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Characterization of Binary Solvent Mixtures

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Solvent mixtures are widely used in chemical and biochemical practice to modify molecular environments in order to modulate interesting phenomena such as chromatographic separation, organic synthesis, reaction kinetics, the color of chromophores, or protein folding−unfolding. Solvents are also often used in mixtures in order to modify physical properties such as viscosity, density, or vapor pressure.

Describing the solvation of a neutral or ionic solute in a solvent mixture is considered to be even more complicated than when the substrate is in the bulk of a pure solvent.[1] This is believed to be mostly the result of solvation in a mixture of solvents involving not only the key solute−solvent interactions but also others between the different species present in the mixture. This leads, among others, to significant deviations in the vapor pressure of a mixture from the ideal behavior as expressed mathematically by Raoult's law.

Research into the solvation of solutes by solvent mixtures has provided evidence suggesting that the explanation for the above-mentioned deviations may be that the solvent ratio is significantly different around the solute and in the bulk solution. This would be the result of the Gibbs energy of solvation becoming more negative by the effect of solute being preferentially surrounded by one of the solvents.[1,2] This would in turn ultimately reflect a difference between the composition of the solvent shell around the solute and the macroscopic ratio. This phenomenon is called "preferential solvation", a term that is usually employed to signify that the solute induces a change in its environment with respect to the situation in the bulk solvent, whether through nonspecific solute−solvent interactions (usually referred to as "dielectric enrichment") or through specific solute−solvent association (e.g., complex formation).

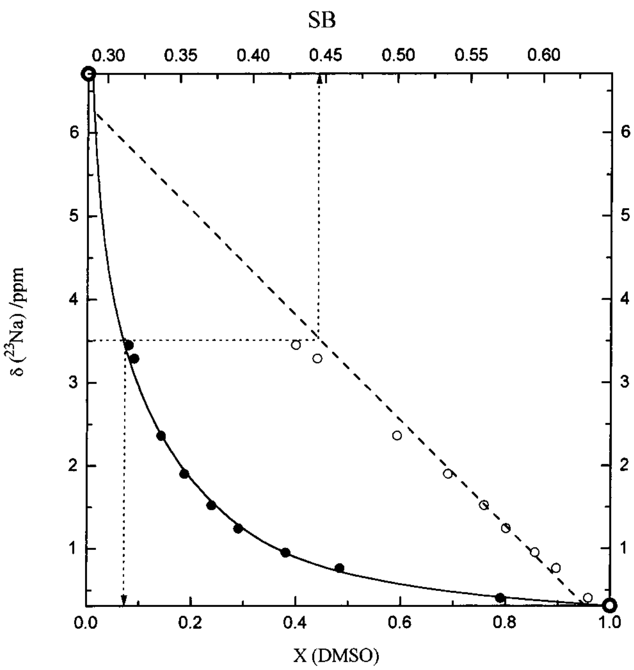

Figure 1. Plot of the NMR chemical shift of ^{23}Na$^+$ vs the mole fraction X(DMSO) (●) and the SB parameters (○) for the DMSO/ACN mixture.

Preferential solvation has been examined with the aid of various methods most of which rely on conductance or transfer measurements,[2] the NMR chemical shift of a nucleus in the solute,[3] or solvatochromic measurements of a solute in the IR[4] or UV−vis region.[5] The variation of these data with the composition of the bulk solvent (usually with the mole fraction) deviates from ideality (Figure 1). The occurrence of deviations is taken as evidence of preferential solvation.

A quantitative description of preferential solvation has been attempted using various methods;[2−6] none of which, however, allows an easy, precise characterization providing a clear view of the situation.

One way of estimating the degree of preferential solvation is through the composition of the bulk solvent, where the solvent molecules in the mixture are assumed to contribute equally to the solvation sphere. Such a mixture composition, usually expressed in terms of mole fractions, is called the "iso-solvation point". According to Greenberg and Popov,[7] ^{23}Na$^+$ dissolved in a dimethyl sulfoxide (DMSO)/acetonitrile (ACN) mixture must be surrounded by identical numbers of DMSO and ACN molecules when the bulk solvent possesses a DMSO mole fraction of 0.10 (see Figure 1). Thus, at a DMSO/ACN

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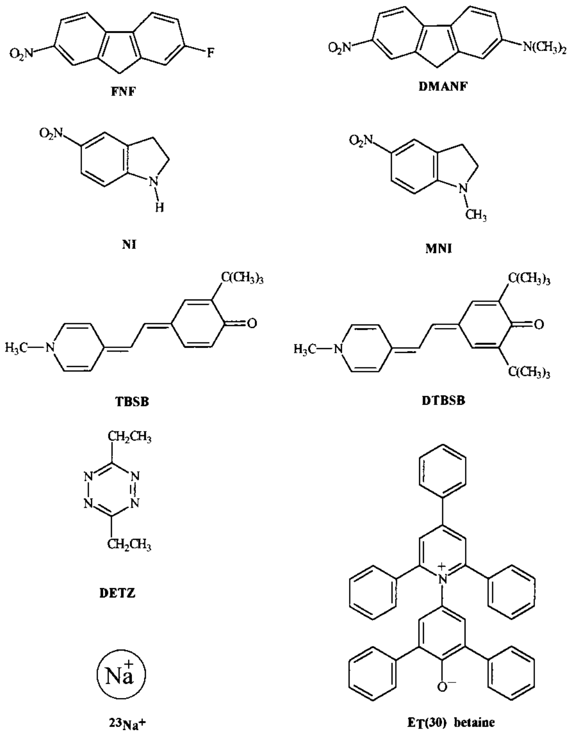
Chart 1. Molecular Structures of the Probes Considered



ratio of about 1:10 in the bulk solvent, the ratio around $^{23}\mathrm{Na}^+$ is approximately 1:1, and the ion is preferentially solvated by DMSO.

In our minds, if preferential solvation were in fact governed by the polar or ionic character of the solute, a solvent mixture could never be characterized by using molecular probes since the behavior observed could only be extrapolated to solutes having not only identical polarity and charge but also similar molecular shape and size.

The experimental evidence provided below allows us to conclude that this is not the actual situation and that solvent mixtures can be characterized in as simple and precise terms as can pure solvents. This is made possible by the pure dipolarity−polarizability (SPP), acidity (SA), and basicity (SB) scales, which were established from suitable probe/homomorph couples (see Chart 1). Thus, the dipolarity−polarizability of a pure solvent can be characterized in terms of the solvatochromism of the probe 2-(*N*,*N*-dimethylamino)-7-nitrofluorene (DMANF) and its homomorph 2-fluoro-7-nitrofluorene (FNF); SPP values range from 0 in the absence of solvent (i.e., in the gas phase) to 1 for DMSO.[8] The SB scale is based on the solvatochromism of the probe 5-nitroindoline (NI) and its homomorph *N*-methyl-5-nitroindoline (MNI); SB values range from 0 for the gas phase to 1 for tetramethylguanidine.[9] Finally, SA is evaluated from the solvatochromism of the probe *o*-*tert*-butylstilbazolium betaine dye (TBSB) and its homomorph *o*,*o*-di-*tert*-butylstilbazolium betaine dye (DTBSB) and encompasses values from 0 for the gas phase to 0.4 for ethanol.[4] The acidity of solvents more acidic than methanol (SA = 0.6) is evaluated by applying the solvatochromic comparison method[11] to solvatochromic measurements of the probe 3,6-diethyl-1,2,4,5-tetrazine (DETZ).[12]

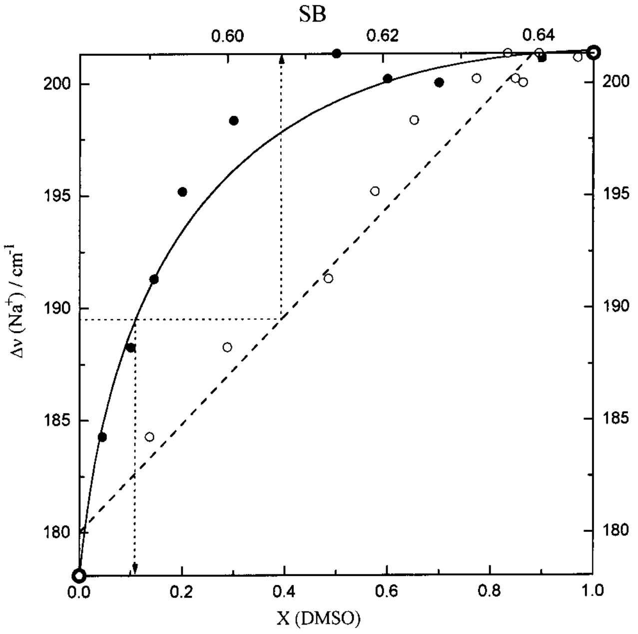


Figure 2. Plot of the variation of the frequency of the Na^+ solvation band vs the mole fraction X(DMSO) (●) and the SB parameters (○) for the DMSO/pyridine mixture.

Experimental evidence obtained by using NMR, IR, and UV−vis spectroscopies, and also by vapor pressure techniques, is analyzed below in relation to data from our solvent scales. The evidence examined provides typical examples of the presence of preferential solvation.

Greenberg and Popov[7] reported evidence of preferential solvation in a series of binary mixtures of nonaqueous solvents that they obtained by analyzing the chemical shift of the cation $^{23}\mathrm{Na}^+$, $\delta(^{23}\mathrm{Na}^+)$. Selected data are shown in Figure 1. Based on its SPP, SA, and SB values, the polarity and basicity of a binary mixture consisting of DMSO (SPP = 1, SA = 0.072, SB = 0.647) and ACN (SPP = 0.895, SA = 0.044, SB = 0.286) will obviously change with the proportions of its components; the changes must therefore account for those in $\delta(^{23}\mathrm{Na}^+)$ (see Figure 1). However, the magnitude of $\delta(^{23}\mathrm{Na}^+)$ are known to be related to Lewis solvent basicity,[13] the Gutmann donor number,[14,15] and solvent basicity (SB).[9] As a result, $\delta(^{23}\mathrm{Na}^+)$ for a solvent mixture should be describable in terms of the corresponding SB values for the DMSO/ACN mixture. Figure 1 shows the variation of the $\delta(^{23}\mathrm{Na}^+)$ values reported by Greenberg and Popov[7] as a function of the mole fraction and SB for the mixture. From the figure it follows that (a) $\delta(^{23}\mathrm{Na}^+)$ exhibits an ideal behavior toward SB and (b) the iso-solvation point corresponds to an SB value of 0.45 [obtained by fitting the SB vs $\delta(^{23}\mathrm{Na}^+)$ plot], which is similar to the mean of the SB values for DMSO and ACN (0.46).

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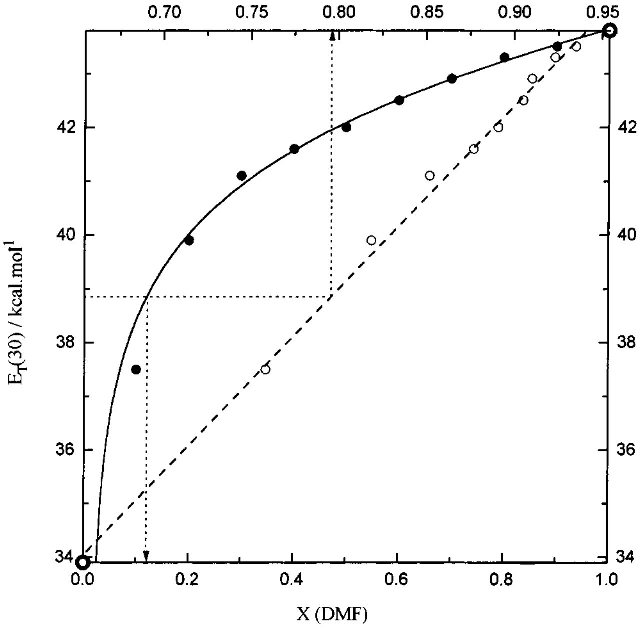

Figure 3. Plot of the $E_T(30)$ data against the mole fraction X(DMF) (●) and the SPP parameters (○) for the DMF/toluene mixture.

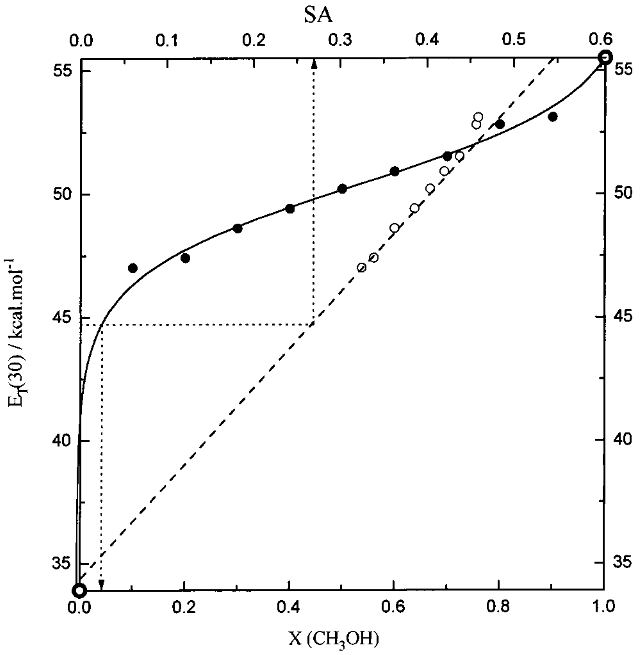

Figure 4. Plot of the $E_T(30)$ data as a function of the mole fraction X(CH_3OH) (●) and the SA parameters (○) for the toluene/methanol mixture.

Erlich et al.[16] provided a clear example of preferential solvation in a binary mixture of DMSO and pyridine (SPP = 0.922, SA = 0.033, SB = 0.581) based on the variation of the frequency of the Na^+ solvation band in the far IR, which was known to appear at 200 cm^{-1} in DMSO[17] and at 180 cm^{-1} in pyridine.[18] Figure 2 shows the variation of the data reported by Erlich et al.[16] as a function of the mole fraction and SB for the mixture. From the figure it also follows that (a) behaves ideally toward SB and (b) the iso-solvation point occurs at SB = 0.607 [obtained by fitting the SB *vs* plot] and is thus quite consistent with the mean of the values for DMSO and pyridine (0.614).

One of the probes most widely used to study the effects of preferential solvation is $E_T(30)$ of Dimroth and Reichardt[19,20] (see Chart 1). This probe[12,19,21] is known to be similarly sensitive to solvent polarity and acidity but not to basicity. Let us first analyze the results obtained by Mancini et al.[22] for this probe in a mixture of *N*,*N*-dimethylformamide (DMF) (SPP = 0.954, SA = 0.031, SB = 0.613) and toluene (SPP = 0.655, SA = 0.0, SB = 0.128) based on their SPP and SA values of the pure solvents. Only the polarity of the mixture should change with its composition. Figure 3 shows a plot of the $E_T(30)$ data reported by Mancini et al.[22] against the mole fraction of DMF and SPP for the mixture. The figure allows us to conclude that (a) $E_T(30)$ behaves ideally toward SPP and (b) the iso-solvation point corresponds to SPP = 0.798 [obtained by fitting the SPP vs $E_T(30)$ plot], which is quite similar to the mean of the SPP values for DMF and toluene (0.805).

Let us now analyze the behavior of $E_T(30)$ as determined by Mancini et al.[22] for a mixture of toluene and methanol (SPP = 0.857, SA = 0.605 and SB = 0.286). Altering the composition of this mixture will obviously change not only its acidity but also its polarity. However, we shall focus on the influence of acidity because, as can be seen from Figure 4, this is the typical situation where a complex is formed via a hydrogen bond [between the $E_T(30)$ betaine and methanol]. Figure 4 shows the $E_T(30)$ data reported by Mancini et al.[22] as a function of the mole fraction of methanol and SA for the mixture. As can be seen, (a) $E_T(30)$ behaves in a *quasi*-ideal manner toward SA and (b) the iso-solvation point corresponds to SA = 0.265 [obtained by fitting the $E_T(30)$ vs SA plot], which is acceptably consistent with the mean of the SA values for methanol and toluene (0.303).

Let us finally analyze the typical deviation of the vapor pressure of a mixture with respect to the ideal behavior expressed by Raoult's law. Figure 5 shows the vapor pressure data reported by Tomila et al.[23] for 2-methyl-2-propanol in aqueous mixtures as a function of the mole fraction of 2-methyl-2-propanol and SB for the mixture. From the figure it follows that (a) the vapor pressure varies in an almost ideal manner with SB and (b) the iso-solvation point corresponds to SB = 0.439 [obtained by fitting the SB vs the vapor pressure plot], which is consistent with the mean of the SB values for water and 2-methyl-2-propanol (0.452).

A global analysis of Figures 1−5 allows us to draw the following conclusions:

(a) The iso-solvation point for all the mixtures considered above occurs at virtually the same mole fraction (0.11 ± 0.02), which is somewhat strange for two solutes

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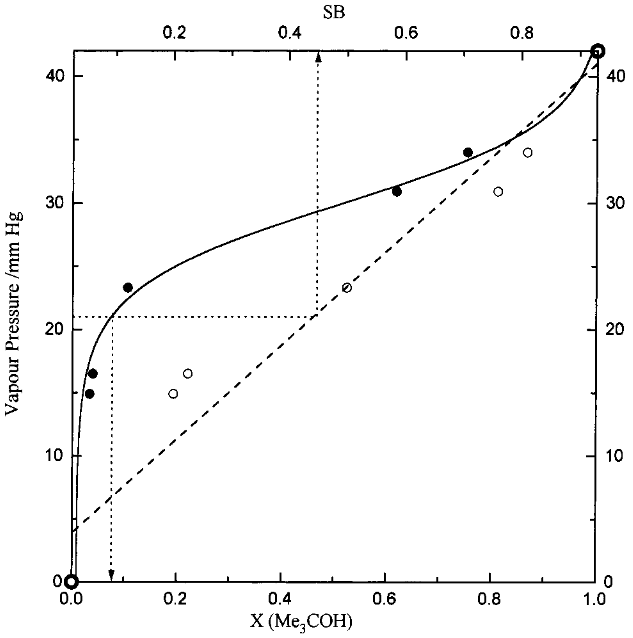

Figure 5. Plot of the vapor pressure data vs the mole fraction X(Me$_3$COH) (●) and the SB parameters (○) for 2-methyl-2-propanol in aqueous mixtures.

so markedly different in size, shape, and charge as Na^+ and $E_T(30)$ betaine (see Chart 1), and for a situation that involves no solute (the vapor pressure of one of the mixture components).

(b) The iso-solvation point occurs at the central point of the solvent scale range used in each case in the five mixtures examined. Thus, the value of $\delta(^{23}Na^+)$ is between those for DMSO and ACN when SB for the mixture corresponds to the mean of the basicities of the two solvents. Likewise, the value of $E_T(30)$ is the mean of those for DMF and toluene when the mixture possesses an SPP value that is the mean of the values for pure DMF and toluene. Finally, the vapor pressure takes its mean value when the mixture basicity does.

Now, that we have shown that the variation of $\delta(^{23}Na^+)$ and $\Delta\nu(Na^+)$ in DMSO/ACN and DMSO/pyridine is due to the basicity of the mixture, and that the variation of $E_T(30)$ in DMF/toluene is due to the polarity (SPP) of the mixture, whereas that in methanol/toluene mixture is due to acidity, one can state that the iso-solvation points of these mixtures correspond to the compositions where the basicity (SB), polarity (SPP), and acidity (SA) equal one-half of the combined values for the pure components. Accordingly, assuming that both mixture constituents contribute identically at the iso-solvation point may be unjustified.

There is one last reflection worth making: how can mixtures possibly be so accurately characterized in terms of SPP, SA, and SB scales constructed from probe/homomorph couples so different in shape, size, and properties (see Chart 1) when preferential solvation is so markedly influenced by features of the solute such as its shape, charge, properties, and size?

We can conclude that this approach provides a method for characterizing solvent mixtures with the same accuracy as pure solvents.[10,12,24−26] Although only one of the mixtures considered is aqueous, we should note that this type of mixture is also accurately described by the proposed approach as it was found to correctly reproduce the rate of solvolysis of 2-chloro-2-methylpropane in 27 pure solvents, the gas phase, and 120 aqueous mixtures.[27] Also, our method has allowed a correct description of the decarboxylation kinetic of the tetramethylguanidinium salt of 3-carboxy-6-nitrobenzisoxazole in 24 pure solvents and 36 dimethyl sulfoxide binary mixtures.[28] It is also worth noting that additional evidence obtained by our group allows us to anticipate that the proposed approach appears to be a useful tool for rationalizing and understanding protein folding−unfolding by denaturing agents.[29]

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Supporting Information Available: Three plots. This material is available free of charge via the Internet at http://pubs.acs.org.

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