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New method for minimum energy path: Application to biological molecules

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Introduction

We implement a method of minimum energy path determination within the GHO QM/MM framework[1,2] based on the constraint optimization with the locally updated planes method[3,4]. To apply the present scheme to chemical reactions in enzymes, we introduce an optimization procedure using adiabatic scheme with microiterations, which fully optimizes the environmental region in each core (QM) macroiteration. We test out implementation on the alanine dipeptide, the catalytic subunit of cAMP-dependent protein kinase (PKA), and the chorismate mutase.

Method

A. Constraint optimization with locally updated planes approach

In the minimum energy path, the potential energy is minimized in all directions except in the reaction path direction, which is expressed as

$$\nabla_{\mathbf{x}}V(\mathbf{X}) - [\nabla_{\mathbf{x}}V(\mathbf{X})\cdot\boldsymbol{\tau}]\boldsymbol{\tau} = 0,$$

where $\boldsymbol{\tau}$ is the unit vector in the direction of the reaction path. Because the rigid body motions can affect the value of $\boldsymbol{\tau}$ and $\nabla_{\mathbf{x}}V$, six linear constraints are added to fix the rigid body translations and rotations during minimization. The rigid body constraints are

$$\sum_{i=1}^{N} m_i(\mathbf{r}_i - \mathbf{r}_i^0) = \mathbf{0} \text{ and } \sum_{i=1}^{N} m_i\mathbf{r}_i \times \mathbf{r}_i^0 = \mathbf{0}$$

In the locally updated planes approach, the reaction path is minimized with the above constraints and $\boldsymbol{\tau}$ is updated every finite number of minimization.

B. New implementation for efficient minimum path determination

We introduce three techniques in the locally updated planes method to enlarge the convergence radius. The first is an improved tangent estimation of the reaction path by using only the neighboring image with higher energy. The new tangent estimation can eliminate the problems with kinks[5]. The second technique is to apply the climbing image algorithm for the highest energy image[6]. The third is a reparametrization of each image using a cubic spline interpolation scheme before updating local tangents. This scheme makes all the images equally

distributed to each other, and the minimum path becomes more reliable[7]. For the efficiency of the program, the second order optimization scheme with Hessian from the internal coordinates is used for the QM region.

Result and Discussion

For the simplest example, we check the reaction profile between two conformers of the alanine dipeptide with pure MM calculation. C7eq and C7ax conformers are chosen as the reactant and product structures[2]. We found that tangent update at finite number of minimization is crucial to get a proper minimum energy path. We also found that reparametrization with cubic spline interpolation with the modified estimation of the tangent enlarges the trust radius of the present method. The use of internal coordinates for initial Hessian improves the efficiency of the optimization, and we could reduce the number of energy/gradient calculation steps.

We test the new implementation on the phosphorylation reaction by cAMP dependent protein kinase (PKA) and the claisen rearrangement of chorismate to prephenate. Our result of the phosphorylation reaction by PKA shows that the proton transfer to the conserved aspartate (D166) occurs after the γ-phosphoryl group of ATP is transferred to the substrate serine (dissociative reaction, Figure 1). The obtained reaction energy barrier 16.4 kcal/mol is in agreement with the experimental data (13.8 kcal/mol) .

For the claisen rearrangement of chorismate to prephenate, the reaction energy barrier 27.6 kcal/mol is somewhat larger than the experimental value (15.4 kcal/mol). The error seems to be due to the level of QM calculation, and we plan to examine the correlation effect for this molecule.
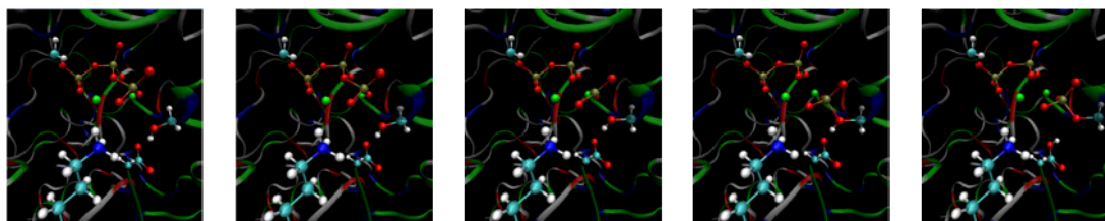

Figure 1. Phosphorylation reaction by PKA

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