Entropic Path Sampling: Computational Protocol to Evaluate Entropic Profile along a Reaction Path

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ABSTRACT: Fleeting intermediates constitute dynamically-stepwise mechanisms. They have been characterized in molecular dynamics trajectories, but whether these intermediates form a free energy minimum to become entropic intermediate remains elusively defined. We developed a computational protocol known as entropic path sampling to evaluate the entropic variation of reacting species along a reaction path based on an ensemble of trajectories. Using cyclopentadiene dimerization as a model reaction, we observed a shallow entropic trap ($-T\Delta S = -0.8$ kcal/mol) along the reaction path which originates from an enhanced conformational flexibility as the reacting species enter into a flat energy region. As the reacting species further approach product formation, unfavorable entropic restriction fails to offset the potential energy drop, resulting in no free energy minimum along the post-TS pathway. Our results show that cyclopentadiene dimerization involves an entropic trap that leads to dynamic intermediates with elongated lifetime, but the reaction does not involve entropic intermediates.

TOC GRAPHICS

KEYWORDS

Entropic Intermediate, Entropic Trap, Reaction Dynamics, Bifurcation, Cyclopentadiene dimerization

Dynamic intermediates are sub-picosecond, reactive intermediates; they have been characterized in quasiclassical direct dynamics with quantum mechanical forces.^{1,2} These intermediates emerge in dynamic trajectories of reactions as a result of zero-point energy effects^{3,4} and/or favorable entropies that become less favorable as additional bonds are formed or broken.⁴⁻⁷ To characterize these dynamic intermediates, Houk and coworkers proposed a timing criterion (60 fs) in pericyclic reactions that was further expanded to other organic transformations.^{2,8,9} Reaction trajectories with a time gap between formation/cleavage of bonds greater than 60 fs are considered to be dynamically stepwise.²

In dynamically stepwise trajectories, restrictions of entropies upon bond rearrangement leads to intermediates with an elongated lifetime and even free energy minima with an entropic barrier^{10,11}. These free energy minima have been rigorously defined as entropic intermediates because they do not correspond to a potential energy minimum.⁸ These intermediates were named by Singleton⁴, Doubleday,¹² and Houk^{5,13}, but have been described as entropy-locked intermediates by Doubleday and McIver,⁶ “caldera” by Doering,¹⁴ Baldwin,¹⁵ and Carpenter¹⁶, fleeting intermediates or long-lived transition states by Jacobsen,¹⁷ and roaming radicals by Bowman and others.^{18,19} Entropic intermediates are increasingly reported in chemical processes such as cycloadditions,²⁰ C–H abstractions,^{21,22} nucleophilic substitutions,^{17,23} and fragmentation reactions^{18,24}. Investigating entropic intermediates enhances fundamental understanding of chemical reactivity and may inspire new strategies to tune reaction selectivity.^{3,25-29}

To define entropic intermediate in thermodynamics, variational transition state theory (VTST) has been employed to compute the free energy profile of chemical reactions.³⁰⁻³³ Truhlar and coworkers reported the first application of VTST to estimate an entropic barrier of the atom-radical reaction: $O + OH$.¹⁰ Hase and coworkers employed canonical VTST to evaluate the rate

for the association of $\text{H} + \text{CH}_3$ that has no potential energy barriers.³² Singleton also applied VTST to evaluate the entropic barrier of the first organocatalyzed Diels–Alder reaction⁴ and SpnF-catalyzed Diels–Alder reaction⁵. Despite the wide application of VTST, how to evaluate entropic profile directly from quasiclassical reaction dynamics trajectories remains an open question. Here we developed a computational protocol known as entropic path sampling (EPS) which integrates quasiclassical direct dynamics simulation and configurational entropy methods^{34,35} to quantify the entropic profile along a reaction path. The EPS protocol enables the differentiation of long-lived dynamic vs. entropic intermediates in dynamically stepwise trajectories and allows the evaluation of an entropic profile for each post-transition state bifurcation path. The method complements the timing criterion and variational transition state theory used in previous work.

Entropic Path Sampling EPS protocol computes the entropy change along a reaction path using a collection of productive quasiclassical trajectories (QCTs) that are propagated using direct dynamics with quantum mechanical forces (Figure 1). The protocol involves four steps: trajectory propagation, trajectory division, entropy computation, and entropy analysis. First, trajectories are initiated in the vicinity of a transition structure and then propagated toward reactants and products to form a collection of productive QCTs (Step-1, Figure 1). Second, the snapshots in the QCTs are divided into several structural ensembles that are consecutively spaced along a user-defined coordinate that depicts a reaction path. (Step-2, Figure 1). Each ensemble is characterized with a specific geometric range for the reacting bond. Third, for each structural ensemble, its configurational entropy is computed with the maximum information spanning tree approximation that was proposed by Tidor et al. and implemented in the PARENT program by Zagrovic et al.³⁴⁻³⁷ The probability density for each degree of freedom (DOF) is

estimated using a histogram-based approach (Step-3, Figure 1). Fourth, the entropy versus coordinate profile is analyzed, which informs whether an entropic barrier and intermediates form along the reaction path.

Figure 1. The protocol of the entropic path method to evaluate the configurational entropy profile along a reaction pathway.

Model Reaction: Cyclopentadiene Dimerization We employed cyclopentadiene dimerization as a model reaction to examine the EPS method (Figure 2). The reaction involves a C2-symmetric bispericyclic (or ambimodal) transition state structure (Figure 2a) that leads to a Cope TS (Figure 2a) and subsequently forms the dimerized product along the intrinsic reaction coordinate (IRC) as reported by Caramella and coworkers in 2002.³⁸ The computational study⁹ validates the two-stage mechanism picture described by Woodward and Katz (WK) in 1959.³⁹ Quasiclassical trajectory simulations by Houk and coworkers further characterize the dynamic nature of the WK two-stage mechanism and identifies the long-lived dynamic intermediates (i.e., up to 240 fs) roaming around the flat potential energy region of the Cope TS (Figure 2b).⁹

Figure 2. (a) Cyclopentadiene dimerization reaction and two transition structures involved in the reaction pathway (i.e., Cycloaddition TS and Cope TS). (b) Electronic energy profile along the post-TS intrinsic reaction coordinate of cyclopentadiene dimerization reactions. The transition structures and intrinsic reaction coordinates are computed using B3LYP/6-31G(d) method.

We employed cyclopentadiene dimerization to benchmark the EPS method for two reasons. First, the two bifurcating paths (i.e., formation of bond 2 or bond 3) are symmetric (Supporting Information, Figure S1), which allows us to examine whether similar entropic profiles can be obtained when separately applying the EPS protocol to either path. Second, long-lived dynamic intermediates have been observed in the trajectories (22% of the trajectories have a time gap greater than 60 fs, Supporting Information, Figure S2). Despite extensive molecular dynamics studies of cyclopentadiene dimerization by Houk⁹ and Singleton,⁴⁰ the quantitative characterization of the entropic profile along the post-TS reaction path still remains unexplored. Quantifying the entropic profile will allow us to assess the thermodynamic outcome of conformational changes during the asynchronous bond formation in the reaction, determining

whether a rigorously-defined entropic intermediate (free energy minimum) exists in the WK two-stage pathway.⁹

Benchmark of Entropic Path Sampling We applied the EPS method to study the post-TS entropic profile for cyclopentadiene dimerization. Among the 5,435 QCTs propagated using the B3LYP/6-31G(d) method in Gaussian 09,⁴¹ we observed approximately equal populations of trajectories that form Bond 2 versus Bond 3 (45.7% for Bond 2 vs. 45.6% for Bond 3, Supporting Information, Figure S1), which reflects the symmetry of the potential energy surface. The formation of either bond leads to practically the same product. The post-TS snapshots for the Bond 2 or Bond 3-forming trajectories were collected and each divided into ten consecutive structural ensembles. The specific range and the number of snapshots falling into each structural ensemble are reported in Table S1 of the Supporting Information.

The post-TS entropic profile for the formation of Bond 2 is highly similar to that of Bond 3 up to around 1.9 Å. Upon further bond formation, we observed deviation between the two profiles because of a small number of geometries incorporated in each of the last two structural ensembles (less than 7,000 geometries, Supporting Information, Table S1). These two entropic profiles feature the presence of an entropic trap with a depth of ca. 0.8 kcal/mol (0.78 kcal/mol for Bond 2 and 0.72 kcal/mol for Bond 3, Figure 3a). Because of the numerical consistency between these two entropic profiles (Supporting Information, Table S2), we emphasize Bond 2 for the rest of the discussion.

We further examined the dependence of the computed entropic profile on two technical parameters: a) the number of sampling points (Supporting Information, Figure S3) and b) the number of structural ensembles used to represent the post-TS reaction path (Supporting

Information, Figure S4). To evaluate the variation of entropic trap under different parametric conditions, we employed the depth of entropic trap (Figure 3b and 3c), which is defined as the difference of $-TS$ between the first post-TS point (i.e., adjacent to cycloaddition TS) and the maximal entropy point (Figure 3a). Figure 3b shows the change of entropic trap depth versus the percentage of sampled geometries in each ensemble. The percentage is used here because the number of sampled snapshots varies in different structural ensembles along the reaction path (Supporting Information, Table S1). The depth of entropic trap drops from ca. 0.9 kcal/mol to ca. 0.8 kcal/mol when the percent of sampled geometries change from 20% to 40%. Over 40%, the value remains at ca. 0.8 kcal/mol with little change even by adding more sampled points.

Figure 3c shows the change of entropic trap depth versus the number of structural ensembles that the QCTs have been segmented into. An optimal number of ensembles should ensure a sufficient resolution of the reaction path while also maintaining sufficient sampling for each structural ensemble. The depth of the entropic trap is ca. 0.5, 0.6, and 0.8 kcal/mol with 5, 8, and 10 ensembles, and remains at ca. 0.8 kcal/mol with 12 ensembles and obtain 0.9 kcal/mol with 15 ensembles. Further increasing the number of ensembles is not feasible because the average number of points for each ensemble will not be sufficient to maintain convergence – this will likely cause a large error in estimating the probability density function for entropy calculation. These results indicate that 10-12 structural ensembles are optimal for describing the post-TS entropic profile. With more than 12 ensembles, the current sampling size (ca. 5000 trajectories) is insufficient to converge the entropic trap observed along the post-TS reaction path. Notably, changing the number of structural ensembles also shifts of the position the first point and maximal entropy points that are used to compute the entropic trap (Supporting Information, Figure S4). To ensure a consistent comparison, we fitted the entropic profile using

polynomial functions (Supporting Information, Figure S5) and computed entropic traps using the difference between the entropic values at the Cycloaddition TS (Length of Bond 2 = 2.90 Å) and the maximal entropy point (Supporting Information, Figure S6). The results also support that 10-12 are most optimal.

Figure 3. (a) Entropic profiles for the formation of Bond 2 (blue) and Bond 3 (grey). The entropy value for each structural window is computed with reference to the entropy of the first post-TS point. The depth of entropic trap is defined as the difference between the first post-TS point and the maximal entropy (minimal $-TS$) point. Benchmark of the depth of entropic trap in cyclopentadiene dimerization reaction against: (b) percent of the sampled geometries in each of the ten ensembles and (c) the number of ensembles.

Post-TS Entropic Profile for Cyclopentadiene Dimerization We demonstrate the variation of electronic energy, entropy, and free energy along the post-TS reaction path in Figure 4 (formation of Bond 2). The reacting species first undergoes a transition from Cycloaddition TS to Cope TS as the length of Bond 2 decreases from 2.90 Å to 2.65 Å (Figure 2a). The reaction path preserves the C2 symmetry with Bond 2 and Bond 3 shortening to the same magnitude simultaneously. In this stage, the electronic energy drops by ca. 2.5 kcal/mol (Figure 2b) accompanying the increase in entropy ($-TS$ reduces by 0.7 kcal/mol, Figure 4). Subsequently, the variation of electronic energy flattens out up until Bond 2 reaches ca. 2.40 Å. The flat electronic energy region characterizes a broader zone of the Cope TS in which the exothermic shortening of Bond 2 compensates for the endothermic lengthening of Bond 3. As Bond 2 further proceeds to formation, the electronic energy starts to drop drastically, which is accompanied by a decrease of entropy (i.e., a rebound of $-TS$).

The trap forms because of the two-stage characteristics of the reaction. The transition from Cycloaddition TS to Cope TS involves enhanced conformational flexibility that results in a favorable entropic change. However, the further formation of the dimerized product inevitably reduces the conformational space, leading to an unfavorable entropy variation in the later stage of the reaction. Notably, along the post-TS reaction path of cyclopentadiene dimerization, the

entropic change appears rather subtle (< 3.0 kcal/mol) compared to the potential energy change (ca. 30.0 kcal/mol). As such, the free energy profile still maintains a monotonically downhill trend without involving a substantial entropic barrier like those reported in asynchronous Diels–Alder reactions by Singleton and Houk.^{4,5} With the absence of a free energy minimum, cyclopentadiene dimerization does not involve a rigorously-defined entropic intermediate. However, the presence of an entropic trap contributes to the presence of dynamic intermediates with elongated lifetime observed in trajectories (Supporting information, Figure S2).

Figure 4. The profiles of electronic energy (top, black), entropy (top, blue), and free energy (bottom) versus the forming bond 2. The first post-TS point, which is in the vicinity of the

cycloaddition TS, is set to be the zero reference point. Two dashed lines represent the position of cycloaddition TS and Cope TS, respectively.

Comparison of Normal Mode Analysis and Entropic Path Sampling Finally, we compare the EPS method against the normal mode analysis in quantifying the entropic difference between the Cycloaddition TS region and the Cope TS region (Figure 5). Cope TS ensembles have been separately defined for both methods. For normal mode analysis, the ensemble is built by randomly sampling the vibrational state along each normal mode of the optimized Cope TS structure. The distributions of Bond 1 and Bond 2 are 1.64 ± 0.10 Å and 2.65 ± 0.14 Å, respectively, which have been known as transition zones (Supporting Information, Figure S4). For entropic path sampling, the Cope TS ensemble is constructed using the snapshots of QCTs along the post cycloaddition TS reaction path. This ensemble contains the snapshots that fall into the transition zone of Bond 1 and Bond 2 (Supporting Information, Figure S7). In each case, the configurational entropy for the Cope TS has been computed, along with the relative difference of entropies between Cope TS and cycloaddition TS (Figure 5). Unlike entropic path sampling that predicts the increase of entropy in the Cope TS region ($-T\Delta S = -0.7$ kcal/mol), normal mode analysis predicts a significant drop in entropy ($-T\Delta S = 1.3$ kcal/mol) for the same process. Noticeably, when comparing the representative geometric overlays obtained in both methods, the ensemble of entropic path sampling appears to exhibit a larger amplitude of inter-ring wagging motion despite both ensembles involving a highly similar distribution for the forming bonds (Supporting Information, Figure S7). These results show the strength of entropic path sampling method – the use of QCTs gives more a realistic description of the molecular conformational distribution along the reaction path. Computation of configurational entropy using histogram-based methods also accounts for the anharmonicity of the vibrational mode. In particular, this

feature complements normal mode analysis for describing the entropy of reacting species on the flat potential energy surface, where normal mode analysis likely involves large error for small-frequency mode due to severe anharmonicity.

In summary, we report a new computational method, entropic path sampling, to evaluate the entropic profile of a reaction path using consecutive structural ensembles segmented from quasiclassical direct dynamics trajectories. Using cyclopentadiene dimerization as a model reaction, we tested the method and identified the presence of an entropic trap along the post-TS reaction path. The depth of the entropic trap was benchmarked against the sample size and number of structural ensembles and was found to converge to ca. 0.8 kcal/mol. The entropic trap is responsible for the elongated lifetime of transient intermediates observed in previous dynamics simulations, but no free energy minimum or entropic barrier was observed along the post-TS reaction path. Comparison between the entropic path sampling and normal mode analysis methods shows the strength of the EPS method in sampling structurally flexible conformational states beyond harmonic approximation. Complementary to the timing criterion and variational transition state theory, the EPS method allows quantitative characterization of the entropic profile of a user-defined reaction path.

Entropic Path Sampling

Normal mode analysis

Figure 5. Structural ensembles derived from quasiclassical trajectories (left) and normal mode sampling (right) with respective entropy values. In both cases, the first post-TS point (sufficiently close to cycloaddition TS) is set to be the zero reference point.

COMPUTATIONAL METHODS

Transition state structure optimization TS geometry optimizations were carried out at the B3LYP/6-31G(d) level of theory using Gaussian 09. The method was selected based on prior benchmark studies. Normal vibrational mode analysis and intrinsic reaction coordinate (IRC) calculation were performed at the same level of theory to validate the computed TS.

Quasiclassical trajectory simulation Quasiclassical trajectory (QCT) simulations were performed for the cyclopentadiene dimerization in vacuum at 298.15 K using (U)B3LYP/6-31G(d) method in Gaussian 09.⁴¹ QCTs were initialized in the vicinity of the cycloaddition TS with normal mode sampling method. The sampled TS geometries conform to a quantum mechanical Boltzmann distribution. For each sampled TS geometry, zero-point energy and thermal energy were added for each real normal vibrational mode. The QCTs were propagated forward and backward for 300 fs with 1 fs step size in each direction with a velocity-Verlet algorithm using Singleton's Progdyn program.^{4, 40, 42} The simulations result in 5,435 QCTs, consisting of 2,485 (45.7%), 2,480 (45.6%), and 470 (8.6%) trajectories that form Bond 2, Bond 3, and are recrossing, respectively. For each QCT, the post-TS snapshots were divided into ten geometric ensembles (Figure 1) characterized by a specific distance range of the reacting bond (Supporting Information, Table S1).

Configurational entropy computation For each ensemble, the configurational entropy of the reacting species was computed using the PARENT program. The program takes in the input

Cartesian coordinates of the structures, converts them to the format of internal coordinates (i.e., bond length, bond angle, and torsion angle), estimates the probability distribution for each degree of freedom (DOF), and eventually integrates the entropy terms. To ensure easy convergence, the analytically exact formula of configurational entropy (eq1) was first truncated to the sum of pairwise interactions and then further treated by second-order maximum information spanning tree (MIST) approximation (eq2) where N refers to the number of DOFs, i refers to an index of a DOF, and j is a conjugate of i .

$$S_N(X_1, \dots, X_N) = S_1(X_1) + S_2(X_2|X_1) + \dots + S_N(X_N|X_1, \dots, X_{N-1}) \quad \text{eq1}$$

$$S_N^{MIST_2}(X_1, \dots, X_N) = \sum_{i=1}^N \left[S_1(X_i) - \max_{j \in \{1, \dots, i-1\}} I_2(X_i; X_j) \right] \quad \text{eq2}$$

For each DOF, a histogram-based approach was applied to estimate the probability density for the 1D and 2D entropy terms using eq3 and eq4, respectively, where $p_i[k]$ refers to the probability density value in the bin k for the DOF i ; $p_{i,j}[k,l]$ refers to the joint probability density in the bin k of DOF i and bin l of DOF j . The binning size was set to be the default value (i.e., 50) based on the prior benchmark.

$$S_i = -\sum_k p_i[k] \ln(p_i[k]) \quad \text{eq3}$$

$$S_{i,j} = -\sum_{k,l} p_{i,j}[k,l] \ln(p_{i,j}[k,l]) \quad \text{eq4}$$

ASSOCIATED CONTENT

Supporting Information. The number of snapshots for each structural ensemble along the trajectory; Benchmark of entropic profile against sampling size and the number of structural ensembles; Transition zone for Bond 1 and Bond 2 in Cope TS. (PDF)

The code and tutorial for the entropic path sampling protocol are open access on GitHub
https://github.com/ZJYgrp/Entropic_Path_Sampling

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Notes

The authors declare no competing financial interest.

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