

Drug Receptor Interactions

- Drug Targets:
 - ✓ Receptors.
 - ✓ Enzymes.
 - ✓ Biomembranes.
 - ✓ Nucleic acids.
 - ✓ Ion channels.



- Ligands are compounds that have affinity for a receptor:
 - ✓ Agonist (intrinsic activity).
 - ✓ Antagonist (lacks intrinsic activity).
- Chemical attractive forces.
- Pharmacological action (efficacy).

- Complementarities assure strong binding:
 - ✓ Three-dimensional characteristics.
 - ✓ Physical and electrochemical properties.
- Strong binding means greater affinity.

- Interaction between the drug and the biologic receptor would be expected to take place by utilizing the same bonding forces involved as those when simple molecules interact.

Bond Type	Bond strength (kcal/mol)	Example
Covalent	40-140	H ₃ C-OH
Reinforced ionic	10	$\begin{array}{c} \text{H} \\ \\ \text{R}-\text{N}-\text{H} \cdots \text{O} \\ \quad \quad \\ \text{H} \quad \oplus \quad \ominus \quad \text{O} \quad \text{R}' \end{array}$
Ionic	5	R ₄ N [⊕] ⋯ ⊖ I
Hydrogen	1-7	-OH ⋯ O=
Ion-dipole	1-7	R ₄ N [⊕] ⋯ :NR ₃
Dipole-dipole	1-7	$\begin{array}{c} \delta^- \text{O}=\text{C} \delta^+ \cdots \text{:NR}_3 \\ \\ \text{C} \end{array}$
van der Waals'	0.5-1	$\begin{array}{c} \diagup \quad \diagdown \\ \text{C} \cdots \text{C} \\ \diagdown \quad \diagup \end{array}$
Hydrophobic	1	

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As organic molecules, drugs bind to their target by:

1- Irreversible bonds:

- Covalent bonds.
- When long lasting effects are desired.
- e.g. antibacterials, anticancers.

2- Reversible bonds:

- Majority of drugs.
- Electrostatic bonds.
- Hydrophobic bonds.
- Drugs can easily leave the receptor site.

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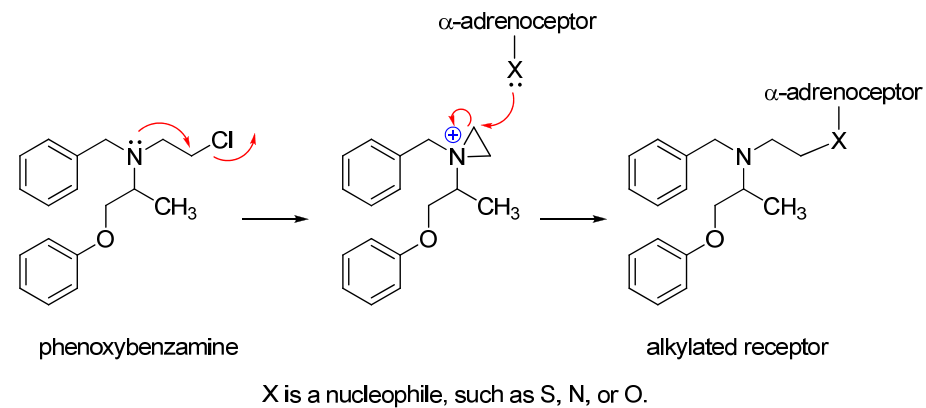
Irreversible Bonds: Covalent Bond

- Ligand and receptor share a pair of electrons.
- Irreversible (50-150 kcal/mole).
- Receptor destruction (suicide binding).
- Aging (Endocytosis and chemical destruction).
- Synthesis of new receptors (recovery).

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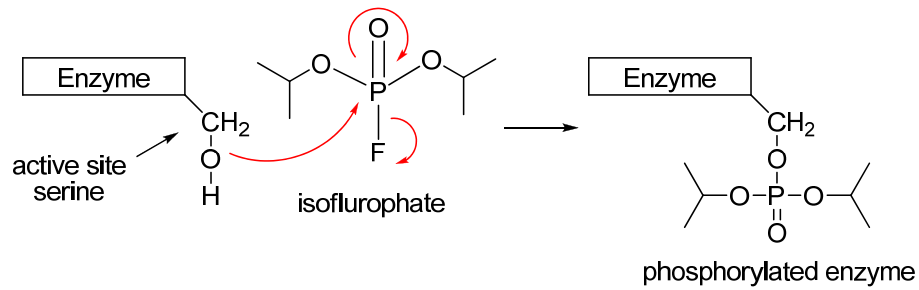
Covalent Bond: Alkylation



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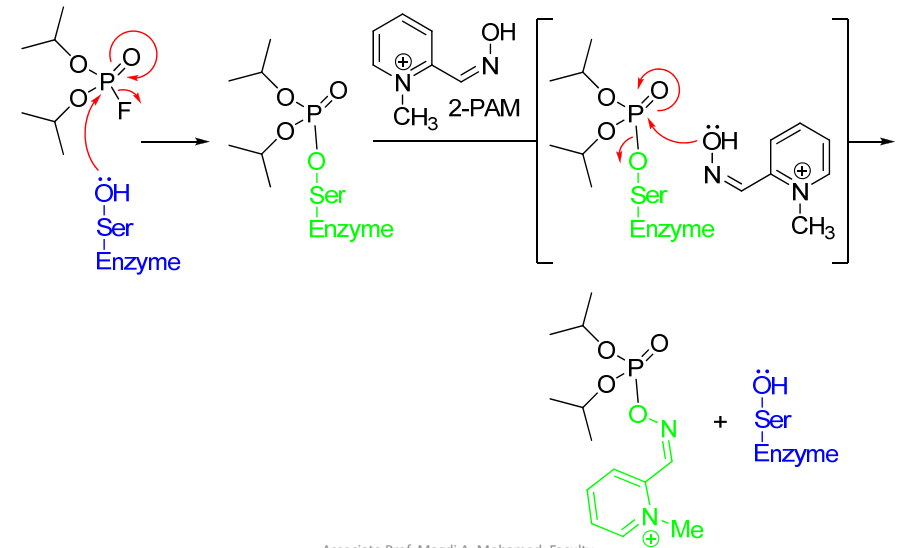
Covalent Bond: Phosphorylation



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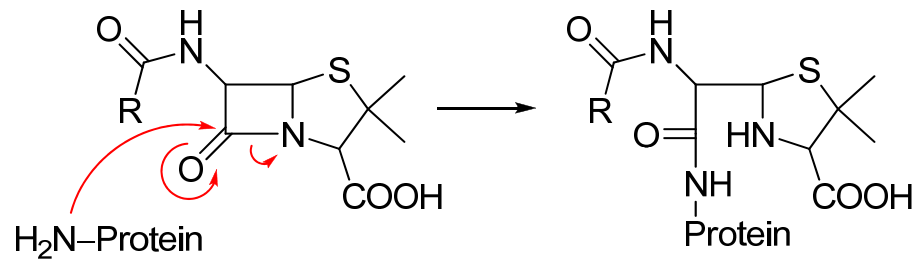
Reactivation of Acetylcholinesterase



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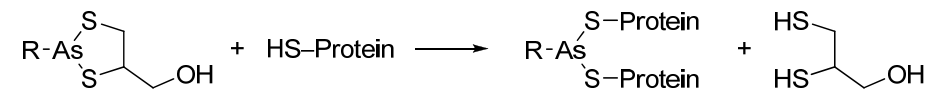
Covalent Bond: Acylation



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Covalent Bond: Metallation

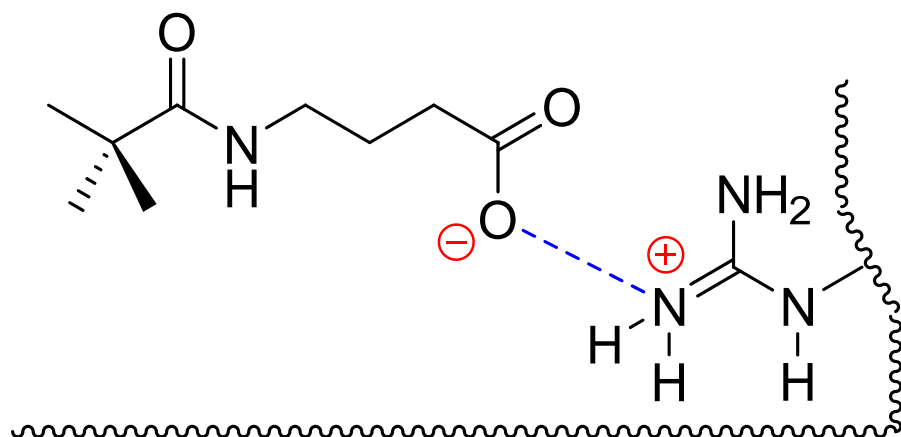
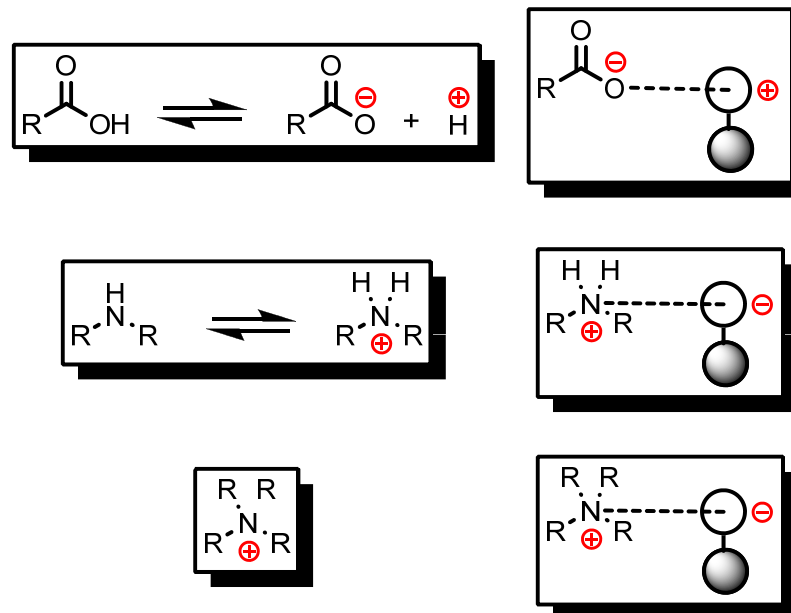


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Reversible Bonds: Ionic Bond

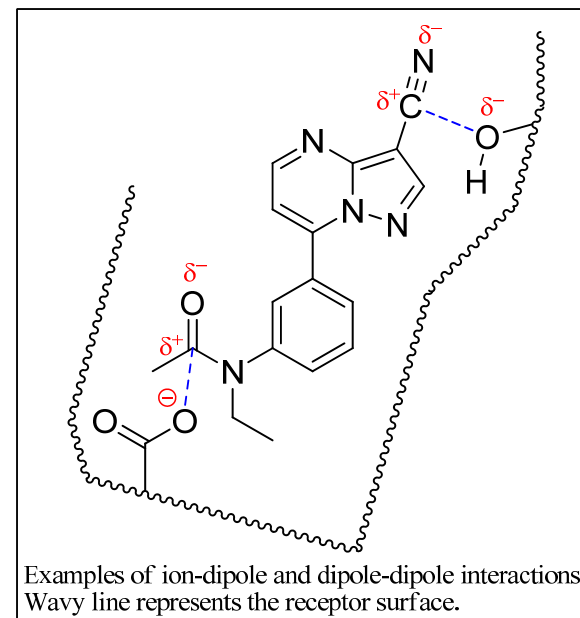
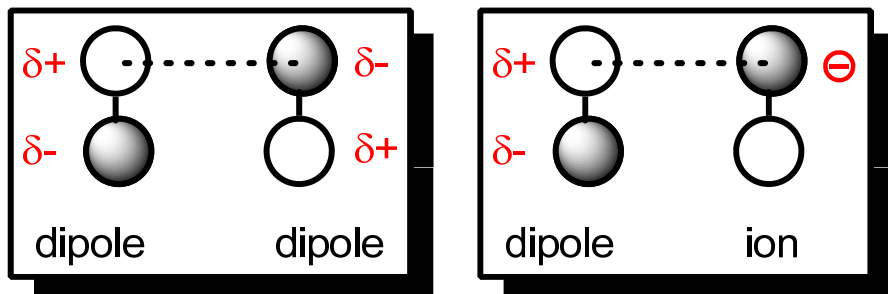
- Ionizable groups at physiological pH:
 - ✓ Carboxyl.
 - ✓ Sulfonamide.
 - ✓ Aliphatic amino.
- Quaternary ammonium group at any pH.



Example of an ionic interaction.
Wavy line represents the receptor surface.

Reversible Bonds: Dipole-Dipole or Ion-Dipole

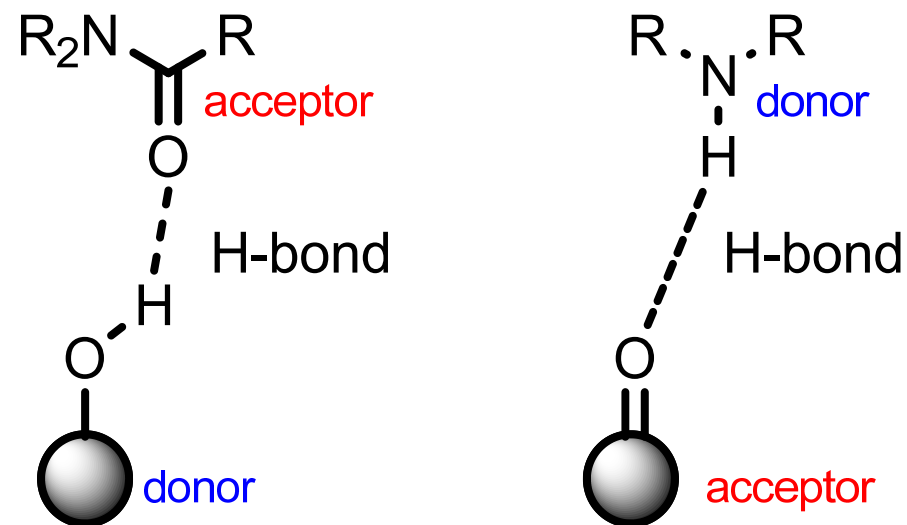
- Electronegativity.
- Dipoles.
- Electrostatic interactions.
- Dipole-dipole or ion-dipole.
- E.g.: Carbonyl, ester, amide, ether, nitrile, and related groups.

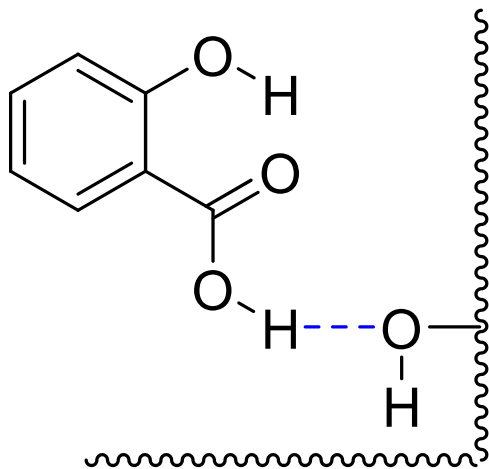


Examples of ion-dipole and dipole-dipole interactions. Wavy line represents the receptor surface.

Reversible Bonds: H-Bond

- Acceptors and donors.
- E.g.: carbonyl, hydroxyl, amino, and imino.

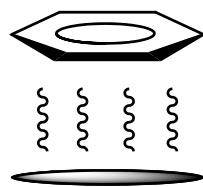




Example of H-bond interaction.
Wavy line represents the receptor surface.

Reversible Bonds: van der Waals' Forces

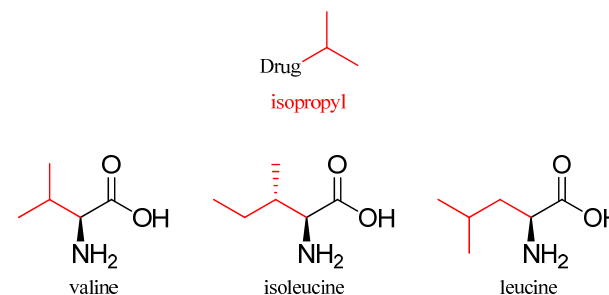
- Non polar compounds.
- Momentary dipolar structure.
- Individually weak.
- Distillation of alkanes ($C > 80$) requires 80 kcal/mol.
- C-C cleavage requires 80 kcal/mol.



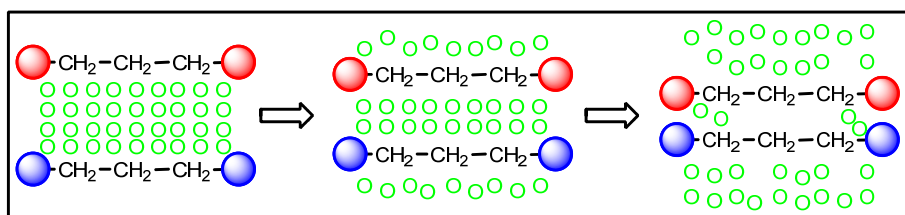
flat hydrophobic region

- The benzene ring binds flat receptor areas via van der Waals.

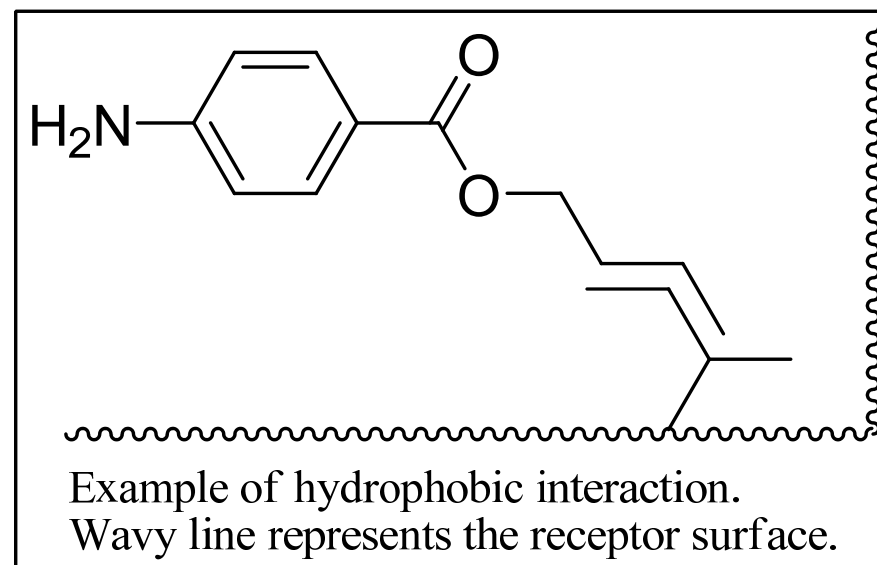
Reversible Bonds: The Hydrophobic Bond



- Non polar group (e.g. isopropyl).
- Hydrophobic cleft on the receptor.
- Hydrocarbon side chains of the amino acid valine, isoleucine, and leucine.



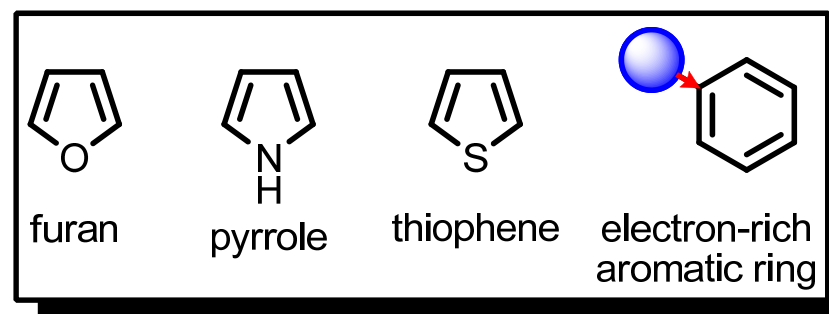
- No H-bonds.
- Not solvated in water.
- Water displacement.
- Van der Waals' forces.



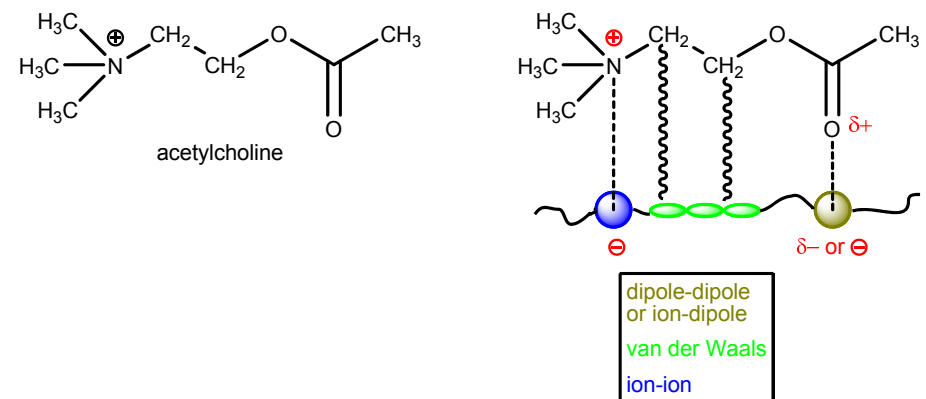
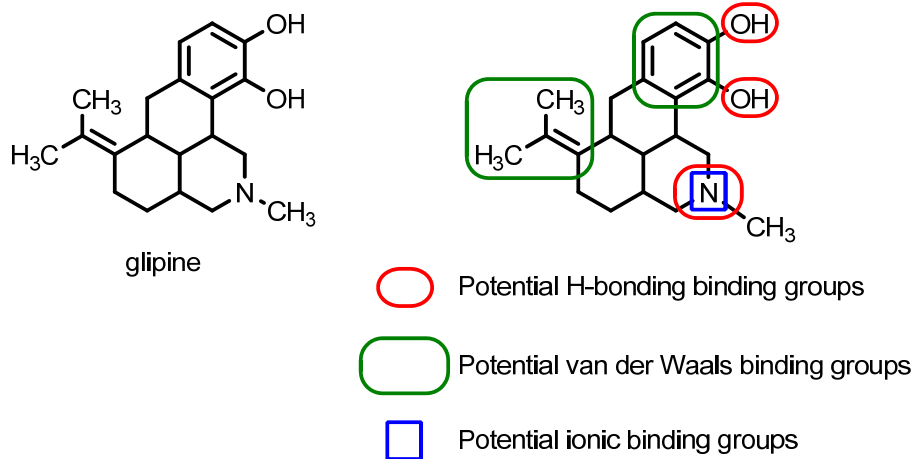
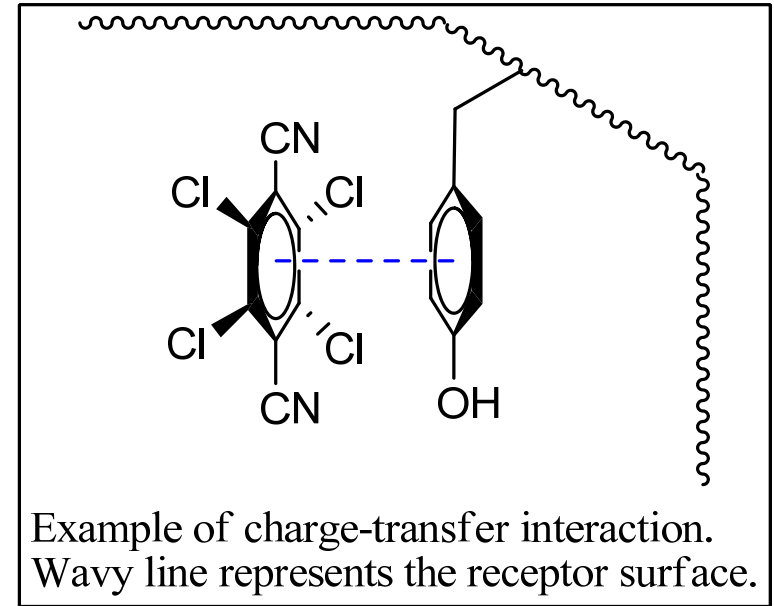
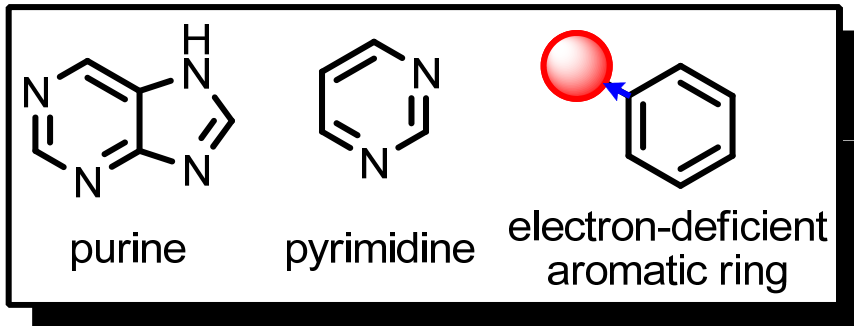
Reversible Bonds: Charge Transfer Complex

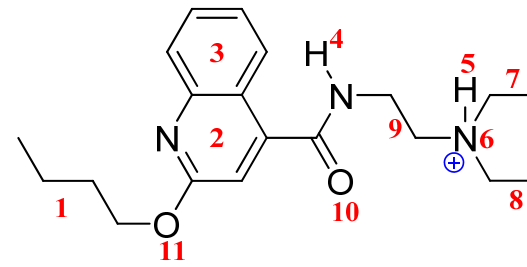
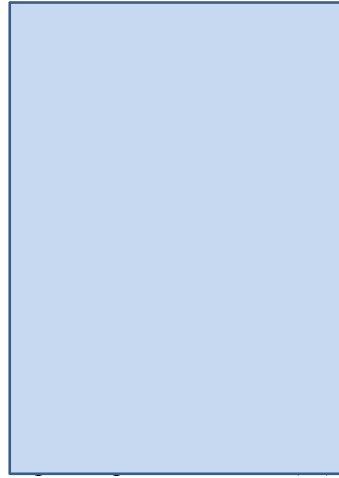
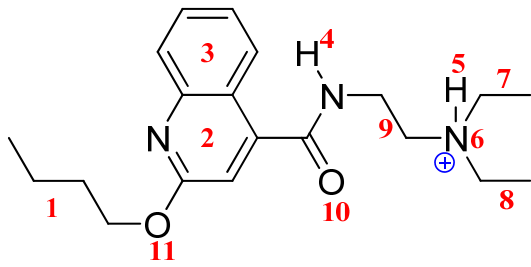
- Electron-rich donor molecules and electron-deficient acceptors.

- Electron-rich donors:



• Electron-deficient acceptors:





- hydrophobic (1)
- charge transfer or H-bond (2)
- hydrophobic (3)
- H-bond (4)
- H-bond (5)
- ionic or ion-dipole (6)
- hydrophobic (7)
- hydrophobic (8)
- hydrophobic (9)
- dipole-dipole or H-bond (10)
- dipole-dipole or H-bond (11)