Inorganic Pharmaceutical Chemistry

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Chapter 1

Atomic and Molecular Structure (Complexation)

1.1 Electronic Structure of Atoms

The fundamental unit of all matter is the atom. The various chemical and physical properties of matter are determined by its elemental composition, and elements are composed of like atoms and their isotopes. In order to be able to predict the properties of matter, molecules, or elements, it is important to understand the structure of atoms.

1.2 Subatomic Particles

Atoms are composed of a central *nucleus* surrounded by *electrons* which occupy discrete regions of space. The nucleus is considered to contain two types of stable particles which comprise most of the mass of the atom. These particles are held within the nucleus by various nuclear forces.

One of these particles is called a *neutron*. It is an uncharged species with a mass of 1.675×10^{-24} g or approximately 1.009 mass units on the atomic scale. The other particle is termed a *proton*. This particle has a positive charge of essentially *one* electrostatic units (e.s.u.). Its mass is close to that of the neutron at 1.672×10^{-24} g or approximately 1.008 atomic units (a.m.u.).

Every stable nucleus contains a certain number of protons (equal to the number of electrons in the neutral atom) and a particular number of neutrons. The sum of the masses of the protons and neutrons accounts for most of the *atomic mass* (or weight) of the element, and the number of protons is equal to the *atomic number*. Isotopic forms of a particular element differ in the number of neutrons, and therefore, in the atomic mass.

A third subatomic particle is the *electron*, which has a *negative* charge of *one* e.s.u. and a mass of 9.107×10^{-28} g or approximately 0.0006 a.m.u. Its charge is opposite in sign and equal in magnitude to that of a proton, so a neutral atom will have the same number of electrons as protons. The mass of the electron is about 1/1840 of that of the proton, thus providing only a small contribution to the atomic mass. Electrons occupy regions of extranuclear space at various distances from the nucleus according to the laws of quantum mechanics.

In addition to these three stable particles, atoms also contain certain unstable species which are observed when atomic nuclei are bombarded with various types of particles. Nuclear physicists have discovered numerous subnuclear particles. Notable among these particles is the *positron*. This might be thought of as the direct counterpart of the electron in that it is similar in mass and opposite in charge. The *betatron* (negatron) or beta particle is an electron emitted from the nucleus. Its site of origin is the major factor distinguishing it from the electron. There are some indications that the positron and beta particle are components of the neutron. The *neutrino* may also be part of the neutron. This is an uncharged species of zero mass.

Its presence can be observed in tracking chambers when nuclei are bombarded with energy or other subatomic particles.

1.3 Atomic Orbitals

The early quantitative description of electronic structure came from Niels Bohr in 1913, and involved a planetary picture of the atom. Electrons were considered as particles which revolved around the nucleus in stationary planar orbits and which had definite energies. Bohr's model involved the use of classical Newtonian mechanics, and suitably predicted the electronic spectrum of hydrogen. However, atoms with more than one electron did not yield satisfactory results.

In the 1920s the theory of quantum mechanics for the description of ultrasmall particles was developed, as was the quantum theory of atomic structure. Although a number of prominent scientists were involved in the historical aspects of the theory, De Broglie's work in 1924, which related velocity and momentum to the dual particle-wave nature of the electron, and Schrödinger's development of the wave equation in 1926 are particularly noteworthy. Relevant to the present discussion is the description of electrons, placing them in discrete volume of space about the nucleus. These volumes of space are referred to by the term *atomic orbitals*, and the electrons contained within their boundaries are described by a set of four numbers called *quantum numbers*.

The uncertainty principle of Heisenberg states that it is not possible to fix simultaneously the momentum and the position of an electron.

1.4 Quantum Numbers

The four quantum numbers set the probability limits within which an electron can be found.

(1) *The Principal Quantum Number (n)*. The principal quantum number describes the relative position of the energy levels of the electrons, their distance from the nucleus and the possibility of discontinuities or points of zero probability in the levels. The value this number can assume are integers from $n = 1, 2, 3, \ldots.., \infty$. When $n = 1$the electron is found in the energy level closest to the nucleus. In older literature, the shells referred to as K, L, M, etc., correspond to $n = 1, 2, 3$, etc.

(2) *The Suborbital Quantum Number (l)*. The suborbital quantum number describes the shape of the orbital, or the "electron cloud". This number can assume integer values limited by the corresponding value of n such that $l = 0, 1, 2, \ldots (n - 1)$. Thus, when $n = 1$, the only permissible value is $l = 0$. When $n = 2$, l can take two values, $l = 0$ and $l = 1$.

The value of *l* is generally designated by the letters *s*, *p*, *d*, and *f* for the orbitals as follows:

l	0	1	2	3
orbital	*s*	*p*	*d*	*f*

Representative shapes for *s*, *p*, *and d*, orbitals are shown in Figure 1-1. The *s* orbitals are spherical, with the nucleus at the center of the sphere. The other orbitals have points with zero probability of finding an electron. These are called *nodes*, and nodal plane pass through the nucleus of the atom. The sign on the lobes are of mathematical significance for determining overlap or bonding between orbitals.

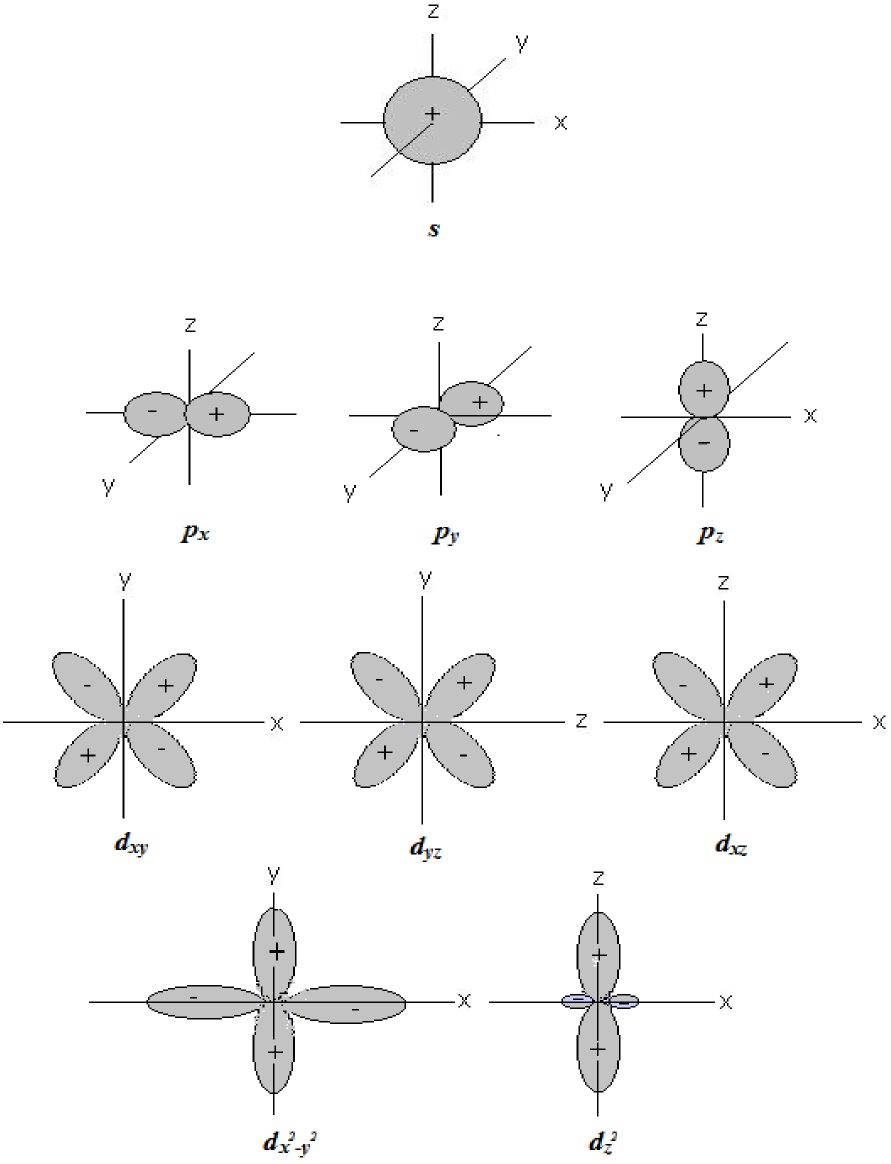


Figure 1-1 Representations of *s*, *p*, and *d* orbitals

(3) *The Magnetic Quantum Number (m_l)*. This number tells which particular orbital the electron occupies within an energy suborbital. Also, it determines the specific orientation in space of the orbital relative to the nucleus. For any value of l, there are ($2l + 1$) allowed values of m_l. The allowed values are restricted by the value of *l* and can be positive or negative integer values according to: m_l = -1, …., 0, …., +1. Obviously, when $l = 0$ the orbital is a (spherical) and can only have one orientation, $m_l = 0$. When $l = 1$, there are three possible orientations of the associated *p* orbital, m_l = -1,0,+1. These correspond to the three *p* orbitals shown in Figure 1-1 along the *x*, *y and z* axes. Likewise, when $l = 2$ there are five possible orientation for the *d* orbital, m_l = -2, -1, 0, +1, +2.

Table 1-1 summarizes the relationship between these quantum numbers. No attempt has been made to assign values of m_l to particular orientations. The choices in Table 1-1 are purely arbitrary.

(4) *The Spin Quantum Number (m_s)*. This number describes the two ways in which an electron may be aligned in a magnetic field, parallel to or opposed to the magnetic field. The electron can be thought of as rotating in either a clockwise or a counterclockwise direction. The spin quantum number, m_s, can have only two values, +½ or -½. The significance of this is that for two electrons to occupy the same orbital they must have opposing spin. If one has m_s = + ½, the other must have m_s = -½.

Table 1-1 Values of Quantum Numbers and Orbital State

Quantum Numbers			***Orbital***
n	***l***	***m_l***	
1	0	0	1*s*
2	0	0	2*s*
	1	+1, 0, -1	$2p_x$, $2p_y$, $2p_z$
3	0	0	3*s*
	1	+1, 0, -1	$3p_x$, $3p_y$, $3p_z$
	2	+2, +1, 0, -1, -2	$3d_{xy}$, $3d_{xz}$, $3d_{yz}$, $3d_{x^2-y^2}$, $3d_{z^2}$
4	0	0	4*s*
	1	+1, 0, -1	$4p_x$, $4p_y$, $4p_z$
	2	+2, +1, 0, -1, -2	$4d_{xy}$, $4d_{xz}$, $4d_{yz}$, $4d_{x^2-y^2}$, $4d_{z^2}$
	3	+3, +2, +1, 0, -1, -2, -3	4*f*

1.5 The Aufbau Process

The electronic structures follow a regular pattern from one atom to the next. Rules can be set down as a guide to determining the structure of any particular atom.

The procedure used has no relationship to physical reality because atoms are not actually formed in a stepwise process of adding electrons to empty orbitals about a nucleus. This process of atom "buildup" is called the *Aufbau process*, and is used only for its convenience.

Before the process can be properly employed, there are some fundamental rules that must be followed. The first of these is known as the *Pauli Exclusion Principle*, which states that: In any atom, no two electrons may be described by the same set of values for the four quantum numbers. In other words, only two electrons may occupy the same atomic orbitals, and these electrons must have opposite spins.

Other rules which apply to the descriptive process are known as *Hund's Rule*. There are two of these which may be paraphrased:

(1) In the ground state of any atom, an electron may inter only the vacant orbital of lowest energy. In other words, lower energy orbitals must be filled before higher energy orbitals.

(2) Electrons must enter degenerate orbitals, (orbitals having the same energy), i.e., $2p_x$, $2p_y$, and $2p_z$, singly and with parallel spins. Stated another way, electrons should remain unpaired in degenerate orbitals as long as possible.

A schematic representation of the order in which orbitals are filled is shown in Figure 1-2. Orbitals in the first and second principal quantum levels (n = 1, 2) are filled in order, as expected. Starting with the third principal quantum level, the *ns* orbital must be filled before electrons can be added to an $(n - 1)d$ orbital. Starting with the third principal quantum level, the $(n - 1)d$ orbitals must be filled before electrons can enter the *np* orbital. In elements where *f* orbitals are being filled, it is probably not practical to state a particular rule. The *f* orbitals are low-lying orbitals, and some of the atoms will have an electron or two in the next highest *d* orbital insetead of in the *f* orbital.

1.6 Ionization

The process of losing one or more electrons by chemical or physical means is known as *ionization*, and the positive ion produced is termed a *cation*. This process is distinctly different from the Aufbau process in that it is based in physical reality, and *should not* be taken as the exact opposite of the process of atom buildup.

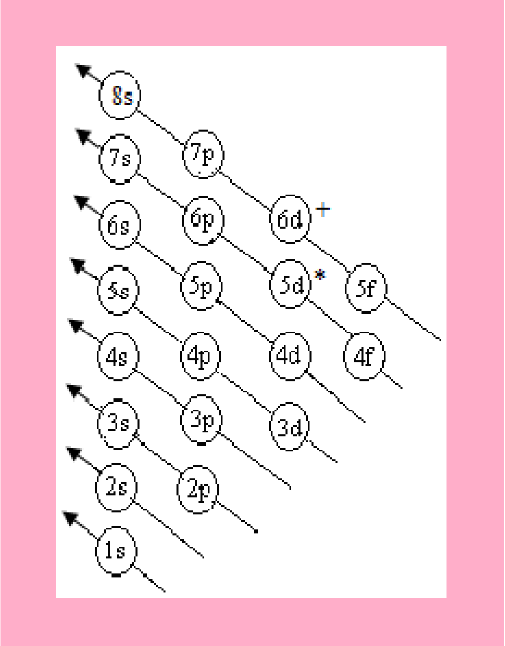


Figure 1-2 Order of filling of orbitals. * A single *5d* is added before the *4f* orbitals can be filled. + One or more *6d* electrons must be add before the *5f* orbitals can be filled.

It is always the most loosely "held" electrons are lost first when an atom ionizes. However, the electronic structure of the ion may not reveal the level from which the electron was lost. This is particularly true for transition elements.

There are several reasons for this. Relative orbital energies are subject to change as electrons are "placed" in them. This means that a high energy orbital in one atom may be of lower energy in a neighboring atom where it might be completely filled. Another phenomenon to be noted is the possibility of rearrangement of the remaining electrons in an ion to a more stable configuration.

Usually atoms in the transition series with incompletely filled *d* orbitals will ionize to leave *d* ions, that is, ions in which the outer "shells" are *d* orbitals which may be contain from one to ten electrons, depending upon the atom in question. For example, cobalt (At. No. 27) would ionize:

$$\begin{array}{ccc} \mathrm{Co}^0 & \xrightarrow{-2e^-} & \mathrm{Co}^{2+} \\ [\mathrm{Ar}]\ 3d^7 4s^2 & & [\mathrm{Ar}]\ 3d^7 \end{array}$$

This does not necessarily mean that both electrons were lost from the 4*s* orbital, even though the structure of the ion would seem to indicate that such was the case. However, one or both electrons could have been removed from the 3*d* orbital followed by rearrangement of all the valence electrons into this orbital.

Atoms in which *s* or *p* orbitals are being filled will usually ionize to form ions with either *inert gas* or *expanded* outer shells. Those which form cations with gas shell structures include elements like sodium (At. No. 11) and magnesium (At. No. 12).

$$\begin{array}{ccc} \mathrm{Na}^0 & \xrightarrow{-1e^-} & \mathrm{Na}^+ \\ [\mathrm{Ne}]\ 3s^1 & & [\mathrm{Ne}] \end{array}$$

$$\begin{array}{ccc} \mathrm{Mg}^0 & \xrightarrow{-2e^-} & \mathrm{Mg}^{2+} \\ [\mathrm{Ne}]\ 3s^2 & & [\mathrm{Ne}] \end{array}$$

Similarly, in periods 2 and 3 of Groups IIIA, IVA, and VA tend to form cations with the preceding inert gas structure. For example, consider aluminum (At. No. 13):

$$\begin{array}{ccc} \mathrm{Al}^0 & \xrightarrow{-3e^-} & \mathrm{Al}^{3+} \\ [\mathrm{Ne}]\ 3s^2 3p^1 & & [\mathrm{Ne}] \end{array}$$

Differences are found in the structures of cations from these same groups when we reach Periods 4, 5, and 6. The cations formed from these atoms tend to have *expanded* or *18-electron* valence shells. Consider the case of gallium (At. No. 31) which is in the same group as aluminum:

$$\begin{array}{ccc} \mathrm{Ga} & \xrightarrow{-3e^-} & \mathrm{Ga}^{3+} \\ [\mathrm{Ar}]\ 3d^{10}4s^2 4p^1 & & [\mathrm{Ne}]3s^2 3p^6 3d^{10} \text{ or } [\mathrm{Ar}]3d^{10} \end{array}$$

The 18 electrons are those contained in 3*s*, 3*p*, and 3*d* orbitals.

Elements in Group VIA and VIIA which have larger numbers of electrons in their *p* orbitals tend to ionize by accepting electrons to form *anions*. These ions have completely filled *p* orbitals so that the valence shell structure is the same as the inert gas in the same period as the neutral element. Example of this can be seen in oxygen (At. No. 8) and bromine (At. No. 35):

$$\begin{array}{ccc} \mathrm{O} & \xrightarrow{+2e^-} & \mathrm{O}^{2-} \\ [\mathrm{He}]2s^2 2p^4 & & [\mathrm{He}]\ 2s^2 2p^6 \text{ or } [\mathrm{Ne}] \end{array}$$

$$\begin{array}{ccc} \mathrm{Br} & \xrightarrow{+1e^-} & \mathrm{Br}^- \\ [\mathrm{Ar}]\ 3d^{10}4s^2 4p^5 & & [\mathrm{Ar}]3d^{10}\ 4s^2 4p^6 \text{ or } [\mathrm{Kr}] \end{array}$$

Other elements which have incompletely filled *f* orbitals (lanthanides and actinides) tend to form cations with electrons remaining in the *f* orbitals.

1.7 Periodic Law

A table of elements in various groups and periods was suggested independently around 1868-1870 by the Russian chemist Mendeleeff and the German chemist Lothar Meyer. They had recorded data that indicated a periodic relationship based on the atomic weights of the elements.

Today it is known that the properties of elements are based primarily upon the outer or valence shell electronic structure. Thus, it can be seen that the periodic table, shown in Table 1-2, listed elements in groups having the same valence orbital structure. However, the table was formulated before much was known about electronic structures. A general statement of *periodic law* is that "the properties of elements are a periodic function of their atomic numbers". Because of the relationship between atomic numbers and the number of electrons, this is equivalent to the original statement concerning valence orbital structures.

There is a large increase in atomic radii (or principal quantum number) as one descends in a particular group. For example, in Group IA, electrons are "lost" (or the elements are oxidized) from each of these elements under certain conditions. The ease with which these elements undergo oxidation increases as the group is descended. In the larger elements, the outer electrons are farther away from the nucleus, and the underlying electrons provide a better shield for these electrons from nuclear influences. These factors produce a gradation in the observed ease of oxidation.

This property may be viewed in another way. An examination of the property of *electronegativity* ,The relative ability of an atom to draw electrons in a bond toward itself, will show that this property increases from left to right across any period and from bottom to top in any group (except VIIIA). The most electronegative element is fluorine, and the last electronegative element is francium. Table 1-3 shows the Pauling electronegativity scale for many of the elements. The opposite concept is that of *electropositivity* which varies in directions opposite to those of electronegativity.

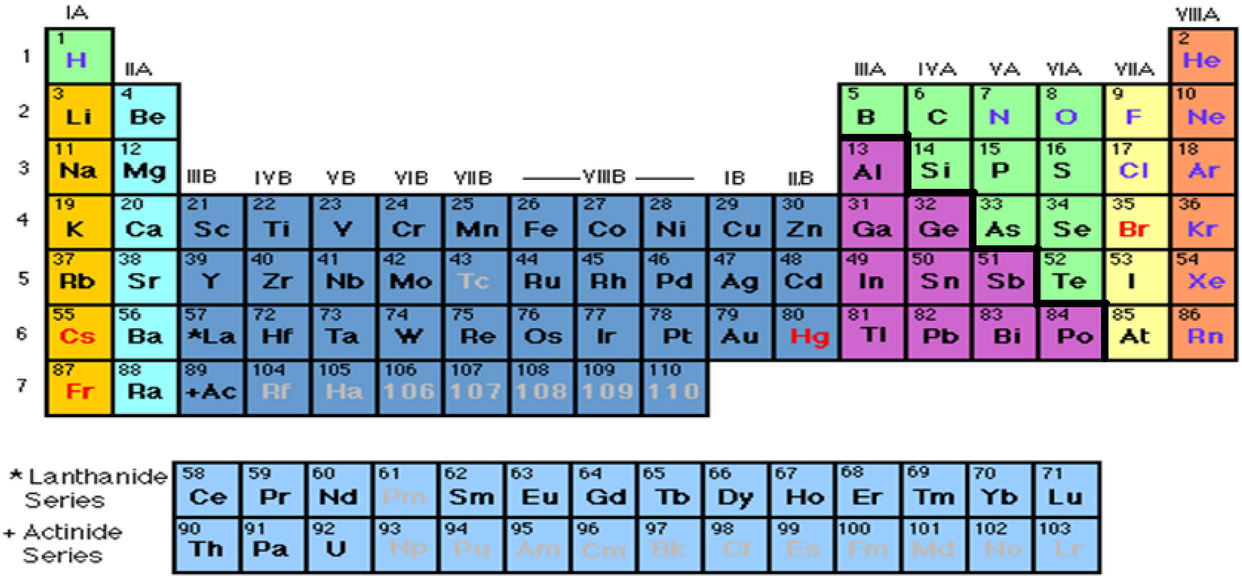
Metallic properties of elements generally decrease in a given period as the atomic number increases. However, this same property seems to increase with increasing atomic number within any particular group.

The heavy line (Table 1-2) passing between elements from boron to polonium represents an amphoteric area. Elements on both sides show both metallic and nonmetallic character.

1.8 Electronic Structure of Molecules

Most of the electrons are in atomic orbitals surrounding the individual nuclei, and the remainder (valence electrons) are in more generalized multinuclear *molecular orbitals*.

Table 1-2 Periodic Table of the Elements



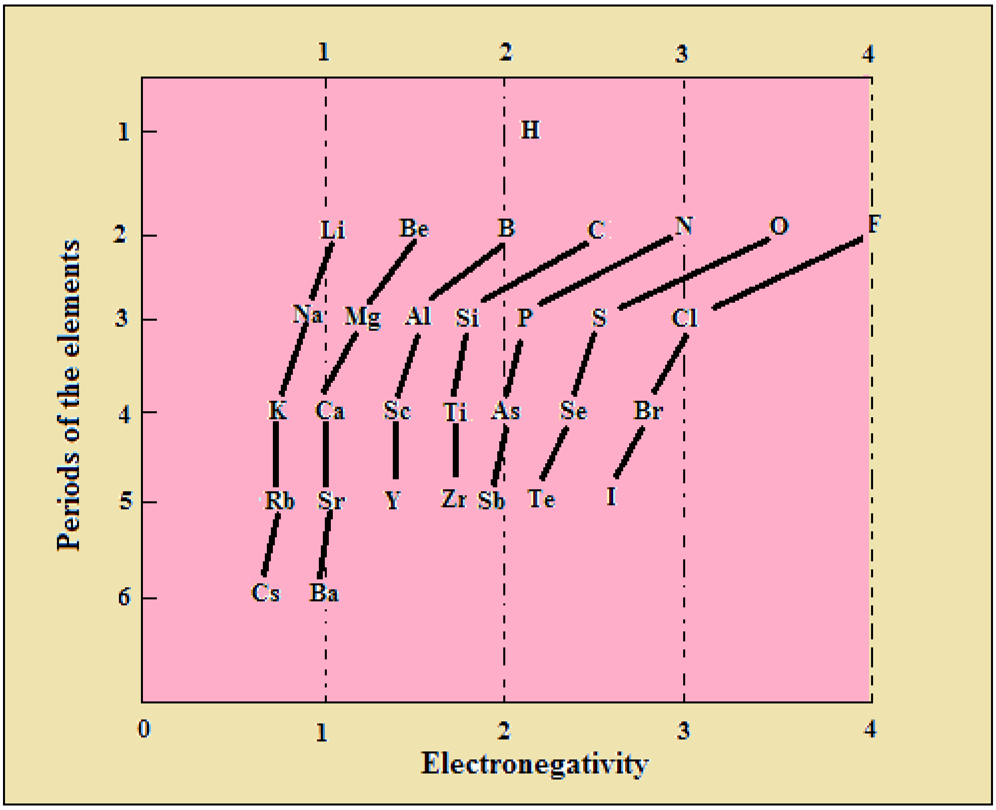
	IA	IIA	IIIB	IVB	VB	VIB	VIIB	VIIIB	VIIIB	VIIIB	IB	IIB	IIIA	IVA	VA	VIA	VIIA	VIIIA
1	1 H																	2 He
2	3 Li	4 Be											5 B	6 C	7 N	8 O	9 F	10 Ne
3	11 Na	12 Mg											13 Al	14 Si	15 P	16 S	17 Cl	18 Ar
4	19 K	20 Ca	21 Sc	22 Ti	23 V	24 Cr	25 Mn	26 Fe	27 Co	28 Ni	29 Cu	30 Zn	31 Ga	32 Ge	33 As	34 Se	35 Br	36 Kr
5	37 Rb	38 Sr	39 Y	40 Zr	41 Nb	42 Mo	43 Tc	44 Ru	45 Rh	46 Pd	47 Ag	48 Cd	49 In	50 Sn	51 Sb	52 Te	53 I	54 Xe
6	55 Cs	56 Ba	57 *La	72 Hf	73 Ta	74 W	75 Re	76 Os	77 Ir	78 Pt	79 Au	80 Hg	81 Tl	82 Pb	83 Bi	84 Po	85 At	86 Rn
7	87 Fr	88 Ra	89 +Ac	104 Rf	105 Ha	106 106	107 107	108 108	109 109	110 110								

* Lanthanide Series	58 Ce	59 Pr	60 Nd	61 Pm	62 Sm	63 Eu	64 Gd	65 Tb	66 Dy	67 Ho	68 Er	69 Tm	70 Yb	71 Lu
+ Actinide Series	90 Th	91 Pa	92 U	93 Np	94 Pu	95 Am	96 Cm	97 Bk	98 Cf	99 Es	100 Fm	101 Md	102 No	103 Lr

Legend - click to find out more...

H - gas	Li - solid	Br - liquid	Tc - synthetic
🟩 Non-Metals	🟦 Transition Metals	🟦 Rare Earth Metals	🟨 Halogens
🟧 Alkali Metals	🟦 Alkali Earth Metals	🟪 Other Metals	🟧 Inert Elements

Table 1-3 Electronegativity of the Elements



When atoms are incorporated into molecules, there are three major forces that are involved in the overall combination. *Coulombic attraction* occurs between the negatively charged electrons in the valence orbitals on one atom and the positive charged nucleus of another atom. As the atoms approach each other, there are two repulsive forces that tend to "push" the atoms away:

(1) *electron-electron repulsion* between valence electrons on neighbor atoms and (2) *nuclear repulsion* between neighboring nuclei. A stable molecule is possible when the proper balance between these forces exists, and the energy of the resulting system of atoms is less than the sum of the energies of the "isolated" atoms. The equilibrium distances that are evident between atoms in molecules (bond distance) are established largely by the interaction of these forces.

However, simply having an overriding attractive force between two atoms does not assure the formation of a bond between them. Depending upon the type of bonding interaction which is likely to occur (eg., ionic, covalent, etc.), there are other criteria based on the differences in electronegativity, availability of electrons, and the nature of the valence state atomic orbitals. Bond formation is also affected by the number of electrons in the valence shell orbitals, and by their orbital distribution.

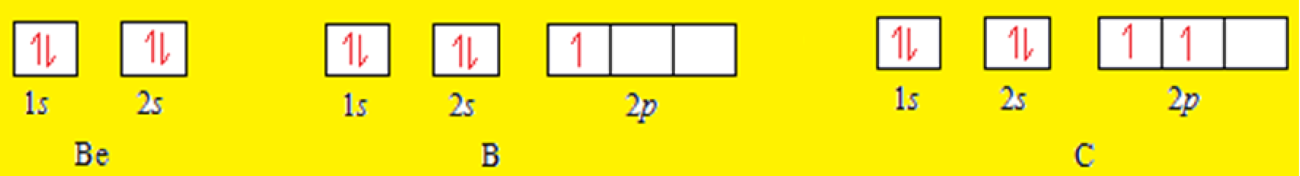
The bonding types that are possible vary with the amount of "sharing" of electrons between the two atoms participating in the bond. *Covalent bonding* ranges from an equal sharing of a pair of electrons in homonuclear diatomic molecules (eg., H_2, Cl_2, I_2, etc.) to a polar or unequal sharing of the electron pair in heteronuclear diatomic molecules (eg., HCl). *Ionic bonding* is more of an electrostatic interaction resulting from the transfer of an electron from an electropositive atom to an electronegative atom (eg., Na^+Cl^-).

1.9 Orbital Hybridization

There are many bonding situations in chemistry which cannot be explained in terms of the ground state valence shell orbitals available in most atoms. In this section, we will briefly discuss the concept of *hybrid orbitals* which is necessary to explain covalent bonding in molecules properly.

Covalent bonding is presumed to occur through the overlapping of atomic orbitals between two atoms. In the usual case, overlapping each orbital will contribute one electron to the electron pair in the resulting molecular orbital or bond. Therefore, bonds formed in this manner must involve atomic orbitals which are singly occupied (contain one unpaired electron).

For a majority of atoms the number of singly occupied orbitals does not corresponding to their covalent bonding capability (or valence) in molecules. For example, the electronic structure of the second row elements (Table 1-2), beryllium, boron, and carbon, illustrate discrepancies common to their groups in the periodic table. From the configurations shown below, Be would be expected to form no covalent bonds, B appears to be monovalent, and C should bond with a maximum of two other elements. In reality, these atoms and the other members of their groups are di, tri, and tetravalent, respectively.



The presumed mechanism allowing these and other elements to increase covalent bonding capacity involves *promotion* to the *valence state*, a situation requiring energy. This is a nonobservable hypothetical state of the atom which is justifiable on certain theoretical ground and on the basis of the stability of the resulting molecules. Figure 1-3 a shows a portion of an energy diagram for the promotion of gaseous beryllium atoms ($Be_{(g)}$) to the divalent valence state. This state is usually viewed as hybrid orbital state and is labeled *sp* in this particular case. Similar diagrams are shown for boron (Figure 1-3 b) and carbon (Figure 1-3 c) indicating that their tri- and tetravalent states also involve hybrid orbitals designated as sp^2 and sp^3, respectively. The tetravalent state for carbon is limited to saturated molecules.

The process of orbital hybridization may be envisioned as a "mixing" of the atomic orbitals to provide a new set of degenerate (energetically equivalent) orbitals having different spatial orientation and directional properties than the original atomic orbitals. The number of hybrid orbitals produced is equal to the number of atomic orbitals involved in the hybridization, and the electrons contained in the original orbitals occupy the hybrids according to Hand's rules.

***sp* hybridization.** This type of hybridization results from combining of an *s* orbital with a *p* orbital having the same principal quantum number. The two *sp* orbitals are equivalent (degenerate), symmetrical about the bonding axis, and oriented 180° away from each other. The largest proportion of the electron density is oriented in a single direction, thus improving overlap with orbitals from other atoms and increasing the strength of the resulting bond. This pair of hybrids is often referred to by the term *digonal* to describe the fact that they are two opposing orbitals.

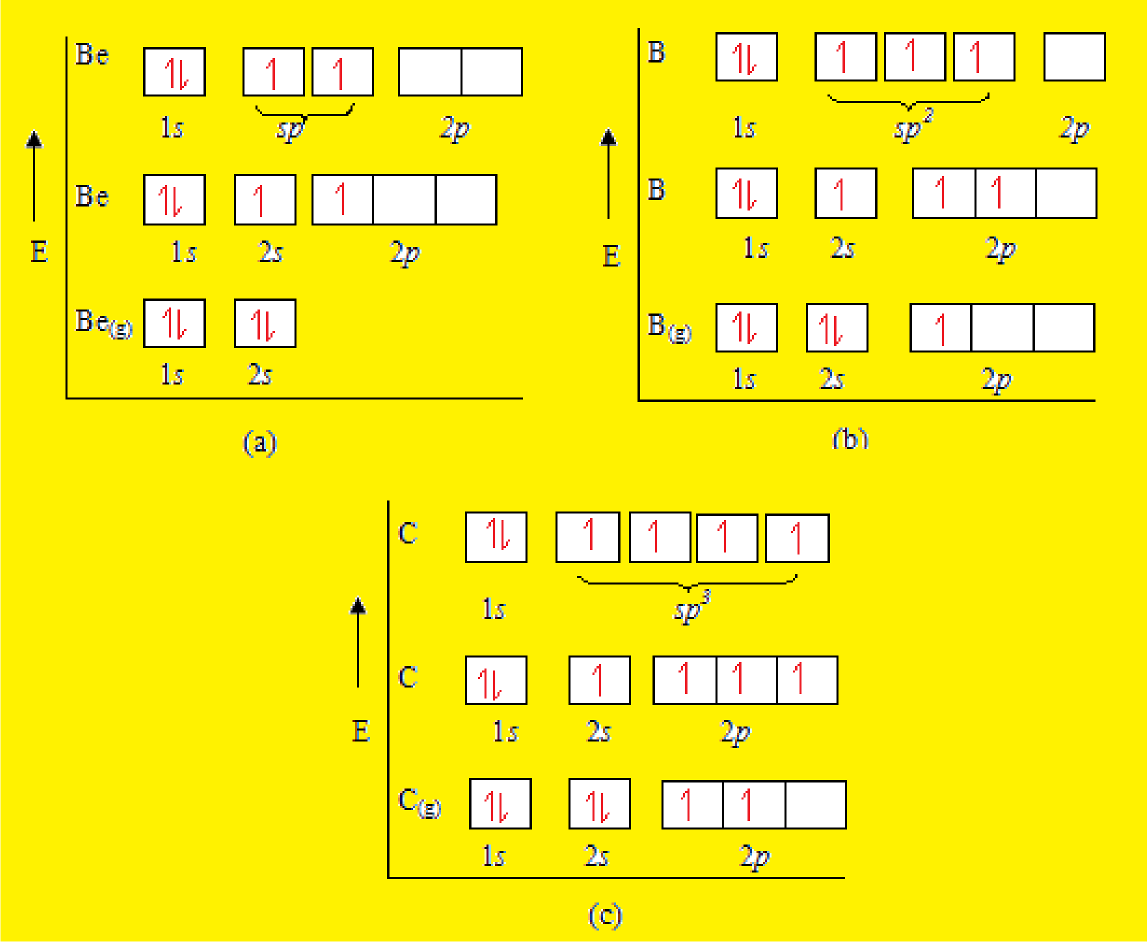


Figure 1-3 Partial energy diagrams showing the promotion of atoms in their gas phase to their valence state configurations. The distances between states are not meant to indicate relative energy barriers.

This *sp* hybridization is evident in the covalent compounds of Group II. Linear covalent molecules of gaseous halides of Be, Mg, and Ca, such as $MgCl_2$, and the solid divalent compounds of Cd and Hg are indicative that the bonds are formed through *sp* hybrids on the Group II element. The energy required to promote the element to its diagonal valence state (Figure 1-3a) is released when the bonds are formed, resulting in stable molecules.

sp^2 **hybridization.** In a manner similar to that described above, elements of Group III may be promoted to a valence state in which singly occupied *s* and two *p* orbitals combine to form three equivalent *sp^2* hybrid orbitals (Figure 1-3b).

The three hybrids are located in the same plane, and are oriented toward the points of an equilateral triangle, 120° apart.

The monomeric covalent compounds of boron, aluminum, and other Group III elements, as well as unsaturated "ethylenic" compounds of carbon, shown *sp^2* hybridization. The empty *p* orbital remaining in the valence state (Figure 1-3b) of the

Group III elements leaves their compounds electron-deficient. These molecules, therefore, react as Lewis acids.

***sp^3* hybridization.** The final extension of hybridization between *s* and *p* orbitals is involved in the tetravalent state of Group IVA elements (Figure 1-3c). When one *s* and three *p* orbitals combine, the result is a set of four equivalent *sp^3* hybrid orbitals pointing to the four corners of a tetrahedron. Therefore, the geometry of a molecule formed through bonding with these orbitals is tetrahedral, and the bond angles are approximately 109°.

Hybridization schemes involving *d* orbitals are involved in transition metal complexes. Two of the more important hybrids in this group include a set of six orbitals with octahedral geometry termed *d^2sp^3* orbitals, and a set of four orbitals with square planar geometry termed *dsp^2* orbitals.

Bond strengths tend to increase as the amount of *s* character in a hybrid decreases. This should be understandable since the *p* character (or *d* character) would alternately increase, thus providing better directional properties to the hybrid.

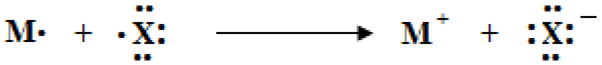
In many molecules, the bond angles will vary from that predicted because repulsive forces will cause changes in the *s* and *p* character leading to some contribution intermediate between those discussed above. Table 1-4 illustrates how the angle between orbitals changes with the various *s* and *p* orbitals contributions. It should be noted that as the *p* character increases the angle becomes smaller until it reaches 90° for two unhybridized *p* orbitals.

Table 1-4 Orbital Contribution and Hybrid Geometry

Orbital	***Geometry***	***Contribution***		***Angle***
		s	***p***	
p^2	(unhybridized *p* orbital)	0	1	90°
sp^3	tetrahedral	¼	¾	109°
Sp^2	trigonal	⅓	⅔	120°
sp	digonal	½	½	180°

1.10 Types of Bonding Interactions

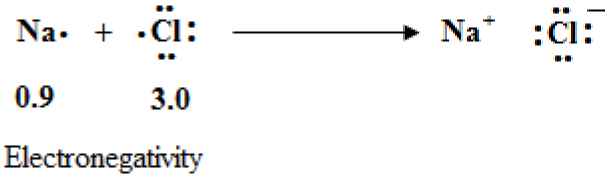
(1) Ionic Bonding. It is the electrostatic force that exists between two chemical entities of opposite charge. The species bearing the positive charge is known as the *cation*, and the negative species is the *anion*. When the two reacting entities are sufficiently far apart in their respective electronegativities (or far apart in the periodic table), the least electronegative entity loses one or more of its valence electrons to the more electronegative entity (or entities) to produce the respective cation and anion.



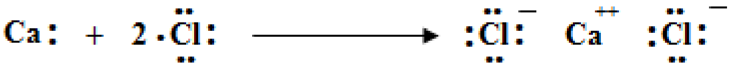
In most cases, when the entities are simple atoms, the ionic species take on inert gas shell electronic structures. Since the valence shell of all inert gases except helium contain eight electrons, this kind of structure is associated with stability, and has led to the octet theory of chemical bonding.

Ionic bonding is usually found in associations between metallic, strongly electropositive elements (Group IA and IIA) and nonmetallic, strongly electronegative elements (Group VIIIA). It is also found in most salts where the anion is complex, such as SO_4^{2-}, PO_4^{3-}, NO_3^-, and the like. Ionic interactions are also present, in many cases, when polar compounds are dissolved in polar solvents.

In sodium chloride, sodium has one electron in its valence shell and an electronegativity on the Puling scale of 0.9 (Table 1-3), while chlorine has seven electrons in its valence shell and Pauling electronegativity of 3.0. The difference in electronegativity is sufficient (more than 1.6) to allow the transfer of one electron from sodium to chlorine, thereby forming two oppositely charged ions, each having the inert gas configuration of eight electrons in their valence shells. The electrostatic attraction between the oppositely charged species is the force holding the ions together.



Similarly, calcium chloride is formed by calcium transferring its two electrons to each of two chlorine atoms.



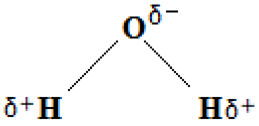
Generally speaking, metals lose electrons to form cations, and nonmetals attract electrons to form anions. Metals that have one electron tend to ionize more readily than those having two or more. The ability to lose electrons increases as we descend in a particular group. This is due to the increased shielding effect of the valence electrons.

(2) Covalent Bonding. Unlike ionic bonding, covalent bonding is the attractive force that exists between two chemical entities due to their "sharing" a pair of electrons. The bonding pair of electrons between two atoms is presumed to be in a *molecular orbital* embracing both nuclei. This type of bonding prevails when the electronegativity difference between the atoms is not sufficient to produce ions. Although quite common in inorganic compounds, covalent bonding is most prevalent in organic chemistry.

The most idealistic covalent bonds occur in homonuclear diatomic molecules such as H_2, Cl_2, N_2, …etc, and also larger systems of atoms like P_4, S_8. In all these situations, the electron pair is shared equally by the two bonded atoms.

$$\mathbf{H}\cdot + \cdot\mathbf{H} \longrightarrow \mathbf{H{:}H} \quad \text{or} \quad \mathbf{H{-}H}$$

Most covalent molecules, however, cannot be presented by an equal distribution of the bonding electrons. The electron density tends to be shifted towards the more electronegative member of the bond. The bond is still covalent rather than ionic, but the molecule is definitely polar. Water is a good example of a primarily covalent molecule which is strongly polar, with the more electronegative oxygen taking the larger share of the bonding electron density. On the structure below, this polarity is indicated by noting partial charges.

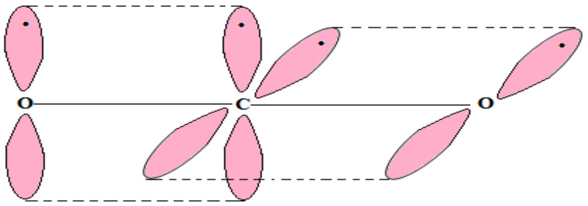


For *sigma* bonds (σ bonds), the molecular orbitals (or electron distributions) are symmetrical about the bond axes. Attention is now directed toward double and triple covalent bonds. These are bonds in which two and three pairs of electrons are being shared, respectively, between two atoms. Only one pair of electrons can occupy a single molecular orbital; therefore, atoms bonded in this fashion need to overlap other valence orbitals to form two and three bonding molecular orbitals, respectively. Further, only one of the bonds can be a σ bond. The other pairs of electrons will occupy molecular orbitals which are distributed on both sides of and perpendicular to a plane (or planes) passing through the bond axis. This type of covalent bond is termed a *pi* bond (π bond).

Carbon dioxide, CO_2, serves as an illustration of a double covalently bonded molecule. Each C–O bond consists of two pairs of electrons, one in the σ bond and one in the π bond.

$$:\ddot{O}::C::\ddot{O}:$$

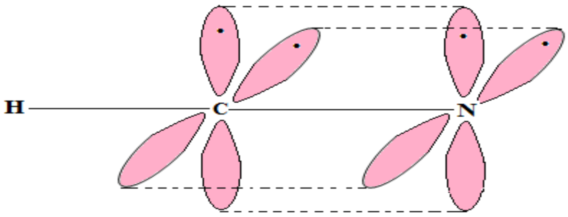
The σ bonds are formed by overlapping *sp* orbitals on the carbon with singly occupied *p* orbitals on the oxygens. This leaves two singly occupied *p* orbitals on the carbon and one such orbital on each of the oxygens. The oxygens can be rotated in turn to bring their *p* orbitals parallel to one of the carbon *p* orbitals. Overlapping of parallel *p* orbitals on carbon and oxygen leads to two volumes of electron density separated by a nodal plane at the bond axis. The carbon thus forms a π bond with each oxygen. The following structure shows the overlapping involved in the π bond formation. The σ bonding orbitals and the lone (nonbonded) pairs of electrons on the oxygens are not shown.



Similarly, hydrogen cyanide, HCN, will serve as an illustration of a triple bonded molecule where two π bonds formed between two atoms.

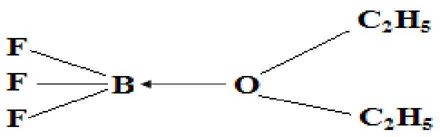
H:C⋮⋮N

The carbon is *sp*-hybridized as in CO_2, but now both p orbitals overlap with two p orbitals on the nitrogen.



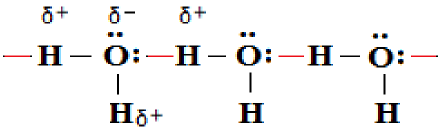
(3) Coordinate Covalent Bonding. This type of bonding is still a covalent interaction but, in this case, both electrons in the bond arise from a single orbital on one of the atoms forming the bond. This type of bonding is found most frequently between complexes. The entity providing the pair of electrons is generally referred to as *donor* species. The *acceptor* species is electron-deficient and has an empty orbital which can overlap with the orbital from the donor.

The representation of the bond, in order to distinguish it from covalent bonds, is an arrow drawn so that it points from the donor atom to the acceptor atom. An example of this type of interaction is the donor-acceptor complex boron-trifluoride etherate.



This type of bond formation also occurs in acid-base chemistry, and is frequently the type of bonding one finds between sulfur and oxygen. In particular, it is found in the oxyacids, e.g., sulfuric, nitric, phosphoric, and chloric.

(4) Hydrogen Bonding. It is a secondary interaction which may be described as an attractive force that occurs between certain types of molecules. When hydrogen is covalently bonded to the more electronegative elements, e.g., O, N, F, Cl, etc., it becomes somewhat electron-deficient taking a partial positive charge. Thus, the hydrogen atom has an increased affinity for the nonbonded electrons on other electronegative atoms in neighboring molecules. This attraction is not usually sufficient to cause the original covalent bond to break.



Hydrogen bonding is responsible for many of the physical and chemical properties of water and similar molecules. For example, the relatively high boiling point of water is due to the strong association between the molecules through hydrogen bonding. This type of association can also occur between unlike molecules.

Hydrogen bonding is also important in interactions between complex molecules, and in the secondary structure of proteins. It is also a secondary binding force in drug-receptor interactions.

(5) Van der Waals (London) Forces. These are very weak electrical forces sometimes referred to as induced dipole-induced dipole interactions. The nature of the interaction can be envisioned as the electron in one atomic or molecular species inducing a repulsive distortion in the electron cloud of a neighboring species. The result is a weak induced dipole. The positive end of the dipole, which is essentially produced by protons in the nuclei, then has an attraction for the oppositely charged electrons in the same or in a neighboring species. Obviously, forces of this nature are active over a very short range, and their strength is dependent upon the polarizabilities of the interacting entities. Van der Waals forces are virtually the only attractive forces between nonpolar molecules. The associations between aromatic hydrocarbon molecules, such as benzene, are due to van der Waals forces. Small disturbances in the electrical balance are present in these molecules because of the motion of the π

electrons. The electron distributions do not always coincide with the center of density of protons in the nuclei, thereby producing weak dipoles. These forces also function in the liquefaction and solidification of the inert gases, a process which requires extremely cold temperatures.

(6) Other Electrostatic Interactions. There are several other interactions between atoms, ions, and molecules. All of these are, of course, attractive forces between oppositely charged species. Ion-dipole and dipole-dipole interactions take place between polar molecules and ions or other polar species, respectively. Ions and polar molecules are also capable of inducing dipole in normally nonpolar species to set up other type of interactions. These interactions are dependent upon a phenomenon known as polarization.

1.11 Polarization

With the exception of homonuclear diatomic molecules and possibly the ionic interaction between Group IA metals and the halogens, pure ionic or covalent bonds are not found in very many inorganic compounds. The common situation is for bonds or molecules to exhibit varying degrees of ionic or covalent character described in terms of *polarity*, which are dependent upon certain factors.

(1) *Polarizability*. The electrons surrounding atomic nuclei in molecules and ions can be influenced by attractive (or repulsive) forces, causing them to shift from a normal distribution to one which is distorted or "lopsided". The more polarizable elements are those which have large atomic radii in which the outer electrons are shielded from the influence of the positively charged nucleus. In general, this property increases from top to bottom in a group of elements. Among ions as might be expected, anions are more polarizable than cations.

(2) *Polarizing Power*. The influence that an atom, ion, or molecule has to cause polarization in another species is determined by its polarizing power. This is generally viewed as the strength of the electric field; for instance, a small cation can produce extreme polarization in an anion with a large ionic radius or in an easily polarizable molecule. In a given period of the Periodic Table, electron attracting power increases from left to right. This is primarily due to an increase in the number of protons without a significant increase in the atomic radii. This same property decreases from top to bottom for a given group of elements.

(3) *Dipole Moment.* The extent of polarization or polarity in a bond or molecule is frequently expressed as the dipole moment. In polar molecules, one portion is relatively positive and the other relatively negative due to the displacement of electrons in relation to the atomic centers. In diatomic molecules, this situation occurs because of the difference in electronegativities of the two atoms. Such a molecule has a positive pole and a negative pole separated by some distance, *d*, and is said to have a dipole moment.

Molecules which exhibit polarization by themselves are termed *permanent dipoles*. The term *induced dipole*, used previously indicates that the polarity in the molecule was created by the polarizing power of surrounding atoms, ions, or molecules.

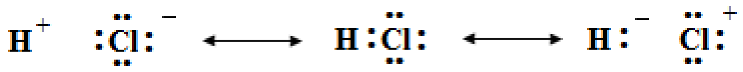
Dipole moments can be experimentally determined and reflected in the measurable quantity known as the *dielectric constant*.

Polarization occurs to a greater extent in anions because of their relatively large size and minimized nuclear attraction. Cations are polarized to a much smaller extent. As ion polarization increases, the electrons begin to be shared to a greater degree, thus increasing the covalent character of the bond.

Each compound would be expected to be affected differently (for instance, different degree of ionization). The larger an ion and the less compact its electronic structure, the more easily the electrons are polarized. Similarly, the smaller ions (fewer electrons) will be less easily distorted. A main point is that small ions have the positive charge from the nucleus nearer the "surface", thus exerting a greater polarizing power. Table 1-5 illustrates the radii of ions.

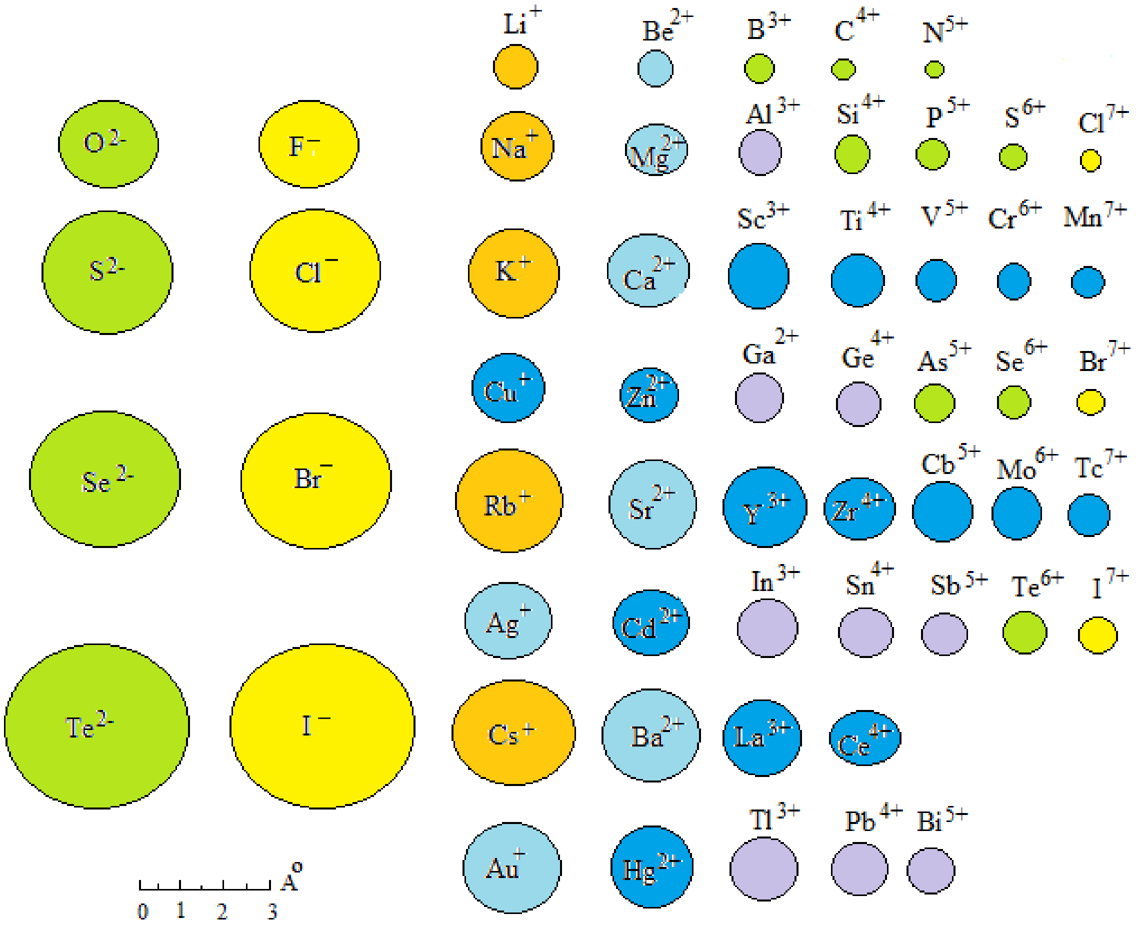
1.12 Resonance

In the above discussions, the dynamic motion of electrons has been mentioned frequently. The impact of this motion is illustrated by the fact that molecules can be represented on paper by various electronic "pictures" known as *canonical structures* or *forms*. Each of these structures makes a certain contribution to the actual structure of the molecule, and the actual structure is said to be a *resonance hybrid* of its canonical forms. The term *resonance* indicates a tendency for the electrons to be somewhat *delocalized*, a further reference to their dynamic properties. Simple covalent molecules tend to be more localized than more complex systems. For example, consider the diatomic molecule HCl as represented by the following canonical structures:



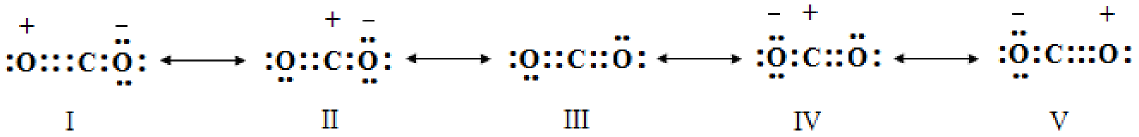
I II III

Table 1-5 The Crystal Radii of Ions



The double-tipped arrows indicate that these structures are in resonance. This is not meant to show an equilibrium situation; in fact, equilibrium between these structures does *not* exist. Structure I and II represent familiar bonding extremes. Structure I is ionic with the more electronegative chlorine taking the bonding pair of electrons. Structure II is the covalent situation with bonding pair being shared between the two atoms; it should be recalled that the greater electronegativity of the chlorine makes structure II a *polar* covalent form. Structure III is not likely to contribute very much to the over-all structure of HCl because of the relatively low electron affinity of the hydrogen for the bonding pair of electrons. For all practical purposes, the structure of HCl can be said to be a resonance hybrid of structures I and II. The structures are not weighted equally, but each makes some mathematical contribution to a valence bond or quantum mechanical description of the molecule.

Unsaturated compounds, due to the greater mobility of the electrons, yield more possibilities for canonical forms. Using carbon dioxide (CO_2) as an example, the following structures can be drawn:



Once again, carbon dioxide is *not* in equilibrium between these structures. Structure III is the one usually drawn for CO_2, but the actual structure is a resonance hybrid in which each of the others makes a weighted contribution to the overall electronic picture. Note that structures I and V and structures II and IV are equivalent on the basis of symmetry.

1.13 Coordination Compounds and Complexation

This is the area of metallic element compounds which we call *coordination chemistry;* it is largely transition metal chemistry, but also involves metals beyond the second period outside the transition series to some extent. The metallic cation appears to be able to bond with additional anions or molecules after the normal valence requirements have been satisfied. The additional bonding species are usually termed *ligands*, and appear to bond directly to the metal cation in accordance with *maximum coordination number*. It is the maximum number of ligands that can be accommodated by a metal ion, and is a property of the metal and its charge. The ligands occupy space about the metal known as the *coordination sphere*, and, although they may be displaced by other ligands, they do not normally dissociate (ionize) from the metal. Therefore, the metal and its associated ligands constitute what is known as a *complex ion*, if charged; the neutral complex or the complex ion with its counter ions is known as a *coordination compound*. Some complexes are stable in crystalline form and decompose in solution, while others are stable only in solution.

The most widely accepted theory of the formation of complex ions was proposed by Alfred Werner, An example of the formation of some coordination compounds can be seen with $FeCl_3$, a simple compound of trivalent iron (III) and chlorine. When this compound is dissolved in water and/or hydrochloric acid the following coordination compounds are formed:

$$FeCl_3 + 3H_2O \longrightarrow [Fe(H_2O)_3Cl_3]$$

$$FeCl_3 + HCl + 2H_2O \longrightarrow H[Fe(H_2O)_2Cl_4]$$
$$= H^+ + [Fe(H_2O)_2Cl_4]^-$$

$$FeCl_3 + NaOH + 2H_2O \longrightarrow Na[Fe(H_2O)_2(OH)Cl_3]$$
$$= Na^+ + [Fe(H_2O)_2(OH)Cl_3]^-$$

The brackets enclose the metal and its coordinated groups or ligands, and the quantities on the right-hand side of the equals sign indicates how the compound would dissociate. The main points of Werner's theory are:

(1) Two types of valence are observed for the metals. One is the primary (ionizable) or principal valence, and the other is the secondary (nonionizable) valence.

(2) Each metal exhibits a specific, maximum number of secondary valences called the coordination number.

(3) The primary valences of metal are filled by anions, but the secondary valence (in the coordination sphere) may be satisfied by anions and/or neutral molecules known as ligands. Cationic groups sometimes (but rarely) are present.

4- The ligands are arranged around the metallic ion in certain characteristic geometries. Those compounds having coordination number 2 are either linear or angular, 3 are trigonal-coplaner or trigonal-pyramidal, 4 are usually tetrahedral or square-planer, 5 are square-pyramidal or trigonal-bipyramidal, and 6 are ligands arranged octahedrally.

The most stable complexes are formed by cations of the transition series, and particularly the transition element in Group VIIIB. The groups immediately preceding and following in Groups VIB, VIIB, IB, IIB, and IIIB also form stable coordination compounds. The major criteria for maximal stability of the metal in a complex involve a high positive charge, a small cationic radius, and unoccupied *d* orbitals. As these criteria become more difficult to meet, the stability of the complexes diminishes. Table 1-6 shows the coordination numbers for some of the more common complex-forming metal ions.

Table 1-6 Metallic Ion Coordination Numbers

Metal	***Coordination number***	***Metal***	***Coordination number***	***Metal***	***Coordination number***
Cr^{+++}	6	Ni^{++}	4	Ag^{+}	2
Mo^{+++}	8	Pd^{++++}	6	Au^{+}	2
Mn^{+++}	6	Pd^{++}	4	Au^{+++}	6
Fe^{++}	6	Pt^{++++}	6	Zn^{++}	4
Fe^{+++}	6	Pt^{++}	4	Cd^{++}	4
Co^{+++}	6	Cu^{+}	2	Hg^{++}	4
Ni^{+++}	6	Cu^{++}	4	Al^{+++}	6

1.14 Properties of Ligands

The ligand species in complexes are generally anions or neutral molecules. Neutral atoms are not usually found as coordinating agents. The one feature that all ligands have in common is the possession of at least one nonbonded pair of electrons which is used to form a coordinate covalent bond with the metal ion. It should be pointed out that although a large body of evidence supports coordinate covalent bonding as the major bonding type in complexes, it is not universally accepted, and some complexes do show other types of ligand bonding (e.g., ionic).

The order of stability of a ligand in a complex follows the order of basicity of the ligand. This actually refers to the strength of the electrostatic field emanating from an anion or, in the case of a neutral molecule, the "availability" of the lone pair of electrons. The basicity may be more correctly related to the Lewis base concept rather than to that of Brönsted. Table 1-7 lists some of the more important neutral and anionic ligands in the order of their stability in complexes.

Table 1-7 Complexing Ligands

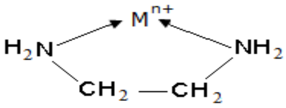
Neutral ligands				*Anionic ligands*	
decreasing stability ↓	NH_3	H_2O	R_3AS	CN^-	**decreasing stability** ↓
	NH_2R	HOR	R_3P	$S_2O_3^{2-}$	
	NHR_2	ROR	R_2S	F^-	
	NR_3	RCOR	PX_3	OH^-	
		RCHO		Cl^-	
				Br^-	
				I^-	

R = Alkyl or aryl radical; X = halogen

For the most part, the ligand in Table 1-7 effectively have one nonbonding pair of electrons to donate to the metal ion; they are termed *unidentate*, indicating that they each form *one* coordinate covalent bond in a complex. Other ligand species may then be classified according to the number of positions on the molecule capable of coordinating with a metal.

Bidentate ligands have two positions arranged so that they both can act simultaneously as donor sites in a complex. Some of these important to pharmacy and medicine are ethylenediamine (en), glycinate (gly), the dianion of oxalic acid (oxalate), and the anion of 8-hydroxyquinoline (oxinate) (Table 1-8). Other polydentate ligands are similarly classified as *tridentate, tetradentate, pentadetate,* and *hexadentate*. Representative examples of some of these are shown in Table 1-8.

When polydentate ligands complex a metal ion a ring structure is produced composed of the metal and the ligand molecule. These ring structures have special significance, and are termed *chelates* from the Greek word *chele*, meaning claw. The structure below shows a simple chelate between a metal ion and ethylenediamine.



In general, the more stable chelates are those where the total number of atoms in the ring including the metal are *five*, *six*, or *seven*. Four- and eight-membered rings are usually unstable.

The process of *chelation* is employed in pharmaceuticals and in drug therapy. The polydentate ligands used for chelate formation are generally referred to as *chelating agents*. The term *sequestering agent* is usually applied when a polydentate ligand is used to improve the solubility and/or stabilize a metal ion by chelation (*sequestration*).

1.15 Bonding in complexes

There are several approaches to a discussion of bonding in metal complexes, none of which is entirely satisfactory in explaining all the properties of these compounds. Working on a coordinate covalent bond concept, Pauling developed a *valence bond theory* which is a useful qualitative picture of bonding in coordination compounds. Around the same time Bethe and Van Vleck independently introduced an electrostatic approach called *crystal field theory*. This theory completely neglected covalent bond formation, but offers more quantitative information. Later, Van Vleck introduced two more comprehensive approaches. One was modification of crystal field theory which includes covalent bond formation through orbital overlap and is called *ligand field theory*. The other is *molecular orbital theory* which probably offers the most complete qualitative and quantitative picture of bonding, but has many computational problems.

Since the primary goal is obtaining a qualitative picture of bonding in complexes, the valence bond approach will be used, recognizing its rather severe limitations in explaining chemical events.

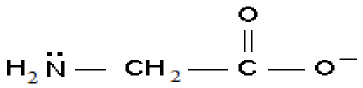
With the above cautions in mind, a valence bond discussion may begin by first reviewing the orientation of *d* orbitals in space. Reference to Figure 1-1 shows that only two of the *d* orbitals are oriented along the axes of a cartesian coordinate system, the $d_{x^2-y^2}$ and the d_{z^2} orbitals. The other three orbitals are directed between the axes.

Table 1-8 Some Common Polydentate Ligands

Bidentate Ligand

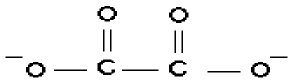
Ethylenediamine (en) $H_2\ddot{N}-CH_2-CH_2-\ddot{N}H_2$

Glycinate (gly)



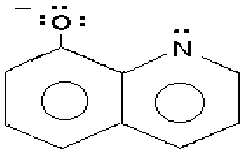
$H_2\ddot{N}-CH_2-\overset{\overset{O}{\|}}{C}-O^-$

Oxalate



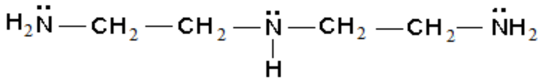
$^-O-\overset{\overset{O}{\|}}{C}-\overset{\overset{O}{\|}}{C}-O^-$

Anion of 8-hydroxyquinoline (oxinate)



Tridentate Ligand

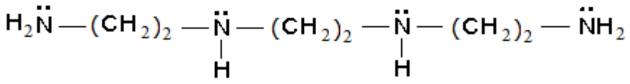
Diethylenetriamine (den)



$H_2\ddot{N}-CH_2-CH_2-\underset{\underset{H}{|}}{\ddot{N}}-CH_2-CH_2-\ddot{N}H_2$

Tetradentate Ligand

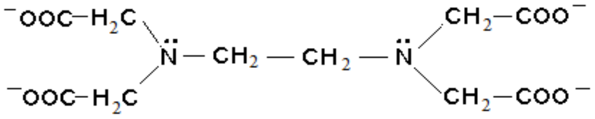
Triethylenetetramine (trien)



$H_2\ddot{N}-(CH_2)_2-\underset{\underset{H}{|}}{\ddot{N}}-(CH_2)_2-\underset{\underset{H}{|}}{\ddot{N}}-(CH_2)_2-\ddot{N}H_2$

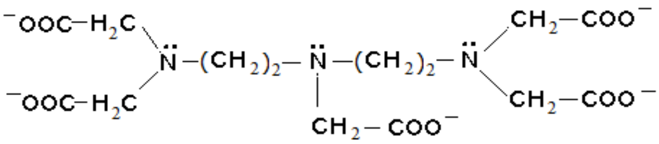
Hexadentate

Ethylenediaminetetraacetate
(EDTA)



Octadentate Ligand

Diethylenetriaminepentaacetate
(DTPA)



Now consider a hexacoordinate complex with the six ligands each located on an axis of the cartesian coordinate system as shown in Figure 1-4. If overlap of the ligand lone pair orbitals with *d* orbitals on the metal ion is to take place, the $d_{x^2-y^2}$ and the d_{z^2} orbitals are the only ones properly oriented. The problem, of course, is that according to Hund's rules these two orbitals cannot accept all of the six pairs of electrons being donated by the six ligands. It is generally accepted that $(n\text{-}1)d$, *ns*, and *np* orbitals are close enough in energy to become hybridized into six bonding orbitals which are directed along the same axes occupied by the ligands. These hybrid orbitals are designated d^2sp^3 hybrids and are equivalent as long as the six ligands are equivalent.

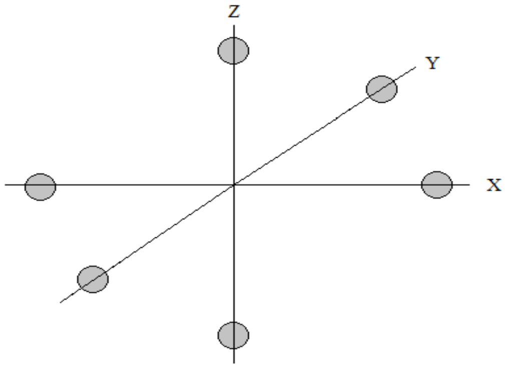
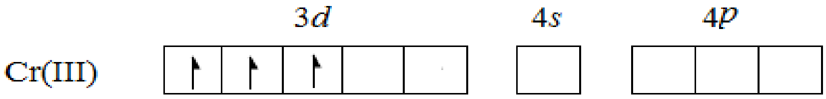
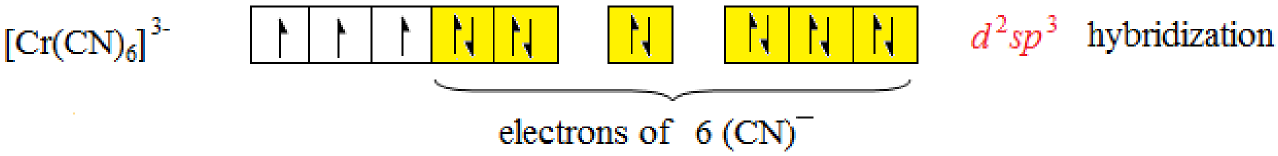


Figure 1-4 Six ligands organized on the axes of a three-dimensional cartesian coordinate system.

The valence bond problem can now be expressed as one involving an examination of the atomic orbitals on the metal ion to discover which ones are occupied by electrons on the ion and which ones are available (empty) for hybridization to accept ligand electrons. Of course, this is an ultrasimplification. Nevertheless, consider the trication of chromium, Cr(III), complexing with six cyanato, CN^-, ions to form $[Cr(CN)_6]^{3-}$. Chromium(III) is a d^3 ion; that is, it contains three electrons in its 3*d* valence orbital as shown below:

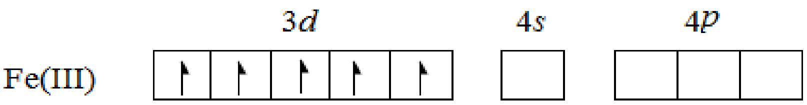


These electrons are unpaired and occupy the three off-axis *d* orbitals (d_{xy}, d_{yz}, d_{xz}) thus leaving two *d*, one *s*, and the three *p* orbitals empty for bonding with the six cyanato groups. If these six orbitals hybridize, a valence bond picture of the complex ion can be drawn:

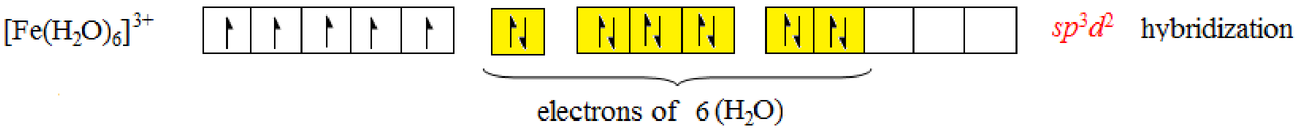


Similar valence bond reasoning can be applied to other complexes formed with metal ions having one to three electrons in their *d* orbitals. A problem arises when there are four or more electrons in these orbitals on the metal. For example, complexes formed with iron(III) (d^5 ion), according to this theory, must alter the normal ground state arrangement of the electrons, use different orbitals for bonding, or bond in a noncovalent manner. If the electronic configuration on the metal was in fact changed from the ground state configuration, it could be measured experimentally by determining the magnetic moment of the complex. This is a measure of the "unpairedness" of electrons in that unpaired electrons are attracted to a magnetic field, *paramagnetic*, and paired electrons are repelled by a magnetic field, *diamagnetic*.

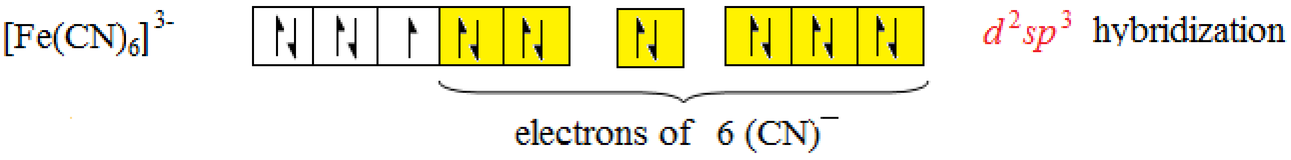
The electronic structure of the valence shell of iron(III) is:



When complexed with water molecules the hexaaquiron(III) ion is formed, and has the same magnetic properties as would be expected from the electronic structure shown above. The magnetic moment is 5.9 B.M. (Bohr magnetons) which is consistent with five unpaired electrons. This is generally referred to as a *high-spin complex* because the electrons are unpaired as much as possible. Within the framework of valence bond theory, the problem of finding six empty atomic orbitals to overlap with the donor water molecules can be accomplished by assuming that the 4*d* orbitals are of appropriate energy to hybridize with 4*s* and 4*p* orbitals. Hybridization of this type is termed *outer orbital* hybridization, and still provides six octahedrally arranged hybrids designated sp^3d^2.



If the water molecules in the last complex are replaced with cyanato groups, the hexacyanoferrate(III) ion results which has distinctly different magnetic properties. The magnetic moment is about 2 B.M,. which is indicative of *one* unpaired electron, and the ion is termed a *low-spin complex*. An explanation of this may be found in the fact that the cyanato anion has a negative electrostatic field of sufficient strength to repel the electrons in the two *d* orbitals which directly oppose the approaching ligands ($d_{x^2-y^2}$ and the d_{z^2}). The repulsive interaction forces the electrons to become paired with those in the other *d* orbitals. The effect of strong field ligands producing low-spin complexes has been noticed with other metals as well. The electronic configuration of this complex involves the 3*d* orbitals in an *inner orbital* hybrid as was seen previously to produce the valence bond picture:



The octahedral arrangement of hexacoordinate complexes is shown in Figure 1-5a.

Metal ions with seven, eight, or nine *d* electrons generally have coordination numbers of 4 which leads to either a square planar or a tetrahedral arrangement of the ligands. Here again the field strength of the ligand and the formation of high-spin and low-spin complexes may be predictive of the type of hybridization and, therefore, the geometry of the complex. For example, a d^8 ion complexing with a ligand having a relatively weak electrostatic field has no *d* orbitals available for bonding. However, the ligands can bond through sp^3 hybrids formed on the metal to give a tetrahedral complex. If the ligand field strength is sufficient to force the metal into a low-spin diamagnetic state, one *d* orbital would be vacant and could be used to form a square planar dsp^2 hybrid (Figure 1-5 b and c).

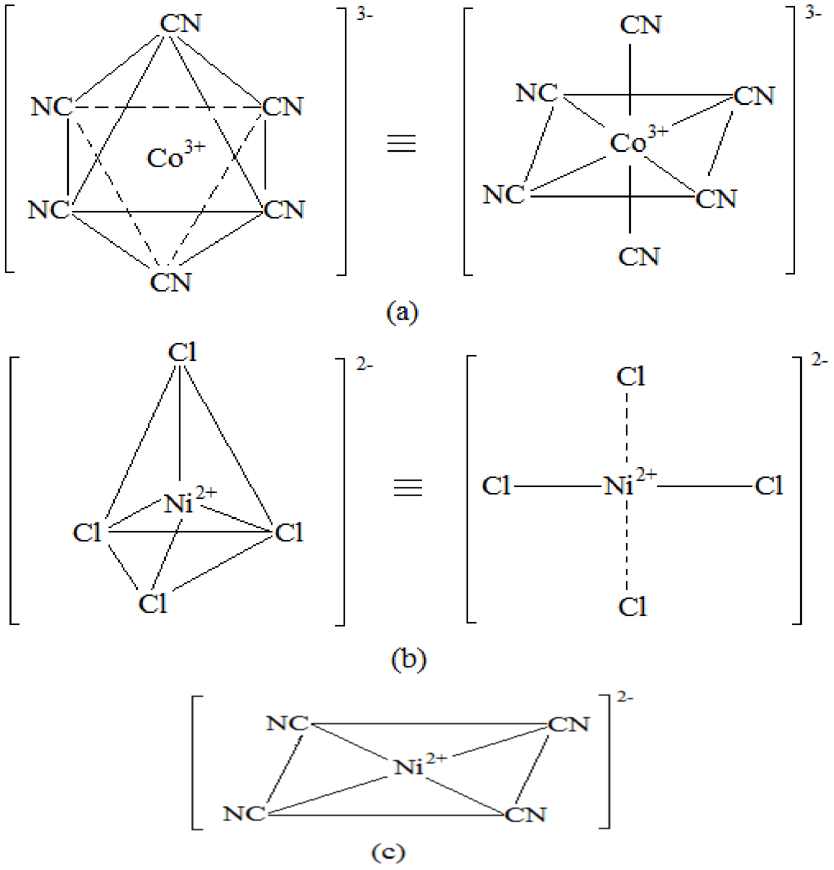


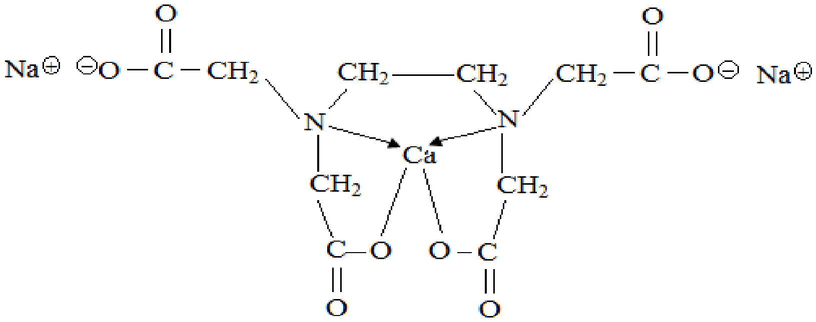
Figure 1-5 Representative complex ion geometry: (a) octahedral; (b) tetrahedral; (c) square planar.

1.16 Complexes and Chelating Agents

Complexes and complexation are important aspects of chemistry and pharmacy. Complexation plays an important role in analytical chemistry where, for example, concentrations of metals can be determined by titration with complexing agent. In some analytical solutions containing metal ions, chelating agents are used to solubilize the metal and to stabilize its oxidation state. Two rather classical examples are found in solutions employed in the identification of reducing substances (e.g., sugars), Benedict's solution and Fehling's solution. Both of these solutions contain copper(II) ions which are chelated by citric acid in Benedict's and by tartaric acid in Fehling's solution. Chelating agents are also found as preservatives in preparations subject to decomposition due to trace quantities of metals, such as preparations containing hydrogen peroxide.

Chelating agents occupy a rather unique place in drug therapy. They are essentially the only compounds which have shown efficacy in the treatment of heavy metal poisonings from such elements as lead, mercury, iron, etc. In addition to their usefulness in toxicological problems such as these, they are also being used to treat certain metabolic disorder where metals such as iron and copper are accumulated in abnormal amounts in various tissues. The particular chelating agents discussed in the sections to follow include calcium disodium edetate (EDTA), dimercaprol (BAL), penicillamine, and deferoxamine.

⇨ **Calcium Disodium Edetate**, U.S.P. XVIII (Calcium Disodium Versenate; Calcium Disodium Ethylenediaminetetraacetate; $C_{10}H_{12}CaN_2Na_2O_8.xH_2O$; Mol. Wt. (anhydrous) 374.28)



This compound is a mixture of the dihydrate and trihydrate (predominantly the dihydrate) which exists as a white crystalline granule or a white crystalline powder. It is odorless, slightly hygroscopic, and has a faint saline taste. It is stable in air, freely soluble in water, and the pH of an aqueous solution is between 6.5 and 8.0.

The compound is actually the calcium complex of the disodium salt of ethylenediaminetetraacetic acid (EDTA). It is used in the treatment of heavy metal poisoning, primarily that caused by *lead* (plumbism). It may also be employed in poisonings due to copper, nickel, cadmium, zinc, chromium, and manganese, but it is of *no value* in the treatment of toxicities produced by mercury, arsenic, or gold. EDTA preparations have a strong affinity for calcium; therefore, the disodium calcium form is used to avoid inducing hypocalcemic states (low serum calcium). This chelating agent removes lead from the tissues by forming an inactive soluble complex which can be removed from the circulation by the kidney and excreted in the urine.

The usual route of administration is by intravenous (I.V.) injection. The official *Calcium Disodium Edetate Injection*, U.S.P. XVIII, contains not less than 180 mg and not more than 220 mg of the compound in each ml. intramuscular (I.M.) administration is employed sometimes in diagnosis of metal poisonings.

Doses

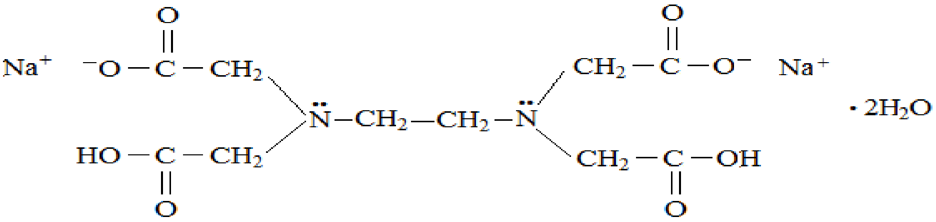
(a) Intravenous infusion of 75 mg/kg of body weight in two divided doses per day, administered in 250 to 500 ml of isotonic sodium chloride or 5% dextrose. One course of treatment would normally last about five days, with up to two-week intervals between courses.

(b) Intramuscular injection of 75 mg/kg administered as a 20% solution in 0.5% to 1.5% procaine which serves to nullify the pain associated with the injection.

Preparations

Calcium Disodium Versenate® (Riker), a solution containing 200 mg/ml for injection.

⇨ **Disodium Edetate**, U.S.P. XVIII (Disodium Ethylenediaminetetra-acetate; $C_{10}H_{14}N_2Na_2O_8.2H_2O$; Mol. Wt. 372.24)



This compound is a white crystalline powder which is soluble in water, providing an aqueous solution of pH between 4.0 and 6.0.

Disodium edetate will chelate the same metals as the disodium calcium form. However, its added affinity for calcium limits its usefulness as an agent for the treatment of toxicities due to these other metals. The chance of hypocalcemia during such therapy definitely exists. The primary use of disodium edetate is in conditions related to *hypercalcemic* states (high serum calcium). The compound may be useful in treating such problems as occlusive vascular disease and cardiac arrhythmias when associated with high blood levels of calcium.

The usual route of administration is by intravenous injection. The official Disodium Edetate Injection, U.S.P. XVIII, contains varying amounts of the disodium and trisodium salts due to the effects of pH adjustment.

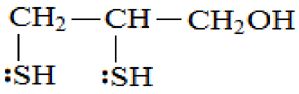
Doses

Intravenous infusion of 50 mg/kg of body weight dissolved in 500 ml of isotonic sodium chloride or 5% dextrose. The infusion is done over a period of three to four hours once a day for a term of five days. Two or three therapeutic courses may be required. There is general disagreement concerning proper dosage and therapeutic value.

Preparations

Endurate® (Abbott), a solution containing 150 mg/ml for injection.

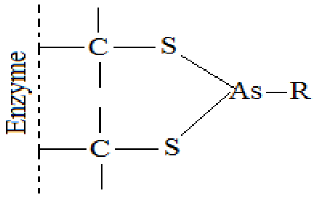
⇨ **Dimercaprol**, U.S.P. XVIII (2,3-Dimercapto-1-propanol; BAL; $C_3H_8OS_2$; Mol. Wt. 124.22)



$$\underset{:SH}{\underset{|}{CH_2}}-\underset{:SH}{\underset{|}{CH}}-CH_2OH$$

This compound is a colorless or almost colorless liquid having a disagreeable, mercaptan-like odor. It is soluble in water, alcohol, and benzyl benzoate.

Certain heavy metals, such as trivalent arsenic, owe their cellular toxicity to the "tying up" sulfhydryl (-SH) groups present in enzymes which are responsible for oxidation-reduction reactions in tissues. Presumably, this inactivation involves covalent bond formation between the metal and the sulfhydryl groups.



Knowledge of this association led to the idea that the use of simple dithiol compounds (those containing sulfhydryl groups) as competitors with the enzymes for these metals might serve to prevent toxic reactions. The idea proved to be successful and subsequent work resulted in the introduction of dimercaprol or BAL (British anti-lewisite) as an effective neutralizing agent for arsenical war gases, such as lewisite. Following the use, the compound was used with marked success in the treatment of mercury and gold poisoning.

The compound forms stable mercaptides of the metals which are excreted in the urine. It appears to be of value in the treatment of toxic reactions due to arsenic and gold. Its effectiveness in the treatment of mercury poisoning is dependent upon its use within a few hours following ingestion. The lapse of a longer period of time diminishes its efficacy. Dimercaprol has also been shown to improve the excretion of lead and copper (Wilson's disease), but it is not the agent of choice for these metals. It is contraindicated in poisonings due to iron, cadmium, or selenium because the resulting complexes have greater renal (kidney) toxicities than do the free metals. Dimercaprol-metal chelates tend to dissociate in acid media; therefore in therapy the urine should be alkalinized (e. g., with sodium bicarbonate) to prevent the release of free metal, producing renal toxicity.

The usual route of administration is by intramuscular injection. The official *Dimercaprol Injection*, U.S.P. XVIII, is a solution of dimercaprol in a mixture of benzyl benzoate and vegetable oil. The solution contains the equivalent of 100 mg of the compound in each ml.

Doses

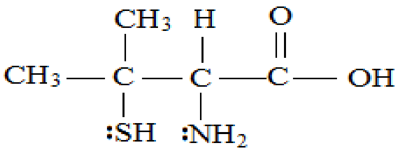
The recommended dosage schedule varies with the severity of the toxicity. In severe arsenic or gold poisoning, intramuscular injection of 3 mg/kg is given six times a day for two days, four times on the third day, then twice daily for the next ten days.

Mercury poisoning requires 5 mg/kg initially (within a few hours of ingestion) followed by 2.5 mg/kg twice daily for ten days.

Preparations

BAL in Oil (Hynson, Westcott and Dunning), a solution containing 100 mg/ml in peanut oil for I.M. injection.

⇨ **Penicillamine**, U.S.P. XVIII (D-(-)-3-Mercaptovaline; *β*, *β*-Dimethyl-cysteine; $C_5H_{11}NO_2S$; Mol. Wt. 149.21)



$$CH_3-\underset{:SH}{\overset{CH_3}{C}}-\underset{:NH_2}{\overset{H}{C}}-\overset{O}{\overset{\|}{C}}-OH$$

This compound is a white or off-white crystalline powder, having a slight characteristic odor. It is freely soluble in water, and slightly soluble in alcohol. The pH of an aqueous solution is between 4.5 and 5.5.

Penicillamine is a chelating agent capable of forming soluble complexes with copper, iron, mercury, lead, gold, and other metals. However, its use has been reserved for the improvement of copper excretion in patients with hepatolenticular degeneration (degenerative changes in the brain associated with increased levels of copper in the tissues and degeneration of the liver, also known as Wilson's disease). This is a rare disease resulting from a familial inability to regulate copper balance, with the consequence that toxic amounts of copper are deposited in tissues such as the eye, liver, brain, and kidney. The disease was customarily treated with calcium disodium edetate or dimercaprol.

Another use of penicillamine which is being investigated is the treatment of gold dermatitis in patients on chronic gold therapy. It has also been used in the treatment of cystinuria (the presence of crystals of the amino acid cystine in the urine) which is not related to its metal chelating abilities.

Unlike the other chelating agents discussed heretofore, the usual route of administration of penicillamine is oral. *Penicillamine Capsules* are official in the U.S.P. XVIII.

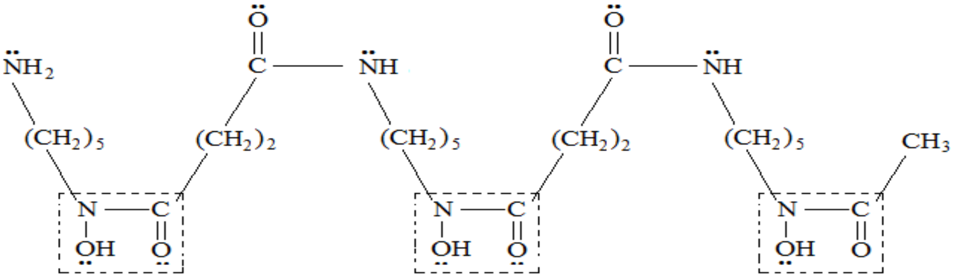
Doses

The usual oral dose is 250 mg given four times a day. Doses may be gradually increased on an individual basis to a maximum of 5 g daily. Low copper diets or a cation exchange resin is frequently employed during therapy. Sulfurated potash (N.F. XIII) has been used in doses of 40 mg to minimize the absorption of dietary copper.

Preparations

Cuprimine® (Merck Sharp and Dohme), capsules containing 250 mg of penicillamine for oral administration.

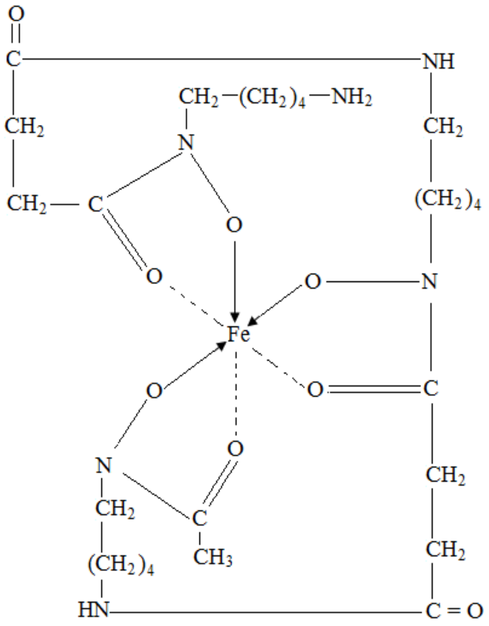
⇨ **Deferoxamine Mesylate**, (Desferrioxamine B; N-(5-[3-[(5-amino-pentyl)hydroxy-carbamoyl]propionamide]pentyl)-3-[[5-(N-hydroxyacet- amido)pentyl]-carbamoyl] propionhydroxamic acid)



This compound is the methylsulfonic acid salt and is usually available as a white, crystalline lyophilized powder. It is soluble in water and the aqueous solution is stable at room temperature for two weeks. The outlined groups in the above structure are involved in the chelation.

Deferoxamine is produced naturally by *Streptomyces pilosus* as a ferric [Fe(III)] complex. After chemical removal of the iron, the chelating agent is purified as the methysulfonate (mesylate) salt.

It is a polydentate ligand with a particular affinity for ferric ions with which it forms stable, water soluble, octahedral complexes (the structure below). It does not have a very strong affinity for ferrous or other divalent metal ions. Deferoxamine is used with other indicated drugs and procedures for the treatment of acute iron toxicity. It is also under investigation for the treatment of iron storage diseases (e.g., hemochromatosis). The compound is poorly absorbed from the gastrointestinal tract. Administration by this route is not generally recommended.



The usual route of administration is by intramuscular or intravenous injection. The former is preferred. Intravenous administration is generally done by slow infusion with isotonic sodium chloride or other electrolyte solution.

Doses

Either route of administration (I.M. or I.V.) has a usual dose of 1 g initially, followed by 500 mg every 4-12 hours which may be given depending on the clinical response of the patient. A total dose of 6 g should not be exceeded in any 24-hour period.

Preparations

Desferal® (Ciba), ampoules containing 500 mg of the lyophilized powder for injection.