Supporting Information for

A Novel Ring-Shaped Reaction Pathway with Interconvertible Intermediates in Chitinase A as Revealed by QM/MM Simulation Combined with One-Dimensional Projection Technique

Tsubasa Iino, Minoru Sakurai,* and Tadaomi Furuta*

Center for Biological Resources and Informatics, Tokyo Institute of Technology, B-62 4259

Nagatsuta-cho, Midori-ku, Yokohama, 226-8501, Japan

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Section 1. Supporting Figures

Figure S1. Comparison between \textit{Sm}ChiA and \textit{Sm}ChiB from the three viewpoints of domains, degrading directions, and subsites.

PDB entries 1EHN\textsuperscript{1} and 1E6N\textsuperscript{2} are used for \textit{Sm}ChiA and \textit{Sm}ChiB, respectively.

Subsites (\textit{Sm}ChiB: -2 to +3 and \textit{Sm}ChiA: -6 to +2) are shown in the bottom close-up views.

References


Figure S2. PMF obtained by the CCV MetaD simulation.

Dotted line and solid line represent the PMF calculated from the first 6.75 ps trajectory (the first backward reaction was observed at 6.75 ps) and that calculated from the whole 20 ps trajectory, respectively.
Figure S3. Time evolution of CV in the CCV and ODP MetaD simulations.

The time evolutions of CVs in the CCV and ODP MetaD simulations are plotted in (a) and (b), respectively. In (a), the values of $d_1$ around 1.7 and 1.1 Å correspond to the reactant and the reaction intermediate, respectively. In (b), the values of $\xi$ around 0.0 and 1.0 correspond to the reactant and the reaction intermediate, respectively.
Figure S4. Changes in distances of $d_{4'}$ (N$_{Nac}$—H$_{Nac}$) and $d_{5'}$ (O$_{Asp313}$—H$_{Asp313}$) along $\xi$.

Each black line represents the average value of each raw data.
Figure S5. Hirshfeld charges of the labelled atoms along $\xi$ at the B3LYP-D3 level.
The structures were obtained by initial 1.1-ps trajectories of the ODP MetaD simulation. Outlier is not plotted. Each black line represents the average value of each raw data.
Figure S6. Changes in the Cremer–Pople puckering angles ($\phi$ and $\theta$) of NAG residue at subsite -1 along $\xi$.
Each black line represents the average value of each raw data.
Figure S7. Time evolution of d4 (H_{NAc}−O_{Asp313}) and d4′ (H_{NAc}−N_{NAs}) in QM/MM MD simulation for the reaction intermediate.

The values of d4 and d4′ of around 1.1 Å correspond to an oxazoline and an oxazolinium ion, respectively. The interconversion of these intermediates is also illustrated on the right side.
Figure S8. Interaction of the NAG residue at subsite -1 with Asp313 and Tyr390.
Here, the NAG residue at subsite -1 is depicted as oxazolinium ion (I⁺).
Figure S9. Two-dimensional topographic maps of the free energy landscape for the reaction intermediate using d3 and d4 as reaction coordinates. Contour lines are at every 0.5 kcal/mol.
Section 2. A geometric aspect of the ODP technique

The ODP technique developed by Baek and Choi is a method for compressing multiple CVs into one CV by using the inner product of a general control parameter of “the advancement of reaction” \( \xi \) and a normalized tangent vector \( \overline{T} \) defined as follows:

\[
\xi = \frac{(\vec{x} - \vec{A}) \cdot (\vec{B} - \vec{A})}{|\vec{B} - \vec{A}|^2}, \tag{1.1}
\]

\[
\overline{T} = \frac{\vec{B} - \vec{A}}{|\vec{B} - \vec{A}|}. \tag{1.2}
\]

Here, we can regard \( \vec{A}, \vec{B}, \) and \( \vec{x} \) as a set of some extracted geometric information, or CVs for an initial structure (reactant), a target structure (product), and an arbitrary structure on the reaction path, respectively, when the structures before/after the reaction are well known. Then, \( \xi \cdot \overline{T} \) represents orthographic projection of \( \vec{x} - \vec{A} \) to \( \vec{B} - \vec{A} \) (Figure S10). Therefore, the ODP technique enables us to perform multi-dimensional sampling in the framework of one-dimensional sampling.

Moreover, this method would make CVs automatically superior to linear combinations of multiple CVs usually chosen in general metadynamics simulations. Let us consider \( \vec{x} \) with components \( d_1, d_2 \) (two distances), and an arbitrary two-dimensional reaction path (Figure S11). In this case, linear combinations of CVs are \( \pm d_1 \pm d_2 \), probably resulting in nearly indistinguishable sampling in some points on the reaction path due to its projected axis being fixed on two-dimensional Cartesian coordinates. On the other hand, the ODP technique can match the projected axis with the line connecting \( \vec{A} \) and \( \vec{B} \), which is the most suitable to distinguish each structure on the reaction path among every imaginable one-dimensional axis. This concept is also true for any dimensional vector \( \vec{x} \). However, note that except for its normalization constant, the ODP technique will become equal to linear combinations of CVs when \( \vec{B} - \vec{A} \) is parallel to one of those. Thus, this method is just an optimized expansion of linear combinations of CVs.
Figure S10. Concept of the ODP technique.

Figure S11. Comparison between the ODP technique and linear combinations of CVs.