

**Progress Report Summary**  
**De Novo Design of Ligands for Metal Separation**  
**(DE-FG07-96ER14693)**  
**9/15/96 - 9/14/97**

**SPECIFIC AIM 1 - Parameterize force field to reproduce geometries and relative energetics of metal-ligand complexes for cesium, strontium, plutonium, uranium, americium and other relevant alkali, transition, lanthanide and actinide metals.**

As an initial attempt to examine parametrization, Dr. Yasuo Takeuchi has examined parameters for iron in combination with the molecular mechanics force field. We realize that most of the current ad hoc methodologies used to model metal interactions in the past do not have a firm theoretical foundation for modeling the d and f orbitals. We have, therefore, started a collaboration with Prof. Anders Carlsson of the Department of Physics to provide a theoretically correct functional form for the metal force field. Prof. Carlsson has an extensive track record in the derivation of the form of angular force fields from analysis of the quantum-mechanical electronic structure. His most important related works have treated the angular forces around transition-metal (TM) atoms in an aluminum host, the angular forces in elemental bcc transition metals, and the origins of angular and torsional forces in well-bonded s-p systems. We propose to apply the basic ideas of these calculations to developing force laws for transition metal ions in biomolecules.

Of particular relevance to the proposed work is his study analyzing angular forces around transition metal (TM) atoms embedded in an aluminum host. Such TM atoms have a profound effect on the host structure, often entirely reassembling the host structure in order to satisfy the angular bonding constraints around the TM atoms. For example, at a concentration of only 1~TM to 12~Al, the transition metals Mn, Mo, Tc, W, and Re form the Al<sup>12</sup>W structure, in which the underlying fcc aluminum lattice is disassembled and reassembled into icosahedra which surround the transition-metal atoms. The Al<sup>12</sup>W structure is a body-centered cubic arrangement of such icosahedra. This behavior is analogous to that of several transition metals in proteins and other potential hosts, for example the formation of square-planar or Jahn-teller distorted octahedral structure by Cu<sup>2+</sup> ions in many proteins. In both cases, the transition metal atom or ion has strong preferences regarding its angular environment. Of course, other effects, such as steric constraints on the ligands, are also important and dominate in some cases.

Nevertheless, the angular preferences are too strong to be ignored and are often essential.

The angular forces calculated for transition metals in aluminum were based on physical mechanisms seen in *ab-initio* electronic-structure calculations of the zero-temperature enthalpy for both the the Al<sup>12</sup>W-structure, Al<sup>12</sup>T compound and a hypothetical fcc-based Cu<sup>3</sup>Au-structure, Al<sup>3</sup>WT compound (plus an amount of Al to preserve stoichiometry). The transition metals with the largest enthalpy difference favoring the Al<sup>12</sup>W structure were (consistent with experiment) those with nearly half-filled d-bands. Analysis of the electronic structure showed that the energy stabilizing the Al<sup>12</sup>W structure for these metals results from a pronounced minimum in the electronic density of states (DOS) which is not present for the fcc-based Cu<sup>3</sup>Au structure. The placement of this minimum is such that the Fermi level of TM with nearly half-filled d-bands lies in the region of the DOS minimum. This energetic stabilization mechanism is closely analogous to the ligand-field splittings of ligated transition-metal ions; in both cases a stabilizing energy results from having a gap (or near-gap) between the empty and occupied states. These studies have provided Prof. Carlsson with the physical insight into the derivation from quantum mechanics of an angular potential for d orbitals. We will incorporate this functional form into our metal force field and parametrize it for the transition metals of interest.

A paper exploring the use of our ferric ion force field to redesign a natural product, enterobactin, which binds ferric ion with high affinity has been submitted to the Journal of Medicinal Chemistry. The parameters and validation of the force field are described in that publication. The goal of our efforts was to understand the basis of the high affinity in hope of generating a synthetically more accessible compound with similar affinity. Synthetic efforts to test our prediction are underway.

Work over the last year by Prof. Ponder has focused on adaptation of the TINKER molecular modeling package to handle the polarizable multipole electrostatics models at the base of the metal/water parameterization strategy outlined in our original proposal.

A refined TINKER water model for use in solvation of metal ions has been finalized (Kong and Ponder, manuscript in preparation). One of the important factors leading to the poor performance of the current effective pair potential models in reproducing the small water cluster properties and other deficiencies is the inaccurate representation of the electrostatic interactions. In most of the

available water models in particular, and the empirical force fields in general, the electrostatic interactions are approximated by atomic partial charge models. The limitation of the partial charge models is two-folded. First, the partial charge model is only the first term in an infinite multipole expansion of the electrostatic potential. To model the electrostatic potential correctly, higher order terms are needed. It has been recognized for a long time that the partial charges intrinsically are unable to accurately model the electrostatic potential around polar molecules. For example, Williams showed that optimally fit partial charges produce a potential with a 10-15% RMS difference from the target ab initio potential, while the average RMS error in an optimal multipole-based potential is usually less than 0.1% relative to the ab initio potential. Sokalski et al. showed that the angular characteristics of the electrostatic potential around functional groups capable of forming hydrogen bonds can be considerably distorted within the partial charge model. The second drawback for the partial charge models lies in the additivity nature of the potentials used and the parameterization procedure of the models. In order to reproduce condensed phase properties, the charges and hence the dipole moment are augmented respect to the gas phase so as to include the average effect of nonadditive induction and other many-body interactions. In this way the bulk properties are reproduced at the expense of the small cluster properties.

In order to overcome the intrinsic limitation of the partial charge models, we have developed the TINKER water model, for the simulation of polarizable, highly charged ions. The force field uses multipole expansion to replace the traditional partial charges. Preliminary parameters for amino acids, various organic functional groups, alkali and alkaline earth metals have also been obtained. At present we are beginning a series of dynamics simulations aimed at refinement of the preliminary parameters. To overcome the second limitation of the additive pair potential models, polarizability is incorporated explicitly in our simulations. It has long been recognized that nonadditive interactions due to electric polarization and many-body effects play an important role in both homogeneous systems such as liquid water inhomogeneous ionic systems. For example, the total dipole moment of a water molecule which changes from 1.855 D in the gas phase to approximately 2.6 D in condensed phase. In a bulk system such as liquid water, the nonadditive effects can be incorporated into a pairwise additive potential in an average way by carefully parameterizing the potential against the thermodynamic properties of the bulk. For isotropic, homogeneous systems this kind of effective potential can give some correct average properties, but for anisotropic, inhomogeneous systems such as solvated cations, as well as water molecules around surfaces, this approach will break down. Several groups have tried to take the nonadditive many-body interactions explicitly into additional special potential functions for single species

in otherwise homogeneous systems such as ions in water. For large ionic systems or systems containing metal ligands, it would be cumbersome to implement this approach. For an empirical force field aiming for general-purpose molecular simulations, a common approach is to incorporate polarizability into the existing molecular mechanics force field. For the sake of simplicity, only dipole polarizability is usually considered. For some models of small molecules such as water, higher order polarizabilities can also be incorporated. Usually the polarization effects are treated in the traditional way through the dipole field tensor, but alternative methods have been proposed, such as the Drude oscillator method and the dynamical fluctuating charge model of Berne. The current TINKER force field incorporates the induced dipole through multipole field tensors, which are an extension of the dipole field tensor used in the partial charge models. Over the last year we have completed a series of simulations comparing the new TINKER model with a number of other current potentials including TIP3P, SPC, SPC/E, TIP4P, DANG, POL3, PSPC and NEMO. Overall the TINKER potential provides the best combined description of bulk and cluster properties (manuscript in prep.). This bodes well for the ability of the new TINKER water potential to accurately solvate metal cations.

An efficient, new reaction field formalism for off-center point multipoles has also been devised to allow inclusion of long range solvation effects (Kong and Ponder, *J. Chem. Phys.*, 107, 481-492, '97). Two general methods for calculating the reaction field generated by a set of off-center point multipoles in a spherical cavity were developed. The methods are a generalization of Kirkwood's original theory for an arbitrary charge distribution. A polytensor formulation, similar to that already used by TINKER for direct multipole interactions, serves to organize the computation and allows straightforward extension to higher derivatives of reaction field energy and gradients of the potential. The computation is reduced to calculation of the Cartesian derivatives of biaxial harmonics. Recursive and explicit formulas have been derived and implemented. For example, the incorporation of reaction field effects in computation of induced dipole moments is now possible. The second procedure, the Central Multipole Method, scales linearly in calculation time with the size of the system. Methods to obtain derivatives analytically based on this method are also available. These developments allow use of reaction field energy terms with atomic multipole-based empirical potential energy functions. Both methods show particular promise for use in simulation of heterogeneous systems, such as metal ions and ligands, where the remainder of the cavity can be filled explicitly with solvent.

**SPECIFIC AIM 2 - Adapt suite of de novo design tools from receptor**

## **structure-based design to metal-ligand design.**

Dr. Chris Ho has recoded most of the systematic search routines in order to improve the efficiency of generation of metal-binding ligands. We have also modified the popular freeware program RASMOL to allow interaction for picking atoms as input. We intend to utilize this modified version of RASMOL along with a HTML- and/or TKL-based graphical user interface (GUI) to the TINKER suite of molecular modeling modules. The lack of a GUI for TINKER has been a serious impediment to its widespread use. While we could have simply written out a file compatible with commercial molecular modeling programs, the lack of a standard file format would require extensive efforts to provide a program which would interface with the wide variety of packages in common use. RASMOL already has some capabilities in this area.

We will test the ability of our programs to generate appropriate ligands with the parameters and force field previously tested by Dr. Takeuchi.

**SPECIFIC AIM 3 - Develop an analogous molecular mechanics/heuristic approach for predicting metal binding affinities to that used by VALIDATE to predict affinities of organic complexes.**

Specific Aim 3 depends on the completion of specific Aim 1. We anticipate serious efforts in this area to begin at the end of this current funding year.