Force Fields

Molecular mechanics

- Model atoms as point-like particles
- Empirical approach
- Adjust model to fit reality, not theory
- The goal is to predict real structure & motion, not to explain it from first principles
- Example: Adjust the size/radius of atoms to reproduce experimental density instead of calculating the size from Quantum chemistry

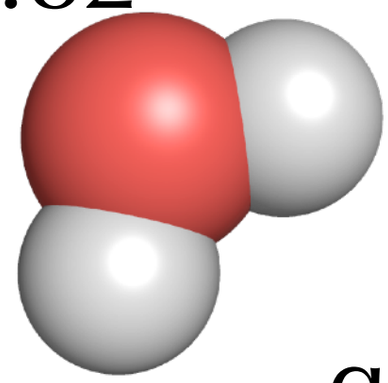
Simulation units

- Length: 1 nm = 10^{-9} m
- Time: 1 ps = 10^{-12} s
- Mass: 1 u = 1.66... x 10^{-27} kg
- Energy: mass x length^2 / time^2:
  1 kJ/mol = 1.66... x 10^{-21} J
- 1 mol = 6.022... x 10^{23}
- Charge (electron): 1 e = 1.602... x 10^{19} C
- Length: 1 Å (Ångström) = 10^{-10} m = 0.1 nm
- Energy 1 kcal/mol = 4.18 kJ/mol

Atom types

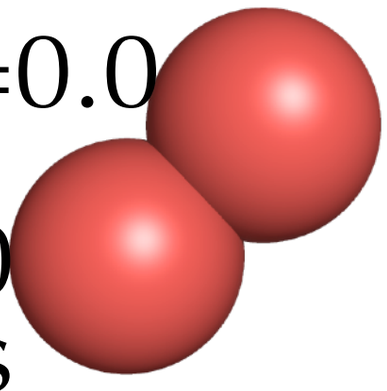
- That's easy right? Most liquids, polymers and proteins typically only contain C,H,N,O,S?
- Yes, but... that doesn't account for the electrons moving between atoms:

q=-0.82



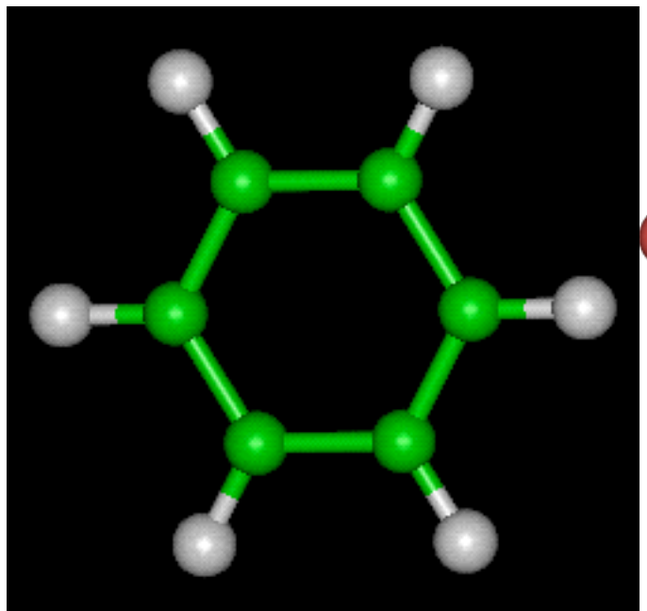
Water

q=0.0



q=0.0

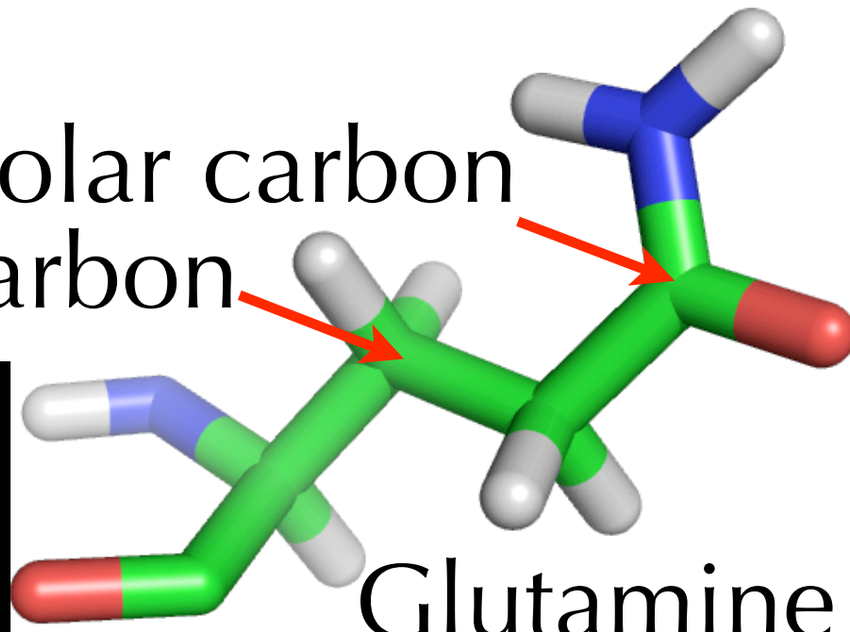
Oxygen gas



Benzene,
Aromatic carbons

Polar carbon

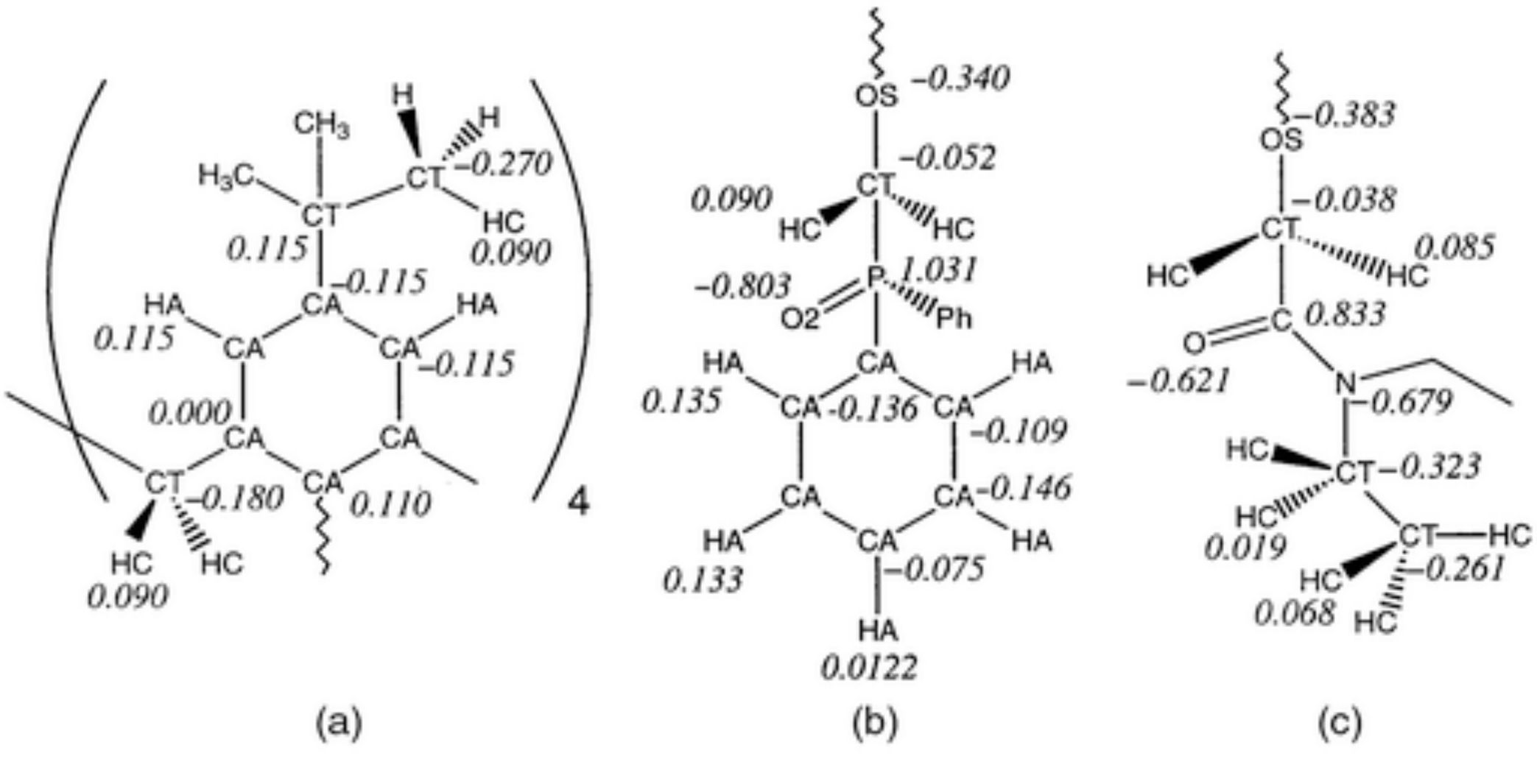
non-polar carbon



Glutamine

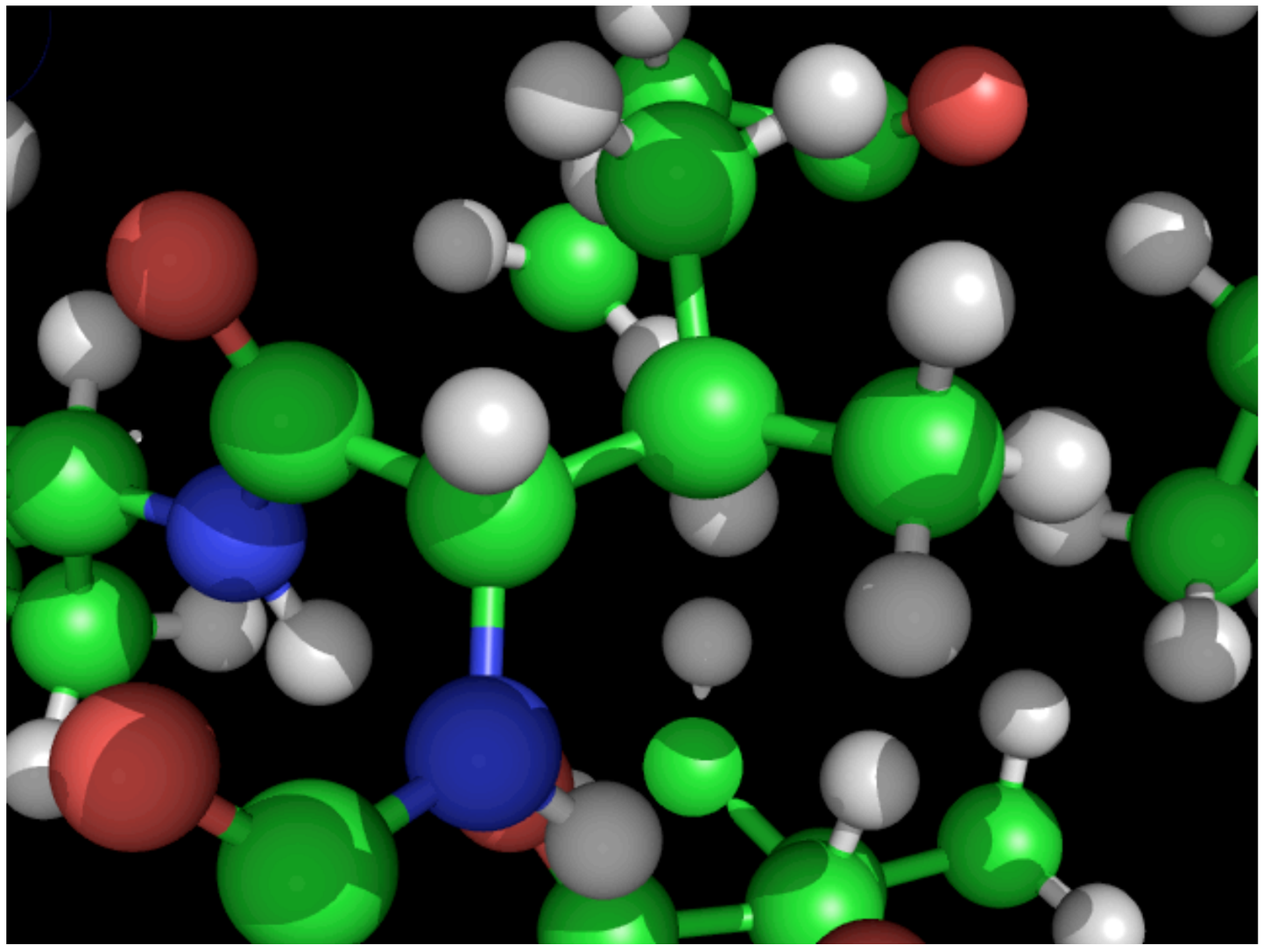
Atom types

- In molecular mechanics, we often use different "atom types" for a given element (e.g. carbon) depending on the environment

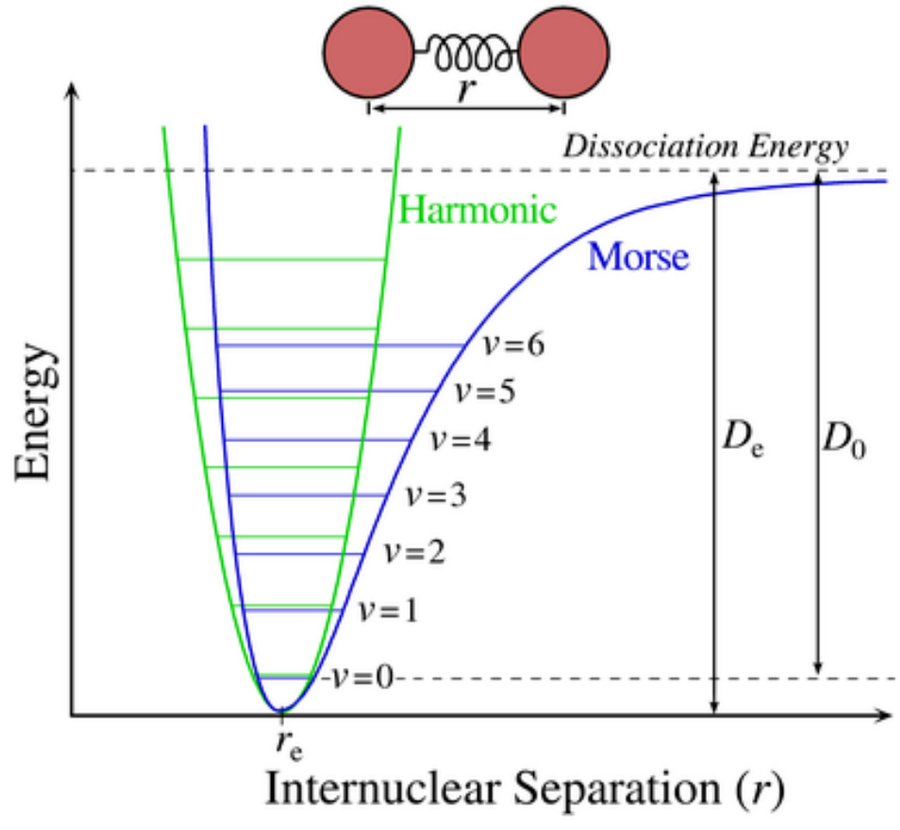


(a) (b) (c)

Bond stretching



- Vibration around average bond length
- Reality: QM oscillator
- Empirical description: Morse bond potential



Bond potentials

- Good illustration of the ideas used in molecular mechanics:
- In practice, bonds never deviate far from the equilibrium value (say, max 5-10%)
  - exp(x) is expensive/slow to calculate
  - Most molecular mechanics models select to use a simple harmonic function instead:

force constant

current bond length

$$U_b(r) = \frac{k_b}{2}(r - r_0)^2$$

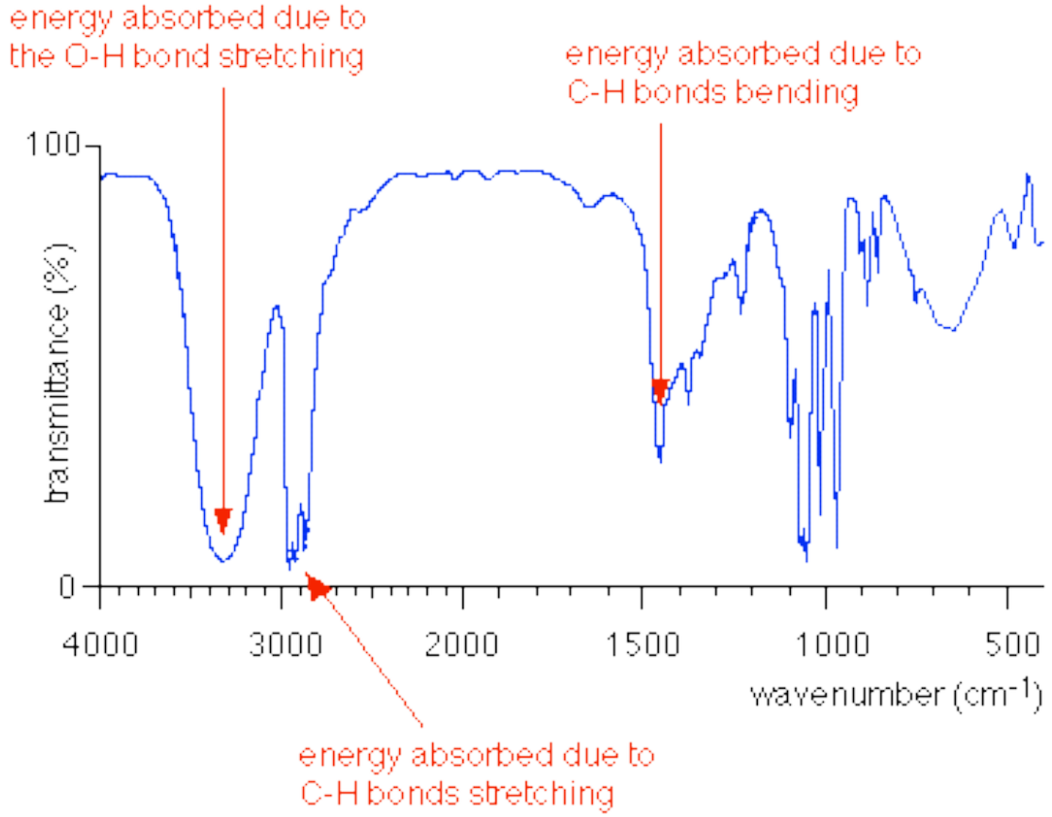
average bond length

Bond parameters

- First principles:
  Quantum chemistry
    - Surprisingly hard, but possible today

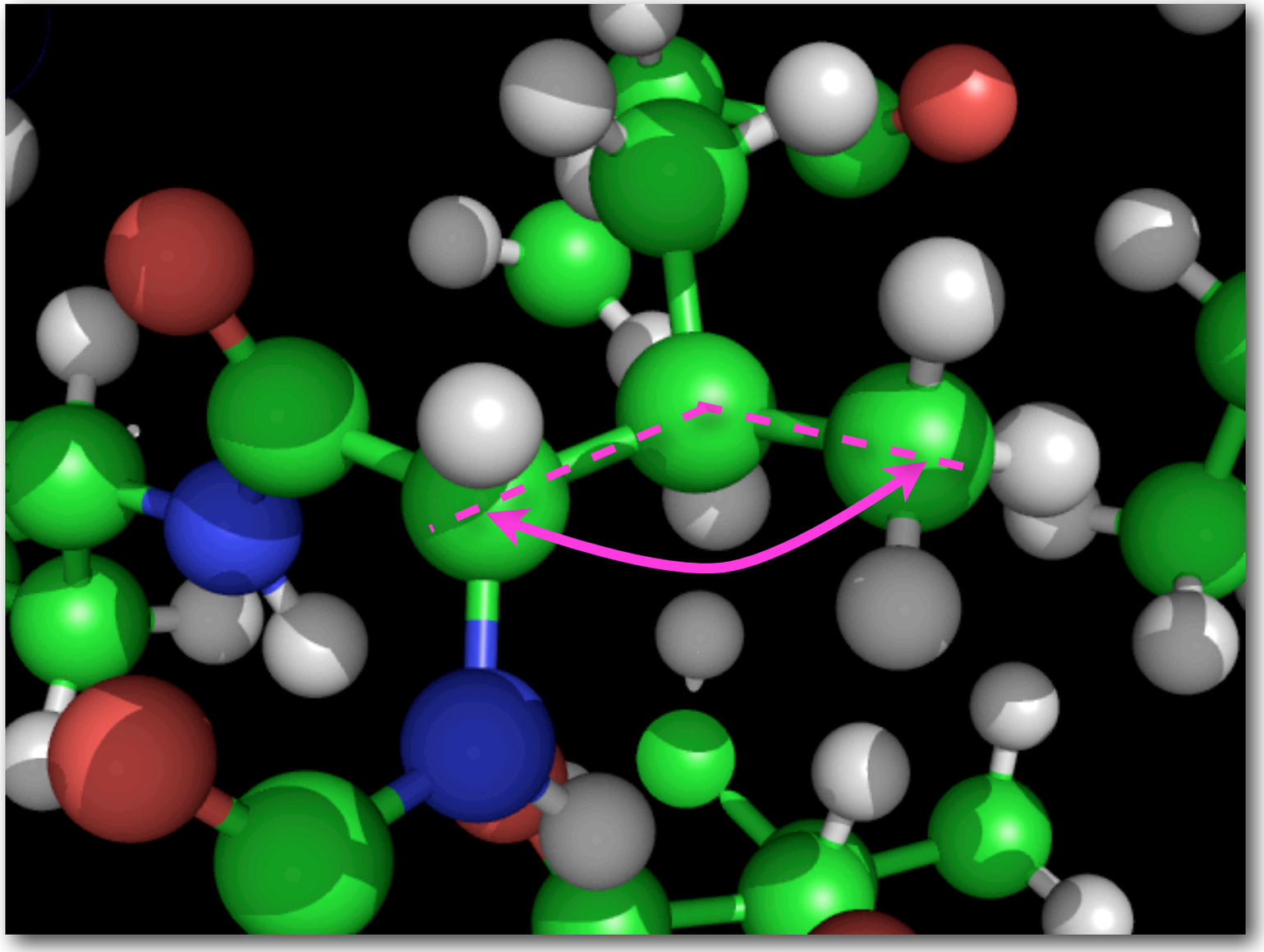
$$\omega = \sqrt{k_b/m}$$

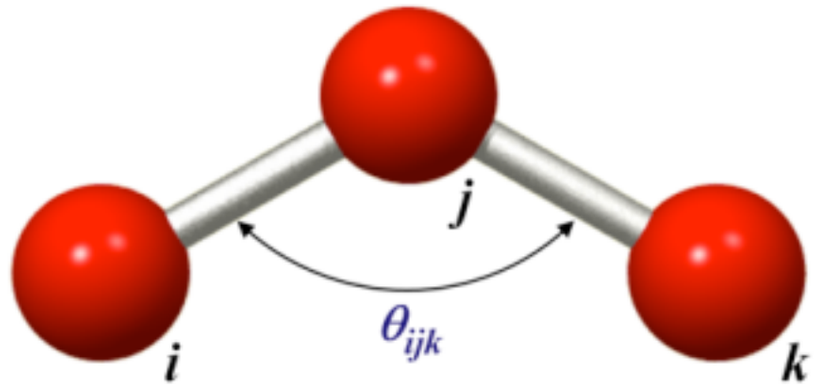
- Classical alternative:
    - r_0 from X-ray crystallography
    - k_b from IR or Raman spectroscopy



k_b ~ 300,000 kJ/mol/nm²

Angle vibrations





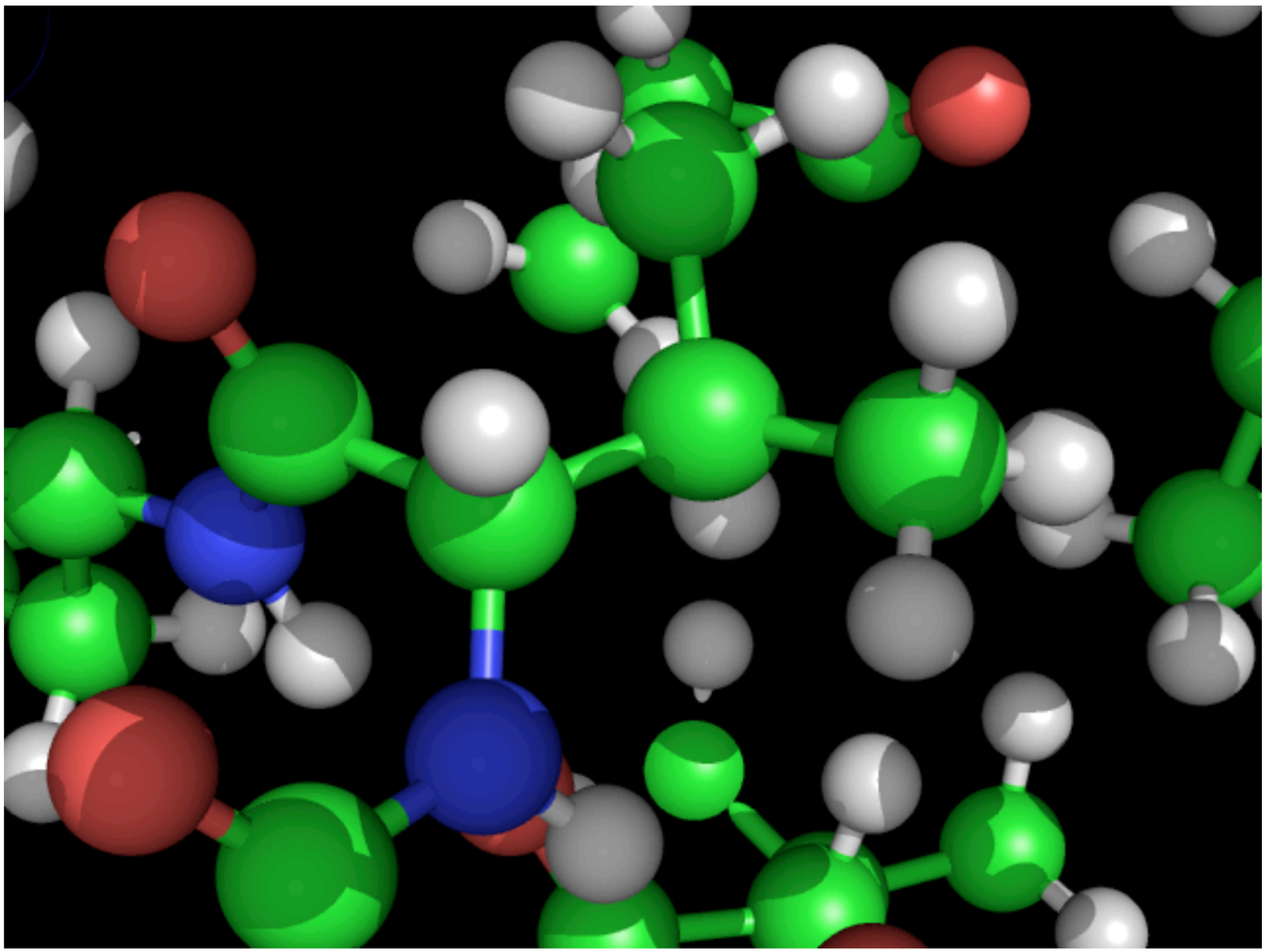
$$\cos\theta = \frac{r_{ij} \cdot r_{kj}}{|r_{ij} \cdot r_{kj}|}$$

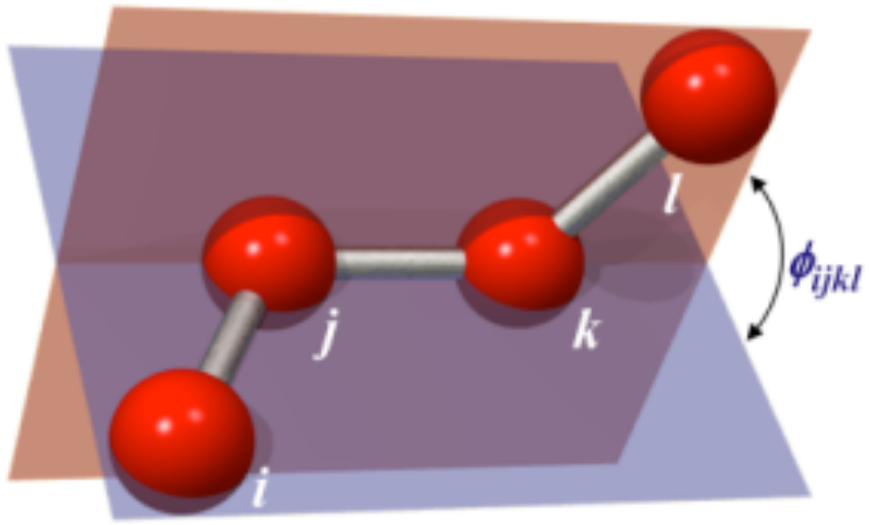
Not quite as rigid as a bond, but almost

$$U(\theta) = \frac{k_\theta}{2}(\theta - \theta_0)^2$$

$k_\theta \sim 300$ kJ/mol/rad^2

Torsion potentials





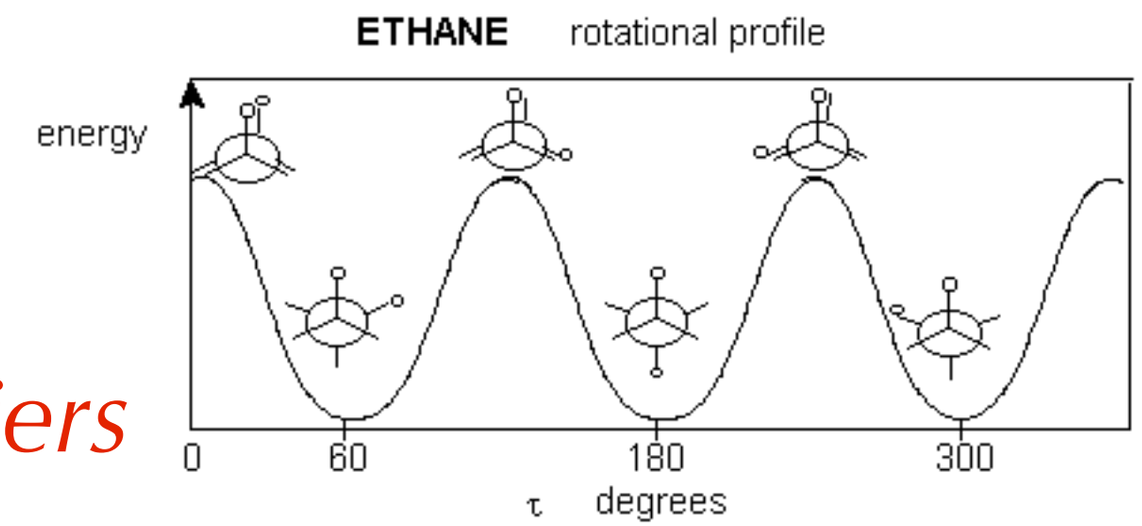
Frequently called "dihedral" angle too

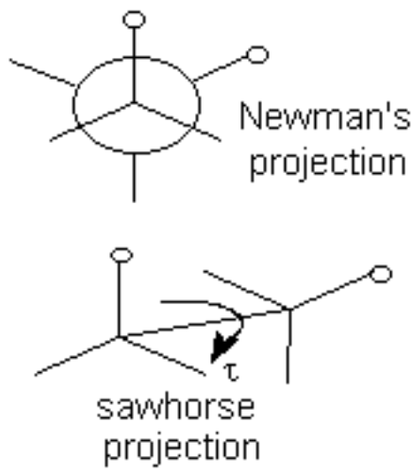
Angle between planes defined by atoms *i-j-k* & atoms *j-k-l*

Torsion potentials / dihedrals

- Changes in torsion angles lead to large/global variations in structure
- Determines conformations e.g. in proteins
- Multiple minima & barriers
- Relatively weak - there will be large variations!

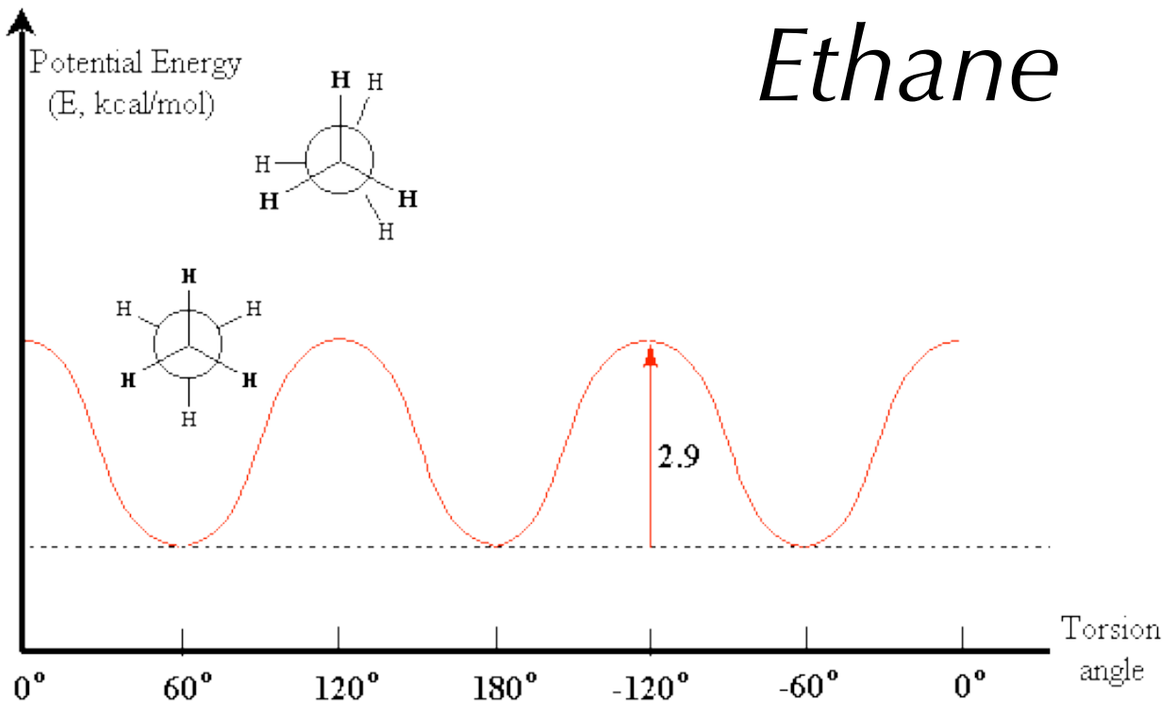
~ 10-20 kJ/mol barriers

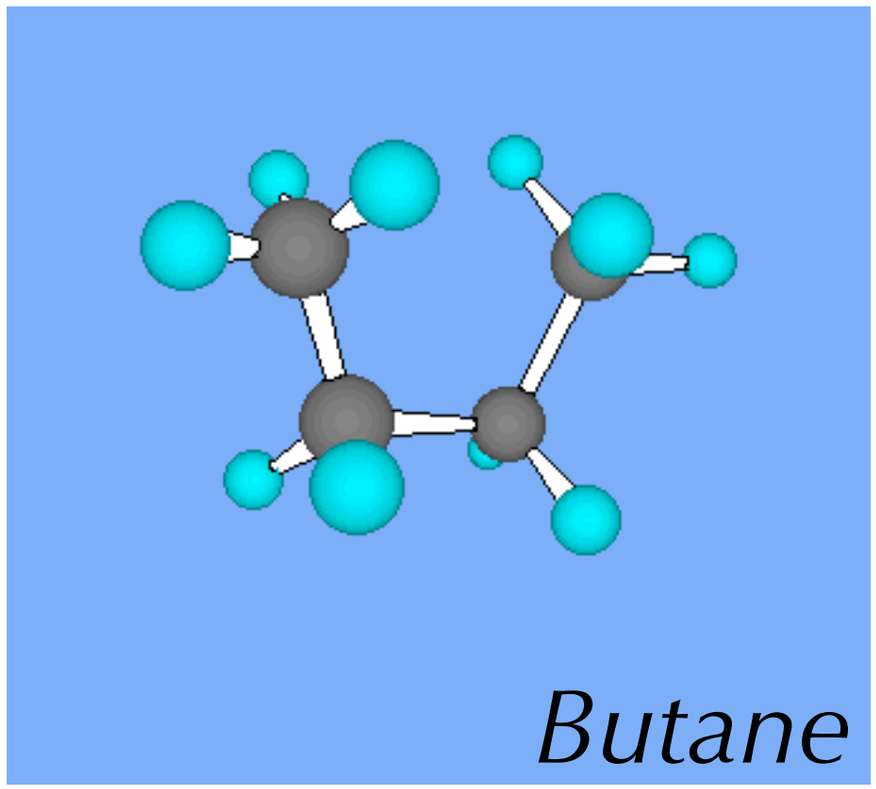




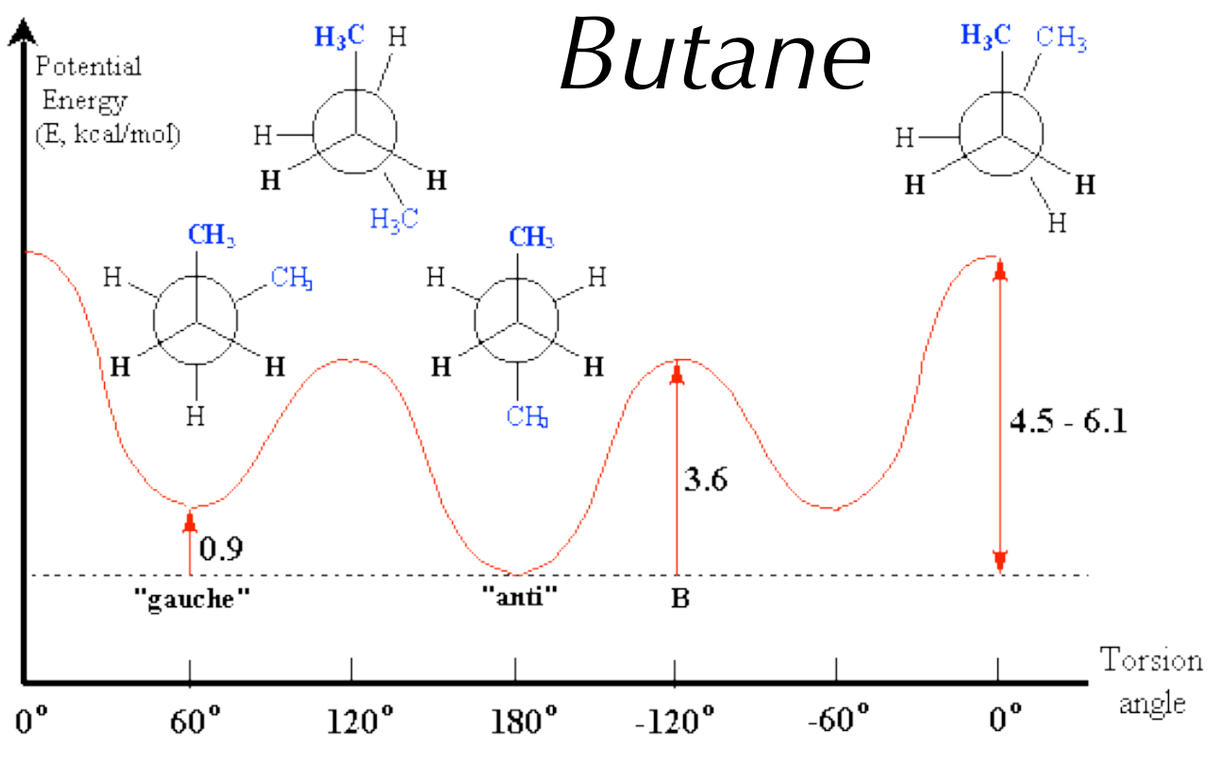
Comparing torsions

Ethane





Butane



Torsion equations

- General form:
  Express it as a series of cos($n\Phi$)

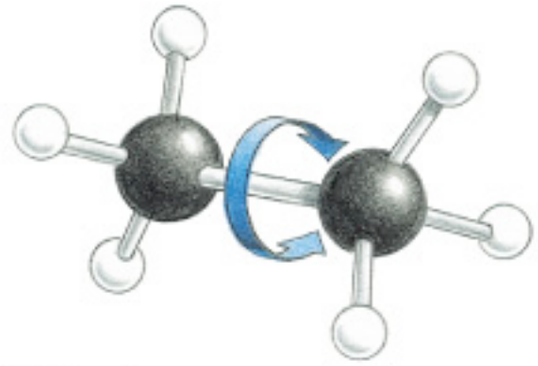
$$U(\phi) = \sum_{n=0} N \frac{k_n}{2} \left[1 + \cos(n\phi - \phi_0)\right]$$

e.g. force constants

$$U(\phi) = \frac{k_1}{2}(1 + \cos\phi) + \frac{k_2}{2}(1 + \cos 2\phi) + \frac{k_3}{2}(1 + \cos 3\phi)$$

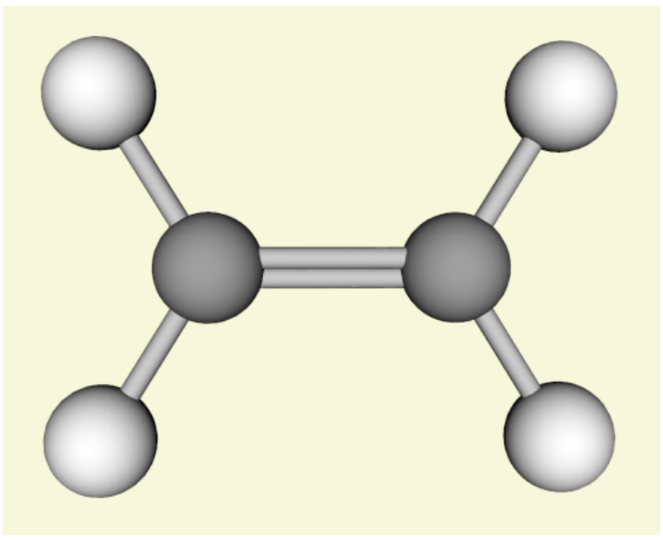
What is a double bond?

- Quantum chemical phenomenon
  - More electrons shared btw. atoms
- Practical effects:
  - Shorter than normal bonds
  - Different bond potential, harder
  - Rigid/planar structure
    - Different torsion potential
    - higher rotation barrier

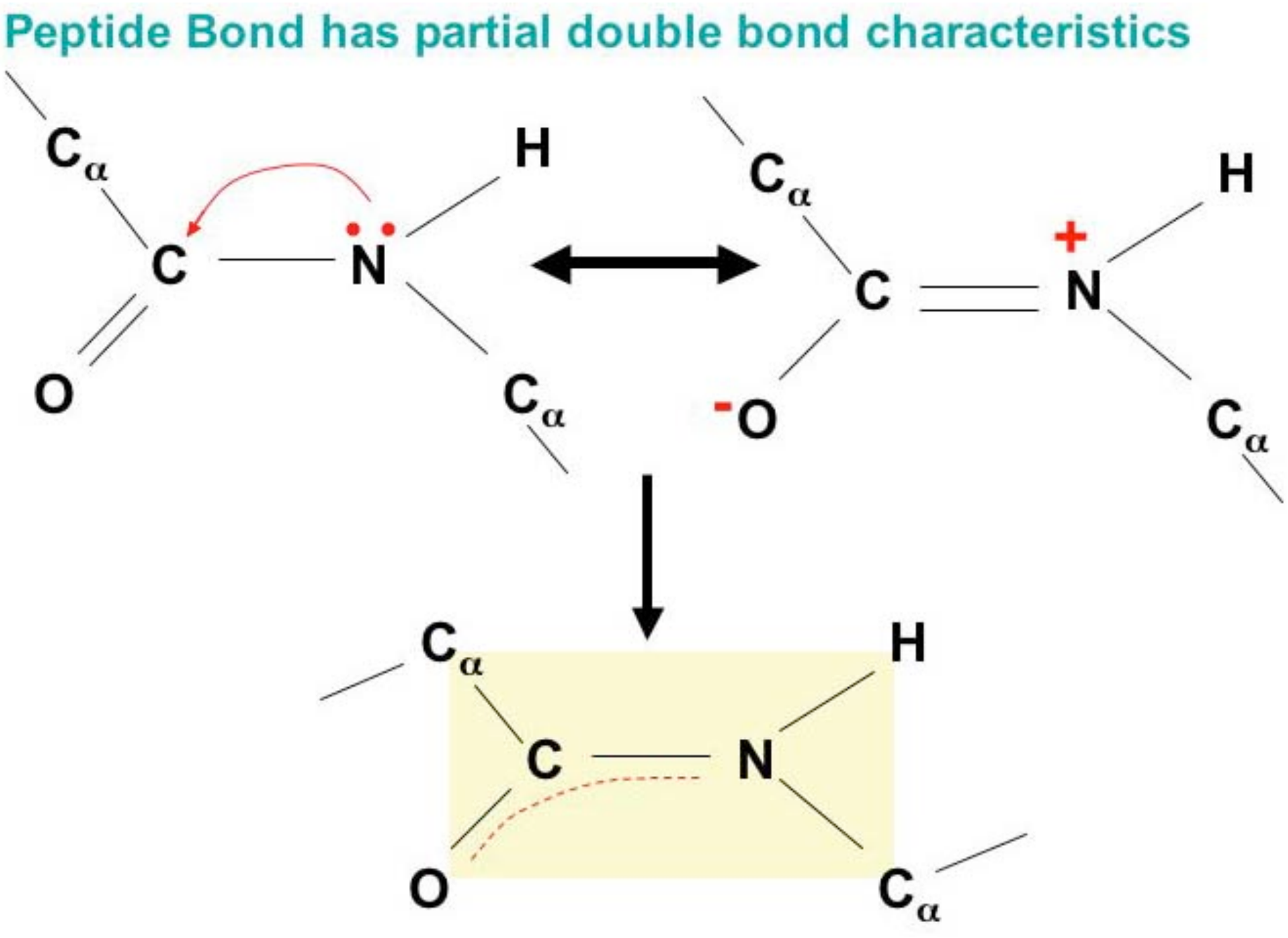


(A) ethane

(B) ethene

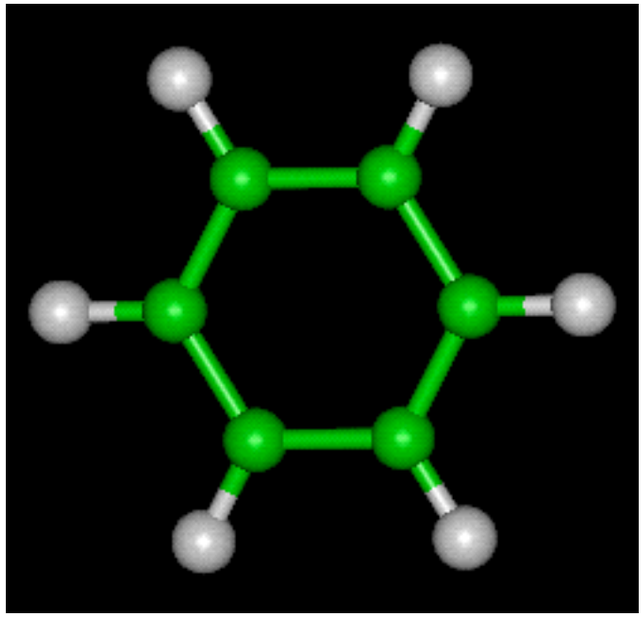


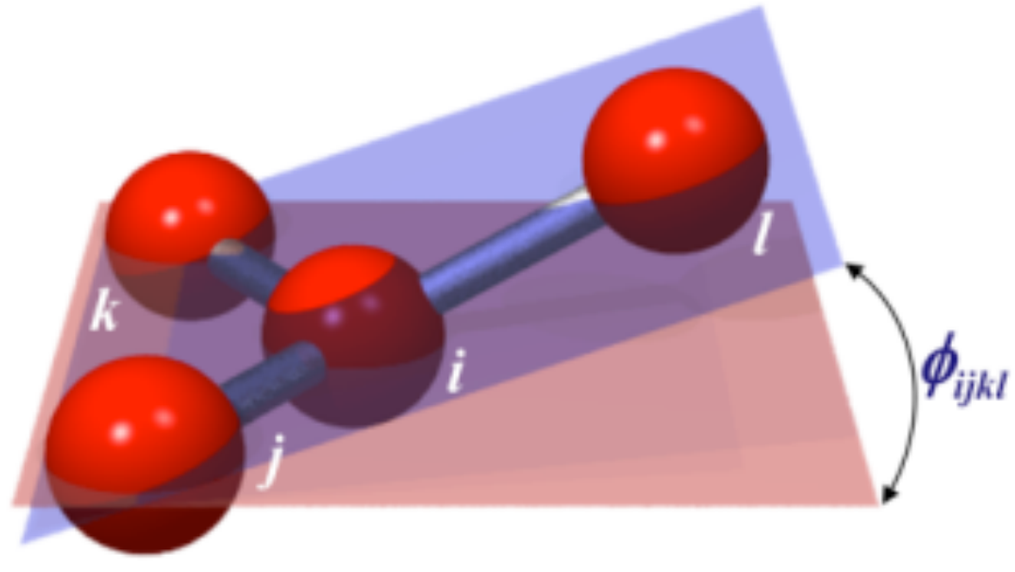
Peptide bond is ‘double’



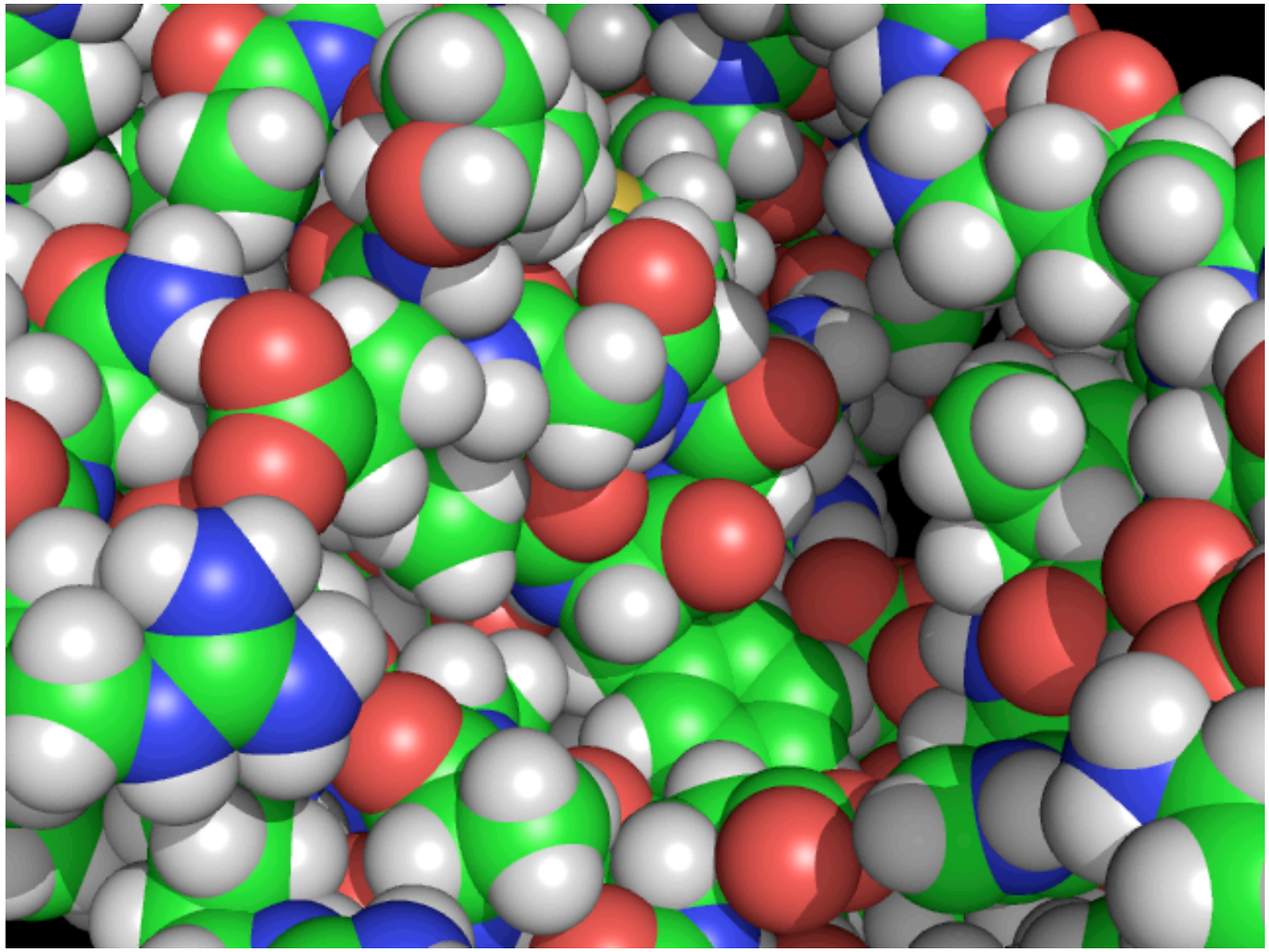
Out-of-plane torsions

- Also known as “Improper” dihedrals
- Used to keep 4 atoms in a plane (e.g. -NH2)
- ...or slightly out of a plane!
- Angle between planes *i-j-k* and *j-k-l*





Non-bonded interactions



- Packing effects (everywhere)
- Electrostatics (e.g. in water)

Coulomb electrostatics

- Interactions between partial charges on all pairs of atoms in the system

$$U_q = \sum_i \sum_j \frac{q_i q_j}{4\pi\epsilon_0 r_{ij}}$$

- Problem 1: Many interactions... what happens if N=1000? (very small protein)
- Introduce a cutoff (say, 1.0 nm / 10 Å)
- Problem 2: Interaction 1/r does not converge (infinite integral, area ~r^2) - we cannot use a cutoff?!

Polarization

- In reality, charges move in response to other charges
- This is what happens with water & a comb!
- Molecular polarization: entire waters rotate/move - works fine with our model
- Dielectric/screening effects - important in water
- Atomic polarization: charges/electrons move along bonds - not included
- Possible solution: Introduce extra electron "particles" with charge on each bond

Van der Waals interactions

- Atoms repel each other at close distance due to overlap of electrons (repulsion)
- All atoms attract each other at longer distance due to induced dipole effects (dispersion)

Example - Buckingham potential:

$$U(r) = A\exp^{-Br} + \frac{C}{r^6}$$

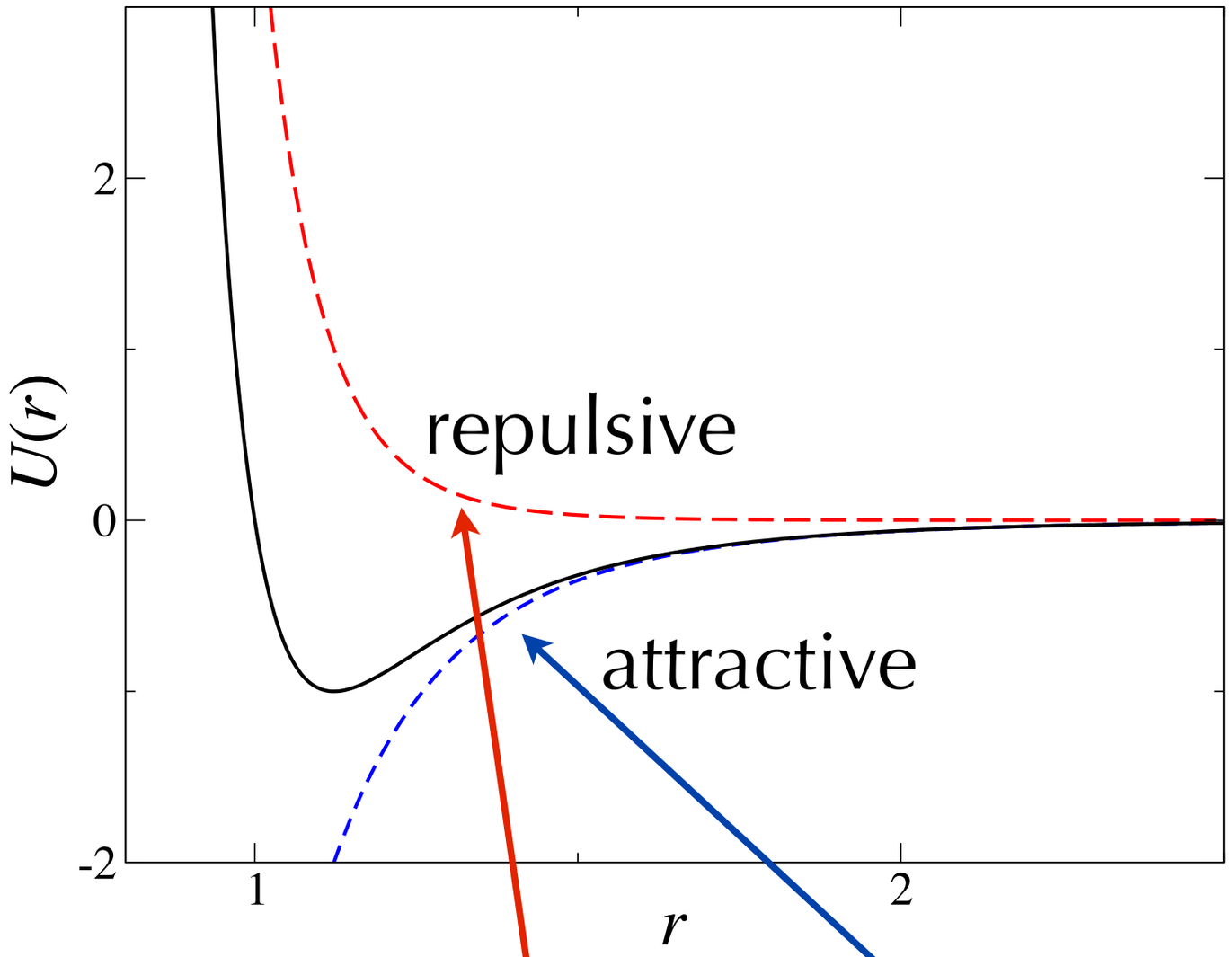
Same problem as before: exp(r) is slow to calculate

Lennard-Jones potential

- Simpler form than Buckingham
- In practice, atoms should never approach really close, so we just want a basic model of the repulsion
- Smart trick: When we have calculated $1/r^6$, it is trivial to get $1/r^{12}$ (1 multiplication)

$$U(r) = 4\epsilon \left[\left(\frac{\sigma}{r} \right)^{12} - \left(\frac{\sigma}{r} \right)^{6} \right]$$

Lennard-Jones potential



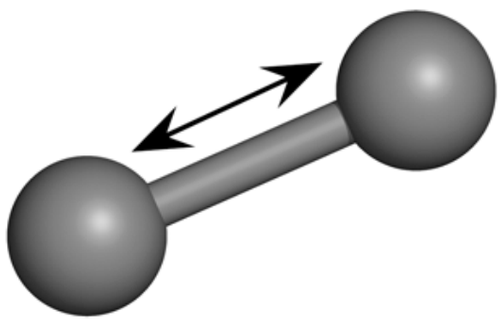
$$U(r) = 4\epsilon\left[\left(\frac{\sigma}{r}\right)^{12} - \left(\frac{\sigma}{r}\right)^{6}\right]$$

Sir John Edward Lennard-Jones

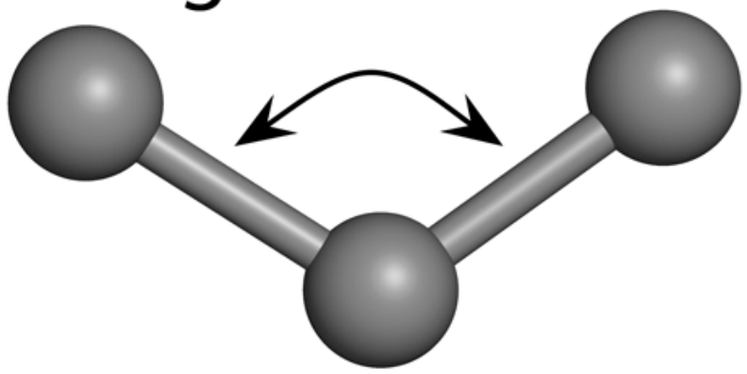
Force constants C6 & C12 are usually parameterized to reproduce experimental density & heat-of-vaporization for simple liquids!

Summary of interactions

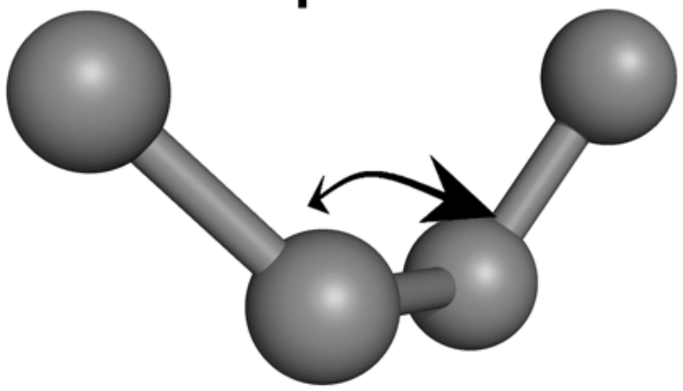
Bond vibration



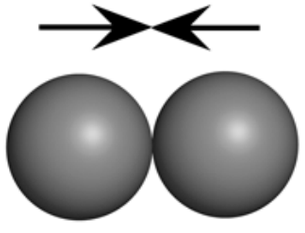
Angle vibration



Torsion potentials



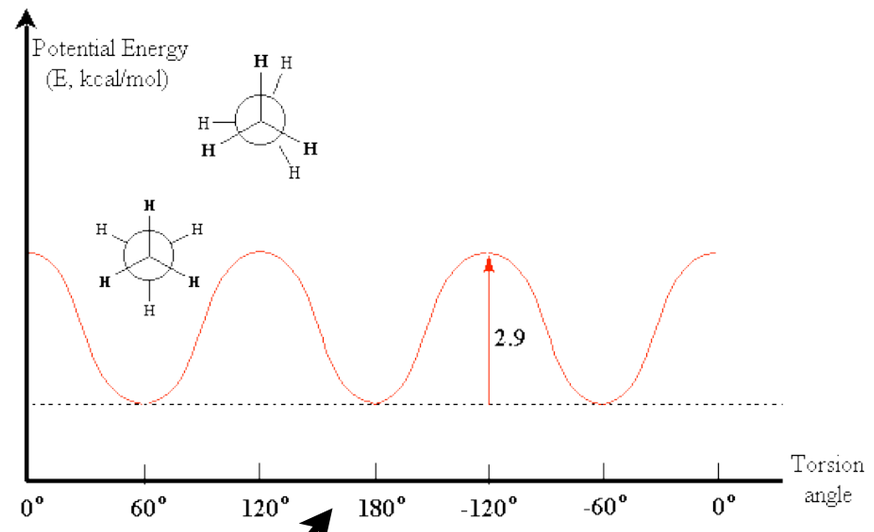
van der Waals interactions

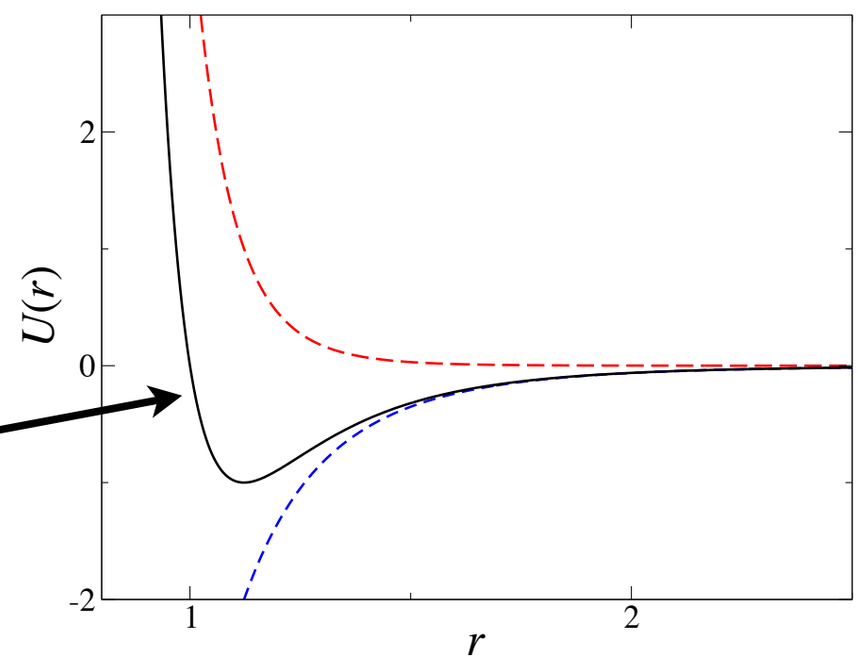


Electrostatics

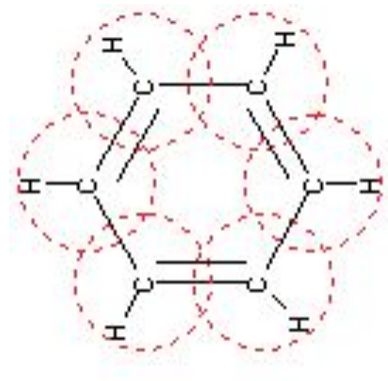
A full ‘force field’

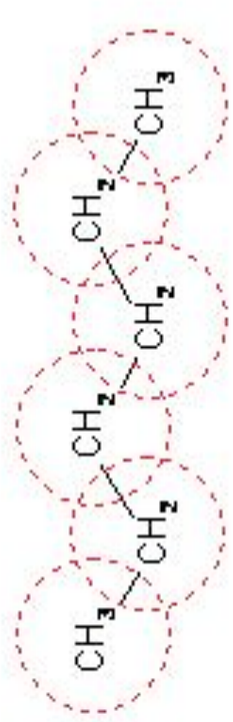
$$
\begin{aligned}
U = & \sum_{\text{bonds}} \frac{1}{2} k^b_{ij} \left(r_{ij} - r^0_{ij} \right)^2 \\
& + \sum_{\text{angles}} \frac{1}{2} k^\theta_{ijk} \left(\theta_{ijk} - \theta^0_{ijk} \right)^2 \\
& + \sum_{\text{torsions}} \left(\sum_n k_\theta \left[1 + \cos(n\phi - \phi^0) \right] \right) \\
& + \sum_{\text{impropers}} k_\xi \left(\xi_{ijkl} - \xi^0_{ijkl} \right)^2 \\
& + \sum_{i,j} \frac{q_i q_j}{4\pi\epsilon_0 r_{ij}} \\
& + \sum_{i,j} 4\epsilon \left[\left(\frac{\sigma}{r} \right)^{12} - \left(\frac{\sigma}{r} \right)^{6} \right)
\end{aligned}
$$





- Hydrogens ubiquitous in organic molecules
- Non-polar hydrogens have very weak interactions
  - Low charges (typically 0.04)
  - Small Lennard-Jones radius
- For efficiency they are sometimes “merged” into the heavy atom they are connected to
- Works surprisingly well

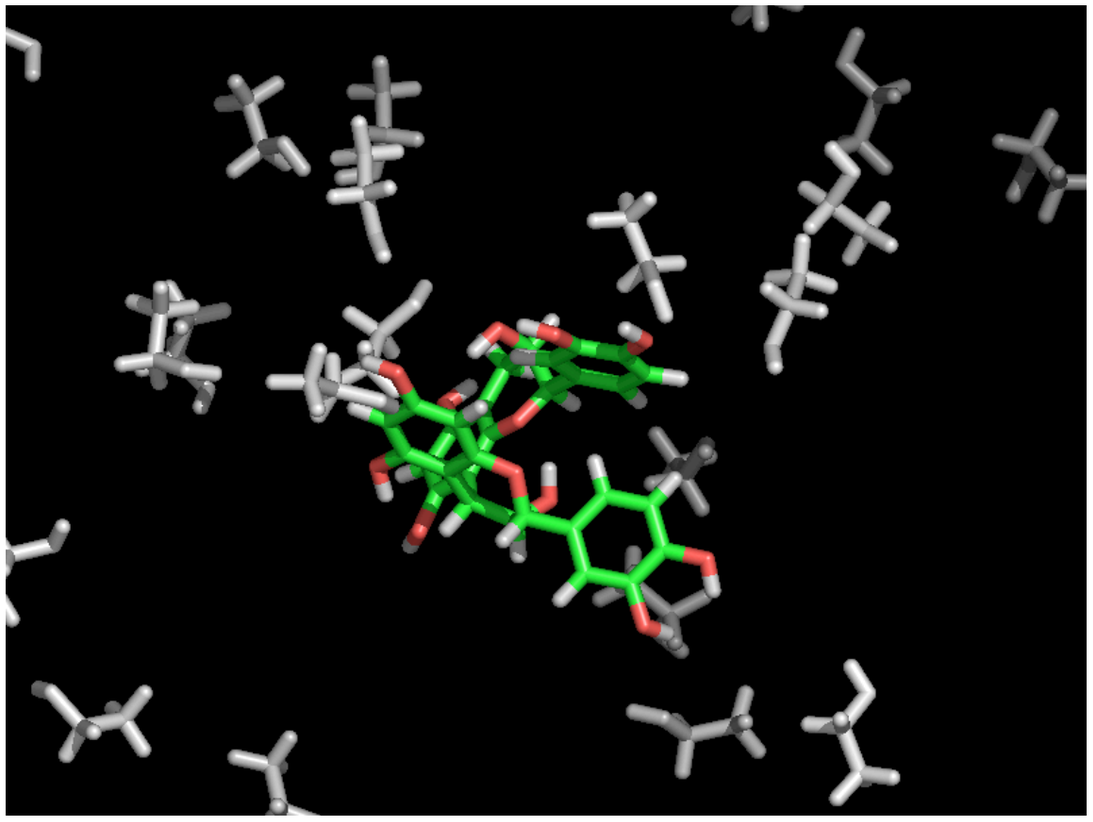




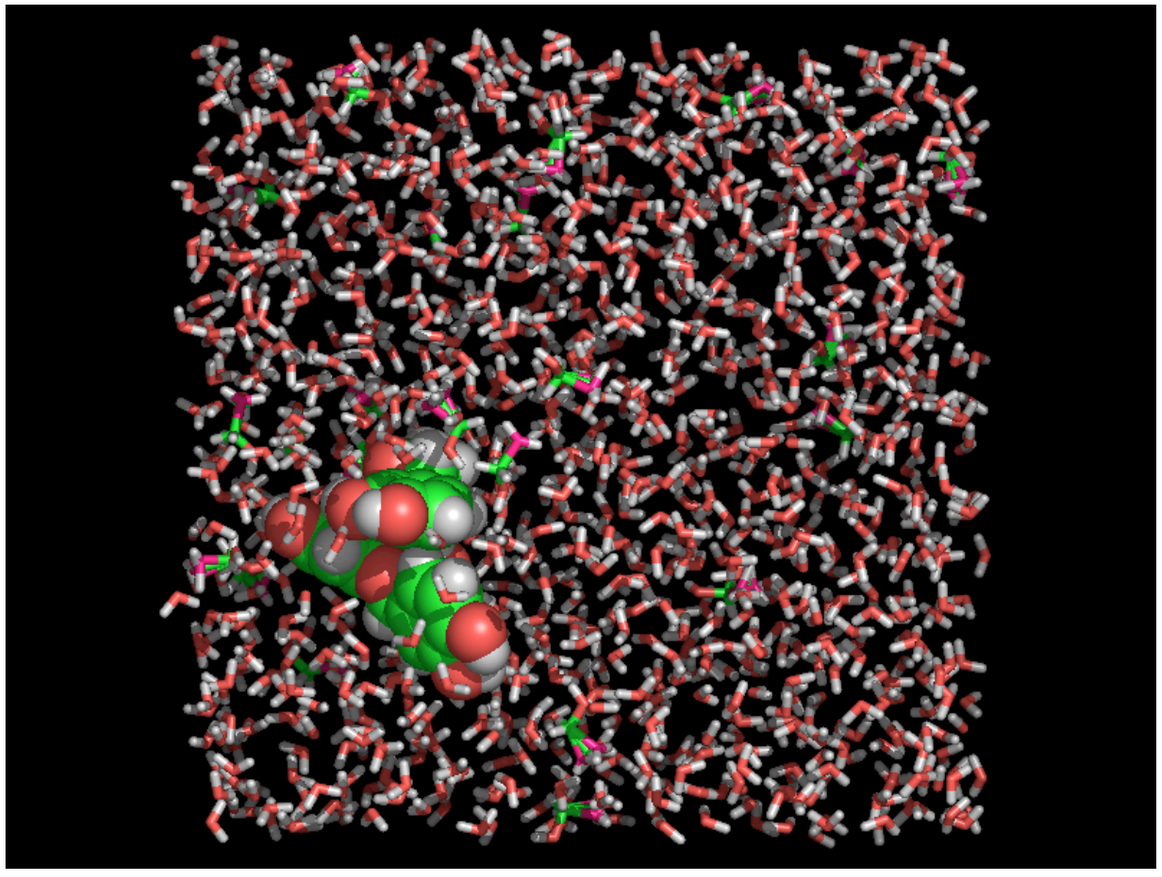
Solvent models?

- Quantum chemists frequently try to model water as a "continuum" in space, with dielectric coefficient ε_r=80
- "Implicit solvent model"
  - Reduces the number of atoms significantly
  - Unfortunately, it is pretty bad...
  - Better: include all waters explicitly in system

Environments



Unrealistic



Realistic

Hydrogen bonds

- Didn't we forget the most important interaction?
- There are special hydrogen bond potentials:

$$U_{\mathrm{HB}}(r) = \frac{A}{r^{12}} - \frac{C}{r^{10}}$$

Problem 1: How do we decide which interactions are hydrogen bonds at each moment?

Problem 2: What happens when hydrogen bonds form/break? Change in potential?

Solution: Modern force fields don't use special H-bond terms, but model it through the general electrostatics

Making a force field

- Critical parameters:
  - bonds, angles: equil. distance, angle
  - dihedrals: V at minima and barriers
  - partial charges for each atom: q_i
- Lennard-Jones parameters: $\sigma_{ij}, \epsilon_{ij}$ different for each type pair!

- Many similar interactions, errors add up
- Example: mixture of polymers with H and D phase separate!

Making a force field, state of the art

- Systematic parametrization:
  - Bonded parameters from quantum mechanics
  - Partial charges from quantum mechanics, fit electrostatic potential on a surface
  - Fit LJ parameters using density, heat of vaporization and other thermodynamic data
- Amount of work:
  - Two ions (in water): a few days
  - Polymers: a few months
  - Proteins: a few years for a whole group!

Polarization

- Charge distribution on molecules in not static, reacts to the “polarity” of the environment
- In many systems groups will not change environment, hydrophilic likes hydrophilic, hydrophobic likes hydrophobic
- But sometimes environments do change:
  - Need for polarizable force fields
  - Adds very large changes to interactions
  - Re-parameterize the whole force field

Protonation

- Surface groups of (bio)molecules often have sites that can (de)protonate
- The protonation state is dynamic and depends on the electrostatic interactions with the local enivornment
  - pH is an important factor
- To simulate dynamic protonation, we have to make proton (dis)appear, taking into the local electrostatic potential