

# Computational Evidence for Heavy-Atom Tunneling in the Bergman Cyclization of a 10-Membered-Ring Eneidyne

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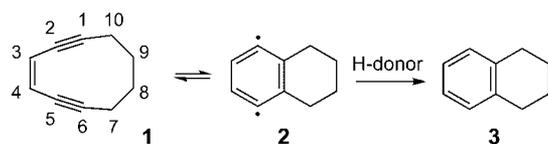
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**S** Supporting Information

**ABSTRACT:** DFT and CASSCF calculations for the cyclization of (3*Z*)-cyclodec-3-en-1,5-diyne were carried out to investigate heavy-atom tunneling. At 37 °C, tunneling was computed to enhance the rate by 38–40% over the transition-state theory rate. Intramolecular <sup>12</sup>C/<sup>13</sup>C kinetic isotope effects were predicted to be substantial, with a steep temperature dependence. These results are discussed in relation to recent experimental findings that show heavy-atom tunneling at moderate temperatures. The calculations point to the possibility of a simple computational test for the likelihood of heavy-atom tunneling using standard quantum-chemical information.

The 10-membered cyclic (3*Z*)-cyclodec-3-en-1,5-diyne **1** is a structure present in a family of antitumor antibiotics<sup>1</sup> whose mechanism of action involves Bergman cyclization<sup>2</sup> to form biradical **2** (Scheme 1). We felt that tunneling could

**Scheme 1. Bergman Cyclization of Cyclodec-3-en-1,5-diyne (1)**



contribute to this reaction because the C<sub>1</sub>–C<sub>6</sub> distance required to traverse the barrier must decrease near the transition state to a range similar to that of other reactions in which carbon tunneling is important.<sup>3</sup> One manifestation of tunneling is a curved Arrhenius plot of ln *k* versus 1/*T*, where *k* is the rate constant and *T* is the absolute temperature. In Nicolaou's study of the cyclization of **1**,<sup>4</sup> the Arrhenius plot over 310–343 K is linear with an activation energy (*E*<sub>a</sub>) of 23.8 kcal/mol. This limited temperature range gives no information on tunneling. A more sensitive experimental criterion for tunneling is the intramolecular <sup>12</sup>C/<sup>13</sup>C kinetic isotope effect (KIE), as recently shown by Borden, Singleton, and co-workers.<sup>3b</sup> If biradical trapping to form **3** is much faster than ring opening of **2**, the intramolecular KIE reflects the cyclization step. In this work, we computed rate constants and intramolecular <sup>12</sup>C/<sup>13</sup>C KIEs including tunneling over the temperature range 200–343 K.

To get an accurate density functional theory (DFT) description, we modified BLYP/6-31G(d)<sup>5</sup> by fitting the local and nonlocal exchange and correlation contributions to experimental<sup>4,6,7</sup> and computational data.<sup>8</sup> The fitting set included energies and computed geometries of stationary points for cyclization of (*Z*)-hex-3-en-1,5-diyne<sup>6–8</sup> and the experimental barrier for cyclization of **1**.<sup>4</sup> Details are given in the Supporting Information (SI). The modified functional is called mBLYP. Since the electronic configuration changes from a closed-shell reactant to a singlet biradical product, mBLYP was used with the unrestricted self-consistent field (SCF) method and a broken-spin initial guess.

After locating the stationary points (Figure 1), however, we found that mBLYP by itself was not suitable for tunneling calculations. Although mBLYP closely approximated the observed barrier, the vibrational zero-point energy (ZPE) along the intrinsic reaction coordinate (IRC) changed discontinuously by 0.3 kcal/mol at the point at which the electronic configuration changed from closed-shell to open-shell. Every DFT functional we examined (BLYP, B3LYP, BPW91, M06-2X) had this characteristic.

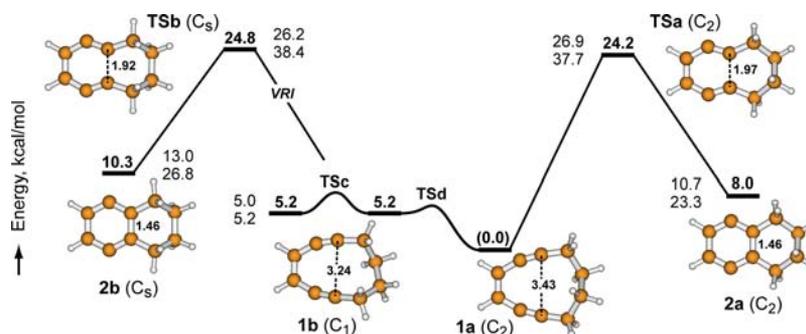
Therefore, we reoptimized the stationary points at the 10,10-CASSCF/6-31G(d) level and corrected the energies using the mBLYP/6-31G(d) and CCSD(T)/cc-pVTZ methods. The ZPE was taken from complete-active-space SCF (CASSCF) frequencies scaled by 0.91 to match the mBLYP ZPE. The mBLYP//CASSCF results (energies in bold type in Figure 1) were in close agreement with the experimental barrier. The CCSD(T)//CASSCF results (upper numbers adjacent to the mBLYP//CASSCF values in Figure 1) gave a barrier that was too high by 2 kcal/mol, and CASSCF (lower adjacent energy values) overestimated the barrier by 14 kcal/mol.

In Figure 1, two enediyne minima, **1a** and **1b**, undergo cyclization via saddle points **TSa** and **TSb** to give biradical products **2a** and **2b**, respectively. The IRC for the **1a**–**TSa**–**2a** path preserves the C<sub>2</sub> point group throughout. On the reactant side of **TSb** (C<sub>s</sub>), the IRC leads through a valley–ridge inflection (VRI) to racemic **1b** (C<sub>i</sub>) via **TSc**, the saddle point for enantiomeric interconversion of **1b**.

Tunneling calculations were carried out using POLYRATE<sup>9</sup> with the GAUSSRATE<sup>10</sup> interface to Gaussian 09.<sup>11</sup> To include CASSCF using GAMESS,<sup>12</sup> GAUSSRATE was modified to read and write GAMESS files. The three levels of theory in

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**Figure 1.** Stationary points for the Bergman cyclizations of **1a** and **1b** (point groups are shown in parentheses). Geometries were optimized at the 10,10-CASSCF/6-31G(d) level. Energies (kcal/mol) are relative to **1a** and include CASSCF vibrational zero-point energies scaled by 0.91. Energies in bold type were corrected using mBLYP/6-31G(d). In the adjacent pairs of energies, the top value was obtained with CCSD(T)/cc-pVTZ and the bottom value with CASSCF. C<sub>1</sub>–C<sub>6</sub> distances are in Å. In **TSa** and **TSb**, this distance corresponds to the maximum in the mBLYP//CASSCF intrinsic reaction coordinate, as described in the SI.

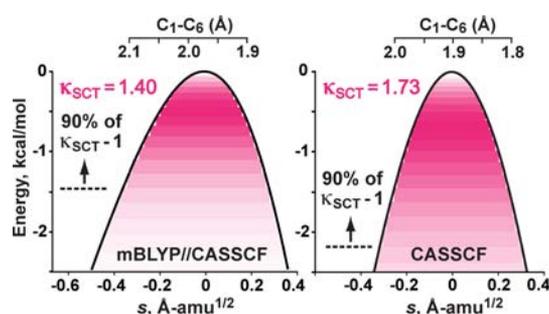
Figure 1 were used in the tunneling calculations. Multidimensional tunneling probabilities were computed with the small-curvature tunneling (SCT)<sup>13</sup> option in POLYRATE. In this method, frequencies are computed along the IRC to define the vibrationally adiabatic ground-state curve ( $V_a^G$ ), which is the IRC plus the ZPE. In the SCT method,  $V_a^G$  is the tunneling path.

In the tunneling calculations, the IRC and  $V_a^G$  curves passing through **TSa** and **TSb** were computed using CASSCF with frequencies scaled by 0.91. IRC energies were corrected at the mBLYP//CASSCF and CCSD(T)//CASSCF levels [called mBLYP and CCSD(T) below] using the variational transition-state theory with interpolated single-point energies (VTST-ISPE) method in POLYRATE. This was done by calculating mBLYP and CCSD(T) energies at 20 points along the CASSCF IRC and interpolating the full IRC at the more accurate level on the basis of these points. The  $V_a^G$  curves were then constructed by adding CASSCF ZPEs to the higher-level interpolated IRC curves. Details are described in the SI.

Tunneling calculations were carried out for the cyclizations of **1a** and **1b** with CASSCF and mBLYP and for **1a** with CCSD(T). POLYRATE computes  $k_{\text{CVT}}$ , the rate constant without tunneling, using canonical VTST (CVT). The SCT tunneling calculation gives  $\kappa_{\text{SCT}}$ , the SCT transmission coefficient, and the rate constant including SCT tunneling is given by  $k_{\text{CVT+SCT}} = \kappa_{\text{SCT}}k_{\text{CVT}}$ .<sup>14</sup>

Figure 2 shows the energy regions of the mBLYP and CASSCF  $V_a^G$  curves over which tunneling contributes to  $\kappa_{\text{SCT}}$  for cyclization of **1a** at 310 K. The color intensity of each energy slice is proportional to its contribution to the Boltzmann-weighted integral over transmission probabilities to give  $\kappa_{\text{SCT}} - 1$ . At 310 K, tunneling was computed to have a substantial effect on the rate, with  $\kappa_{\text{SCT}}$  values of 1.40 (mBLYP) and 1.73 (CASSCF). CCSD(T) gave  $\kappa_{\text{SCT}} = 1.38$  at 310 K, and its  $V_a^G$  curve was nearly superimposable on the mBLYP curve in Figure 2 (see the SI). The much higher  $\kappa_{\text{SCT}}$  for CASSCF is due to its narrower  $V_a^G$  curve compared with mBLYP and CCSD(T), which may be the result of the large CASSCF barrier.<sup>15</sup>

The information in Figure 2 is useful for a reaction like the Bergman cyclization, whose barrier is both high and wide. The wide barrier prevents tunneling at low energies. Tunneling contributes to the rate only within a specific energy range near the top of the barrier where the barrier is sufficiently narrow. Figure 2 allows one to identify that energy range, and the



**Figure 2.** mBLYP//CASSCF and CASSCF tunneling contributions to the SCT transmission coefficient  $\kappa_{\text{SCT}}$  for cyclization of **1a** at 310 K as functions of energy on the  $V_a^G$  curves. The color intensity of each energy slice is proportional to its contribution to  $\kappa_{\text{SCT}}$ , normalized to maximum intensity at the maximum contribution. Dotted lines at the left indicate the energy above which 90% of the tunneling contribution occurs. Bottom scale: mass-weighted path length  $s$  in terms of which  $\kappa_{\text{SCT}}$  was computed. Top scale: C<sub>1</sub>–C<sub>6</sub> distance in Å.

barrier widths over that range, to understand how thermally activated tunneling affects rates and KIEs as a function of temperature.

Three differences between the mBLYP and CASSCF results in Figure 2 stand out: the mBLYP curve is wider, tunneling contributes to  $\kappa_{\text{SCT}}$  over a much smaller energy range with mBLYP, and  $\kappa_{\text{SCT}}$  is smaller for mBLYP. In terms of the horizontal scales, the contribution of tunneling to  $\kappa_{\text{SCT}}$  in both curves is largely confined to energies at which the C<sub>1</sub>–C<sub>6</sub> distance (top scale) changes by <0.2 Å [or  $s$  (bottom scale) changes by <0.6 Å amu<sup>1/2</sup>] from one side of the barrier to the other. The larger value of  $\kappa_{\text{SCT}}$  computed by CASSCF is the result of a larger energy range over which the width is appropriately narrow: 2.2 kcal/mol for CASSCF versus 1.5 kcal/mol for mBLYP. The essential information in Figure 2 is that  $\kappa_{\text{SCT}}$  is sensitive to the energy range over which the barrier is narrow enough for tunneling to contribute to the rate.

A similar relation among transmission coefficient, barrier width, and energy range may be applicable to heavy-atom tunneling in other reactions as well. The form of this relation is unknown, but Figure 2 gives a rough estimate of the likely magnitudes involved. If such a relation could be established, screening an arbitrary reaction for tunneling would require only a few IRC points on either side of the saddle point. Then, if the barrier width and energy range criterion is met, the application

of POLYRATE would be warranted. Further examination of this approach is planned.

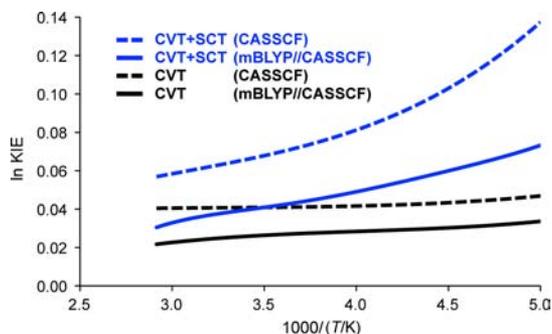
A consequence of the high barrier that widens rapidly at lower energy is that the Arrhenius plot was computed to be linear over the temperature range 200–343 K, even though 60% of the rate at 200 K is due to tunneling. A curved Arrhenius plot would require the energy range of tunneling to spread to much lower energies as the temperature is lowered. However, the widening of the barrier at lower energies restricts the tunneling range. On the energy scale of Figure 2, 90% of the mBLYP tunneling contribution to  $\kappa_{\text{SCT}}$  occurs at energies above  $-1.5$  kcal/mol at 343 K. At 200 K, this energy range expands only slightly, down to  $-2.3$  kcal/mol. There is even less change in the energy of the maximum mBLYP tunneling contribution to  $\kappa_{\text{SCT}}$ , which changes from  $-0.5$  kcal/mol at 343 K to  $-0.7$  kcal/mol at 200 K. Tunneling is suppressed below  $-2.5$  kcal/mol by the widening barrier.

The rate constant  $k$  for cyclization of an equilibrium mixture of **1a** and **1b** is given by  $k = f^a k^a + f^b k^b$ , where  $f^a$  and  $f^b$  are the mole fractions and  $k^a$  and  $k^b$  are the  $k_{\text{CVT+SCT}}$  cyclization rate constants of **1a** and **1b**, respectively. The mBLYP-computed  $f^a k^a$  value was found to constitute 68% of  $k$  at 310 K. The intramolecular KIE for  $^{13}\text{C}$  substitution at  $\text{C}_1$  versus  $\text{C}_{10}$  in an equilibrium mixture of **1a** and **1b** is defined as<sup>3b</sup>

$$\text{KIE} = \frac{k_{12\text{C}}/k_{13\text{C}} \text{ for } ^{13}\text{C}_1}{k_{12\text{C}}/k_{13\text{C}} \text{ for } ^{13}\text{C}_{10}} = \frac{k_{13\text{C}} \text{ for } ^{13}\text{C}_{10}}{k_{13\text{C}} \text{ for } ^{13}\text{C}_1} \quad (1)$$

where the rates are obtained from  $k$  for the equilibrium mixture. The KIE would be observable experimentally as the  $^{13}\text{C}$  abundance at position  $\text{C}_1$  relative to  $\text{C}_{10}$  in the trapped product **3**, provided that trapping is fast and that the measurements are carried out at low conversion or extrapolated to 0% conversion. POLYRATE calculations of isotopically substituted **1a** and **1b** were carried out by recomputing the CASSCF and mBLYP//CASSCF IRCs to get  $k^a$  and  $k^b$  for the  $^{13}\text{C}_1$  and  $^{13}\text{C}_{10}$  isotopomers. Figure 3 shows the Arrhenius plots for the KIEs computed using CVT+SCT (blue lines) and CVT (black lines) at the mBLYP//CASSCF (solid lines) and CASSCF (dotted lines) levels.

Tunneling has a large effect on the KIE. The magnitudes and slopes of the KIE curves are clearly different for CVT+SCT versus CVT. This result is qualitatively similar to that reported by Borden, Singleton, and co-workers for ring opening of cyclopropylmethyl radical.<sup>3b</sup> Because  $\text{C}_1\text{--C}_6$  motion is the largest component of the reaction path, the increase in mass at



**Figure 3.** Arrhenius plots of  $\ln \text{KIE}$  vs  $1000/T$ , where the KIE is defined in eq 1, computed using CVT+SCT (blue) and CVT (black) at the mBLYP//CASSCF (solid lines) and CASSCF (dotted lines) levels.

$\text{C}_1$  due to  $^{13}\text{C}$  substitution decreases the tunneling, and therefore the reaction rate, more than the mass increase due to  $^{13}\text{C}$  substitution at  $\text{C}_{10}$ . The CVT+SCT (blue) slopes are larger because the tunneling contribution increases at lower temperature.

We estimate that the lowest practical temperature for a KIE measurement is ca. 250 K, where  $\text{KIE} = 1.028$  (CVT) and 1.049 (CVT+SCT) as computed using mBLYP. Singleton's 95% confidence intervals for the cyclopropylmethyl case are  $\pm 0.002\text{--}0.004$ ,<sup>3b</sup> which would make the two predictions distinguishable. The mBLYP CVT+SCT slope over the range 250–343 K in Figure 3 is 2.5 times the CVT slope, which would also be distinguishable. The region of strong KIE curvature lies below 250 K.

In summary, mBLYP//CASSCF and CCSD(T)//CASSCF calculations that include multidimensional tunneling predict substantial intramolecular  $^{12}\text{C}/^{13}\text{C}$  KIEs for the cyclization of **1**. The tunneling is thermally activated, occurring mainly within 1.5 kcal/mol of the classical threshold at 37 °C [mBLYP and CCSD(T) calculations]. The result is an enhancement of the rate relative to that calculated using CVT by a factor of 1.38–1.40 at 37 °C. If the KIE predictions are confirmed experimentally, it would suggest that the efficacy of enediyne antibiotics rests partly on tunneling.

Recent studies of allylboration of aldehydes<sup>3c</sup> at  $-78$  °C and linoleic acid oxidation with soybean lipoxygenase 1<sup>3d</sup> at 21–23 °C indicate significant heavy-atom tunneling at the temperatures at which these reactions are normally carried out. In these and other studies,<sup>3</sup> the variety of reactions and temperatures suggests that heavy-atom tunneling may be much more common than previously thought, as proposed recently by Veticatt and Singleton<sup>3c</sup> and Schreiner and co-workers.<sup>3e</sup> The current calculation supports this view by showing that tunneling enhances the CVT rate of a Bergman cyclization by 38–40% at 37 °C, even though the reaction has a substantial barrier. The rate enhancement occurs within 2 kcal/mol of the transition state, where the barrier is sufficiently narrow. This observation suggests the possibility of a simple computational test for the likelihood of thermally activated heavy-atom tunneling using standard quantum-chemical information.

## ■ ASSOCIATED CONTENT

### 📄 Supporting Information

Additional computational details and complete refs 9 and 11. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

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- (14) In *POLYRATE*,  $k_{\text{CVT+SCT}} = \kappa_{\text{SCT}}\kappa_{\text{CAG}}k_{\text{CVT}}$ , where  $\kappa_{\text{CAG}}$  is a classical correction factor for  $k_{\text{CVT}}$ . In this work,  $\kappa_{\text{CAG}} \approx 0.97$ . To simplify the current discussion,  $\kappa_{\text{SCT}}$  is defined to be the product  $\kappa_{\text{SCT}}\kappa_{\text{CAG}}$  in Truhlar's notation.
- (15) A referee asked why there is no tunneling contribution to  $\kappa_{\text{SCT}}$  at the top of the barrier (white space), where the transmission probability is highest. It should be noted that  $\kappa_{\text{SCT}}$  is not the transmission probability but rather the Boltzmann-weighted integral of transmission probability over energy. The tunneling contribution to  $\kappa_{\text{SCT}}$  must go to zero at the top, where the reaction becomes classically allowed.