Chapter 9. Integrated Molecular Modeling, Synthesis, and Characterization Experiments for the Undergraduate Inorganic Chemistry Laboratory. Introduction

Statement of the Problem.

As computational chemistry techniques are becoming widely used in the chemical sciences, students need exposure to this technology at the undergraduate level. Yet, there are few published examples of efforts made toward integrating and/or evaluating molecular modeling into the undergraduate curriculum. As such, the goal of this research is to develop an experiment for the undergraduate inorganic laboratory in which computational methods are used to strengthen, inform, supplement, and improve the depth of understanding that the students will gain from a project that has synthesis and characterization at its core. The integrated molecular modeling, synthesis, and characterization laboratory experiments are incorporated into the undergraduate inorganic laboratory curriculum, and subsequent evaluation is used to modify this curricular approach.

Molecular Modeling.

Chemistry is an experimental science. Much of the chemist's effort is spent making complexes and investigating the relationships between molecular structure, and the physical, chemical, or biological properties of various substances. Synthesis, characterization, and measurement of properties are repeated in a cycle until a complex with the desired properties is found. The introduction of molecular modeling techniques may aid the chemist in reaching the same goal - design of a useful system - while eliminating the mass production of potentially feasible complexes, as illustrated in Figure 9.1.[100] By investigating the properties computationally, time and resources may be saved. Computational modeling potentially minimizes:

1.) the time necessary to develop a new catalyst, drug, or polymer;

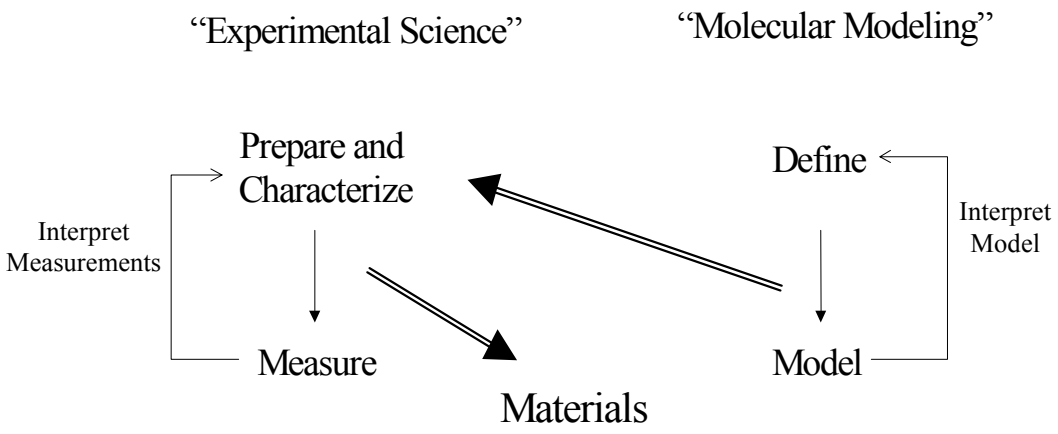
2.) the materials and laboratory spaces needed for research; and

3.) the production of hazardous wastes.

A wide variety of structural analogues can be easily investigated; only the most promising are then synthesized and characterized. Currently available computational software and theories are, however, limited in their capabilities; as such, although it is a useful tool, modeling can't be the mainstay of chemical research. In the book Using Computers in Chemistry and Chemical Education, Peter Lycos states,

> "In my view, the core of chemistry is organic plus inorganic chemistry, and its practice involves the determination of: (1) algorithms for synthesizing molecules, (2) mechanisms of (2) chemical reactions, and (3) models of molecular structure… I believe the advent of the computer not only gives us a major enhancement to the practice of chemistry but, in the process, offers a path to the refocusing and renormalization of the structure of chemistry as a discipline."[101]

Figure 9.1. Experimental Science Versus Molecular Modeling.[97]



There are many properties of chemical systems that can be studied with the use of molecular modeling techniques. A partial list of these properties is presented in Table 9.1. They will be discussed in the context of the computational technique(s) with which they correspond in Chapter 10. The focus of this molecular modeling literature discussion will remain on techniques used in the research at hand. Statistical dynamics, Monte Carlo,

MOPAC, and other computational techniques not pertinent to the research at hand will not be presented in any depth.

Table 9.1. Properties of Molecules that can be Studied Using Molecular Modeling, Select Examples.[100,102,103]

- Most stable geometry
- Bond lengths and angles
- Electron affinity and density
- Molecular orbitals
- Barriers to rotation
- Property mapping (e.g. electronegativity)
- Partial charges

Molecular Mechanics Calculations.

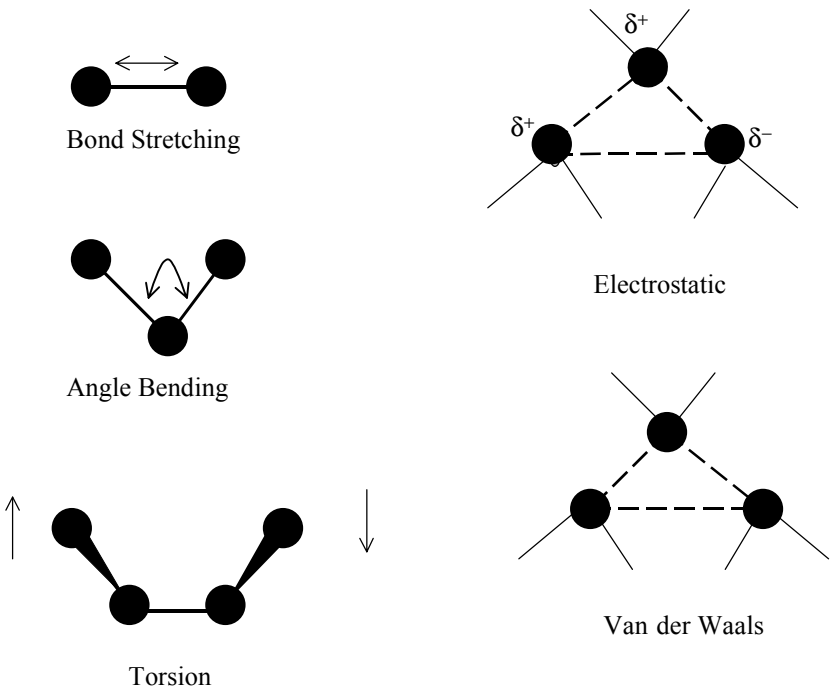
Molecular mechanics or "force field" calculations make use of techniques from Newtonian (classical) physics to calculate molecular geometries.[102-104] Force field methods calculate the energy of a molecule solely as a function of nuclear position.[104] All electronic motions and interactions of the systems are ignored. Therefore, molecular mechanics calculations are not used to calculate electronic properties such as the highest occupied molecular orbital (HOMO), which depend on the electronic structure. The molecule's potential energy is calculated by treating it (the molecule) as a set of spheres (atoms) and springs (bonds), and regarding the motion of this set. Molecular mechanics is still used for molecules with large numbers of atoms, where including the electronic factors for each would be tedious.

Most molecular mechanics algorithms can be described in terms of four components, which consist of the intermolecular and intramolecular forces taking place in the molecule.[104] These forces are described as: bond stretching, angle bending, torsion (bond rotation), and non-bonded interactions (electrostatic and van der Waals forces)

(Figure 9.2). How these terms are defined is called the "functional form" and depends on the calculational method used. The functional form and the force field constants (parameters) determine the potential energy of the molecule. The energy of the molecule is minimized by varying the coordinates of the spheres to find the global minimum.[100,104]

One of the most widely used sets of molecular mechanics force fields are Allinger's MM2 and MM3.[103,105-108] This thesis uses MM2 force fields. These force fields have been parameterized for sp, sp^2, sp^3, carbonyl, cyclopropane, cyclopropene, radical, and carbonium ion carbon atom types.[103,104] CAChe augments MM2 routine with additional parameters for square planar, trigonal bipyramidal, and octahedral atoms.[103]

Figure 9.2. Intramolecular and Intermolecular Terms in Molecular Mechanics Calculations.[100,104]



Spheres represent atoms, lines represent bonds within the plane, wedges represent bonds outside of the plane, and dotted lines represent intermolecular forces.

Quantum Mechanics Calculations.

Whereas force field techniques calculate the energy of a molecule solely as a function of nuclear position, quantum mechanics calculations address the system's electronic interactions. Quantum mechanics techniques are based upon the following principles:

1. the electrons and nuclei of a system are distinguished from each other;
2. electron/electron and electron/nuclei interactions are discrete;
3. interactions are governed by nuclear charges, electronic charges, and electron motions; and
4. interactions determine the spatial distribution of nuclei, electrons, and their respective energies. [100,104]

Obviously the foundations for quantum mechanical techniques lie in quantum theory. Quantum theory in based on Schroedinger's Equation (Equation 5).[105]

$$H\Psi = E\Psi \qquad (5)$$

Electrons are regarded as wave-like particles, whose wave properties are mathematically represented by a set of wavefunctions (Ψ) obtained by solving Schroedinger's equation.[100,109] As exact solutions to Schroedinger's equation can only be found for a few situations (e.g. harmonic oscillator, hydrogen atom, etc.), approximations must be made. The quantum mechanical approximation techniques used in molecular modeling are generally classified as either *ab initio* or semi-empirical approximations.[104]

The *ab initio* method makes use of the entire Hartree-Fock/Roothaan-Hall equations and does not ignore or approximate any of the Hamiltonian terms.[104, 110-111] This technique can be time- and computer - resource consuming and is generally limited to smaller molecules. This quantum mechanical method is not suited to our work.

Semi-empirical quantum mechanical calculation techniques neglect and approximate some of the terms used in the *ab initio* calculation, and add parameters to compensate for this. These approximations are done in part by considering only the valence electrons in the molecule, as these are mainly used in bonding and are

responsible for chemical phenomena. Two types of semi-empirical quantum mechanical calculation techniques are used in this research: Extended Huckel and ZINDO. It should be noted that there are many other semi-empirical quantum mechanics methods available. These vary widely in parameters and computational capabilities (for examples, see references 103,109,112).

Extended Huckel Theory.

Extended Huckel theory evolved from Huckel theory.[104] Huckel theory isolates a molecule's π-system and builds molecular orbitals for those specific electrons in accordance with the Aufbau principle.[104,109] As this technique can only be used for conjugated π-systems, it does not have many current applications in molecular modeling. However, the Extended Huckel theory, developed by Hoffmann in 1963, makes use of all of the valence electrons in a system.[109,113] Extended Huckel calculations are not restricted to conjugated π-systems. Extended Huckel calculations use ionization potentials that have been experimentally determined, and the calculations are therefore not as computationally tedious as other techniques.[104] Extended Huckel theory is noted for its ability to model metal complexes.[104]

ZINDO.

The ZINDO algorithm was developed by M. C. Zerner, ZINDO being the abbreviation for Zerner's Intermediate Neglect of Differential Overlap.[101,111] ZINDO makes use of the INDO/1 technique, developed by Pople, Beveridge, and Dobosh in the late 1960s.[104,115,116] The INDO/1 method allows for the interaction between electrons on the same atom with parallel spins to be at a lower energy than interactions between electrons with opposite spins.[104,115] This has been advantageous in energy/electron density calculations.[109] Like the Extended Huckel technique, ZINDO is an all-valence electron method. Wavefunctions used to optimize structure are single determinants.[110] ZINDO provides two different valence electron semi-empirical procedures: a technique to calculate molecular geometries (conformation and structure), and a technique to calculate electronic spectroscopic properties.[103] The elements for which the ZINDO

(INDO/1) algorithm are parameterized are presented in Chapter 10. Common limitations of the ZINDO algorithm occur in energy minimization calculations. With the ZINDO method, small strained rings are calculated to be very stable.[114] Therefore, molecules with multiple carbonyl ligands may find that the ZINDO optimized geometry converts the carbonyl carbons into a small strained ring instead.

Internet Resources for Molecular Modeling.

There is a ever-growing amount of information about the theory, applications, and available software for molecular modeling on the Internet. Although a comprehensive review of Internet sites for molecular modeling will not be presented, selected websites are provided here. The URL for each will be given in the body of this section. The links have been checked and were found to be active April 27, 2001.

1. National Institutes of Health (NIH) Center for Molecular Modeling (CMM).
http://cmm.info.nih.gov/modeling/

The NIH Center for Molecular Modeling website offers a wide range of computational chemistry resources. This site has links to tutorials, computational chemistry literature materials, hardware, software and general science information.

2. The NIH offers an additional resource titled "The NIH Guide to Molecular Modeling". This is listed separately because it is very difficult to find using the above address. This offers valuable information of computational theory.
http://cmm.info.nih.gov/modeling/guide_documents/background.html

3. The CAChe Molecular Modeling software package (Oxford Molecular, Ltd.) has recently been acquired by Fujitsu, Ltd. CAChe's new homepage is located at:
http://www.cache.fujitsu.com/

4. The Wilson-Squier Group at University of California, San Diego, has a site with materials on quantum mechanics presented at several different levels.

http://wilson-squier.ucsd.edu/education/

Molecular Modeling in Chemical Education.

As one might imagine, there are a variety of ways that molecular modeling techniques can be integrated into the undergraduate level curriculum. Several instructors have reported their efforts in incorporating as a discrete unit into the classroom or laboratory.[117-119] H. Dugas presented a report for the undergraduate molecular modeling course that he developed at the Universite de Montreal.[120] This paper was comprehensive, detailing topics, computer time, and approaches used.

Integrated molecular modeling experiments for use in the undergraduate laboratory have also been presented in the literature. These experiments have been largely organic/biochemical in nature, and have used molecular modeling with synthesis and/or characterization techniques. Lee and co-workers[121], Poon and co-workers[122], and Wigal and co-workers[123] have integrated molecular modeling techniques into laboratory experiments for organic chemistry. These authors have made use of molecular mechanics calculations as an investigational tool to aid students in understanding the reactivity and structure of organic molecules. Wolfson, Hall, and Branham have used computational techniques to study enzyme mutations in the biochemistry laboratory curriculum.[124] V. Box has published two papers discussing his use of molecular modeling techniques.[125-126] In his work, literature or laboratory-obtained values of bond length and bond order of aromatic systems are investigated for incorporation into both the organic laboratory curriculum and undergraduate research program.

There is also a series of examples sited in the literature for the educational use of molecular modeling in inorganic chemistry. Only a few will be cited here, these are the most relevant to the work at hand. It should be noted, however, that many educators do not publish their laboratory work, so there are most likely additional instances of integrated molecular modeling work that is not currently present in the literature. Aduldecha and co-workers have developed a series of modeling exercises for integration

into the inorganic chemistry curriculum.[127] These cover topics such as, inorganic stereoisomerization, space group model building, and plotting molecular structures. Modeling exercises are completed in tandem with their standard curricular material to enhance the level of student understanding and interaction. Zimmer and co-workers have also developed molecular modeling exercises for incorporation into the inorganic laboratory curriculum.[128] These modeling exercises are used with characterization techniques in the laboratory and classroom to improve the level of student understanding.

Evaluation Techniques in Chemical Education.

Evaluation in educational research is loosely defined. Methods are chosen according to the type of research (program) being carried out, the individuals involved (population), and the kind of information desired.[129,130] Research evaluations are classified as either formative or summative.[129] The formative style is qualitative, detailing the strengths and weaknesses of the research in question. This method is used if detailed comments and feedback about the project are the goal of evaluation. The summative style is quantitative, providing information as to the validity of the research in question. Whatever evaluation technique is utilized, biases, neutrality, and other seemingly external factors must be acknowledged by the interviewer. Common evaluation techniques include questionnaires, interviews, observations, and journals.[129,130]

Although new experiments and teaching techniques are continually introduced into the chemical education literature, few projects undergo a formal evaluation. This excludes standard course evaluations completed at the end of each offering. Evaluation styles used by chemical educators include questionnaires, testing, observation, and interviews. Williamson and Abraham completed a detailed statistical evaluation of their computer animation research.[131] This approach is of particular interest to those who prefer quantitative means of evaluation. It provides a thorough statistical treatment of student response.

However, if detailed comments and feedback from the students are desired, a statistical treatment is not the evaluation style of choice. Ram makes use of an interesting evaluation style[132]: self-evaluation and self-study logs are kept by each student and

studied by the instructor to see the progression of these traits over the course of the semester. These are reviewed at the completion of the semester to assess student response to topics, learning styles, and to obtain specific student thoughts. In addition, questionnaires are completed by the students, evaluating specific points about the laboratory. These three units are combined to produce the (qualitative) project evaluation. This evaluation technique provided detailed student comments, as well as response to specific questions posed by the instructor. The interview evaluation style has also been utilized, both in the research detailed herein and elsewhere.[133-135]