Ion-Dipole S_N2 Reaction in Acetone−Water Mixtures. Electrostatic and Specific Solute−Solvent Interactions

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The rate constants of the S_N2 reaction of sodium 4-nitrophenoxide (**1**) and iodomethane were determined by UV−visible spectrophotometry in acetone−water mixtures at 25, 30, and 35 °C. The rate−X_{water} (mole fraction of water) profile shows that the reaction depends strongly on the medium. The fastest rate constant was obtained in pure acetone, and a minimum occurred at X_{water} = 0.4, whereas the observed second-order rate constants k_2' increases again in the water-rich region. In pure acetone, in the presence of dicyclohexano-[18]-crown-6, k_2' increases linearly with the concentration of the crown ether as a result of the complexation of the sodium ion (K_S = 104.8 M) of the ion-pair and the increase in the effective concentration of free 4-nitrophenoxide ion, which was assumed to be the only reactive species. Ion-pairing was also detected at X_{water} = 0.65 with a dissociation constant K_d = 7.82 × 10^{-4} M^{-1}. The solvatochromic behaviors of 2,6-diphenyl-4-(2,4,6-triphenyl-1-pyridinio)-1-phenoxide (**2**), 4-[(1-methyl-4(1H)-pyridinylidene)ethylidene]-2,5-cyclohexa-dien-1-one (**3**), and 1-methyl-8-oxy-quinolinium betaine (**4**) were investigated in the entire range of acetone−water mixtures. The dyes presented an increasing order of hydrophilicity compatible with their chemical structure, i.e., **2** < **3** < **4**. Kinetic parameters for the methylation of **1** and the E_T values of the dyes show a linear correlation of the polarity in the region of X_{water} = 1.0−0.40 for **3** and **4**, and it was observed that the more hydrophilic the dye the better the correlation coefficient, because of the structural similarity with **1**. The activation parameter−X_{water} profile shows extrema at X_{water} < 0.4, reflecting an important change in the structure of the solvent that is responsible for the changes in the solvation of the reactive species including ion-pairs. These results suggest that the addition of water to acetone reduces abruptly the rate of substitution due to the preferential solvation (PS) of the phenoxide ion by the hydrogen-bonding donor (HBD) solvent. Nevertheless, the real second-order rate constant is "masked" by the association involving Na$^+$ and 4-nitrophenoxide that extends even to water-rich mixtures. A model, based on the assumption that the free-energy terms involved in the second-order rate constant and the dissociation constant of the ion-pair have two components, is invoked to explain the kinetic data. One of the components depends on electrostatic interactions for which the main variable is the dielectric constant of the solvent mixture, and the other depends on the specific solute−solvent interactions, expressed by the activity coefficients of transfer of the species involved. The model indicates that in the range of X_{water} = 1.0−0.40 the interactions are exclusively electrostatic, while for the rest of the acetone-rich region they are specific with a large contribution of the 4-nitrophenoxide ion.

Introduction

It has been widely recognized that the rates and courses of many chemical reactions are deeply influenced by the solvent used in these processes.[1] These effects are interpreted as resulting from changes in the specific and nonspecific or polar interactions, which cover the overall solvating capability of the solvent.[2] Physicochemical studies of solvent properties normally include an interest in mixed solvents, which has increased in recent years.[3,4] The possibility of preferential solvation makes the solute−

solvent interactions more complex in mixed solvents than in pure solvents.[3−6] Preferential solvation (PS) occurs when the solute has in its microenvironment more of one solvent than another, in comparison with the bulk composition. This concept is relevant because it enables

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us to explain spectroscopic, equilibrium, and kinetic data in mixed solvents.

Inasmuch as most transition states in chemical processes imply different charge distributions in comparison with the reactant species, it is likely that PS of reactants and/or transition states will occur by one of the components of the binary mixture and, as a result, will change the rate of reaction.[6] Solvation of each reactant, product, and transition state will contribute to a change in the intrinsic barrier of the reaction.[7] A mixture of water and an organic cosolvent is often used as a medium for many organic reactions.[8] For solvolyses in mixtures of protic solvents, no preferential solvation has so far been detected.[9] However, the water-catalyzed hydrolysis of a cellulose xanthate ester in aqueous acetone showed that the rate constant does not change when the molarity of water is higher than 30 M, suggesting that the tight cybotactic region induced by the cellulose expels the aprotic cosolvent.[10] Systematic studies over the whole spectrum of solvent mixtures are scarce, especially for ion-dipolar molecule S_N2 mechanisms. In the present work, we report the study of the alkylation of sodium 4-nitrophenoxide by iodomethane (eq 1) in acetone−water
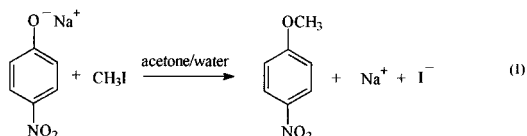

mixtures in order to investigate the influence on the rate of this reaction of the continuous change of the polarity of the medium and the microenvironment of the reactants. We also studied the PS of solvatochromic dyes in the same mixed-solvent system in order to understand better the role of the media in the kinetic parameters. The results are interpreted in terms of electrostatic and specific solute−solvent interactions.

Experimental Section

Materials. All reagents were of analytical grade and were purchased from Aldrich, unless otherwise specified, and the solvents were purified following methodologies described in the literature.[11] The crown ether *cis*-dicyclohexano-[18]-crown-6 was a mixture of syn-cis and anti-cis. Glass double-distilled water was used in all measurements and was boiled, bubbled with nitrogen, and subsequently kept in nitrogen atmosphere to avoid the presence of carbon dioxide. The phenoxide **1** was obtained by mixing equimolar amounts of 4-nitrophenol with sodium hydroxide in methanol as solvent. The resulting solution was rotary evaporated, and the yellow residue was solubilized in hot ethanol, filtered, and reprecipitated in benzene. The solid was separated and dried under vacuum (1 mmHg) for 8 h at 56 °C. Iodomethane (Merck, Darmstadt) was dried over phosphorus pentoxide, distilled, and stored in an ambar bottle.

Dyes 2,6-diphenyl-4-(2,4,6-triphenyl-1-pyridinio)-1-phenoxide (**2**), 4-[(1-methyl-4(1*H*)-pyridinylidene)ethylidene]-2,5-cyclohexadien-1-one (**3**), and 1-methyl-8-oxy-quinolinium betaine (**4**) were synthesized and purified according to published procedures.[11−13]
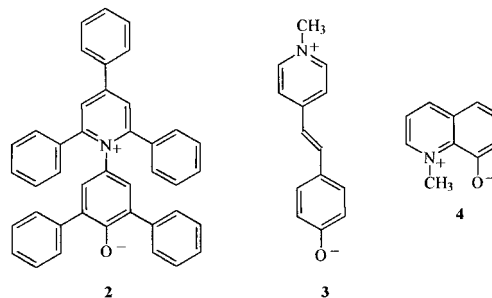
Solvatochromic Measurements. All spectra were recorded using a Beckman DU-65 or a Metrolab 1700 spectrophotometer. The concentration of the dyes in the binary mixtures was 5×10^{-4} M, and the solutions were prepared just prior to use. The measurements were made after thermal equilibration at 25.0 °C in the cell holder of the spectrophotometer. The visible absorption band (λ_{max}) of longest wavelength was transformed into the E_T scale, by means of the following relationship:[1,2]

$$E_T(\text{dye})/\text{kcal mol}^{-1} = 28591/\lambda_{max} \text{ (nm)} \qquad (2)$$

Kinetics. Kinetic measurements for the reaction between **1** and iodomethane were carried out using a Varian 634 spectrophotometer by following the disappearance of sodium 4-nitrophenoxide at $\lambda_{max} = 407$ and 420 nm in the aqueous solutions and pure acetone, respectively. The cell temperature was kept constant with a Haake thermostat within the limits of ±0.1 °C. Pure solvents were mixed by weight to give binary solvent mixtures of various compositions. Kinetic solutions of sodium 4-nitrophenoxide were about 10^{-5} M, and iodomethane, in excess, was added to the thermostated cell with a microsyringe so that the final concentration in the cuvette would be in the range of 50−200 mM. All runs gave strict first-order kinetics over more than three half-lives. Observed first-order rate constants (k_{obs}) were calculated from linear plots of $\ln(A_\infty - A_t)$ against time using an iterative least-squares program; correlation coefficients r were better than 0.999 for all kinetic runs, except for the reaction in pure acetone where a deviation from linearity after the second half-life was observed. This deviation disappeared after addition of the crown ether.

Second-order rate constants k_2' were obtained from the linear plots of k_{obs} versus the concentration of iodomethane.

Activation parameters were calculated from k_2' values at 25.0, 30.0, and 35.0 °C by least-squares fitting from the Eyring equation.

Analyses of the reaction products (after 10 half-lives) in acetone and in a binary mixture with $X_{water} = 0.65$ were performed. Concentrations of the solutions of **1** and iodomethane were 10^{-2} M. 4-Nitroanisol was identified by comparison with an authentic sample by TLC using silica gel 60 HF$_{254}$ from Merck, and 1:9 diethyl ether/petroleum ether (bp 40−60 °C). The R_f values for 4-nitrophenol and 4-nitroanisol were 0.17 and 0.83, respectively.

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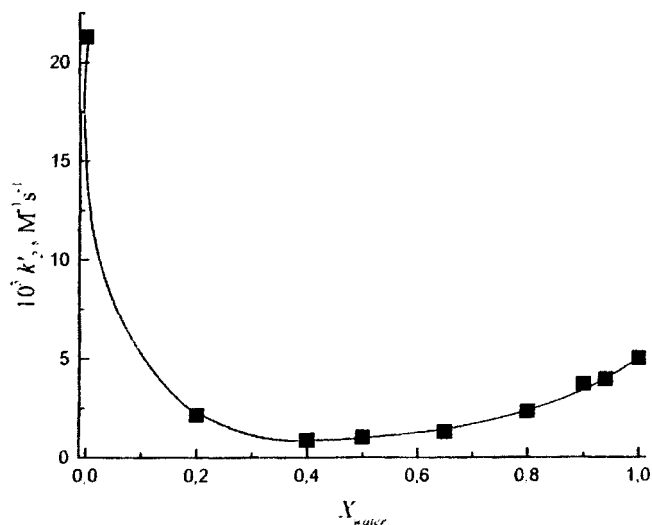
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Table 1. Second-order Rate Constants for the Reaction of 1 with Iodomethane in Various Acetone−Water Mixtures and at Different Temperatures^a

	$10^3 k_2'$, M^{-1} s^{-1}		
X_{water}	25 °C	30 °C	35 °C
0.00	13.4	21.3	28.6
0.20	1.32	2.16	3.49
0.40	0.57	0.87	1.42
0.50	0.63	1.03	1.61
0.65	0.77	1.30	2.14
0.80	1.34	2.34	4.13
0.90		3.73	
0.94	1.81	3.95	7.05
1.00		5^b	

^{a} $n = 4-6$, average standard deviation 3.3%. ^{b} Extrapolated value.

Figure 2. Effect of the addition of dicyclohexano-[18]-crown-6 on k_2' in acetone at 30 °C.
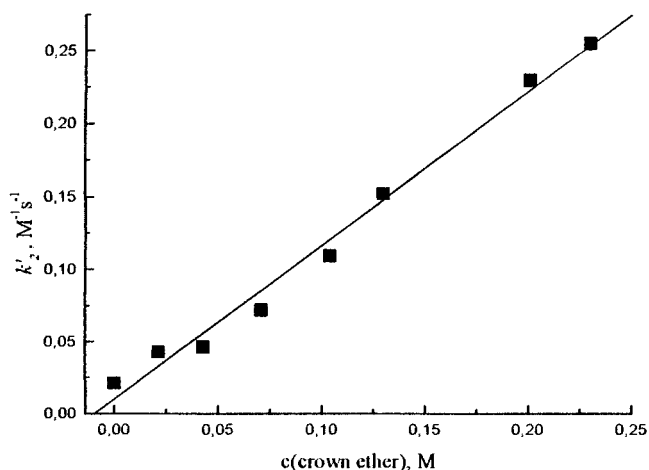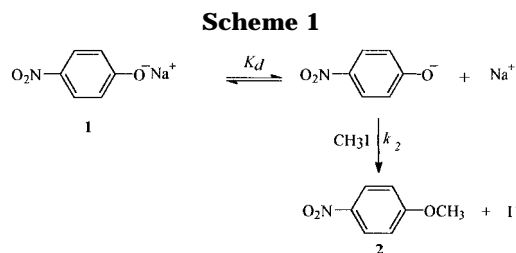
Scheme 1

Figure 1. Profile of the observed second-order rate constants k_2' as a function of the mole fractions of water at 30 °C.

Results and Discussion

Kinetics. Plots of the pseudo-first-order rate constants k_{obs} as a function of iodomethane concentration were linear for the different compositions of mixed solvents. The second-order rate constants k_2' were obtained from these plots at 25, 30, and 35 °C, and are presented in Table 1.

Figure 1 shows the effect of the binary mixture composition on the k_2' values at 30 °C. Similar trends were obtained at 25 and 35 °C. These data show the high influence of the media on the reaction rate. The highest k_2' value was obtained for acetone as solvent. Addition of water produced an abrupt retardation in the rate constant until the water mole fraction $X_{water} \approx 0.4$. At higher values of X_{water}, k_2' values rose steadily with the increase of the water content in the solvent mixture. The profile presented in Figure 1, with an inversion of behavior in k_2' values with the increase in X_{water}, indicates a change in the nature of the factors that influence the reaction rate.

Effect of Dicyclohexano-[18]-crown-6. In pure acetone, the real value of the second-order rate constants may be depressed by the formation of ion-pairs involving the phenoxide ion and Na$^+$.[14] An important tool for the

investigation of this question involves the measurement of the rate constant in the presence of macrocyclic complexing agents.[15] Thus, a sequence of experiments was performed to study the influence of dicyclohexano-[18]-crown-6 on the reaction of **1** with iodomethane. Data shown in Figure 2 demonstrate that the addition of the crown ether increases considerably the reaction rate in acetone, and the linear relationship suggests that the ion-pairs were not reactive. Only the free phenoxide ion reacts with iodomethane.

The reaction is therefore represented as shown in the Scheme 1, where K_d is the dissociation constant for the ion-pair formed from sodium ion and 4-nitrophenoxide, and k_2 is the second-order rate constant for the formation of 4-nitroanisol.

For different solvent mixtures, solutions of sodium 4-nitrophenoxide show only one absorption maximum in the UV−vis spectrum, suggesting that the molar absorptivities of the ion-pairs were approximately the same. Consequently, the observed pseudo-first-order rate constant follows the disappearance of the total concentration of 4-nitrophenoxide ([PNP]$_t$) because of the impossibility to distinguish spectrophotometrically between free and associated 4-nitrophenoxide ([PNP]$_{free}$ and [PNP]$_{assoc}$, respectively). The rate of product formation was dP/dt = k_2[CH$_3$I][PNP]$_{free}$, where by substituting [PNP]$_{free}$ = [PNP]$_t$·K_d $/$([Na$^+$]+K_d), the observed second-order rate constant k_2' can be expressed as eq 4 , where [Na$^+$] is the

$$k_2' = k_2 K_d/([Na^+] + K_d) \qquad (4)$$

concentration of free sodium ions. The value of the equilibrium constant K_d depends on the medium under consideration. In acetone or in acetone-rich mixtures, the

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K_d values may be small, making k_2' smaller than k_2. In water, or in water-rich mixtures, however, k_2' may be equal or close to k_2 because $K_d > [Na^+]$.

The stability constant K_S between Na^+ and the crown ether was calculated as being equal to 104.8 ± 7.9 from eq 5 , considering $[Na^+] = [Na^+]_0/(1 + K_S[CE])$, where

$$k_2' = k_2 K_d/([Na^+]_0 + K_d) + k_2 K_d K_S[CE]/([Na^+]_0 + K_d) \quad (5)$$

$[Na^+]_0$ is the concentration of free sodium ion in the absence of crown ether, and $[CE]$ is the concentration of crown ether. The value of k_2' in the presence of a solution containing 0.23 M of crown ether was 0.26 M^{-1} s^{-1}, or ca. 12 times greater than the value obtained in the absence of crown ether. These results shed light on the strong inhibition due to the cation association with the nucleophile, as has been described elsewhere,[16,17] and are consistent with the assumption that only the free phenoxide is able to "attack" the electrophilic center in order to generate the product.

The great effect on the reaction rate by addition of small amounts of water to acetone is the result of the opposite effect on the dissociation constant K_d and the rate constant k_2. The "isolated" molecules of the HBD solvent strongly interact with the negatively charged nucleophilic center under these conditions. In a recent work, Linert et al. demonstrated that the rate of methylation of a pyridiniophenoxide dye in acetonitrile is also highly dependent on the water content.[18] Preferential solvation of pyridiniophenoxide dyes by water in acetonitrile-rich mixtures is well established in the literature, and their use has been proposed as a rapid procedure for the determination of water content in organic solvents.[19]

Effect of Ionic Strength. To investigate the importance of the association Na^+-4-nitrophenoxide in the water-rich region, a kinetic study of the reaction at 30 °C was performed, in mole fraction of water equal to 0.65 with increasing amounts of sodium iodide (Figure 3). The presence of the salt inhibits the reaction rate. For instance, the addition of sodium iodide up to 1.06×10^{-3} M decreases the observed rate constant from 4.26×10^{-4} to 1.88×10^{-4} s^{-1}. It is also possible to calculate k_2 and K_d from these data and eqs 4 and 6. The plot of $1/k_{obs}$ vs

$$1/k_{obs} = 1/k_2[CH_3I] + [Na^+]/k_2 K_d[CH_3I] \quad (6)$$

[NaI] was linear ($r = 0.99$) and gave values of k_2 and K_d equal to 1.43×10^{-3} M^{-1} s^{-1} and 7.82×10^{-4} M^{-1}, respectively, for $X_{water} = 0.65$. These results show that even in the water-rich region, K_d values are still small in magnitude and should not be disregarded.

Solvatochromism in Acetone−Water Mixtures. It is interesting to investigate the polarity scales, such as the E_T values, in binary solvent mixtures, especially when
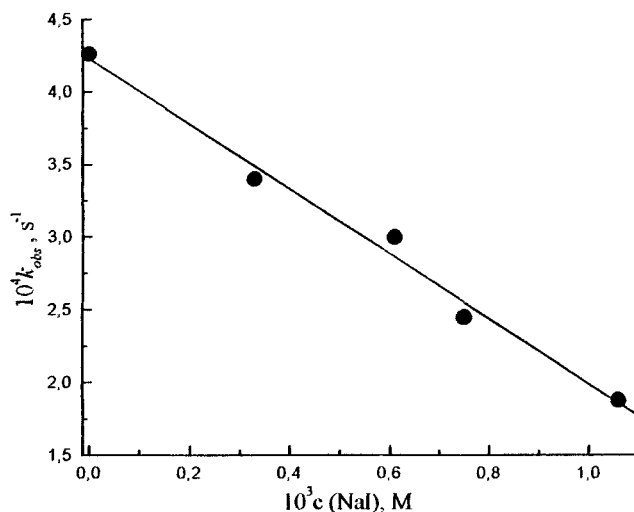
Figure 3. Effect of the addition of NaI on the observed pseudo-first-order rate constant in $X_{water} = 0.65$ at 30 °C. The concentration of MeI was 0.32 M.

preferential solvation of reactants and/or transition state takes place by one of the components. This information is relevant because it offers an explanation of the spectroscopic, equilibrium, and kinetic data in mixed solvents. Dawber and co-workers[6] have studied the relationship between PS and certain solvolytic processes in mixed solvents using a solvatochromic pyridinium betaine. Mancini and co-workers[20] have successfully interpreted the effect of solvents on the aromatic nucleophilic substitution reaction in binary mixtures, by comparison with the $E_T(30)$ parameter in the same solvent mixtures.

We studied the PS of the solvatochromic dyes **2−4** in order to get a better understanding of the role of the media in the kinetic parameters. These probes are well-known for their solvatochromic properties.[1,4,21−23] Thus, considering that they present a phenoxide moiety in their structure, it is reasonable to suppose that they might provide an insight into the solvation of **1**.

Figure 4 shows the E_T values of the three solvatochromic dyes in acetone−water mixtures as a function of X_{water}. Experimental data were accurately fitted by a nonlinear least-squares method to a fourth-order polynomial (eq 7). Values for the coefficients a, b, c, d, and e

$$E_T \text{ (dye)} = a + bX_{water} + cX_{water}^2 + dX_{water}^3 + eX_{water}^4 \quad (7)$$

for each curve shown in Figure 4 are given in Table 2.

Figure 4 shows that the PS phenomenon is present in binary solutions of all three dyes. Reichardt's betaine **2** is preferentially solvated by water in the acetone-rich mixtures, whereas in the water-rich region the PS is still observed but this time by acetone. These results agree

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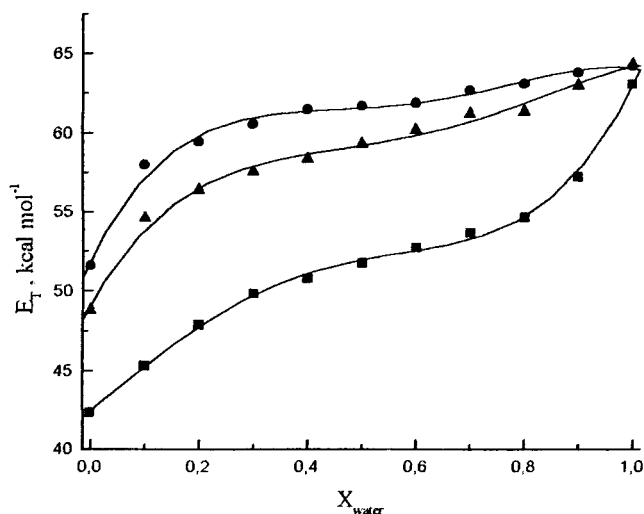
Figure 4. Relationship of E_T(dye) versus X_{water} for compounds **2** (■), **3** (▲), and **4** (●).

Table 2. Polynomial Dependence of E_T(dye)$_{mixture}$ (kcal mol^{-1}) on the Mole Fraction of Water (X_{water}) for Acetone−Water Mixtures According to Eq 7

dye	a	b	c	d	e	r	sd^a
2	42.42	28.30	4.85	−80.49	67.83	0.999	±0.30
3	49.12	59.99	−145.32	162.47	−62.03	0.996	±0.52
4	51.94	67.46	−177.22	203.34	−81.38	0.994	±0.51

^{a} Standard deviation.

Table 3. Estimated Local Mole Fraction of Water (X^L_{water}) in the Solvation Shell of Dyes 2−4 for Different Bulk Water Mole Fractions^a

dye	X_{water} 0.25	0.50	0.75
2	0.31	0.47	0.56
3	0.54	0.67	0.81
4	0.71	0.80	0.90

^{a} These values were obtained from the fourth-order polynomials given in Table 2.

with earlier studies by Krygowski et al.[13] Dyes **3** and **4** are preferentially solvated by water over the entire range of these mixtures, and the PS is more accented for dye **4**. For dye **4**, a very small PS by acetone in water-rich mixtures has been reported.[23]

The degree of solvation of dyes **2−4** by water in aqueous acetone may be more easily visualized comparing the data in Table 3. These data represent the local mole fractions of water (X^L_{water}) in the solvation shell of each dye, when the bulk water mole fraction in the solvent mixture is 0.25, 0.50, and 0.75, using the data from Table 2 and eq 8, where E_T^0(dye) and $E_T^{1.0}$(dye) are

$$X^L_{water} = [E_T^X(dye) − E_T^0(dye)]/[E_T^{1.0}(dye) − E_T^0(dye)] \quad (8)$$

the E_T values for the dye at mole fractions of water 0 and 1.0 respectively, and E_T^X(dye) is the value at the corresponding X_{water}.

In an acetone−water mixture containing 25 mol % of water, 31% of the molecules surrounding the dye **2** are water, indicating a PS of **2** by the HBD solvent. For dyes **3** and **4**, PS by water is also observed, but dye **4** turns out to be the more hydrophilic dye because in this case 71 mol % of water is in the dye's cybotactic region. In
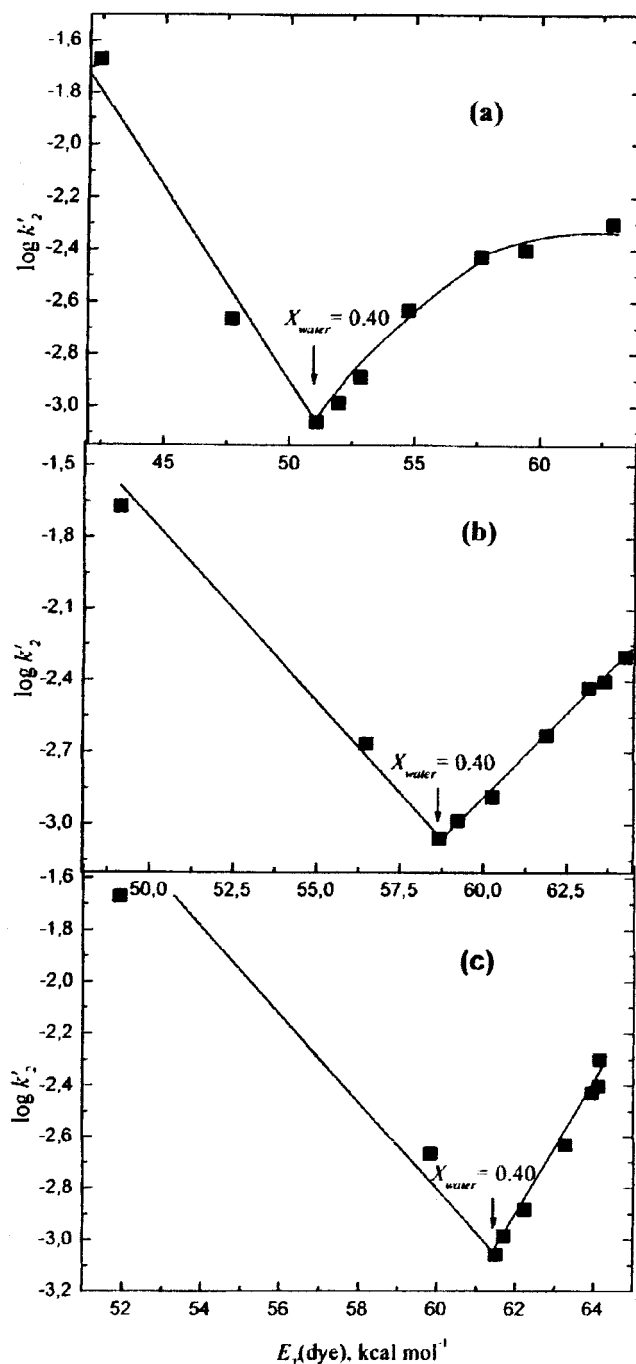
Figure 5. Plots of log k_2' vs E_T(**2**) (a), E_T(**3**) (b), and E_T(**4**) (c).

contrast, when the bulk molar composition in water is 75%, the solvation shell of dyes **2**, **3**, and **4** present 56, 81, and 90 mol % of water, respectively. These results show that compound **2** is preferentially solvated by acetone in water-rich mixtures, whereas the more hydrophilic dyes **3** and **4** are preferentially solvated by water. It is apparent from Table 3 that for all ranges of acetone−water mixtures the increasing order of hydrophilicity of the dyes is **2** < **3** < **4**, as expected from their molecular structures.

Figure 5 shows the plot of log k_2' as a function of the E_T values of dyes **2−4** for all binary mixtures. It can be observed that for binary mixtures with X_{water} > 0.40, there is a linear correlation between the kinetic and solvatochromic data for dyes **3** and **4** but not for dye **2**, probably because of the lack of structural similarity when

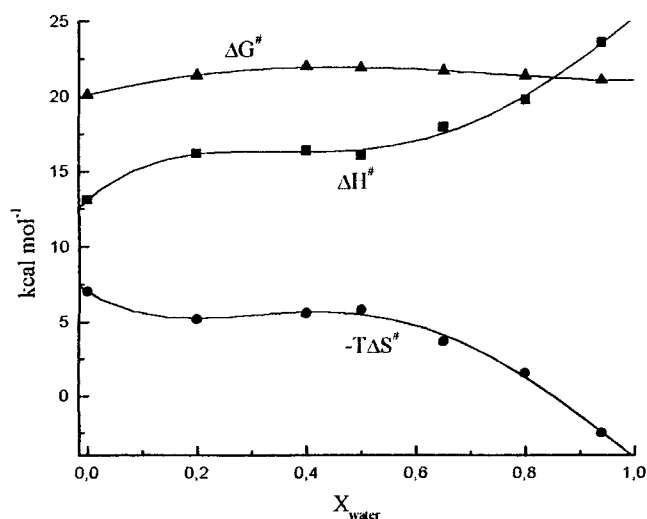**Table 4. Activation Parameters for the Reaction of 1 with Iodomethane in Various Acetone−Water Mixtures**

X_{water}	$\Delta G^{\ddagger}$ kcal mol^{-1}	$\Delta H^{\ddagger}$ kcal mol^{-1}	$\Delta S^{\ddagger\,a}$ cal mol^{-1} K^{-1}	$-T\Delta S^{\ddagger}$ kcal mol^{-1}
0.94	21.1 ± 0.06	23.6 ± 1.9	8.4 ± 6.7	-2.5 ± 2
0.80	21.4 ± 0.03	19.8 ± 2.1	-5.37 ± 7.05	1.60 ± 2.1
0.65	21.7 ± 0.06	18.0 ± 1.0	-12.4 ± 3.19	3.70 ± 0.95
0.50	21.9 ± 0.12	16.1 ± 3.9	-19.5 ± 13.1	5.81 ± 3.90
0.40	22.0 ± 0.12	16.4 ± 2.3	-18.8 ± 7.7	5.6 ± 2.29
0.20	21.4 ± 0.06	16.2 ± 1.9	-17.4 ± 6.4	5.19 ± 1.91
0.00	20.1 ± 0.1	13.1 ± 1.0	-23.5 ± 3.4	7.00 ± 1.0

^{a} At 25 °C.

dye **2** is compared to the nucleophile **1**. It is apparent that the correlations are better with increasing hydrophilicity of the dye. Thus, for the range $X_{water} = 0.40−1.0$, the strong hydrophilic dye **4**, structurally more similar to **1**, gave an excellent relationship ($r = 0.999$), while Brooker's merocyanine **3** presents a lower correlation ($r = 0.992$). The experimental data also fit well in the same range of water mole fraction with the Z parameter of Kosower.[24] It is well-known that both specific and nonspecific interactions of the solvent with the ground state of 1-ethyl-4-methoxycarbonyl-pyridinium iodide determine the changes in the position of its charge-transfer band.[24,25] The property of the dye to recognize the different kinds of interactions may be the reason for the observed good relationship.

The change of the trend observed in acetone-rich mixtures is consistent with the division of the kinetic data into two parts. Kinetic data from the binary mixtures between $X_{water} = 0.40$ to $X_{water} = 1.0$ reflect the increase of the dielectric constant and the interaction of "isolated" molecules of acetone with **1**, leading to higher values of the dissociation constant (K_d) of the ion-pair and consequently to a discrete change in the rate constants. The linear relationship between the solvatochromic parameters and the observed rate constants is observed under these conditions because of the large effect of the highly structured water on reactant **1**. In pure acetone, however, the increase in the reactivity outbalances the decrease in the dissociation of the ion-pair because of dehydration of 4-nitrophenoxide. Strong PS by water produces a sharp decrease in reactivity for increasing values of X_{water}, until a full solvation cage is attained. There should be a larger effect on the 4-nitrophenoxide than on the dispersed charge of the transition state, producing the observed break in Figure 5. Chemical probes constitute a very important tool in the study of binary mixtures. If there is a structural similarity with a reactant in a given process, it may be expected that the "reportage" effectuated by the probes on their microenvironment corresponds to the solvation of the reactant in the process under consideration.

Activation Parameters. Activation parameters calculated for the reaction in different water−acetone mixtures are shown in Table 4. Addition of water causes a large change on the $\Delta S^{\ddagger}$ values from -23.5 in acetone to $+8.4$ cal mol^{-1} K^{-1} for $X_{water} = 0.94$. The experimental data in the range of pure acetone to $X_{water} = 0.4$ can be explained by the increase of the dielectric constant as expected by the Hughes−Ingold rules,[26] but the prediction is of a small decrease with increasing solvent polarity.

Figure 6. Activation parameters for the reaction of **1** and iodomethane in acetone−water mixtures.

The high negative $\Delta S^{\ddagger}$ value in acetone is consistent with a bimolecular mechanism between the phenoxide and the iodomethane. Anions are less solvated in aprotic dipolar solvents than in water where strong hydrogen bonding occurs.[8d] However, the existence of ion-pairing of **1** observed in the presence of crown ether makes this interpretation oversimplified. The positive value of $\Delta S^{\ddagger}$ in nearly pure water medium, where ion-pairing should be negligible and the anion is strongly solvated (Table 3), suggests that the water molecules freed on the formation of the transition state counterbalance the negative value of $\Delta S^{\ddagger}$.

Activation data presented in Figure 6 show that the near linear change of $\Delta G^{\ddagger}$ with a smooth maximum near $X_{water} = 0.4$ is a result of the increase in the entropic contribution $-T\Delta S^{\ddagger}$ balanced by a decrease in $\Delta H^{\ddagger}$. The behavior of these two terms observed at $X_{water} < 0.4$ reflects the important change in the structure of the solvent that is responsible for changes in the solvation of the reactive species including ion-pairing. Extrema in $\Delta G^{\ddagger}$ are relatively rare, and in aqueous binaries they often conceal large solvation effects.[8a]

An acceleration of the reaction would result either from interactions that destabilize the ground state or stabilize the transition state.[27,28] The remarkable effect of added water in acetone may also result from stronger hydrogen-bonding interactions involving 4-nitrophenoxide ion and this HBD solvent in comparison with the transition state dipole.

Electrostatic and Specific Interactions. Changes of reactivity of the reactive species with the variation of the medium can be analyzed by considering the standard state in pure water and by assuming that these changes are the consequence of two main components, one due to electrostatic effects and the other related to specific solvation.[29,30] The activation energy (E_A) for the reaction

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between **1** and iodomethane becomes then equal to $E_n +$ E_e, where one term is independent (E_n) and another dependent (E_e) on electrostatic effects.[31] Values of k_2 can be expressed by means of eq 9, at very low ionic strength

$$k_2^\circ = Z^0 \exp(-E_n/kT) \exp[(\epsilon\mu_c \cos\theta)/(Dr^2 kT)] \quad (9)$$

or infinite dilution, where Z^0 refers to the standard collision frequency, k is the Boltzmann constant, μ_c is the dipole moment of iodomethane, D is the dielectric constant, r is the distance between the charge on the ion and the center of the dipole in the transition state, and θ is the angle of approach to the positive end of the dipole. The factor $Z^0 \exp(-E_n/kT) = k_2^\infty$ depends on the nonelectrostatic component or specific solute−solvent interactions and represents the rate constant when the dielectric constant is infinite. According to the Brönsted−Bjerrum[32] equation $k_2 = k_2^\circ \gamma_k$, where γ_k is the activity coefficient dependent factor. Equation 10 is obtained by substitution

$$k_2 = k_2^\infty \gamma_k \exp(\beta/D) \quad (10)$$

of k_2° and $(\epsilon\mu_c \cos\theta)/r^2 kT = \beta$.

In a medium of dielectric constant D and ionic strength near to zero or at infinite dilution, the dissociation constant K_d° is given by eq 11,[31b,33,34] where, ϵ is the

$$K_d^\circ = K^\infty \exp(-\epsilon^2/DakT) = K^\infty \exp(-\alpha/D) \quad (11)$$

charge of the proton, k is the Boltzmann constant, and a is the nearest distance approach. K^∞ is the dissociation constant of the ion-pair into uncharged products or dissociation in a medium of infinite dielectric constant, and it represents the specific interaction-dependent term, which is independent of the electrostatic interactions. The expression of the equilibrium constant K_d° can be simplified substituting $\alpha = \epsilon^2/akT$. The exponential term $\exp(-\alpha/D)$ expresses the dependence of K_d on the electrostatic interactions. The equilibrium constant K_d depends on K_d, the equilibrium constant in terms of concentration, and K_γ, which depends on the activity coefficients (eq 12).

$$K_d = K^\infty K_\gamma \exp(-\alpha/D) \quad (12)$$

Considering the standard state as pure water, the change of K_d when the ion-pair is transferred from water to any other solvent mixture is expressed by eq 13.

$$^\circ K_d^S = {}^\circ K_\gamma{}^S \exp(\alpha/D_0 - \alpha/D_S) \quad (13)$$

Extending the same treatment to k_2, eq 10 becomes eq 14.

$$^\circ k_2{}^S = {}^0\gamma_k{}^S \exp(\beta/D_S - \beta/D_0) \quad (14)$$

An increase in the dielectric constant will increase the K_d value, according to eq 12, but it will decrease the reactivity of the reactant anion as shown by eq 10. There is an increase of the reaction rate in the water-rich mixtures and in order to observe this effect, [Na$^+$] should be larger than or of the same magnitude as K_d, and eq 4 can be approximated to $K_2' \cong k_2 K_d/[Na^+]$. Substitution of $^\circ k_2^S$ and $^\circ K_d^S$ according to eqs 13 and 14, in the observed second-order rate constant of transfer produces eq 15.

$$\log {}^\circ(k_2')^S = \log {}^0\gamma_k{}^{S\ 0}K_\gamma{}^S + [(\alpha - \beta)/2.3](1/D_0 - 1/D_S) \quad (15)$$

The value of $^\circ(k_2')^S$ can be calculated from the relative rate constants in a solvent of S composition and in the standard state (pure water). The second term, $\log {}^0\gamma_k^S {}^0K_\gamma^S$, contains the activity coefficients of transfer of all the species involved, where $^0\gamma_k^S {}^0K_\gamma^S$ is equal to $^\circ[(\gamma_{PNP^-})^2(\gamma_{MeI})(\gamma_{Na^+})/\gamma_{\neq}\gamma_{PNP^-\cdot Na^+}]^S$ and the 4-nitrophenoxide ion has higher weight in determining the value of the term. As has been pointed out by Engberts[8a] and Parker,[35] activity coefficients of transfer depend on the specific solvation of the species involved. They will be equal to zero in pure water or when the specific interactions are weak. The last term, $[(\alpha - \beta)/2.3](1/D_0 - 1/D_S)$, represents the electrostatic contributions of both the dissociation equilibrium of the ion-pair and the reaction rate between 4-nitrophenoxide and iodomethane. Equation 15 is important because it separates the electrostatic and specific interactions.

An excellent linearity ($r = 0.998$) was obtained in the range of $X_{water} = 1.0-0.4$ from the plot of $\log k_2'$ vs $(1/D_0 - 1/D_S)$. This result is also consistent with the E_T correlation in this region and the preferential solvation of water in acetone-rich mixtures. According to eq 15, the increase in this last term with the dielectric constant is a consequence that in the case of a reaction of an anion and a dipolar molecule the sign of $(\alpha - \beta)$ is positive. The smooth change of $\Delta H^\ddagger$ and $-T\Delta S^\ddagger$ in this region might be due to the fact that the electrostatic model is being followed and that the dielectric constant of the medium in this range of solvent mixture is determinant for the rate of reaction.

The electrostatic contributions were calculated for the whole range of water−acetone mixtures (Figure 7). The contribution of the term that depends on the activity coefficients ($\log {}^0\gamma_k^S {}^0K_\gamma^S$) is practically zero in the water-rich mixtures, but it increases rapidly for water mole fractions less than 0.4. A change in the trend of $\Delta H^\ddagger$ and $-T\Delta S^\ddagger$ values is observed exactly in this region, suggesting that the increase of the activity coefficients is due to changes in the solute−solvent interactions because of the dehydration of the ionic and polar species, especially, as mentioned above, in the case of the 4-nitrophenoxide ion. These results are similar to those obtained for the reaction between 4-nitrophenoxide and iodomethane in methanol/dimethylformamide mixtures,[28] but in the present work we have managed to offer a more complete explanation of the main factors involved in the changes of solute−solvent interactions and the rate of the reaction. Preferential solvation might not be important solely

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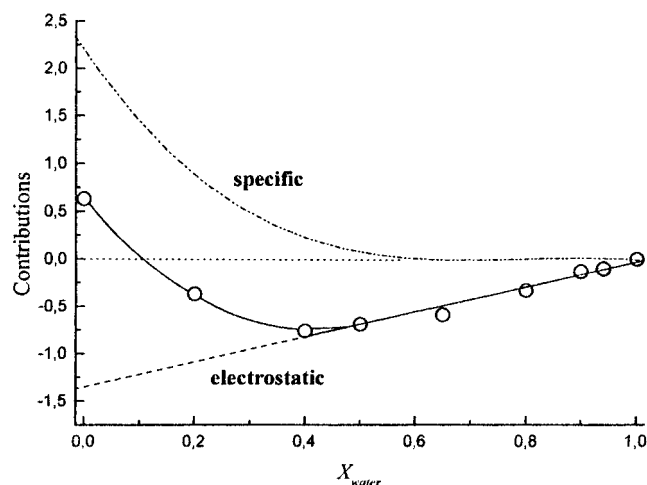
Figure 7. Contributions to the observed second-order rate constant of transfer [$\log^0(k_2')^S$], $\bigcirc$; - - -, electrostatic term [$(\alpha - \beta)/2.3(1/D_0 - 1/D_S)$]; $- \cdot \cdot -$, specific interactions term (log $^0\gamma_k^S \ ^0K_\gamma^S$).

when an ion is involved but also when a tight cybotactic region has been induced by a strong hydrophilic substrate.[10]

Conclusions

The S_N2 reaction between **1** and iodomethane in aqueous acetone is strongly dependent on the medium, and the observed second-order rate constant k_2' is "masked' by the ion-pairing of Na^+ and 4-nitrophenoxide ion, decreasing the effective concentration of free 4-nitrophenoxide ion that constitutes the reactive species.

For all ranges of acetone–water mixtures the dyes **2**, **3**, and **4** present a crescent order of hydrophilicity compatible with their chemical structure. Kinetic parameters for the methylation of **1** and the E_T values of the dyes show a linear correlation with the polarity in the region of $X_{water} = 1.0-0.40$ for **3** and **4**. The more hydrophilic the dye the better the correlation coefficient, because of its structural similarity with **1**.

Extrema of the activation parameters at $X_{water} < 0.4$ reflect an important change in the structure of the solvent that is responsible for the changes in the solvation of the reactive species and ion-pairs.

The addition of water to acetone reduces abruptly the rate of the reaction mainly as a result of preferential solvation (PS) of the phenoxide ion by the hydrogen-bonding donor (HBD) solvent. A model based on the assumption that the free-energy terms involved in the second-order rate constant and the dissociation constant of the ion-pair have two components can be used to explain the kinetic data. One of the components depends on electrostatic interactions for which the main variable is the dielectric constant of the solvent mixture, and the other depends on the specific solute–solvent interactions, expressed by the activity coefficients of transfer of the species involved. The model, consistent with experimental observation, indicates that in the range of $X_{water} = 1.0-0.40$ the interactions are exclusively electrostatic and k_2' increases with the dielectric constant of the mixture (which goes against Ingold's rule) because $(\alpha - \beta)$ is positive. In the acetone-rich region, $X_{water} < 0.40$, the interactions are specific, with important contribution of the activity coefficient of 4-nitrophenoxide ion.