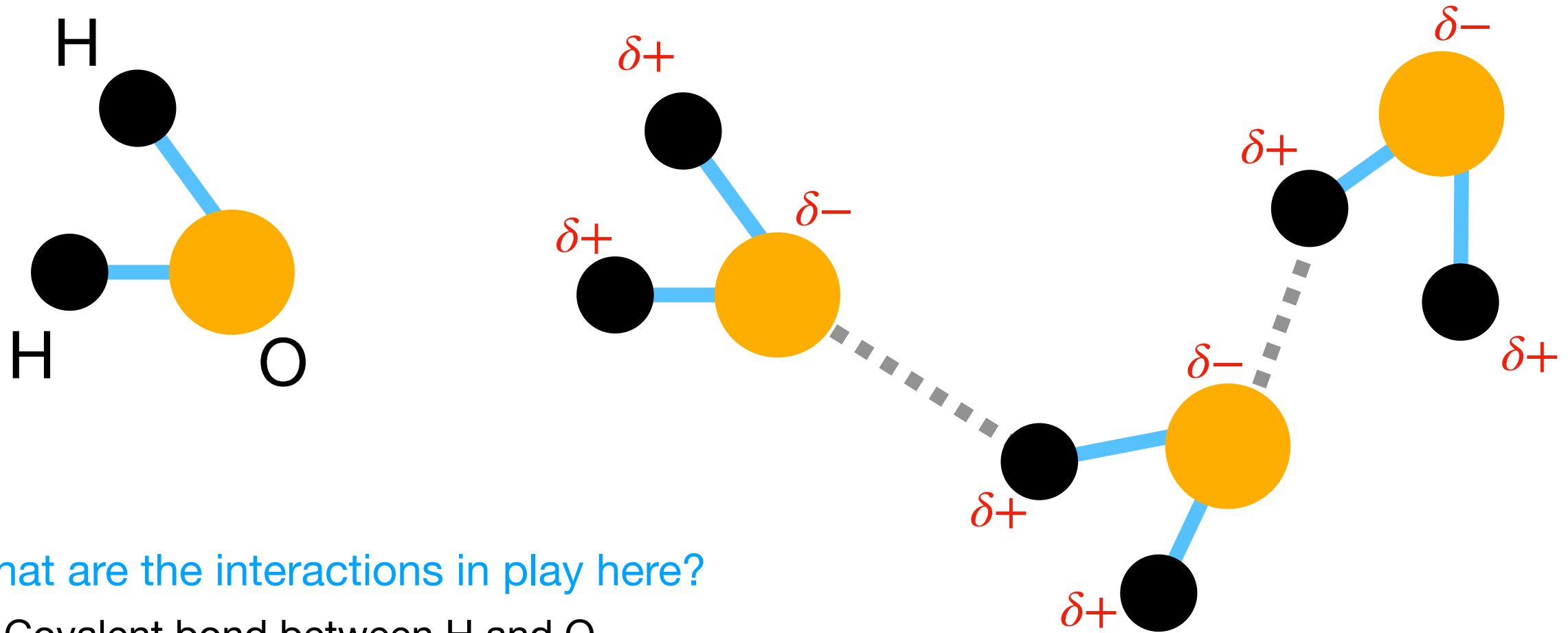


Today's class:

Molecular forces in Biology

*Majority of this lecture follows the chapter 24 from the book
'Molecular Driving Forces' by Dill and Bromberg, Garland Science, 2nd Ed*

Chemical bonds vs intermolecular forces



What are the interactions in play here?

- Covalent bond between H and O
- H-O bond is polarized to form dipoles
- Dipole-dipole interactions between H-O bonds of different water molecules
- Dispersion forces among all molecules

Takeaways

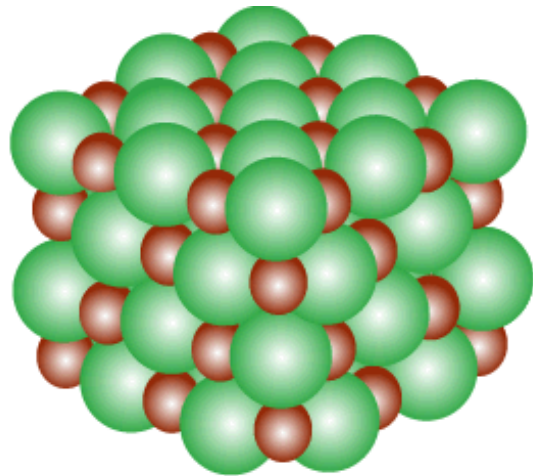
- Chemical bonds are almost exclusively 'intra'-molecular
- Intermolecular forces are much weaker than chemical bonds

41 kJ to vaporize 1 mole of water (inter)

930 kJ to break all O-H bonds in 1 mole of water (intra)

Types of intramolecular forces

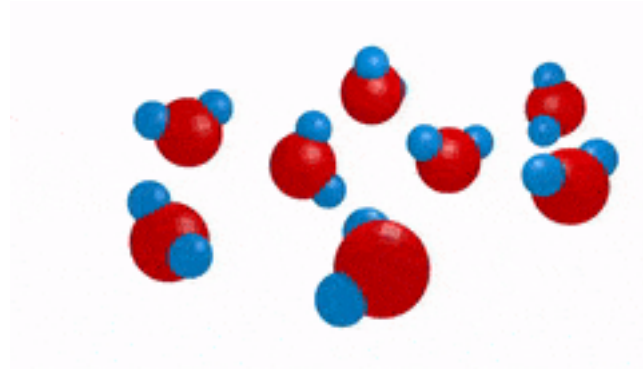
Ionic bonds



Solid state

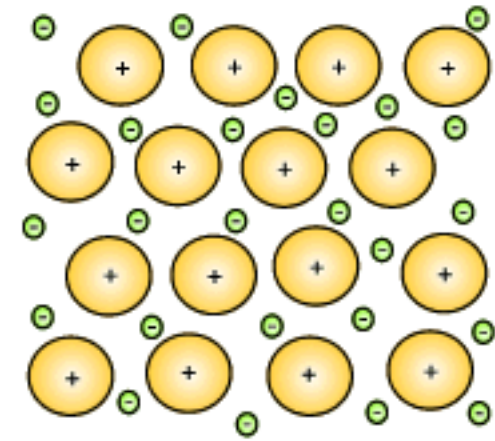
interaction between cations and anions

Covalent bonds



interaction between adjacent atoms through shared electrons

Metallic bonds



interactions between metal cations through delocalized electrons

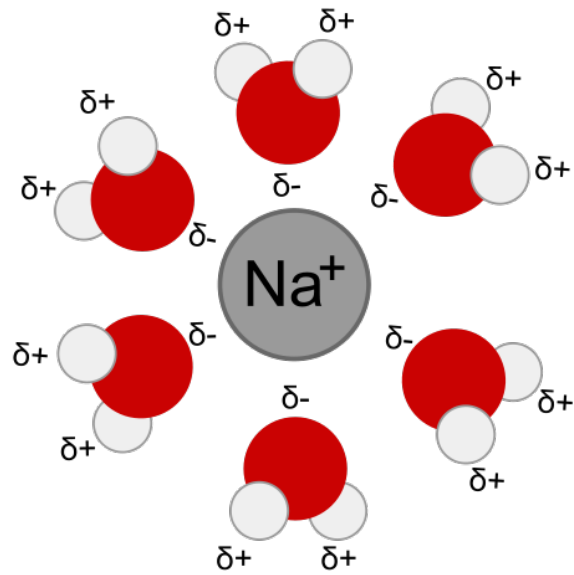
All biomolecules are covalently bonded.

Life on earth is primarily made of C, H, O, N, S & P

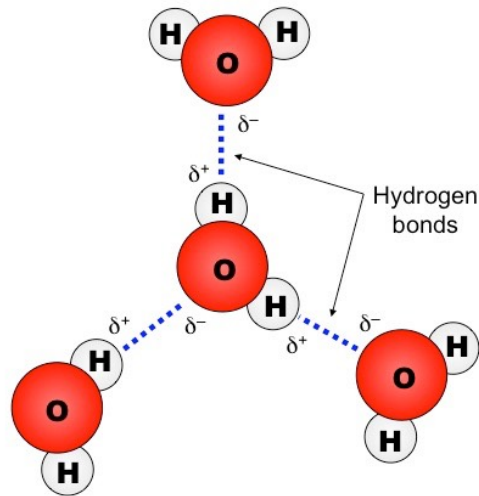
Types of intermolecular forces

A story of charge distributions and polarizabilities

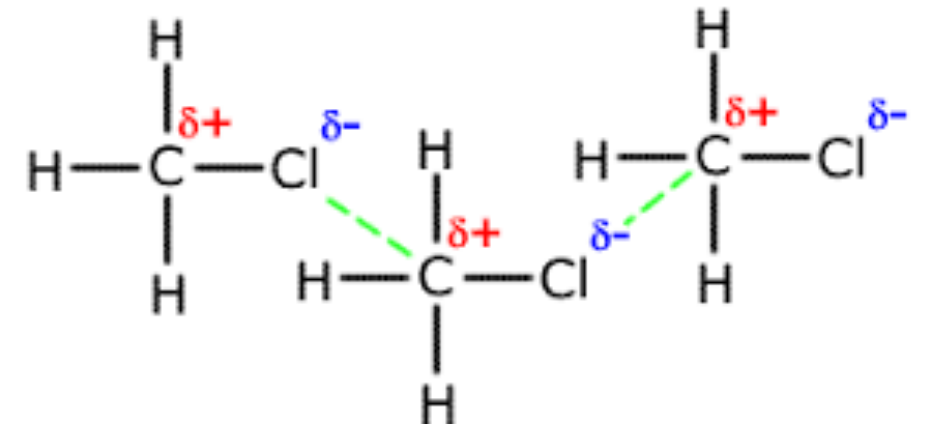
Ion-dipole



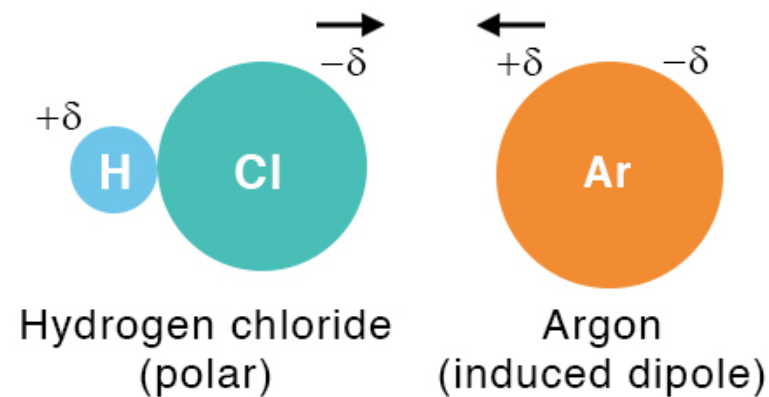
Hydrogen bond



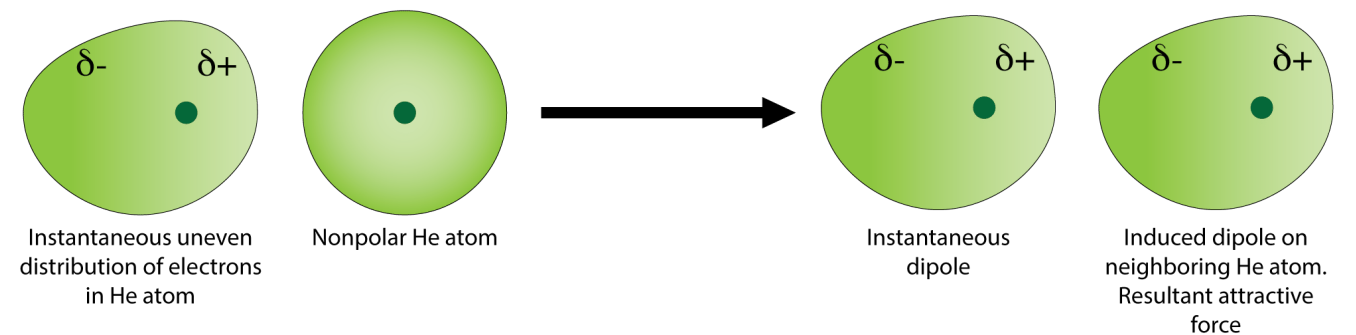
Dipole-dipole



Dipole-induced dipole

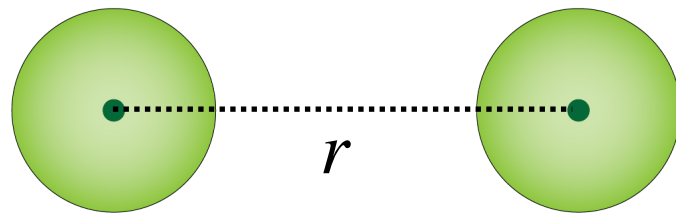


London dispersion forces



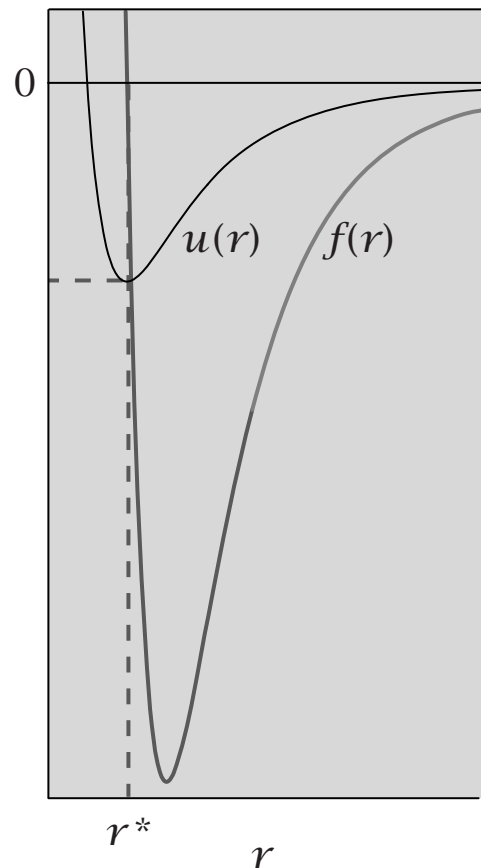
Intermolecular interactions are the driving forces for so much diversity in biology

Understanding intermolecular forces



Any intermolecular ‘bond’ can be described by pair potential $u(r)$

$$\text{Intermolecular force, } f(r) = -\frac{du(r)}{dr}$$



Main features of $f(r)$

- $u \rightarrow 0$ & $f \rightarrow 0$ as $r \rightarrow \infty$ — no interaction when too far
- $f < 0$ as r decreases — attraction when close enough
- $f > 0$ when $r \lesssim r^*$ — repulsion when too close
- at $r = r^*$, u reaches minimum, so $f = 0$ — equilibrium bond length

Universal feature for all kinds of bonds:

No interaction at very long range, attraction at short range and repulsion at very short range

Figure 24.1 The energy of interaction $u(r)$ between two particles as a function of their separation r , and the corresponding force $f = -du/dr$; r^* is the equilibrium bond length.

Classification of intermolecular forces

Based on the behaviors of pair potential $u(r)$ as a function of intermolecular separation r

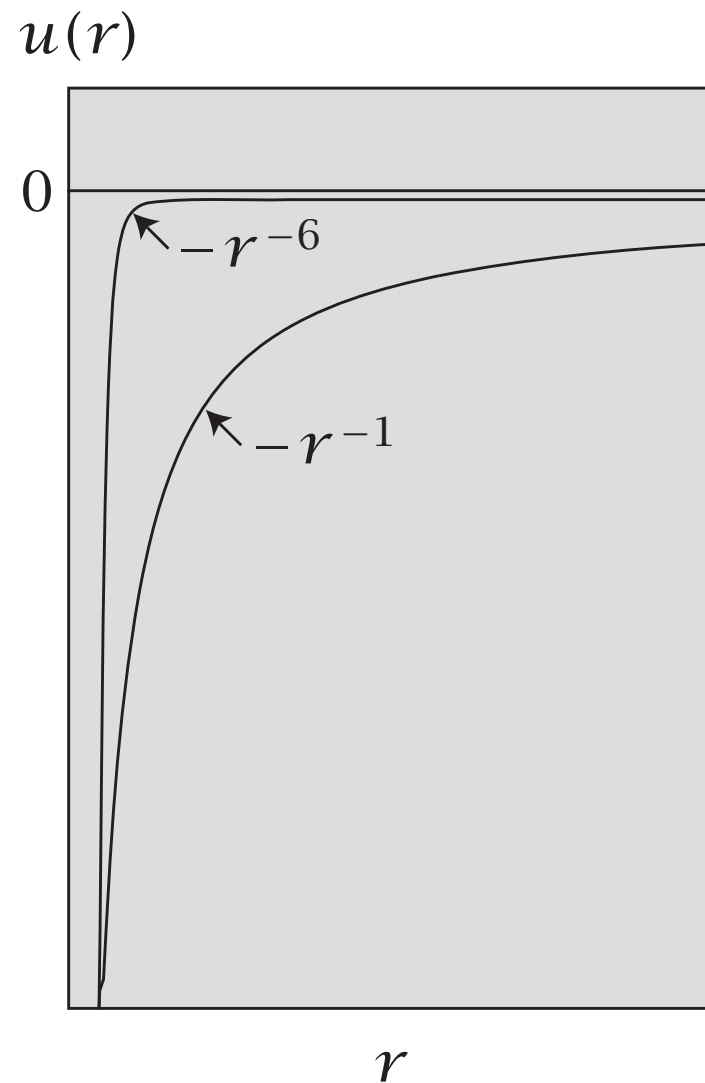


Figure 24.2 The range of an interaction. r^{-1} is long-ranged and r^{-6} is short-ranged.

Long-ranged

Short-ranged

$$u(r) = \text{constant} \times r^{-p} \quad \text{General power law form}$$

$$p \leq 3 \rightarrow \text{long-ranged}$$

$$p > 3 \rightarrow \text{short-ranged}$$

E.g. Coulombic interaction $\propto \frac{1}{r}$

E.g. van der Waals interaction $\propto \frac{1}{r^6}$

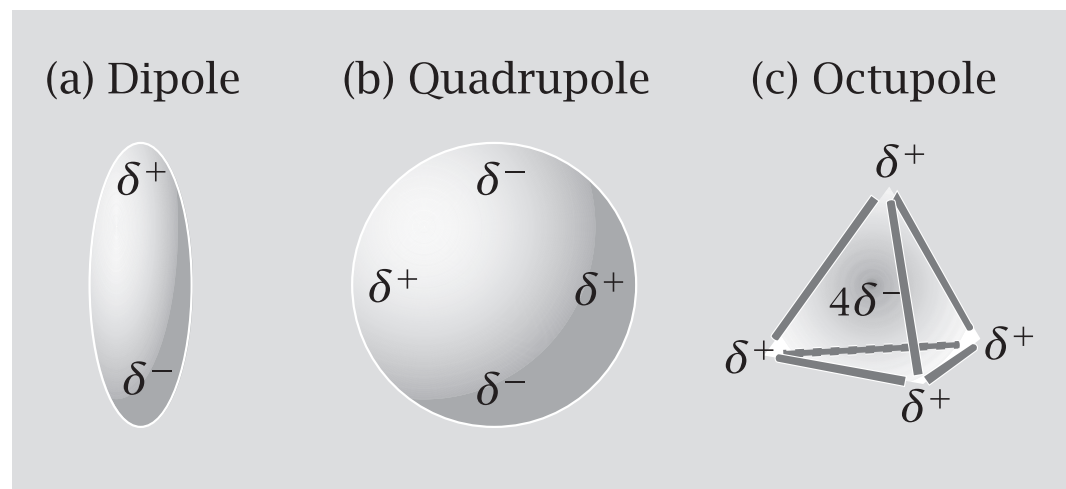
What about very short-ranged repulsion?

Violation of Pauli exclusion principle: electrons in the same state can't occupy the same space. These repulsions are described by $p = 9, 12$, or 14

Short-Ranged attractions essentially arise from Electrostatic interactions

Electrostatic interactions are long-ranged.

But when the interacting molecules represent charge-distributions the net interaction can become short-ranged



Any spatial charge distribution can be expressed as a multiple expansion

$$\rho(x, y, z) = \rho(\vec{r})$$

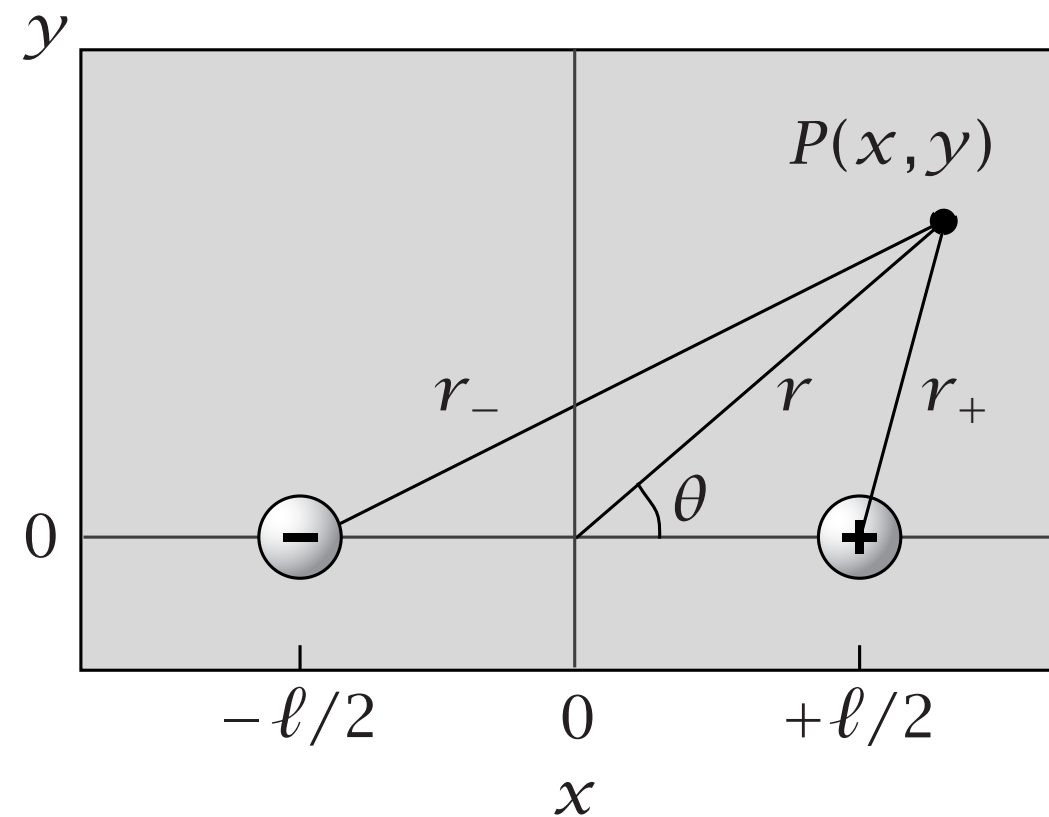
$$= \rho_{mon}(\vec{r}) + \rho_{dip}(\vec{r}) + \rho_{quad}(\vec{r}) + \rho_{oct}(\vec{r}) + \dots$$

Monopole term $\int \rho(\vec{r}) dV$
- describes the net charge

Dipole term $\int \vec{r} \rho(\vec{r}) dV$
describes a symmetric arrangement of equal amounts of +ve and -ve charge separated by \vec{r}
lowest term with no net charge

Quadruple term
 $\int \rho(\vec{r}) [3(\hat{r}\hat{r})^2 - r^2] dV$
lowest term with no net dipole moment

Interaction between ion and a dipole is short-ranged than Coulombic



D = medium
dielectric constant

The interaction energy for an ion with charge at point P and a dipole at origin is $\rightarrow u(r, \theta) = \frac{\mu Q \cos \theta}{4\pi\epsilon_0 D r^2}$ Shorter ranged than pure Coulombic

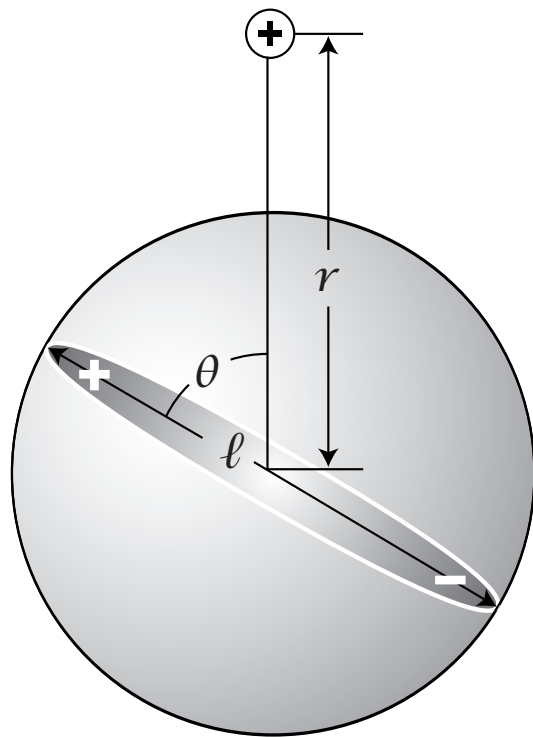
Where $\Psi = \frac{\mu \cos \theta}{4\pi\epsilon_0 D r^2}$ is the total electrostatic potential for this system

Next tutorial problem set

Similarly, when two dipole's interact the energy becomes: $u(r) \propto r^{-3}$

Orientational averaging can also reduce the range of interactions

Ion-dipole interaction energy for a fixed dipole $\rightarrow u(r, \theta) = \frac{\mu Q \cos \theta}{4\pi\epsilon_0 D r^2}$



If the dipole is free to rotate, the average interaction energy becomes

$$\langle u(r) \rangle = \frac{\int_0^\pi u(r, \theta) e^{-u(r, \theta)/kT} \sin \theta d\theta}{\int_0^\pi e^{-u(r, \theta)/kT} \sin \theta d\theta}.$$

Here we have assumed a Boltzmann distribution of energy

If energy is small $u/kT \ll 1$, we can show that $\langle u(r) \rangle = -\frac{1}{3kT} \left(\frac{\mathcal{C} Q \mu}{D} \right)^2 \frac{1}{r^4}.$

Even shorter ranged than dipole-dipole interactions

Next tutorial problem set

$$\mathcal{C} = \frac{1}{4\pi\epsilon_0}$$

Generalizing this result,

energy of fixed dipoles interacting is $u(r) \sim 1/r^{-3}$

So, energy of two freely rotating dipoles interacting is $u(r) \sim 1/r^{-6}$

Continuing the discussion on freely rotating dipoles

Energy of interaction for two freely rotating dipoles with dipole moment μ_A & μ_B

$$\langle u(r) \rangle = -\frac{2}{3kT} \left(\frac{\mu_A \mu_B}{4\pi \epsilon_0 D} \right)^2 \frac{1}{r^6},$$

Using this compute the energy of interaction for ethanol

Consider average separation of ethanol molecules to be 10\AA , dipole moment $\sim 1.7 D$

$$1 \text{ Debye} = 3.33 \times 10^{-30} \text{ C m}$$

$$\epsilon_0 = 8.85 \times 10^{-12} \text{ C}^2 \text{ J}^{-1} \text{ m}^{-1}$$

$$T = 300 \text{ K}$$

$$\langle u(r) \rangle = -8.27 \text{ J mol}^{-1}$$

<< ion-dipole or fixed dipole-dipole energy

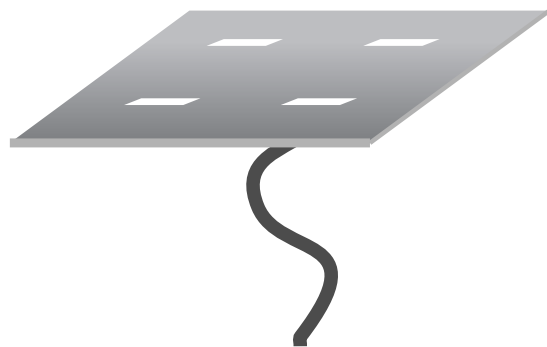
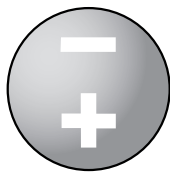
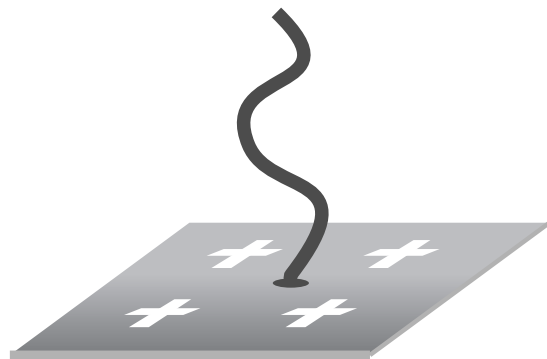
Table 24.3 Various types of energy u (at 5\AA) and the dependence on distance r .

Type of Interaction	u (kcal mol ⁻¹)	Distance r Dependence
Ionic	66	$1/r$
Ion/dipole	4	$1/r^2$
Dipole/dipole	0.5	$1/r^3$
Dipole/induced dipole	0.012	$1/r^6$

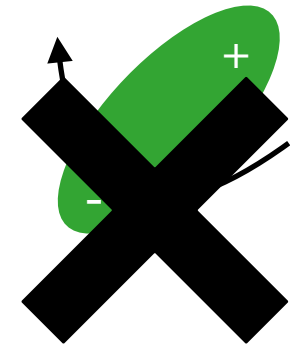
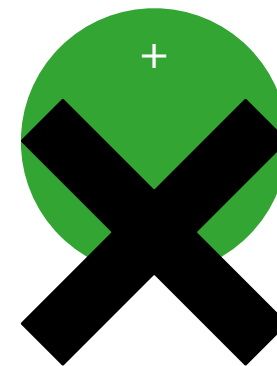
Source: RS Berry, SA Rice, and J Ross, *Physical Chemistry*, Wiley, New York, 1980.

London dispersion forces are due to polarizability of atoms

Attractive interactions are universal



Induced dipolar charge distribution under an applied electric field



Even spherically uncharged inert gas atoms also condense to liquid at very low temperatures. There is always a basic attractive force!

Such interactions are called London dispersion forces F London (1937)

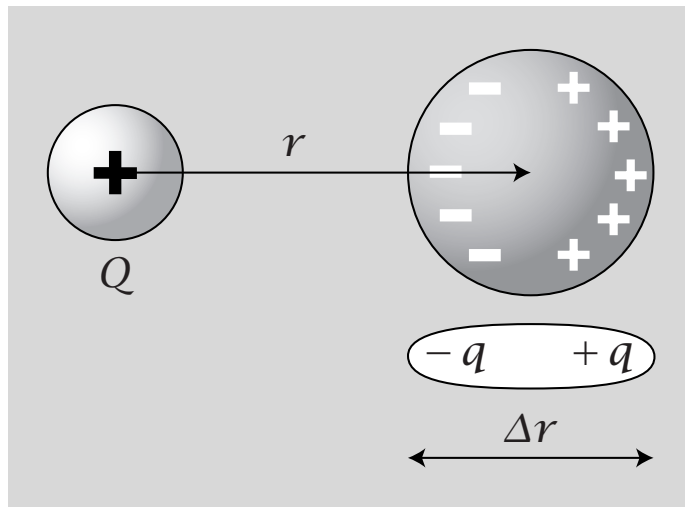
London dispersion forces arises due to polarizability of atoms

A polarizable atom or medium is one that responds to an applied electric field by redistributing its internal charge.

Induced dipole on a polarizable atom, $\vec{\mu} = \alpha \vec{E}$

α is the polarizability expressed in unit of volume

A charge will polarize a neutral atom and attract it



Force on the atom, $f = \text{charge} \times \text{electric field} = q \times E_{tot}$

$$E_{tot} = E(r - \Delta r/2) + E(r + \Delta r/2) \approx \frac{dE}{dr} \Delta r$$

Using Taylor's expansion

$$f = q \Delta r \frac{dE}{dr} = \mu_{ind} \frac{dE}{dr} = \alpha E \frac{dE}{dr}$$

$$E(r) = \frac{Q}{4\pi\epsilon_0 D r^2}$$

$$\therefore f = \frac{2\alpha}{r^5} \left(\frac{Q}{4\pi\epsilon_0 D} \right)^2 \quad \Rightarrow \quad u(r) = - \int f(r) dr = - \frac{\alpha}{2} \left(\frac{Q}{4\pi\epsilon_0 D} \right)^2 \frac{1}{r^4}$$

This interaction energy is always attractive and increases with polarizability

Similarly, for two neutral atoms the interaction energy of induced dipoles would be

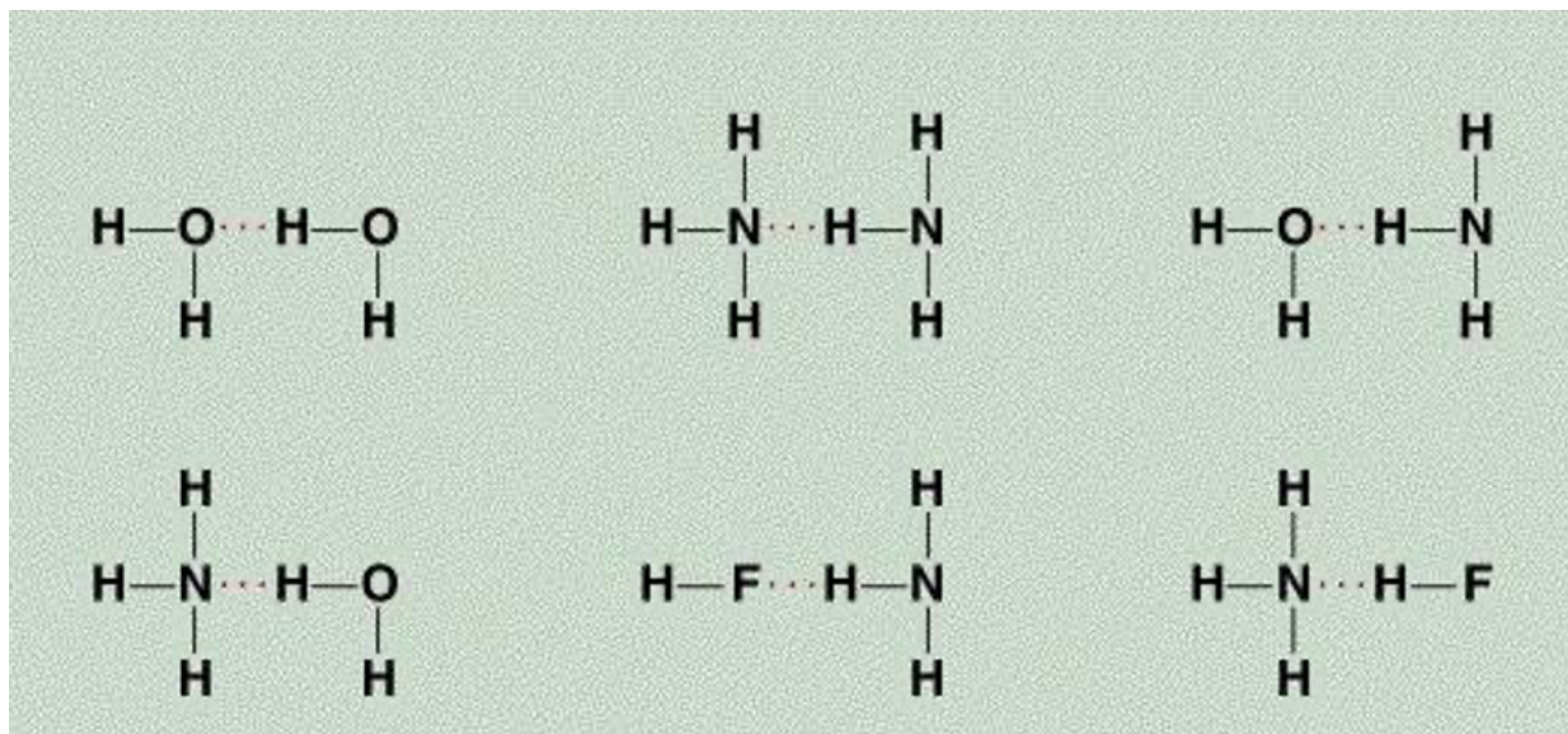
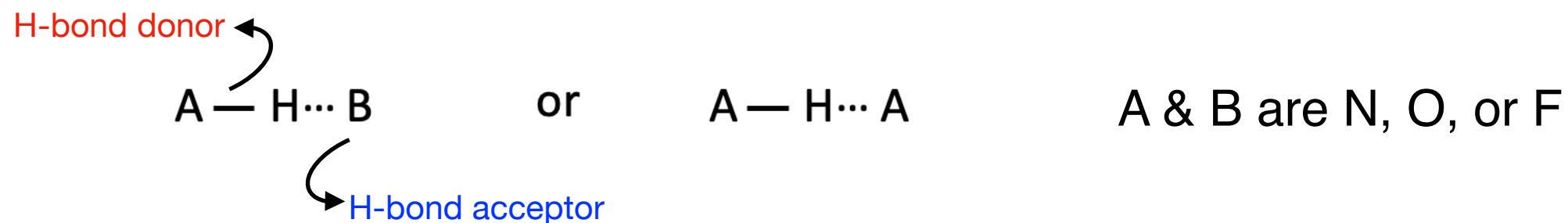
$$u(r) \propto - \frac{1}{r^6}$$

This provides a physical basis for the famous Lennard-Jones potential: $u(r) = \frac{A}{r^{12}} - \frac{B}{r^6}$

Determine A and B: next tutorial problem set

Hydrogen bonds are dipole-dipole interactions

hydrogen bond is a special dipole-dipole interaction between the hydrogen atom in a polar N-H, O-H, or F-H bond and an electronegative O, N, or F atom.



Empirical energy functions for molecular systems

A popular approach to modeling the interactions and conformations of large molecules, particularly in solution, is to assume an energy U that is a sum of terms:

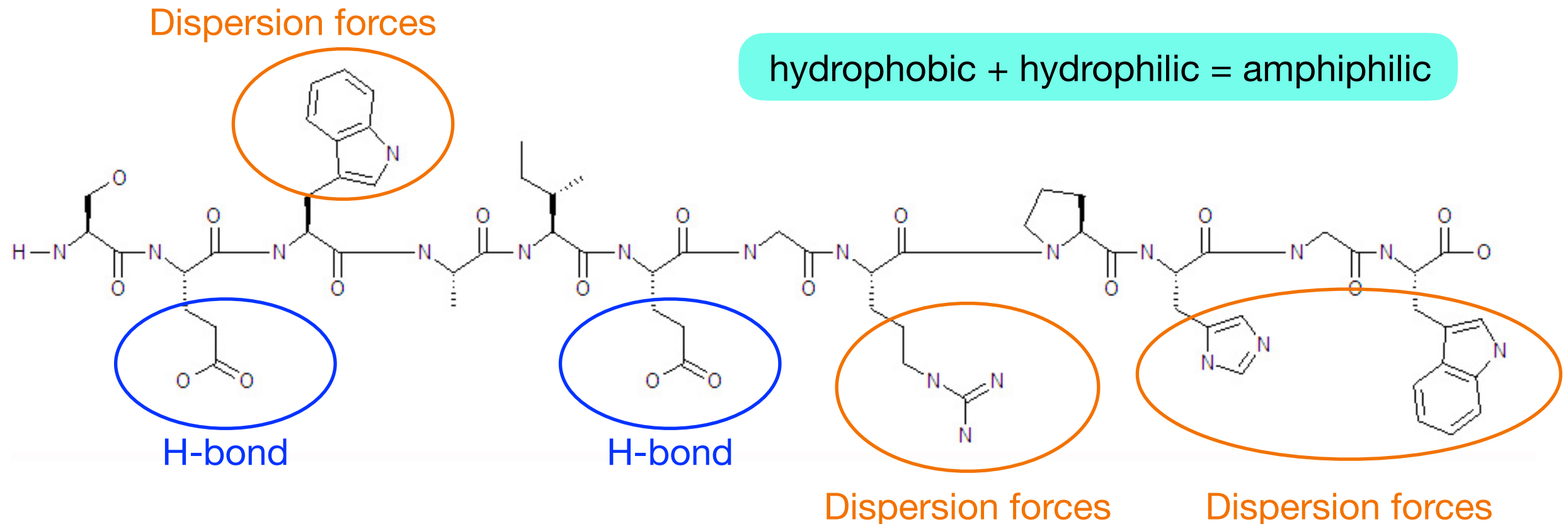
- (1) Coulombic interactions between charged atoms,
- (2) spring forces that stretch and bend bonds,
- (3) periodic potentials for torsional rotations around bonds, and
- (4) a Lennard–Jones potential for nonbonded interactions

$$\begin{aligned} U = & \sum_{\text{bond lengths } b} \frac{K_b}{2} (b - b_0)^2 + \sum_{\text{bond angles } \theta} \frac{K_\theta}{2} (\theta - \theta_0)^2 \\ & + \sum_{\text{dihedral angles } \phi} K_\phi [1 + \cos(n\phi - \delta)] \\ & + \sum_{\text{nonbonded pairs } i < j} \left(\frac{a_{ij}}{r_{ij}^{12}} - \frac{b_{ij}}{r_{ij}^6} + \frac{c q_i q_j}{D r_{ij}} \right), \end{aligned}$$

Softwares like NAMD, GROMACS, LAMMPS, HOOMD have this kind of energy function built in for simulations of biopolymers

Intermolecular forces in proteins

Identify the dominant forces on the side chains



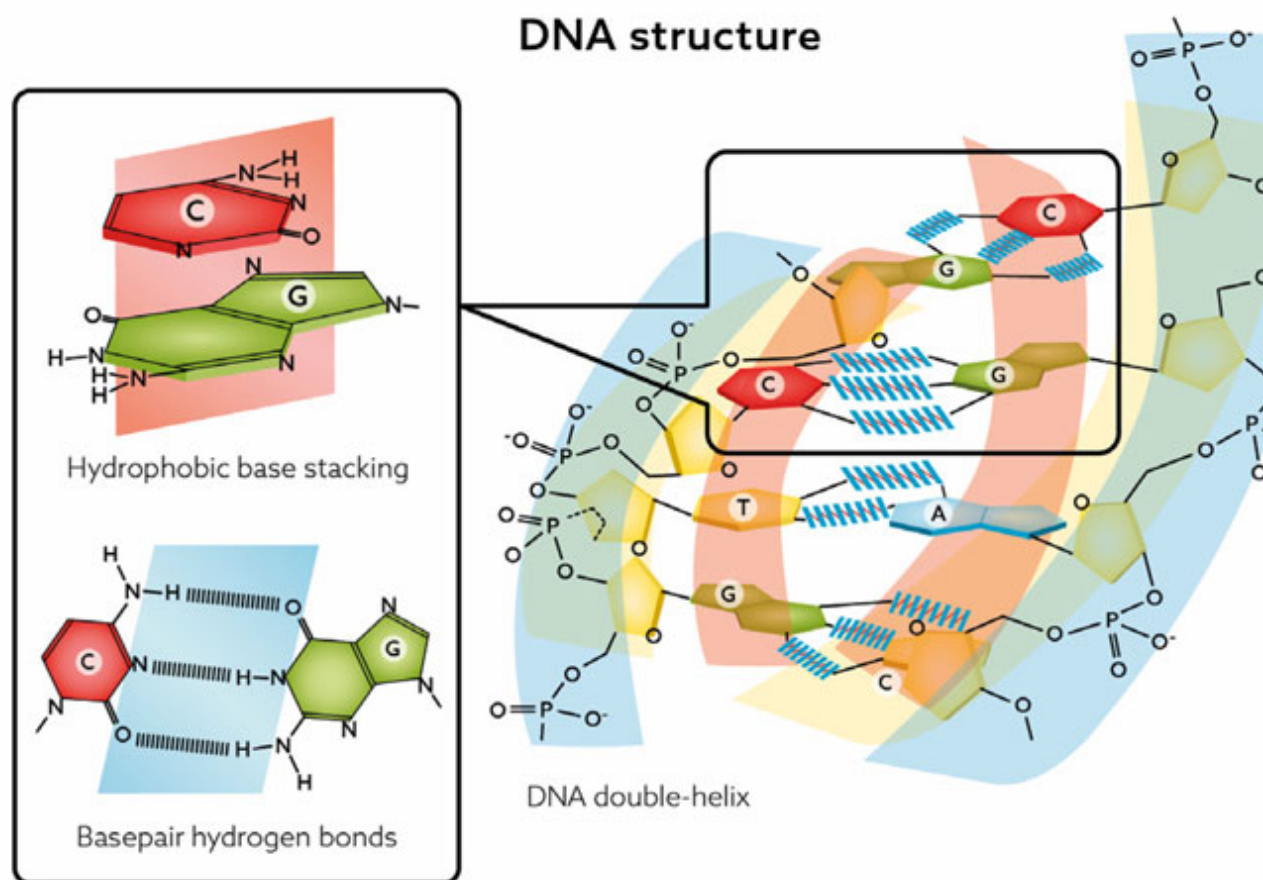
In aqueous medium, all will come together and hide away from water

all will be hydrated and remain exposed in solution

In which medium the reverse will happen?

Non-polar medium, e.g. oil, organic solvents like benzene

Intermolecular forces in nucleic acids



The three most important interactions in nucleic acids are

1. stacking interactions between the aromatic bases — **hydrophobic**
2. Electrostatic interactions between the charged phosphates of the polymer backbone, and water — **hydrophilic**
3. hydrogen bonds in Watson–Crick base pairs — **hydrophilic**

DNA is also an amphiphilic molecule

For single-stranded nucleic acids, like RNA

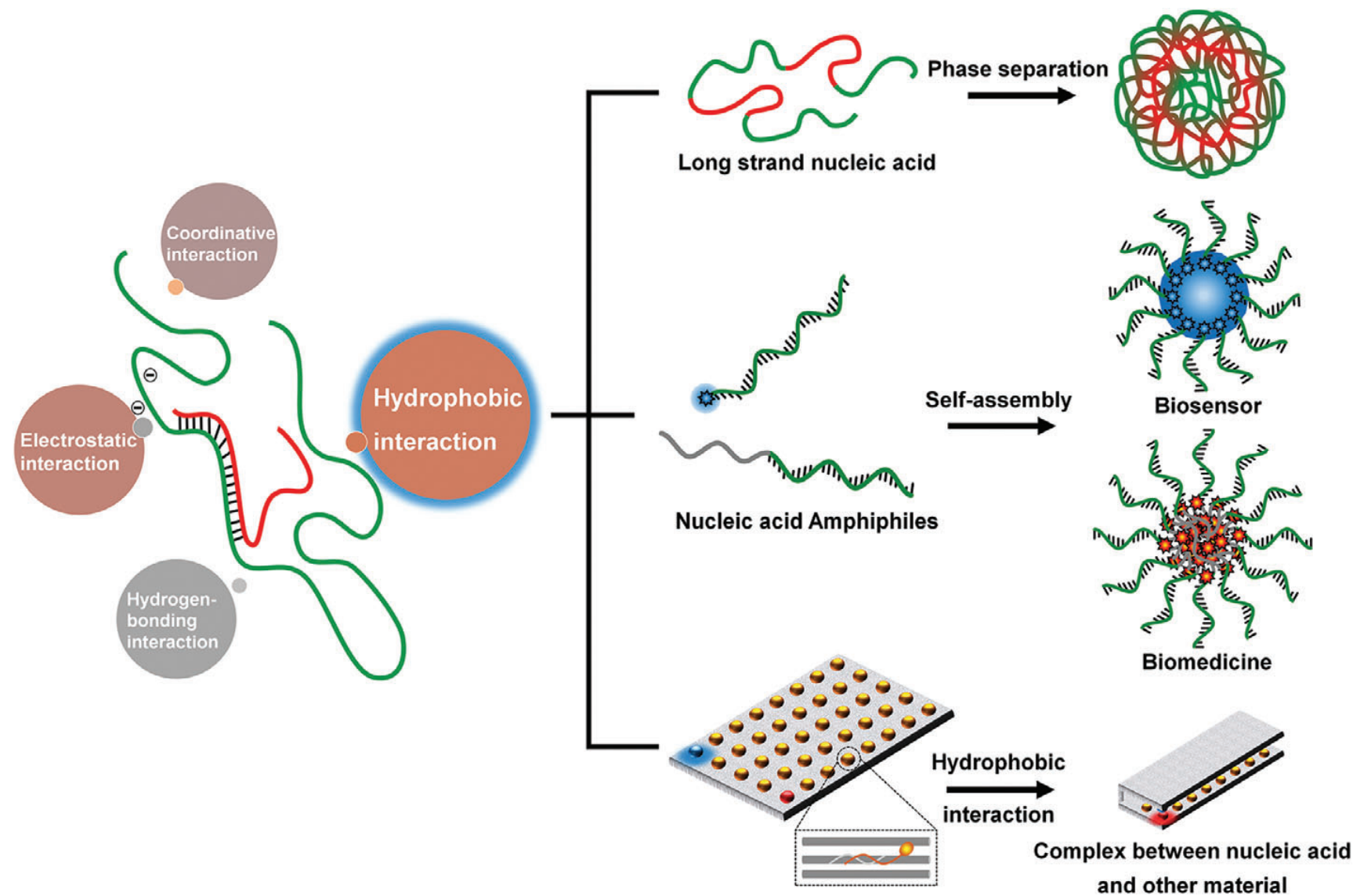
In dilute condition, the repulsive force between the charged phosphate groups tends to straighten the molecule out, increasing their **persistence length**



Distance along the polymer for which it is straight

However, if there are many such RNA or a protein the hydrophobic interactions can drive condensate formation

Leveraging hydrophobic interactions in biomedical applications



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Hydrophobic Interaction: A Promising Driving Force for the Biomedical Applications of Nucleic Acids

Fan Xiao, Zhe Chen, Zixiang Wei, and Leilei Tian*

Adv. Sci. **2020**, *7*, 2001048