

Non-covalent interactions and how macromolecules fold

Lecture 2: More attractive forces. Repulsive forces. Torsion angles and the Ramachandran plot

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First-year Biophysics course

Objective:

Describe the properties of an electrical dipole

Understand how the differences in polarisabilities of atoms leads to polar molecules and how non-polar molecules may induce dipoles in one another leading to the London dispersion interaction

Examine the origins of why molecules don't collapse and combine with the London dispersion interaction to form the Lennard-Jones 6-12 potential

How do the repulsive forces limit the conformational space of polypeptides?

What conformations can polysaccharides and nucleic acids adopt?

Summary:

Two equal but opposite charges separated by a small distance can be described by a dipole

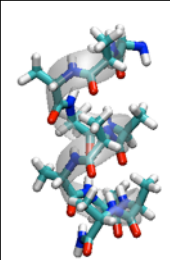
The electronegativity of an atom characterises its ability to attract electrons towards themselves

Dipoles can interact with point charges and other dipoles; they may be permanent or induced.

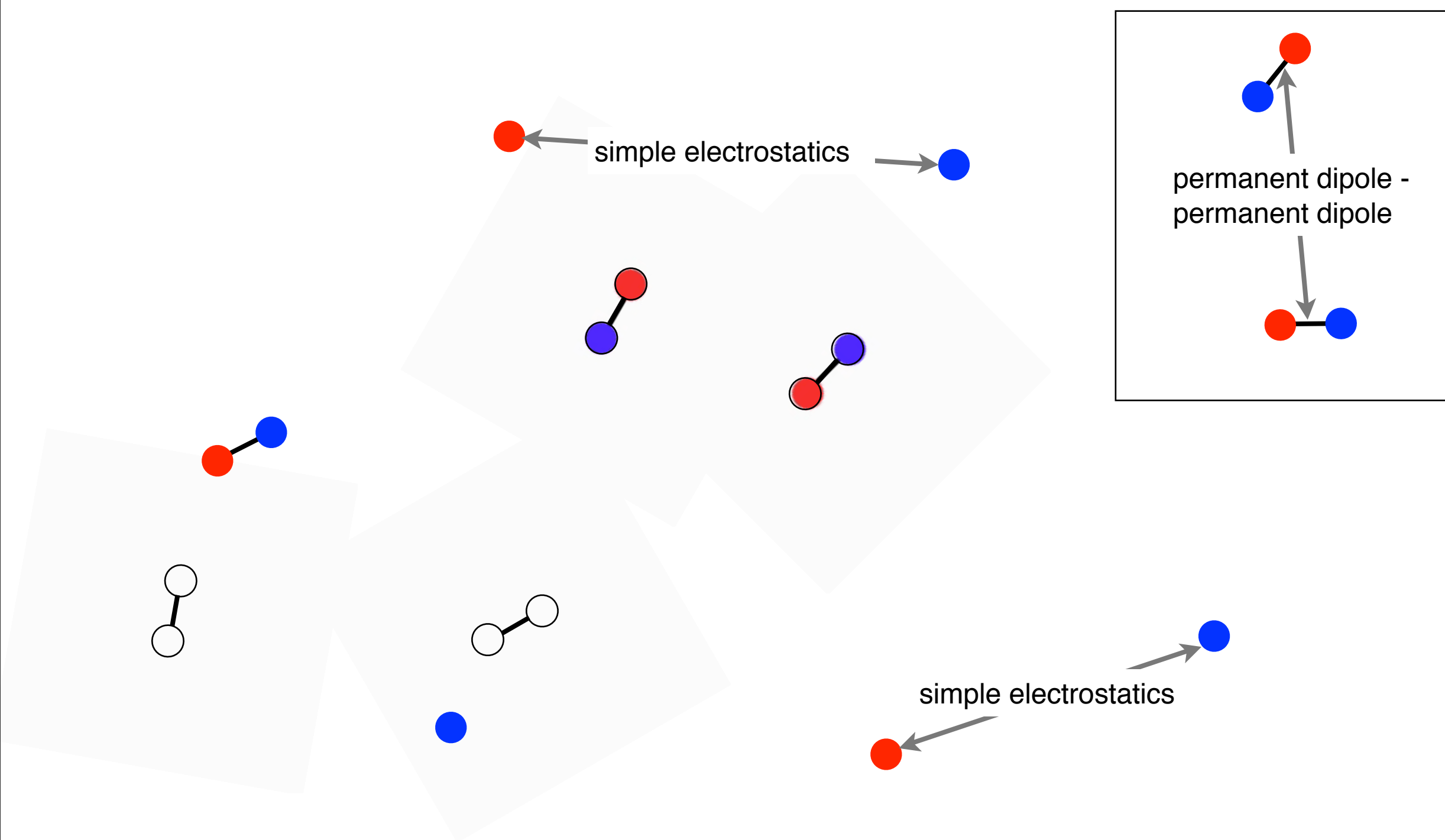
The Lennard-Jones 6-12 potential contains a repulsive term that has its origins in the Pauli Exclusion Principle and an attractive term that models London dispersion interactions.

The backbone conformation of polypeptides can be described by two angles: ϕ and ψ . Only ~22% of $\phi\psi$ combinations are permitted due to steric clashes

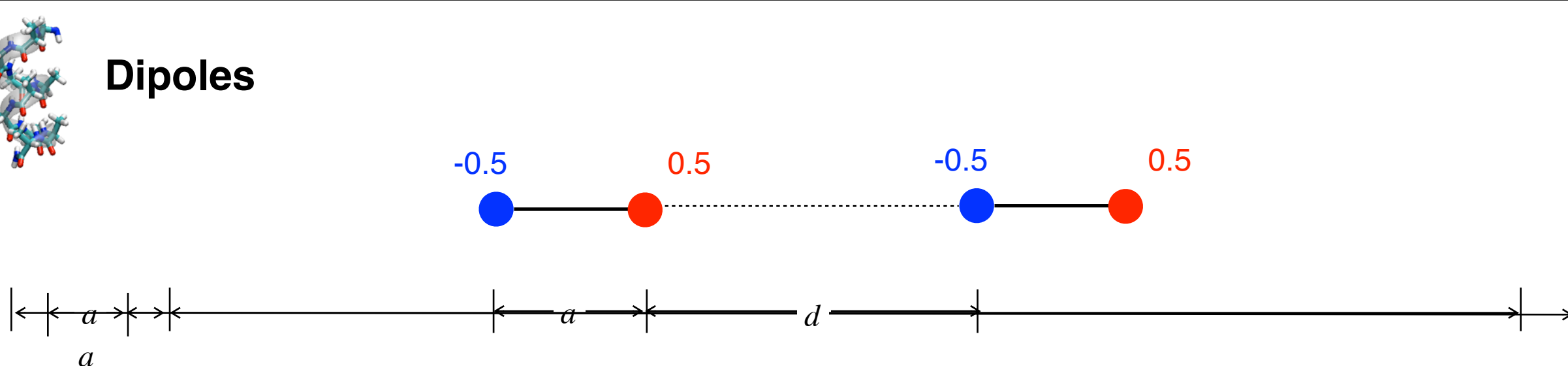
The structures of polysaccharides and nucleic acids can also be described by torsional angles and each has its own characteristic structures



Permanent dipoles



Dipoles



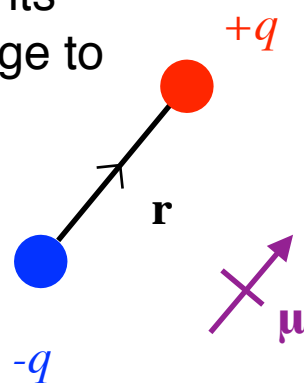
when $d \sim a$ we must explicitly calculate all interactions between all charges

when $d \gg a$ we can describe each pair of charges by a **dipole**

Electrical dipole a dipole is two electrical charges with opposite signs, $\pm q$, separated by a small distance

the dipole moment points from the negative charge to the positive charge

a dipole is usually drawn as an arrow



$$\mu = q \cdot \mathbf{r}$$

dipole moment (vector)

charge

distance vector between charges

Example: what is the magnitude of the dipole moment of two charges, $\pm 1e$, separated by 1 Å?

$$\mu = 1.6 \times 10^{-19} \times 1 \times 10^{-10}$$

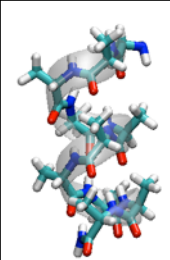
$$\mu = 1.6 \times 10^{-29} \text{ C m}$$

$$\mu = 4.8 \text{ D}$$

the dipole moment is the analogous quantity to the electrical charge but it is a vector due to the relative positioning of the charges

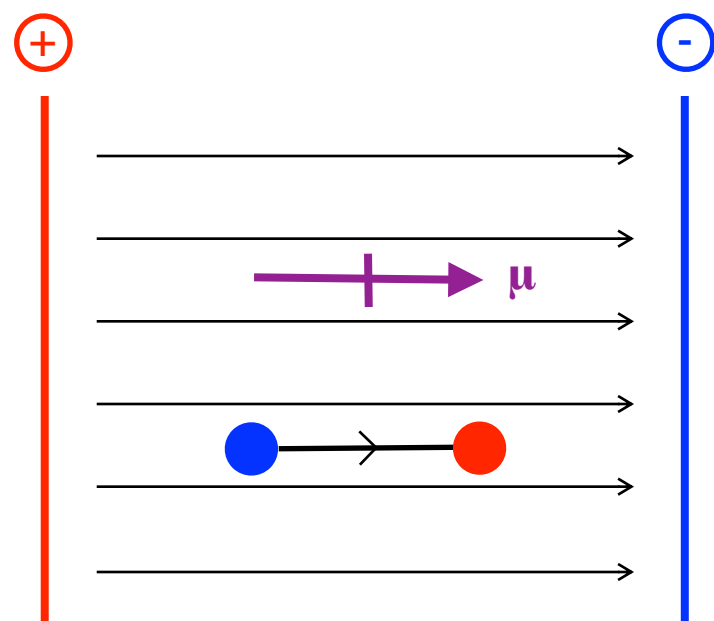
Units: C m or D (Debye)

1 D = 3.34×10^{-30} C m



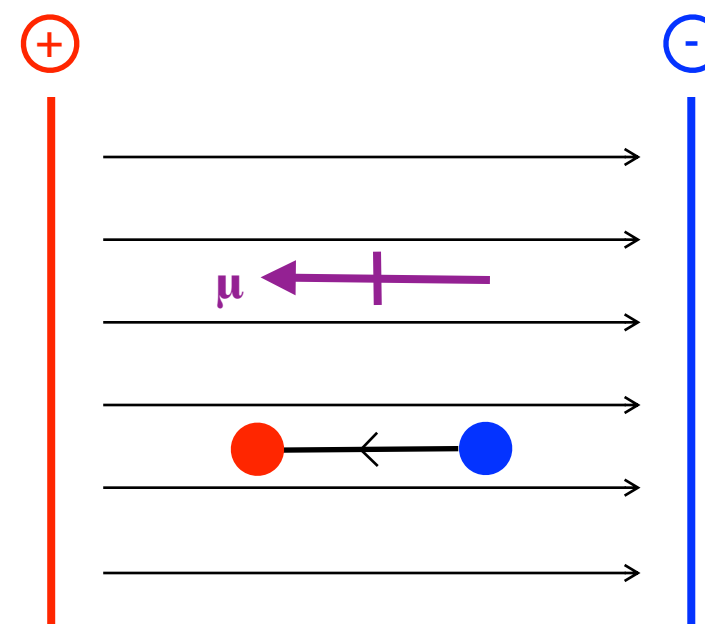
The properties of a dipole can be understood if we think of it as two charges separated by a small distance

in an electric field



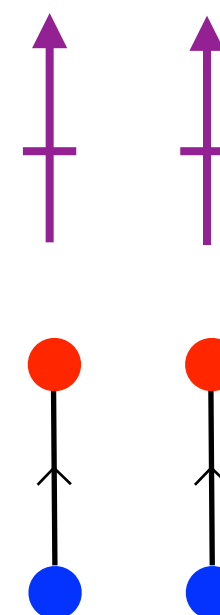
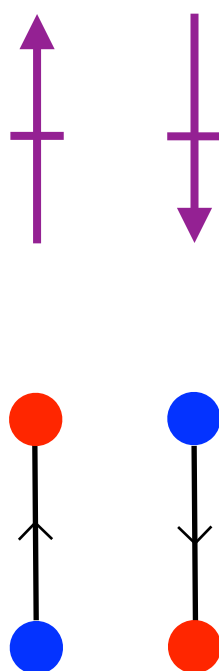
lowest potential energy (stable)
maximum attraction

$$\Delta U = 2\mu E$$



highest potential energy (unstable)
maximum repulsion

parallel to another dipole



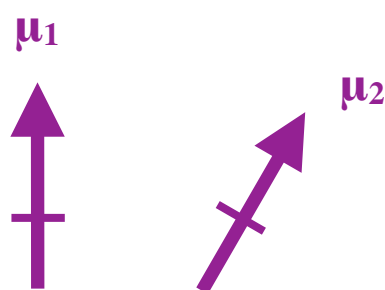
caution: remember $d \gg a$

Dipole-dipole interaction energies

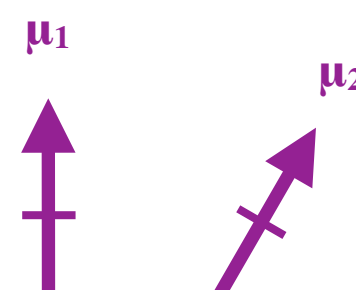
(a) dipole - ion



(b) fixed dipole - fixed dipole



(c) free dipole - free dipole



———— drops off faster with r i.e. shorter range —————→

$$\Delta U \propto \frac{\mu_1 q_2}{r^2}$$

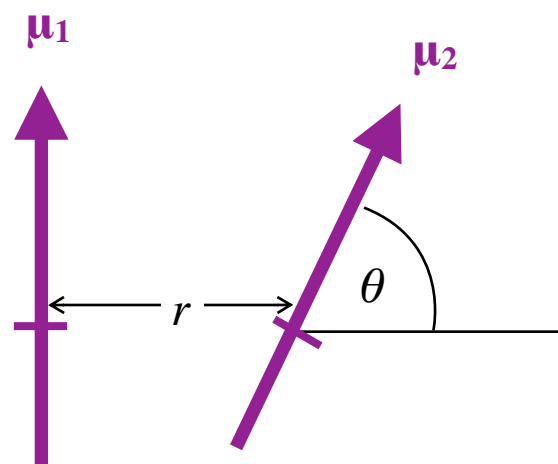
$$\Delta U \propto \frac{\mu_1 \mu_2}{r^3}$$

$$\Delta U \propto \frac{(\mu_1 \mu_2)^2}{r^6}$$

what does the constant of proportionality depend upon?

The variation with angle is complex

Consider the general case when two dipoles are **fixed** at an angle θ

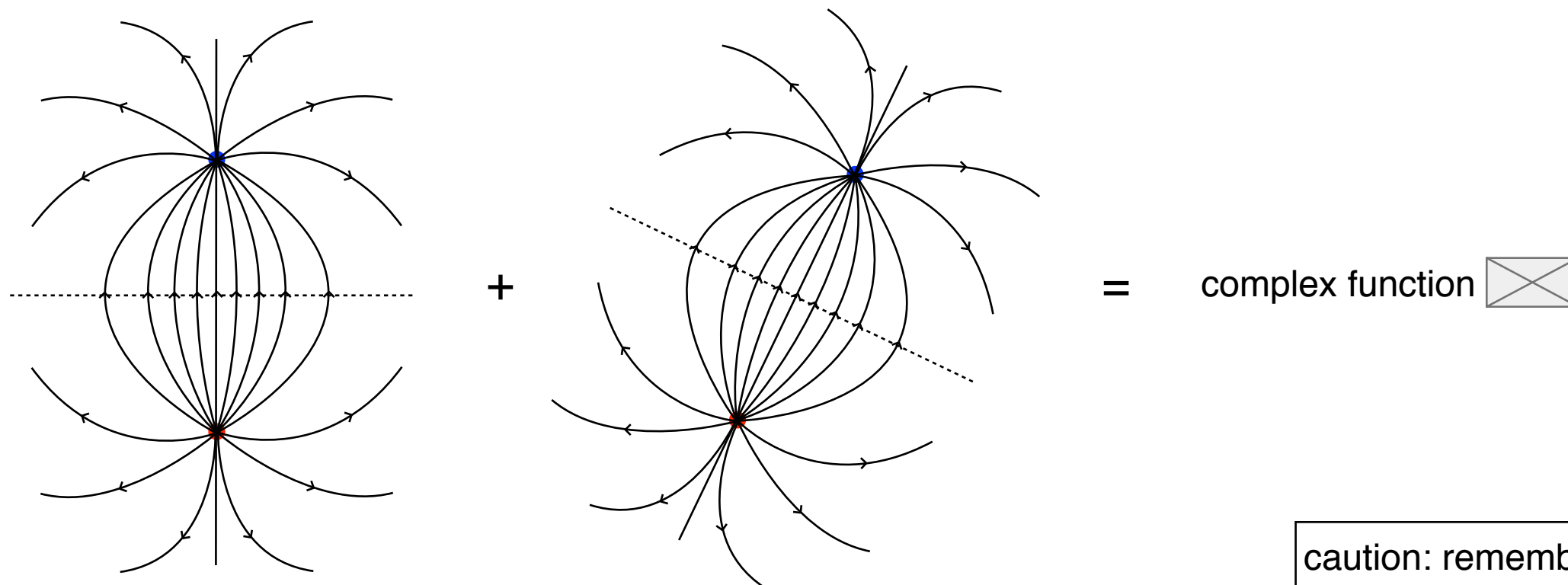


$$\Delta U = \frac{1}{4\pi\epsilon\epsilon_0} \frac{\mu_1\mu_2 f(\theta)}{r^3}$$

this is a complicated trigonometric term where $f(\theta) = 1$ when $\theta = 0$

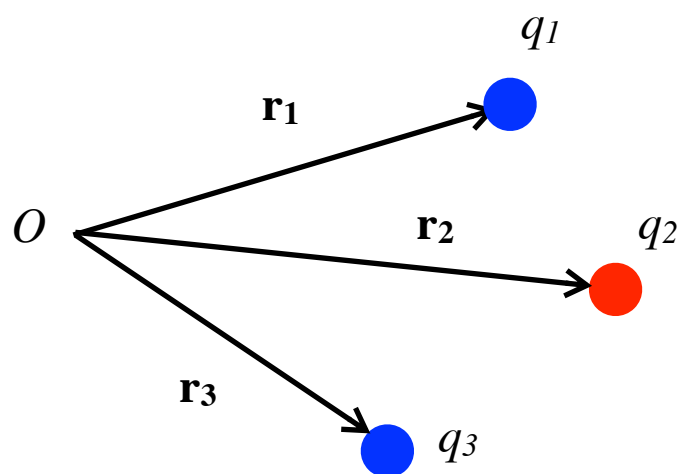
falls off faster with distance than single charges

We can intuitively see that $f(\theta)$ is complex by imagining adding the electric fields of two dipoles. This is like when we added the electric fields of two point charges



caution: remember $d \gg a$

Can combine multiple charges to form one dipole

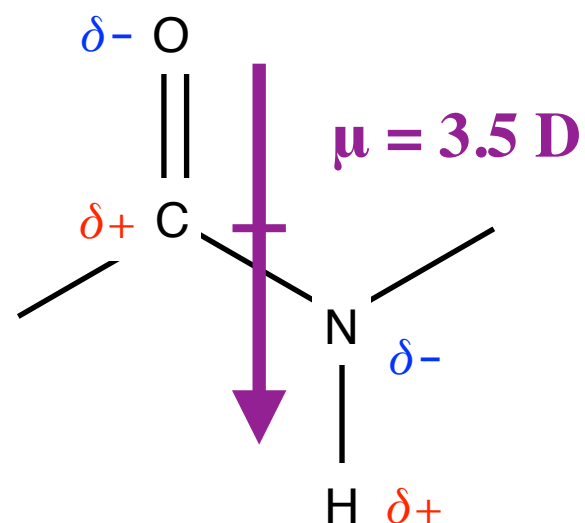


$$\mu = q_1 \mathbf{r}_1 + q_2 \mathbf{r}_2 + q_3 \mathbf{r}_3$$

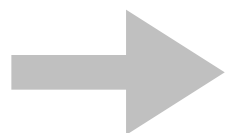
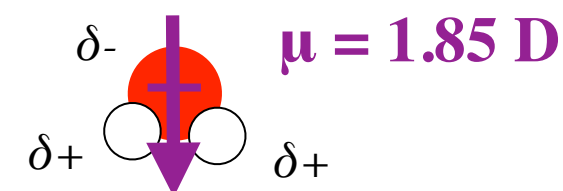
$$\mu = \sum_i q_i \mathbf{r}_i$$

Examples

(1) the peptide bond



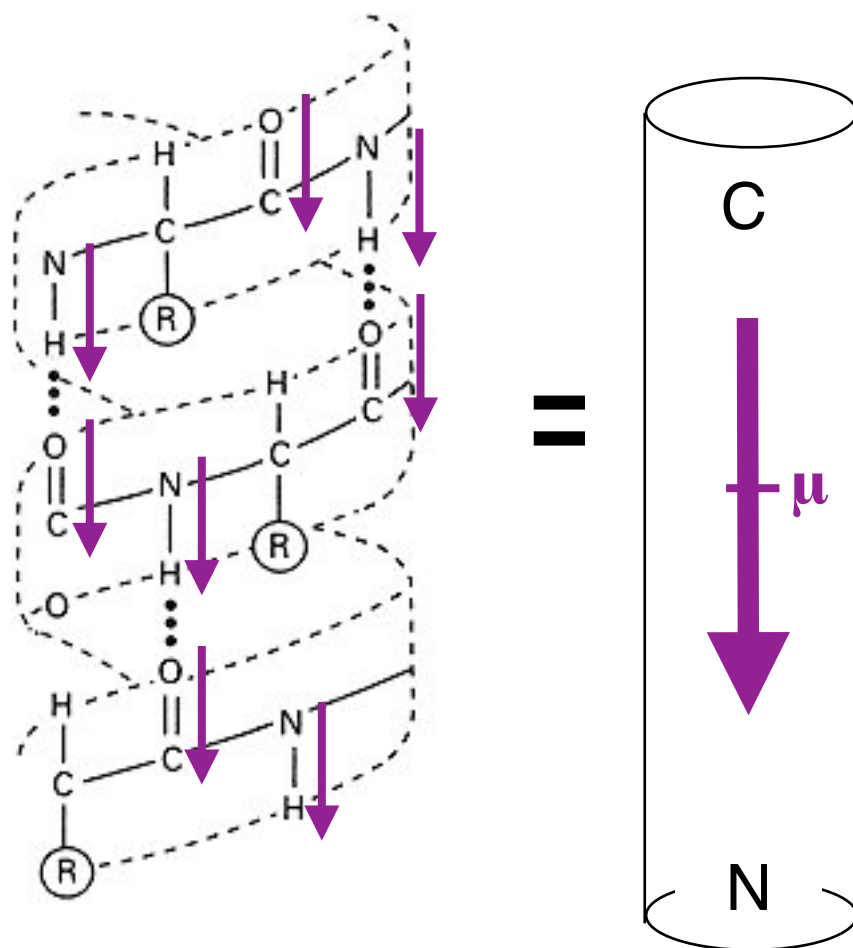
(2) water



don't have to stop there: calculate the **molecular dipole** of a whole protein or an alpha helix if we know the structure

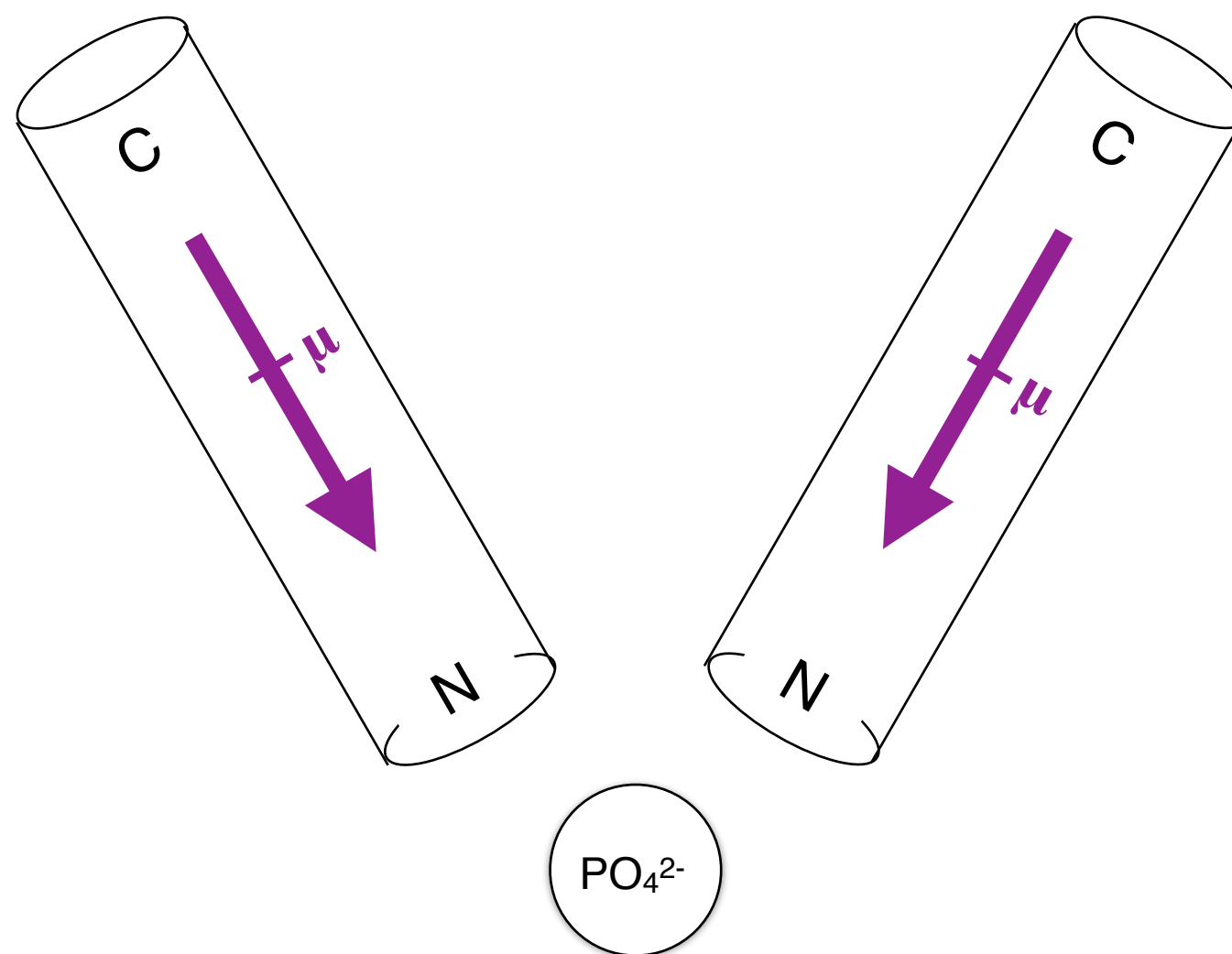
Consequences of the α -helix dipole moment

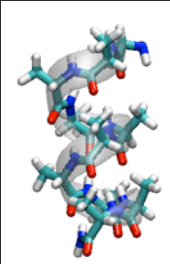
The C=O and N-H groups are generally aligned with the axis of the helix



Each a helix has a net dipole moment pointing towards its N-terminus

The net dipole moments can stabilise ion binding sites in proteins (e.g. -50 kJ mol^{-1})



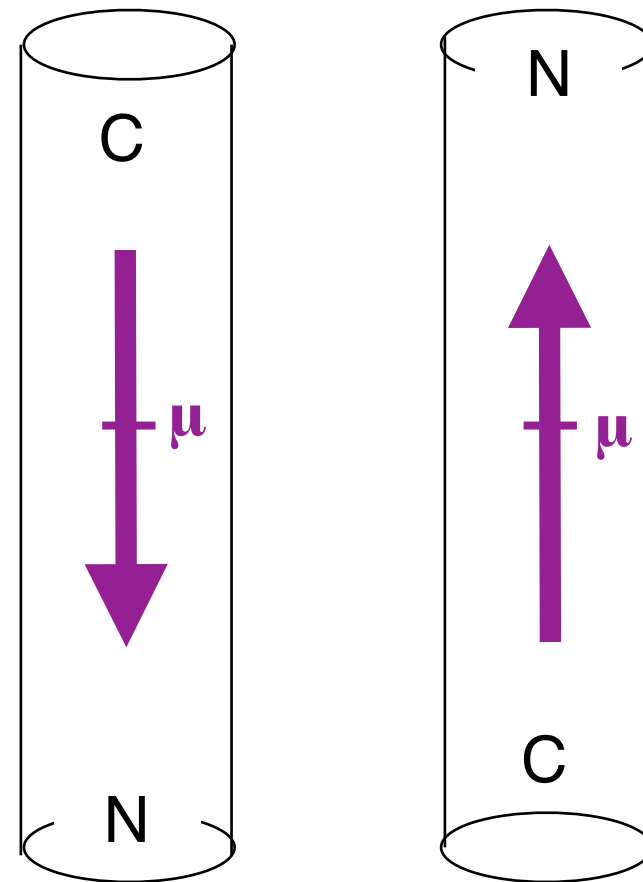
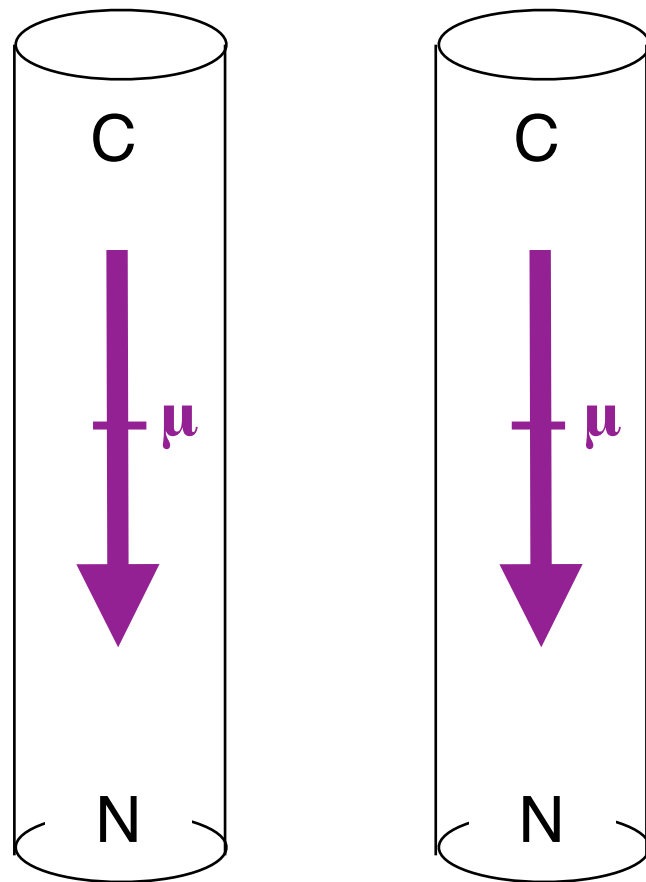


Antiparallel helix packing in proteins

parallel α -helices

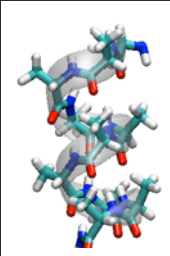
..are less stable than...

antiparallel α -helices

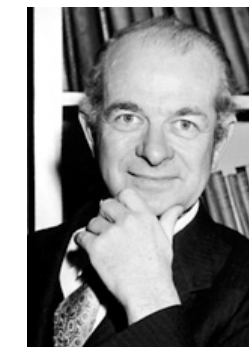


To understand this, remember each dipole can be represented as two charges separated by a small distance...





Polar molecules



Elements differ in their ability to attract electrons towards themselves (when forming covalent bonds)

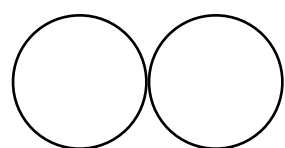
This is called the **electronegativity**, χ , and is often characterised using the **Pauling scale**

Elements with a high electronegativity have a high tendency to attract electrons (e.g. Group VII)

Elements with a low electronegativity have a low tendency to attract electrons (e.g. Group I)

Consider diatomic molecules

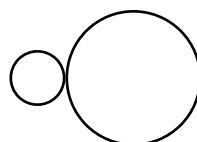
(i) Homonuclear (e.g. O_2)



no difference in χ

electrons evenly shared between atoms

(ii) Heteronuclear (e.g. HCl)



difference in χ

electrons not evenly shared between atoms

separation of centres of charge

net permanent dipole moment

H 2.2							He
Li 1.0	Be 1.6	B 2.0	C 2.6	N 3.0	O 3.4	F 4.0	Ne
Na 0.93	Mg 1.3	Al 1.6	Si 1.9	P 2.2	S 2.6	Cl 3.2	Ar
K 0.82	Ca 1.3	Ga 1.6	Ge 2.0	As 2.2	Se 2.6	Br 3.0	Kr
Rb 0.82	Sr 0.95	In 1.8	Sn 2.0	Sb 2.1	Te 2.1	I 2.7	Xe
Cs 0.79	Ba 0.89	Tl 2.0	Pb 2.3	Bi 2.0	Po 2.0	At	Rn

Electronegativity

4.0– 3.0–3.9 2.0–2.9 1.0–1.9 0–0.99

$$\mu \sim \Delta\chi$$

magnitude of dipole (D)

difference in Pauling electronegativities

For example: HCl

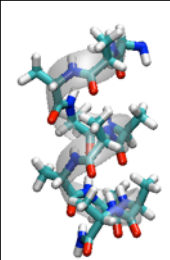
from scale:

$$\mu = 3.2 - 2.2$$

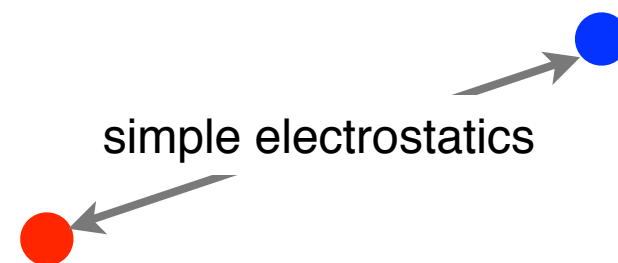
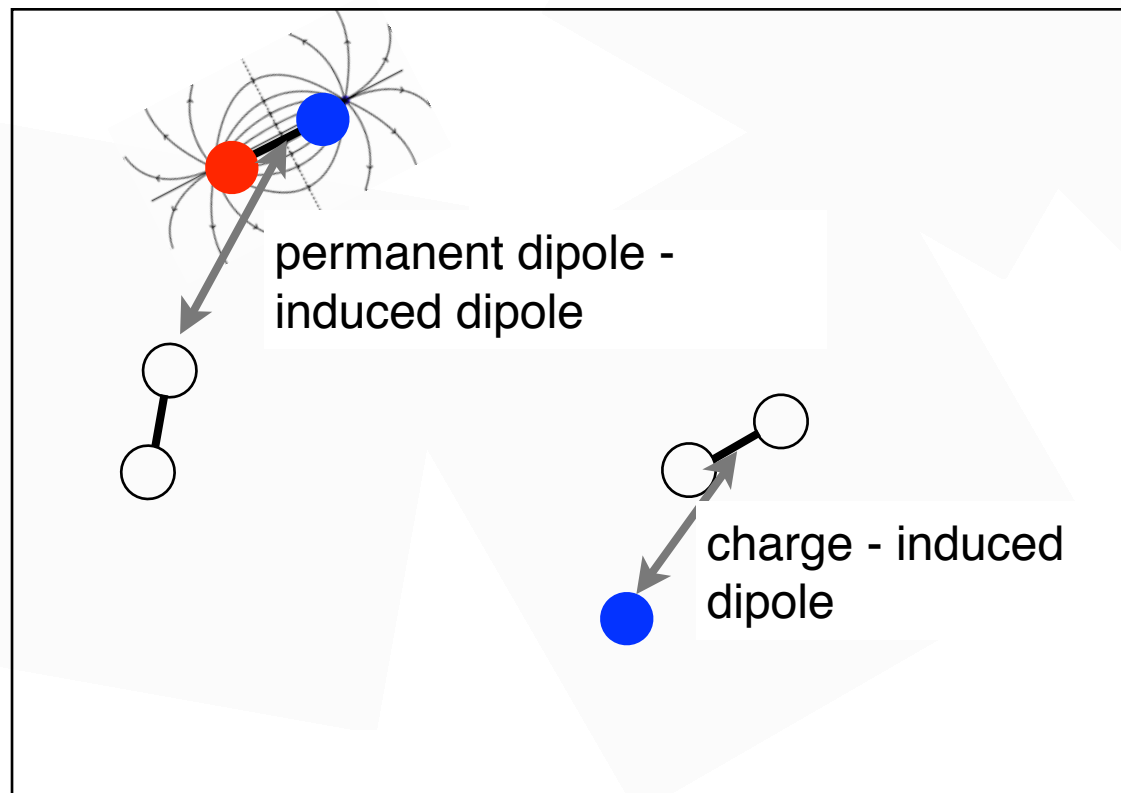
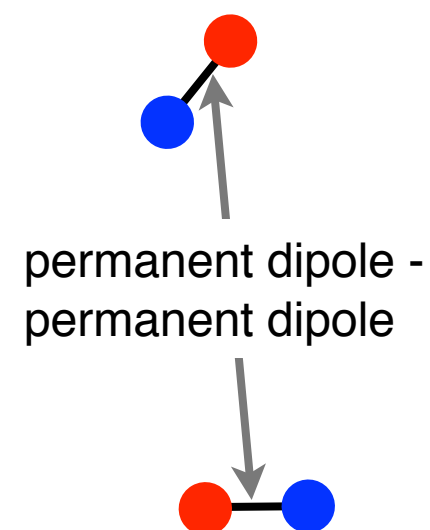
$$\mu = 1.0 \text{ D}$$

from experiment:

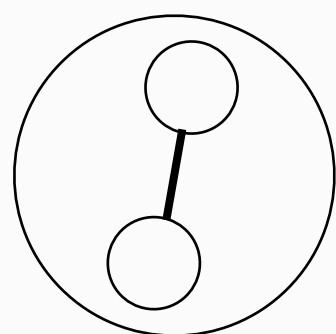
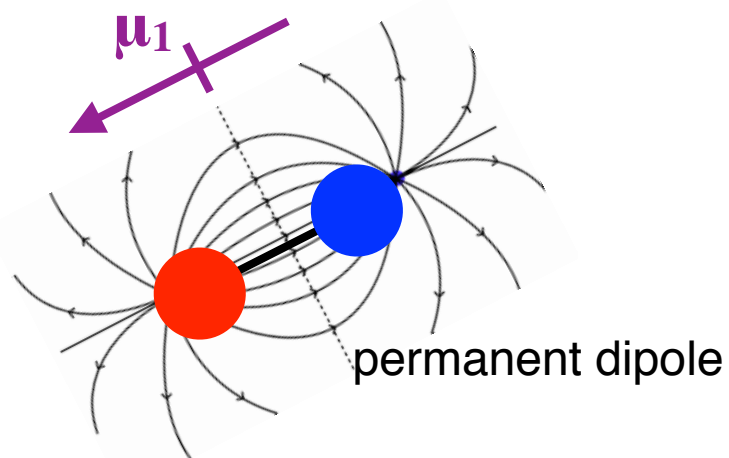
$$\mu = 1.08 \text{ D}$$



Induced temporary dipoles



The magnitude of the induced dipole depends on the polarizability of the molecule



electric field could be due to either a permanent dipole or an ion

non-polar molecule or atom

polarizability and polarizability volume

$$\mu^* = \alpha E$$

magnitude of induced dipole

magnitude of applied electric field

polarizability of molecule Units: C m² V⁻¹

(this is a simplification since it also depends on the orientation of the molecule)

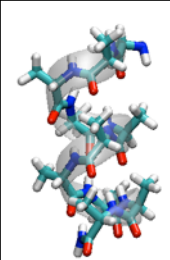
define the **polarizability volume** for a particular molecule as

$$\alpha' = \frac{\alpha}{4\pi\epsilon_0}$$

Units: m³

for induced dipoles the electric potential energy is

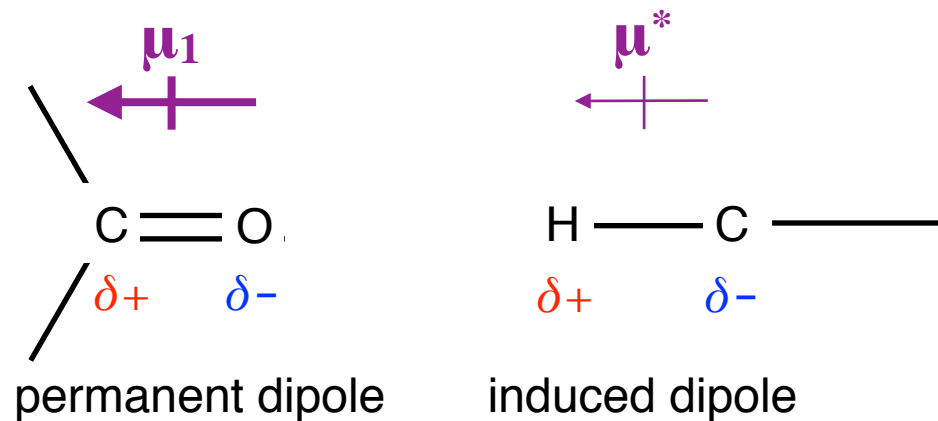
$$\Delta U = -\frac{\mu_1^2 \alpha'_2}{r^6}$$



Polarisability volumes

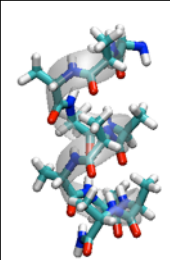
Polarisability volumes

Example

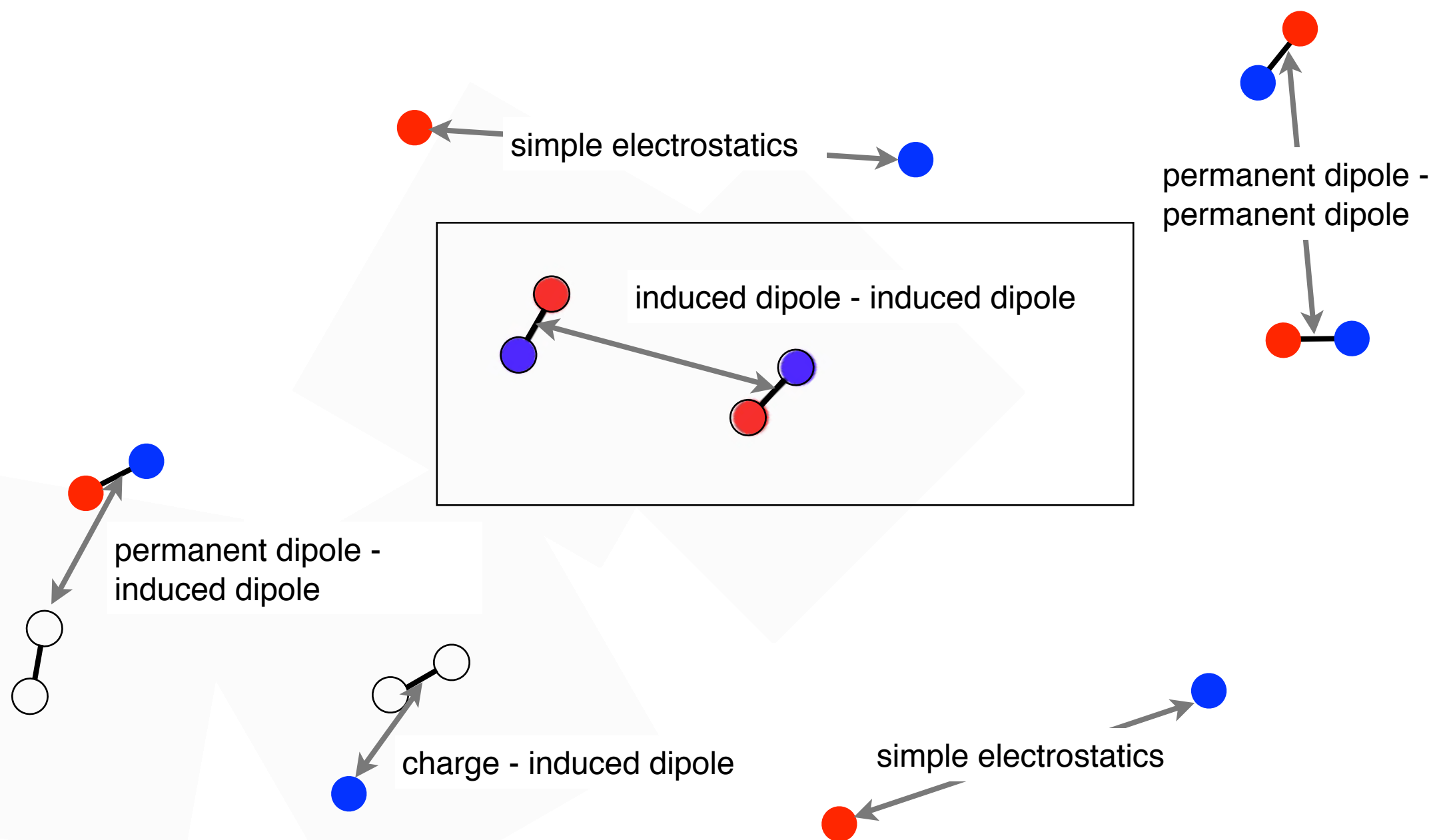


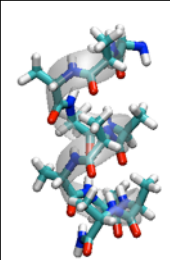
	μ (D)	α'	
argon	0	1.66	
CCl	0	10.5	
C	0	10.4	
H	0	0.819	← homonuclear
H	1.85	1.48	
NH	1.47	2.22	
HCl	1.08	2.63	heteronuclear
HBr	0.8	3.61	
HI	0.42	5.45	

α' is an average over all orientations of the molecule (compare CCl₄ and H₂O)



Induced dipole - induced dipole interactions





London dispersion interactions

also called dispersion interaction or
induced dipole - induced dipole interaction

1. molecules have no **net** charge or permanent dipole (e.g. H₂)

6. there is a small **net attraction** between the two molecules

2. the instantaneous electron positions **fluctuate**

3. creates a small, **transient dipole**

4. this then **induces** another transient dipole in the second molecule

5. the magnitude and direction of this dipole remains **correlated** with the fluctuating transient dipole in the first molecule

polarizabilities of
molecules 1 and 2

ionisation energies

$$\Delta U \propto -\frac{C}{r^6}$$

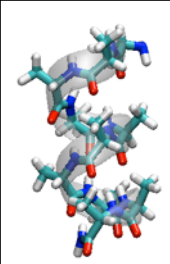
where

$$C \propto \frac{\alpha_1 \alpha_2 I_1 I_2}{I_1 + I_2}$$

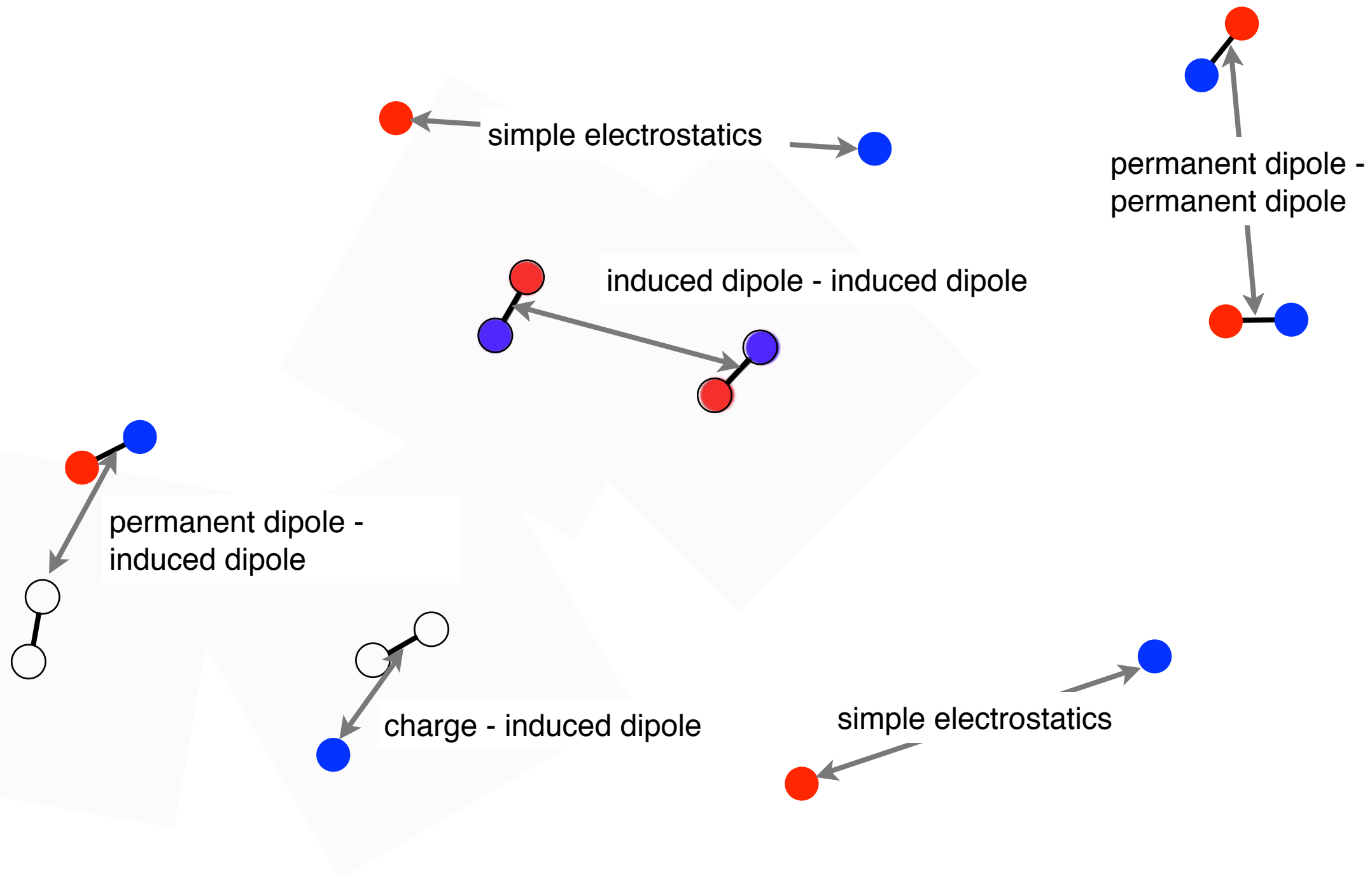
dispersion interactions are small
(~ -0.1 kJ mol⁻¹)

It is present in all materials

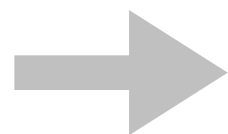
This is the only non-covalent interaction if the molecules are non-polar (e.g. the Noble gases)



All these interactions are electrostatic in nature and attractive...



...so why don't molecules collapse?



There are also **repulsive forces** that act at very **short range**

These arise from

(1) electrostatic repulsion between electron orbitals (classical effect)
(can no longer consider an atom as a simple point at short distances)

(2) the Pauli Exclusion Principle (quantum effect)
“no two electrons can have the same quantum numbers”

i.e. no electrons can occupy the same space

The combined effect of these repulsive forces is therefore usually modelled by a term like

$$\Delta U \propto \frac{1}{r^n}$$

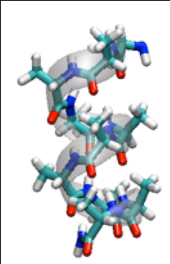
n is usually taken to be 12

Why is this a “principle”?

Overlap of electron clouds results in splitting into **bonding** and **antibonding** molecular orbitals, with the latter dominating. The overlap can only be calculated for some simple systems and varies generally as

$$\Delta U \propto \frac{1}{r^n}$$

with $9 \leq n \leq 12$

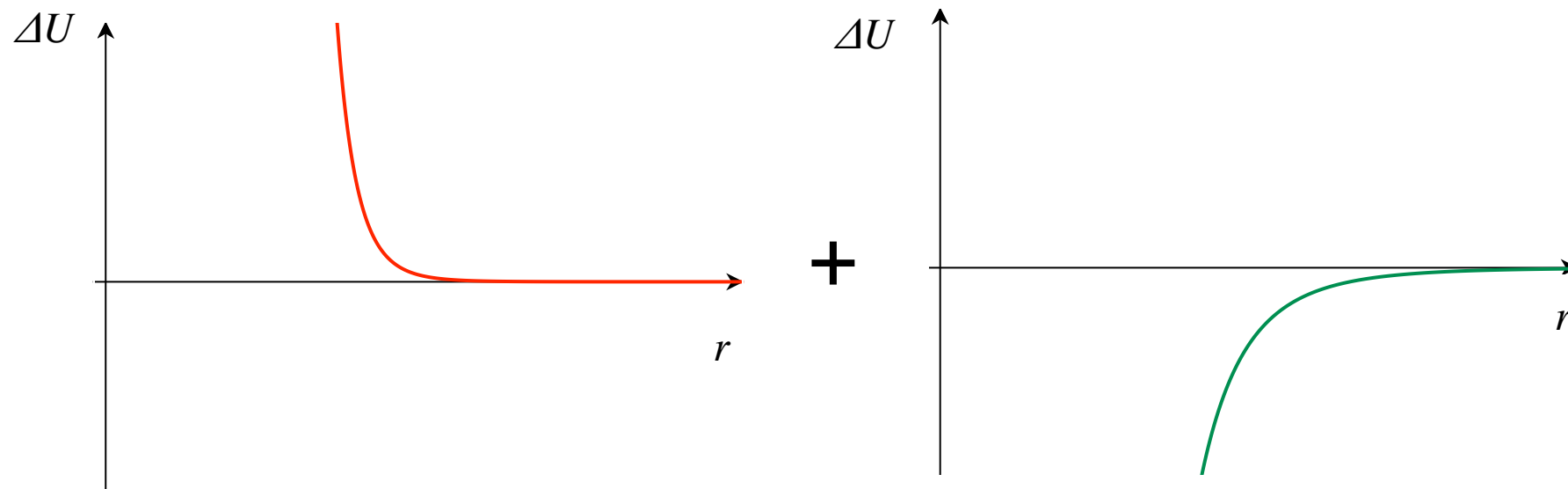


The Lennard Jones 6-12 potential

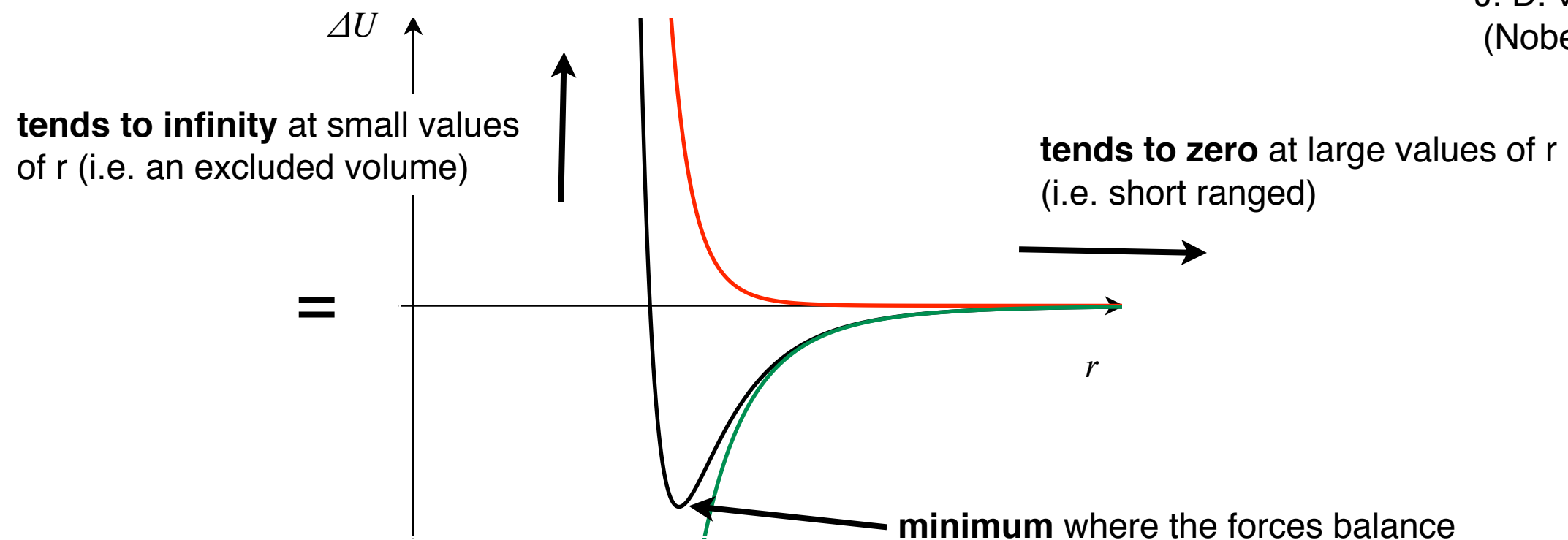
for non-polar molecules this **repulsive term** is balanced by the **attractive London dispersion forces**

if n is taken to be 12 we get the **Lennard Jones 6-12 potential**

$$\Delta U = \frac{A}{r^{12}} - \frac{B}{r^6}$$



J. D. van der Waals
(Nobel prize 1910)



Where do the forces balance?

usually written instead as

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

note that when $r = \sigma$, $\Delta U = 0$
so σ is the radius when ΔU is 0

since $F = -\frac{dU}{dr}$ differentiating...

$$-\frac{dU}{dr} = -4\epsilon^* \left[-\frac{12\sigma^{12}}{r^{13}} + \frac{6\sigma^6}{r^7} \right]$$

at the stationary point, $\frac{dU}{dr} = 0$

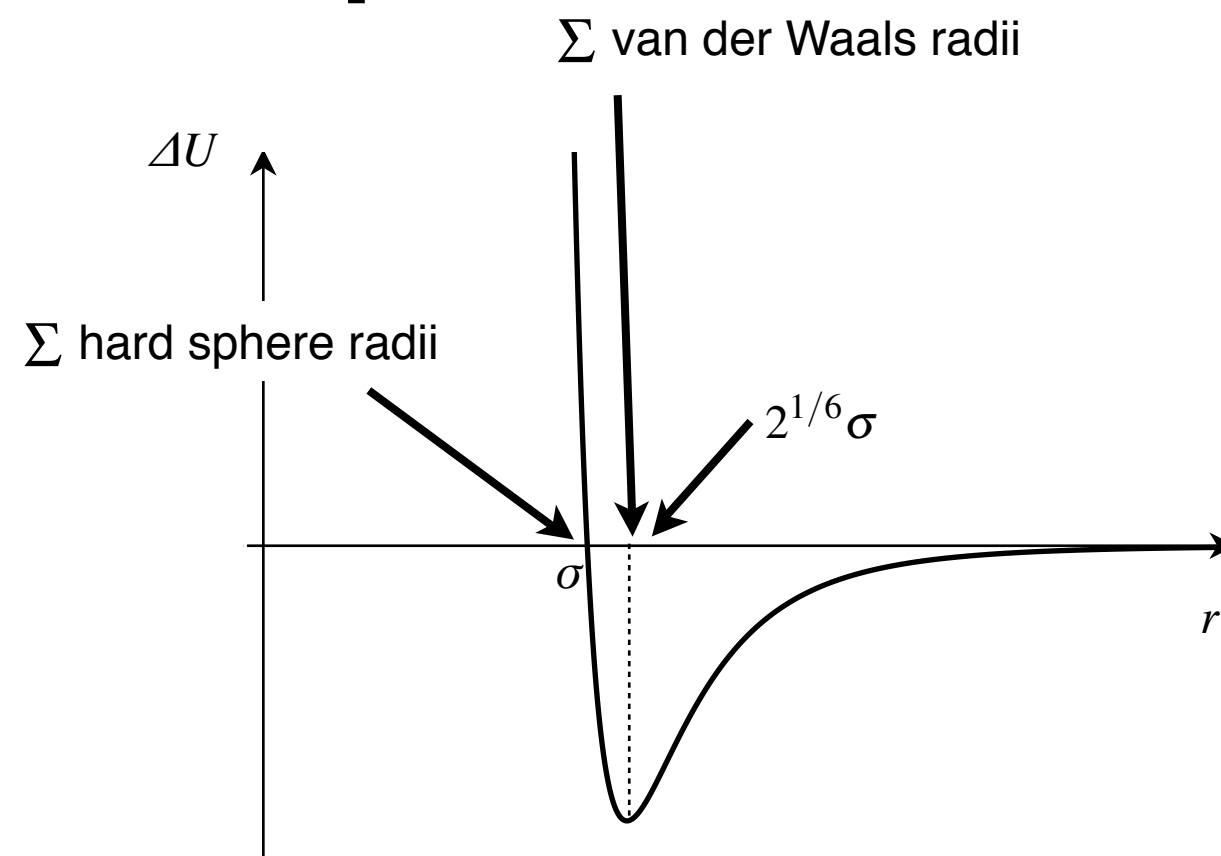
$$0 = -4\epsilon^* \left[-\frac{12\sigma^{12}}{r^{13}} + \frac{6\sigma^6}{r^7} \right]$$

$$\frac{6\sigma^6}{r^7} = \frac{12\sigma^{12}}{r^{13}}$$

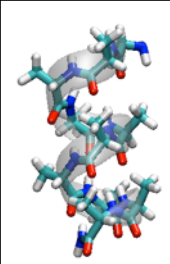
$$r^6 = 2\sigma^6$$

the forces balance when

$$\left| \begin{array}{l} r = 2^{1/6}\sigma \\ r = 1.123\sigma \end{array} \right.$$



σ is the sum of the “hard-core” radii
of the two interacting atoms



What is the depth of the minimum?

substitute $r = 2^{1/6}\sigma \longrightarrow \Delta U = 4\epsilon^* \left[\left(\frac{\sigma}{r} \right)^{12} - \left(\frac{\sigma}{r} \right)^6 \right]$

$$\Delta U = 4\epsilon^* \left[\frac{\sigma^{12}}{(2^{1/6})^{12}\sigma^{12}} - \frac{\sigma^6}{(2^{1/6})^6\sigma^6} \right]$$

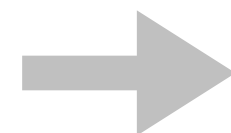
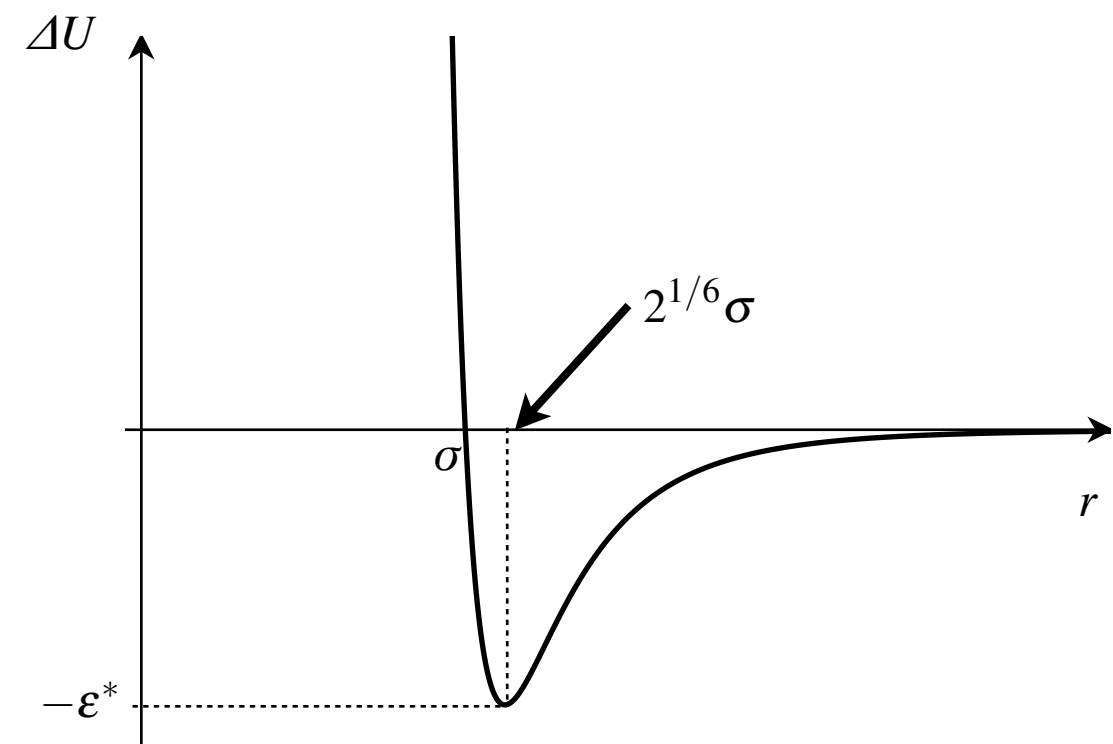
$$\Delta U = 4\epsilon^* \left[\frac{1}{2^2} - \frac{1}{2} \right]$$

$$\Delta U = 4\epsilon^* \left[\frac{1}{4} - \frac{1}{2} \right]$$

$$\Delta U = -\frac{4\epsilon^*}{4}$$

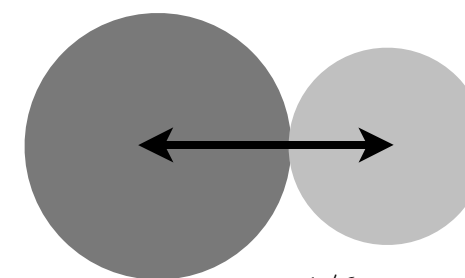
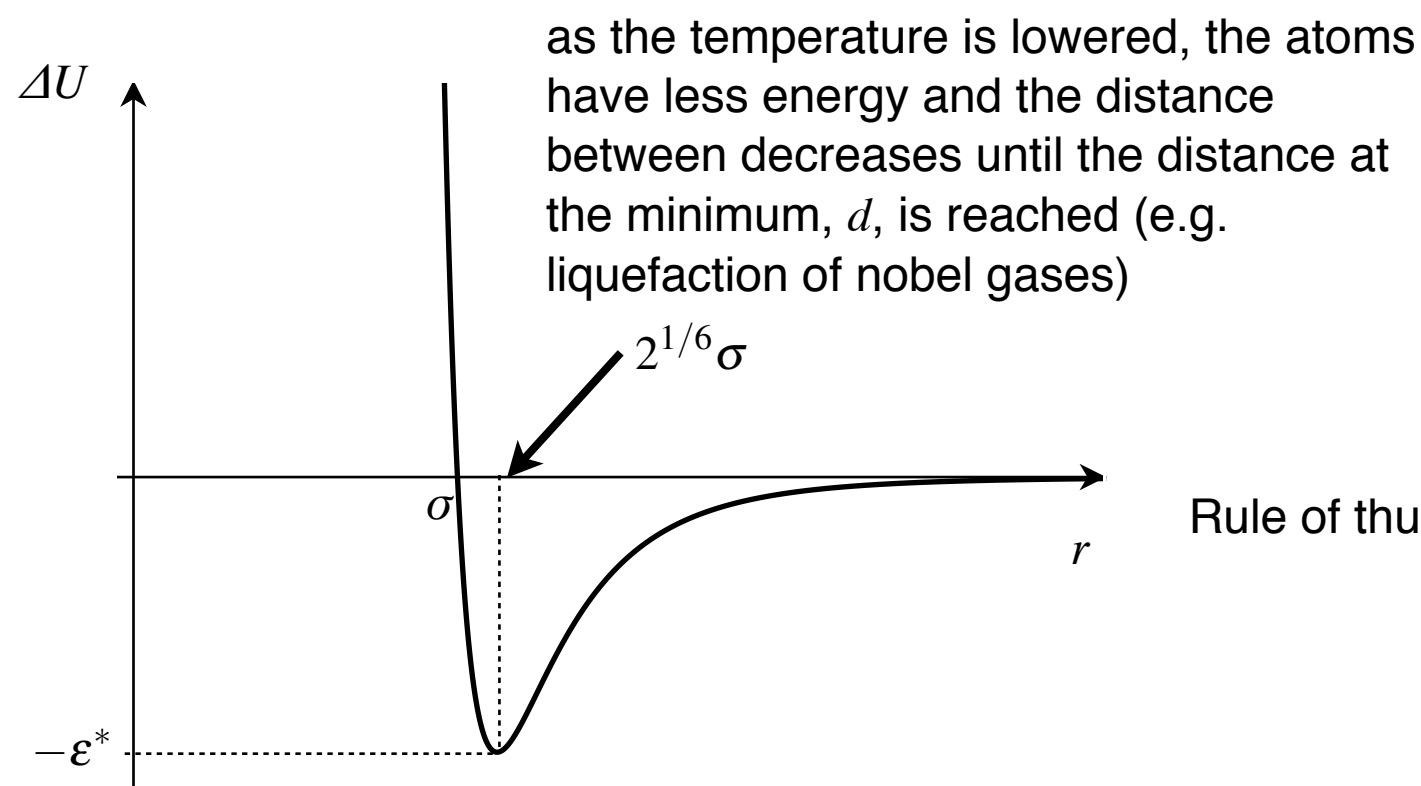
$$\Delta U = -\epsilon^*$$

could show this is a minimum by examining the sign of $\frac{d^2U}{dr^2}$



ϵ^* is the depth of the minimum

van der Waals radii



$$d = 2^{1/6}\sigma$$

$$d = \sum \text{sum of van der Waals radii}$$

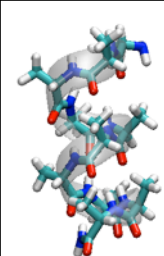
Rule of thumb: van der Waals radii > atomic radii

van der Waals radii (in Å)

				can also measure for		CH ₃	2.0
				atomic groups:		H ₂ O	1.6
H	1.1						
C	1.7						
N	1.5	P	1.9			Ar	1.7
O	1.4	S	1.85				
F	1.35	Cl	1.8	Br	1.85	I	2.2

← the more electronegative the atom, — the smaller the vdW radius

How could we describe all these interactions?



...attractive London dispersion forces

...repulsive forces

1. model all charges explicitly

$$\Delta U = 4\epsilon^* \left[\left(\frac{\sigma}{r} \right)^{12} - \left(\frac{\sigma}{r} \right)^6 \right] + \frac{1}{4\pi\epsilon\epsilon_0} \frac{q_i q_j}{r_{ij}}$$

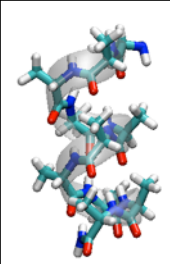
Lennard Jones potential

Coulomb electrostatics

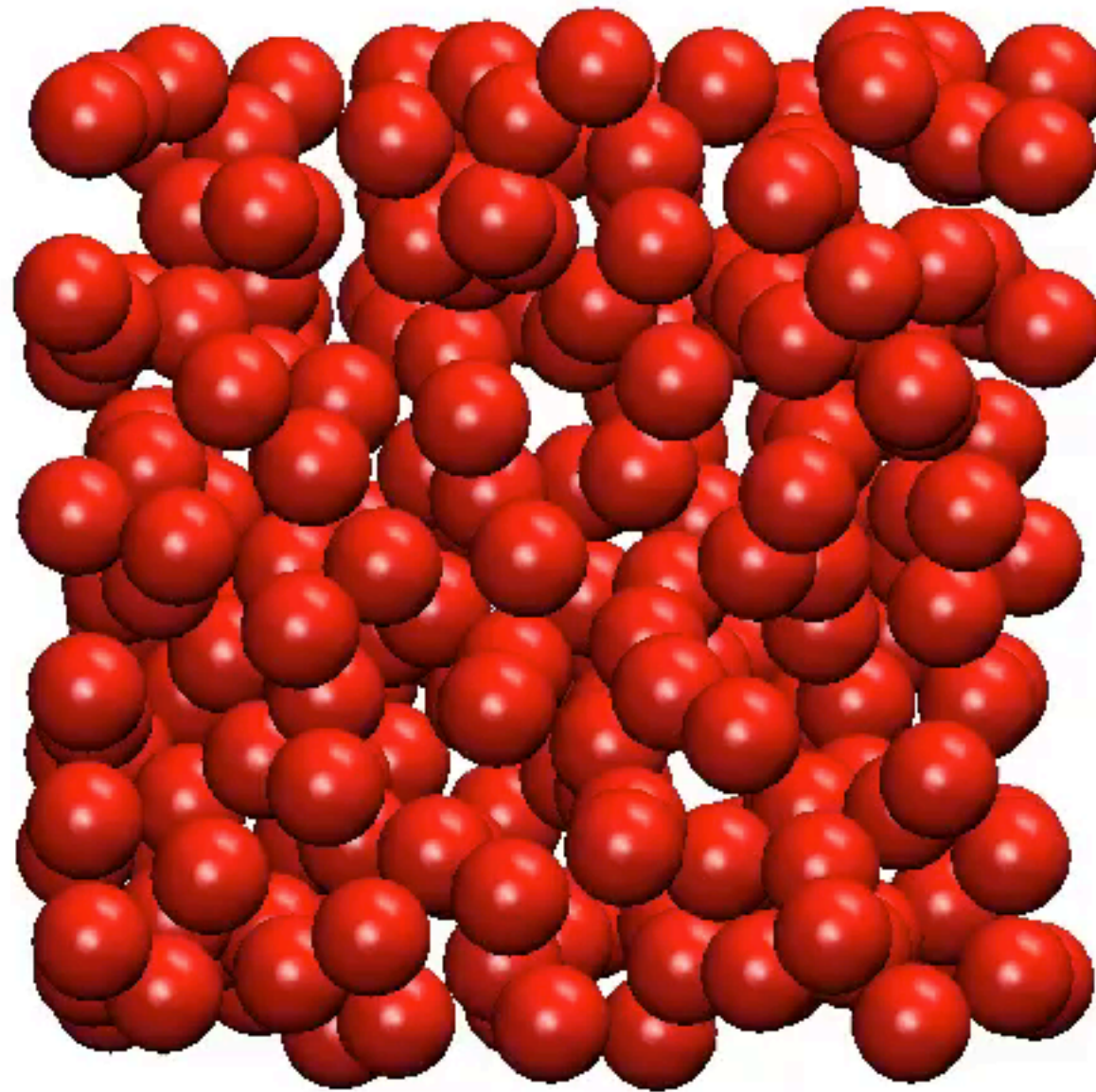
more, simpler calculations

2. reduce the number of interactions by describing charges separated by a small distance as dipoles. e.g. include permanent dipole - permanent dipole interaction term

fewer, more complex calculations



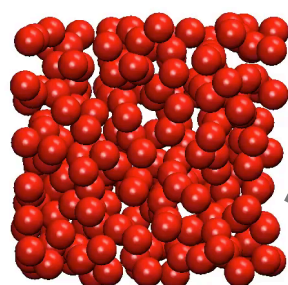
Movie: liquid Argon



Radial distribution functions

incident X-rays or
neutrons

sample solution



scattering angle

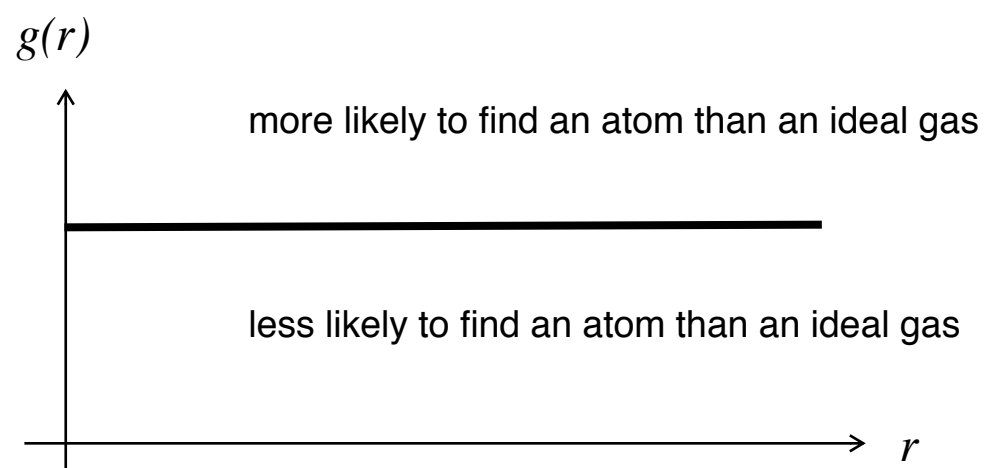
$g(r)$

0

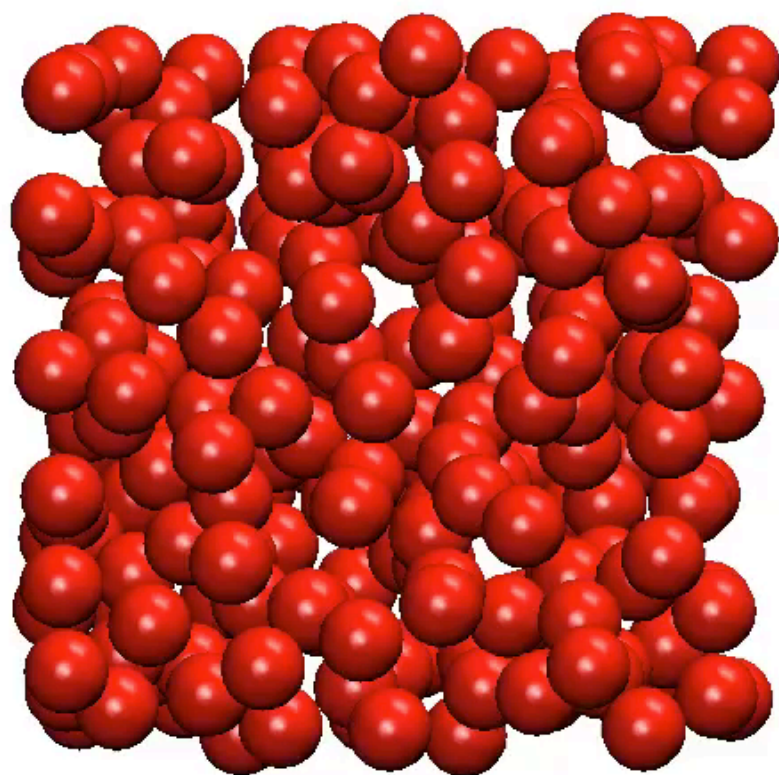
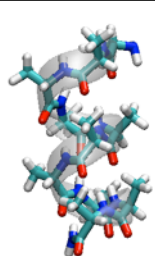
r

From the scattering data we can construct the
radial distribution function $g(r)$

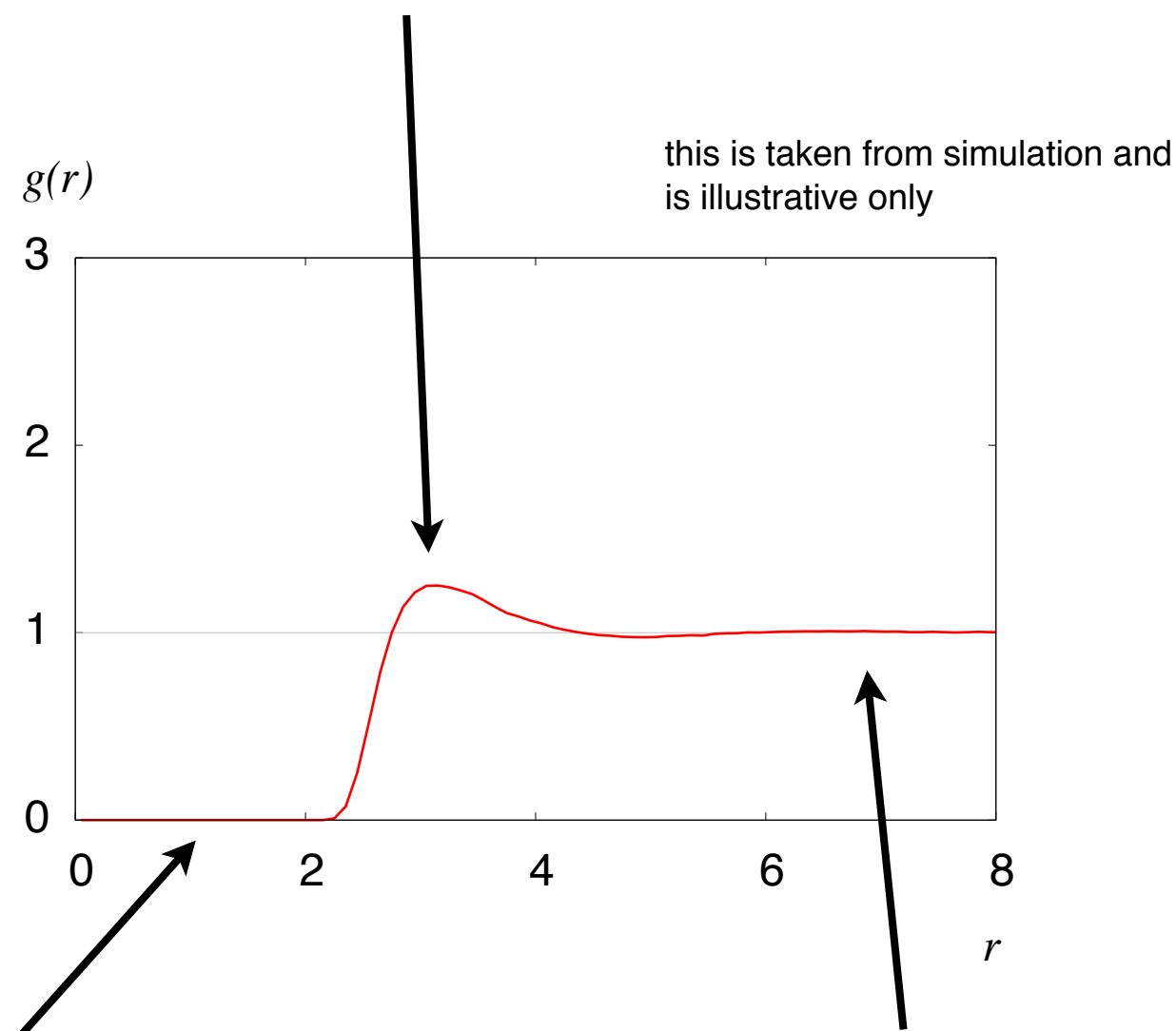
➔ This is the probability of finding a second atom at a
distance r from the first normalised w.r.t an ideal gas



liquid Argon radial distribution functions



slightly enhanced probability of finding another Argon atom at $\sim 3\text{\AA}$ due to London dispersion forces

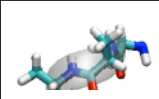


zero probability of finding another Ar atom within $\sim 2.2\text{\AA}$ due to repulsive forces in Lennard Jones 6-12 potential

same as ideal gas at large r



how can we describe / model more complex molecules?



Deca-alanine: a simple model

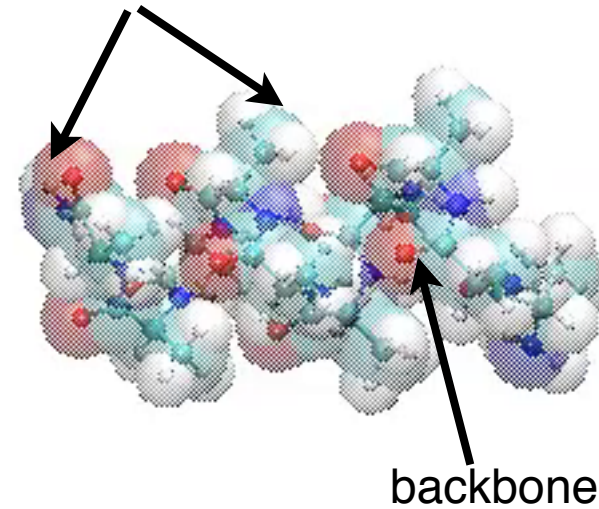


sequence: AAAAAAAAAA

short α -helix

cartoon representation

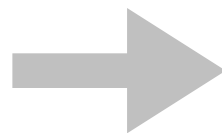
CH₃ sidechains



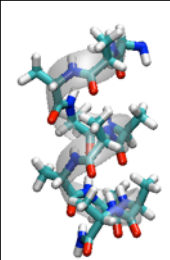
backbone

CPK + VDW representation

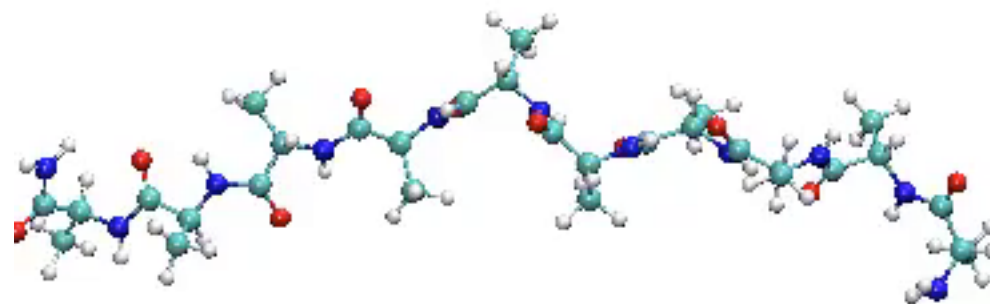
van der Waals radius \sim length of covalent bond



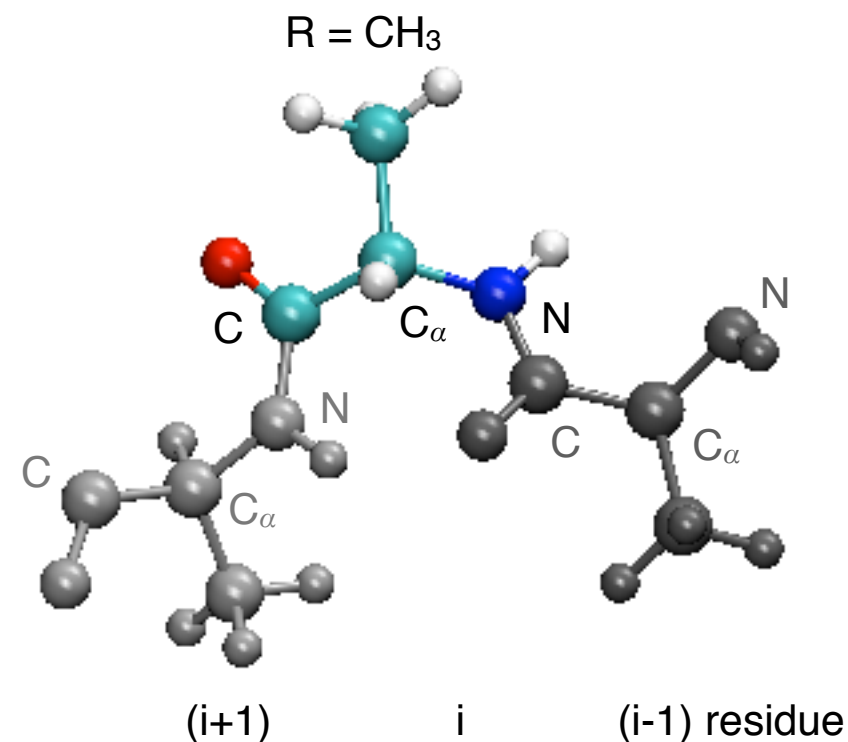
van der Waals spheres tightly packed against one another



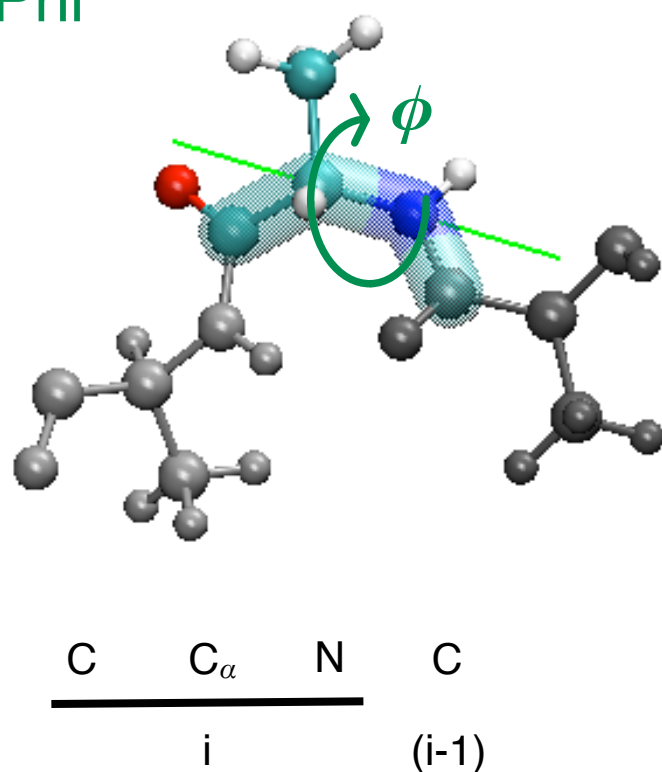
Torsion angles



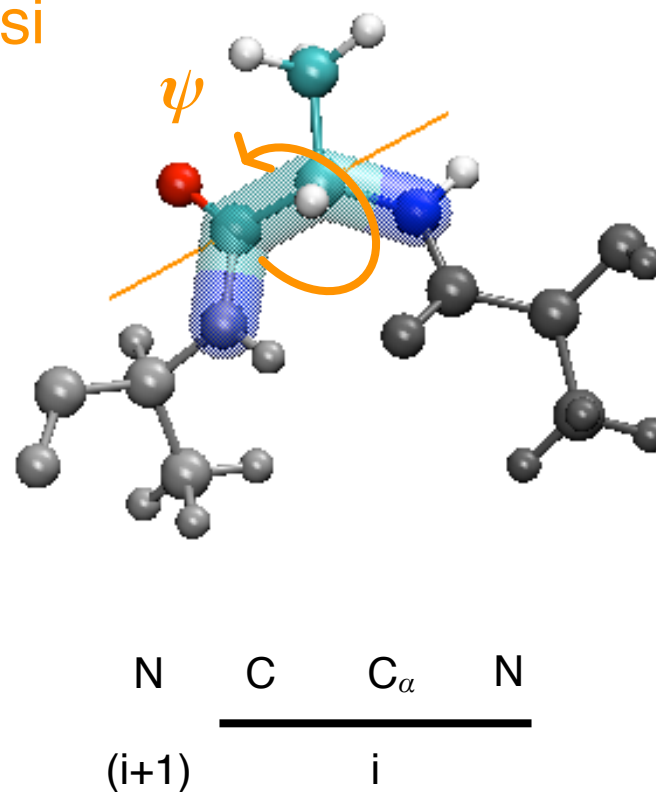
Torsion angles



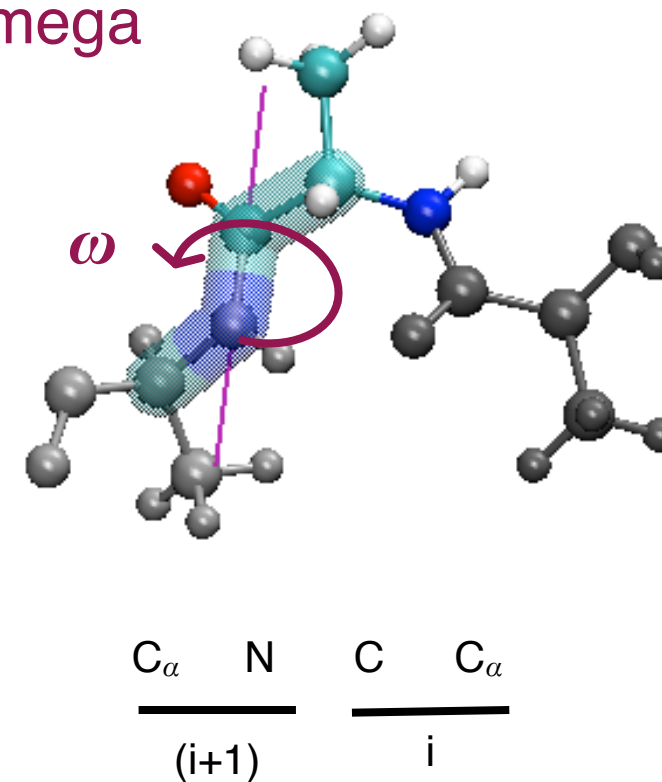
Phi



Psi



Omega



Convention: all angles measured **clockwise** when looking from the N-terminus to the C-terminus. When **eclipsed** the angles are zero, when **extended** they are 180°. This was altered in 1969 and is incorrect in Voet and Stryer. It is correct in Branden and Tooze. <http://www.chem.qmul.ac.uk/iupac/misc/pprep4.html>

ω measures the rotation around the **peptide bond** which we know is rigid due to resonance

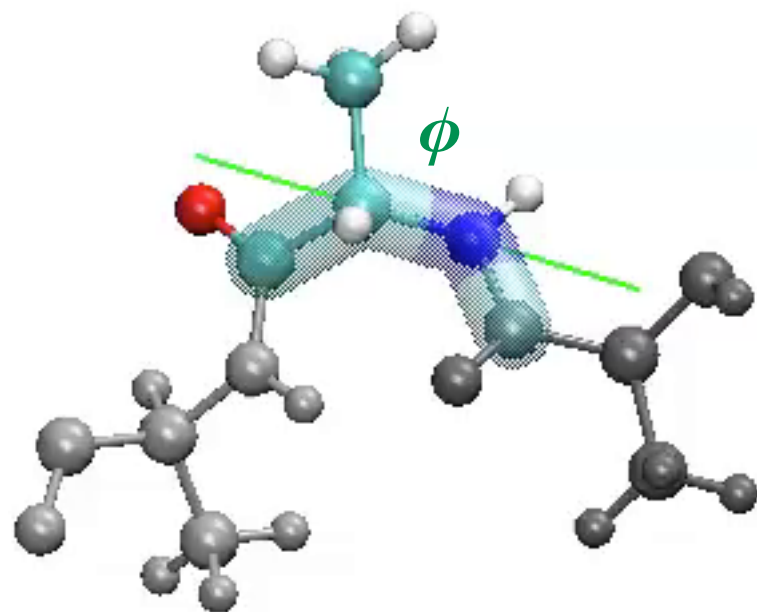
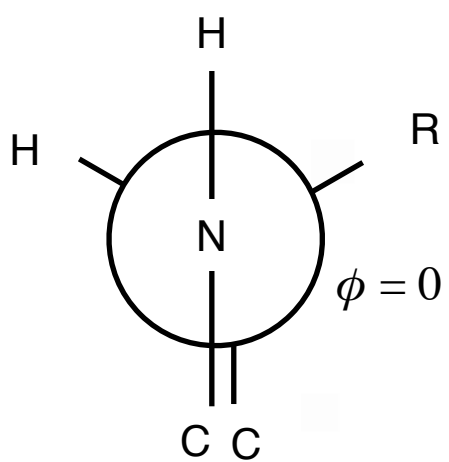
ω does not vary significantly

Phi and Psi

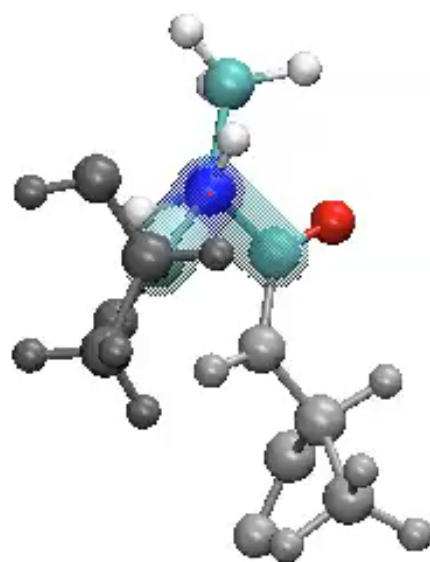
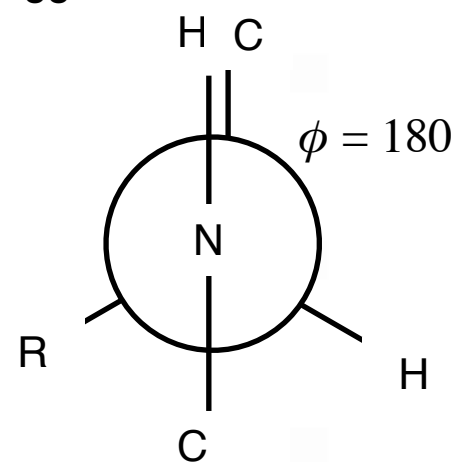
Phi

Psi

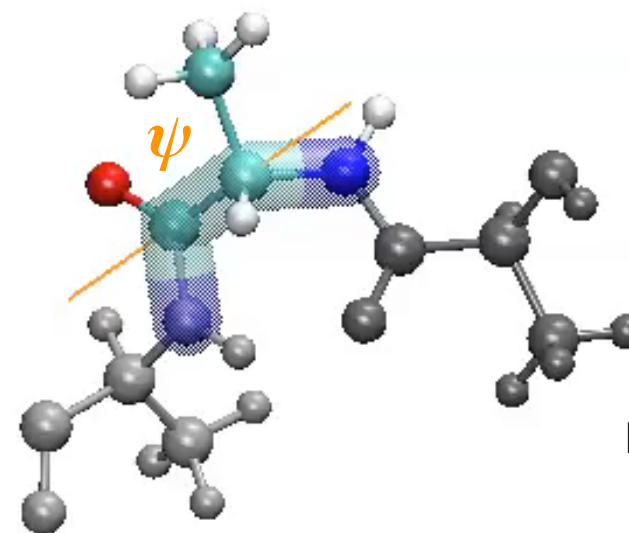
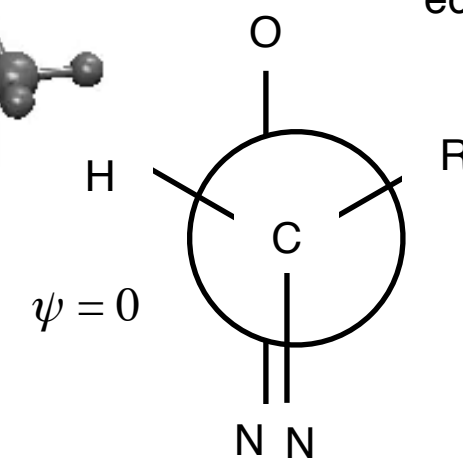
eclipsed



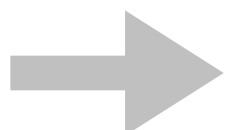
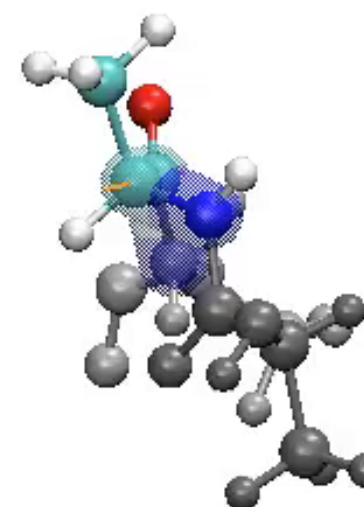
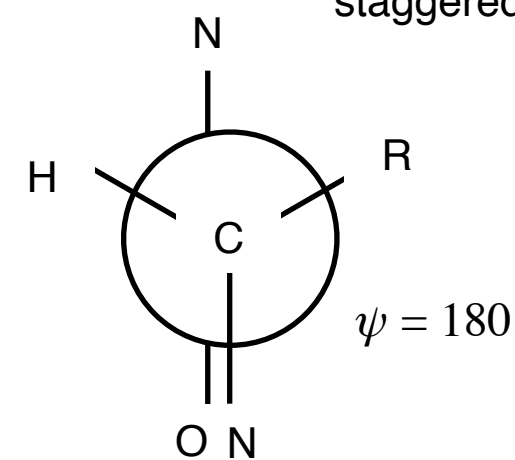
staggered



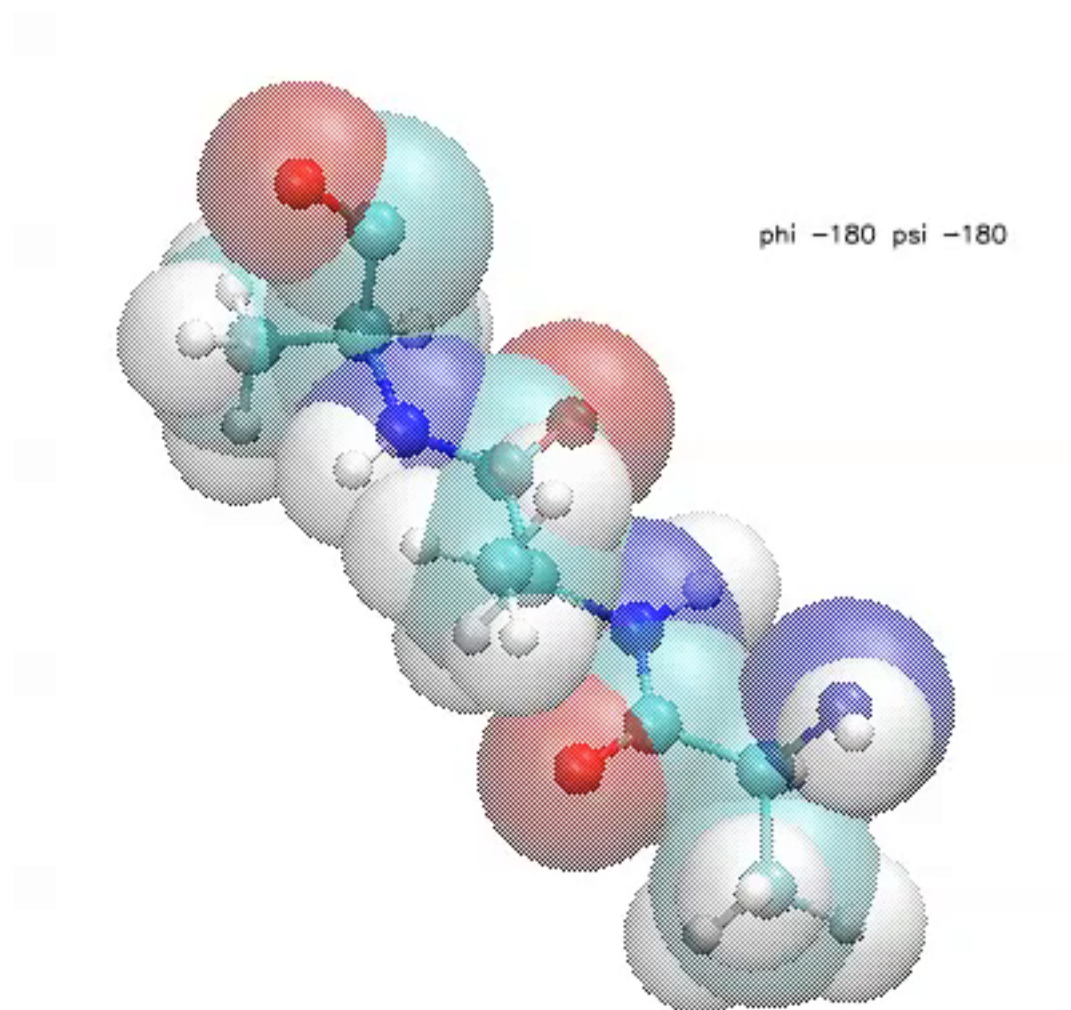
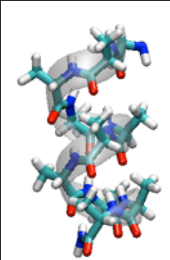
eclipsed



staggered

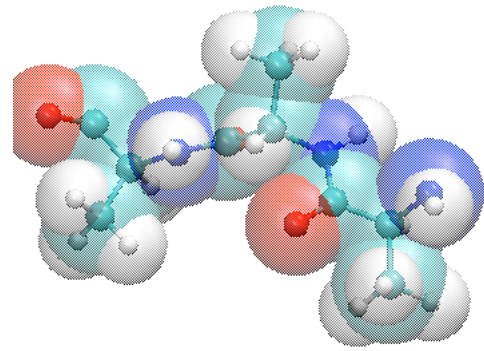


some combinations of (ϕ, ψ) result in e.g. the CO and NH groups coming close to one another and therefore the energy increasing due to the repulsive nature of the van der Waals potential



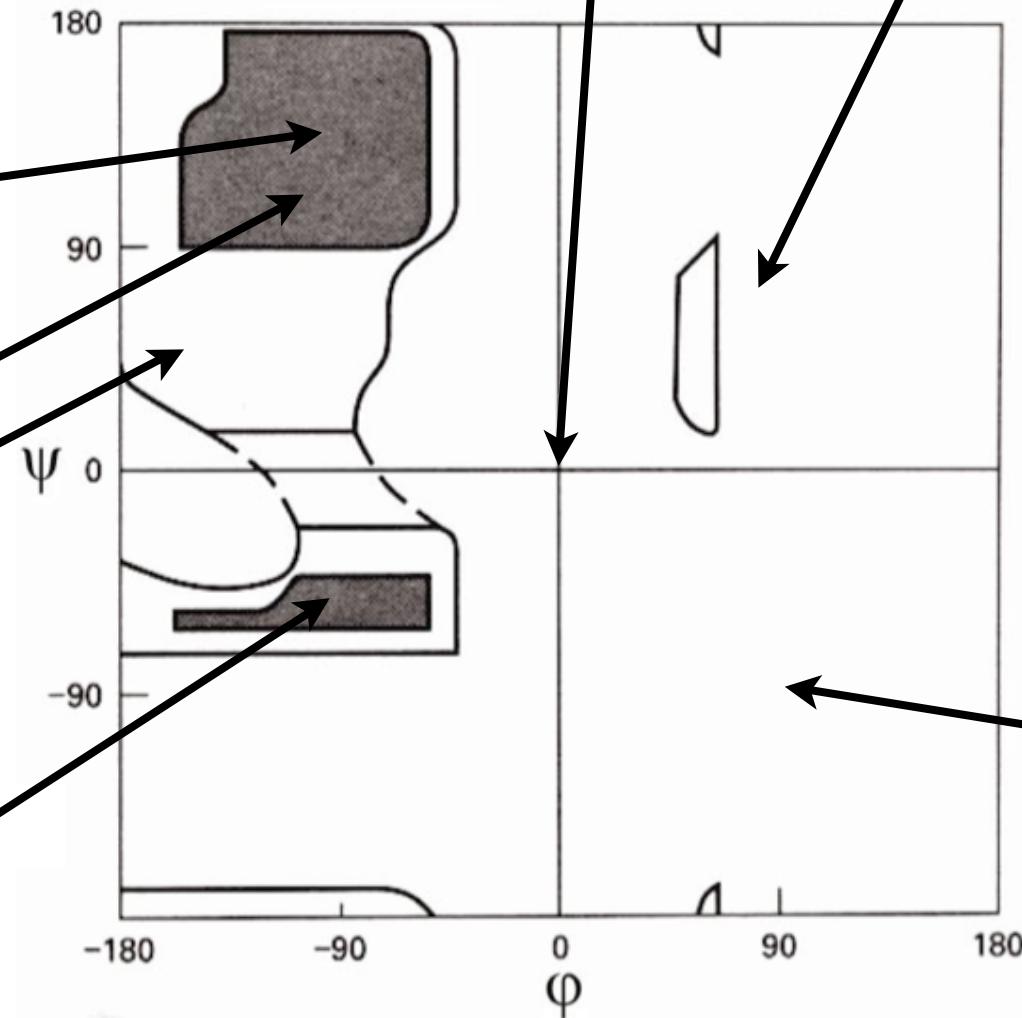
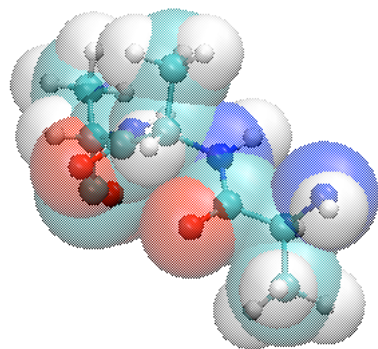
Ramachandran plots

Ramachandran et al. assumed the atoms were hard-spheres and used a computer to systematically study which combinations of (ϕ , ψ) were possible



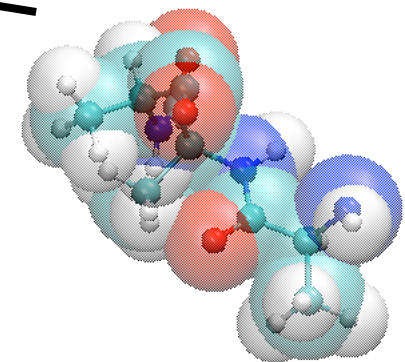
favoured region

allowed region



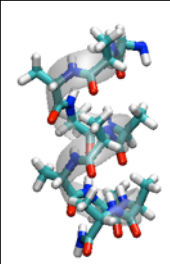
All residues except glycine

Practical: what are the steric interactions that rule out most of $\phi > 0$?



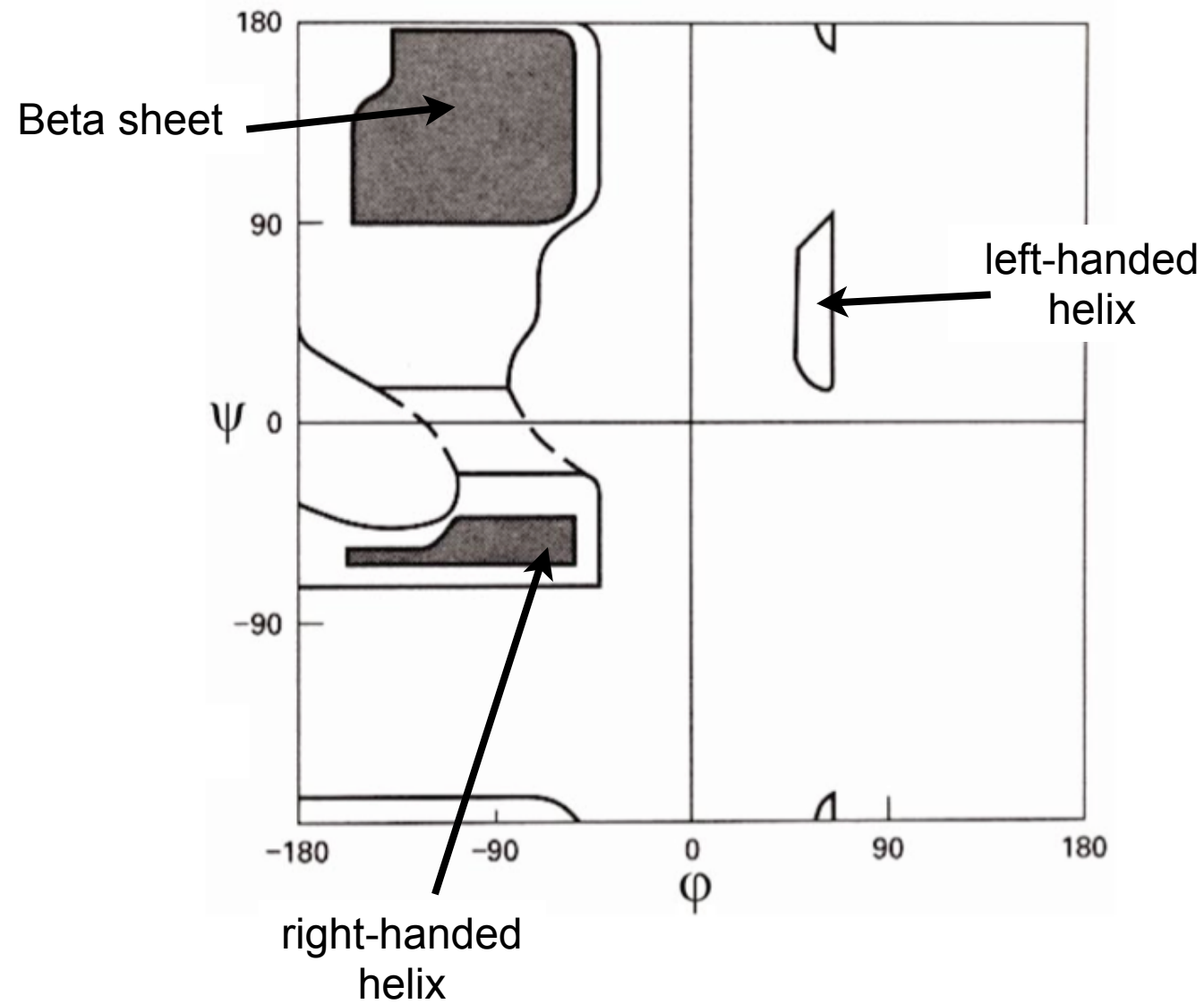
22% of the area is allowed and only 7% of the area is favoured

We can identify the favoured regions with protein secondary structure

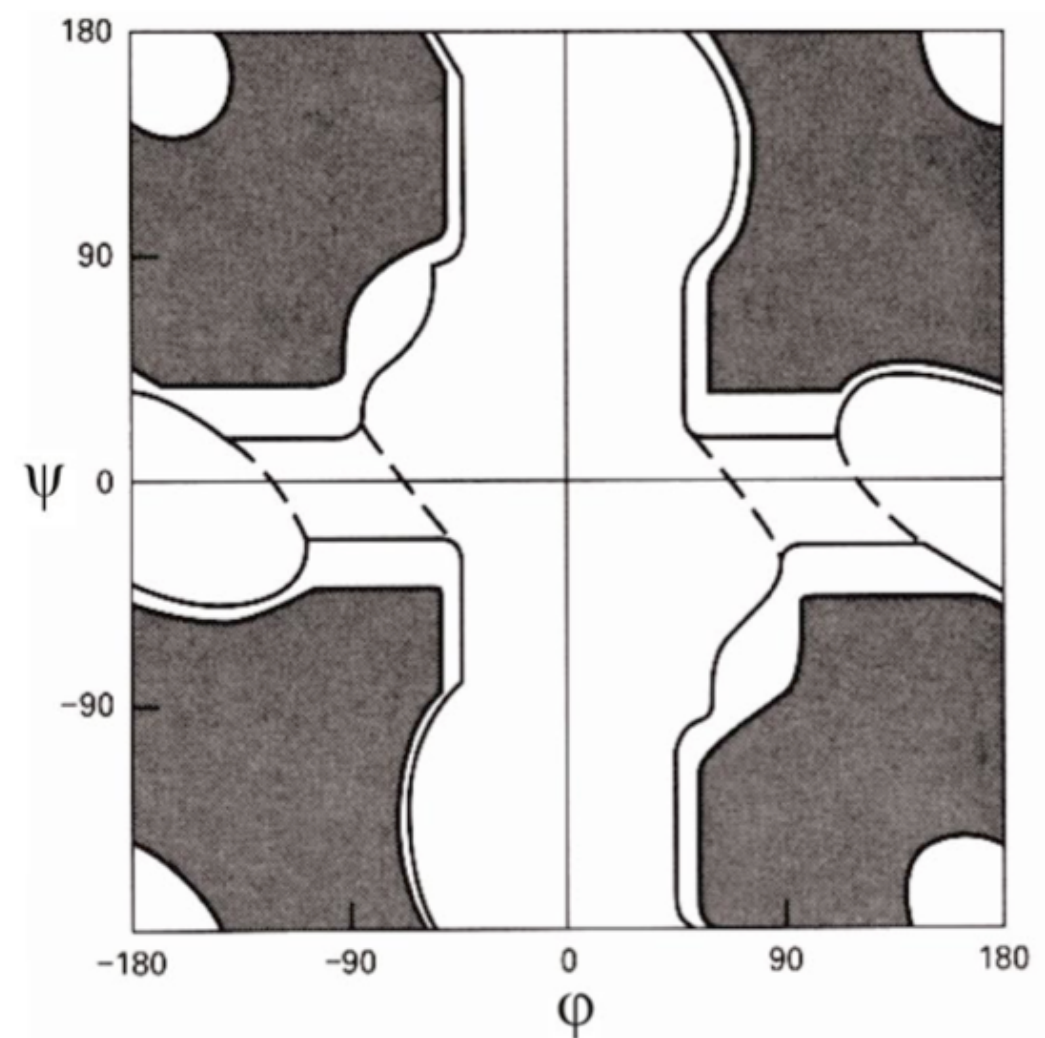


Regions of secondary structure

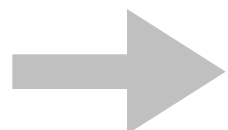
All residues except glycine



Glycine



But the atoms are not “hard”-spheres and this also ignores temperature and other effects



Replot using many experimental structures of different proteins

A more recent Ramachandran plot: RAMPAGE

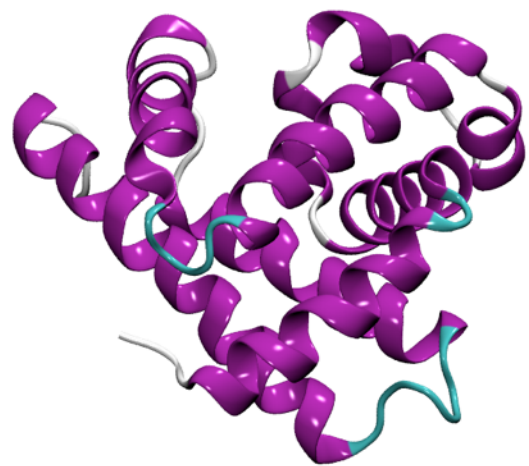
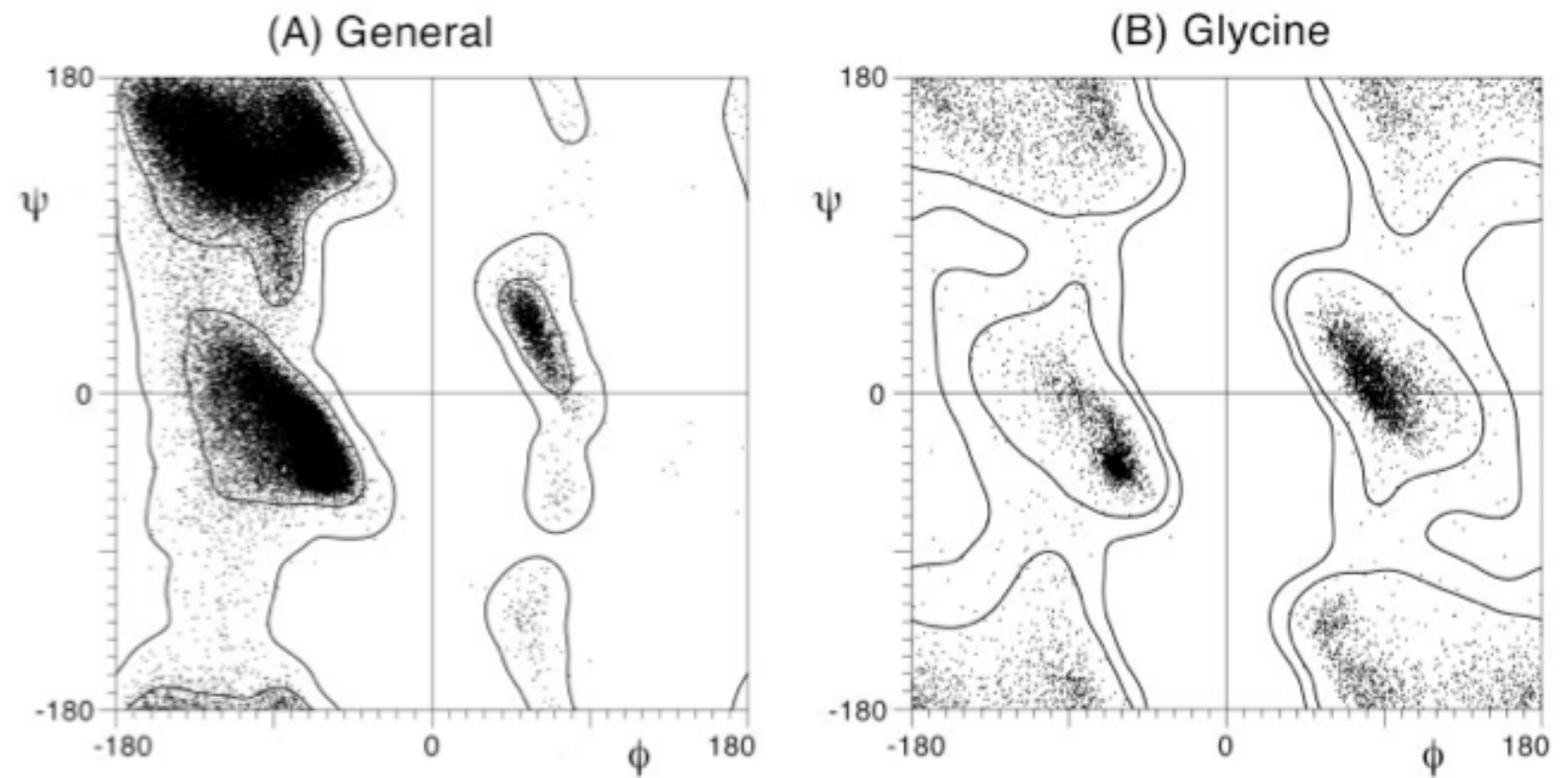
Proteins (2003) **50** 437

Figure Legend:

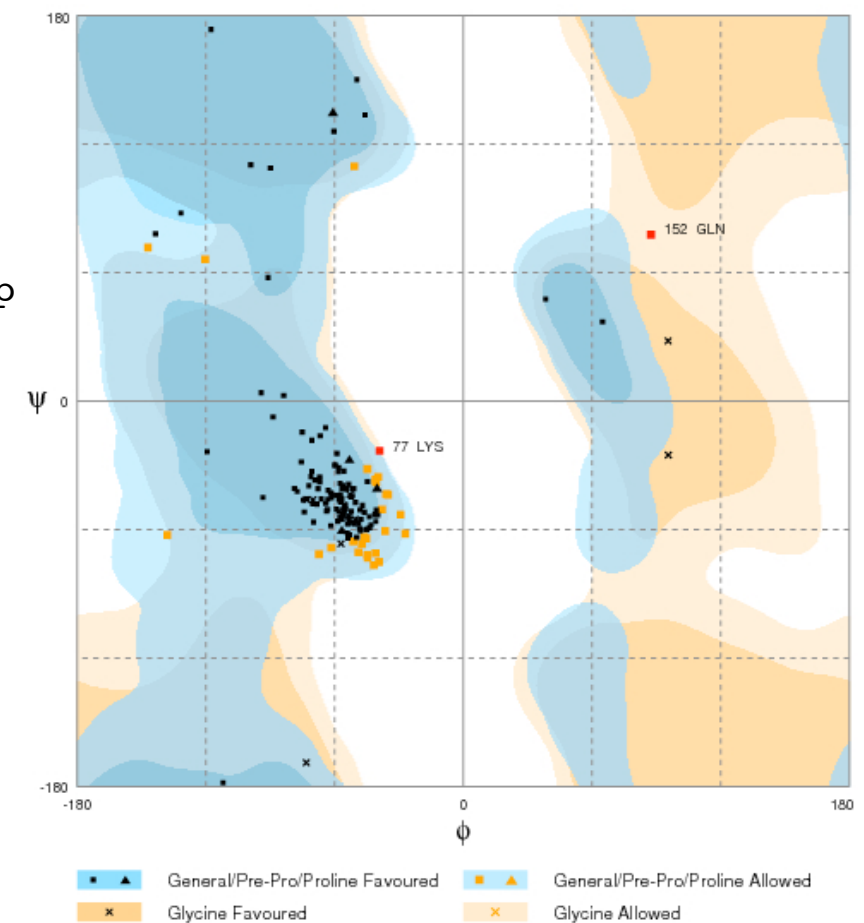
(ϕ, ψ) angle distributions for 97,368 residues.

(a) The general case of 81,234 non-Gly, non-Pro, non-prePro residues.

(b) The 7705 Gly residues



<http://mordred.bioc.cam.ac.uk/~rapper/rampage.php>



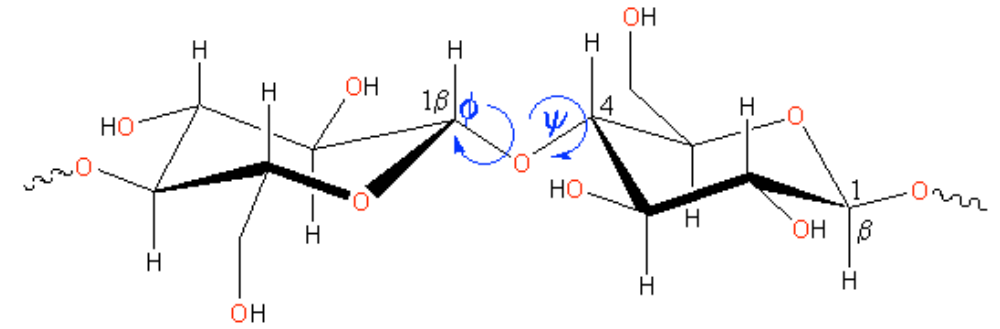
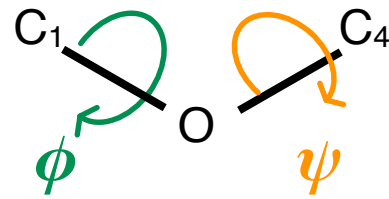
Myoglobin (PDB:1MBN)

Prog. Stereochem. (1969) **4** 299

Polysaccharides: torsion angles

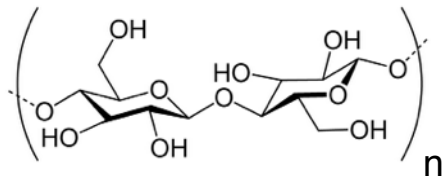
Analogous to proteins we can define torsional angles ϕ and ψ

For 1 \rightarrow 4 linked glycoside:



Examples

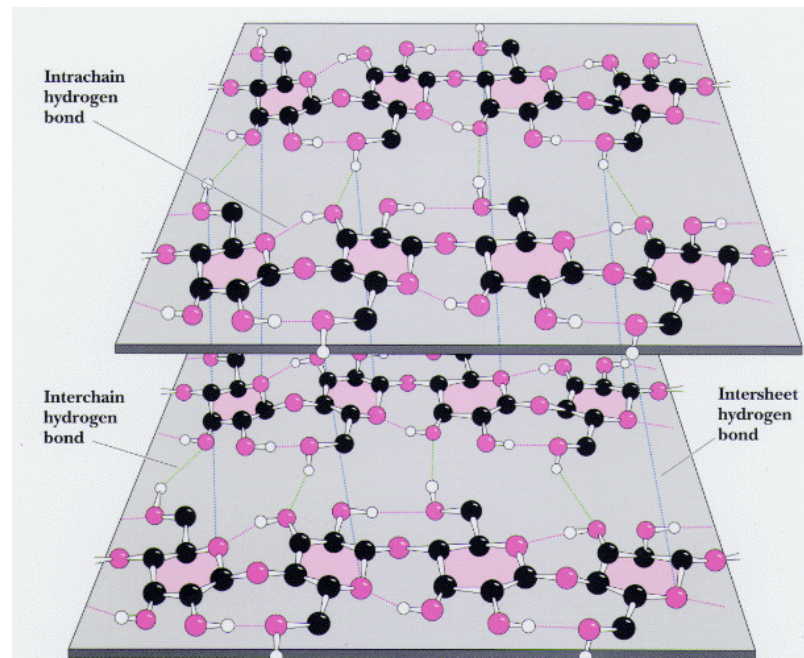
1. Cellulose is a polymer of β (1 \rightarrow 4) linked D-glucose



1. forms a chain of glucans (each flipped 180° relative to preceding one)

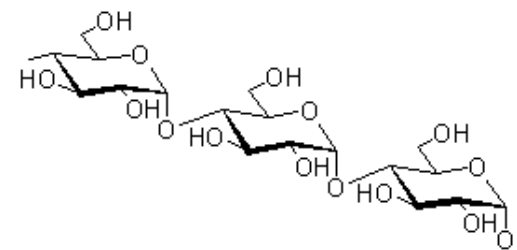
2. parallel extended chains form sheets

3. sheets stack to form fibres



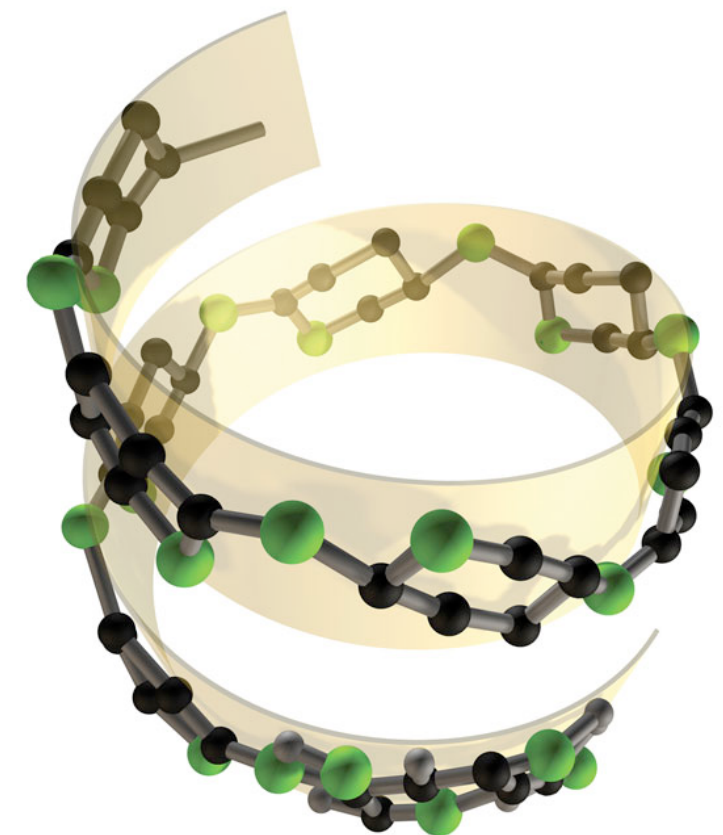
Voet (3rd ed) Fig 8-8, pg 229

2. α -Amylose is a polymer of α (1 \rightarrow 4) linked D-glucose



is an isomer of cellulose

forms left-handed helix



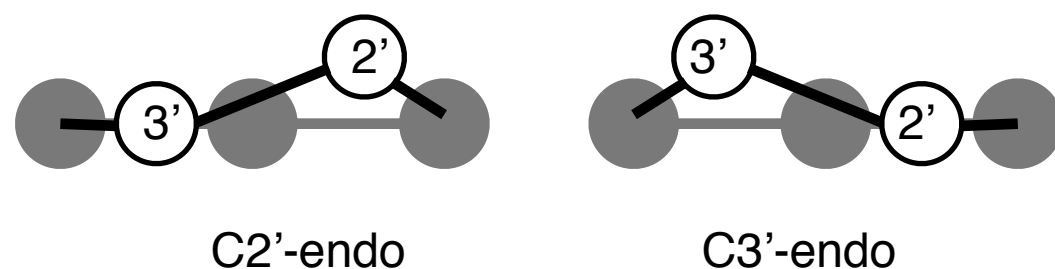
Voet (3rd ed) Fig 8-10, pg 231

Nucleic acids

Bases adopt planar structure

Different conformations of the double helix come result from

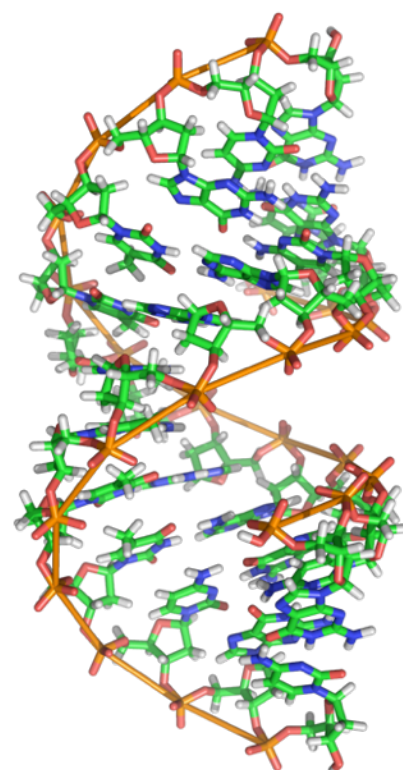
1. pucker of sugar



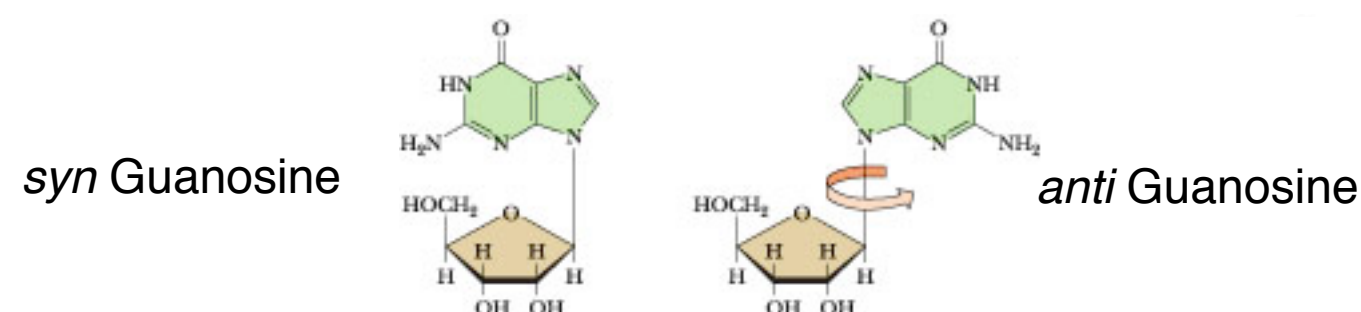
standard RNA structure
(A-DNA)

nucleotides all *anti*

sugars primarily C3'-endo



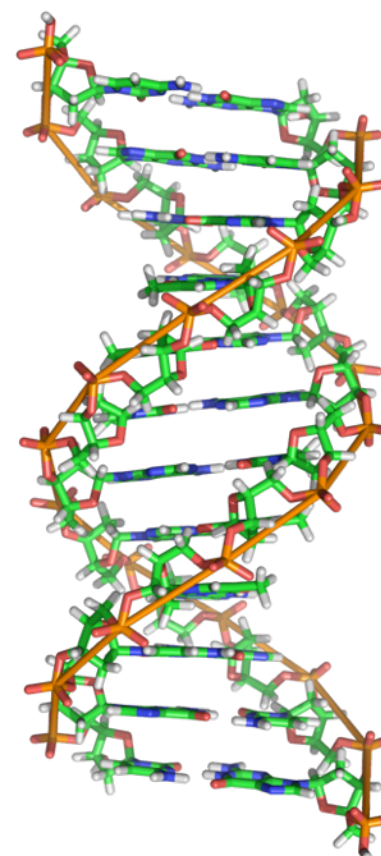
2. rotation of N-glycosidic bond



standard DNA structure
(B-DNA)

nucleotides all *anti*

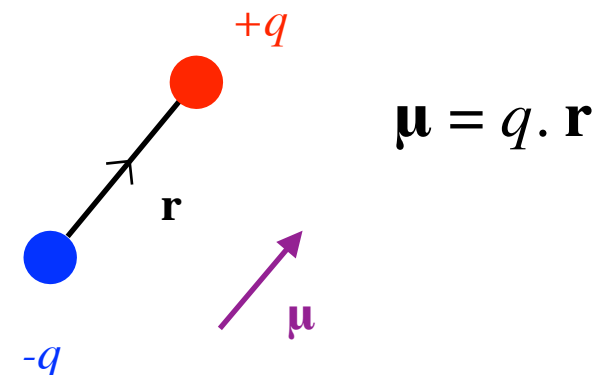
sugars primarily C2'-endo



What is the other structure
DNA and RNA can adopt and
how is it different?

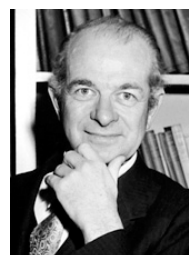
Lecture 2: Summary

Two equal but opposite charges separated by a small distance can be described by a dipole

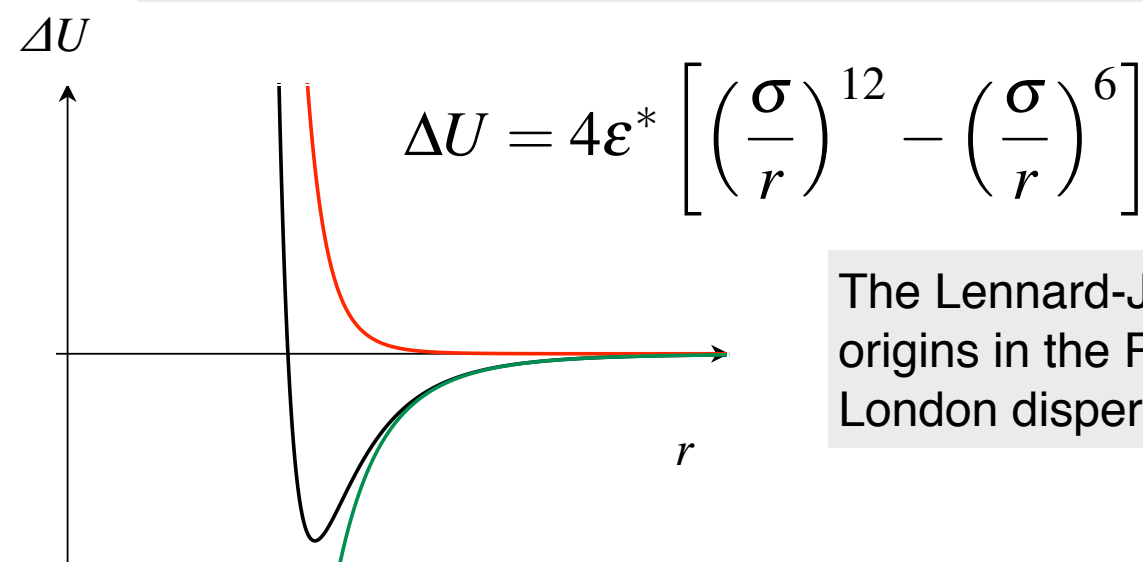
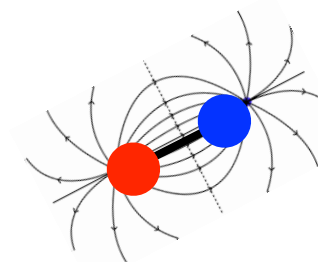


$$\mu \sim \Delta\chi$$

The electronegativity of an atom characterises its ability to attract electrons towards themselves



Dipoles can interact with point charges and other dipoles; they may be permanent or induced.



The Lennard-Jones 6-12 potential contains a repulsive term that has its origins in the Pauli Exclusion Principle and an attractive term that models London dispersion interactions.

The backbone conformation of polypeptides can be described by two angles: φ and ψ . Only ~22% of (φ, ψ) combinations are permitted due to steric clashes

The structures of polysaccharides and nucleic acids can also be described by torsional angles and each has its own characteristic structures

