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Solvent Polarity and Organic Reactivity in Mixed Solvents: Evidence Using a Reactive Molecular Probe To Assess the Role of Preferential Solvation in Aqueous Alcohols

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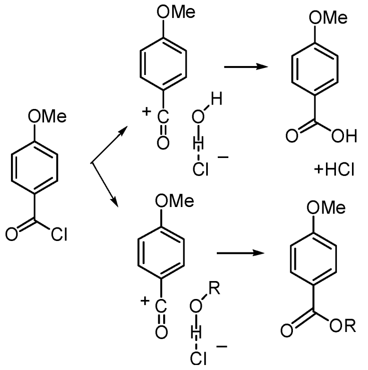

Product selectivities [S = ([ester product]/[acid product]) × ([water]/[alcohol solvent])] are reported for solvolyses of *p*-methoxybenzoyl chloride (**2**) in aqueous methanol, ethanol, 2,2,2-trifluoroethanol, *n*-propyl alcohol, isopropyl alcohol, and *tert*-butyl alcohol at 25, 35, and 45 °C. S values are small and depend significantly on the alcohol cosolvent, varying from 1.3 in methanol to 0.1 in *tert*-butyl alcohol, but S depends only slightly on the solvent composition, and on the temperature. As S adjusts the product ratios for changes in bulk solvent compositions, it is suggested that preferential solvation by either alcohol or water at the reaction site is not a major factor influencing rates or products. Logarithms of rates of solvolyses of **2** correlate well with Kosower Z values (based on solvatochromism). In contrast, another solvatochromic polarity index, $E_T(30)$, shows "dispersion" in correlations with the solvent ionizing power parameter, Y_{OTs}, probably due to aromatic ring and other solvation effects.

Introduction

Organic reactions are frequently carried out in aqueous/organic solvent mixtures for practical reasons: e.g., to increase solubilities for reactions in aqueous media or to increase rates of reactions in organic media. For kinetic and mechanistic studies, mixed solvents have an advantage in providing the opportunity to vary continuously the reaction conditions, in contrast to the more abrupt changes arising from studies of substituent effects or the very subtle changes arising from secondary kinetic isotope effects. The main disadvantage of mixed solvents is that interpretations of the data are more complex, but an important advantage of studies of nucleophilic substitutions in aqueous alcohols is that two products are formed, and quantitative product studies provide additional data helping to unravel the complexity.[1]

We now report an investigation of the possibility that rates and products of organic reactions in mixed alcohol/water mixtures could be influenced by preferential solvation, alternatively referred to as solvent sorting,[1] in which one or more solvation shells differ significantly in molar composition from the bulk solvent mixture. As might be expected, preferential solvation is particularly important for salts in mixtures of water and organic cosolvents,[2a] but it also occurs for the polar probe dye

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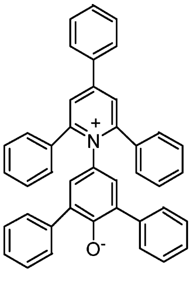
indicators used to determine solvation indices:[2b] e.g., for the solvent polarity index $E_T(30)$, based on the solvent dependence of electronic transitions (solvatochromism) of the pyridinium *N*-phenolate betaine dye (**1**). There is a relatively large increase in $E_T(30)$ when small amounts of water are added to aprotic solvents (e.g., acetonitrile[3a] and dioxane[3a]), providing strong evidence for preferential solvation by water. Aprotic organic cosolvents would be expected to be more prone to preferential solvation than alcohol cosolvents, but ^{1}H and ^{13}C NMR of **1**[4] and recent intermolecular ^{1}H-NOESY NMR of small neutral organic solutes[5] provided evidence for preferential solvation for various binary solvents including aqueous alcohols.

There is much current interest in preferential solvation from observations of solvatochromism of binary aqueous mixtures,[3b] but it is very difficult to separate preferential solvation from other solvent effects.[6] The possible role of preferential solvation in solvolytic reactivity is relevant to innumerable mechanistic studies of organic substrates in mixed solvents, and has been considered previously,[1,7−9] but was not thought to be a "major factor".[1] Recent developments[5,6] have led us to investigate further.

Inert chemical probes are often used for the characterization of solvent mixtures.[10] A completely independent and direct probe of the solvent composition around the reaction site is the product ratio, when alcohols or water react competitively as nucleophiles with a reactive molecular probe via an extremely short-lived intermediate. We now report applications of this alternative approach to studies of solvent effects in binary mixtures of water and various alcohols, and we discuss solvent effects other than preferential solvation, which could influence solvatochromism of **1**.



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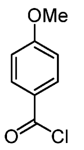

2

The chosen probe substrate was *p*-methoxybenzoyl chloride (**2**), which reacts in alcohol/water mixtures to form a mixture of an ester and an acid. Product studies and salt effects are consistent with such rapid reactions of solvent-separated ion pair intermediates with protic solvents that reaction via a more dissociated ("free") cation is not a major product-determining step.[11−13] When product selectivities (*S*) are defined by using eq 1, where

$$S = ([\text{ester product}]/[\text{acid product}]) \times ([\text{water}]/[\text{alcohol solvent}]) \quad (1)$$

the square brackets refer to concentrations in moles/liter, product ratios are adjusted for changes in bulk solvent compositions (i.e., ignoring preferential solvation). *S* values were found to be approximately independent of solvent composition for solvolyses of **2** in methanol/water and ethanol/water at 25 °C.[11] We now extend our previous work, and discuss the implications for the effect of preferential solvation on reactivity in alcohol/water mixtures.

TABLE 1. Product Selectivities (*S*, Eq 1) for Solvolyses of *p*-Methoxybenzoyl Chloride (2) in Methanol/Water (% v/v)

	25 °C			35 °C	45 °C
% v/v	set A[a]	set B[b,c]	set C[b]	set C[b]	set C[b]
90	1.36	1.35	1.39	1.39	1.25
80	1.31	1.24	1.19	1.36	1.34
70		1.26	1.31	1.32	1.27
60	1.23	1.31	1.32	1.31	1.19
50		1.32	1.25	1.31	1.25
40	1.35	1.37	1.26	1.34	1.18
30		1.39	1.27	1.40	1.52
20	1.43	1.37	1.30	1.32	
10		1.40	1.28	1.47	

[a] Data from from ref 11. [b] From at least duplicate HPLC analyses of at least two independent samples; typical errors ±3%. [c] Reference 14.

TABLE 2. Product Selectivities (*S*, Eq 1) for Solvolyses of *p*-Methoxybenzoyl Chloride (2) in Ethanol/Water (% v/v)

	25 °C			35 °C	45 °C
% v/v	set A[a]	set B[b]	set C[c]	set C[c]	set C[c]
90	0.71	0.71	0.55	0.64	0.66
80	0.64	0.66	0.57	0.51	0.66
70	0.71	0.70	0.60	0.67	0.62
60	0.70	0.75	0.64	0.74	0.69
50	0.72	0.74	0.68	0.76	0.85
40	0.73	0.76	0.75	0.82	0.90
30	0.75	0.78	0.74	0.85	0.84
20	0.77	0.78	0.77	0.85	
10		0.78	0.80	0.82	

[a,b,c] As for Table 1.

Results

Product selectivities (*S*, eq 1) are shown for solvolyses in aqueous methanol (Table 1) and ethanol (Table 2) at three temperatures, and for methanol/ethanol mixtures at 25 °C in Table 3; there are also data for aqueous mixtures of *tert*-butyl alcohol (Table 4), and 2,2,2-trifluoroethanol (TFE), *n*-propyl alcohol, and isopropyl al-

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(13) Several other substrates (e.g. adamantyl, classified[1b] as the first group) behave similarly, but are more hydrophobic and do not possess a UV chromophore, and so cannot be investigated over a wide range of aqueous mixtures.

TABLE 3. Product Selectivities (S) for Solvolyses of *p*-Methoxybenzoyl Chloride (2) in Methanol/Ethanol (% v/v) at 25 °C

% v/v	20	40	60	80
S^a	1.54	1.51	1.50	1.51

[a] Refers to methanol/ethanol product ratios in eq 1; data from ref 14.

TABLE 4. Product Selectivities (S, Eq 1) for Solvolyses of *p*-Methoxybenzoyl Chloride (2) in *tert*-Butyl Alcohol/Water (% v/v)

	25 °C		35 °C	45 °C
% v/v	set B[a]	set C[b]	set C[b]	set C[b]
90	0.12	0.11	0.11	0.14
80	0.12	0.12	0.11	0.13
70	0.12	0.12	0.12	0.21
60	0.12	0.12	0.14	0.28
50	0.12	0.14	0.15	0.31
40	0.12	0.17	0.17	0.33
30	0.13	0.14	0.15	0.22
20	0.11	0.13		
10	0.12			

[a] Data from ref 14.; the mobile phase for HPLC contained 0.1% triethylamine instead of acetic acid. [b] As for Table 1.

cohol (Table 5) at 25, 35, and 45 °C. All data were obtained by response calibrated HPLC, and were then converted to selectivities (S, eq 1).

Product ratios were constant after 8−10 half-lives (up to several hours) and after longer times (up to 2 days), showing that products did not slowly interconvert during the reaction. Also, the ester products were shown to be stable in acidified 50% alcohol/water, and the acid product (*p*-methoxybenzoic acid) was stable in acidified 90% alcohol/water mixtures, showing that rapid interconversion of products did not occur. Two different HPLC analyses of the acid were employed to resolve the acid signal from the relatively large solvent signals; addition of 0.1% acetic acid to the eluent (ionization suppression), or alternatively 0.1% triethylamine (ion pairing), gave very similar S values.[14]

Three independent measurements in our laboratories are shown in Table 1 (for methanol/water) and in Table 2 (for ethanol/water). Agreement is within ±5%. Two independent measurements of S at 25 °C for *t*-BuOH/water (Table 4) and for *i*-PrOH (Table 5) agree satisfactorily, with two exceptions (30% and 40% *i*-PrOH). A possible source of error, leading to anomalously high values of S, occurs for very rapid reactions in highly aqueous media due to insufficiently rapid dispersal after mixing.[11] Independent results for *n*-PrOH (Table 5) agree well, except for 90% alcohol, which also shows an anomalous temperature dependence.

Discussion

Trends in S Values. First, we consider whether S values for individual alcohol/water mixtures are constant within experimental uncertainties or show consistent variations with composition or temperature. Results for methanol (Table 1) appear to be close to constant, for all nine solvent compositions and all three temperatures; deviations from the average value of 1.32 (23 values at 25 °C) show no consistent trends. Even at 35 and 45 °C, there are only two slightly high S values for the most rapid reactions in the more aqueous media, possibly due to insufficiently rapid mixing. A similar lack of variation in S is observed for TFE, and the average of 24 values is 0.135 (Table 5); possibly S decreases in more aqueous media at 25 °C.

New results for ethanol (B and C, Table 2) show a small but consistent increase in S for more aqueous solvents at all three temperatures, a trend less convincingly discernible in previous data (A, Table 2). For data set C, the extreme values at 25 °C (0.55 and 0.80) differ by <20% from the average value of 0.68 (other averages: 0.74 at 35 °C and 0.75 at 45 °C). All results for *n*-PrOH (Table 5) show similar but more marked trends. Results for *i*-PrOH (Table 5) and *t*-BuOH (Table 4) are approximately constant (except for some values at 45 °C), although the low values of S automatically compress the range of values.

There are few previous studies of S for solvolyses in a wide range of alcohol/water mixtures, but values of $1/S$ for solvolyses of 2-bromoadamantane at 120−150 °C defined the dimensiosolvatic parameter (D, Table 6), for which steric effects had a major role.[15a] Steric effects are apparent from the following order of S for solvolyses of **2** in aqueous alcohols at 25 °C—MeOH (1.32, Table 1) > EtOH (0.71, Table 2) > *i*-PrOH (0.36, Table 5) > *t*-BuOH (0.12, Table 4)—and from selectivities for solvolyses of 1-bromoadamantane in 70 and 80% aqueous alcohols at 100 °C (Table 6).[15b,c] By definition $S = 1$ for water, so water is not in the correct sequence for two of the entries in Table 6, and other factors such as the number of hydrogen bonds and/or electrophilicities must contribute.[15]

Other minor solvent effects are also needed to explain why the ratio of S values at 25 °C for methanol/water and ethanol/water (1.32/0.71 = 1.86) is not the same as the value of 1.52 obtained in methanol/ethanol mixtures (Table 3); taking only set B data from Tables 1 and 2, the ratio of S values is 1.33/0.74 = 1.80, so the discrepancy is about 20%. Also, for 1-bromoadamantane, the ratio of the selectivities for water/TFE and water/ethanol (1.04/1.26 = 0.83) is not the same as the average selectivity of 0.68 for ethanol/TFE.[15b] Selectivities for TFE could be low because the CF_3 group is oriented toward the positive charge, so that trapping cannot occur unless there is time for a rotation.[16]

Implications. Solvent effects on solvolyses of **2** are similar to those for 2,6-dimethylbenzoyl chloride[11] and *p*-methoxybenzyl chloride,[17a] and solvolyses of *p*-methoxybenzoyl bromide correlate well with Y_{BnBr}.[17b] These

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TABLE 5. Product Selectivities (*S*, Eq 1) for Solvolyses of *p*-Methoxybenzoyl Chloride (2) in *n*-Propyl Alcohol, Isopropyl Alcohol, and 2,2,2-Trifluoroethanol/Water (% v/v)

	n-PrOH				*i*-PrOH				TFE		
	25°C		35°C	45°C	25°C		35°C	45°C	25°C	35°C	45°C
% v/v	set B[a]	set C[b]	set C[b]	set C[b]	set B[a]	set C[b]	set C[b]	set C[b]	set C[b]	set C[b]	set C[b]
90	0.61	0.32	0.81	0.37	0.33	0.36	0.28	0.22	0.15	0.17	0.12
80	0.56	0.42	0.67	0.51	0.31	0.35	0.29	0.30	0.15	0.16	0.11
70	0.55	0.47	0.68	0.64	0.32	0.34	0.31	0.35	0.15	0.14	0.10
60	0.63	0.53	0.82	0.64	0.33	0.36	0.32	0.47	0.14	0.12	0.11
50	0.60	0.60	0.75	0.79	0.35	0.39	0.31	0.53	0.15	0.13	0.12
40	0.66	0.60	0.85	0.98	0.36	0.43	0.29	0.56	0.13	0.15	0.14
30	0.70	0.67	0.90	0.91	0.35	0.44	0.30	0.74	0.15	0.15	0.12
20	0.73	0.75			0.34		0.32	0.49	0.11	0.16	
10	0.78	0.82			0.32		0.28	0.49	0.11		

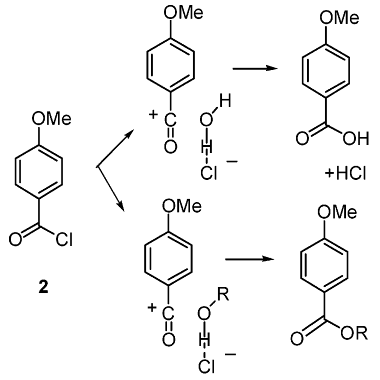
[a] Data from ref 14. [b] As for Table 1.

TABLE 6. Comparison of 1/*S* with D Values from Dimensiosolvatic Effects

	solvent				
	MeOH	EtOH	*n*-PrOH	*i*-PrOH	*t*-BuOH
$1/S$[a]	0.76	1.4	1.6	2.8	8.3
D[b]	1.5	1.7	2.5	2.6	10
1-AdBr[c]	1.0	1.3		4.9	8.7

[a] Relative to water ($S = 1$), for solvolyses of *p*-methoxybenzoyl chloride (**2**) at 25 °C. [b] Defined as $1/S$ for solvolyses of 2-bromoadamantane at 150 °C (from ref 15a). [c] Average of selectivities for 1-bromoadamantane in 70% and 80% v/v alcohol/water at 100 °C, quoted in ref 15b as k(water)/k(alcohol), so the values are equivalent to $1/S$ in eq 1.

SCHEME 1. Proposed S_N1 Mechanism for Solvolysis of *p*-Methoxybenzoyl Chloride (2) in Alcohol/Water, with Product Formation via Front-Side Collapse of Water- or Alcohol-Separated Ion Pairs



results are consistent with S_N1 reactions for solvolyses in ethanol and in more polar solvents. As there is a tendency for aromatic acid chlorides to undergo a mechanistic change to addition−elimination, depending on the substituent and solvent,[17c,d] it is possible (but unproven) that the mechanism of solvolyses of **2** could change in solvents of lower polarity (e.g. *tert*-butyl alcohol); also, the transition state may be weakly solvated nucleophilically.[17c,e]

From the lack of trapping by fluoride ion, the rate of reaction of the *p*-methoxyphenyl acylium ion with water was estimated at $k > 10^{11}$ s^{-1},[12] which corresponds to a lifetime of the "cation" even shorter than typical lifetimes (ns) of solvents in coordination spheres of for example lithium or sodium cations.[2d] Reactions occurring via "free" carbocations give $S > 1$ for alcohol/water mixtures.[1c,18] As S values for solvolyses of **2** are generally low, and $S < 1$ (except for MeOH), it is assumed that all or most of the product is formed when a molecule of protic solvent acts as a nucleophile and attacks a solvent-separated ion pair intermediate (Scheme 1).[1b,11,12,15] This leads us to propose the following. ***Assumption 1*: *Product ratios for solvolyses of* 2*, in any particular binary mixture of protic solvents*, *will depend on the solvent composition adjacent to the reaction site at the instant when the product-forming reaction occurs*** (as discussed above, product ratios in a range of binary mixtures will also depend on properties of the two competing solvents such as electrophilicity, nucleophilicity, steric bulk, and number of hydrogen bonds). ***Assumption 2*: *Preferential solvation is negligible in mixtures of similar alcohols.*** This assumption is intuitively reasonable, and is supported experimentally by $E_T(30)$ data for methanol and ethanol showing close to ideal behavior.[19a] ***Assumption 3*: *Solvolyses of* (2) *will show a constant value of S* (*eq 1*) *if preferential solvation is absent.*** This assumption is supported by the constant S values for solvolyses of **2** in methanol/ethanol (Table 3), when preferential solvation is assumed to be absent (assumption 2).

If the above three assumptions are accepted, based on the arguments and experimental evidence discussed above, it follows that the relatively constant S values for solvolyses of **2** in alcohol/water mixtures (Tables 1, 2, 4, and 5) can be explained by similar solvent compositions at the reaction site and in the bulk solvent (except for *n*-PrOH). Although there are not large variations in selectivities,[1c] our experimental probe (S values) should be sensitive to solvent composition at the reaction site because the mass law effect of concentration on rates should apply.

Our results are not in clear agreement with independent studies of preferential solvation.[5,19] S for each binary mixture varies within a factor of 2 in all cases except two (90% *n*-PrOH at 25 and 45 °C, Table 5). In contrast, for equimolar mixtures of water and *n*-PrOH, ^{1}H NOESY

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NMR data show a 5-fold preference for *n*-PrOH solvating phenol,[5] and data analyzed by the 1-step (2 state) exchange model imply a 12-fold preference for *n*-PrOH solvating **1**;[19b] perhaps even more remarkable is the predicted 4.4-fold preference for MeOH solvating **1** in aqueous methanol.[19b]

A possible source of discrepancies is that S values only measure changes (they are not absolute). If, as suggested,[19] the mole ratio of solvent in the solvation shell is proportional to that in the bulk solvent, constant S values would be observed because the solvent ratio (eq 1) is unchanged. Another possibility is that the "true" mole ratio of water/alcohol at the reaction site could be say 4-fold less than the ratio in the bulk solvent, and then the true S (eq 1) would also be 4-fold lower. Our counterarguments are the following: (i) S values (based on bulk solvent compositions) are already surprisingly low, because alcohols are more nucleophilic than water;[20] (ii) contrary to the expected reduction in preferential solvation caused by decreasing hydrogen bonding as temperatures are increased,[21] our S values tend to increase at increased temperatures and our $1/S$ values at 25 °C parallel D values at 150 °C within a factor of 2 (Table 6).

A more plausible explanation of the above discrepancies is that organic groups distant from the reaction site may be preferentially solvated. As the reaction site is only a small part of a typical organic substrate, preferential solvation of more distant hydrophobic groups within the substrate will not be reflected in S values: e.g., as preferential solvation at the molecular level was detected for phenol in alcohol/water,[5] so perhaps only the phenyl ring is solvated preferentially by the more hydrophobic alcohol. Although "resolution" at the atomic level would be desireable,[5] product ratios provide experimental evidence at an intermediate level of "resolution", but crucially solvent effects at the reaction site are probed (i.e., solvent effects on reactivity).

Investigations of other reactive probe substrates are desirable, especially if additional, positive rather than negative evidence could be obtained in some cases. Choices are limited by mechanistic changes, involving for example either more stable, dissociated carbocations,[1b] or prior nucleophilic attack.[12,17d] Suitable substrates should also dissolve rapidly in highly aqueous media. Cationic substrates provide possible water-soluble alternative reactive probes, although they may be more susceptible to effects of preferential solvation. Solvolyses of 2-, 3-, and 4-methylphenyldiazonium ions were shown to have constant selectivities (with $S < 1$) in both methanol/water and ethanol/water mixtures. Unexpectedly[18b] $S_{\mathrm{EtOH/water}} > S_{\mathrm{MeOH/water}}$, explained by immediate reaction of a highly destabilized cation with a solvent nucleophile in the first solvation shell;[22a] preferential solvation by ethanol would also lead to greater S values for ethanol.

Detailed selectivity data for solvolyses of derivatives of 2-deoxyglucosoyl isoquinolinium tetrafluoroborates at 65 °C indicate that the 2-deoxyglucosoyl oxacarbenium ion is so reactive that it is not solvent-equilibrated in typical alcohol/water mixtures.[22b] As in our work,[18b] $S_{\mathrm{MeOH/water}} > S_{\mathrm{EtOH/water}}$, but S varies up to 2-fold with solvent composition; S increases as water is added to ethanol or methanol (possibly due to preferential solvation at the positively charged, relatively hydrophobic reaction site), but is constant or decreases for TFE.[22b] Solvolysis of α-D-glucopyranosyl fluoride in 55/45 v/v water/methanol gives <1% yield of methyl β-D-glucopyranoside, possibly because the hydrophilic reaction site is preferentially solvated by water.[22c,d]

Solvolyses of 1-adamantyl substrates also proceed via highly unstable intermediates, but data are usually available only for more highly alcoholic v/v compositions; S values (shown as k_W/k_E rather than $k_E/k_W = S$) for dimethylsulfonium salts vary little (between 1.11 and 1.36) for solvolyses over a wide solvent range (20–90% v/v ethanol/water) at 70.6 °C;[23a] chloroformates[23b] vary between 1.11 and 1.66 for 96–40% v/v ethanol/water at 25 °C. Other S values (k_E/k_W) for 1-bromoadamantane in ethanol/water are also close to constant.[1d]

Comparisons of Solvent Effects on Rate Constants and on Solvatochromism in Alcohol/Water Mixtures. Preferential solvation has been investigated in detail through solvent effects on solvatochromism,[3b,19] and it could also influence solvent effects on reactivity. For applications of the Grunwald–Winstein equation for solvent-ionizing power (Y,[24] a measure of solvent polarity[25]), plots of logarithms of rate constants (k) for various solvolyses in aqueous alcohols versus various solvent functions were examined, and mole fraction was selected empirically as the most suitable for interpolations.[24] However, there is no theoretical basis for the expectation[26] that there should be a linear relationship between logarithms of rate constants and mole fractions for the full composition range of a binary aqueous mixtures[2c]—volume fraction has recently been advocated for aqueous mixtures,[6,27] and preferential solvation is not the sole cause of deviations from a linear relationship (as proposed[26]) because many other solvent effects are possible.[6]

When Y (based on logarithms of rates of solvolyses of *tert*-butyl chloride) is plotted against Y_{Cl} (based on solvolyses of the much more hydrophobic 1-chloroadamantane), there is very little "dispersion" into separate correlation lines for aqueous acetone, ethanol, and methanol,[28] consistent with little or no effect of preferential solvation on solvolytic reactivity. Dispersion depends on the number of electrons adjacent to the sites of positive

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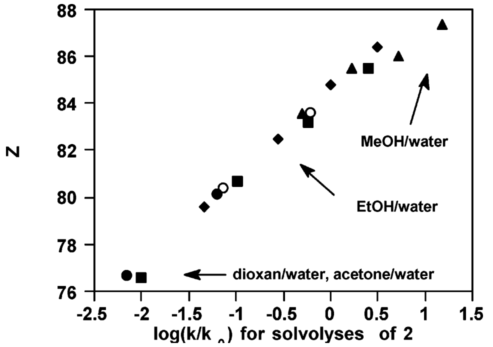
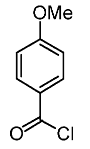


FIGURE 1. Correlation of Z values (kcal/mol) with logarithms of rate constants for solvolyses of *p*-methoxybenzoyl chloride (**2**), relative to 80% v/v ethanol/water (k_0) at 25 °C; all solvent compositions refer to % v/v organic solvent; slope = 3.44 ± 0.12, intercept = 84.23 ± 0.13, $r = 0.991$, $n = 16$; Z values are from ref 31, with additional data for 70% and 80% methanol/water and 80 and 90% acetonitrile/water (open circles) from a correlation between Z and the transition energy of the charge-transfer absorption band of *N*-ethyl-4-cyanopyridinium iodide (ref 32); kinetic data are from ref 17a.

charge,[29] and this can be accounted for quantitatively by using the aromatic ring solvation parameter (I).[30]

We now consider the extent to which a special solvation effect of aromatic rings (and other π-electron systems) could influence solvatochromic measures of solvent polarity. For Z values, based on the transition energy of the charge-transfer absorption band of the solvatochromic dye (**3**),[31] a plot (Figure 1) against logarithms of rate constants for solvolyses of **2** shows very little dispersion into separate correlation lines for aqueous acetone, methanol, and ethanol. Both substrates (**2** and **3**) contain only one aromatic ring, and the difference in anion does not significantly affect the correlation because the three binary solvent mixtures have very similar electrophilicities (e.g., see the good correlation of Y_{Cl} with Y_{I} based on solvolyses of 1-iodoadamantane[33]).



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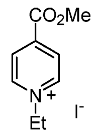

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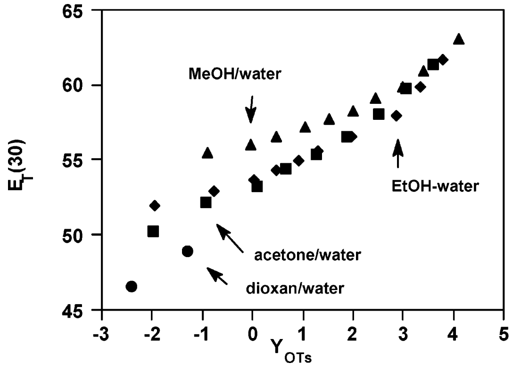

FIGURE 2. Correlation of $E_T(30)$ with Y_{OTs} at 25 °C; values of $E_T(30)$ are calculated from the published transition energies (ref 38; see also refs 19b and 39); Y_{OTs} values are from ref 40; all solvent compositions are % v/v; slope = 2.0 ± 0.2, intercept = 53.9 ± 0.4, $r = 0.942$ for the 19 solvents in Figure 2 for which I values are available (ref 30); an improved correlation is $E_T(30) = (2.38 \pm 0.14)Y_{\mathrm{OTs}} + (6.0 \pm 1.3)I + (54.5 \pm 0.3)$, $r = 0.975$.

Earlier plots of Z vs Y showed dispersion and linearity over a limited solvent range,[31] but plots of $E_T(30)$ vs Y not only showed dispersion but were also nonlinear.[34] We previously reported a plot (showing very little dispersion, but for a less extensive range of solvents) of Z vs logarithms of rate constants for solvolyses of *p*-methoxybenzyl chloride;[17a] extrapolation gave a Z value for pure water of 95.4 ± 0.7 kcal/mol, higher and with a more realistic uncertainty than the original value of 94.6 ± 0.1.[31]

The Z value for pure water has attracted much attention, and significantly lower Z values of 92.5,[10] 91.8,[25,35] and 91.4[32] have also been proposed from various correlations. An extrapolation of the data in Figure 1, based on a very recent direct measurement[36] giving $k = 58\ \mathrm{s}^{-1}$ for solvolyses of **2** in ca. 4% acetonitrile/water at 25 °C, gives a value of $Z = 96.0 \pm 0.6$ kcal/mol; because of the presence of acetonitrile, and from our data for **2** in less aqueous media,[17d] it is likely that k in water at 25 °C is greater than $58\ \mathrm{s}^{-1}$, thus giving a slightly higher Z value. A value of $Z = 95.3 \pm 0.7$ is obtained from a correlation ($r = 0.99$ for 11 solvent compositions of dioxane/water, ethanol/water, and methanol/water) of Z vs solvolyses of α-phenylethyl chloride (kinetic data from ref 37—data for water required a small extrapolation). All of the quoted errors are standard errors, so the upper and lower limits (at 95% confidence) are wider.

As the lower values[10,25,32,35] of ca. 92 kcal/mol were obtained from correlations in which dispersion was observed, additional solvent effects were present, and so extrapolations are more uncertain. From published data,[19b] extrapolations of $E_T(30)$ vs mole fraction (x) of the approximately linear regions from pure methanol or ethanol up to $x = 0.5$ would give an $E_T(30)$ value of pure water, too low by ca. 5 kcal/mol. Consequently, the discrepancy of ca. 4 kcal/mol between our estimate of Z = ca. 96 kcal/mol and the lower values is not surprising.

In contrast to the lack of dispersion in Figure 1, a plot of Z vs Y_{I} gave substantial dispersion (>4 kcal/mol difference between acetone/water and methanol/water).[33] Also, a plot (Figure 2) of $E_T(30)$ vs Y_{OTs} (based on solvolyses of 1- or 2-adamantyl tosylate)[40] shows similar dispersion. Plots such as Figures 1 and 2 converge automatically to the data point for pure water, but

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dispersion cannot be due solely to preferential solvation in the aqueous organic mixtures, because for each alcohol/water mixture the data for the two pure organic solvents (methanol and ethanol) show the largest dispersion. The pattern of dispersion (MeOH > EtOH > acetone−water) can be explained by using the aromatic ring solvation parameter (*I*).[30] Water has the lowest *I* value (−0.45), and others are in the order 90% acetone/water (−0.17), 90% dioxane/water (−0.12), 100% ethanol (0.20), and 100% methanol (0.41);[30] details of correlations (given in the legend to Figure 2) indicate a substantial dependence of $E_T(30)$ on *I*.

Conclusions

Low and approximately constant product selectivities for solvolyses of **2** (S, eq 1, Tables 1−5) for a wide range of aqueous alcohol solvent compositions and at several temperatures, typically employed in kinetic and mechanistic studies, are consistent with previous conclusions[1a,8,9] that the solvent compositions *at the reaction site* do not vary greatly from those of the bulk solvents. However, small increases in *S* in more aqueous solvents, particularly for ethanol (Table 2) and *n*-propyl alcohol (Table 5) indicate that preferential solvation may occur. Overall, these results provide further evidence that preferential solvation/solvent sorting is not a major factor influencing reactivity for nucleophilic substitutions of neutral organic substrates in aqueous alcohols (i.e. at the reaction site), even though substantial preferential solvation may be observed by NMR.[5] Cationic substrates[22a,b] may be more prone to preferential solvation at the reaction site.

Logarithms of rate constants for solvolyses of **2** correlate well with *Z* values (based on electronic transition energies for **3**) with little or no "dispersion" into separate correlation lines for each binary mixture (Figure 1); extrapolation leads to an upward revision of the original *Z* value for water (from 94.6 to ca. 96 kcal/mol), contrary to literature reports of lower estimates (ca. 92).[10,25,32,35] Neither solvatochromism of *N*-alkyl pyridinium iodides (such as **3**) in alcohol/water mixtures (up to C_3)[32] nor solvolyses of **2** in alcohol/water mixtures (Tables 1−5) are considered to involve substantial preferential solvation. Also, structural similarities between **2** and **3** lead to similar effects of aromatic ring solvation, so the good correlation (Figure 1) is explained. In contrast $E_T(30)$ does not correlate well with Y_{OTs} (Figure 2), probably because of differences in aromatic ring solvation, one of the possible solvent effects other than preferential solvation also contributing to the observed[6,19] nonlinear plots of E_T(30) vs mole fraction[19] or volume fraction[34] for alcohol/water mixtures; when these and other possible solvent effects are ignored,[19] the role of preferential solvation is overemphasized.[6]

Experimental Section

Materials. Commercial samples (Aldrich) of *p*-methoxybenzoyl chloride (**2**) were purified by reduced pressure distillation, and were checked for purity by HPLC analysis of methanolysis products; *p*-methoxybenzoic acid (Aldrich) was recrystallized from ethanol. Alcohols for selectivity measurements were dried by reaction with magnesium, except for *tert*-butyl alcohol, which was distilled from sodium. Solvents for HPLC were AR grade. HPLC response factors were obtained from standard solutions of esters, prepared by injecting 10.0 μL of a 5% solution of **2** in dry acetonitrile into 5.00 mL of alcohol or 40% acetonitrile/water.

Selectivities. A few microliters (5−50) of dilute solutions (0.2−5%) of **2** in dry acetonitrile was mixed rapidly with thermostated solvolysis solvent (5−8 mL) in an air-driven, turbostirred apparatus.[41] Swansea procedures and equipment were used to obtain the results coded B in Tables 1−5;[14,41] Jinju results, coded C, were obtained by using the equipment described earlier.[42] The chromatography columns were Spherisorb ODS2, and the mobile phase was typically 70% methanol/water, containing 0.1% acetic acid.

Many experiments were carried out to check that the products were those formed under kinetic control. An illustration is a study of a 4×10^{-3} M solution of *p*-methoxybenzoic acid in 90% methanol/water, containing the same amount or a 2-, 4-, or 20-fold excess of HCl; after 1 day only the latter solution contained any ester (0.6%).

Correlations. Statistical analyses were performed with Microsoft Excel, and graphs were plotted with KaleidaGraph (Synergy Software, Reading, PA).

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Note added in proof: Professor A. Bagno has kindly informed us of a paper (Halle, B. *J. Chem. Phys.* **2003**, *119*, 12372−12389) showing that intermolecular NOEs may contain substantial contributions by spins from the bulk solution, which may complicate the evaluation of the results (e.g., ref 5).

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