

Understanding Enzymes: Gateway Concepts of Structure from Chemistry

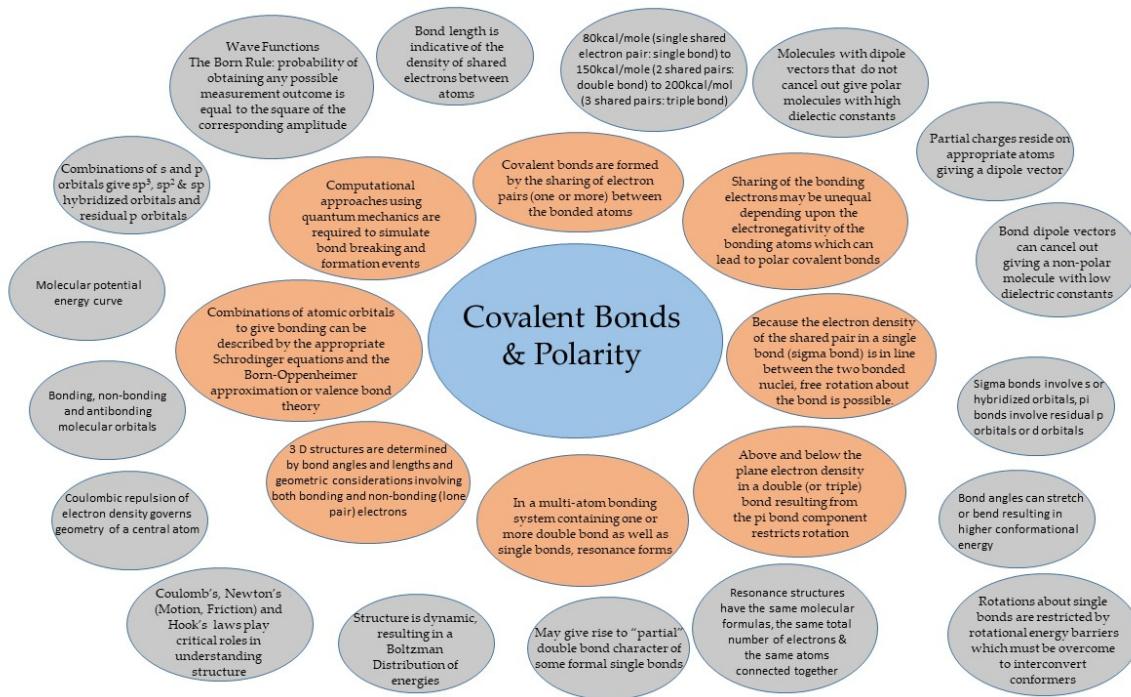
Ellis Bell

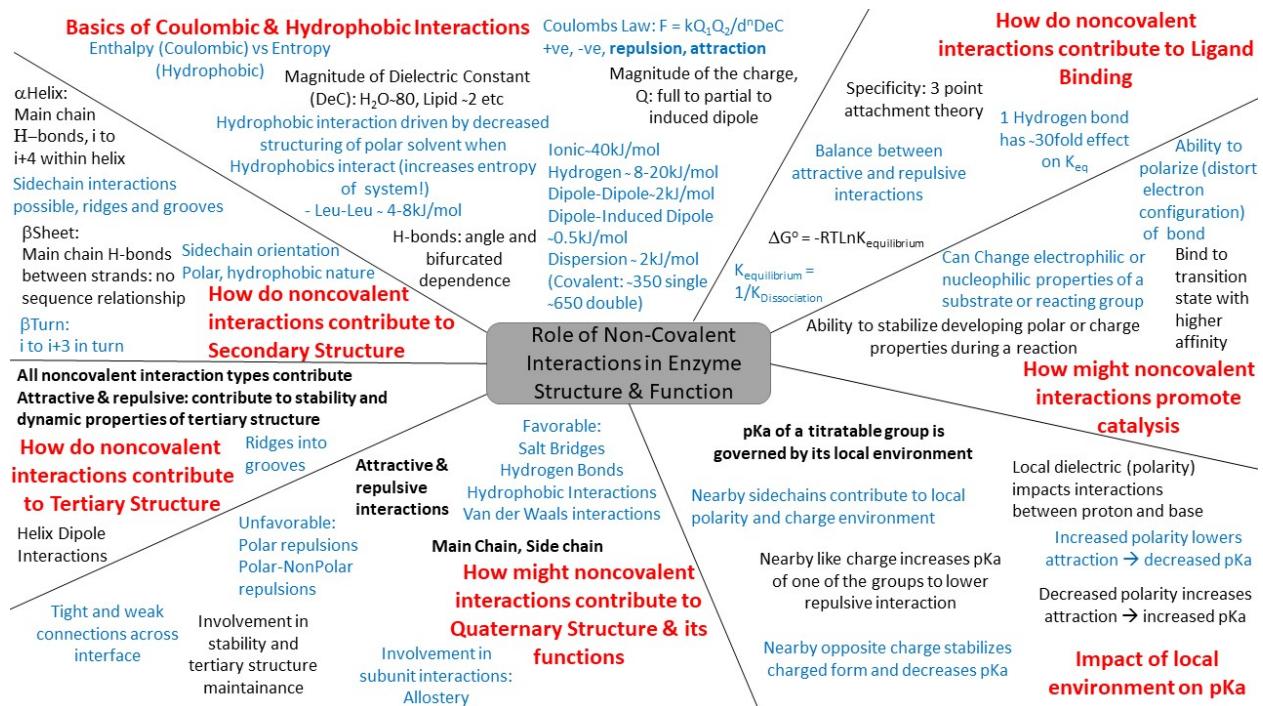
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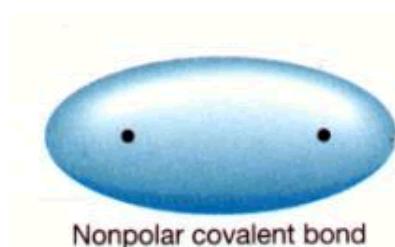




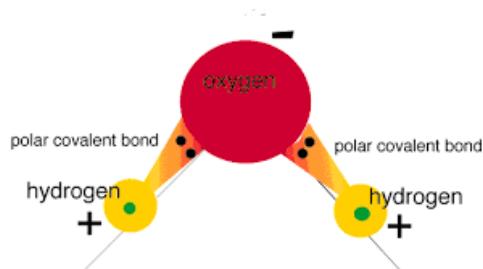
Synopsis

The structure (both in terms of through bond connectivity (covalent bonds) and through space interactions (non-covalent interactions, both favorable and repulsive)) of a molecule determine its dynamic properties and reactivity (chemical and physical): ie its function. 5 gateway concepts of bonding and interactions lay the foundation for understanding protein structure function relationships and the structure, activity and regulation of enzymes.

1: Core Concepts of Covalent Bonds and Polarity

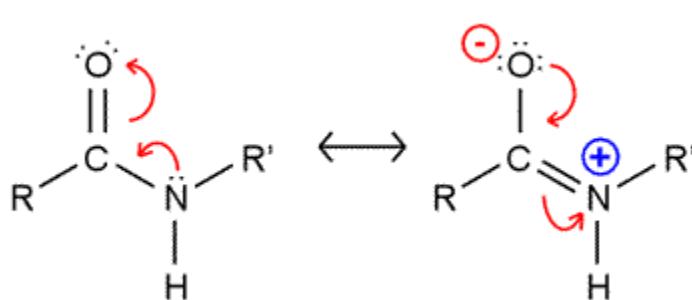
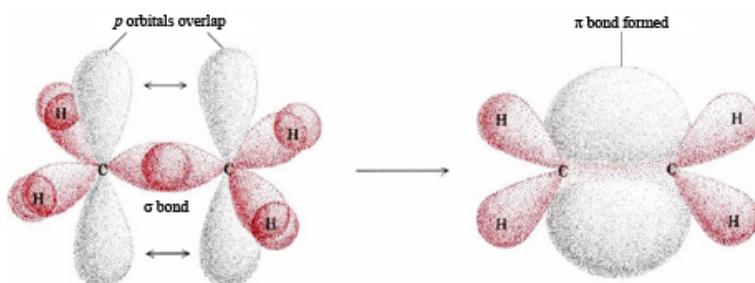


Covalent bonds are formed by the **sharing of electron pairs (one or more)** between the bonded atoms to give strong bonds with energies ranging from around 80kcal/mole (single shared electron pair: single bond) to 150kcal/mole (2 shared pairs: double bond) to 200kcal/mol (3 shared pairs: triple bond), compared to the thermal energy at room temperature of about 0.6kcal/mole.

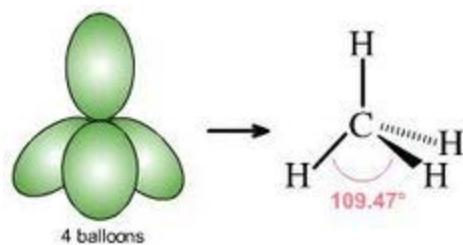


The **sharing of the bonding electrons may be unequal depending upon the electronegativity of the bonding atoms** [Periodic Table and Trends] which can lead to polar covalent bonds where partial charges can reside on the appropriate atoms [Dipoles etc].

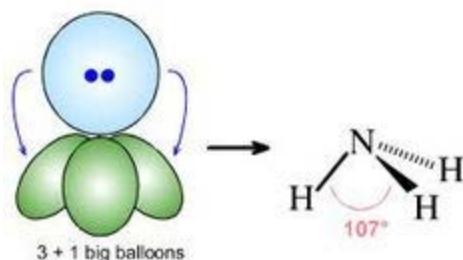
Because the **electron density of the shared pair in a single bond (sigma bond) is in line between the two bonded nuclei, free rotation about the bond is possible**. However the above and below the plane electron density in a double (or triple) bond resulting from the **pi bond component restricts rotation** since rotation would result in negative Coulombic interactions between the component electron densities.[Sigma and Pi bond electron density]

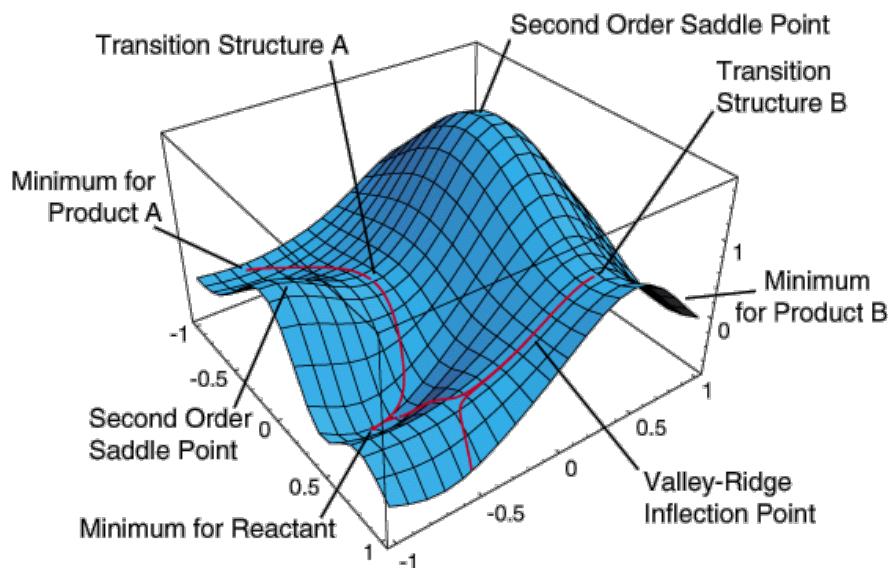


In a multi-atom bonding system containing one or more double bond as well as single bonds, **resonance forms may give rise to “partial” double bond character** of some formal single bonds.[Peptide Bond resonance forms etc]



For small molecules (1 or a limited number of “central” atoms), **3 Dimensional structures are determined by bond angles and lengths and geometric considerations involving both bonding and non-bonding (lone pair) electrons based upon Coulombic repulsion of electron density**[Lewis Dot Diagrams and VSEPR].

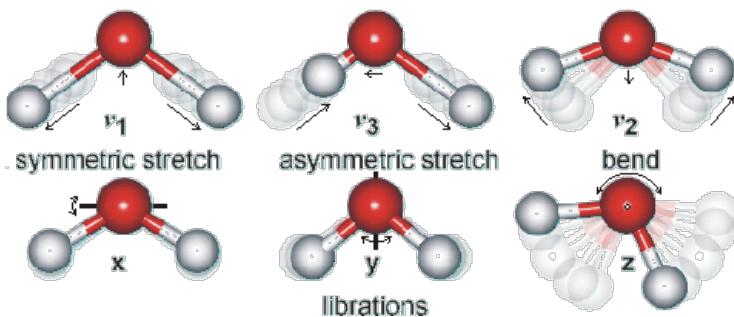




Combinations of atomic orbitals (usually s, p or hybridized in biochemical systems) to give bonding can be described by the appropriate Schrodinger equations [Wave-functions] and the Born-Oppenheimer approximation [scheme] or valence bond theory [scheme] to give

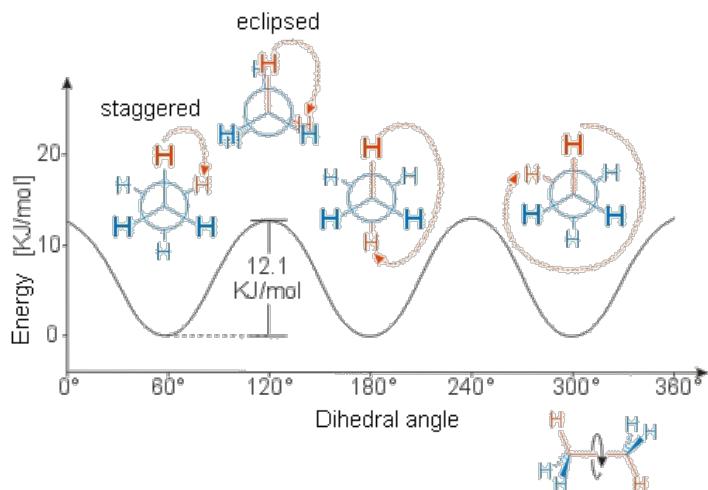
bonding and antibonding molecular orbitals [energy levels] and can be used to construct a molecular potential energy surface.

2: Bond rotations and vibrations



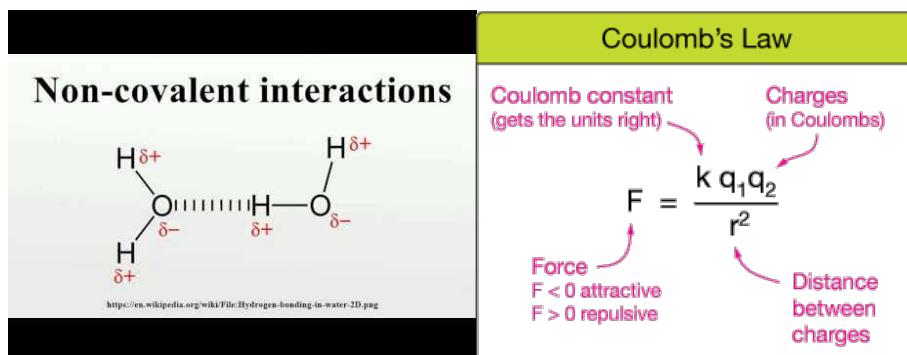
The chemical bond between 2 atoms vibrates as a harmonic oscillator to allow **bond stretching**. [diagram] Such stretching may be **symmetric or asymmetric** in a molecule with a central atom. In such molecules bending motions may also occur [Energy of a Molecule].

The time scale of such **bond vibrations** is on the order of 10^{-13} - 10^{-14} seconds. As a result of the high energy cost of deforming bond lengths and angles such vibrations are usually of small amplitude.



Rotations about single covalent bonds can occur with energy barriers to rotation on the order of 10-12 kJ/mole in simple molecules without steric hindrance, and time scales on the order to 5×10^{-10} seconds.

3: Hydrogen bonds and other noncovalent interactions

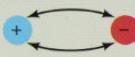
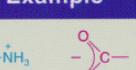
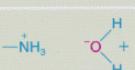
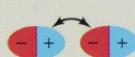
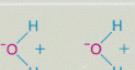
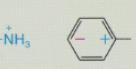
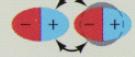
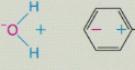
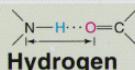


A variety of **non-covalent interactions** are based upon Coulombic interactions between opposite (attraction) or like (repulsion) charges involving either full (ionic) or

partial (Van der Waals or Hydrogen Bond) charges rather than sharing of electrons as in covalent bonds.

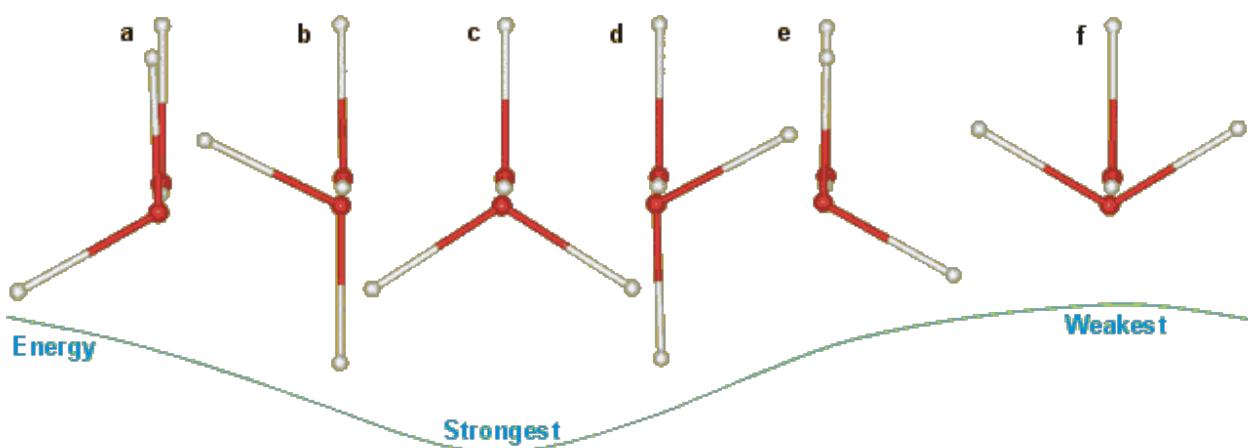
Such interactions can involve **Charge-Dipole**, **Dipole-Dipole** or **Induced Dipole** interactions and the magnitude of the interaction energy, as a result of Coulomb's Law, shows a dependence on both distance and the local dielectric environment.

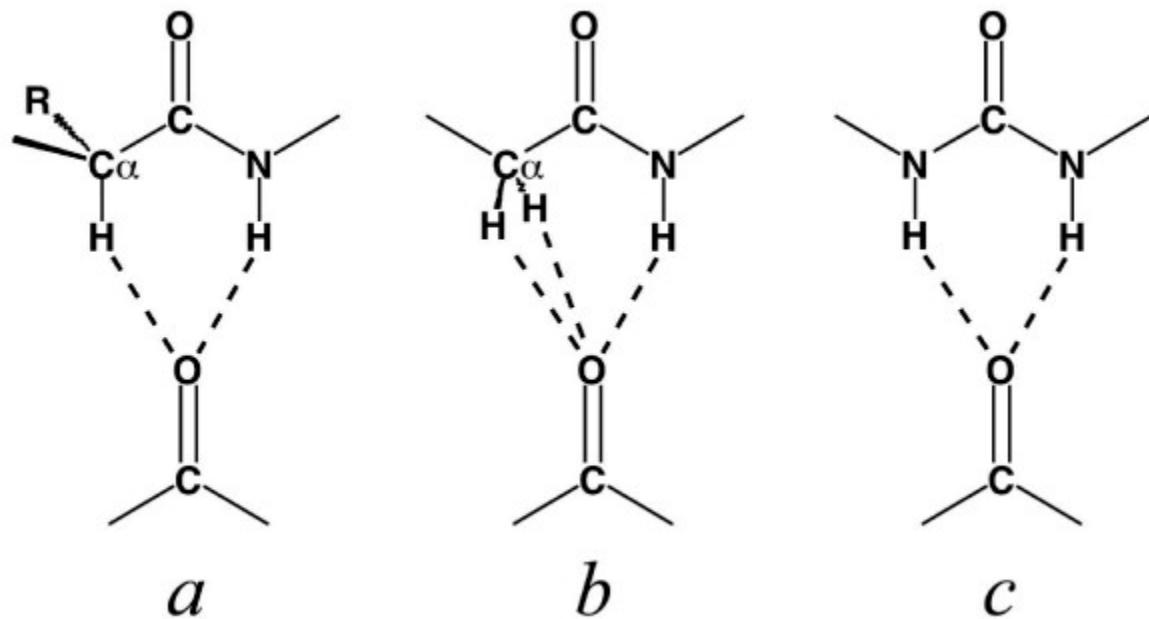
Figure 2.2 Noncovalent interactions

Type of Interaction	Model	Example	Dependence of Energy on Distance
(a) Charge–charge Longest-range force; nondirectional		--NH_3^+ 	$1/r$
(b) Charge–dipole Depends on orientation of dipole		--NH_3^+ 	$1/r^2$
(c) Dipole–dipole Depends on mutual orientation of dipoles			$1/r^3$
(d) Charge–induced dipole Depends on polarizability of molecule in which dipole is induced		--NH_3^+ 	$1/r^4$
(e) Dipole–induced dipole Depends on polarizability of molecule in which dipole is induced			$1/r^5$
(f) Dispersion Involves mutual synchronization of fluctuating charges			$1/r^6$
(g) van der Waals repulsion Occurs when outer electron orbitals overlap			$1/r^{12}$
(h) Hydrogen bond Charge attraction + partial covalent bond	 Donor Acceptor	 Hydrogen bond length	Length of bond fixed

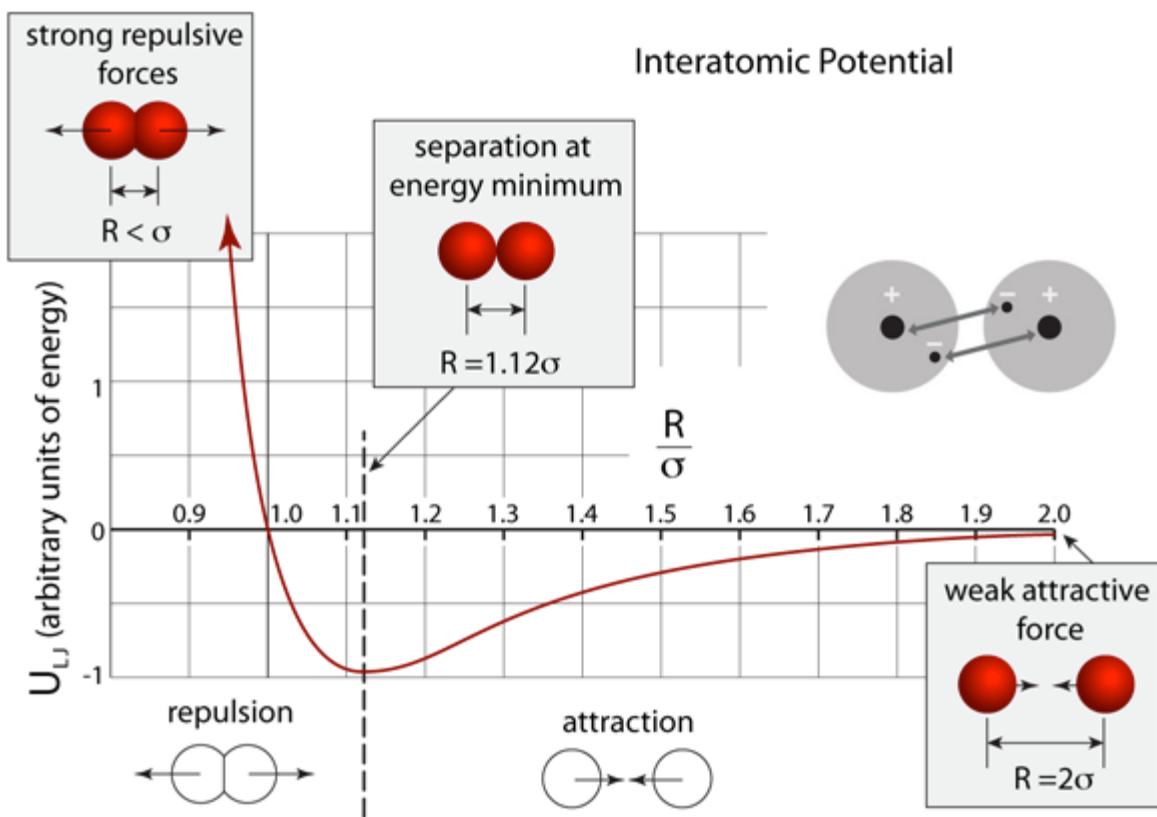
From Mathews and van Holde: *Biochemistry 2/e*. © The Benjamin/Cummings Publishing Co., Inc.

Hydrogen bonds can be classified as Strong ($2.2\text{--}2.5\text{\AA}$, $\Delta G = 40\text{--}14\text{kcal/mole}$), Moderate ($2.5\text{--}3.2\text{\AA}$, $\Delta G = 15\text{--}4\text{kcal/mole}$) and weak ($3.2\text{--}4.0\text{\AA}$, $\Delta G < 4\text{kcal/mole}$), with the **strength of the bond progressively decreases as the angle between the involved atoms deviates from 180° .** **Hydrogen Bonds may be bifurcated.** There appears to be a potential “covalent” contribution





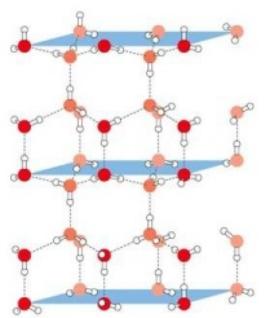
(sharing of electron density) in some strong Hydrogen Bonds.[Comparison to Covalent and Ionic Bond strengths]



The force between two atoms in Non-Covalent interactions can be described by **the Lennard-Jones Potential** involving the equilibrium distance of the two atoms (the van der Waals radius), the attractive interactions and the repulsive forces resulting from overlapping atomic orbitals.

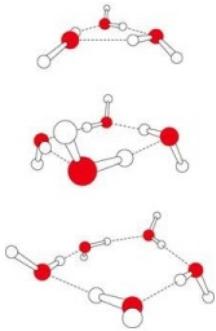
4: The Hydrophobic effect

Non-polar molecules, as a result of their local dielectric constant structure a cage of polar solvent molecules around them, resulting in a decrease in the entropy of the system.



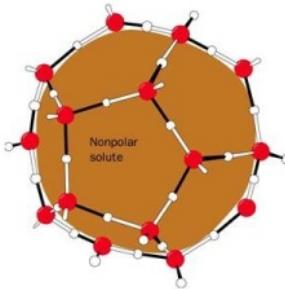
tetrahedral structure of ice

after L. Pauling, *The Nature of the Chemical Bond* (Cornell University Press 1960)



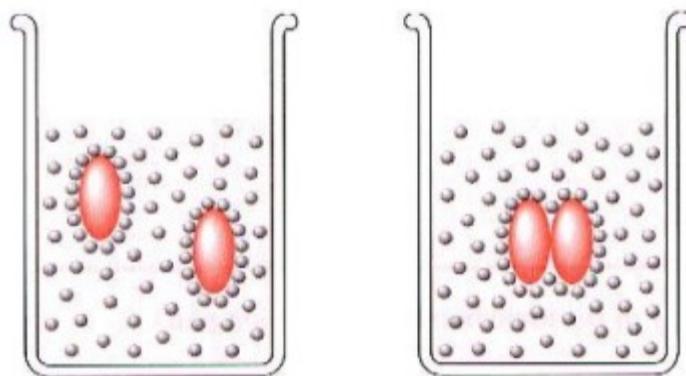
hydrogen bond networks in liquid water

Liu, K., Cruzan, J.D. and Saykally, R.J. *Science* **271**, 930 (1996)



ordering of water around a nonpolar solute

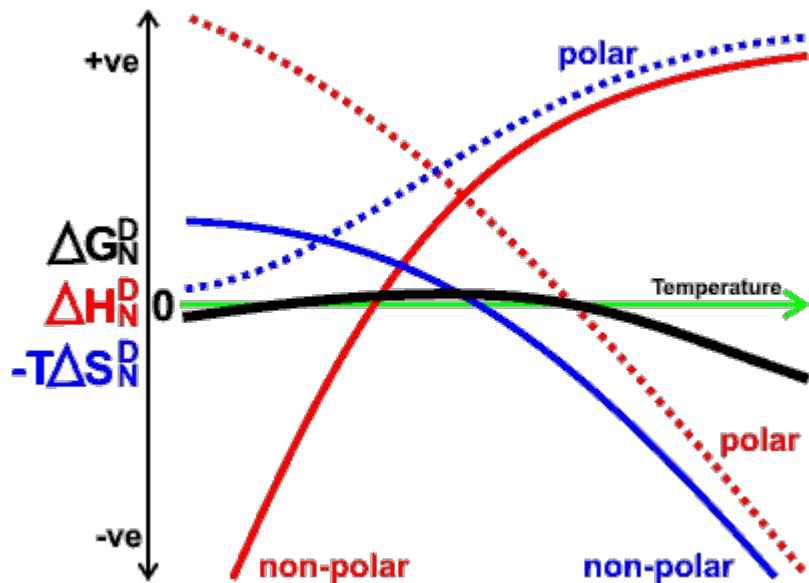
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The hydrophobic effect is the coming together of 2 or more non-polar molecules in a high dielectric solvent with a **concomitant decrease in the overall structuring of solvent molecules and an increase in the entropy of the system**.

The **magnitude of the hydrophobic effect is proportional to the number of C-H bonds** in the molecule excluded from the polar solvent by the interaction.

The ΔG for the interaction of two non-polar molecules comes predominantly from the entropy increase in the polar solvent molecules of the system: $\Delta G = \Delta H - T\Delta S$, with ΔS being large and positive overall with the resultant ΔG being negative.



5: Dynamic aspects of molecular structure

The potential energy of a molecule can be written

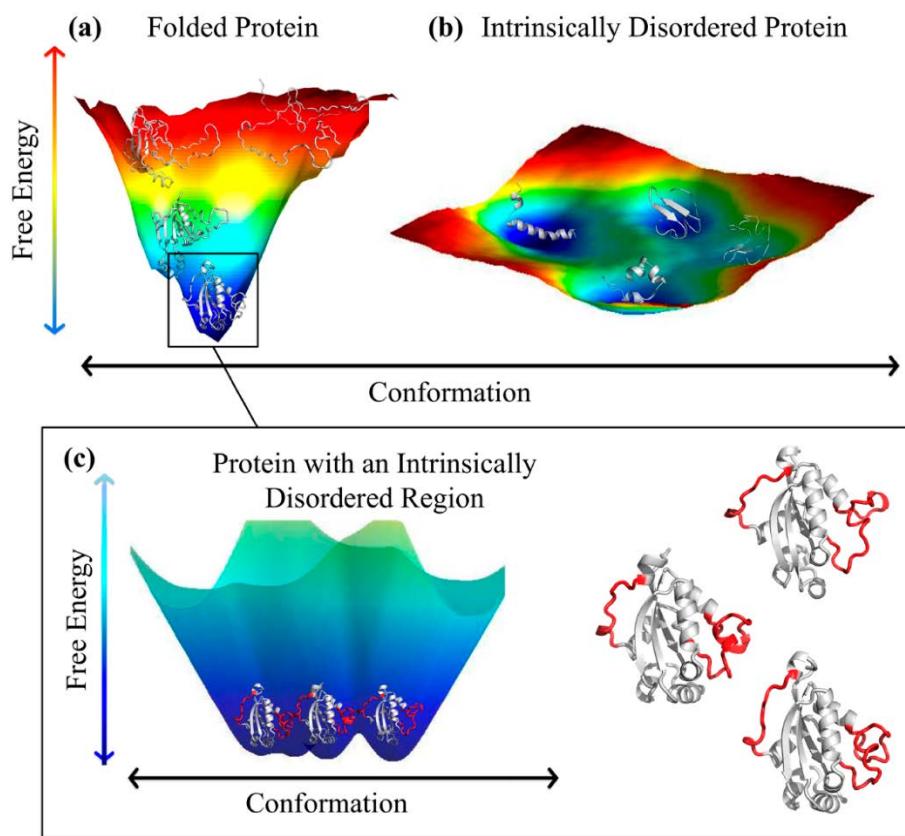
$$E = \sum_{bonds} E_{stretch} + \sum_{angles} E_{bend} + \sum_{dihedrals} E_{torsion} + \sum_{pairs} E_{nonbond}$$

As a result of the properties of bonds and interactions **a molecule is not a static structure.**

Bond rotations and vibrations combined with inter-molecular non-covalent interactions (attractive and repulsive) allow **a potential energy surface to be calculated**
(approximated for large molecules)

The potential energy of a molecule (which is the sum off all of the possible bonded and non-bonded interactions) determines the “structure” of a molecule which can be described in terms of **Potential Energy minima**, the local equilibrium structures, and **saddle points** which represent transition states from one local equilibrium structure to another.

Molecular motion can be described in terms of small amplitude motions (within an energy well on the surface) or large amplitude (between energy wells on the surface)



An ensemble of chemically identical molecules will be distributed between accessible (depends upon the temperature of the system) potential energy minima on the surface proportional to the depths of the minima and can freely interchange between these local energy minima

Images from Google Image

Mindmap from Project Mindmap, <https://www.molecularlifesciences.org/>