

The PIMM Force Field - Recent Developments

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Introduction

Even though the steady advances in computing power and algorithms continue to increase the competition by semi-empirical and *ab initio* methods, they also serve to open new realms for modern force fields. Among the key advantages of the classical molecular mechanics approach is their ability to handle systems with a large number of atoms and degrees of freedom. A second and increasingly important feature lies in the fact that they can often provide a simple but efficient means of modeling metal complexes.

In recent years, our PIMM force field [1] for organic molecules has found successful application in a number of problems in organic and bio-organic chemistry. Examples range from peptide complexes of alkaline earths cations to porphyrin complexes of the transition metals. In its traditional field, the conformational analysis of organic molecules, satisfying results have been reported especially for carbohydrates [2]. Besides conventional energy minimization techniques and systematic permutations, molecular dynamics calculations have gained increasing importance.

In its current form, the program fills the niche between the small-molecule force fields and the protein modeling packages. Even on the pc platform, systems of up to 2000 atoms can readily be studied without simplifications. This entails not only an all-atom representation, but also a semiempirical SCF calculation of the pi electrons and a Hessian matrix-based optimization algorithm. Current projects address the specific continuum effects in con-

densed phases, i.e. a model representation of solvent and packing effects.

Parameters

Metal complexes can in theory be modeled by two conceptually different approaches. While some authors favor an explicit parametrization of metal-ligand bonds, we have achieved good results based on electrostatic and van der Waals interactions alone. At first glance, the bonded approach offers the advantage of prescribing exact bond angles and torsional angles in addition to distances. On the other hand, this requires a great number of parameters and will usually lead to a very stiff model, where e.g. the number of ligands is defined by the starting structure.

The flexible non-bonded model used in PIMM naturally benefits greatly from the strong contribution of charge interactions in the force field. Its disadvantages become apparent only in cases where orbital interactions have a dominating influence on the 3D structure of a complex. Results for porphyrin complexes, metallocenes and carbonyl complexes generally display good agreement between calculated and experimental geometries.

Catering especially to the growing interest in coordination chemistry, the parameter set has been extended over the past year to include several new classes of compounds. Besides the ferrocenes, this now includes zirconocenes as well as chromium carbonyls. Parameters for covalently bound boron have been added to allow modelling of pyrazolylborate complexes and tetraalkylborate salts. As the parameter set is extended mainly in conjunction with

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specific projects, the current set as depicted in figure 1 does not reflect a fundamental limitation of the program.

H																	He				
Li	Be															B	C	N	O	F	Ne
Na	Mg															Al	Si	P	S	Cl	Ar
K	Ca	Sc	Ti	V	Cr	Mn	Fe	Co	Ni	Cu	Zn	Ga	Ge	As	Se	Br	Kr				
Rb	Sr	Y	Zr	Nb	Mo	Tc	Ru	Rh	Pd	Ag	Cd	In	Sn	Sb	Te	I	Xe				
Cs	Ba	Lan	Hf	Ta	W	Re	Os	Ir	Pt	Au	Hg	Tl	Pb	Bi	Po	At	Rn				
Fr	Ra	Act																			
La	Ce	Pr	Nd	Pm	Sm	Eu	Gd	Tb	Dy	Ho	Er	Tm	Yb	Lu							
Ac	Th	Pa	U	Np	Pu	Am	Cm	Bk	Cf	Es	Fm	Md	No	Lw							

Figure 1: Chemical elements available in the current parameter set

Algorithms

Until recently, the molecular dynamics code in PIMM constituted one of its major weaknesses. As a relatively recent addition originally intended for the generation of starting conformations rather than true MD, it contained a number of shortcomings that impaired its performance. The revised algorithm has shown vastly improved performance in calculations of cyclodextrins and peptides. Conformational analysis of larger molecules has been facilitated by a Metropolis Monte Carlo algorithm. Irrespective of the type of starting coordinates, this can be used to vary torsional angles as well as the cartesian coordinates of individual atoms. For cyclic systems, variation of a torsional angle is

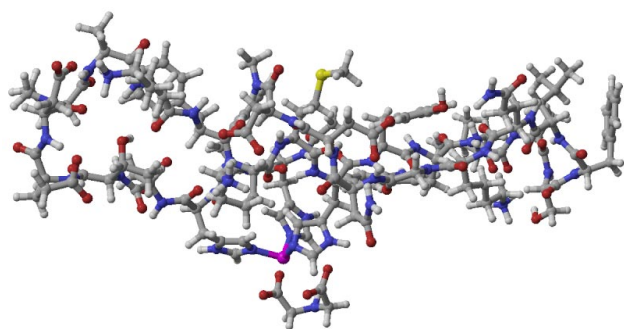


Figure 2: Peptide fragment encompassing the Zn binding region

automatically transformed into the appropriate puckering or folding motion.

The concomitant changes to the torsional angle driver have also removed the previous restrictions in the systematic variation of torsional angles. Thus it is no longer necessary to include a torsional angle in the Z-matrix in order to permute it, and substituents can have arbitrary reference atoms. Periodic boundary conditions have been introduced to allow the realistic modeling of molecular crystals. While the full crystallographic symmetry can be taken into account, it is currently necessary for the asymmetric unit to contain a complete molecule. Although this precludes the study of covalently linked polymers, hydrogen bonding networks are already treated correctly.

Although the code has primarily been tested in energy minimization runs, it can be used as well for molecular dynamics and monte carlo simulations. The results obtained so far generally indicate a good agreement of experimental and calculated heats of formation, though in some cases coupled with a small contraction of the unit cell.

Sample Applications

These snapshots of current research projects are meant to serve only as illustrations of the versatility of the program. In-depth discussions of the individual topics will be published elsewhere.

A. Mutational study of zinc binding sites

Based on previous modeling work with calcium-binding proteins, the goal of this project is the prediction of zinc

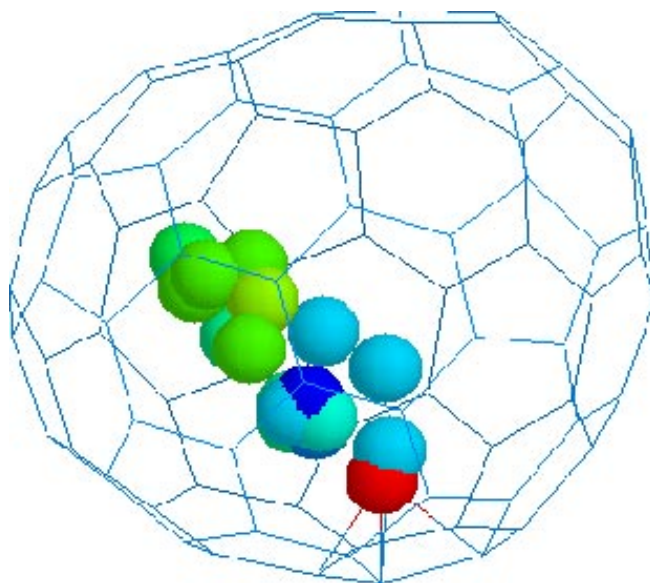


Figure 3: Trajectory of Fe color-coded by binding energy

binding affinities in active site mutants of carbonic anhydrase A2 (CA2) [3] and a chimeric protein [4] composed of the retinol binding protein (RBP) and the zinc site of CA2. Preliminary calculations on protein fragments as depicted in figure 2 yield a good correlation between experimental binding constants and calculated binding energies.

B. Fullerene complexes

Molecular dynamics and monte carlo calculations are being employed to locate energetically favourable positions for divalent iron ions in the cage structure of C82. The results obtained with PIMM appear to be in good agreement with spectroscopic data and *ab initio* calculations that used a minimal basis set (figure 3).

C. Porphyrin complexes

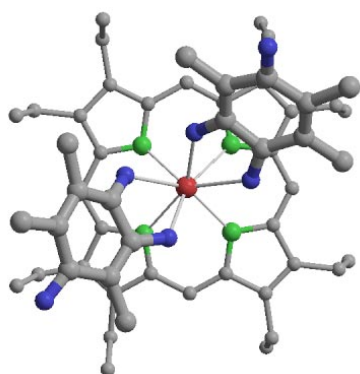


Figure 4: Model structure of $Fe(OEP)(hquin)_2$

The structure of a novel zirconium complex [5] with axial hydroxyquinone ligands was modeled by combined MM and MD techniques, allowing the interpretation of spectroscopic features even though no crystals suitable for an x-ray analysis could be obtained.

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