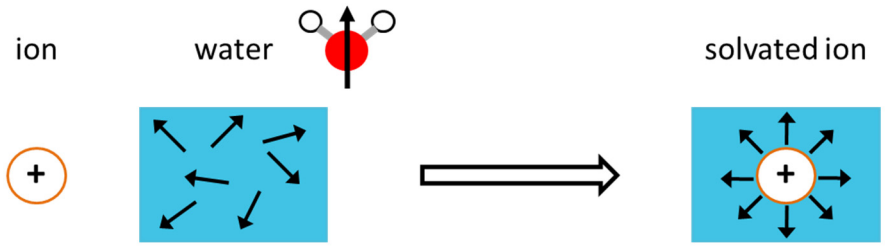
4. Solvation

Solvation describes the intermolecular interactions of a molecule or ion in solution with the surrounding solvent, which for our purposes will refer to water. Aqueous solvation influences an enormous range of problems in molecular biophysics, including (1) charge transfer and charge stabilization; (2) chemical and enzymatic reactivity; (3) the hydrophobic effect; (4) solubility, phase separation, and precipitation; (5) binding affinity; (6) self-assembly; and (7) transport processes in water. The terms solute and solvent commonly apply to dilute mixtures in the liquid phase in which the solute (minor component) is dispersed into the solvent (major component). For this reason, the concept of solvation is also at times extended to refer to the influence of any surrounding environment in which a biomolecule is embedded, for instance, a protein or membrane.

There are numerous types of interactions and dynamical effects that play a role in solvation. Typically, solute–solvent interactions are dominated by electrostatics (interactions of charges, dipoles, and induced dipoles), as well as hydrogen bonding and repulsion (both of which have electrostatic components). Therefore there is a tendency to think about solvation purely in terms of these electrostatic interaction energies. A common perspective—polar solvation—emphasizes how the dipoles of a polar liquid can realign themselves to energetically stabilize solute charges, as illustrated here for the case of ion solvation in water. The extent of solute stabilization in the liquid is the reorganization energy.



Unlike most solvents, the presence of water as a solvent for biological molecules fundamentally changes their properties and behavior from the isolated molecule. This means that water influences the conformation of flexible molecules, and sometimes hydrogen bonding interactions with water can be strong enough that it is hard to discern where the boundary of solute ends and water begins. But there is also a significant energetic cost to disrupting water's hydrogen bonding network in order to insert a solute into the liquid. Furthermore, the fluctuating hydrogen bond network of water introduces a significant entropy to the system which can be competitive or even the dominant contributor to the free energy of solvation. As a result, there are competing interactions involving both solute and water that act to restructure the solute and solvent relative to their isolated structures.

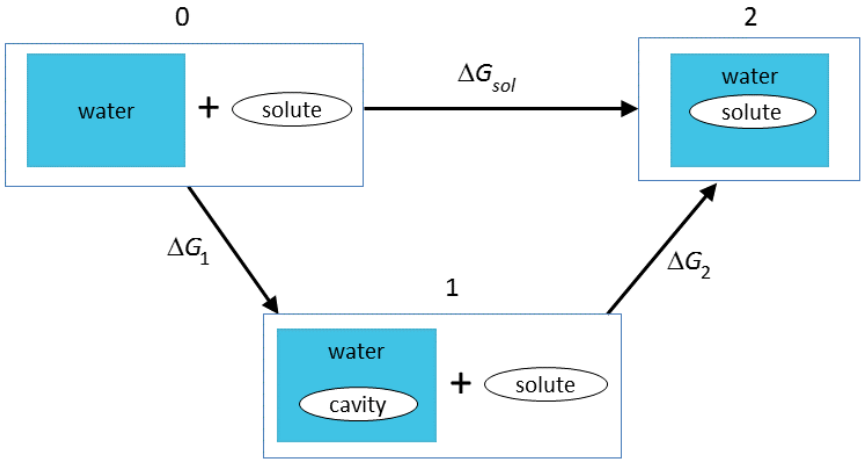
It is also important to remember that solvation is a highly dynamical process. Solvation dynamics refers to the time-dependent correlated motions of solute and solvent. How does a solvent reorganize in response to changes in solute charge distribution or structure? Conversely, how do conformational changes to the intermolecular configuration of the solvent (i.e., flow) influence changes in structure or charge distribution in the solute? The latter perspective views the solute as "slaved" to the solvent dynamics. These coupled processes result in a wide variety of time-scales in the solvation of biological macromolecules that span timescales from 10^{-14} to 10^{-7} seconds.

Solvation Thermodynamics

Let's consider the thermodynamics of an aqueous solvation problem. This will help identify various physical processes that occur in solvation, and identify limitations to this approach. Solvation is described as the change in free energy to take the solute from a reference state, commonly taken to be the isolated solute in vacuum, into dilute aqueous solution:

$$\text{Solute}(g) \rightarrow \text{Solute}(aq)$$

Conceptually, it is helpful to break this process into two steps: (1) the energy required to open a cavity in the liquid, and (2) the energy to put the solute into the cavity and turn on the interactions between solute and solvent.



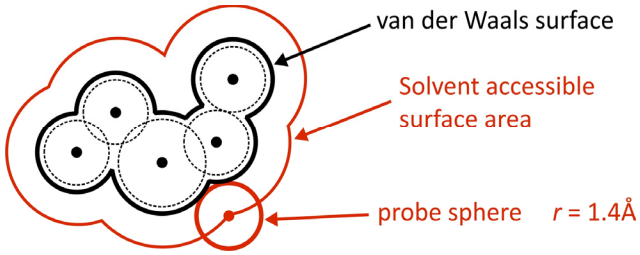
Each of these terms has enthalpic and entropic contributions:

$$\Delta G_{\text{sol}} = \Delta H_{\text{sol}} - T\Delta S_{\text{sol}}$$

$$\begin{aligned}\Delta G_{\text{sol}} &= \Delta G_1 + \Delta G_2 \\ &= \Delta H_1 - T\Delta S_1 + \Delta H_2 - T\Delta S_2\end{aligned}$$

ΔG_1: Free energy to open a cavity in water. We are breaking the strong cohesive intermolecular interactions in water (ΔH_1), creating a void against constant pressure, and reducing the configurational entropy of the water hydrogen-bond network (ΔS_1). Therefore ΔG_1 is large and positive. The hydrophobic effect is dominated by this term.

In atomistic models, cavities for biomolecules are commonly defined through the solute's solvent accessible surface area (SASA). In order to account for excluded volume on the distance scale of a water molecule, the SASA can be obtained by rolling a sphere with radius 1.4 Å over the solute's van der Waals surface.

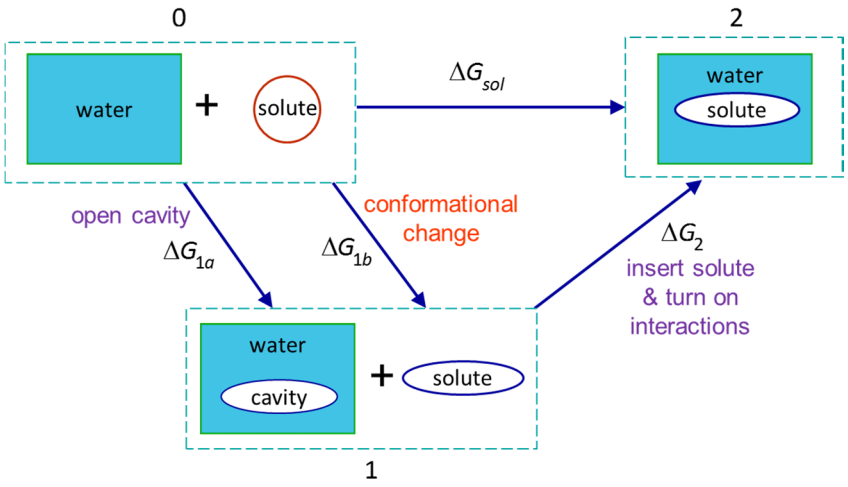


ΔG_2: Free energy to insert the solute into the cavity, turn on the interactions between solute and solvent. Ion and polar solvation is usually dominated by this term. This includes the favorable electrostatic and H-bond interactions (ΔH_2). It also can include a restructuring of the solute and/or solvent at their interface due to the new charges.

The simplest treatment of this process describes the solvent purely as a homogeneous dielectric medium and the solute as a simple sphere or cavity embedded with point charges or dipoles. It originated from the Born–Haber cycle first used to describe ΔH_{rxn} of gas-phase ions, and formed the basis for numerous continuum and cavity-in-continuum approaches to solvation.

Given the large number of competing effects involving solute, solvent, and intermolecular interactions, predicting the outcome of this process is complicated.

Looking at the cycle above illustrates many of the complications from this approach relevant to molecular biophysics, even without worrying about atomistic details. From a practical point of view, the two steps in this cycle can often have large magnitude but opposite sign, resulting in a high level of uncertainty about ΔG_{sol}—even its sign! More importantly, this simplified cycle assumes that a clean boundary can be drawn between solute and solvent—the solvent accessible surface area. It also assumes that the influence of the solvent is perturbative, in the sense that the solvent does not influence the structure of the solute or that there is conformational disorder or flexibility in the solute and/or solvent. However, even more detailed thermodynamic cycles can be used to address some of these limitations:



ΔG_{1a}: Free energy to create a cavity in water for the final solvated molecule.

ΔG_{1b}: Free energy to induce the conformational change to the solute for the final solvated state.

ΔG_2: Free energy to insert the solute into the cavity, turn on the interactions between solute and solvent. This includes turning on electrostatic interactions and hydrogen bonding, as well as allowing the solvent to reorganize around the solute:

$$\Delta G_2 = \Delta G_{\text{solute–solvent}} + \Delta G_{\text{solvent reorg}}$$

Configurational entropy may matter for each step in this cycle, and can be calculated using[1]

$$S = -k_B \sum_i P_i \ln P_i$$

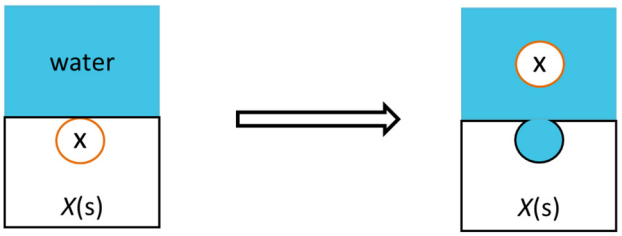
Here sum is over microstate probabilities, which can be expressed in terms of the joint probability of the solute with a given conformation and the probability of a given solvent configuration around that solute structure. In step 1, one can average over the conformational entropy of the solvent for the shape of the cavity (1a) and the conformation of the solute (1b). Step 2 includes solvent configurational variation and the accompanying variation in interaction strength.

With a knowledge of solvation thermodynamics for different species, it becomes possible to construct thermodynamic cycles for a variety of related solvation processes:

1) **Solubility.** The equilibrium between the molecule in its solid form and in solution is quantified through the solubility product K_{sp}, which depends on the free energy change of transferring between these phases.

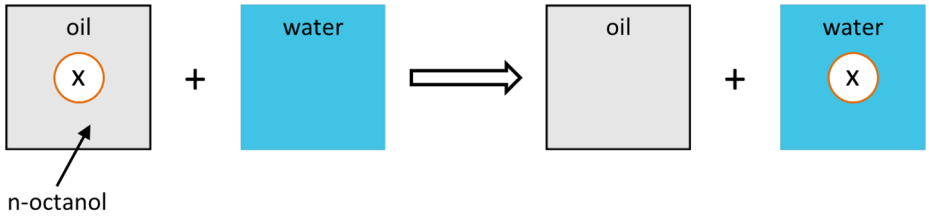
1. See C. N. Nguyen, T. K. Young and M. K. Gilson, Grid inhomogeneous solvation theory: Hydration structure and thermodynamics of the miniature receptor cucurbit[7]uril, J. Chem. Phys. **137** (4), 044101 (2012).

$X(s) + H_2O \rightarrow X(aq)$ $\quad K_{sp}=[X(aq)]=\exp[-\Delta G_{sp}/k_BT]$



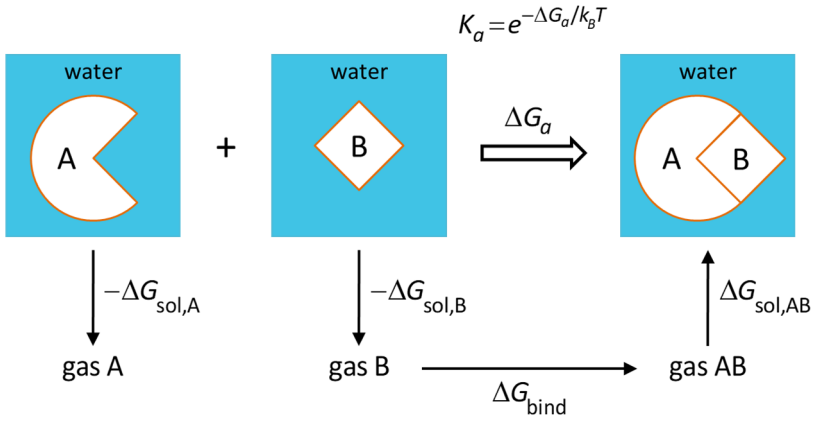
2) **Transfer free energy.** The most common empirical way of quantifying hydrophobicity is to measure the partitioning of a solute between oil and water. The partitioning coefficient P is related to the free energy needed to transfer a solute from the nonpolar solvent (typically octanol) to water.

$X(oil) \rightarrow X(water)$ $\quad P = [X(oil)]/[X(aq)] =\exp[-\Delta G_{transfer}/k_BT]$

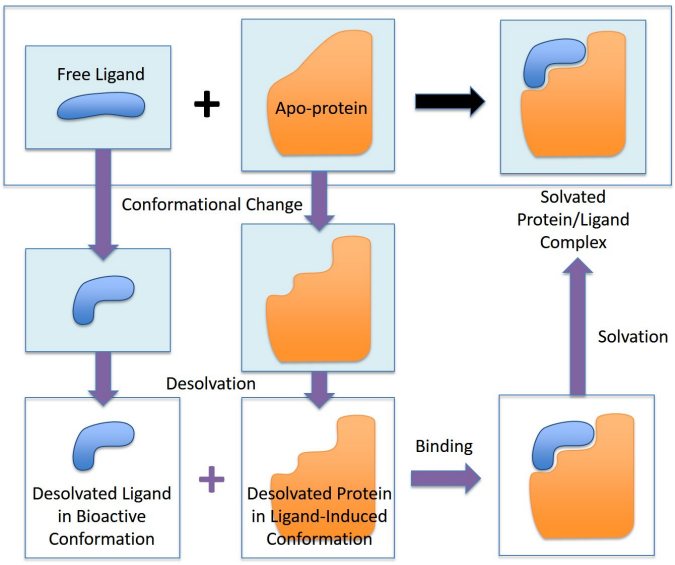


3) **Bimolecular association processes**

Association/Dissociation	$2X(aq) \rightarrow X_2(aq)$	$K_a = [X_2]/[X]^2$
Binding	$A(aq) + B(aq) \rightarrow AB(aq)$	$K_a = [AB]/[A][B]$



Binding with conformational selection



Solvation Dynamics and Reorganization Energy

Some of the practical challenges of describing solvation through thermodynamic cycles include dealing with strong solute–solvent interactions, flexible solutes, and explicit solvents. Additionally, it does not reflect the fact that solvation is a highly dynamic process involving motion of the solvent. Perhaps the most common example is in charge transfer processes (i.e., electrons and protons) in which water's dipoles can act to drive and stabilize the position of the charge. For instance, consider the transfer of an electron from a donor to an acceptor in solution:

$$D + A \rightarrow D^{+} + A^{-}$$

We most commonly consider electron transfer as dependent on a solvent coordinate in which solvent reorganizes its configuration so that dipoles or charges help to stabilize the extra negative charge at the acceptor site. This type of *collective* coordinate is illustrated in the figure to the right. These concepts are reflected in the Marcus' theory of electron transfer. The free energy change to relax the solvent configuration after switching the charges in the initial configuration is known as the reorganization energy λ.