Chapter 7:

Intermolecular Interactions

"Corpora non agunt nisi fixata', i.e. molecules do not react if they do not bind."
– Paul Ehrlich

7-1. Introduction:

Intermolecular forces (IMF) are non-covalent bonding forces of attraction that operate over large distances between interacting molecules. Generally, intermolecular forces have a greater dependence on distance of interaction and much less of a dependence on geometry for the strength of their interactions. This is typically not true for covalently bonded atoms because the strength of covalent bonding interactions strongly depend upon both distance and the geometry of orbital overlap between bonded atoms as determined by their atomic electronic structures.

Intermolecular forces are responsible for the 'stickiness' exhibited between Noble gas atoms (e.g. He, Ne, etc.) and molecules. Although weak compared to bond strength energies, these weakly attractive forces are responsible for the formation of liquids, solids, and the organization of bulk matter. The term intermolecular interactions or **Intermolecular forces (IMF)** refer to several types of weak forces of attraction occurring **between molecules**.

Chemical bonds generally are both stronger than IMF interactions and covalent bonds also occur between atoms within a molecule (i.e. bonds generally are point-to-point in their interactions). This point-to-point criteria for chemical bonds is not a hard line in the sand because we already know that ionic bonds can occur between atoms or even between oppositely charged molecular ions. Chemical bonds also have a much larger range of bond energies that range from weak for purely covalent bonds (e.g. Li-Li or F-F) to very strong for ionic bonds (e.g. NaCl or NaOAc).

**It is strongly recommended at this point that the reader take, at least, a quick look at Appendix: Ch 21-2 on thermochemistry. This provides a review of terms, including definitions of energy, enthalpy, entropy, and free energy that are particularly relevant to discussions of various topics in Organic Chemistry, like this chapter on IMF.

7-2. What will be presented:

1. What are the types of intermolecular forces (IMF) typically operating between organic molecules and how do they differ from chemical bonds?

2. Examples of different intermolecular interactions.

3. What are the energy ranges for these different types of intermolecular interactions?

4. What are the relative orientations expected for Dipole-Dipole interactions?

5. What is required for H-bonding?

6. What are the different types of H-Bonds?

7. What structural factors affect the strength of London Dispersion forces?

8. A flow diagram to aid in identifying the types of intermolecular forces between molecules.

9. Why intermolecular forces are important to both chemistry and especially biology.
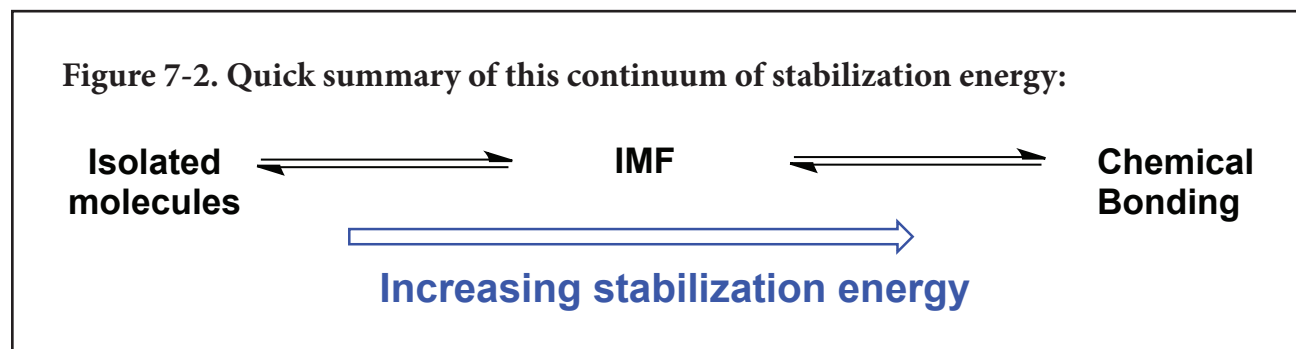
7-3. What differentiates intermolecular forces (IMF) from chemical bonds:

Intermolecular forces are stabilizing attractive forces occurring between molecules; however, the stabilization energy produced by such non-bonding attractive forces are considerably less than that produced by covalent bonds. For example, there even are non-covalent bonding interactions (IMF) operating even between atoms of the Noble gases that permits them to be condensed into liquids.

Figure 7-1. Distance and strength of PE changes resulting from chemical bonding as compared to the PE resulting from Intermolecular forces:

Structure   Energy

Reactivity
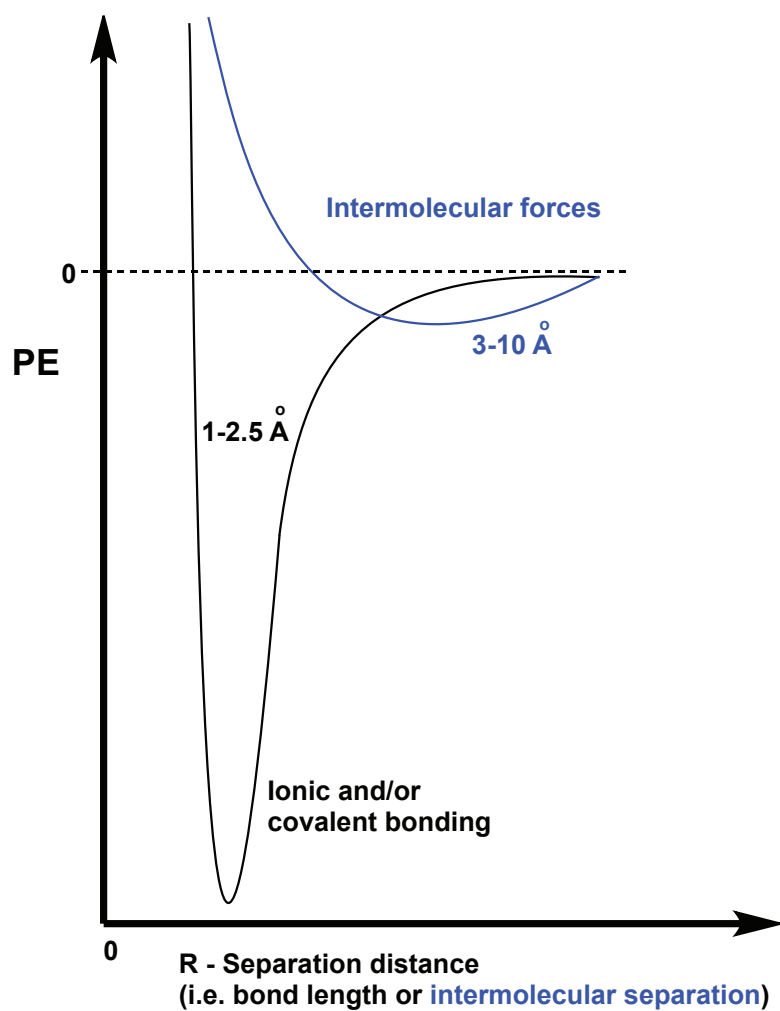
As indicated in Fig. 7-1, intermolecular forces (IMF) although weaker also "switch-on" to provide stabilization over distances much greater than those observed for typical chemical bonds. In a way, IMF are a chemical version of compound interest; although IMF are weak, they also are both cumulative and often non-linear in their impact on a physical properties. Without such non-bonding attractive forces operating between molecules, there would be no intermolecular interactions such as solvation, and without the possibility of interactions like solvation, most reactions would require much higher activation energies. In biology these non-covalent bonding interactions also are the basis for both cellular organization and also contribute to physiological control of cellular functions.

Figure 7-2. Quick summary of this continuum of stabilization energy:

Isolated molecules ⇌ **IMF** ⇌ **Chemical Bonding**

Increasing stabilization energy

In addition to distance of interaction, just what are other types of differences between intermolecular interactions and chemical bonds? A simple comparison is shown in Table 7-1:

Structure Energy

Reactivity

Table 7-1. Intermolecular interactions versus Chemical Bonds:

Intermolecular Forces:	Chemical Bonds:
Intermolecular-between molecules and sometimes even intramolecular if operating between non-bonding (i.e. non-adjacent) molecular segments.	Intramolecular point-to-point between atoms.
Areas of electrostatic attraction-not as directional as a covalent bond: IMF have a stronger dependence on distance than on geometry of interaction. IMF are non-directional	Points of electrostatic attraction- typically have dependence on both distance and geometry of their interaction. Covalent bonds are directional
Affects magnitude of physical properties.	Creates chemical reactivity.
Weak Binding Energy: < 100 kJ/mol	Strong Binding Energy: > 100 kJ/mol
IMF generally have no direct vibrational structure. This result likely is a measurement limitation. However, IMF often have small measurable effects on the vibrational and rotational structure of molecules.	Chemical bonds have strong characteristic vibrational structures.
Generally transient in duration	Not transient

7-4. General energy and distance dependence for different types of Intermolecular Interactions:

As you might recall, a first step towards understanding intermolecular interactions was taken back in Chapter 2, when the relationship between bond polarity and polar molecules was discussed. However, intermolecular interactions have a greater impact on molecular properties than just a rudimentary characterization of molecules as either polar or non-polar.

A tabulation of IMF interaction energies in Table 7-2 along with their stabilization energies are collected along with the strengths of different types of chemical bonds:
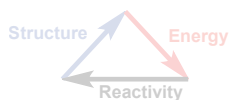
Structure   Energy

Reactivity

Table 7-2. Types of intermolecular interactions and their stabilization energies:

Type of Interaction	Range of energy values (kJ/mol)[1]:	How energy varies as a function of separation (r):
Chemical Bonds		
Ionic	400-4000	$-1/r$
Covalent	150-1100	
Metallic	75-1000	
Intermolecular Interactions		
Ion-Dipole	40-600	$-1/r^2$
H-bond	4-40	$-1/r^3$
Dipole-Dipole	5-25	$-1/r^3$
Ion-Induced Dipole	3-15	
Dipole-Induced Dipole	2-10	$-1/r^6$
Dispersion (London) induced dipole-induced dipole	0.05-40	$-1/r^6$

1) 1 kcal/mol = 4.184 kj/mol

The right column of Table 7-2 also illustrates how these various types of interaction energies vary as a function of separation distance (r) between molecules. This separation data (r) also is graphed in Fig. 7-3 in order to permit a visual and relative comparison of the dependence for these different components of IMF on separation distance (r). The larger the exponential value for n, the shorter the separation distance (r) between molecules before a specific type of interaction develops- i.e. "switches on". In Fig. 7-3, one observes that dipole-dipole interactions with a $-1/r^2$ dependence "switch on" sooner than do London/ Dispersion forces with their $-1/r^6$ variation with distance. Here too one again encounters a more quantitative treatment of an old acquaintance: Van der Waals repulsion (i.e. in Ch 6 this interaction was identified as Steric or Van der Waals strain), has a $\sim+1/r^{12}$ dependence on separation distance:

Structure

Energy

Reactivity

Figure 7-3. Dependence of intermolecular PE as a function of $1/r^n$ for different values of n:

1/r^{12} Van der Waals steric repulsion

0

PE

-1/r^2

-1/r

-1/r^3

-1/r^6

Separation distance (r)
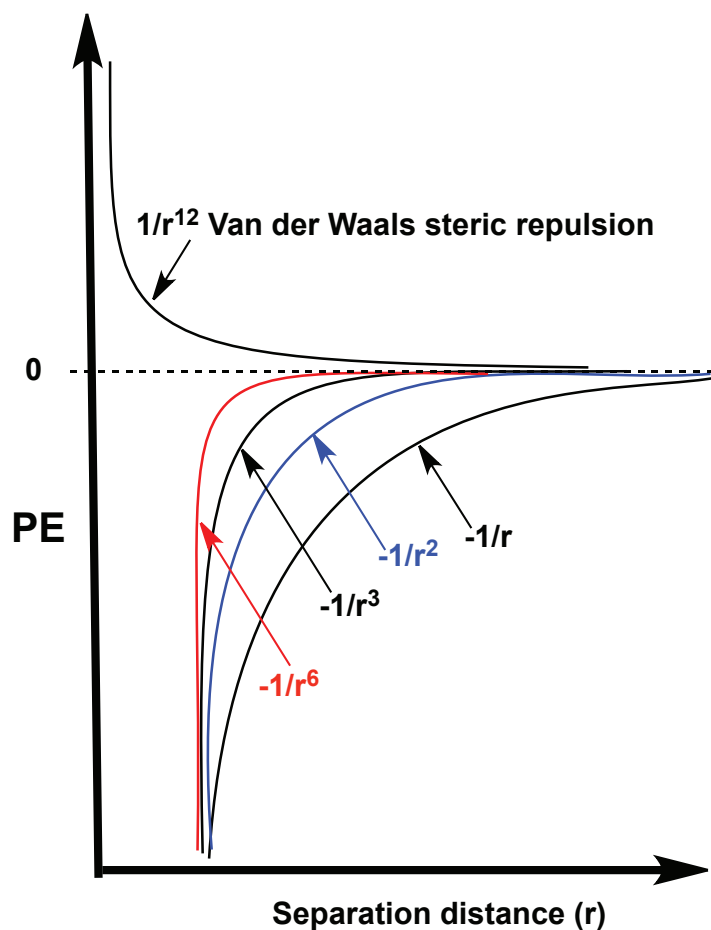
Ionic Bonding: -1/r (long range)

Ion-Dipole: -1/r^2

Dipole-Dipole: -1/r^3

Dipole-Induced Dipole: -1/r^6

London: -1/r^6 (short range)

The Van der Waals repulsion (Ch 6): 1/r^{12}

* Remember separation distance is measured in angstroms:

$$1A° = 1 \times 10^{-8} \text{ cm}$$

Since each of these IMF components has a different functional dependency on r, a maximum value for the total IMF between two or more molecules will be a net sum of all those specific components of an IMF that contribute to that particular intermolecular interaction (See Table 7-2). As a result, IMF (i.e. total sum) does not have a simple relationship between intermolecular separation (r) and the strength of an IMF interaction between two or more molecules like that illustrated for covalent bonds back in Ch. 4 (Fig. 4-19). For a covalent bond, the smaller the value of its r (i.e. its bond length), the stronger its bond (i.e. bond energy).

Structure

Energy

Reactivity

Examples of different types of IMF components:
This section contains both descriptions of these various components of IMF and also several examples of structures that are dominated by that specific type of IMF.

Fig. 7-4, provides several examples of structures and their structural components that are dominated by either ion-ion or ion-dipole interactions. As one might have expected, there is a continuum between ionic bonding and those coulombic interactions that contribute to the IMF within a salt bridge. An important factor used to differentiate ionic bonding from salt bridge formation has to be the distance of separation between specific ions. The range of ion separation distances for a salt bridge appears to be anywhere from >2.5- to ~4.5 A° with typical values hovering around 2.8 A°.

Examples of ion-dipole interactions, such as those in Fig. 7-4, are identified readily because these interactions involve ions interacting with polar molecules:
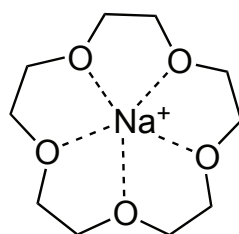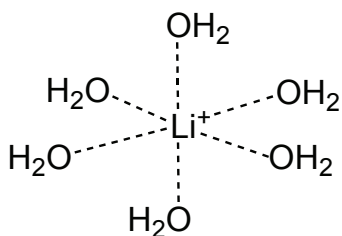
Figure 7-4. Examples of non-covalent Ionic interactions that also include salt bridges and ion-dipole interactions and their individual dependences on separation distance (r):

Ion-ion or (Coulombic) : E ~ -1/r

Ion-dipole : E ~ $-1/r^2$
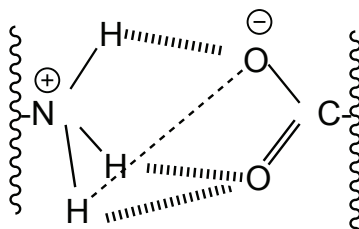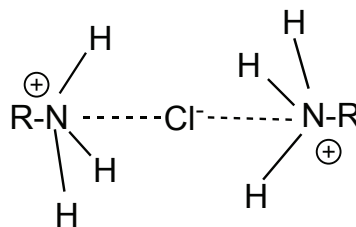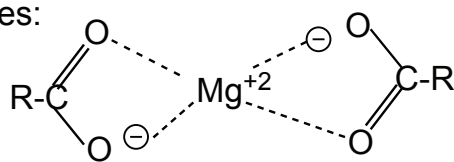
Structure
Energy
Reactivity

Salt-bridge ionic interactions generally are more commonly encountered in structural Biochemistry rather than in Organic chemistry. However, as we'll see later in this text, ion-dipole interactions frequently are encountered in Biochemistry and also used for advantage in synthetic Organic chemistry.
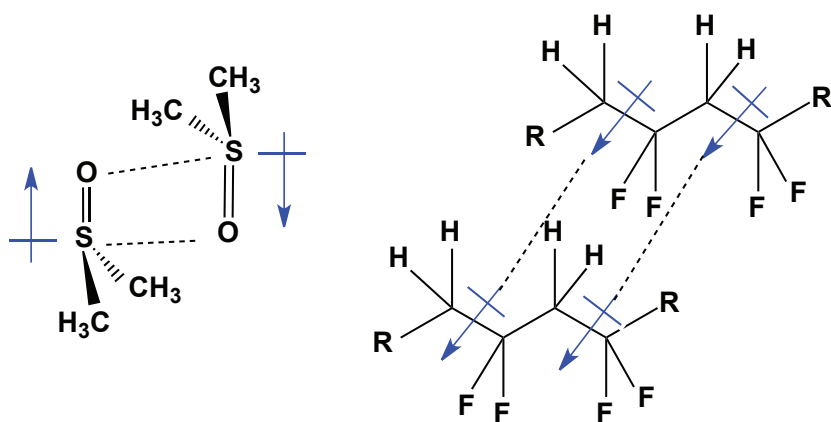
Those intermolecular interactions (IMF) of particular importance to both Organic and Biochemistry include: H-bonding, dipole-dipole, dipole-induced dipole, and London Dispersion forces. This discussion will start with dipole-dipole interactions and then finish with the London Dispersion forces-typically the weakest of these important IMF.

Figure 7-5. Energy dependence on molecular Dipole-Dipole Interactions and some examples of these Dipole-Dipole interaction geometries:
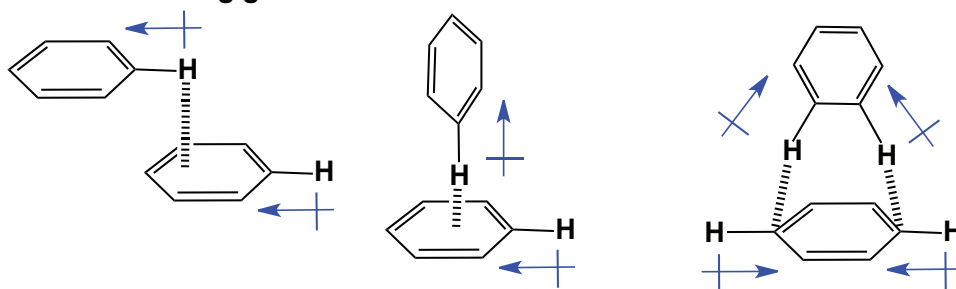
Dipole-Dipole interaction E(r) varies as -1/r³

dipole-dipole : E ~ -1/r³

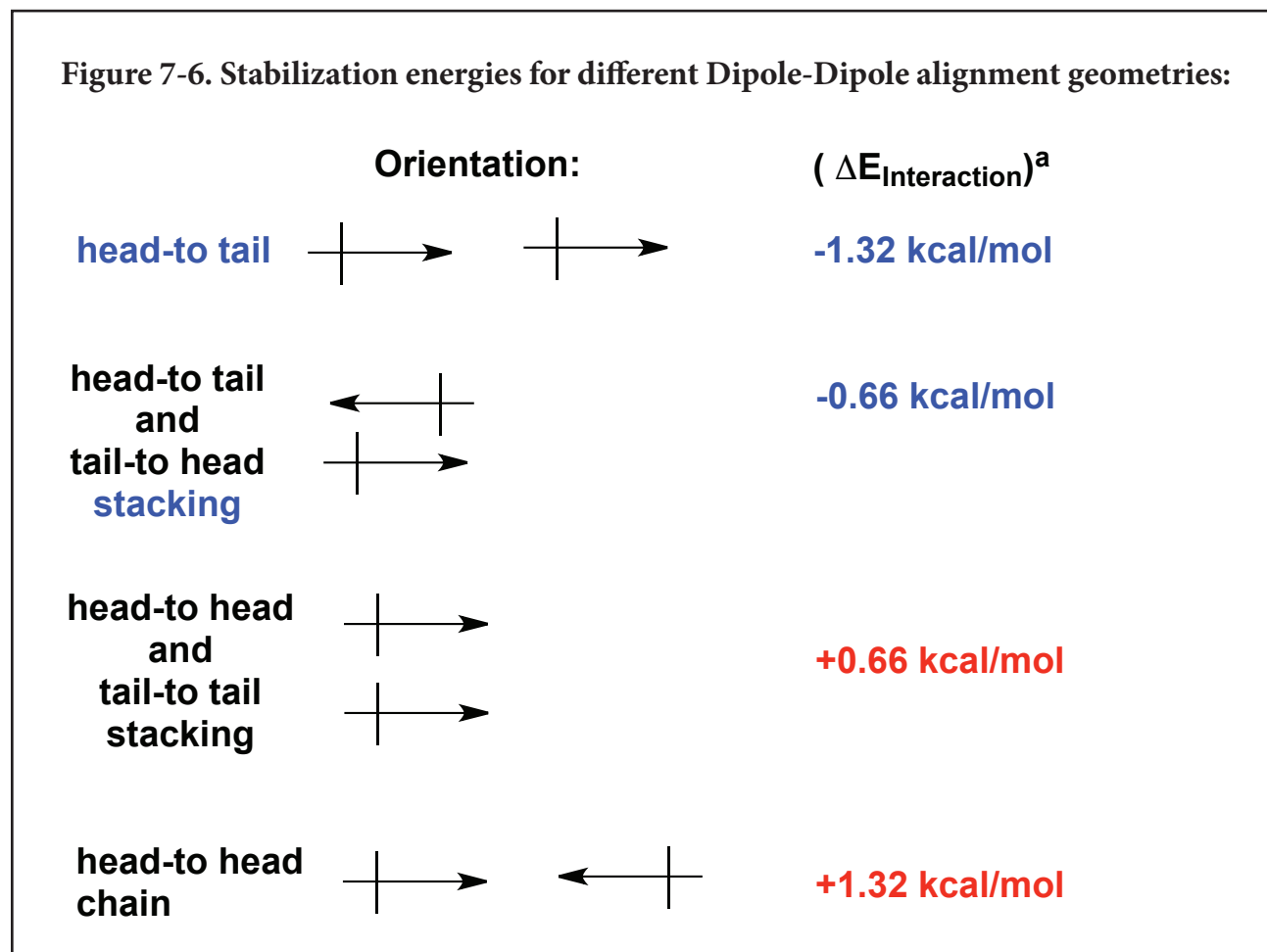**typical head-to-tail dipole-dipole interactions**

possible π-stacking geometries

head-to-tail dipole-dipole interaction geometries don't have to be parallel or co-planar

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Dipole-dipole interactions like those in Fig. 7-5 are one of the most important intermolecular interactions in both Organic and Biochemistry. *Dipole-dipole interactions* result from attractions between permanent molecular dipoles. A molecular dipole moment is produced from a net sum of a molecule's bond dipoles. As you should recall (from Ch 2), bond dipoles result from the displacement of electron pairs within their covalent bonds to create polar covalent bonds. Unlike many of the other types of IMF, dipole-dipole interactions **do** depend on both dipole magnitude and relative geometry of intermolecular orientation. As data in Fig. 7-6 illustrate, dipole-dipole interactions typically favor head-to-tail dipole-dipole orientations over head-to-tail "stacking":

Figure 7-6. Stabilization energies for different Dipole-Dipole alignment geometries:

Orientation:		$(\Delta E_{Interaction})^a$
head-to tail		**-1.32 kcal/mol**
head-to tail and tail-to head stacking		**-0.66 kcal/mol**
head-to head and tail-to tail stacking		**+0.66 kcal/mol**
head-to head chain		**+1.32 kcal/mol**

a. These $\Delta E_{Interaction}$ were calculated for two dipoles of 1 Debye each at 5 A^0 separation in in a medium with a dielectric constant ε = 4 (almost equivalent to the solvent diethyl ether with an ε = 4.3); For points of reference: water has ε = 78.4 (very very polar) and cyclohexane has ε = 2.0 (very very nonpolar).

H-bonding is a special type of dipole-dipole interaction:

Although H-bonds (i.e. hydrogen bonds) are just a special type of dipole-dipole interaction, this particular type of dipole-dipole interaction is considered by many in both Organic and Biochemistry to be the most important of all these possible intermolecular interactions. The reason for this importance is that the stability provided by H-bonding also depends on both geometry and distance between H-donors (A-H) and H-bond acceptors (B:). Table 7-3 provides ranges of energies for H-bonding interaction and the energy implications implied by such adjectives as strong, moderate, and weak that are used to describe specific examples of H-bonding:

Structure Energy

Reactivity

Table 7-3. Types of H-bonds:

Types of Hydrogen Bonds		
Strong	15 - 40 kcal/mol	63 - 167 kJ/mol
Moderate	4 - 14	16.7 - 58.6
Weak	0 - 4	0 - 16.7

Weak hydrogen bonds generally are the type most commonly encountered. H-bonds can be strengthened or weakened by other concurrent electrostatic interactions (e.g. salt bridges, see Fig. 7-4).

Figure 7-7. Examples of both intra- and intermolecular H-bonding interactions:

H-bonding PE(r) is a dipole-dipole interaction and it too varies as $-1/r^3$

Hydrogen-bonds : E ~ $1/r^3$
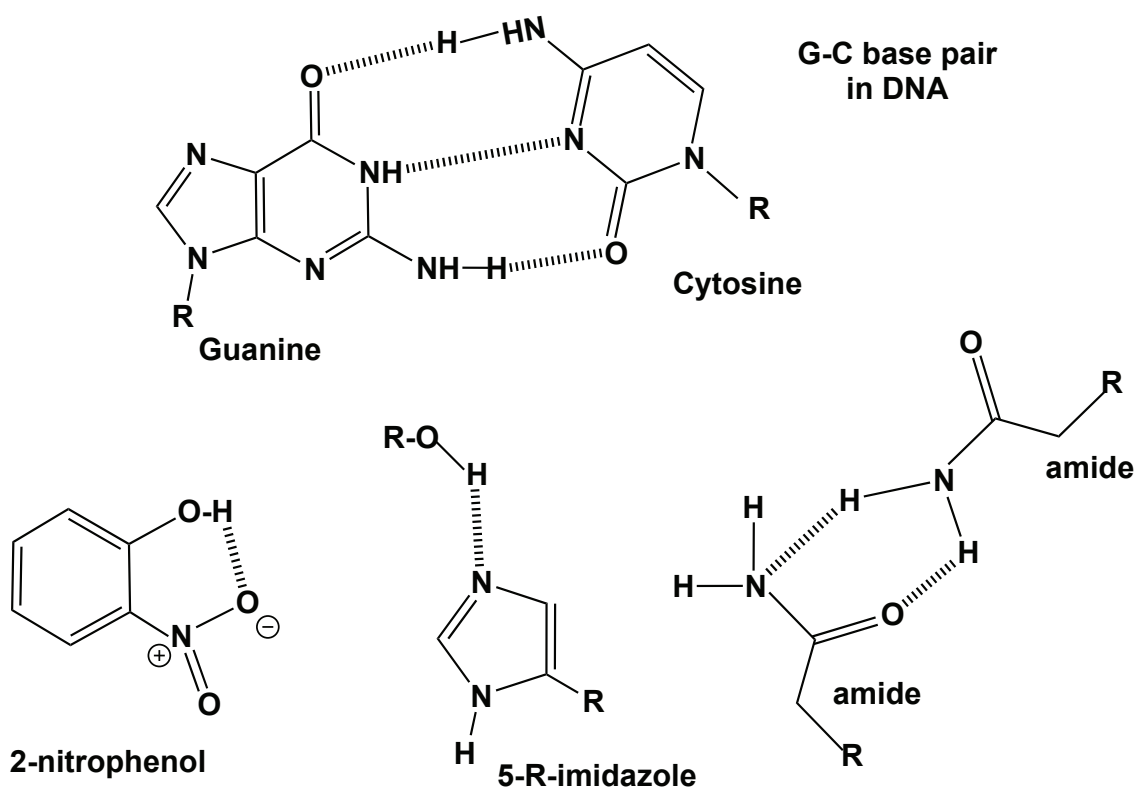
As Fig. 7-7 shows, H-bonds can be intermolecular or even intramolecular (e.g. 2-nitrophenol). Intermolecular H-bonds lead to formation of dimers (e.g. amides) and even 3D oligiomers (e.g. structure of liquid water). In addition to bulk physical properties, intramolecular H-bonds also can influence both molecular geometry and stereochemistry by restricting rotation about sigma bonds, which also can affect relative conformational energies.

Structure
Energy
Reactivity

Enthalpy of formation (i.e. $\Delta H_{H\text{-bond}}$) for intermolecular H-Bonds $(\Delta H_{H\text{-bond}})_{\textbf{Inter}}$, although small, generally are more negative (i.e.more stable) than the enthalpy of formation for intramolecular H-bonds $(\Delta H_{H\text{-bond}})_{\textbf{Intra}}$. This typical result is observed because geometric constraints imposed by intramolecular H-bonding also can limit the ability of intramolecular H-bonds to attain that combination of optimal distance and geometry necessary to maximize H-bond strength (as measured by $\Delta H_{H\text{-bond}}$). However, there is more to H-bond strength than enthalpy (i.e. $\Delta H_{H\text{-bond}}$).

For small changes in enthalpies, one now also has to consider the effects of entropy. H-bonding interactions decrease entropy (i.e. $\Delta S_{H\text{-bond formation}}$ is neg). These H-bonding decreases in entropy are a bit more negative for intermolecular H-bonds (**inter**) than for intramolecular H-bonds (**intra**).

The change in intramolecular H-bond entropy, $\Delta S_{H\text{-bond form}}$ (**intra**) is less negative than changes in intermolecular H-bond entropy, $\Delta S_{H\text{-bond form}}$ (**inter**) because intramolecular (**intra**) interactions have a smaller impacts on rotational and translational molecular motions than do intermolecular H-bonds. The formation of complexes or agglomerations resulting from intermolecular H-bonds decreases entropy, $\Delta S_{H\text{-bond form}}$ (**inter**), because their dimers and oligomers reduce the translational degrees of freedom (i.e. motion in x,y,z directions) and also affect rotational motions (e,g. translation and rotation of agglomerated molecules (e.g. a dimer vs two independent molecules). These molecular motions would be unrestricted for both monomeric (i.e. isolated) H-bond donors and for their isolated H-bond acceptor molecules. These differences between changes in entropy for intra- vs intermolecular H-bonds makes free energy changes ($\Delta G_{H\text{-bond form}}$) for **intramolecular** H-bonds slightly **more negative** (i.e. **more stabilizing**) than those changes in $\Delta G_{H\text{-bond form}}$ for **intermolecular** H-bonds.

Formation of a hydrogen bond requires two partners: an H-bond donor (A-H) and an H-bond acceptor (B:). An H-bond donor (A-H) "donates" the hydrogen end of its A-H bond dipole to an H-bond acceptor (B:). An H-bond acceptor (e.g. B:) is an atom in a molecule that most often has at least one pair of non-bonding electrons.

Increasing the electonegativity of A in an A-H bond donor group increases the strength of an H-bond donor, [i.e. strength of donor increases with EN(A)]. Thus trends for H-bond strengths for A-H are: S-H <<< N-H < O-H < F-H. The strength of H-bonding also increases with base strength (i.e. the availability) of an electron pair on the H-bond acceptor (e.g. B:).

Structure Energy
Reactivity

Electron availability for B: from weakest (left)-to-strongest (right):

π-electrons <non-bonding electrons on halides < non-bonding electrons on nitriles e.g. **:NC-R** <
**:S=CR$_2$ (in thiocarbonyls and thioesters) < :O=CR$_2$ (in carbonyls and esters) and C-O-C(ethers) <
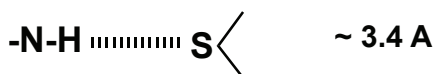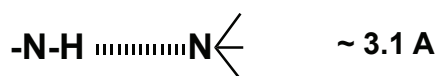:N=CR$_2$ (Imines) and :NR$_3$ amines**

H-bond strength trends and commonly encountered types of H-bonding interactions are illustrated in Table 7-4:

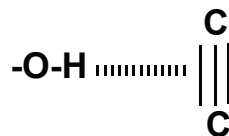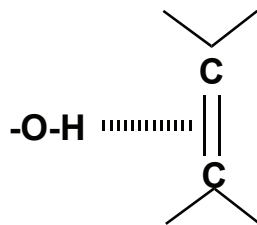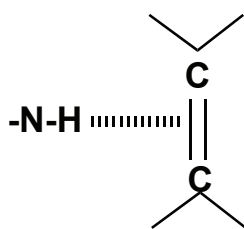**Table 7-4: General types of different types of H-bond donor-acceptor combinations[1]:**

Strong H-bonds (2.4-2.9 A; 16-35 kJ/mol)

-O-H ⨿⨿⨿⨿O〈   ~ 2.7 A

-O-H⨿⨿⨿⨿S〈   ~ 2.8 A

-O-H⨿⨿⨿⨿N〈   ~ 2.8 A

-N-H ⨿⨿⨿⨿O〈   ~ 2.9 A
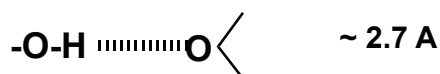
Moderate H-bonds (3.0-3.5 A; 8-16 kJ/mol)

-N-H ⨿⨿⨿⨿N〈   ~ 3.1 A

-N-H ⨿⨿⨿⨿ S〈   ~ 3.4 A

-O-H⨿⨿⨿⨿ F   ~ 2.1 A , (one example)

Weak H-bonds (>3.0 A; 2-8 kJ/mol)

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*1) Data and organization from B. Testa, Principles of Organic stereochemistry,1979, p28;
Conversion factor: 4.184 kJ/mol = 1 kcal/mol*

The more polar an A-H donor bond (notice that strongest A's in Table 7-4 are **all** from the second row) and the more basic its H-bond acceptor (e.g. B:), the stronger the resulting H-bonding interaction. Not only are H-bonding interactions typically stronger attractive forces than London dispersion forces, but they also can be cooperative. This cooperativity among multiple H-bond makes the net strength of multiple H-bonds, unlike London dispersion interactions (see below), non-linear in their stabilizing effects — that is the total intermolecular (i.e. net) interaction energy for multiple H-bonds between two molecules often is more than just a sum of their individual H-bonding pairs of contacts. A classic example of this cooperative effect is the base pairing within DNA structures.

London dispersion interactions:

What makes London dispersion forces so important is that they operate, to a greater or lesser extent, between Noble gas atoms and molecules alike — whether or not the molecules are polar or non-polar. London forces are a foundation for all non-covalent bonding interactions. London forces are directly proportional to a property identified as polarizability. Polarizability is a measure of the ease with which electron clouds around atoms or molecules can be distorted from their "equilibrium" positions by an adjacent electric field. The easier it is to distort this valence electron density, the higher the value for polarizability, the stronger the London forces that arise from this polarizable electron density. London dispersion forces drive aggregation between the atoms of Noble gases and molecules, and as a consequence, these dispersion forces also are a fundamental factor affecting both macroscopic order and self-organization within the Universe.

Adding together both the VDW (Van der Waals) repulsion to these different stabilizing components of IMF (Fig. 7-3) will generate a potential energy (PE) diagram with a familiar shape like that shown in Fig. 7-8. The PE diagram for IMF for an argon dimer (Ar••••Ar) is relatively "simple" because it's IMF consists only of London dispersion forces. The strength of the "stickiness" between these two atoms has a stabilization energy of about -0.286 kcal/mol at an argon-argon separation of about 3.75 Aᵒ.

Figure 7-8. PE for London Forces between two Argon atoms in a dimer*:
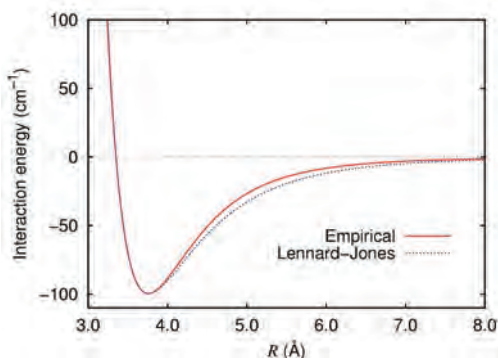
Interaction energies in this example are so small that the y-axis energy units are in cm^{-1}:
$$E = h\nu$$

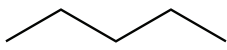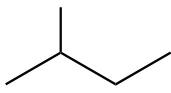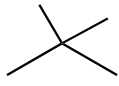$1cm^{-1} = 2.86 \times 10^{-3} kcal/mol;$

$100cm^{-1} = 0.286$ kcal/mol

Notice that the optimal distance for maximum London forces between these argon atoms is around 3.75 Aᵒ

Lennard-Jones refers to a theoretical description of PE for these London forces that describes London forces in terms of a stabilizing $-1/r^6$ attractive component and the detabilizing $1/r^{12}$ (i.e. van der Waals) steric strain component.
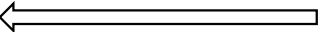
Structure   Energy

Reactivity

London forces increase with atomic size and molecular surface area [i.e. which generally is proportional to molecular weight (MW)]. Molecules with more atoms and larger molecular weights will have larger polarizabilities than smaller molecules with fewer atoms. If MW and functional groups are equivalent, then those molecules with larger surface areas (e.g. chains) are more polarizable and will have larger London forces than similarly constituted molecules with smaller surface areas (e.g. branched chains). This effect of surface area is dramatically illustrated in Table 6-5 for a selection of pentane isomers:

Table 7-5. Physical properties of pentane isomers that are determined by variations in London Dispersion interactions[1]:

	pentane	isopentane	neopentane
bp (C^0)	36.0	27.7	9.5
H^0_{vap} (kJ/Mol 25C)	26.4	24.85	21.84
Density: g/L	621	616	586
Heat capacity (J/K^0mol)	167.2	164.9	121.0
Vapor Pressure (kPa)	57.9	77.0	gasseous
Mp (C^0)	-129	-159	-16*

* effect of symmetry on packiing of crystal

Molecular Properties:

London Forces:	Larger ⟸	Smaller
Surface area:	Larger ⟸	Smaller
Branching:	None ⟹	Largest

1) MW is constant across this series of molecular structures.

Structure

Energy

Reactivity

Figure 7-9. The relationship between Valence electron polarization and creation of instantaneous dipole-dipole interactions:

Electron distribution averaged over time- appears to be evenly distributed along and around molecule or atom:
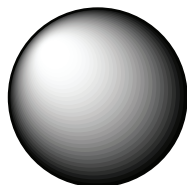
However, in any one instant, fluctuations of electron density do occur. These fluctuations "dislocate" the symmetrical electron distribution around a molecule and this creates-for just an instant-an instantaneous dipole:
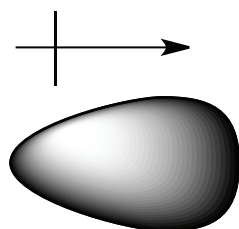
In closer contact with other molecules, these fluctuations become synchronized between molecules creating an "attraction" between these induced dipole-induced dipole interactions. These istantaneous dipoles create stabilizing IMF between molecules and even between atoms:

and

Structure   Energy

Reactivity
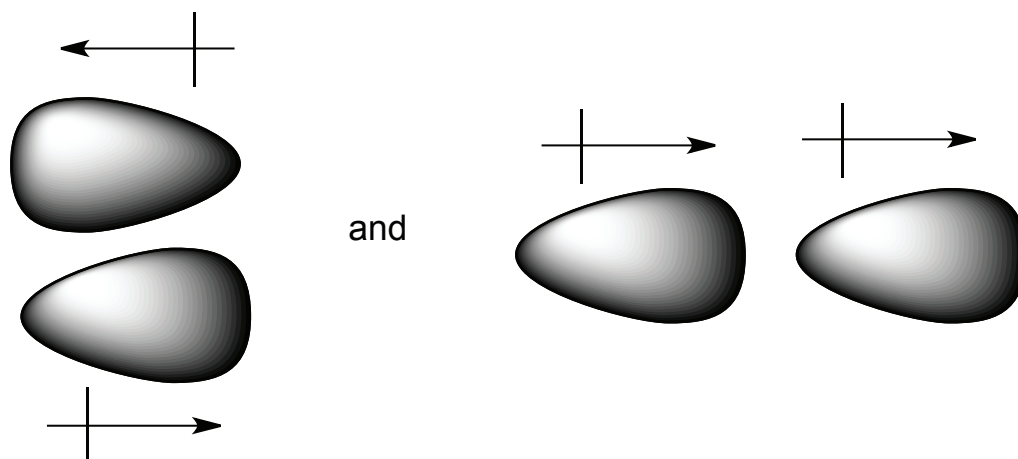
The larger a molecule's surface area, the larger the London forces that are generated by its electron density fluctuations, which lead to transient associations or stickiness between molecules. Although not terribly large for small mo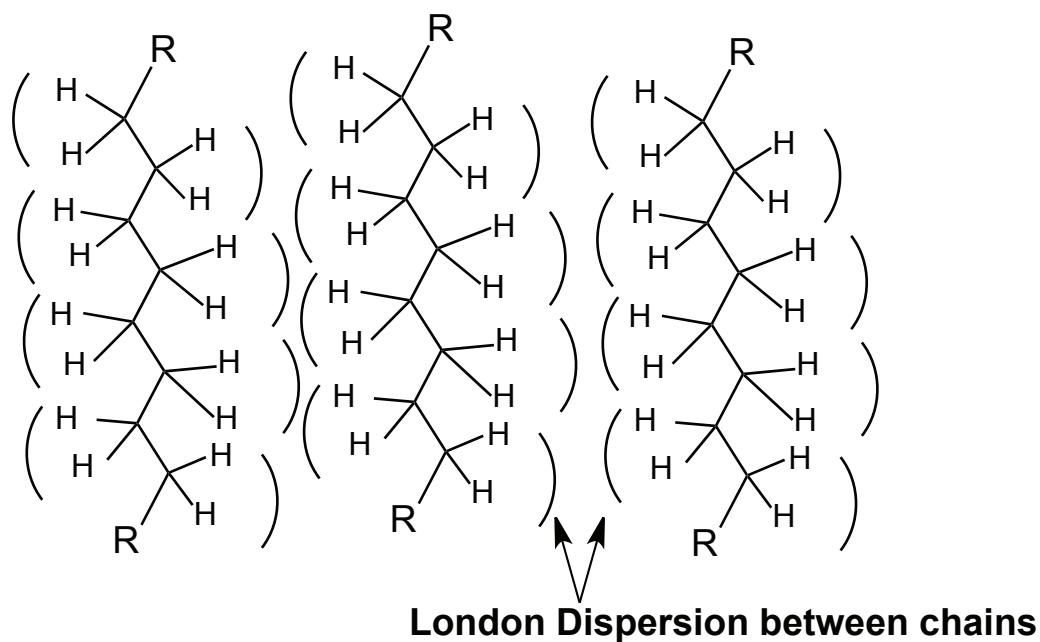lecules, these attractive forces increase in significance for large molecules. London Dispersion forces are the reason why one can condense a Noble gas like helium into a liquid state.

Figure 7-10. Examples of London Dispersion Interactions:

London Dispersion E(r) varies as -1/r^6

London Dispersion between chains

Increasing molecular "stickiness" increases physical properties that depend on IMF, such as: boiling point, enthalpy of vaporization, density, surface tension and heat capacity. Increasing the strength of IMF also decreases vapor pressure. The stronger the intermolecular forces (IMF) between molecules, the stickier the molecules are to each other, and this increases the amount of energy required for molecular separation.

The contribution of London forces relative to the other types of intermolecular non-covalent interactions are illustrated rather dramatically for small molecules like those shown in Table 7-6:

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Table 7-6: Resolution of non-covalent bonding into IMF components:

| Substance	Bp (C⁰)	Dipole Moment (D)	Polarizability	% from dipole-induced dipole	% from dipole-dipole	% from London dispersion
He	-270	0	0.2	0	0	100
Ar	-186	0	1.6	0	0	100
CO	-190	0.1	2.0	0	~0	~100
HCl	-84	1.0	2.6	4.2	14.4	84.1
HBr	-67	0.8	3.6	2.2	3.3	94.5
HI	-35	0.4	5.4	0.4	0.1	99.5
NH$_3$	-33	1.5	2.6	5.4	44.6	50.0
H$_2$O	100	1.8	1.5	4.0	77.0	19.0

Even for a very polar molecule like water (H$_2$O), London forces still account for about 19% of those intermolecular forces of attraction between water molecules. From an analysis of alkane boiling point data, one also observes that London forces generally scale in a linear fashion with increases in surface area (i.e. molecular weights). This is why Bp's of alkane chains generally increase in a very regular fashion with increasing molecular weight (See Fig. 7-13).

Q; Identify the polar groups in the molecules below and then determine if the molecule itself is polar:
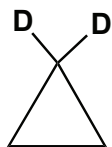
C-D
same polarity as
C-H

Not a Polar molecule
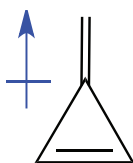
(cis) C-C=C-C
smaller dipole
than
(C)₂C=C

Net molecular dipole-thus a Polar molecule
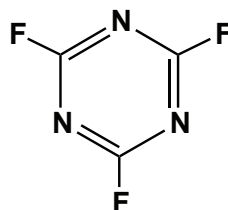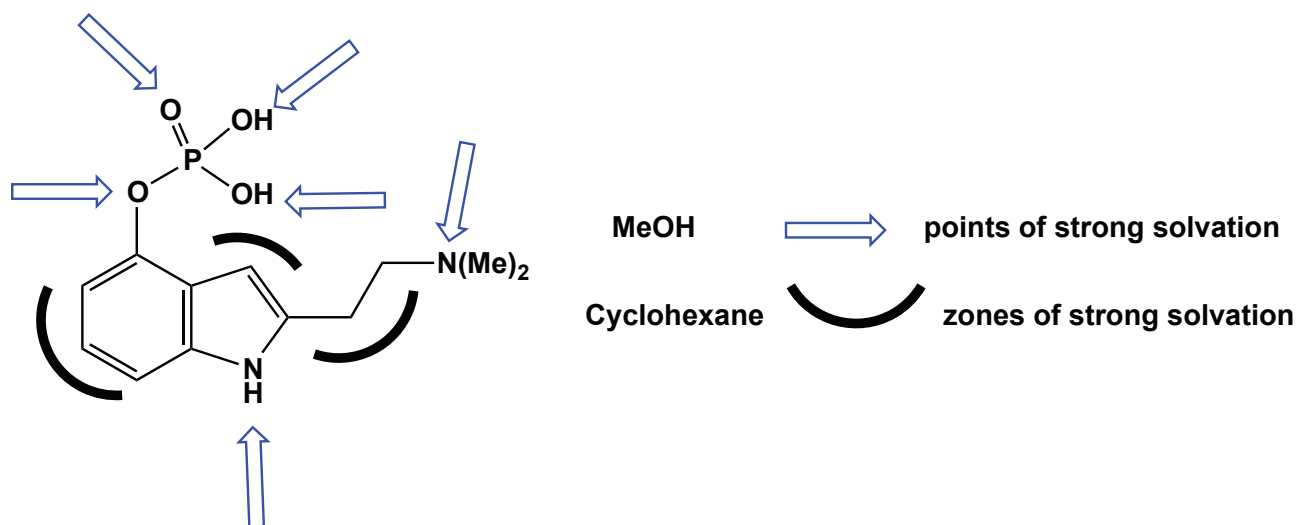
C-F dipole
larger than
C=N dipole

Bond dipoles cancel each other,
No net molecular dipole-thus NOT a Polar molecule
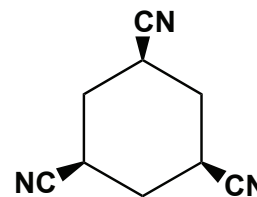
CN dipole
larger than
C-H dipole

All -CN in equatorial positions
No net molecular dipole-thus NOT a Polar molecule

Q: For a molecule of psilocybin shown below, consider in more detail how this molecular structure is likely to be solvated in two different solvents. Try to find the strongest points of solvation for methanol and also cyclohexane:

MeOH is a very polar solvent; its strongest solvent-solute interactions involve strong dipole-dipole and H-bonding interactions. Expect very tight solvation due to H-bonding between solvent and solute. There should be strong interactions between groups that can function as both strong H-bond donors and H-bond acceptors (i.e. MeOH-----OH groups). As a result, one expects the solvation cavity or "sphere" for methanol to be tight and very irregular in its cavity volume due to these different points of strong H-bonding contacts.

Cyclohexane is a very non-polar solvent and much larger in size than methanol. Cyclohexane's strongest solvent-solute interactions will be of the London dispersion type. Those groups on psilocybin with strong bond dipoles also will induce dipoles within cyclohexane, there is no dipole-dipole or H-bonding between cyclohexane and psilocybin. These London forces and induced dipole interactions with cyclohexane will be weak when compared the dipole-dipole and H-bonding interactions with methanol. Thus expect the solvation cavity for cyclohexane to be much larger, much looser that a solvation cavity created for psilocybin by a solvent like methanol.

In common discourse, the terms London dispersion and Van der Waals force often are used interchangeably. However, this can be confusing, because the term Van der Waals force is a generic contextual term that often refers to all types of non-bonding attractive forces (e.g. IMF) such as those shown in Table 7-2 and this term also is even used to describe those steric repulsion forces also operating between all molecules or groups (i.e. Van der Waals repulsion or steric strain). As the data in Table 7-2 shows, London forces often are just one component of all the different types of IMF interactions that also may be described collectively as Van der Waals forces of attraction.

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7-5. Impact of intermolecular interactions on selected physical properties:

Mp- (melting point) is the temperature at which a solid is in equilibrium with its liquid state. Thus the stronger a material's intermolecular forces the higher its Mp. However, it should be noted that the more symmetrical a molecule and its attached functional groups also will increase its Mp- because symmetrical molecules produce solids with tighter packing of molecules within their unit cells (see data bottom of Fig.7-5). Thus Mp trends among different compounds often can be confounded (i.e. confused or complicated) by contributions from both IMF and increases in packing efficiency within a solid's unit cell. A thermodynamic property that directly assesses the IMF within a solid is its enthalpy of fusion (ΔH^0_{fusion}). Like Mp, the heat of fusion also contains contributions from both IMF and unit cell packing effects. The greater the Mp of a solid, the greater its enthalpy of fusion.

Bp- (boiling point) is the temperature at which a liquid is in equilibrium with its gas (vapor). Unlike Mp, Bp is only a function of intermolecular forces. The stronger the intermolecular forces between molecules, the more energy is required to move molecules from their liquid state into their vapor state. The thermodynamic property that directly measures the energy required to move molecules from a liquid phase into a gas phase is the enthalpy of vaporization (ΔH^0_{vap}). The higher the Bp for a liquid, the greater is its enthalpy of vaporization and also the lower its vapor pressure.

Solubility is the extent to which one compound — a solute — dissolves into a liquid — the solvent. The general rule of solubility is that like-dissolves like, because for good solubility, a solvent needs to have attractive intermolecular forces that match-up with those same types of attractive forces found within a liquid or solid solute. Understanding intermolecular interactions not only will permit one to predict which solvents are best at dissolving a given solute, but there also are numerous examples where solvation also affects both the rate and very often the mechanistic nature of a reaction. Solvation effects on rates of reactions and reaction pathways will be of particular interest in subsequent chapters.
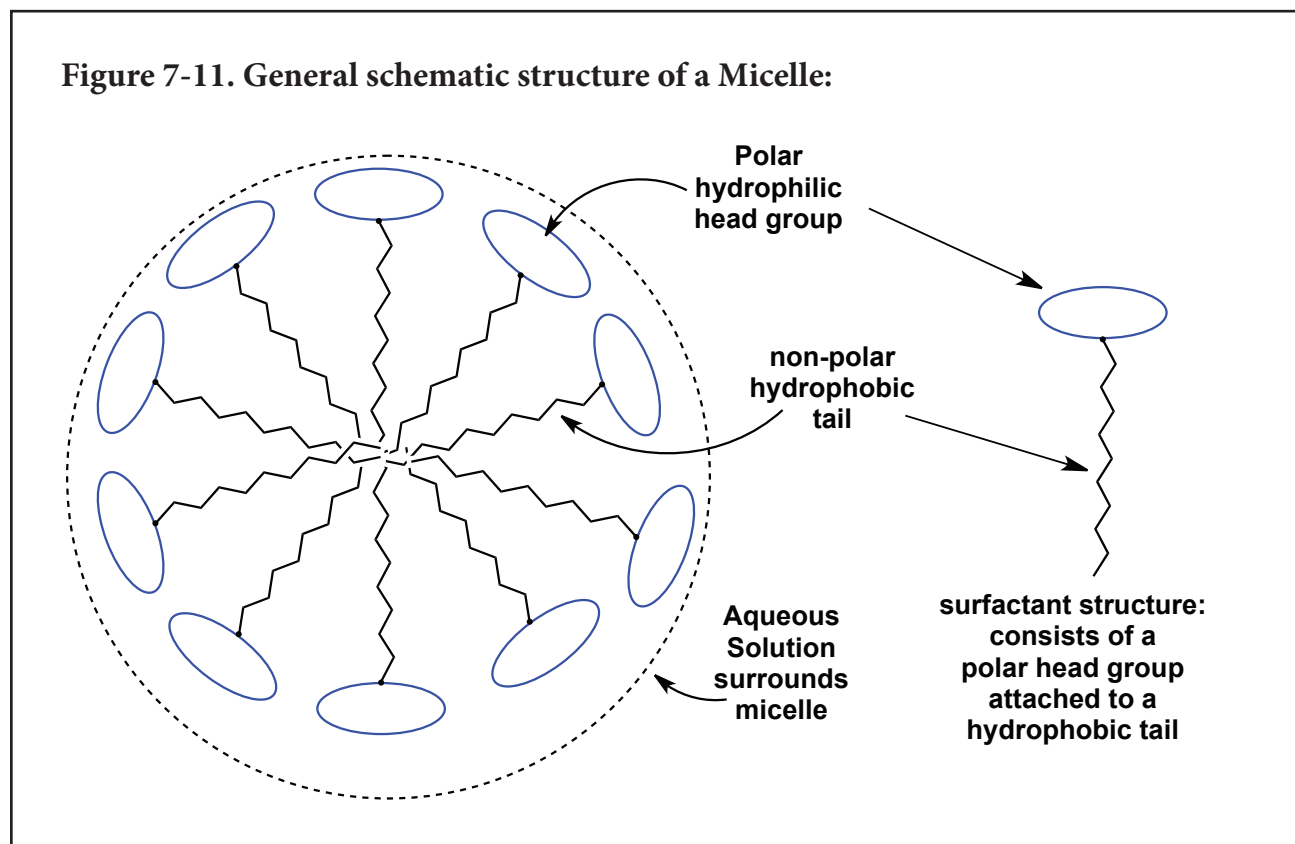
Solids always have a limited solubility in a solvent because those Intermolecular forces holding a solid together are greater than those forces that hold a liquid together. The closer a solid is to its melting point, the less energy required to break-up its unit cell — the more likely that entropic effects will exceed any enthalpy differences between its solid phase and its solvated molecules. It's for this reason that low melting solids, as a general rule, often possess greater solubility in a given solvent than do higher melting solids.

One of the more interesting applications of intermolecular interactions is in the area of surfactants-these are compounds that decrease surface tension, especially the surface tension of water. Surface tension is the energy required to increase the surface area of a liquid (i.e. the energy required to spread out molecules in a liquid to form a film of liquid vs a droplet). The greater the intermolecular forces holding a liquid together, the higher a liquid's surface tension. Surface tension has units of force per unit length (dynes/cm) or energy per unit area (ergs per cm^2). Water has a surface tension of 72.8 dynes/cm compared to 22.3 for ethanol (CH_3CH_2-OH) or 465 for liquid mercury.

Surfactants:

Amphiphilic molecules such as surfactants consist of alkyl chains containing anywhere from C14-C30 carbons attached to a terminal polar head group. This type of molecular structure creates two rather extreme zones of polarity within the same molecule: The polar head group zone is *hydrophilic* (literally water loving) and the non-polar zone, created by its long alkyl tail, is hydrophobic (literally water hating). This schizophrenic structure within a single molecule produces some rather unusual properties. Typically surfactants are added to liquids like water, to decrease surface tension. Surfactants, both naturally occurring (i.e. soaps) and synthetic (i.e. detergents), will in higher concentrations also form micro aggregated globular structures such as micelles, lipid bilayers, and liposomes. Liposomes are especially interesting because they are models for the basic building blocks for cell wall structures.
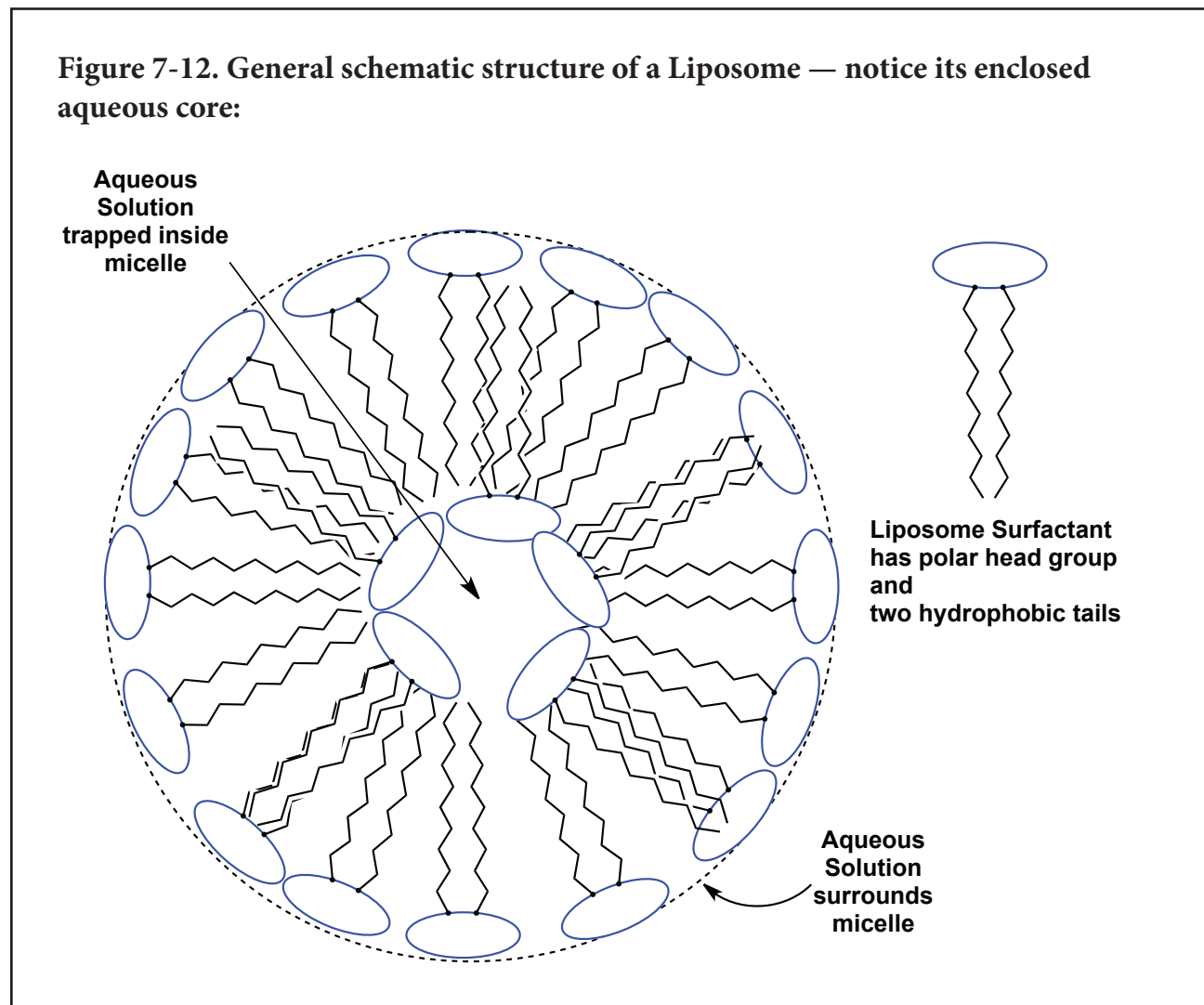
Normal micelles are globular structures that consist of an outer surface occupied by polar hydrophilic head groups, with an interior containing their hydrophobic tail groups:

Figure 7-11. General schematic structure of a Micelle:

Polar hydrophilic head group

non-polar hydrophobic tail

Aqueous Solution surrounds micelle

surfactant structure: consists of a polar head group attached to a hydrophobic tail

In effect a micelle uses its hydrophilic polar head groups to shield their interior hydrophobic tails from their aqueous environment.

Since surfactants disrupt bulk H-bonding in water, micelles decrease the surface tension of water. As a result, surfactants find extensive application as wetting agents (soaps and detergents), as well as emulsifiers, and also are utilized in organic synthesis as phase transfer catalysts that essentially facilitate both mixing and contact on a molecular scale. We'll talk a bit more about phase transfer catalysis when substitution reactions are discussed later in Ch 14.

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A lipid bilayer and globular liposomes (Fig. 17-12) have their hydrophobic tails in a layer that is sandwiched between two pairs of hydrophilic heads on their exposed outer and interior core surfaces. A liposome has an exterior like a micelle, but it also encloses an aqueous core inside its globular organic structure:

Figure 7-12. General schematic structure of a Liposome — notice its enclosed aqueous core:

Aqueous Solution trapped inside micelle

Liposome Surfactant has polar head group and two hydrophobic tails

Aqueous Solution surrounds micelle

This enclosed volume of water is why liposomes are considered as models for proto cells.

The competition or tension between hydrophobic and hydrophilic interactions also contribute to the structure and function of many important biological molecules structures.

Table 7-7. Affects of H-bonds and Hydrophobic Interactions on Structural and Properties of classes of Biomolecules:

Biomolecule Class	H-Bonds Effect	Hydrophobic Effects
Carbohydrate ($C_n(H_2O)_n$	Major; H-bond donor and acceptor	Minor
Lipid (R-CO-O-R')	Minor; H-bond acceptor	Major
Protein (polyamides)	Major; H-bond donor and acceptor	Expect to be Minor[1]
Nucleic acid (RNA and DNA)	Major; H-bond donor and acceptor	Expect to be Minor[1]

1) Hydrophobic effects indirectly impact the larger globular macro structure. Hydrophobic groups will tend to cluster together and orient themselves towards the interior of globular structural form to get away from an exterior surface and its aqueous solvation interactions.

Many globular proteins possess tertiary structures that orient their polar side chains outward towards their aqueous environments and also cluster their hydrophobic groups together into their non-aqueous interiors away from their surrounding aqueous environments.

7-6. Final comments on Intermolecular Interactions:

It is worth emphasizing that inter/intra molecular non-bonding interactions (i.e. what we call IMF) are a sum of different types of non-covalent bonding interactions. Although one often can identify a dominant intermolecular interaction between two molecules, one should not forget such identifications also must consider the overall structure of the interacting molecules in order to accurately assess the impact of a particular polar group on a given set of IMF interactions. Keep in mind that the dominant interaction in a small molecule may not be as dominant an IMF in much larger molecules containing the same functional groups. As is shown in Fig. 7-13, the impact of even a polar functional group like an alcohol (R-OH) can be "washed-out" by simply increasing molecular size of its attached alkyl residue or tail.

The plots in Fig. 7-13 are Bp curves are for four different types of organic structures that collectively illustrate the impact of functional group polarity on a physical property as a function of alkyl chain length.

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Figure 7-13: BP data for alkanes, alkyl halides, and alcohols as a function of alkyl chain length:

Boiling Pt C⁰

R-OH

R-Cl

R-H

R-Z where Z= -OH, -H and -Cl; molecular weight
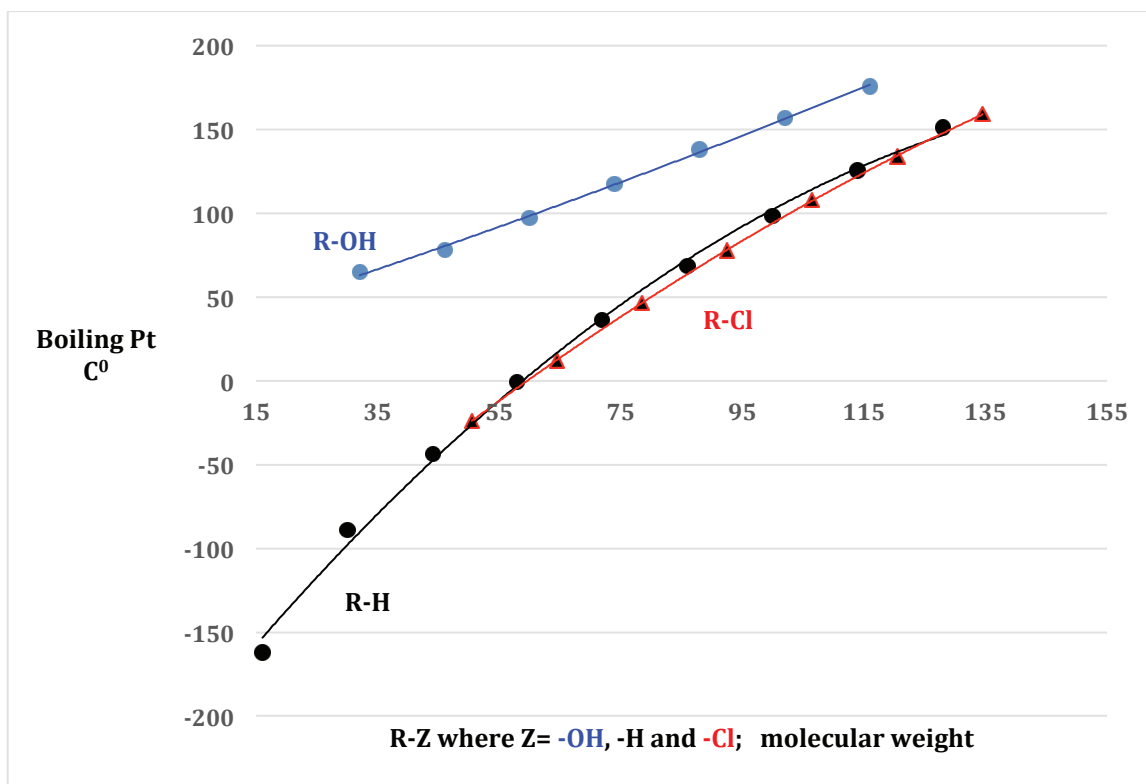
Typically, as is shown in Fig. 7-13, for a given MW, the more polar molecule has the higher BP. The impact of an OH group is especially dramatic when one compares lower MW alcohol vs alkane structures. However, as their alkane chain lengths increase, the London forces also continue to increase, and eventually London dispersion forces will exceed the strength of interactions between alcohol's polar head groups. At some given chain length these two different Bp curves will intersect. From this graph, the estimated chain length for this intersection will lie somewhere between chain lengths of C25-C35. At this point of intersection, the polar effect of an attached OH group (i.e. its dipole-dipole and H-bonding) effectively vanishes or is "washed out" by the now dominant London forces.

Q: How could one use these "wash-out" points to determine a polarity scale for different types of polar functional groups?
Expect that the more polar a functional group, the longer the chain length required before the effect of that group to get "washed-out" by the increasing London dispersion forces.

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In addition to issues of solvation, transport, and segregation, one also can hijack intermolecular interactions to do what is known as *template directed synthetic chemistry*. Template chemistry uses non-covalent interactions between ions and dipoles to create what are known as "knotted" molecules (i.e. catenanes and rotaxanes). Templates often have charged cationic centers and their ionic interactions are used to pre-position or better pre-orient ligand molecules in order to enable them to react and form new bonds between the ends of these bound ligands. An early and practical application of this concept is shown below for the synthesis of a cyclic polyether (18-crown-6):

Figure 7-15. Using Intermolecular interactions as templates for synthetic chemistry:

Structure / Energy

Reactivity
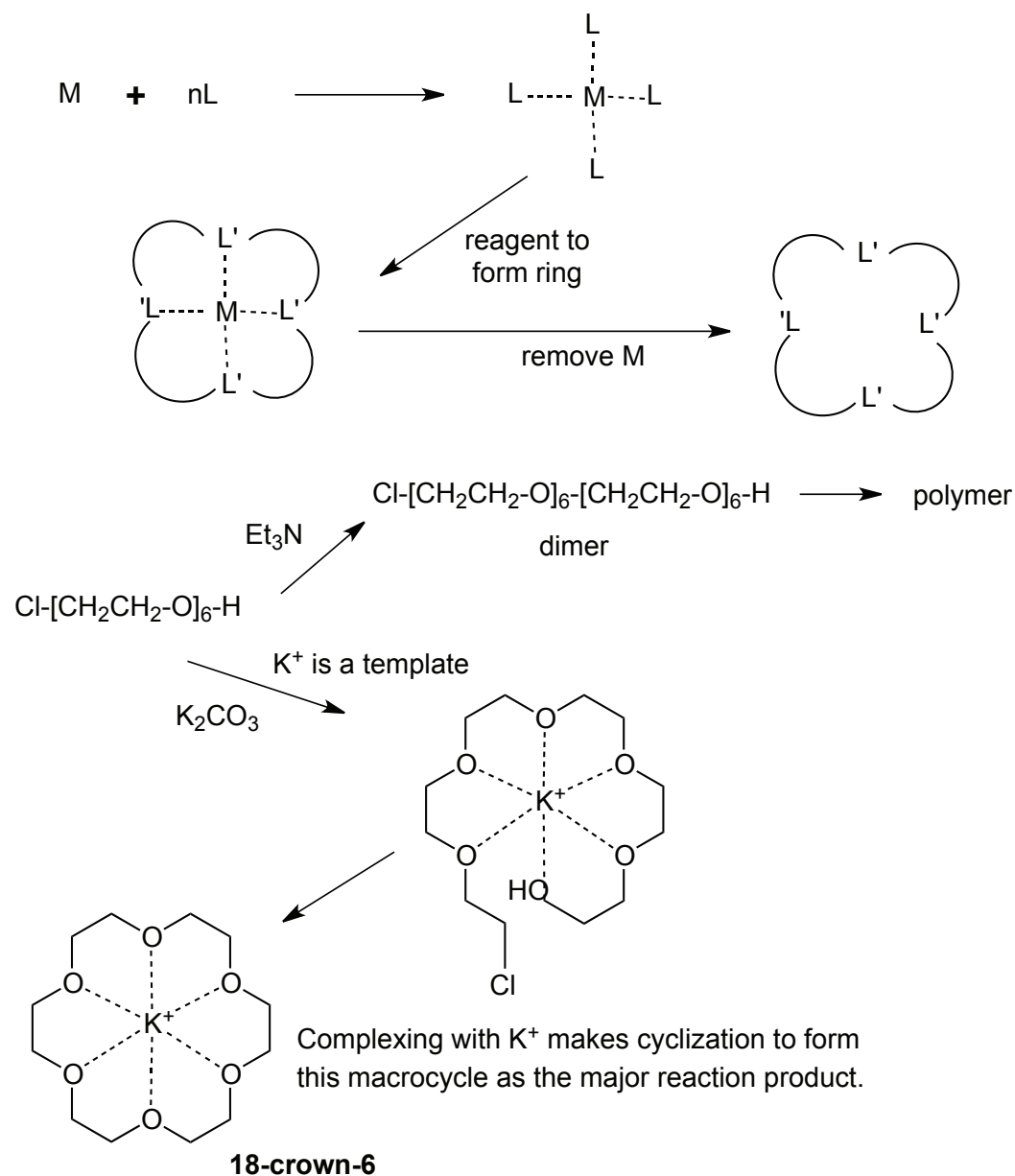
The potassium cation is used to bind or complex that polyether chain through its ion-dipole interactions, first with a diol and then with a polyether ring. This complex then makes it synthetically feasible to form a macro ring of 18 atoms by essentially transforming this almost impossible 18-membered ring cyclization proble into just connecting up six 5-membered rings organized and oriented by a commonly shared potassium cation. As Fig. 7-15 shows, ring formation does not occur in the absence of potassium cations — the templates for this reaction. This is just one of many such examples that use intermolecular interactions to achieve a synthetic goal, the inorganic and organometallic chemists have many more examples than can be presented here.
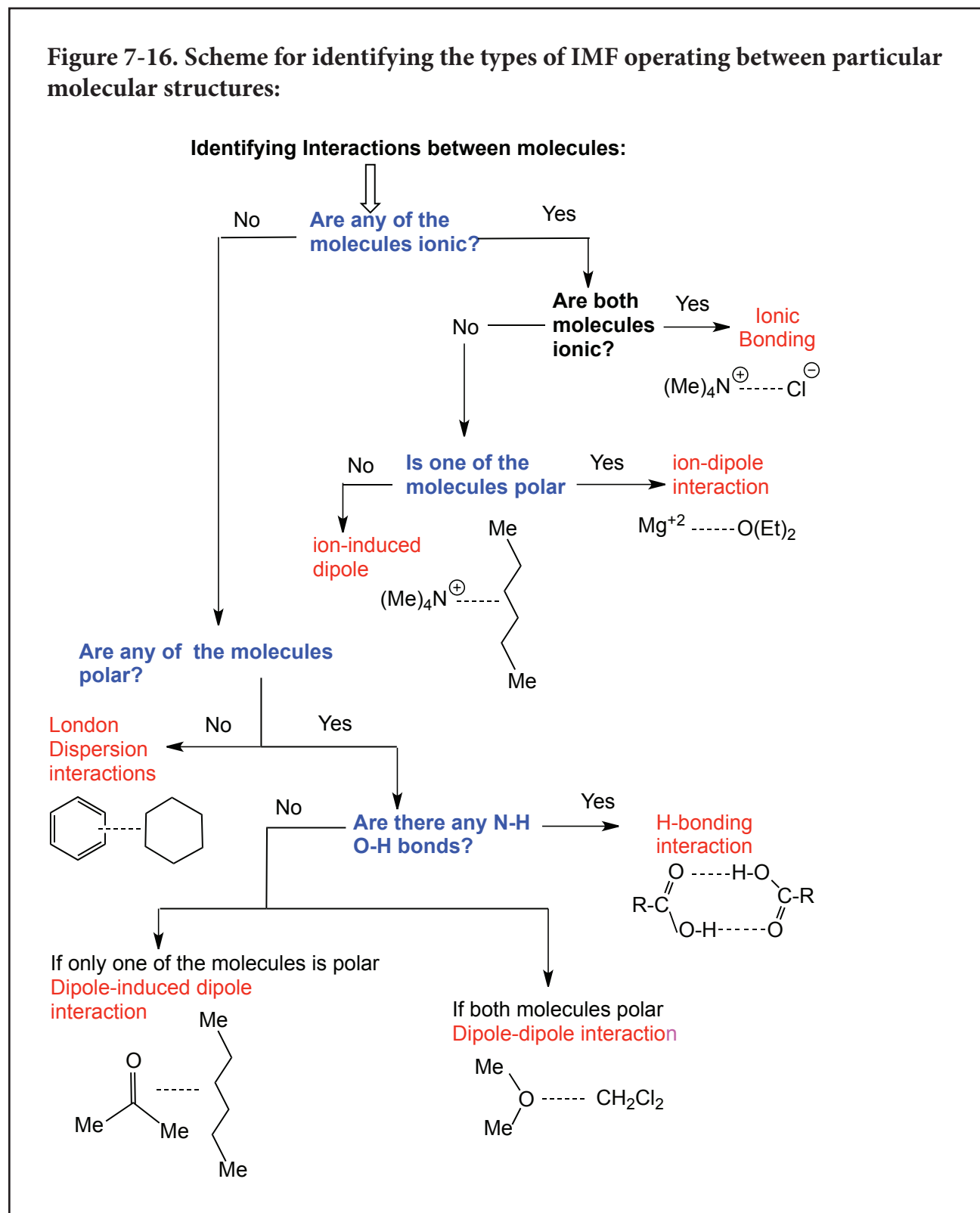
The other end of this application spectrum uses intermolecular interactions to manipulate bulk physical properties. One of the major recent developments in Polymer Chemistry involves an ability to manipulate intermolecular interactions in order to provide what are called "smart" materials. Smart materials are polymers that respond to specific changes in their molecular environments.

In biochemistry, one also will hear a great deal about hydrophilic and hydrophobic interactions. The forces generated by these water-substrate interactions are especially important in their effects on biological aggregation and organization. Hydrophilic interactions favor structures that cluster their hydrophilic (i.e. polar) functional groups together and also try to place these polar groups facing outward in closer contact with their aqueous environment. The hydrophobic interactions with their non-polar groups instead tend to cluster their non-polar functional groups together into the interior of a biological structure in order to shield these non-polar molecular regions from their aqueous environments. Those IMF that contribute to hydrophilic interactions include all of the polar intermolecular interactions shown in Table 7-2. London dispersion forces dominate what are commonly identified as hydrophobic interactions.

Although the Big Bang created space, time, and matter, it was these non-covalent intermolecular interactions that made the condensation of matter possible. It is not the Big Bang, but rather the forces of condensation; driven by these non-covalent intermolecular interactions that are fundamental driving forces for order in the Universe, as we know it now.

7-7. General conclusions about intermolecular interactions:

Fig. 7-16 is a flow chart to aid in identification and also to more systematically analyze possible intermolecular interactions:

Figure 7-16. Scheme for identifying the types of IMF operating between particular molecular structures:

Identifying Interactions between molecules:

No ← **Are any of the molecules ionic?** → Yes

No — **Are both molecules ionic?** → Yes → Ionic Bonding

$(Me)_4N^{\oplus}\text{------}Cl^{\ominus}$

No — **Is one of the molecules polar** → Yes → ion-dipole interaction

$Mg^{+2}\text{------}O(Et)_2$

ion-induced dipole

$(Me)_4N^{\oplus}\text{------}$

Me ... Me

Are any of the molecules polar?

London Dispersion interactions ← No — Yes

No — **Are there any N-H O-H bonds?** → Yes → H-bonding interaction

$R-C \overset{O\ \text{-----}\ H-O}{\underset{O-H\ \text{------}\ O}{}} C-R$

If only one of the molecules is polar
Dipole-induced dipole interaction

Me
O
Me   Me ------ Me ... Me ... Me

If both molecules polar
Dipole-dipole interaction

Me
O ------ CH_2Cl_2
Me

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This flow chart provides a systematic approach that one can use as an aid in identifying specific intermolecular forces that contribute to an IMF. This chart is NOT a hierarchical guide to the strength of these components to IMF. Those general trends expected for the strengths of these specific IMF interactions are summarized in Figure 7-17. Level 1 is typically-though not always, the weakest of these IMF interactions and the fourth level of IMF interactions (e.g. ionic) are expected to be the strongest.

Figure 7-17. Hierarchy for the energy of stabilization from IMF interactions:

First Level (Weakest IMF): London Dispersion
This interaction is at the core of ALL intermolecular interactions

Second Level: Dipole-Dipole or Dipole-Induced Dipole
dipole-dipole interaction will be present if both molecule are polar
For a polar molecule interactiong with a non-polar molecule
the interaction will be Dipole-Induce Dipole

Third Level: H-Bonding
If there is an N-H or O-H covalent bond
in one or both molecules

Fourth Level (Strongest): Ionic interaction
If these molecules have functional groups
**with opposite charges**

It is important to remember that this model for partitioning the IMF into their components contains a rather diverse set of IMF components. However, no matter what the structure is for a specific molecule there ALWAYS will be a contribution to its IMF from London dispersion forces:

$$PE_{int} (e.g. IMF) = E_{London} + (E_{dipole-dipole} \text{ or } E_{dipole-induced Dipole}) + E_{H-bond} + E_{ionic}$$

All of the other contributions to IMF will depend on whether the molecule also happens to be polar, and in addition, whether or not there is any ionic functionality.

Unlike bond lengths, there is a much stronger dependence of non-covalent bonding interactions on the distance of molecular separation (r). These forces can begin having an impact with separations as great as 5-7 A^0 (i.e. 500-700 pm) as is illustrated by the PE diagram in Fig. 7-18. This IMF compilation superimposes the PE data for several total or net IMF interactions between small molecules onto one graph: This set includes a neon gas dimer and dimers of several other small inorganic and organic molecules derived from hydrogen and other second row atoms of the periodic table:

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Figure 7-18. PE curves of IMF interactions[1] for sveral small molecules and atoms:
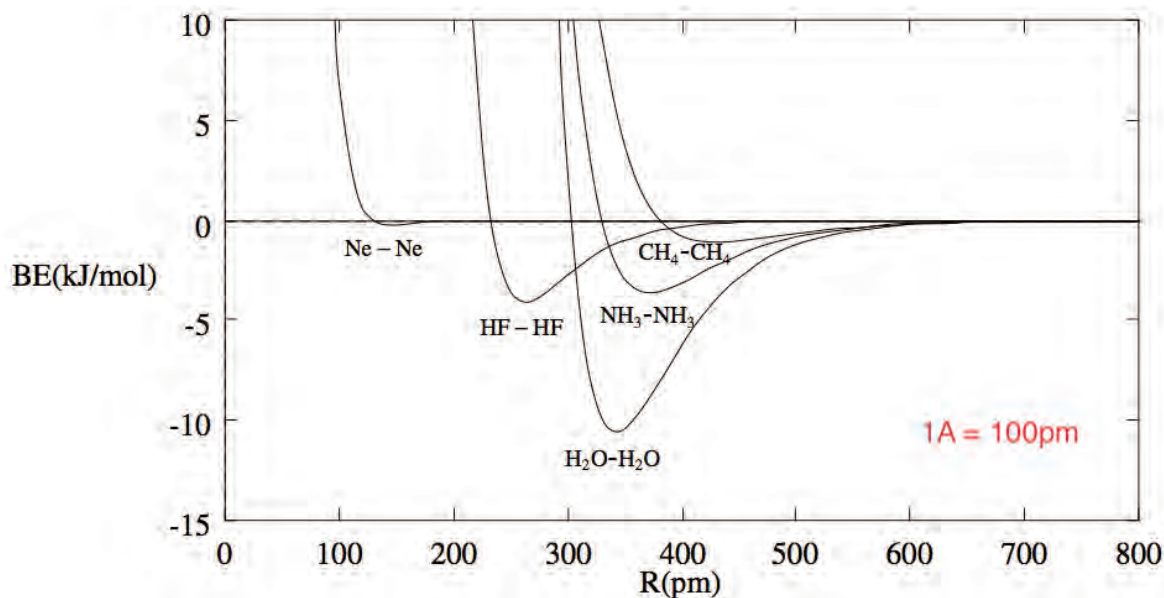
1) This image from Univ. New Mexico, Dept. of Chemistry; Ch 14

Even for molecules like water or hydrazine, intermolecular interactions only have shallow potential energy minima (i.e. binding energy (BE), where1 kcal = 4.18kJ). Typically these non-covalent bonding minima are located somewhere between 3-6 A^0 (i.e. 300-600pm) of molecular separation (r). Notice that the stronger the non-covalent forces, the deeper their parabolic potential energy wells. This trend also was observed for chemical bonds (Ch 4). However, **DO NOT** try to make a broader connection between intermolecular separation distance (r) and the strength of an IMF non-covalent binding energy (i.e. depth of a PE well). For example, compare the optimal molecular separation of a water dimer to that optimal separation distance for an HF dimer. The water dimer has a larger IMF than a H-F dimer, but the internuclear separation distance (r) for an H-F dimer is smaller than that for a water dimer. Again recall that the net or total IMF depicted in Fig. 7-28 is a function of its individual IMF components and those different components also have different dependences on intermolecular separation (r):

$$E_{int} \propto [(-1/r^6)_{London} + (-1/r^6)_{induced\ Dipole} + (-1/r^3)_{dipole\text{-}dipole\ and\ H\text{-}bond} + (+1/r^{12})_{VDW\ repulsion}]$$

This is why net IMF (e.g. E_{int}) do not conform to a simple rule: The stronger the stabilizing strength of an interaction, the shorter the distance of separation(r) between interacting molecules.

7-8. Conclusion:

Intermolecular forces are much weaker and generally much less directional than those forces that produce covalent or ionic bonds. A reasonable rule of thumb is: As the strength of an IMF decreases, its sensitivity to geometry of interaction also decreases. Although IMF are weaker, they also operate

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over longer distances than typical chemical bond lengths. Despite their small binding energies, IMF remain important factors in their contributions to bulk physical properties, and IMF also are the basis of, and driving forces for all biological organization.

Important intermolecular forces are classified into the following categories;
1. **Ionic**
2. **Ion-dipole**
3. **Hydrogen-bonding**
4. **Dipole-dipole**
5. **Induced dipole-induced dipole (London dispersion forces)**

The strength of these "sticky" binding interactions between molecules most likely to be encountered in this course on Organic chemistry are:

1 > 2 > 3 > 4 > 5

All atoms and molecules have contributions from London dispersion forces as part of their intermolecular interactions. London forces operate even between atoms of the Noble gas Helium. The essential question is: Are there other additional components to a molecule's intermolecular forces that also contribute to a particular molecule's net or total intermolecular forces of attraction?

General rules for assessing relative impact of intermolecular interactions:
1. The more of these different types of intermolecular forces that operate between molecules, the stronger the expected IMF of attraction operating between molecules.

2. If two molecules have the same set of intermolecular forces, then look to see which specific forces might be stronger for one set of molecular interactions over those similar forces found for the other set of molecular interactions.

7-9. What you should know and be able to do:

1. Be able to name and identify specific intermolecular interactions that contribute to non-covalent binding between molecules (i.e. IMF).

2. Understand the origins and relative strengths of these various intermolecular forces operating between molecules.

3. Be able to identify which specific type(s) of IMF contribute to the IMF between a given set or pair of interacting molecules.

4. Understand how the structures of H-bond donor and acceptor molecules contribute to the strengths of their H-bonding interactions.

5. Predict trends in the physical properties of materials (e.g. mp, bp, viscosity, surface tension, and heat of vaporization and solubility) based on your understanding of the relative strengths of these various intermolecular interactions.

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7-10. Problems:

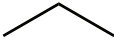1. See if you can answer the following questions:

a) Describe why non polar molecules are attracted to one another?

b) What structural features result in an increase of the London dispersion forces?

d) List the general characteristics of functional groups that can be hydrogen bond acceptors:

e) List the general characteristics of those functional groups that can be hydrogen bond donors:

2. Given the following enthalpy data decide which compound in each pair has the highest bp:

		Enthalpy of vaporization (kJ/mol)
	N_2	5.6
a)	or	
	O_2	6.8
	F_2	6.6
b)	or	
	CH_4	8.2
	⌃	19.0
c)	or	
	Cl_2	20.4

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3. Using your knowledge about functional groups and the dipole moment data shown for the selected molecules below, decide which molecule in each pair should have the higher bp.

a) CH_3CN 3.9D   or CH_3CHO 2.7D

b) NH_3 1.47D   or H_2O 1.85D
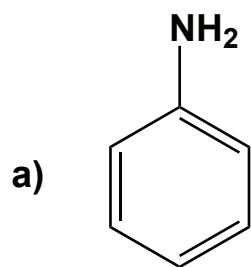
c)   n-butanol   1.7D   or   2-butanol   1.7D

d)   Me-O-Et   1.22D   or   Me-Cl   1.9D

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4. Which molecule in each pair below should have higher IMF?

a) SiF$_4$ or SiO(O-CH$_3$)$_2$

b)

or

c)

or

d)

or

e)

or

f)

or

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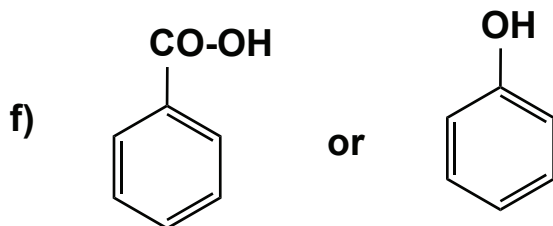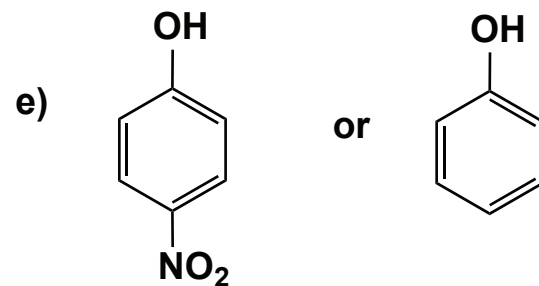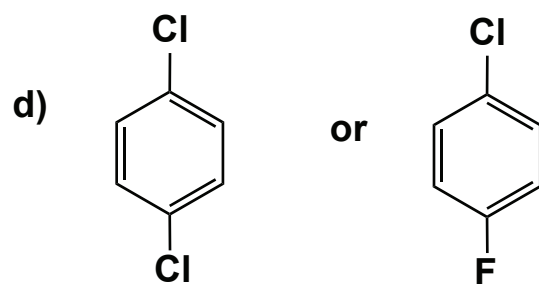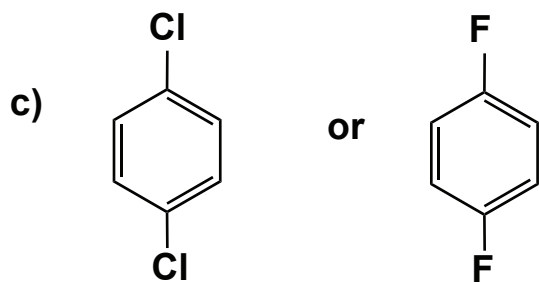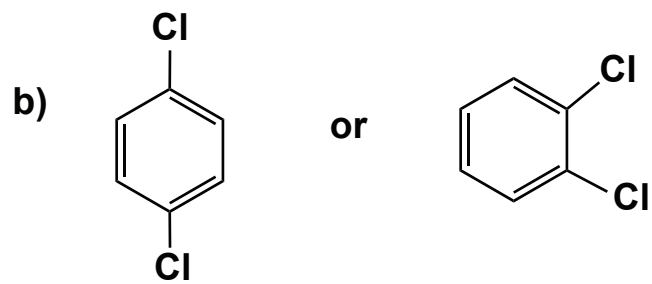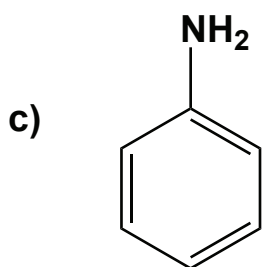
5. Examine each pair of molecules below and decide which molecule in each pair will have a greater solubility in water. Then explain why.

a)

NH₂

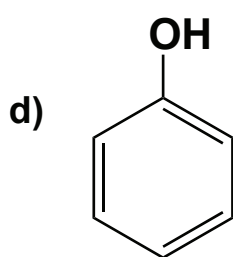b)

OCH₃
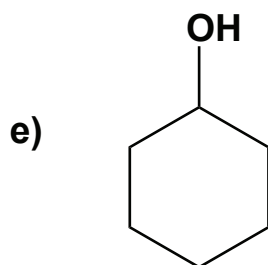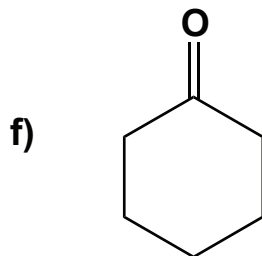
dipole: 1.5-1.6D   1.4D

c)

NH₂

d)

OH

dipole: 1.5-1.6D   1.45D

e)

OH

f)

O

dipole: 1.9D   2.9D

Structure   Energy

Reactivity
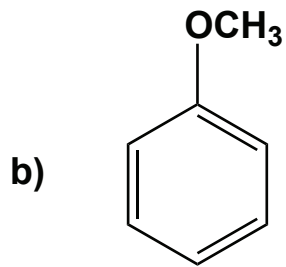
6. Which molecule in each pair of molecules in question 5 has the higher boiling point and explain why?

7. Why is SO$_2$ polar but CO$_2$ is non-polar?

8. Use wedge-dash representations to draw the dimers of methanol (CH$_3$-OH) and also for hypochlorous acid (Cl-OH):

9. How do you explain the following trends in water solubility for these following alcohols (R-OH) ?

| Alcohol	Solubility in water: (g/100g water)
n-butanol	7.7
2-pentanol	4.5
n-pentanol	2.2

10.
a) Identify both the hydrophobic (using squares) and hydrophilic components (using circles) of the molecules shown below:

a)

□   **hydrophobic**

○   **hydrophilic**

b)

Psilocybin

c)

Lorazepam

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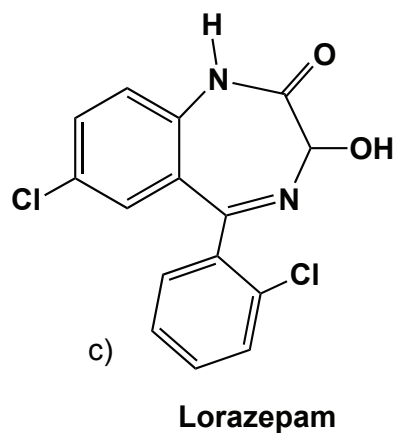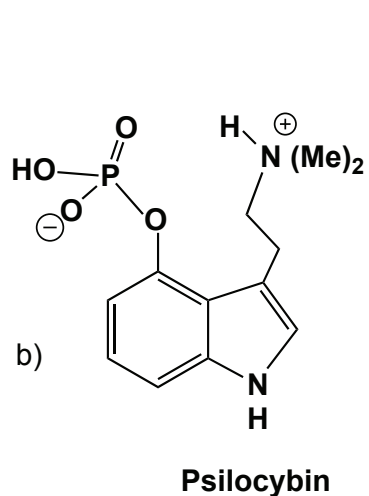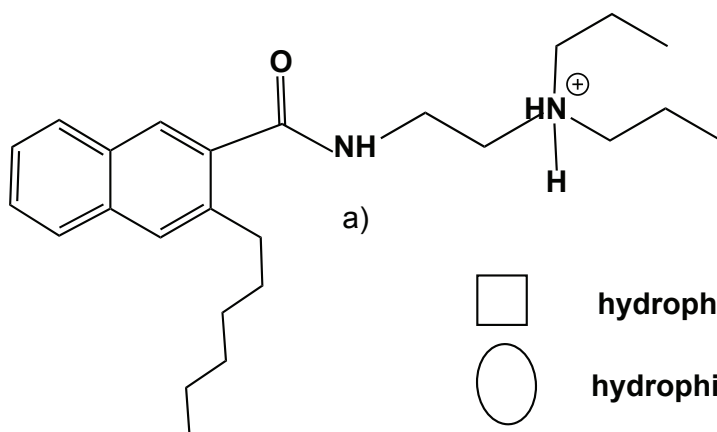
b) In the molecules above list all the types of intermolecular interactions in each of the hydrophobic and also in their hydrophilic zones:

11. Consider the two molecules 2-nitrophenol and 4-nitrophenol:

3.01D

bp 217⁰ C

2-nitrophenol

5.43D

bp 279⁰ C
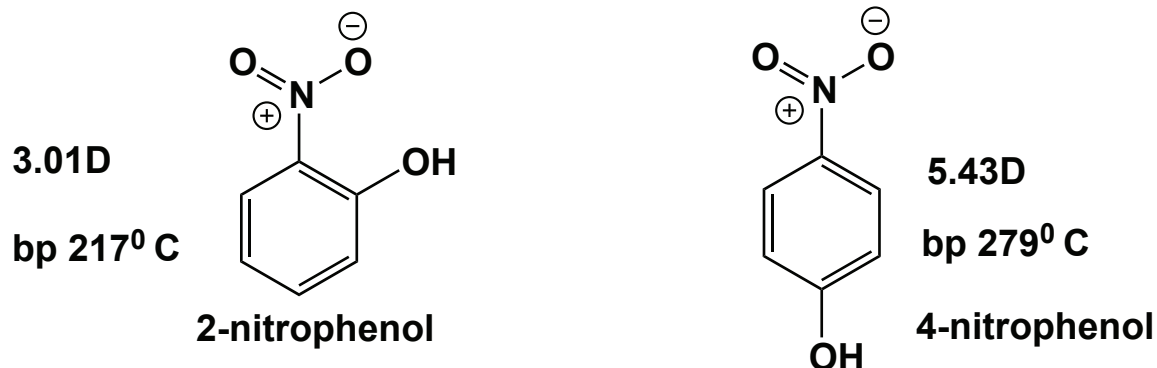
4-nitrophenol

Why should 4-nitrophenol boil at a higher temperature than 2-nitrophenol (229^0C vs 217^0C).

12. Why is carbon monoxide (i.e.CO) less polar than formaldehyde (i.e. H_2CO)?

Compound	Dipole Moment (D)
CO	0.122
H_2CO	2.33

(Hint: draw Lewis structure for both molecules and examine the atomic sources for the valence electrons in these two structures);

Structure   Energy

Reactivity