Solvent Organisation in Biomacromolecule–Water Systems: Theoretical Approaches *via* Model Building and Computer Simulation

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As part of a broader experimental and theoretical programme aimed at understanding the role of solvent effects in the folding, stability, interactions and operation of globular proteins [1, 2], we are investigating in detail the possible solvent organisation and dynamics around several proteins and other biologically interesting macromolecules whose crystal structures have been refined to high resolution (1.5 Å or better) by either X-ray and/or neutron diffraction techniques.

Two major, complementary theoretical approaches are used to predict solvent organisation in the *crystal,* and the predictions checked rigorously against the indications (which are often uncertain even at such high resolution) from the crystal structures.

(*1*) By examining in detail the nature of the exposed surface of the protein, correlations between internally unsatisfied hydrogen bonding and surface-exposed area have been found [2, 3] which allow tentative placings of water molecules on the protein surface; further stereochemically allowable manipulations *either* on three-dimensional models *and/or* a sophisticated interactive computer graphics system facilitate modifications of the solvent shell with respect to neighbouring solvent molecules and polar groups. The resulting 'first solvent shell' shows good agreement with the crystal structure studies, and also correlates remarkably well with related infra-red, calorimetric and NMR measurements made in parallel [4].

(*2*) Using a previously developed *non-pair-additive* potential for the water molecule [5–7], Monte Carlo calculations have been performed on the solvent organisation in crystals of three molecules in particular – pancreatic trypsin inhibitor (1.5 Å resolution), insulin (1.5 Å) and coenzyme B_{12}, whose structure is currently under refinement from both neutron (0.9 Å resolution) and X-ray (0.8 Å) data. Macromolecule–water potentials are obtained by molecular orbital calculations on chemically sensible fragments of the molecule. Both semi-empirical and *ab initio* calculations are made with particular emphasis being made on the sensitivity of the solvent structure on the potentials used. The importance of non-pair additivity of both water–water and water–polar group interactions is strongly underlined.

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Quantum Chemical Description of Ions in Solution

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The application of the MESQUAC-MO method, a mixed electrostatic quantum chemical approach [1, 2], allows the calculation of models simulating ions in solution including one, two, three or more explicitly considered solvation shells, *i.e.* up to the level, where the region of the bulk solvent begins. Such calculations have been performed for most metal ions up to the atomic number 30 (Zinc).

Since these calculations have been carried out mainly for aqueous solutions, values for binding energies of water molecules in the various hydration layers could be obtained, allowing a theoretical prediction of the size of the hydration spheres of these ions. The total binding energies can be compared well to the experimentally determined hydration energies and reflect well known effects as the 'ligand field stabilization' within the transition metal ions.

A comparison of the calculated binding energies at various coordination numbers with experimental data for the kinetics of solvent exchange in the first hydration layer allowed to discuss some models for the mechanism of exchange, indicating an important role of the water molecules in the second layer, which is confirmed by some tentative calculations on the corresponding transition state.

Finally, some first calculations on a model pathway for the ionic dissociation in solution have been carried out giving some theoretical background on the basis of quantum chemistry for this fundamental process of solution chemistry.

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Solute–Solute Interactions by NMR of Molecules Dissolved in Liquid Crystal Solvents: Pyridine – Iodine Molecular Complex in Nematic Phase

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NMR spectra of pyridine [^{14}N] and pyridine [^{15}N] partially oriented in nematic phase IV in presence of iodine show an increasing width as a function of the I_2 concentration. The observed spectral changes can be interpreted assuming that, as the molecular complex between iodine and pyridine is formed, a considerable variation in the orientation of pyridine moiety is produced.

Spectral analysis, performed by means of LEQUOR programme, reveals that the direct dipolar couplings (D_{ij}) are linearly dependent on the iodine concentration.

Our attempts to interpret the measured couplings on the basis of an average geometry and orientation of pyridine were unsuccessful leading to dramatic distortion effects on the apparent geometry. These results suggest that a two sites exchange mechanism is operating in the nematic phase, the two sites being the free pyridine and the complexed one.

By taking account of this exchange and using ^{15}N enriched pyridine an attempt was made to obtain the geometry and orientation of the pyridine–I_2 molecular complex.

Nuclear Quadrupole Coupling Constants of Small Ions in Aqueous Solution

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An atomic nucleus with a spin quantum number $I > ½$ possesses a nuclear quadrupole moment, which, when interacting with an external electric field gradient, gives the so-called quadrupole coupling. This coupling plays a dominating role for the relaxation rates of NMR signals of quadrupolar ions [1], but it can also give additional splittings of signals in systems, where the field gradient does not average to zero at the nuclear site.

However, for a dilute aqueous solution of ions, the field gradient is caused by the surrounding water molecules, which, due to their motion, will average it to zero. Hence, there is no splitting, but the fluctuation of the field gradient will contribute to the relaxation. From the NMR experiment it is possible to estimate the product between the field gradient fluctuation, $\langle V_{zz}^2\rangle_{eq}$, and a correlation time τ_c, associated with the motion of the water molecules.

In this work we have focused our interest on the field gradient at the ion nuclear site, and the origin of it. Therefore, calculations with the Monte Carlo simulation technique have been performed on systems consisting of 50 water molecules surrounding an ion (Li^+, Na^+ and Cl^-). The configurations generated in the simulation have been used to calculate the field gradient fluctuation at the nuclear site of the ion. The results have been compared with experimental and other theoretical data.

The analytical expressions for the intermolecular pair-potentials used in the Monte Carlo program, have been obtained from fittings of accurately calculated quantum mechanical (near Hartree–Fock) energies and field gradients of *ca.* 80 ion–water molecule configurations.

In Table I the calculated electric field gradient at the nuclear site of a lithium ion, and its fluctua-

TABLE I.

N	$\langle V_{zz}\rangle_{eq}$ (a.u.)	$\langle V_{zz}^2\rangle_{eq}$ (a.u.)
4	$2.2 \cdot 10^{-4}$	$0.3 \cdot 10^{-4}$
5	$2.9 \cdot 10^{-4}$	$0.5 \cdot 10^{-4}$
10	$-13.0 \cdot 10^{-4}$	$1.1 \cdot 10^{-4}$
50	$23.0 \cdot 10^{-4}$	$1.3 \cdot 10^{-4}$
exp.	–	$0.14 \cdot 10^{-4}$