

Trajectory Calculations for Bergman Cyclization Predict H/D Kinetic Isotope Effects Due to Nonstatistical Dynamics in the Product

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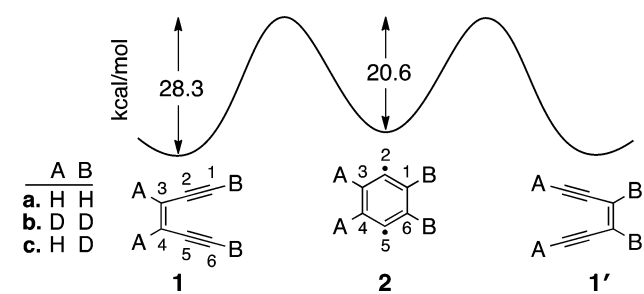
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S Supporting Information

ABSTRACT: An unusual H/D kinetic isotope effect (KIE) is described, in which isotopic selectivity arises primarily from nonstatistical dynamics in the product. In DFT-based quasiclassical trajectories of Bergman cyclization of (*Z*)-3-hexen-1,5-diyne (**1**) at 470 K, the new C₁C₆ bond retains its energy, and 28% of nascent *p*-benzynes recrosses back to the enediyne on a vibrational time scale. The competing process of intramolecular vibrational redistribution (IVR) in *p*-benzyne is too slow to prevent this. Deuteration increases the rate of IVR, which decreases the fraction of recrossing and increases the yield of statistical (trapable) *p*-benzyne, **2**. Trapable yields for three isotopomers of **2** range from 72% to 86%. The resulting KIEs for Bergman cyclization differ substantially from KIEs predicted by transition state theory, which suggests that IVR in this reaction can be studied by conventional KIEs. Leakage of vibrational zero point energy (ZPE) into the reaction coordinate was probed by trajectories in which initial ZPE in the CH/CD stretching modes was reduced by 25%. This did not change the predicted KIEs.

In studying the gas phase dynamics of the Bergman cyclization¹ of (*Z*)-3-hexen-1,5-diyne (**1**) to *p*-benzyne (**2**), Scheme 1, we found an unusual H/D kinetic isotope effect

Scheme 1. Enediyne Cyclization Energetics (ΔH^\ddagger in kcal/mol at 470 K) Computed by mBLYP/6-31G*



(KIE), in which isotopic selectivity arises from nonstatistical dynamics in the product. *para*-Benzyne is formed with ca. 20 kcal/mol of vibrational excitation, and it has two choices: (a) undergo intramolecular vibrational redistribution (IVR) to form statistical (trapable) *p*-benzyne or (b) recross back to **1** (or **1'**, a minor path at short times) on a vibrational time scale, before IVR of **2** is complete. In quasiclassical trajectory

calculations, we find that potential energy release from the transition state (TS) goes mainly into the new C₁C₆ bond of **2**, which cannot dissipate its energy fast enough to prevent recrossing. Deuteration increases the rate of IVR in **2**, which reduces the amount of recrossing. The result is a substantial predicted H/D isotope effect on the trapable yield of **2**, and a corresponding kinetic isotope effect (KIE) on the thermal cyclization rate. If confirmed by experiment, this finding would indicate that slow IVR affects the rate of Bergman cyclization under normal reaction conditions and that conventional KIEs can yield information on IVR in this reaction.

The calculations were carried out with a previously described modified BLYP density functional, mBLYP/6-31G*, parametrized to reproduce experimental and ab initio data.² Scheme 1 shows the mBLYP/6-31G* enthalpies at 470 K. Initial coordinates and momenta for the trajectories were chosen by TS normal mode sampling³ of the TS for **1** → **2** at 470 K, using a modified version of Hase's Venus program.⁴ Trajectories were integrated using Gaussian 09⁵ with the BOMD option and were stopped when enediyne **1** or **1'** was formed, with either C₁C₆ or C₃C₄ > 2.5 Å. Trajectories were retained if they conserved energy to <0.1 kcal/mol. We examined trajectories for cyclization of **1a**–**c** to **2a**–**c**.

Figure 1 shows survival probabilities for **2a**–**c**, i.e., the fraction of trajectories that remains at a given time. The zero of time is the sampled TS point. The decays are due to recrossing

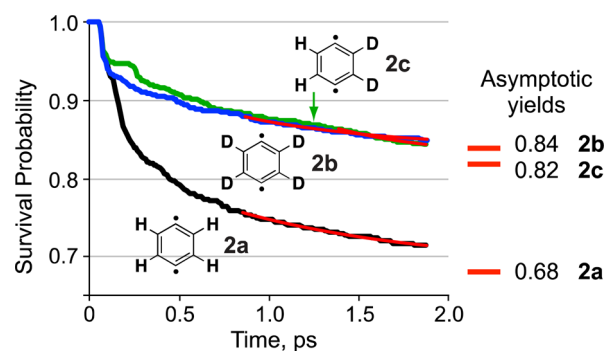


Figure 1. Survival probabilities of *p*-benzyne **2a**–**c** (fraction of **2a**–**c** remaining vs time) initialized at the TS at 470 K (**2a** black, **2b** blue, **2c** green). Decays are due to formation of **1** or **1'**. Superimposed red lines are exponential fits to the long-time regions. Yields of statistical (trapable) **2a**–**c** are given by asymptotic limits shown in red at right. These yields must be refined by the procedure in Figure 3.

Received: April 4, 2016

Published: June 13, 2016

of **2** to form **1**, and to a lesser extent **1'**. In the initial fast decay, recrossing occurs within 1 to 3 C_1C_6 vibrational cycles. During this time, vibrational energy in the remaining **2** is transferred to a few modes strongly coupled to C_1C_6 , but it is not fully redistributed. The slow decays at longer times are assumed to monitor the approach to a statistical distribution.⁶ From exponential fits at long times (superimposed red lines), the asymptotic limits give the yields of statistical, or trapable, *p*-benzynes (short red lines at right): 68%, 84%, and 82% for **2a**, **2b**, and **2c**, respectively. These yields are classical transmission coefficients, which scale the rate constants for cyclization, and they imply substantial KIEs on the thermal cyclization rate. The nearly identical asymptotic yields of **2b** and **2c** imply that the KIEs are dominated by the alkynyl hydrogens. This is not unexpected for hydrogens bound directly to the nascent C_1C_6 bond. Dynamic KIEs were first reported by Singleton,⁷ who has identified two types, Newtonian^{7b,c} and recrossing.^{7d} The present case is clearly one of the latter, in which isotopic selectivity occurs mainly in *p*-benzynes and to a smaller extent in the TS region.

In addition to KIEs, the calculation makes a prediction about the yield of **1'c**, which is distinct from **1c**. We find that 30% of recrossed **2c** forms **1'c**, equivalent to a 5% yield of **1'c** based on initial **1c**. This 5% cannot be prevented by trapping and should be measurable by extrapolation to 0% conversion.

In studies of the gas phase S_N2 reaction of $CH_3Cl + Cl^-$, Hase reported dynamics analogous to Figure 1.⁸ When CH_3Cl and Cl^- become trapped in an ion-dipole minimum, multiple recrossings over the central barrier occur between the two minima. Substitution of D for H decreases the rate of recrossings by a factor of 3.5.^{8c} Hase suggested that lower frequencies in $CD_3Cl + Cl^-$ lead to faster IVR, which decreases the recrossing rate. Computational precedent for recrossing from a deep minimum has been reported for the isomerization of vinylidene to acetylene.⁹ In classical trajectory calculations by Carter^{9a} and quantum dynamics by Schork and Köppel,^{9b} the reverse barrier of 48 kcal/mol is repeatedly recrossed to regenerate vinylidene.

The isotope effects on the trapable yields in Figure 1 are due to a phase space bottleneck to IVR in **2a** that is partly relieved in **2b** and **2c**. IVR competes with recrossing and is known to be sensitive to H/D substitution in the case of benzene.¹⁰ To explore vibrational energy transfer in **2a–c**, and the nature of the bottleneck in **2a**, we computed their normal mode energies vs time.^{11,12} One trajectory was propagated for each isotopomer, initialized at the saddle point with no vibrational energy and 0.9 kcal/mol in the reaction coordinate. Trends in energy partitioning derived from this single trajectory method have been shown to track the mean energy partitioning derived from quasiclassical simulations.^{12,13}

Figure 2 shows the energies of normal modes in **2a** and **2b** that receive most of the potential energy release in the single trajectories. The plot for **2c** is similar to **2b** and is shown in the Supporting Information (SI). In both **2a** and **2b**, the energy initially goes into the nascent C_1C_6 bond, a local mode whose energy is the sum of symmetric and antisymmetric CC stretching normal mode energies (blue and red in Figure 2). In **2a**, the energy remains in those modes for 1.4 ps. Instead of transferring energy to other modes such as CH stretches and bends, they exchange energy with each other as the hot CC bond oscillates. In contrast, the same two CC stretching modes in **2b** rapidly transfer energy to other modes, especially the CD stretches. Fermi resonances have been shown to be important

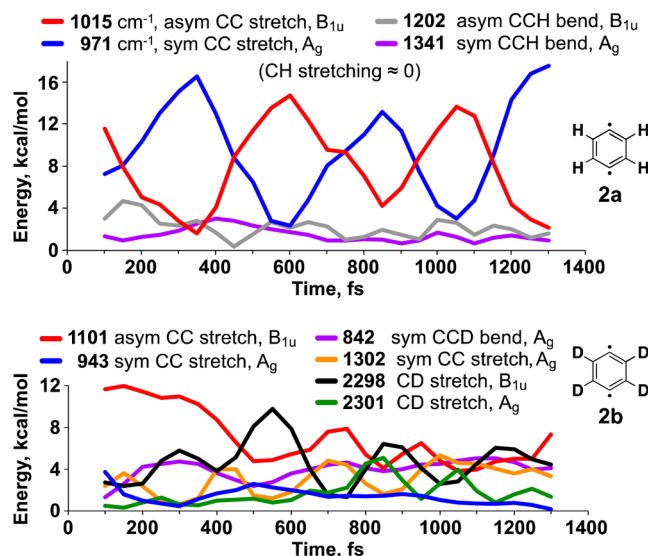


Figure 2. Prominent normal mode energies of **2a** (top) and **2b** (bottom) computed from single trajectories, initialized at the saddle point without vibrational energy and with 0.9 kcal/mol in the reaction coordinate. Frequencies are in cm^{-1} . Total vibrational energy is 23.4 kcal/mol (= potential energy release + 0.9).

in IVR of benzene.¹⁰ In that respect, a clear difference between **2a** and **2b** is the $\sim 2:1$ resonance in **2b** between the CD stretch ($\sim 2300\text{ cm}^{-1}$) and the B_{1u} CC stretch (1101 cm^{-1}), vs a less effective $3:1$ resonance between CC and CH stretching in **2a**.

To estimate the full yield of *p*-benzynes, we checked for consecutive recrossing, $2 \rightarrow 1 \rightarrow 2$. The **2a** trajectories that recrossed to **1a** and the **2b** trajectories that recrossed to **1b** were continued for up to 2 ps. The percents of regenerated **1a** and **1b** that recrossed a second time to form **2a** and **2b** were 17% and 8%, respectively (survival probabilities are shown in the SI). **2c** was not similarly examined; its second recrossing fraction is taken to be 12% (mean of 17 and 8).

Multiple recrossings $2 \rightarrow 1 \rightarrow 2$ imply that the yield of statistical **2** accumulates in repeated cycles of forward and reverse reaction. Figure 3 shows one such cycle. f is the asymptotic yield of **2** in Figure 1; f' is the fraction of $2 \rightarrow 1$ trajectories that does not recross a second time; $1 - f$ and $1 - f'$ are first and second recrossing fractions. If the same fractions

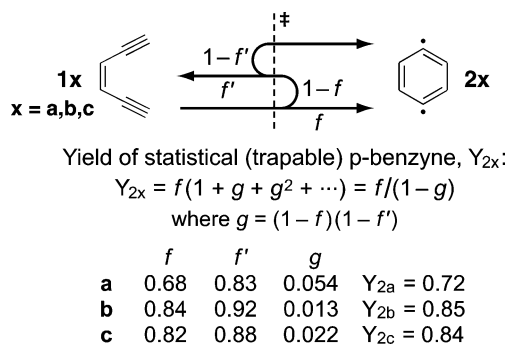


Figure 3. Correction scheme for multiple recrossings. Top: one cycle of forward/reverse motion between **1** and **2**. f = asymptotic yield of **2** from Figure 1. f and f' are nonrecrossing fractions; $1 - f$ and $1 - f'$ are recrossing fractions. Bottom: recrossing and nonrecrossing fractions and trapable yields Y_{2a} , Y_{2b} , Y_{2c} .

apply to subsequent cycles, the geometric series in Figure 3 gives the yield Y_{2x} of statistical (trapable) $2x$ ($x = a, b, c$).

Trajectory-based KIEs are given by

$$\text{KIE}(a/b)_{\text{Traj}} = (Y_{2a}/Y_{2b}) \text{KIE}(a/b)_{\text{CVT}}$$

$$\text{KIE}(a/c)_{\text{Traj}} = (Y_{2a}/Y_{2c}) \text{KIE}(a/c)_{\text{CVT}}$$

where Y_{2a}/Y_{2b} and Y_{2a}/Y_{2c} are the ratios of trapable yields and $\text{KIE}(a/b)_{\text{CVT}}$, $\text{KIE}(a/c)_{\text{CVT}}$ are the H/D KIEs computed by canonical variational transition state theory (CVT).¹⁴ For the latter calculation we used Polyrate¹⁵ with the Gaussrate¹⁶ interface to Gaussian 09. At 470 K, $\text{KIE}(a/b)_{\text{CVT}} = 0.93$ and $\text{KIE}(a/c)_{\text{CVT}} = 0.92$; trajectory-based KIEs are $\text{KIE}(a/b)_{\text{Traj}} = (0.72/0.85) 0.93 = 0.79$, and $\text{KIE}(a/c)_{\text{Traj}} = (0.72/0.84) 0.92 = 0.79$. These results are shown in the second column of Table 1. They predict that KIEs based on CVT are substantially altered by H/D-dependent IVR in *p*-benzynes.

Table 1. Trapable Yields of 2a, 2b, 2c and KIEs for 1 → 2^a As a Function of Initial CH/CD Stretching ZPE; Y_{2a} and Y_{2b} at 500 fs

	100% ZPE	75% ZPE ^b
2a trapable yield, Y_{2a}	0.72 ± 0.02 ^{c,d}	0.76 ± 0.03 ^{d,e}
2b trapable yield, Y_{2b}	0.85 ± 0.02 ^{c,d}	0.90 ± 0.03 ^{d,e}
2c trapable yield, Y_{2c}	0.84 ± 0.02 ^{c,d}	–
Y_{2a}/Y_{2b}	0.85 ± 0.04	0.85 ± 0.06
Y_{2a}/Y_{2c}	0.86 ± 0.04	–
$\text{KIE}(a/b)_{\text{Traj}}$	0.79 ± 0.04	0.79 ± 0.06
$\text{KIE}(a/c)_{\text{Traj}}$	0.79 ± 0.04	–
At 500 fs		
Survival prob. for 2a	0.79	0.79
Survival prob. for 2b	0.90	0.92

^aFast thermal trapping of statistical 2 is assumed. ^bInitial CH/CD stretching ZPE reduced by 25%. ^cFrom Figures 1 and 3. ^dVariances are 95% binomial confidence intervals. ^eAsymptotic yields as in Figure 1, corrected for multiple recrossing.

In quasiclassical simulations, vibrational zero-point energy (ZPE) can flow into the reaction coordinate to create spurious results. To investigate the possibility that the KIEs are artifacts of ZPE leakage, we focus on the 4 CH/CD stretching modes, which comprise 40% of the ZPE. IVR involving excited CH stretches of benzene is well documented.^{10,17} Direct measurement of ZPE leakage is impractical,¹⁸ but we can measure the response of trapable yields and KIEs to a reduction of the initial ZPE of the CH/CD stretching modes. If ZPE leakage from CH/CD stretching is required for recrossing, then a reduction of initial CH/CD ZPE should give a reduced recrossing yield, $1 - Y_{2a,b}$. To examine this, we chose to reduce the CH/CD ZPE by an amount at least as large as the mean kinetic energy in the reaction coordinate at the time of recrossing, E_{RC} . For 2a, $E_{\text{RC}} = 2.1 \pm 2.0$ kcal/mol (± 1 standard deviation), and for 2b $E_{\text{RC}} = 1.9 \pm 2.0$ kcal/mol. A reduction of CH/CD ZPE by 25% would decrease the initial ZPE of 2a and 2b by 4.6 and 3.4 kcal/mol respectively, in each case greater than E_{RC} .¹⁹

We initialized trajectories for 2a and 2b by TS normal mode sampling at 470 K with 75% ZPE in the 4 CH/CD stretching modes (all other modes with full ZPE) and ran them for 2 ps. Results are shown in the third column of Table 1, corrected for multiple recrossings with f' values from Figure 3. The effect of ZPE on recrossing is best discussed in terms of recrossing yields $1 - Y_{2a}$ and $1 - Y_{2b}$. Relative to 100% ZPE, recrossing yields

with 75% ZPE are 14% lower for 2a (24% vs 28% recrossing) and 29% lower for 2b (10% vs 14% recrossing). CH/CD ZPE leakage therefore occurs in both, to a larger extent in 2b than 2a. Nevertheless, the KIE value of 0.79 is unchanged by lowering the ZPE, consistent with a KIE that is not an artifact of ZPE leakage.

Table 1 also shows survival probabilities for 2a and 2b at 500 fs, which gives information on the rate of ZPE leakage. For 2a, lowering the ZPE has no effect on recrossing; by this measure ZPE leakage in 2a is negligible at 500 fs. For 2b, however, lowering the ZPE reduces the recrossing fraction at 500 fs from 10% to 8% in Table 1, a 20% reduction, indicating faster ZPE leakage in 2b than 2a. This, as well as the isotope effects on trapable yields of 2, both derive from the stronger coupling of reaction coordinate motion with CD stretching than with CH stretching shown in Figure 2.

The effect on E_{RC} of reducing the ZPE is small to negligible: with 75% ZPE, E_{RC} is 1.8 ± 1.8 kcal/mol for 2a and 1.9 ± 1.9 kcal/mol for 2b. Despite the removal of several kcal/mol of CH/CD stretching ZPE, 2a and 2b still have about the same amount of energy available for recrossing.

In preliminary results for other Bergman cyclizations, we found 50% recrossing in 2 ps for cyclization of 1,2-diethynylbenzene, 30% recrossing in 850 fs for 2,3-diethynylpyridine, and 10% recrossing in 350 fs for cyclonon-3-en-1,5-diyne. KIEs have not yet been examined. A reviewer asked how solvent would change the results. We expect collisions with solvent to reduce recrossing but not eliminate it. Simulations with explicit solvation are planned.

In summary, the rate of IVR can affect the competitive balance between reaction paths. In the current example, slow IVR is predicted to affect the product yield, giving rise to a KIE. A phase space bottleneck to IVR in 2a is identified in Figure 2 by the weak coupling of the reaction coordinate to other modes. The predicted KIEs of 0.79 would be readily distinguishable from the KIEs of 0.93 and 0.92 predicted by CVT. Trajectories were also computed with CH/CD stretching ZPE reduced by 25%. The reduced ZPE results serve both as a test for the presence of ZPE leakage and as a partial correction for it,¹⁹ by removing some of the initial ZPE that would later be leaked. ZPE leakage from CH/CD modes is detected in these calculations, but it does not appear to contribute in a crucial way to the KIEs, which remain unchanged when ZPE is reduced by several kcal/mol.

■ ASSOCIATED CONTENT

📄 Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b03466.

Full refs 5 and 15, computational details and procedures (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the National Science Foundation for financial support, Grants CHE-1213976 and CHE-1465040. For

computational support, we acknowledge Grant TG-CHE09007 from XSEDE on Gordon at SDSC.

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