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# Illuminating the Interactions of Small Solutes in Liquid Water

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The rich and complex solvating properties of liquid water have entertained scientists for over a century<sup>1-5</sup>. Water is distinct from other common liquids in the tendency for individual molecules to engage in tetrahedrally coordinated hydrogen bonding. Indeed this tendency is reflected in the microscopic structure, dynamics and hydrating properties of liquid water. The hydrogen bonding interactions between water molecules are so energetically favorable that at ambient conditions the network of hydrogen bonds is nearly saturated<sup>6</sup> (i.e., a small fraction of individual molecules are missing a hydrogen bond). To avoid the loss of hydrogen bonds the solvation of small solutes can be enabled by microscopic distortions in water's hydrogen bonding network, whereby individual solutes occupy the disordered hydrogen bond cages formed between adjacent water molecules<sup>7-8</sup>. Solutes with an effective diameter of less than about 1nm can be accommodated in this way. For larger solutes the geometric constraints of hydrogen bonding necessitate the costly sacrifice of water-water hydrogen bonds. In fact, it is this length scale crossover that provides the driving force for many aqueous phenomena, such as the demixing of oil and water<sup>8</sup>.

In solvation thermodynamics solute-solute interactions include a balance of water-solute, water-water, and solute-solute interactions. When solutes are similar in size to water molecules their interactions are mediated by a flexible but solute-distorted hydrogen bonding network. In this regime simulation studies seem to indicate that thermodynamic properties, such as the solute-solute potential of mean force, can depend quite sensitively on model details<sup>9-10</sup> (e.g., force field parameters, polarizability, etc.). This sensitivity can signal that a delicate balance is at play in the underlying molecular physics. When this is the case experimental insight is required in order to resolve the apparent ambiguity.

This issue contains two *perspective* articles that confront the delicate balance of forces that govern the water-mediated interactions of small solutes in aqueous solutions. Both perspectives combine experiment and simulation in order to generate molecular-level insight into their respective system of interest, which represent two entirely different classes of aqueous solute particles. Specifically, one perspective focuses on the interactions of small hydrophobic molecules while the other perspective focuses on the interactions of oppositely charge ions.

In the first perspective article, Dor Ben-Amotz considers the aqueous solvation of small oily molecules, the type that spontaneously demix in sufficient concentration. Ben-Amotz addresses a common misconception related to the hydration of small hydrophobic molecules, namely that the tendency of such molecules to associate in solution is dominated by water-mediated forces. On the contrary, both vibrational spectroscopy and molecular simulations indicate that the water-mediated contribution to the overall binding free energy of these small oily molecules decreases with solute size, becoming negative (meaning water-mediated interactions are driving molecules apart) for compact alkanes

composed of more than about 5 carbons. This result demonstrates that when it comes to the interaction of hydrophobic solutes, water's contribution is most vivid when hydrogen bonds are at stake. This also serves to highlight that the tendency for oil and water to demix is an inherently collective phenomenon.

In the second perspective article, Miriam Kohagen and co-workers explore the interactions of the ionic components of water-soluble salts. In this case a delicate balance of strong attractive ion-ion and ion-water interactions govern the dissolution of oppositely charged ion pairs. Consequently, as Kohagen and coworkers highlight, the ion-pairing statistics generated using classical molecular simulation can depend sensitively on the details of the force field being used. This sensitivity reflects the importance of polarizability in the aqueous solvation of ions<sup>11</sup>, which, as they highlight, can be described accurately and efficiently using non-polarizable force fields with pre-screened ionic charges. This mean field treatment of electronic polarizability has been successfully used to treat a variety of problems in ionic solvation<sup>12</sup>. Here, benchmarked by experimental neutron scattering data, Kohagen and coworkers apply this efficient charge-scaling approach to carry out explicit simulations of ion-pairing in biological systems.

Both of the perspective articles described above are able to gather experimental information related to solute-solute interactions through a kind of subtractive data analysis. More specifically, the relevant but practically invisible experimental features, those pertaining to the minority solute-solute and solute-water interactions, are brought forward by subtracting away the dominant water-water contributions. This technique for systematically bringing forward specific subtle experimental signatures seems to provide a powerful and promising route to better understanding the rich and complex problem of aqueous solvation.

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