Medicinal Chemistry and Enzyme Kinetics

Elizabeth Amin and C. R. Wagner, Medicinal Chemistry
Jiali Gao, Chemistry
Don Truhlar, Chemistry
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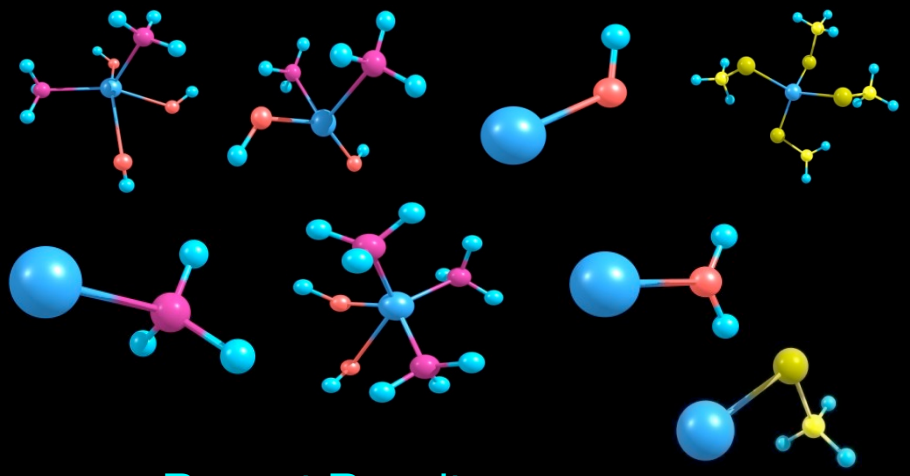
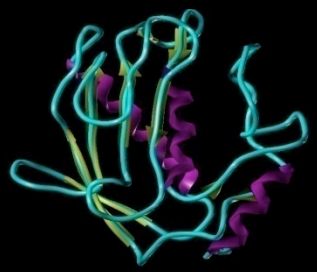
Zn Metalloprotein Force Field Design

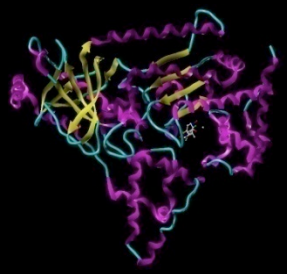
Prof. Elizabeth A. Amin, Department of Medicinal Chemistry, College of Pharmacy
Prof. Donald G. Truhlar, Department of Chemistry, February 2007

- Zn: unusual coordination, charge distribution at transition states in important metalloenzymes such as MMP-3, ATLF, phosphotriesterase
- Poorly represented in current force fields
- Need new functional forms and parameters for MM, QM/MM work





MMP-3



Anthrax Toxin Lethal Factor

Recent Results

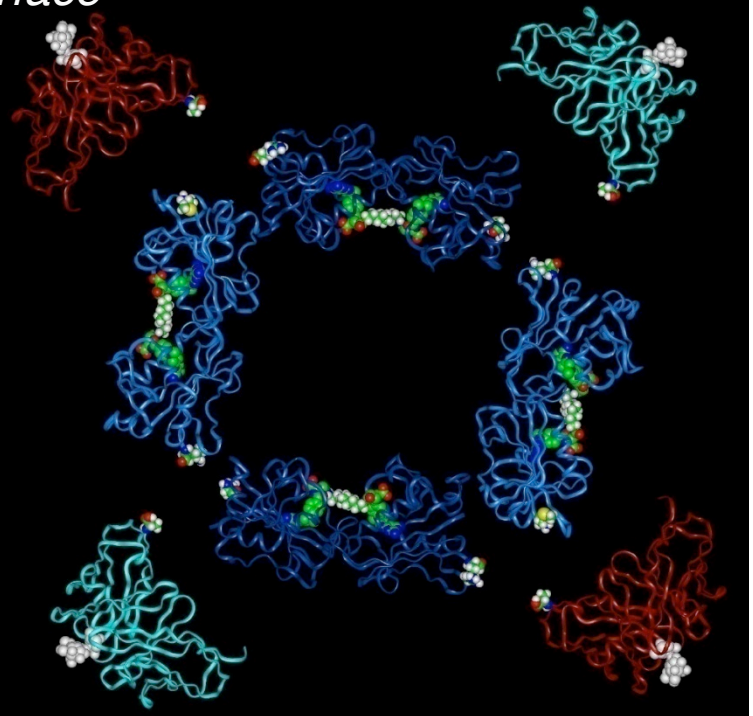
- Novel analytic function not requiring diagonalization/iterations
- More accurate parameters based on hybrid DFT on Zn model compounds
- Best overall DFT and semiempirical methods for Zn structures: geometries, bond dissociation energies, dipoles

Modeling of Protein Nanorings

Brian White, Carston R. Wagner, Elizabeth A. Amin, and Donald G. Truhlar, February 2007

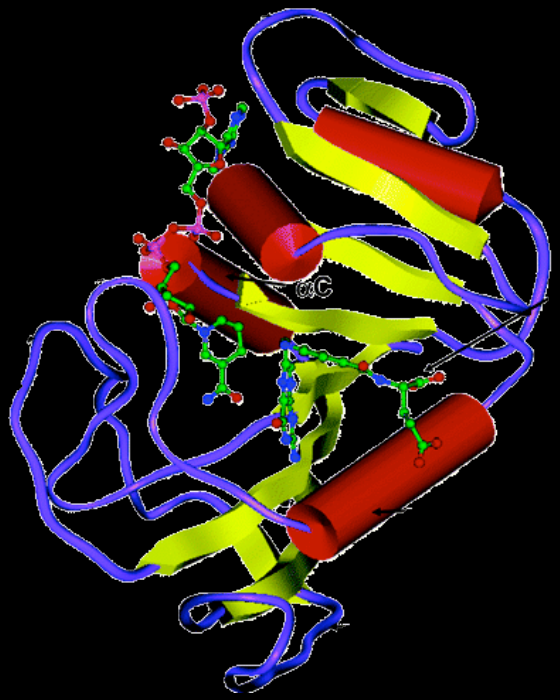
- *Protein Nanorings - Novel Therapeutic Delivery Tools*
  - *Clean, chemically-induced self assembly due to bivalent ligand*
  - *Multivalent targeting possible*
  - *Necessary to exert control over nanoring formation by utilizing heterodimeric pairs to introduce multiple, ring-tethered targeting agents*
  - *This is achieved by mutating the dimer interface*

We are in the initial stages of developing a computational model to predict mutation effects on heterodimer stability. By understanding mutation effects, we will increase our control over the assembly of nanorings via the introduction of mutants at the protein interface. We are utilizing Wave Function, Density Functional, Semi-empirical Molecular Orbital, and Molecular Mechanics theories to develop a set of parameters that will accurately describe both proteins and their bivalent ligand in solution.



Enzyme Kinetics

Neil Young, Rudolf Allemann, *University of Cardiff*
Mireia Garcia-Viloca,*University of Barcelona*
Javier Ruiz, and Iñaki Tuñón, *University of Valencia*
Jingzhi Pu, *Harvard University*
Wangshen Xie, Shuhua Ma, Sudeep Bhattacharyay, Marian Stankovich,
Jiali Gao, and Donald G. Truhlar, *University of Minnesota*
February 2007



Kinetic isotope effects

Variational transition state theory

Multidimensional tunneling

Ensemble averaging

Electrostatics

Polarization effects

Reduction potentials

Solvation modeling of bioavailability and ADMETox in drug design

See a separate research highlight on solvation for further medicinal chemistry research.