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Review Commentary

Probing the solvation shell of organic molecules by intermolecular ^{1}H NOESY†

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ABSTRACT: The solvation of some neutral and charged organic molecules (phenol, nitroanilines, tetraalkylammonium) in binary solvent mixtures was investigated by means of intermolecular ^{1}H-NOESY NMR spectroscopy. The solvation shell of the solute is, in most cases, selectively enriched in one of the cosolvents (preferential solvation). The origin of preferential solvation is discussed in terms of solute–solvent interactions and microheterogeneity in the solvent mixture. Copyright © 2002 John Wiley & Sons, Ltd.

KEYWORDS: binary solvent mixtures; NMR spectroscopy; NOESY; preferential solvation

INTRODUCTION

When a substance is dissolved in a solvent mixture, the composition of the solvation shell may be different from that of the bulk; this situation is pictorially represented in Fig. 1.

This phenomenon is commonly denoted preferential (or selective) solvation[1–4] and has an obvious bearing on all solvation-related properties, since the environment of solutes and solvents may be substantially different from that expected on the basis of the bulk composition. Ultimately, then, reactivity changes may ensue.[5] Apart from practical implications, an understanding of the factors that drive the system towards an enrichment in one component is obviously desirable. The basic question connected with preferential solvation is, therefore, the extent to which it is due to molecular properties (such as the capabilities to be engaged in hydrogen bonding, dipole–dipole and dispersive interactions) rather than collective/cooperative phenomena that involve large ensembles of molecules.

Not surprisingly, preferential solvation has been investigated with a variety of experimental and theoretical methods.[3,4] Most studies have been concerned with electrolytes like metal ions, and employed methods which are not easily applicable, e.g. to neutral molecules. However, notably Wakisaka and co-workers probed the solvation shell of neutrals determining the mass spectra of clusters obtained by evaporation of solution droplets.[6]

A few NMR methods have also been tailored to probe the association of neutral species, notably those based on the A_{ij} parameter[7] or 2D intermolecular HOESY (mapping heteronuclear NOEs).[8] However, in general, intermolecular interactions are best probed through the nuclei that point towards the outside, in most cases hydrogen atoms. When coupled with the high sensitivity of ^{1}H compared with those of heteronuclei, the

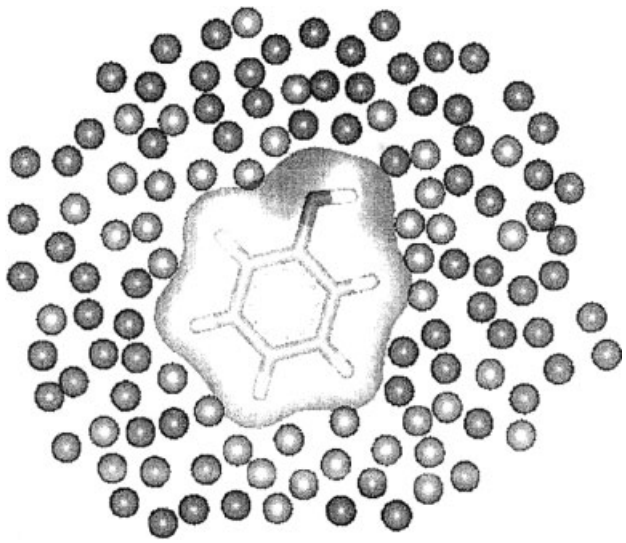

Figure 1. Pictorial representation of preferential solvation. The solute molecule (phenol) is embedded in a schematic solvent mixture portrayed by the light- and dark-grey spheres, which are in equal number. The solvation shell is represented as being enriched in the light-grey solvent

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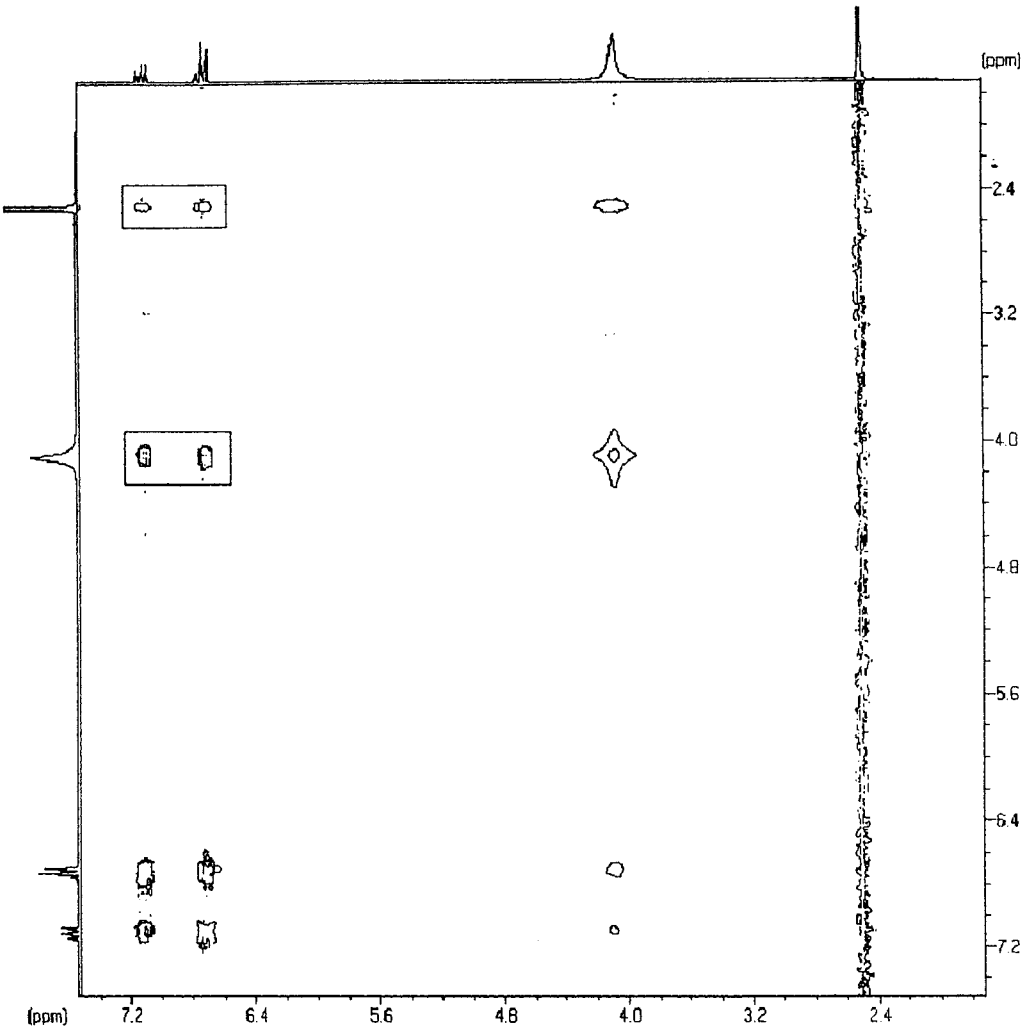


Figure 2. 200 MHz ^{1}H NOESY phase-sensitive spectrum of phenol in 1:1 water–DMSO. Spectral window, 1.6 kHz; mixing time, 3.4 s; 230 FIDs acquired in 4K data points, 96 scans each. Cross (i.e. off-diagonal) peaks indicate the onset of dipolar cross-relaxation, arising from NOE, between spins at the ν_1 and ν_2 frequencies. Intermolecular cross-peaks, observed at solute and solvent frequencies, are highlighted

advantages of exploiting ^{1}H NOEs (by the ^{1}H NOESY sequence) become clear.

The latter method exploits the NOE between spatially close protons, a well-established technique for probing structure and conformation. However, perhaps owing to its great success when applied in this fashion, considerably less attention has been paid to the fact that NOEs can in principle be observed also when the involved spins belong to different molecules, which of course opens a path for investigating solute–solvent interactions at an atomic resolution level. Part of this neglect stems from the fact that the methods for preparing the samples for NOE measurements recommend deuterated solvents, precisely aiming at suppressing intermolecular NOEs.[9] Such effects consequently become very weak or unobservable.

The longitudinal relaxation of ^{1}H (and of other spin-$\frac{1}{2}$ nuclei) takes place mostly through the fluctuation of nuclear dipoles in the surrounding spins. For small molecules in non-viscous solvents,[9] the intermolecular dipole–dipole relaxation rate is proportional to the spin concentration reached by the solvent (N), the diffusion coefficient (D) and the approach distance (r) as $1/T_1^{\mathrm{DD,inter}} \propto N/Dr$. Even this qualitative expression highlights that the factors that appear therein are related to solvation, and therefore that the NOESY technique may furnish valuable information thereon.

In previous work,[2–4] we showed that one can emphasize intermolecular NOEs by a careful choice of acquisition parameters of standard 2D ^{1}H NOESY sequences, and thus extract the useful information contained therein. Related approaches have been advocated for the study of biomolecules.[10]

NOESY spectra obtained under appropriate conditions (solvents with low deuterium content, mixing time tailored to the very slow relaxation rates in such

solutions) indeed show cross-peaks at the solute and solvent frequencies. One such example is given in Fig. 2.

NOESY cross-peaks arise from dipolar cross-relaxation between the spins involved. Intermolecular cross-peaks, therefore, yield information on the efficiency of solute–solvent dipolar cross-relaxation. These cross-peaks have different integrated intensities; the question then becomes whether such differences may be related to the composition of the solvation shell. In order to do this, one must have theoretical expressions for such intensities, which we have evaluated[3] following the theory developed by Macura and Ernst,[11,12] lifting some constraints built into the original formulation.

If we denote our system as being made of a solute (A) present at a very low concentration in a mixture of two solvents (B and C), according to the Macura–Ernst theory, the intensity of the intermolecular cross-peak between spins i and j as a function of the mixing time τ_m, $a_{ij}(\tau_m)$, is given by

$$a_{ij}(\tau_m) = \frac{n_j M_0}{N} [\exp(-\mathbf{R}\tau_m)]_{ij} \quad (1)$$

where n_j is the concentration of spin j, M_0 is the equilibrium magnetization, N the total spin concentration ($N = n_A + n_B + n_C$) and $[\exp(-\mathbf{R}\tau_m)]_{ij}$ a matrix element of $\exp(-\mathbf{R}\tau_m)$.[12] The evaluation of Eqn. (1) requires diffusion coefficients (D) and approach distances (r); such parameters were estimated by means of the microviscosity theory,[9a] with the aid of experimentally available viscosities.

Thus, if a_{AB} and a_{AC} are the cross-peak intensities between solute A and solvents B and C, respectively, their ratio can be calculated as seen above. The ratio of cross-peaks due to each individual solute–solvent interaction (a_{AB}/a_{AC}) is given by

$$\left(\frac{a_{AB}}{a_{AC}}\right)_{calc} = \frac{n_B}{n_C} \frac{\exp(-\mathbf{R}\tau_m)_{AB}}{\exp(-\mathbf{R}\tau_m)_{AC}} \quad (2)$$

Values of a_{AB}/a_{AC} are calculated setting all spin concentrations to the values imposed by the composition of the mixture (i.e. the solvent mole fractions x_B and x_C; x_A is much smaller, and its effect is negligible). If there is preferential solvation, this will be reflected in a different experimental a_{AB}/a_{AC} value. Thus, if, e.g., $(a_{AB}/a_{AC})_{exptl} > (a_{AB}/a_{AC})_{calc}$, then the solute will be preferentially solvated by solvent B.

This qualitative result can also be put on a semiquantitative basis. One can numerically invert Eqn. (2), thus finding a new set of solvent mole fractions (x'_B, x'_C) that render $(a_{AB}/a_{AC})_{exptl} = (a_{AB}/a_{AC})_{calc}$.[3] These new mole fractions x'_B, x'_C may be viewed as providing a semiquantitative description of the extent to which preferential solvation has altered the solvation shell.

PREFERENTIAL SOLVATION OF SOME ORGANIC NEUTRAL AND CHARGED SPECIES

Throughout the following presentation, we will assume a 1:1 mole fraction binary mixture as solvent, the solute being present at very small mole fraction (ca 10^{-2}), and we will show NOESY data obtained by adding up the integrals of all signals from non-exchangeable protons in the solute (i.e. the solvation of the whole solute molecule).[2,3]

Solvation in isotopomeric solvent mixtures

Even though the results obtained by this technique are consistent with available data independently obtained (see below), we strived to validate the method by studying a system having a known behavior. A good benchmark would be provided by a solute that is *not* preferentially solvated; however, this is easier said than done. Even though one can make this assumption for some real-world mixtures, there is hardly any bona fide such case known with certainty. We worked around this problem by adopting a mixture of isotopomers of the same chemical entity as solvent.[3] Thus, e.g., a mixture of CD_3CH_2OH (B_1) and CH_3CD_2OH (B_2) is guaranteed to give NMR signals from different molecules because the chemical species, and its solvating characteristics, are essentially the same. If a 1:1 mixture is used, a_{AB1}/a_{AB2} should be equal to the ratio of the respective spin concentrations, in this case 2:3. Figure 3 reports the results of this experiment with phenol as solute; the ratio of intermolecular cross-peaks was 2:3, as expected for non-selective solvation.

Phenol

In 1:1 aqueous mixtures with CH_3CN, DMSO, EtOH and *n*-PrOH, phenol is preferentially solvated by the respective organic cosolvent. Conversely, in a CH_2Cl_2–Et_2O mixture hardly any preference was observed. Inverting Eqn. (2) as described before yields values of x'_B and hence a semiquantitative insight on the extent of preferential solvation (see Table 1).

In aqueous CH_3CN and DMSO, the bulk mole fraction of water ($x_B = 0.5$) is locally decreased to $x'_B = 0.4$. For H_2O–CH_3CN, self-association of both components is known to cause microheterogeneity at $x_B \approx 0.5$.[13] Hence the existence of prearranged regions strongly enriched in acetonitrile suggests that phenol can favorably fit into such clusters. In H_2O–DMSO, self-association seems implicated only at $x_B > 0.8$.[7a,13] Hence, preferential solvation in this system is dictated mainly by individual solute–solvent interactions, and the result is consistent with a preference for the stronger HB acceptor (DMSO).

More strikingly, when the organic cosolvent is EtOH

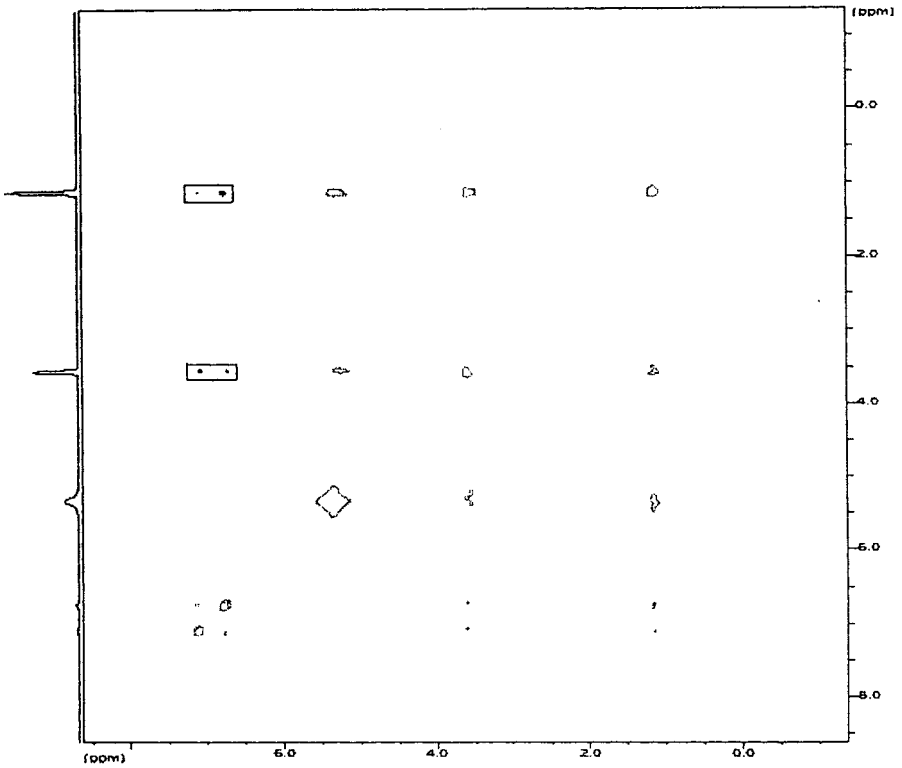


Figure 3. 250 MHz ^{1}H NOESY phase-sensitive spectrum of phenol in 1:1 CH_3CD_2OH–CD_3CH_2OH. Spectral window, 2.5 kHz; mixing time, 3.3 s; 256 FIDs acquired in 4K data points, 32 scans each. Intermolecular cross-peaks are highlighted

or *n*-PrOH, $x'_B = 0.1$–0.2. This marked preferential solvation probably stems from the ability of both alcohols to solvate phenol through both HB and dispersive interactions, as well as microheterogeneity due to self-association of both alcohols.[7a,b,13] The results obtained by Wakisaka *et al.* through the analysis of the composition of molecular clusters by mass spectrometry[6b] are in agreement with the NOESY results. It should be noted, however, that the solvolytic behavior of structurally related compounds (substituted benzyl and benzoyl chlorides) in water–alcohol mixtures has been interpreted differently.[14]

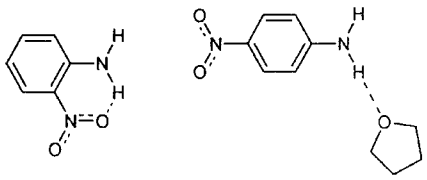
Data obtained in Et_2O–CH_2Cl_2 indicate no preference for either solvent. This result is at variance with the better HB accepting power of Et_2O, and suggests that dispersive interactions with the more polarizable chlorine atoms compensate.

In conclusion, the overall solvation shell of phenol is of a hydrophobic nature, despite the well-known HB donor ability of its OH group. However, it must be kept in

Table 1. Preferential solvation of phenol and nitroanilines in binary solvent mixtures[a]

Solute (A)	Solvent mixture (B–C)	x'_B [b]	Preferred solvent
Phenol	H_2O–CH_3CN	0.4	CH_3CN
Phenol	H_2O–DMSO	0.4	DMSO
Phenol	H_2O–EtOH[c]	0.2	EtOH
Phenol	H_2O–*n*-PrOH[c]	0.1	*n*-PrOH
Phenol	CH_2Cl_2–Et_2O	0.5	None
o-Nitroaniline	Cyclohexane–THF	0.5	None
m-Nitroaniline	Cyclohexane–THF	0.4	THF
p-Nitroaniline	Cyclohexane–THF	0.4	THF
Me_4N^+ Cl^-	H_2O–CH_3CN	0.6	H_2O
n-Bu_4N^+ I^-	H_2O–CH_3CN	0.2	CH_3CN

[a] The bulk composition (1:1) is $x_A \approx 2 \times 10^{-2}$, $x_B = x_C = 0.5$.
[b] From inversion of Eqn. (2) (see text).
[c] The intensity of phenol–water cross-peaks may be overestimated owing to proton exchange with the alcohol.



Scheme 1

mind that the NOESY method only obtains information from the relaxation of the ring protons, many of which are somewhat removed from the OH group.

Nitroanilines

The solvation of *o*-, *m*- and *p*-nitroaniline was investigated in cyclohexane–THF. For the *meta* and *para* isomers THF is preferred over cyclohexane ($x'_B = 0.4$; Table 1), whereas for *o*-nitroaniline there is hardly any preference, in agreement with UV results.[15] Hence, in general their solvation is dominated by dipole–dipole and NH···O hydrogen-bonding interactions between the amino group and the oxygen ether of THF, whereas cyclohexane can only solvate through dispersion. The behavior of *o*-nitroaniline is probably due to the engagement of the NH hydrogen in an intramolecular HB with a nitro oxygen (Scheme 1), thus reducing its requirement for solvent stabilization.

Tetraalkylammonium salts

Me_4N^+ and *n*-Bu_4N^+ were studied in H_2O–CH_3CN, in order to investigate the combined effect of ionic charge and a non-polar surface on the nature of the solvation shell, since their charge is symmetrically located with respect to the probe protons and not directly exposed to the solvent. The results for Me_4N^+ and *n*-Bu_4N^+ in H_2O–CH_3CN (Table 1) were opposite (preference for water and CH_3CN, respectively), which agrees with the values of single-ion transfer activity coefficients.[16] Hence the positive charge of Me_4N^+ is relatively accessible to the solvent, so that solvation is dominated by electrostatic forces and hydration is favored, whereas the surface of *n*-Bu_4N^+ is essentially hydrophobic, and solvation is controlled by the solvent that can best stabilize the solute by dispersion (CH_3CN). However, since the dielectric permittivity of these solutions is relatively small, some degree of ion pairing may not be ruled out, so that the observed result may partly reflect the solvation of the anion. While the NOESY technique is not applicable to quadrupolar halide anions such as Cl^-, Br^- and I^-, the effect of the anion could be profitably probed through anions such as F^-, BF_4^- or simple organic anions.

CONCLUSION

Enrichment of the solvation shell in a given solvent is dictated by the balance of several factors, which may be broadly classified as solute–solvent or solvent–solvent interactions. In aqueous–organic solvent mixtures, the solute–solvent stabilization provided by water is dominated by polar and HB interactions. Depending on its nature, the organic solvent may be able to provide similar stabilizing interactions, but (unlike water, which has a very low polarizability) it can also interact via dispersive interactions[17] with non-polar regions. However, when electrostatic forces are strong, as in the case of Me_4N^+, preferential hydration is apparent. On the other hand, preferential solvation is also favored if the mixed solvent has regions enriched in a self-associated component, i.e. a pre-organized environment with which the solute may interact favorably. If should finally be mentioned that preferential solvation is affected also by a size mismatch in the solvents[18] and entropic effects.[19]

Most of these phenomena, notably those pertaining to microheterogeneity, are collective in nature and cannot be understood through the study of the interaction between single molecules. The simulation of molecular dynamics in bulk, mixed-solvent systems[20,21] is probably the most appropriate theoretical method available for elucidating the structure of the solvation shell at atomic resolution, and its results should usefully complement those obtainable by NMR.

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