Application of Semi-Empirical Methods to the Study of Biological Molecules

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The recent advances in microprocessor technology, parallel programming and availability of supercomputer clusters have allowed computational chemists to apply a broader range of methods to systems of ever increasing size and complexity. As a natural consequence, the use of quantum mechanical methods in computational studies of biological molecules is becoming more popular, and native implementations of semi-empirical methods in popular biomolecular simulation programs such as AMBER and CHARMM promise to make the use of hybrid quantum mechanics / molecular mechanics (QM/MM) even more widespread.

In such an environment, it is important to ask the question of which methods are the most appropriate for the problems under consideration. While there is no doubt QM methods are required for situations where intrinsically quantum processes such as bond breaking and forming, tunneling or charge redistribution are important, the semi-empirical methods currently available have been parameterized against small molecules and reactions, usually to reproduce gas-phase data. The parameters thus obtained are not guaranteed to be fully transferable to biological molecules in their natural surroundings and the potential improvements for the calculation of structural properties that could be obtained by using semi-empirical methods over classical force fields have not been established yet.

We applied molecular dynamics to compare the performance of a series of commonly used semi-empirical Hamiltonians to the reproduction of structural properties of peptides, when used as part of a hybrid QM/MM scheme, for the simulation of biological molecules in water. We present results for blocked alanine dipeptide (Ace-Ala-NMe, Ala_2) and unblocked alanine trimer (ALA-ALA-ALA, Ala_3), both immersed in water, where the peptides are either treated quantum mechanically or with classical force fields, and the water molecules are treated classically with the TIP3P model. We show conformational distributions in the (ϕ,ψ) space, dipolar couplings and radial distribution functions (RDF), and compare with available experimental data. We show that none of the currently available semi-empirical methods is able to satisfactorily reproduce experimental data, and discuss possible reasons for the discrepancy.