FREE ENERGY CALCULATION IN ENZYMATIC REACTIONS USING SEMIEMPIRICAL REFERENCE POTENTIALS

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Abstract

The computation of free energy of activation of chemical reactions in enzymes at ab initio level with current technology requires the use of hybrid strategies that involve coarse approximations at parts of the system away from the reaction site and usually also at intermediary steps between reactant, transition states and products. The idea is to use the QM/MM method where only a small part of the system is treated using quantum mechanics (QM) while the remaining of the system is treated using classical molecular mechanics (MM). However, this is not enough as there is the need to generate several thousands of samples at each iteration while moving along the reaction path and even QM/MM methods, using ab initio QM methods, are still too demanding for most practical applications because they are hindered by the expensive QM ab initio computations. One strategy is to work with two levels of QM approximations. At the coarse level, for example semiempirical methods or empirical valence bond is used as reference potential and at fine leve a more accurate QM method. A few strategies have been tested, and in this work the strategy known as paradynamics was implemented using the semiempirical methods PM3 and PM6, respectively, as coarse and fine physics approximations. The idea of the paradynamics is to refine the coarse physics potential by adding gaussians until it resembles the fine physics potential, then the computationally expensive sampling is done in the reference coarse physics potential to obtain the potential of mean force (PMF) with umbrella sampling/WHAM, and, at selected locations along the reaction path, the fine physics free energy differences are calculated using a thermodynamic cycle and free energy perturbation or its corresponding linear response approximation (LRA). The paradynamic protocol was implemented using the pDynamo molecular modeling package and tested with a reaction catalyzed by the enzyme haloalkane dehalogenase with the substrate 1,2-dicloroetane (DCE). The system consisted of the enzyme and substrate surrounded by a 40Å radius water box. The QM region included 12 atoms near the reaction center and all the remaining atoms were treated with classical mechanics. The potential of mean force was computed using a distance reaction coordinate between the three atoms involved in the reaction at the PM3 level and after the identification of reactant state, transition state and product state, the linear response approximation was used to compute free energy variations at PM6 level. The PMF at PM6 level was also

obtained for comparison and it was verified that the results obtained with our procedure are in good agreement.

Palavras-chave: QM/MM, Free energy, Enzymes.