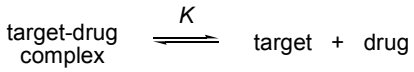
DavidsonX – D001x – Medicinal Chemistry
Chapter 9 – Binding, Structure, and Diversity
Part 1 – Intermolecular Forces
Video Clip – Binding Energy

DAVIDSONX

Drug-target binding is often measured through dissociation equilibrium constants, such as K_i for an enzyme inhibitor or K_D for a receptor ligand.



Equilibrium constants can be easily converted into a binding energy.

$$\Delta G^{\circ}_{bind} = -2.3RT \log \frac{1}{K} = 2.3RT \log K$$

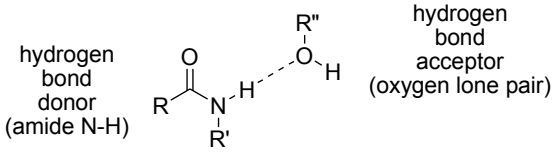
The calculated value for ΔG°_{bind} is the free energy of binding. If a value of 0.00199 kcal/mol•K is used for R with a temperature (T) of 298 K, then the binding energy has units of kcal/mol. More negative values for ΔG°_{bind} indicate a stronger binding energy.

Free energy changes (ΔG) are a combination of both changes in enthalpy (ΔH) and entropy (ΔS), and both enthalpy and entropy must be considered in binding. One interaction that controlled by enthalpy changes is **hydrogen bonding**. An interaction that is dominated by changes in entropy is the **hydrophobic effect**.

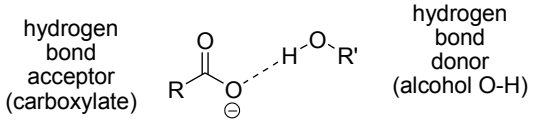
hydrogen bonding

For our purposes, hydrogen bonds are generally limited to the interaction of an N-H or O-H bond (the **hydrogen bond donor** – HBD) with a nitrogen or oxygen lone pair (the **hydrogen bond acceptor** – HBA). Both a donor and acceptor are required for a hydrogen bond. Hydrogen bonds can be divided into three types.

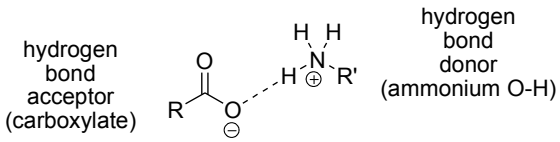
- Both the HBD and HBA are neutral. This type of hydrogen bond can contribute up to 1.5 kcal/mol to binding energy.



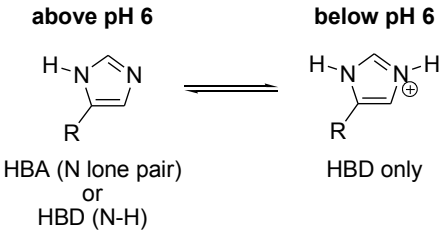
- Either the HBD or HBA has a charge. This type of hydrogen bond is somewhat stronger with a strength of up to 3.0 kcal/mol.



- Both the HBD and HBA have a charge. This type of hydrogen bond is strongest with a strength of up to 4.0 kcal/mol. In fairness, the strength of this interaction is a combination of both hydrogen bonding and an electrostatic attraction between the two opposite charges.



The pH of the environment has a significant impact on any hydrogen bond that involves a charged species. As the pH changes, some functional groups can gain or lose a proton and change in their ability to serve as a HBD or HBA. An example is imidazole, which is part of the side chain of the amino acid histidine. Above a pH of around 6, the ring is neutral and can act as either a HBD or HBA. Below 6, the ring is protonated and can only act as a HBD.



hydrophobic effect

Most drugs, as organic molecules, are somewhat non-polar. In an aqueous medium, the non-polar drug interacts poorly with the surrounding water molecules, which form an *ordered* solvent shell around the drug. After the drug binds its target, most of the water molecules are released and free to go their separate ways in solution. The disorder of the system increases ($\Delta S > 0$) with binding of the drug, and this entropy increase makes ΔG for the binding process more negative (more favorable).

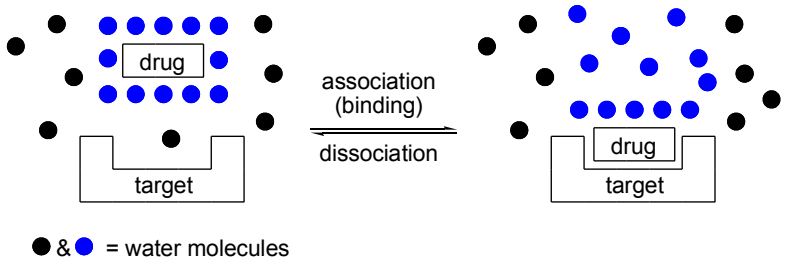


Image credit: Pearson Education

The greater the surface area of a drug that is freed of water molecules during binding equals a greater hydrophobic effect. For this reason, energy changes for the hydrophobic effect are often measured by surface area. The approximate contribution of the hydrophobic effect to binding energy is 0.03 kcal/mol/Å^2. A single CH_2 group in a binding pocket provides about 0.8 kcal/mol. A phenyl ring contributes about 2.0 kcal/mol.