Development and Application of Quantum Mechanical/ Molecular Mechanical Coupled Potentials

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In order to fully exploit combined quantum mechanical/molecular mechanical (QM/MM) coupled potentials (CP) in molecular dynamics (MD) and free energy perturbation (FEP) simulations several technical problems need to be overcome. These problems as well as ou solution to these problems will form the first part of our presentation. In the second part of the presentation we will describe recent applications of QM/MM CP methods to reactivity in condensed phases.

We have found that temperature control during a QM/MM MD simulation can be difficult, which results in unstable MD trajectories. To solve this problem we make use of a sophisticated T control procedure called the Nosé-Hoover Chain method. In this method multiple thermostats can be "chained" to different degrees of freedom in the system. Thus, we can coup our QM region of a system to one thermostat, while we attach another thermostat to the surrounding MM environment. We find that this procedure works very effectively in controlling temperature in QM/MM simulations, while the more traditional Berendsen T controlling method fails. This now allows us to routinely carry out MD, FEP and potential of mean force (PMF) simulations on reactive processes where we not able to do so in the past.

When carrying out a FEP simulation using a QM/MM CP several situations can arise. In simple perturbations (CH_4 -> NH_4^+) the basis set parameters can be altered to mutate one ato type into another. Thus, for CH_4 -> NH_4^+ we simply alter the basis set parameters for C into those for N. In more complex perturbations the number of electrons can change during the cours of the FEP run. In purely MM simulations changing the number of electrons is trivial to do, since in the MM representation no electrons are present. However, in QM simulations this can be a problem. To solve this problem we have developed the fractional electron method (FEM). In this procedure the orbital occupancy, as governed by the density matrix, becomes a variable in th FEP simulation. For example, if a molecular orbital is doubly occupied at the start of the FEP simulation and becomes unoccupied at the end of the simulation we simply introduce a variable (N_k) which goes from two to zero and scales the molecular orbital occupancy. Thus, by slowly altering the value of N_k during the FEP simulation we can calculate the free energy change associated with this conversion. The application of this method as well as its relationship to othe methods will be discussed.

The final part of our presentation will be the application of or QM/MM CP methods to reactive processes. In particular, we will focus on the use of a density functional theory (DFT)/MM approach to study the proton transfer between water and hydroxide using the 6-31G** basis set in conjunction with gradient corrections. To study this system we have developed a novel sampling strategy in order to reduce the computational expense of the PM simulations we have used to assemble the 2-dimensional free energy profile for this reaction. Th final example, will be the proton transfer between ionizable groups within the active site of human carbonic anhydrase II (HCAII). In HCAII there is a Glu-His-metal motif, which is related to the well known Asp-His-Ser motif seen in serine proteases. It has been suggested that the Glu His-metal motif is important in governing the reactivity of HCAII by shuttling a proton between the Glu and the His residues much like what is observed in serine proteases. In order to address the importance of this we have carried out PMF simulations that examine the energetics involved in transferring a proton between Glu and His in HCAII. From these studies we will discuss the importance of this proton transfer to the catalytic mechanism of HCAII.