Trends in Chemistry

CellPress
REVIEWS

Special Issue: Big Questions in Chemistry

Review

Mechanisms and Dynamics of Reactions Involving Entropic Intermediates

Zhongyue Yang,[1,3] Cooper S. Jamieson,[1] Xiao-Song Xue,[1,2] Marc Garcia-Borràs,[1] Tyler Benton,[1] Xiaofei Dong,[1] Fang Liu,[1] and K.N. Houk[1,*]

An entropic intermediate is defined as a free energy minimum that is not a potential energy minimum; the favorable entropy in this region of the potential surface is responsible for the increased lifetime of this species. Enabled by molecular dynamics simulations, entropic intermediates have been identified for several types of reactions, particularly pericyclic reactions. This review highlights recent advances in the mechanistic and dynamic investigations of organic and biosynthetic pericyclic reactions that involve entropic intermediates. We have proposed timing criteria to differentiate dynamically concerted from dynamically stepwise mechanisms. These criteria complement the usual definitions of concertedness based on energetics and bonding changes along the potential surface.

Highlights

Unlike conventional intermediates that are local minima on a PES, entropic intermediates involve a flat region on the potential surface (favorable entropically) and the necessity to decrease entropy to exit from this region of the PES. Entropic intermediates are not potential energy minima.

We have proposed timing criteria to differentiate dynamically concerted from dynamically stepwise reactions. A mechanism is described as dynamically concerted if all bonding changes are complete in less than 60 fs, but dynamically stepwise otherwise. This criterion is complementary to the usual definition of concerted based on potential energy surface (one or two barriers). Entropic intermediates are often involved in dynamically stepwise reactions.

Entropic Intermediates and Time-Resolved Mechanisms

Understanding the mechanisms and dynamics of chemical transformations has been the principle goal of many chemists [1,2], from the early physical theorists and kineticists to physical organic chemists [3]. Reactive intermediates, such as radicals, diradicals, carbenes, carbocations, carbanions, and zwitterions play vital roles in determining reactivity and selectivity [4]. Reactive intermediates are energy minima on the **potential energy surface (PES)** (see Glossary), in principle detectable, depending on their lifetimes. In recent decades, experimental advances in spatial and temporal resolution [5,6] have expanded the range of reactive intermediates that can be characterized [7–9]. A new form of 'transient intermediate' has recently become prominent on the basis of quantum mechanical direct dynamics simulations [10,11]. These intermediates have sub-picosecond lifetimes, exist on a relatively flat potential energy surface, and are not minima on the PES. In 1983, Doubleday, McIver, and coworkers showed that the tetramethylene diradical (formed from two ethylenes or from cyclobutane) is what they called an 'entropy-locked intermediate' [12], a free energy minimum dominated by entropy 'even though it lacks a potential energy minimum'. (The first mention of such a species was suggested to be in the Caltech Ph.D. Thesis of Jeffrey Hay in 1972. [J. Hay, PhD thesis, California Institute of Technology, 1972, p. 74, footnote 18]). Such species emerge in dynamics simulations of reactions as a result of favorable entropies that become less favorable as additional bonds are formed or broken, leading to a free energy minimum arising primarily from restrictions of entropies upon bond formation [12,13–15]. Such restrictions have been described in the literature as leading to entropic barriers [16,17].

Entropic intermediates are discussed in this article. They have many descriptive names, like 'caldera' by Doering [18], Baldwin [19], and Carpenter [20], roaming radicals by Bowman and others [21,22], fleeting intermediates or long-lived **transition states (TS)** by Jacobsen [8], entropy-locked intermediates by Doubleday and McIver [12], and entropic intermediate by

[1] Department of Chemistry and Biochemistry, University of California, Los Angeles, CA 90095, USA
[2] Department of Chemistry, Nankai University, Tianjin, 300071, China
[3] Current address: Department of Chemical Engineering, Massachusetts Institute of Technology, Cambridge, MA 02138, USA

*Correspondence:
houk@chem.ucla.edu (K.N. Houk).

10.1016/j.trechm.2019.01.009

Singleton [13], Doubleday [23], and Houk [14]. Entropic intermediates are increasingly implicated in fundamental chemical processes, including nucleophilic substitutions [8,24], C–H abstractions [25,26], cycloadditions [3], and fragmentation reactions [21,27]. Exploration of entropic intermediates enriches our fundamental knowledge of reactivity and may lead to new synthetic strategies to control selectivity [28–31].

Predicting the behavior of entropic intermediates is an inviting challenge for theory [1]. Current computational capabilities permit the study of chemical-reaction dynamics with reasonably accurate quantum-mechanical methods [2,32]. The resulting reactive trajectories enable visualization of chemical processes on a femtosecond timescale and reveal fundamental dynamic features of entropic intermediates on a single-molecule level [3]. In the course of systematic molecular dynamics (MD) studies of cycloaddition reactions, Houk and colleagues proposed a timing criterion [3] to differentiate between dynamically stepwise and dynamically **concerted** mechanisms. The mechanism is considered as dynamically concerted if all bonding changes are complete in less than 60 fs, but dynamically stepwise otherwise. The criterion was defined as the lifetime of the TS [33] derived from Eyring's TS theory equation (Equation 1; since the inverse of the pre-exponential factor, h/k_BT is equal to 60 fs at $T = 298$ K) [34]

$$k = \frac{k_BT}{h}e^{-\frac{\Delta H^{\neq}}{RT}}e^{\frac{\Delta S^{\neq}}{R}} \qquad [1]$$

This criterion is complementary to the usual definition of concertedness based on potential energy surface (one or two barriers) [35]. Dynamically stepwise reactions with bond-formation lifetimes of 60–200 fs often have entropic intermediates, as discussed in this review. Notably, one reviewer of this article pointed out that Michael Dewar suggested a definition of concerted versus **synchronous**, in which ‘concerted’ refers to kinetics. Synchronous does mean ‘at the same time’. Our ‘dynamically concerted’ and ‘dynamically stepwise’ are what Dewar related to what he called ‘synchronous’ and ‘**asynchronous**’, but his definitions referred to the nature of the concerted TS, not directly to dynamics [36]. Our terms were introduced to avoid confusion with ‘synchronous’ and ‘asynchronous’, which are widely used by organic chemists [and indeed the International Union of Pure and Applied Chemistry (IUPAC), see Glossary] to describe the nature of the bond lengths in computed transition structures, where two identical forming bond lengths in a TS is termed a ‘synchronous concerted TS’ and two different lengths in the TS is termed an ‘asynchronous concerted TS’.

We first review the definition and discovery of entropic intermediates. We then describe the involvement of entropic intermediates in **pericyclic reactions** (specifically cyclopentadiene dimerization [37] and the **Cope rearrangement** [38]) and many recently discovered biosynthetic reactions, including SpnF-catalyzed **Diels-Alder reactions** [29], LepI-catalyzed cycloadditions [e.g., hetero-Diels-Alder (HDA), intramolecular Diels-Alder (IMDA), and hetero-Claisen rearrangement] [39], and trispericyclic reactions [40]. We also discuss the likely role of entropic intermediates in other types of organic reactions.

Definition and Discovery of Entropic Intermediates

Unlike conventional intermediates that are local minima on a PES, entropic intermediates occur because of a relatively flat region [41] on a potential surface (favorable entropically) and the necessity to decrease entropy [17] to exit from this region of the PES [12]. The entropic intermediate has an even less well-defined structure than a normal minimum that has zero point and thermal vibrational energies. An entropic intermediate involves an ensemble of dynamical structures (Figure 1, Key Figure) residing in a shallow free-energy well. The occurrence of an

Glossary

Adduct: a new chemical species AB, each molecular entity of which is formed by direct combination of two separate molecular entities A and B in such a way that there is change in connectivity, but no loss, of atoms within the moieties A and B. [IUPAC Gold Book (https://doi.org/10.1351/goldbook.A00138)].

Asynchronous and synchronous: there is some difference in the English meaning (occurring at different times or the same time, respectively) and how this word is used in chemistry. First we give the IUPAC definition: a concerted process in which the primitive changes concerned (generally bond rupture and bond formation) have progressed to the same extent at the transition state is said to be synchronous. The term figuratively implies a more or less synchronized progress of the changes. However, the progress of the bonding change (or other primitive change) has not been defined quantitatively in terms of a single parameter applicable to different bonds or different bonding changes. The concept is therefore in general only qualitatively descriptive and does not admit an exact definition except in the case of concerted processes involving changes in two identical bonds. [IUPAC Gold Book (https://doi.org/10.1351/goldbook.S06219)]. This is basically the definition used by Dewar [36], but a proper use of the term would be to equate synchronous to our dynamically concerted, and asynchronous to our dynamically stepwise. This however, is not the general usage of this terminology at this time.

Bifurcating surface: (or post-transition state bifurcation); ‘a bifurcating surface is one for which a single transition-state structure leads to two products. For such a situation, intrinsic reaction coordinate (IRC) calculations often indicate that this transition-state structure is directly connected to a second transition-state structure that is itself connected directly to both of the two products. In some cases where bifurcations are suspected, reaction coordinates generated in this way lead directly to one product, but flat plateau regions are often entropic intermediate is related to the consequences of variational transition state theory (VTST) [42,43], which determines the TS dividing surface that maximizes the reactive flux from reactants to products. When multiple bonds are formed in a reaction, the deviation of a TS dividing surface from the vicinity of saddle point likely indicates a significant contribution of entropy to the free energy profile. The free energy surface, also known as the potential of mean force [44,45], is the theoretical foundation for the existence of an entropic intermediate. The concept of an entropic barrier, which implies the presence of what we now call an entropic intermediate, was proposed by Truhlar and coworkers who reported the first application of VTST to estimate an entropic barrier of the atom-radical reaction: O + OH [16].

Singleton and coworkers obtained computational and experimental evidence that suggests the existence of an entropic intermediate on the **bifurcating surface** for the reaction of dichloroketene with *cis*-2-butene [13]. An unusual heavy-atom **kinetic isotope effect (KIE)** was observed and was rationalized by a model in which the cycloaddition is stepwise with a rate-determining entropic barrier [16,46] for formation of the second C–C bond. A short-lived dynamic intermediate is thus entrapped between the cycloaddition barrier and the entropic barrier [16,46], termed ‘entropic intermediate’. Singleton identified another entropic intermediate using the first organocatalyzed Diels-Alder reaction, vinyliminium ion with cyclopentadiene, which was reported by MacMillan [47] and computationally investigated by Houk and coworkers [48]. The reaction involves a concerted but highly asynchronous TS on the PES (Figure 2). Along the reaction coordinate, two canonical variational transition states (VTS) were found at 25°C; an entropic intermediate resides between these VTSs. The two VTSs are labeled in Figure 2, corresponding to the formation of the first and the second C–C bond, respectively. The VTS1 is close to the barrier located on the PES and the VTS2 represents the hidden rate-limiting entropic barrier that determines the apparent chemical reactivity, selectivity, and isotope effects.

The properties of entropic intermediates, especially their atomic-level dynamic behavior, are difficult to probe experimentally but can be characterized computationally from MD. MD shows how individual trajectories undergo reactions and provides the bond-formation timing for each trajectory [11]. Entropic intermediates are found in those trajectories with time gaps between sequential formation of bonds (i.e., longer than several vibrational periods of a C–C bond) that is greater than 60 fs (as discussed above). These trajectories have dynamically stepwise character. In contrast, trajectories with a shorter time gap are dynamically concerted. To differentiate between these mechanisms, a lifetime of TS (60 fs at 298 K, corresponding to two periods of C–C bond vibration and the inverse of Eyring’s pre-exponential factor) was employed as the borderline between dynamically concerted and stepwise trajectories. This dynamical dichotomy complements the conventional classification of concerted versus stepwise mechanisms based on potential energy diagrams or surmises about bonding sequences [35]. We note, however, that this timing borderline is an arbitrary (but reasonable) boundary. Dynamically complex mechanisms (i.e., the coexistence of dynamically concerted and stepwise trajectories) have been observed in reactions with asynchronous concerted TS [14,49,50] or even those with a shallow potential energy intermediate [51,52]. Jacobsen and coworkers [8] recently investigated the concerted versus stepwise mechanisms in nucleophilic aromatic substitution (S_NAr) reactions based on a new ^{19}F-based technique that they developed; this enables a sensitive measurement of KIE for reactions involving the breaking or formation of C–F bonds. Jacobsen and colleagues found F^- substitution of 1-chloro-2,4-dinitrobenzene to be the borderline between a concerted and a stepwise mechanism. A concerted TS was located, and no Meisenheimer complex was found along the intrinsic reaction coordinate (IRC), but a complex was observed from MD simulations with a mean lifetime of 233 fs. Although they

encountered along such a pathway. Navigating along a bifurcating surface presents a molecule with a choice as to which branch of the bifurcating pathway to follow, a more complicated situation than following a surface with a single pathway downhill from a transition-state structure, and a choice that determines which product will ultimately predominate’ [82].

Concerted: two or more primitive changes are said to be concerted (or to constitute a concerted process) if they occur within the same elementary reaction. Such changes will normally (though perhaps not inevitably) be ‘energetically coupled’. (In the present context the term ‘energetically coupled’ means that the simultaneous progress of the primitive changes involves a transition state of lower energy than that for their successive occurrence). In a concerted process the primitive changes may be synchronous or asynchronous. [IUPAC Gold Book (https://doi.org/10.1351/goldbook.C01234)].

Cope rearrangement: the Cope rearrangement is the thermal isomerization of a 1,5-diene leading to an isomeric 1,5-diene. The main product is the thermodynamically more stable regioisomer.

Diels-Alder reaction: the formation of a cyclohexene from the cycloaddition of a diene and a dienophile (alkene, alkyne, or hetero analog). The reaction may be concerted or stepwise.

Fulvene: a 5-alkylidenecyclopentadiene.

Kinetic isotope effect (KIE): the effect of isotopic substitution on a rate constant is referred to as a kinetic isotope effect. For example, in the reaction of A + B to C, the effect of isotopic substitution in reactant A is expressed as the ratio of rate constants k^l/k^h, where the superscripts l and h represent reactions in which the molecules A contain the light and heavy isotopes, respectively. Within the framework of transition state theory and with neglect of isotopic mass on tunneling and the transmission coefficient, k^l/k^h can be regarded as if it were the equilibrium constant for an isotope exchange reaction between the transition state $[TS]^\ddagger$ and the characterized this as a fleeting intermediate or a long-lived TS, we describe this species as an entropic intermediate. These results further exemplify the complexity of fundamental organic reactions and highlight the necessity of quantum mechanics and MD simulations for the mechanistic and dynamic understanding of chemical transformations.

Recent studies show many examples of entropic intermediates in organic and biosynthetic reactions, as briefly summarized in Table 1. The subsequent sections will discuss specifically how dynamical trajectories reveal the time-resolved mechanisms of reactions.

Pericyclic Reactions Involving Entropic Intermediates

Cyclopentadiene Dimerization

In 1959, Woodward and Katz described the dimerization of cyclopentadiene in the seminal paper '*The Mechanism of the Diels-Alder Reaction*' [53]. They envisioned the similarity between the TS of cycloaddition and that of the Cope rearrangement (Figure 3A), proposing a two-stage mechanism for the Diels-Alder reaction. The two-stage mechanism (an alternative to the concerted and stepwise mechanisms) first involves the formation of the C–C bond through a concerted TS with high asynchronicity, leading to the Cope TS. The second stage involves the facile formation of the second bond to generate the product. No intermediate was proposed. The reaction was later studied computationally by Caramella and coworkers in 2002 (Figure 3B) [54]. They showed that the transition structure has C_2 symmetry that they called 'bispericyclic', referring to a merger of [4 + 2] and [2 + 4] pathways, both of which give the cyclopentadiene dimer. The intrinsic reaction path leads downhill to the formation of the Cope TS on the PES; the reaction path bifurcates to two identical products that can be interconverted by the Cope rearrangement.

Houk and coworkers performed MD simulations to investigate the dynamics of cyclopentadiene dimerization [37]. Due to the high asynchronicity of the TS (Figure 3B), the formation of the second bond undergoes substantial reduction of conformational space after the formation of the first bond; the flat PES region in the vicinity of the Cope TS causes the lifetimes of some trajectories to exceed several C–C vibration periods. These results show that both dynamically concerted and dynamically stepwise two-stage (in Woodward-Katz terminology) pathways were involved in the reaction (Figure 3C). The concerted pathway (dashed line) directly gives the final product after passing the TS. The dynamically stepwise two-stage pathway (solid line) undergoes several vibrations before forming the final product, and it explores the Cope TS region during these vibrations, exhibiting the characteristics of an entropic intermediate. Typical snapshots for both concerted and two-stage trajectories are shown in Figure 3D and E, respectively. Statistically, 70% of trajectories are dynamic, while 30% are dynamically stepwise. A 'two-stage' mechanism was found in 13% of the trajectories (Figure 3E), which follow pathways through the Cope TS, as hypothesized by Woodward and Katz in 1959 [53]. Entropic intermediates were also observed in the Cope-TS region in these trajectories.

Cope Rearrangement

The Cope rearrangement, which eventually became a classic example of a pericyclic sigmatropic rearrangement, was first discovered in the 1940s by Cope and Hardy [55]. The mechanism of this reaction was debated into the 1990s. The debate centered on the associative or dissociative nature of the TS and whether the reaction involved an intermediate [55–57]. Besides being widely applied in organic synthesis, the Cope rearrangement is involved in the PES bifurcation for dimerization of cyclopentadiene [37,54], where it serves to connect the two products that result from the ambimodal TS.

isotopically substituted reactant A, and calculated from their vibrational frequencies as in the case of a thermodynamic isotope effect. Isotope effects like the above, involving a direct or indirect comparison of the rates of reaction of isotopologues, are called 'intermolecular', in contrast to intramolecular isotope effects, in which a single substrate reacts to produce a non-statistical distribution of isotopomeric product molecules [IUPAC Gold Book (https://doi.org/10.1351/goldbook.K03405)].

Pericyclic reaction: a reaction in which all bonding changes occur in concert on a closed curve.

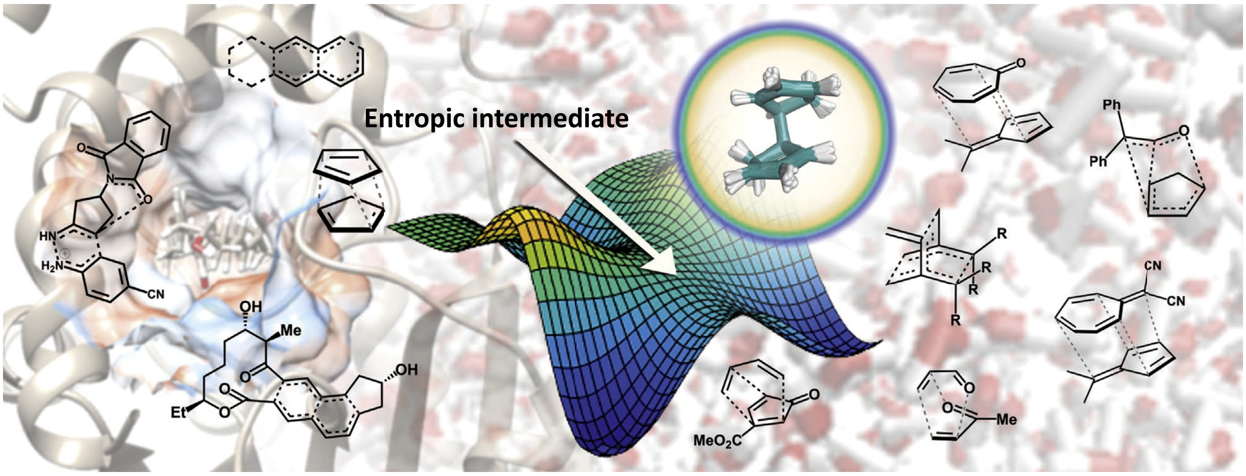
Potential energy surface (PES): (synonymous with energy hypersurface); a geometric hypersurface on which the potential energy of a set of reactants is plotted as a function of the coordinates representing the molecular geometries of the system. Such a diagram is often arranged so that reactants are located at the bottom left corner and products at the top right.

Retro-Claisen rearrangement: the aliphatic Claisen rearrangement is a [3,3]-sigmatropic rearrangement in which an allyl vinyl ether is converted thermally to a 4-pentenal.

Transition state (TS): in Evans-Polayni or Eyring theories describing elementary reactions it is usually assumed that there is a transition state between the reactants and the products through which an assembly of atoms (initially composing the molecular entities of the reactants) must pass on going from reactants to products in either direction. In the formalism of 'transition state theory' the transition state of an elementary reaction is that set of states (each characterized by its own geometry and energy) in which an assembly of atoms, when randomly placed there, would have an equal probability of forming the reactants or of forming the products of that elementary reaction. The transition state is characterized by one and only one imaginary frequency (corresponding to a negative force constant). Adapted from the IUPAC Gold Book (https://doi.org/10.1351/goldbook.T06468).

Key Figure

The Prototype Potential Energy Surface Involving Ambimodal Transition State, Entropic Intermediate, and Subsequent Bifurcation in the Dimerization of Cyclopentadiene

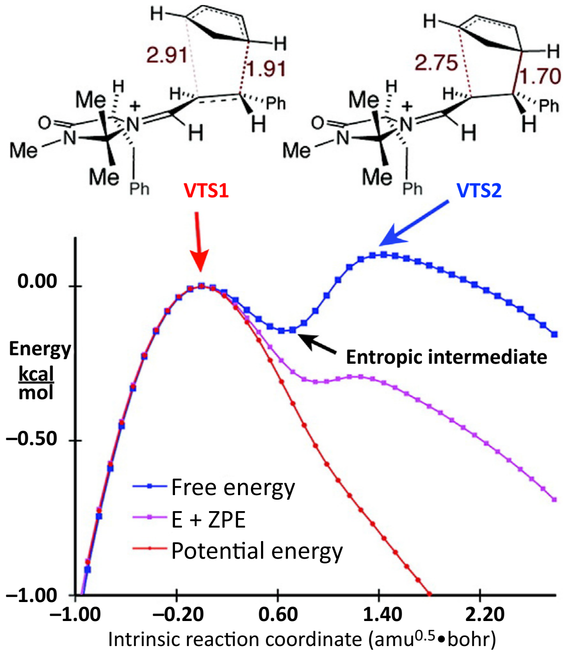


Trends in Chemistry

Figure 1. The structures shown are schematic renditions of nine entropic intermediates discussed in this article for gas phase, solution, and enzyme, depicted as the background of the figure.

A Cope rearrangement also interconnects the [4 + 2] and [6 + 4] **adducts** formed from an ambimodal TS in the biosynthesis of heronamide [58] and in SpnF-catalyzed Diels-Alder reactions (discussed later) [14]. Although the nature of the TS [57,59–63] and substituent effects for the Cope rearrangement have been well investigated [64–66] the timing of bond formation had not been investigated until the dynamics of the degenerate rearrangement of 1,5-hexadiene (i.e., the simplest Cope rearrangement) were studied in the Houk group.

The concerted transition structure for the parent Cope rearrangement involves a chair conformation with C_{2h} symmetry (Figure 4). Trajectories were initiated on the TS dividing surface at the sampled TS geometries (blue dots in Figure 4). The transition zone was defined as that region of the PES that embraces 98% of the sampled TS geometries [10]. The transition zone for either bond is 1.97 Å ± 0.15 Å, and the included area is shown as the white oval in Figure 4. To characterize the dynamical features, the time to traverse the transition zone was employed as the criterion to differentiate dynamically concerted and stepwise mechanisms for each trajectory. A Cope rearrangement trajectory is considered dynamically concerted if the time in the transition zone is $\leq$60 fs at 298 K. Note that this is different from cycloadditions where the time gap between formation of two bonds (r <1.6 Å) was utilized. Both dynamically concerted and dynamically stepwise trajectories are illustrated in Figure 4 as green and purple lines, respectively. The dynamically concerted trajectory directly passes through the transition zone in 29 fs, which is comparable with a normal C–C bond vibration period. In contrast, the dynamically stepwise trajectory surfs the TS dividing surface and remains in transition zone for 81 fs

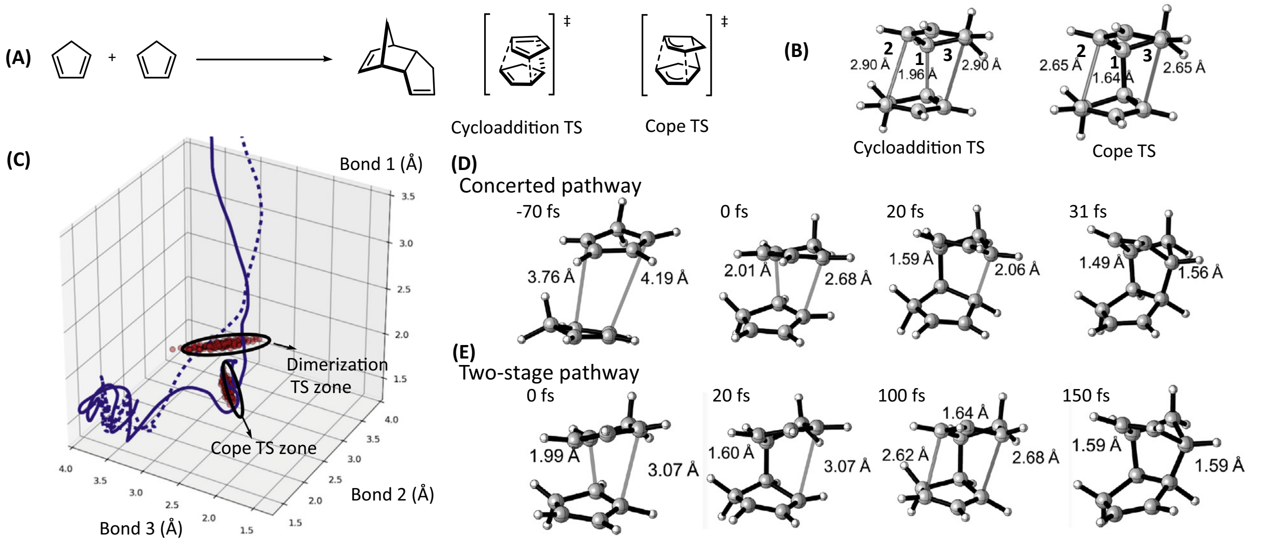


Trends in Chemistry

Figure 2. Energy Profiles Along the Intrinsic Reaction Coordinate through the Transition State, with the Saddle Point Taken as the Zero of Energy. The free-energy profile is based on generalized free energies of activation obtained from GAUSSRATE [83]. Reproduced with permission from [13]. VTS1 and VTS2 are two transition states that were located using the variational transition-state method. ZPE, Zero-point energy.

Table 1. Averaged Time Gap between Bond Formation in All Reactive Trajectories and Percentage of Dynamically Stepwise Trajectories from MD Simulations of Typical (Ambimodal [85]) Pericyclic Reactions

Reaction	Method	Average time gap (fs)	Percentage of dynamically stepwise (%)	Refs
Diels-Alder: butadiene + ethylene	B3LYP/6-31G*	4	0	[11]
Cope rearrangement: 1,5-hexadiene	B3LYP/6-31G*	35	6	[38]
Cyclopentadiene dimerization	B3LYP/6-31G*	44	30	[37]
[4 + 2]/[6 + 4] cycloaddition: butadiene + hexatriene	B3LYP/6-31G*	86	87	[58,86]
[4 + 2]/[6 + 4] cycloaddition: tethered-butadiene + hexatriene	B3LYP/6-31G*	60	39	[58,86]
[6 + 4]/[4 + 6] cycloaddition: tropone + dimethylfulvene	B3LYP-D3/6-31G*	95	53	[49,86]
SpnF-catalyzed Diels-Alder (gas-phase model-reaction)	M06-2X/6-31G*	65	51	[29,87]
SpnF-catalyzed Diels-Alder (water)	M06-2X/6-31G*/TIP3P	48	34	[29,88]
SpnF-catalyzed Diels-Alder (enzyme)	M06-2X/6-31G*/FF99SB	74	67	[29,89]
Pericyclase LepI-catalyzed cycloadditions	B3LYP-D3/6-31G*	99	74	[39]
Tripericyclic cycloaddition [6 + 4]/[4 + 6]/[8 + 2]	ωB97X-D/6-31G*	102	72	[40]



Trends in Chemistry

Figure 3. Quantum Mechanical Direct Dynamics Simulations of Cyclopentadiene Dimerization. (A) Reaction scheme of cyclopentadiene dimerization with putative cycloaddition transition state (TS) and Cope TS proposed by Woodward and Katz. (B) Transition structures of cycloaddition and Cope rearrangement optimized by B3LYP/6-31G(d) [84]. (C) Typical trajectories propagated for the reaction of cyclopentadiene dimerization. The dashed line and solid line represent the trajectories that are dynamically concerted and dynamically stepwise, respectively. Red dots show the transition-state geometries sampled by normal mode sampling method in the vicinity of transition structure. The typical snapshots along the trajectories of concerted pathway (D) and two-stage pathway (E). Reproduced with permission from [37].

(corresponding to roughly three periods of a normal C–C single bond vibration). This shows the characteristics of an entropic intermediate, albeit short-lived and undetectable by current methods. Of the 220 reactive trajectories obtained from MD simulations, 6% of the trajectories were found to be dynamically stepwise and involve entropic intermediates. Statistically, the time in the transition zone was calculated to be 35.0 ± 16.0 fs.

Biosynthetic Reactions Involving Entropic Intermediates

SpnF-Catalyzed Diels-Alder Reaction

Despite the wide applications of the Diels-Alder reaction since its discovery in 1928 [67], the identification of natural enzymes that catalyze Diels-Alder reactions has been difficult. In recent decades, thousands of natural products have been identified to contain six-membered unsaturated carbocycles or heterocycles, many with potential to be formed by enzyme-catalyzed pericyclic reactions [68–70]. In 2011, Liu and coworkers demonstrated the first monofunctional Diels-Alderase (SpnF) that catalyzes a Diels-Alder reaction in the biosynthetic pathway of tetracyclic polyketide spinosyn A (Figure 5A) [71]. *En route* to spinosyn A, SpnF catalyzes the transannular Diels-Alder reaction of a macrolactone precursor to form the 5,6-bicyclic of the natural product 500-fold faster than the nonenzymatic background reaction in water [71,72]. The crystal structure of SpnF was reported in 2015 [73], which allowed further investigations of atomic-level and time-resolved mechanisms for the SpnF-catalyzed Diels-Alder reaction in the enzyme with quantum mechanics/molecular mechanics (QM/MM) and MD simulations.

The groups of Singleton, Liu, and Houk found that the reaction involves an ambimodal TS that leads directly to the observed Diels-Alder-([4 + 2]-) cycloadduct and to an unobserved [6 + 4]-

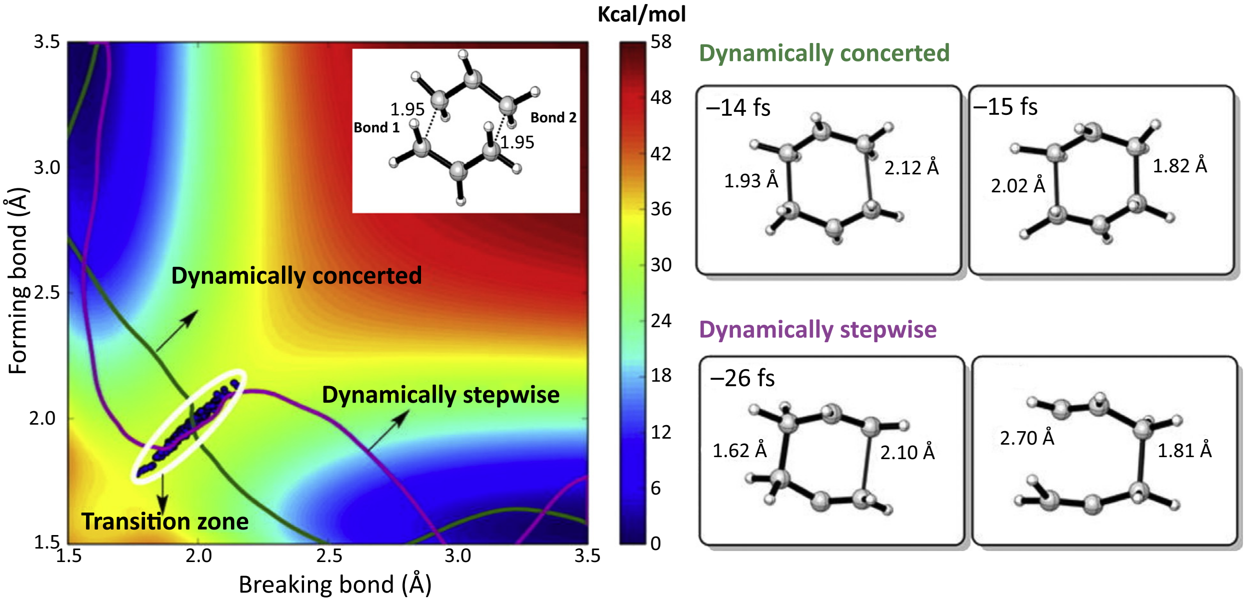
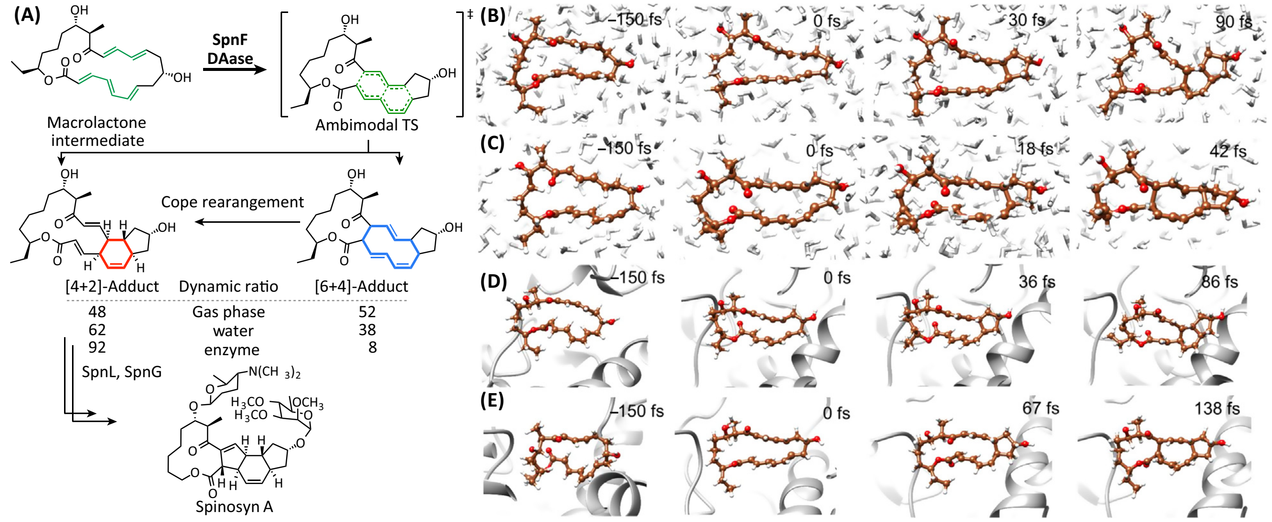


Figure 4. Typical Dynamically Concerted (Green) and Dynamically Stepwise (Purple) Trajectories of the Cope Rearrangement. The typical snapshots along the trajectories are also presented. Inset is the concerted transition structure for Cope rearrangement. The dots in blue show the transition state geometries sampled by normal mode sampling method in the vicinity of transition structure. Reproduced with permission from [38].

cycloadduct (Figure 5A) [14]. The unobserved [6 + 4]-adduct has higher free energy than the Diels-Alder adduct and can spontaneously convert to the Diels-Alder adduct via a Cope rearrangement. The IRC leads to the Diels-Alder adduct via a flat region on the PES, and no intermediate was located on the PES. A variational TS theory calculation revealed two free energy barriers corresponding to the formation of the first and the second C–C bond of the [4 + 2]-adduct, respectively. An entropic intermediate exists between the two free energy barriers.

Environment-perturbed transition-state sampling [29], a QM/MM MD method that Houk, Doubleday, and Yang developed, was applied to investigate how solvent water [74,75] or SpnF enzyme dynamically alter the reaction pathways and the time gaps of bond formation. The formation of both [4 + 2] and [6 + 4] adducts was observed in trajectories initiated from the ambimodal TS with a ratio of 1:1 in the gas phase (M06-2X), 1:1.6 in water (M06-2X/TIP3P), and 1:11 in the enzyme (M06-2X/ff99 sb). Typical snapshots from trajectory simulations are shown in Figure 5B–E. From the gas phase to water, the formation of [4 + 2]-adduct is more favored by high polarity solvent, due to a larger dipole moment of [4 + 2]-adduct than that of the [6 + 4]-adduct [76]. The enzyme SpnF alters the ambimodal TS geometry [77,78] and the post-TS bifurcation dynamics in the active site via hydrophobic repulsion exerted by residue V26, L30, and L198. Both dynamically concerted and dynamically stepwise trajectories were observed in all media. The percentage of dynamically stepwise trajectories that involve an entropic intermediate was found to be 51% in the gas phase, 34% in water, and 67% in enzyme. The average time gaps of all reactive trajectories are 65, 48, and 74 fs, respectively. The time gap of bond formation in the enzyme is longest, but still much too small to be observed by current experimental methods.



Trends in Chemistry

Figure 5. Direct Dynamics Simulations Using Quantum Mechanical Forces for the SpnF-Catalyzed Diels-Alder Reaction in the Gas Phase, Water, and Enzyme. (A) SpnF-catalyzed transannular Diels-Alder reaction. This is a step in the biosynthesis of spinosyn A. Typical trajectories for the formation of (B) [4 + 2] adduct in water, (C) [6 + 4] adduct in water, (D) [4 + 2] adduct in enzyme, and (E) [6 + 4] adduct in enzyme. 1.6 Å is taken as the criterion for C–C bond formation. DAase, Diels-Alderase; TS, transition state.

LepI-Catalyzed Diels-Alder/HDA Reaction

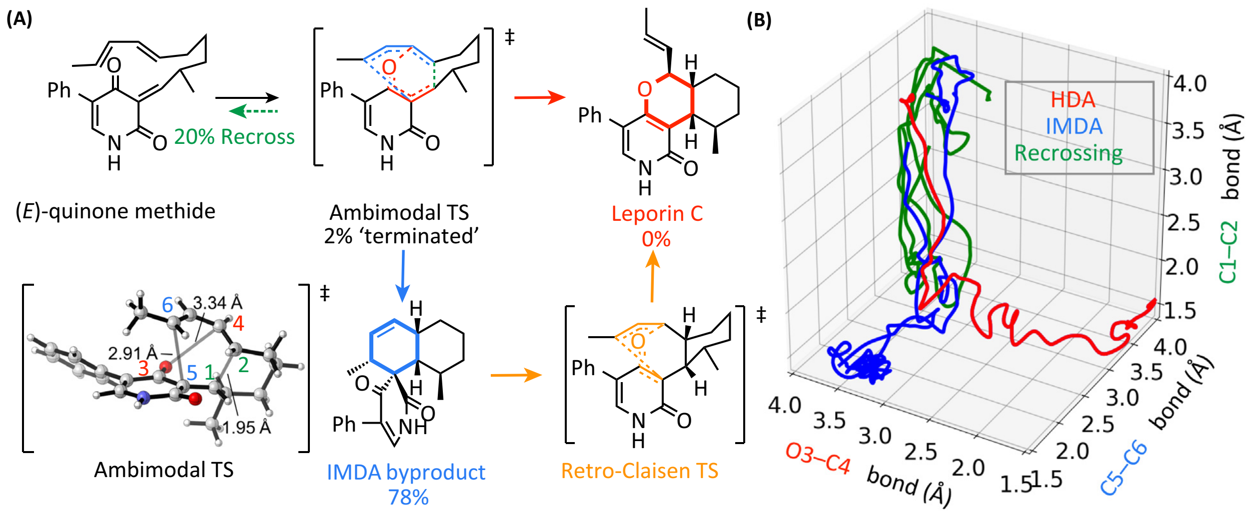
In collaboration with the Yi Tang lab, Houk and colleagues studied the biosynthetic pathway of formation of leporin B and discovered a new multifunctional SAM-dependent pericyclase [79], LepI [39], that catalyzes a stereoselective *trans*-dehydration reaction and three pericyclic reactions: HDA, IMDA, and **retro-Claisen rearrangement**. As shown in Figure 6A, leporin C could be formed from two pathways: (i) the direct pathway from (*E*)-quinone methide via a HDA reaction, and (ii) a competing pathway in which an IMDA byproduct is formed first, followed by a retro-Claisen rearrangement.

QM calculations were performed at the B3LYP-D3 level [80]. The HDA and IMDA cycloaddition reactions of (*E*)-quinone methide share a single ambimodal TS structure. Trajectory simulations were performed on the spontaneous reaction (Figure 6A, ambimodal TS). Typical trajectories are exemplified in Figure 6B. The resulting HDA:IMDA ratio is 1:74. Among the reactive trajectories, 74% are dynamically stepwise and involve entropic intermediate. The average time gap between formation of two bonds is 99 fs with the extrema of 38 fs and 271 fs.

Trispericyclic Cycloaddition

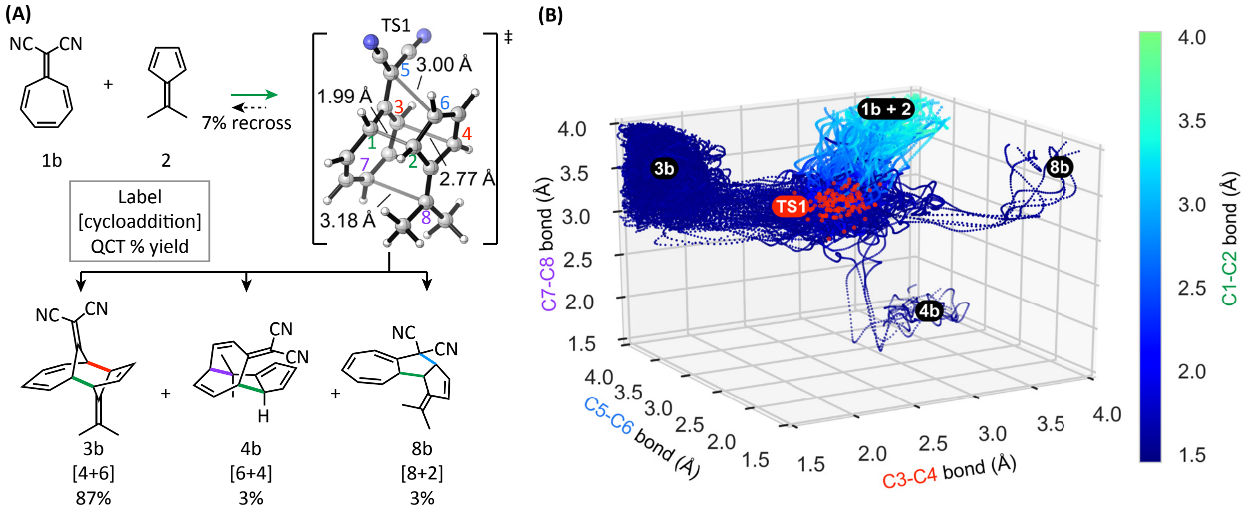
Houk and coworkers recently discovered the first examples of an ambimodal trispericyclic TS that leads to three different cycloaddition products [40]. In 1992, Liu and Ding studied experimentally the reactions between 8,8-dicyanohepta**fulvene** 1b or 8-cyano-8-(methoxycarbonyl)heptafulvene and 6,6-dimethylfulvene (2) [81]. They observed the formation of [6 + 4]- and [8 + 2]-cycloadducts and respective hydrogen-shift derivatives with product ratios dependent on substituents, reaction time, solvent, and temperature.

Houk and colleagues had previously characterized the reaction between tropone and dimethylfulvene to proceed through an ambimodal TS that leads to both [6 + 4] and [4 + 6]



Trends in Chemistry

Figure 6. Quantum Mechanical Direct Dynamics Simulations of an LepI-Catalyzed Pericyclic Reaction. (A) LepI-catalyzed pericyclic reactions of (*E*)-quinone methide forming leporin C and spirobicyclic intramolecular Diels-Alder (IMDA) byproduct. (B) Representative dynamic results from 50 quasiclassical trajectories propagated from ambimodal transition state (TS). Reproduced with permission from [39]. HDA, Hetero-Diels-Alder.



Trends in Chemistry

Figure 7. Quantum Mechanical Direct Dynamics Simulations of the First Tripericyclic Reaction in the Gas Phase. (A) Dynamic reaction scheme of heptafulvenes 1b and 2 forming 3b, 4b, and 8b from ambimodal tripericyclic transition structure TS1. (B) A 4-dimensional plot of 142 trajectory geometries propagated from TS1 ensemble at ωB97X-D/6-31G(d) level of theory. The common bond among all products is mapped to the color bar where 1.5 Å is blue and 4 Å is green. Reproduced with permission from [40]. QCT, quasi-classical trajectory.

adducts [49]. This result, together with experimental observations from Liu and colleagues, encouraged computational investigation to determine if one single ambimodal TS could lead to the formation of three products ([6 + 4], [4 + 6], and [8 + 2]) when different 8,8-disubstituted heptafulvenes are considered instead of tropone. The transition structure (TS1,

Figure 7A) for the reaction of 1b with 2 was found to be highly asynchronous with four partially formed σ-bonds, as compared with the three partially formed bonds observed in the parent ambimodal TS for the reaction between tropone and dimethylfulvene. Quasiclassical trajectories were initiated from TS1 and lead to three different products, 3b, 4b, and 8b (Figure 7B), thus confirming the ambimodal nature of the TS. Analysis of the reaction dynamics determined average time-gaps of 90, 74, and 141 fs for formation of [4 + 6]-, [6 + 4]-, and [8 + 2]-cycloadducts, respectively. The reaction exhibits an overall mean time-gap of 102 fs, where 28% of the trajectories are dynamically concerted and 72% are dynamically stepwise forming an entropic intermediate *en route* to products. Our preliminary analysis suggests that a bifurcation occurs after the TS, and each of the new paths further bifurcate as they approach to TS2 and TS3, which correspond to Cope TSs for interconversions of pairs of adducts. Interestingly, both TS2 and TS3 are also found to be ambimodal, interconnecting the three cycloadducts through the formation of this entropic intermediate [40]. This fascinatingly complicated trispericyclic reaction further broadens our knowledge of pericyclic ambimodality.

How General Are Entropic Intermediates?

Besides the pericyclic reactions that we have emphasized in this article, entropic intermediates have been implicated in many other types of chemical reactions. For instance, our previous study of dimethyldioxirane C–H oxidation [25] showed that the open-shell singlet radical pair has no barrier to reaction under implicit acetone solvent, and an entropic intermediate is involved in 65% of the trajectories initiated from the C–H abstraction TS. In the non-adiabatic dynamic studies, Vacher, Lindh, and coworkers [27] observed frustrated dissociation of 1,2-dioxetane caused by an entropy trap. The dissociation occurs between 30 and 140 fs in the ground state, and between 30 and 250 fs when the singlet excited state is involved in non-adiabatic dynamics. Systematic work on the roaming radical mechanisms [21] observed in the decomposition of formaldehyde also shares the same spirit of entropic intermediate that we discussed here.

Concluding Remarks and Future Perspectives

From fundamental organic reactions to biosynthetic transformations, the involvement and importance of entropic intermediates has been recognized. Empowered by direct dynamics simulations with quantum mechanical force calculations, the dynamical processes of prototypical pericyclic reactions and of biosynthetic reactions have been elucidated. The first trispericyclic reactions have also been identified, which involve the formation of an entropic intermediate that leads to the formation of three different cycloadducts.

A timing criterion was proposed to classify dynamically concerted and stepwise trajectories and to help to qualitatively identify the degree by which an entropic intermediate is involved in the reaction. Entropic intermediates have the signature of lifetimes of 60–200 fs or more, but with no potential energy barrier to bond formation to give stable products.

These studies demonstrate how molecules undergo chemical transformations in a time-resolved fashion, and also emphasize the need for further computational and experimental development to probe the influence of environments, such as solvents and enzymes, on geometries and lifetimes of entropic intermediates.

Outstanding Questions

Is the lifetime of transition state (60 fs at 298 K) a proper timing boundary to differentiate dynamically concerted versus dynamically stepwise mechanisms for different types of organic reactions?

How do different levels of computational methods influence the study of entropic intermediates? Is density functional theory a trustworthy approach, or is it necessary to apply coupled-cluster and multiconfigurational methods in the description of entropic intermediates?

How do the properties of entropic intermediates influence the branching ratios for reactions with post-transition state bifurcations? How can we transform the dynamical studies of entropic intermediates into predictive models of branching ratios?

How are entropic intermediates influenced by the environments, including solvent, enzyme, crystalline state, surfaces, or interfaces? How is the motion of the entropic intermediate coupled to the dynamical variations of the environment, like solvent reorganization or protein residue motion? How do long-range electrostatic interactions change the dynamics of entropic intermediates?

How can the free energy profile and dynamical behavior of entropic intermediates be derived from experiments?

Acknowledgements

We are grateful to the National Science Foundation (CHE-1361104) for financial support of our research.

References

1. Houk, K.N. and Liu, F. (2017) Holy grails for computational organic chemistry and biochemistry. *Acc. Chem. Res.* 50, 539–543
2. Krylov, A. *et al.* (2018) Perspective: computational chemistry software and its advancement as illustrated through three grand challenge cases for molecular science. *J. Chem. Phys.* 149, 180901
3. Yang, Z. and Houk, K.N. (2018) The dynamics of chemical reactions: atomistic visualizations of organic reactions, and homage to van't Hoff. *Chem. Eur. J.* 24, 3916–3924
4. Carpenter, B.K. *et al.* (2016) The study of reactive intermediates in condensed phases. *J. Am. Chem. Soc.* 138, 4695–4705
5. Carrascosa, E. *et al.* (2017) Imaging dynamic fingerprints of competing E2 and S(N)2 reactions. *Nat. Commun.* 8, 25
6. Yang, X. *et al.* (2017) Chemical reaction dynamics. *Chem. Soc. Rev.* 46, 7481–7482
7. De Feyter, S. *et al.* (1999) Femtosecond dynamics of diradicals: transition states, entropic configurations and stereochemistry. *Chem. Phys. Lett.* 303, 249–260
8. Kwan, E.E. *et al.* (2018) Concerted nucleophilic aromatic substitutions. *Nat. Chem.* 10, 917–923
9. Xie, J. and Hase, W.L. (2016) Rethinking the Sn2 reaction. *Science* 352, 32–33
10. Liu, Y.P. *et al.* (1993) Direct dynamics calculation of the kinetic isotope effect for an organic hydrogen-transfer reaction, including corner-cutting tunneling in 21 dimensions. *J. Am. Chem. Soc.* 115, 7806–7817
11. Black, K. *et al.* (2012) Dynamics, transition states, and timing of bond formation in Diels-Alder reactions. *Proc. Natl. Acad. Sci. U. S. A.* 109, 12860–12865
12. Doubleday, C. *et al.* (1984) Is tetramethylene an intermediate? *J. Am. Chem. Soc.* 106, 447–448
13. Gonzalez-James, O.M. *et al.* (2012) Entropic intermediates and hidden rate-limiting steps in seemingly concerted cycloadditions. Observation, prediction, and origin of an isotope effect on recrossing. *J. Am. Chem. Soc.* 134, 1914–1917
14. Patel, A. *et al.* (2016) Dynamically complex 6 + 4 and 4 + 2 cycloadditions in the biosynthesis of spinosyn A. *J. Am. Chem. Soc.* 138, 3631–3634
15. Doubleday, C. (1993) Tetramethylene. *J. Am. Chem. Soc.* 115, 11968–11983
16. Rai, S.N. and Truhlar, D.G. (1983) Variational transition state theory calculations for an atom–radical reaction with no saddle point: O+ Oh. *J. Chem. Phys.* 79, 6046–6059
17. Zhou, H.X. and Zwanzig, R. (1991) A rate process with an entropy barrier. *J. Chem. Phys.* 94, 6147–6152
18. Doering, W.V. *et al.* (2002) Fate of the intermediate diradicals in the caldera: stereochemistry of thermal stereomutations, (2 + 2) cycloreversions, and (2 + 4) ring-enlargements of *cis-* and *trans-*1-cyano-2-(E and Z)-propenyl-*cis*-3,4-dideuteriocyclobutanes. *J. Am. Chem. Soc.* 124, 11642–11652
19. Baldwin, J.E. (2003) Thermal rearrangements of vinylcyclopropanes to cyclopentenes. *Chem. Rev.* 103, 1197–1212
20. Collins, P. *et al.* (2014) Nonstatistical dynamics on the caldera. *J. Chem. Phys.* 141, 034111
21. Bowman, J.M. and Houston, P.L. (2017) Theories and simulations of roaming. *Chem. Soc. Rev.* 46, 7615–7624
22. Bowman, J.M. (2014) Roaming. *Mol. Phys.* 112, 2516–2528
23. Doubleday, C., Jr *et al.* (1988) Singlet biradicals as intermediates. Canonical variational transition-state theory results for trimethylene. *J. Phys. Chem.* 92, 4367–4371
24. Pratihar, S. *et al.* (2017) Direct chemical dynamics simulations. *J. Am. Chem. Soc.* 139, 3570–3590
25. Yang, Z. *et al.* (2016) Molecular dynamics of dimethyldioxirane C-H oxidation. *J. Am. Chem. Soc.* 138, 4237–4242
26. Carlsen, R. *et al.* (2018) Dynamical mechanism may avoid high-oxidation state Ir(V)-H intermediate and coordination complex in alkane and arene C-H activation by cationic Ir(iii) phosphine. *J. Am. Chem. Soc.* 140, 11039–11045
27. Vacher, M. *et al.* (2017) Dynamical insights into the decomposition of 1,2-dioxetane. *J. Chem. Theory Comput.* 13, 2448–2457
28. Hare, S.R. and Tantillo, D.J. (2017) Post-transition state bifurcations gain momentum - current state of the field. *Pure Appl. Chem.* 89, 679–698
29. Yang, Z. *et al.* (2018) Influence of water and enzyme Spnf on the dynamics and energetics of the ambimodal 6 + 4/4 + 2 cycloaddition. *Proc. Natl. Acad. Sci. U. S. A.* 115, E848–E855
30. Carpenter, B.K. (2014) Effect of a chiral electrostatic cavity on product selection in a reaction with a bifurcating reaction path. *Theor. Chem. Acc.* 133, 1525
31. Carpenter, B.K. *et al.* (2015) Prediction of enhanced solvent-induced enantioselectivity for a ring opening with a bifurcating reaction path. *Phys. Chem. Chem. Phys.* 17, 8372–8381
32. Mardirossian, N. and Head-Gordon, M. (2017) Thirty years of density functional theory in computational chemistry: an overview and extensive assessment of 200 density functionals. *Mol. Phys.* 115, 2315–2372
33. Horn, B.A. *et al.* (1996) Retro-Diels-Alder femtosecond reaction dynamics. *J. Am. Chem. Soc.* 118, 8755–8756
34. Eyring, H. (1935) The activated complex in chemical reactions. *J. Chem. Phys.* 3, 107–115
35. Firestone, R.A. (1968) A. Mechanism of 1,3-dipolar cycloadditions. *J. Org. Chem.* 33, 2285–2290
36. Dewar, M.J.S. (1977) Studies of the mechanisms of some organic reactions and photoreactions by semiempirical SCF MO methods. *Faraday Discuss. Chem. Soc.* 62, 197–209
37. Yang, Z. *et al.* (2018) Molecular dynamics of the two-stage mechanism of cyclopentadiene dimerization: concerted or stepwise? *Chem. Phys.* 514, 120–125
38. Mackey, J.L. *et al.* (2017) Dynamically concerted and stepwise trajectories of the Cope rearrangement of 1,5-hexadiene. *Chem. Phys. Lett.* 683, 253–257
39. Ohashi, M. *et al.* (2017) Sam-dependent enzyme-catalysed pericyclic reactions in natural product biosynthesis. *Nature* 549, 502–506
40. Xue, X.-S. *et al.* (2019) Ambimodal tripericyclic transition state and dynamic control of periselectivity. *J. Am. Chem. Soc.* 141, 1217–1221Published online January 9, 2019. DOI: 10.1021/jacs.8b12674
41. Carpenter, B.K. *et al.* (2018) Dynamics on the double Morse potential: a paradigm for roaming reactions with no saddle points. *Regul. Chaotic Dyn.* 23, 60–79
42. Truhlar, D.G. and Garrett, B.C. (1980) Variational transition-state theory. *Acc. Chem. Rev.* 13, 440–448
43. Truhlar, D.G. and Garrett, B.C. (1984) Variational transition-state theory. *Annu. Rev. Phys. Chem.* 35, 159–189
44. Kim, Y. *et al.* (2010) Free-energy surfaces for liquid-phase reactions and their use to study the border between concerted and nonconcerted A, B-elimination reactions of esters and thioesters. *J. Am. Chem. Soc.* 132, 11071–11082
45. Klippenstein, S.J. *et al.* (2014) Chemical kinetics and mechanisms of complex systems: a perspective on recent theoretical advances. *J. Am. Chem. Soc.* 136, 528–546
46. Bao, J.L. *et al.* (2016) Barrierless association of Cf2 and dissociation of C2f4 by variational transition-state theory and system-specific quantum Rice–Ramsperger–Kassel theory. *Proc. Natl. Acad. Sci. U. S. A.* 113, 13606–13611
47. Ahrendt, K.A. *et al.* (2000) New strategies for organic catalysis: the first highly enantioselective organocatalytic Diels–Alder reaction. *J. Am. Chem. Soc.* 122, 4243–4244
48. Gordillo, R. and Houk, K.N. (2006) Origins of stereoselectivity in Diels–Alder cycloadditions catalyzed by chiral imidazolidinones. *J. Am. Chem. Soc.* 128, 3543–3553
49. Yu, P. *et al.* (2017) Mechanisms and origins of periselectivity of the ambimodal 6 + 4 cycloadditions of tropone to dimethylfulvene. *J. Am. Chem. Soc.* 139, 8251–8258

50. Xu, L. *et al.* (2011) Dynamics of carbene cycloadditions. *J. Am. Chem. Soc.* 133, 17848–17854
51. Jimenez-Oses, G. *et al.* (2014) Competition between concerted and stepwise dynamics in the triplet di-pi-methane rearrangement. *Angew. Chem. Int. Ed.* 53, 8664–8667
52. Toerk, L. *et al.* (2015) Molecular dynamics of the Diels-Alder reactions of tetrazines with alkenes and N-2 extrusions from adducts. *J. Am. Chem. Soc.* 137, 4749–4758
53. Woodward, R. and Katz, T.J. (1959) The mechanism of the Diels-Alder reaction. *Tetrahedron* 5, 70–89
54. Caramella, P. *et al.* (2002) An unexpected bispericyclic transition structure leading to 4 + 2 and 2 + 4 cycloadducts in the endo dimerization of cyclopentadiene. *J. Am. Chem. Soc.* 124, 1130–1131
55. Cope, A.C. *et al.* (1941) The rearrangement of allyl groups in three-carbon systems. I. 1. *J. Am. Chem. Soc.* 63, 1843–1852
56. von E. Doering, W. and Roth, W.R. (1962) The overlap of two allyl radicals or a four-centered transition state in the Cope rearrangement. *Tetrahedron* 18, 67–74
57. Gajewski, J.J. and Conrad, N.D. (1979) Variable transition state structure in 3,3-sigmatropic shifts from alpha-secondary deuterium isotope effects. *J. Am. Chem. Soc.* 101, 6693–6704
58. Yu, P. *et al.* (2015) Transannular [6 + 4] and ambimodal cycloaddition in the biosynthesis of heronamide A. *J. Am. Chem. Soc.* 137, 13518–13523
59. Gajewski, J.J. and Emrani, J. (1984) Origin of the rate acceleration in the Ireland-Claisen rearrangement. *J. Am. Chem. Soc.* 106, 5733–5734
60. Gajewski, J.J. (1980) Energy surfaces of sigmatropic shifts. *Acc. Chem. Rev.* 13, 142–148
61. Gajewski, J.J. (1979) Substituent effects in concerted reactions. A nonlinear free-energy relationship for the 3,3-shift and the Diels-Alder reaction. *J. Am. Chem. Soc.* 101, 4393–4394
62. O'Ferrall, R.A.M. (1970) Relationships between E2 and E1cB mechanisms of B-elimination. *J. Chem. Soc. B Phys. Org.* 274–277
63. Kreevoy, M.M. and Ridl, B.A. (1981) Isotopic fractionation factor and hydrogenic potential in 2-hydroxy-1, 1, 1, 5, 5, 5-hexafluoro-2-penten-4-one. *J. Phys. Chem.* 85, 914–917
64. Houk, K. *et al.* (1992) Theoretical secondary kinetic isotope effects and the interpretation of transition state geometries. 1. The Cope rearrangement. *J. Am. Chem. Soc.* 114, 8565–8572
65. Hrovat, D.A. *et al.* (1999) A Becke3LYP/6-31G* study of the Cope rearrangements of substituted 1, 5-hexadienes provides computational evidence for a chameleonic transition state. *J. Am. Chem. Soc.* 121, 10529–10537
66. Hrovat, D.A. *et al.* (2000) Cooperative and competitive substituent effects on the Cope rearrangements of phenyl-substituted 1, 5-hexadienes elucidated by Becke3LYP/6-31G* calculations. *J. Am. Chem. Soc.* 122, 7456–7460
67. Diels, O. and Alder, K. (1928) Synthesen in der hydroaromatischen reihe. *Justus Liebigs Ann. Chem.* 460, 98–122
68. Ose, T. *et al.* (2003) Insight into a natural Diels–Alder reaction from the structure of macrophomate synthase. *Nature* 422, 185
69. Townsend, C.A. (2011) A "Diels-Alderase" at last. *ChemBioChem* 12, 2267–2269
70. Minami, A. and Oikawa, H. (2016) Recent advances of Diels–Alderases involved in natural product biosynthesis. *J. Antibiot.* 69, 500
71. Kim, H.J. *et al.* (2011) Enzyme-catalysed 4 + 2 cycloaddition is a key step in the biosynthesis of spinosyn A. *Nature* 473, 109–112
72. Jeon, B.-S. *et al.* (2017) Investigation of the mechanism of the Spnf-catalyzed [4 + 2]-cycloaddition reaction in the biosynthesis of spinosyn A. *Proc. Natl. Acad. Sci.* 114, 10408
73. Fage, C.D. *et al.* (2015) The structure of Spnf, a standalone enzyme that catalyzes [4 + 2] cycloaddition. *Nat. Chem. Biol.* 11, 256
74. Yang, Z. *et al.* (2015) QM/MM protocol for direct molecular dynamics of chemical reactions in solution: the water-accelerated Diels-Alder reaction. *J. Chem. Theory Comput.* 11, 5606–5612
75. Grayson, M.N. *et al.* (2017) Chronology of Ch . . . O hydrogen bonding from molecular dynamics studies of the phosphoric acid-catalyzed allylboration of benzaldehyde. *J. Am. Chem. Soc.* 139, 7717–7720
76. Medvedev, M.G. *et al.* (2017) Quantifying possible routes for Spnf-catalyzed formal Diels-Alder cycloaddition. *J. Am. Chem. Soc.* 139, 3942–3945
77. Chen, N. *et al.* (2018) Biosynthesis of spinosyn A: a [4 + 2] or [6 + 4] cycloaddition. *ACS Catal.* 8, 2353–2358
78. Zheng, Y. and Thiel, W. (2017) Computational insights into an enzyme-catalyzed [4 + 2] cycloaddition. *J. Org. Chem.* 82, 13563–13571
79. Jamieson, C.S. *et al.* (2019) The expanding world of biosynthetic pericyclases: cooperation of experiment and theory for discovery. *Nat. Prod. Rep.* Published online October 12, 2018. DOI: 10.1039/c8np00075a
80. Grimme, S. *et al.* (2010) A consistent and accurate *ab initio* parametrization of density functional dispersion correction (DFT-D) for the 94 elements H-Pu. *J. Chem. Phys.* 132, 154104
81. Liu, C.Y. *et al.* (1993) Steric effects in the cycloaddition reactions of electron-deficient unsymmetrically 8,8-disubstituted 8-cyano-8-(methoxycarbonyl)heptafulvene with electron-rich 6,6-diphenyl- and 6,6-dimethylfulvenes. *J. Org. Chem.* 58, 1628–1630
82. Hong, Y.J. and Tantillo, D.J. (2009) A potential energy bifurcation in terpene biosynthesis. *Nat. Chem.* 1, 384–389
83. Zheng, J. *et al.* (2010) *Gaussrate, Version 2009-A,* University of Minnesota
84. Lee, C. *et al.* (1988) Development of the Colle-Salvetti correlation-energy formula into a functional of the electron density. *Phys. Rev. B* 37, 785
85. Pham, H.V. and Houk, K.N. (2014) Diels-Alder reactions of allene with benzene and butadiene: concerted, stepwise, and ambimodal transition states. *J. Org. Chem.* 79, 8968–8976
86. Yang, Z. *et al.* (2018) Relationships between product ratios in ambimodal pericyclic reactions and bond lengths in transition structures. *J. Am. Chem. Soc.* 140, 3061–3067
87. Zhao, Y. and Truhlar, D.G. (2008) The M06 suite of density functionals for main group thermochemistry, thermochemical kinetics, noncovalent interactions, excited states, and transition elements: two new functionals and systematic testing of four M06-class functionals and 12 other functionals. *Theor. Chem. Acc.* 120, 215–241
88. Jorgensen, W.L. *et al.* (1983) Comparison of simple potential functions for simulating liquid water. *J. Chem. Phys.* 79, 926–935
89. Lindorff-Larsen, K. *et al.* (2010) Improved side-chain torsion potentials for the amber Ff99sb protein force field. *Proteins* 78, 1950–1958