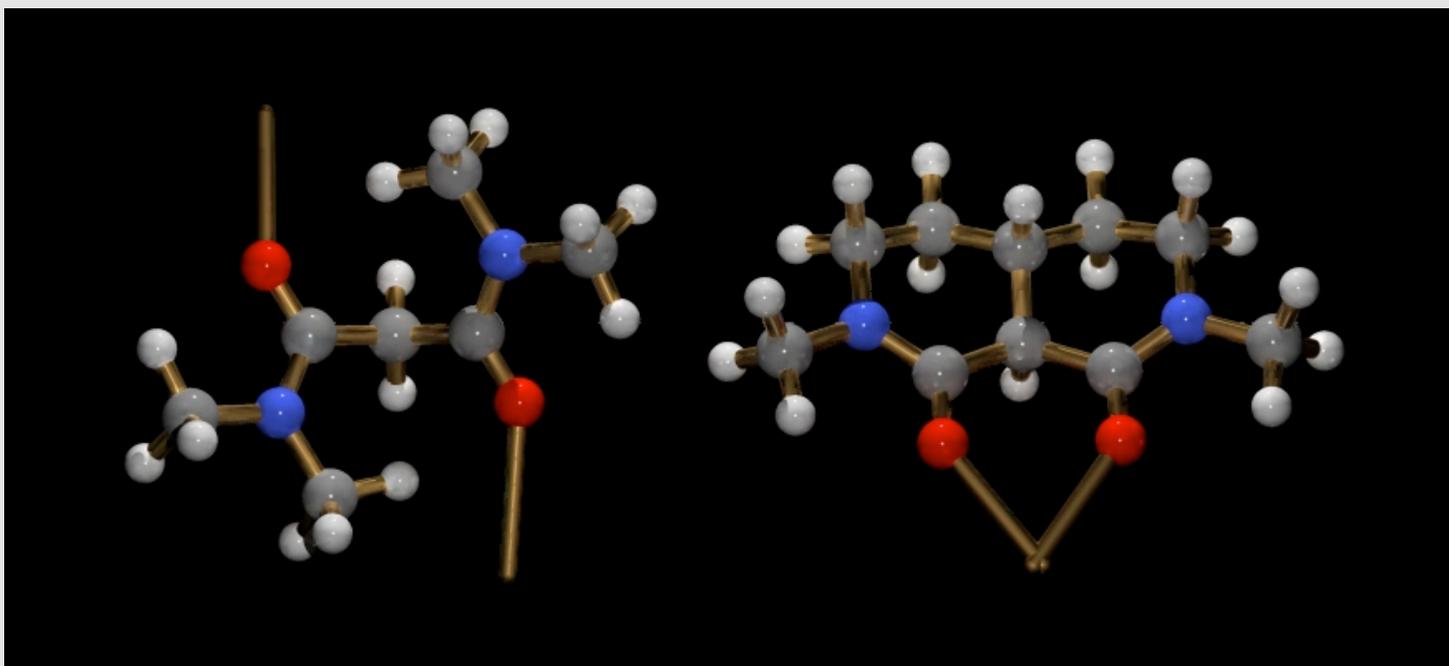


# Computational Design of Metal Ion Sequestering Agents



EMSP Project 73759

Benjamin P. Hay, January, 2004

## Relevance to DOE mission

**In 2003, site technology needs documented widespread potential uses for more selective and effective metal ion sequestering agents**

<b>Areas</b>	<b># Needs</b>
Metal ion partitioning (solvent extraction/ion exchange)	27
Metal ion specific sensors	24
Decontamination of metals, pipes, small parts, etc.	17
Remediation of contaminated soil and groundwater	13

([www.srs.gov/general/scitech/stcg/needstmt.htm](http://www.srs.gov/general/scitech/stcg/needstmt.htm), [tmfa.inel.gov/Needs](http://tmfa.inel.gov/Needs), [www.oakridge.doe.gov/em/stcg](http://www.oakridge.doe.gov/em/stcg), [web.ead.anl.gov/chstcg](http://web.ead.anl.gov/chstcg), [www.hanford.gov.boards/stcg](http://www.hanford.gov.boards/stcg), [www-emtd.lanl.gov/doeal/stcg.html](http://www-emtd.lanl.gov/doeal/stcg.html))

<b>EMSP has responded to these technology needs</b>	<b># Projects</b>
Development of organic hosts for targeted metal ions	11
Host-based technologies for metal ion sequestration	11
Host-based technologies for metal ion detection	12

## EMSP support

| FY97 | FY98 | FY99 | FY00 | FY01 | FY02 | FY03 | FY04 | FY05 | FY06 |

**54679, Hay 2.6 FTE**  
Architectural Design Criteria for  
Metal Ion Sequestering Agents

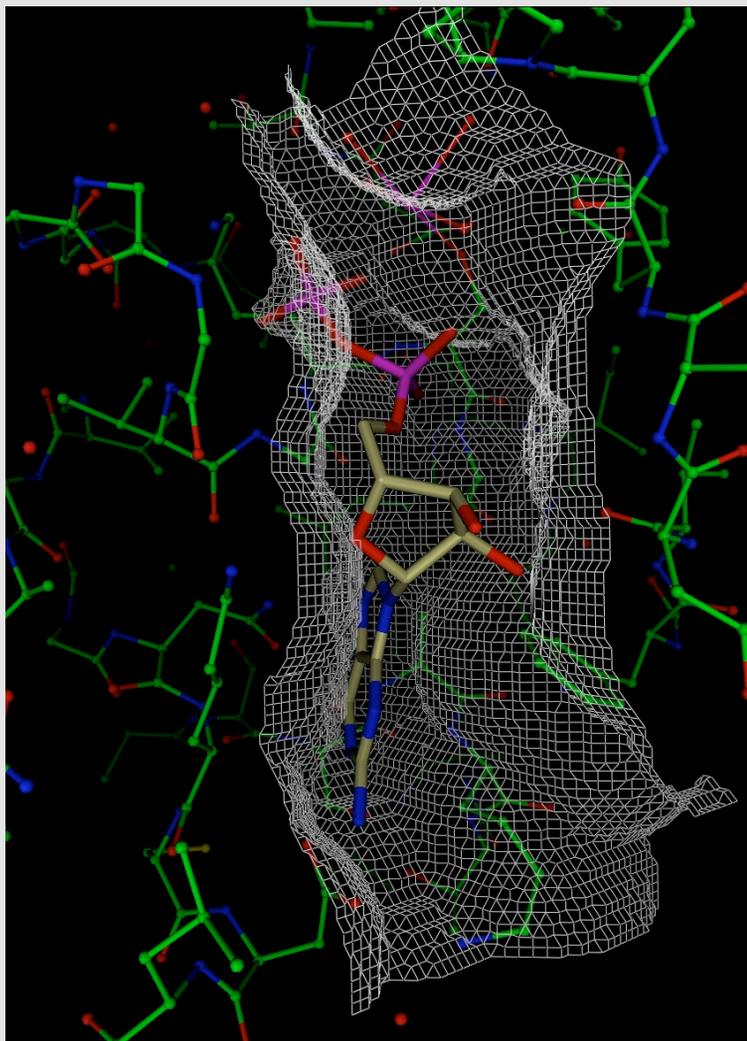
**73759, Hay 0.9 FTE**  
Computational Design of Metal  
Ion Sequestering Agents

**73759, Hay 0.9 FTE**  
Computational Design of Metal  
Ion Sequestering Agents

**55087, Moyer 0.4 FTE**  
Design and Synthesis of the  
Next Generation of Crown . . .

<b>64949, Ainsworth, 0.3 FTE</b> Contaminant-Organic Complexes. Structure and Energetics in . . .	<b>82773, Ainsworth, 0.1 FTE</b> Contaminant-Organic Complexes. Structure and Energetics in . . .
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## De novo structure-based drug design



### Known host structure

- steric constraints
- H-bond regions
- hydrophobic regions

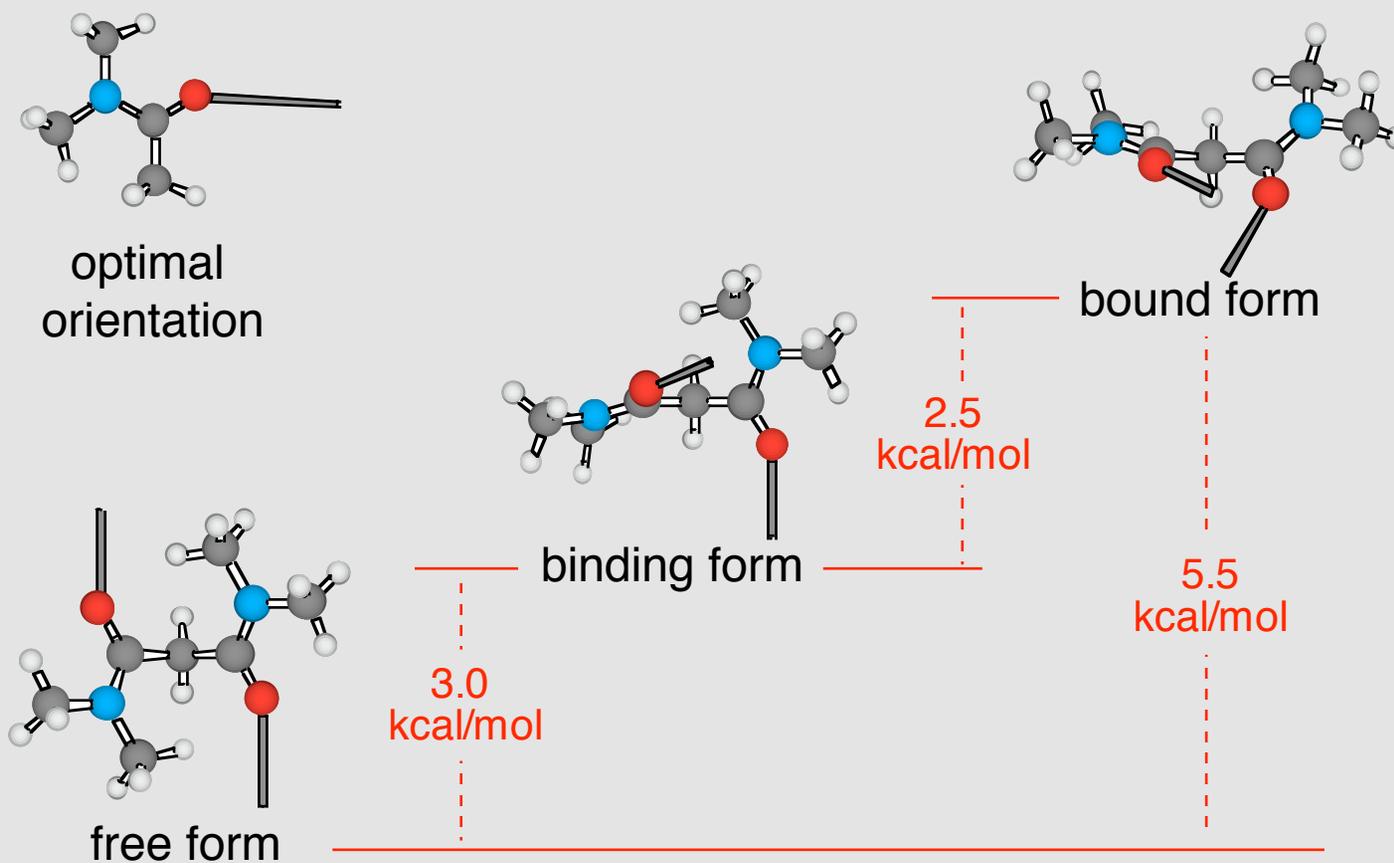
### Step 1: Build candidate guests

- position functional groups
- link with spacer fragments

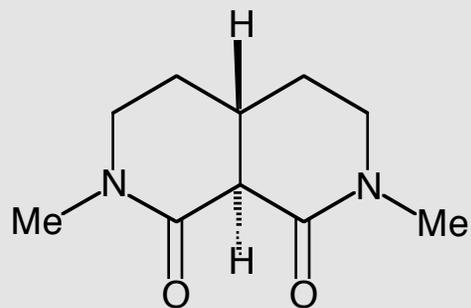
### Step 2: Score the candidates

- number of H-bonds
- hydrophobic contact area
- entropic factors
- conformational strain energy

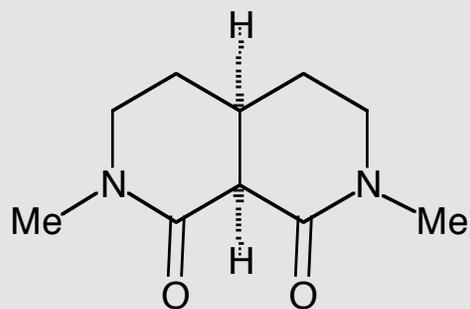
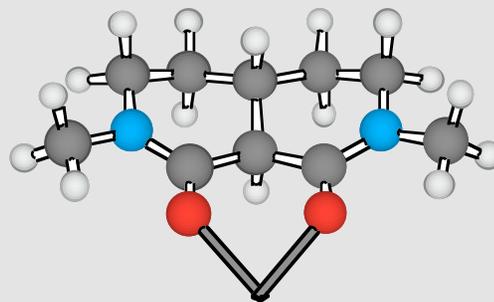
# Structure-based design of metal ion receptors



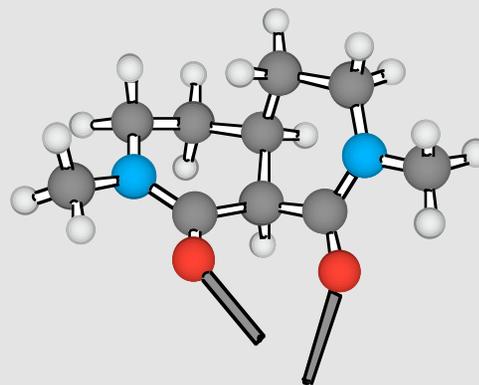
## Improved architecture



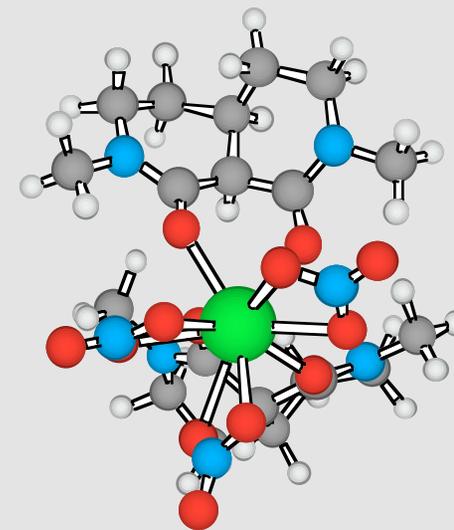
*trans*



*cis*



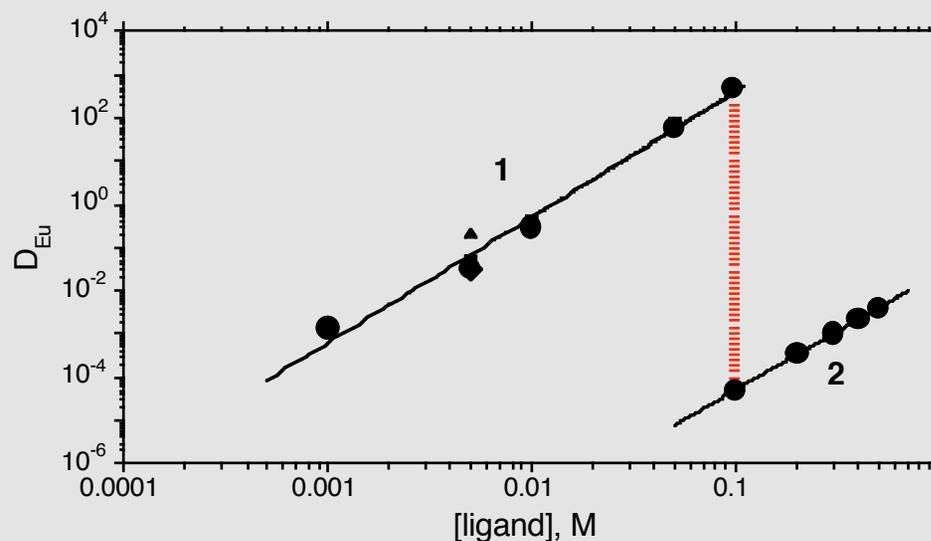
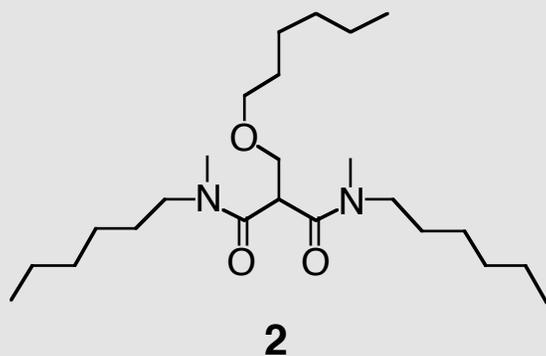
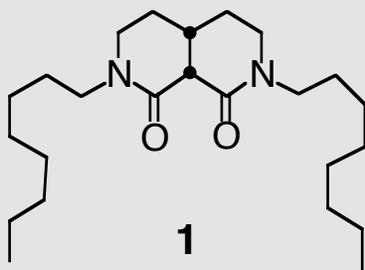
Synthesis yields only the *cis* form



X-ray structure of  
 $[\text{Eu}(\text{L})_2(\text{NO}_3)_3]$

## Proof of principle

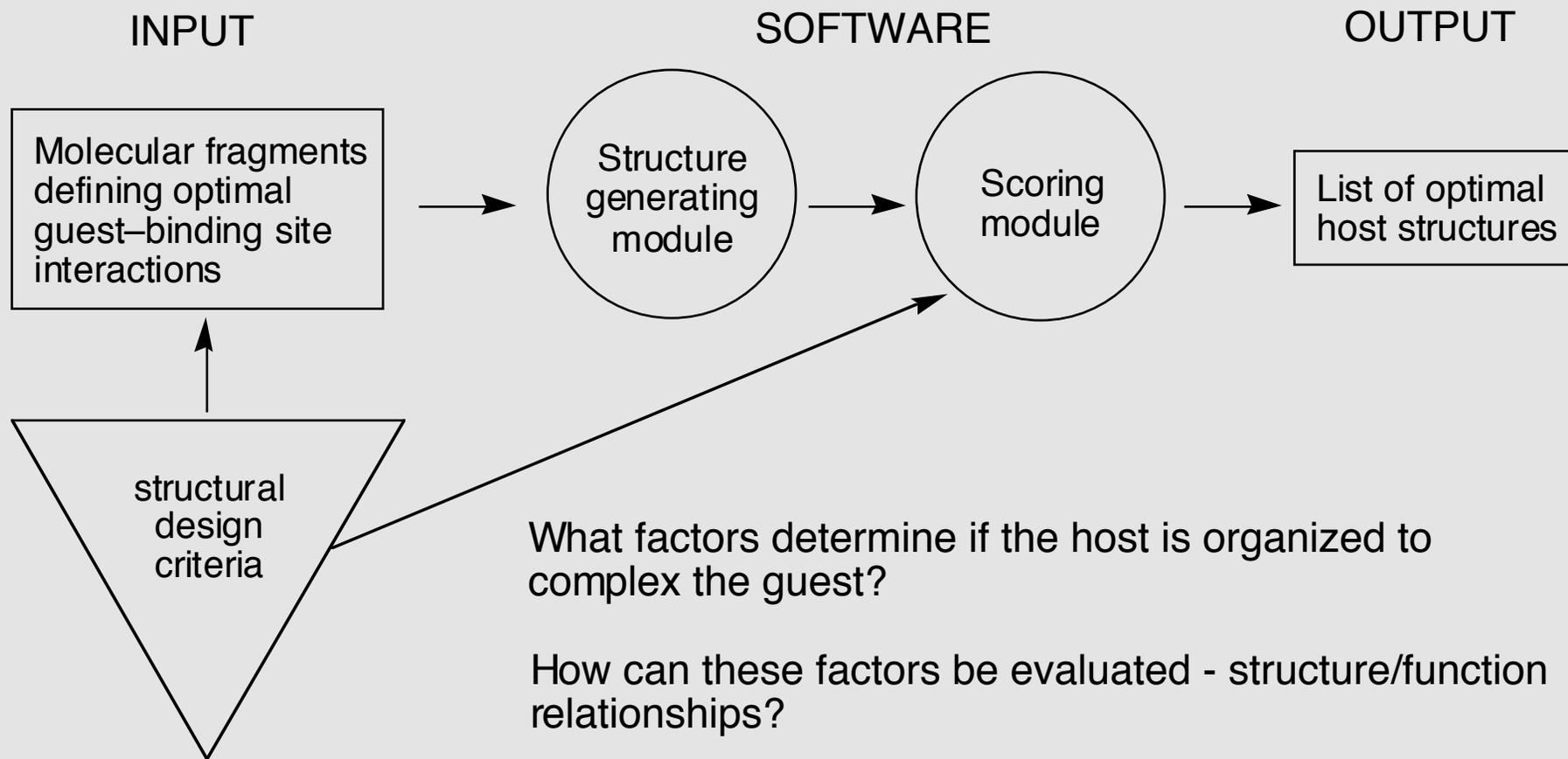
Extraction into t-butylbenzene from aqueous solution containing consisting of 1 M NaNO<sub>3</sub>, 1.5 mM HNO<sub>3</sub>, 0.1 mM Eu(NO<sub>3</sub>)<sub>3</sub>, and 1- $\mu$ L of <sup>155</sup>Eu tracer solution.



10 million times more effective

“Deliberate Design of Ligand Architecture Yields Dramatic Enhancement of Metal Ion Affinity.” *J. Am. Chem. Soc., Comm. Ed.* **2002**, *124*, 5644-5645. Highlighted in *Science Magazine* (**2002**, *296*, 985), *Chemical and Engineering News* (**2002**, *80*(20), 37), and the Office of Science Website (Feature Article, 7/29/02)

# Research goal - automated *de novo* structure-based host design



What factors determine if the host is organized to complex the guest?

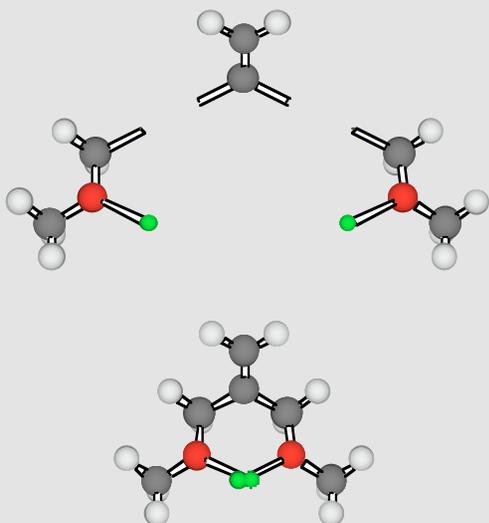
How can these factors be evaluated - structure/function relationships?

How can we obtain structures for evaluation?

## Structure generating module - HostDesigner

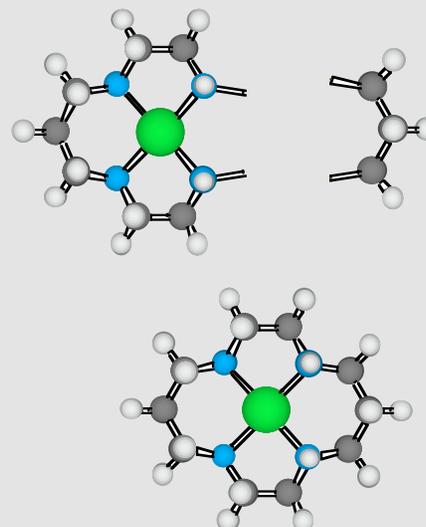
(free download @ <http://hostdesigner.emsl.pnl.gov>)

### 3-body algorithm



structures scored by degree  
of "metal" superposition

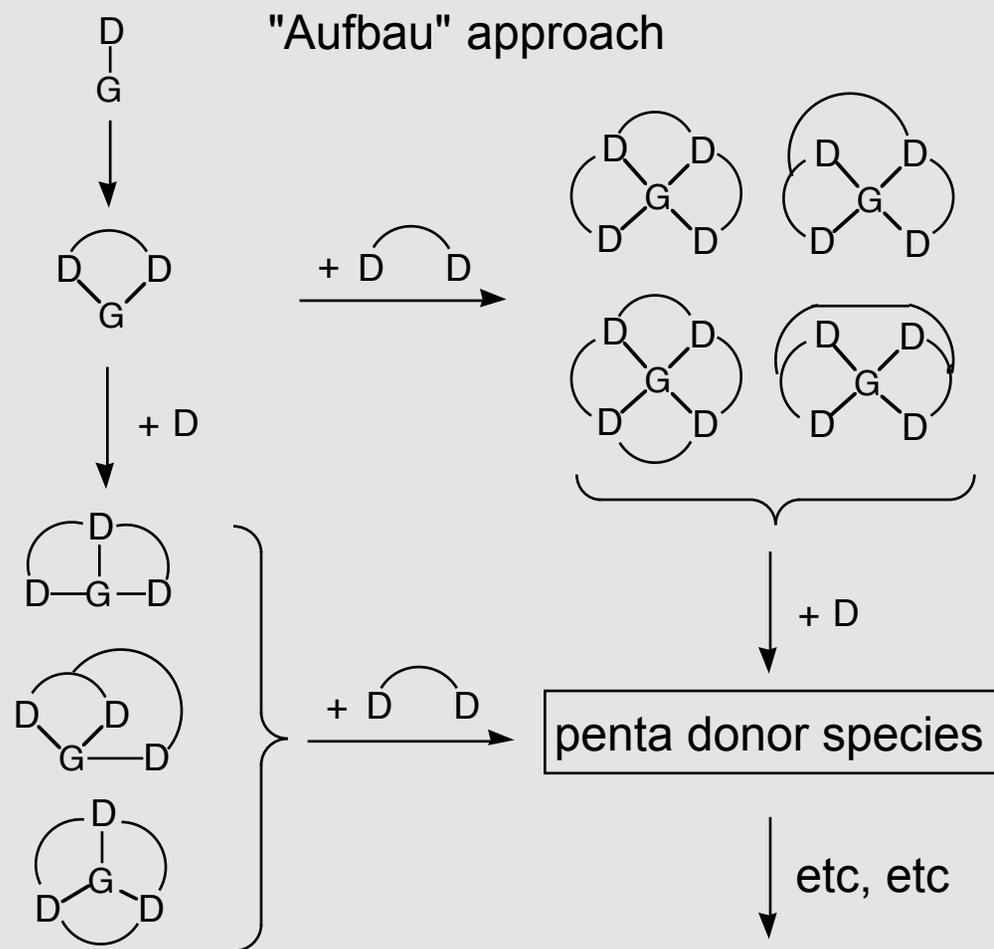
### 2-body algorithm



structures scored by degree  
of bond superposition

- Fragment database contains 20,705 hydrocarbon linkages
- Structures constructed at a rate of > 1,000,000 per minute on desktop PC

## Filtering the fragment database - *completed FY04*



Each database link now has three descriptors:

C = Chiral?

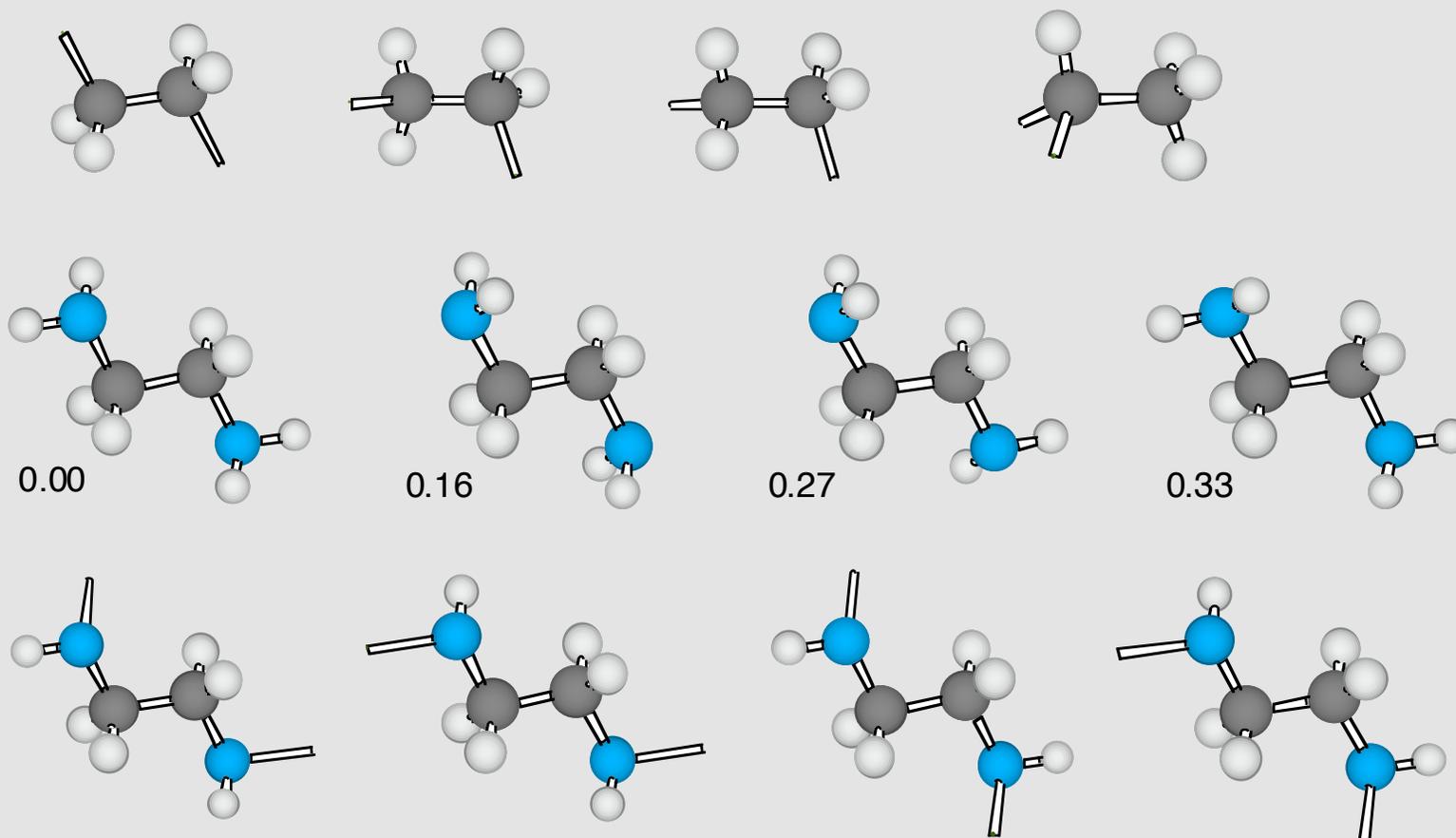
P = Prochiral?

L = Linkage Isomers?

C	P	L	example
F	F	F	
F	F	T	
F	T	T	
T	F	F	
T	F	T	

## Increasing scope of fragment database - *planned*

Expand database by adding functional groups to existing fragments



## Improved scoring via molecular modeling - *in progress*

### HostDesigner builds millions of structures

score based on structure and conformational energy estimates

8 min

### identify top 5000 hits

optimize complex and host (molecular mechanics)  
score based on interaction energy

3 hrs

### identify top 500 hits

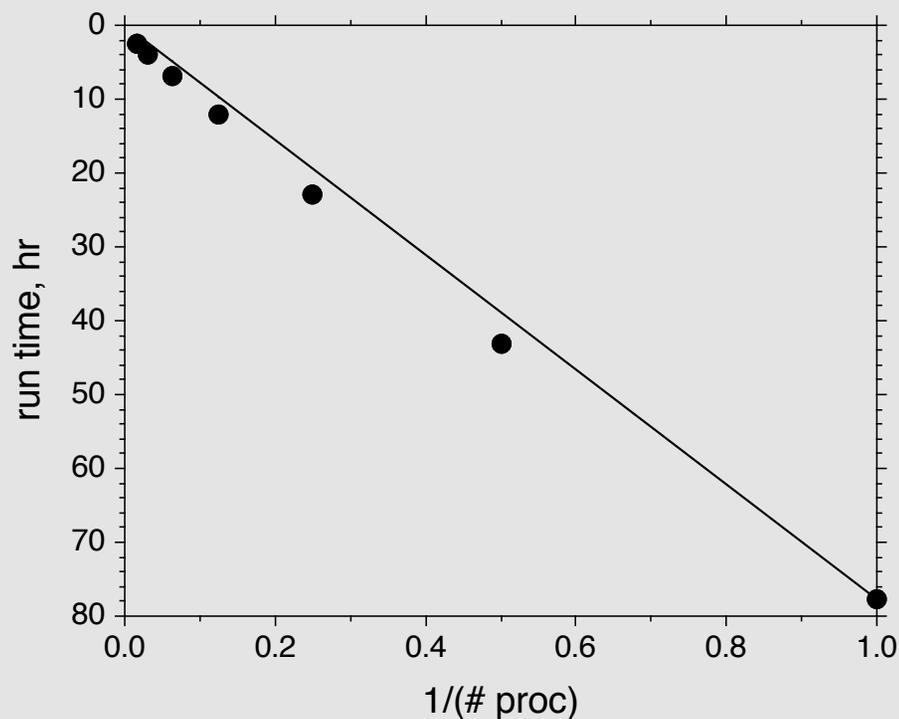
conformer search free host (molecular mechanics)  
score based on binding energy

75 hrs

Beta version of software to automate the post-processing is now being tested. Choice of MMX, MM3, MMFF94, AMBER, and OPLSAA force fields (collaboration with Dr. Kevin Gilbert, started October 2003).

(MacOSX, G5)

## Decrease run times by parallelizing the code - *in progress*



~ 2 hrs, 64 procs



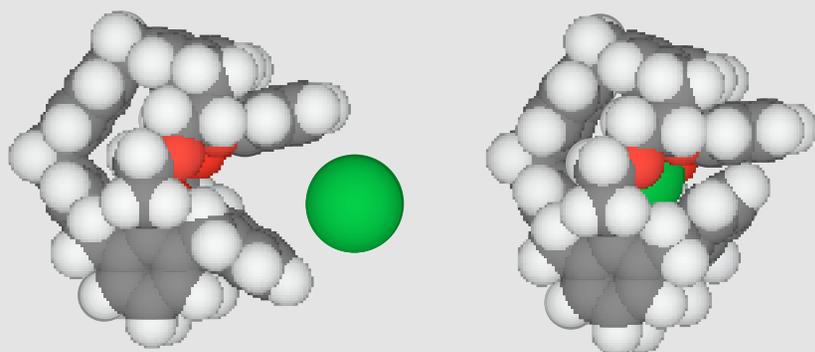
78 hrs, 1 proc

Calculations performed using the Molecular Science Computing Facility (MSCF) in the William R. Wiley Environmental Molecular Sciences Laboratory, a national scientific user facility sponsored by the Department of Energy's Office of Biological and Environmental Research and located at Pacific Northwest National Laboratory.

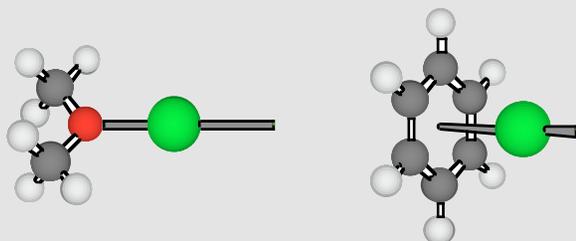
# CAD application in collaboration with experimental groups

Dr. Bruce Moyer, ORNL

Cs, Sr, Ra using ethers and arenes



"trap-door" calix[4]crown ethers

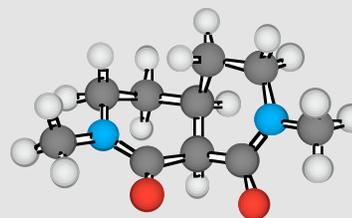


identify optimal building blocks  
(chelating structures) bearing  
ether and arene donor groups

Prof. Jim Hutchison, University of Oregon

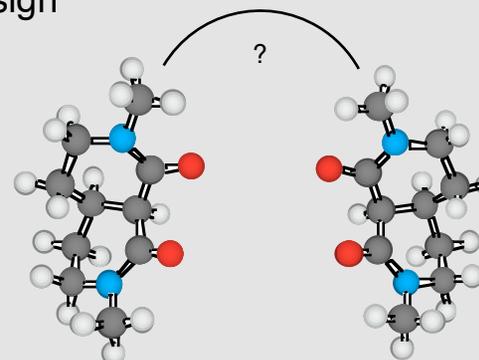
f-elements using amides

Experimental



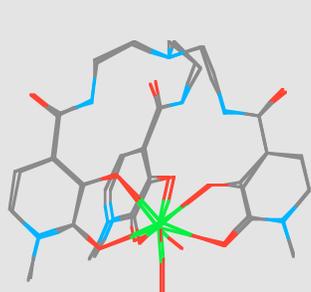
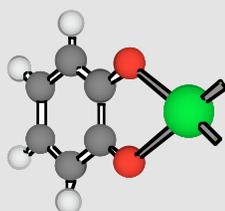
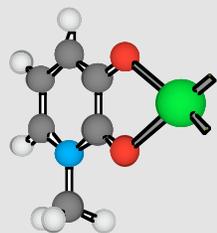
Aqueous phase  
binding constants for  
Nd(III), Am(III), Pu(IV),  
Np(V), U(VI), Pu(VI)

Design

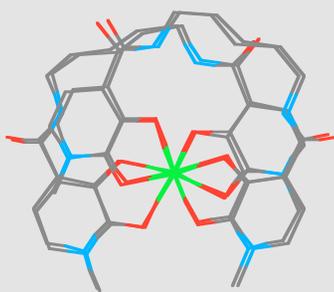


# CAD application in collaboration with experimental groups

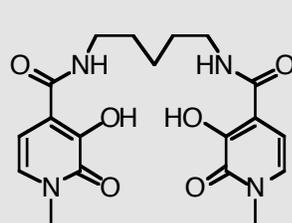
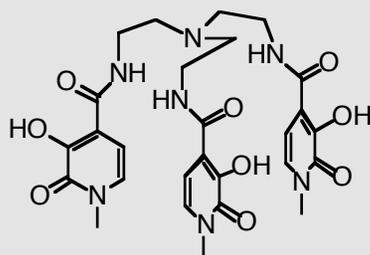
Prof. Ken Raymond, UC-Berkeley  
f-elements using HOPO and catechol



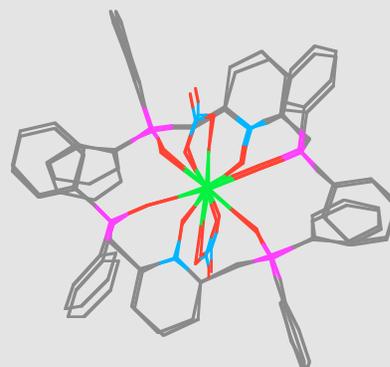
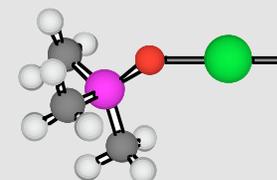
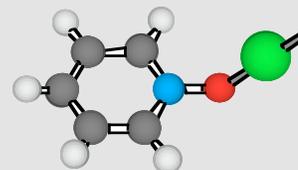
ZAXQAQ Gd(III)  
(0.192 Å)



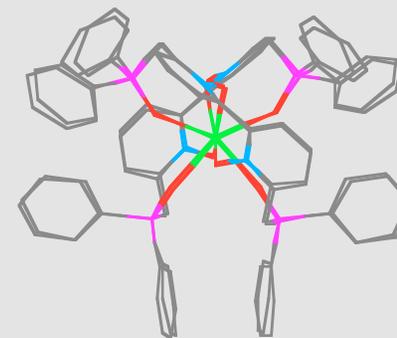
GOVNIO Ce(IV)  
(0.288 Å)



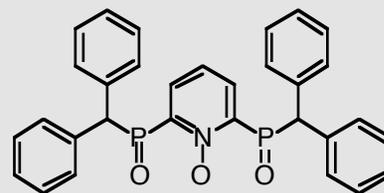
Prof. Robert T. Paine, University of New Mexico  
f-elements using N-oxides and phosphine oxides



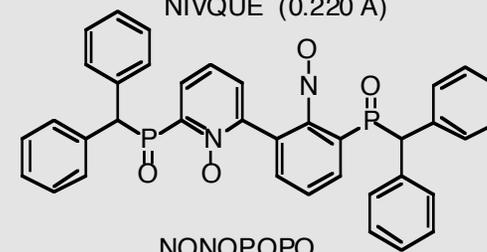
[Pu(NOPOPO)<sub>2</sub>(NO<sub>3</sub>)<sub>2</sub>]<sup>2+</sup>  
WOHYIP (0.254 Å)



[Er(NONOPOPO)<sub>2</sub>]<sup>3+</sup>  
NIVQUE (0.220 Å)



NOPOPO



NONOPOPO

## Staff, collaborators, postdocs, and students who have received funding from EMSP projects 54679 and 73759

### **PNNL Staff**

(FY04, FY05)

Mikhail Alnajjar

David Dixon

Ben Hay

Gregg Lumetta

Brian Rapko

Linfeng Rao

Sergei Sinkov

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Kevin Gilbert (U Indiana)

Jim Hutchison (U Oregon)

Robin Rogers (U Alabama)

Max Roundhill (Texas Tech)

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Robert Gilbertson

Tom Klinckman

Bruce McNamara

Giovanni Sandrone

Alex Oliferenko

Jamal Uddin

Rubi Vargas

Pierre-Luigi Zanonato

Cungen Zhang

### **Graduate Students**

Matt Stavis

Eric Werner

## Publications resulting from Project # 73759

1. "How Strong is the C(alpha)-H...O=C Hydrogen Bond?" Vargas, R.; Garza, J.; Dixon, D.A.; Hay, B.P. *Journal of the American Chemical Society* **2000**, *122*, 4750-4755 and highlighted in *Chemical & Engineering News*, News of the Week Article "Protein Folding. Weak Hydrogen Bonds in Peptide Backbones May Play Significant Role."
2. (2000, 78, 15) "Conformational Analysis of N,N,N',N'-Tetramethylsuccinamide: Importance of C-HO Hydrogen Bonds?" Vargas, R.; Garza, J.; Dixon, D.A.; Hay, B.P. *Journal of Physical Chemistry, A* **2000**, *104*, 5115-5121.
3. "Coordination of Lanthanide Ions Containing Non-Coordinating Counteranions with N,N,N',N'-Tetramethylsuccinamide (TMSA). I. Preparation and Characterization of [(TMSA)<sub>4</sub>Ln][A]<sub>3</sub>, A = ClO<sub>4</sub><sup>-</sup>, CF<sub>3</sub>SO<sub>3</sub><sup>-</sup>" Rapko B.M.; McNamara, B.M.; Lumetta, G.J.; Rogers, R.D.; Broker, G.; Hay, B.P. *Inorganic Chemistry* **2000**, *39*, 4858-4867.
4. "Synthesis and Characterization of Mono- and Bis-(tetraalkyl-malonamide) Uranium(VI) Complexes" Lumetta, G.J.; McNamara, B.K.; Rapko, B.M.; Sell, R.L.; Rogers, R.D.; Broker, G.A.; Hutchison, J.E. *Inorganica Chimica Acta* **2000**, *309*, 103-108.
5. "The Role of Donor Group Orientation as a Factor in Metal Ion Recognition by Ligands" Hay, B.P.; Hancock, R.D. *Coordination Chemistry Reviews* **2001**, *212*, 61-78.
6. "Molecular Recognition by Cesium Tetrabenzo-24-crown-8" Bryan, J.C., Hay, B.P. *Structural Chemistry* **2001**, *12*, 283-290.
7. "Tribenzo-18-crown-6 Acetonitrile Solvate" Bryan, J.C.; Engle, N.L.; Sachleben, R.A.; Hay, B.P. *Acta Crystallographica, C* **2001**, *57*, 1359-1360.
8. "Deliberate Design of Ligand Architecture Yields Dramatic Enhancement of Metal Ion Affinity" Lumetta, G.J.; Rapko, B.M.; Garza, P.A.; Hay, B.P.; Gilbertson, R.D.; Weakley, T.J.R.; Hutchison, J.E. *Journal of the American Chemical Society, Communication to the Editor* **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 Office of Science Website (Feature Article, 7/29/02).

9. "Refinement of the Crystal Structure of (9,10-triptyceno)-25-crown-7 measured at 173K" Bryan, J.C.; Gahk, A.A.; Sachleben, R.A.; Hay, B.P. *Zeitschrift fur Kristallographie* **2002**, *217*, 225-227.
10. "A Novel Bicyclic Diamide with High Binding Affinity for Trivalent f-Block Elements" Lumetta, G.J.; Rapko, B.M.; Hay, B.P.; Garza, P.A.; Hutchison, J.E.; Gilbertson, R.D. *Solvent Extraction and Ion Exchange* **2003**, *21*, 29-39.
11. "Design, Synthesis, and Structure of Novel Cesium Receptors" Bryan, J.C.; Sachleben, R.A.; Eagle, C.T.; Hay, B.P.; Zhang, C.; Bonnesen, P.V. *Journal of Chemical Crystallography* **2003**, *33*, 349-355.
12. "Rational Design of Cesium-Selective Ionophores and Chemosensors: Dihydrocalix-[4]arene Crown-6 Ethers" Sachleben, R.A.; Bryan, J.C.; Brown, G.M.; Dabestani, R.; Engle, N.L.; Haverlock, T. J.; Hay, B.P.; Ji, H.F.; Urvoas, A.; Moyer, B.A. *European Journal of Organic Chemistry* **2003**, 4862-4869.
13. "Bicyclic and Acyclic Diamides. Comparison of Aqueous Phase Binding Constants with Tetra- and Hexavalent Actinides" Sinkov, S.I. *Actinide Research Quarterly*, 3<sup>rd</sup>/4<sup>th</sup> quarter, **2003**, 19-21.
14. "Eight-coordinate Stereochemistries of U(IV) Catecholate and Aquo Complexes" Hay, B.P.; Uddin, J.; Firman, T.K. *Polyhedron* **2004**, *23*, 145-154.
15. "Toward the Computer-Aided Design of Metal Ion Sequestering Agents" Hay, B.P.; Firman, T.K.; Lumetta, G.J.; Rapko, B.M.; Garza, P.A.; Sinkov, S.I.; Hutchison, J.E.; Parks, B.W.; Gilbertson, R.D.; Weakley, T.J.R. *Journal of Alloys and Compounds* **2004**, *374*, 416-419.
16. "Bicyclic and Acyclic Diamides: Comparison of Their Aqueous Phase Binding Constants with Am(III), Pu(IV), Np(V) and U(VI)" Sinkov, S.I.; Rapko, B.M.; Lumetta, G.J.; Hay, B.P.; Hutchison, J.E.; Parks, B.W. *Inorganic Chemistry* **2004**, *43*, 8404-8413.
17. "Estimating the Number of Bound Waters in Gd(III) Complexes Revisited. Improved Methods for the Prediction of q-Values" Hay, B.P.; Werner, E.J.; Raymond, K.N. *Bioconjugate Chemistry*. **2004**, *15*, 1496-1502.
18. "The Synthesis and Lanthanide Coordination Chemistry of 2,6-Bis[(dicyclohexyl)phosphino- methyl]pyridine N,P,P'-trioxide. The Crystal Structure of 2,6-Bis[(dicyclo-hexyl)phos-phinomethyl] Pyridine N,P,P'-trioxide Erbium(III) Nitrate" Gan, X.; Rapko, B.M.; Duessler, E.N.; Benjamin, I.; Paine, R.T.; Hay, B.P. Accepted for publication in *Polyhedron*.