Computational Design of Metal Ion Sequestering Agents

EMSP Project No. 73759

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Research Objective

Organic ligands that exhibit a high degree of metal ion recognition are essential precursors for developing separation processes and sensors for metal ions. Since the beginning of the nuclear era, much research has focused on discovering ligands that target specific radionuclides. Members of the Group 1A and 2A cations (e.g., Cs, Sr, Ra) and the f-block metals (actinides and lanthanides) are of primary concern to DOE. Although there has been some success in identifying ligand architectures that exhibit a degree of metal ion recognition, the ability to control binding affinity and selectivity remains a significant challenge. The traditional approach for discovering such ligands has involved lengthy programs of organic synthesis and testing that, in the absence of reliable methods for screening compounds before synthesis, have resulted in much wasted research effort.

This project seeks to enhance and strengthen the traditional approach through computer-aided design of new and improved host molecules. Accurate electronic structure calculations are coupled with experimental data to provide fundamental information about ligand structure and the nature of metal-donor group interactions (design criteria). This fundamental information then is used in a molecular mechanics model (MM) that helps us rapidly screen proposed ligand architectures and select the best members from a set of potential candidates. By using combinatorial methods, molecule building software has been developed that generates large numbers of candidate architectures for a given set of donor groups. The specific goals of this project are:

• further understand the structural and energetic aspects of individual donor group- metal ion interactions and incorporate this information within the MM framework
• further develop and evaluate approaches for correlating ligand structure with reactivity toward metal ions, in other words, screening capability
• use molecule structure building software to generate large numbers of candidate ligand architectures for given sets of donor groups
• screen candidates and identify ligand architectures that will exhibit enhanced metal ion recognition.

These new capabilities are being applied to ligand systems identified under other DOE-sponsored projects where studies have suggested that modifying existing architectures will lead to dramatic enhancements in metal ion binding affinity and selectivity. With this in mind, we are collaborating with Professors R. T. Paine (University of New Mexico), K. N. Raymond (University of California, Berkeley), and J. E. Hutchison (University of Oregon), and Dr. B. A. Moyer (Oak Ridge National Laboratory) to obtain experimental validation of the predicted new ligand structures. Successful completion of this study will yield molecular-level insight into the role that ligand architecture plays in controlling metal ion complexation and will provide a computational approach to ligand design.
Research Progress and Implications

This project is a renewal of EMSP Project No. 73759 "Architectural Design Criteria for f-Block Metal Sequestering Agents" that began in September 2000 and ended in September 2003. This report summarizes progress after the first 8 months of the current 3-year period. Research focuses on two major areas. These are (1) expanding the functionality of our de novo structure-based design program, HostDesigner, and (2) application of computational methods to ligand design.

To bring the powerful concepts embodied in de novo structure-based drug design to the field of coordination chemistry, we have developed a computer program named HostDesigner with support from PNNL LDRD and Chemical Sciences, Office of Basic Energy Sciences, Office of Science, US DOE. This software builds millions of potential host structures from molecular fragments, screens the candidate structures with respect to their complementarity for a targeted metal ion guest, and outputs a list of lead candidates for further evaluation. One of the goals of this EMSP project is to couple the HostDesigner software with subsequent MM analyses to provide a more accurate prioritization of the candidates.

In a collaboration with Dr. Kevin E. Gilbert (Serena Software), we are working to automate fully the MM post-processing by breaking it into two steps. In the first step, a set of up to 10,000 top hits are evaluated and re-sorted with respect to calculated guest binding energies. In the second step, a smaller subset of the top hits are conformationally searched and the candidates are sorted to give a final ranking on the basis of total reorganization energy. To accomplish this, we have developed an interface to a new MM post-processing software module that provides access to five force field models including MMX, MM3, AMBER, MMFF94, and OPLSAA.

Because force field parameters for metal complexes are limited, an important subtask is to extend parameter sets to treat donor group-metal ion interactions. We are working toward extending these models to treat the interaction of f-block metal ions with hydroxypyridinonates, catecholates, phosphine oxides, and pyridine N-oxides. A series of electronic structure calculations are in progress to elucidate the nature of these metal-ligand bonding interactions and to understand the geometric features that are observed in crystal structures.

HostDesigner experiences two limitations that are common to all fragment-based molecule building approaches: (1) synthesis of some candidate structures may be difficult or impossible and (2) the number of structures that can be generated is limited by the contents of the linking fragment database. We have addressed the first issue by adding descriptors to the fragment database that allow the user to exclude links with synthetically undesirable properties, for example, those that would lead to linkage isomers or give rise to chiral molecules. We are planning to address the second issue over the next year.

A second goal of this EMSP project is apply and test the computer-aided design methodologies being developed under this project through continuing collaborations with experimental research groups. In recent interactions with the Raymond group, we have (1) further validated the ability of our extended MM models to predict the structure of catecholate
and hydroxypyridinonate complexes with trivalent and tetravalent f-block metals, (2) benchmarked the accuracy of the density functional theory model (B3LYP/DZVP2) by showing that it correctly predicts barrier heights for stereochemical inversion in tris-catecholate complexes, (3) applied HostDesigner to design supramolecular assemblies composed of actinide complexes, and (4) initiated the design of actinide receptors formed by connecting multiple chelate groups. Raymond graduate students, Eric Werner and Matt Stavis, visited PNNL for two weeks in May 2004 to learn how to set up and perform HostDesigner calculations.

In recent interactions with the Paine group and Prof. Jeff Bryan (University of Wisconsin – LaCrosse), we have (1) conducted a detailed analysis of the Cambridge Crystallographic Database to establish geometric parameters for the interactions between metal ions and neutral oxygen donor groups, phosphine oxide and pyridine N-oxide, (2) used our MM model to help rationalize observed reactivity in several lanthanide NOPOPO complexes, and (3) initiated the application of HostDesigner to identify optimal ligand architectures containing these neutral oxygen donor groups.

Experimental research on our “designer” bicyclic diamide extractant, conducted at the University of Oregon and PNNL, has confirmed that the dramatic 10^7 increase in Ln(III) distribution coefficients observed in liquid-liquid extraction experiments is directly correlated with the increased metal ion binding affinity exhibited by this ligand architecture in the aqueous phase. The application of HostDesigner to identify optimal tris- and tetrakis-amide extractants is planned for next year.

### Planned Activities

- Complete the testing and validation of automated MM post-processing capability.
- Expand HD fragment library.
- Continue the application of computer-aided design methods to identify improved metal ion host architectures.
- On-site visits with all experimental collaborators. The first visit, to UC-Berkeley, occurred January 2004. The next visit, to the University of Oregon, is scheduled for this fall.
**Information Access**

To date, project 73759 has resulted in 15 publications and 32 presentations at meetings, workshops, and conferences. In addition, two manuscripts are submitted for publication and two abstracts are submitted to future conferences.

**Recent publications (2002 to date):**


- "Bicyclic and Acyclic Diamides. Comparison of Aqueous Phase Binding Constants with Am(III), Pu(IV), Np(V) and U(VI)," SI Sinkov, BM Rapko, GJ Lumetta, BP Hay, JE Hutchison, and BW Parks, (Submitted to *Inorganic Chemistry*).


**Publications from 2000 – 2002:**


- "Coordination of Lanthanide Ions Containing Non-Coordinating Counteranions with N,N,N’,N’-Tetramethylsuccinamide (TMSA). I. Preparation and Characterization of
Recent Presentations (2002 to date):

Presentations (2000 to 2002):

- AV Davis, TK Firman, BP Hay, and KN Raymond. “Isomerization of tris-Catecholate Complexes: The Twisted Sisters of Ti(IV), Ga(III), and Ge(IV) Octahedral Coordination.” Submitted to the 36th International Conference on Coordination Chemistry to be held in Merida, Mexico, July 2004.

Presentations (2000 to 2002):


