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Pharmacy department

Physical pharmacy II

lec3

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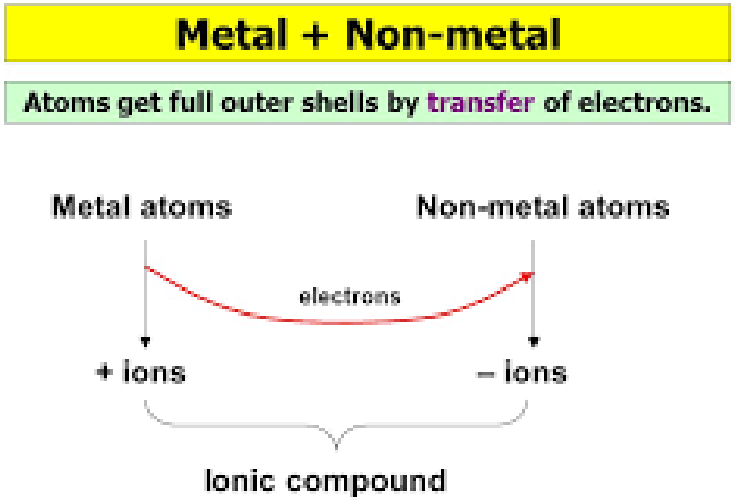
Complexation and Protein binding

Objective

1 Define the three classes of complexes (coordination compounds) and identify pharmaceutically relevant examples.
2 Describe chelates, their physically properties, and what differentiates them from organic molecular complexes.
3 Describe the types of forces that hold together organic molecular complexes and give examples.
4 Describe the forces involved in polymer–drug complexes used for drug delivery and situations where reversible or irreversible complexes may be advantageous.
5 Discuss the uses and give examples of cyclodextrins in pharmaceutical applications.
6 Determine the stoichiometric ratio and stability constant for complex formation.
7 Describe the methods of analysis of complexes and their strengths and weaknesses.
8 Discuss the ways that protein binding can influence drug action.
9 Describe the equilibrium dialysis and ultrafiltration methods for determining protein binding.
10 Understand the factors affecting complexation and protein binding.
11 Understand the thermodynamic basis for the stability of complexes

- Complexes or coordination compounds, according to the classic definition, result from a donor- acceptor mechanism or Lewis acid base reaction between two or more different chemical constituents

- Any nonmetallic atom or ion, whether free or contained in a neutral molecule or in an ionic compound, that can donate (give)an electron pair can serve as the donor
- The acceptor, or constituent that accepts a share in the pair of electrons is frequently a metallic ion, although it can be a neutral atom



note

Elements that tend to gain electrons to form anions during chemical reactions are called nonmetallic

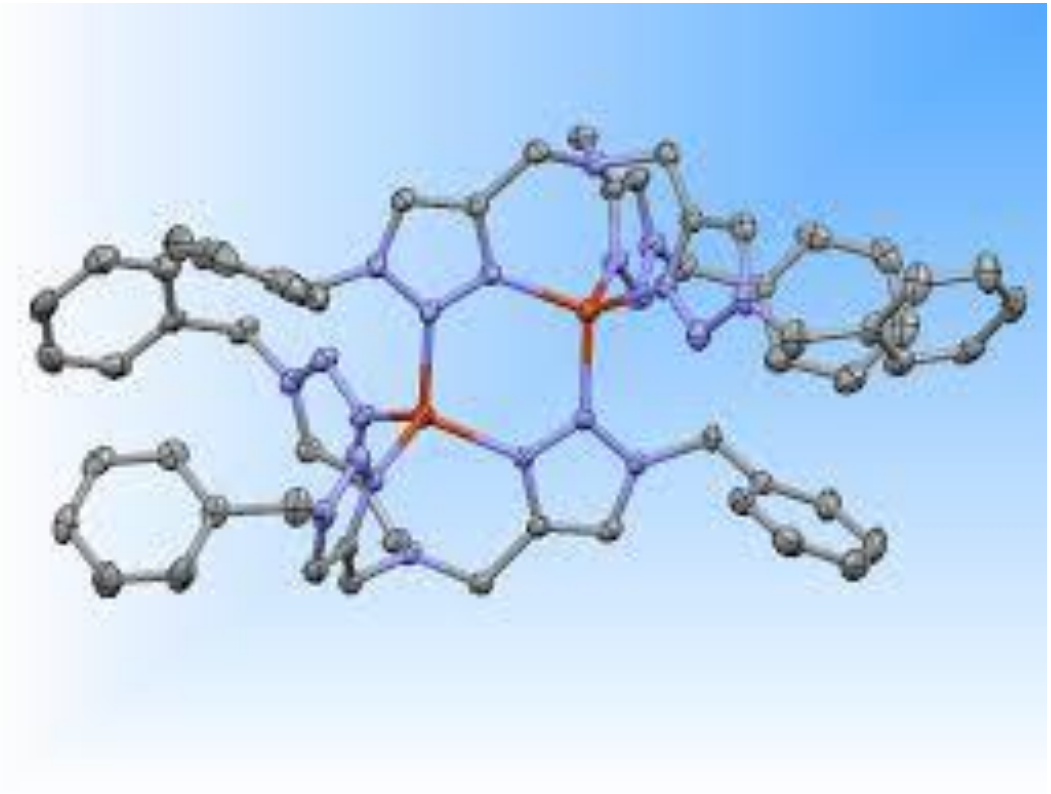
Complexes can be divided broadly into two classes depending on whether the acceptor component is a metal ion or an organic molecule; third class, the inclusion/ occlusion compounds, involving the entrapment(caught) of one compound in the molecular framework of another

CLASSIFICATION OF COMPLEXES*

I. Metal ion complexes
  A. Inorganic type
  B. Chelates
  C. Olefin type
  D. Aromatic type
    1. Pi (π) complexes
    2. Sigma (σ) complexes
    3. "Sandwich" compounds
II. Organic molecular complexes
  A. Quinhydrone type
  B. Picric acid type
  C. Caffeine and other drug complexes
  D. Polymer type
III. Inclusion/occlusion compounds
  A. Channel lattice type
  B. Layer type
  C. Clathrates
  D. Monomolecular type
  E. Macromolecular type

I-Metal Complexes

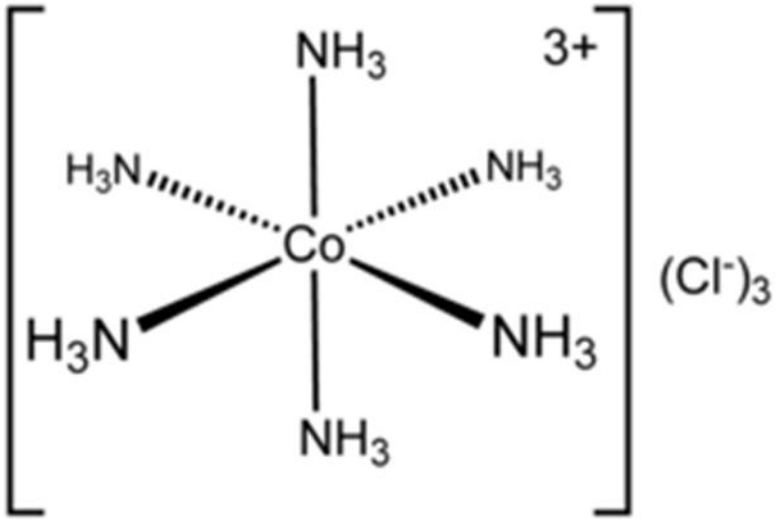
A. Inorganic type
B. Chelates
C. Olefin type
D. Aromatic type
1. Pi (π) complexes
2. Sigma (σ) complexes
3. “Sandwich” compounds



A-Inorganic Complexes

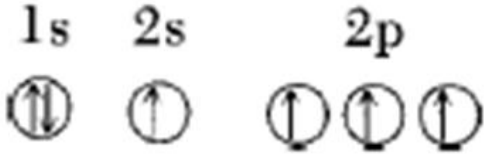
The ammonia molecules in hexamminecobalt (III) chloride, as the compound $\mathbf{[Co(NH_3)_6]^{+3}\ Cl^{-3}}$ is called, are known as the **ligands** and are said to be **coordinated** to the cobalt ion. The coordination number of the cobalt ion, or number of ammonia groups coordinated to the metal ions, is six. Other complex ions belonging to the inorganic group include **silver $\mathbf{[Ag(NH_3)2]^{+}}$, iron$\mathbf{[Fe(CN)_6]^{-4}}$**, and $\mathbf{[Cr(H_2O)_6]^{+3}}$ ·Each ligand donates a pair of electrons to form a coordinate covalent link between itself and the central ion having an incomplete electron shell. For example,

$$Co^{3+} + 6\ddot{N}H_3 = [Co(NH_3)_6]^{3+}$$



Hybridization plays an important part in coordination compounds in which sufficient bonding orbitals are not ordinarily available in the metal ion .The ground state configuration of carbon is

This cannot be the bonding configuration of carbon, however, because it normally has four rather than two valence electrons Pauling suggested the possibility of hybridization to account for the quadrivalence .According to this mixing process, one of the 2 s electrons is promoted to the available 2 p orbital to yield four equivalent bonding orbitals the structure is known as an $\underline{sp^3}$ hybrid because it involves one **s** and three **p** orbitals

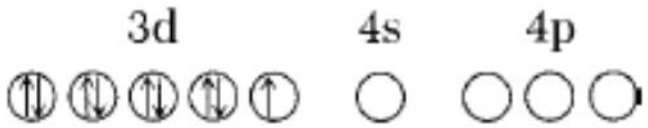


Orbitals other than the 2s and 2p orbitals can become involved in hybridization . The transition elements, such as iron, copper, nickel, cobalt, and zinc, seem to make use of their 3d, 4s, and 4p orbitals in forming hybrids.

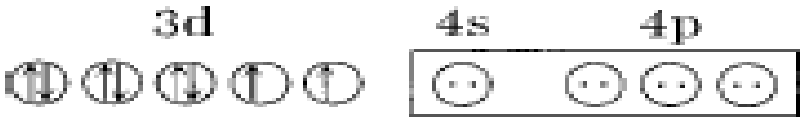
Ligands such as $H_2\ddot{O}$ $H_3\ddot{N}$, $C\ddot{N}^-$, or $\ddot{C}l^-$ donate a pair of electrons in forming a complex with a metal ion, and the electron pair enters one of the unfilled orbitals on the metal ion. A useful but not perfect rule to follow in estimating the type of hybridization in a metal ion complex is to select that complex in which the metal ion has its 3d levels filled or that can use the lower-energy 3d and 4s orbitals primarily in the hybridization.

For example, the ground-state electronic configuration of Ni^+ can be given as

Ni 28

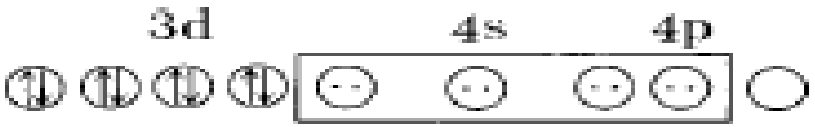


In combining with $4C\ddot{N}^-$ ligands to form $[Ni(CN)4]^{-2}$, the electronic configuration of the nickel ion may become either



sp^3 Tetrahedral structure

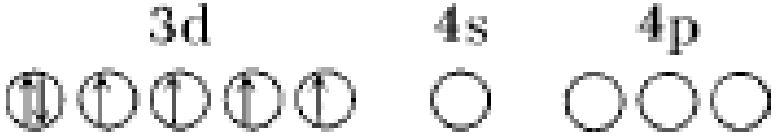
or



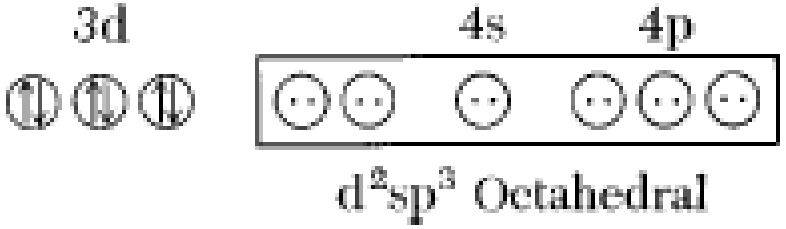
dsp^2 Planar structure

in which the electrons donated by the ligand are shown as dots. The **dsp^2** or square planar structure is predicted to be the complex formed because it uses the lower-energy 3d orbital.

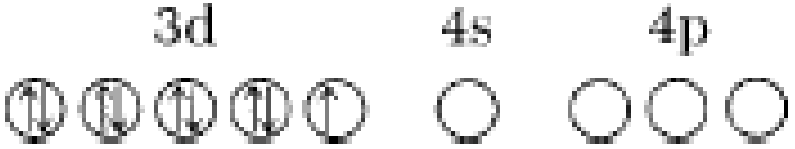
Similarly, the trivalent cobalt ion, Co(III), has the ground state electronic configuration



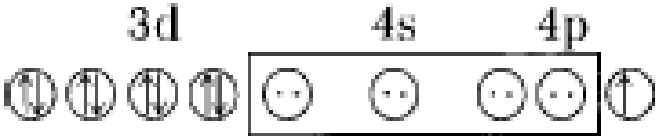
and one may question into the possible geometry of the complex $[Co(NH3)6]^{+3}$. The electronic configuration of the metal ion leading to filled 3d levels is



In the case of divalent copper, Cu(II), which has the electronic configuration

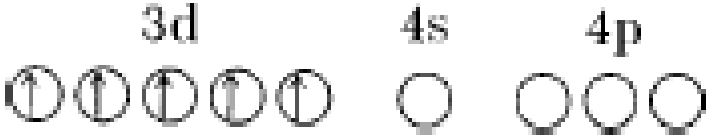


the formation of the complex $[Cu(NH_3)_4]^{+2}$ requires the promotion of one d electron of Cu2+ to a 4p level to obtain a filled 3d configuration in the complexed metal ion, and a dsp2 or planar structure is obtained

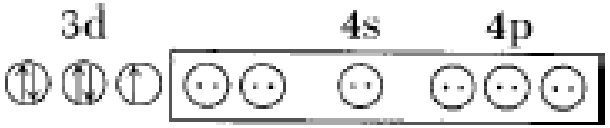


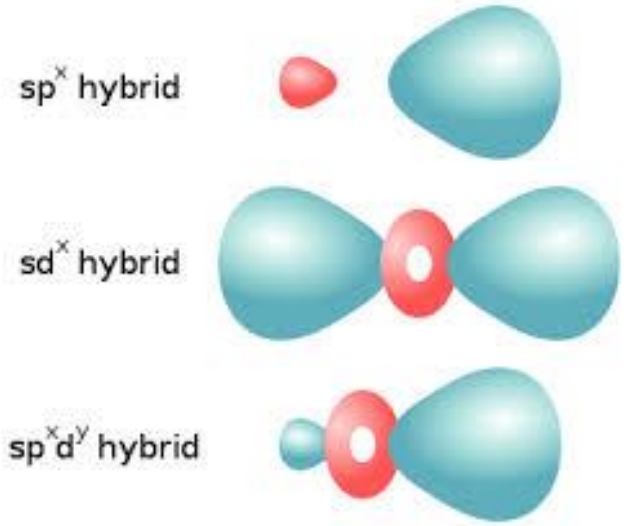
Although the energy required to elevate the **d** electron to the 4p level is considerable, the formation of a planar complex

The metal ion Fe(III) has the ground-state configuration

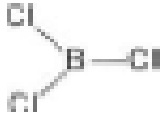
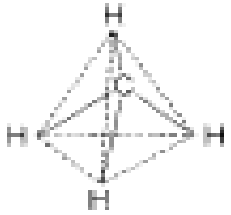
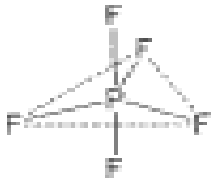
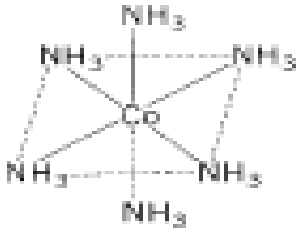


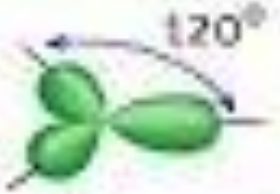
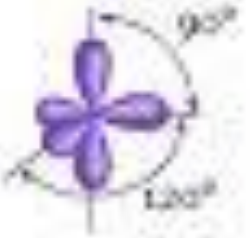
and in forming the complex $[Fe(CN)_6]^{-3}$, no electron promotion takes place,





BOND TYPES OF REPRESENTATIVE COMPOUNDS

Coordination Number	Orbital Configuration	Bond Geometry	Example	
			Formula	Structure
2	sp	Linear	O_2	
3	sp^2	Trigonal	BCl_3	
4	sp^3	Tetrahedral	CH_4	
4	dsp^2	Square planar	$Cu(NH_3)_4^{2}$	
5	dsp^3	Bipyramidal	PF_5	
6	d^2sp^3	Octahedral	$Co(NH_3)_6^{3}$	

Pure atomic orbitals of central atom	Hybridization of the central atom	Number of hybrid orbitals	Shape of hybrid orbitals
s,p	sp	2	Linear 
s,p,p	sp^2	3	Trigonal Planar 
s,p,p,p	sp^3	4	Tetrahedral 
s,p,p,p,d	sp^3d	5	Trigonal Bipyramidal 
s,p,p,p,d,d	sp^3d^2	6	Octahedral 

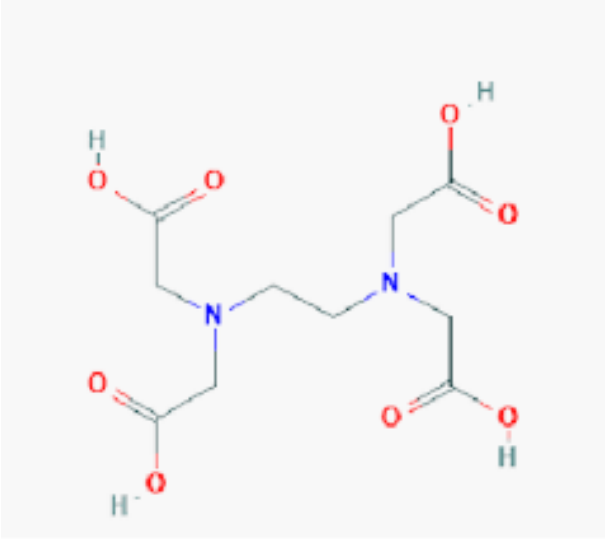
B-Chelates

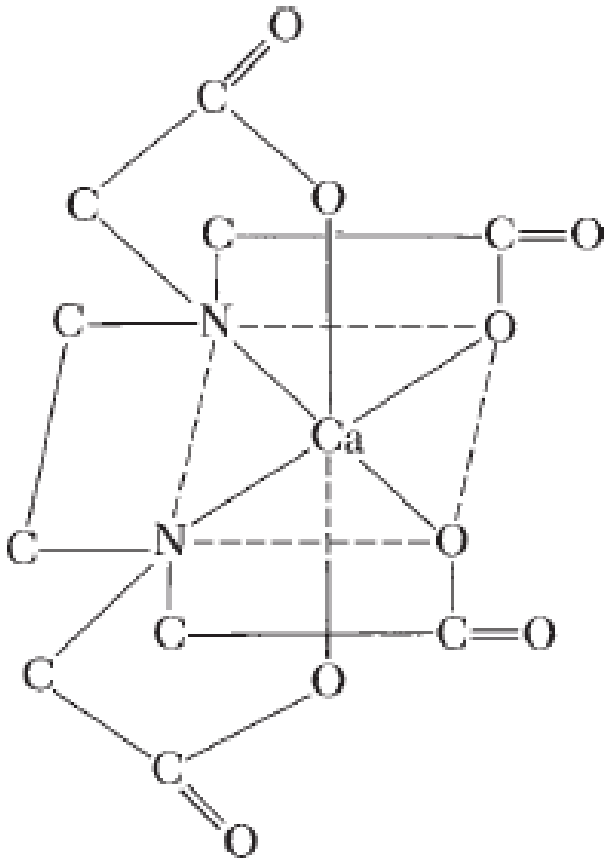
- ✓ A substance containing two or more donor groups may combine with a metal to form a special type of complex known as a chelate

- ✓ Some of the bonds in a chelate may be **ionic** or of the primary **covalent** type, whereas others are **coordinate covalent links**.

- ✓ When the ligand provides one group for attachment to the central ion, the chelate is called **monodentate**
- ✓ Molecules with two and three donor groups are called **bidentate** and **tridentate**, respectively.

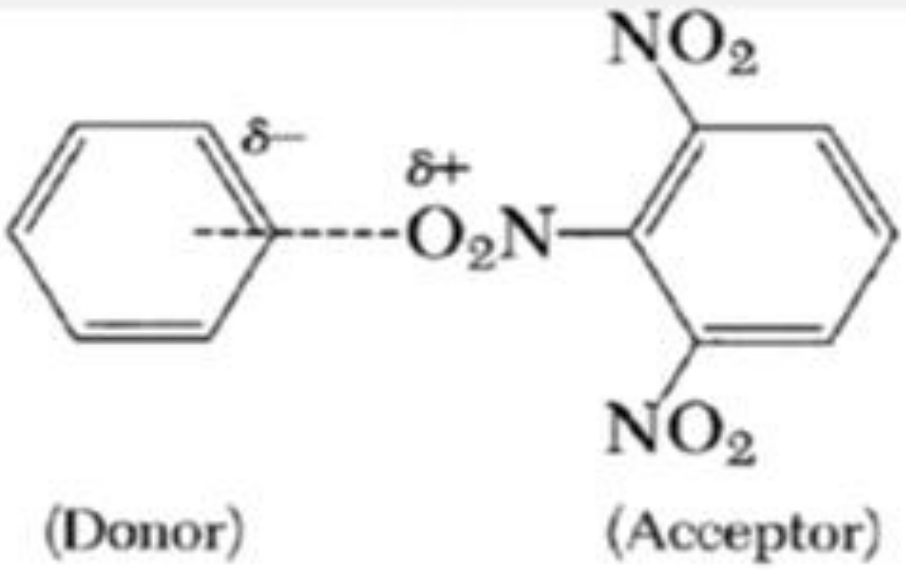
Ethylenediaminetetraacetic acid(EDTA) has six points for attachment to the metal ion and is accordingly hexadentate however, in some complexes, only four or five of the groups are coordinated





Calcium ions sequestered by ethylendediaminetetraacetic acid.

- ✓ **Chlorophyll and hemoglobin,** two extremely important compounds, are naturally occurring chelates involved in the life processes of plants and animals.
- ✓ **Albumin** is the main carrier of various metal ions and small molecules in the blood serum. The amino terminal portion of human serum albumin binds Cu(II) and Ni(II) with higher affinity than that of dog serum albumin. This fact partly explains why humans are less susceptible to copper(Cu) poisoning than are dogs.
- ✓ The binding of copper to serum albumin is important because this metal is possibly involved in several pathologic conditions.
- ✓ The synthetic chelating agent EDTA has been used to tie up or sequester iron and copper ions so that they cannot catalyze the oxidative degradation of ascorbic acid in fruit juices and in drug preparations .
- ✓ EDTA is widely used to sequester and remove calcium ions from hard water



Electron drift or partial electron transfer by polarization (π bonding)

22

19

II. Organic molecular complexes

A. Quinhydrone type

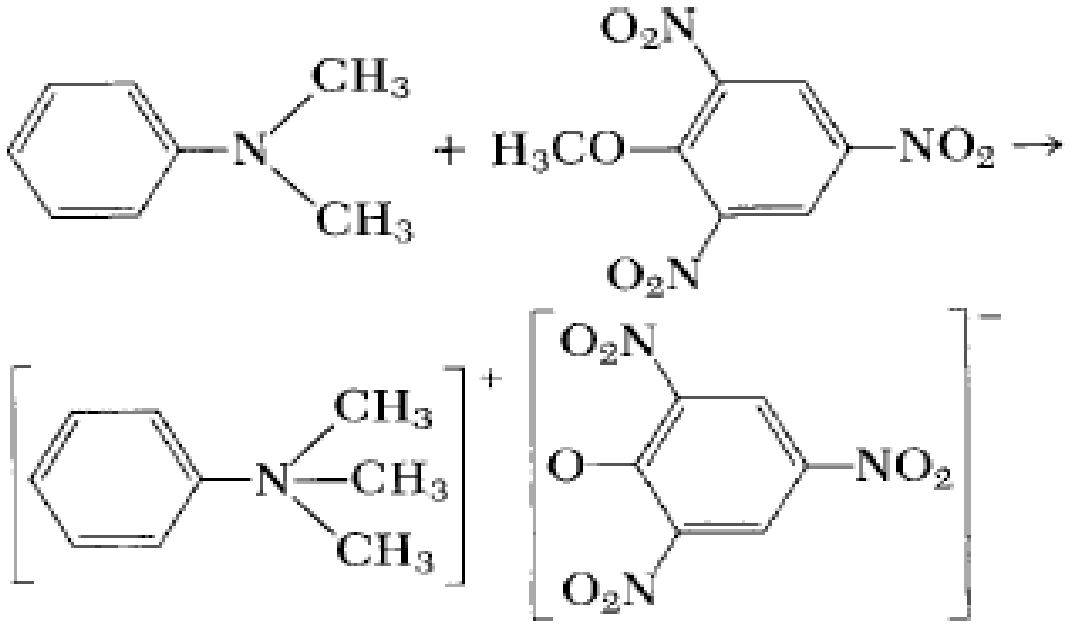
B. Picric acid type

C. Caffeine and other drug complexes

D. Polymer type

- ✓ An organic coordination compound or molecular complex consists of constituents held together by weak forces of the donor–acceptor type or by hydrogen bonds.
- ✓ The difference between complexation and the formation of organic compounds has been shown in figures below
- ✓ The compounds dimethylaniline and 2,4,6-trinitroanisole react in the cold to give a molecular complex

On the other hand, these two compounds react at an elevated temperature to yield a salt, the constituent molecules of which are held together by primary valence bonds

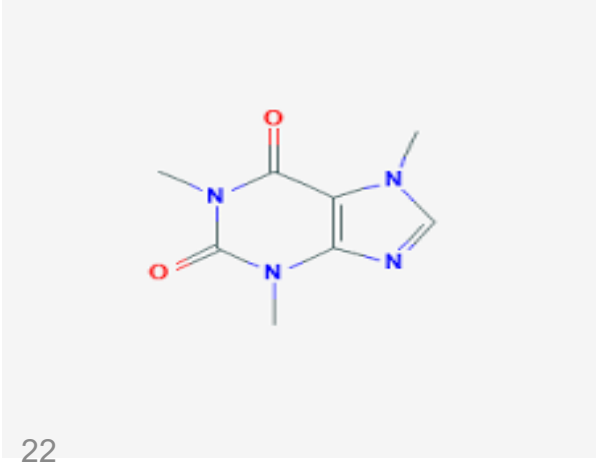


Drug Complexes

Higuchi and his associates investigated the complexing of **caffeine with a number of acidic drugs**.

They attributed the interaction between caffeine and a drug such as a sulfonamide or a barbiturate to **a dipole–dipole force or hydrogen bonding between the polarized carbonyl groups of caffeine and the hydrogen atom of the acid**.

A secondary interaction probably occurs between the **nonpolar parts** of the molecules, and the resultant complex is “squeezed out” of the aqueous phase owing to the great internal pressure of water. These two effects lead to a high degree of interaction.



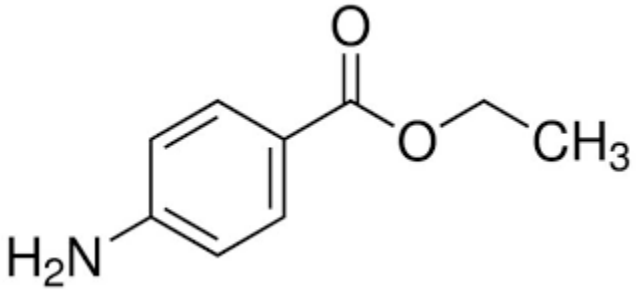
caffeine

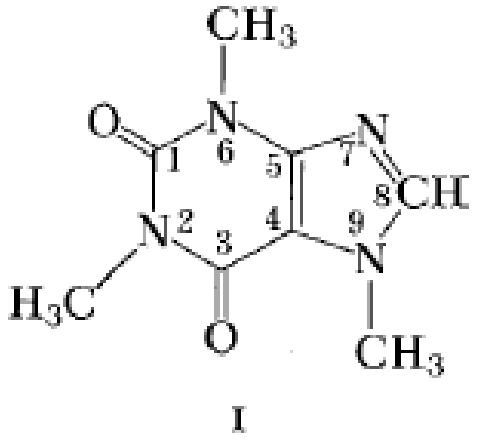
Complexation of esters such as benzocaine with caffeine

The caffeine observed in formula II, the nitrogen at the 2 position can become strongly electrophilic or acidic, owing to the withdrawal of electrons by the oxygens at positions 1 and 3. An ester such as benzocaine also becomes polarized (formula III) in such a way that the carboxyl oxygen is nucleophilic or basic.

The complexation can thus occur as a result of a dipole–dipole interaction between the nucleophilic carboxyl oxygen of benzocaine and the electrophilic nitrogen of caffeine

benzocaine

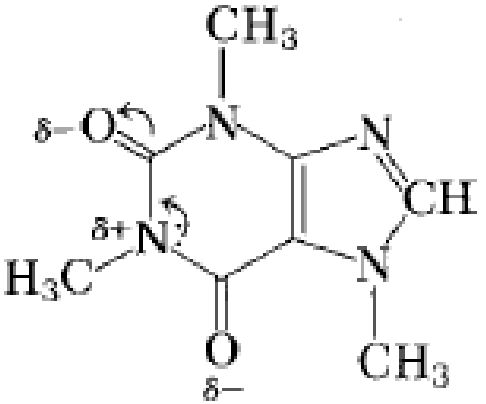




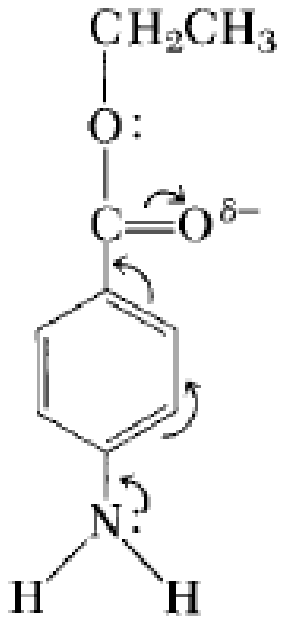
I

caffeine

Complexation between caffeine and benzocaine



II



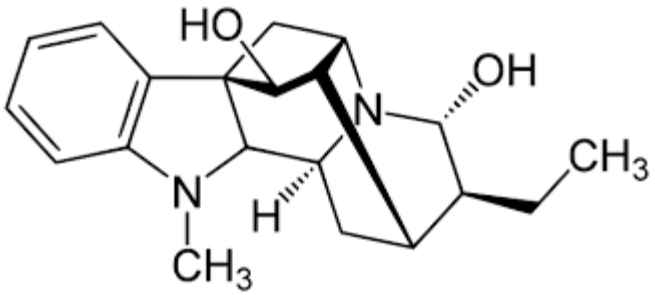
III

Polymer Complexes

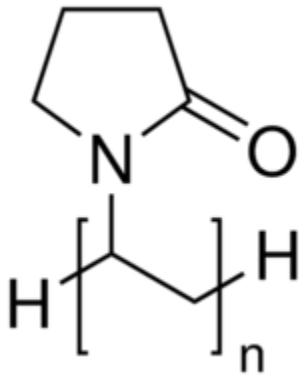
Polyethylene glycols, polystyrene, carboxymethylcellulose, and similar polymers containing nucleophilic oxygens can form complexes with various drugs. The incompatibilities of certain polyethers, such as the Carbowaxes, Pluronics, and Tweens with tannic acid, salicylic acid, and phenol, can be attributed to these interactions. Marcus reviewed some of the interactions that may occur in suspensions, emulsions, ointments, and suppositories. The incompatibility may be manifested as a precipitate, flocculate, delayed biologic absorption, loss of preservative action, or other undesirable physical, chemical, and pharmacologic effects.

Polymer–drug complexes are used to modify biopharmaceutical parameters of drugs; the dissolution rate of ajmaline is enhanced by complexation with Polyvinylpyrrolidone (PVP). The interaction is due to the aromatic ring of ajmaline and the amide groups of PVP to yield a dipole–dipole-induced complex

Ajmaline



PVP



Note

Ajmaline is an alkaloid that is classified as a 1-A antiarrhythmic agent.

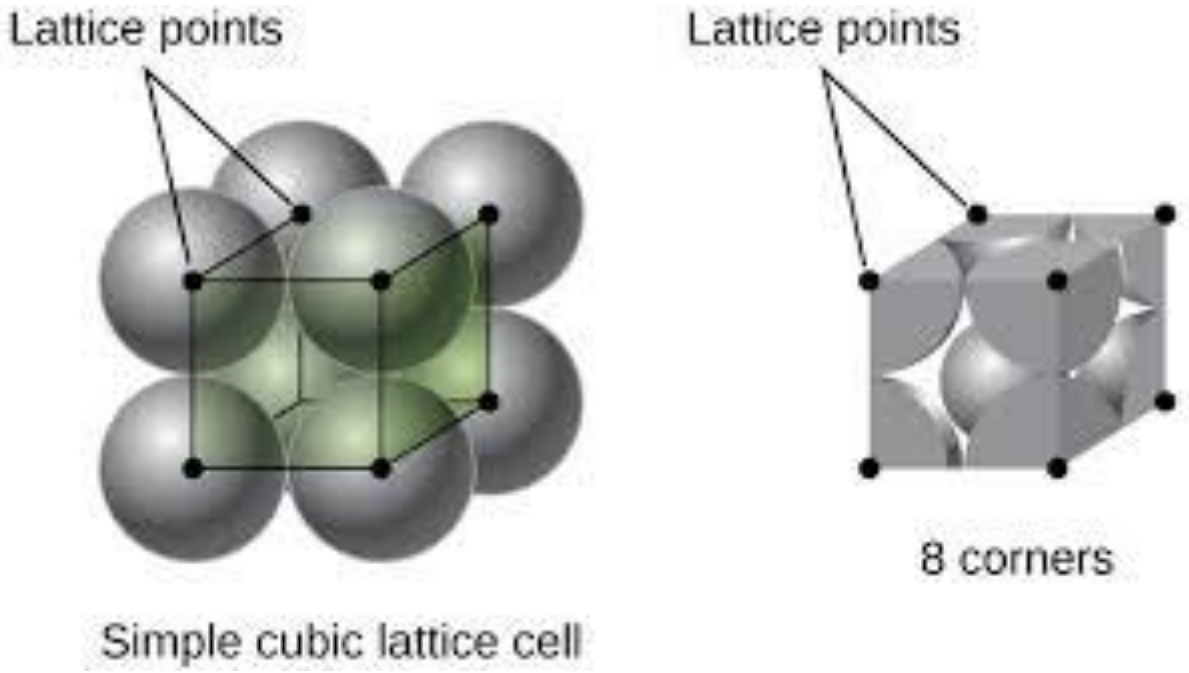
III-Inclusion / occlusion Compounds

The class of addition compounds known as *inclusion* or *occlusion* compounds results more from the architecture of molecules than from their chemical affinity. One of the constituents of the complex is trapped in the open lattice or cagelike crystal structure of the other to yield a stable arrangement..

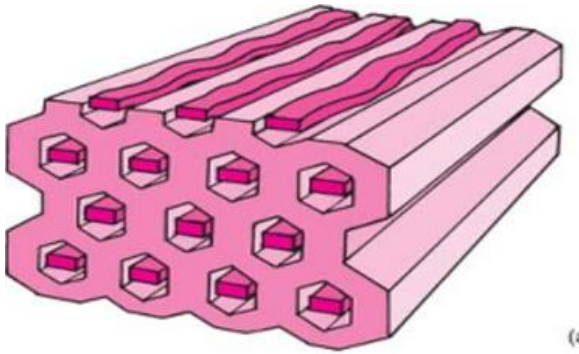
Inclusion/occlusion compounds
A. Channel lattice type
B. Layer type
C. Clathrates
D. Monomolecular type
E. Macromolecular type

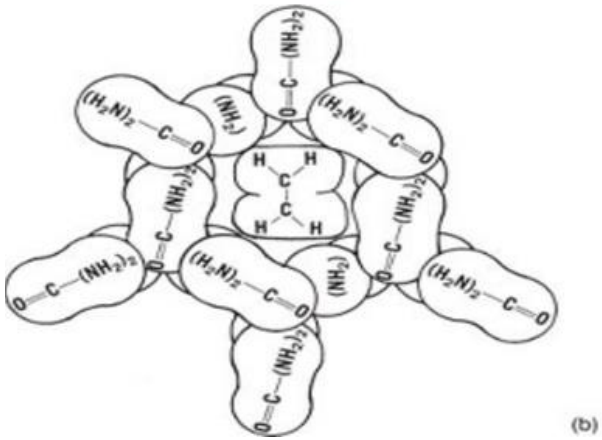
A-Channel Lattice Type

The *cholic acids* (bile acids) can form a group of complexes principally involving deoxycholic acid in combination with paraffins, organic acids, esters, ketones, and aromatic compounds and with solvents such as ether, alcohol, and dioxane



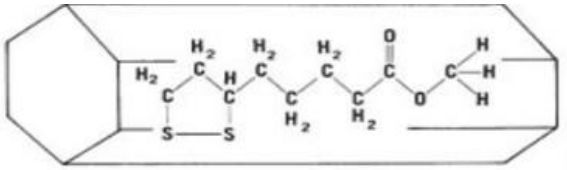
a) A channel complex formed with urea molecules as the host

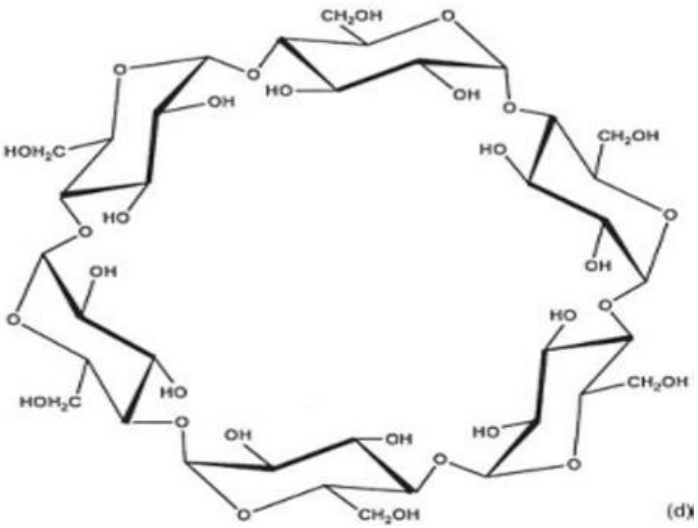




b)packed in an orderly manner and held together by hydrogen bonds between nitrogen and oxygen atoms. The hexagonal channels

c)A hexagonal channel complex of methyl α-lipoate and 15 g of urea in methanol prepared with gentle heating





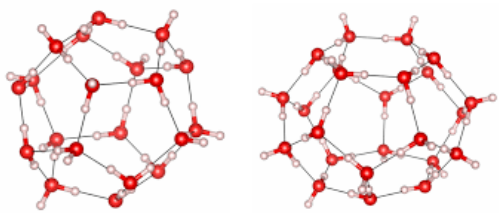
d)Cyclodextrin (cycloamylose)

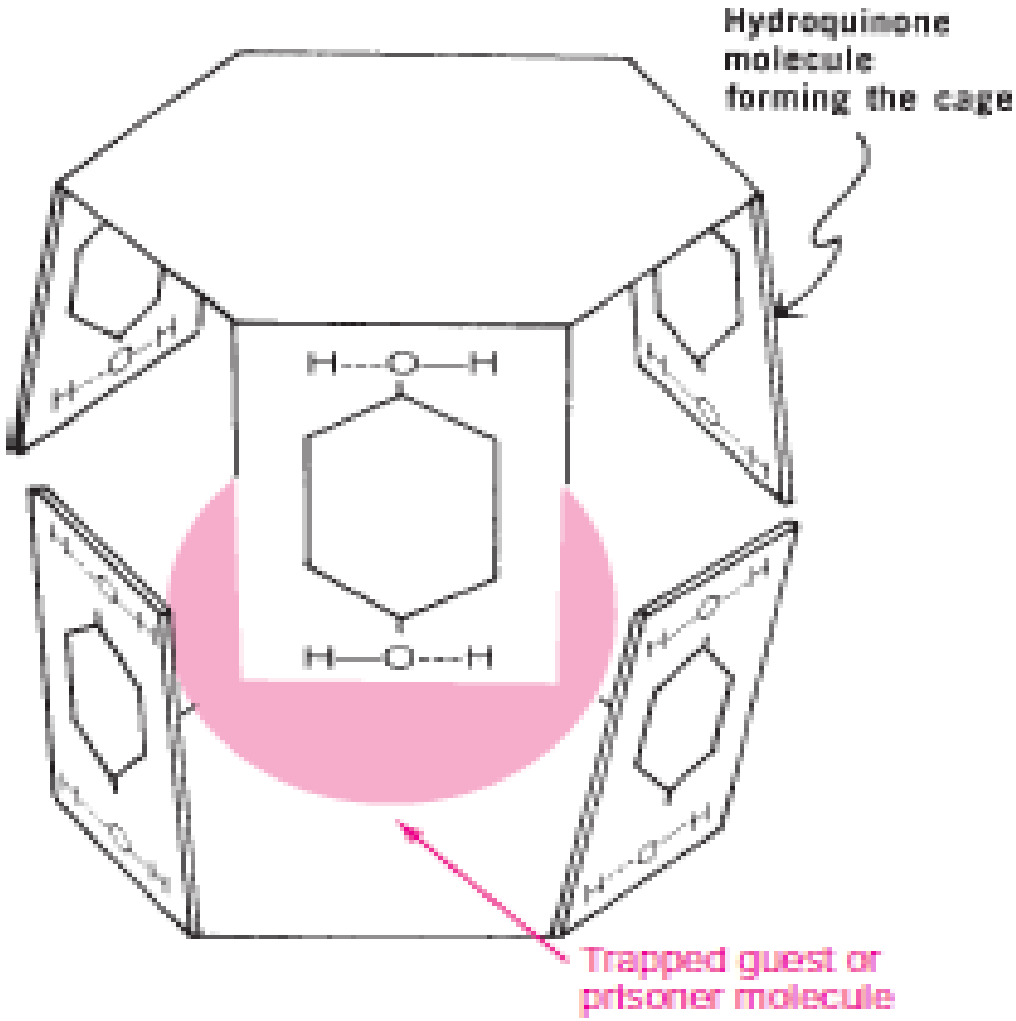
B-Layer Type

Some compounds, such as the clay montmorillonite , the principal constituent of bentonite, can trap hydrocarbons, alcohols, and glycols between the layers of their lattices . Graphite can also insert compounds between its layers

C-Clathrates

The clathrates crystallize in the form of a cagelike lattice in which the coordinating compound is entrapped. Chemical bonds are not involved in these complexes, and only the molecular size of the encaged component is of importance. The stability of a clathrate is due to the strength of the structure, that is, to the high energy that must be expended to decompose the compound, just as a prisoner is confined by the bars that prevent escape.

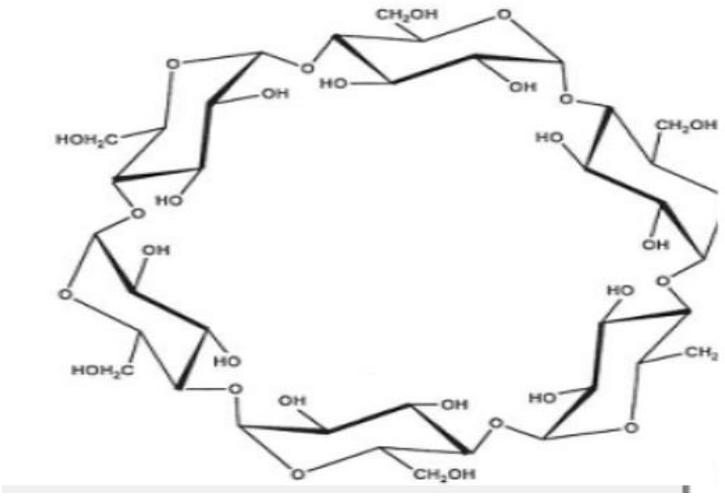




Cagelike structure formed through hydrogen bonding of hydroquinone molecules

D-Monomolecular Inclusion Compounds :
Cyclodextrins

"Cyclodextrins are cyclic oligomers of glucose that can form water-soluble inclusion complexes with small molecules and portions of large compounds. These biocompatible, cyclic oligosaccharides do not stimulate immune responses and have low toxicities in animals and humans. Cyclodextrins are used in pharmaceutical applications for numerous purposes, including improving the bioavailability of drugs.



Protein binding

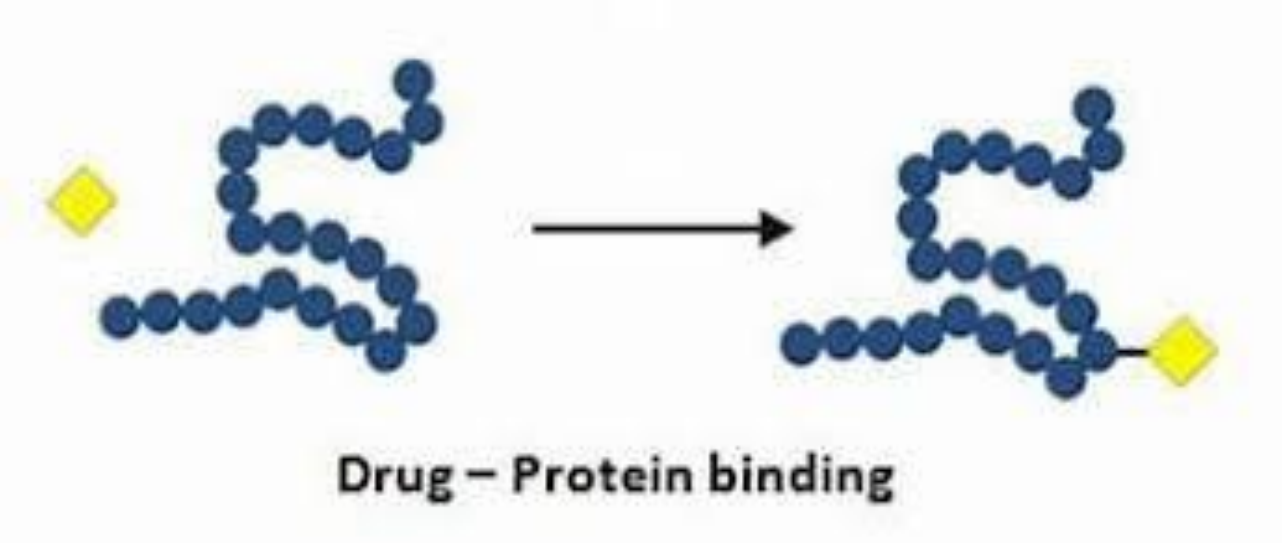
Drug–protein binding

The binding of drugs to proteins contained in the body can influence their action in a number of ways. Proteins may

(*a*) facilitate the distribution of drugs throughout the body,

(*b*) inactivate the drug by not enabling a sufficient concentration of free drug to develop at the receptor site, or

(*c*) retard the excretion of a drug.



The interaction of a drug with proteins may cause

(a) the displacement of body hormones or a coadministered agent,

(b) a configurational change in the protein, the structurally altered form of which is capable of binding a coadministered agent, or

(c) the formation of a drug–protein complex that itself is biologically active.

Among the plasma proteins, albumin is the most important owing to its high concentration relative to the other proteins and also to its ability to bind both acidic and basic drugs. Another plasma protein, α1- acid glycoprotein, has been shown to bind numerous drugs; this protein appears to have greater affinity for basic than for acidic drug molecules.


THANK YOU