I
Theory

In Part I of this book, we describe methods for molecular modeling, with special emphasis on empirical force field calculations. Molecular mechanics is an interpolative procedure, and its justification is that it works. However, there is a theoretical basis for force field calculations, and this will be provided in this Part of the book. The fact that molecular mechanics is a rather simplistic method implies that there are a number of dangers and limitations, and these must be discussed in detail to provide the reader with the ability to judge not only where these methods are applicable, but also what quality the predictions might be expected to have. Since the aim of Part I is to demonstrate these problems in an explicit manner, we might create a rather pessimistic view in terms of the accuracy, reliability, general applicability and scientific basis of the methods presented. This certainly is not our aim, as the applications discussed in Part II clearly reveal the potential of molecular modeling, enabling useful predictions to be made in many areas of inorganic chemistry.

Molecular Modeling of Inorganic Compounds. Third Edition.
Peter Comba, Trevor W. Hambley and Bodo Martin

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1
Introduction

1.1
Molecular Modeling

Advances in computing, and in the development of new methods in the area of computational chemistry, have greatly increased interest in computer-based molecular modeling. Today, molecular modeling is widely used as an aid in the interpretation of experimental results, and also in the design of new materials with desirable properties. Examples drawn from the area of inorganic chemistry include studies of the interaction of metal ions with proteins and DNA, as well as the design of new metal-based drugs, magnetic materials, metal-ion-selective ligands and stereospecific catalysts.

The basis of molecular modeling is that all important molecular properties – such as stabilities, reactivities and electronic properties – are related to the molecular structure (Figure 1.1). Therefore, if it is possible to develop algorithms that are able to calculate a structure with a given stoichiometry and connectivity, it must be possible to develop algorithms for the computation of the molecular properties based on the calculated structure, and vice versa. There are many different approaches and related computer programs, including *ab-initio* calculations, various semi-empirical molecular orbital (MO) methods, density functional theory (DFT) calculations, ligand–field calculations, molecular mechanics, molecular dynamics, quantitative structure–activity relationships (QSARs), neural networks and genetic algorithms that can be used to calculate structures and one or more additional molecular properties.

Before any computational study on molecular properties can be carried out, a molecular model needs to be established. This can be based on an appropriate crystal structure, or derived using any technique that can produce a valid model for a given compound, whether or not it has been prepared. Molecular mechanics is one such technique and, primarily for reasons of computational simplicity and efficiency, it is one of the most widely used. Quantum-mechanical modeling is far more computationally intensive, and has only recently been used routinely for metal complexes. The development of effective-core potentials (ECP) and DFT methods has made the use of quantum mechanics a practical alternative. This is particularly so when the electronic structures of a small number of compounds or isomers are required, or when transition states or excited states – which are not usually available in molecular

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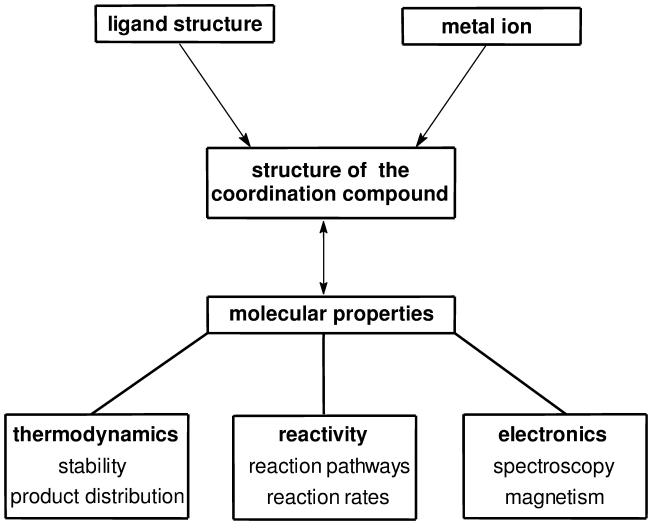

Figure 1.1 The relationship between the ligand and metal ion preferences, the resulting molecular structure, and the molecular properties.

mechanics – are to be investigated. However, molecular mechanics is still orders of magnitude faster than *ab-initio* quantum mechanics and therefore, when large numbers of compounds or isomers are to be investigated, molecular-mechanical methods are still preferred. Also, because of the speed of molecular-mechanics calculations, it is possible to highly optimize the force-field parameterization against a large set of compounds. With slower quantum-mechanical calculations the optimization and testing of basis sets, functionals and other variables against more than a few compounds is less feasible and, perhaps as a consequence, the balance between bonded and non-bonded forces is often better in molecular mechanics than in quantum mechanics. For example, DFT at the present time does not adequately describe dispersion interactions.

Molecular mechanics can be considered to arise from the Born–Oppenheimer approximation, which assumes that the motions of the nuclei of a molecule are independent of the motions of the electrons. In molecular-mechanics calculations, the arrangement of the electrons is assumed to be fixed and the positions of the nuclei are calculated. The basis of many quantum-mechanical calculations is, in contrast, that the electronic states can be calculated if the nuclei are assumed to be in fixed positions.

The basis of the molecular-mechanics method is that a good estimate of the geometry of a molecule can be obtained by taking into account all the forces between the atoms, calculated using a mechanical approach. For example, bonded atoms are treated as if they are held together by forces that behave as mechanical springs, while non-bonded interactions are taken to be made up of attractive and repulsive forces that together produce the typical van der Waals curve. The parameters that define the strength of the springs or the steepness of the van der Waals curves are derived, in the

first instance, from experimental observables such as infrared vibrational frequencies and gas compressibility data, or from quantum-mechanical calculations. However, the parameters are usually modified empirically to enhance the reproduction of experimentally determined geometries. In order to optimize the geometry of a molecule, the total energy that arises from these forces, or stresses, is minimized by computational methods. The minimized total energy is taken to be an indication of the strain present in the molecule. It is frequently referred to as the "strain energy" or "steric energy", and is related to the molecule's potential energy and stability. Some of the potential energy functions used to calculate the total strain energy of a molecule are similar to the functions used in the analysis of vibrational spectra. Because the parameters used to derive the strain energies from these functions are fitted quantities that are based on experimental data (e.g., X-ray structures or vibrational spectra), molecular mechanics may be referred to as "*empirical* force-field calculations" (more often the simplification "force-field calculations" is used). The quality of such calculations is strongly dependent on the reliability of potential energy functions and the corresponding parameters (the force field). Thus, the selection of experimental data to fit the force field is one of the most important steps in a molecular mechanics study. An empirical force-field calculation is, in essence, a method where the structure and strain energy of an unknown molecule are *interpolated* from a series of similar molecules with known structures and properties.

Molecular modeling of transition metal compounds is complicated by the partially filled d-orbitals of the metal ions that are responsible for the multifarious structures of coordination compounds with a large variety of possible coordination numbers and geometries. The coordination geometry of a metal complex is always a compromise between the size and electronic structure of the metal ion, and the type, size, geometry and rigidity of the coordinated ligands (see Figure 1.1). The fact that ligand–metal–ligand angles vary over a much larger range than corresponding parameters of organic molecules indicates that the competition between the ligand and metal ion in terms of coordination geometry is generally dictated by the ligand. Thus, the structure of a coordination compound – and therefore its thermodynamics, reactivity and electronics – is strongly influenced by the ligand structure. Since empirical force field calculations have been shown to be a powerful tool for estimating the structures of organic molecules, there is reason to expect that molecular mechanics may be a viable tool for modeling coordination compounds.

For a molecular-modeling technique to be useful and to achieve widespread application, it must readily and reliably reproduce molecular properties that closely resemble experimentally determined data. The molecular mechanics method has been successfully applied to a wide variety of problems in inorganic chemistry, and many of these are outlined in detail in Part II of this book. However, the varied chemistry – particularly of the transition metal elements – greatly complicates the molecular-mechanical analysis of such systems, and in some cases molecular mechanics alone is unable to predict the geometry of a metal complex. For example, the assumption that the nature of the bonding does not change with the structure may not be valid when there is π–bonding between the metal and the ligand, or when there is an equilibrium between two spin-states with similar energies. Coupling of the

molecular mechanics method with quantum-mechanical or ligand-field calculations has led to new models that can overcome some of these restrictions. The limitations of the classical molecular mechanics method as applied to metal complexes are discussed further in all three parts of this book.

1.2 Historical Background

Chemists in the 19th century were aware of the connectivity and the basic geometries of their molecules, and therefore of structural formulae, but they were unable to quantify the structures of molecules on a metric basis. In addition to chemical bonds, they were aware of van der Waals interactions, electrostatic interactions, steric hindrance, Kekulé conjugation, and donor–acceptor interactions. However, detailed information on electronic and molecular structure was lacking.

The 20th century brought two important advances. With the development of diffraction techniques, the arrangement of atoms could be determined on a metric basis. Depending on the size of the molecule, the quality of the crystal and the accuracy of the experiment, well-defined bond lengths, valence and torsional angles, as well as non-bonded contacts, could be determined.

The other development with far-reaching consequences was the Schrödinger equation ($H\Psi = E\Psi$). The problems encountered when solving the Schrödinger equation for complex molecular systems have resulted in the development of various approximations. The most important of these is the Born–Oppenheimer approximation, whereby the total energy of the molecular system is related to the coordinates of the nuclei. A quantitative description of a Born–Oppenheimer potential energy surface may solve many – if not most – chemical problems, although there is no efficient theoretical way to compute such a surface. The alternative, which has been developed during recent years, is to use empirical models, based on experimental data, to calculate potential energy surfaces, and molecular mechanics is the least computationally intensive method that is able to compute energetic and structural information (Figure 1.2).

The application of molecular mechanics to metal complexes developed in parallel with its application to organic molecules. Indeed, the earliest report that considered the importance of non-bonded interactions in determining the relative stabilities of isomeric molecules was a 1944 study of the six isomers of the coordination compound $[Co((S)\text{-pn})_2(NO_2)_2]$ (pn = propane-1,2-diamine) [1]. A number of similar, though more detailed, studies performed during the 1950s and 1960s [2–4] led to the

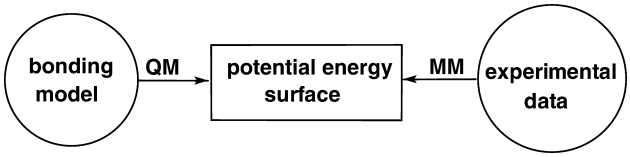

Figure 1.2 Computation of the potential energy surface.

full application of molecular mechanics to metal complexes. The common theme in these early studies was the measurement of non-bonded contacts, from physical (Dreiding) models, or their determination by vector analysis. The van der Waals energies of the shortest non-bonded interactions for a series of isomers were calculated and compared, the hypothesis being that the isomer with the fewest short, high-energy contacts would be the most stable. It was realized in these early investigations that this was a rather crude approach, with no account being taken of how other internal coordinates, such as bond angles, might adjust to accommodate and avoid close contacts, nor of the energy cost associated with the deformation of these internal coordinates.

In a series of more advanced studies, this problem was partially addressed by systematically adjusting a limited number of internal coordinates (bond lengths, valence angles and torsion angles) to find the geometry of metal chelates with the lowest energy [5–8]. However, due to the computational limitations of the time, the approach was limited in that only a small number of internal coordinates could be adjusted simultaneously. It became clear that methods for calculating the energy costs associated with deforming all of the possible internal coordinates (bond lengths, valence angles, torsional angles, non-bonded contacts), and for finding the geometry with the lowest deformation or strain energy were required.

At that time, the first applications of the currently employed molecular mechanics techniques, to organic molecules, were being reported [9–12]. In particular, the first report of the use of the Newton–Raphson method for strain–energy minimization appeared [13]. Subsequently, new force fields for modeling cobalt(III) complexes were developed and used with the Newton–Raphson method to determine the strain energies and minimum energy geometries of a number of complexes [14–16]. Since then, molecular mechanics has been used to model increasingly diverse metal-containing systems, and numerous reviews of these studies have been published (see Appendix 4).