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.

References

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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