

Metals in Medicine

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A John Wiley and Sons, Ltd., Publication

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*To my wife, Tatiana, 'Tati'
without whose love, support and understanding
this book would not have been possible*

Barnett (Barney) Rosenberg, the discoverer of cisplatin, was a remarkable scientist. He transformed a laboratory discovery into one of the most important drugs for treating cancer and he did it in an era with no previous success of a metal-based anticancer drug. The story of cisplatin will always be inspirational to the budding scientist, sustaining to those doing research in the field and motivational to all pursuing the unknown. Barney Rosenberg passed away on August 8, 2009. He will be greatly missed.

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Preface

Metals in Medicine is a textbook for undergraduate and graduate students in chemistry, biochemistry, biology and the related areas of biophysics, pharmacology and bioengineering. The first chapter of the book presents basic bonding concepts in inorganic chemistry and provides a brief overview of the physical and chemical properties of metal complexes using concepts and ideas presented in general chemistry. The more demanding concept of quantum mechanics, although not generally discussed in beginning level chemistry courses, is also briefly covered at an easy-to-understand level in Chapter 1. Chapter 2 emphasizes the nature and structure of biological targets, the reactivity of metal complexes in the biological milieu, and methods for measuring the efficacy and toxicity of agents. The steps from drug discovery to marketplace are also briefly outlined and discussed in this chapter.

The remaining six chapters of *Metals in Medicine* focus on individual metallo-drugs, drug candidates and metal-containing agents used to treat and diagnose disease, their synthesis, structures, formulations, pharmacokinetics and known mechanisms of action, and important physical and chemical principles that apply, while the last chapter addresses the role of inorganic chemistry in the emerging and exciting field of nanomedicine.

No attempt was made to cover all of the metal-containing compounds that are actively being used or being considered for use in medicine, but rather select topics were focused upon, in order to present a brief overview of the area, stressing important chemical, physical and biological principles, and pointing out where the area might be headed. It was felt that this was the best way to prevent 'saturation' and leave room for the motivated student to discover more on their own.

Chapter 3 of the text covers cisplatin, which is arguably the most important metal-containing agent used in medicine and without which this book would not be possible. In this chapter, the student is introduced to how cisplatin was discovered, its physical and chemical properties, and possible methods by which it may kill cancer cells, covering mechanisms that involve DNA as well as protein targets in the cell. Chapter 4 discusses the later-generation cisplatin analogues, carboplatin and oxaliplatin, which are in worldwide use for treating cancer, as well as other platinum drugs that have gained regional approval and a select number of platinum drug candidates that are in clinical trials. The huge success of cisplatin prompted the search for other metal complexes with antitumor properties and Chapter 5 addresses compounds of ruthenium, titanium and gallium that exhibit anticancer activity. In order to emphasize the breadth of application of inorganic chemistry in medicine, the use of gold complexes for treating arthritis, cancer and other diseases is presented in Chapter 6, while the use of vanadium for treating diabetes, copper in Wilson's, Menkes and Alzheimer's diseases, and zinc-bicyclam as a stem-cell mobilizing agent and for potentially treating AIDS are covered in Chapter 7.

Although metal-containing agents have had a major impact on treating disease, they are also widely used for disease detection. Chapter 8 outlines the importance of radioactive technetium complexes in diagnostic nuclear medicine and discusses the use of paramagnetic gadolinium compounds as contrast enhancing agents in magnetic resonance imaging, MRI. This chapter also briefly discusses the use of radioactive agents for palliative care and cancer treatment in radioimmunotherapy.

Chapter 9 covers the design and construction of nano-size structures for biomedical applications in nanomedicine. Since nanomedicine is one of the most dynamic areas of science, presenting all of the developments in the field with an inorganic theme proved impossible, so a limited number of examples, chosen

largely because they extend the information in previous chapters, are presented and discussed. Although nanomedicine has enormous potential, the fact that nanomaterials are totally alien to the biological system has raised serious questions about the health risks that they may pose to humans. This topic is also discussed in Chapter 9.

Throughout the book are Feature Boxes that expand important concepts in metals in medicine, including relevant physical techniques, structures of biological targets and transport molecules, the discovery of cisplatin, synthesis of compounds, special assays and principles behind medical techniques. Although the Feature Boxes were not intended to be comprehensive, they provide sufficient information to show 'how things work', with additional information being found in the extensive list of references at the end of each chapter. Following each chapter are specifically designed problems, with solutions, that allow the student to apply the laws of thermodynamics and the principles of equilibrium and kinetics to problem solving in the topic being addressed.

While this textbook is designed for teaching a one-semester course on the role of metal complexes in medicine, it could also be used to teach basic coordination chemistry against the exciting backdrop of metals in medicine. It has been the author's experience that students with no previous background in inorganic chemistry and with sights on careers in medicine will easily accept learning some of the most challenging aspects of inorganic chemistry as long as the ultimate goal is learning how metal-containing agents are used in medicine. It is also clear that those students who are committed to chemistry and its related disciplines find the subject matter totally intoxicating and easily acclimatize to the many biochemical and medical aspects that metals in medicine involves.

In reading the extensive volume of literature needed to write this book, the author was impressed, indeed humbled, by the huge body and quality of work produced by investigators in the field. Clearly, many decisions needed to be made about what or what not to include, but in the end the guiding principle was on what to tell students wishing to gain an overview of an exciting area of science and, most importantly, to let them see how they might fit into the area and ultimately how they could help to move it forward. Since selection was of course carried out by the author, he accepts full responsibility for the emphasis of the book and any omissions and inaccuracies that it may contain.

James C. Dabrowiak
May 2009

Web Site

PowerPoint slides of all figures from this book, along with the solutions to the problems, can be found at <http://www.wiley.com/go/dabrowiak>.

Acknowledgments

It is difficult to write any book without the help, encouragement and support of many people. Special thanks to a professional colleague and personal friend, Jerry Goodisman, who read and commented on various parts of the manuscript for its substance and technical accuracy, and thanks also to many professional colleagues and support staff at Syracuse University for their insight and suggestions. Dr Matthew D. Hall at the National Institutes of Health suggested many important concepts and ideas in the development stage of the book that were ultimately incorporated into the finished manuscript. Through the years a number of outstanding graduate students, because they often focused thinking in unexpected directions, have helped shape the views of the author, and thus their influence is also in this work. Gratitude is also expressed to the graduate and undergraduate students in the 2009 edition of the course 'Metals in Medicine', who helped to make many sections of the book stronger as the manuscript was being written. Spending countless hours reading and writing is a strain on a relationship and my wife, Tatiana, deserves enormous credit for understanding what needed to be done and, most importantly, for 'being there' when things were not going as well as they might.

1

Inorganic Chemistry Basics

No description of the metal-containing compounds that have found their way into medicine would be useful without first providing basic information on the bonding in metal complexes, their spectral and magnetic properties and, most importantly, the manner in which they react with water and biological targets in the cell. The approach taken in this chapter assumes background knowledge of general and organic chemistry with no previous exposure to inorganic chemistry, as would occur in a junior- or senior-level course at most universities. The concepts presented are for the most part intuitive, requiring basic knowledge of chemistry and physics, but sometimes more abstract issues like quantum mechanics – which explains the spectral properties of metal complexes – will also need to be covered. The overall goal of this chapter is to bring all readers to a common level, providing them with the ‘core’ of information needed to understand how and why, from the chemical perspective, metal complexes play important roles in medicine.

1.1 Crystal field theory

The bonding that exists in metal complexes, their spectral and magnetic properties and their chemical reactivity are not easily explained using a single theory. However, one approach that is often used in a basic presentation of bonding concepts in transition metal chemistry is crystal field CF theory, which because it is based on simple electrostatic arguments, is relatively easy to understand. In CF theory and MO theory the interactions between the metal ion (M) and the groups attached to it (called ligands and denoted by L) are considered to be electrostatic in nature and the bonding in the compound is described as being salt-like in character. The metal ion, a *cation*, electrostatically interacts with a series of surrounding ligands, which are usually negatively charged or, if they are uncharged, have the negative end of a dipole directed toward the metal ion. Barring any serious steric interactions between the ligands, the arrangements about the metal ion generally have high-symmetry geometries. For example, a 6-coordinate complex – that is, a compound with six ligands attached to the metal ion – has an octahedral arrangement of ligands, while five-coordinate complexes have square or trigonal bipyramidal arrangements, four-coordinate structures are tetrahedral and square planar, and so on. These geometries, along with compounds and intermediates commonly encountered in metal complexes used in medicine, are shown in Figure 1.1.

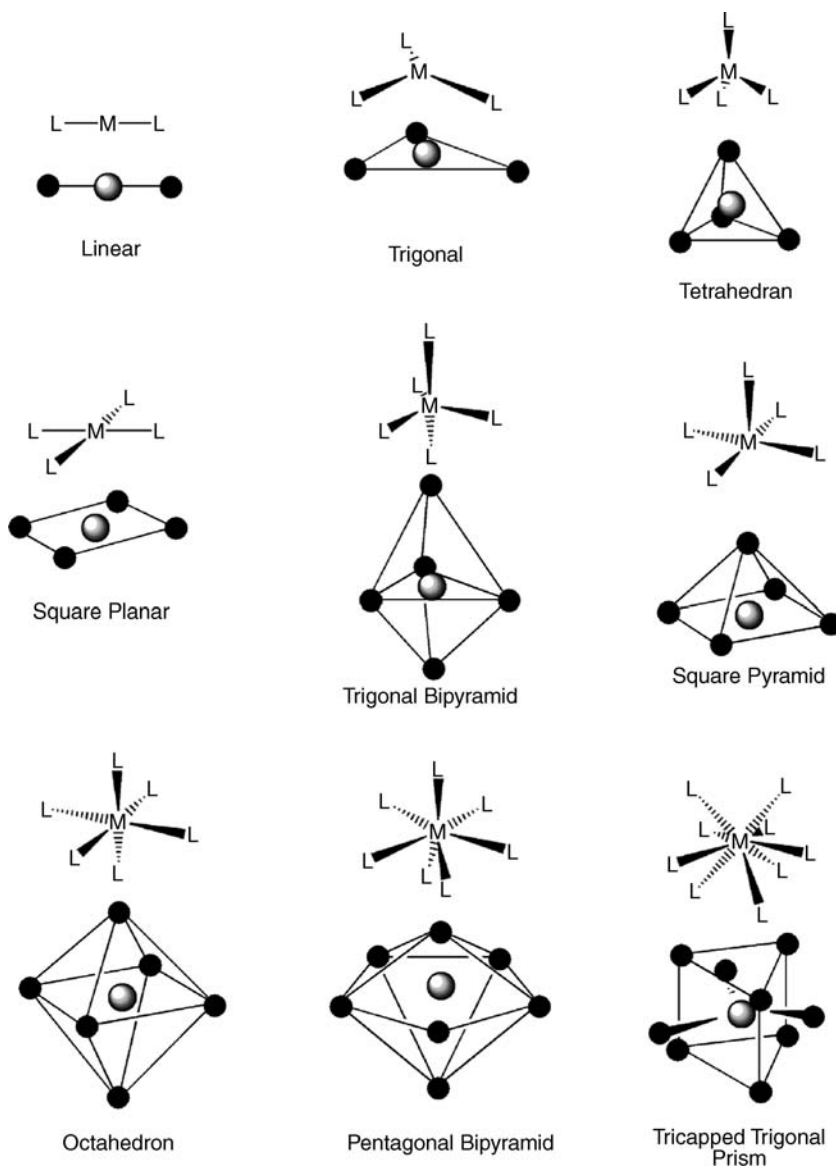


Figure 1.1 Common geometries of metal complexes and intermediates found in inorganic chemistry

1.1.1 Octahedral crystal field

The first-row transition metal series, which begins with scandium, Sc, fills the $3d$ level of the atom, while the second- and third-row transition metal series, which begin with yttrium, Y, and lanthanum, La, respectively, fill the $4d$ (second row) and $5d$ (third row) orbitals of the atom. The transition metal ions and the electronic configurations of common oxidation states are shown in Figure 1.2. Since ions of these elements have electron occupancies in the d level, which is considered the ‘valence’ level of the ion, CF theory focuses on the change in energy of the d -orbitals when charges representing the ligands approach the metal ion and form salt-like bonds.

	3 3B	4 3B	5 5B	6 6B	7 7B	8 8B	9 8B	10 8B	11 1B	12 2B
Ions	+2, d^1 +3, d^0	+2, d^2 +3, d^1 +4, d^0	+2, d^3 +3, d^2 +4, d^1 +5, d^0	+2, d^4 +3, d^3 +4, d^2 +5, d^1 +6, d^0	+1, d^6 +2, d^5 +3, d^4 +4, d^3 +5, d^2 +6, d^1 +7, d^0	+2, d^6 +3, d^5 +4, d^4	+2, d^7 +3, d^6 +4, d^5	+2, d^8 +3, d^7 +4, d^6	+1, d^{10} +2, d^9 +3, d^8	+2, d^{10}
1 st Row $3d^n$	21Sc	22Ti	23V	24Cr	25Mn	26Fe	27Co	28Ni	29Cu	30Zn
2 nd Row $4d^n$	39Y	40Zr	41Nb	42Mo	43Tc	44Ru	45Rh	46Pd	47Ag	48Cd
3 rd Row $5d^n$	57La	72Hf	73Ta	74W	75Re	76Os	77Ir	78Pt	79Au	80Hg

Figure 1.2 Transition metal ions and their electronic configurations for various oxidation states

The spatial arrangements of the five d -orbitals on a Cartesian coordinate system are shown in Figure 1.3. The shapes shown represent the probability of finding an electron in a volume of space about the nucleus of the metal ion. If the metal ion has no bonded ligands – this is referred to as a *free ion* – the energies of all five d -orbitals will be the same and are said to be *five-fold degenerate* in energy. This situation is shown on the left side of Figure 1.4. Let's suppose that instead of existing as a free ion, the metal ion is part of a stable complex consisting of six negatively-charged ligands bound to the metal ion in an octahedral array. The way that crystal field theory approaches this situation is to consider what happens to the five d -orbitals in the

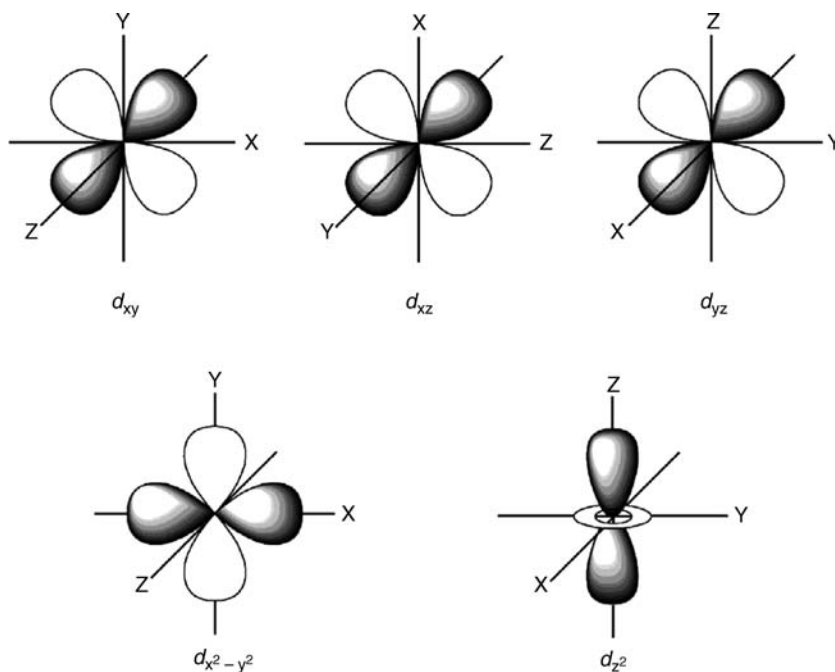


Figure 1.3 Boundary surfaces of the five d -orbitals

electrostatic field set that is up by the ligands. The first thing that the theory does is to consider a situation in which the total negative charge of the ligands is ‘smeared’ equally over the surface of a sphere with a radius equal to the metal–ligand bond distance and with the metal ion at its center. Since the d -orbitals have electrons in them and the surface of the sphere is negatively charged, the energies of the d -orbitals will be raised; that is, they will become less stable relative to the free ion, due to electrostatic repulsion between the d -electrons and the negatively-charged surface of the sphere. Since the charge on the sphere has no ‘directionality’ – that is, the negative charges are equally distributed over the entire surface of the sphere – all five d -orbitals must experience the same electrostatic perturbation from the sphere and move as a group to a new energy, E_o (see Figure 1.4). The next step is to redistribute the charge on the surface of the sphere and concentrate it at the six points where the axes penetrate the sphere. If the charge at each of the six points is identical, this will produce a perfect octahedral crystal field about the central metal ion and simulate what the d -orbitals experience in an octahedral metal complex. It should be evident that since $d_{x^2-y^2}$ and d_{z^2} are pointed directly at the charges (ligands), they must experience a different perturbation than the three orbitals, d_{xz} , d_{yz} , d_{xy} , that are directed between the charges. While it may not be obvious that both $d_{x^2-y^2}$ and d_{z^2} should experience an identical perturbation from the octahedral field, quantum mechanics shows that d_{z^2} , which has a ring of electron density in the xy plane (Figure 1.3), is actually a composite of two orbitals that are identical to $d_{x^2-y^2}$ except that they lie in the yz and xz planes. Thus, since d_{z^2} is a composite of two orbitals that look like $d_{x^2-y^2}$, it makes sense that the crystal field will affect d_{z^2} and $d_{x^2-y^2}$ identically, as shown in Figure 1.4. It should also be evident that since these orbitals are pointed directly at the ligands, they feel the electrostatic repulsion directly, and thus their energies are *raised* relative to the energy of the spherical field, E_o . It is possible to show that if the total charge on the sphere is simply rearranged or ‘localized’ to certain positions on the sphere, the energy of the system cannot change; that is, E_o for the sphere and the octahedral field must be the same. This is the *center of gravity* rule, which applies to electrostatic models of this type. The consequences of this is that if two orbitals,

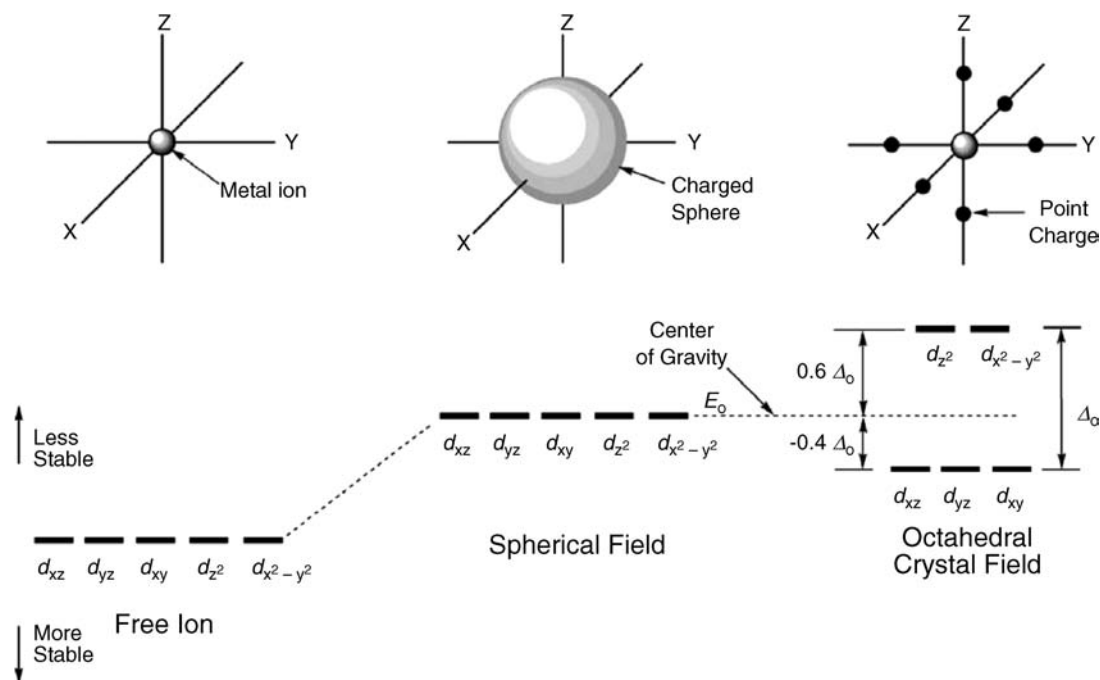


Figure 1.4 Generation of the octahedral crystal field from the free ion

$d_{x^2-y^2}$ and d_{z^2} , are raised by a certain amount, the remaining three, d_{xz} , d_{yz} , d_{xy} , must be *lowered* by a certain amount. Inspection of the shapes and orientations of d_{xz} , d_{yz} , d_{xy} shows that since these orbitals are directed 45° to the axes of the system, and each is related to the others by a simple rotation, all must experience exactly the same perturbation from the charges which are on the axes of the system. This set of orbitals, which are ‘triply degenerate’, is often referred to as the ‘ t_{2g} ’ set due to its symmetry properties. In a similar fashion, the orbitals, $d_{x^2-y^2}$ and d_{z^2} which are ‘doubly degenerate’ are referred to as the ‘ e_g ’ set. The labels t_{2g} and e_g are products of the application of *group theory*, a mathematical tool for characterizing the symmetry properties of molecules.

Simple electrostatic arguments show that the spacing between the t_{2g} and e_g levels depends on the distance that the charge is from the origin of the system and the magnitude of the charge. If the distance is decreased or if the magnitude of the negative charge is increased, the splitting between t_{2g} and e_g will increase. As we will see, metal complexes can be made with a wide variety of attached ligands, some of which are negatively charged, for example, Cl^- , CN^- and so on, and some of which are electrically neutral, for example, H_2O , NH_3 and so on. However, one thing that all ligands have in common is that they direct electrons, usually a lone pair, toward the metal ion, and these electrons become the ‘point charges’ in the crystal field model describing the electronic structure of the complex. Since the ability of different ligands to perturb the d -orbitals varies considerably, the splitting between the t_{2g} and e_g sets of orbitals can be quite different for different complexes. In order to address this, crystal field theory denotes the splitting between the t_{2g} and e_g sets as Δ_o , which is the *crystal field splitting parameter*. The subscript ‘o’ in Δ_o indicates that a crystal field of octahedral symmetry is being addressed. If there are no attached ligands – that is, in the free ion case – there can be no crystal field and Δ_o is zero. Since the splitting between the levels is different for different metal complexes, Δ_o , which carries units of energy usually expressed in wavenumbers (cm^{-1}), varies over a wide range. However, the relative displacement of the t_{2g} and e_g levels *in terms of* Δ_o from the center of gravity, E_o , is the same for all octahedral complexes with the e_g level at $0.6 \Delta_o$ and the t_{2g} level at $-0.4 \Delta_o$. These values arise because $(2 \text{ orbitals}) \times (0.6 \Delta_o) + (3 \text{ orbitals}) \times (-0.4 \Delta_o) \equiv 0$, which satisfies the center of gravity rule. It should be evident that E_o is the *average crystal field*.

1.1.2 Other crystal fields

Numerous anticancer drugs containing Pt^{+2} have a square planar geometry in which four ligands at the corners of a square are bonded to the metal ion (Figure 1.1). The best way to generate the square planar crystal field splitting pattern for the d -orbitals is to first consider an intermediate field called the *tetragonal crystal field*. Suppose that the charge on each of the two point charges on the plus and minus z -axis of the octahedral crystal field is slightly reduced in magnitude relative to the other four charges in the plane or, the equivalent situation, wherein the magnitude of the charges on the plus and minus z -axis remain unchanged but the charges are moved to greater distance from the metal ion than the four charges in the plane. In this case, the electrostatic field on the z -axis is *less than* the field seen by the metal ion on the x - and y -axes of the system. As a consequence of this *asymmetry* or non-equivalence in the field, all orbitals with z -components – that is, d_{xz} , d_{yz} and d_{z^2} – will have their energies *lowered*; that is, they will become *more stable* in the applied field (Figure 1.5). Since d_{z^2} is pointed directly at the weaker charges on the z -axis, it must experience greater stabilization – that is, more lowering – than d_{xz} , d_{yz} , which are directed away from the point charges. As a consequence of the center of gravity rule, if some levels go down in energy, others – that is, $d_{x^2-y^2}$ and d_{xy} – must become *less stable* and their energies must be raised.

The limiting case of the tetragonal distortion is the *square planar geometry* in which the two charges on the z -axis have been reduced to zero; that is, there are only four charges in the plane of the system. The removal of the axial charges causes a significant stabilization in d_{z^2} , which moves downward in the energy diagram and passes below (becomes more stable than) the d_{xy} orbital. Since d_{xz} , d_{yz} also have z -components, they are also stabilized by the loss of the axial charges, but to a lesser extent than d_{z^2} . The resulting crystal field splitting diagram, sometime called the *square planar limit*, is shown in Figure 1.5.

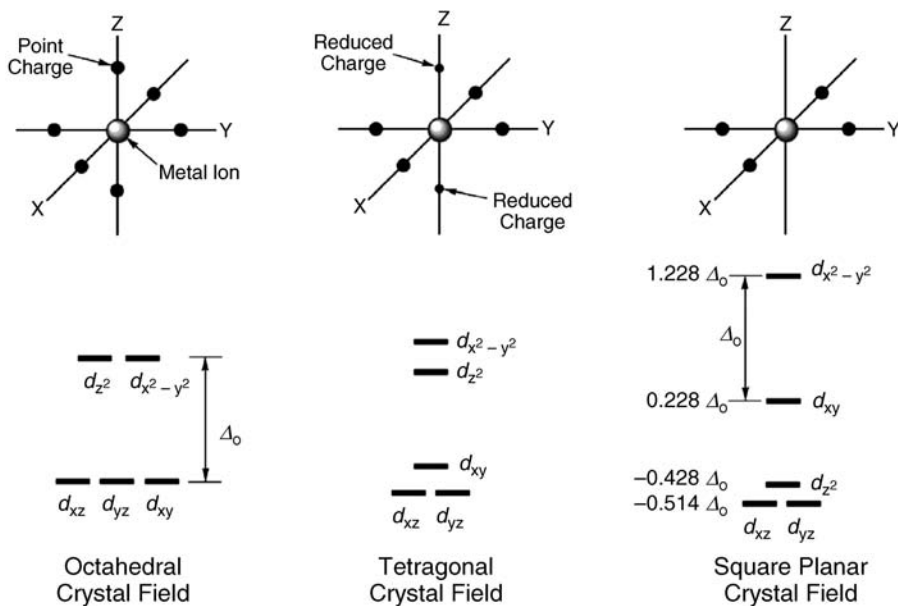


Figure 1.5 Octahedral, tetragonal and square planar crystal field

A second very common structure for metal complexes with four groups bonded to the central metal ion is the *tetrahedral* geometry (Figure 1.1). Compared to the previous examples, rationalizing the *d*-orbital splitting pattern for the tetrahedral geometry is less straightforward. Figure 1.6 shows a Cartesian coordinate system in the center of a cube. Placement of charges at opposite corners of opposite faces of the cube and hypothetically connecting them to the metal ion in the center of the cube generates the tetrahedral geometry; that is, all charge–metal–charge angles are 109.5° . It should be evident from the figure that none of the *d*-orbitals point directly at the charges, and although other relative arrangements of the cube on the *d*-orbital coordinate system are possible, all lead to the conclusion given for the splitting pattern shown in Figure 1.6. The tetrahedral crystal field has a doubly degenerate set of orbitals, the d_{z^2} and $d_{x^2-y^2}$, termed for symmetry reasons the ‘*e*’ set, which is *lowest* in energy, and a triply degenerate set, d_{xz} , d_{yz} and d_{xy} , called the ‘*t*₂’ set, which is *highest* in energy. While this pattern is exactly the opposite of the octahedral case, the labels *e* and *t*₂, which also come from group theory, are missing the subscript ‘*g*’. This is because the octahedron has a symmetry element called the *center of inversion* (*i*), which is associated with a mathematical operation in which each point charge of the

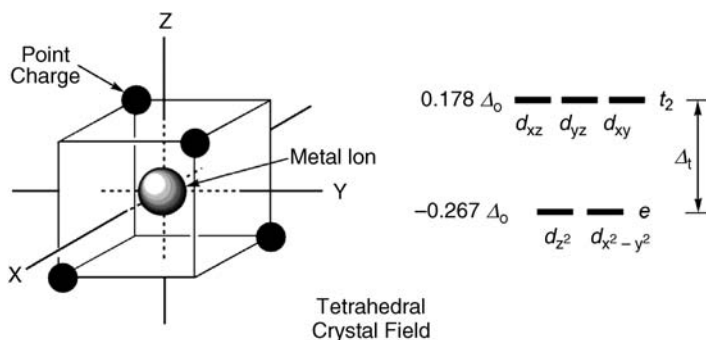


Figure 1.6 Tetrahedral crystal field

Table 1.1 Relative energies of the *d*-orbital in various crystal fields^a

CN	Structure	d_{z^2}	$d_{x^2-y^2}$	d_{xy}	d_{xz}	d_{yz}
2	Linear ^b	1.028	-0.628	-0.628	0.114	0.114
3	Trigonal ^c	-0.321	0.546	0.546	-0.386	-0.386
4	Tetrahedral	-0.267	-0.267	0.178	0.178	0.178
4	Square Planar ^c	-0.428	1.228	0.228	-0.514	-0.514
5	Trigonal Bipyramid ^d	0.707	-0.082	-0.082	-0.272	-0.272
5	Square Pyramid ^d	0.086	0.914	-0.086	-0.457	-0.457
6	Octahedron	0.600	0.600	-0.400	-0.400	-0.400
7	Pentagonal Bipyramid ^d	0.493	0.282	0.282	-0.528	-0.528
9	Tricapped Trigonal Prism	-0.225	-0.038	-0.038	0.151	0.151

^aValues given are in units of Δ_o .

^bLigands or charges are along the z-axis.

^cLigands or charges are in the xy plane.

^dPyramid base in xy plane. From Table 9.14, p. 412 of Huheey, J.E. (1983) *Inorganic Chemistry: Principles of Structure and Reactivity*, 3rd edn, Harper & Row Publisher, New York.

structure can be passed along a straight line through the central metal ion to reach an identical point charge (Figure 1.5). Since *i* is not present in the tetrahedron, the subscript ‘g’ is missing from the labels. Although the tetrahedral pattern is the exact opposite of the splitting pattern for the octahedron, the magnitude of the splitting between the *e* and t_2 levels for the tetrahedral geometry, denoted as Δ_t , is only 4/9 the value of the splitting between t_{2g} and e_g of the octahedron; that is, $\Delta_t = 4/9 \Delta_o$ or $0.445 \Delta_o$. Thus, for the tetrahedron, the t_2 orbital set is at $0.178 \Delta_o$ and the *e* orbital set is at $-0.267 \Delta_o$.

Table 1.1 gives the energies of the five *d*-orbitals for common geometries in terms of the octahedral crystal field splitting parameter, Δ_o . The values in the table, which were calculated using a point charge crystal field model, can be used to determine the orbital energy diagrams for geometries other than the octahedral, tetrahedral and square-planar geometries discussed above. The entries in the table assume that if there is more than one electron in the pattern, which is almost always the case, there is no interaction between the electrons, which is never the case. The energies given are the so-called *one electron energies* for the various orbitals in the different crystal fields. If there is more than one electron in the pattern, the electrons can be in the same or different orbitals and will ‘see’ each other through what are called *configuration interactions*, and the energies of levels given in Table 1.1 will be adjusted to new values. Since determining the new energies of the orbitals is beyond the scope of our work, and changes are in most cases small, the entries in Table 1.1 are reasonable approximations for all multiple-electron systems encountered in this text.

1.1.3 Factors affecting the crystal field splitting parameter, Δ

1.1.3.1 Spectrochemical series

As was earlier pointed out, the point charges used to generate the splitting patterns for various geometries simulate the electrostatic effects of ligands that are bonded to the metal ion. Extensive spectral and magnetic studies on a large number of transition-metal complexes showed that the electronic effect exerted by a specific ligand on the *d*-orbitals of the metal ion is essentially a property of that ligand and independent of the geometry of the complex, the nature of the metal ion or its oxidation state. This characteristic allowed ranking of common ligands in terms of their ‘*d*-orbital splitting power’, to produce a series called the *spectrochemical*

Table 1.2 Factors affecting the crystal field splitting parameter, Δ

The Ligand ^a	<i>Spectrochemical Series, Increasing Δ</i> $I^- < Br^- < S^{2-} < NCS^- < Cl^- < NO_3^- < N_3^- < F^- < OH^- < C_2O_4^{2-} \approx H_2O < \underline{NCS}^-$ $< CH_3CN < NH_3 < en < bipy < phen < \underline{NO}_2^- < PPh_3 < \underline{CN}^- < \underline{CO}$
The Metal Ion	<i>Principal Quantum Number, n</i> First-row transition metal ion, 3d level, Δ^{3d} Second-row transition metal ion, 4d level, $\Delta^{4d} \sim 1.5 \Delta^{3d}$ Third-row transition metal ion, 5d level, $\Delta^{5d} \sim 1.75 \Delta^{3d}$
The Metal Ion	<i>Oxidation State, Increasing Δ</i> $M^+ < M^{+2} < M^{+3} < M^{+4} < M^{+5}$

^aThe underscored atom is the donor atom to the metal ion. *en*, ethylenediamine, 1, 2 diaminoethane; *bipy*, 2, 2' bipyridine; *phen*, 1, 10 phenanthroline.

series (Table 1.2). Ligands on the left of the series, which are referred to as *weak field ligands*, for example I^- and Br^- , cause a small splitting in the *d*-orbitals, while ligands on the right of the series, for example CN^- (cyanide), CO (carbon monoxide) – *strong field ligands* – cause a large splitting in the orbitals. While there is little doubt that the order of the ligands in the series is correct (the order is obtained from experiment), the series does not seem to follow our intuitive feeling about which ligands should be high in the series and which should be low. For example, CO, which is uncharged, is highest in the series but iodide, I^- , which is negatively charged, is lowest in the series. Based on the electrostatic arguments put forth in connection with the crystal field this makes little sense: I^- should have a *greater* perturbation on the *d*-orbitals than uncharged CO. Clearly, factors other than simple electrostatic effects must influence Δ_o . While the crystal field model works well for most of the cases encountered in this text, complexes which have considerable overlap between the orbitals on the metal and ligand – that is, when covalent bonding is present – cause the theory to ‘bend’ but not completely break down. How basic crystal field theory needs to be modified to accommodate this will be addressed in a later section.

1.1.3.2 Principal quantum number, n

While the spectrochemical series rank orders the experimentally-measured effects of ligands on the splitting of the *d*-orbitals, it is also possible to make some general statements concerning the effects of the metal ion on the magnitude of Δ . If one moves down a given column in the periodic chart, the quantum number n , which is called the *principal quantum number*, increases. For example, the first-row transition metal series elements have electrons in the 3d ($n = 3$) level, the second-row in the 4d ($n = 4$) level and the third-row in the 5d ($n = 5$) level of the atom. Experimentally, it has been found that the magnitude of the crystal field splitting parameter Δ increases in the order $3d < 4d < 5d$, with $\Delta^{4d} \sim 1.5 (\Delta^{3d})$ and $\Delta^{5d} \sim (1.75 \Delta^{3d})$ (Table 1.2). The effects of this increase with n can easily be seen for the series $[Co(NH_3)_6]^{3+}$, $3d^6$, $[Rh(NH_3)_6]^{3+}$, $4d^6$ and $[Ir(NH_3)_6]^{3+}$, $5d^6$, which have identical geometries (octahedral), ligands (ammonia) and metal ion oxidation states (+3), and belong to the same family (column) of the periodic chart. The values of Δ_o for these complexes are $\sim 22\,000\text{ cm}^{-1}$, $\sim 34\,000\text{ cm}^{-1}$ and $\sim 41\,000\text{ cm}^{-1}$, respectively, which shows that moving down a given column in the periodic chart does indeed cause the values of the crystal field splitting parameter to *increase* by the approximate amounts given. Since atoms, and ions, become larger with atomic number, M–L bond lengths increase in moving from the first to the second and third rows of the transition metal series. Simple point-charge arguments would predict that if the M–L distance were increased, the magnitude of Δ would *decrease*, not increase as observed. The fact that the opposite is found is further proof that the simple point-charge model cannot be entirely correct and that other factors are important in determining the magnitude of Δ .

1.1.3.3 Metal ion oxidation state

Experimentally, it can be shown that *increasing* the charge on the metal ion – that is, increasing its oxidation state – causes the *d-d* absorption bands of the complex to shift toward the UV region of the spectrum, which means that Δ has *increased* (Table 1.2). Since the ionic radius of any ion decreases with an increase in the net positive charge on the ion, the *distance* between the metal ion and its bonded ligands must decrease when oxidation state is increased. Since decreased distance would lead to greater electrostatic repulsions between electrons on the metal ion and the ligands, the observed trends in Δ (with changes in oxidation state on the metal ion) *are* predicted by simple crystal field arguments.

1.1.4 High- and low-spin complexes

When considering the ways in which electrons can occupy energy levels of an atom, ion or molecule, *Hund's rule* states that the electronic configuration with the lowest overall energy is one for which the spins for the electrons are unpaired, even if it means placing electrons in a nearby less-stable orbital (level) in order to do so. For the free ion, the five *d*-orbitals are degenerate in energy and electrons are added to the orbitals by *maximizing the number of unpaired spins*. If, for example, there are four electrons in the *d*-level of a free ion, it is possible to place the electrons in the level in a number of different ways, some of which are shown in Figure 1.7. Experimentally, Figure 1.7a, which has the maximum amount of spin unpairing, is known to be the lowest-energy (most stable) configuration. When describing the electron spin of any system, it is best to use the value of the magnetic spin quantum number, m_s , associated with the spin angular momentum of the electron. Each electron has spin angular momentum of $\pm 1/2$ in units of $h/2\pi$. With n electrons, the maximum possible value of the *total magnetic spin quantum number* S is $n/2$ (all electrons unpaired) and the minimum possible value of S is zero (if n is even) or $1/2$ (if n is odd). For simplicity, the term $h/2\pi$, where h is Planck's constant, is usually dropped. Thus, for the configuration shown in Figure 1.7a, $S = (4)(1/2) = 2$, while S for Figure 1.7b is $(+1/2 - 1/2 + 1/2 + 1/2) = 1$ and for Figure 1.7c is $(+1/2 - 1/2 + 1/2 - 1/2) = 0$. Two factors associated with electronic configurations, *coulombic interactions* and *spin correlations*, form the basis for Hund's rule. Since placement of two electrons in the same orbital forces them to occupy the same regions of space, the coulombic repulsion between the electrons will be high, thus destabilizing the system. This obvious electrostatic repulsion makes it easy to see why maximum spin unpairing, maximum S , is desirable. While coulombic considerations are important, the ability to exchange one electron with another in a given configuration *without changing* S is even more important. This aspect of Hund's rule, which is a product of quantum mechanics, is called *spin correlation* or *exchange energy*. Both of these factors – coulombic (electrostatic) and spin correlation (exchange energy) – drive the system to obtain maximum spin unpairing,

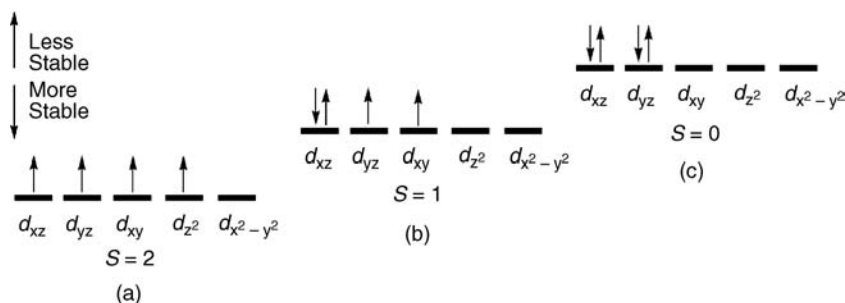


Figure 1.7 Some possible electronic configurations for the d^4 free ion and their respective values of S

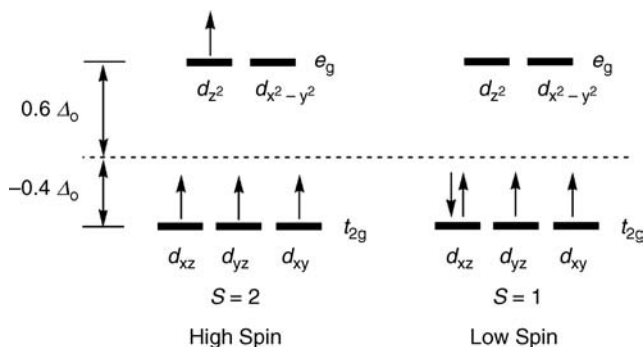


Figure 1.8 High and low spin possibilities for d^4 in an octahedral crystal field

and for the free ion case, where all of the d -orbitals have the same energy, *the configuration with the largest value of S always has the lowest, most negative, energy.*

In the presence of an octahedral crystal field the five d -orbitals are not degenerate in energy, and a decision needs to be made on how to place the electrons into the d -orbital pattern to create the lowest energy configuration. For example, d^4 in an octahedral crystal field can have two possible electronic configurations, which are shown in Figure 1.8. One situation, called the *high-spin* case, has one electron in each of the three t_{2g} orbitals and the fourth electron in one of the d -orbitals of the e_g level, giving $S = 2$. The energy gained by the system due to the presence of the crystal field is called the *crystal field stabilization energy* or *CFSE*, which in this case is $CFSE_{hs} = (3 \text{ electrons})(-0.4 \Delta_o) + (1 \text{ electron})(0.6 \Delta_o) = -0.6 \Delta_o$. This possibility can be written as $t_{2g}^3 e_g^1$. An alternative possibility for arranging the electrons in the levels is also shown in Figure 1.8. In this case all four electrons are in the t_{2g} set of orbitals and since *Pauli's principle* must be obeyed, two of the electrons in the same orbital must have their spin oppositely aligned. This gives $S = 1$ for the configuration, which is called the *low-spin* case. The crystal field crystallization energy for this configuration is $CFSE_{ls} = (4 \text{ electrons})(-0.4 \Delta_o) = -1.6 \Delta_o + P$, where P is the energy required for pairing two of the electrons in one of the orbitals. This possibility can be written as t_{2g}^4 . Since P is the energy *lost* due to coulombic and exchange effects, its sign is *positive*, meaning that it *destabilizes* the system. Which possibility is found – high-spin or low-spin – clearly depends on which CFSE – $CFSE_{ls}$ or $CFSE_{hs}$ – has the larger *negative* value. This can be found by equating $CFSE_{ls}$ to $CFSE_{hs}$, which gives $-1.6 \Delta_o + P = -0.6 \Delta_o$ or $P = \Delta_o$. If the ligands bonded to the metal ion produce a splitting in the d -orbitals with $\Delta_o > P$, the *low-spin* possibility, $S = 1$, will be more stable. If the ligands produce a splitting with $\Delta_o < P$, the *high-spin* situation, $S = 2$, will be more stable.

The electronic configuration, value of S and CFSE for weak and strong octahedral fields are given in Table 1.3. A point to make concerning the entries in Table 1.3 is that the value of CFSE given is the stabilization energy that the system accrues as a result of the presence of the crystal field. This means that the ‘reference point’ for determining the CFSE is the free-ion case. For example, for the strong-field configuration, t_{2g}^6 , which has $S = 0$, the value of CFSE in Table 1.3 of $-2.4 \Delta_o + 2P$ was determined by first writing the electronic configuration for the free-ion case and determining its energy in terms of P , the pairing energy. With six d -electrons and five orbitals, there must be one paired set of electrons or one unit of P for the free ion. Next, the energy of the system due to the presence of the crystal field, in terms of Δ_o and P , was written, which in this case is $-2.4 \Delta_o + 3P$. There are three pairs of electrons in the t_{2g} set of orbitals, hence $3P$, and the extra energy in terms of Δ_o due to the crystal field is $-2.4 \Delta_o$. Taking the difference between the energy in the presence of the field and the energy of the free ion gives $CFSE = -2.4 \Delta_o + 3P - P$ or $-2.4 \Delta_o + 2P$. The remaining entries in Table 1.3 were calculated in a similar fashion. The values of CFSE for crystal fields of other symmetries can easily be obtained using the energies of the orbitals given in Table 1.1. As described above, calculation of S and CFSE assumes that there is no configuration interaction; that is, electrons in the pattern operate as independent