Fragment-based Optimization of Large System Using Quantum Mechanics

Matthias Trautwein, Thomas E. Exner

Universität Konstanz, Theoretische chemische Dynamik

The calculation of properties of proteins is essential for the understanding of biochemical processes. Quantum mechanics allow calculations with very high accuracy, but they scale in the third or higher power with the size of the system. Thus, today it is not possible to calculate large molecules like proteins using standard methods. A solution to this problem are fragment-based approaches. One of these, on which this work is based, is the adjustable density matrix assembler (ADMA) [1-4]. ADMA divides a macromolecule into fragments of only 5-10 atoms surrounded by additional regions (surroundings) to include short-ranged interactions up to 3 Å to 12 Å depending on the desired accuracy. By combining the results from each separately performed fragment calculation, the electron density matrix, the forces acting on each atom and the total energy can be obtained. This information can now be used for the energy optimization of large molecules by interfacing ADMA with DL-FIND [5], a library of optimization procedures especially developed for quantum-mechanical calculations.

An interesting application of this new method is to study influences of structural changes on calculated NMR chemical shifts. The Trp-cage miniprotein is used here as an examples. In earlier work [6] it has been shown, that calculated NMR chemical shifts for a tyrosine side chain show larger deviations from the experiment than nuclei from any other amino acid. To analyze if these deviations result from an incorrect orientation of this side chain, it was energetically optimized keeping the remaining protein fixed and the NMR chemical shift calculations were rerun on these optimized structures.

[1] T.E. Exner, P.G. Mezey, *J. Phys. Chem A.,* **2002**, *106*, 11791-11800
[2] T.E. Exner, P.G. Mezey, *J. Comp. Chem,* **2003**, *24*, 1980-1986
[3] T.E. Exner, P.G. Mezey, *J. Phys. Chem A.,* **2004**, *108*, 4301-4309
[4] T.E. Exner, P.G. Mezey, *Phys. Chem. Chem.,* **2005**, *7*, 4061-4069
[5] J. Kästner, J.M. Carr, T.W. Keal, W. Thiel, A.Wander, P.Sherwood, *J. Phys. Chem. A.,* **2009**, *113*, 11856-11865
[6] A. Frank, I. Onila, H.M. Möller, T.E. Exner *Proteins,* **2011**, *79*, 2189-2202