Hybrid quantum mechanics/molecular mechanics calculations (QM/MM) for the limiting step dealkylation reaction catalyzed by ALKBH3 Erik Antonio Vázquez-Montelongo¹, Hatice Gökcan¹, Alice. R. Walker^{1,2}, G. Andrés Cisneros^{1*}



Abstract

QM/MM simulations have become a powerful tool to model chemical processes in solution and biomolecular systems, at a reasonable computational time with the necessary accuracy. It has been applied in drug design [1], enzyme/protein engineering [2] and complex systems like ionic liquids[3]. One of the main applications of QM/MM simulations is to investigate the kinetics of chemical processes. We have used our QM/MM software package [4], LICHEM (Layered Interacting CHEmical Models), to performed geometry optimizations and minimum-energy path (MEP) transition state (TS) search using the nudged elastic band (NEB) method and the quadratic string (QSM) method to study the limiting step dealkylation reaction catalyzed by ALKBH3.

Background and Purpose





After performing MD simulations, ten stable structures were extracted from the MD trajectory to perform QM/MM optimizations on the reactant state. All the QM/MM calculations were performed using LICHEM software package [4]. The QM region (70 atoms) was modeled at ω B97XD/6-31+G(d,p)/ level of theory. The boundary atoms were modeled by the pseudobond approach [8], which provides a smooth connection at the QM/MM interface. The MM region (35,305 atoms) was modeled using the AMBER99 force field. Long-range electrostatic (LRE) effects were taken into account using the long-range electrostatic correction (LREC) approach [9], with a LREC exponent of 2 and a cutoff radius of 25 Å.

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Minimum energy path (MEP) Transition State (TS) Search

The initial guess for the MEP was obtained by a linear interpolation between the reactant and product structure (Figure 1). The nudged elastic band (NEB) method was used to minimize the path and approximate the TS structure (Figure 2). The reaction energy is -3.23 kcal/mol, and the reaction barrier is 18.44 kcal/mol. This energy is lower compared with the one previously calculated for AlkB (22.4 kcal/mol), but is in aggrement with the approximate free energy barrier using transition state theory from the experimental results for AlkB (19.8 kcal/mol) [10]. Additionally, the MEP posses one intermediate structure that correspond to the H-bonding formation between the Fe–O–H and the neighbor Aspartate.



Comparison between NEB and QSM

Initially, LICHEM only had implemented the NEB method for MEP optimization. Recently, one of us include the QSM method. This method has the advantage that it is independent of the integration step-size and the spring constant, and it can be used in reactions with multiple barriers.

The reaction barrier calculated with the QSM method is 15.43 kcal/mol, which is slightly lower compared with the one calculated with the NEB method (18.44 kcal/mol).

Future Work

QM/MM calculations require a sequential sampling and optimization approach that helps to accurately determine the reaction path and thermodynamic properties of complex reaction systems (biological such as enzymes or condensed-phase ones likes ionic liquids). An alternative for this approach is the QM/MM minimum free-energy path (QM/MM–MFEP) method [11], where a sequential MM sampling and QM optimization is iterated until convergence. The thermodynamics are described by evaluation of the QM potential of mean force and its gradient within the ensemble. The AMOEBA force field (FF), is a polarizable potential that uses atomic multipoles (up to quadrupoles) and provide a more accurate description of the MM enviroment. Unfortunately, MD simulations using the AMOEBA FF are expensive. Software packages that use GPU-acceleration (Tinker-OpenMM) or highly parallel implementations (Tinker-HP) help to mitigate this disadvantage. The current implementation for NEB and QSM methods in LICHEM is primarily parallelized with OpenMP. One of us is working in the implementation of a hybrid parallel scheme for the QSM method.



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