Theoretical Approaches to the Intermolecular Nature of Water [and Discussion]

F. H. Stillinger, J. B. Hasted and A. Warshel

Phil. Trans. R. Soc. Lond. B 1977 **278**, 97-112
doi: 10.1098/rstb.1977.0033

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

Phil. Trans. R. Soc. Lond. B. **278**, 97–112 (1977)
Printed in Great Britain

Theoretical approaches to the intermolecular nature of water

By F. H. Stillinger
Bell Laboratories, Murray Hill, New Jersey 07974, *U.S.A.*

A brief review is presented of recent advances in theoretical understanding of liquid water. These advances include detailed quantitative specification of water-molecule interaction potentials, and development of several techniques in statistical mechanics for predicting molecular order in the liquid. Specifically, computer simulation now plays a particularly important rôle. A labile, defective, random network picture for the liquid is the only consistently supported possibility. Implications of this picture for an explanation of hydrophobic solvation and bonding are mentioned. Furthermore, the apparent cooperative restructuring of the random network near the supercooling limit suggests that a dielectric anomaly might exist in this régime. Several areas for future development of water theory are suggested, bearing specifically on phenomena of biological interest.

1. Introduction

Water is often described as 'unique' among liquids. However, that is not an informative description. In fact all liquids are unique, as are all humans. Each human possesses an individualistic set of physiological and psychological traits, and similarly each liquid reveals its own 'personality' as a set of measurable physical and chemical properties. Some humans obviously stand out from the crowd, though, and in analogy we might aptly describe water as a 'talented eccentric'.

Theoretical chemistry has the task of explaining the sources and ramifications of these eccentricities. This paper undertakes briefly to outline present theoretical approaches to understanding liquid water, to assess implications for the biological sciences, and to present prospects for future development.

The anomalous physical properties of pure water are widely known. Included among them are:

(1) contraction upon melting,
(2) density maximum for the orthobaric liquid,
(3) isothermal compressibility minimum,
(4) high dielectric constant,
(5) high constant-volume heat capacity,
(6) viscosity reduction upon pressurization.

Needless to say, successful theory must at least rationalize these observations, if not predict them quantitatively from first principles.

With respect to its rôle in biology, water needs to be understood as a solvent and as a constituent of interfaces. It is important to document its rôle in the production and maintainance of active forms of biological molecules. Prevention of the freezing of water in tissues by cryoprotective agents requires deep understanding of the molecular basis of *both* biology *and* phase transitions. Theoretical insights have been (and continue to be) sought into alterations in water structure during anaesthesia. And perhaps most basic of all, we seek to know if water is the only medium in which life can arise, and subsequently evolve to higher forms.

Fundamental research on the molecular properties of water and aqueous systems has accelerated markedly during the last seven or eight years. On the theoretical side, this reflects the impact of rapid digital computers. It has become possible to start with the Schrödinger wave equation for electrons, and hydrogen and oxygen nuclei, to derive *ab initio* the molecular structure and intermolecular forces for water molecules, then to use those properties to infer by the methods of statistical mechanics how the material acts in bulk. Perhaps we are witnessing operation of a reductionist procedure that will eventually encompass all of biochemistry.

Prior to the advent of this recent period, many 'theories' or 'explanations' of the molecular nature of water were offered, which have now become obsolete. Most of them have been articulated in widely available reviews (Kavanau 1964; Eisenberg & Kauzmann 1969; Horne 1972). By hindsight we can say that their authors, often clever and intelligent, were forced to work with woefully inadequate information about the molecular nature of water interactions, which has only subsequently become available. In addition, water is a sufficiently complex substance that it seemed possible to explain its behaviour, with equal precision, in any of several mutually contradictory ways.

Unfortunately there has been a tendency for these early notions to persist in the biochemical community. Some changes in that situation are warranted.

2. INTERMOLECULAR FORCES

The manner in which molecules are arranged in condensed phases represents a compromise between the ordering influence of intermolecular forces, and the entropic drive toward disorder provided by thermal motion. Since the former predominates at low temperature, valuable insights into the character of the forces (particularly for water) result from study of the crystal structures of solid phases.

Consequently, the determination of the structure of ordinary hexagonal ice (ice Ih) has exerted a powerful influence on the way that subsequent work on the liquid has been conceived and implemented (Bragg 1922; Bernal & Fowler 1933; Peterson and Levy 1957). Basically, ice Ih consists of intact water molecules arranged so as to form a three-dimensional network of linear hydrogen bonds. Each molecule in the perfect crystal has at distance 0.276 nm four nearest neighbours, toward two of which it donates its protons, and from two of which it accepts protons. At each molecule the four hydrogen bonds radiate outward in a tetrahedral pattern (i.e. toward vertices of a regular circumscribing tetrahedron). The formation of the ice Ih lattice is obviously encouraged by the fact that the HOH bond angle in an isolated molecule (104.5°) is close to the ideal tetrahedral angle ($\arccos -\frac{1}{3} = 109.5°$).

The entropy of melting ice to liquid at 1 atm (10^5 Pa) is 5.2581 cal/mol K (Rossini *et al.* 1952). This indicates that each molecule has 14.08 times the configurational freedom after melting as it did in ice. Nevertheless, it has always seemed attractive to suppose that a remnant of ice Ih order persists into the liquid. X-ray diffraction studies of the liquid are at least consistent with the hypothesis (Narten, Danford & Levy 1967).

Significantly, the requirement of tetrahedral hydrogen bonding can be met in a wide variety of ways. Pauling pointed out (Pauling 1935) that there are approximately $(3/2)^N$ ways that N water molecules can be oriented so as to form the required ice Ih network. In addition, the molecules can be made to form a cubic crystal (ice Ic) by vapour phase condensation at low temperature, which has the same local tetrahedral pattern of hydrogen bond coordination. To this must be added the diverse collection of tetrahedral water networks present in clathrate hydrates (Jeffrey & McMullan 1967; Jeffrey 1969). Even under external pressure sufficient to cause transformation between numerous ice polymorphs, the existence of fourfold hydrogen bond coordination remains a constant theme (Eisenberg & Kauzmann 1969).

In formation of a crystal, the collection of water molecules is constrained to produce a spatially periodic structure. Even under this severe restriction, we observe that the intermolecular forces permit a wide range of hydrogen-bond 'architectures'. Melting removes the periodicity constraint, so one must expect a substantially wider range of hydrogen-bond patterns to qualify for inclusion in the liquid.

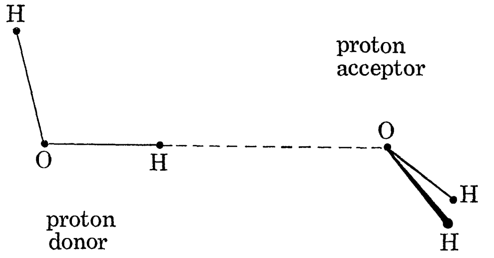


FIGURE 1. Stable form of the water dimer.

Recent quantum-mechanical studies of water-molecule interactions have reinforced and amplified these ideas. Figure 1 shows the most stable arrangement inferred for two molecules from high-accuracy calculations of the Hartree–Fock (all electron) type. A single linear hydrogen bond links the participants; its length is 0.300 nm, and its strength about 5 kcal (21 kJ)/mol (Hankins, Moskowitz & Stillinger 1970, 1973; Lentz & Scheraga 1973; Popkie, Kistenmacher & Clementi 1973). Molecular beam resonance experiments confirm these theoretical results (Dyke & Muenter 1974). It should be stressed that the water dimer hydrogen bond involves some covalency and charge transfer, so it cannot be explained by electrostatics alone.

Even when the participating monomers are rigidly held in their undeformed geometries, there remain five angles of possible distortion for the dimer in figure 1. Two of these will move the donated proton off the oxygen–oxygen axis, and they are costly in terms of stabilization energy. The other three describe rotation of the acceptor molecule about its oxygen, and are considerably less costly in energy. This latter set of 'easy' motions is important in transforming from one hydrogen-bond network topology to another.

Theoretical calculations using the Hartree–Fock approximation also show the extent to which molecules can be crowded together in non-bonding orientations. The resulting inferred molecular sizes are such that the proton acceptor molecule in figure 1 can easily accept a second proton from another donating neighbour molecule. While thus acting doubly as an acceptor, it can simultaneously donate its own two protons to the rear of third and fourth neighbours. This completes a tetrad of linear hydrogen bonds to an uncrowded retinue of four nearest neighbours that are unbonded among themselves. By building outward from a central molecule in this fashion, the ice and clathrate networks can be produced naturally.

On account both of molecular size, and of the angular and length requirements on well-formed hydrogen bonds, one can infer from the available quantum-mechanical results on water interactions that five fold hydrogen bonding to a central molecule is unfavourable. It is satisfying that such structures are not seen crystallographically.

Although the major portion of the binding energy in any space-filling hydrogen bond network of water molecules may be explained in terms of pair interactions between first neighbours other contributions are present. Second, third, ..., neighbours interact as well, primarily through dipolar forces. In addition, the overall potential energy has a significant component that is not of additive-pair origin, but is instead associated with close groupings of three, four, ..., molecules. The result of these additional interactions is overall increase in binding energy of the networks, and reduction in hydrogen-bond length (Hankins *et al.* 1970, 1973).

3. STATISTICAL-MECHANICAL TECHNIQUES

As a result of the considerations just outlined, a comprehensive and quantitative understanding of intermolecular forces between water molecules is now available. It is subsequently the task of statistical mechanics to convert that information into predictions about the behaviour of water in bulk.

At present, three rather distinct approaches to the statistical mechanics of liquid water are under active development. For the most part they are confined to the régime of classical statistics. Although it is clearly desirable to examine quantum corrections, little has systematically been done along these lines, and in any event the chemical and physical similarity of H_2O and D_2O suggest that these quantum corrections have modest magnitudes.

(*a*) *Lattice and cell theories*

Lattice models for fluids constrain the particles to reside at a discrete set of sites, in place of the full spatial continuum. If the sites are sufficiently dense, both ordered crystalline and disordered fluids can be adequately accommodated in the same lattice model. The major advantage of this approach is that a variety of combinatorial techniques is available (Domb 1960) for evaluating the classical lattice-model partition function. By contrast, the continuum problem presents a more formidable challenge in evaluation of its corresponding partition function.

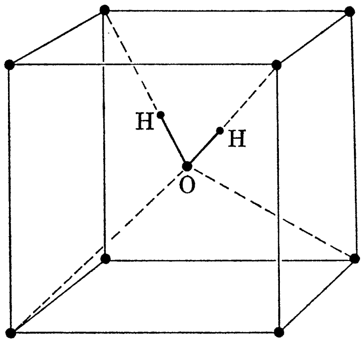


FIGURE 2. Body-centred cubic arrangement of sites used in lattice gas models for water.

The natural lattice choice for water is body-centred cubic, shown in figure 2. Its nearest-neighbour separation would be that corresponding to a fully formed hydrogen bond. Although the ice Ih crystal cannot be fitted onto these sites, the closely related cubic modification Ic can, with half of the sites occupied. Two such networks, interpenetrating but unconnected by hydrogen bonds, can also reside on this lattice to produce the high-pressure structure of ices VII and VIII. Melting of the ice Ic crystal on the lattice occurs partly by motion of molecules to the unoccupied half of the lattice sites, and partly by orientational disorder.

Several studies of the lattice gas model for water have already been published (Bell 1972; Fleming & Gibbs 1974*a*, *b*). Although only short-range interactions are admitted in these calculations, a reasonable account can be given of the thermodynamic properties of the real liquid. Perhaps most interesting is the demonstration that with suitable choice of interaction parameters, both the density maximum and compressibility minimum can be made to occur in the lattice gas model for water.

The b.c.c. lattice suffers the topological shortcoming that only hydrogen-bond polygons with even numbers of sides can occur. That is adequate for ordinary ice (hexagons). But mindful of the fact that pentagons occur frequently in clathrate crystals, one must suspect that odd polygons frequently occur in the liquid. There are in fact denser lattices (of which the b.c.c. lattice sites constitute a subset) which would permit formation of polygons with both parities (Stillinger 1975). To date, however, no serious use has been made of these more elaborate lattice gas models.

An attempt has recently been made (O'Reilly 1974) to combine the lattice model with aspects of the 'scaled-particle theory' of fluids. The results are claimed to have value in explaining both thermodynamic and molecular kinetic properties of water.

It should also be noted that a class of 'interstitial' lattice models has recently been examined, in which two distinct types of sites are employed (Perram & Levine 1974).

Whereas the lattice models rigidly constrain the molecules to discrete positions and orientations, the related 'cell model' method attempts to restore at least some of the motional freedom. Specifically, water molecules nominally assigned to the b.c.c. lattice shown in figure 2 can be allowed to translate and librate in the force field supplied by neighbour molecules (Weres & Rice 1972). While still providing an adequate description of thermodynamic behaviour, the cell method offers a richer description of local molecular order in the liquid (e.g. the extent of hydrogen-bond bending) than does the bare lattice approach. Furthermore, it seems to be capable of explaining gross features of infrared and Raman spectra in pure water (Denley & Rice 1974).

The lattice and cell theories predict considerable disorder in the liquid compared to the solid, which agrees qualitatively with the previously cited melting entropy. That disorder is due to hydrogen-bond breakage, and to occasional occurrence of more than four nearest neighbours around some molecules.

(*b*) *Molecular distribution function theories*

From its earliest development, molecular pair distribution functions have played a central rôle in fundamental liquid state theory (Kirkwood 1935). In part this was due to experimental determination of these functions for monatomic substances by X-ray diffraction. It was also due to the fact that all thermodynamic properties could be expressed rigorously as quadratures involving molecular pair distribution functions, provided the intermolecular forces were pairwise additive. With that background it is natural to seek a quantitative description of polyatomic liquids, including water, in terms of molecular distribution functions.

In an isotropic, monatomic fluid with number density ρ, the statistical distribution of particle pairs can be described fully by a single function of the pair distance r. Specifically, the pair correlation function $g(r)$ is defined so that in a spherical shell of radius r and width dr centred about any one particle the expected number of other particle centres will be $4\pi\rho r^2 g(r)\mathrm{d}r$. For large r, g becomes unity. But when r is comparable to the range of intermolecular forces, deviations of $g(r)$ from unity reflect the preferred modes of particle packing in the fluid, i.e. the 'structure'.

In the case of water, not only distance but relative orientation is important in describing the 'structure' of the liquid in terms of molecular pair occurrences. Just as was the case for the molecular pair interaction, five angles are necessary to specify that orientation. The full pair correlation function (for rigid water molecules) thus requires six variables, $g(r, \theta_1 \dots \theta_5)$. Although no combination of known experimental methods could determine this elaborate function, theoretical techniques promise to supply the desired information.

An alternative to the full water pair correlation function would be the set of three *nuclear* pair correlation functions, $g_{OO}(r)$, $g_{OH}(r)$, and $g_{HH}(r)$. They specify the relative occurrence probabilities, at the distance r, for pairs of nuclei of the subscripted species. In the case of g_{OH} and g_{HH}, both intramolecular and intermolecular correlations would be manifest.

The three nuclear pair correlation functions can be derived (by integration) from $g(r, \theta_1 \dots \theta_5)$; unfortunately the inverse procedure is not possible. Still, a rather detailed and informative picture of molecular ordering in liquid water would emerge from knowledge of the three nuclear correlation functions. It is relevant to note that a combination of X-ray and neutron diffraction experiments (the latter using different isotopic waters) could in principle determine g_{OO}, g_{OH}, and g_{HH} experimentally.

One of the standard generic methods for calculating molecular distribution functions in monatomic substances has been 'cluster expansions'. In this approach $g(r)$ is expressed as a series of integrals, whose integrands involve products of Mayer f functions:

$$f(r) = \exp[-v(r)/k_B T] - 1,$$

where v is the pair potential, k_B is the Boltzmann constant, and T is absolute temperature (Van Leeuwen, Groeneveld & DeBoer 1959). Leading terms in the resulting cluster series suffice to represent correlations at low density (vapour), and approximate series summation methods are available for the liquid range.

Difficulty in application of the cluster method to water resides in the strong directionality of hydrogen-bond interactions, and the fact that the magnitude of the pair potential when a hydrogen bond forms exceeds thermal energy $k_B T$ by roughly a factor 10. Consequently the Mayer f function at its maximum is enormous for water in comparison with its monoatomic analogues. This causes severe difficulties in securing convergence in the cluster series (terms are very large but vary in sign).

Nevertheless, a systematic procedure must exist for summing the cluster series. Andersen has carried out a careful analysis of the cluster series for $g(r, \theta_1 \dots \theta_5)$, and has shown in principle how the terms must combine to describe the hydrogen-bond 'saturation effect' that limits full-bonding coordination number to four (Andersen 1973, 1975). The resulting formalism should be sufficiently tractable soon to produce an explicit (albeit approximate) set of predictions for g and the equation of state.

An alternate approach to determining molecular order in liquid water (and other polyatomic fluids) has been devised by Chandler & Lowden (Lowden 1975). Their 'RISM' technique (acronym for 'reference interaction site model') postulates a rigid complex of seven force centres for each water molecule. These sites are assigned positions and collision diameters to ensure that pairs of neighbouring water molecules can adopt hydrogen-bond configurations. At present, the RISM computations (which require solving simultaneous integral equations) predict only the nuclear correlation functions g_{OO}, g_{OH}, and g_{HH}. Since only repulsive forces are present, causing structure to arise as a result of carefully manipulated steric hindrance, this approach does not yield thermodynamic functions (however attractive forces could probably be included as first-order perturbations).

The Chandler–Lowden calculations produce molecular order that is characteristic of random hydrogen bonding. At least as judged by their g_{OO}, the average number of nearest neighbours in the liquid lies between 4 and 5, and there is a clear tendency for second neighbour oxygens to occur at a position required by successive hydrogen bonds at the tetrahedral angle. This theory predicts an X-ray diffraction pattern for water in moderately good agreement with experiment. The corresponding theoretical neutron diffraction result is less accurate, probably indicating that hydrogen positions are not yet adequately described by the RISM technique. The results obtained thus far are sufficiently encouraging that refinements in the model parameters should actively be sought.

A third approach to theoretical study of molecular distribution functions in water is supplied by a class of 'central force models' (Lemberg & Stillinger 1975). Here water is formally treated as a binary mixture of H and O particles, subject to suitable central interaction potentials $V_{OO}(r)$, $V_{OH}(r)$, and $V_{HH}(r)$. No fundamental distinction is drawn between intramolecular and intermolecular forces; the same potential functions serve for both. The three functions are chosen in such a way that individual water molecules automatically form in the correct non-linear geometry, and interact as molecular units to form hydrogen bonds.

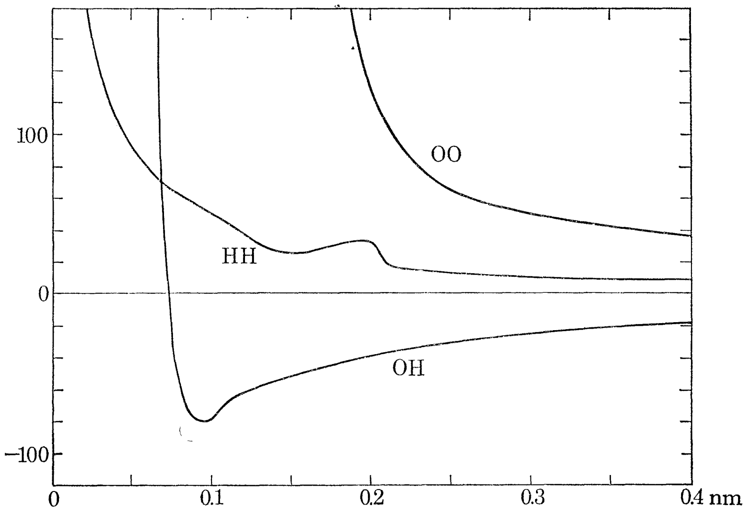


FIGURE 3. Potential functions for the central-force model of liquid water in kcal/mol.

Figure 3 illustrates the types of potential functions that must be used. The non-monotonic behaviour shown for V_{HH} ensures that the individual water molecules remain nonlinear. It should be stressed that vibrations are present in each molecule, and that dissociation into H^+ and OH^- fragments is possible as a result of a strong thermal fluctuation.

The primary theoretical advantage offered by the central force model is the applicability of standard integral equation methods for self-consistent determination of the three nuclear pair correlation functions. Lemberg & Stillinger have numerically integrated the so-called h.n.c., or 'hypernetted chain' integral equations (Van Leeuwen *et al.* 1959) for one version of this model. In order to achieve convenient rates of convergence, it has thus far been necessary to limit attention to very high temperatures ($T > 1000$ °C), but even with this restriction it is possible to observe the development of intermolecular correlation as T declines, and density increases.

(c) *Computer simulation*

Rapid digital computers can be programmed to simulate the static and dynamic behaviour of collections of interacting molecules, using specified potential energy functions as input. This capacity currently offers the most powerful non-experimental method for the study of liquid water. Although computer speed and memory size limit the simulations to several thousand molecules or fewer (at present!), use of periodic boundary conditions in the calculations permit the studies to probe macroscopic behaviour.

Two standard formats have been used. The 'Monte Carlo' method (Sarkisov, Dashevsky & Malenkov 1974; Lie & Clementi 1975) generates an ensemble of molecular configurations representative only of thermal equilibrium. By contrast, the 'molecular dynamics' method (Stillinger & Rahman 1974) traces the full mechanical motion of the molecular system in time, given suitable initial conditions. Both approaches can be used to study molecular arrangements in the liquid, and thermodynamic properties. However, the latter alone provides kinetic properties (such as self-diffusion constants, rotational relaxation rates, viscosity, etc.).

Computer simulation offers several notable advantages. It is capable of handling states of matter at temperature and pressure extremes unattainable in the laboratory. In addition, it offers a wealth of molecular detail far beyond present resolving powers of experimental techniques. Finally, it permits careful study of the effects of variations in the intermolecular forces acting between the simulated molecules.

For the most part, the computer simulations carried out thus far have treated the individual water molecules as rigid asymmetric rotors. However, a recent exception has been the molecular dynamics study (Rahman, Stillinger & Lemberg 1975) of the central force model, in which vibrational motions were present in each molecule.

In the pure water simulations, greatest attention has been devoted to calculation of the nuclear correlation functions g_{OO}, g_{OH}, and g_{HH}. In spite of some differences in assumed molecular interactions, the results of various workers constitute a broad consensus on the extent and type of order present. It seems clear in all cases that a marked tendency toward hydrogen-bond order exists, but with far less predictable geometry than study of ice crystallography alone would suggest. Under ordinary temperature and pressure conditions, the simulations indicate that each water molecule has 4–5 near neighbours, to contrast with *ca.* 12 found in simple liquids (such as argon). The nuclear correlation functions seem to be consistent with X-ray and neutron diffraction measurements, though some minor discrepancies (of uncertain origin) remain.

The computer simulations have succeeded at least qualitatively in affirming the unusual thermodynamic properties of water. High heat capacity, a density maximum, and a compressibility minimum have been reported (Stillinger & Rahman 1974).

Concerning experimentally inaccessible information, it has been possible to study various geometrical aspects of hydrogen bonding in liquid water through computer simulations. One possibility lies in visual examination of stereoscopic photograph pairs prepared from molecular configurations generated in the simulations (Rahman & Stillinger 1971). For quantitative studies, however, it is necessary to define the existence of an 'hydrogen bond' between two molecules precisely in terms of their relative configuration; a convenient way is to demand that the corresponding pair potential lie below some fixed value (for example −3.5 kcal (14.5kJ) mol). Having decided upon such a bonding criterion, it is then possible to compute the fraction of molecules engaging in 0, 1, 2, 3,...hydrogen bonds at any given instant (Stillinger & Rahman 1972). Furthermore, it has been possible to enumerate the frequencies of occurrence of hydrogen-bond polygons in the liquid, to observe that, unlike ice, no preference seems to exist for polygons with an even number of sides at the expense of those with an odd number of sides (Rahman & Stillinger 1973).

Some recent computer simulations have begun to examine aqueous solutions (Dashevsky & Sarkisov 1974; Watts, Clementi & Fromm 1974; Vogel & Heizinger 1975). Uncertainty about the nature of solute-water potential energy functions has thus far been a noticeable limitation on extension of the method to wider classes of solutions.

4. Conclusions about water

The various descriptions of liquid water offered by the theoretical techniques outlined in §3 differ in emphasis, richness of detail, and reliability. At present, greatest weight must be accorded the computer simulation results. But in spite of the disparity in approaches, a uniformly supported theme seems to emerge: *Liquid water consists of a random hydrogen-bond network, with frequent strained and broken bonds, that is continually subject to spontaneous restructuring.*

In view of the history of the subject, it seems nearly as important to state what is *not* supported by recent theoretical studies. Specifically, notions of compact ‘icebergs’ or clusters floating in unbonded water are ruled out (Némethy & Scheraga 1962). Likewise, the concept of an ice-like framework heavily invaded by distinguishable interstitials must be rejected (Narten & Levy 1969). The modern results make it clear that partitioning of molecules into two (or more) discrete states or classes is unnecessary in order to explain, for example, infrared and Raman bands in water. Since hydrogen-bond lifetimes are normally much longer than vibrational periods, it should be possible to distinguish between vibrating OH groups that respectively do or do not participate in hydrogen bonds, merely depending on how they are incorporated into the random network.

Solvation by water now may be construed as response of the labile and geometrically diverse random network to various perturbations caused by the various solutes. Aside from the obvious fact that solutes may induce hydrogen bonds to form (‘structure makers’) or to break (‘structure breakers’), more subtle changes can also occur. In particular, solutes can locally alter the distribution of hydrogen-bond polygons, or perhaps alter the frequency with which different portions of the random network interpenetrate.

Alteration of water structure by non-polar groups, and the associated phenomenon of hydrophobic bonding, are important topics for biochemistry. The most obvious attribute of inert non-polar groups is that they occupy space. Within surprisingly wide limits, water networks can be rearranged to accommodate such space-filling entities, without the necessity for breaking bonds. However, this requirement obviously limits the diversity of ways by which hydrogen-bond linkages occur. It has been pointed out that water molecules next to a convex cavity preferentially orient so that (*a*) three of their fundamental tetrahedral directions straddle the cavity while the fourth points radially outward, and (*b*) pairs of such water molecules bond in an ‘eclipsed’ configuration (Stillinger 1973). Thermodynamically these geometric restrictions on network structure must appear as negative solution entropies. Of course this is exactly what is observed for hydrocarbons in water (Franks 1973).

As is well-known, this negative solution entropy for non-polar entities suffices to explain the 'hydrophobic bond'. Two such solutes can minimize the entropic 'discomfort' created in the water by coming together, and sharing a cavity with smaller surface than the total attributable to two separated cavities. Once one grasps the notion of geometric restrictions on cavity-forming water molecules, there is no need to postulate ice-like sheaths (Frank & Evans 1945). Any reduction in motion of these solute-contacting water molecules need not be due to local strengthening of hydrogen bonds at all, but can arise merely because fewer orientational and translational options are available for moving about.

The ability to supercool liquid water nearly to −40 °C has interesting relevance. It means that at least above this temperature, 1 cm^3 of liquid would not be expected to have a *single* seed with sufficient size and order of ice Ih character to permit a macroscopic crystal to begin to grow. Near the lower end of this supercooling régime, the critical nucleus would only have to contain about 190 molecules (Fletcher 1970). Even on experimental grounds alone, one must therefore conclude that strict ice-like order is not present in the random network to any marked extent. In any case one should realize that nuclei structurally could be cubic-ice-like either wholly or in part; the hexagonal form could easily grow epitaxially on the [111] faces of a cubic seed, which present the requisite chair-form hexagons.

On the basis of density, heat capacity, isothermal compressibility, and relaxation rate measurements, Angell and his collaborators (Angell, Shuppert & Tucker 1973) have suggested that the anomalous properties of strongly supercooled water can best be interpreted as a λ-type transition (centred at the just-unreachable temperature −45 °C). The strongly under-cooled random network evidently develops large particle- and energy-density fluctuations characteristic of critical phenomena, and it seems important to identify the cooperative process involved.

Evidently the supercooling permits reduction in breakage and strain in the hydrogen-bond network (note that activation energy for kinetic processes increases strongly) by allowing re-structuring in more open forms. It is attractive to suppose that the restructuring might be accompanied by tendency to proton ordering of ferroelectric type. This is plausible in view of proton ordering that exists in some ice polymorphs (Eisenberg & Kauzmann 1969), and in view of indications that ice Ih itself may be ferroelectric below 100 K (Onsager 1967). If the postulated λ anomaly is connected with low-density, strongly bonded ferroelectric domains, then the static dielectric constant ϵ_0 should also rise to very large values upon strong super-cooling. These considerations lend considerable importance to the task of measuring ϵ_0 in the supercooling régime.

It should be mentioned in this connection that among the possible unbroken hydrogen-bond network structures, the cubic-ice structure alone can be perfectly polarized (i.e. all molecular dipoles can be parallel). This leads directly to the possibility that the same fluctuations which seed crystallization near −40 °C, are also the source of the 'λ' anomalies – namely ferro-electric regions with a rough approximation to cubic-ice bonding geometry. It would then follow that cryoprotective agents specifically should suppress formation of those regions, and should suppress the thermodynamic anomalies. It will be interesting to see if cryoprotective agents are particularly potent in reducing the expected dielectric constant divergence.

5. Open problems

Thus far, none of the theories for water mentioned in §3 has turned its attention to the freezing phenomenon. Surely an important test of the validity of any theory for water must be the accuracy with which the freezing temperature, 0 °C, is reproduced. It is possible that good account of liquid-phase properties might be achieved in a theoretical model with certain choices of molecular interactions, while inadvertently the freezing point becomes displaced to an unacceptable extent. Since one biologically important area of application for theoretical models of water concerns freezing in restricted geometries (capillaries, films, cell interiors, etc.), assurance should exist that the macroscopic freezing behaviour of bulk water will be correctly reproduced.

An adequate molecular theory of ionic solvation has yet to be constructed and analysed. The chief barrier is the presence of strong electronic polarization induced in solvent molecules by the ions. These polarization effects cannot be properly handled without introducing three, four, five, ..., molecule interactions. Even computer simulation studies at present would be severely retarded by this complication.

Dissociation of the water molecule into H^+ and OH^- ions, and subsequent solvation of those ions, constitute basic processes that are little understood at present. Some quantum-mechanical studies of small H^+ and OH^- solvation complexes have been carried out (Newton & Ehrenson 1971), but it remains to be seen how closely these finite cluster calculations represent the structure present around the ions in an extended hydrogen-bond network. In order to account quantitatively for the dissociation constants of H_2O and D_2O, and for the mobilities of the ions formed, it will surely be necessary to invoke a full quantum-statistical formalism. It is presently unclear whether a proper treatment of the solvated proton will support existence of discrete units such as $H_9O_4^+$ (Eigen & De Maeyer 1959), or whether description in terms of a more diverse set of structures and species (including short, symmetrical hydrogen bonds) is warranted.

In order to develop a comprehensive understanding the solvation of biological molecules, detailed information will have to be accumulated (principally from quantum theory and from crystallography) about the way that water molecules interact with the usual catalogue of functional groups encountered. This catalogue would have to contain alkyl groups, hydroxyl and sulphydryl units, amines, carboxyl groups, and so forth. Just as large biopolymers are covalently constructed from these modular units, so would the full water-molecule-plus-biopolymer-molecule potential energy be synthesized from the appropriate modular unit potentials.

Beyond the obvious features of gross hydrophilicity and hydrophobicity for subunits in biopolymers, there are doubtless more subtle effects that are important in determining native-state conformations and reactivities for biological molecules. These subtleties should be amenable to theoretical study once the appropriate potential energy functions become available. Certainly one of the subjects of great interest will be the explicit rôle of water in the catalytic properties of enzymes. There exists substantial evidence for specific binding of water at the active sites of the enzymes carboxypeptidase A, carbonic anhydrase C, and ribonuclease S (Berendsen 1975). It seems likely that this water acts as a 'place-holder' for the substrate, interacting strongly enough with the enzyme to aid in maintaining its active form, but not so strongly as to retard its displacement by the substrate. We should eventually observe study of this water binding and displacement by suitably designed computer simulations, if not by techniques of a more analytical nature.

It has occasionally been suggested (Pauling 1961; Di Paolo & Sandorfy 1974) that the physiological effects of anaesthetics are due to their ability to alter water structure in specific ways. At the moment we can confidently do no more than to admit that intriguing possibilities exist. A complete understanding of anaesthesia will require first an understanding of how water is involved in signal transmission along nerve axons, and across synapses. Subsequently the interference of anaesthetics (if that is actually the case) in these rôles of water would have to be documented. Evolving theoretical techniques should become powerful allies in this documentation.

Finally, we have to consider the fascinating question of whether water alone can serve as the fluid medium for support of life. Two inequivalent versions of this question need to be distinguished:

(1) Have all cases of spontaneous chemical evolution of 'life' in the universe occurred in the essential presence of liquid water?

(2) Considering all conceivable chemical and physical environments, in how many ways can evolution to a recognizably 'living' world proceed?

(The matter of what one does, or should, mean by 'life' and 'living' leads to endless debate, which we leave aside. It seems reasonable to assume that an informal consensus could be reached covering most cases of interest.)

In connection with question one, it is important that the elements of the periodic system have a very non-uniform frequency of occurrence in the universe. Furthermore, stellar evolution seems to be rather more systematic than diverse, suggesting that few scenarios are available for planetary development. Under these restrictive circumstances, then, liquid water may be the only fluid medium present in the universe in which life actually has arisen. Perhaps liquid ammonia provides an alternative, but it may occur only on outer planets with temperatures so low that the reactions necessary for chemical evolution are too slow to produce anything biologically noteworthy.

Question two in some respects may turn out to be the more interesting. Synthetic chemistry has at its disposal a far wider range of atomic and molecular compositions than planetary surfaces can exhibit. Furthermore, delicate control over pressure, temperature, radiation and electrical discharge conditions can be exercised in the laboratory, to compare with random and often chemically destructive conditions occurring in the cosmological régime.

There is nothing present in the theory for water as yet to suggest that it is uniquely qualified to support life. Although it is true that biochemical structures and processes as we know them often exist due to exquisitely balanced aqueous influences, we have no basis for believing that analogous structures and processes (entailing similar balance between competing influences) could not exist in rather different chemical environments. For an example, we can cite the (energetically driven) tendency for fluorocarbons to cluster together in a liquid hydrocarbon as an analogue to the (entropically driven) hydrophobic interaction of non-polar substances in water. Perhaps it is possible that laboratory 'life' could be based primarily on elements H, C, and F.

It seems reasonable to speculate that within the next century, not only will we develop a comprehensive understanding of how water quantitatively contributes to terrestrial biochemistry, but also how other liquids might serve as hospitable media for the laboratory production of exotic 'life'.

References

Andersen, H. C. 1973 Cluster expansions for hydrogen-bonded fluids. I. *J. chem. Phys.* **59**, 4714–4725.

Andersen, H. C. 1975 Cluster expansions for hydrogen-bonded fluids. II. *J. chem. Phys.* **61**, 4985–4992.

Angell, C. A., Shuppert, J. H. & Tucker, J. C. 1973 Anomalous properties of supercooled water. *J. phys. Chem.* **77**, 3092–3099.

Bell, G. M. 1972 Statistical mechanics of water: lattice model with directed bonding. *J. Phys. C: Solid State Phys.* **5**, 889–905.

Berendsen, H. J. C. 1975 Specific interactions of water with biopolymers. In *Water, a comprehensive treatise* (ed. F. Franks), vol. 5, pp. 293–330. New York: Plenum Press.

Bernal, J. D. & Fowler, R. H. 1933 A theory of water and ionic solution. *J. chem. Phys.* **1**, 515–548.

Bragg, W. H. 1922 The crystal structure of ice. *Proc. phys. Soc. Lond.* **34**, 98–103.

Dashevsky, V. G. & Sarkisov, G. N. 1974 The solvation and hydrophobic interaction of non-polar molecules in water. *Molec. Phys.* **27**, 1271–1290.

Denley, D. & Rice, S. A. 1974 A model calculation of the intramolecular vibration spectrum of liquid water. *J. Am. chem. Soc.* **96**, 4369–4374.

Di Paolo, T. & Sandorfy, C. 1974 Fluorocarbon anaesthetics break hydrogen bonds. *Nature, Lond.* **252**, 471–472.

Domb, C. 1960 On the theory of cooperative phenomena in crystals. *Adv. Phys.* **9**, 149–361.

Dyke, T. R. & Muenter, J. S. 1974 Microwave spectrum and structure of hydrogen bonded water dimer. *J. chem. Phys.* **60**, 2929–2930.

Eigen, M. & De Maeyer, L. 1959 Hydrogen bond structure, proton hydration, and proton transfer in aqueous solution. In *The structure of electrolytic solutions* (ed. W. J. Hamer), pp. 64–85. New York: Wiley.

Eisenberg, D. & Kauzmann, W. 1969 *The structure and properties of water.* Oxford University Press.

Fleming, P. D. & Gibbs, J. H. 1974*a* An adaptation of the lattice gas to the water problem. *J. Stat. Phys.* **10**, 157–173.

Fleming, P. D. & Gibbs, J. H. 1974*b* An adaptation of the lattice gas to the water problem. II. *J. Stat. Phys.* **10**, 351–378.

Fletcher, N. H. 1970 *The chemical physics of ice*, p. 96. Cambridge University Press.

Frank, H. S. & Evans, M. W. 1945 Free volume and entropy in condensed systems. III. *J. chem. Phys.* **13**, 507–532.

Franks, F. 1973 The solvent properties of water. In *Water, a comprehensive treatise* (ed. F. Franks), vol. 2, pp. 1–54. New York: Plenum Press.

Hankins, D., Moskowitz, J. W. & Stillinger, F. H. 1970 Water molecule interactions. *J. chem. Phys.* **53**, 4544–4554.

Hankins, D., Moskowitz, J. W. & Stillinger, F. H. 1973 Erratum: water molecule interactions. *J. chem. Phys.* **59**, 995.

Horne, R. A. (ed.) 1972 *Water and aqueous solutions.* New York: Wiley-Interscience.

Jeffrey, G. A. & McMullan, R. K. 1967 The clathrate hydrates. *Prog. inorg. Chem.* **8**, 43–108.

Jeffrey, G. A. 1969 Water structure in organic hydrates. *Accounts. chem. Res.* **2**, 344–352.

Kavanau, J. L. 1964 *Water and solute-water interactions.* San Francisco: Holden-Day.

Kirkwood, J. G. 1935 Statistical mechanics of fluid mixtures. *J. chem. Phys.* **3**, 300–313.

Lemberg, H. L. & Stillinger, F. H. 1975 Central-force model for liquid water. *J. chem. Phys.* **62**, 1677–1690.

Lentz, B. R. & Scheraga, H. A. 1973 Water molecule interactions. Stability of cyclic polymers. *J. chem. Phys* **58**, 5296–5308.

Lie, G. C. & Clementi, E. 1975 Study of the structure of molecular complexes. XII. *J. chem. Phys.* **62**, 2195–2199.

Lowden, L. J. 1975 *Theory of the intermolecular pair correlations in molecular liquids.* Doctoral thesis, University of Illinois (unpublished).

Narten, A. H., Danford, M. D. & Levy, H. A. 1967 X-ray diffraction study of liquid water in the range 4–200 °C. *Discuss. Faraday Soc.* **43**, 97–107.

Narten, A. H. & Levy, H. A. 1969 Observed diffraction pattern and proposed models of liquid water. *Science, N.Y.* **165**, 447–454.

Némethy, G. & Scheraga, H. A. 1962 Structure of water and hydrophobic bonding in proteins. *J. chem. Phys.* **36**, 3382–3400.

Newton, M. D. & Ehrenson, S. 1971 *Ab initio* studies on the structures and energetics of inner- and outer-shell hydrates of the proton and the hydroxide ion. *J. Am. chem. Soc.* **93**, 4971–4990.

Onsager, L. 1967 Ferroelectricity of ice? In *Ferroelectricity* (ed. E. F. Weller), pp. 16–19. Amsterdam: Elsevier.

O'Reilly, D. E. 1974 Self-diffusion coefficients and rotational correlation times in polar liquids. VI. Water. *J. chem. Phys.* **60**, 1607–1618.

Pauling, L. 1935 The structure and entropy of ice and of other crystals with some randomness of atomic arrangement. *J. Am. chem. Soc.* **57**, 2680–2684.

Pauling, L. 1961 A molecular theory of general anesthesia. *Science, N.Y.* **134**, 15–21.

Perram, J. W. & Levine, S. 1974 Recent theoretical work on the structure of water. *Adv. Mol. Relaxation Processes* **6**, 85–122.

Peterson, S. W. & Levy, H. A. 1957 A single-crystal neutron diffraction study of heavy ice. *Acta Cryst.* **10**, 70–76.

Popkie, H., Kistenmacher, H. & Clementi, E. 1973 Study of the structure of molecular complexes. IV. *J. chem. Phys.* **59**, 1325–1336.

Rahman, A. & Stillinger, F. H. 1971 Molecular dynamics study of liquid water. *J. chem. Phys.* **55**, 3336–3359.

Rahman, A. & Stillinger, F. H. 1973 Hydrogen-bond patterns in liquid water. *J. Am. chem. Soc.* **95**, 7943–7948.

Rahman, A., Stillinger, F. H. & Lemberg, H. L. 1975 Study of a central-force model for liquid water by molecular dynamics. *J. chem. Phys.* **63**, 5223–5230.

Rossini, F. D., Wagman, D. D., Evans, W. H., Levine, S. & Jaffe, I. 1952 *Chemical thermodynamic properties* (National Bureau of Standards Circular 500). Washington: U.S. Government Printing Office.

Sarkisov, G. N., Dashevsky, V. G. & Malenkov, G. G. 1974 The thermodynamics and structure of liquid water. The Monte Carlo method. *Molec. Phys.* **27**, 1249–1269.

Stillinger, F. H. & Rahman, A. 1972 Molecular dynamics study of temperature effects on water structure and kinetics. *J. chem. Phys.* **57**, 1281–1292.

Stillinger, F. H. 1973 Structure in aqueous solutions from the standpoint of scaled-particle theory. *J. Solution Chem.* **2**, 141–158.

Stillinger, F. H. & Rahman, A. 1974 Improved simulation of liquid water by molecular dynamics. *J. chem. Phys.* **60**, 1545–1557.

Stillinger, F. H. 1975 Theory and molecular models for water. *Adv. chem. Phys.* **31**, 1–101.

Van Leeuwen, J. M. J., Groeneveld, J. & DeBoer, J. 1959 New method for the calculation of the pair correlation function. I. *Physica* **25**, 792–808.

Vogel, P. C. & Heizinger, K. 1975 A molecular dynamics study of aqueous solutions. II. Cesium chloride in H_2O. *Z. Naturf.* **30a**, 789–796.

Watts, R. O., Clementi, E. & Fromm, J. 1974 A theoretical study of the lithium fluoride molecule in water. *J. chem. Phys.* **61**, 2550–2555.

Weres, O. & Rice, S. A. 1972 A new model of liquid water. *J. Am. chem. Soc.* **94**, 8983–9002.

Discussion

J. B. HASTED. (*Department of Physics, Birkbeck College, Malet Street, WC1E 7HX*). The magnitude of a dielectric relaxation process possessing very small activation enthalpy (~1 kcal (4 kJ)/mol) such as we have recently reported in the submillimetre waveband (Zafar & Hasted 1973; Chamberlain *et al.* 1975) should be very sensitive to proportions of zero- and one-bonded molecules n_0, n_1. We believe that this process corresponds to the initial steep part of your dipole direction correlation function $\Gamma_2(t)$. Comparison of experimental data with your calculations of n_0, n_1 ($j = 7$, but more especially $j = 6$) appears most encouraging. What are the prospects of obtaining values at further temperatures, and in solutions?

References

Chamberlain *et al.* 1975 *Nature, Lond.* **255**, 319.

Zafar, M. S. & Hasted, J. B. 1973 *Nature Phys. Sci.* **243**, 129.

F. H. STILLINGER. The fractions n_j of molecules engaging in exactly j hydrogen bonds have been computed at a few distinct temperatures. Professor Hasted's suggestion seems to warrant more such computations under conditions of optimum numerical precision. The prospects are good for these soon to be done for pure water, and also to be done in the longer range for selected aqueous solutions.

With respect to the second-order spherical harmonic relaxation function $\Gamma_2(t)$, there exists a possible contribution to the short-time relaxation due to fully bonded librating molecules. The extent of this latter effect could be estimated by evaluating $\Gamma_2(t)$ for ice, where essentially all molecules fit this description, and then comparing with liquid-state results.

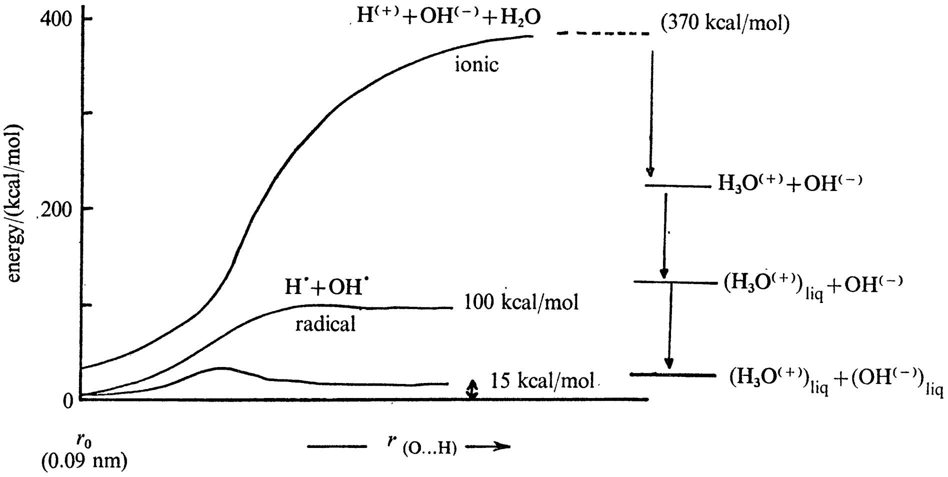
In order to test Professor Hasted's hypothesis in the depth it deserves, separate Γ_2 values should, and can, be computed via molecular dynamics for molecules initially ($t = 0$) involved in 0, 1, 2,...hydrogen bonds. If the hypothesis is correct, only the first two molecule populations should exhibit the rapid inital relaxation. Needless to say, several temperatures should also be examined to infer activation energies.

I must stress that these calculations are not trivial tasks. However, even the fact that we can consider them as serious possibilities for future study illustrates the inherent power of the molecular dynamics simulation technique!

A. Warshel

A microscopic dielectric model for reaction in water

I would like to comment about the possibility of performing reliable quantum mechanical calculations of chemical reactions in solution. As you know quantum mechanical calculations describe properly reactions in vacuum but this has no direct relevance to the corresponding ionic reactions in solution. Let us examine this point on the simple and yet unique test case of dissociation of H_2O molecules in water solution. The experimental energy balance of this process is described in figure 4. It is seen that in vacuum water dissociates as a diradical and this costs ~100 kcal (420 kJ)/mol. The corresponding dissociation in water is of ionic nature and costs only ~18 kcal (75 kJ)/mole. The problem is to reproduce this effect with the available quantum mechanical calculation schemes.



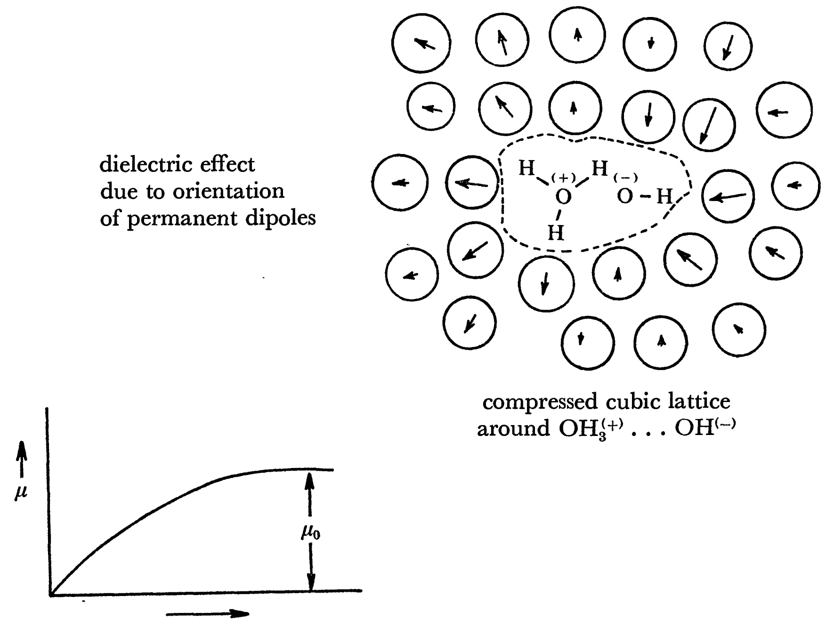
quantum treatment in external field

$$F_{ii} = F^0_{ii} - \sum_j Q_j e^2/R_{ij} - \sum_j \boldsymbol{\mu}_j \mathbf{R}_{ij}/R^3_{ij}$$

Figure 4. Dissociation of H_2O.

Recently Dr M. Levitt & I developed a simple microscopic dielectric model which teaches the quantum mechanical computer programs to perform reactions in water. This model is described in figure 5. In our model we chose the simplest representation for the water solution by treating it as a distorted cubic lattice of point dipoles which formed cavity around the reacting molecules. The idea is that the main effect of the water on the reactants can be simulated by evaluating the interaction between the water dipoles to the reactants charges. If the orientation of the water dipoles in the field of the reactants charges can be evaluated by some indirect way, then the problem is solved (even without detailed understanding of the overall factors which determine the apparent orientation). Clearly the average orientation of the water dipoles obey some unique law, the problem is to find this law. In our model we find the average orientation by the following empirical approach: we assume that the water dipoles are oriented according to the well known Langevin formula.

$$\mu_i = \mu_0(\coth(x_i) - i/x_i)\, \mathbf{E}_i/E_i, \quad x_i = v_i/kT$$



$$\mu_i = \mu_0(\coth(\alpha) - 1/\alpha)\frac{\mathbf{E}_i}{|E_i|}$$

$$\alpha = \mu_0 E_i/kT\epsilon(r)$$

where μ_0 is permanent water dipole
E_i is applied field due to charges in cavity on ith water
$\epsilon(r)$ is effective dielectric to allow for interaction of water dipoles.

FIGURE 5. Water model.

The average effective V_i is described as

$$v_i = \mu_0 E_i/\epsilon(r),$$

where $\epsilon(r)$ is an empirical function which describes the effective dielectric. The function $\epsilon(r)$ was determined by using the above model and calculating the interaction of water with various ions with different radii and different charges and by fitting the results to the observed solvation energies.

The resultant function $\mu(\mathbf{E})$ was used for quantum mechanical calculations of different reactions in water. It was found that our model produces the observed reaction energies and the correct charge distribution of ionic process. It is needless to stress the practical importance of this model in view of the fact that the biological reactions occur in water (and in enzymes) rather than in vacuum.