Computer Simulations on Aqueous Solutions of Some Non-electrolytes

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1 Introduction

Water is a very good solvent for many kinds of substance. If we confine the scope of solutes to non-electrolyte molecules, we can construct a series of solutes according to the magnitude of the cohesive energy density of the molecule in question. One example of such energy density series is shown in Figure 1, where one can see that the position of water is at the upper end (the highest energy density). By contrast, rare gases, fluorocarbons, and hydrocarbons are near the other (lower energy density) end of the series. It is well known that the latter substances show only a low solubility in water and that, although the composition ranges of their aqueous solutions are severely limited, there occurs a remarkable change in the structure of solvent water. The structure promotion in such dilute aqueous solutions is known as 'hydrophobic hydration'.[1]

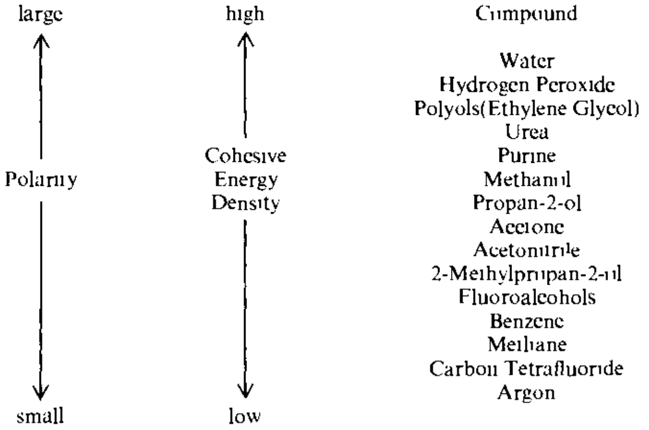

Figure 1 Cohesive energy density series for water and organic non-electrolytes.

On the other hand, the positions of polar and associated molecules, such as urea, polyols, and hydrogen peroxide, are located near the position of water. Such molecules can be accommodated into water structure rather easily and their aqueous solutions can be treated as normal mixtures.[2] In such aqueous solutions, structure enhancement of water might not exist, but rather a structural disruption has been suggested, as in the case of urea. Only hydrogen bonding interactions should be predominant.

There are many other organic compounds between these two extremes. Detailed thermodynamic studies indicate that, except for some highly hydrophilic compounds mentioned above, their aqueous solutions can be characterized by the behaviour of the non-polar group in the molecule. Rare gases and alcohols behave similarly as far as the thermodynamic excess properties are concerned, and the role of polar groups in the latter molecules is simply to lower the free energy and to promote a high miscibility with water.

Although important progress has been achieved experimentally in thermodynamic studies, knowledge at the molecular level is still insufficient. Recently, there has been much progress in molecular simulation because of rapid developments in supercomputers as well as in the techniques for calculating static and dynamic properties of molecular ensembles. The method of molecular simulation,[3] which consists of molecular dynamics (MD) and Monte Carlo (MC) calculations, can serve as a complementary method to traditional macroscopic approaches.

In this review we first give a brief description of how we can execute MD and/or MC calculations for aqueous solutions in which the hydrogen bonding interaction is predominant. We then discuss the results of molecular simulations of aqueous solutions of, mainly, 2-methylpropan-2-ol (TBA) and urea. There exist several reasons for the choice of solutes. First, these two molecules represent highly hydrophobic and hydrophilic compounds, respectively. Secondly, their molecular structures are such that conformational changes are relatively unimportant. In other words, the internal rotations do not cause large conformational changes in the molecules. One may consider that if these two rather extreme cases can be fully understood, then the intermediate molecules might be more easily interpreted. We shall show in a later part of this review, however, that one of the intermediate cases, acetonitrile-water mixtures, is actually highly complicated and interesting.

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2 Method of Molecular Simulation

The method of molecular simulation as applied to aqueous solutions of non-electrolytes consists of the following several processes.

2.1 Selection of Potential Functions

In almost all of the molecular simulations attempted so far, the pairwise additivity of molecular interactions is adopted. Thus, three kinds of pair potentials are necessary for binary mixtures. In the present case, one component is always water. For water–water interactions, some empirical and non-empirical models are available. We adopt the so-called TIP4P potential proposed by Jorgensen,[4] and also the MCY potential by Clementi *et al.*[5] We should point out that, although many water–water dimer potential functions including the above have been proposed,[6] we are still looking for a better one. If we term the second component 'solute', though somewhat ambiguously, we must have water–solute and solute–solute potential functions. They are not available, except for some limited cases. In the case of non-polar molecules, solute–solute potentials can be expressed by the simple Lennard-Jones potential. Otherwise, we must use semi-empirical methods or derive potential functions for a dimer (super-molecule) on the basis of quantum chemical molecular orbital (MO) calculations. As a semi-empirical method, Jorgensen and co-workers have proposed a useful set of potential parameters called TIPS or OPLS for various kinds of atoms and atomic groups, in order to avoid the unnecessary repetition of MO calculations. This is essentially a potential energy version of the group contribution concept. Thus, semi-empirical potential functions can be prepared easily by combining their parameters. The TIP4P potential for the water dimer mentioned above is a typical example. OPLS potentials are adopted for the acetonitrile dimer[7] and water–acetonitrile interactions.

2.2 Preparation of the Potential Function

In the general case where the above-mentioned semi-empirical potentials cannot be utilized, or are shown to be inappropriate, one must proceed to the so-called 'super-molecule method', with the aid of extensive MO calculations. Potential functions for TBA dimer,[8] urea dimer,[9] TBA–water,[10] and urea–water[11] have been developed in this manner. The method consists of the following procedures.

(i) The molecular conformation of each molecule concerned should be known. Sometimes information is available from molecular spectral data. Otherwise, the most stable one can be determined by the energy gradient method in MO calculations.

(ii) Energies of the two molecules concerned, say, 1 and 2, and of the super-molecule (1 + 2) are determined by MO calculations, using the appropriate basis set. Then intermolecular interactions between 1 and 2, $\phi_{12}(r)$, can be obtained by

$$\phi_{12}(r_1, r_2) = E_{12}(r_1, r_2) - E_1(r_1) - E_2(r_2) \qquad (1)$$

where molecules 1 and 2 are identical in the case of pure fluids.

(iii) The determination of $\phi_{12}(r)$ is repeated for each different mutual configuration of (1 + 2) and simultaneous optimization of parameters in an assumed potential function. The functional form of potential implies the proposition of a model. In this manner, an assumption is introduced into the potential function.

(iv) When the further addition of different configurations does not lead to an improvement in the potential parameter set, we can assume that a reasonable 'non-empirical' potential function has been obtained.

A representative example of this procedure may be found fully described in literature for the case of TBA-water.[10]

2.3 MD and MC Simulations

The methodology of molecular simulation for liquids and liquid mixtures is now well documented.[3] Only some important points will be commented upon. Monte Carlo calculations have usually been done in NTV and NPT ensembles by the use of the Metropolis scheme.[12] The number of molecules N is 256 and the temperature T of the system is 298.15 K throughout the present calculations. In addition, either the volume of the cell V, from the density data, or the pressure P (normally 1 atm.) is kept constant. The Metropolis scheme is essentially the generation of the configurations of a molecular ensemble under certain restrictions, and the total potential energy of the ensemble tends to decrease normally until a stationary state is established. One needs at least 10^6 N configurations for the equilibrium of the system and a further 2×10^6 N configurations for the formation of a meaningful statistical mechanical ensemble. Various structural and thermodynamic properties of the system studied can be obtained from MC ensemble data.

Conventional molecular dynamics calculations have normally been performed for systems with spherical symmetrical potentials in a microcanonical (NEV) ensemble by the use of the Verlet scheme.[13] Since the temperature T is obtained as a result of the calculation, the constant temperature MD, proposed by Andersen, is sometimes used.[11] The molecular dynamics calculation is essentially a numerical integration of the Newton–Euler equation of motion for the molecular ensemble. The time step is 0.005 picoseconds and the number of steps is as large as 10^5. The integration extends to a total of 20 ~ 40 ps. The result of calculations, namely the position and velocity of each molecule as a function of time, forms a statistical MD ensemble description, from which various static and dynamic properties of the system studied can be derived.

In the present case, attention is focused mainly on the structure of the solution. The fundamental property used to describe structural characteristics is the radial distribution function (RDF) $g(r)$. In addition, one can make use of various kinds of energy–structure distribution functions, among which the pair interaction distribution function, PIDF, might be the most useful. PIDF is the distribution of the interaction energy of each pair of molecules in the system.

3 Aqueous Solutions of TBA

Among aliphatic alcohols miscible with water in all proportions, TBA has the largest and most compact hydrophobic group. The minimum in the partial molar volume–composition relation in TBA aqueous solution is the most characteristic among organic non-electrolytic solutes. This means that hydrophobic effects are largest in this solution. Results of extensive MC and constant temperature MD calculations are available for 0.5, 3.0, 8.0, and 17 mol % aqueous solutions of TBA with the potential models described above.[8,10,14]

In the case of an infinitely dilute solution (1 TBA in 215 water ≃ 0.5 mol %), a hydration structure is clearly formed. Figure 2 shows density diagrams for the distribution of the water molecules surrounding TBA. For a comparison, similar density diagrams are included in the figure for water molecules around methanol or one specified water molecule.[15] This is essentially a graphic representation of the angle-dependent $g(r)$ (or more exactly, pair correlation functions between the centres of mass of alcohol and water). It is seen that, while the hydration structure around methanol is spherical, around TBA it is rather spot-like, suggesting the formation of a stable hydration shell in the latter case. Moreover, it is interesting to note that, as seen in Figure 3, the average potential energy of water molecules in the hydration shell of the hydrophobic groups of TBA is lower than that near the hydroxyl group of TBA. Although qualitative observations, they are evidence for the existence of hydrophobic hydration.

Similar information can be obtained from the RDF itself. Indeed, the first peak of the water–water RDF becomes significantly higher when a small amount (3 mol %) of TBA is introduced into pure water. This is direct evidence for the structure enhancement of water in such dilute solutions.

Kauzemann proposed three different liquid structures for pure water (ice), depending on the time scale of observation.[16] They are I(instantaneous)-structure, V(vibrationally-averaged)-structure, and D(diffusionally-averaged)-structure. Both V- and I-structures obtained from the results of MD calculation will give useful information on hydrophobic hydration and interaction(HI). The V-structure can be seen in the trajectory diagram obtained from the results of the MD calculation.

Here HI implies a kind of self-association of non-polar molecules in aqueous solution or of the tendency of non-polar groups to interact with each other. Although not to be discussed in more detail here, this kind of hydrophobic interaction is proved to be of solvent-separated type(SSHI), suggested by Franks.[17] The presence of HI can be seen most definitely in the PIDF shown in Figure 4a, where a large peak for TBA–TBA interactions appears between − 5 to + 10 kJ mol^{-1} and the distribution completely disappears in the lower energy region, indicating the lack of hydrogen bonding interactions between TBA molecules. However, as shown in Figure 4b, the TBA–TBA interaction has a small but definite peak between − 10 and − 20 kJ mol^{-1} in a more concentrated (17 mol %) solution, indicating the presence of hydrogen bonding between TBA molecules in such a TBA/water molar ratio.

Summarizing the general impression obtained from MD and MC data, the introduction of TBA into water leads to an

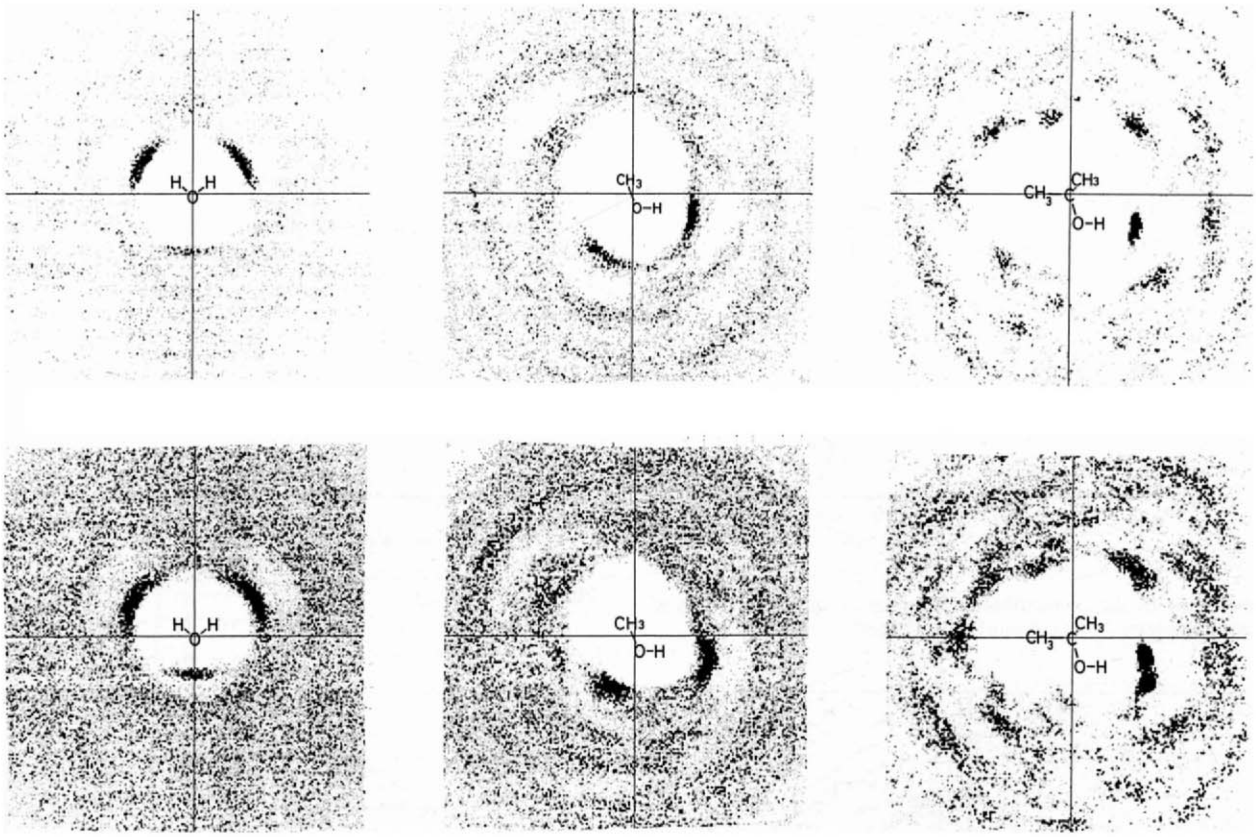

Figure 2 Density distribution diagrams of water molecules around water, methanol, and 2-methylpropan-2-ol: (upper) oxygen atom, (lower) hydrogen atoms.

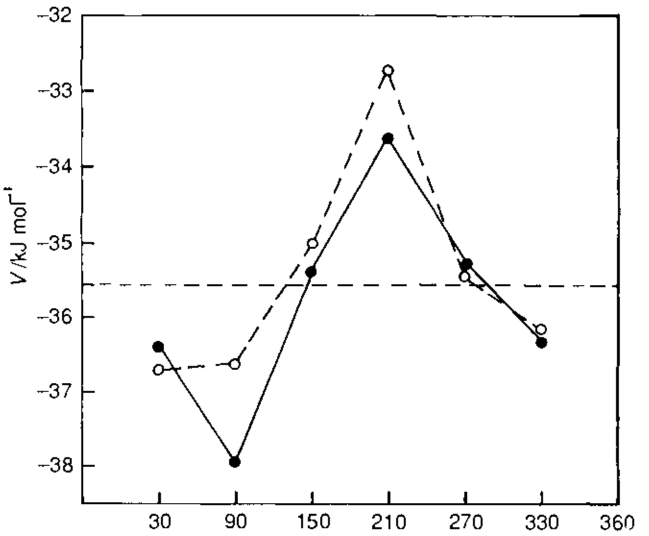

Figure 3 Angular dependence of the potential energy of water molecules hydrated around 2-methylpropan-2-ol (for details see ref. 10).

enhancement of aqueous structure, an energetic stabilization of water molecules near hydrophobic groups of TBA, and solvent-separated hydrophobic interactions between TBA molecules. With an increase in TBA concentration, hydrophobic interactions, namely contacts between hydrophobic groups, are predominant below 10 mol % solution. The formation of hydrogen bonding between TBA molecules cannot be observed in this region. It is only above 10 mol % that the hydrogen bonds appear between TBA molecules.

4 Aqueous Solutions of Urea

Effects of urea and its alkyl derivatives on water structure have been studied extensively by experimental and model approaches.[18] Conflicting interpretations are given for the results of these studies: one insists that urea may destroy water structure, while another suggests that urea may promote water structure. In addition, urea behaves as a protein denaturing agent in concentrated aqueous solutions. It is thus important to clarify at the molecular level the influence of urea on hydrophobic effects.

As previously noted, urea occupies a position on the hydrophilic side of the series given in Figure 1. Urea seems to be a good partner of TBA, because of the conflicting effects on water structure. The procedure of determining a potential function, as explained in Section 2, is quite suitable for urea because it is a rather rigid molecule, internal rotations being unimportant, and there are strong hydrogen bonding interactions.

There exist non-empirical potential functions for urea–water[11] and urea–urea[9] interactions, and the results of MD simulations are available.[9,11,19] According to quantum mechanical MO calculations, water and urea form a ring-like dimer and the intermolecular energy is estimated to be as large as − 40 kJ mol^{-1}. However, an MD simulation of a 0.5 mol % (1 urea in 215 water) urea solution indicates that the structure of water is practically identical to that of pure water, except for a few water molecules attached to hydrogen bonding sites of urea. In Figure 5, the density distribution diagram for the distribution of water molecules around urea(D-structure) is superimposed on an isoenergy contour map for the urea–water potential. It is seen that the water distribution outside the hydration shell around urea has no special structural characteristics. There seems to be five strong hydrogen bonding sites in the hydration shell. Of these, one is at the potential minimum between two amino groups. The other four sites near the carbonyl group do not correspond to the minima in the urea–water potential. The resultant disadvantage in the energetic stabilization can be compensated by the harmonious connections between the hydration shell and the surrounding water structures.

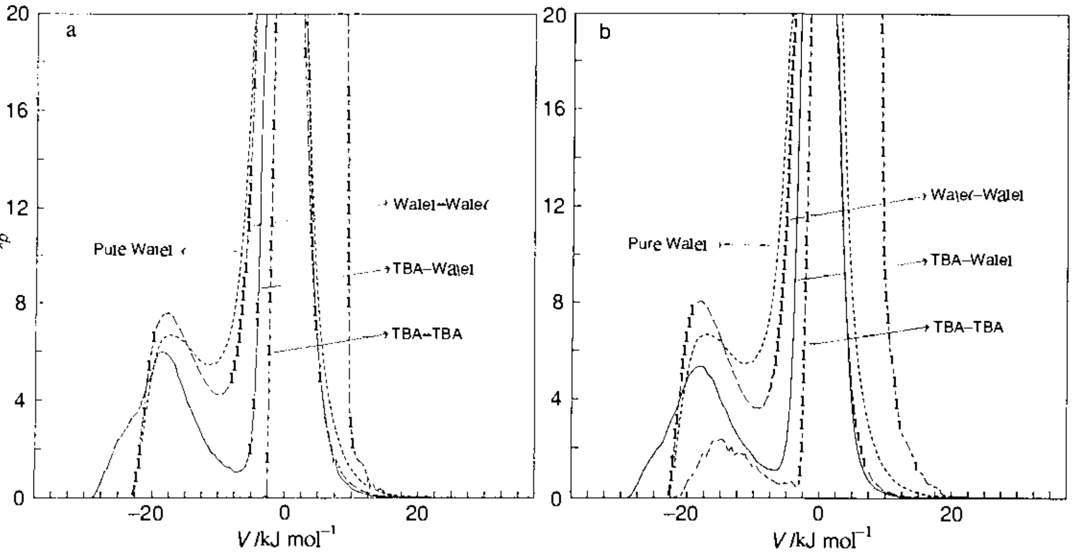

Figure 4 Pair interaction distribution functions in aqueous solutions of 2-methylpropan-2-ol: (a) 8 mol%, (b) 17 mol%.

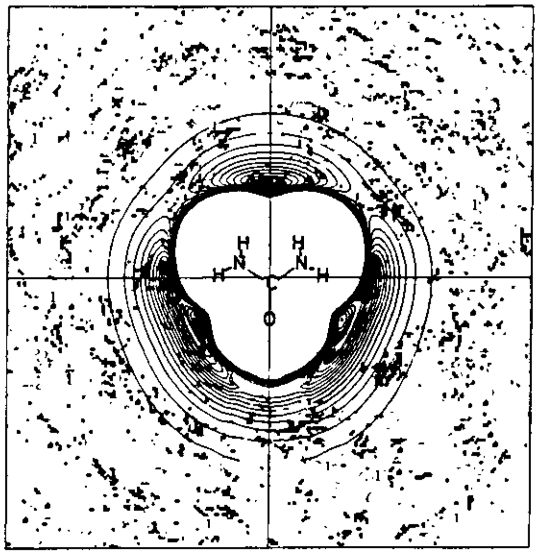

Figure 5 Comparison of density distribution diagram of water molecules around urea with the isoenergy contour map of urea + water potential.

In more concentrated solutions (8 and 17 mol % solutions), urea molecules tend to self-associate as seen by graphical presentations of l- and V-structures.[9-11] The pair interaction distribution functions plotted in Figure 6 can also afford interesting information on the self-association of urea. One can see two large peaks for urea–urea interactions near $-20 \sim -40$ and $-60 \sim -80$ kJ mol^{-1}, respectively. These are due to the self-association of urea. In contrast to the hydrophobic interaction in dilute TBA solution, it is through these strong hydrogen bonding interactions that urea can self-associate in water.

5 Aqueous Solutions of Acetonitrile

As has been shown in the above two sections, TBA and urea represent two extreme cases of solutes in water and one expects that the behaviour of many other amphiphiles may easily be understood as intermediate between them without any special complication. This expectation has not been borne out in recent studies on acetonitrile (AN), however.[20,21]

There are many studies dealing with the thermodynamic properties and solution structure for aqueous mixtures of this useful solvent. Computer simulation studies have also been carried out.[22] It has been suggested that AN may form dimers in dilute aqueous solution. This should have a close connection with the fact that, although there is endothermic mixing for almost all compositions of AN–water mixtures, mixing is slightly exothermic in the highly dilute region of AN.[23]

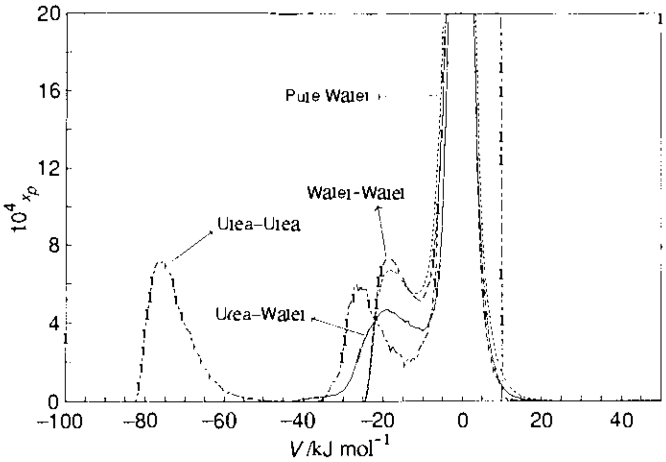

Figure 6 Pair interaction distribution functions in aqueous solutions of urea.

The results of standard NPT Monte Carlo calculations are available for the following conditions and models.[20] The temperature and pressure of the systems are 298.15 K and 1 atmosphere; the total number of molecules in the system is 216; the TIP4P model water–water potential and a three-site model for AN–AN were used. The water–AN potential used is of the conventional LJ × Coulomb type and the unlike interactions assumed are the geometric mean of each set of LJ parameters. This is somewhat different from the usual Lorent–Berthelot combining rule, but the difference is of a minor degree. Some details of molecular models are shown in Figure 7.

Monte Carlo simulations cover the whole composition range of water + AN mixtures with 12 different molar concentrations. Particular emphasis is placed on the water-rich region. Much energetic and structural information has been obtained.

The most direct results from the MC calculation are the excess molar enthalpies H^E of water + AN solutions. In Figure 8, computer generated H^E values are compared with experimental results.[23] It is seen that the real mixtures are less endothermic but the tendency of exothermic mixing in the water-rich region can be well reproduced. The potential functions used are the best ones available for the two pure fluids and the results may

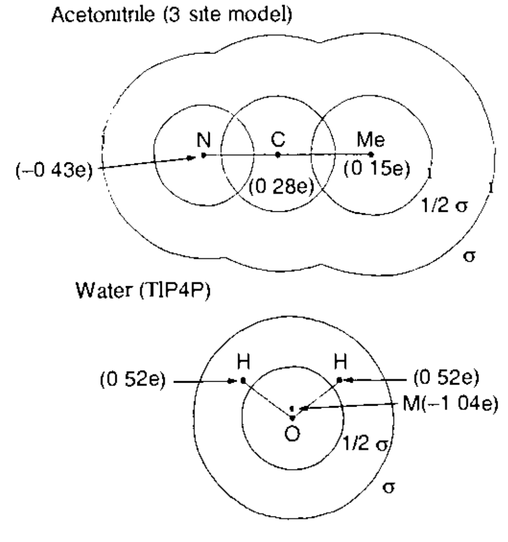

Figure 7 Model for acetonitrile + water interactions

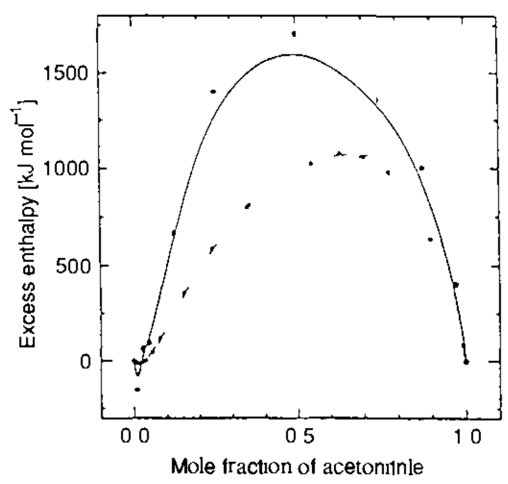

Figure 8 Molar excess enthalpies of acetonitrile + water mixtures Comparison between Monte Carlo(—) and calorimetric( ) results

indicate that there is room for improving the agreement between simulation and experiment by using a more appropriate combining rule for unlike interactions

The solution structure can be quantitatively discussed by calculating various energetic and structural distribution functions However, a graphic display can furnish more impressive information Figures 9 and 10 show solution structures of some water–AN mixtures It is clearly seen that in water-rich regions, where the excess enthalpy is negative, two AN molecules tend to associate It is also observed that in the equimolar region both water and AN molecules show clustering of the same kind, in other words, they are not in monodisperse states The presence of such 'local heterogeneity' might have a close relation with a large positive excess enthalpy

The further analysis of pair formation of AN in dilute aqueous solutions would be impossible by conventional thermodynamic approaches Instead, one can use a statistical mechanical approach, namely, RISM(reference interaction site model) theory [14] Although this RISM theory has been applied to pure fluids, there is difficulty in its application to fluid mixtures However, dilute solutions containing only two AN molecules could be treated in the following manner [21]

(i) Consider two AN solutes with a fixed mutual configuration as a super-molecule $(AN)_2$, the RISM calculation can be applied to the infinite dilution state of this molecule

(ii) The hydration energy is calculated for an infinite dilution state of $(AN)_2$

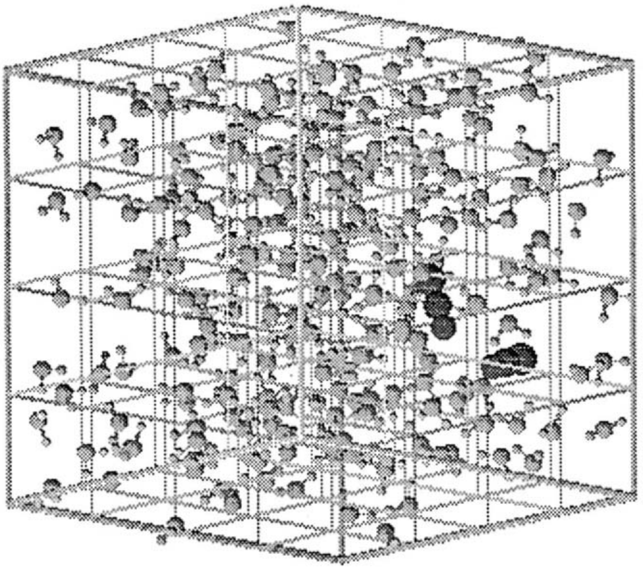

Figure 9 Structure of acetonitrile + water mixture Two AN molecules in 214 water molecules

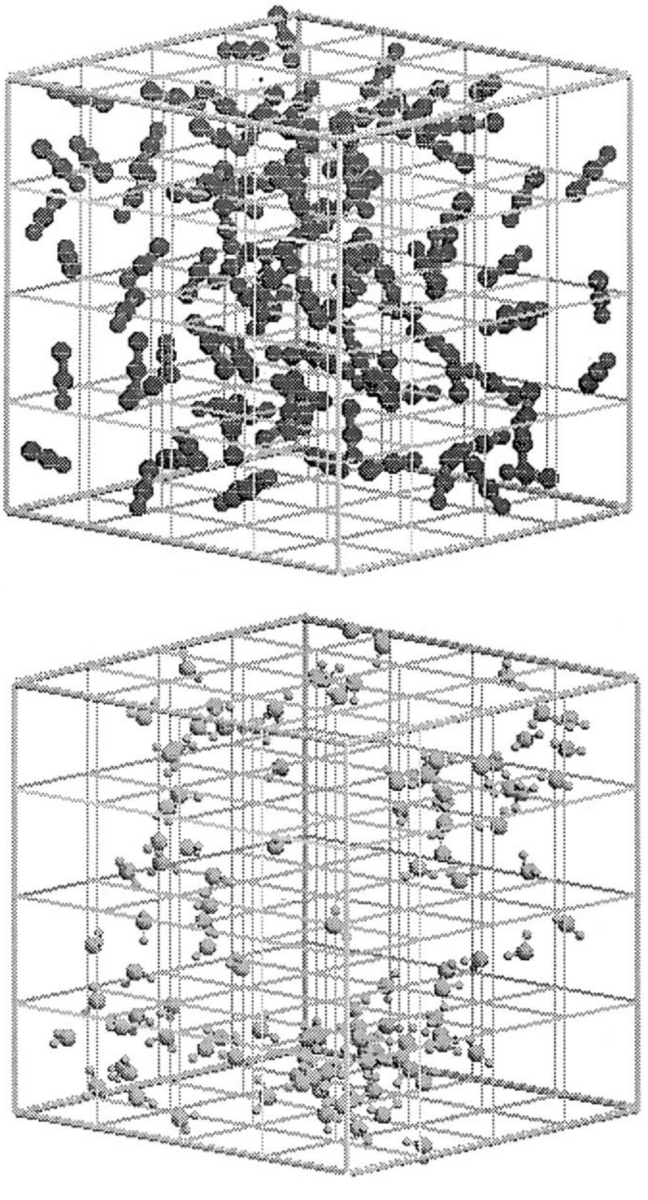

Figure 10 Structure of acetonitrile + water mixture Clustering of AN(upper) and water(lower) in equimolar solution

(iii) The above calculations are repeated by changing the configuration of the super-molecule.

The most stable configuration of $(AN)_2$ obtained from this calculation is such that the angle between two AN molecules is 60° and the distance between centres of mass is 0.4 nm (see Figure 11). Contrary to expectation, the CN group in one AN molecule comes into close contact with the CN group in the other AN molecule. This kind of 'parallel' orientation is the result of the potential of mean force from the surrounding water; the solute–solute interaction is repulsive (~ 11 kJ mol^{-1}); contributions from solvent water are as large as -25 kJ mol^{-1}, and resultant net energetic stabilization due to the pair formation is thus about -14 kJ mol^{-1}.

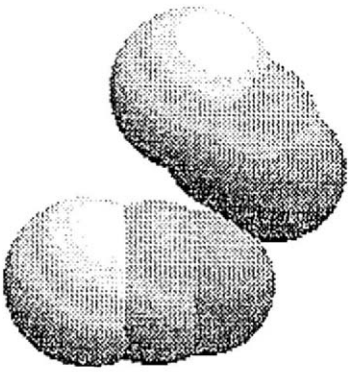

Figure 11 Stable structure of acetonitrile dimer in water.

In order to confirm such unexpected pair formation, an MD simulation has also been done under the same conditions as those in the above RISM study.[21] The result clearly shows a long contact period between two CN groups. Figure 12 is a plot of the site–site distance as a function of time steps in the MD simulation.

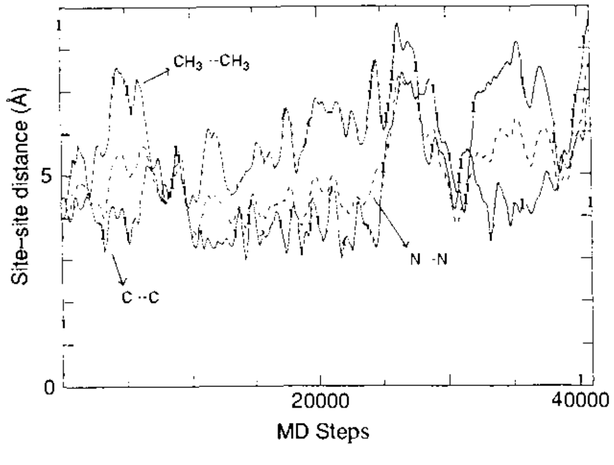

Figure 12 Molecular dynamics results of two acetonitrile molecules in dilute aqueous solution.

6 Concluding Remarks

Recent advances in computer simulation have made it possible to calculate various thermodynamic and transport properties of aqueous solutions of non-electrolytes. If calculated values of many physical properties agree consistently with experimental results, then various types of information on the molecular level obtained concurrently should generally give a valid picture. The MD and MC studies for TBA and urea solutions described in Sections 3 and 4 furnish not only complementary information to various experimental studies but also give a more detailed insight at the molecular level. Similar studies on methanol[15,25] and some other solutes (*e.g.* non-polar molecules,[26] fluoroalcohols,[27] *etc.*) in water have already been performed. As an example, one can also see reasonable agreement of the calculated excess enthalpy of AN–water mixtures with the experimental data.

However, further improvement and extensions of the method of molecular simulation are required because, for example, the calculation of the excess free energy cannot always be performed with confidence. Furthermore, new molecular approaches cannot be complete unless fluctuations and dynamics in liquid mixtures are discussed on a sound theoretical basis. Examples of this kind of approach, namely, one-particle dynamics, local equilibrium searches, and normal mode analysis, are already being applied to aqueous solutions of non-polar molecules.[28]

7 References

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