Non-covalent interactions

Electrostatics, Solvation, Transfer to a membrane or to a solvent, (continued)

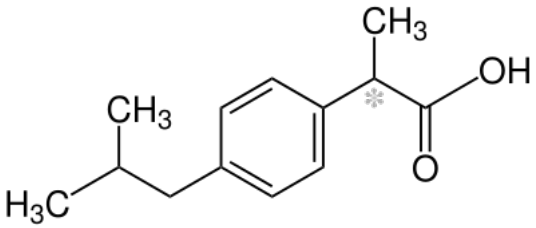
Types of electric charges in drugs

- Permanent formal charges due to covalent structure and [e-] [p+] balance

- **pH**-dependent Charges due to acid-base equilibrium:

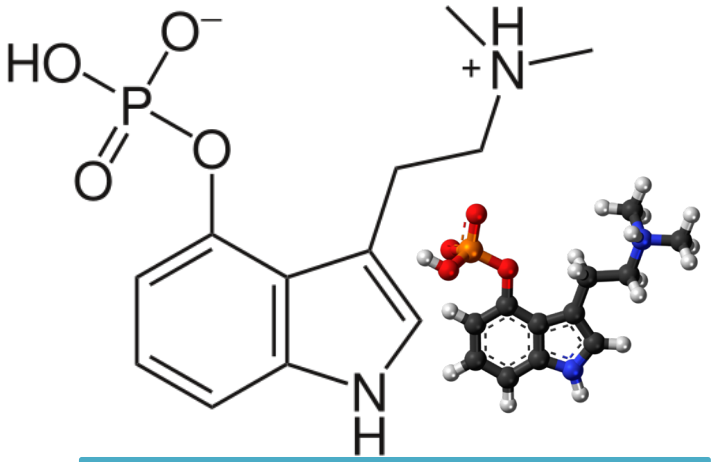
  $[AH] \leftrightarrow [A^-] + [H^+]$

  $[BH^+] \leftrightarrow [B] + [H^+]$



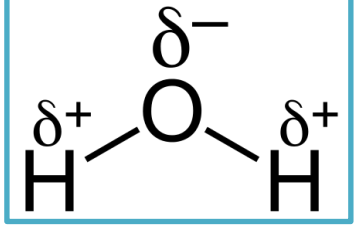
- A partial charge due to different electronegativity, e.g. water

- Transiently induced dipoles due to intermolecular interactions (van der Waals attraction)



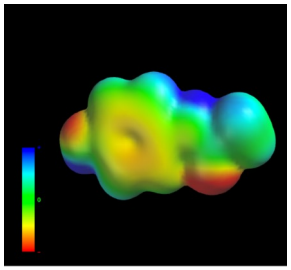
Psilocybin hallucinogen: illicit with the lowest harm, similar to serotonin

Ibuprofen: non-steroidal anti-inflammatory drug (NSAID)



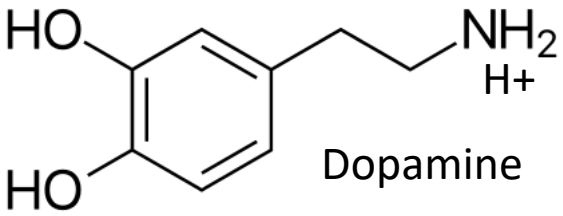
High solvation energies of ions and charged groups in a drug block passive permeability

- *Biological membranes are practically impermeable to anything charged*
- Even polar compounds can not go through



  ADME Lipinski's rule of 5
  - **No more than 5 hydrogen bond donors**
  - **No more than 10 hydrogen bond acceptors** (all N and O's)
  - MW < 500 Da; Log P < 5
  - Gut: **PSA < 120-140** A^2 , BBB: PSA < 70 A^2

- How Drug-N+ gets transported in a cell? Some amines are transported with special transporters, e.g. DAT, SERT, NET

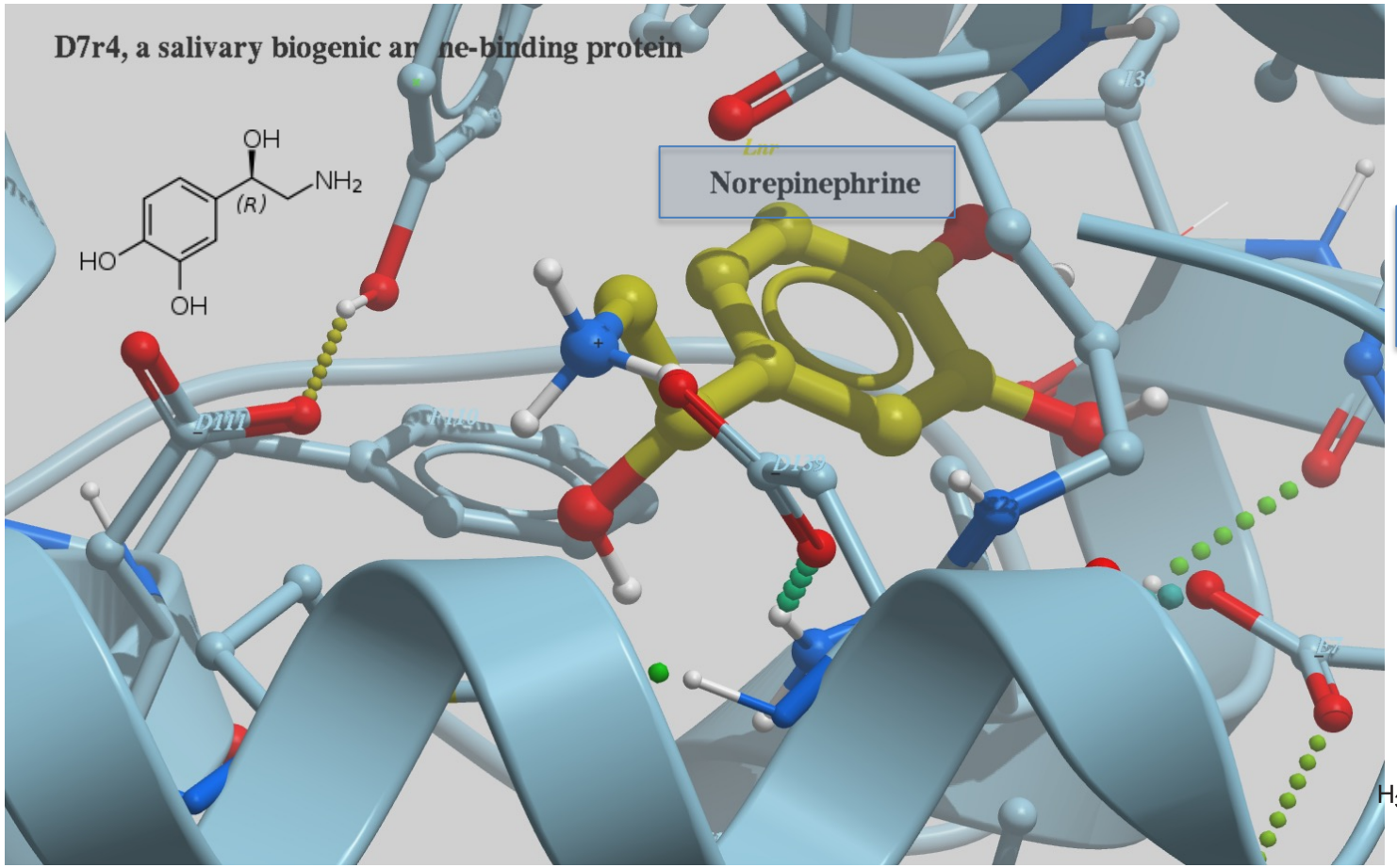


Dopamine

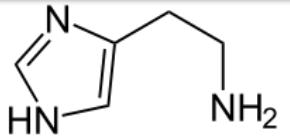
How mosquito calms you down?

biogenic amines and drugs

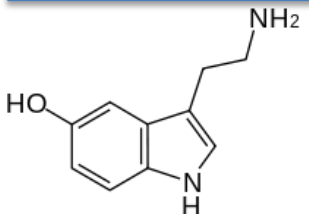
D7r **proteins** of the malaria vector Anopheles gambiae **binds** the **biogenic amines** serotonin, norepinephrine, and histamine with high affinity



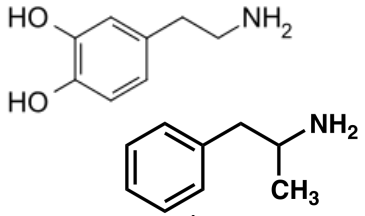
Histamine:
Arousal, inflammation



Serotonin
Happiness, appetite

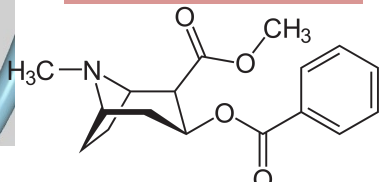


Dopamine
Reward. Lacking in Parkinsons, Schizophrenia



Amphetamine/Adderall

Cocaine inhibits reuptake of S,D,N

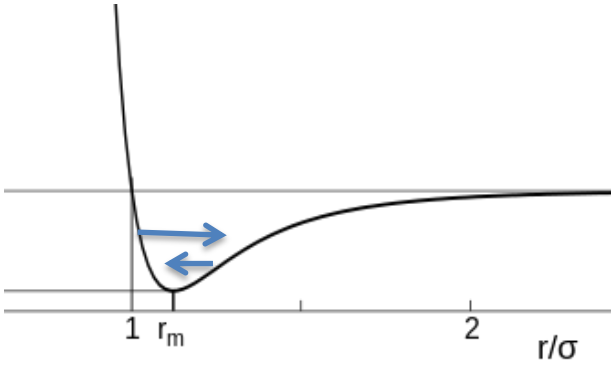


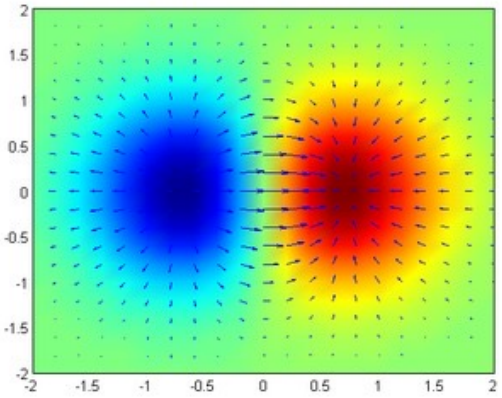
Energy and Force

$$U = C\frac{q_1 q_2}{\varepsilon r} \qquad dU = -\vec{F}d\vec{x} \qquad F = C\frac{q_1 q_2}{\varepsilon r^2}$$

$$\vec{F} = -\vec{\nabla}U$$

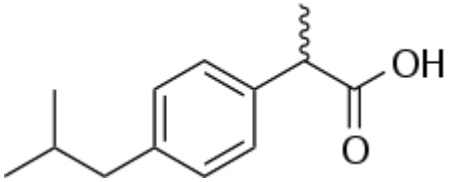
- Don't mix up Energy and Force
- Energy is primary, Force is literally a *derivative* of the Energy





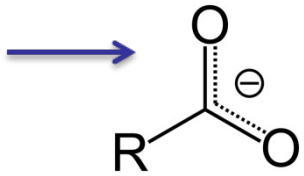
- Force is a negative *gradient* of the Energy function (a slope)
- Force causes instability and acceleration

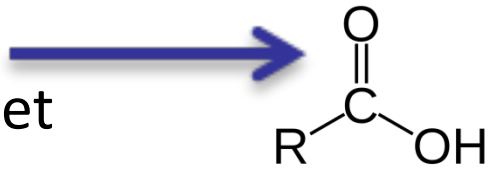
Charges in Drug Molecules



Ibuprofen, pKa=4.91

Which atoms in ibuprofen are charged?

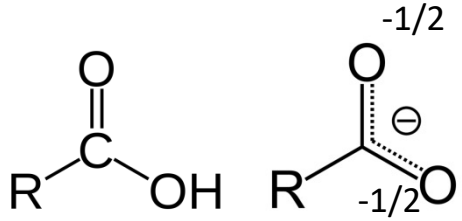


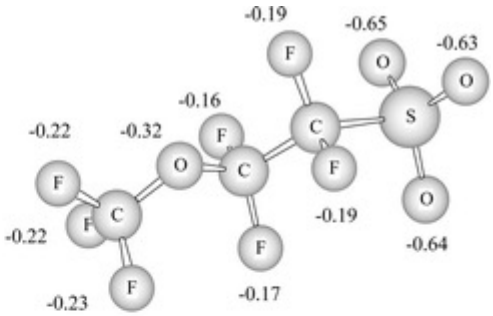


- At neutral pH ibuprofen's oxygens in solution are charged
- In acidic gastric acid the carboxyl gets uncharged
- The neutral form gets absorbed
- Then it gets charged again and binds to its target COX2
- In both charged and uncharged forms the electron density is redistributed with respect to the positively charged nuclei.
- The balance projected on the nuclei can be described as 'partial charges'.

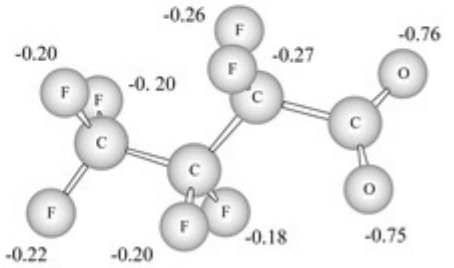
Formal and Partial atom charges

- Physical reality: a *molecule* can have a different number of protons and electrons. The **integer** difference gives the formal charge of the molecule.
- Formal Charge (FC): If an atom has more or less electrons in a molecule than in a free, neutral state, FC +1, -1, +2,..-1/2 … Fractions result from a redistribution of an integer number between several atoms
- Partial charges: the formal charge gets redistributed so that each atom gets an effective fractional charge. Another source of partial charges is due to the bond polarization, electrons moving closer to more electro-negative atom, e.g. in R-OH

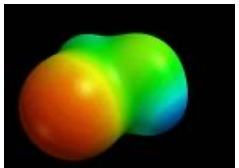




(b) $CF_3OCF_2CF_2SO_3^-$

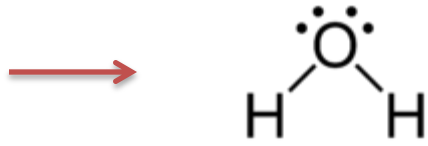


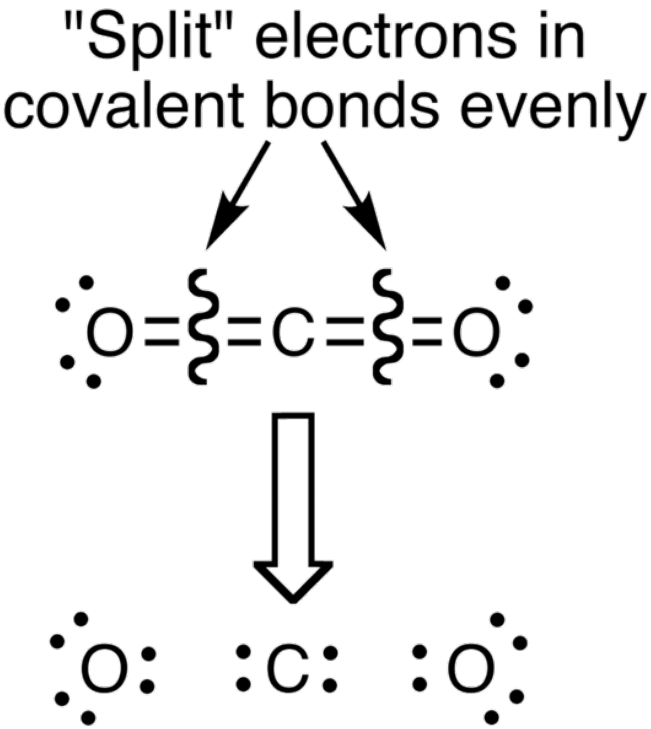
(d) $CF_3CF_2CF_2COO^-$



The Bond Splitting Method

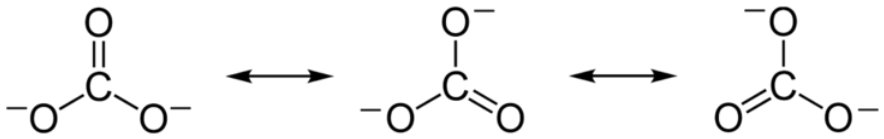
- Draw a Lewis structure, e.g.
- Split bonds into two electrons
- Count electrons and compare with the valence number (C:4, N:5, O:6,..)
- Be aware of the resonance structures creating fractional formal charges, e.g.



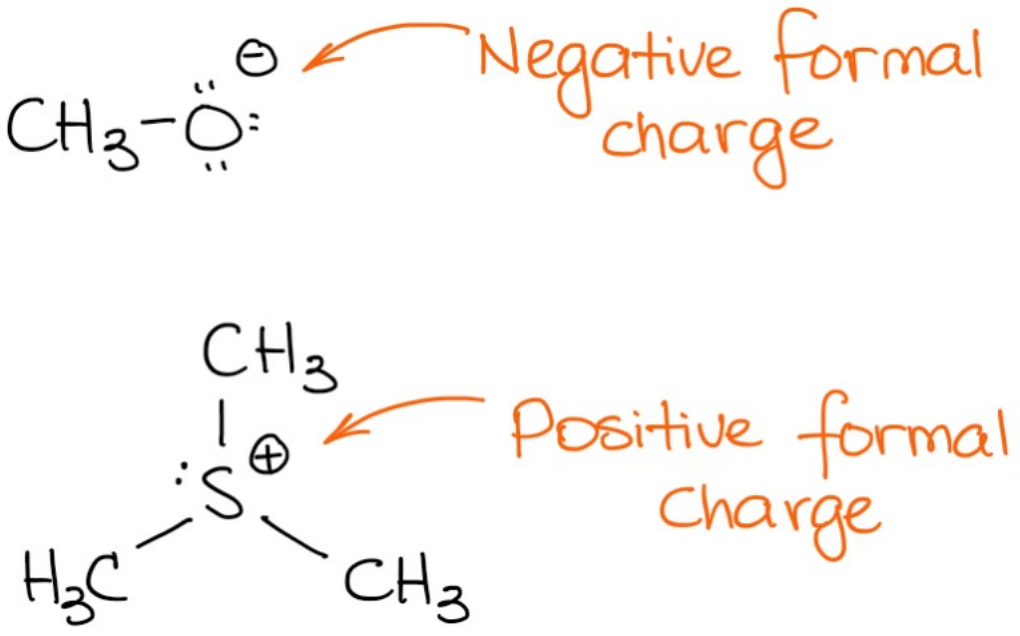


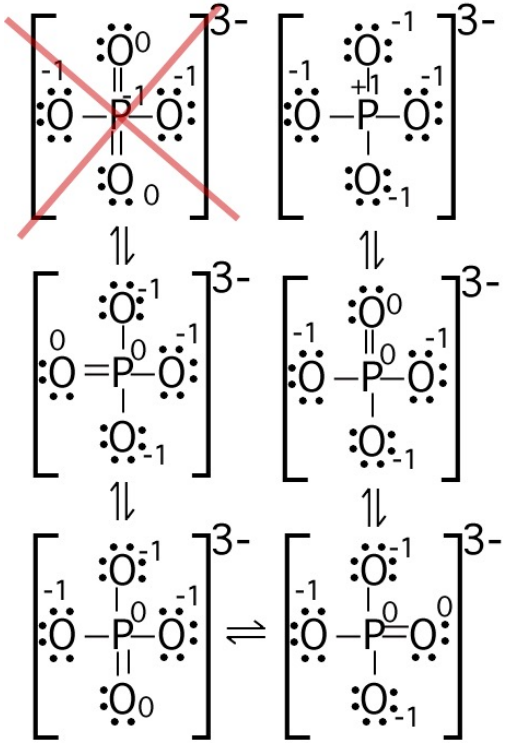
-1/2

-2/3



A phosphate PO_4^{3-} and biphosphate HPO_4^{2-}



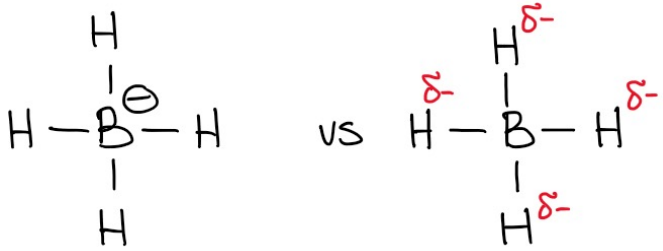


Resonance leads to fractional formal charges

Another formula

Formal Charge = + Valence Electrons
- ½ Bonding Electrons (#sticks)
- Nonbonding Electrons (#dots)

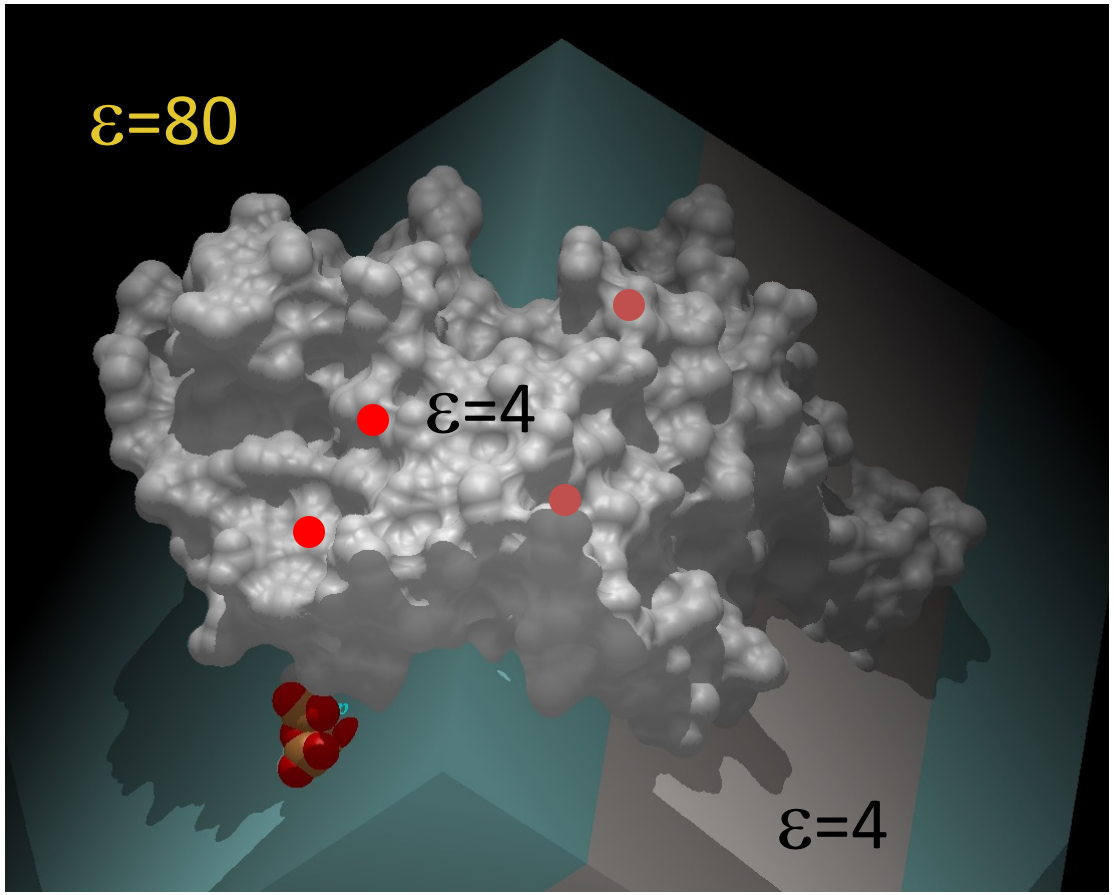
Valence e- : **C**(4), **N**,**P**(5), **O**(6), **F**,**Cl**,**Br** (7)



Formal charge vs Real electron distribution

In protein 3D structures the formal charges are at the surface, or form salt bridges

- N-,C-termini, Lys, Arg, Glu, Asp,some His, Cys .. have formal charges
- Water may be represented by a polarizable continuum, $\varepsilon = 80$
- Proteins, membrane, .. are geometric shapes with low dielectric medium ε=2-10



- Atomic charges are immersed in low dielectric medium at a particular locations inside or on the surface of the shapes

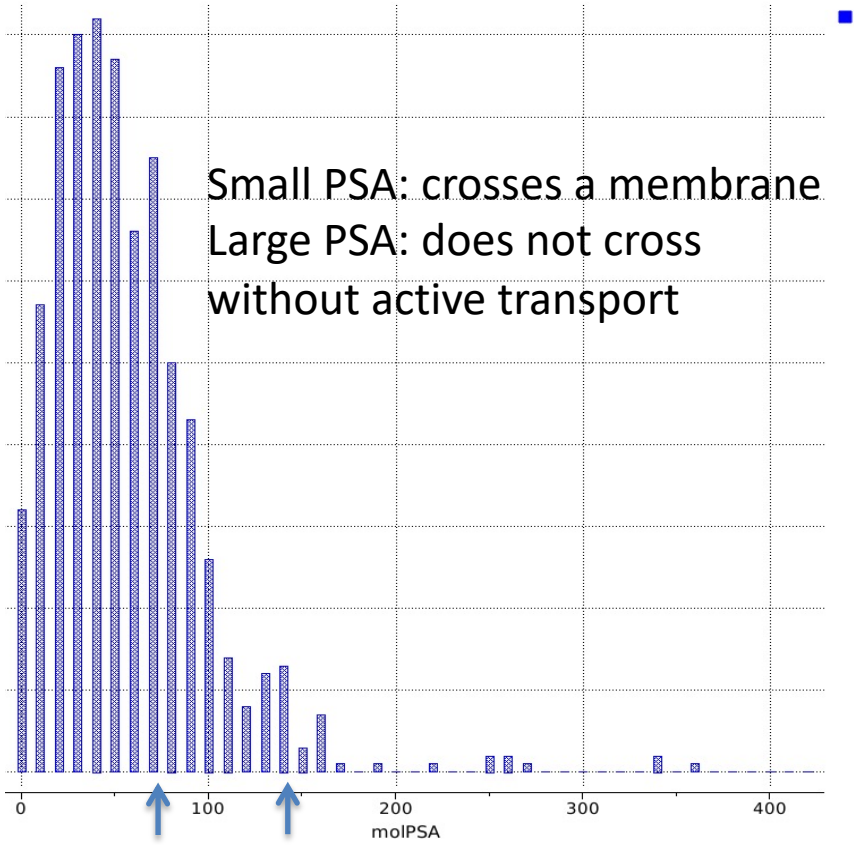
Polar Surface Area (PSA) for CNS and systemic drugs

- Charged compounds do not passively cross BBB

$$U_{transfer}^{molar} = 40\frac{Z^2}{r_q}[kcal/mol]$$

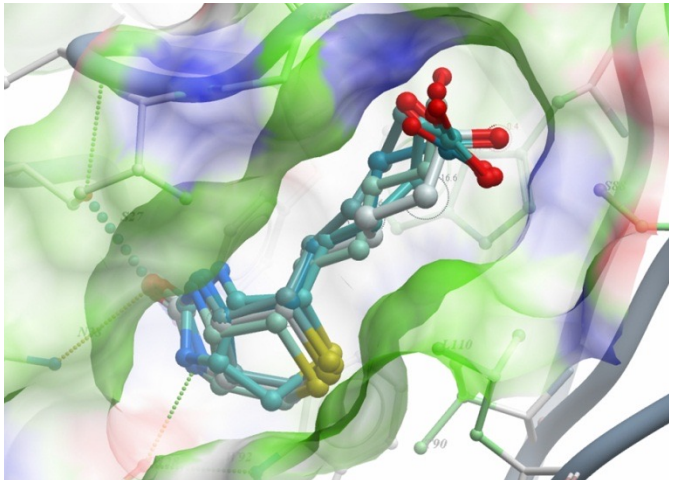
Even partial charges near polar atoms O,N,P,S affect membrane energy barrier:

- Oral: PSA < 140A^2 safe: PSA < 120A^2
- Blood-brain barrier: 40 < PSA < 75 (90?) A^2
- Additional CNS filters:
  - logP<3, logD<2, MW<360, HbD<0.5, basic pKa < 8
  - Need at least 4 ouf of 6

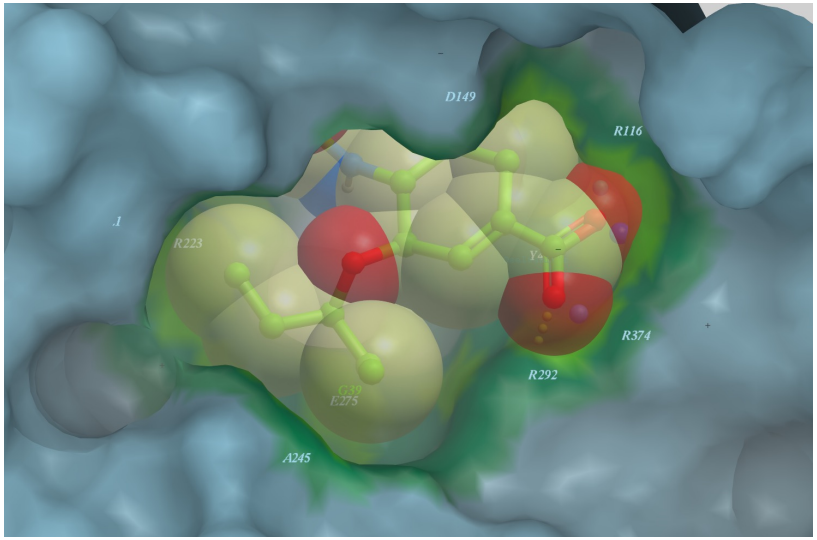


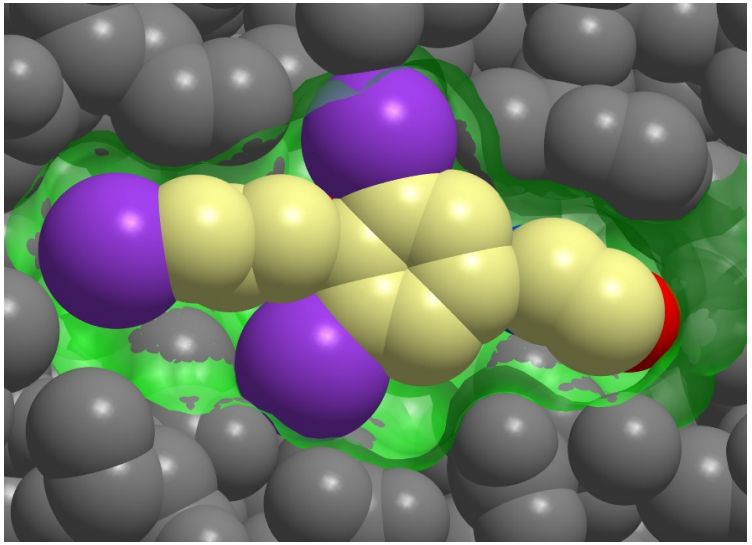
Van der Waals Interactions

- Drugs fit very well into their binding pockets
- They also fit well into water
- Why?



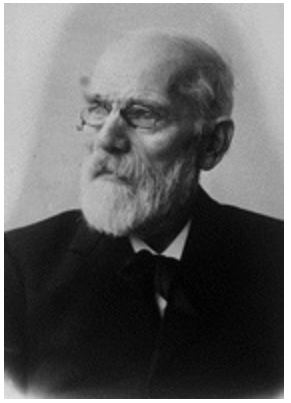
Oseltamivir with Flu-viral Neuraminidase



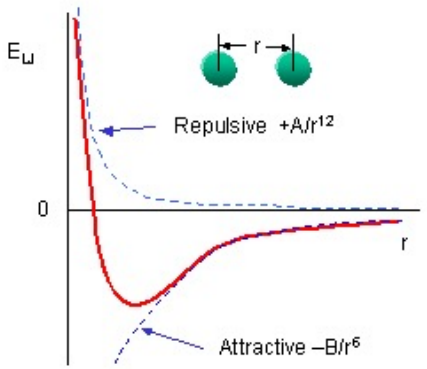


Van der Waals Interactions Attraction of neutral atoms due weak induced electrostatics.

- Interaction between any two atoms including the uncharged ones
- Consists of two parts:
  - Strong repulsion after atoms bump into each other (Pauli principle)
  - Attraction at contact distances and quickly vanishing weak attraction at larger distances (fluctuating dipoles)

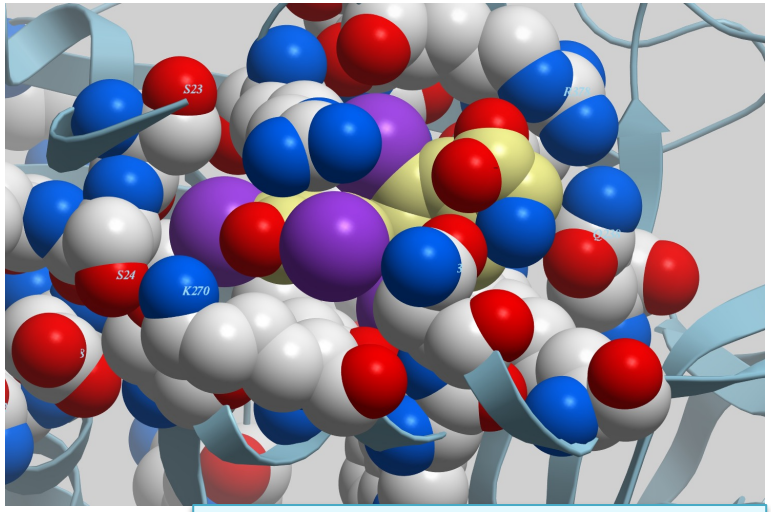


Johannes Diderik van der Waals

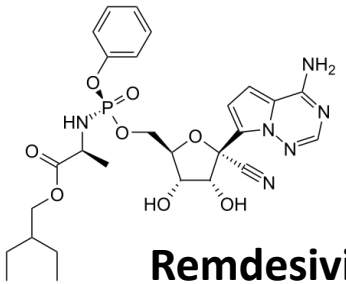


Atomic composition of drugs

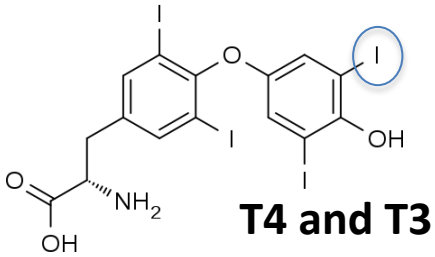
- **H,C,N,O** - in most drugs
- **S** in many (disulfiram)
- **P** eg in nucleoside analogs
- Halogens: **F, Cl, Br, I**
  - **F** Lipitor, 5-Fluorouracil, ..
  - **Cl** Midazolam, Gefitinib/Iressa, ..
  - **Br** Brompheniramine, Brodimoprim
  - **I** Diatrizoate, Levothyroxine, Amiodarone
- **B** (bortezomib), **Se** (Ebselen), **Au** (auranofin), **Co** (B12), ..



Thyroxine (T4) with the human *thyroxine binding globulin* (large iodines)

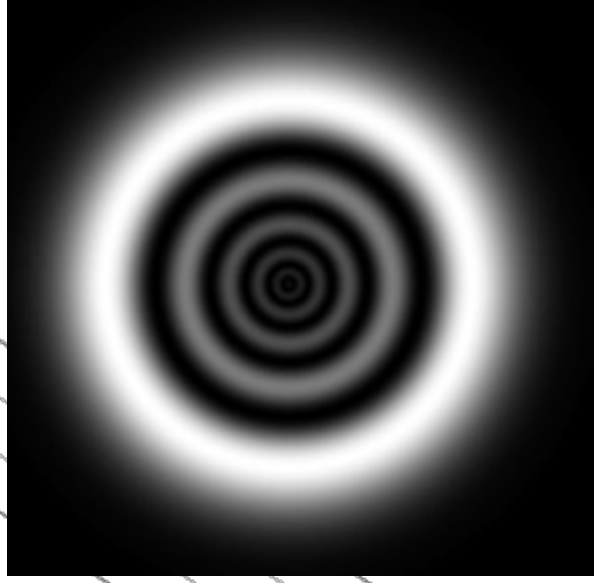


Remdesivir



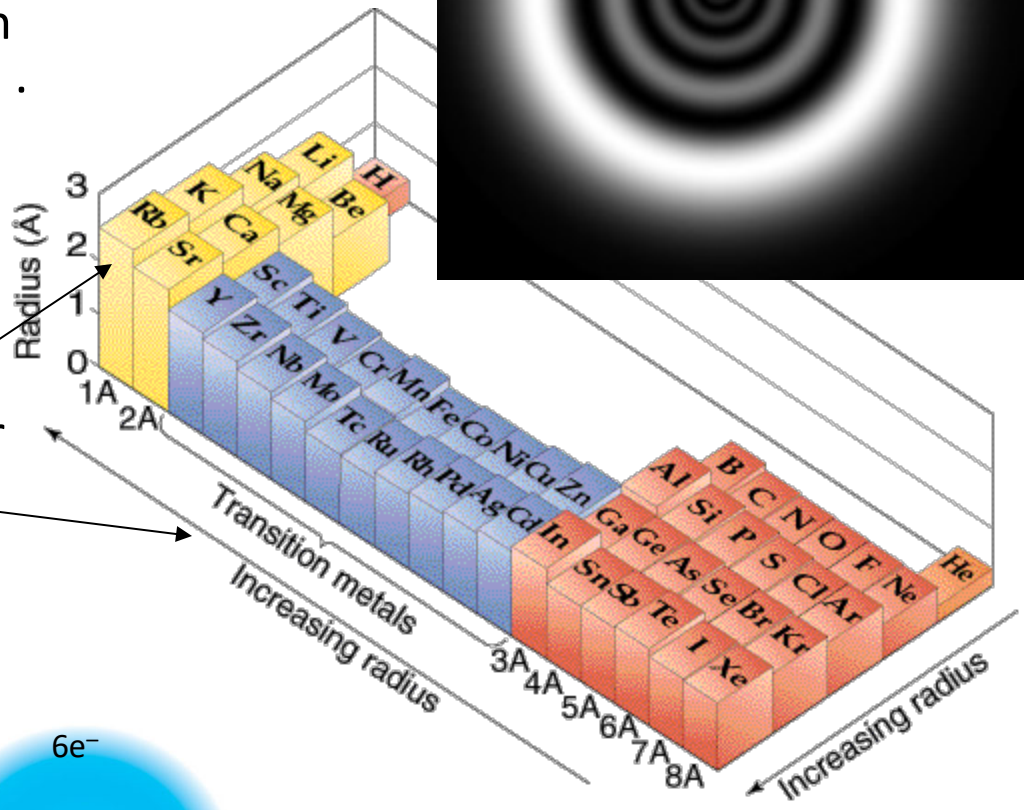
T4 and T3

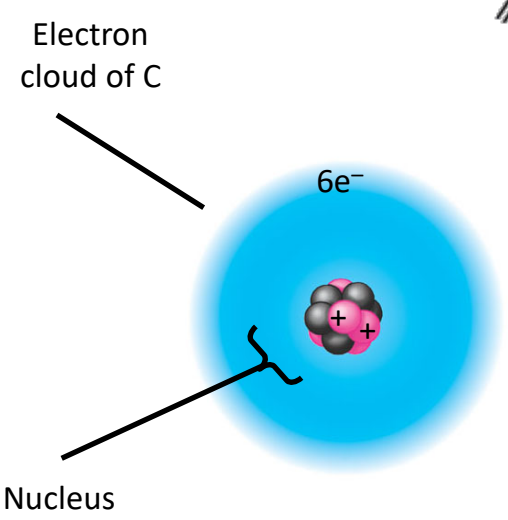
Van Der Waals radii



- Atom size depends on the electron orbitals interacting with the nuclei .
- The radius of an atom is not a uniquely defined property

- Radii increase as main quantum number, n, increases
- Radii decrease as effective nuclear charge increases
- Some radii in Angstroms:
  - H 1.
  - C 1.7
  - O 1.5
  - N 1.6
  - S 1.8

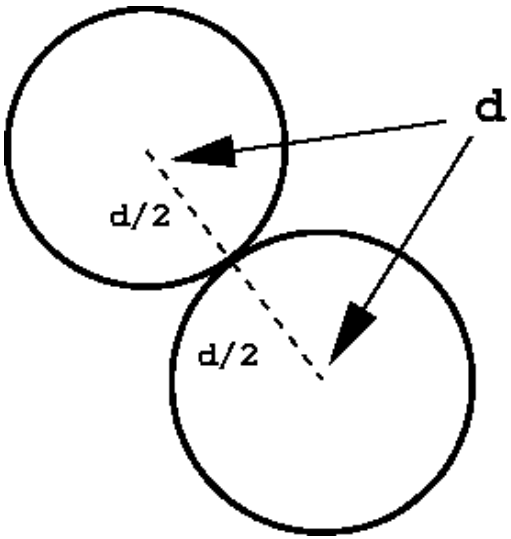


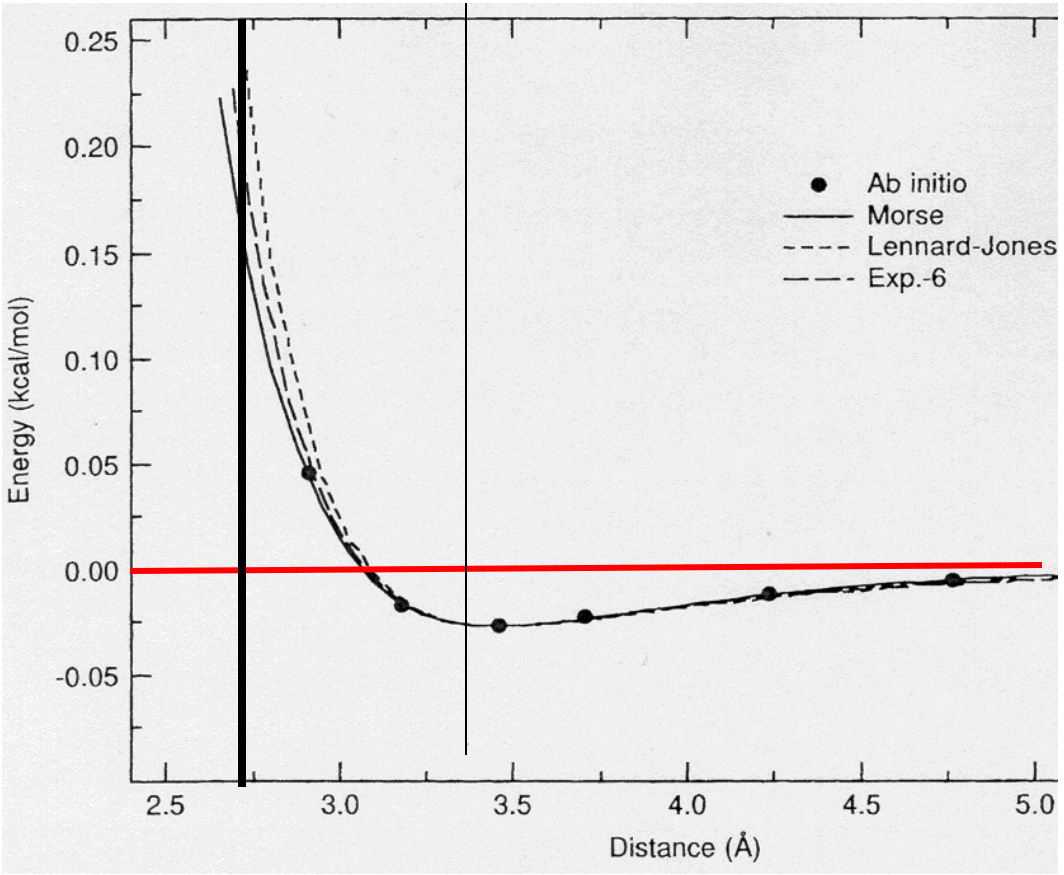


Repulsion is steep

- The Lennard-Jones form of the repulsive potential:

$$E_{vw}^{repulsion} = \frac{A}{r^{12}}$$

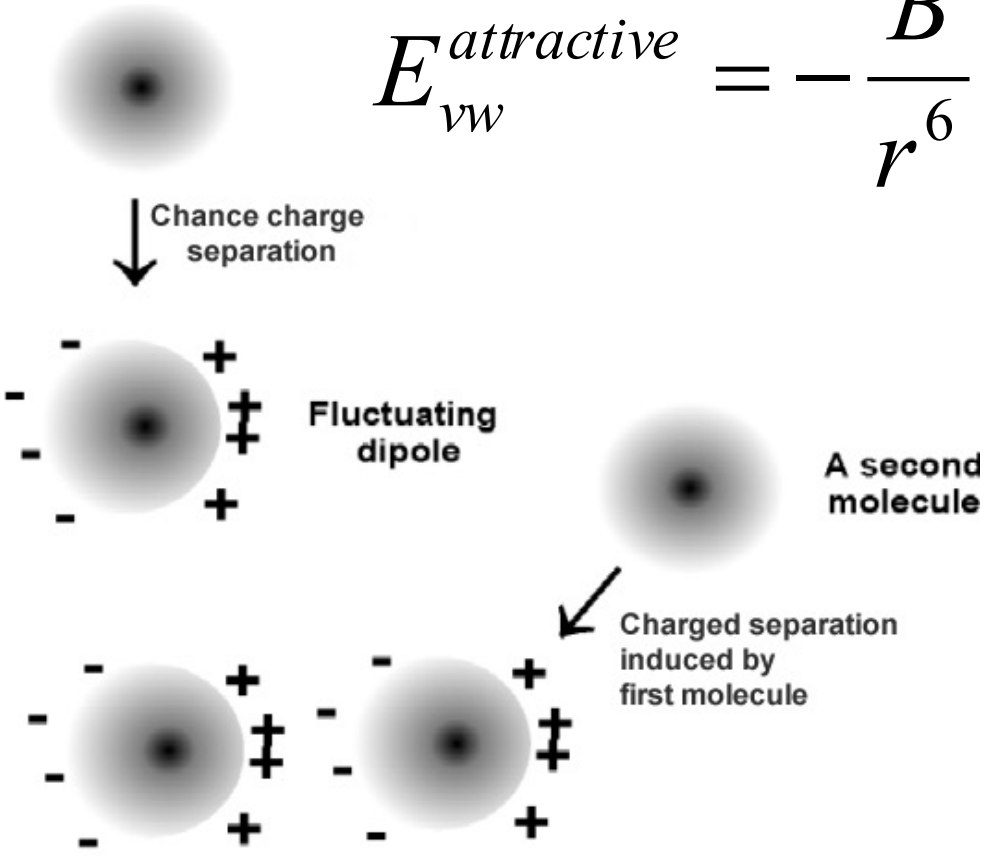




Van der Waal's attraction

- The weak attraction is due to two mutually fluctuating dipoles.

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



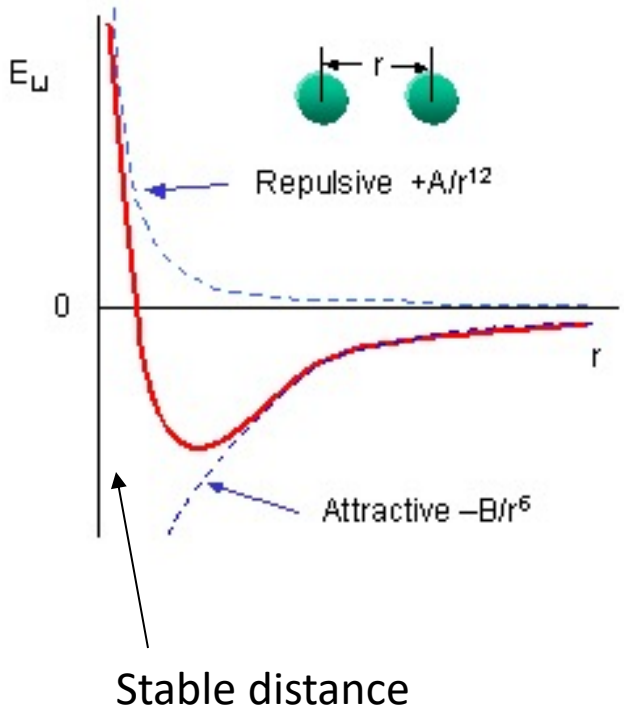
$$E^{Coulomb} = C\frac{q_1 q_2}{r}$$

Van der Waals energy approximation: Lennard Jones Potential

- Properties
  - Strong repulsion at $r < r_A + r_B$
  - Weak attraction at $r \approx r_A + r_B$
  - Zero at large distances

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

- A_{IJ}, and B_{IJ} values are tabulated for different *I* and *J* pairs of atom types, e.g. sp3 carbon and sp2 nitrogen.
- $E_{IJ} \approx -0.15$ kcal/ mol at the vw contact distances for two methane molecules (vaporization enthalpy of 2kcal/mole), n_packing ~ 12
- The attraction between two carbons at a distance of around 3.3A is around **30-40 cal/mol**



VdW and shape complementarity

- Van der Waals interactions are weak but there are many of atom pairs.
- Shape complementarity between a drug and a receptor