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 (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 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 MM3 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. 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 on October 2000, and this report summarizes progress after 2 year and 8 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 Pacific Northwest National Laboratory (PNNL), 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 single crystal X-ray diffraction of their metal complexes verify 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 PNNL. A communication of these results, published in the *Journal of the American Chemical Society*,

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.

has been highlighted in *Science Magazine* (**2002**, 296, 985), *Chemical and Engineering News* (**2002**, 80(20), 37), and US DOE Office of Science website as a Feature Article “Designer Molecules Set the Trend for Advancing Science” (7/29/2002).

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 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. Progress has been made toward extending the MM3 model to treat the interaction of f-block metal ions with aminocarboxylates, hydroxypyridinonates, catecholates, phosphine oxides, and pyridine N-oxides.

The computer-aided design technologies being developed in this project are now being applied in collaborations with three 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. The 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. The third application, initiated this year with the University of New Mexico, brings computer-aided ligand design methods to phosphine oxide and pyridine-N-oxide based ligands for f-block elements in collaboration with Prof. R.T. Paine.

Planned Activities

- Continue development and testing of computational tools for host design.
- Continue the application of computer-aided design methods to identify improved metal ion host architectures in collaboration with Oak Ridge National Laboratory, the University of California-Berkeley, and 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 12 publications and 26 presentations. In addition, abstracts are submitted for two presentations at future conferences.

Publications since May 2000:

- R. Vargas, J. Garza, D.A. Dixon, and B.P. Hay. "How Strong is the C(α)-H $\cdots$ O=C Hydrogen Bond?" *J. Am. Chem. Soc.* **2000**, 122, 4750-4755 and highlighted in a *Chemical and Engineering News* News of the Week article "Protein Folding. Weak Hydrogen Bonds in Peptide Backbones May Play Significant Role." (**2000**, 78(19), 15).
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- B.M. Rapko, B.K. McNamara, G.J. Lumetta, R.D. Rogers, G.A. Broker, and B.P. Hay. "Coordination of Lanthanide Ions Containing Non-Coordinating Counteranions with N,N,N',N'-Tetramethylsuccinamide (TMSA). I. Preparation and Characterization of [(TMSA) $_4$ Ln][A] $_3$, A = ClO $_4^-$, CF $_3$ SO $_3^-$." *Inorg. Chem.* **2000**, 39, 4858-4867.
- G.J. Lumetta, B.K. McNamara, B.M. Rapko, R.L. Sell, R.D. Rogers, G.A. Broker, and J. E. Hutchison, "Synthesis and Characterization of Mono- and Bis-(tetraalkyl-malonamide)uranium(VI) Complexes," *Inorg. Chim. Acta* **2000**, 309, 103-108.
- L. Rao, P. Zanonato, P. Di Bernardo, and A. Bismondo, "Calorimetric and Spectroscopic Studies of Eu(III) Complexation with Tetramethylmalonamide and Tetramethylsuccinamide in Acetonitrile and Dimethylsulfoxide." *Inorg. Chim. Acta* **2000**, 306, 49-64.
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- G.J. Lumetta, B.M. Rapko, P.A. Garza, B.P. Hay, R.D. Gilbertson, T.J.R. Weakley, and J.E. Hutchison. "Deliberate Design of Ligand Architecture Yields Dramatic Enhancement of Metal Ion Affinity." *J. Am. Chem. Soc., Comm. Ed.* **2002**, 124, 5644-5645 and highlighted in *Science Magazine* as an Editors' Choice article "Designer Bindings" (**2002**, 296, 985), in *Chemical and Engineering News* as a Science Concentrate "Designed Ligands Boost Metal Binding" (**2002**, 80(20), 37), and on the US DOE Office of Science Website as a Feature Article "Designer Molecules Set the Trend for Advancing Science" (7/29/2002).
- G.J. Lumetta, B.M. Rapko, B.P. Hay, P.A. Garza, J.E. Hutchison, and R.D. Gilbertson. "A Novel Bicyclic Diamide with High Binding Affinity for Trivalent f-Block Elements." *Solv. Extr. Ion Exch.* **2003**, 21, 29-39.
- R.A. Sachleben, J.C. Bryan, G.M. Brown, R. Dabestani, N.L. Engle, T.J. Haverlock, B.P. Hay, H.-F. Ji, A. Urvoas, and B.A. Moyer. "Rational Design of Cesium-Selective Ionophores and Chemosensors: Dihydrocalix[4]arene Crown-6 Ethers." *European J. Org. Chem.* in press.
- J.C. Bryan, R.A. Sachleben, C.T. Eagle, B.P. Hay, C. Zhang, and P.V. Bonnesen. "Design, Synthesis, and Structure of Novel Cesium Receptors." *J. Chem. Crystallogr.* in press.
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- B.P. Hay. "Building a Better Mousetrap: Ligand Design with Molecular Mechanics." American Chemical Society, Pacifichem 2000 Meeting in Honolulu, Hawaii, December 2000.
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- R.D. Gilbertson, B.M. Rapko, B.P. Hay, J.E. Hutchison, and T.J.R. Weakly. "Synthesis of a Conformationally Constrained Malonamide and Its Coordination Chemistry with Uranyl Nitrate." 221st American Chemical Society National Meeting, San Diego, California, April, 2001.
- G. J. Lumetta, B.K. McNamarra, B.M. Rapko, R.D. Rogers, G.A. Broker, and J.E. Hutchison. "Extraction of U(VI) with Malonamides: What's Really Going On?" 221st American Chemical Society National Meeting, San Diego, California, April, 2001.
- B.P. Hay. "HostBuilder: A Combinatorial Structure Generator for Host Discovery", Separations Group Seminar, Oak Ridge National Laboratory, Oak Ridge, Tennessee, June 2001.
- B.P. Hay, D.A. Dixon, B.M. Rapko. "Computational Design of Metal Ion Sequestering Agents." EMSP Symposium, 222nd American Chemical Society National Meeting, Chicago, Illinois, August 2001.
- T.R. Klinckman, D.A. Dixon, and B.P. Hay. "An MM3 Force Field for Metal Complexes with Amines, Carboxylates, and Aminocarboxylates." Inorganic Poster Session, 222nd American Chemical Society National Meeting, Chicago, Illinois, August 2001.
- B.P. Hay. "Toward the Computer-Aided Design of Metal Ion Hosts." Departmental Seminar, Georgia Institute of Technology, Atlanta, Georgia, October 2001.
- B.P. Hay. "Toward the Computer-Aided Design of Metal Ion Hosts." Departmental Seminar, University of Memphis, Memphis, Tennessee, October 2001.
- B.P. Hay. "HostBuilder: A Combinatorial Molecular Structure Generator and Its Application to the Design of Metal Sequestering Agents." Raymond Group Seminar, University of California-Berkeley, Berkeley, California, December 2001.
- B.P. Hay. "Computer-Aided Design of Ion Receptors." Chemical and Analytical Division Seminar, Oak Ridge National Laboratory, Oak Ridge, Tennessee, May, 2002.
- B.M. Rapko, G.J. Lumetta, B.P. Hay, P.A. Garza, J.E. Hutchison, R.D. Gilbertson, T.R. Weakly. "Bicyclic Diamides Exhibit Exceptional Affinity for Europium(III)." Actinides Separation Conference, Berkeley, California, June, 2002.
- B.P. Hay. "Extending the MM3 Force Field for Application to the Structure-Based Design of Metal Ion Hosts." Symposium on New Developments in Force Fields for Molecular Modeling, Computers in Chemistry Division, 224th American Chemical Society National Meeting, Boston, Mass., August 2002.
- B.P. Hay, G.J. Lumetta, B.M. Rapko, P.A. Garza, R.D. Gilbertson, T.R.J. Weakley, and J.E. Hutchison. "Deliberate Design of Ligand Architecture Yields Dramatic Enhancement in Metal Ion Affinity." Inorganic Poster Session, 224th American Chemical Society National Meeting, Boston, Mass., August 2002.
- C. Zhang and B.P. Hay. "Computer-Aided Design of Cesium Receptors Based on Calix[4]arene Scaffolds." Inorganic Poster Session, 224th American Chemical Society National Meeting, Boston, Mass., August 2002.
- J. Uddin, T.K. Firman, and B.P. Hay. "Computer Aided Design of Complementary Chelate Ring Architecture." Coordination Chemistry Symposium, Inorganic Chemistry Division, 224th American Chemical Society National Meeting, Boston, Mass., August 2002.
- R.D. Gilbertson, J.E. Hutchison, T.J.R. Weakley, B.M. Rapko, and B.P. Hay. "Efficient Synthesis and Coordination Complexes of a New Ligand Architecture with High Affinity for f-Block Elements." Inorganic Poster Session, 224th American Chemical Society National Meeting, Boston, Mass., August 2002.

- B.P. Hay. "Toward the Computer-Aided Design of Host Molecules." Seaborg Institute Seminar Series, Los Alamos National Laboratory, Los Alamos, New Mexico, October 2002.
- B.P. Hay. "Toward the Computer-Aided Design of Host Molecules." Department of Chemistry, University of New Mexico, Albuquerque, New Mexico, October 2002.
- B.P. Hay. "Computer-Aided Host Design." Molecular Interactions and Transformations Seminar, Pacific Northwest National Laboratory, Richland, Washington, December 2002.
- J.E. Hutchison, R.D. Gilbertson, B.W. Parks, B.P. Hay, and B.M. Rapko, "Preorganized Malonamide Ligands: New Ligands and Materials for f-Block Ion Binding." Division of Nuclear Chemistry and Technology, 225th American Chemical Society National Meeting, New Orleans, Louisiana, March 2003.
- J. Uddin and B.P. Hay. "The Computer-Aided Design of Receptors for Tetravalent Actinides." Division of Computers in Chemistry, 225th American Chemical Society National Meeting in New Orleans, Louisiana, March 2003.
- B.P. Hay. "Computer-aided design of ion receptors." Department of Chemistry, University of North Texas, Denton, Texas, April 2003.
- B.P. Hay. "Computer-aided design of ion receptors." Department of Chemistry, Texas Tech University, Lubbock, Texas, April 2003.
- B.P. Hay. "Computer-aided design of ion receptors." Department of Chemistry, University of Texas, Austin, Texas, April 2003.
- B.P. Hay. "Computer-Aided Design of Metal Ion Hosts." Science Lecture, Biological and Environmental Research Advisory Council, Washington, D.C., April 2003.
- J. Uddin, T.K. Firman, and B.P. Hay. "Computer-Aided Design of Complementary and Preorganized Chelate Ring Architectures for Ether and Amine Donor Atoms." Abstract submitted to the 226th American Chemical Society National Meeting to be held in New York City, New York, September 2003.
- B. P. Hay, T.K. Firman, G.J. Lumetta, B.M. Rapko, P.A. Garza, J.E. Hutchison, R.D. Gilbertson and T.J.R. Weakley. "Toward the Computer-Aided Design of Metal Ion Sequestering Agents." Invited speaker at the Fifth International Conference on f-Elements to be held in Geneva, Switzerland, August 2003.