Energies

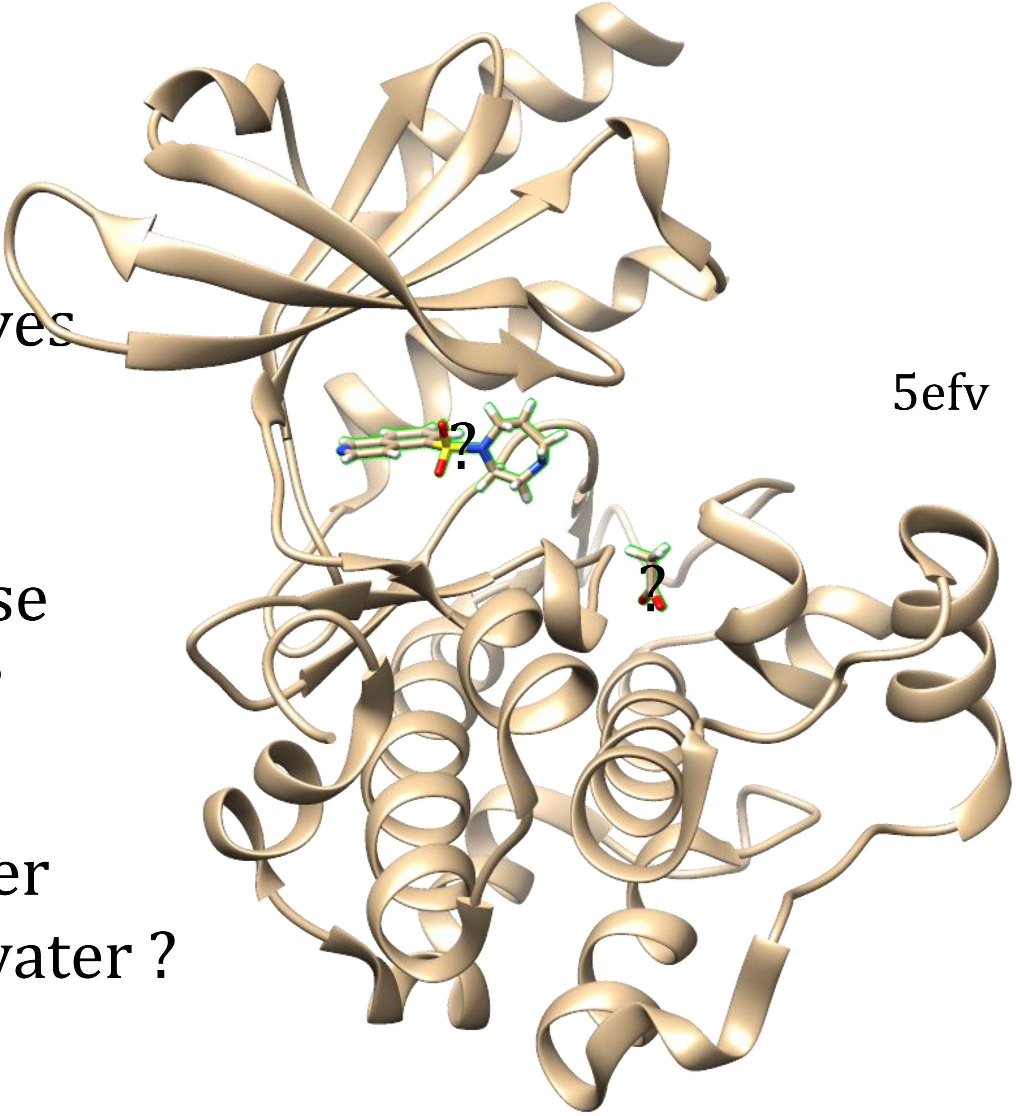
Where do you think
your drug is binding ?

- necessary if you want
  to think about alternatives

If I modify the ligand

- will it bind better ? worse
- will a side chain rotate ?

- Would a side chain prefer
  to H-bond to ligand or water ?



5efv

Andrew Torda, Wintersemester 2018 / 2019

more energy questions

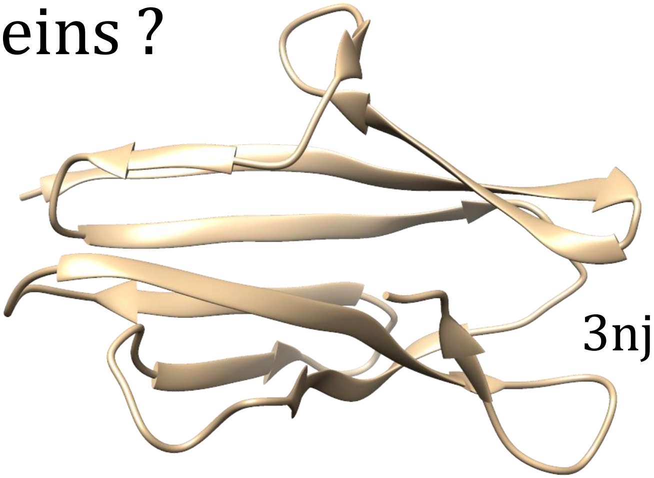
Anfinsen's hypothesis

- Proteins fold to lowest (free) energy conformation

If I can predict energies

can I predict the structure of proteins ?

Does it work ? Later…



3njf

Things we want to predict

- conformations of proteins, nucleotides
- binding constants (strong / weak binding)
- binding sites

What drives the world ?

- energies

What do we learn about energy states ?

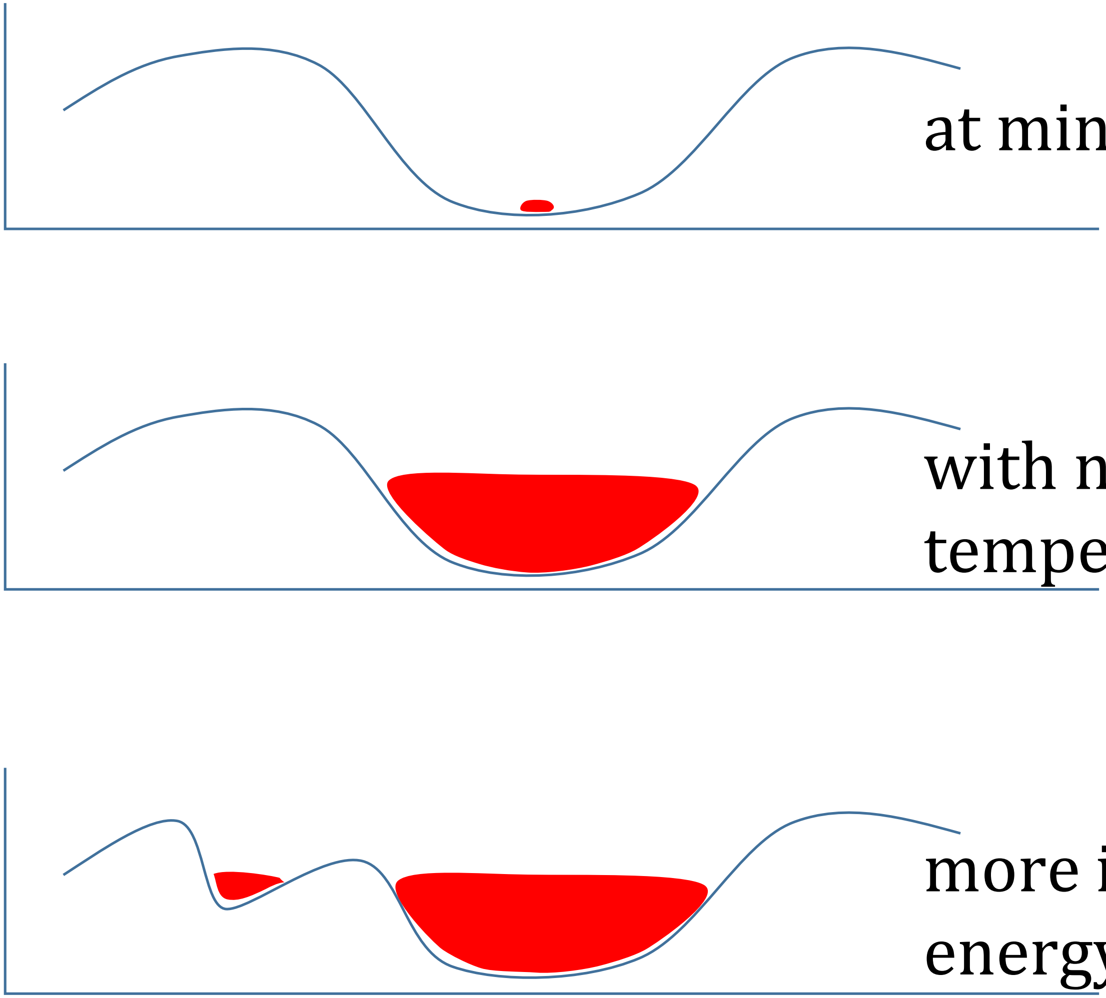
- Things tend to go down in energy
- electrons fall down and emit a photon
- high energy states decay via vibrations – gives off heat

Two complications

- equilibria and temperature
- free energy and entropy

Energies and distributions

Do we end up in the lowest energy conformation ?



$U(\{\vec{r}\})$
energy

at minimum

$U(\{\vec{r}\})$

with non-zero temperature

$U(\{\vec{r}\})$

more interesting energy landscape

conformations $\{\vec{r}\}$

Energies and distributions

The lowest energy state is not the only relevant one

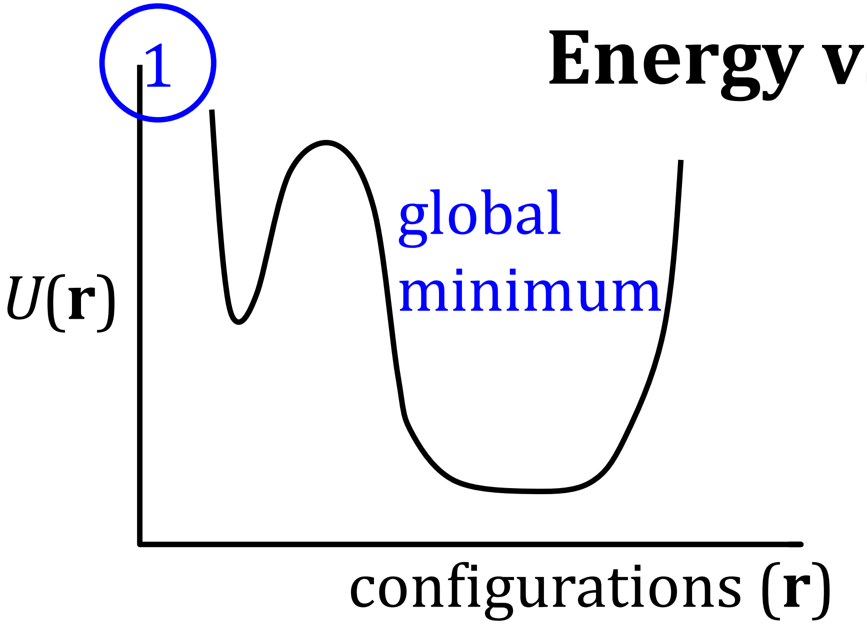
- but it is the most populated – what we are normally interested in

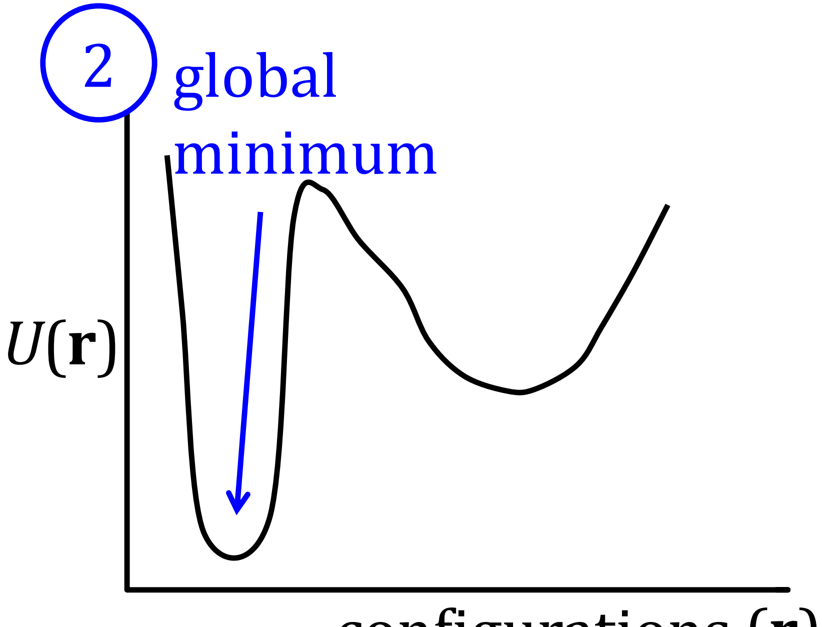
What is the term used in 1st year chemistry ?

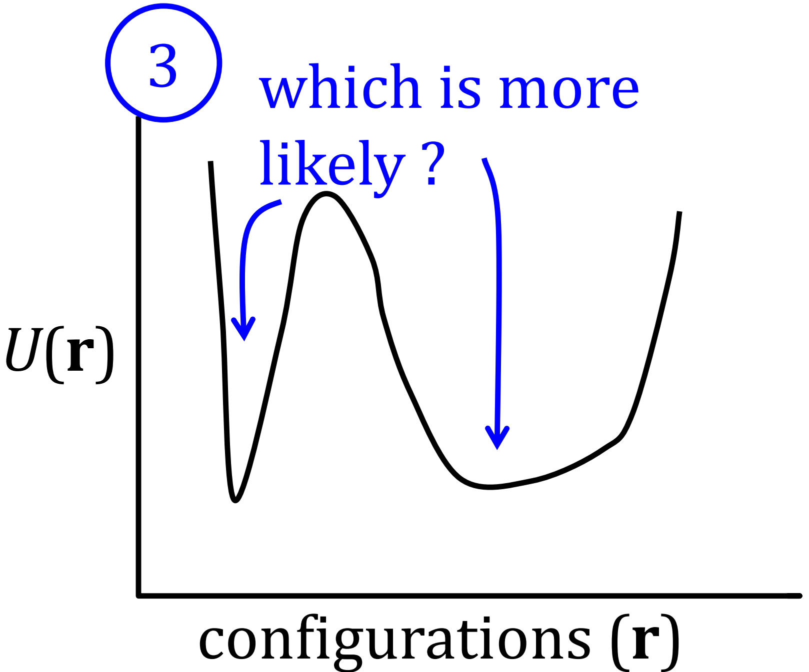
- Energy or free energy (ΔG) ?

What is the practical meaning ? …

Energy vs free energy







Energy / potential energy / free energy

Potential energy

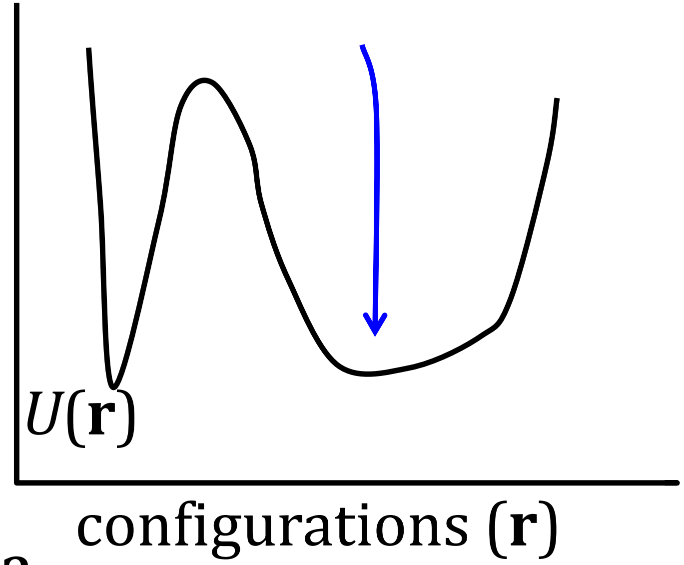
- is easy
- important
- not the whole story

Systems

- like to go downhill in potential energy
- likely to go towards bigger (less ordered) regions
- net effect – potential energy and entropy are both important

formalise a bit ..

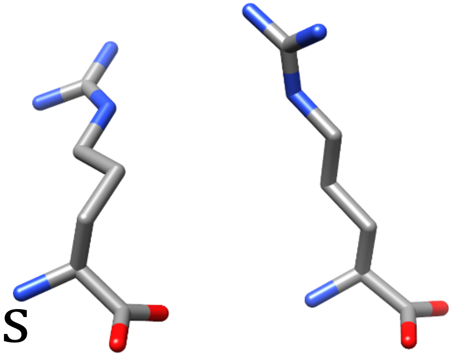
Entropy contribution



$\Delta G = \Delta H - T\Delta S$

- let us say ΔH is potential energy
- T temperature
- ΔS change in entropy

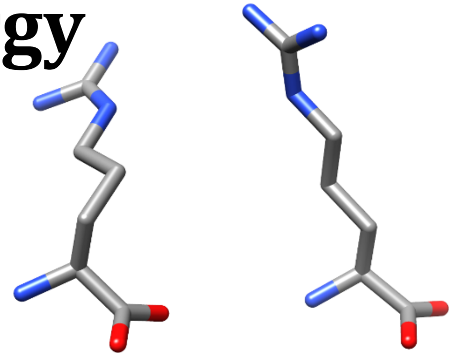
Why is entropy so difficult to estimate ?



- these two conformations have different potential energies
- they are part of the same set of conformations
- entropy is a property of all states / conformations

- entropy of a conformation has no meaning

models for potential energy



Why talk about potential energy ?

- we have models for potential energy

Can I model entropic effects ?

- entropic effects ?
  - simulation methods
  - ugly approximations

- today we discuss potential energy

- start with fundamental physics

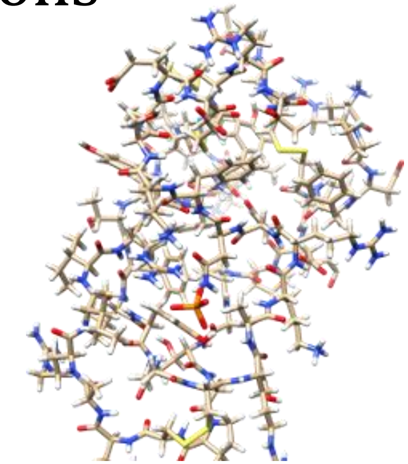
Chemistry is a approximations

Physics is not helpful

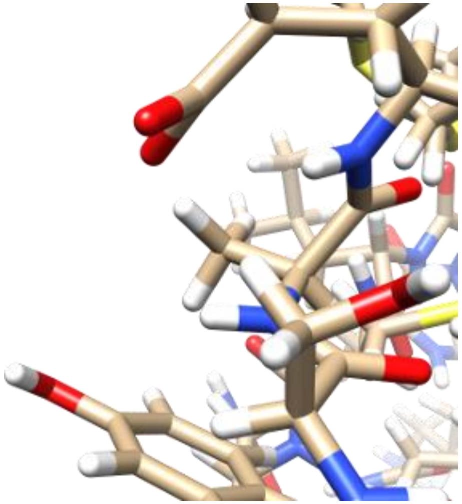
strong	particle physicists
weak	
gravity	astronomers
electromagnetic	chemists

True – not helpful – chemists use approximations

- I have coordinates and names of atoms
    - want potential energies
        - electrostatics
        - lennard-jones
        - bonds
        - angles
        - torsion angles



electrostatics

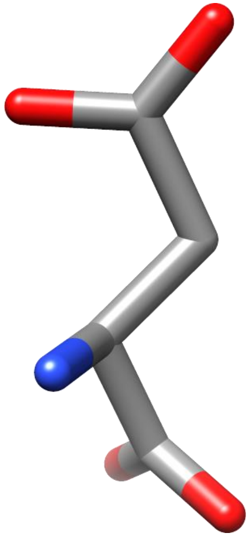


Can we just use Coulombs Law ?

$$U(\vec{r}_i, \vec{r}_j) = \frac{q_i q_j}{4\pi\epsilon_0 r_{ij}}$$

- charges q_i, q_j
- distance r_{ij}
- constants $4\pi\epsilon_0$

Yes, but what are the charges ?



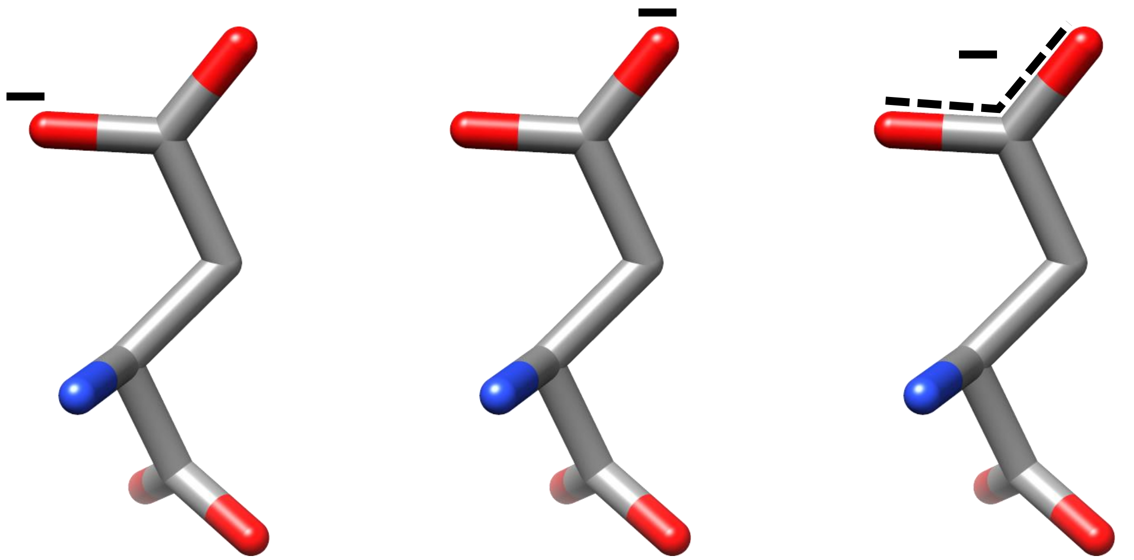
Look at asp

- I know it has a charge of −1, but where ?

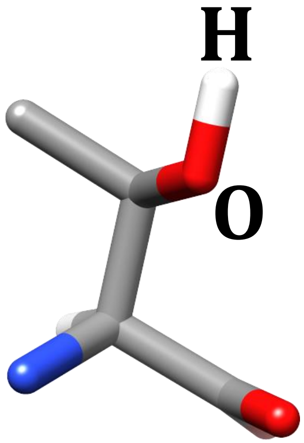
charges

where is the charge ?

- spread around



A neutral
but polar sidechain



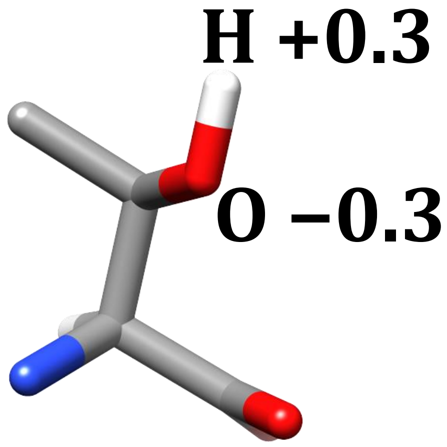
an OH group

- is neutral
- likes water

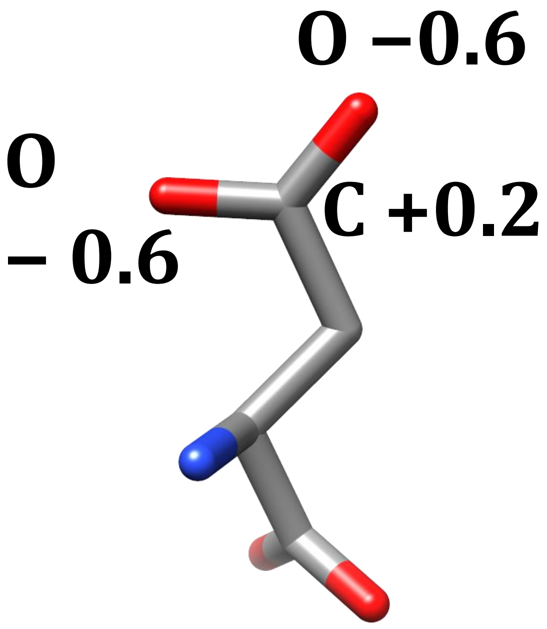
how does one model these properties ?

partial charges

- assign a value like $q_{\mathrm{H}} = 0.3$ or $q_{\mathrm{O}} = -0.3$
- overall correct charge
- locally we have correct properties
  - imagine two OH groups come together
  - only sensible geometries are preferred



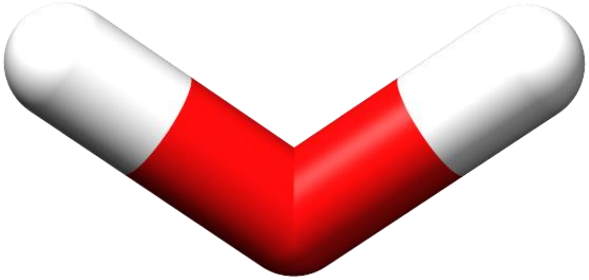
- similar rules for all atoms in polar and charged environments

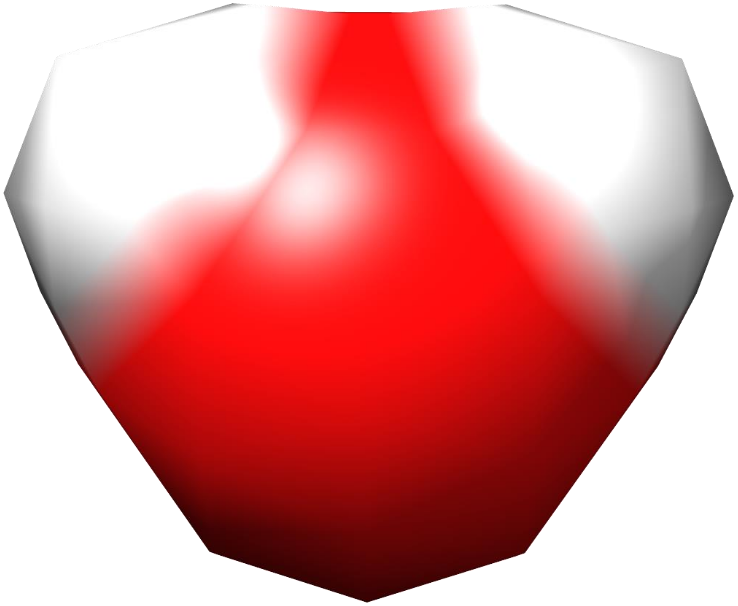


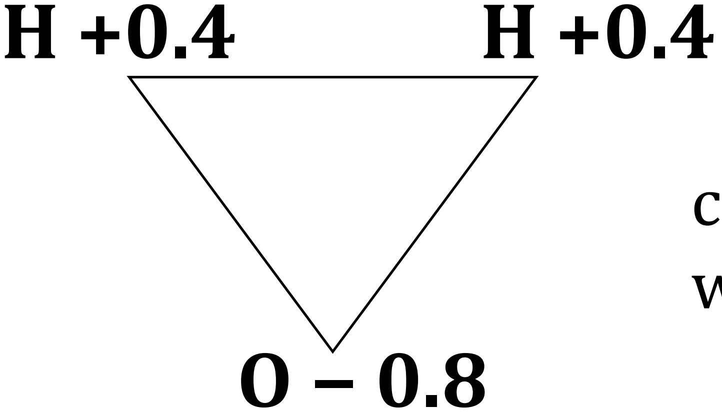
- famous example

a water model

water







H +0.4 **H +0.4**

O – 0.8

common model for
water electrostatics

partial charges

Weak physical basis

- there is no such thing as 0.4 of an electron
- they are a good approximation

Distances

- electrostatic interactions are very small after about 15 Å

What next ?

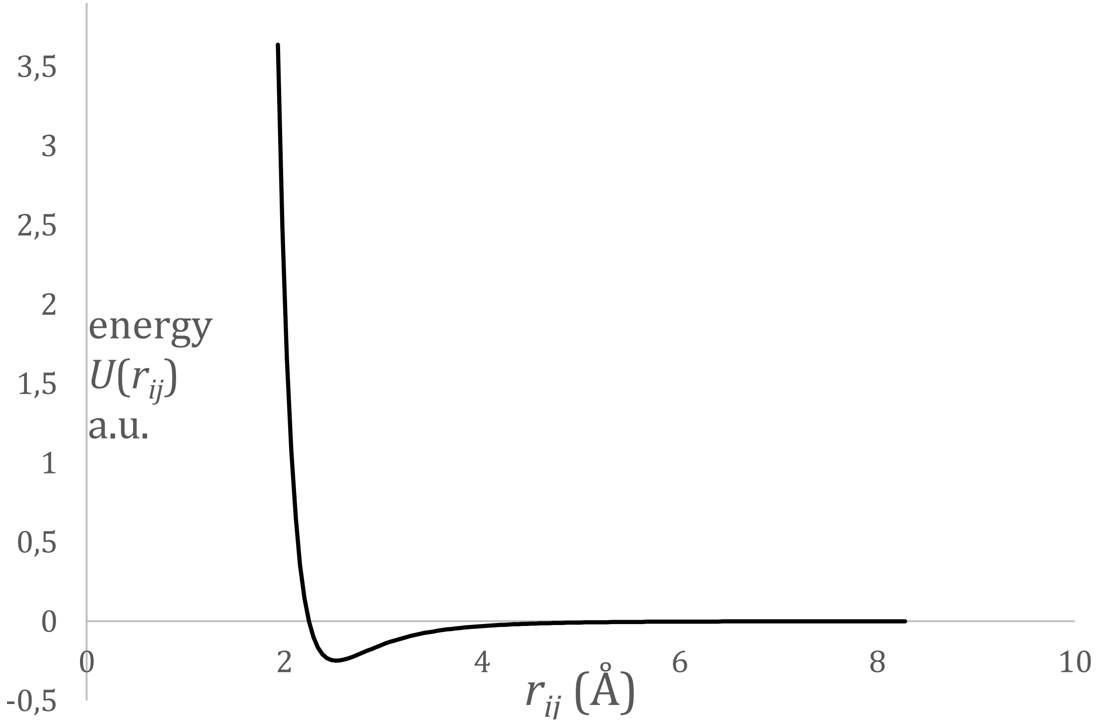
- why does argon form a liquid ?

Lennard-Jones / van der Waals

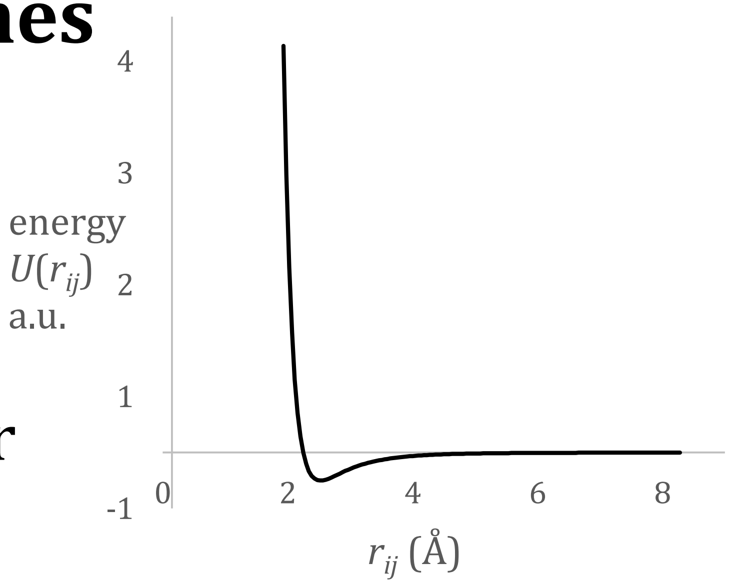
argon / methane / benzene / N_2

- completely neutral / non-polar
- do form liquids

- electrostatic effect, but complicated



Lennard-Jones



- weak
- between all atoms not connected by bonds or bond angles
- all atoms like to be near each other
- atoms do not want to be on top of each other
- at long distance atoms do not know about each other
- short range (disappears $r_{ij} > 8$ Å)
- only important energy term in middle of proteins

- ask me why I do not write a formula
- summarise …

non-bonded energies

so far - two contributions to energies

1. electrostatics (energy= $q_i q_j / Dr$)
2. lennard-jones

Call them "non-bonded" energies

Distances – after about 10 or 15 Å nearly zero

- medium size protein – lots of atoms do not directly interact

What else is there ?

- bonded contributions
  - bonds
  - angles
  - torsion angles

Bond energies ?

Push two bonded atoms together ?

- the Lennard-Jones term would go up

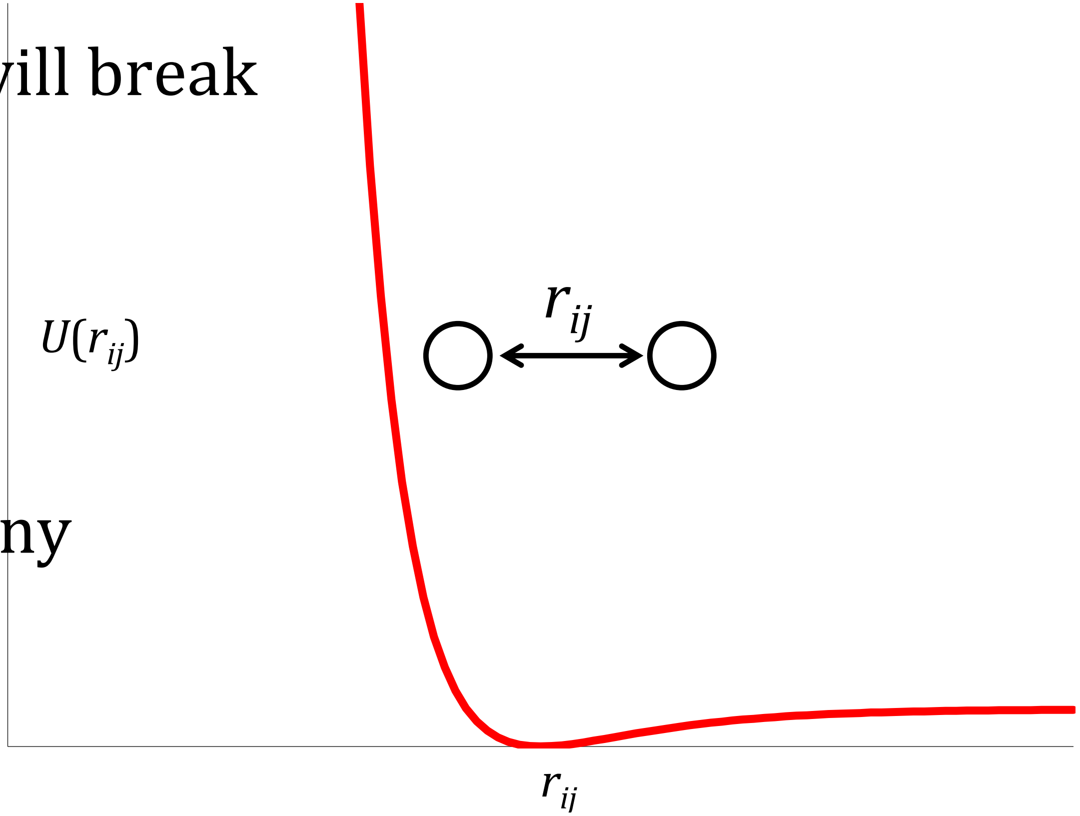
Pull them apart

- eventually the bond will break

Will you meet this ?

- hopefully no

- bond vibrations are tiny



Bonds

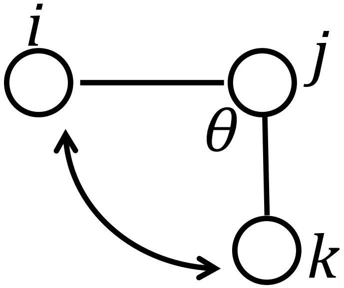
- at room temperature we can treat them as fixed
- if you have a model with bad bonds, energy is not so helpful
  - you have a very bad model
    - very bad or very very bad is usually not important

Who cares about bond energies ?

- maybe people simulating chemical reactions

What about angles ?

Angles



Are they interesting ?

- not very
- a bit more flexible than bonds
- might fluctuate a bit at room temperature

If you have a tetrahedral carbon

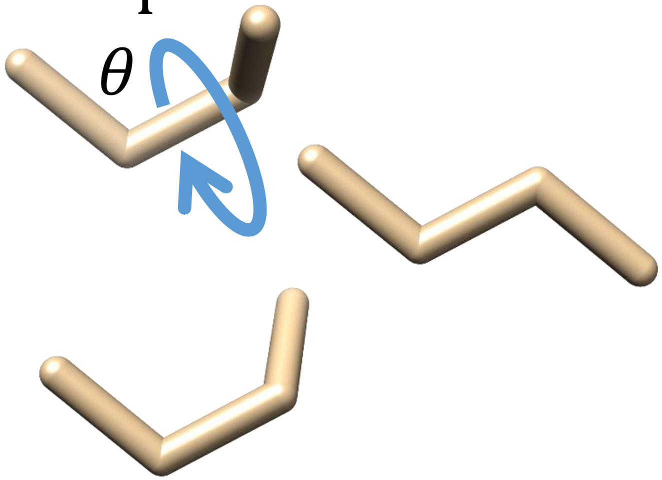
- an angle is 115° instead of 109.5° it is not just high energy It is broken

What is more interesting ?

torsion angles

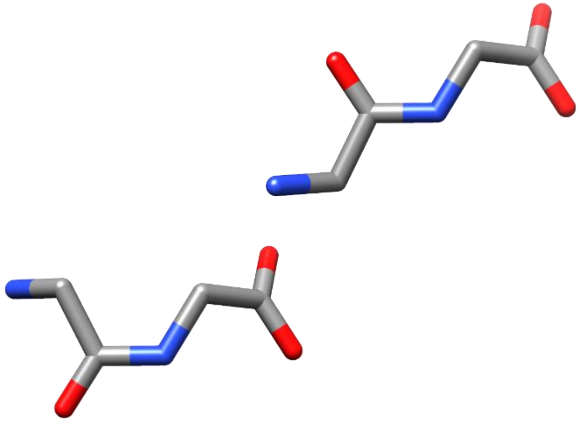
More interesting

- most single bonds can rotate at room temperature
- there are preferred conformations



- number of minima varies
- butane 3
- peptide bond 2 (*cis* / *trans*)

What would the form look like ?



Form of torsion terms

a periodic function

$$U(\theta) = \sin(\theta)$$

with a shift of ν

$$U(\theta) = \sin(\theta - \nu)$$

with periodicity n

$$U(\theta) = \sin\big(n(\theta - \nu)\big)$$

how high are the barriers ?

$$U(\theta) = k_{torsion}\sin\big(n(\theta - \nu)\big)$$

no physics – just created

summarise energies

A classic force field has..

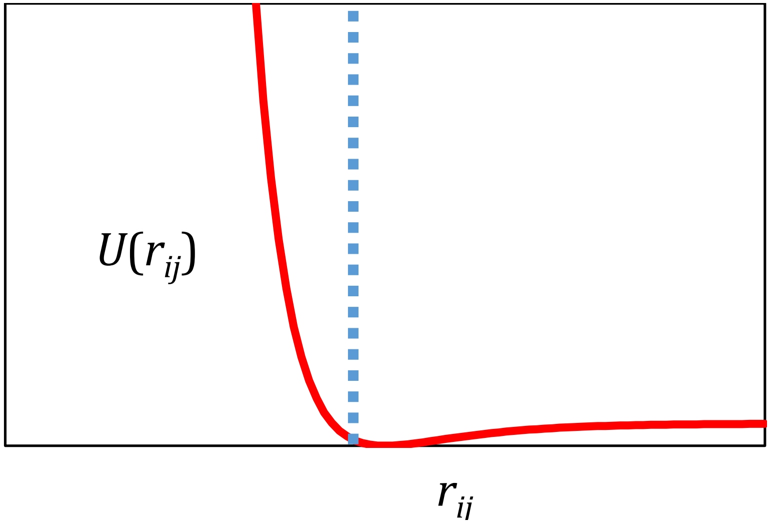
electrostatics	important	varies as atom move
lennard-jones	important	real meaning of steric effects / collisions
bonds		do not change much
angles		
torsions	important	

Not all force fields are the same

Parameters differ (partial charges, barriers)

Forms differ

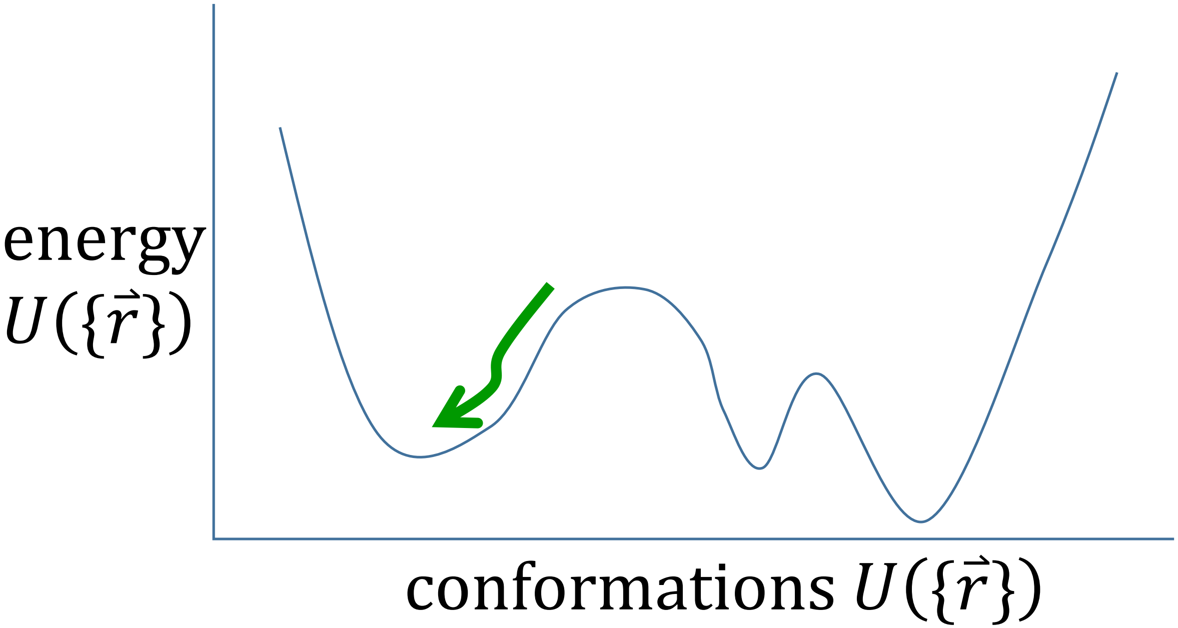
- one often does not care about details
- drop terms that are not interesting
  - treat bonds and angles as rigid



How do you use them ? (1)

3 or 4 ways

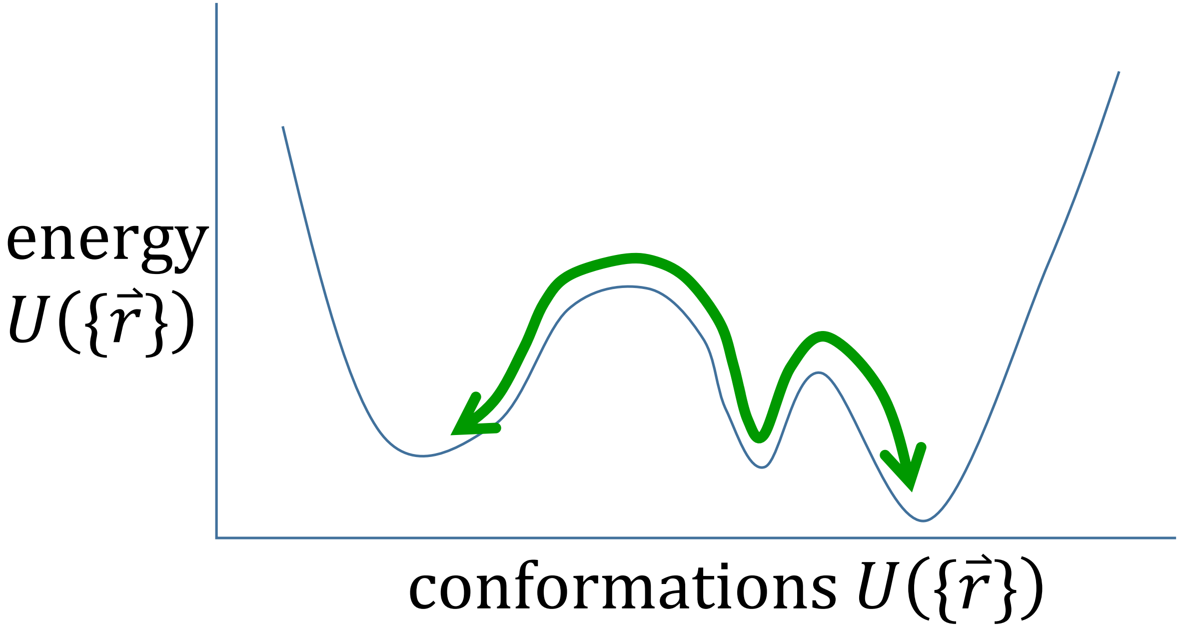
I have coordinates and just want to remove clashes and small problems



1. energy minimisation / gradient descent

How do you use them ? (2)

I want to search a big space or simulate dynamics

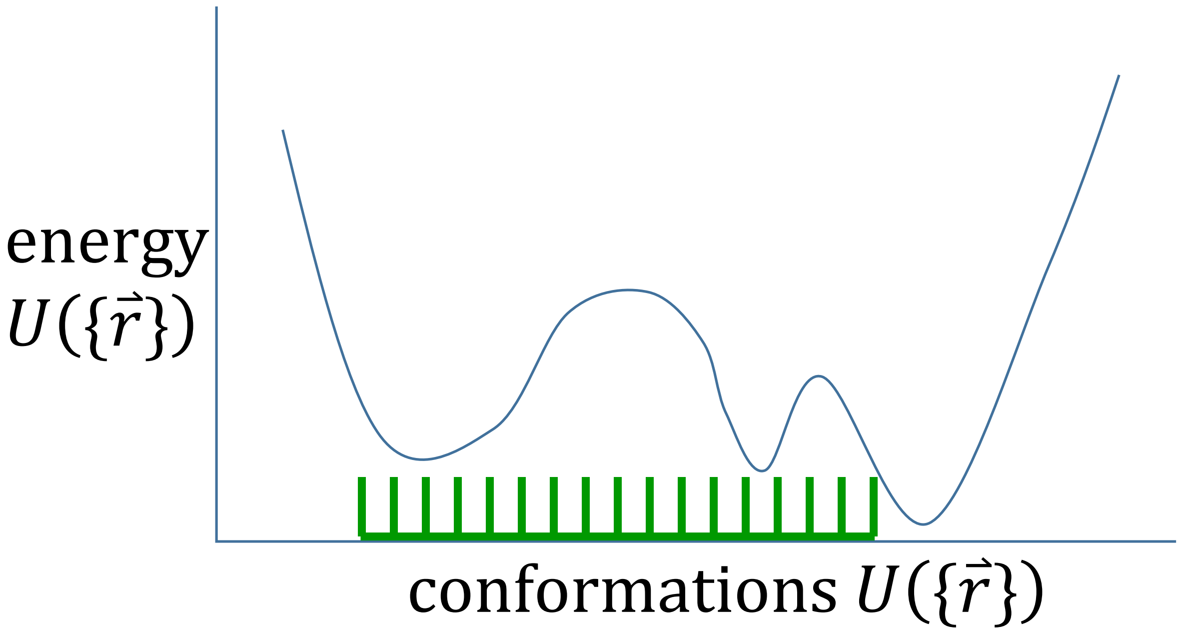


2. molecular dynamics (or Monte Carlo)

computationally expensive

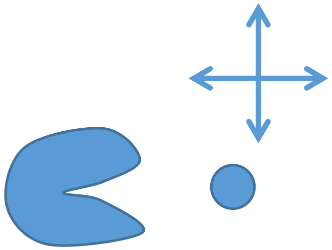
How do you use them ? (3)

small set of possibilities



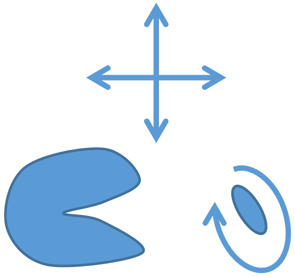
3. grid (gitter) search

How big is the search space ?
protein + ligand

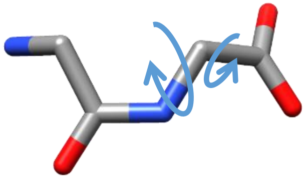


Imagine

- rigid ligand and spherical
- n possibilities in each dimension
- n^3 is search space size (3 degrees of freedom)



- if ligand is not round – rotation about x, y, z
  - extra n^3 rotations
  - total search space is $n^3 n^3 = n^6$ (6 degrees of freedom)



- what if there are internal torsion rotations ?
  - we have m angles each with n possibilities = n^m
  - space is now $n^6 n^m$ let us say n^{6+m}

conformational space for protein

Previous slide assumed protein was rigid

How big is the space for a protein ?

- say bonds and angles are fixed
- we have m torsion angles
- if each has n possibilities, we have n^m search space
- chemistry simplification
  - -there are 3 sidechain conformations then 3^m search space
- for a protein with n residues we have ϕ and ψ angles
- total space is $(2 \cdot 3)^m$
- for a protein of 100 residues $= 6^{100}$ possibilities

- cannot visit them all

the set of conformations is very big

Answer to question at start

- if I can calculate energies – can I predict protein structure ?

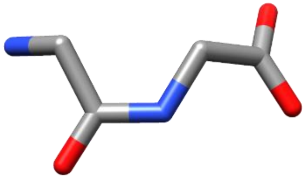
Entropy

Everything I have said was focussed on potential energy, but

$$\Delta G = H - T\Delta S$$

How important is entropy ?

- protein folding – HUGE – there are many unfolded states higher entropy – preferred
  - you need a lot of favourable potential energy
- ligand binding
  - free ligand can
    1. rotate freely
    2. visit much of space (drift around in solution)
  - many of these states (entropy) are lost when a ligand binds



summary of energies

- remember components of potential energy and which are important

- why potential energy is not sufficient to predict behaviour

- even if you could predict energies, could you predict structure ?