Molecular Interactions

Fall 2004, AMS-691 Section 2
Topics in Applied Mathematics

Introduction to Computational Structural Biology and Drug Design

Meeting 05, 09/15/04, Topics 1 and 2

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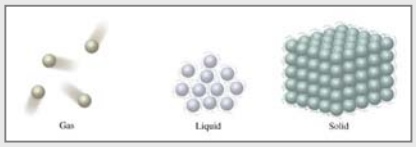
Molecular interactions influence states of matter and drive protein-ligand binding



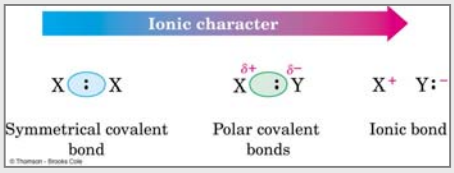
Physical interactions that determine properties of proteins and recognition

- Covalent interactions (bonding)
- Non-covalent interactions
  - Electrostatic
  - Short-range repulsion
  - Van der Waals interactions (attraction)
  - Hydrophobic effects
  - Hydrogen bonds

Approximate strengths of molecular interactions

Type	strength (kcal/mol)
covalent bonds	-50 to -100
salt bridge	-80 to -120
hydrogen bonds	-3 to -6
van der waals forces	-0.5 to -1
hydrophobic forces	-0.5 to -3

Ionic character of interacting atoms



Electrostatic energy

- Intermolecular forces are thought to be essentially electrostatic in nature
- The most fundamental non-covalent attraction is between electrostatics charges
- Coulomb's law for a vacuum: $\Delta E = \frac{q_i q_j e^2}{r_{ij}}$

Electrostatic energy

- Varies inversely with the first power:
  - effective over large distances
  - very strong interaction
- Charges of opposite sign:
  - energy decreases as species approach (favorable)
- Charges of same sign:
  - energy increases as species approach (repulsion)
- Na+ with Cl- at optimal contact 2.76 ang apart yields $E_{coulombic}$ = 120 kcal/mol

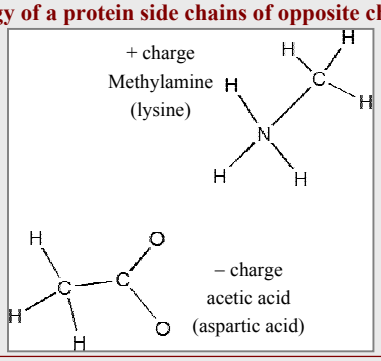
Screened electrostatic interactions

- Dielectric constant always greater than unity
- For homogeneous environments (i.e. bulk water) electrostatic interactions are decreased by a dielectric constant ε
- Coulomb's law then becomes: $\Delta E = \frac{q_i q_j e^2}{\varepsilon r_{ij}}$
- Larger dielectric constants = increased screening

Experimental dielectric constants

Solvent	T (°C)	ε	bp (°C)
vacuum		1.0	
argon	–191	1.5	–185.9
water	25	78.3	100.0
methanol	25	32.66	64.5
ethanol	25	24.55	78.3
formamide	20	111.0	210.5
NMA	32	191.3	206.7
acetic acid	20	6.17	117.9
acetonitrile	25	35.94	81.6
DMSO	25	46.45	189.0
dichloromethane	25	8.93	39.6
chloroform	20	4.81	61.2
carbon tetrachloride	25	2.23	76.6
dimethyl ether	25	5.02	–24.8
diethyl ether	25	4.20	34.4
THF	25	7.58	66.0
benzene	25	2.27	80.1

A model system for computing the interaction energy of a protein side chains of opposite charge



Solvent (water) dramatically reduces the interaction energy between the two species

species	gas phase MP2 energy	water phase MP2 energy
deprotonated acetic acid	-227.8637194	-227.9812541
protonated methylamine	-95.9123453	-96.0254008
complex	-323.9679131	-324.0099847
Einteraction (hartrees)	-0.1918484	-0.0033298
Einteraction (kcal/mol)	-120.39	-2.09

$$\Delta E = C - (A + B)$$

$$\Delta E = \text{Complex} - (\text{Acetic acid} + \text{methylamine})$$

$$\Delta E = \text{Complex} - (\text{receptor} + \text{ligand})$$

Short range repulsion

- Electrostatics ignores the size of atoms
- As atoms approach atomic orbitals may overlap
- Bound electrons in each molecule are forbidden from entering the same state as the electrons in the other molecules (Pauli exclusion principle)
- Repulsive energy increase with the inverse of the 12th power of distance between the center of the two atoms

Short range repulsion

- Molecules and atoms treated as:
  - defined dimensions
  - occupying volume
  - impenetrable to other atoms and molecules
- Atoms modeled as spheres with impenetrable volumes defined by the van der Waals radius

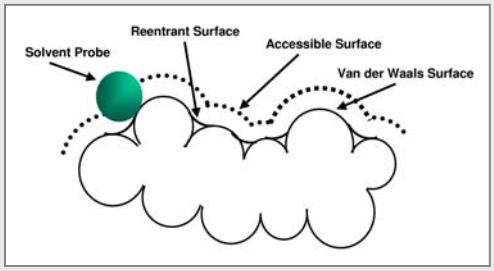
Commonly used van der Waals radii (angstroms)

	Pauling	E/H	OPLS	Bondi
C	1.7-2.0	1.87	1.88-1.96	1.7-2.0
N	1.5	1.43	1.63	1.65-1.75
O	1.4	1.43	1.48-1.54	1.5
S	1.85	1.68	1.78	1.80

Surface area and volume

- The VDW radius defines the volumes for atoms and chemical groups
- Volumes and surface areas of small molecules can be estimated by summing constituent parts (if molecules is not too strained)
- VDW surface includes many nooks and crannies not accessible
- More practical concept of surface is the "solvent accessible surface area"

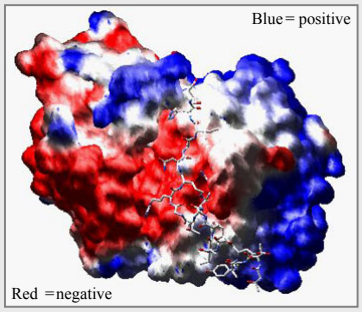
Solvent accessible surface area



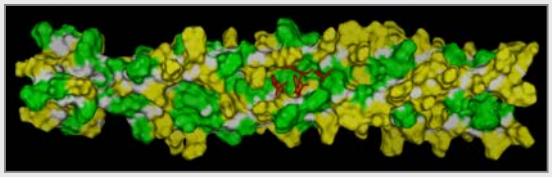
Solvent accessible surface area and thermodynamic properties

- Gas to water-phase partitioning (free energy of hydration)
- Solvation of amino acid side chains (D. Eisenburg's atomic solvation parameters)
- Binding energies methods which incorporate a SASA like term
  - Linear response method
  - Enthalpy of binding (Ernesto Freire)
  - MM-PBSA, MM-GBSA
  - Docking scoring functions

Solvent accessible surface area can be mapped with an electrostatic potential



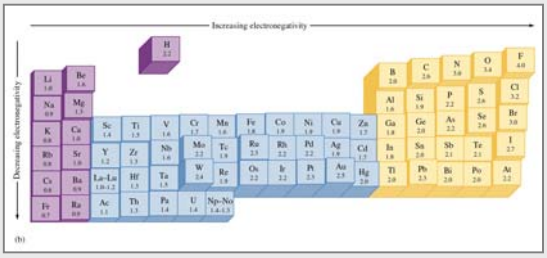
Solvent accessible surface area of a coiled-coil surface with hydrophobic (nonpolar) regions in green



Electronegativity

- Electron density have uneven distributions about molecules
- Electronegativity: The ability of an atom in a molecule to attract shared electrons to itself.
- Electronegativity can be defined in many ways. Pauling model is widely used.
- Compare the bond energy of an "HX" molecule to that of the average of an HH bond and an XX bond.
- Unequal sharing in the covalent bond (a dipole) gives stability to the bond.

Pauling electronegativity table

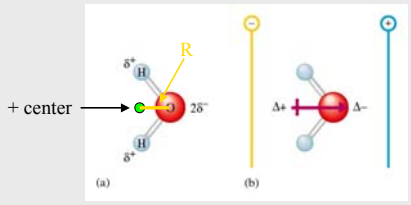


HF bond energy 569 kJ/mol
HH bond energy 436 kJ/mol

Dipole moment

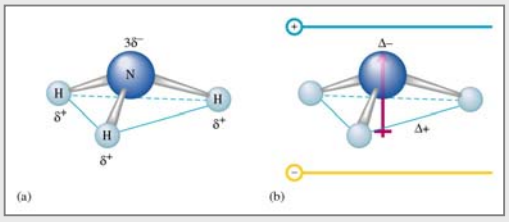
- Separation of charge in a molecule gives rise to the dipole moment.
- The dipole moment (μ) is defined as the product of the magnitude of the separated excess charge Q and the distance R:

$$\mu = QR$$

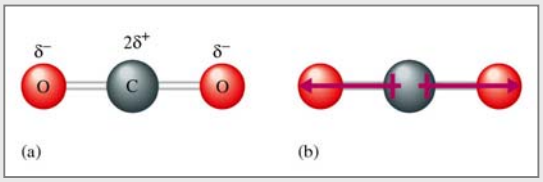


Dipole moment

- Molecular geometry is a critical factor in determining if a molecule has a dipole moment
- Unique conformations of a single molecule will have different computed dipole moments



Dipole moment



No net dipole moment. Dipoles add vectorally and cancel

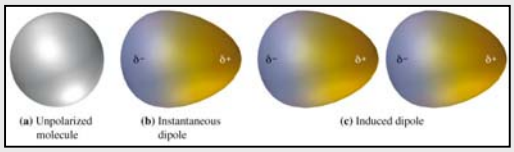
Dipoles

- Dipoles can interact with point charges and other dipoles
- The interactions of four partial charges of two dipoles is analogous to those between two bar magnets
  - parallel side by side dipoles repel each other
  - anti-parallel side by side dipoles attract each other
- Dipole dipole interactions are less strong than coulombic (monpole) interactions
- Dipole interactions decrease inversely to the 6th power
- Dipoles can perturb the electron density about an atom to create an induced dipole

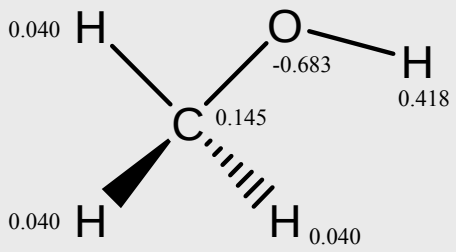
Van der Waals interactions

- The **polarizability** of an atom or molecule is a measure of the ease with which electron charge density is distorted by an external electrical field.
- The greater the polarizability of molecules, the stronger the intermolecular forces between them.
- VDW interactions are a collection of these dipole effects:
  - dipole-dipole
  - dipole-induced dipole
  - induced dipole-induced dipole (dispersion forces)
- Also called a *London* force after Fritz London who offered a theoretical explanation of these forces in 1928

Van der Waals interactions (London forces)

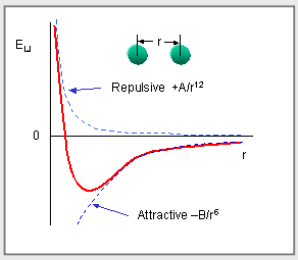


A fixed partial charge model can be "preloaded" to include bulk polarization effects in an average sense (dipole moments enhanced 10-20% over gas phase)

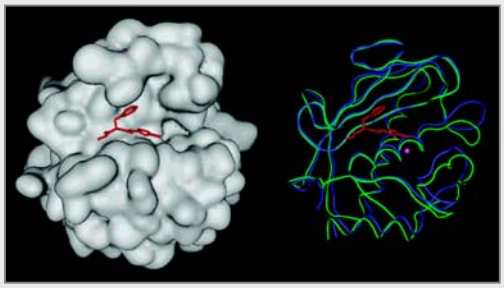


Repulsive and attractive Van der Waals interactions together is the Lennard-Jones potential

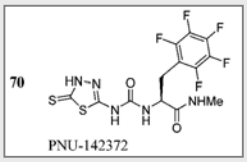
$E_{LJ} \propto A/r^{12} - B/r^6$



Binding for thiadiazole inhibitors with matrix metalloproteinases relies on favorable van der Waals interactions

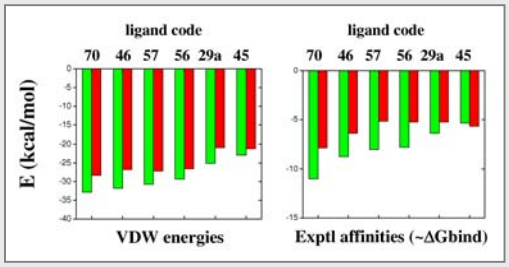


Van der Waals interaction energies (kcal/mol) of ligands with stromelysin (breast cancer target)

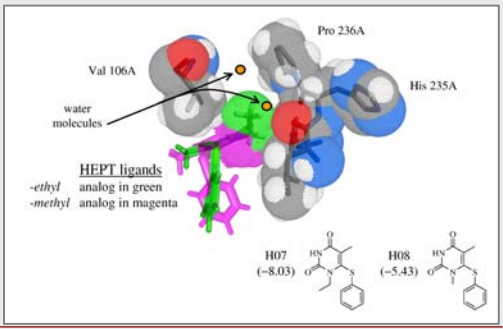


system	ΔE_{vdw} $(N = 201)$ A
str **70**	-32.84 ± 0.15
str **46**	-31.78 ± 0.13
str **57**	-30.73 ± 0.14
str **56**	-29.34 ± 0.14
str **29a**	-25.11 ± 0.14
str **45**	-22.94 ± 0.11

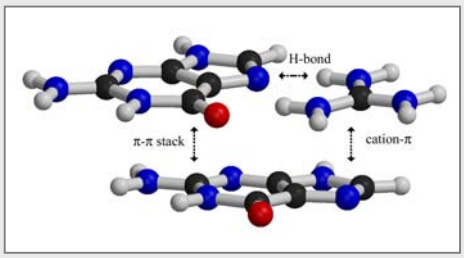
Van der Waals interaction energies correlate strongly with the observed activities (binding affinities). Energies in kcal/mol



A larger functional group yields more favorable Van der Waals packing interactions. Energies in kcal/mol.



Pi-Pi stacking is another type van der Waals interactions experimentally observed



Hydrogen Bonds

- A H-bond occurs when two electronegative atoms compete for the same hydrogen atom:

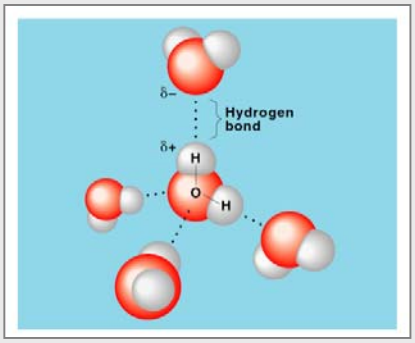
$$-D-H\bullet\bullet\bullet\bullet\bullet\bullet A-$$

- The H atom is formally bonded to one atom the donor D and interacts favorable with the acceptor atom A

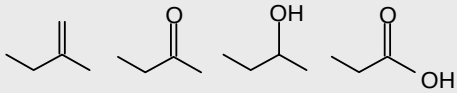
$$-D^{\delta-}-H^{\delta-}\bullet\bullet\bullet\bullet\bullet\bullet^{\delta-}A-$$

- Oxygen atoms frequently participate in two hydrogen bonds

Hydrogen Bonds Stabilize Liquids

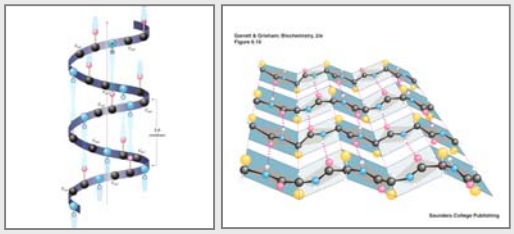


Carboxylic Acids - High Boiling Points

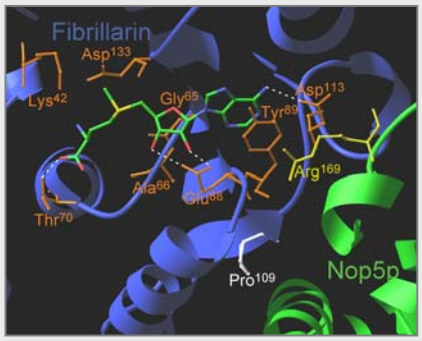


bp (1 atm) 31°C 80°C 99°C 141°C

Hydrogen Bonds Stabilize Proteins

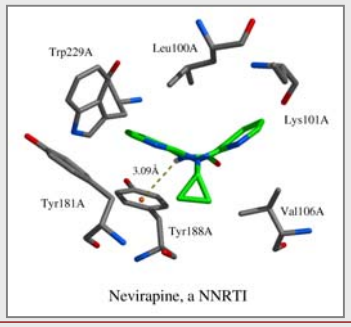


Hydrogen Bonds Mediate Ligand Binding

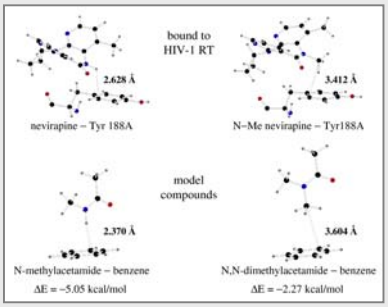


Water Molecules can Mediate Ligand Binding

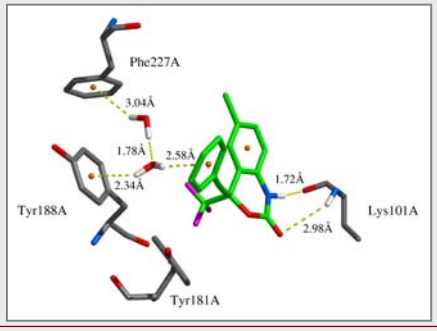
Example of a Hydrogen Bond Donated by a Ligand to an Aromatic Ring in the Binding pocket



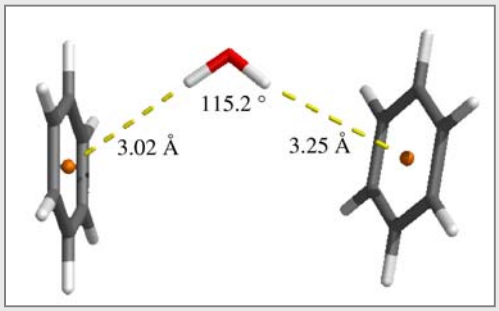
A key π-type hydrogen bond explains the otherwise surprising activity of the secondary amides and the poor activity of nevirapine against the Y188C mutant.



Water-mediated Hydrogen Bonds Between Aromatic Systems



Optimized ab initio structure of a π-water-π system (structure identified as a local minimum)



The importance of hydrogen bonding in drug discovery

- Interactions between drug and solvent
  - Permeability, solubility, potency
- Interactions between drug and target
  - Potency, efficacy, affinitty
- Interactions between drug molecules in crystal lattice
  - Solubility

Hydrophobic effect

Hydrophobic interactions minimizes interactions of non-polar residues with solvent.

Nonpolar regions of biological macromolcules are often buried in the molecules interior to exclude them from the aqueous phase.

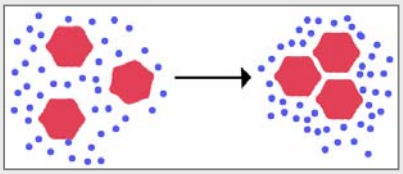
However non-polar residues can also be found on the surface of a protein. They may participate protein-protein interactions.

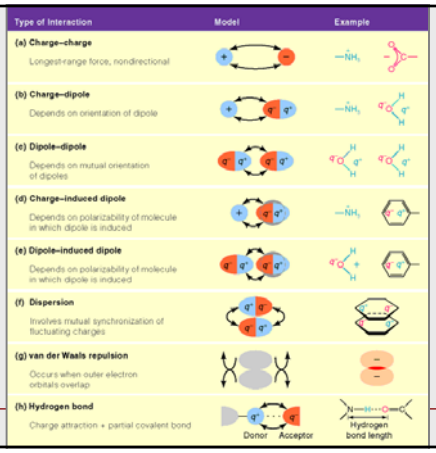
This type of interaction is entropy driven (solvent structure disrupted).

Hydrophobic effect include surface area effects

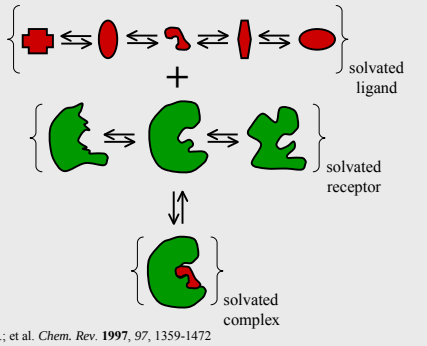
Hydrophobic interactions : each hydrophobic molecule (mainly nonpolar solute) when introduced into water provokes the decrease of the entropy of the system ("iceberg" or "cage" model).

Thus hydrophobic molecules will tend to self-associate in water, because doing so will decrease their total surface area in contact with the solvent and the unfavorable entropy decrease will be minimized. Aggregation on nonpolar solutes in water is 'entropy-driven'.



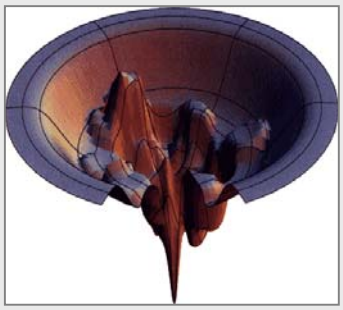


Molecular recognition* (ΔG_{bind})



*Babine, R. E.; et al. *Chem. Rev.* **1997**, *97*, 1359-1472

Protein-ligand binding energy potential surface has many local minima and one (?) global minima



Molecular recognition* (ΔG_{bind})

$$P + L \underset{}{\overset{K_a}{\rightleftharpoons}} P - L$$

$$K_a = \frac{[P-L]}{[P][L]}$$

$$K_d = 1/K_a$$

$$\Delta G_{binding} = -RT \ln K_a$$

What is ΔG? The thermodynamics of a system

•Biological systems can be usually described as having constant pressure *P* and constant temperature *T*

–the system is free to exchange heat with the surrounding to remain at a constant temperature

–it can expand or contract in volume to remain at atmospheric pressure

Gibbs free energy

•At constant pressure P and constant temperature T the system is described by the Gibbs free energy:

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

–H is the enthalpy or heat content of the system

–S is the entropy of the system (disorder)

–a reaction occurs spontaneously only if $\Delta G < 0$

–for $\Delta G > 0$ the input of energy is required to drive the reaction

Changes of the Gibbs free energy ΔG of an reaction

$$a\mathrm{A} + b\mathrm{B} + \ldots \rightleftarrows g\mathrm{G} + h\mathrm{H} \ldots$$

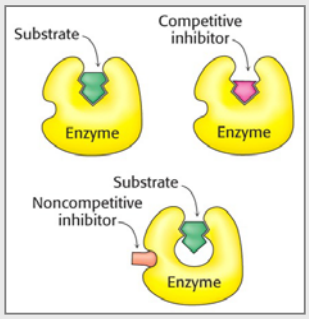
$$\Delta G = G(\text{final state}) - G(\text{initial state})$$

$$\Delta G = \Delta G^0 + RT \ln \frac{[\mathrm{G}]^g[\mathrm{H}]^h \ldots}{[\mathrm{A}]^a[\mathrm{B}]^b \ldots}$$

At equilibrium $\Delta G = 0$

$$\Delta G^0 = -RT \ln \left(\frac{[\mathrm{G}]^g[\mathrm{H}]^h \ldots}{[\mathrm{A}]^a[\mathrm{B}]^b \ldots} \right)_{\mathrm{Eq}} = -RT \ln K$$

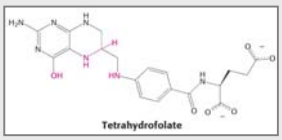
Molecular recognition: Competitive vs non-competitive inhibition



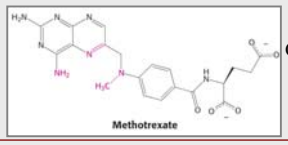
pp. 209

Competitive inhibitor example

Dihydrofolate reductase (DHFR) inhibitors slow down DNA synthesis by inhibiting regeneration of tetrahydrofolate (anti-cancer)



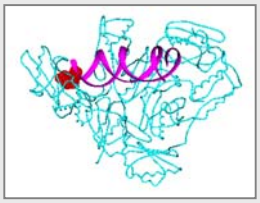
Substrate



Competitive inhibitor

Non-competitive inhibition

Non-nucleoside reverse transcriptase inhibitors slow down RNA to DNA reverse transcription through an allosteric mechanism (anti-AIDS)

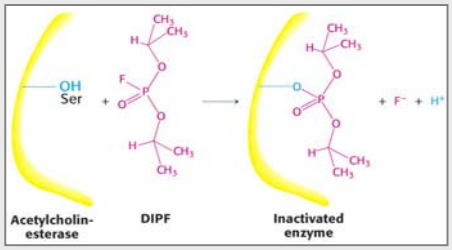


HIVRT complexed with RNA substrate

HIVRT complexed with allosteric inhibitor

Irreversable Inhibition

DIPF acts as a potent nerve gas by blocking acetylcholinesterase, the enzyme responsible for breaking down the neurotransmitter acetylcholine after signals are passed from nerve cells to muscle cells.



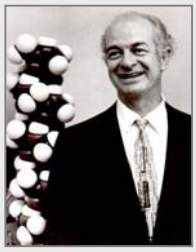
pp. 211

Enzymes stabilize the transition state

Pauling's Hypothesis

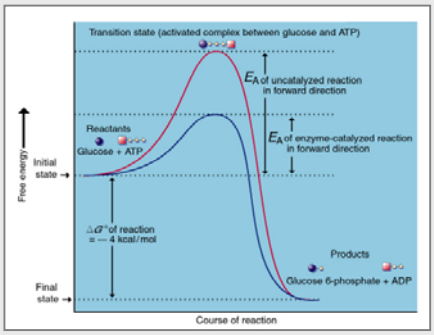
"I think that enzymes are molecules that are complementary in structure to the activated complexes of the reactions that they catalyse, that is, to the molecular configuration that is intermediate between the reacting substances and the products of reaction for these catalysed processes.

The attraction of the enzyme molecule for the activated complex would thus lead to a decrease in its energy and hence to a decrease in the energy of activation and to an increase in the rate of reaction."

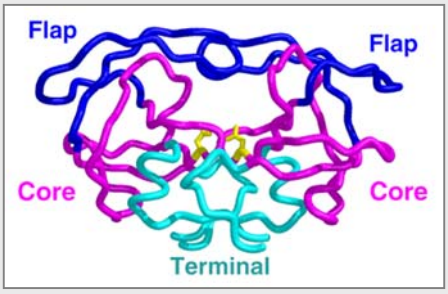


Linus Pauling
Nature **161**, 707 (1948)

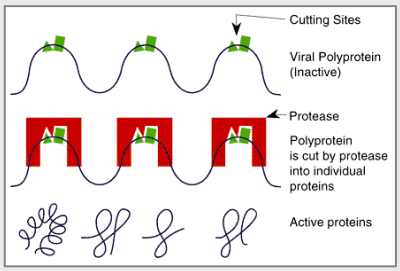
Enzymes (proteins) act as a reaction catalyst



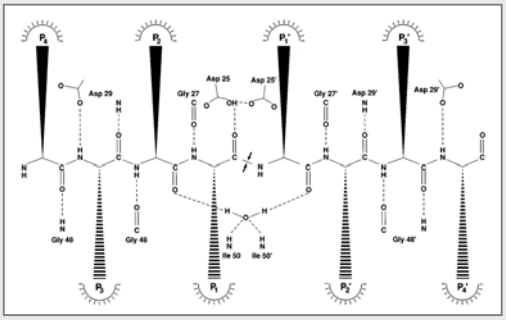
The three subdomains of HIV protease. Catalytic functional groups (Asp) shown in yellow



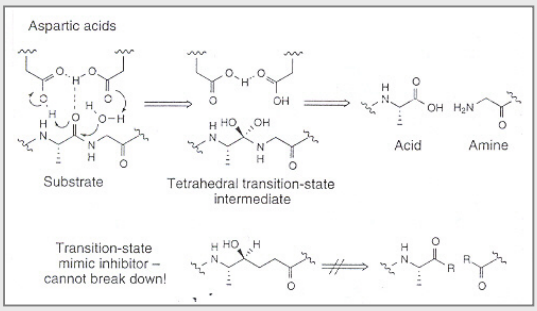
Transition state inhibitors: HIV protease cleaves peptide bonds (Tyr-Pro or Phe-Pro)



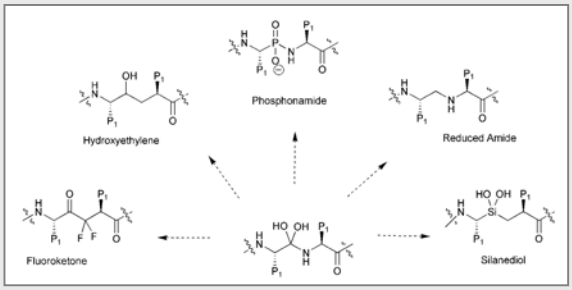
Schematic diagram showing hydrogen bonding between HIV protease and a model substrate



Proposed mechanism for the peptide bond cleavage by the HIV protease enzyme.

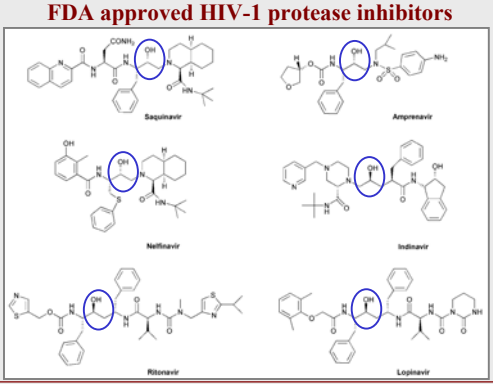


Non-cleavable transition state peptide bond isosteres

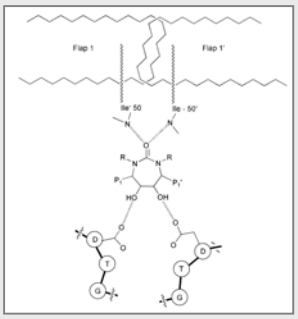


transition state
tetrahedral intermediate

FDA approved HIV-1 protease inhibitors



A unique cyclic urea-based inhibitor is a pseudo transitions state mimic (diol functionality)



Protein-ligand binding can be a physically understandable process

Molecular recognition includes many effects:
electrostatics, van der Waals, H-bonds, hydrophobic, entropy

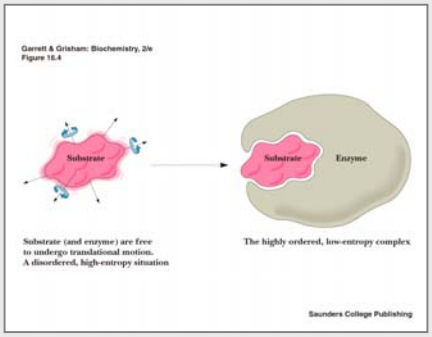
Complexation is driven by changes in free energy ΔG of the system

$\Delta G = \Delta H - T\Delta S = -RT \ln(K_a)$

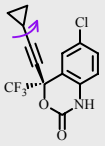
Note: A *very* crude approximation: $\Delta G \approx \Delta E_{potential} = -RT \ln(K_a)$

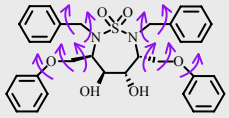
Complexation is always in competition with the unbound state

A decrease in entropy disfavors binding



Rigid vs. flexible ligands



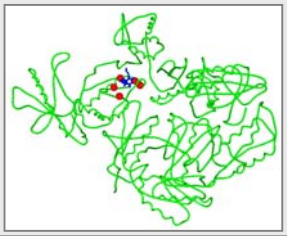


1 rotatable bond
($3^1 = 3$ possible conformers)

12 rotatable bonds
$3^{12} = 531{,}441$ possible conformers

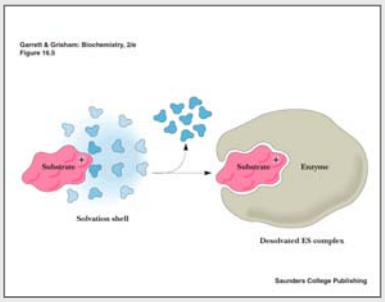
Pre-organization can be an effective drug design strategy

But…….. What about mutational effects ?

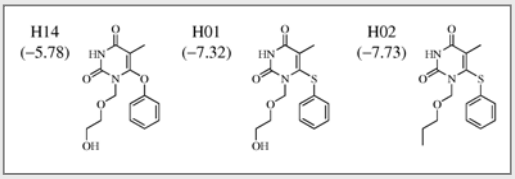


Compounds which are too rigid may not be able to accommodate point mutations and therefore only be effective against wildtype strains

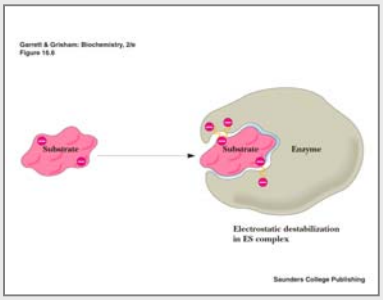
Desolvation penalties must be considered (the competing unbound state)



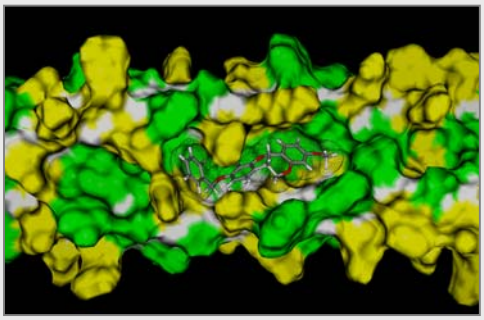
HEPT ligands structure-activity-relationship (estimated binding energy ΔG ≈ -RT ln (activity) in kcal/mol



Unfavorable electrostatic interactions may be offset by very favorable VDW interactions



Van der Waals interactions are a measure of good steric packing



Binding affinity calculation methods to be discussed ……

- Free energy perturbation (Jorgensen, Kollman)
- Linear Response (Aqvist, Jorgensen)
- Molecular Mechanics Poisson Boltzmann Surface Area (Case, Kollman)