Comparison of QM cluster calculations and QM/MM calculations for reactions in proteins

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During the latest decades, quantum mechanical (QM) calculations have become an important complement to experiments for the study of the structure and function or proteins. However, there is still no consensus on how such calculations should be performed. Instead, two schools have emerged: In the first, a small model (50–200 atoms) of the active site is cut out from the protein and is studied in isolation by QM methods. The effect of the surrounding is typically modelled by fixing a few atoms at the periphery to their crystal positions and by running the calculations in a continuum solvent with a dielectric constant of ~4 [1]. In the second approach, the entire protein, including some surrounding water molecules are explicitly studied by the combined QM and molecular mechanics (QM/MM) approach, in which the active site (again 50–200 atoms) is studied by QM methods, whereas the rest is modelled at the MM level [2].

We have studied the convergence of the QM cluster approach with respect to the size of the QM system and compared various methods to select atoms to include in the calculations [3]. For our test system, a simple proton-transfer reaction in [Ni,Fe] hydrogenase, various approaches to add groups to the QM system converge after ~15 groups have been added and the effect of the continuum solvent becomes unimportant at the same size. Unfortunately, different approaches to add groups converge to different results that differ by up to ~60 kJ/mol. In fact, it seem to be necessary to include all groups within 4–5 Å of the active site, as well as all charged groups that are buried inside the protein.

Likewise, we have studied the accuracy of QM/MM calculations, compared to pure QM calculations on a 446-atom model of [Ni,Fe] hydrogenase, again systematically increasing the size of the QM system [4]. This gave us the opportunity to study also the influence of different charge-distribution schemes around the junctions and different ways to correct the errors introduced by the junctions, including variants of both mechanical and electrostatic embedding. The results show that the junctions introduce inaccuracies that are hard to correct if they are too close to the reactive centre. Moreover, instabilities in the wavefunction, caused by nearby point charges can give rise to large errors. In fact, the best results are obtained by mechanical embedding. With the best approaches, the QM/MM results are more accurate than those with the QM cluster approach.

Finally, we will discuss how the two approaches may be combined to obtain the most reliable results.

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