B. An Introduction to (Bio)inorganic Chemistry

The goal of this introduction is to familiarize you with issues associated with metal ion coordination in biochemistry. Roughly one-third of all enzymes require metal ions for their function, and metals play key roles in a variety of regulatory processes within the cell. Also, they play substantial roles in stabilizing both protein and nucleic acid structure. The following is intended to provide a basic understanding of bonding and stability of metal ions in the biochemical setting.

The Metal-Ligand Interaction

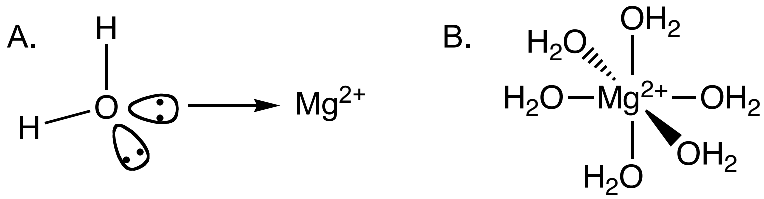

Figure B.1. (A) Electron pair donation from a water ligand to the magnesium ion. (B) The hexaaquo complex of Mg^{2+}, which predominates in aqueous solutions of magnesium.

Species that bond to metals are referred to as **ligands**. Metal ions are the prototypical Lewis acids – species that accept electron pairs, and the ligands are the electron pair donors, Lewis bases. In aqueous solution, the most common metal-ligand interaction is through electron pair donation from water to the metal ion (Figure B.1.A), but a variety of other biochemical species, including amines, carboxylates, thiolates, imidazoles and even purines and pyrimidines are capable of donating electrons to metals, forming **coordination complexes**. For example, in Figure B.1, $Mg^{2+}_{(aq)}$ is shown as the hexaaquo[1] species that is found in solution, with six bound water ligands. The coordination complex can also be written as $Mg(H_2O)_6^{2+}$.

Table B.1. Potential metal ligands in the protein environment.

Electron donating species	**Atom group involved**
Aspartate and Glutamate	Side chain carboxylate oxygens
Histidine	Imidazole nitrogen (unprotonated)
Cysteine, Methionine	Thiolate and thioether on side chains
Asparagine, Glutamine	Side chain amide oxygens
Peptide backbone	Amide carbonyl oxygen, α-amine and carboxylate
Asparagine, Glutamine	Side chain amide oxygens
Serine, Threonine	Hydroxyl oxygen
Tyrosine	Phenolate oxygen
Lysine	Neutral side chain amine

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[1] All Inorganic Chemistry texts describe the nomenclature rules for simple coordination complexes. I won't go into that here.

There are other small dissolved molecules in the biochemical environment that can act as metal ligands, such as hydroxide, carbonate and phosphate, but chiefly we will be interested in the interaction of metals with coordination environments in protein binding sites. The atom groups capable of acting as metal ligands include all protein functional groups with oxygen and sulfur, and some of those containing nitrogen (see Table B.1).

Ligand Selection and Hard/Soft Acid/Base Theory (HSAB)

Given the variety of interactions that a protein can have with a metal ion (Table B.1), much can be done to tailor the choice of ligands to the nature of the metal ion to be bound. Observation has shown that certain types of metals prefer particular atoms groups as ligands, and these preferences can be categorized along the lines of the "hardness" or "softness" of the metal ion and ligands involved. Those terms refer, in some sense, to the polarizability of the electrons in the metal ion and ligands, and likewise correlate to the degree of ionic vs. covalent character in the bonding. Hard acids (metal ions in this instance) bond with a large degree of ionic character to hard bases (ligands), while soft metal ions bond with a greater degree of covalent character to soft ligands. Typically, metal ions and ligands are classified as hard, soft or borderline. The hard metals are typically highly charged, smaller and come from the upper left side of the periodic table. Soft metals typically carry a lower charge and come from the lower right side of the periodic table. But, these are generalizations. The categorization is largely based on empirical evidence rather than theoretical grounds. In a biochemical setting, there are predominantly only three elements involved in metal ion coordination. Ligands that bond through oxygen (carboxylates, phenolates, carbonyls and hydroxyls) are hard. The only common soft ligands in biology are thiolates and thio ethers, while most nitrogen-containing ligands are classified as borderline, being capable of ligating both hard and soft metals (Table B.2.).

Table B.2. A table of hard and soft acids and bases in bioinorganic chemistry.

Category	Metal Ions	Ligands
Hard	Na^+, K^+, Mg^{2+}, Ca^{2+}, Mn^{2+}, Fe^{3+}, Al^{3+}, Co^{3+}	H_2O, HO^-, carboxylates, phenolates, carbonyls, hydroxyl groups, amines
Borderline	Fe^{2+}, Cu^{2+}, Ni^{2+}, Zn^{2+}, Pb^{2+}	imidazole
Soft	Cu^+, Ag^+, Cd^{2+}, Hg^{2+}	RS^-, R_2S, CN^-,

While these categories generally work, they're not completely prescriptive. Calcium and magnesium binding sites are generally oxygen rich, while proteins that are designed to bind and detoxify cadmium and mercury are generally sulfur rich. On the other hand, iron sulfur clusters abound in biochemistry, pairing the hard ferric ion (Fe^{3+}) with soft sulfide ligands.

The Geometries of Metal Ion Coordination Compounds[2]

Although the shapes of coordination complexes are much more flexible than those of simple organic compounds, which typically only see small deviations from geometric ideals, certain geometric patterns are observed with some frequency, depending on the **coordination number** of the complex (Figure B.2). The coordination number is the number of ligands in the complex. The most common coordination numbers for metal ions in biochemical settings are between four and six.

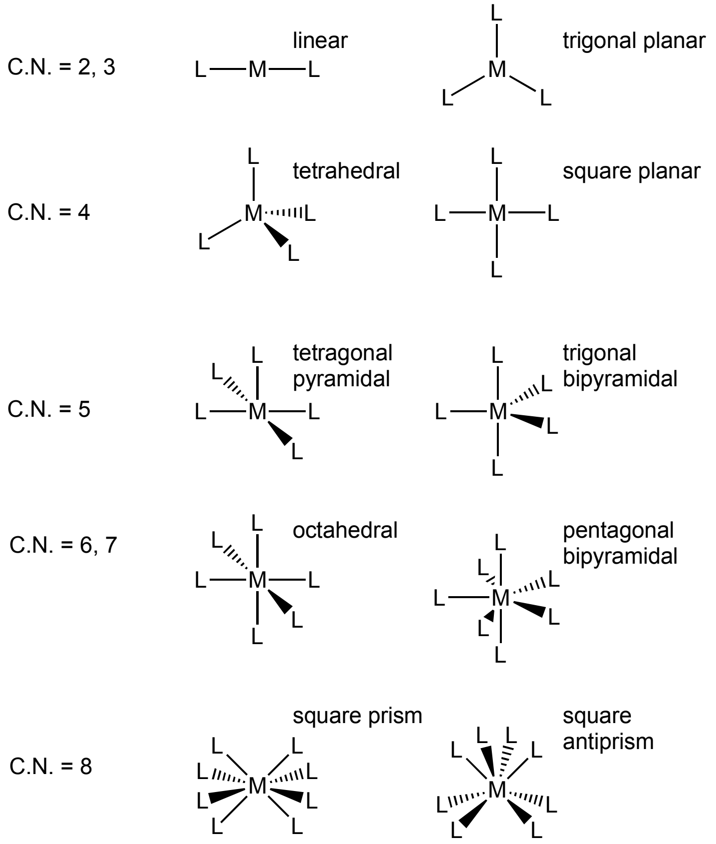

Figure B.2. Some common coordination geometries associated with metal ion complexes in biochemistry.

The geometries of coordination compounds are linked to the ionic size of the metal and to bonding issues associated with the d electrons (see below).

Ionic Size

In the simplest relationship, coordination number can be generally related to the size of the metal ion. If we remove the dependence on electronic interactions with d electrons on the metal, by

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[2] For a more thorough and interactive description of coordination geometries, see: http://www.d.umn.edu/~pkiprof/ChemWebV2/Coordination/CN1.html (accessed 11/14/04).

focusing on the alkali and alkaline earth metals, we see that coordination number increases with ionic radius (Table B.3.) The larger the ionic radius, the more ligands that can crowd around the metal to stabilize its positive charge through lone pair donation.

Table B.3. Ionic radius and coordination number for hydrated ions of the alkali and alkaline earth metals.

Metal ion	Ionic Radius	Coordination Number
Li^+	0.71 Å	4: $Li(H_2O)_4{}^+$
Na^+	1.16 Å	6: $Na(H_2O)_6{}^+$
K^+	1.65 Å	8: $K(H_2O)_8{}^+$
Mg^{2+}	0.86 Å	6: $Mg(H_2O)_6{}^{2+}$
Ca^{2+}	1.26 Å	8: $Ca(H_2O)_8{}^+$

There are some good general trends to remember with respect to ionic size. First, it decreases with charge. Thus Fe^{2+} is larger than Fe^{3+}. Second, it increases as you go down a column in the periodic table (see Table B.3 again). And third, it *tends* to decrease as you go from left to right on the periodic table. Thus Zn^{2+} is a smaller cation than Mn^{2+}.

Electronics[3]

Metal ions are typically be classified by their d electron configuration, since these orbitals play a significant role in their chemistry. The key thing to remember is that, although the neutral electron configuration of many transition metals includes a filled or partially filled s orbital (the 4s orbital for first row transition metals), those electrons are the first lost in the formation of metal ions. Thus, in Table B.4 we see that the remaining valence electrons are the d electrons.

Table B.4. Some sample metal ions, their neutral electron configurations and the electron configurations of the ionic form.

Metal Ion	Electron Configuration of Neutral Metal Atom	Ionic Electron Configuration	d Electron Configuration
K^+	$[Ar]4s^1$	$[Ar]$	d^0
Ca^{2+}	$[Ar]4s^2$	$[Ar]$	d^0
Cr^{3+}	$[Ar]4s^13d^5$	$[Ar]3d^3$	d^3
Mn^{2+}	$[Ar]4s^23d^5$	$[Ar]3d^5$	d^5
Fe^{2+}	$[Ar]4s^23d^6$	$[Ar]3d^6$	d^6
Fe^{3+}	$[Ar]4s^23d^6$	$[Ar]3d^5$	d^5
Ni^{2+}	$[Ar]4s^23d^8$	$[Ar]3d^8$	d^8
Cu^+	$[Ar]4s^13d^{10}$	$[Ar]3d^{10}$	d^{10}
Zn^{2+}	$[Ar]4s^23d^{10}$	$[Ar]3d^{10}$	d^{10}
Hg^{2+}	$[Xe]6s^25d^{10}$	$[Ar]5d^{10}$	d^{10}

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[3] A good website for more on this material is at http://www.unine.ch/chim/chw/Chapter%204.html (accessed 11/17/04).

In those instances where the d orbitals are empty (K^+ and Ca^{2+} are d^0) or full (Cu^+ and Zn^{2+} are d^{10}), electron configuration doesn't play a significant role in defining a specific coordination geometry, except to say that it is permissive with respect to geometry. The defining characteristics of those metal ion complexes tends to be size, as discussed above. However, when d electrons are present, bonding is largely defined by those electrons, and the geometry of the coordination shell is influenced by how stable the d electrons are in that geometry. To provide a rationale for how a given geometry can stabilize a given electron configuration, we will look at the explanation provided by **crystal field theory** (CFT). To apply CFT, we need to describe d electron orbital shape and geometry (Figure B.3). Note that there are two ways we can group the orbitals. One group (heretoforward to be described as the e_g orbitals) includes the d_{z2} and d_{x2-y2} orbitals, which both place electron density on the principal x, y and z axes. The t_{2g} orbitals (d_{xy}, d_{yz} and d_{xz}) place electron density in the planes defined by their subscripts, but place no electron density directly on the axes.

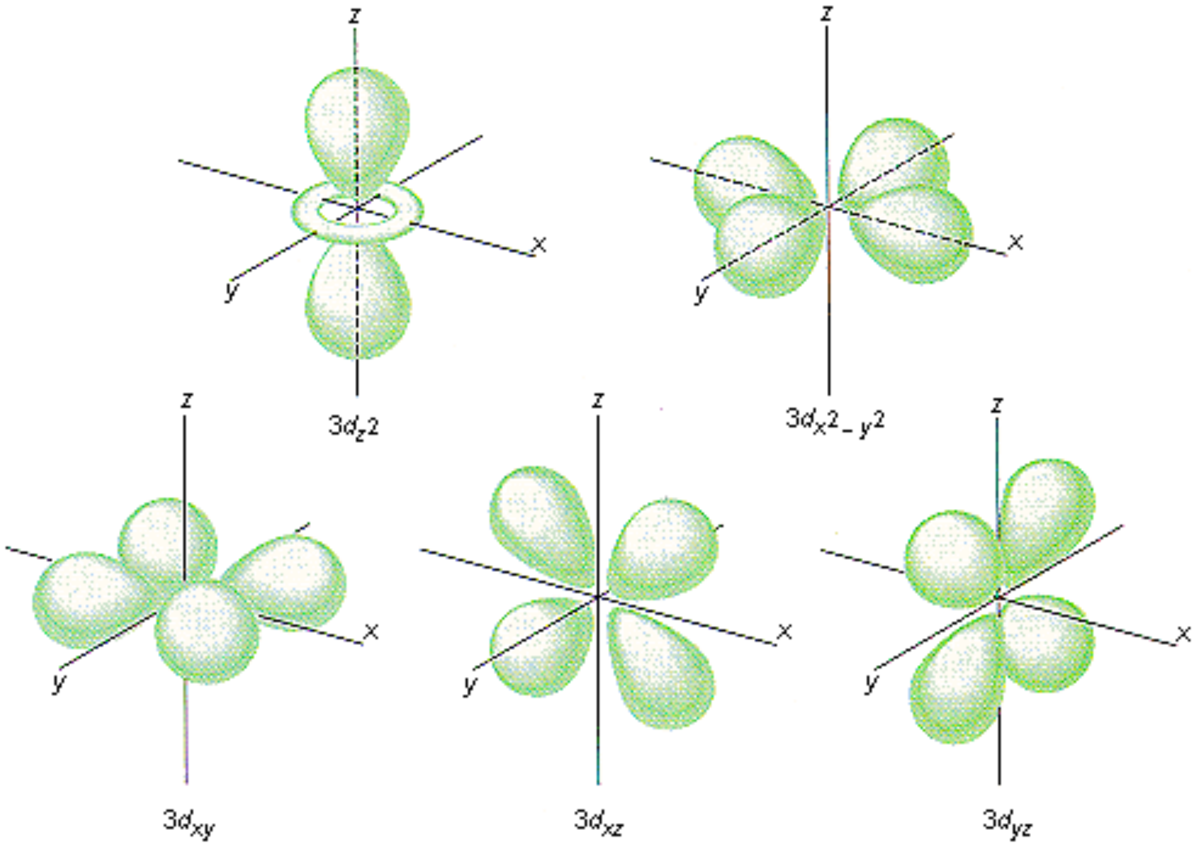


Figure B.3. Shapes of the d orbitals. The e_g orbitals are shown on top and the t_{2g} orbitals below.

CFT describes d electron energetics in response to field of negative electric charge. Imagine an isolated metal ion all of a sudden dropped into a symmetric sphere of negative charge. As the sphere of negative charge contracts all electrons in d orbitals will be equally destabilized by charge repulsion, leading to a universal increase in orbital energy (Figure B.X.A and B). Now imagine that the negative charge condenses from its spherical distribution and concentrates along the principal axes (see the top left of Figure B.X). This is meant to approximate the case in which six electron rich electrons approach the metal ion along the three axes to form an octahedral coordination geometry. At this point, the individual d orbitals are differently affected. The d_{z2} and $d_{x2\text{-}y2}$ have density **on** those axes and so they feel greater repulsion from the negative charges than do the e_g orbitals, which don't lie on the axes. As a result, the e_g orbitals rise to a higher energy than the t_{2g} orbitals, with the energy gap described as the octahedral splitting energy (Δ_o). The split is achieved by raising the e_g orbitals 0.6 Δ_o and lowering the t_{2g} orbitals 0.4 Δ_o. The particular value of Δ_o is determined by the actual ligands involved.

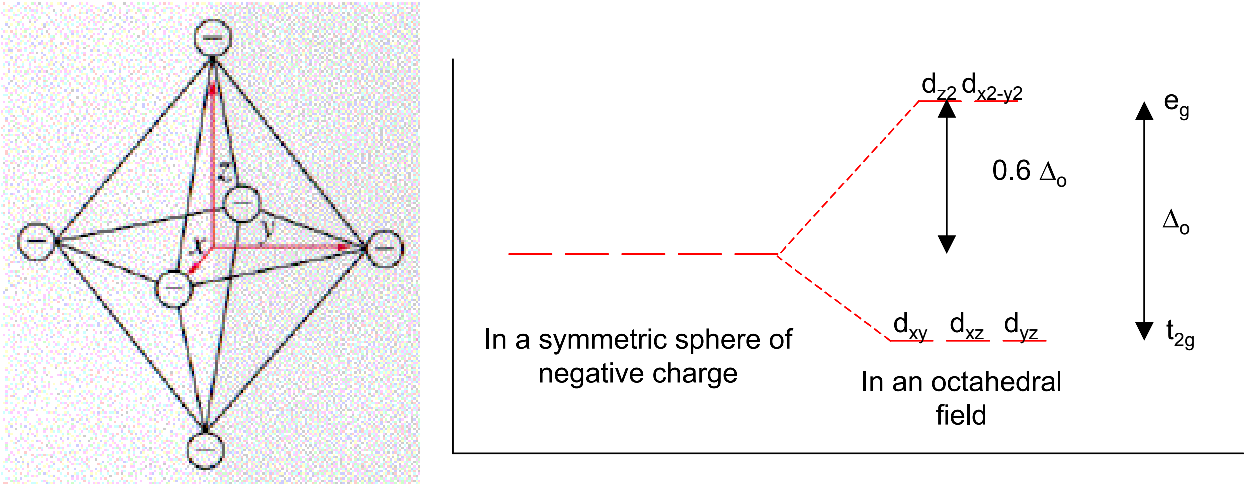
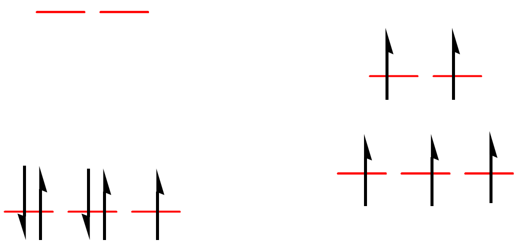


Figure B.4. The crystal field splitting due to an octahedral geometry. The distribution of negative charge is shown on the left with respect to the three axes. The splitting for the five d orbitals is shown on the right.

When the metal ion has four or more d electrons, there are two possible electron configurations in the d orbitals: **low spin** or **high spin** (Figure B.5). These two different configurations depend on the total value of stabilization provided by occupying the lower lying t_{2g} orbitals vs. the Coulombic repulsion of putting two electrons in the same orbital and by losing the exchange energy (a quantum phenomenon that says its good to have electron spins oriented in the same direction). When Δ_o is big, you get low spin configurations and when Δ_o is smaller, you tend to get high spin electron configuration. As a rule, d^5 species like Mn^{2+} and Fe^{3+} prefer high spin even in cases where the orbital splitting is sizable.



Low spin d^5 High spin d^5

Figure B.5. Low vs. high spin configurations for a d^5 metal ion in an octahedral crystal field. Note that Δ_o is smaller for the high spin configuration.

In a comparable situation we could imagine a tetrahedral geometry, in which the negative charge concentrates to the points of a tetrahedron. If we assume that the axes intersect at the faces of a cube, and that the points of the tetrahedron are at the corners of the cube, then we see that the t_{2g} orbitals feel greater repulsion than the e_g orbitals, and the splitting pattern in reversed, with the t_{2g} orbitals being higher in energy (Figure B.6). In this instance, the crystal field splitting energy for the tetrahedral geometry (Δ_t) is $4/9^{th}$'s the value of Δ_o for the octahedral geometry, because the negative charge concentrates less strongly on the three t_{2g} orbital positions. Finally, I leave it as an exercise for you to determine the identities of the five d orbitals in the square planar geometry, where the negative charge, provided by the ligands, is concentrated on the x and y axes (See Figure B.8 at end of these notes)

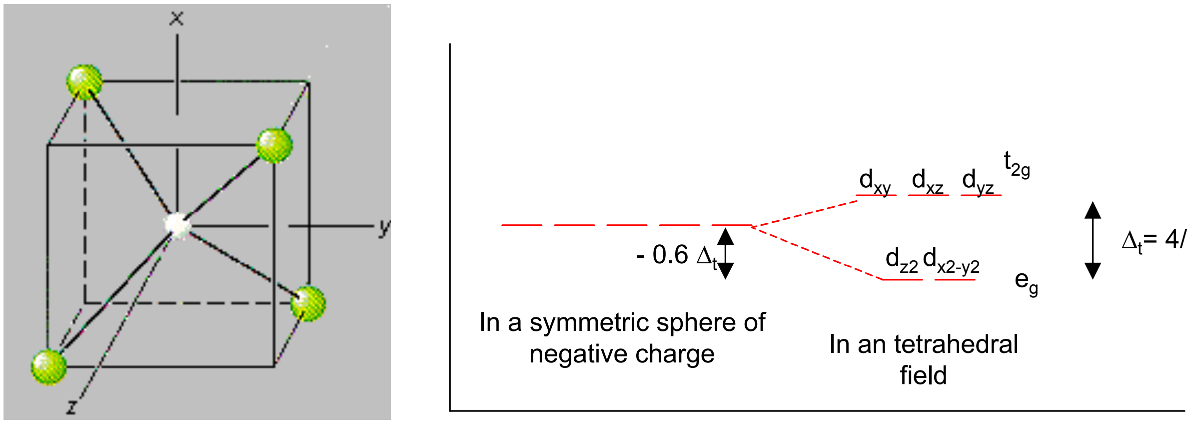


Figure B.6. Crystal field splitting in a tetrahedral coordination geometry. Note that the overall splitting is less than in an octahedral field ($4/9^{th}$'s as much) and that the e_g orbitals are stabilized by 0.6 Δ_t.

As a result of these different splitting patterns, different geometries are more suitable for some electron configurations than others. In general, the stabilization of the d electrons in the octahedral field comes about by placing them in the low lying t_{2g} orbitals, so species that are d^1, d^2 and d^3 will always prefer to be in octahedral geometries. But in some situations, the tetrahedral geometry is as good or preferable to the octahedral geometry. For example, Co^{2+} is a d^7 metal ion. When Δ_o is small for a given set of ligands, it will adopt a high spin configuration placing two electrons in the e_g orbitals (at a cost of 1.2 Δ_o) and five in the t_{2g} orbitals (at a benefit of 2.0 Δ_o). In a high spin tetrahedral geometry, there will be three electrons in the high energy t_{2g} orbitals (at a cost of 1.2 Δ_t) and four in the low energy e_g orbitals (at a benefit of 2.4 Δ_t). The difference is thus a net stabilization of 0.8 Δ_o vs. 1.2 Δ_t. Since Δ_t is still only 44% as big as Δ_o, octahedral is preferred – but only barely, and one often finds tetrahedral Co^{2+} complexes because you can get the four ligands closer to the metal ion in the tetrahedral conformation, thus increasing the crystal field splitting.

A more frequent set of geometric preferences based upon electron configuration is found in Ni^{2+} and Cu^{2+} complexes (d^8 and d^9, respectively). Both achieve good stabilization through a square planar geometry, which is not typically adopted by other first row transition metal ions.

As an aside, it is the d electrons that give metal ions their color. Transitions between d orbitals are typically in the visible range. Thus we see colors that arise when an electron can be advanced from a lower energy d orbital to a higher *energy orbital. The exceptions are high spin* d^5 *metals, like* Mn^{2+} *and* Fe^{3+} *which are very faintly colored because the transition requires a spin to flip (a "forbidden" transition). Also,* d^{10} *and* d^0 *species are colorless, for the most part, because of the absence of allowed d to d transitions.*

Entropic Issues in Metal Ion Binding: The Chelate Effect

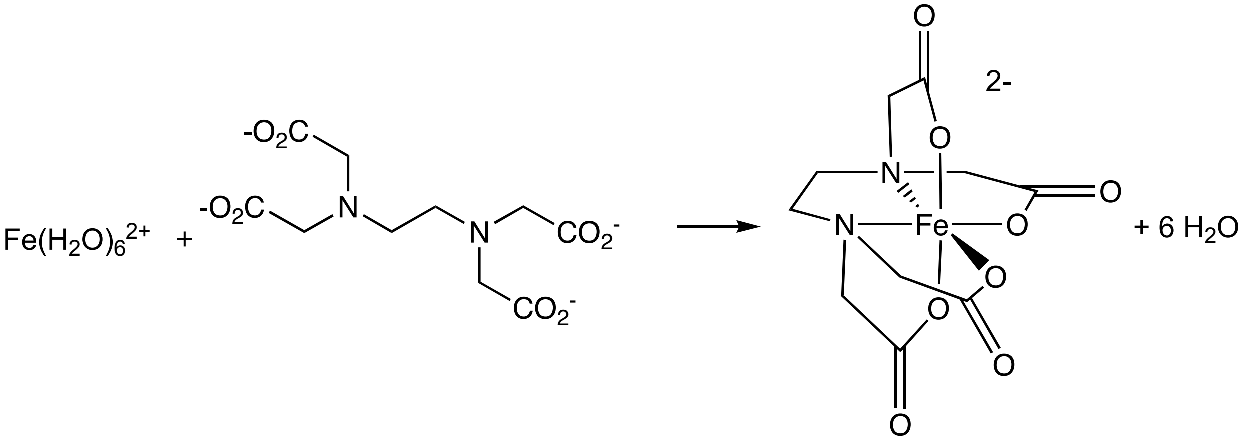


Figure B.7 The hydrated ferrous ion reacts with $EDTA^{4-}$ to produce $Fe(EDTA)^{2-}$ and six solvent molecules.

Inorganic coordination chemistry involves a significant number of synthetic (and natural) ligands that make more than one electron pair donation to the metal. These are called **polydentate** ("many-toothed") ligands, which are said to **chelate** the metal. The simplest chelators are bidentate ligands involving functional groups like carboxylates and phosphate, which are capable of donating two lone pairs to a single metal (Figure B.X). In addition, a variety of synthetic species have been developed that place electron donating groups in a geometry that is well-suited to the geometric preferences of a given metal ion. For example, EDTA is a hexadentate ligand that can donate six electron pairs in an octahedral geometry (Figure B.7). Chelators bind metals tightly in part because of the favorable entropy of association. When the hexadentate ligand ethylenediamine tetraacetate (EDTA) binds to a metal that had previously been solvated by six solvent molecules, the ΔS value reflects the change from two independent dissolved species to seven.

Proteins frequently act as chelators. There are instances in which the fully solvated metal ion is bound intact, but much more frequently metal binding sites in proteins replace the water ligands of the solvated metal ion with atom groups from the protein. Thus, it is possible to see an endothermic binding event driven by the entropy of the "chelate effect".