $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ are discussed in this paper, the problem of the choice of the standard state in the calculation of $\Delta S^{\ddagger}$ is not relevant.

Thermodynamic Quantities of Transfer. Heats of transfer ($\Delta H_{tr}{}^{\circ}$) for **3** (Table V) were obtained from solubility measurements between 15 and 30 °C following the procedure of Jolicoeur and Lacroix[47] with small modifications. (1) Saturated solutions were prepared by stirring the solution containing excess of **3** for 8–12 h. No solvolysis of **3** was observed during this period. (2) For the measurements of the absorbance, the samples were diluted with 96% ethanol (λ_{max} 223.5 nm, 20-mm quartz cells).

Since the transfer parameters for **3** are being discussed in connection with activation parameters for hydrolysis of **1** and **2**, we note that the corresponding thermodynamic quantities for transfer of one water molecule will be very small in comparison with the values listed in Table V.

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Registry No.—**1**, 26452-84-6; **1a**, 59711-29-4; **2**, 14894-56-5; **3**, 31081-09-1.

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