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Theoretical and Computational Studies of Biomacromolecule–Water Interactions

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Although it is conventional wisdom that water plays a very significant role in the structure, stability, dynamics and interactions of many biochemical systems, the operation of such solvent effects at the molecular level is very poorly understood. Any adequate theoretical or computational approach to *e.g.* the statics and dynamics of protein–solvent interactions at this microscopic level necessarily requires knowledge of the various interatomic potential functions. That such chosen functions should be realistic is underlined by the very marginal stability of native protein structures, their free energies being generally only around 10–20 kcal mol^{-1} lower than their denatured conformations; this represents the energy of only 2–4 hydrogen bonds.

Within this context, our recent work has been directed at (*a*) the effects of changes in water structure itself, and in solvent organisation around ions and macromolecules, as the model potentials are varied, and (*b*) the establishment of reliable potential functions, largely through quantum mechanical calculations. Particular stress is placed on a thorough testing of these potentials at relatively well-defined macromolecule–solvent interfaces, such as are found in protein crystals whose structures have been refined to *very* high (1.5 Å or better) resolution. Computer simulation and model-building studies of several suitable systems (*e.g.* insulin, pancreatic trypsin inhibitor, coenzyme B_{12}) will be described, and the current problems and possible solutions discussed. The particular importance of the cooperative nature of the hydrogen bond is emphasised, especially as it may seriously affect solvent–ion and solvent–macromolecule interactions.

An Experimentalist Point of View on Quantitative Elaboration of Theoretical Models

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In a number of problems of solute–solute–solvent interaction, information on the geometrical structure of solvent in the near neighbourhood of solute is now available. This was obtained from a variety of experiments as well as from numerical calculations. The present trend in computer simulation as well as in experimental techniques seems to appropriately be towards an extension of this information to include thermal disorder.

Despite these efforts, other aspects of solute–solute–solvent interaction do not seem likely to find exhaustive answers through a study of the geometrical configurations of solvent molecules around the solute.

More detailed calculations of inter- and intramolecular dynamical behaviour would not only add appreciably to our knowledge and description of the behaviour of water in the phase-space. It would also provide ampler grounds for comparison between theoretical expectations and experimental findings, now available in this area. In turn, this could hopefully provide a better insight on the possible role of solvent motional modes on solute–solute–solvent interaction.

Molecular Dynamics Simulations of Aqueous Electrolyte Solutions

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In the molecular dynamics simulations the classical equations of motion are solved numerically for a

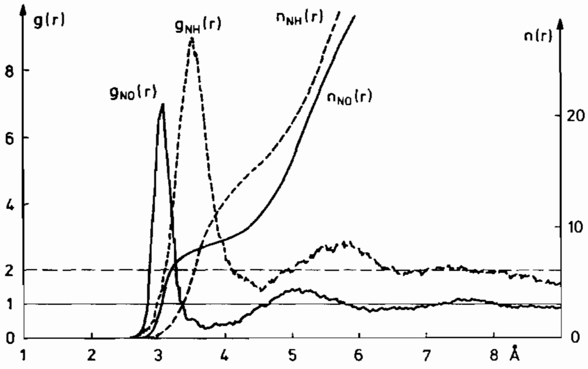

Fig. 1. Radial distribution functions and running integration numbers n(r) for NH_4^+-hydrogen (dashed) and NH_4^+-oxygen (full) in a 2.2 molal NH_4Cl solution.

certain number of particles, usually a few hundred. The interactions between the particles are described by pair potentials and it is assumed that the total potential can be developed as a sum of these pair potentials. From the resulting knowledge of position and velocity as well as orientation and angular velocity, if molecules are involved, as a function of time for each of the particles thermodynamical, structural and dynamical properties are calculated with the help of statistical mechanics.

Results from the simulation of aqueous alkali halide and an NH_4Cl solution are reported. The pair potentials are based on models for the ions and the water molecule. The alkali and halide ions are described by Lennard–Jones spheres with a point charge in the center [1] while the NH_4^+ is modelled as a regular tetrahedron with an N–H distance of 1.05 Å and 4 point charges at the position of the hydrogen atoms each 0.25 of an elementary charge [2]. For the water molecule the rigid four point charge model (ST2) proposed by Stillinger and Rahman [3] is employed. The basic periodic cube contained 200 water molecules and 8 ions of each kind, equivalent to 2.2 molal solutions. The equations of motion are integrated in time steps of 2×10^{-16} sec. The simulations extended mostly over about 10000 time steps.

The structural properties of the solutions are discussed on the basis of radial distribution functions g(r) (Fig. 1) and the orientation of the water molecules in the hydration shells of the ions. The structure function derived from the g(r) can be compared directly with results from X-ray and neutron diffraction studies.

Dynamical properties of the solutions such as self-diffusion and rotational diffusion coefficients, reorientation times of the dipole moment vector and residence times of the water molecules in the hydration shells of the ions are calculated from the simulation through autocorrelation functions and are compared with experimental results. The spectral densities of the hindered translational and librational motions have been calculated by Fourier transformation from the corresponding autocorrelation functions and are compared with IR and Raman measurements.

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