

Two faces of water

David Chandler

Water and oil famously don't mix: the term hydrophobic (water-fearing) is commonly used to describe substances that, like oil, do not mix with water. Although it may look as if water repels oil, in reality the separation of oil and water in ambient conditions is not due to repulsion between water and oil molecules, but to particularly favourable hydrogen bonding between water molecules. Each water molecule can participate in four such bonds, sharing its two hydrogen atoms with two neighbouring water molecules and sharing two further hydrogen atoms associated with two other neighbours. Ice is a tetrahedrally ordered array, and liquid water a disordered network, of such hydrogen-bonded molecules.

Oil and water molecules actually attract each other, but not nearly as strongly as water attracts itself. Mixing enough oil with water therefore leads to a reduction in favourable bonding. Strong mutual attractions between water molecules induce segregation of oil from water and result in an effective oil–oil attraction, in the same way that groups of people segregate when one subgroup prefers to associate with its own kind. This water-induced attraction between oil molecules is called the hydrophobic interaction.

In the 1950s, Walter Kauzmann identified hydrophobic interactions as a primary source of protein stability. Proteins are chains of amino acids that fold into specific, functional, three-dimensional structures that are determined by the order of the amino-acid sequence. Kauzmann reasoned that as amino acids are either water-like or

oil-like, a given linear sequence would fold into the structure that best segregates oil-like amino acids from water. Later, when protein structures were deduced with the help of X-ray crystallography, Kauzmann's general predictions were found to be correct. Yet subsequent attempts to quantify his ideas by identifying a single parameter or function that characterizes the strength of hydrophobic interactions have been unsuccessful.

This difficulty has to do with length scales. Under the right conditions, hydrophobicity of the traditional Kauzmann sort can appear, but only for large oily surfaces in water. A different, weaker hydrophobic interaction occurs for small assemblies of oil molecules. Because the mutual attraction between water molecules is so strong, water–water interactions persist even in the presence of small oily species, perhaps a single alkane chain with, say, 10 or fewer carbon atoms. Hydrogen bonding simply goes around hydrophobic species. In the close vicinity of the oily molecules, the possible configurations of hydrogen bonding may be restricted, but the overall amount of hydrogen bonding remains relatively unchanged. Thus, the cost of hydrating a small, hydrophobic solute has more to do with the number of ways in which hydrogen bonds can form than with their strength. That is, the solvation free energy of the system is largely entropic and not enthalpic. However, this geometric picture breaks down for an extended oily region, because not all hydrogen bonds can persist near to its surface (see picture). The nature of hydrophobicity therefore changes when the size of oily surfaces depletes the number of hydrogen bonds. This energetic effect — the loss of hydrogen bonding — drives the segregation of oil from water.

What molecule size characterizes this crossover between small and large hydrophobic solute hydration? For a small solute where hydrogen bonding occurs adjacent to it, the number of water molecules that are affected by the solute is proportional to solute volume, and hence the solvation free energy is also proportional to this volume. The solvation free energies of ethane, propane and other similar molecules indicate that the proportionality constant is roughly 1×10^8 joules per cubic metre.

In contrast, the free energy of a large solute with an extended hydrophobic surface is proportional to the surface area of the interface between the solute and water. Here, the proportionality constant can be estimated from the surface tension of oil–water interfaces — about 6×10^{-2} joules per square metre. Thus, when the assembly interface extends beyond 1 nanometre, the energetic cost of assembling hydrophobic units is significantly more

Hydrophobicity

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favourable than the entropic cost of keeping them separate. The hydrophobic stabilization of smaller assemblies, however, is insufficient to overcome thermal agitation.

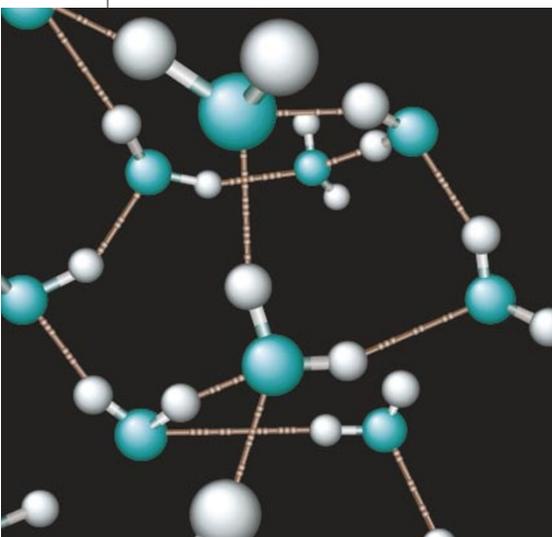
The crossover to assembly of hydrophobic units involves the nucleation of an interface with broken hydrogen bonds, such as that between water and its vapour. The assembly of hydrophobic structures requires the removal of water from regions between these groups; this is the same as vaporization. Hence, the closer water is to the liquid–vapour phase transition, the stronger is the tendency for hydrophobic assembly. I believe this explains why proteins are denatured by cold and by high pressure: lowering temperature and raising pressure both move water away from its liquid–vapour phase transition. Furthermore, raising the temperature increases the solvation free energy of small, disassembled hydrophobic units because hydration costs are entropic for such solutes, but it reduces the solvation free energy of larger, oily clusters because the costs here are enthalpic. Finally, in aqueous solutions with no assemblies of 1 nanometre or more in size, such as mixtures of water and simple alcohols, hydrogen bonding persists much as it does in pure water.

Without an aqueous environment, hydrophobic interactions cannot occur. But the free energetic cost of dissolving large, oily molecules in water is formidable. This cost can be successfully compensated for, however, by attaching sufficient numbers of polar and charged groups. In this way, large, oily molecules can easily mix with water, and nature can then exploit the phenomenon responsible for phase separation to create local assemblies of oily structures. These assemblies can exist on scales down to nanometres (but no smaller), because this threshold size coincides with the critical radius at which oil separates from water. This seems to explain the existence of cooperativity during protein folding, an idea that is worthy of experimental study. ■

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FURTHER READING

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Closing ranks: water's strong hydrogen-bonding network (thin lines) can exclude other species.