



## CHEMISTRY: Water from First Principles

Anthony J. Stone, *et al.*

*Science* **315**, 1228 (2007);

DOI: 10.1126/science.1140758

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experimental evolution study of viral parasites (bacteriophage) of bacteria (4). Bacteriophage invade bacteria after a random encounter, reproduce inside the host, and then burst out, killing the bacteria in the process. The experimental design for this study involved nearly 200 individual media-filled “wells,” some of which were inoculated with either bacteria or bacteriophage. Dispersal was manipulated by moving samples of bacteria and phage between different wells. Where dispersal was limited to only neighboring wells, clusters of wells containing only phage formed. This reflects “self-shading” by the phage, because they quickly killed bacteria in a well. As expected, this favored the evolution of prudent phage, which in turn reduced the rate of phage reproduction. Because this allowed more growth of the bacterial “resource,” there was an increase in total bacteriophage yield from a well. This in turn increased the probability of bacteriophage infecting new bacterial wells. In contrast, when the bacteriophage and bacteria could disperse to any well, the authors argue that there was a much higher chance of encountering a bacterial well, so prudence was less beneficial.

Prudence, when considered a form of cooperation, is open to cheating. Regardless of the long-term benefits to the group of prudent behavior, a faster exploiting “cheat”—an individual that reproduces more rapidly in the short term—that invades a patch of prudent individuals is likely to have an advantage. What prevents such cheats from joining patches of prudent individuals in the limited-dispersal conditions in the above examples? On the one hand, it could be chance; some pathogen populations simply don’t contain cheats. However, limited dispersal also means that viruses within a localized patch are more likely to share the same immediate ancestors than would viruses between patches. The benefits of prudent behavior are therefore most directed toward close kin, which themselves are likely to be cooperators, causing genes for cooperation to spread throughout a population (5, 6). This process of kin selection (7) is likely to be an important determinant of many cooperative traits.

However, when there is greater dispersal, there will be much more interaction between individuals of different immediate ancestry, and hence between cheats and cooperators. Of

course, it is impossible to know the importance of kin selection in explaining the results of Boots and Meador because dispersal and the likelihood of viruses interacting with their closest relatives are necessarily correlated. Independent manipulation of these two variables would provide fascinating insights into the mechanisms responsible for the evolution of parasite infectivity.

Regardless of the precise details of the theoretical explanation, there is now, for the first time, some very convincing experimental data that parasites are likely to evolve to be less prudent when they get to travel. Less prudent can mean various things: more infectious, more disease-causing, and more likely to kill. None of which is likely to be very good for hosts.

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10.1126/science.1139839

## CHEMISTRY

# Water from First Principles

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The water molecule is very simple, yet water in its various forms is one of the most complicated substances. Its anomalous behavior, such as its expansion on freezing and other more subtle properties, is related to the detailed form of the interaction between its molecules, which is still imperfectly understood. For more than 70 years, scientists have been trying to understand the behavior of water in its different forms from first principles—that is, based on the fundamental properties of the water molecule. Much progress has been made in this task in recent years, and the report by Bukowski *et al.* on page 1249 of this issue (1) marks an important step.

For some substances, the properties of the bulk solid, liquid, or gas can be deduced with reasonable accuracy once one knows the pair potential—that is, the function that describes how the energy of a pair of molecules depends on their relative geometry. For molecules like

water, this function depends on six coordinates: the position (three coordinates) and orientation (three more) of either molecule relative to the other. The energy of an assembly of molecules is then taken to be a sum of all pair interactions in the assembly.

For water, and for many other substances, however, the pair potential is not enough. The energy of an assembly of water molecules cannot be described adequately as a sum of pair potentials. The interaction between any two molecules leads to a distortion of both molecules, which in turn modifies their interactions with a third molecule (see the figure). A three-body function is needed to take such effects into account. The three-body correction is a function of 12 coordinates: the position and orientation of two molecules relative to the third. Even this is not enough: In principle, there are four-body and five-body corrections, and so on. These are smaller, but are thought to be important for the tetrahedral structure of liquid water (2). Most of these many-body corrections can be accounted for by a careful description of the polarization of

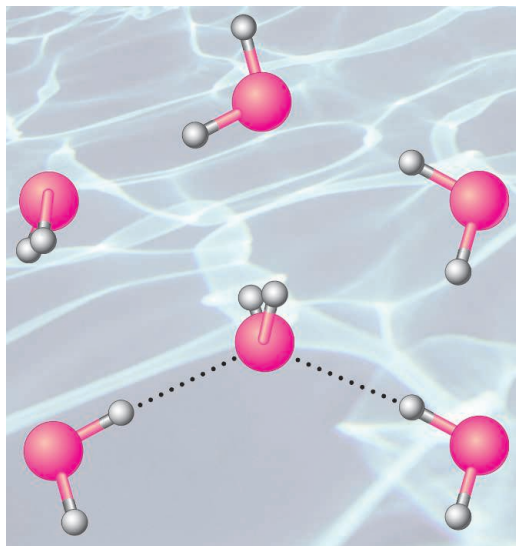
It has been hard to reproduce some of the properties of water starting only with the basic laws of physics. A description of water derived entirely from theory now succeeds in this task.

each molecule by its neighbors (3). There are other many-body effects that are not included in this way—for example, the three-body correction to the van der Waals attraction (4)—but they are smaller and can often be ignored.

For simulations of liquid water and of biological systems in the presence of water, very simple descriptions are needed because of computational constraints. They usually approximate the many-body effects by modifying the pair potential, typically by enhancing the molecular dipole moment. These models are quite successful in modeling liquid water at ambient temperature and pressure, but give a very poor account of the water dimer, because the modified pair potential is incorrect.

In recent years, several research groups have tried to obtain a description of water that gives a good account of the water dimer, small clusters of water molecules, and the bulk liquid (5–7). Such a comprehensive task requires a much more elaborate potential. Traditionally, the intermolecular potential has been determined from experimental data, but experimen-

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**Three-body effects.** The two hydrogen bonds may act cooperatively, each reinforcing the other (**top**), or they may oppose each other (**bottom**). The top configuration is bound more strongly than the bottom one. Three-body effects of this kind play an important role in water clusters and liquid water. Bukowski *et al.* (1) describe a potential derived entirely from first principles that captures these and other properties of water.

quality, has not been met. This is what Bukowski *et al.* have been able to do. They have used perturbation theory to determine the form of the potential function, and fitted the parameters in it using data points for the water dimer calculated by the CCSD(T) method.

An advantage of this approach is that the CCSD(T) data points cover the energy surface much more completely than the spectroscopic data, which describe only the region in the neighborhood of the energy minimum and the barriers to neighboring minima. The CCSD(T) calculations were carried out only for the dimer, but with a good functional form the resulting potential is able to give a good account of the many-body interactions and hence of the liquid properties as well as the dimer spectrum.

This work is not the end of the story. The

calculated properties are good, but leave room for improvement. The form of the potential function omits some of the smaller terms. Ideally, one would wish to obtain accurate numbers as well as the functional form from perturbation theory. Nevertheless, Bukowski *et al.* have been able to show that a good description of water from first principles is becoming feasible.

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10.1126/science.1140758

tal properties are averages over the potential surface, and it is difficult or impossible to extract the details of the potential surface unambiguously from such properties. Alternatively, the intermolecular potential can be calculated from first principles. The most accurate method in current use is coupled-cluster theory with inclusion of single, double, and triple excitations, the triples noniteratively. Unfortunately, this CCSD(T) method gives only the total pair potential energy, and only at isolated points. It provides no information about the functional form of the pair potential, which is needed for most applications.

Perturbation theory, on the other hand, does give information about the functional form, but is very complex and computationally demanding, and cannot yet achieve the same accuracy. Recent practice has been to refine the details of the potential by fitting to experimental data.

Fitting is a well-established technique in many fields of science, but it has pitfalls: It may improve some properties at the expense of others. For example, in the case of the simple potentials mentioned above, enhancement of the molecular dipole moment improves the calculated properties of the liquid but ruins the description of the dimer. In that case, however, the form of the potential is known to be inadequate. Careful use of perturbation theory can give the right functional form, and the numerical parameters can be refined by fitting to the very accurate experimental data that have been obtained from high-resolution spectroscopy on the dimer and small clusters. This approach can lead to potentials that give a good account of both small clusters and the bulk liquid (7).

Nevertheless, the challenge to obtain a good intermolecular potential energy function entirely by calculation from first principles, using experimental data only as a test of its

## BIOCHEMISTRY

# A Missing Link in Membrane Protein Evolution

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Discerning the orientation of subunits of an unusual bacterial membrane protein suggests how the particular topology of other membrane proteins may have evolved.

Most proteins embedded in biological membranes have vectorial functions, such as transporting molecules into or out of cells or transducing signals. It is thus essential that these membrane proteins have unique orientations in the lipid bilayer. To achieve a unique orientation, membrane proteins carry signals in their amino acid sequences that are recognized during the membrane insertion process. Intriguingly, some membrane proteins have structurally similar, homologous regions with opposite orientations in the membrane, raising questions about their evolution. On page 1282 of this issue, Rapp *et al.* (1) offer a com-

puting explanation for how such proteins may have evolved.

One of the best-understood signals for membrane protein topology is the “positive-inside rule”: Positively charged residues such as lysine (K) and arginine (R) tend to be most abundant (“K+R bias”) in loops located at the cytoplasmic side of plasma and endoplasmic reticulum membranes (2). Crystallography has shown that many membrane proteins contain homologous domains with opposite (antiparallel) membrane orientation, leading to proteins with a quasi-two-fold axis in the plane of the membrane. Well-known examples are the members of the aquaporin family, in which the first three transmembrane segments are homologous to the last three but with opposite membrane orientation. Exactly how such quasi-symmetrical proteins have come about has been puzzling. Rapp *et al.*

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