Non-covalent interactions
Hydrogen Bonds, Hydrophobicity

Donors and Accepting Lone Pairs

Competition with water

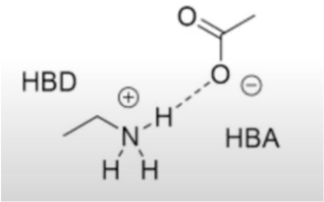
Cooperativity and directional nature

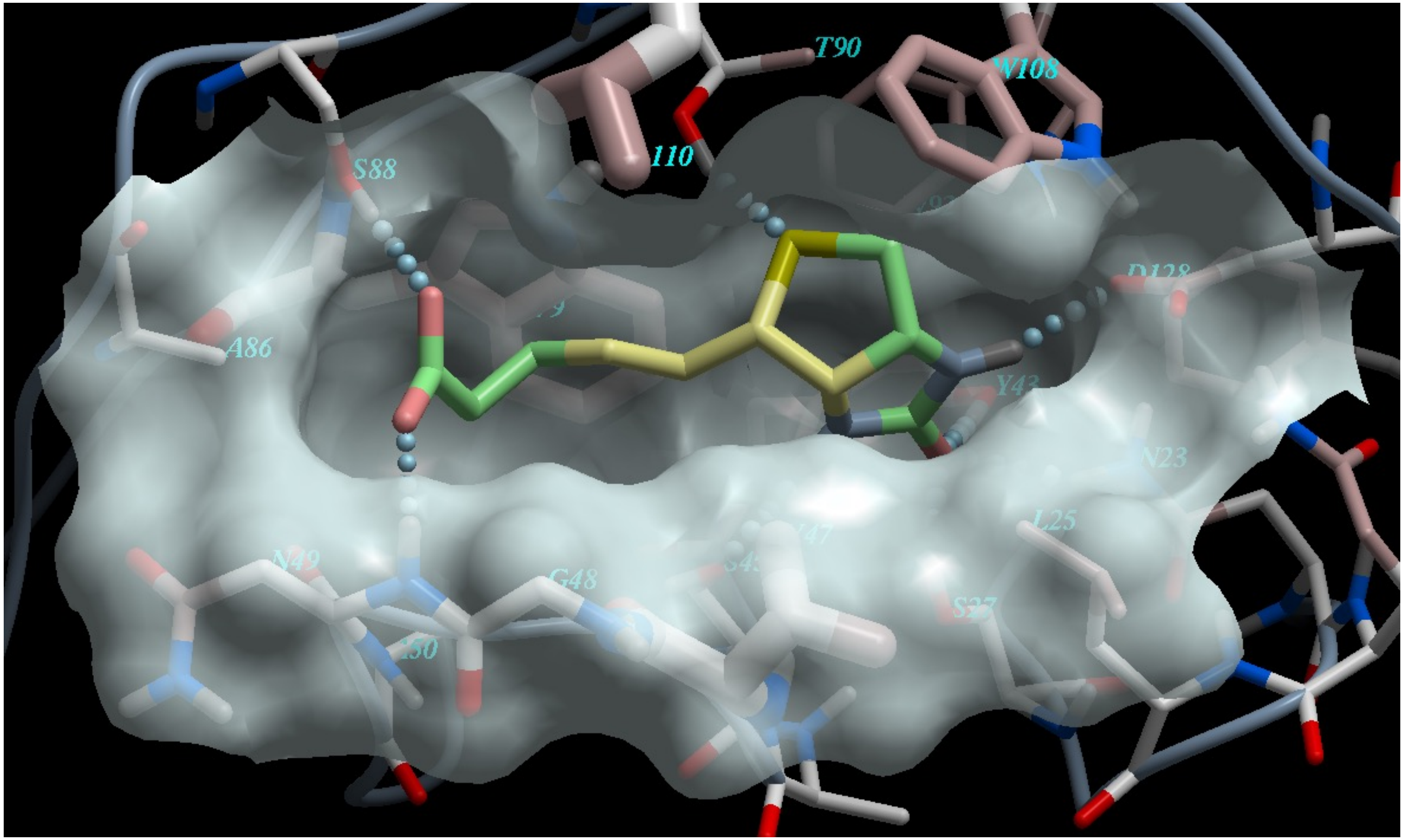
Penalty for burying a donor or an acceptor

Hydrogen Bonds

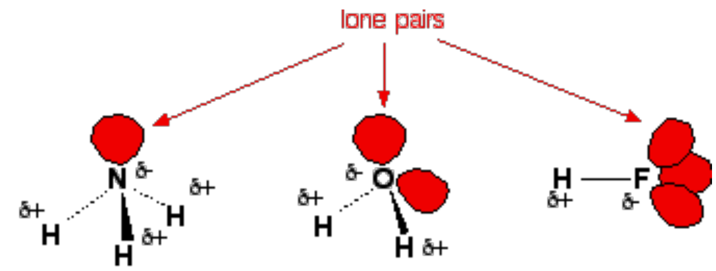
Donor (HBD): e.g. O-H , N-H **Acceptor**: O, N, .. , with a lone pair **Energy**: ~ 1-7 kcal/mol

The strongest hydrogen bonds between charged donors and acceptors
For drug-receptor binding: when unbound, hydrogen bonds with water

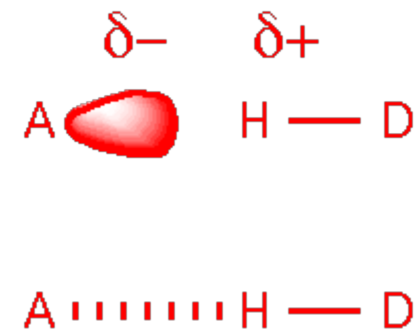




Donors, Lone Pairs and Acceptors



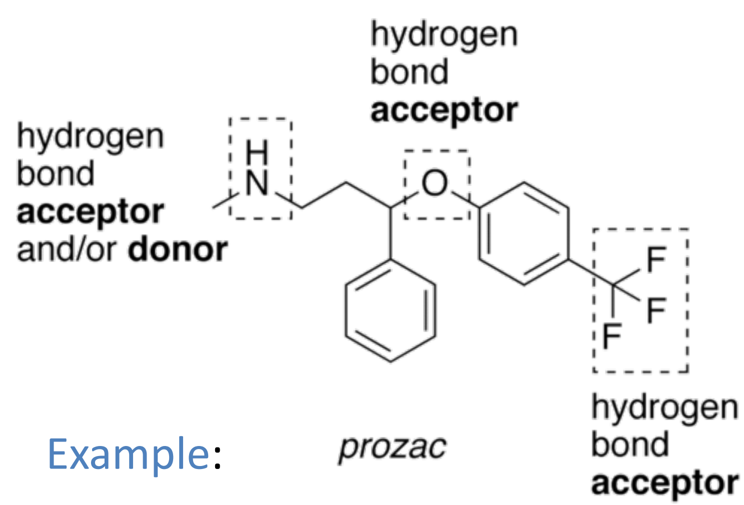
- An acceptor atom (A) that bears a basic lone pair of electrons can interact favorably with the acidic hydrogen (H) of a donor atom (D)
- A stable hydrogen bond requires that both atoms A and D are *electronegative* atoms, e.g. C=O•••H-O-C
- Hydrogen bonded atoms are CLOSER to each other than normal pair of interacting atoms: 1.6 to 2A
- Amines: neutral amine can be an *acceptor* due to a lone pair, it can also serve as an H-*donor*.



Acceptor: O, N, S, *anion*

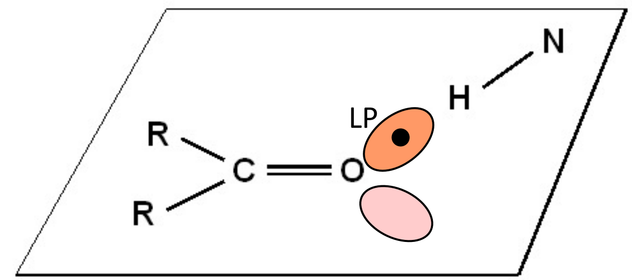
H-bond **D**onor: [O,N,S]-H

Example:

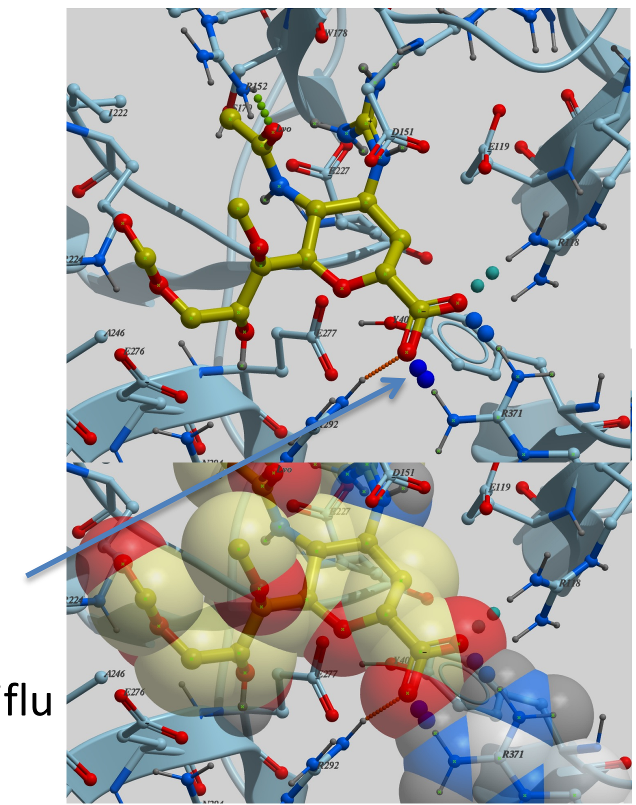


The strength of an H-bond

$-D^{\delta-} - H^{\delta+} \cdots\cdots {}^{\delta-}A -$



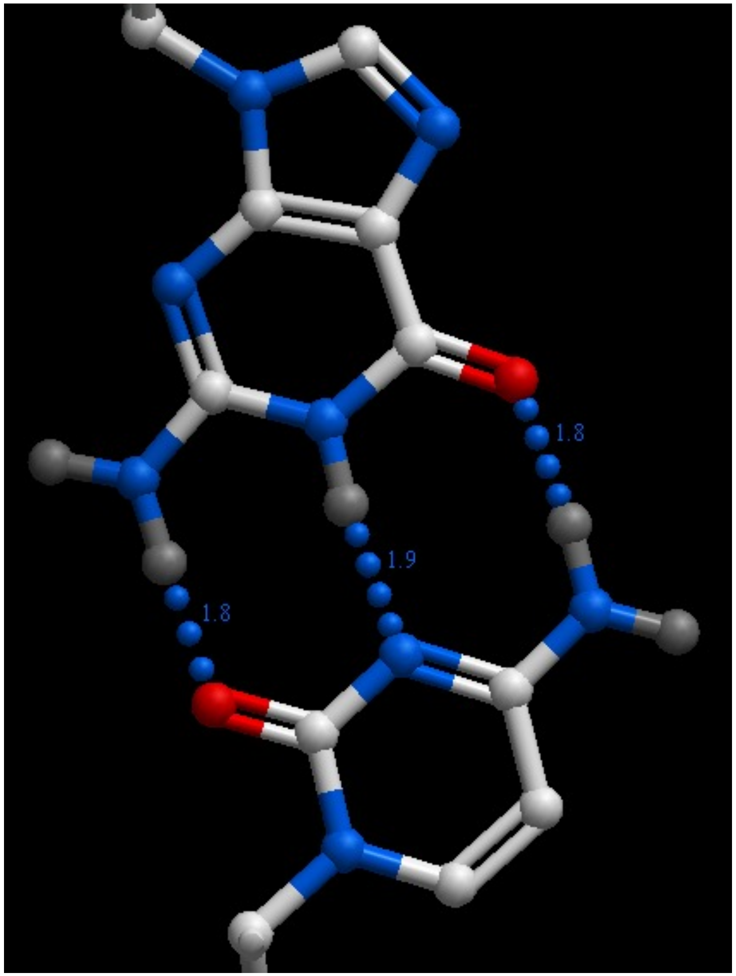
- Depends on the nature (element's electronegativity and covalent neighbors) of D and A
- Depends on DH--A distance. 1.6-2 strong, > 2. weak, >2.5=0.
- Depends on D-H-A$_{LP}$ angle: ideal geometry corresponds to 180° between 3 points: lone-pair (LP) of acceptor, the polar hydrogen, and its donor (at optimal distance)

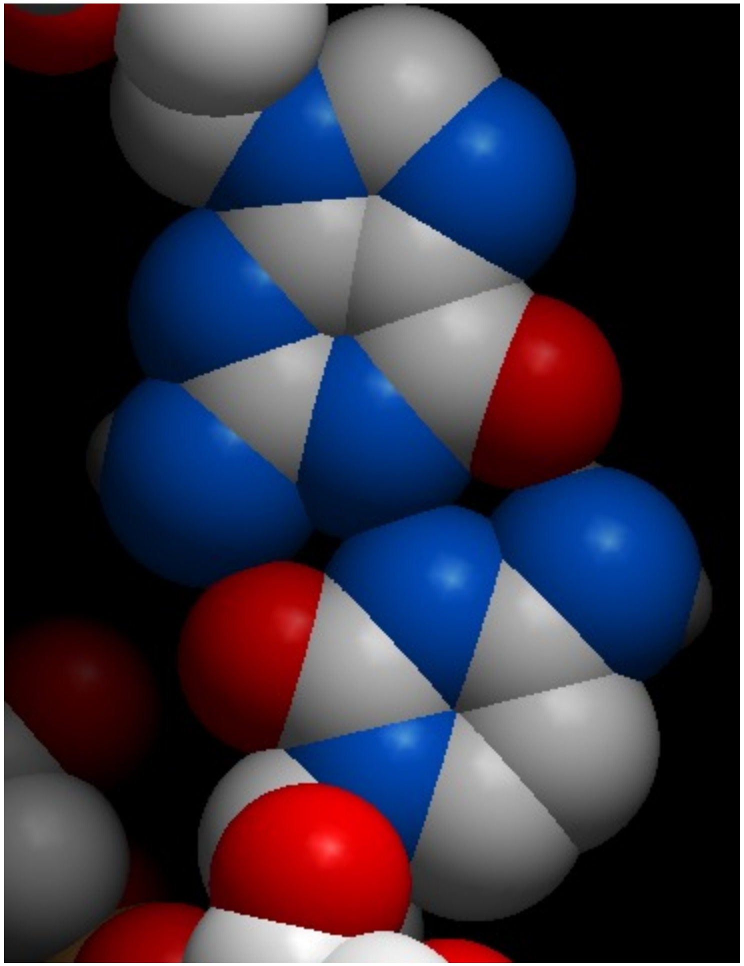


Neuraminidase with Tamiflu
Distance (O,H)=1.8A

Shorter interatomic distances

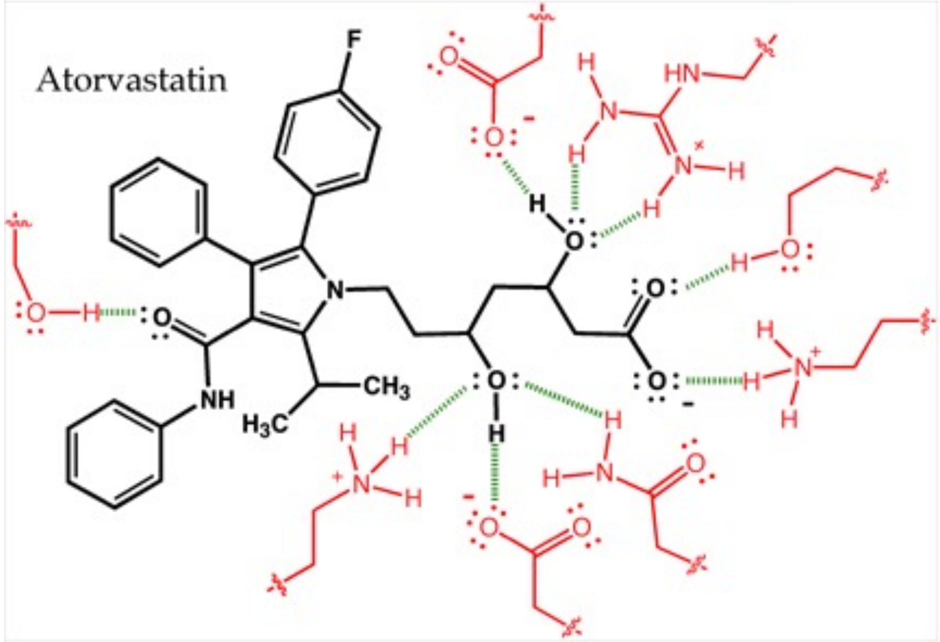
- Bonded Hydrogens are not even visible in CPK





Cooperativity of H-bonds

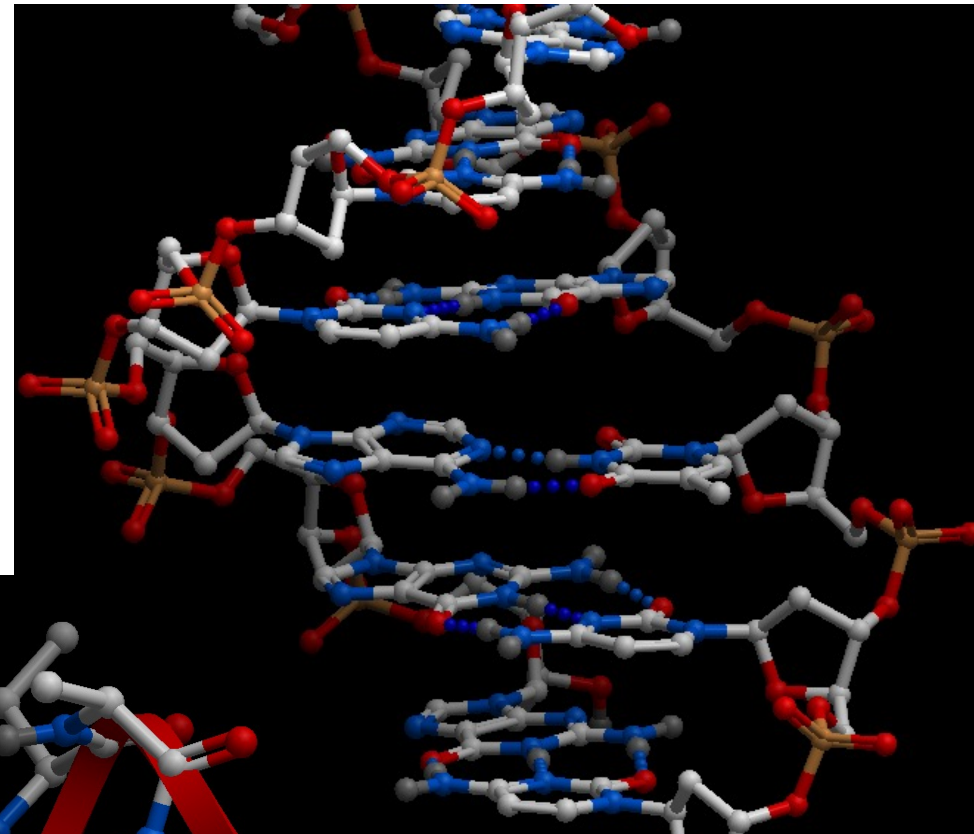
- **Cooperativity**. Once *one* hydrogen bond is formed, the probability of a *second* one may be *increased*, leading to an *increased* probability of a *third* forming, etc.
- This can lead to a very strong and stable set of bonds, even though it is made up of individually weak hydrogen bonds.
- This phenomenon is very common and important in the structure and function of both proteins and nucleic acids
- Reason: each bond increases polarization around HB-acceptor atom

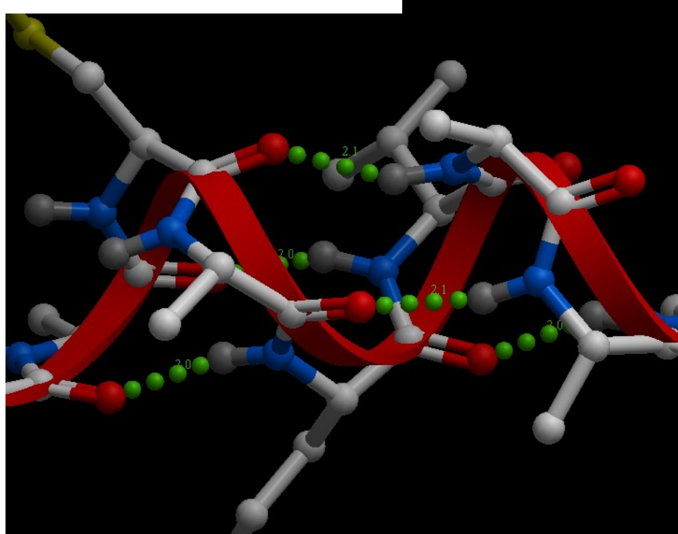


Target: 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase (HMGR, or HMG reductase)

Hydrogen bonds in DNA and proteins

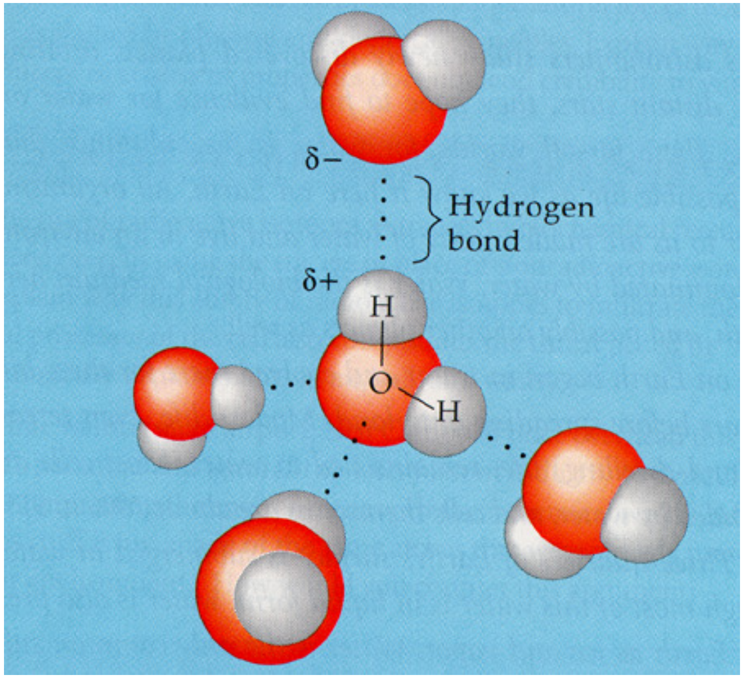
- Complementary bases in double stranded NA
- H-bonds define helices and β–sheets in proteins





Hydrogen Bonds in Water

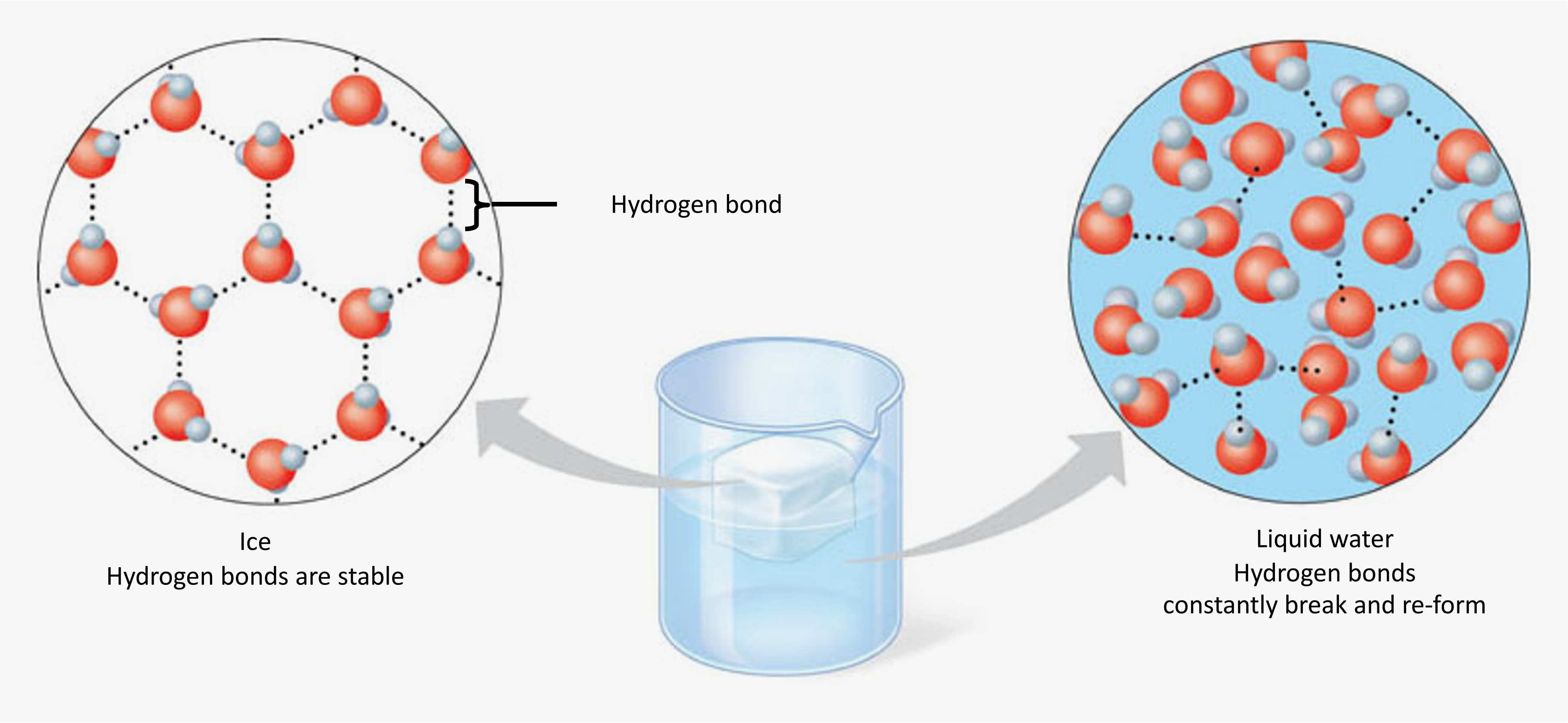
- Hydrogen bonds in water aver very strong.
- Up to four H-bonds are formed
- H-bonds are responsible for high boiling T of water
- $\Delta H_{vap} \approx 10$ kcal/mole (9.72)
- 3 to 4 bonds lost upon transition from water to vapor, it means that it is ≈ 2.5kcal/mol per bond



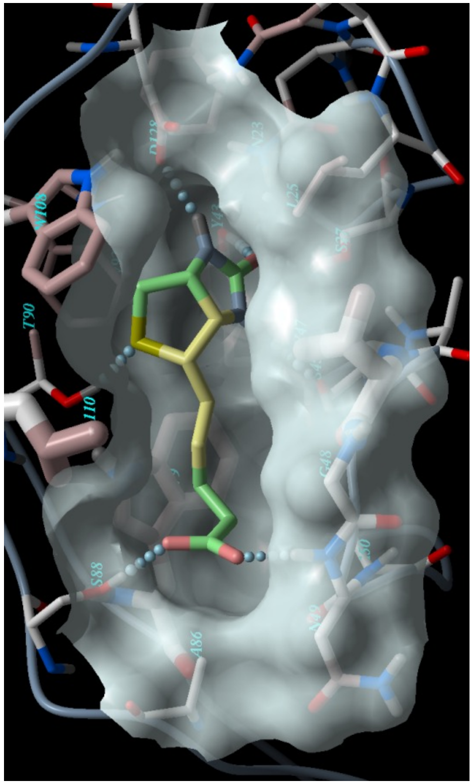
ΔH_{vap} = 40.657 kJ mol^{-1} at 100 °C

Ice is less dense than water

- Ice (4 bonds per molecule) and water (3 to 4)



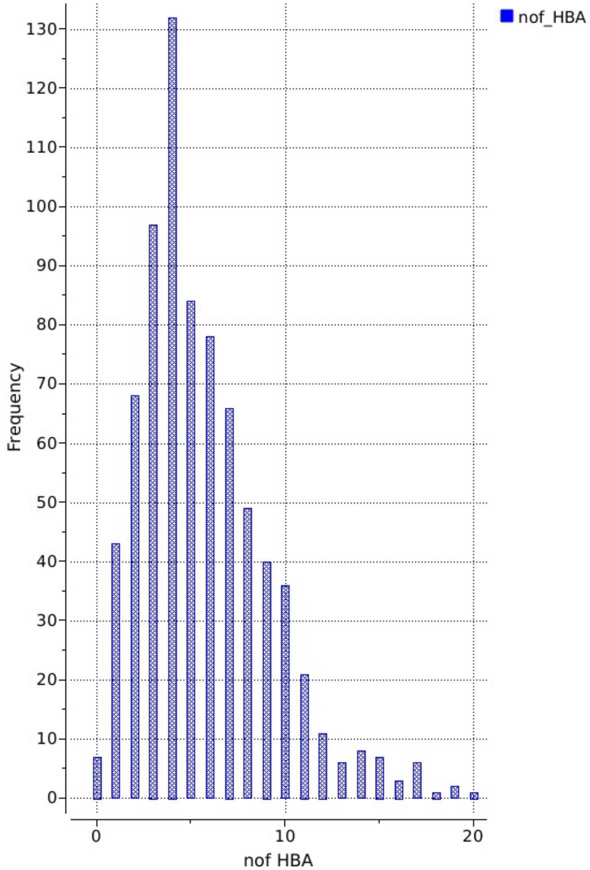
Hydrogen Bonds in Drug Complexes

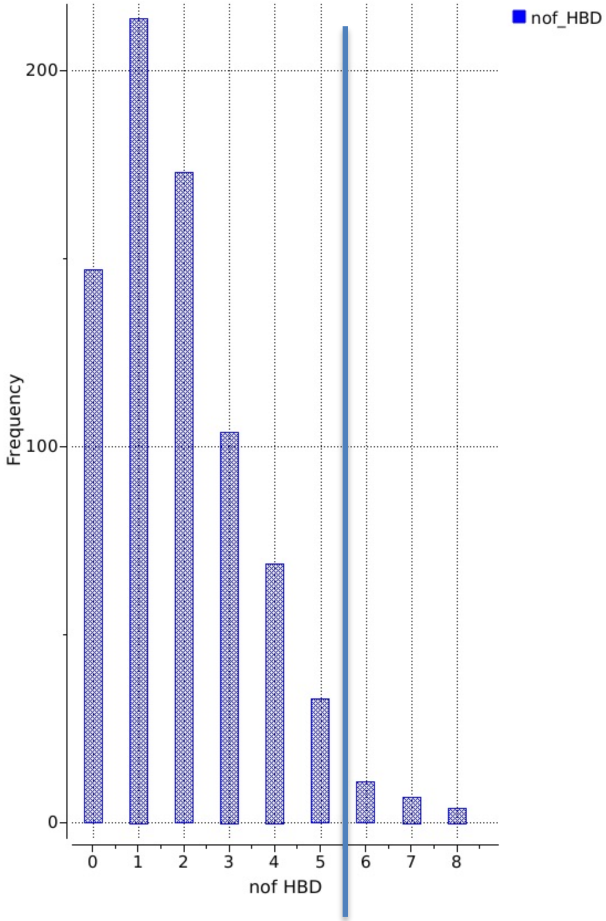


- Hydrogen bonds can be inter- and intra- molecular
- Energies: if we exclude Fluorine, the strength of a hydrogen bond is 2 -7 kcal/mol
- Water vs receptor: Drug – receptor hydrogen bonds may or may *not* be stronger than drug-water bonds. The buried ones matter more.
- *Unsatisfied* buried hydrogen bonding donors or acceptors are strongly destabilizing. Fixing that problem can improve K_d up to ***100 fold*** (~2.8 kcal/mol = 2*1.4 kcal//mole).
- A H-bond can stabilize by 0 to 1.5 kcal/mol, but even non-stabilizing H-bonds may improve **specificity**

Distribution of H-bonds in Drugs

Distribution of hydrogen bonding donors and acceptors/donors in 676 oral drugs

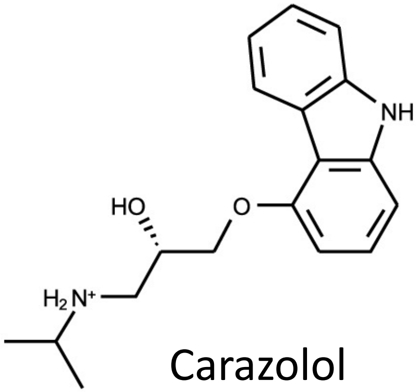




Hbond related Rule of 5 for Oral drug candidates:
- nHBD <= 5 (O,N,S with Hydrogen atoms)
- nHBA <= 10 (O, N, S atoms)

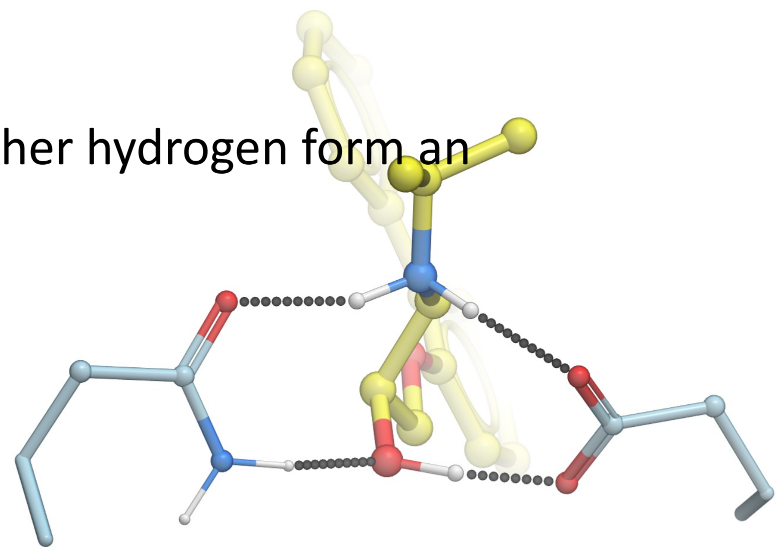
Hydrogen bonding

- ***Problem***: In target-drug interactions, a hydroxyl (-OH) group can participate in hydrogen bonds (HB) as follows:
  - A. a HB donor only
  - B. a HB acceptor only
  - C. a HB donor and a HB acceptor at the same time
  - D. either a HB donor or a HB acceptor, but not both
  - E. a hydroxyl group does not form HBs



Carazolol

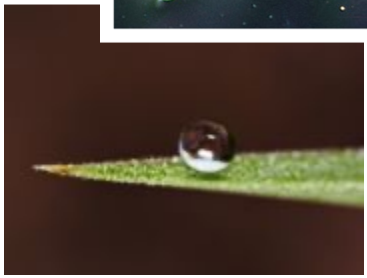
- ***Answer***:
  - In OH, O still has **two lone pairs**
  - It can donate a hydrogen and accept another hydrogen form an outside donor simultaneously



Hydrophobicity

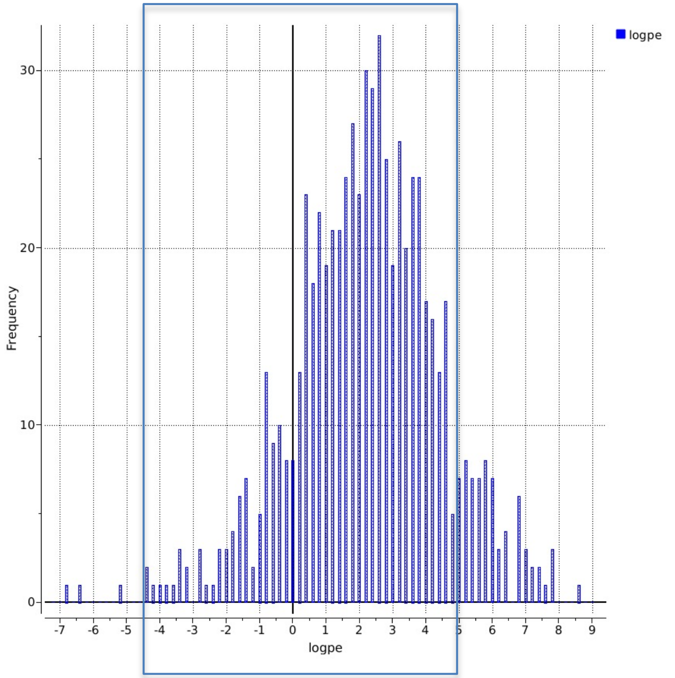
"Fear of water" groups in drugs

- The main contributor to the drug binding free energy
- However, does not provide binding specificity (all grease is alike).
- from the Greek *(hydros)* "water" and *(phobos)* "fear"
- Hydrophobic molecules tend to be nonpolar and thus prefer other neutral molecules and nonpolar solvents.
- Hydrophobic molecules, i.e. alkanes, oils, fat, in water often cluster together.
- Hydrophobic ~ lipophilic



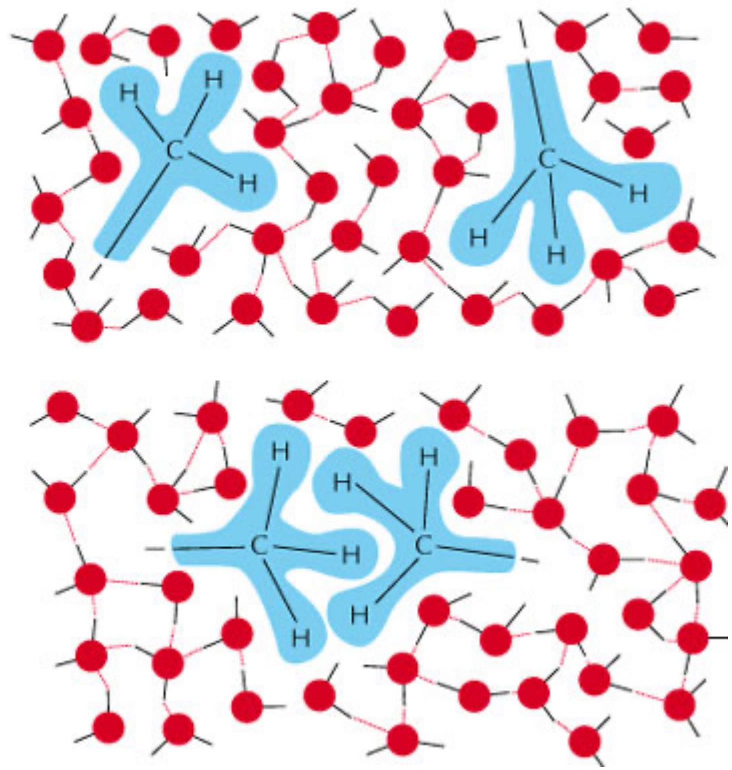
Dew drop on a hydrophobic leaf surface

Experimental LogP values of 676 drugs



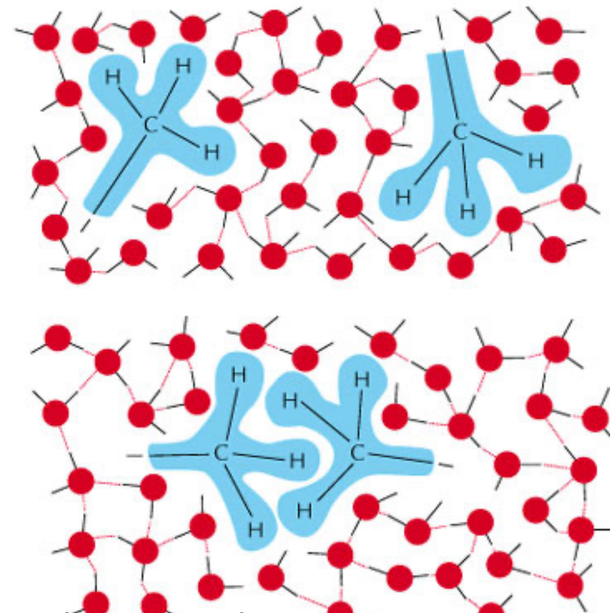
Hydrophobic interactions

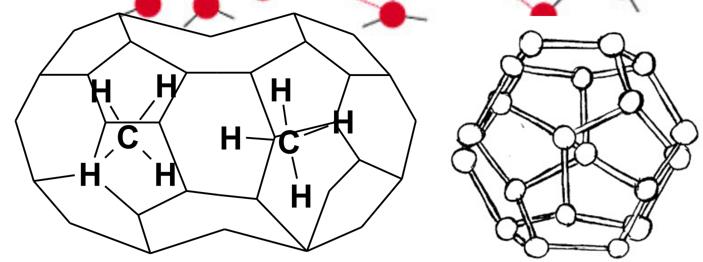
- At a boundary of a hydrophobic molecule water molecules lose free energy.
- Bringing two hydrophobic surfaces together reduces that boundary area.
- The more polar the solute molecule, the easier it goes into water (less hydrophobic).
- Methane (CH4) gas to water:
- ΔG^{o}= 6.5 kcal/mol, (for Na+ ≈ –100 kcal/mol),
- $\Delta G^{\text{Me-Me in water}} \approx$ 0.5 kcal/mol



Hydrophobic interactions : origin

- Entropic detriment: the possible orientations of water molecules in the first hydration shell of a hydrophobic solute are limited: the water molecules can not have their hydrogen-bond donating or accepting groups point toward the solute without losing one of their hydrogen bonds.
- Molecules forming the water cages have reduced entropy (frozen surfaces): reducing the number of 'frozen surfaces' leads to the hydrophobic effect



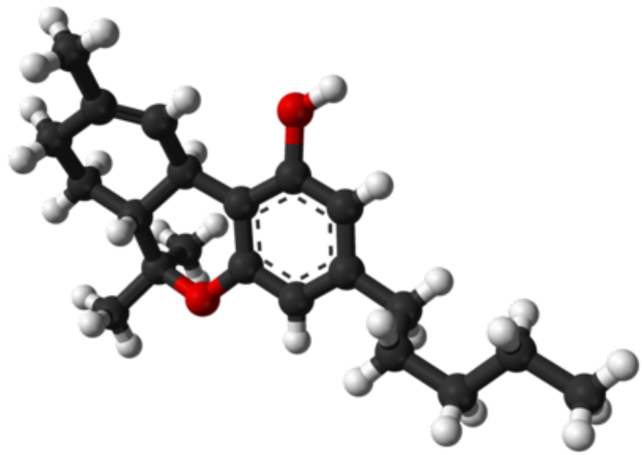


$$\Delta E_{hp} = \sigma \, \Delta \, Area$$

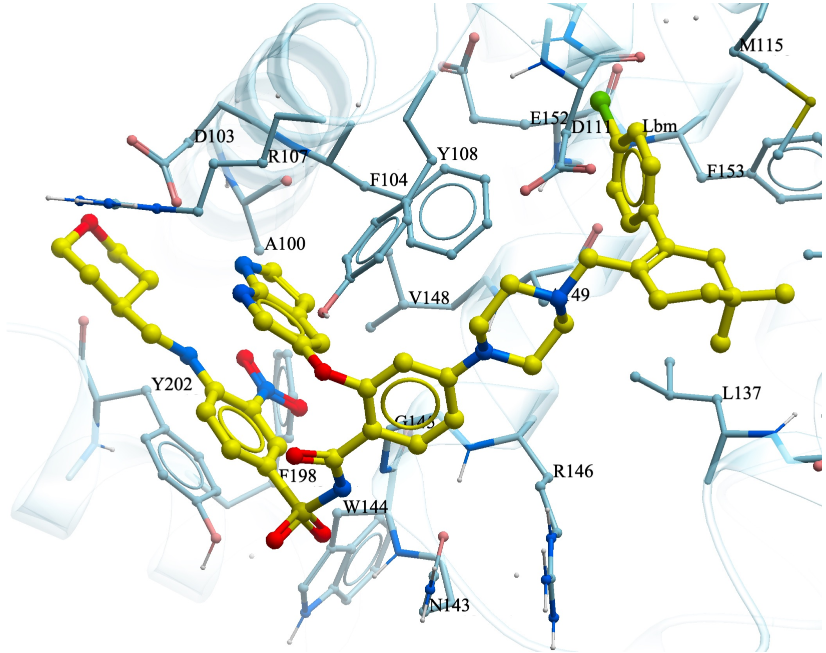
$$\Delta \, Area = A_{complex} - (A_{drug} + A_{target})$$

Drugs that are too hydrophobic

- **Tetrahydrocannabinol (THC), LogP=5.65**



- **Venetoclax, cLogP is close to 7, subnanomolar Ki (0.01 nM)!**



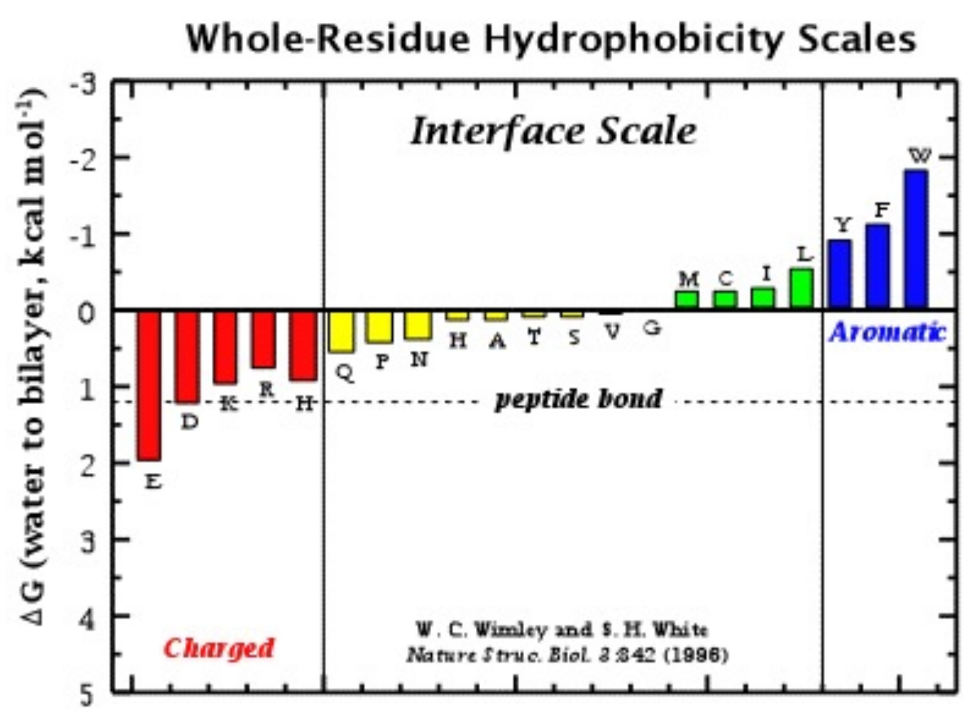
Energy and concentration

- 0.6 kcal/m ↔ *e* times
- 1.4 kcal/m ↔ 10-fold
  - 2.8 kcal/m : 100 fold
  - 14 kcal/m : 10^{10} fold
- Conclusion: add a hydrophobic group and decrease the needed drug concentration 10 times!

$$\frac{[B]}{[A]} = e^{-\frac{\Delta G_{AB}}{RT}}$$

Proteins: bury hydrophobic residues inside the protein core

Drugs: bury hydrophobic groups by the hydrophobic patches of pockets



Hydrophobicity increases with temperature

- Proteins denature at both high and low temperatures for different reasons
- Stingray venom proteins are heat-labile, botulinum toxin is denatured at T>80 °C (176 °F)
- Therapeutic mABs may denature at storage temperatures near −20°C (pH 6.3) [Lazar et al., **Cold denaturation of monoclonal antibodies** *MAbs*. 2010 Jan-Feb; 2]

Stingray bite treatment (45 °C)

$$-T\Delta S$$

- Because the hydrophobic effect is, at least in part, entropic, it becomes stronger at higher temperatures!
- Cold denaturation of proteins.
- ***Lower*** **solubility of hydrophobic substances at** ***higher*** **temperature**

FDA approved therapeutic antibodies

Abciximab ReoPro
Adalimumab Humira
Alemtuzumab Campath
Basiliximab Simulect
Belimumab Benlysta
Bevacizumab Avastin
Brentuximab Vedotin
Canakinumab Ilaris
Cetuximab Erbitux
Certolizumab Cimzia
Daclizumab Zenapax
Denosumab Prolia/Xgeva
Eculizumab Soliris
Efalizumab Raptiva

Gemtuzumab Mylotarg
Golimumab Simponi
Ibritumomab Zevalin
Infliximab Remicade
Ipilimumab Yervoy
Natalizumab Tysabri
Ofatumumab Arzerra
Omalizumab Xolair
Palivizumab Synagis
Panitumumab Vectibix
Ranibizumab Lucentis
Rituximab Rituxan/Mabthera
Tocilizumab Actemra/RoActemra
Tositumomab Bexxar
Trastuzumab Herceptin

Review of Energy Contributions to the non-covalent Binding Energy

- **q-q**: Coulomb: (+) or (-) , strong in non-polar medium and weak in water. Long range (r^{-1}).
  - C=332 (kcal Å/mole Z-charge units)
- **q-water**: *Ion and (induced) dipole* Solvation. Born energy, Large.
- **D-H..A**: H-bonds. Medium, short range.
- **Atom-Atom**: Van der Waals interaction Weak (< -0.2 kcal/mole per pair of atoms), but many. Short range (r^{-6}).
- **Apolar-Apolar** in water: Hydrophobic energy

$$E_{el} = C\frac{q_1 q_2}{\varepsilon r}$$

$$E^{solv}_{m\text{-}w} = \frac{Cq^2}{2r_q}\left(\frac{1}{\varepsilon_w} - \frac{1}{\varepsilon_m}\right)$$

$$E_{hb} = f(r_{HA}, \alpha_{A_{LP}HD})$$

$$E_{vw} = \frac{A}{r^{12}} - \frac{B}{r^6}$$

$$E_{hp} = \sigma \cdot Area$$

$$\Delta E_{hp} = \sigma\, \Delta\, Area$$