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Significance of Nonstatistical Dynamics in Organic Reaction Mechanisms: Time-Dependent Stereoselectivity in Cyclopentyne−Alkene Cycloadditions

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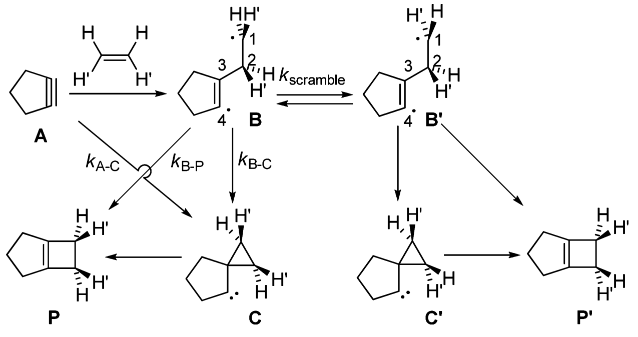
The failure of statistical models (transition state and RRKM theories) to satisfactorily rationalize the outcomes of some organic reactions is increasingly well recognized.[1,2] In particular, Carpenter has suggested that understanding the failure of such models for thermally generated intermediates on diradical potential energy surfaces may help resolve the longstanding debate within mechanistic chemistry concerning whether reactions occur in a concerted or stepwise fashion.[3] In the following work, we have used dynamics analysis to examine the stereospecificity in the cycloaddition of cyclopentyne and alkenes, and we demonstrate that the probability of retaining stereochemistry is in fact time dependent, with 100% stereochemical retention occurring at short times but stereochemical scrambling being observed at longer times.

The thermal [2+2] cycloaddition of cyclopentyne with alkenes is a formally forbidden process according to the Woodward−Hoffmann rules but has nevertheless been shown experimentally to proceed in a stereospecific manner with retention of alkene geometry.[4] Various explanations have been advanced,[4b,c,5,6] and increasingly accurate electronic structure theory treatments have discredited a direct [2+2] addition mechanism.[6] The stereospecific formation (by a [2+1] cycloaddition) and rearrangement of carbene **C** (Scheme 1) has been proposed as an alternative mechanistic explanation,[6b] but there is conflicting evidence regarding whether the direct conversion of **A** to **C** is significantly lower in energy than the formation of diradical **B**.[6b−d] This diradical can itself potentially either close directly to product **P** or proceed via formation of carbene **C**, as suggested by Bachrach and Gilbert.[6c]

Scheme 1. Possible Reaction Pathways Leading to Cycloaddition with Retention or Inversion of Stereochemistry



Implicit in any mechanism involving the diradical **B**, however, is the requirement that the forward reaction of **B** must proceed faster than the rate of rotation around the C1−C2 bond (i.e., $k_{\text{B−C}}$ or $k_{\text{B−P}}$ > k_{scramble}) for the reaction to be stereospecific (i.e., to avoid formation of the stereoisomeric **P′** through **B′** and/or **C′**). Given the low barriers to torsion around the C1−C2 bond, this is far from certain. Nevertheless, in an attempt to rationalize the experimentally observed retention of stereochemistry, we have investigated this possibility.

The structures of the intermediates and transition states shown in Scheme 1 have been calculated at a CASPT2//CASSCF(6,6)/cc-pvdz model chemistry. Figure 1, which shows a 2D potential energy surface (PES) with respect to the 1−2−3 and 1−2−3−4 angles, reveals the C_s symmetry of the system and several of the minima and transition states in Scheme 1. The diradical **B** exists on a plateau region of the PES where large amplitude motion may occur on a relatively flat PES. Between the C_s related geometries of **B** is a very deep product chasm which corresponds to the cycloadduct **P**. Flanking the product chasm **P** are high energy passes containing TS-**BC** and minima corresponding to the symmetry related geometries of the carbene **C**. The calculated zero point energies for transition states TS-**AB** (linking structures **A** and **B**), TS-**BP**, and TS-**BC** lie ~100, 6, and 40 kJ mol^{-1} above the zero-point energy of **B**, while the barrier to rotation about the C1−C2 bond is less than 2 kJ mol^{-1}.

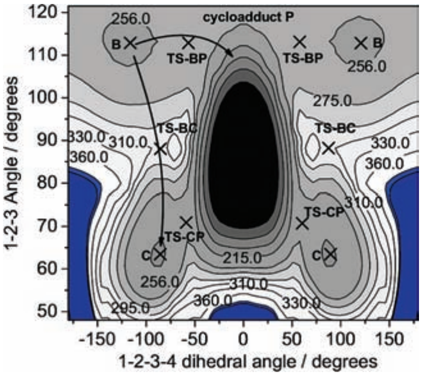


Figure 1. CASPT2//CASSCF(6,6)/cc-pvdz 2d PES.

The approximate minimum energy reaction paths are shown as arrows in Figure 1. Calculations of the rate coefficients using RRKM theory with the energy of **B** equal to 100 kJ mol^{-1} (i.e., no collisional relaxation following passage over TS-AB) give k_{scarmble} ~10^{13} s^{-1}, while k_{BP} is ~2.5×10^{12} s^{-1} and k_{BC} ~10^{9} s^{-1}. Calculations based on this statistical model using a master equation analysis give a **P**:**P′** product ratio of 56:44, corresponding to much less stereochemical retention than that observed experimentally (>99:1). The experimental results therefore appear clearly inconsistent with a statistical model.

To investigate nonstatistical effects, we carried out Born−Oppenheimer molecular dynamics using a Hessian based algorithm and the UHCTH93 functional with a reduced basis set (RBS). A careful comparison was made of the UHCTH93/RBS and CASPT2 energies over large portions of the molecular phase space by running multidimensional relaxed PES scans. 1027 trajectories were examined using local normal mode sampling at a temperature of 200 K to mimic experimental conditions. The trajectories were initiated at TS-**AB** and were run until passage via TS-**BP** or TS-**BC** occurred.

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Figure 2 shows a plot of the integrated stereochemical excess (for retention) as a function of time obtained from statistical rate theory and from the dynamics results. The former reveals a low and constant stereochemical retention excess (12%), due to TS-**BP** passage. The latter shows close to 100% retention of stereochemistry over the first 400 fs of reaction, decaying to a stereorandom process at long times (ca. 1400 fs). The origin of the short time stereochemical excess has been analyzed by examining the redistribution of energy within the complex **B** and the relaxation of the geometry following passage over TS-**AB**.

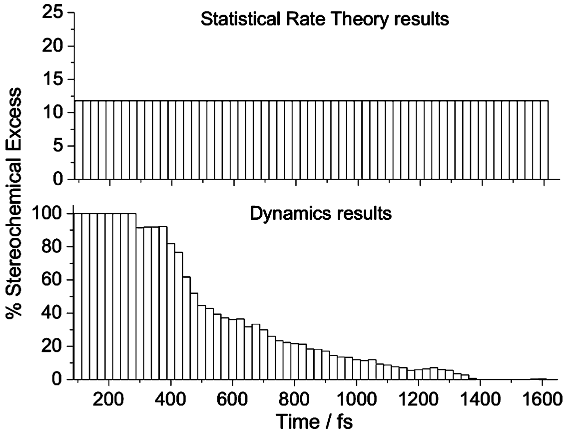

Figure 2. Comparison of time dependent stereochemical excess for retention obtained from (1) statistical rate theory and (2) dynamics results.

At short times the energy is located in the **A**−**B** reaction coordinate corresponding to the C2−C3 vibration. The lifetime for energy relaxation in this mode is ∼35 fs, which is close to its reciprocal vibrational frequency of 32 fs. A Fourier analysis shows close coupling between the C2−C3 and C1−C3 stretches; the latter, which corresponds to the reaction coordinate for carbene formation, thus has a substantial probability of containing sufficient energy to overcome the ∼40 kJ mol^{-1} energy barrier presented by TS-**BC**, over the first 400 fs.

Analysis of the time dependent evolution of the torsional coordinates show that the time scales of geometry relaxation also favor formation of **C** at short times. The initial geometry in the C1−C2 torsion, following passage over TS-**AB**, retains the stereochemical orientation of the alkene, and the loss of this orientation (by rotation about the C1−C2 bond) occurs on a time scale of ∼300 fs. On this time scale, therefore, the system has both sufficient energy and the appropriate geometry for carbene formation with retention of stereochemistry, accounting for the initial stereochemical excess shown in Figure 2. Angular relaxation about the C2−C3 torsion, which is required for barrierless passage over TS-**BP**, occurs much more slowly (i.e., on a 1−2 ps time scale) because of the heavier substituents attached to this bond. Thus, passage via TS-**BP** occurs significantly more slowly at short times before the C2−C3 torsion has relaxed.

These dynamical arguments provide an explanation of the observed short time stereochemical excess, which arises from a combination of (i) high initial energy in the C1−C3 vibration, through close coupling with the C2−C3 vibration that initially contains the excess energy following formation of **B**, and (ii) a favorable early orientation for formation of **C** with retention of stereochemistry (i.e., before C1−C2 bond rotation), coupled with a much slower angular motion to form nonstereospecific product **P** via TS-**BP**. Restated, the nonstatistical behavior of the reaction at short times (i.e., on the order of a few C−C vibrational periods) derives from fast reaction with respect to both energy and geometry relaxation.

These gas phase results show that ∼5% of the trajectories pass over TS-**BC** with stereochemical retention; however, this yield will likely be larger for the *actual* solution phase experiments, performed with 1,2-disubstituted alkenes (but-2-ene and 1-methoxyprop-1-ene). With bulkier substituents, relaxation about the C1−C2 and C2−C3 bonds will be slower, extending the time during which the geometry of **B** will be favorable to forming **C** with stereochemical retention, and this may be further enhanced by solvent friction. Carpenter has argued that experiments on diradical plateaus may only observe products from the short time dynamics;[7] this explains the observed stereochemistry and is consistent with experimental yields substantially less than unity.

Experimental verification of the behavior predicted here might be possible using stereospecifically labeled deuterated ethene, where C1−C2 rotation will be more competitive with bond formation and may lead to a lower retention of stereochemistry than that found by previous workers. The dynamics discussed herein occur on a 51 dimensional PES, but the analysis we describe above is in terms of only a few dynamical features, a more detailed description of which is in preparation. It should be possible to extend the more general principles that arise from this sort of analysis more widely within mechanistic organic chemistry and begin to qualitatively determine the likelihood of large departures from statistical rate theory in other systems.

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Supporting Information Available: Details and data pertinent to the calculations, including optimized geometries. This material is available free of charge via the Internet at http://pubs.acs.org.

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