

# Computational Design of Metal Ion Sequestering Agents

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## Research Objectives

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 the U.S. Department of Energy (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 (MM3) 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 objectives of this project are as follows:

- Further understand the structural and energetic aspects of individual donor group- metal ion interactions and incorporate this information within the framework of MM3.
- 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 in which 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 researchers at the University of New Mexico, University of California at Berkeley, University of Oregon, and Oak Ridge National Laboratory to obtain experimental

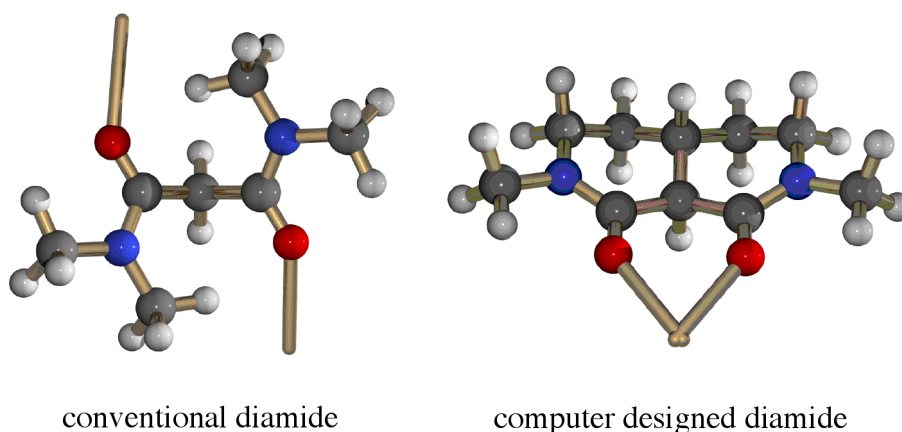
validation of the predicted new ligand structures. Successful completion of this study will yield molecular-level insight into the role that ligand architecture plays in controlling metal ion complexation and will provide a computational approach to ligand design.

## Research Progress and Implications

This project is a renewal of EMSP Project No. 54679, “Architectural Design Criteria for f-Block Metal Sequestering Agents,” that began in September 1996 and ended in May 2000. Funding for the project was renewed in October 2000, and this report summarizes progress after 1 year and 7 months of a 3-year period. Research has focused on three areas. These are 1) the completion of diamide studies, 2) coupling molecular mechanics screening methods with a *de novo* structure-based design program, HostDesigner, and 3) application of computational methods to ligand design.

Over the past decade, there has been a worldwide effort to develop processes for separating trivalent transuranic elements from nitric acid media based on the use of lipophilic diamide ligands. Because the sequestering agents contain only C, H, O, and N atoms, diamide process solvents are completely incinerable, resulting in less secondary waste than alternative systems that use phosphorous-containing ligands. However, the weak extraction efficiency of conventional diamides necessitates the use of high ligand concentrations, resulting in increased costs as well as difficulties with third-phase formation and hydraulic behavior of process solvents. Using theoretical models developed at the W. R. Wiley Environmental Molecular Sciences Laboratory, we have designed a new class of bicyclic diamide structures that are highly organized for complexation with trivalent f-block elements (see Figure 1). The designer ligands differ from conventional diamides only in the way that the two amide binding sites are connected. Single-crystal x-ray diffraction of their metal complexes verifies that the new diamides bind to f-block metal ions in the expected manner. Liquid-liquid extraction measurements reveal that the computer-designed architecture yields a dramatic performance enhancement, exhibiting a partitioning of Eu(III) to a ligand-containing organic phase that is *10 million times more effective* than that observed for conventional diamides. An invention report on the bicyclic diamide compounds, 3,9-diaza-3,9-dialkylbicyclo[4.4.0]decane-2,10-diones, was filed at Pacific Northwest National Laboratory (PNNL).

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 Laboratory-Directed Research and Development and Chemical Sciences, Office of Basic Energy Sciences, DOE Office of Science. 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



**Figure 1.** A comparison of the three-dimensional structure of a conventional diamide ligand with that of the new bicyclic diamide. The vectors on each oxygen atom, which indicate the direction required for optimal interaction with a metal ion, diverge in the malonamide structure and converge in the computer-designed structure.

further evaluation. One of the goals of this project was to couple the HostDesigner software with a molecular mechanics program (MM3) to provide a more accurate ranking of structures in terms of their complementarity for the targeted metal ion. This task was successfully completed, and post-processing of the HostDesigner output with MM3 strain energy analyses is now automated, provided the force field parameters for the system under study are available. Because force field parameters for metal complexes are limited, another task within this project is to extend the MM3 model to treat additional donor group-metal ion interactions. Research to extend the MM3 model to amines, carboxylates, and aminocarboxylates, was initiated in the first year of this project.

The computer-aided design technologies being developed in this project are now being applied in collaborations with two research groups. One application, with Oak Ridge National Laboratory, focuses on the design of new calix[4]crown ether architectures that provide more effective and more selective interactions with the cesium cation. The approach involves 1) using HostDesigner to add binding sites to existing scaffolds and/or to add structure to preorganize the host molecule, 2) MM3 analysis of lead structures for complementarity, and 3) conformational analysis of the most complementary structures to evaluate their degree of preorganization. In addition, HostDesigner is being used to identify optimal molecular structure for combining unidentate donor groups, for example ethers and amines, to form multidentate host structures that complement metal ions of different sizes. A second application, with the University of California, Berkeley, uses a similar approach to identify optimal ways to link bidentate chelates, such as catecholamides and hydroxypyridinones, in order to design more efficient receptors for trivalent and tetravalent f-block metal ions.

## Planned Activities

- In collaboration with Oak Ridge National Laboratory and the University of California-Berkeley, we will continue application of computer-aided design methods to identify improved host architectures.
- Beginning in November 2002, we will apply computer-aided ligand design methods to phosphine oxide and pyridine-N-oxide based ligands for f-block elements in collaboration with the University of New Mexico.

## Information Access

The original project, which combined theoretical and experimental approaches to investigate the interactions of amide ligands with metal ions, resulted in 28 presentations at meetings, workshops, and conferences, and 14 journal articles. Since the renewal of the original project, there have been an additional eight publications and eleven presentations. In addition, abstracts are submitted for six presentations at future conferences.

## Publications since May 2000

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Lumetta GJ, BK McNamara, BM Rapko, RL Sell, RD Rogers, GA Broker, and JE Hutchison. 2000. Synthesis and Characterization of Mono- and Bis-(tetraalkyl-malonamide)uranium(VI) Complexes, *Inorganica Chimica Acta* 309:103-108.

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