

1 Water

1.1 Water: The molecule

Let's start with a brief reminder from your molecular physics class. The water molecule is composed by an oxygen atom with eight electrons ($1s^2 2s^2 2p^4$) and by two hydrogen atoms, for a total of 10 electrons. Assuming the two $1s^2$ electrons are non involved in the binding (forming a full inner shell) there are eight electrons which mix together to determine the electronic properties of the molecule. Within a LCAO-MO approach oxygen will contribute with $2s$, $2p_x$, $2p_y$ e $2p_z$ orbitals while each H with a $1s$.

Defining as z the symmetry axis of the molecule (dipole moment) and yz the plane where the molecule is sitting, orbitals partition in three groups with different symmetry

$$A_1 : \quad a_1 = c_1(H1s_A + H1s_B) + c_2(O2p_z) + c_3(O2s)$$

$$B_1 : \quad b_1 = c_4(O2p_x) \quad \text{always antibonding, since does not mix with H orbitals}$$

$$B_2 : \quad b_2 = c_5(H1s_A - H1s_B) + c_6(O2p_y)$$

Then, the matrix $H - ES$ will be a block matrix with a 3x3, a 1x1 and a 2x2 block. The resulting levels are indicated in the figure

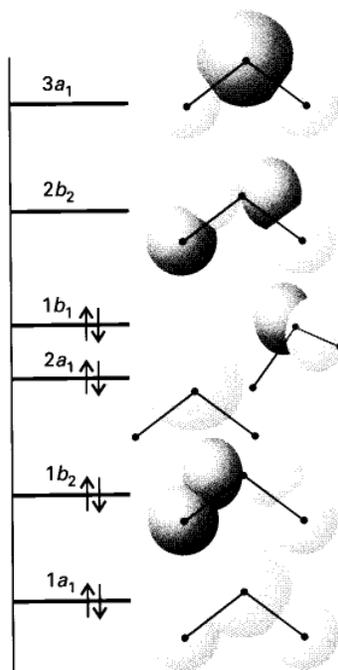


Fig. 8.24 The molecular orbitals of H_2O at its equilibrium bond angle of 104° .

The ground state combination is achieved by filling these molecular orbitals

$$1a_1^2 1b_2^2 2a_1^2 1b_1^2$$

where the last two orbitals are bonding. The resulting configuration shows that the $H\hat{O}H$ angle is larger than 90° but smaller than the tetrahedral angle. The equilibrium value is $H\hat{O}H = 104^\circ$. The intramolecular O–H distance is about 0.10 nm, as expected for a covalent bond. The dipole moment of an isolated molecule (gas phase) is $\mu = 1.85$ Debye.

1.1.1 Dimer

A dimer of water can assume several configurations. The lowest energy state is shown in the figure. In this configuration, which as you can see is not the one predicted by aligned dipoles, one OH bond points straight into the O of the other molecule, pushing the two H to lay on the opposite side.

The energy of this configuration is about 10 kJ/mol, more or less $4k_B T$ ($k_B T = 2.5$ kJ/mol at $T = 300\text{K}$). This physical bond is commonly named **hydrogen bond** (HB), since the hydrogen atom lays between the two oxygens. The intermolecular O–O distance is 0.28 nm.

The ice structure shows the linear HB pattern in full glory. Each water molecule donates and accepts two H, participating in four HB. These HB, are oriented tetrahedrally (a reminiscence of the sp^3 hybridization) resulting into an open crystal in which the O atoms occupy a hexagonal diamond lattice. In ice I_h , the standard ice, the protons are disordered, contributing to a residual entropy associated to the number of different positioning of the protons in the network of bonds, satisfying the two-acceptor, two-donor rule.

1.2 The HB

The previous section indicates that some unusually strong and orientation-dependent bonds are involved in the interactions between water molecules. Hydrogen bonds are not unique to water; they exist to varying degrees between electronegative atoms (e.g., O, N, F and Cl) and H atoms covalently bound to similar electronegative atoms. These bonds are special in that they only involve hydrogen atoms, which, by virtue of their tendency to become positively polarized and their uniquely small size, can interact strongly with nearby electronegative atoms resulting in an effective H-mediated 'bond' between two electronegative atoms. Originally, it was believed that the hydrogen bond was quasi-covalent and that it involved the sharing of an H atom or proton between two electronegative atoms. But it is now accepted that the hydrogen bond is predominantly an electrostatic interaction. With few exceptions, the H atom is not shared but remains closer to and covalently bound to its parent atom; accordingly, the hydrogen bond between two groups XH and Y usually denoted by X–H ... Y. Nevertheless, certain characteristics of hydrogen bonds do make them appear like weak covalent bonds. For example, they are not only fairly strong but also (fairly)

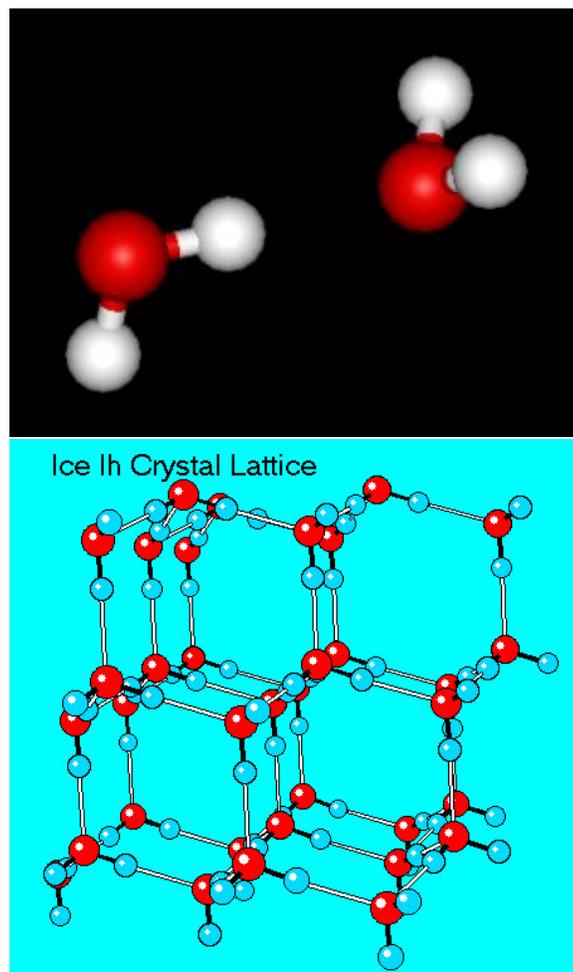


Figure 1: (top) Lowest energy state of a water dimer; (bottom) A cartoon of (a proton ordered) Ice I_h

directional. This endows them with the ability to form weak three-dimensional 'structures' in solids, whereas in liquids the short-range order can be of significantly longer range whenever hydrogen bonds are involved hence the term associated liquids. The strengths of most hydrogen bonds lie between 10 and 40 kJ/mol (which makes them stronger than a typical van der Waals 'bond' (~ 1 kJ/mol) but still much weaker than covalent or ionic bonds (~ 500 kJ mol/mol). Hydrogen bonds can occur intermolecularly as well as intramolecularly and can happily exist in a non-polar environment. They are consequently particularly important in macromolecular and biological assemblies, such as in proteins, linking different segments together inside the molecules, and in nucleic acids, where they are responsible for the stability of the DNA molecule (holding the two helical strands together). Their involvement in setting up one-, two- and three-dimensional macromolecular structures is sometimes referred to as hydrogen-bond polymerization.

1.2.1 Bulk

In the bulk, water molecules attempt to maximize the number of their hydrogen bonds. Each water molecules can provide two protons (donors). It can also accept a certain number of donors (acceptors). Steric conditions limit this number to two, in low energy states (linear HB). It is possible also to form one or two more distorted HB. X-rays static scattering experiments demonstrate that water at ambient T and P , has a number of nearest neighbour around 4.5. The phase diagram of water is also shown in the figure.

1.3 The Physics of Water.

What makes water special compared with other liquids is the strong directional character of the intermolecular interaction potential. The dominant contribution, called the hydrogen bond (HB), has a strength intermediate between the stronger covalent bond and the weaker dipole-induced interaction. In addition, the HB strength is significantly larger than the thermal energy at room T . An HB requires a hydrogen atom pointing toward a close-by oxygen atom. The strength of the HB is maximized when the hydrogen atom is collinear with the acceptor and donor oxygen and progressively weakens on increasing the HOO angle. The strength of the HB and its directionality are key elements in controlling liquid water's thermodynamic and dynamic behavior. If the HB interaction did not exist, water would behave just like all other H_2X triatomic molecules, with X representing any chalcogen, and it would be gaseous at room T . If the interaction between water molecules was isotropic and described by an attraction comparable to the HB strength, the gas-liquid critical T would be located at about one order of magnitude higher temperature than the real experimental value (647 K). What makes water a liquid at ambient T is the directionality of the HBs and the limited number of linear HBs that a molecule can form (at most four). Such limited valence significantly lowers the critical T compared with the isotropic case. This originates a liquid phase at room T in which the number of nearest neigh-

bours is around four, significantly lower than the typical value observed in simple liquids, namely 12. The liquid phase can be described as a percolating network of HBs, constantly restructuring itself on a picosecond time scale.

The directionality of the interaction is responsible for the peculiar correlation between local energy, density, and entropy. The establishment of four linear HBs (a state of low energy) is possible only for well-defined orientations of the water molecule (low entropy and density). The formation of such a state is driven by the decrease in enthalpy but it is contrasted by the decrease in entropy. Similarly, the formation of locally denser arrangements, associated with the presence of additional molecules in the first coordination shell, generates distorted HBs and states with higher local enthalpy and entropy. The formation of these more dense local environments is driven by entropy and contrasted by the energy loss. Both of these structural motifs are found in liquid water. The most prominent examples are environments characterised by four and three linear HBs together with two more distorted ones. In the first case the local arrangement is to a good approximation tetrahedral, while in the second case a fifth neighbour, locally distorting the HB pattern, is present in the first coordination shell.

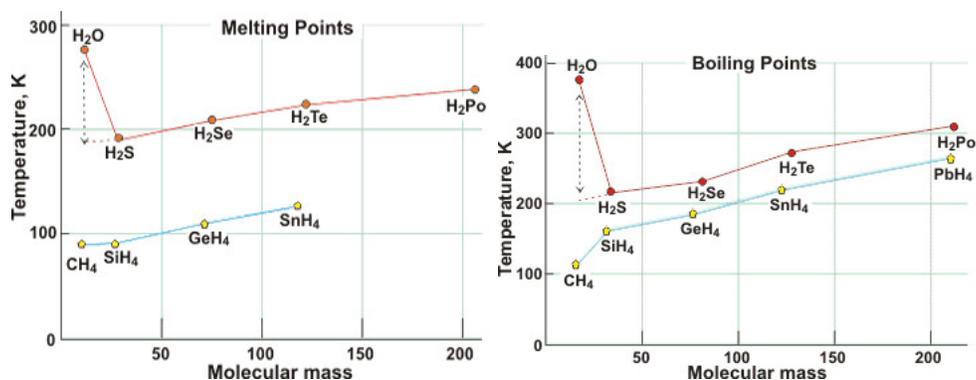


Figure 3: Melting and boiling points of X₂O molecules

1.4 Water anomalies

Water is such an unusual substance that it has been accorded a special place in the annals of phenomena dealing with intermolecular forces, and two types of 'special interactions' — the hydrogen bond and the hydrophobic effect — are particularly relevant to the interactions of water. The literature on the subject is vast, not only because water is the most important liquid on earth, but also because it has so many interesting and anomalous properties. For a liquid of such a low molecular weight, water has unexpectedly high melting and boiling points and latent heat of vaporization. There are, of course, many other substances of low molecular weight and high melting and boiling points, but these are invariably ionic

crystals or metals whose atoms are held together by strong Coulombic or metallic bonds. These properties of water point to the existence of an intermolecular interaction that is stronger than that expected for ordinary, even highly polar, liquids.

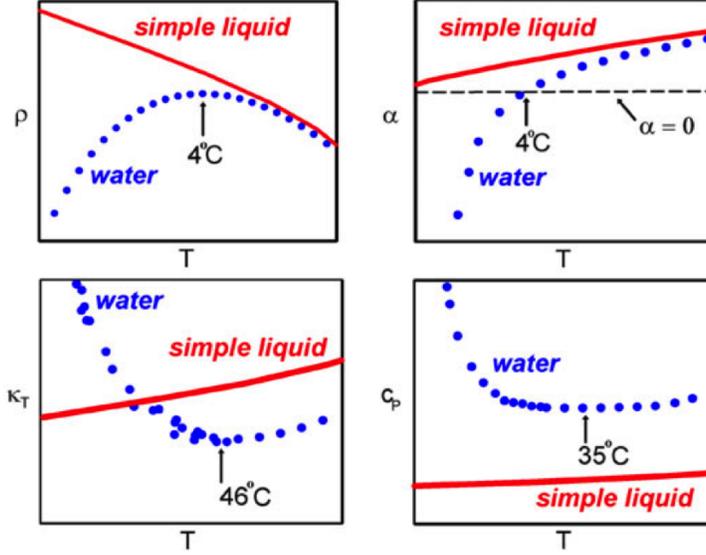


Figure 3. A schematic comparison of the isobaric temperature dependence of the density ρ , thermal expansion coefficient α , isothermal compressibility κ_T and isobaric heat capacity c_p for water and a simple liquid.

The density maximum at 4C exhibited by liquid water, and the unusual phenomenon that the solid (ice) is lighter than the liquid, indicates that in the ice lattice only the tetrahedral (more open) structure is explored. We may further conclude that the strong intermolecular bonds formed in ice persist into the liquid state and that they must be strongly orientation-dependent since water adopts a tetrahedral coordination (four nearest neighbours per molecule) rather than a higher packing density (cf. 12 nearest neighbours characteristic of close-packed van der Waals solids where the 'bonds' are non-directional). Water has other unusual properties, such as a very low compressibility and unusual solubility properties both as a solute and as a solvent.

Particularly informative are the T -dependence of some relevant response functions, the constant pressure specific heat C_p , the isothermal compressibility κ_T , the coefficient of thermal expansion α . As shown in the appendix, these response functions provide a direct evidence of the importance (and T dependence) of the microscopic fluctuations.

Indeed we find (see appendix)

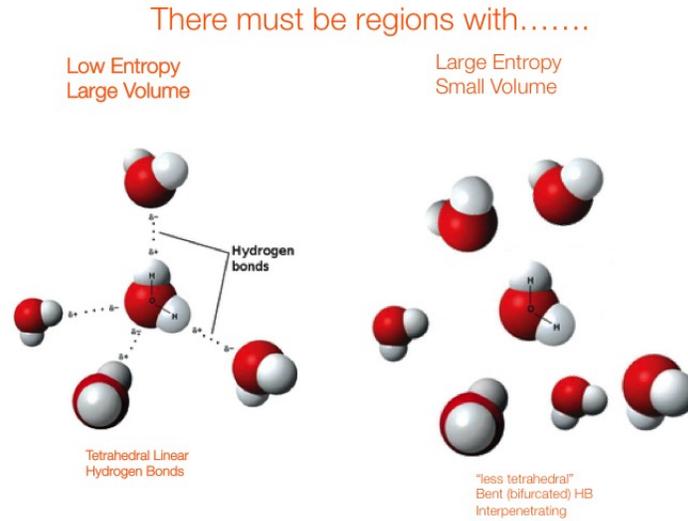
$$\kappa_T \equiv -\frac{1}{V} \frac{\partial V}{\partial P_T} \sim \langle \Delta V^2 \rangle$$

$$C_p \equiv \frac{\partial H}{\partial T}_P \sim \langle \Delta H^2 \rangle$$

$$\alpha \equiv -\frac{1}{V} \frac{\partial V}{\partial T}_P \sim \langle \Delta V \Delta S \rangle$$

where $H = U + PV$ is the enthalpy and S is the entropy.

As shown in the figure, the fluctuations (as revealed by κ_T , C_p) increase on cooling, differently from standard liquids. Such increase reveals the competition in the liquids between structures with different enthalpy and volume.



It is also important to recall one more anomaly: applying pressure to cold water makes it flow easier. In other words, the viscosity decreases with P .

1.5 MODELS OF WATER AND ASSOCIATED LIQUIDS

Hydrogen bonds play a particularly prominent role in water since each oxygen atom with its two hydrogens can participate in four such linkages with other water molecules—two involving its own H atoms and two involving its unshared (lone-pair) electrons with other H atoms. To see exactly how this arises we require some picture of the charge distribution within the water molecule. Various models have been proposed of which the so-called ST2 model of water (named after a modified model by Stillinger and Rahman, 1974) will be described. Other models also exist, but it is recognized that as yet no single model has been able to account satisfactorily for the properties of water in all three phases (ice, liquid and vapour). However, the main features of ST2 water are simple and quite similar to some of the other models and so provide a good introduction to the various

conceptual approaches that are being applied in attempts at understanding water. In ST2 water the water molecule is modelled with charges of $+0.24e$ centred on each hydrogen atom and two compensating charges of $-0.24e$ on the opposite side of the oxygen atom, representing the two unshared electron pairs. The four charges are located along four tetrahedral arms radiating out from the centre of the O atom. The interaction between any two water molecules is assumed to involve an isotropic Lennard-Jones potential and 16 Coulombic terms representing the interaction between each of the four point charges on one molecule with the four on the other. The net Coulombic interaction obviously depends on the mutual orientation of the two molecules. When many molecules are involved their equilibrium configuration can only be solved on a computer, and when this is done the model can account for a number of the unusual properties of water, such as the highly open ice structure and the density maximum in the liquid state. Computer simulations show that this comes about because of the strong preference for the molecules to order into a lattice where each oxygen is tetrahedrally coordinated with four other oxygens, with a hydrogen atom lying in the line joining two oxygen atoms. It is this preferred linearity of the O–H ... O bond in water that endows it with its strongly directional nature. In liquid water the tendency to retain the ice-like tetrahedral network remains, but the structure is now disordered and labile. The average number of nearest neighbours per molecule rises to about five (hence the higher density of water on melting), but the mean number of H bonds per molecule falls to about 3.5 whose lifetimes are estimated to be about 10^{-11} s. Other strongly hydrogen-bonding molecules, such as formamide, ammonia and HF, also retain some of their ordered crystalline structure in the liquid state over short distances. Such liquids are known as associated liquids. It is also believed that the H-bond structure in such liquids is cooperative in the sense that the presence of H bonds between some molecules enhances their formation in nearby molecules, thereby tending to propagate the H-bonded network. If so, the interaction is non-pairwise additive, which presents serious problems in theoretical computations of aqueous and other systems involving cooperative associations. It is instructive to note that the tetrahedral coordination of the water molecule is at the heart of the unusual properties of water, much more than the hydrogen bonds themselves. As a rule of thumb, molecules that can participate in only two H bonds can link up into a one-dimensional chain or ring (e.g., HF and alcohols, as shown in Fig. 8.2). Likewise, atoms of valence two such as selenium and tellurium can form long chains of covalently bonded atoms. Atoms that can participate in three bonds (e.g., arsenic, antimony and carbon in graphite), can form two-dimensional sheets or layered structures held together by weaker van der Waals forces. But only a tetrahedral, or higher, coordination allows for a three-dimensional network to form. For example, it is the tetrahedral coordination characteristic of carbon and silicon that results in their almost infinite variety of atomic association whether in chain molecules (e.g., polymers, surfactants, polypeptides), cyclic compounds or two- and three-dimensional crystals (e.g., diamond, silica, sheet silicates).

2 Aqueous solutions

So far in this chapter we have considered the interactions of water molecules with other water molecules. In the rest of this chapter we shall investigate the equally interesting interactions of water with other compounds, i.e., when water acts as a solvent or as a solute.

First of all let's discuss some basic solubility data. Consider a salt, like NaCl. It dissolves in water up to 358 g/liter. This means, considering that the molar mass of NaCl is 58 g, that in a liter of water one can mix about 6 moles of NaCl. Since in a liter there are 55.5 moles of water ($1000/18=55.5$), this means that one can dissolve NaCl up to the point that there are 9 water molecules for each NaCl, e.g. about 4.5 water per ion !!! On passing, we note that in a physiological solution there are 9 g of NaCl for each liter, 40 times less than maximum solubility, equivalent to 180 water molecules per ion.

Other molecules are also highly soluble. H_2O_2 and small alcohols are completely soluble.

Let's next consider longer alcohols (C_4H_9OH , or longer). Fig. 2 shows the solubility of different alcohols as a function of T . What we note clearly is that the solubility (in mass) decreases significantly (roughly a factor of 3 for each added CH_2), providing evidence that long non-polar molecules are not quite welcome in the water network. In addition we note that the solubility goes down with T , indicating that it becomes progressively harder to solvate (surround by water) a non-polar group.

To quantify a little bit better what is controlling solubility, let's consider the process of transferring a solute from its bulk to water. Assuming there is a membrane allowing for the transfer of the solute, equilibrium will be reached when the chemical potential of the solute is identical in the bulk and in water. The chemical potential is the sum of an ideal gas part ($k_B T \ln c$) and an excess part μ_{ex} . Measuring the difference in concentration in the pure solute and in the solute in water, one obtain an experimental measure of the difference in excess chemical potential $\Delta\mu$.

From the analysis of the T dependence of $\Delta\mu$ it is possible to infer information on the entropic and enthalpic contribution to the transfer process. Indeed, assuming no explicit T dependence in S and H , one can write

$$\Delta G = N\Delta\mu = \Delta H - T\Delta S$$

so that ΔS is the slope of $\Delta\mu$ vs T . From the slope, $\Delta H = N\Delta\mu + T\Delta S$.

The data in Fig. 2 shows the complexity of the transfer process. At low T (below 50 C), the dominant contribution is entropic. But at higher T , the enthalpic change becomes progressively more relevant. Note that the two temperatures where ΔS and ΔH cross zero are points in which the entire process is controlled respectively by enthalpy or entropy. In many molecules of biological relevance, the T at which ΔH crosses zero is close to 25 C.

The strong inclination of water molecules to form H bonds with each other influences their interactions with non-polar molecules that are incapable of forming H bonds (e.g.,

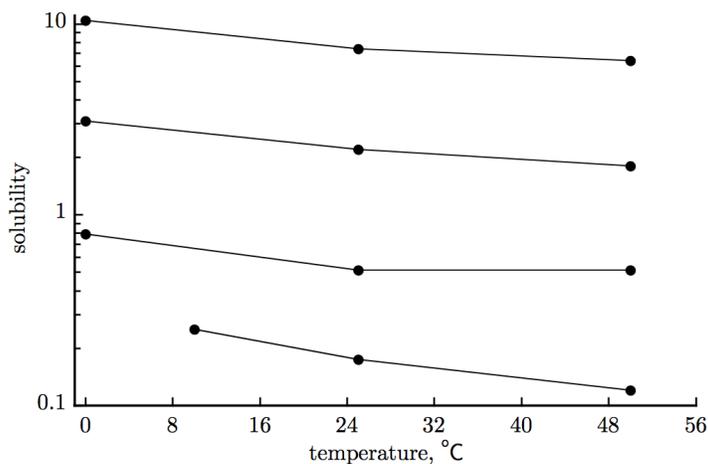


Figure 7.14: (Experimental data.) Solubilities of small nonpolar molecules in water, as functions of temperature. The vertical axis gives the mass percentage of solute in water, when water reaches equilibrium with the pure liquid. *Top to bottom*, butanol (C₄H₉OH), pentanol (C₅H₁₁OH), hexanol (C₆H₁₃OH), and heptanol (C₇H₁₅OH). Note that the solubilities decrease with increasing chain length. [Data from Lide, 2001.]

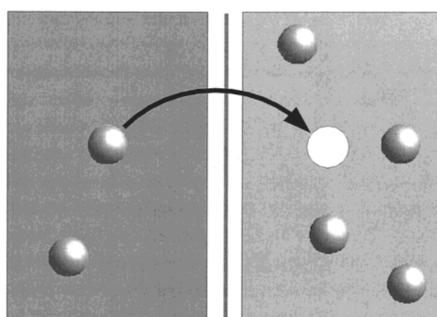


Figure 1. Partitioning is a balance. Hydrophobicity is measured by oil/water partitioning of solutes. At equilibrium, the chemical potentials in the two phases, 1 and 2, are equal $\mu_1^\circ + RT \ln C_1 = \mu_2^\circ + RT \ln C_2$. Measuring the solute concentrations c_1 and c_2 in the two phases give the difference in chemical affinities between phases, $\Delta\mu^\circ = -RT \ln C_1/C_2$.

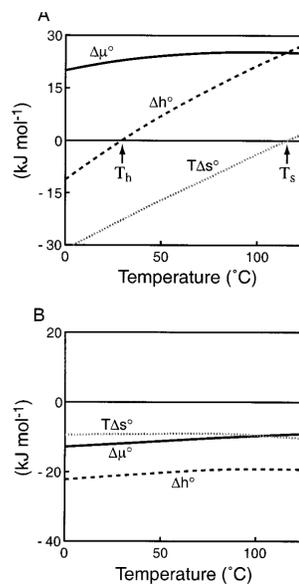


Figure 2. Hydrophobic Effect is the anomalous mixing thermodynamics of nonpolar solutes with water. (A) The transfer of neopentane from its own neat phase into water, and (B) a regular solution: the transfer of neopentane from the gas phase into a neopentane neat phase. T_s is the temperature where the entropy of transfer is zero, T_h is where the enthalpy of transfer is zero. Data adapted from Lee, B. *Biopolymers* 1991, 31, 993.

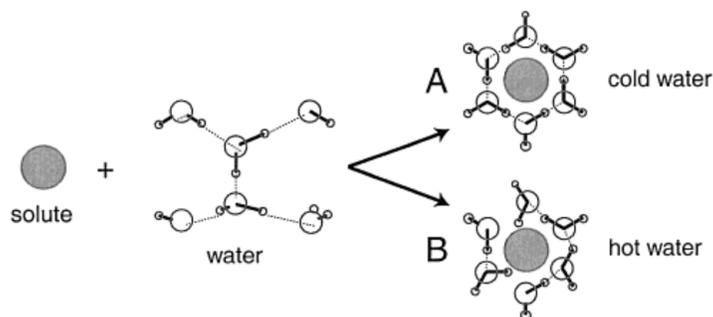


Figure 8. “Iceberg” model for the large heat capacity of transfer of nonpolar solutes into water. (A) At room temperature the water molecules surrounding a nonpolar solute adopt only a few orientations (low entropy) to avoid wasting hydrogen bonds. Most water configurations are fully hydrogen bonded (low energy). (B) In hot water, more conformations become accessible (higher entropy), but at the cost of breaking hydrogen bonds (high energy).

alkanes, hydrocarbons, fluorocarbons, inert atoms). When water molecules come in contact with such a molecule they are faced with an apparent dilemma: whichever way the water molecules face, it would appear that one or more of the four charges per molecule will have to point towards the inert solute molecule and thus be lost to H-bond formation. Clearly the best configuration would have the least number of tetrahedral charges pointing towards the unaccommodating species so that the other charges can point towards the water phase and so be able to participate in H-bond attachments much as before. There are many options to salvaging lost H bonds. If the non-polar solute molecule is not too large, it is possible for water molecules to pack around it without giving up any of their hydrogen-bonding sites. The main effect of bringing water molecules and non-polar molecules together is the reorientation of the water molecules so that they can participate in H-bond formation more or less as in bulk water (i.e., without necessitating any breakage of H bonds).

The immiscibility of inert substances with water, and the mainly entropic nature of this incompatibility is known as the hydrophobic effect (Kauzmann, 1959; Tanford, 1980), and such substances, e.g., hydrocarbons and fluorocarbons, are known as hydrophobic substances). Similarly, hydrophobic surfaces are not ‘wetted’ by water; when water comes into contact with such surfaces it rolls up into small lenses and subtends a large contact angle on them.

2.1 Hydrophobic forces - From Cleri

Despite the fact that the hydrophobic effect includes also a substantial enthalpy contribution, the largest part of the force in water at standard pressure and temperature comes

from the entropy of the rearrangement of the tridimensional network of hydrogen bonds between water molecules. A hydrogen bond between two molecules involves a donor species, whose charge distribution is slightly unbalanced so as to appear slightly positive, and an acceptor species, whose charge distribution appears in turn slightly negative. However, because of charge conservation, if some part of a molecule becomes negatively charged, some other part must get positively charged (thus generating a dipole moment in the polar molecule). This means that every molecule is at the same time a donor and an acceptor, depending on the geometry of bonding. Water molecules are quite unique in their capability of forming hydrogen bonds with similar molecules. In fact, their chemical structure with two "lone" electrons makes each water molecule capable of accepting two such bonds from two neighbouring molecules (one lone electron from each molecule being attracted to one of its slightly positive H atoms), while at the same time donating two more bonds to two other molecules (its two lone electrons being attracted toward two H atoms from two different molecules). Other H-bond-forming molecular species have a reduced capability in this respect: for example hydrofluoric acid, HF, could accept three bonds but can donate only one; ammonia, NH₃, could donate three but accepts only one. Under such conditions, species like HF and NH₃ in a dense, liquid-like environment can only form chains of molecules. On the other hand, water molecules can form a symmetric tetrahedral structure, in which each molecule is at the center of a tetrahedron, with four other molecules (the two donors and the two acceptors) situated at the four corners of the tetrahedron. In such a tridimensional structure, water in the liquid phase maintains a rather regular geometrical structure, with a constant O-O bond length of about 2.8 Å, and tetrahedral angles between each triplet of molecules equal to about 109.5°. Since water in these conditions is a liquid its molecules are highly mobile, and constantly exchange their location at the tetrahedral sites, however keeping the tetrahedral geometry with a remarkable regularity. Note that mixing two polar molecules, such as acetone and water, gives similar results since, being both polar, the two types of molecules can mix and maintain a more or less compact network of hydrogen bonds. We say in this case that acetone is readily dissolved in water. On the other hand, if we mix an assembly of polar and non-polar molecules, for example water and gasoline (which is a combination of many different hydrocarbons), such molecules try to avoid each other. Droplets of pure gasoline form in water (or vice versa, depending on which one is the majority component) to minimise the contact surface. Ideally, all the minority molecules would like to form a single spherical bubble, whose shape has the minimum surface to volume ratio.

Introducing a non-polar (for example, a plastic) object in water (Fig. 5.3a) partially destroys the ordered tetrahedral structure, since non-polar surfaces, with their molecules being insensitive to charge displacement, do not allow the formation of hydrogen bonds. As a consequence, the water molecules in direct contact with the plastic surface lose part of their hydrogen bonds, and try to adjust their configuration in order to minimise the number of broken H-bonds. The result is an interface structure in which some water molecules are constrained in a sort of cage, their mobility is reduced and, consequently, their entropy

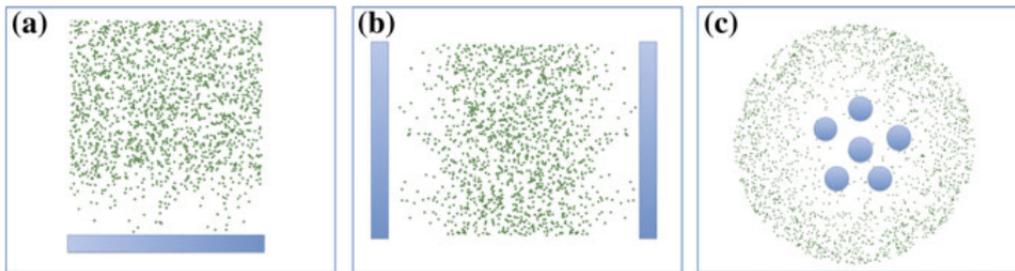


Fig. 5.3 The hydrophobic effect between water molecules (*green*) and a non-polar (*blue*) material. **a** A non-polar surface (for example, a plastic sheet) is introduced in water; as a result, the water molecules tend to maximise their entropy by retreating from the plastic surface. **b** Two non-polar surfaces in water have the effect of creating two such regions of reduced density: as soon as the two surfaces are approached, water molecules tend to escape from the region between the two. **c** The effect of introducing in water several non-polar surfaces, for example a bunch of plastic microspheres, leads to a kind of voiding effect in the space comprised between the plastic surfaces, thus promoting an effective *hydrophobic attraction* between the non-polar objects

is also decreased in comparison with the free liquid. Seeking to maximise their entropy, such constrained water molecules try to reduce their contact with the non-polar surface by escaping this region, thus creating a layer of reduced density. Now, let us think of two non-polar surfaces immersed in water (Fig. 5.3b). If these surfaces are approached, the simultaneous density reduction in the space comprised between the two surfaces will result in an effective attraction between the two objects.

The effect of introducing in water several non-polar surfaces, for example a bunch of plastic microspheres, leads to a kind of voiding effect in the space comprised between the plastic surfaces, thus promoting an effective hydrophobic attraction between the non-polar objects. By following this same pattern, if several non-polar particles are immersed in water (Fig. 5.3c) they tend to aggregate because of this effect of reduced density: it is like water "escapes" from the region comprised between the particles, which now seem to attract each other as if in the presence of some force. In fact, there is no force at all: the thermodynamic drive coming just from the requirement of maximising the solvent entropy. This is the basis of the hydrophobic attraction between non-polar objects in water. The hydrophobic effect is at the basis of the spontaneous formation of biological membranes starting from amphiphilic molecules.

2.2 Hydrophobic effect - Nelson - The hydrogen-bond network affects the solubility of small molecules in water.

Solvation of small nonpolar molecules: We have described liquid water as a rather complex state, balancing energetic and entropic imperatives. With this picture in mind, we can now sketch how water responds to — and in turn affects — other molecules immersed in it. One way to assess water's interaction with another molecule is to measure that molecule's solubility. Water is quite choosy in its affinities, with some substances mixing freely (for example hydrogen peroxide, H_2O_2), others dissolving fairly well (for example sugars), while yet others hardly dissolve at all (for example oils). Thus when pure water is placed in contact with, say, a lump of sugar the resulting equilibrium solution will have a higher concentration of sugar than the corresponding equilibrium with an oil drop. We can interpret these observations by saying that there is a larger free energy cost for an oil molecule to enter water than for sugar

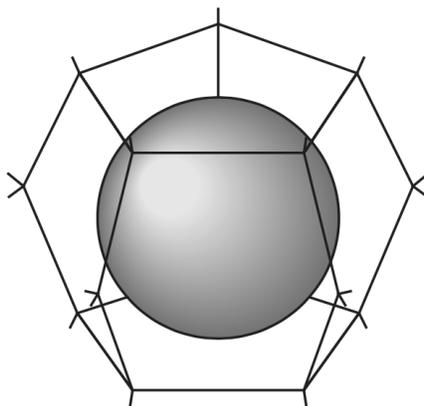


Figure 7.13: (Sketch.) Clathrate cage of H-bonded water molecules, shown as vertices of a polyhedron surrounding a nonpolar object (gray sphere). Four lines emerge from each vertex, representing the directions to the four water molecules H-bonded to the one at the vertex. This idealized structure should not be taken as a literal depiction; in liquid water some of the H-bonds will always be broken. Rather, the figure demonstrates the geometrical possibility of surrounding a small nonpolar inclusion without any loss of H-bonds.

To understand these differences, we first note that hydrogen peroxide, which mixes freely with water, has two hydrogen atoms bonded to oxygens, and so can participate fully in water's hydrogen-bond network. Thus introducing an H_2O_2 molecule into water hardly disturbs the network, and so incurs no significant free energy cost. In contrast, hydrocarbon chains such as those composing oils are nonpolar (Section 7.5.1), and so offer no sites for H-bonding. We might at first suppose that the layer of water molecules sur-

rounding such a nonpolar intruder would lose some of its energetically favorable H-bonds, creating an energy cost for introducing the oil. Actually, though, water is more clever than this. The surrounding water molecules can form a "clathrate cage" structure around the intruder, maintaining their H-bonds with each other with nearly the preferred tetrahedral orientation (Figure 7.13). Hence the average number of H-bonds maintained by each water molecule need not drop very much when a small nonpolar object is introduced. But energy minimization is not the whole story in the nanoworld. To form the cage structure shown in Figure 7.13, the surrounding water molecules have given up some of their orientational freedom: They cannot point any of their four H-bonding sites toward the nonpolar object and still remain fully H-bonded. Thus the water surrounding a nonpolar molecule must choose between sacrificing H-bonds, with a corresponding increase in electrostatic energy, or retaining them, with a corresponding loss of entropy. Either way, the free energy $F = E - TS$ goes up. This free energy cost is the origin of the poor solubility of nonpolar molecules in water at room temperature, a phenomenon generally called the hydrophobic effect.

The change in water structure upon entry of a nonpolar molecule (or "hydrophobic solvation") is too complex for an explicit calculation of the sort given for electrostatics. Hence we cannot predict a priori which of the two extremes above (preserving H-bonds or maintaining high entropy) water will choose. At least in some cases, though, we can reason from the fact that some small nonpolar molecules become less soluble in water as we warm the system beyond room temperature. At first this observation seems surprising: Shouldn't increasing temperature favor mixing? But suppose that for every solute molecule that enters, gaining some entropy with its increased freedom to wander in the water, several surrounding water molecules lose some of their orientational freedom, for example by forming a cagelike structure. In this way, dissolving more solute can incur a net decrease in entropy. Raising the temperature accentuates this cost, making it harder to keep solute in solution. In short, solubility trends like the ones shown previously imply a large entropic component to the free-energy cost of hydrophobic solvation. More generally, detailed measurements confirm that at room temperature the entropic term $-T\Delta S$ dominates the free energy cost ΔF of dissolving any small nonpolar molecule in water. The energy change ΔE may actually be favorable (negative), but in any case it is outweighed by the entropic cost. For example, when propane (C_3H_8) dissolves in water the total free energy change is $+6.4 k_B T$ per molecule; the entropic contribution is $+9.6 k_B T$, while the energetic part is $-3.2 k_B T$. (Further evidence for the entropic character of the hydrophobic effect at room temperature comes from computer simulations of water structure, which confirm that outside a nonpolar surface the water's O-H bonds are constrained to lie parallel to the surface.) The short range of the hydrogen bond suggests that the H-bond network will get disrupted only in the first layer of water molecules surrounding a nonpolar object. The free energy cost of creating an interface should therefore be proportional to its surface area, and experimentally it's roughly true. For example the solubilities of hydrocarbon chains decrease with increasing chain length (see Figure 7.14). Taking the free energy cost of introducing

a single propane molecule into water and dividing by the approximate surface area of one molecule (about 2nm^2) gives a free energy cost per surface area of $\approx 3 k_B T \text{ nm}^{-2}$.

Solvation of small polar molecules. The preceding discussion contrasted molecules like hydrogen peroxide, which make H-bonds and mixes freely with water, with nonpolar molecules like propane. Small polar molecules occupy a middle ground between these extremes. Like hydrocarbons, they do not form H-bonds with water, and so in many cases their solvation carries an entropic penalty. Unlike hydrocarbons, however, they do interact electrostatically with water: The surrounding water molecules can point their negative sides toward the molecule's positive parts, and away from its negative parts. The resulting reduction in electrostatic energy can compensate the entropic loss, making small polar molecules soluble at room temperature.

Large nonpolar objects: The clathrate cage strategy only works for sufficiently small included objects. Consider the extreme case of an infinite, planar surface, for example the surface of a lake, an interface between air and water. Air itself can be regarded as a hydrophobic substance, since it too disrupts the H-bond network; the surface tension of the air-water interface is about 0.072 Jm^{-2} . Clearly the water molecules at the surface cannot each maintain four H-bonds directed tetrahedrally! Thus the hydrophobic cost of introducing a large nonpolar object into water carries a significant energy component, reflecting the breaking of H-bonds. Nevertheless the free energy again goes up. In fact, the magnitude of the hydrophobic effect in the large-object case is roughly the same as that of small molecules:

Nonpolar solvents: Although this section has been mainly concerned with solvation by water, it is useful to contrast the situation with nonpolar solvents, like oil or the interior of a bilayer membrane. Oils have no network of H-bonds. Instead, the key determinant of solubility is the electrostatic self-energy of the guest molecule. A polar molecule will prefer to be in water, where its self-energy is reduced by water's high permittivity. Transferring such a molecule into oil thus incurs a large energy cost and is unfavorable. Nonpolar molecules, in contrast, have no such preference and pass more easily into oil-like environments. Fatty acids like hexanoic acid, with their hydrocarbon chains, dissolve more readily in the membrane, and hence permeate better, than do polar molecules like urea.

2.2.1 Water generates an entropic attraction between nonpolar objects: hydrophobic interaction

W. Kauzmann proposed in 1959 that any two nonpolar surfaces in water would tend to coalesce, in order to reduce the total nonpolar surface that they present to the water. Since the cost of hydrophobic solvation is largely entropic, so will be the corresponding force, or hydrophobic interaction, driving the surfaces together. It's not easy to derive a quantitative, predictive theory of the hydrophobic interaction, but some simple qualitative predictions emerge from the picture given above. First, the largely entropic character of the hydrophobic effect suggests that the hydrophobic interaction should increase as

we warm the system starting from room temperature. Indeed in vitro the assembly of microtubules, driven in part by their monomers' hydrophobic preference to sit next to each other, can be controlled by temperature: Increasing the temperature enhances microtubule formation. Like the depletion interaction, the hydrophobic effect can harness entropy to create an apparent increase in order (self-assembly) by coupling it to an even greater increase of disorder among a class of smaller, more numerous objects (in this case the water molecules). Since the hydrophobic interaction involves mostly just the first layer of water molecules, it is of short range, like the depletion interaction. Thus we add the hydrophobic interaction to the list of weak, short-range interactions that are useful in giving macromolecular interactions their remarkable specificity. Later on will also argue that the hydrophobic interaction is the dominant force driving protein self-assembly.

2.3 Two hard spheres in water: a picture of the hydrophobic interaction

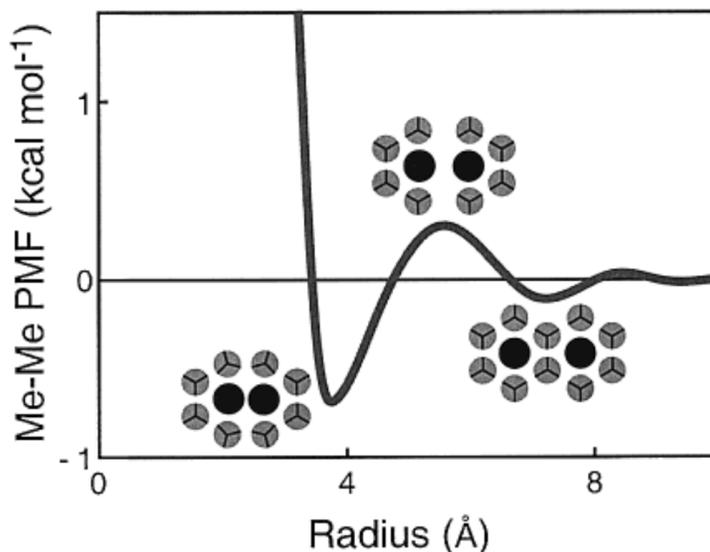


Figure 15. Methane–methane potential of mean force. Idealized potential of mean force between two methanes as a function of distance in angstroms. Left: methanes (in black) at contact, middle: at the barrier distance (which has an unfavorable free energy), and right: in a solvent-separated configuration. Adapted from D. E. Smith, and A. D. J. Haymet, *J. Chem. Phys.* **1993**, 98, 6445.

Numerical simulations provide a detailed picture of the effective interactions between two sphere which can not form HB immersed in water. The simulation results show that

indeed sphere prefer to stay in contact or at a distance in which just one water molecule separate them. This effective interaction fully arises by the restructuring of the solvent in its attempt to maximize the number of hydrogen bonds.

The effective potential in this example is about 4 kJ/mol, hence comparable to $k_B T$. Hence, one can also consider macroscopic effects associated to the collective behavior of hard-spheres in water (phase separation). This simple model also give us an hint of the role that hydrophobic effect has on the folding of proteins.

3 Appendix - Compressibility and Volume Fluctuations

The response function

$$\kappa_T \equiv -\frac{1}{V} \frac{\partial V}{\partial P} \Big|_T$$

In the constant pressure ensemble, the partition function $\Delta(P, T, N)$ is defined as

$$\Delta(P, T, N) = \frac{1}{V_0} \int_0^\infty dV e^{-\beta PV} Q(N, V, T)$$

and it is associated to the Gibbs free energy

$$\beta G(P, T, N) = -\ln \Delta(P, T, N)$$

Let's evaluate the average volume and the average squared volume in this ensemble

$$\langle V \rangle = \frac{\frac{1}{V_0} \int_0^\infty V dV e^{-\beta PV} Q(N, V, T)}{\Delta(P, T, N)} = -k_B T \frac{\frac{1}{V_0} \int_0^\infty \frac{\partial}{\partial P} e^{-\beta PV} dV Q(N, V, T)}{\Delta(P, T, N)}$$

where we have used the fact that P enters only in the exponential $e^{-\beta PV}$. Then

$$\langle V \rangle = -k_B T \frac{\partial}{\partial P} \ln \Delta(P, T, N) = \frac{\partial G}{\partial P} \Big|_T \quad (1)$$

Performing a similar analysis for $\langle V^2 \rangle$ we find

$$\begin{aligned} \langle V^2 \rangle &= \frac{\frac{1}{V_0} \int_0^\infty V^2 dV e^{-\beta PV} Q(N, V, T)}{\Delta(P, T, N)} = (k_B T)^2 \frac{\frac{1}{V_0} \int_0^\infty \frac{\partial^2}{\partial P^2} e^{-\beta PV} dV Q(N, V, T)}{\Delta(P, T, N)} \\ &= (k_B T)^2 \frac{1}{\Delta(P, T, N)} \frac{\partial^2}{\partial P^2} \frac{1}{V_0} \int_0^\infty e^{-\beta PV} dV Q(N, V, T) = (k_B T)^2 \frac{1}{\Delta(P, T, N)} \frac{\partial}{\partial P} \frac{\Delta(P, T, N)}{\Delta(P, T, N)} \frac{\partial}{\partial P} \Delta(P, T, N) = \\ &= (k_B T)^2 \frac{1}{\Delta(P, T, N)} \frac{\partial}{\partial P} \Delta(P, T, N) \frac{\partial}{\partial P} \ln \Delta(P, T, N) = -k_B T \frac{1}{\Delta(P, T, N)} \frac{\partial}{\partial P} \Delta(P, T, N) \frac{\partial}{\partial P} G \end{aligned}$$

$$\begin{aligned}
&= -k_B T \frac{1}{\Delta(P, T, N)} \left[\frac{\partial \Delta(P, T, N)}{\partial P} \frac{\partial}{\partial P} G + \Delta(P, T, N) \frac{\partial^2}{\partial P^2} G \right] \\
&= \left[\frac{\partial}{\partial P} G \right]^2 - k_B T \left[\frac{\partial^2}{\partial P^2} G \right] \\
&= \langle V \rangle^2 - k_B T \left[\frac{\partial^2 G}{\partial P^2} \right]
\end{aligned}$$

Then, remembering from the Maxwell relations (Eq. 1)

$$\left. \frac{\partial G}{\partial P} \right|_T = V$$

we obtain

$$\langle V^2 \rangle - \langle V \rangle^2 = -k_B T \left. \frac{\partial V}{\partial P} \right|_T = k_B T V \kappa_T$$

4 Appendix - Specific Heat and Enthalpy Fluctuations

The response function

$$C_P \equiv \left. \frac{dQ}{dT} \right|_P$$

We can repeat the derivation for κ_T to evaluate the fluctuations in Enthalpy.

In the constant pressure ensemble, the partition function $\Delta(P, T, N)$ is defined as

$$\Delta(P, T, N) = \frac{1}{V_0} \int_0^\infty dV e^{-\beta PV} Q(N, V, T)$$

and it is associated to the Gibbs free energy

$$\beta G(P, T, N) = -\ln \Delta(P, T, N)$$

Let's evaluate the average enthalpy and the average squared enthalpy in this ensemble

$$\langle H \rangle = \frac{\frac{1}{V_0} \int_0^\infty (\mathcal{H} + PV) dV e^{-\beta PV} Q(N, V, T)}{\Delta(P, T, N)} = -\frac{\frac{1}{V_0} \int_0^\infty \frac{\partial}{\partial \beta} e^{-\beta PV} dV Q(N, V, T)}{\Delta(P, T, N)}$$

Then

$$\langle H \rangle = -\frac{\partial}{\partial \beta} \ln \Delta(P, T, N) = \left. \frac{\partial(-\beta G)}{\partial \beta} \right|_P$$

Performing a similar analysis for $\langle H^2 \rangle$ we find

$$\langle H^2 \rangle = \frac{\frac{1}{V_0} \int_0^\infty (\mathcal{H} + PV)^2 dV e^{-\beta PV} Q(N, V, T)}{\Delta(P, T, N)} = \frac{\frac{1}{V_0} \int_0^\infty \frac{\partial^2}{\partial \beta^2} e^{-\beta PV} dV Q(N, V, T)}{\Delta(P, T, N)}$$

$$\begin{aligned}
&= \frac{1}{\Delta(P, T, N)} \frac{\partial^2}{\partial \beta^2} \frac{1}{V_0} \int_0^\infty e^{-\beta PV} dV Q(N, V, T) = \frac{1}{\Delta(P, T, N)} \frac{\partial}{\partial \beta} \left[\frac{\Delta(P, T, N)}{\Delta(P, T, N)} \frac{\partial}{\partial \beta} \Delta(P, T, N) \right] = \\
&= \frac{1}{\Delta(P, T, N)} \frac{\partial}{\partial \beta} \left[\Delta(P, T, N) \frac{\partial}{\partial \beta} \ln \Delta(P, T, N) \right] = \frac{1}{\Delta(P, T, N)} \frac{\partial}{\partial \beta} \left[\Delta(P, T, N) \frac{\partial}{\partial \beta} G \right] \\
&= \frac{1}{\Delta(P, T, N)} \left[\frac{\partial \Delta(P, T, N)}{\partial \beta} \frac{\partial}{\partial \beta} (-\beta G) + \Delta(P, T, N) \frac{\partial^2}{\partial \beta^2} G \right] \\
&= \left[\frac{\partial}{\partial \beta} (-\beta G) \right]^2 + \left[\frac{\partial^2}{\partial \beta^2} (-\beta G) \right] \\
&= \langle H \rangle^2 + \left[\frac{\partial^2 (-\beta G)}{\partial \beta^2} \right]
\end{aligned}$$

Then, remembering from the Maxwell relations that

$$\frac{\partial G}{\partial T} \Big|_P = -S \quad \text{and} \quad d\beta = -\frac{1}{T^2} dT$$

we obtain

$$\begin{aligned}
\left[\frac{\partial^2 (-\beta G)}{\partial \beta^2} \right] &= \frac{\partial}{\partial \beta} \frac{\partial}{\partial \beta} (-\beta G) = \frac{\partial}{\partial \beta} \left[-G - \beta \frac{\partial G}{\partial \beta} \right] = \\
\frac{\partial}{\partial \beta} \left[-G + \frac{k_B T^2}{k_B T} \frac{\partial G}{\partial T} \right] &= -k_B T^2 \frac{\partial}{\partial T} [-G - TS] = -k_B T^2 \frac{\partial}{\partial T} [-(U - TS + PV) - TS] = k_B T^2 \frac{\partial}{\partial T} H
\end{aligned}$$

such that

$$\langle H^2 \rangle - \langle H \rangle^2 = k_B T^2 C_P$$