

Water? What's so special about it?

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What is so special about water? Why does it have the properties it has, and how might these reasons be relevant to its apparent biological importance? By exploring the structure and dynamics of water, from the isolated molecule and its interactions, through its many crystalline phases and to its so-called anomalous liquid phase, some of its apparently unusual behaviour is rationalized. The way in which it interacts with some relatively simple interfaces is also discussed. As a result of this exploration, a checklist of possible molecular-level reasons for its biological importance is devised.

Keywords: water molecule; water–water interactions; ices; liquid water; anomalous properties

1. INTRODUCTION

Water is implicated in many biomolecular processes. So much so that a great deal of mystique has grown up around this molecule. It has been called the ‘molecule of life’, the ‘matrix of life’, ‘life’s natural habitat’ and similar descriptions that underline its received biological importance. Although much effort has gone into trying to understand the ways in which water is involved in these processes—for example, protein folding and stability, enzyme–substrate interactions—there has been much less focus on trying to identify the specific molecular characteristics of water that ‘Nature’ exploits, and that evolution has capitalized upon. Although we pay lip service to the biological importance of water, we do not understand what it is about the molecule that makes it a particularly ‘fit’ molecule to form the ‘matrix of life’.

In the context of its biological relevance, much is made of the so-called ‘anomalies’ of water. That it is a liquid at all, at the conditions we find on the Earth’s surface, is only one of these anomalies, though clearly an important one as far as life here is concerned. These anomalies are, unfortunately in my view, sometimes termed the ‘mysteries’ of water, suggesting that we do not understand the reasons underlying them. This erroneous impression tends to feed into ideas about the ‘magic’ of water in relation to its role in life processes. Some demystification of water might help us to understand more clearly its role in the molecular-level processes that are important for maintaining life.

To focus attention on the characteristics of water that may be important in this context, this paper offers a summary at the molecular level of the water molecule and its interactions. As a backdrop to the papers and discussion that follow, this is an attempt to identify candidate molecular properties that may be critical in enabling water to be particularly effective in supporting biomolecular

processes. If we could identify what these biologically important characteristics actually are, we would be in a better position to suggest how other non-water-based systems might be developed.

In § 2, the focus is on the characteristics of the water molecule itself, while § 3 looks at the way water molecules interact with each other. Building on this background, § 4 looks at the molecular sociology of water—its structure and dynamics in condensed phases. It also considers current knowledge on electrical processes such as proton conduction that have often been implicated in certain aspects of protein activity. A simple explanation of the so-called anomalies is offered. An intermediate summary collects together something of a ‘checklist’ of water properties that we might like to consider when we try to identify the critical molecular reasons for water’s biological effectiveness. Some comments on water in other relatively simple environments follow. Finally, some suggestions of those properties that might be particularly important biologically are made.

2. THE WATER MOLECULE

(a) *The water molecule as nuclei*

Our view of the water molecule tends to be influenced by how we draw it. Yet how we depict it depends on the aspects we want to emphasize, for example the nuclei, the electrons or the distribution of charge.

For example, figure 1 emphasizes the nuclei that make up the molecule, and their relative geometry in the molecule. First, we might note that it consists of one *heavy* nucleus (oxygen) and two *light* ones (hydrogen). It is worth emphasizing the lightness of the hydrogen nucleus in the context of possible quantum effects. We should note also the molecular geometry (see figure 2). The bonded O–H distance is just slightly less than 1 Å (Benedict *et al.* 1956). Perhaps more interestingly, the HOH angle is accepted to be 104.52° (Benedict *et al.* 1956). This is close to not only the tetrahedral angle of *ca.* 109.5°, but also to the internal angle of the pentagon (108°). As we shall see later (§§ 4 and 5), when water molecules hydrogen bond

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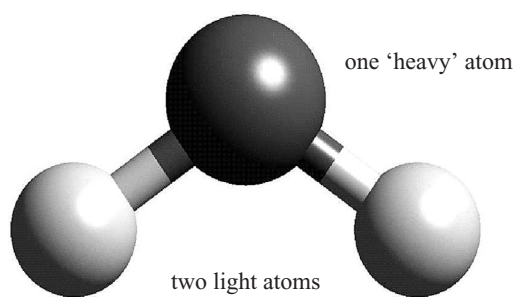


Figure 1. One schematic picture of the water molecule, emphasizing the nuclei.

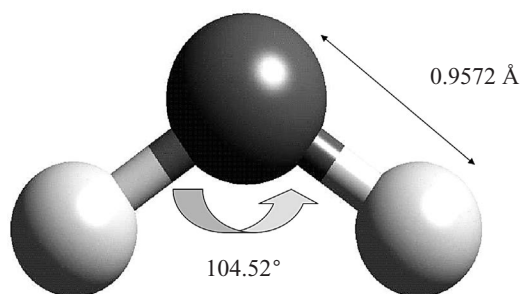


Figure 2. The average geometry of the water molecule.

to one another, the puckered hexagonal and near-planar pentagonal ring structures that are frequently observed could thus be considered as a natural consequence of the water molecule geometry.

But this static picture, though it serves a function at one level, is too simple—the water molecule is never static. Its vibrational motion can be characterized by its three normal modes of vibration (figure 3). Even at absolute zero, there is still zero-point motion; a zero-point vibrational frequency of 4634 cm^{-1} corresponds to a zero-point energy of 55.4 kJ mol^{-1} ($13.25\text{ kcal mol}^{-1}$) (Eisenberg & Kauzmann 1969). It may seem a little odd to emphasize this point in the context of biological processes at ambient temperature, but as will be discussed later (see § 4d), the quantum nature of the molecule may well be important in some fundamental processes that may be biologically relevant.

(b) *The molecule as a distribution of charge*

Another drawing of the water molecule might show the density of valence electrons in the molecule (figure 4), a picture that parallels the nuclear structure of figures 1 and 2. A somewhat different view is seen when we look at the total electron density; figure 5 shows a section cut through the oxygen and hydrogen centres to allow comparison with figures 1 and 4.

An obvious way to quantify the charge distribution is in terms of a multipole moment expansion. The first term—the dipole moment—for water is *ca.* 1.85 D (Clough *et al.* 1973; Xantheas & Dunning 1993). If we place the molecule in an electric field, it will not only respond through the interaction of its dipole moment with that field. As the molecule has a significant dipole polarizability, its dipole moment will be enhanced in the presence of this field. However, this is a property common to many small molecules. Neither the individual magnitude of the dipole

moment for water nor its dipole polarizability are unusual for a small molecule.

The dipole moment is, however, only the first term in the multipole expansion of its charge distribution, and higher terms in this expansion cannot be ignored. The quadrupole moment is significant, and relates to the standard simple model of the water molecule as having two regions of positive charge centred close to the hydrogen nuclei, and two centres of negative charge ('lone pair electrons') tetrahedrally displaced with respect to the positive charge. This classical picture is illustrated by the cartoon in figure 6, in which the positively and negatively charged regions are depicted as having tetrahedral symmetry. High-quality quantum mechanical calculations (e.g. Hermansson 1984; Buckingham 1986 and references therein) show this to be an oversimplification. On the basis of such calculations, a more realistic representation of the relative dispositions of the notional charge centres is shown in figure 7a: the lone-pair (negative) charge regions (L) appear to be much closer in to the molecular centre than the positively charged regions close to the hydrogens (H). In fact, there is good evidence to suggest that we should regard the negative charge as not separated into two distinguishable lobes, but rather as a single zone of negative charge. Thus, the charge distribution might more realistically be thought of as near trigonal rather than tetrahedral, as perhaps indicated by the section shown in figure 7b.

This near trigonality of the charge distribution is echoed in the more successful potential functions that have been developed for computer simulation calculations of water. Some of the earlier potentials developed, such as the BNS (Ben-Naim & Stillinger 1972) and ST2 (Rahman & Stillinger 1971) potentials of Ben-Naim and Stillinger and Stillinger, respectively, reflected strong tetrahedrality of the electron distribution. The results they gave are now generally recognized as predicting angular dependences that are too strong. By contrast, the more successful potential functions (interestingly all bearing a strong resemblance to the charge distribution inherent in the early water work of Bernal & Fowler (1933)) are more trigonal. Some, in fact the most successful ones, represent the lone-pair region by a single negative point charge close to or even at the molecular (oxygen) centre.

Before leaving the electron density of the water molecule, we should remember that molecules will repel each other when their electron distributions begin to overlap. The simple bent dumb-bell picture of the molecule as shown in figures 1 and 4 can be highly misleading if we use them to inform us about the geometry of the repulsive core. This is perhaps indicated in figure 7, where an attempt is made to represent the repulsive core in terms of the calculated total electron distribution. Whether the molecular shape can be sufficiently well represented by spheres centred on the centres of positive and negative charge, as implied in that figure, remains to be seen. What we can say is that it can be described reasonably well by a slightly non-spherical surface. Experimental data from high-resolution crystal structure analyses of a range of hydrates support such a slight non-sphericity, as well as allowing some rationalization of apparently complex water network geometries in terms of the non-spherical

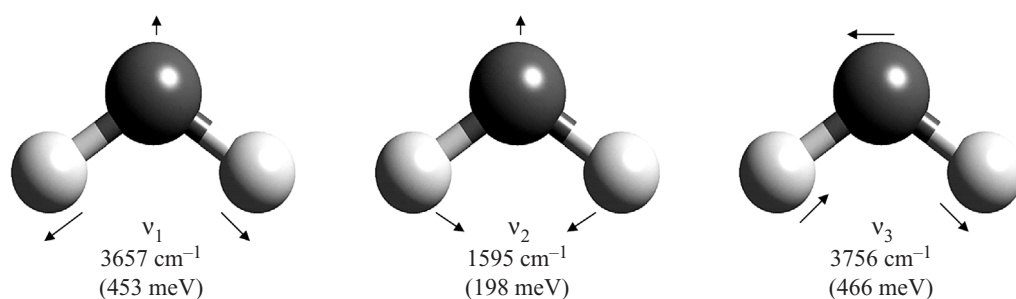


Figure 3. The three normal modes of vibration of the isolated water molecule. The frequencies quoted are from Benedict *et al.* (1956).

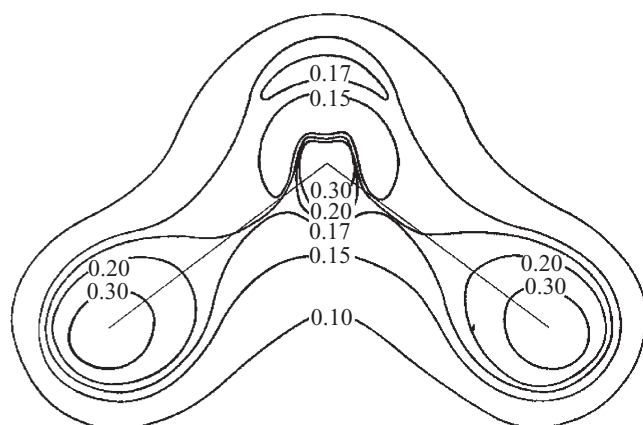


Figure 4. Contours of valence electron density (in atomic units) of the water molecule in the HOH plane. (Reproduced from Bader & Jones (1963), with permission.)

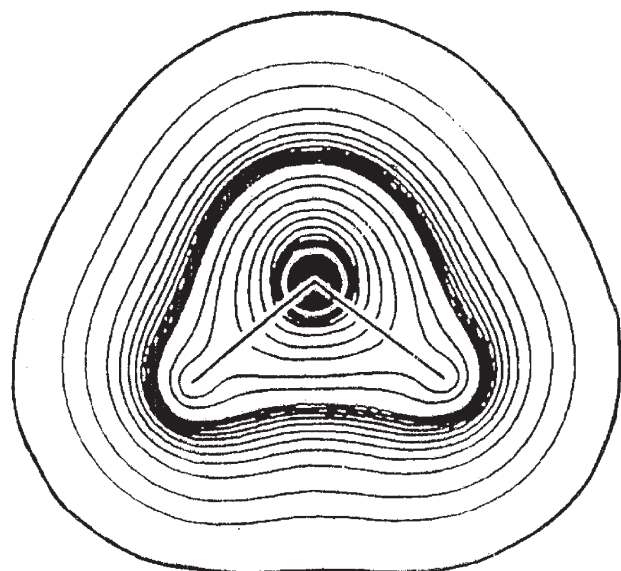


Figure 5. Contours of total electron density of the water molecule in the HOH plane, from quantum mechanical calculations by Hermansson (1984).

geometry of the repulsive core (Savage 1986*a,b*; Savage & Finney 1986; Finney & Savage 1988).

(c) *The molecule: a summary*

In summary, the following points are emphasized. First, the water molecule comprises one heavy and two light

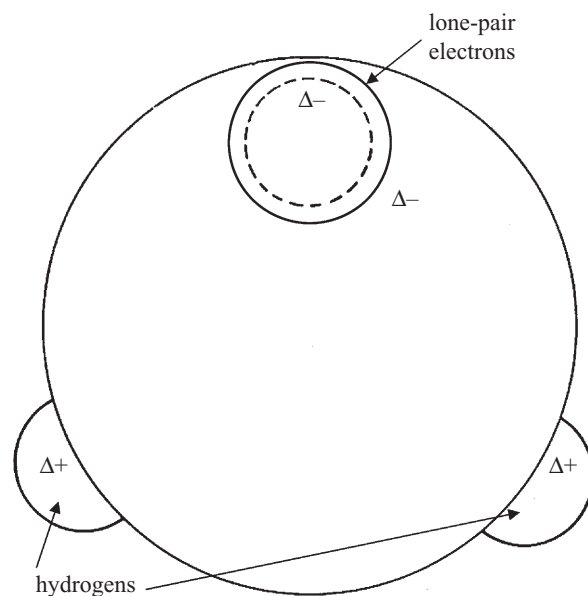


Figure 6. The classical symmetrical picture of tetrahedrally disposed hydrogen (Δ^+) and lone-pair (Δ^-) regions.

atoms. The HOH angle of its average geometry is, at *ca.* 104.5° , close to both the tetrahedral angle and the internal angle of a planar pentagon. This molecular geometry is, however, only an average—the molecule's internal motions can be described by three normal modes of vibration, and the zero-point motion is significant. The molecule has a significant dipole moment and a significant dipole polarizability, though neither is out of line with many other small molecules. Its overall charge distribution is best thought of as being near trigonal rather than tetrahedral, the elementary textbook picture of a tetrahedral disposition of two positively and two negatively charged regions being oversimplistic and, if used as the basis of quantitative potential functions, overemphasizes the angular dependence of the intermolecular potential. Finally, the molecule's repulsive core is nearly spherical, though the departure from sphericity may be important in controlling the detailed geometry of assemblies of water molecules.

In summary, it is apparently an unremarkable small molecule.

3. INTERACTIONS BETWEEN WATER MOLECULES

Water molecules interact with each other through hydrogen bonding. Whether we should consider this

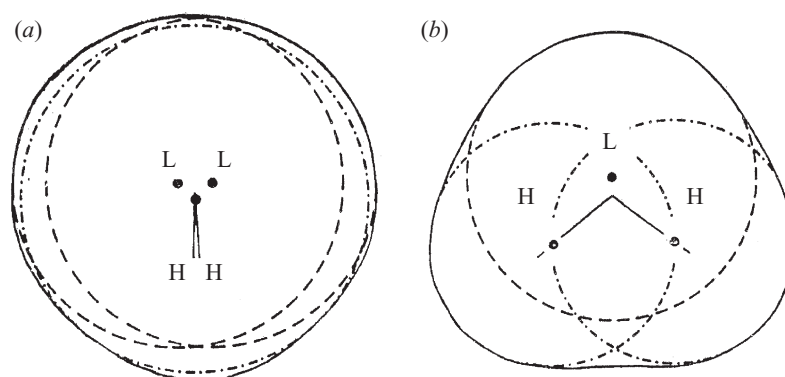


Figure 7. Representation of the centres of charge in the isolated water molecule based on quantum mechanical calculations of Hermansson (1984) (a) normal to and (b) parallel to the HOH plane. Note that the lone-pair 'centres' (L) are located much closer to the molecular centre, and to each other, than the centres of positive charge (H). The outer solid circles approximate to the outline of the molecule (c.f. the lowest electron density contour level in figure 5). The dashed and dash-dot circles are centred on the negative (L) and positive (H) charge centres, respectively.

interaction in the case of water as purely electrostatic, and hence prescribed by the electron distribution and repulsive core discussed in § 2, or including a significant covalent contribution, remains controversial. What is not controversial is the order of magnitude of the strength of the interaction between two water molecules of *ca.* 20 kJ mol^{-1} (*ca.* 5 kcal mol^{-1}). This is intermediate between a simple van der Waals interaction and an ionic one. It is equivalent to approximately 10 times a typical thermal fluctuation at room temperature ($kT_{\text{room}} \sim 0.5 \text{ kcal mol}^{-1}$), and this relative strength gives a simple rationalization of one of the so-called anomalies: that it is liquid at ambient temperature, while many other molecules of similar molecular mass remain gaseous.

There is, of course, more to the water–water hydrogen bond than its strength: there is its directionality and the number of molecules that can interact with each other. Assuming the simple idea of the hydrogen bond resulting from the attraction between the positive charge of one molecule and the negative charge of another, and vice versa, the oversimplified picture of a tetrahedral charge distribution (see figure 6) suggests each water molecule will be surrounded ideally by four hydrogen-bonded neighbours. In two of these interactions, the central water molecule will act as hydrogen-bond donor through pointing its (positively charged) hydrogens at a lone-pair (negative) region of each of two neighbouring waters. In the other two interactions, the central molecule will act as a hydrogen bond acceptor of two neighbouring waters pointing their hydrogens towards the lone-pair regions of the central water molecule. On this simple model, we build up the four-coordinated motif shown in figure 8.

Even though we have emphasized in § 2 that this highly tetrahedral picture of the water molecule's charge distribution is oversimplified, the classical four-coordinated motif of figure 8 is a good representation of the preferred mutual arrangement of hydrogen-bonding water molecules. This approximate tetrahedrality is, however, forced by more than the tetrahedral aspect of the charge distribution. High-resolution crystallographic studies on hydrates (e.g. Olovsson & Jönsson 1976) show that water hydrogens almost always participate as hydrogen-bond donors. Thus, even though the negative lone-pair region is not realistically described by two separate lobes of negative

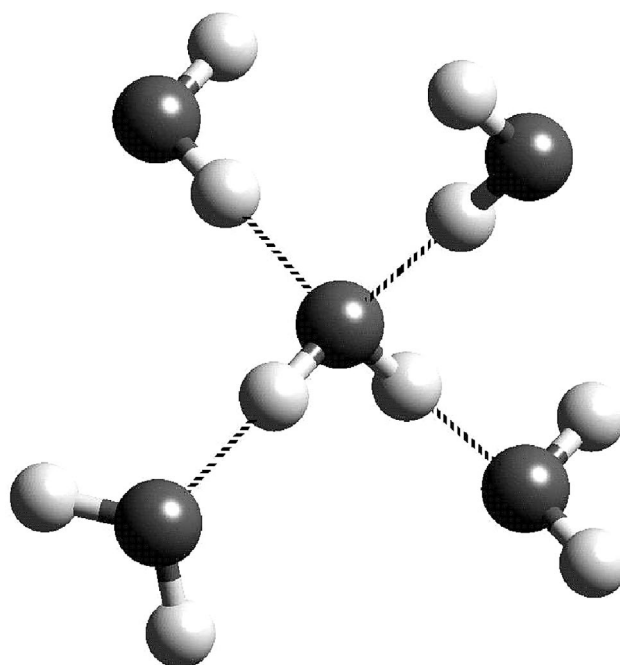


Figure 8. A four-coordinated water molecule showing the classic tetrahedral arrangement of the first-neighbour environment of a water molecule hydrogen bonding to four neighbours. The central molecule 'donates' two hydrogen bonds to its two lower neighbours and 'accepts' a hydrogen bond from each of its two upper neighbours.

charge, the fact that the donor : acceptor ratio is 2 : 2 for an assembly of water molecules, taken together with the availability of space to accommodate two donor hydrogens in the lone-pair region, will tend to result in the tetrahedral coordination seen in this fourfold motif. Structure minimization calculations using good potential functions to describe the water–water interaction reproduce this motif, even though the angular dependence of the energy of the hydrogen bond donating to the lone-pair region shows a single broad minimum corresponding to an extended lone-pair negative charge region as argued in § 2b (see figure 9a). By contrast, the 'reverse' angular dependence of the 'reverse' hydrogen bond does indeed show two minima (figure 9b), reflecting the separation of the positive charges associated with the hydrogen atoms.

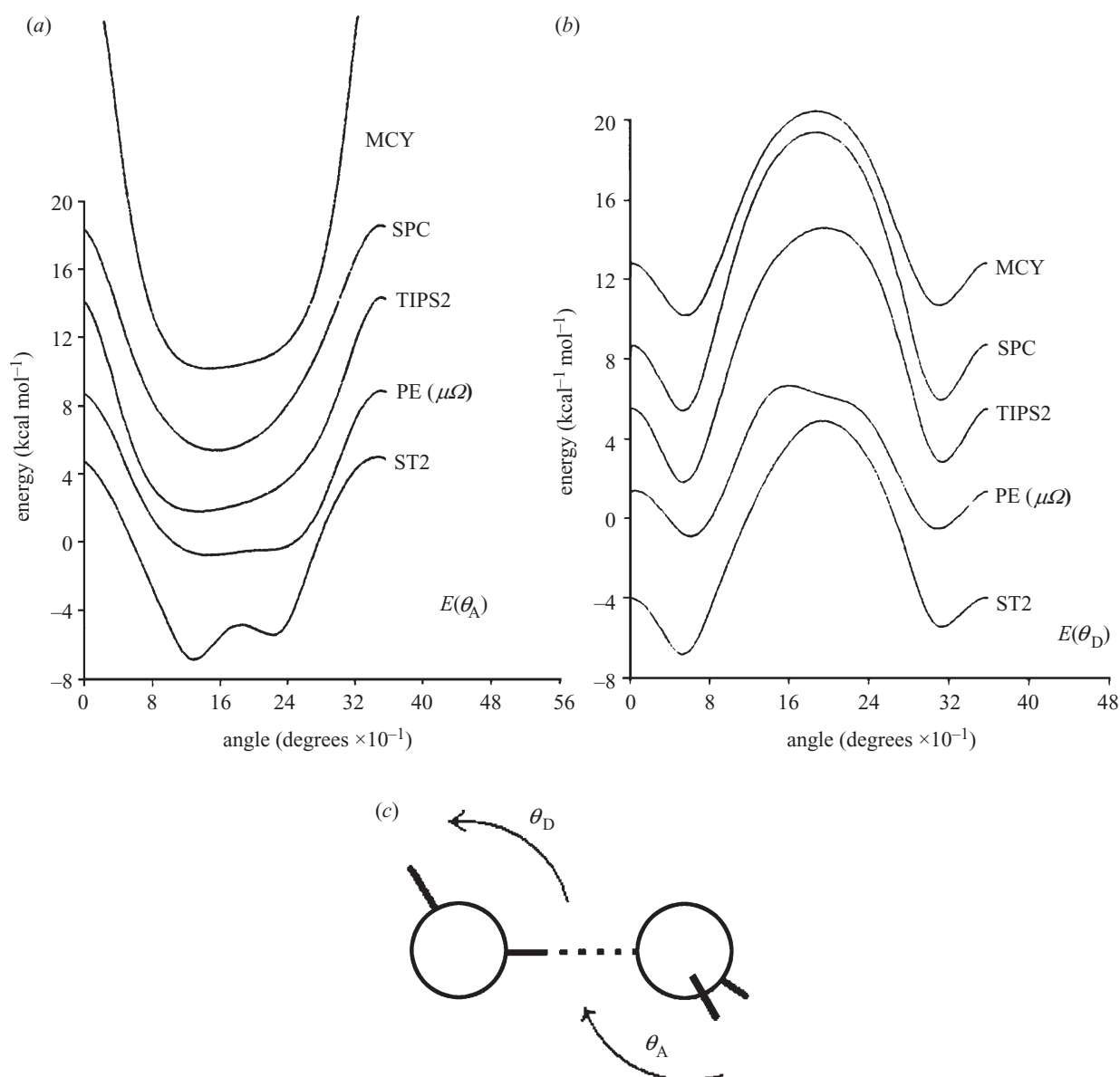


Figure 9. (a) Acceptor and (b) donor sections of the energy surface of the water molecule dimer calculated using a number of different model potential functions. For the acceptor section, θ_D is set to its value for the minimum-energy dimer; for the donor section, θ_A is set to its minimum-dimer energy value. The dimer motif indicates the minimum-energy dimer and the rotation angles used in (a) and (b). (From Finney *et al.* (1985).)

4. CONDENSED PHASES OF WATER

(a) *The structures of ices*

The four-coordinated motif of figure 8 is central to the structures of water in its condensed phases. For example, consider ordinary hexagonal ice, ice Ih—the ice we are familiar with from the freezer and frozen lakes. In considering its structure, we can ask the question: how can we connect together a number of water molecules in the manner indicated by figure 8 to form a crystalline structure that fills the correct volume at a given temperature? The answer is the structure shown in figure 10.

We can note perhaps three main points from this structure. First, it is formed from connecting together molecules according to the four-coordinated motif of figure 8. Thus, each water molecule is four-coordinated. Second, the structure is very open: in the orientation shown in figure 10, there are open channels through the structure. Even though the amount of ‘empty space’ is exaggerated

by drawing the water molecules as nuclei (figure 1) rather than their space-filling electron density (figure 7), the structure really is open and of low density. Compared with an equivalent close packing of spherical molecules centred on each water oxygen and making contact with neighbours along the hydrogen-bond direction shown in figure 7, this structure is only approximately half the maximum possible density. This lower density is a consequence of the angular constraints forced on the assembly by the directionality of the water–water interaction. Third, we should note that the hydrogen-bonded O–O distances are all almost identical at 2.759 Å and 2.761 Å at 223 K (Kuhs & Lehmann 1986; see also Petrenko & Whitworth 1999, p. 23). Similarly, the OOO angles vary only slightly between 109.36(4)° and 109.58(4)° (Kuhs & Lehmann 1986), comfortably close to the ideal tetrahedral angle (109.47°) and the average HOH angle of the individual water molecule (104.52°).

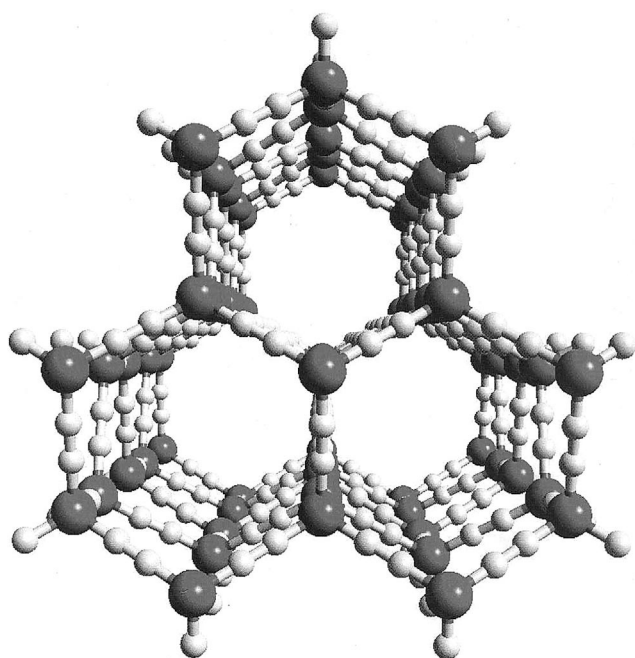


Figure 10. The structure of ice Ih looking down the crystallographic c axis. As the hydrogen positions in this structure are disordered, each possible hydrogen position is represented in the figure (by a small white sphere), though in the actual structure, only one of each pair of possible sites between two hydrogen-bonded oxygens can be occupied.

But there are many more ices than this familiar one (see figure 11). As we know their structures, what else might we learn about the molecular sociology of water from these other crystalline phases? In each of these structures, we have to arrange the water molecules to occupy less volume as pressure is increased. How does the basic four-coordinated motif respond to such demands?

Under moderate pressure of *ca.* 5 kbar (1 kbar is equivalent to a pressure of *ca.* 1000 atm.), we observe ice II. As shown in figure 12, this structure is still quite open, though some of the sixfold rings evident in the ice Ih structure of figure 10 appear to have collapsed to form smaller rings (Lobban *et al.* 2002). The basic four-coordinated motif is, however, retained. A further consequence of the structural rearrangement made to enable the molecules to occupy less volume is an increase in the spread of both bond lengths and bond angles. The former range between 2.74 Å and 2.83 Å, whereas the bond angle variation increases quite markedly to a range of 80–129°. This latter variation underlines the relative softness of the orientational part of the water–water potential function, which apparently allows deviations of up to 30° from the ideal tetrahedral angle of the ideal four-coordinated motif.

As we increase the pressure further, do we induce even greater variations in bond lengths and angles? Interestingly, the water system has another way of adapting to the lower volume forced by increased pressure, one example of which is shown by ice IV, one of the metastable phases of ice. Again, the four-coordinated motif is retained, but the structure accommodates to a reduced volume by threading hydrogen bonds through some of the open hydrogen-bonded hexagonal rings (see figure 13). This is accompanied by a slight increase in the bond length distortion, with a range from 2.74 Å to 3.08 Å (Lobban

1998). The OOO bond angle range of 85–128° is slightly less than for ice II.

This idea of threading is taken further in the higher-pressure ices VI, VII and VIII, in all of which we find two interpenetrating sub-lattices of four-coordinated motifs. In the high-symmetry cases of ices VII and VIII, essentially all the empty space formed by the open structures such as in ice Ih (figure 10) is taken up in an interpenetrating diamond-type structure (figure 14). In the ordered form ice VIII, as the interpenetration has removed much of the driving force to bond distortion, we find all hydrogen bonds to be of identical length (2.88 Å), with a relatively narrow range in OOO angles of 107.9–110.2°, a narrow range including the ideal tetrahedral angle (Kuhs *et al.* 1984).

Thus, in all the crystalline water structures determined so far, the ordered arrangements of water molecules all show four-coordinated geometry, consistent with the four-coordinated motif of figure 8. The same is also true of a number of other crystal structures involving water (Savage 1986*b*), for example the gas hydrates. There are, however, considerable variations in both hydrogen bond lengths and OOO angles in the high-pressure ice structures. The angular part of the water–water potential in particular seems to be relatively soft, accommodating quite significant deviations from an ideal near-tetrahedral value.

When considering the molecule itself, we concluded that it appeared rather unremarkable. After considering its crystalline phases, perhaps we should comment on the molecule's remarkable versatility in structure forming, and also perhaps on the fact that other systems whose interaction geometry is essentially tetrahedral (e.g. Si, SiO₂) also form a wide range of crystal structures. However, perhaps water is the only one that does so through hydrogen bonding, with an equality between the number of hydrogen-bond donors and acceptors?

(b) *Liquid water: structure*

To form the various ice structures, we imagined connecting together water molecules to occupy a given volume in a manner consistent with the water–water interaction and the existence of a crystal lattice. In considering the structure of liquid water, we can imagine following the same procedure, but discarding the crystal lattice constraint. This reflects the important fact that a liquid is *not* a crystal—even a highly disordered crystal. It is an inherently disordered structure that cannot be referred to any lattice.

An illustration of the inherent structural difference between a simple liquid and a crystal of the same spherical molecules is given in figure 15. This model, taken from the early work of Bernal (1964), contrasts snapshots of the inherently disordered structure of a hard-sphere liquid (the 'heap' of spheres making up the upper part of the picture) with the regular ordered structure of a hard-sphere crystal (the 'pile' of spheres at the bottom). The liquid region is consistent with the potential function between the 'atoms' (a spherical hard sphere repulsion), the absence of an underlying lattice and the correct (here closely packed) density.

For water, we can perform the same thought experiment, though here we have to take account of the *directional* interaction between the molecules. The result in a

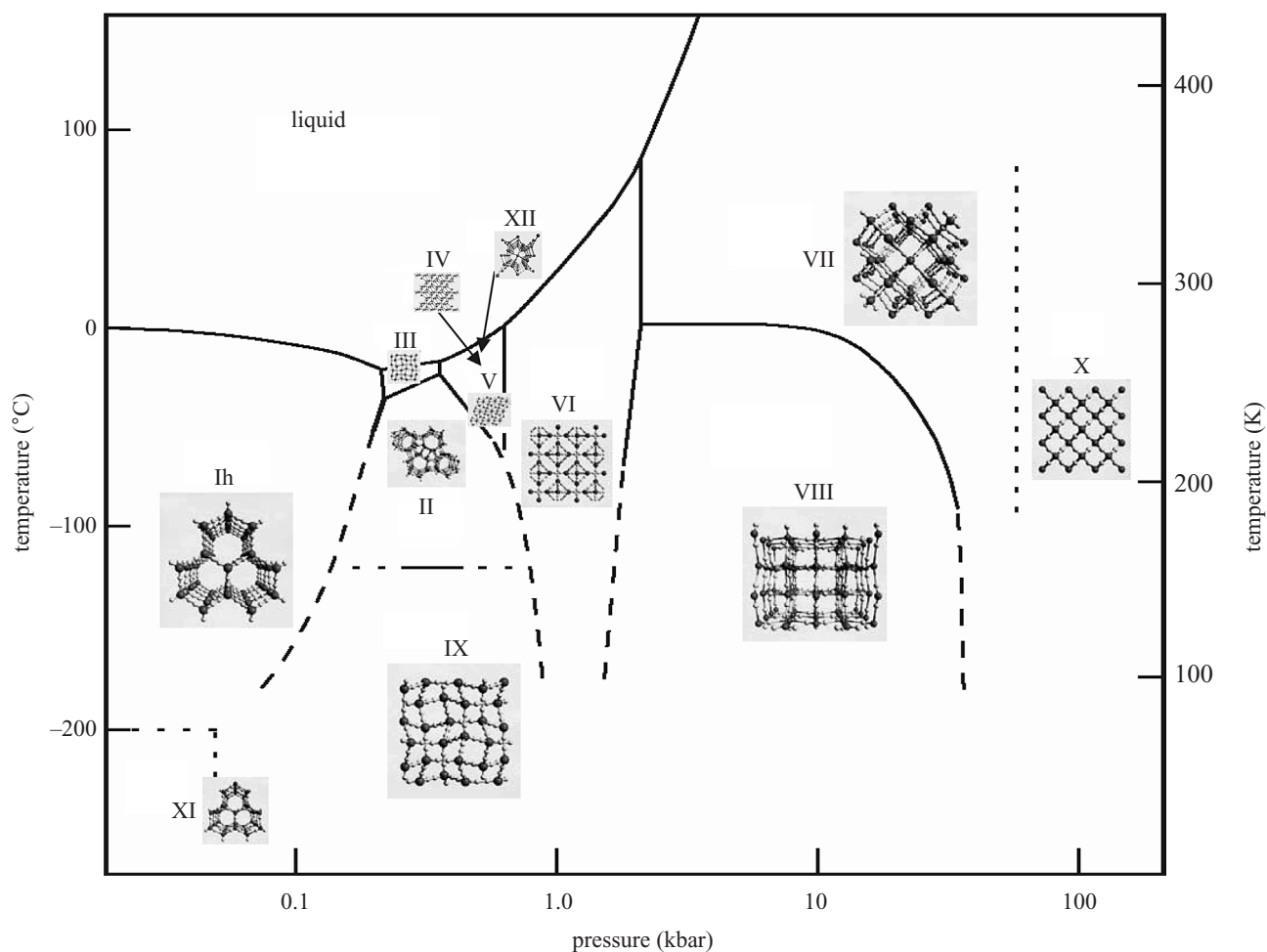


Figure 11. The phase diagram of ice. Note that ices IV and XII are metastable phases that can be found within the stability region of ice V. The thumbnails are of the structures of each phase.

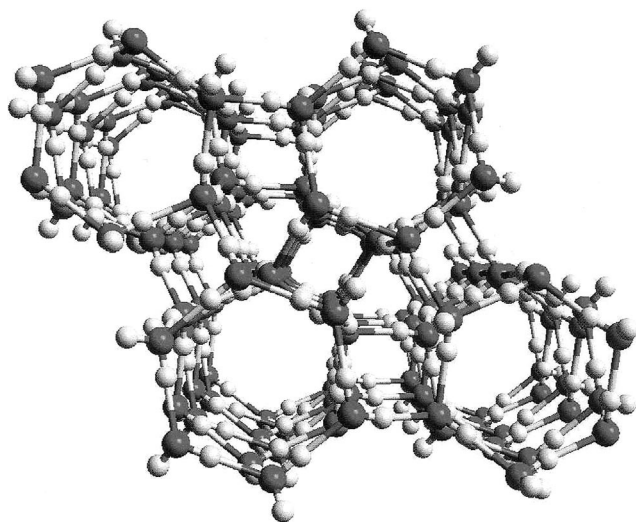


Figure 12. The structure of ice II. Note that as this is a hydrogen-ordered phase, only one hydrogen is shown between pairs of hydrogen-bonded neighbours.

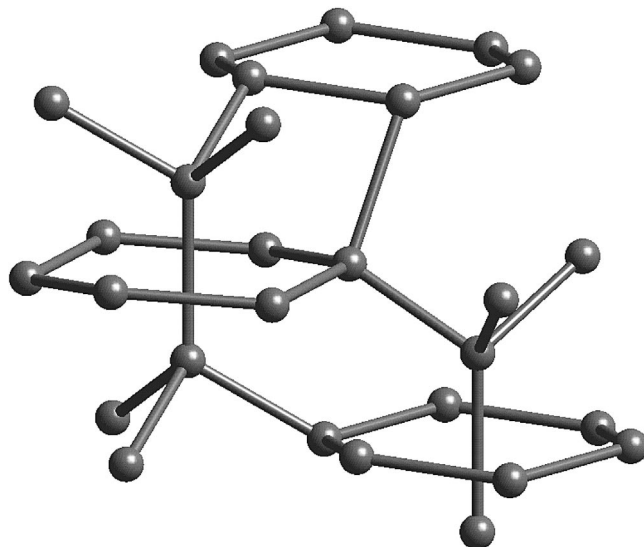


Figure 13. The structure of ice IV. Only the oxygen atoms of the water molecules are shown, with lines indicating hydrogen bonds between neighbouring waters.

two-dimensional analogue as shown in figure 16. Because of the two-dimensionality of this analogue, we have reduced the coordination to trigonal, but the concept is similar to that in three dimensions. In the disordered liquid snapshot of figure 16b, we consistently have three-

fold coordination (with some bond angle variability). Looking at ring structures, these include five-, six- and sevenfold rings (and might well include smaller and larger rings depending on the degree of bond angle distortion

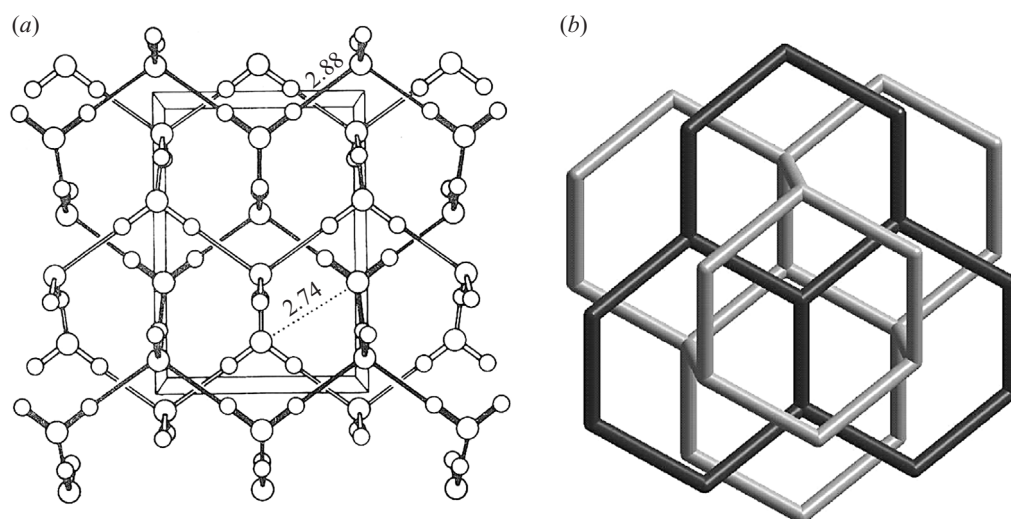


Figure 14. The structure of ice VIII. In (b) the two interpenetrating sub-lattice structure of this crystal is emphasized.

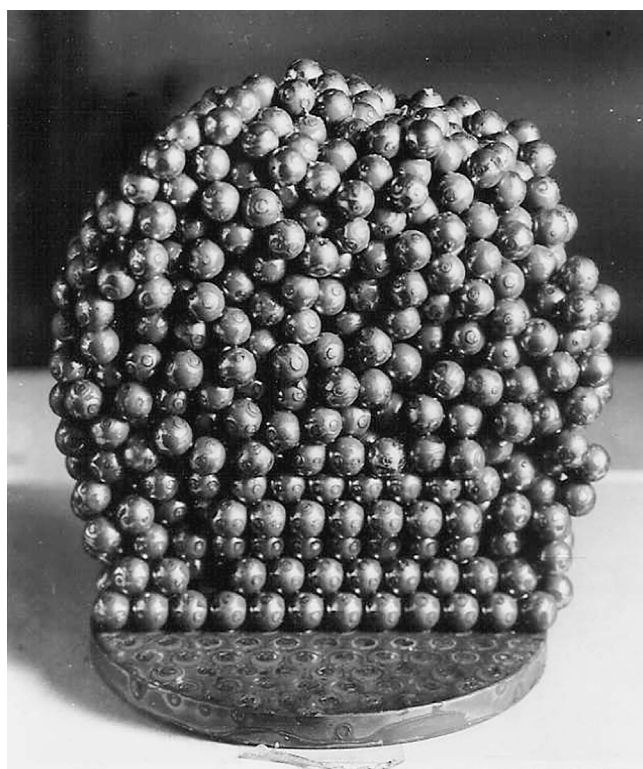


Figure 15. A simple model of a liquid of hard spheres (upper part) compared with the regular array of a hard sphere crystal (lower part), as modelled by Bernal (1964).

allowed). By contrast, the two-dimensional crystal of figure 16a has only sixfold rings (c.f. ice Ih), but is still three-coordinated. We can extend this thought process to three dimensions and build up a non-crystalline arrangement of the fourfold motif of figure 8, allowing appropriate degrees of bond bending. This would give an idealized picture of the basic liquid water structure as a random network of four-coordinated hydrogen-bonded water molecules.

But what about *real* water?

Figure 17 shows what a box of liquid water looks like. This picture was derived to be consistent with state-of-the-art neutron diffraction measurements. To explore its

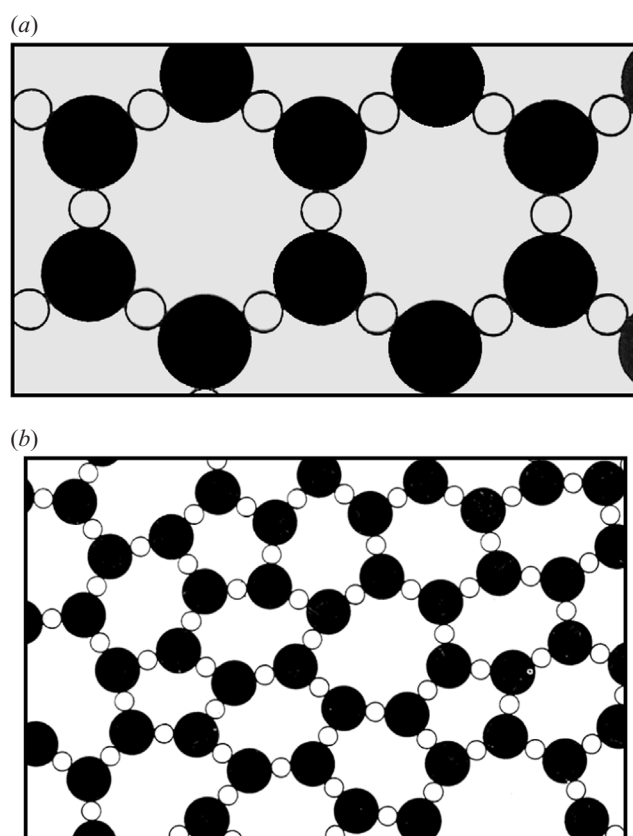


Figure 16. Two-dimensional analogues of the structures of (a) ice and (b) liquid water. To accommodate the two-dimensionality, the coordination has been reduced from four to three. (After Ziman (1979).)

detailed structural characteristics, we can home in on a limited region of this snapshot (figure 18).

From this blow-up, we can see that the four-coordinated motif is retained as the dominant coordination. However, there is significant three-coordinated 'trigonal' coordination (see figure 19a), consistent with the underlying trigonal geometry of the water's electron density distribution. A detailed examination of hydrogen-bond angles shows a wide range of values as in the high-pressure ice

structures, though the variation is broader and more continuous as would be expected of a liquid (see figure 19*d*). Inspection of the snapshots shows there are four-, five-, six- and sevenfold ring structures—all of which are consistent with the range of bond angles observed in the ice structures.

One local structure that should be noted is the so-called bifurcated threefold interaction of which an example is labelled on figure 18. In this 'defect', one hydrogen appears to be unsure of which lone-pair region of two neighbouring molecules it should interact with (see inset to figure 18). Assuming the other hydrogen makes a normal hydrogen bond and the molecule's lone-pair region accepts two molecules, such a molecule could have a local fivefold coordination—and the coordination histogram of figure 19*a* shows that such five-coordinations are relatively frequent. We shall return to this kind of configuration later (see § 4c) in the context of the molecular dynamics of the liquid.

Finally, an impression of the *average* environment of each water molecule is given by the *spatial distribution function* in figure 20. In this diagram, the lobes above and below the central water molecule represent population densities of water molecules at those positions and orientations. The average fourfold motif is clearly reflected in this function, the two lobes capping the hydrogens of the central water molecule showing the range of locations of neighbouring waters accepting hydrogen bonds from the central molecule. Below the central molecule, we have a *continuous* band of density. This reflects the lack of separation of the negative charge in the lone-pair regions of the molecule, and underlines the point made above that water molecules approaching in the direction of the lone-pair region can take on a wider variety of orientations (cf. the potential function sections of figure 9).

Before leaving the structural aspect of liquid water, we recall from § 2 that the water molecule has a significant dipole polarizability. In the liquid, each water molecule will experience a fluctuating electric field from its neighbours, which would be expected to lead to an enhancement of the dipole moment of each molecule. Although there are no easily interpretable measurements of the degree of dipole moment enhancement in the liquid, there are *ab initio* computer simulations that give an indication of what may happen. One recent such calculation (Silvestrelli & Parrinello 1999) shows a distribution of dipole moments ranging from *ca.* 2 D to *ca.* 4 D. Compared with the isolated molecule value of 1.85 D, this is a very significant enhancement. We note in this context the potential relevance of this to the relatively high dielectric constant of liquid water, a property that makes it particularly effective in dissociating ionic species. Without this polarizability, the permittivity would be expected to be significantly less.

In summary, we emphasize that liquid water is a liquid, with the structural characteristics of a liquid—no long-range order, and local variability of environment consistent with the intermolecular potential. On average, the first-neighbour environment is tetrahedral, though there are significant local defects where the coordination is either greater or less than 4. There is a wide distribution of OOO bond angles. And its dielectric permittivity is

particularly high partly because of the molecular polarizability.

(c) *Liquid water: molecule dynamics*

Experimental measurements report typical water molecule reorientation times in the liquid of *ca.* 2 ps at ambient temperature (Texeira *et al.* 1985). Furthermore, the mean time for a water molecule to move a distance of approximately one molecular diameter is *ca.* 7 ps (Denisov & Halle 1996). Recalling the typical hydrogen-bond energy of *ca.* 20 kJ mol⁻¹—equivalent to *ca.* 10 kT_{room} —these times are remarkably short. We would expect them to be several orders of magnitude greater than these if the molecular motion involved breaking two or three hydrogen bonds. The implication is that some other mechanism must be in play to allow more rapid motions of this linked hydrogen-bonded network structure.

One possibility was suggested 20 years ago from looking at certain pathways in model potential surfaces that involved cooperative motions (Finney *et al.* 1985). Such cooperative motions may not involve discontinuous breaking of hydrogen bonds. Rather, several neighbouring molecules may move cooperatively to avoid the assembly passing over thermally significant barriers between neighbouring configurations. More recently, a detailed examination, using computer simulations, of possible 'transition states' has implicated local hydrogen-bond defect structures in the diffusion mechanism (Sciortino *et al.* 1991, 1992).

We recall the concept of a bifurcated bond discussed in § 4b. Sciortino and colleagues estimated the energy of one 'normal' hydrogen bond to be about the same as two bifurcated ones. Looking at the details of the simulations, they also found that there was preferential exchange of molecules close to five-coordinated defects. They concluded that bifurcated hydrogen bonds offer a transition state between two different configurations. Thus, although the hydrogen-bond network is relatively robust with respect to typical thermal fluctuations at ambient temperature, such a defect mechanism offered a viable mechanism that could explain the anomalously high diffusion rate observed. We thus have an interesting situation of a relatively rigid framework—the water network structure; yet this framework has the ability to act as the good room-temperature fluid that is essential in performing its biomolecular functionality.

(d) *Proton conduction in liquid water*

Water ionizes—there is always some H⁺ and OH⁻ (or various hydrated versions of these ions) present in the liquid. In addition to molecular diffusion being anomalously high in liquid water, so also is the conduction of an excess proton. Much is often made of this ability, particularly with respect to moving protons both to and from a protein for whose action it is necessary, and along hydrogen-bonded chains (which may sometimes be linear 'water wires') to and from the relevant site on the protein.

There is much controversy over the mechanism of this proton motion. Most explanations rely on the basic Grotthuss mechanism (von Grotthuss 1806), which has its double centenary in 2006. According to this mechanism, a proton from an H₃O⁺ ion moves rapidly along a hydrogen bond to a neighbouring water, so recreating the H₃O⁺ on

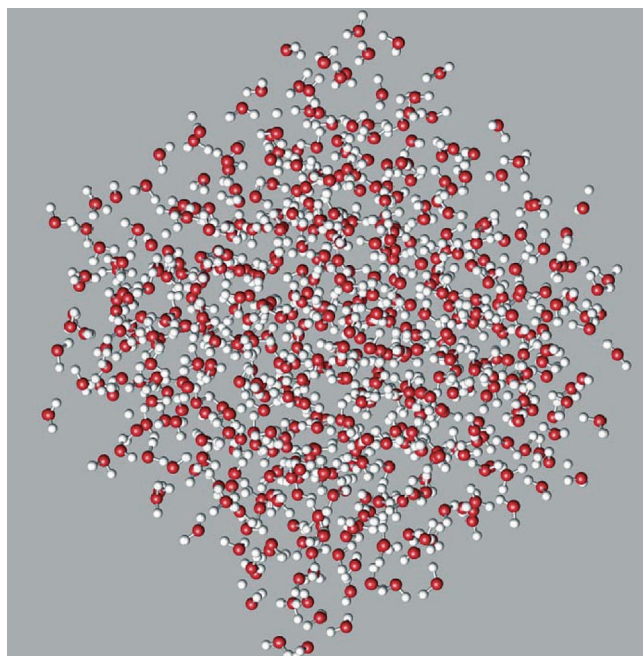


Figure 17. A snapshot of liquid water at 298 K.

the neighbouring molecule. Another proton from the receiving water molecule then translocates similarly to another neighbour, etc. This basic mechanism has been 'refined' in a number of ways, perhaps including concepts of proton tunnelling along the hydrogen bond, or involving a rate-limiting water molecule rotation step to present a lone-pair site to the translocating proton. Some explanations invoke proton delocalization over large clusters of water molecules. However, the experimental evidence is in conflict with these simple ideas (e.g. Agmon 1995).

Recent progress in understanding proton conduction has been made using developments in *ab initio* computer simulations (Tuckerman *et al.* 1997; Marx *et al.* 1999). As a result, we now have a viable picture of the proton conduction process that is consistent with the range of experimental data available. A detailed graphical picture of what may happen is given in Marx *et al.* (1999), though the essence of the process is illustrated in figure 21. The excess proton is initially localized on one water molecule (A in figure 21), which thereby becomes three-coordinated. For this proton to move along a hydrogen bond, the receiving neighbour (B in figure 21) has to lose one of its four neighbours (molecule C) in the second-coordination shell of the molecule with the excess proton. This thermally induced hydrogen-bond breaking process is thought to control the proton diffusion rate. Once the proton has shifted to the neighbour B, another water molecule (D in figure 21) coordinates to the molecule A that originally hosted the excess proton. The process can thus be thought of as a one propelled by hydrogen-bond cleavage in front of the moving proton with subsequent hydrogen-bond formation at the back. Such a model is indeed consistent with the existing experimental evidence.

A further point is relevant to proton conduction in water. Contrary to much speculation over at least 30 years, the recent calculations do not support the idea of proton tunnelling through a classical barrier as being of significant importance. What the calculations do show is

that the barrier to proton motion along a hydrogen bond is washed out by zero-point motion. This zero-point motion effectively reduces a classical barrier to proton motion of *ca.* $1 kT$ to a much lower quantum barrier of *ca.* $kT/4$ (Marx *et al.* 1999). That water has two light atoms as part of its make-up appears to be important for this effective proton transfer in the liquid.

(e) *The so-called anomalies of water*

Much is made of the so-called anomalous properties of water. The first anomaly that we are usually introduced to is the fact that water is a liquid at all at ambient temperature, where most other molecules of similar mass remain in the gaseous state. As mentioned previously at the beginning of § 3, this property is simply explained by the strength of the hydrogen bond operating between water molecules, which, as we have already seen, is equivalent to several times a typical thermal fluctuation at room temperature. By contrast, many other small molecules interact mainly through the much weaker van der Waals interaction, the typical energy of which would be of the order of kT .

More interesting, and less simple to explain, are what we might call the 'structural' (or 'thermodynamic') and the 'dynamic' anomalies of liquid water. These include the observations that water is denser than ice (in contrast to most other systems where the liquid phase is less dense than the crystalline phase), and that cold water *expands* on cooling—with a temperature of maximum density at 277 K. Thus ice floats on water, meaning that lakes freeze from the top rather than the bottom, and cold lakes stratify. Both of these consequences of these unusual properties have potential climatological and biological importance. It is often suggested that the overall biological importance of water is specifically related to its anomalous properties. Whether this is so or not remains a matter of argument. What is not a matter of argument are the molecular reasons for the so-called anomalous behaviour. We now summarize the features of the water molecule interactions that explain, both qualitatively and (through appropriate modelling) quantitatively, the so-called anomalous behaviour.

To anticipate the conclusion, it is generally accepted that the underlying reason for liquid water's anomalous behaviour relates to the four-coordinated local geometry that reflects the directionality of the hydrogen-bond interaction (figure 8). Consider now the normal 'close-packed' liquid idealized in figure 15. In this latter case, removing the crystallinity constraint on the hard-sphere crystal forces the spherical molecules to occupy a larger volume, with the liquid therefore being less dense than the crystal. For water, however, we have already seen that the structure of the normal crystalline phase, hexagonal ice, is expensive on space occupation. Figure 10 shows the presence of open channels that arise as a consequence of the tetrahedral geometry of the water coordination. On melting, we remove the crystallinity constraint so the molecules are able to explore a wider range of local geometries that are consistent with the water–water interaction, and as we have already seen in the liquid, a range of different local structures are found. For example, looking at the liquid in terms of ring structures, ice Ih contains only six-fold rings. The liquid contains a range of ring structures

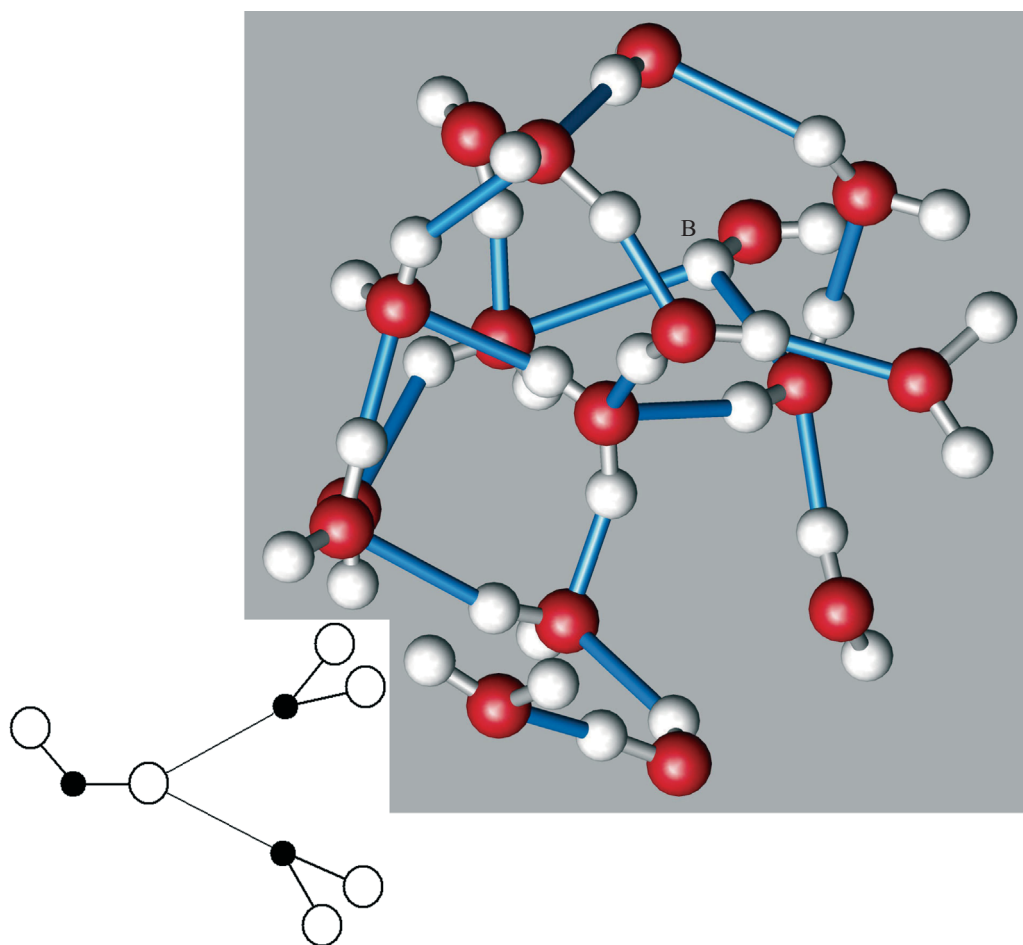


Figure 18. A close-up of the configuration shown in figure 17, including lines indicating likely hydrogen bonds between neighbouring molecules. Note the existence of both four- and three-coordinated molecules, as well as a bifurcated interaction (marked B) in which one hydrogen apparently donates to two neighbouring lone pair regions (indicated also in the inset).

including five- and fourfold ones, each of which will be less space demanding than the sixfold rings in ice Ih. Thus, the removal of the crystallinity constraint allows the molecules to take up a range of local structures, many of which occupy less volume per molecule than the crystal. The overall result, as is perhaps implied in the two-dimensional cartoon of figure 16, is a liquid of a higher density than the corresponding crystal.

We can make a similar qualitative argument to justify the low-temperature thermal expansion behaviour. As we heat a simple liquid, the anharmonicity of the potential well results in an increasing average first-neighbour separation. For water, we have an additional variable in the local structures, namely the OOO angles. As we increase temperature, we expect an increase in the bond-angle variations, an increase that may enable the exploration of denser local structures—remember the above qualitative rationalization of water being denser than ice. Thus, we have two effects operating as we increase the temperature—a ‘normal’ thermal expansion from the anharmonicity of the hydrogen bond potential well, and an increasing angular variation that could lead to denser rather than expanded structures. As we increase the temperature, the volume variation observed will be the result of the resolution of these two competing tendencies. At low temperature (below 277 K) the bond-angle variation dominates, leading to an overall contraction, whereas

above 277 K the normal thermal expansion mechanism dominates.

This explanation is rather qualitative, and it would be useful to formalize it a little more. Consider as an example of an anomalous property the isothermal compressibility, whose temperature dependence is compared schematically with that for a ‘normal’ liquid in figure 22. Whereas for a normal liquid the compressibility increases with increasing temperature (it becomes less dense), with water at low temperature the compressibility first decreases, passes through a minimum at 319 K, and then continues to increase similarly to a normal liquid. The anomalous behaviour is most obvious at low temperature, as is seen also in the other thermodynamic anomalies such as the isobaric heat capacity (with a minimum at 308 K) and the thermal expansion coefficient (which, as already mentioned above, changes sign at the temperature of maximum density of 277 K).

It is useful to think of these three anomalous properties in terms of the fluctuations to which they can be related (see e.g. Debenedetti & Stanley (2003) for a fuller discussion of this). The isothermal compressibility is proportional to volume fluctuations $\langle(\delta V)^2\rangle$, the isobaric heat capacity is proportional to the entropy fluctuations at fixed pressure $\langle(\delta S)^2\rangle$, while the thermal expansion coefficient relates to the cross correlations between entropy and volume fluctuations $\langle(\delta S\delta V)\rangle$. In simple liquids, both density

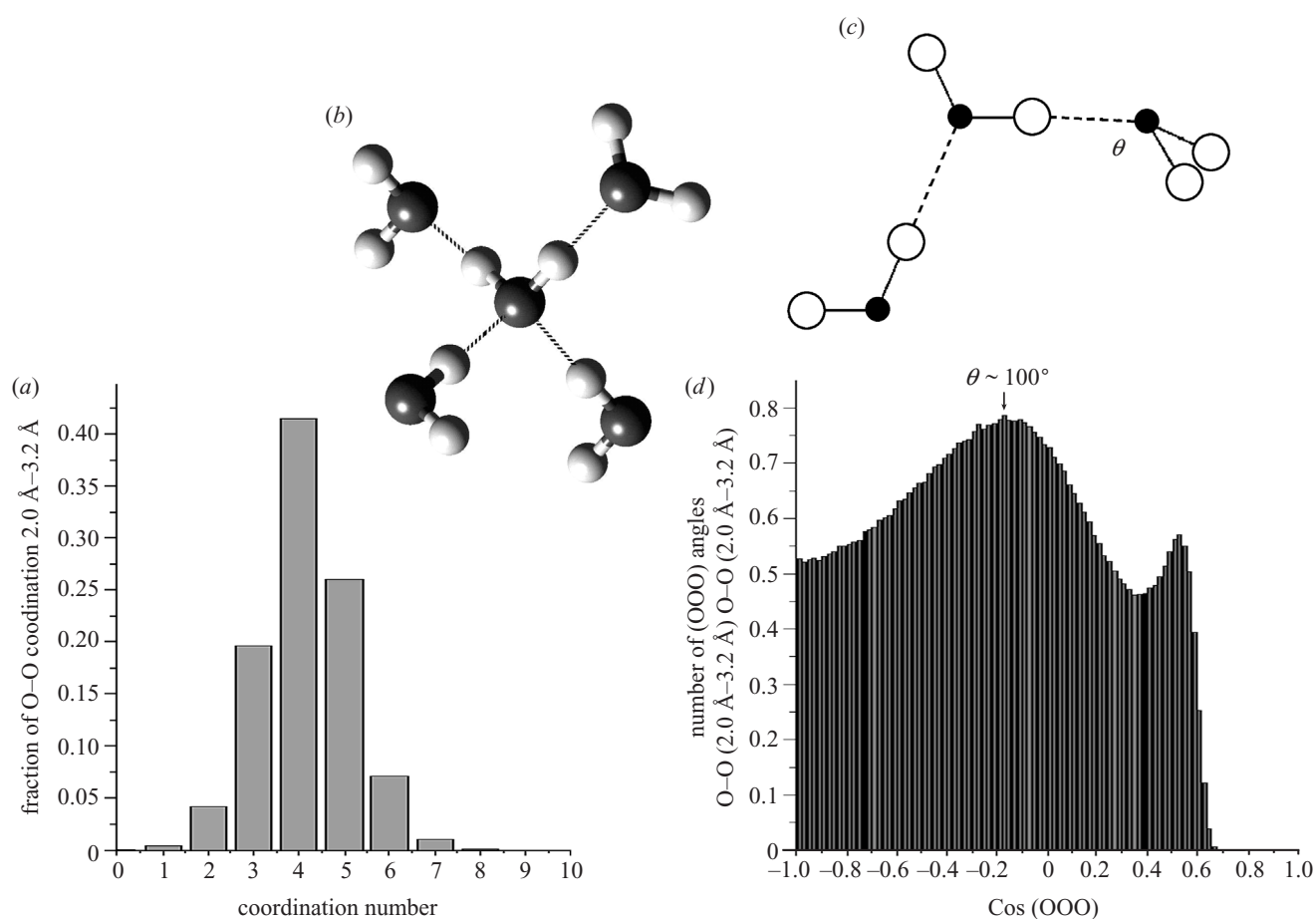


Figure 19. Distribution of coordination numbers and OOO angles in water at 298 K. The average coordination number is 4.4. The criteria used in defining the contacts are given in the ordinates of the graphs.

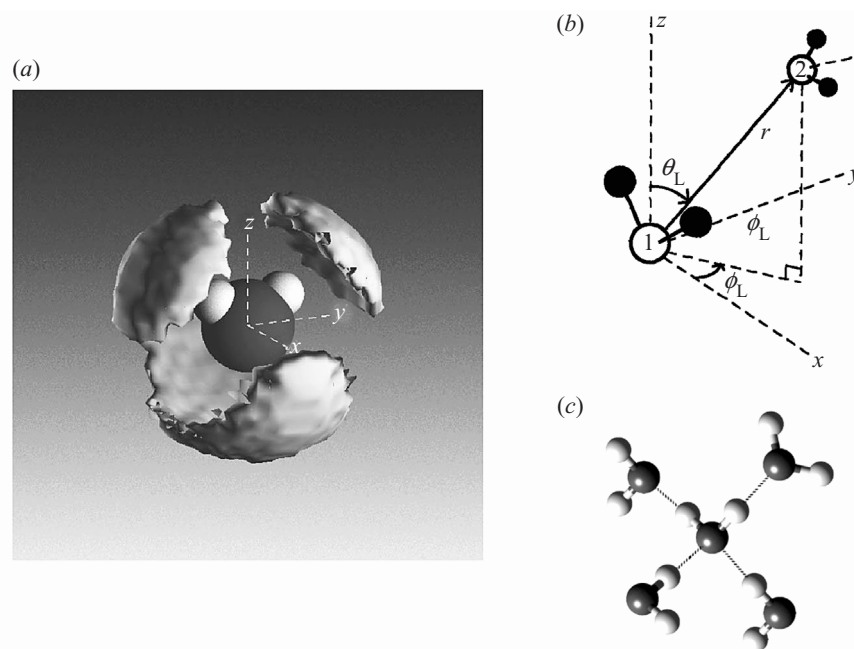


Figure 20. The average first-neighbour environment in liquid water. (a) The spatial distribution function, which illustrates, through the lobes, the average distribution of neighbouring waters (molecule '2' in (b)) around the central molecule (molecule '1' in (b)). The two distinct lobes above the central molecule correspond to waters accepting a hydrogen bond from the central molecule. The single broader lobe below corresponds to neighbours donating hydrogen bonds to the lone-pair region of the central molecule (as in the fourfold motif reproduced again in (c)). The fact that this 'acceptor' lobe is a single one reflects the asymmetry of the electron distribution discussed in § 3.

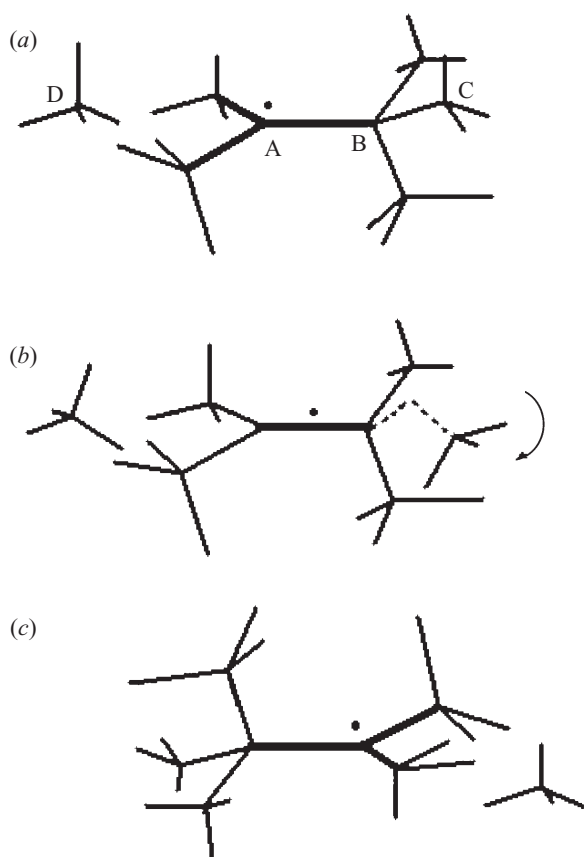


Figure 21. A mechanism for proton conduction in liquid water that is consistent with both experimental data and recent quantum mechanical modelling calculations. The filled circle denotes the location of the excess proton in each of the three panels. See text for details. After Agmon (1995).

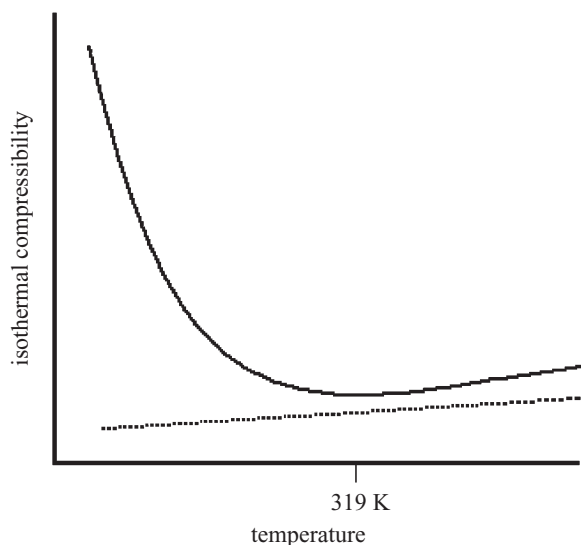


Figure 22. Schematic temperature dependence of the isothermal compressibility of water (solid line) and of a 'normal' (dashed line) liquid.

and entropy fluctuations reduce with reducing temperature. Moreover, entropy and volume fluctuations in normal liquids are positively correlated—increasing the volume results in an increase in entropy. We thus have the normal temperature dependence of the properties that

relate to these fluctuations: the compressibility, heat capacity and thermal expansion all become smaller as the temperature is lowered.

For water, however, density and entropy fluctuations increase as we lower the temperature (figure 22 shows schematically the increase in volume fluctuations, directly related to the isothermal compressibility, as temperature is reduced below 319 K). Furthermore, below 277 K, an increase in volume gives rise to a decrease in entropy—the volume and entropy fluctuations are *anticorrelated*. The cause of this anticorrelation can be found in the local tetrahedral geometry of the water molecule interactions. Starting from the liquid at, say, room temperature, reducing the temperature will gradually 'tighten up' the angular variability around the ideal tetrahedral angle, causing the local geometrical structure to increase its degree of orientational 'order'. In contrast to simple liquids, where the local ordering results in occupying less volume per molecule, in water's case an increased order in the local orientational structure will result in an *increased* local specific volume. We thus have a natural geometrical explanation of the anticorrelation between entropy and volume; an anticorrelation that allows the thermal expansion to become negative.

If this explanation of the thermodynamic anomalies is valid, then we would expect similar 'anomalous' behaviour in other liquids that show local tetrahedral symmetry, such as silica. Our expectations are correct. It is the local tetrahedral geometry that is ultimately responsible for the thermodynamic anomalies observed in liquid water and in other liquids with similar underlying local geometrical structures.

This explanation can be put on a quantitative basis by defining two different order parameters (e.g. Errington & Debenedetti 2001). The first of these—'spatial order'—relates to the tendency of pairs of molecules to adopt preferential separations, while the second—'orientational order'—quantifies the extent of the local tetrahedral arrangement (see figure 23). Using these order parameters, we can consider the behaviour of both normal liquids and water as the volume is increased. In normal liquids, both the spatial and orientational order *increase* as the volume is decreased. In water at low temperature, however, the spatial order and orientational order both *decrease*—the bonds are forced to bend (it is perhaps useful here to recall the increased dispersion in both bond angles and bond lengths as we compress ice—recall the high-pressure ice discussion in § 3a). Thus, again we see that the local tetrahedral structure is the key to the thermodynamic anomalies of both water and other tetrahedral liquids.

We can draw a similar conclusion with respect to the 'dynamics' anomalies such as the observation that as pressure is increased, diffusivity initially increases. This is opposite to the behaviour of typical liquids, where increase of pressure (which also reduces the specific volume) limits the ability of the molecules to move. In the case of water and other tetrahedral liquids, increase in pressure will tend to break down the local orientational order through increased hydrogen-bond bending and, ultimately, breakage. Using the model for diffusion involving the defects discussed previously, pressure will be expected to increase

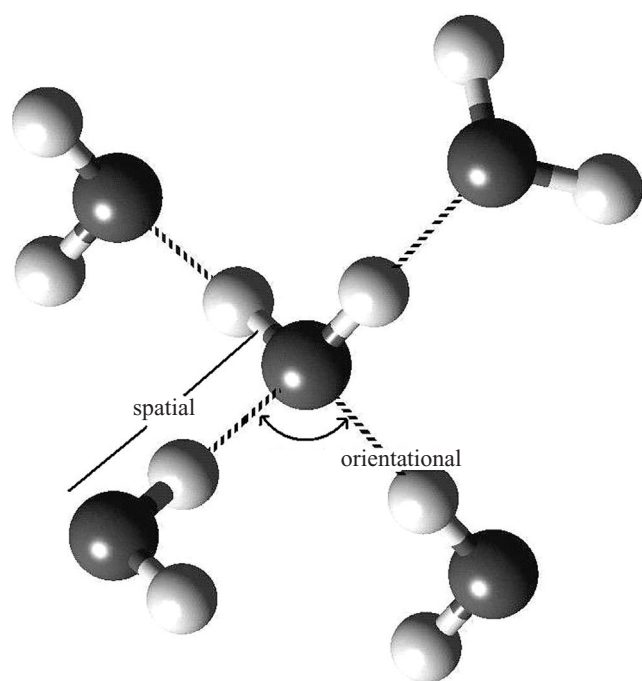


Figure 23. Spatial and orientational order parameters for the local structure of liquid water can be defined in terms of (spatial) the extent to which a molecule adopts a preferential separation and (orientational) the extent to which the neighbours of a given molecule subtend tetrahedral angles about it.

the defect concentration, and thus increased diffusivity will be expected.

In summary, the so-called anomalies of water arise from the orientational local order that results from the underlying tetrahedral bonding geometry. A similar behaviour is found in other tetrahedrally bonded systems. Despite frequent claims to the contrary, there is no real 'mystery' about the origin of water's physical properties.

(f) Intermediate summary: a checklist of water properties?

As background to the discussion, it may be worthwhile to bring together here a 'checklist' of water properties that we might bear in mind when trying to identify molecular reasons for water's biological importance. We might ask if any of these properties—of the molecule, of the condensed phases—are likely to be important in enabling biomolecular processes. If so, could we perhaps replace water with some other specific molecule with similar characteristics that could maintain that functionality? Or perhaps even design a completely different architecture based on another molecule that has similar generic properties that might be built on?

We focus first on the molecule itself.

- (i) The water molecule consists of one oxygen atom plus two hydrogen atoms. As hydrogen is the lightest atom, quantum effects are possibly significant.
- (ii) The water molecule has an (average) internal angle of 104.5° . This is close to both the tetrahedral angle of 109.5° and the internal angle of a pentagon (108°), suggesting comfortable formation of structures with which these angles are consistent

(e.g. puckered hexagonal rings, near-planar pentagons).

- (iii) The water molecule is not static. Its atoms are in constant motion, and the molecule has a significant zero-point energy.
- (iv) Its dipole moment of *ca.* 1.85 D is not particularly remarkable for a small molecule. Similarly, its dipole polarizability is significant though not particularly large for a small molecule.
- (v) The overall charge distribution in the molecule is *not* perfectly tetrahedral. Rather, there is asymmetry between the charge distributions relating to the positively charged regions (around the hydrogens) and the negatively charged lone-pair regions. The classic picture of fully separated lone pairs is an oversimplification. Rather, we should consider the negatively charged region as a single diffuse region, with the overall charge symmetry of the molecule more trigonal than tetrahedral. This deviation from good tetrahedrality might be compared with the greater tetrahedrality in other network liquids such as silica.
- (vi) The repulsive core of the molecule is slightly but significantly non-spherical.

Potentially interesting aspects relating to condensed phases include the following.

- (i) The interaction between two water molecules (hydrogen bonding) is stronger than that operating between most other small molecules. The hydrogen-bond energy is significant with respect to typical thermal fluctuations at ambient temperature (*ca.* $10 kT_{\text{room}}$).
- (ii) In condensed phases, local structures can be characterized with respect to a reference four-coordinated motif (figure 8). Ideally, the central molecule of this motif can donate two hydrogen bonds and accept two hydrogen bonds from neighbours. This 'two donor, two acceptor' potential, allied to possible variations from it, may be significant.
- (iii) Low-pressure ices and the liquid at ambient conditions have open network structures consistent with the underlying tendency to tetrahedral local order. The underlying tetrahedral motif appears to be highly versatile in forming a range of structures.
- (iv) The so-called anomalies of water relate to this underlying tetrahedral motif. Similar 'anomalies' are found in other tetrahedral network liquids.
- (v) There are significant bond angle and bond length variations found in liquid structures. There is a significant population of threefold 'trigonal' local coordinations, and a range of ring structures (e.g. four-, five-, six- and sevenfold).
- (vi) There are also local fluctuating coordination defects in the liquid state; these 'bifurcated interactions' may explain the fact that the diffusivity of liquid water is much higher than expected for a system whose intermolecular interactions are so strong with respect to typical thermal fluctuations.
- (vii) The average local first-neighbour structure seen in liquids seems resilient to perturbations.
- (viii) The molecular polarizability leads to a 50–60% enhanced average dipole moment in the liquid. This

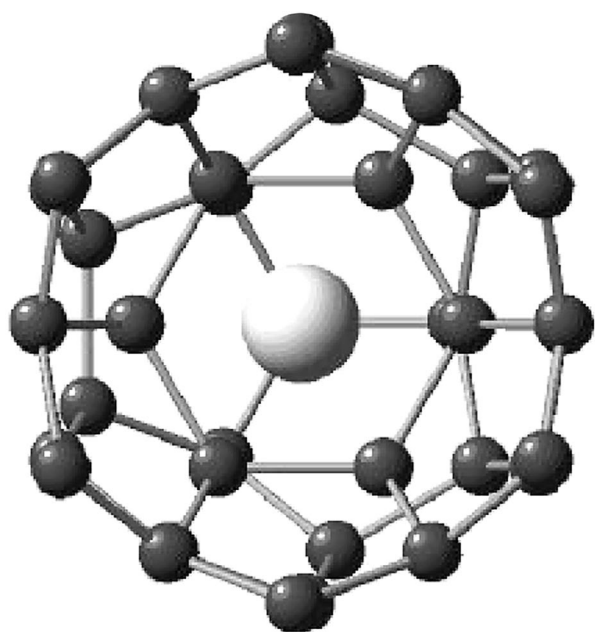


Figure 24. One arrangement of water molecules about an inert gas atom in a simple cage in a clathrate hydrate crystal. Each water molecule retains four neighbours, three of them within the shell shown, with the fourth connecting to water molecules in neighbouring shells.

is relevant to the high dielectric constant that makes liquid water particularly effective in dissociating ionic species.

- (ix) Liquid water has a high proton conductivity, in which both zero-point motion and thermally induced hydrogen-bond breaking appear to play important roles.

5. WATER IN DIFFERENT ENVIRONMENTS

So far, this discussion has been limited to considering water as either an isolated molecule or in interaction with other water molecules. The other papers presented in this discussion will consider the nature of, and response to, water in a range of different environments of potential biological interest. Partly as a background to what follows, partly to illustrate the 'operation' of certain of the properties emphasized previously, and partly to try to focus on which of the above checklist of properties might be particularly relevant to water's biological fitness, I conclude with a brief discussion of some examples of water in a number of, generally simple, environments. Despite the simplicity of some of these environments, there is much active controversy about how water responds to them, which we may need to bear in mind in trying to identify water's critical biological roles.

(a) *Water near 'inert' boundaries: non-polar interfaces*

Looking first at *curved* non-polar interfaces such as those around single non-polar atoms, the water structure appears to adapt easily to the non-polar interface. For example, in gas hydrate structures, the water molecules form so-called 'clathrate cages' round the inert gas molecule as indicated in figure 24. Looked at in terms of ring

structures, we see both five- and sixfold rings that are consistent with the 104.5° average internal water molecule angle. Looked at in terms of coordination, each molecule donates and accepts two hydrogen bonds to neighbouring water molecules. When we look at water at curved non-polar interfaces in the liquid, we see significant distortions from an idealized clathrate cage structure, as we indeed should expect for a liquid (e.g. Soper & Finney 1993; Bowron *et al.* 1998; Finney *et al.* 2003). However, the first-neighbour water structure is unchanged from that in pure water: water in this environment still thinks it is liquid water. Thus, both in the crystalline and liquid states, we see further illustrations of the versatility and resilience of the underlying tetrahedral geometry stressed earlier.

A more complex example of water structure around a non-polar moiety in crystals of coenzyme B₁₂ is shown in figure 25 (Bouquiere *et al.* 1994). Focusing on the water network around the benzimidazole group, we see a sixfold ring (a 'partial clathrate cage') capping the B10 methyl group. The remainder of the water network surrounding the benzimidazole shows examples of both fourfold and threefold coordination of water molecules. In addition to further underlining the versatility of the tetrahedral interaction in enabling water molecules to accommodate themselves to different environments, we also see the utility of the molecule's ability to deal with an imbalance of the donor/acceptor ratio through the presence of trigonally coordinated molecules that accept only one hydrogen bond from their neighbours—e.g. waters 216, 220 and 215. Had the water molecule been symmetrical in terms of its donor/acceptor interactions, it might not be so easy to accommodate such imbalances.

Considering the considerable controversy surrounding the issue at the present time, it is not possible to discuss water in non-polar environments without referring to the problem of its structure at a planar non-polar surface. For many years, there has been experimental evidence that has been interpreted in terms of a long-range interaction between two planar non-polar surfaces immersed in water (Israelachvili & Pashley 1982; see also Christenson & Claesson 2001 for a recent review). This interaction is argued to occur over distances of *ca.* 100 nm. This being equivalent to several hundred water molecule diameters, we have difficulty in arguing for a realistic source of such a long-range interaction through the liquid. If it is a real long-range effect, what is its source, and could this be biologically relevant?

There is both theoretical and experimental evidence that bears on this problem. Unfortunately, there is significant conflict in this evidence (e.g. Ball 2003). For example, neutron reflectivity measurements of Steitz *et al.* (2003) investigated the contact between water and polystyrene and concluded that there is a surface layer 2–5 nm thick with a density 6–12% lower than that of the bulk. Other workers (Jensen *et al.* 2003) using X-ray reflectivity also found a depletion layer next to an alkane monolayer, with a similar density deficit of *ca.* 10%; the layer thickness is, however, less than 1.5 nm. Other neutron reflectivity work (Schwendel *et al.* 2003) shows a depletion layer of *ca.* 2 nm, but one with such a density deficit as to be unphysical. One possible interpretation of this is that nanobubbles or other air inclusions may be present—and

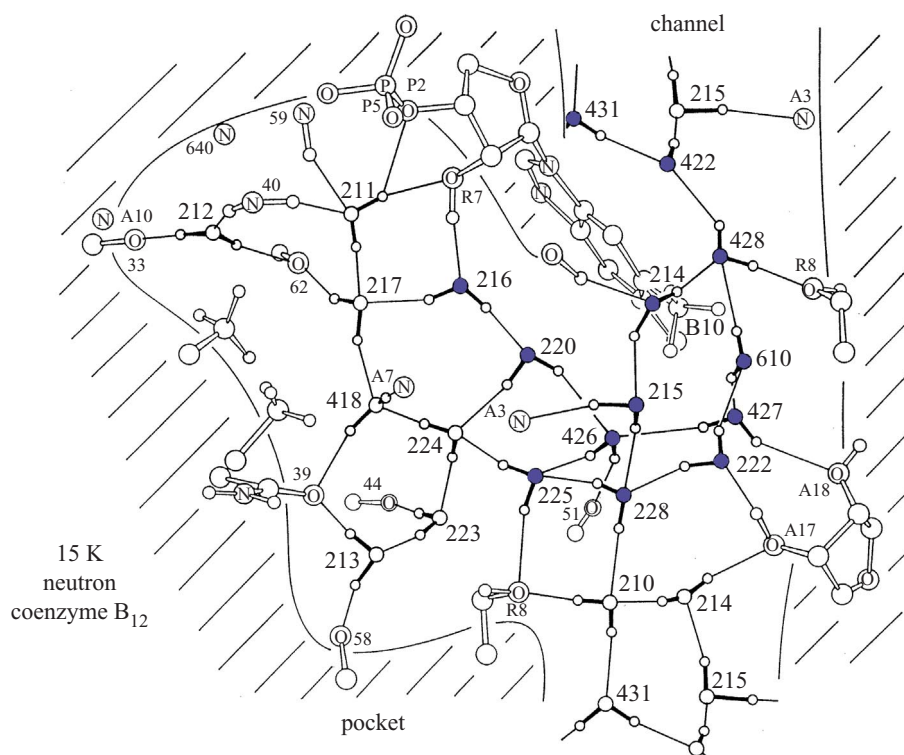


Figure 25. A more disordered cage of water molecules surrounding the benzimidazole group in the coenzyme B_{12} structure. Note that the water cage (shaded oxygen centres) fails to bond directly to the benzimidazole group (which has no available hydrogen-bonding sites) but is anchored to the molecule in other hydrogen-bonding sites such as to the OH group of R7. (From Bouquiere *et al.* (1994).)

nanobubbles have been suggested to be present by other workers (Tyrell & Attard 2001; Steitz *et al.* 2003) using AFM.

This experimental work was preceded by theoretical predictions that a gas-like layer could form between two extended planar surfaces in water (Lum *et al.* 1999), and suggestions (Parker *et al.* 1994) that the long-range force might arise from the bridging of sub-microscopic bubbles between the surfaces. That such nanobubbles have been observed may appear to support this hypothesis, and perhaps explain at least some of the depletion zone results from neutron reflectometry. However, observations of nanobubbles using AFM are subject to the objection that the AFM tip itself might nucleate the bubbles. Moreover, other workers have argued (Yaminsky & Ohnishi 2003) that experimental imperfections such as surface protrusions may be the cause of the long-range force, and that nothing more than the standard theory of colloidal interactions is needed to explain it.

The jury has not even retired to consider its verdict on this controversy, but one possible picture (Ball 2003) might be that there is a thin (*ca.* 1–5 nm thick) layer of density *ca.* 10% lower than bulk water. This depletion zone may precede capillary evaporation between the surfaces that may nucleate nanobubbles, which may then explain the capillary attraction. However, in all this, there may be nothing unique to the nature of water. All that may be needed is relatively unfavourable interactions between the fluid and the surface, and these can occur for other liquids apart from water.

(b) Water at polar interfaces

This is much easier, as there is a wide range of good quality crystallographic data on water in contact with biomolecule interfaces, as will be discussed in several of the other papers. These data tell us similar things to those pointed out earlier (§ 5a) in commenting on the water surrounding the benzimidazole group in coenzyme B_{12} , which also have to accommodate themselves with respect to the nearby polar interfaces. Figure 26 shows again the water network in coenzyme B_{12} , but also includes a second water network in the channel region at the right-hand side of the figure (Bouquiere *et al.* 1994). One network is shown as solid thin lines, the other as dotted lines. Both of these experimentally observed water networks match the polar interfaces they attach to, and are consistent with the water–water interaction geometry, again underlining the versatility of the underlying (asymmetric) tetrahedral geometry of the molecular interactions.

In summarizing the interaction of water with polar interfaces from a wide range of studies, we can comment that water structures apparently fit in comfortably with available hydrogen-bonding sites. Water molecules can accommodate irregular interfaces, and can, through three-fold coordination, mop up significant donor–acceptor imbalances. The versatility of the interaction geometry is further underlined by the fact that a set of polar interfaces can be bridged by more than one distinct water network—two are shown in the case of B_{12} at 15 K, though earlier work at 279 K identified four different networks (Savage 1986a).

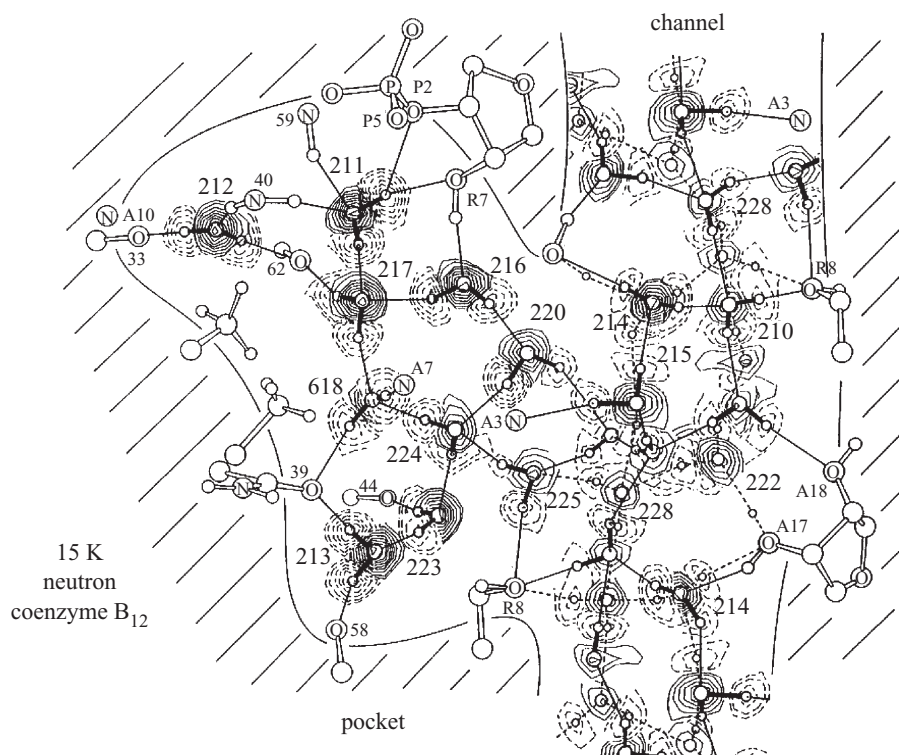


Figure 26. The water organization in the coenzyme B_{12} crystal structure at 15 K, showing the possible existence of two different water networks in the channel region (denoted, respectively, by thin solid and thin dotted lines connecting neighbouring hydrogen-bonded waters). (From Bouquiere *et al.* (1994).)

(c) Water dynamics in confined geometry

So far we have considered only structural aspects of water interactions with other surfaces. What about dynamics? Again, this will be discussed in detail in other papers, but it seems worthwhile to raise the general issue of water dynamics in confined geometry in the context of the earlier discussion on diffusivity and its pressure dependence. Again, this is an area in which water seems to behave differently from more 'normal' liquids, and if this behaviour is of biomolecular relevance, we might usefully look for the molecular reason for this.

An example of relevant work (Raviv *et al.* 2001) uses surface-force balance measurements to extract information on relative viscosities of liquids confined between two surfaces. For both standard organic liquids and water, for a film thickness of greater than 8–10 molecular diameters, the viscosities are essentially the same as those in the bulk. As the confinement is increased so that we are looking at thin layers of liquid between five and eight molecular diameters, the results for typical organic liquids and for water diverge dramatically. For the organic liquids, the effective viscosities increase greatly, as would be expected if the additional compression of the liquid between the two approaching surfaces increased the degree of ordering in the (simple) liquid—because increasing pressure increases the viscosity and diffusivity of simple liquids, as mentioned in § 4e. For water, the effect of further confinement is very much smaller: Raviv *et al.* (2001) conclude that it remains within a factor of three of its bulk value. In the context of the discussion above (§ 4e) of the effect of increasing pressure on the diffusivity of water (below a threshold value the diffusivity rises as the pressure breaks down the orientational order and increases the defect

population), this result is not unexpected. If this retention of relatively high fluidity in confined geometry is of biological relevance, then again it would seem that the underlying tetrahedral geometry is also of importance.

6. SO WHY MIGHT WATER BE SPECIAL?

It was the job of this meeting to try to come to some answers to this question, and a checklist of possible characteristics was offered in § 5. In the light of this quick survey of water interacting with other interfaces, can we perhaps begin to pin down some promising molecular-level candidates?

First, we have repeatedly come across the underlying ideal tetrahedral geometry of the local order. This was central to understanding the so-called anomalies, but those may be incidental to the molecular-level biological fitness of water. But this geometry does appear to be central to the structural versatility of the molecule, a versatility that was considerably enhanced by its imperfectness or asymmetry. The positively charged end of the molecule is more orientationally constrained than in the negative lone-pair region, allowing both trigonal and tetrahedral local structures and enabling hydrogen bonding to be satisfied even in situations, which occur all the time in macromolecular structures, where there is a mismatch between the number of available donors and acceptors to link to. If, therefore, this tetrahedral geometry is biologically critical, so may be its imperfect nature; other 'more perfect' tetrahedrally coordinated systems such as silica, silicon or germanium may therefore lack an important characteristic that water possesses.

Second, the water network itself would appear to be relatively 'rigid' with respect to typical thermal fluctuations at ambient temperature. With a bond energy of *ca.* 10 *kT*, we would expect the molecular mobility to be much less than it is found to be. As discussed earlier (§ 4c), the existence of a significant population of local coordination defects has been postulated to explain the observed molecular mobility. We thus appear to have a relatively strong molecular framework, yet one that has a much higher mobility than we would expect. Again, the reason for this seems to relate to the details of the imperfect tetrahedral geometry. Thus, if biomolecular processes require a relatively stable framework with an inbuilt ability to allow relatively rapid molecular motions, then water seems to have put itself in pole position to do the job effectively.

Finally, liquid water is a good proton conductor, and proton conduction is relevant to certain biomolecular processes. The conduction process seems to require a relatively resilient framework, but one that is relatively labile at the individual molecular level (see the previous paragraph). Moreover, the proton transfer step itself is across a barrier whose height has been effectively washed out by zero-point motion.

Whether or not the above characteristics are essential to any biomolecular process we might envisage built on a different chemistry is, of course, arguable, but with respect to the way life has developed in water, a case might be made for it adapting to exploit these particular characteristics, as well as more obvious ones such as the solution properties of a high dielectric constant. One might envisage other molecules that have some of the above characteristics, but can we envisage one that has them *all*?

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Discussion

M. W. Ho (*Institute of Science in Society, London, UK*).

- (i) Do other substances have the flexibility of water? That is, in terms of allowed bond angle of OOO?
- (ii) Can you detect a relationship between the various allowed bond angles in ice?
- (iii) Can you derive large-scale hydrodynamic properties of water from the molecular properties?

J. L. Finney. With respect to the first point, I would expect similar flexibility in other small molecules that hydrogen bond. You also get similar spreads in OOO bond angles in vitreous silica, and therefore presumably also in liquid silica. Secondly, I am not sure what you mean by a relationship between the bond angles in ice—a relationship to other angles or to some other property? If you look at the various ices, you find a range of bond angles that depend on the particular phase; these are presumably forced by the space-filling constraints and the energy cost of bond bending. With respect to your third point, I am not aware that anyone has connected the

hydrodynamic properties of liquid water quantitatively with molecular properties, though computer simulations using appropriate potential functions can reproduce properties such as diffusion and dielectric constant.

R. P. Rand (*Department of Biological Sciences, Brock University, St Catharines, Ontario L2S 3A1, Canada*). Is there an answer to your last question? Are there other liquids that have *all* three of the three properties you mentioned in your last paragraph?

J. L. Finney. I think the answer is no—but that may be lack of imagination on my part.

F. Franks (*BioUpdate Foundation, London, UK*). You have provided an interesting description of what properties are special, although not necessarily unique, to water. Would you agree that what makes water unique is the *combination* of some of these special properties, primarily the molecular structure, combining the sp^3 hybridization with the 3D weakly hydrogen-bonded system, the equal number of proton donors and acceptors (unique!) and all that entails, the reactivity and the amphipathic behaviour. Most other properties that make the ecosphere fit for life, as we know it, arise from this combination.

It is interesting that most forms of life that can withstand partial dehydration, whether by freezing, salinity or drought, do so by the synthesis of molecules that resemble water in several respects: the carbohydrates $C_n(\text{H}_2\text{O})_n$. Like water, they form 3D hydrogen-bonded networks in their crystalline and amorphous states, they are flexible, non-toxic and interact with substrates to form solutions that vitrify on cooling.

Can you offer an explanation for some remaining mysteries about water, e.g. the H/D isotope effects on thermodynamics, kinetics and physiology? Specifically, why is the temperature of maximum density of D_2O so high? Why do the vapour pressure curves of the two isotopic species cross over at 215 °C, giving D_2O a lower critical point than H_2O ? Also, probably more important for life: do we have an explanation of the inordinately high kinetic isotope effect on chemical reactions, diffusion and other transport properties?

J. L. Finney. I tried to suggest at the end of my talk that it may well be the *combination* of a number of properties that is particularly important. Particularly important I suspect is the network structure based on the underlying ideal, but distortable, tetrahedral geometry that provides a robust (in terms of kT) framework, but one that somehow has the ability to allow the molecules in the framework to move more easily than the strength of the hydrogen bonds suggests it should. A remarkable combination of rigidity and flexibility that may be unique? The ability of water to both donate and accept two hydrogen bonds I think also may be one of its most chemically and biologically important attributes. I do not know of any other simple molecule that has this 2+2 facility. But perhaps more than that, water's ability to *vary* its hydrogen bonding, for example by only accepting one hydrogen bond without apparently a significant penalty, enables it to mop up hydrogen-bonding imbalances.

I plead ignorance with respect to understanding the reasons behind the remaining characteristics you mention.

L. Pettersson (*Department of Physics, Stockholm University, Sweden*). The view that the molecules in the liquid are mainly tetrahedrally coordinated must be seriously

questioned. In a combined experimental (Anders Nilsson) and theoretical effort we have obtained high-resolution X-ray absorption (XAS) (Cavalleri *et al.* 2002; Myneni *et al.* 2002) as well as X-ray Raman scattering spectra of water (H_2O , D_2O) in its liquid state. Density functional theory (DFT) calculations of spectra and experimental comparison with the spectra of bulk ice Ih (tetrahedral) and surface (Nordlund *et al.* 2004) (free OH) show that the liquid is dominated by molecules with only one hydrogen involved in a strong hydrogen bond. This is only weakly affected by temperature, i.e. raising the temperature from room temperature to 90 °C increases the fraction of these species from about 85% to 90% (Wernet *et al.* 2004); neither the coordination nor the effect of temperature is reproduced by any of the present simulation techniques. In fact, direct calculation of the absorption spectrum from Carr–Parrinello molecular dynamics simulations yields a bulk-ice-like spectrum in agreement with the high degree of connectivity obtained combining our XAS data with radial distribution functions from neutron scattering we can conclude that the weakening of the second donating hydrogen bond is mainly due to strong angle distortion. We must tentatively conclude that the liquid has some hitherto unobserved additional structure compatible with each molecule being involved in only two stronger hydrogen bonds, one donating and one accepting.

D. T. Bowron (ISIS Facility, Rutherford Appleton Laboratory, Didcot, UK). The questioner wishes to challenge the conventional picture of the local structure in liquid water, based exclusively upon recently reported work attempting to analyse oxygen K-edge XANES quantitatively. Though this new experimental work is a considerable technical achievement, much controversy surrounds the structural interpretation of the XANES data, this analysis being based exclusively on DFT calculations. The analytic route was chosen because the conventional means to analyse such spectral information is known to be highly unreliable for the cases under consideration. In the framed question and its supporting references, it is tacitly assumed that the DFT analysis method is not subject to the serious difficulties that prevent conventional data processing, but in no way do they demonstrate this or give any quantitative estimate as to the extent that systematic and methodological uncertainties affect the results.

To put the problem into context it is worth summarizing how structural results are obtained in a conventional analysis of near edge spectra. The data are known to be highly sensitive to the model adopted for the electronic potential of the photo-absorbing atom, and also to be highly subject to extensive long-range multiple scattering effects typically arising from structure out to beyond 6 Å in radial distance from the photocentre. In this formalism, the analysis of the data is typically pursued using electron scattering potentials based on overlapped relativistic-atom muffin-tin approximations and curved-wave multiple scattering expansions. Such an approach is known to be inadequate for analysis of XANES data collected at the oxygen K-edge. This fact is exacerbated by the relatively long lifetime of the 1 s core hole excited state of the oxygen photocentre and its marked effect on the potential. It would be a rather fortuitous finding if the relatively simplistic DFT methods currently under discussion could indeed describe the complex local structure and electronics of X-ray

absorption data without any concerns as to the effect of the considerable number of approximations upon which they are based. However, at the current time and given the very limited number of studies using this new technique, this finding remains far from proven.

With regards to the local structure of liquid water there is a huge body of experimental evidence relating to the fourfold, near-tetrahedral, hydrogen-bonding environment. In fact, and in direct contradiction to the claims in the questioner's referenced work, diffraction methods are sensitive to local molecular orientational order (Gray & Gubbins 1984). Detailed analyses of neutron-scattering data from liquid water, based on higher body correlation functions and using different analytical approaches, have consistently shown the dominance of the near tetrahedral hydrogen-bonding motif (e.g. Soper 1994, 2001). Furthermore, conventional analysis of oxygen K-edge extended X-ray absorption fine-structure spectroscopy data, which is intimately related with the XANES data under discussion, but considerably less subject to uncertainties in the precise form of the atomic potential due to the higher energy of the photoelectron, shows that the local structure is fully consistent with the accepted fourfold coordinated models of water (Bowron *et al.* 2000).

In summary, the data raised for discussion are certainly very interesting, yet a key challenge remains for this developing experimental technique, i.e. it is first necessary to establish an unambiguous ability to reproduce the results of known systems. Without this, claims of 'new' insight have no foundation as the balance between measuring established fact and providing new sensitivity have not been established. Even with conventional XANES analysis the proof that it is an unambiguous structural probe has yet to be fully achieved. In that case it is well known that most derived structural models are entirely dependent upon the selected atomic potential used to fit the data. The current status of XANES/DFT methods is even less established and it is therefore premature to claim that there is a need for a comprehensive re-evaluation of what is known about the local hydrogen-bonding structural order in liquid water.

J. B. F. N. Engberts (*Physical Organic Chemistry Unit, University of Groningen, The Netherlands*). In your excellent lecture, you put all emphasis on hydrogen-bonding interactions. My question is concerned with London dispersion interactions. A single water molecule has a small volume and consequently London dispersion interactions will be weak.

Would it be conceivable that the rapidly changing electric field originating from the extremely fast proton migration could couple with the electronic motion of a much bigger apolar molecule, leading to some sort of attractive London dispersion interaction? In other words, could it be that the fast intermolecular proton conduction has consequences for the Gibbs energy of apolar solute–water interactions? This might contribute to the unusually favourable enthalpy of transfer of apolar molecules from the gas phase to water.

J. L. Finney. I agree with your implication that non-hydrogen bonding interactions may be more important to biomolecular structures and dynamics than is generally thought. For example, when we were elucidating the water

networks in coenzyme B₁₂, Hugh Savage showed quite convincingly that the apparently chaotic (to a crystallographer) network structures in all kinds of systems from ices to proteins could be rationalized very well by the (non-spherical) shape of the water molecule (Savage & Finney 1986), rather than trying to explain it in terms of hydrogen-bond directionality. Moreover, the polarizabilities of groups such as CH₃ are quite significant and potentially capable of making significant (in terms of kT at room temperature) dipole-induced-dipole interactions with polar or charged groups. Whether or not proton conduction could lead to quantitatively significant effects is an interesting suggestion. I am not aware of any calculations that might relate to this.

P. Ball (*Nature, London*). As well as the physical properties, should we consider the chemical properties of water as contributing to the unique role that it seems to play in mediating life's processes—for example, its amphoteric nature?

J. L. Finney. Being a physicist, I would be tempted to say that the chemical properties all come down eventually to the physics of the molecule and its interactions. So yes, we should consider the chemical properties, and if we think particular chemical properties may be critical to biological functionality, then I would want to pin those down to properties at the molecular level. Its amphoteric nature, for example, relates in essence to the ability of the molecule to facilitate proton transfer in one direction or the other, which is essentially a physical property. I do not see water as being particularly outstanding in this context—there are other molecules that are also amphoteric.

G. Zaccai (*Institut de Biologie Structurale, 38027 Grenoble Cedex 1, France*). Perhaps life is possible without water but it is not possible without salt! Is there any other liquid in which salt will ionize? We know that most of the energy consumed by a living organism (from bacteria to nerve cells) is to activate ion pumps.

J. L. Finney. Yes, there are liquids in which salts are ionized, but solubility can be very low and of course they do not have the other properties that water has.

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GLOSSARY

- AFM: atomic force microscopy
XANES: X-ray absorption near edge structure