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Molecular dynamics of the intramolecular 1, 3-dipolar ene reaction of a nitrile oxide and an alkene: non-statistical behavior of a reaction involving a diradical intermediate*

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ABSTRACT

Potential energy surfaces and molecular dynamics of the intramolecular 1, 3-dipolar cycloaddition and ene reaction of a nitrile oxide with an alkene were performed in the gas phase and in dichloromethane with density functional theory. One hundred trajectories were propagated in the gas phase and in dichloromethane, respectively. Twenty percent of the trajectories in the gas phase involve bicyclic intermediate and the mean time gap is 472fs. A dynamically stepwise reaction is observed. In dichloromethane, more reactive trajectories were obtained and the time gap is larger than that in the gas phase.

ARTICLE HISTORY

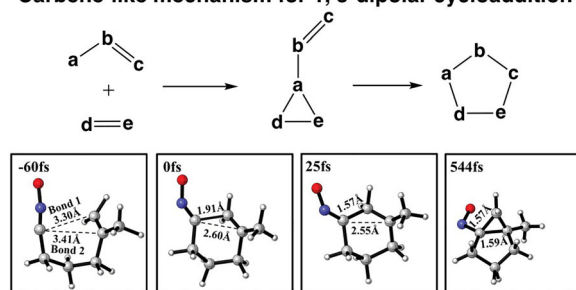
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Molecular reaction dynamics; intramolecular 1, 3-dipolar cycloaddition; carbene-type mechanism; diradical intermediate

Carbene-like mechanism for 1, 3-dipolar cycloaddition



1. Introduction

Many 1, 3-dipolar cycloadditions have been applied to the synthesis of five-membered heterocyclic products [1–3]. In recent years, these reactions have played vital roles in bio-orthogonal reactions and click chemistry [4,5]. The concerted versus stepwise character of 1, 3-dipolar cycloadditions have been extensively debated. In 1963, Huisgen first proposed a single-step concerted mechanism for the 1, 3-dipolar cycloadditions (Scheme 1(a)) [6]. In this mechanism, two σ -bonds are formed simultaneously during the cycloaddition, although not necessary at equal rates. Stereoselectivity is generated in the concerted 1, 3-dipolar addition.

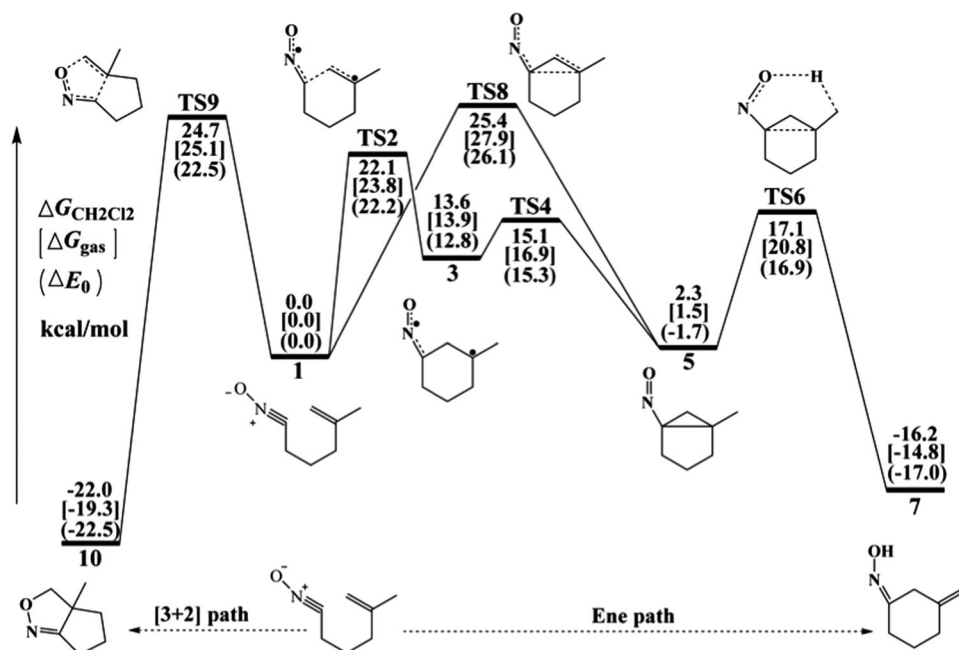
Contrary to Huisgen's one-step mechanism with a single transition state, Firestone proposed a two-step stepwise mechanism in 1968 (Scheme 1(b)) [7]. He hypothesised that the reaction is a two-step process separated by a diradical intermediate between reactant and product [8,9]. The first bond formation is rate-determining, generating a diradical intermediate. After several decades of debate, it seems that both concerted and stepwise mechanisms are probable, depending on the specific reaction condition. Huisgen found that the 1, 3-dipolar cycloaddition of an electron-rich thiocarbonyl ylide with a highly electron-poor tetracyano alkene is a stepwise process with a zwitterionic intermediate [10]. In addi-

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*Dedicated to the memory of the great theoretician and friend, Dieter Cremer.

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Scheme 1. Energy profile of the intramolecular 1, 3-dipolar cycloaddition reaction between a nitrile oxide and an alkene. $\Delta G_{CH_2Cl_2}$ is the free energy in dichloromethane, and ΔG_{gas} is the free energy in the gas phase. ΔE_0 is the zero-point energy (ZPE)-corrected relative electronic energy in the gas phase, with (U)B3LYP/6-31G(d).

tion, Huisgen also discussed a carbene-type mechanism (Scheme 1(c)) [11,12]. The outer part of the 1, 3-dipole first combines with the double bond to form a three-membered ring, and then a rapid intramolecular rearrangement leads to the five-membered ring. This mechanism was disproved experimentally for intermolecular cycloadditions by Huisgen, but was found later in intramolecular cycloadditions by Padwa, Steglich, Miyashi, and others [13,14]. In the carbene-type mechanism, the 1, 3-dipole acts as a carbene or nitrene in a cheletropic 1, 1-cycloaddition to form a three-membered ring intermediate. A heterovinylcyclopropane rearrangement ensues to generate the final (3 + 2) cycloadduct. An intramolecular ene-like reaction of a nitrile oxide with an alkene was reported by Ishikawa and Saito [15]. Previously, our group performed quantum mechanical calculations to explore the mechanism of intramolecular 1, 3-dipolar cycloadditions. The theoretical studies uncovered a three-step mechanism, involving a carbene-like 1, 1-cycloaddition mechanism to form bicyclic nitrocyclopropane intermediate, 5, followed by a retro-ene reaction to give cyclic oxime *cis*-product (Figure 1) [16]. The formation of intermediate 5 involves a stepwise pathway where a shallow diradical intermediate 3 converts readily to the bicyclic intermediate 5. Intermediate 3 can be energised by excess kinetic energy as a result of the formation of the first C-C bond. In this case, non-statistical dynamic effects [17–19] are likely involved to drive the conversion from intermediate 3 to bicyclic adduct 5. Molecular

dynamics are essential to elucidate the time-resolved mechanism of this process. Previously, we have employed this powerful simulation tool to study the dynamics of Diels-Alder reaction [20–23], intermolecular 1, 3-dipolar cycloadditions [24], Cope rearrangements [25], C-H oxidation [26] and cyclopentadiene dimerisation [27], and to explore the environmental influences on the dynamics of reactions in solvent and in enzyme [28,29]. In these studies, we have found several energetically stepwise reactions in which the trajectories quickly bypass the intermediate region within several periods of bond vibration and lead to the product [20]. The lifetime of the intermediates in these reactions are much shorter than what is predicted by transition state theory.

Here we conducted molecular dynamics simulations of the intramolecular 1, 3-dipolar ene reaction between the nitrile oxide and alkene. Specifically, we focused on the intrinsic time-resolved transformation from the reactant 1 to the bicyclic intermediate 5. For the conversion from intermediate 3 to 5, the barrier is lowered by 1.5 kcal/mol with CH_2Cl_2 solvation (Figure 1). This motivates us to explore how implicit dichloromethane solvation influences the dynamical behaviours.

2. Computational methods

We performed density functional theory (DFT) computations using Gaussian 09 [30]. The development of density functional theory allows an accurate assessment of

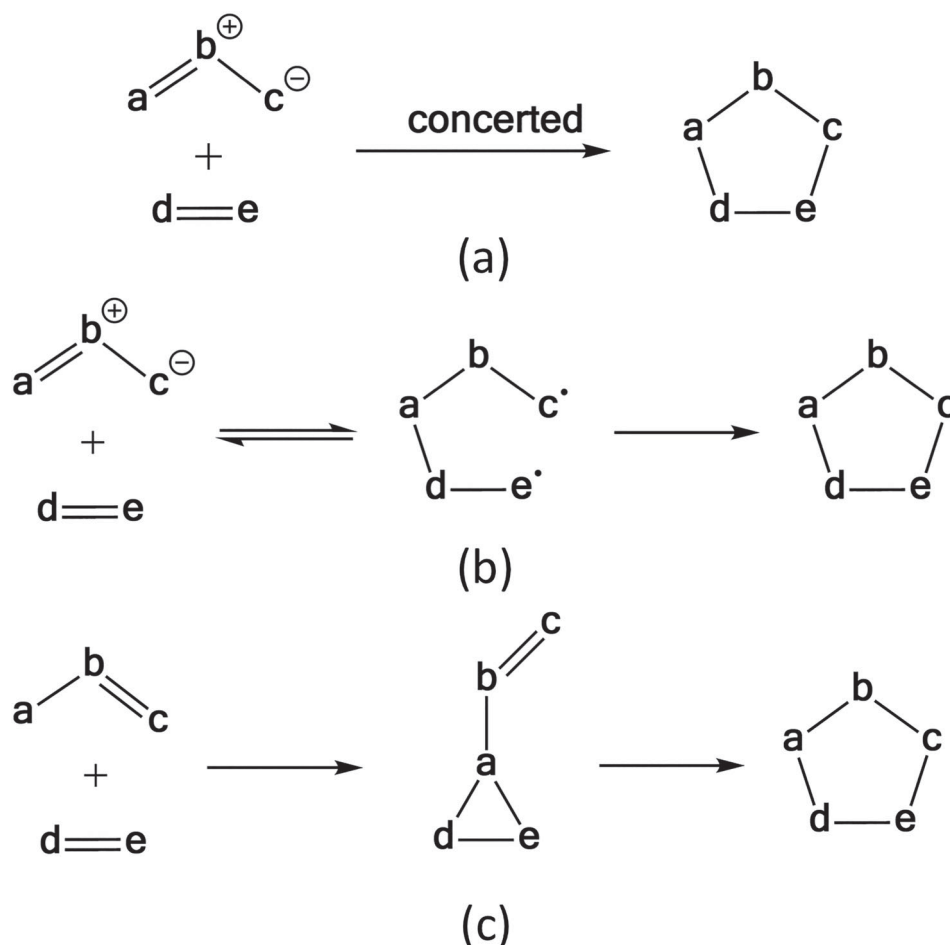


Figure 1. Mechanisms of 1,3-dipolar cycloaddition, (a) concerted, (b) stepwise, and (c) carbene-type.

various chemical properties, especially thermodynamics and kinetics. Recent benchmarks by Head-Gordon *et al.* [31] and Grimme *et al.* [32] thoroughly document the performance of different functionals for applications of main group chemistry. In this work, geometry optimizations were carried out at the (U)B3LYP/6-31G(d) level of theory [33,34], to be consistent with our previous studies [16]. Normal vibrational mode analysis confirms the optimised structures are minima or transition structures (TS). We benchmarked the reaction energetics calculated with the (U)B3LYP/6-31G(d) method with those obtained using (U)B3LYP/6-311 + G(d,p), (U)M06-2X/6-311 + G(d,p), and (U) ω B97X-D/6-311 + G(d,p) (Table S1). We looked specifically into the barrier energy from intermediate **3** to transition structure TS4; the process that is highly relevant to the dynamics of three-membered ring closure. The barriers were computed to be 4.6, 4.2, 5.3 and 5.3 kcal/mol for (U)B3LYP/6-31G(d), (U)B3LYP/6-311 + G(d,p), (U)M06-2X/6-311 + G(d,p), and (U) ω B97X-D/6-311 + G(d,p), respectively. These energies are all qualitatively consistent, justifying our use of B3LYP

functional in the current study, although we should note that the B3LYP functional might be problematic in other applications [32]. Direct molecular dynamics (MD) simulations were performed for the intramolecular 1,3-dipolar ene reaction of nitrile oxide and the alkene in the gas phase and in implicit dichloromethane at 298.15 K. Solvent effects were computed by the PCM model [35]. Because of the large computational expense of quantum calculations required in the dynamics simulations, the reaction trajectories were performed at the (U)B3LYP/6-31G(d) level of theory with guess = mix to capture the diradical character of dynamical species. In both the gas phase and dichloromethane solvation, one hundred quasiclassical trajectories (QCTs) [36] were initialised in the region of the potential energy surface near the TS with the normal mode sampling method, which involves first adding zero-point energy and thermal energy for each real normal mode in the TS, and then randomly sampling a set of geometries and velocities that follow a Boltzmann distribution of energies. No additional velocities were added other than vibrations along modes that are perpendicular to the reaction coordinate. The trajectories

were propagated forward and backward for 1000 fs in each direction. The classical equations of motion were integrated with a velocity-verlet algorithm using Singleton's programme Progdyn [37], with the energies and derivatives computed on the fly by the (U)B3LYP method using Gaussian 09. The step length for integration was 1 fs.

3. Results and discussion

In both the gas phase and dichloromethane, quasiclassical trajectories calculations were performed at 298.15 K to study the dynamics of the intramolecular 1, 3-dipolar ene reaction between the nitrile oxide and the alkene. Trajectories were initiated in the vicinity of the TS2 (Figure 2), and were propagated forward and backward

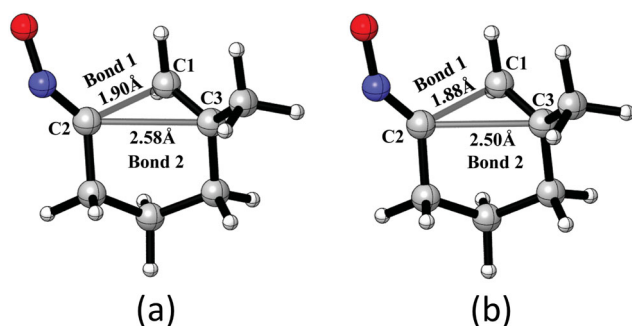


Figure 2. Transition structures of TS2 (a) in the gas phase and (b) in dichloromethane.

for 1000 fs in each direction. A total of 100 trajectories were collected in each medium.

3.1. Snapshot of representative trajectory

Reactive trajectories (reactant **1** to intermediate **3** or **5**) and recrossing trajectories (reactant **1** back to reactant **1**) were observed from our dynamics simulations in both media. Figure 3 shows typical snapshots of reactive trajectories in the gas phase. Figure 3(a) illustrates the formation of the bicyclic intermediate **5**. Atoms C2 and C1 approach mutually, and reach 1.91 Å for bond 1 and 2.60 Å for bond 2 at the TS geometry (0 fs). We defined 1.60 Å as the distance at which the C-C bond is formed. Bond 1 forms at 25 fs. Bond 2 vibrates around 2.60 Å for hundreds of femtoseconds, and forms at 544 fs to give the bicyclic intermediate **5**. The time gap between formation of both bonds is 519 fs. Figure 3(b) shows a trajectory that also involves the formation of bond 1 at about 22 fs, but the trajectory remains in the intermediate geometry **3** and does not generate **5** within 1000 fs.

3.2. Distribution of trajectories and time gap between formation of two bonds

We analysed the distribution of trajectories. For trajectories propagated in the gas phase, 20% trajectories lead to bicyclic intermediate **5**, 66% are intermediate **3**, and 8% are recrossing (Figure 4(a)). In contrast, for trajectories in implicit dichloromethane, 35% trajectories lead to bicyclic intermediate **5**, 45% remain as intermediate **3**,

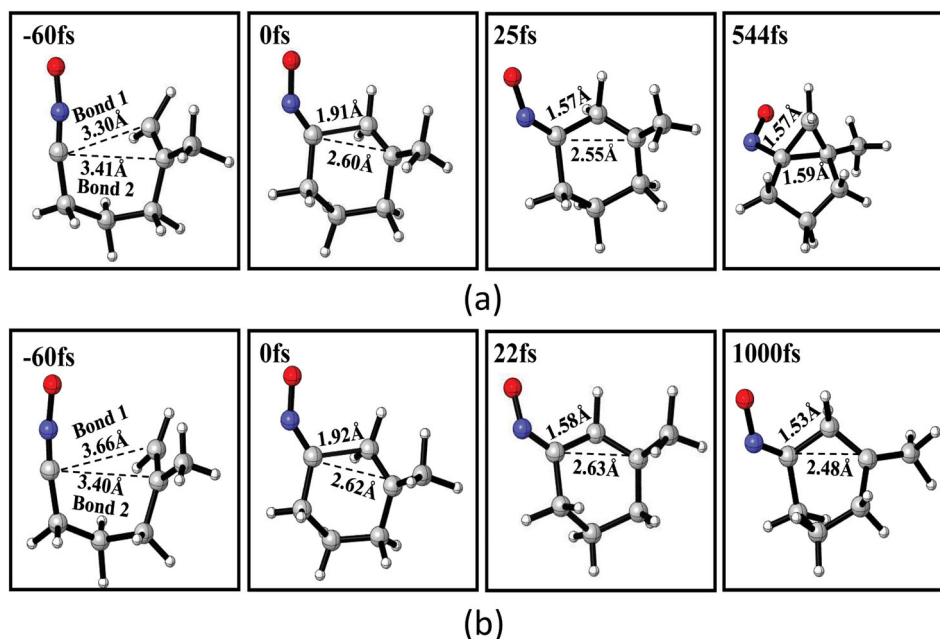


Figure 3. Snapshots of representative trajectory in the gas phase, (a) from reactant to intermediate **5**, (b) from reactant to intermediate **3**.

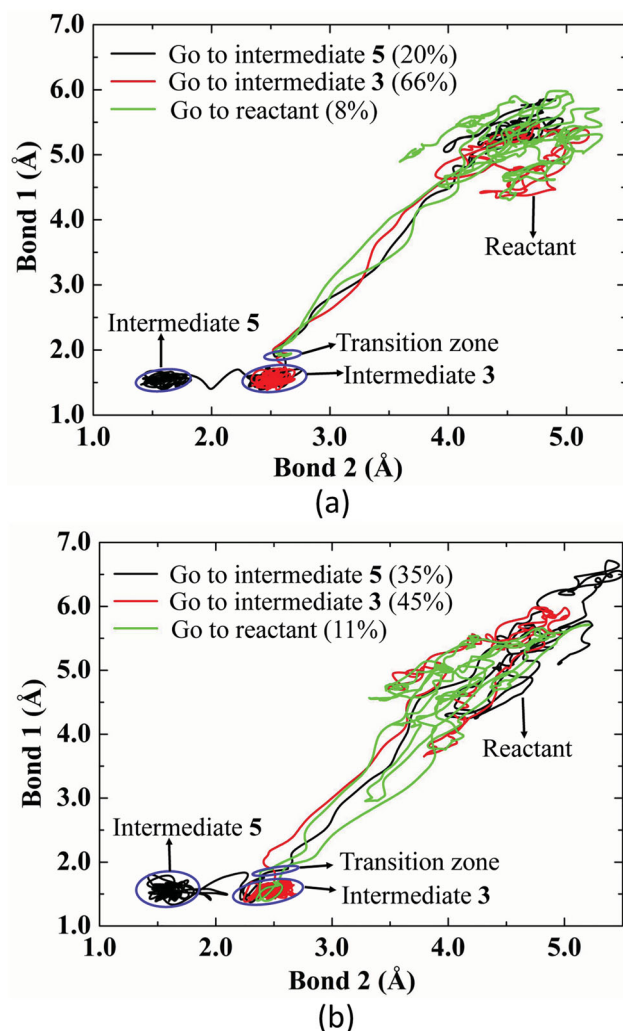


Figure 4. Molecular dynamics trajectories (a) in the gas phase, and (b) in dichloromethane. The black and red lines represent the reactive trajectory from reactant 1 to intermediate 5, and to intermediate 3, respectively. The green line represents the recrossing trajectory from reactant to reactant.

and 11% are recrossing (Figure 4(b)). The implicit solvent environment lowers the barrier of intermediate 3 to TS4 from 3 kcal/mol in the gas phase to 1.5 kcal/mol in dichloromethane, allowing more formation of bicyclic intermediates 5.

Previously, we proposed a dynamical criterion to differentiate dynamically concerted and stepwise mechanisms in cycloadditions. We describe a mechanism as dynamically concerted if the time gap between formation of two bonds are less than 60 fs, but dynamically stepwise otherwise. The criterion was defined as the lifetime of transition state derived from Eyring's equation for zero activation free energy. ($h/k_B T$ with $T = 298$ K) Here, the time gaps between formation of bond 1 and bond 2 are shown in Figure 5. The time gap also represents the lifetime of intermediate 3. In the gas phase, the distribution

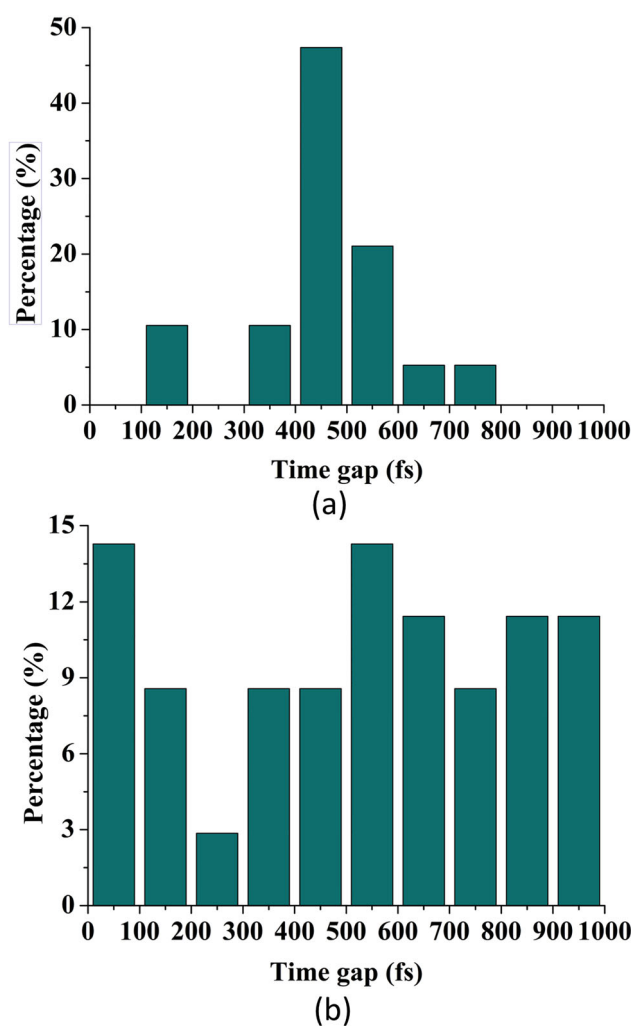


Figure 5. Distributions of time gap between formation of bond 1 and 2 for trajectories propagated at 298.15K (a) in the gas phase and (b) in dichloromethane.

of time gaps ranges between 100 fs and 800 fs, and peaks at ~ 450 fs. The time gaps in the gas phase trajectories are all above 60 fs, revealing that the intrinsic mechanism is both energetically and dynamically stepwise. The lifetime of the intermediate 3 estimated from transition state theory is about 10 ps (3 kcal/mol barrier) in the gas phase, which is much longer than what was observed from dynamics. This indicates that non-statistical dynamic effects facilitate the formation of bicyclic intermediate 5. In dichloromethane, the distribution of time gaps are flat, ranging from 34 fs to 944 fs with a mean value of 518 fs. One out of 35 trajectories were found to involve a time gap less than 60 fs, suggesting the involvement of energetically stepwise but dynamically concerted trajectories, albeit with its low probability. The lifetime of the intermediate 3 estimated from transition state theory is about 750 fs (1.5 kcal/mol barrier), which is comparable to the average we obtained (518 fs). In both media, a significant

number of trajectories that stay around intermediate 3 over the 1000fs trajectory.

4. Conclusion

The dynamics of the intramolecular 1, 3-dipolar ene reaction between nitrile oxide and alkene was investigated with quasiclassical trajectory simulations. In the gas phase, 20% trajectories lead to the formation of bicyclic intermediate from the reactant via bypassing the diradical intermediate. These trajectories were found to be both energetically and dynamically stepwise. In implicit dichloromethane, the percentage of productive trajectories increases to 35%. One trajectory involves energetically stepwise but dynamically concerted fashion, while all others are stepwise both energetically and dynamically.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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