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Solvent Effects on the Spontaneous Hydrolysis of 2-(Aryloxy)tetrahydropyrans in Some Water-rich, Typically Nonaqueous Solutions

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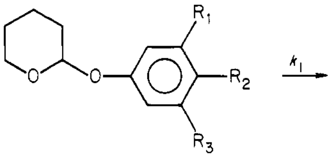
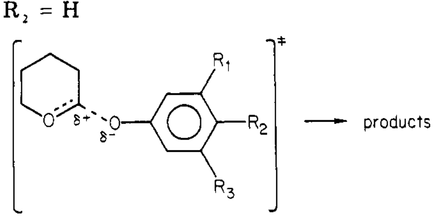
First-order rate constants (k_1) and thermodynamic activation parameters have been measured for the pH-independent hydrolysis of 2-(4-nitrophenoxy)tetrahydropyran (1) in water-rich MeCN–H_2O, Me_2SO–H_2O, and 1,4-dioxane–H_2O. All cosolvents retard the rate of hydrolysis. Excellent linear correlations are found between ln k_1 and the mole fraction of the cosolvent (n_{cs}), ln [H_2O], and δ_w (the chemical shift of the water protons). The linear correlation between ln k_1 and the Kirkwood function is somewhat less satisfactory. In the three solvent systems, isodielectric rate constants exhibit an inverse relationship with the polarizability of the medium, despite the fact that the highly dipolar transition state is much more polarizable than the initial state. However, dispersion effects do not always increase with increasing polarizability, as shown by an analysis indicating the prevailing contribution of the ionization potentials. It appears that the kinetic solvent effects are to a large extent determined by dipolar interactions involving extensive hydrogen bonding. The solvent effects on the thermodynamic activation parameters for hydrolysis of 1 reveal that the medium strongly affects $\Delta S^\ddagger$ but leaves $\Delta H^\ddagger$ almost unchanged. These findings are rationalized by invoking the importance of cosolvent–water interactions in the solvation of the transition state. Rate measurements using 2-(3,5-dinitrophenoxy)tetrahydropyran reveal essentially similar results.

Chemists have been intrigued by the effect of solvents on chemical reactivity for more than a century.[1,2] Many approaches have been used to interpret these solvent effects, and these attempts are usually couched in terms of transition-state theory. Among the large number of solvent systems that have been examined, water and water-rich mixed aqueous solvents often exhibit the most peculiar behavior.[3] In the latter systems, initial states and transition states may interact differently with the medium via hydrogen-bonding, dipole–dipole, dipole-induced dipole, London dispersion, and hydrophobic interactions. A quantitative dissection into contributions of these types of interactions has not been achieved for any system. For all molecules the only omnipresent interaction mechanism involves London dispersion forces.[4,5] Although their importance has been recognized in such processes as liquefaction and crystallization of hydrocarbons and substrate–enzyme binding, surprisingly little attention has been focused on their role in solvent effects.[6] In these studies of medium effects it is frequently assumed that the polarizability (α) of the solute and solvent is the only important parameter. For example, a "polarizability function" has been proposed to rationalize solvent effects on a quantitative basis.[7]

Very few systematic studies have been made to assess the importance of London dispersion forces in mixed aqueous solvents. In a series of important papers, this problem was addressed by Grunwald et al.,[8] who showed, inter alia, that the relative acid strength of picric acid relative to acetic acid is increased by almost 2 orders of magnitude in the solvent series water, methanol, ethanol.[8a] This behavior contrasts with the dissociation constant of trichloroacetic acid, which remains nearly constant. These observations were explained in terms of an increase in London dispersion interactions with the highly polarizable picrate anion upon displacement of water by ethanol in its solvation shell. This interpretation was supported by model calculations on a related equilibrium process.



1, $R_1 = R_3 = H$; $R_2 = NO_2$
2, $R_1 = R_3 = NO_2$; $R_2 = H$



We have examined a simple organic reaction in an effort to single out the contribution of London dispersion forces to a kinetic solvent effect. The reaction involves the spontaneous (i.e., pH independent) hydrolysis of the 2-(aryloxy)tetrahydropyrans 1 and 2. The solvent deuterium isotope effect of about unity,[9] the small entropy of activation,[9] the large dependence of the first-order rate constant (k_1) on solvent polarity,[9] the large ρ^- value (2.7 ± 0.1),[10] and the small and negative volume of activation in

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Table I. First-Order Rate Constants and Thermodynamic Activation Parameters for the pH-Independent Hydrolysis of 1 in Some Mixed Aqueous Solvents at 40 °C

solvent system	n_{cs}[a]	$10^5 k_1$,[b] s^{-1}	$\Delta H^\ddagger$, kJ mol^{-1}	$\Delta S^\ddagger$, J mol^{-1} K^{-1}
H_2O	0.000	31.2 ± 0.7[c]	105 ± 2	24 ± 8
MeCN-H_2O	0.030	23.6 ± 0.7		
MeCN-H_2O	0.060	15.4 ± 0.4	99 ± 4	-3 ± 12
MeCN-H_2O	0.090	8.91 ± 0.09	98 ± 1	-8 ± 3
MeCN-H_2O	0.149	3.65 ± 0.06	99 ± 2	-13 ± 6
MeCN-H_2O	0.210	1.72 ± 0.03	100 ± 3	-17 ± 11
Me_2SO-H_2O	0.049	16.5 ± 0.5		
Me_2SO-H_2O	0.099	9.2 ± 0.2	100 ± 1	-4 ± 3
Me_2SO-H_2O	0.153	5.33 ± 0.09		
Me_2SO-H_2O	0.200	2.61 ± 0.05	104 ± 1	-2 ± 4
Me_2SO-H_2O	0.251	1.52 ± 0.01		
Me_2SO-H_2O	0.300	0.861 ± 0.003	97 ± 2	-34 ± 5
Me_2SO-H_2O	0.346	0.53 ± 0.02		
Me_2SO-H_2O	0.397	0.320 ± 0.006	104 ± 3	-18 ± 9
dioxane-H_2O	0.010	26.4 ± 0.6		
dioxane-H_2O	0.020	20.0 ± 0.3	104 ± 2	16 ± 5
dioxane-H_2O	0.030	15.7 ± 0.3		
dioxane-H_2O	0.040	12.5 ± 0.3	99 ± 2	-3 ± 7
dioxane-H_2O	0.050	10.1 ± 0.2		
dioxane-H_2O	0.060	8.2 ± 0.2	96 ± 2	-17 ± 5
dioxane-H_2O	0.080	5.0 ± 0.1	100 ± 2	-9 ± 7

[a] Mole fraction of the organic solvent component. All solutions contained 10^{-3} M of NaOH. [b] The estimated errors have been obtained from at least three measurements. [c] Lit.[10] 32.2 × 10^{-5} s^{-1} at 39.2 °C, $\Delta H^\ddagger$ = 101 ± 0.8 kJ mol^{-1}, $\Delta S^\ddagger$ = 9 ± 3 J mol^{-1} K^{-1}.

water[11] are all consistent with a unimolecular, S_N1-type reaction proceeding via a dipolar and late transition state.[10] We envisioned the possibility that the substantial negative charge delocalization in the transition state might show up in a relative large contribution of London dispersion forces in the overall solvent effects. In order to avoid complications arising from hydrophobic interactions, we have studied the hydrolysis of 1 and 2 in three typically nonaqueous (TNA) solvent systems,[12] i.e., in mixtures of water with acetonitrile, dimethyl sulfoxide (Me_2SO), and 1,4-dioxane. In these binary systems, the organic component is "water-structure breaking" and participates in appreciable hydrogen-bonding interactions with water, thus hampering the formation of hydrophobic hydration shells around apolar solutes.

Results and Discussion

First-order rate constants (k_1) for the spontaneous hydrolysis of 1 in MeCN-H_2O, Me_2SO-H_2O, and 1,4-dioxane-H_2O at 40 °C are listed in Table I. The mole fraction range of the organic cosolvent (n_{cs}) was chosen to give a nearly equal change in the dielectric constant. The three cosolvents all retard the hydrolysis. The ln k_1 values (which are proportional to $\Delta G^\ddagger$) in the three solvent systems have been correlated with five solvent parameters and the results are shown in Table II. Generally, there is an excellent linear correlation between ln k_1 and n_{cs} (Figure 1). However, the slopes of the lines are quite different (dioxane > MeCN > Me_2SO). Thus, the solvent effect on $\Delta G^\ddagger$ does not simply reflect the replacement of water molecules by non-hydrogen-bond donating cosolvent molecules in the medium. The linear correlations between $\Delta G^\ddagger$ and ln [H_2O] are equally satisfactory. In several previous studies, the slope of such regression curves has been given mechanistic significance. For example, in the hydrolysis of p-nitrotrifluoroacetanilide Haake et al.[13]

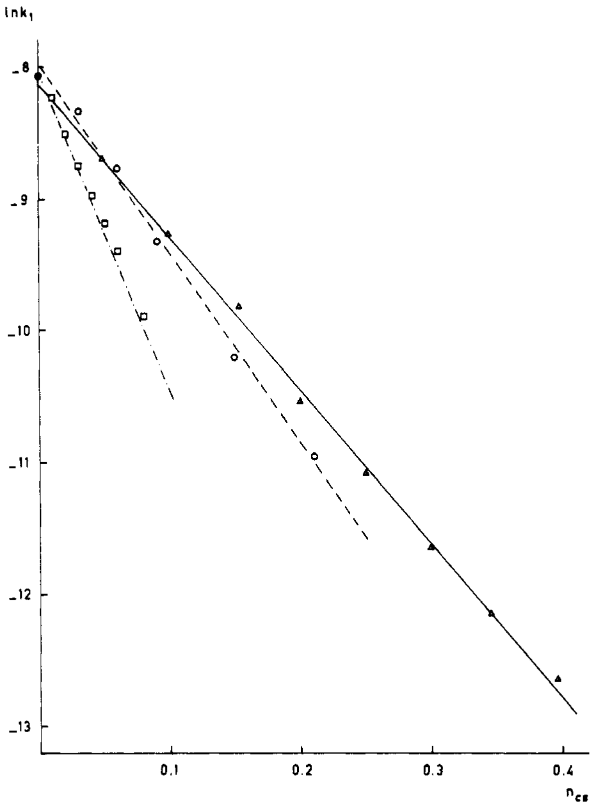

Figure 1. Plot of ln k_1 vs. mole fraction of the cosolvent (n_{cs}) for the spontaneous hydrolysis of 1 at 40 °C: ○, MeCN-H_2O; △, Me_2SO-H_2O; □, 1,4-dioxane-H_2O.

Table II. Correlation of the Gibbs Free Energy of Activation with Solvent Parameters for the Spontaneous Hydrolysis of 1 at 40 °C in Some Mixed Aqueous Solutions

solvent system	solvent parameter[a]	slope[c]	r	standard error
MeCN-H_2O	n_{cs}	-14.4 ± 0.3	0.9979	0.033
Me_2SO-H_2O	n_{cs}	-11.6 ± 0.1	0.9992	0.023
dioxane-H_2O	n_{cs}	-23.0 ± 0.2	0.9994	0.008
MeCN-H_2O	ln [H_2O]	5.3 ± 0.1	0.9976	0.035
Me_2SO-H_2O	ln [H_2O]	3.65 ± 0.03	0.9993	0.022
dioxane-H_2O	ln [H_2O]	5.35 ± 0.06	0.9989	0.011
MeCN-H_2O	$(\epsilon_r - 1)/(2\epsilon_r + 1)$	1090 ± 40	0.9947	0.053
Me_2SO-H_2O	$(\epsilon_r - 1)/(2\epsilon_r + 1)$	2900 ± 180	0.9723	0.132
dioxane-H_2O	$(\epsilon_r - 1)/(2\epsilon_r + 1)$	345 ± 6	0.9975	0.016
MeCN-H_2O	δ_w	0.127 ± 0.005	0.9921	0.064
Me_2SO-H_2O	δ_w	0.17 ± 0.01	0.9605[b]	0.157
dioxane-H_2O	δ_w	0.242 ± 0.003	0.9990	0.011
MeCN-H_2O	$E_T(30)$	0.51 ± 0.05	0.9653	0.134
Me_2SO-H_2O	$E_T(30)$	0.41 ± 0.01	0.9917	0.072
dioxane-H_2O	$E_T(30)$	0.33 ± 0.01	0.9871	0.038

[a] n_{cs} = mole fraction of the organic solvent component. [b] If the points n_{cs} = 0.00–0.05 are left out, the correlation is greatly improved, see text. [c] Errors in the slope estimated on basis of the standard error.

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(11) (a) Haak, J. R.; Engberts, J. B. F. N., to be published. (b) Stereoelectronic factors demand that the hydrolysis is much faster for the substrate with an axial leaving group. Compare: Chandrasekhar, S.; Kirby, A. J.; Martin, R. J. *J. Chem. Soc., Perkin Trans. 2* **1983**, 1619.

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Table III. Values of ln k_1 for the Spontaneous Hydrolysis of 1 (40 °C) in Some Mixed Aqueous Solvents at Constant Dielectric Constant. Effect of Polarizability[a]

ϵ_r	MeCN-H_2O		Me_2SO-H_2O		dioxane–H_2O	
(40 °C)	ln k_1	α	ln k_1	α	ln k_1	α
73	−8.07	1.455	−8.59	1.702	−8.06	1.444
70	−8.73	1.591	−10.45	2.750	−8.26	1.504
68	−9.09	1.666	−11.24	3.189	−8.40	1.547
66	−9.46	1.749	−12.02	3.634	−8.51	1.583
64	−9.82	1.817	−12.73	4.034	−8.65	1.626

[a] Obtained from $\alpha = n_w\alpha_w + n_{cs}\alpha_{cs}$ (see text).

identify these slopes with the order in water and changes in slope are used to assign changes in the reaction mechanism. We emphasize, however, that the usefulness of these slopes as kinetic parameters is at present rather poorly understood. Apart from such complications as preferential solvation of the substrate,[14] Langford et al.[15] have discussed the theoretical and practical difficulties in defining higher order rate constants for solvolytic reactions.

The use of the Kirwood function[16] $(\epsilon_r - 1)/(2\epsilon_r + 1)$ as a solvent parameter is based on the assumption that purely electrostatic solvent effects are adequately expressed by this equation.[3] For our systems, the linear correlation is mediocre for MeCN-H_2O and Me_2SO–H_2O but rather good for dioxane–H_2O (Figure 2). These findings are not unexpected since it is known that particularly mixed aqueous reaction media may even show freakish results.[17]

Interestingly, the changes in ΔG^* for hydrolysis of 1 in MeCN-H_2O and dioxane–H_2O correlate quite well with the chemical shift of the water protons (δ_w) in the binary mixtures.[18] These chemical shifts largely reflect changes in the strengths and average number of hydrogen bonds per water molecule, upfield shifts indicating weakening of hydrogen bonding.[19] Therefore, the linear relationships are consistent with the idea that the rates mainly reflect the capability of the medium to stabilize the dipolar transition state by hydrogen-bonding interactions. The modest correlation for Me_2SO–H_2O can be greatly improved if δ_w values between $n_{cs} = 0.00$ and 0.05 (very small change of δ_w in this region) are omitted in the correlation. We then find a linear relationship (slope 0.144 ± 0.004, $r = 0.9962$, standard error 0.044) which is as good as those for the two other solvent systems.

A really microscopic solvent parameter is the $E_T(30)$ value.[2] Now the best linear relationship is found for Me_2SO–H_2O. Generally, the correlations are somewhat less satisfactory than those with the Kirkwood function. However, for the latter solvent parameter the individual slopes differ more widely than those for the correlations with $E_T(30)$.

The first question to be asked is as to whether dispersion effects contribute significantly to the trends in the solvent effects. In order to make meaningful comparisons between the three binary solvents, isodielectric rate constants were calculated via plots of ln k_1 vs. n_{cs} using n_{cs} values directly read from plots of ϵ_r vs. n_{cs}.[20] Of course, the definition of polarizability of a mixed aqueous solvent constitutes a problem. For the three mixtures we have calculated "effective" polarizabilities from those of water (α_w) and of the cosolvent (α_{cs}) assuming ideal behavior, i.e., $\alpha = n_w\alpha_w + n_{cs}\alpha_{cs}$. For MeCN-$H_2O$ and dioxane–H_2O the obtained values[21] can be compared with those calculated by using the Lorentz–Lorenz equation:[22]

$$\alpha = \left(\frac{3(n^2-1)}{4\pi(n^2+2)}\right)\left(\frac{M}{\rho N}\right)$$

in which n is the refractive index, M the molecular mass, ρ the density, and N Avogadro's number. Individual values in the two sets of α's did not differ by more than 1%, thus affording some physical basis for the supposed ideal behavior.

Isodielectric rate constants (k_1^{ϵ}) and α values for the three aqueous mixtures are listed in Table III. In contrast to expectation, the rate constants *decrease* with increasing α, the deviation from linearity of ln k_1^{ϵ} with α becoming larger with decreasing dielectric constant (Table IV).

Table IV. Correlation of ln k_1 (at Constant ϵ_r) vs. Polarizability for the Spontaneous Hydrolysis of 1 in MeCN-H_2O, Me_2SO-H_2O, and Dioxane-H_2O at 40 °C

ϵ_r	slope[a]	r	standard error, %
73	−2.08 ± 0.06	0.9996	0.7
70	−1.6 ± 0.2	0.9899	13.4
68	−1.6 ± 0.3	0.9855	20.5
66	−1.6 ± 0.3	0.9800	29.5
64	−1.5 ± 0.3	0.9780	35.8

[a] See note for Table II.

Table V. Values of ln k_1 for the Spontaneous Hydrolysis of 1 (40 °C) in Some Mixed Aqueous Solvents at Constant $E_T(30)$. Effect of Polarizability[a]

	MeCN-H_2O		Me_2SO-H_2O		dioxane–H_2O	
$E_T(30)$	ln k_1	α	ln k_1	α	ln k_1	α
62.0	−8.08	1.458	−8.16	1.460	−8.11	1.458
61.0	−8.39	1.522	−8.37	1.578	−8.26	1.504
60.0	−8.70	1.586	−8.63	1.722	−8.58	1.605
59.0	−9.14	1.678	−8.94	1.900	−8.92	1.709
58.0	−9.76	1.804	−9.29	2.095	−9.32	1.834
57.0	−10.69	2.000	−9.66	2.305	−9.73	1.963

[a] See note a for Table III.

Table VI. Correlation of ln k_1 (at Constant $E_T(30)$) vs. Polarizability for the Spontaneous Hydrolysis of 1 in MeCN-H_2O, Me_2SO-H_2O, and Dioxane-H_2O at 40 °C

$E_T(30)$	slope[a]	r	standard error, %
62.0	−36 ± 10	0.9593	0.9
61.0	−1.1 ± 1.3	0.5759	4.8
60.0	0.2 ± 0.7	0.2617	4.7
59.0	0.5 ± 0.8	0.5234	8.7
58.0	1.0 ± 1.1	0.6314	16.4
57.0	1.4 ± 2.4	0.4740	41.2

[a] See note c for Table II.

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(13) (a) Henderson, J. W.; Haake, P. *J. Org. Chem.* **1977**, *42*, 3989. (b) Shaskus, J.; Haake, P. *Ibid.* **1983**, *48*, 2036.

(14) Remerie, K.; Engberts, J. B. F. N. *J. Phys. Chem.* **1983**, *87*, 5449.

(15) Langford, C. H.; Tong, J. P. K. *Acc. Chem. Res.* **1977**, *10*, 258.

(16) Kirkwood, J. G. *J. Chem. Phys.* **1934**, *2*, 351.

(17) Abraham, M. H. *Prog. Phys. Org. Chem.* **1974**, *11*, 1.

(18) These shifts were determined relative to the methyl signal of bis(methylsulfonyl)methane: Karzijn, W.; Engberts, J. B. F. N. *Recl. Trav. Chim. Pays-Bas* **1976**, *96*, 95. Subsequent measurements of δ_w in 1,4-dioxane–H_2O using Me_4Si and DSS as inert references did not reveal significant differences: Remerie, K. Ph.D. Thesis, Groningen, 1984.

(19) Wen, W.-Y.; Hertz, H. G. *J. Solution Chem.* **1972**, *1*, 17.

(20) These isodielectric rate constants are probably more reliable than those obtained directly from plots of ln k_1 vs. $(\epsilon_r - 1)/(2\epsilon_r + 1)$.

(21) Unfortunately, no sufficiently accurate data are available for Me_2SO-H_2O.

(22) Moelwyn-Hughes, E. A. "Physical Chemistry"; London: Cambridge University Press: 1940; p 382.

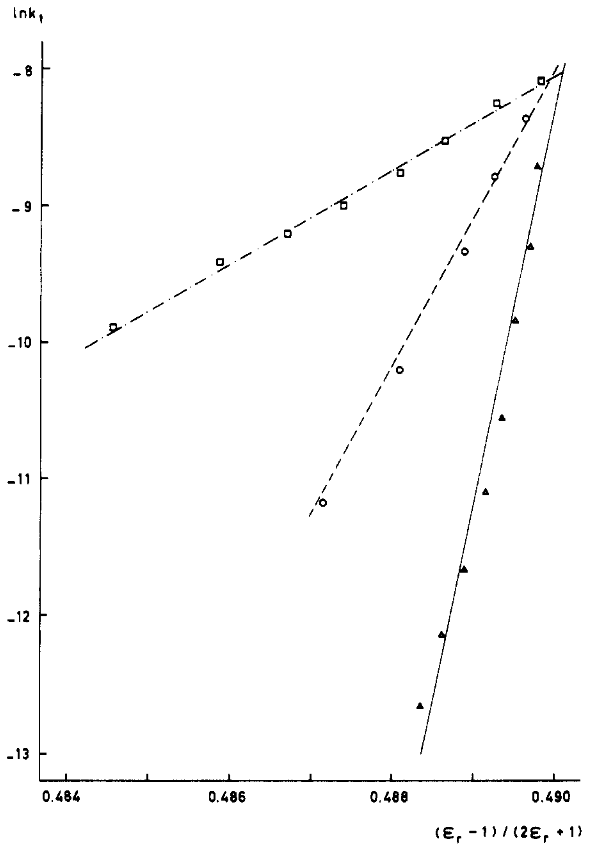

Figure 2. Plot of $\ln k_1$ vs. the Kirkwood function for the spontaneous hydrolysis of 1 at 40 °C: ○, $MeCN-H_2O$; △, Me_2SO-H_2O; □, 1,4-dioxane–H_2O.

A similar analysis was performed by using the microscopic solvent parameter $E_T(30)$. As can be seen from the data in Tables V and VI, there is no significant correlation between the isosolvatochromic free energies of activation and α.

In order to rationalize these results, the factors that determine the dispersion cohesive energy (E_L) between two molecules A and B are examined more closely:[5]

$$E_L = \left(\frac{-3I_A I_B}{2(I_A + I_B)}\right)\left(\frac{\alpha_A \alpha_B}{r^6}\right)$$

Herein, A refers to solvent and B to the solute, I is the ionization potential, α the polarizability, and r the intermolecular distance. In discussions of the influence of London dipersion forces on solvent effects,[2] commonly, most attention is paid to the $\alpha_A\alpha_B$ term, but the more complex dependence on I_A and I_B is important as well. For the three cosolvents the variation in ionization potential is rather small. However, there is a large change in ionization potential during the activation process. Based on the ionization potentials[23] of 4-nitrobenzene, phenol, and diethyl ether of 9.9, 8.8, and 9.5 eV, respectively, we estimate that for the substrate 1 the ionization potential will be about 9.5 eV. Since the transition state for the spontaneous hydrolysis of 1 occurs late on the reaction coordinate (vide supra), its ionization potential will resemble that of the 4-nitrophenoxide anion. Taking into account the electron affinity of the phenyl radical (2.36 eV)[24] and the electron-withdrawing properties of the 4-nitro substituent, we estimate an ionization potential of ca. 3 eV for the transition state.[25] Thus, the contribution of the changes in polarizability in the solvent effects will be clearly overcompensated by the term arising from the ionization potentials, consistent with the inverse relation between $\ln k_1^{\epsilon}$ and α (Table IV). The absence of any correlation between the isosolvatochromic rate constants and α (Table VI) probably finds its origin in the fact that the $E_T(30)$ values already contain contributions from dispersion forces.[2]

Table VII. First-Order Rate Constants for the Spontaneous Hydrolysis of 2 in Some Mixed Aqueous Solvents at 39.3 °C[a]

solvent system	n_{cs}	$10^5 k_1$, s^{-1}
H_2O	0.000	58.5 ± 1.0[b]
$MeCN-H_2O$	0.030	42.8 ± 0.4
$MeCN-H_2O$	0.060	28.4 ± 0.8
$MeCN-H_2O$	0.090	18.9 ± 0.4
Me_2SO-H_2O	0.050	29.4 ± 0.3
Me_2SO-H_2O	0.100	19.5 ± 0.1
Me_2SO-H_2O	0.150	10.6 ± 0.2
Me_2SO-H_2O	0.200	5.90 ± 0.04
dioxane–H_2O	0.010	46.9 ± 0.3
dioxane–H_2O	0.020	35.8 ± 0.8
dioxane–H_2O	0.030	28.6 ± 0.3
dioxane–H_2O	0.040	23.4 ± 0.1

[a] See footnotes a and b for Table I. [b] Lit.[10] 65 × 10^{-5} s^{-1} at 39 °C and ionic strength 1.0 M (KCl).

We conclude that the difference in polarizability or, in Grunwald's terms,[8] delocalization of virtual electronic oscillators, between initial and transition state in the spontaneous hydrolysis of 1 is not large enough to induce rate accelerations due to dispersion effects if a more polarizable organic cosolvent is added to water. Instead, the correlation between $\Delta G^{\ddagger}$ and the Kirkwood function or δ_w values provides evidence that the solvent effects are largely dipolar in nature and strongly dominated by hydrogen bonding. The overwhelming importance of solvation of the dipolar transition state is further substantiated by the solvent effects on the thermodynamic activation parameters (Table I). Contrary to many organic reactions in water-rich binary mixtures which show strong $\Delta H^{\ddagger} - \Delta S^{\ddagger}$ compensation effects,[3] the solvent effects on $\Delta G^{\ddagger}$ for hydrolysis of 1 are strongly dominated by changes in $\Delta S^{\ddagger}$. Addition of the cosolvent to water is accompanied by a strong decrease of $\Delta S^{\ddagger}$ while $\Delta H^{\ddagger}$ is hardly affected. In the absence of thermodynamic parameters for the transfer of the substrate from water to the mixed solvents, an interpretation of these data can only be speculative. We suggest that the reduced polarity and water content of the medium upon addition of the cosolvent is partly offset by water polarization effects[26] as a result of water–cosolvent hydrogen-bond interactions. Solvation of the transition state by these water–cosolvent complexes costs entropy[26,27] but will be favorable in enthalpy, thereby keeping $\Delta H^{\ddagger}$ almost constant.

First-order rate constants and correlations with solvent parameters for the spontaneous hydrolysis of 2-(3,5-dinitrophenoxy)tetrahydropyran (2) are listed in Tables VII and VIII, respectively. This substrate is slightly more reactive than 1 but lacks the direct resonance interaction

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(25) The difference in ionization potential between phenol and 4-nitrophenol is ca. 1 eV, see ref 23.

(26) Compare: (a) Remerie, K.; Engberts, J. B. F. N. *J. Org. Chem.* **1981**, *46*, 3543. (b) Menninga, L.; Engberts, J. B. F. N. *J. Am. Chem. Soc.* **1976**, *98*, 7652.

(27) Compare: Cox, B. G.; Parker, A. J. *J. Am. Chem. Soc.* **1973**, *95*, 408.

Table VIII. Correlation of First-Order Rate Constants with Solvent Parameters for the Spontaneous Hydrolysis of 2 at 39.3 °C in Some Mixed Aqueous Solvents

solvent system	solvent parameter[a]	slope	r	standard error
$MeCN-H_2O$	n_{cs}	-12.6 ± 0.4	0.9982	0.018
Me_2SO-H_2O	n_{cs}	-11.2 ± 0.3	0.9979	0.030
dioxane–H_2O	n_{cs}	-23.3 ± 0.4	0.9989	0.009
$MeCN-H_2O$	ln $[H_2O]$	4.5 ± 0.2	0.9975	0.021
Me_2SO-H_2O	ln $[H_2O]$	3.3 ± 0.1	0.9976	0.032
dioxane–H_2O	ln $[H_2O]$	5.20 ± 0.08	0.9992	0.008
$MeCN-H_2O$	$(\epsilon_r - 1)/(2\epsilon_r + 1)$	1180 ± 50	0.9948	0.021
Me_2SO-H_2O	$(\epsilon_r - 1)/(2\epsilon_r + 1)$	4500 ± 500	0.9726	0.107
dioxane–H_2O	$(\epsilon_r - 1)/(2\epsilon_r + 1)$	380 ± 10	0.9971	0.014
$MeCN-H_2O$	δ_w	0.093 ± 0.006	0.9930	0.035
Me_2SO-H_2O[b]	δ_w	0.25 ± 0.05	0.9087	0.191
dioxane–H_2O	δ_w	0.243 ± 0.005	0.9987	0.010
$MeCN-H_2O$	$E_T(30)$	0.30 ± 0.02	0.9911	0.040
Me_2SO-H_2O	$E_T(30)$	0.32 ± 0.02	0.9909	0.062
dioxane–H_2O	$E_T(30)$	0.27 ± 0.02	0.9971	0.027

[a] n_{cs} = mole fraction of the organic solvent component. [b] See note b of Table II.

in the transition state (1, $\sigma_{p\text{-}NO_2} = 1.27$; 2, $2\sigma_{m\text{-}NO_2} = 1.42$). Despite this difference in the details of charge delocalizability in the transition state, the trends in the correlations between ln k_1 and n_{cs}, ln $[H_2O]$, the Kirkwood function, δ_w, and $E_T(30)$ for $MeCN-H_2O$, Me_2SO-H_2O, and dioxane–H_2O are very similar for hydrolysis of 1 and 2. Correlations with solvent polarizability were carried out in a similar fashion as for 1 (Tables IX–XII) and again the conclusions fully substantiate those drawn above for the hydrolysis of 1.

Experimental Section

Materials. The 2-(aryloxy)tetrahydropyrans 1[28] and 2[10] were prepared according to literature procedures and were stored at -40 °C. Acetonitrile (Baker) was of the best grade available and was used as such. Dimethyl sulfoxide (Baker analyzed grade) was stored on molecular sieves before use. 1,4-Dioxane (Merck, Uvasol) was filtered through active, basic alumina and stored in the dark at -40 °C. Water was demineralized and distilled twice in an all-quartz distillation unit. All solvent mixtures were made up by mass and contained 10^{-3} M of NaOH to suppress acid catalysis and to allow hydrolysis to be followed by the appearance of the phenoxide anion.

Kinetic Measurements. First-order rate constants (k_1) were measured by following the appearance of 4-nitrophenoxide anion (at 400 nm) or 3,5-dinitrophenoxide anion (at 400 nm) in a Cary 210 or a Beckman Model 24 spectrophotometer equipped with a thermostated cell compartment. In a typical experiment 3–10 μL of a stock solution in MeCN containing 10^{-2} M of substrate was added to 3 mL of the solvent mixture. For half-lives less than 10 h the reactions were followed to completion. Otherwise the reactions were followed for at least 3 half-lives and Guggenheim's method was employed for the calculation of the k_1 values. All rate constants were at least measured in triplicate. Thermodynamic activation parameters were obtained from rate constants in the range 40–60 °C for the binary mixtures and 30–50 °C for water. Analysis in terms of the Eyring equation was carried out by using a least-squares program. Errors in ΔH^* and ΔS^* were estimated from the standard deviation of the regression.[29]

Solvent Parameters. These were taken from the literature, occasionally via graphical interpolation of data presented as a function of mole fraction or temperature.[30]

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Supplementary Material Available: Rate constants for the spontaneous hydrolysis of 2 (39.3 °C) in $MeCN-H_2O$, Me_2SO-H_2O, and 1,4-dioxane–H_2O at constant ϵ_r and $E_T(30)$ and correlations with polarizability (Tables IX–XII) (4 pages). Ordering information is given on any current masthead page.

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