

Figure 1. ORTEP drawing of the SCF/6-31G\* transition structure. Arrows show motion in the normal mode of imaginary frequency.

of diastereotopically distinct secondary deuterium kinetic isotope effects for a prototypical concerted pericyclic reaction, the thermal isomerization of hexa-1,3Z,5-triene (**1**) to 1,3-cyclohexadiene (**2**);<sup>4</sup> these effects, which have been uncovered in both experimental and theoretical work, point toward a more detailed level of understanding of such reactions and transition-state structures.

The stereospecifically deuterium-labeled hexatrienes **3** and **4** were prepared from hex-3Z-en-1,5-diyne.<sup>5</sup> Hydroboration using disiamylborane followed by deuterionolysis with CH<sub>3</sub>COOD<sup>6</sup> gave the 1E,5E-<sup>2</sup>H<sub>2</sub> isomer **3**, while exchange of the acetylenic hydrogens in the enediyne<sup>7</sup> using NaOD/D<sub>2</sub>O in di(2-ethoxyethyl) ether, followed by hydroboration and protonolysis, provided the 1Z,5Z-<sup>2</sup>H<sub>2</sub> triene **4**. The <sup>1</sup>H NMR spectra of these trienes show the C1,6 protons in **3** as a doublet ( $J = 16.7$  Hz) at 5.24 ppm, while in **4** the doublet for C1,6 protons ( $J = 10.1$  Hz) is seen at 5.15 ppm.

Competitive thermal isomerizations of hexa-1,3Z,5-triene **1** and the deuterium-labeled analogues **3** or **4** were run in the gas phase in a conditioned 1-L Pyrex bulb at 140 °C; analyses of reaction mixtures at given times by GC/MS gave  $m/e$  80/82 data as functions of time, from which [1]/[3] and [1]/[4] ratios and relative rate constants were readily derived.<sup>2</sup> The secondary isotope effects ( $k_H/k_D$ ) for the electrocyclic reactions of **3** and **4** are  $1.05 \pm 0.03$  and  $0.88 \pm 0.02$ , respectively. Diastereotopically distinct hydrogens in starting material **1** manifest different secondary deuterium isotope effects on the rate of electrocyclic isomerization.

In order to gain a better understanding of these remarkable secondary isotope effects, ab initio SCF/6-31G\* calculations were performed with the program CADPAC<sup>8</sup> on an SCS 40 computer. The triene **1** was found to be nonplanar ( $C_2$  symmetry) in the s-cis,s-cis conformation. The  $C_s$ -symmetric transition structure for this disrotatory ring closure was located (Figure 1).<sup>9</sup> Ab initio force constants were computed, then scaled<sup>10</sup> by 0.8, and used to compute vibrational frequencies which in turn gave theoretical secondary isotope effects at 140 °C (no tunneling) of 1.00 for **3** and 0.87 for **4**. Use of Bell's tunneling correction as applied by Saunders<sup>11</sup> increased these to 1.01 for **3** and 0.88 for **4**, in reasonable agreement with experiment.

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Diastereotopically distinct secondary deuterium kinetic isotope effects imply diastereotopically distinct changes in force constants between ground and transition states, which may be associated either with different changes in hybridization or with different changes in nonbonded interactions.<sup>12</sup> From the geometry of **1** and of the transition structure (Figure 1) and the relationship  $\lambda_i \lambda_j \cos \theta_{ij} = -1$ , one may conclude that the  $\pi$  orbitals at C1 and C6 in the transition state remain of high p character (93%) and that the hybrid orbitals from C to A and B hydrogens experience approximately equal changes in hybridization from ground state to transition state. But as the geometry and the normal mode of imaginary frequency (Figure 1) emphasize, A and B hydrogens are associated with very different stereochemical environments in the transition structure, and the A hydrogens may be subject to a substantially greater degree of steric crowding. An increase in intramolecular nonbonding interactions on passage to the transition state may increase force constants for the A hydrogens and give rise to the inverse  $k_H/k_D$  effect observed.

Such electrocyclic reactions involve more than a simple rotation of the two methylene groups and a change in hybridization of C1 and C6. The calculated transition structure and the different rates of cyclization shown by **3** and **4** underscore the fact that progress toward C-C bond formation in the transition state is associated with different roles played by the diastereotopically distinct C-H(A) and C-H(B) bonds.

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### Diastereotopically Distinct Secondary Deuterium Kinetic Isotope Effects on the Thermal Isomerization of Cyclobutene to Butadiene

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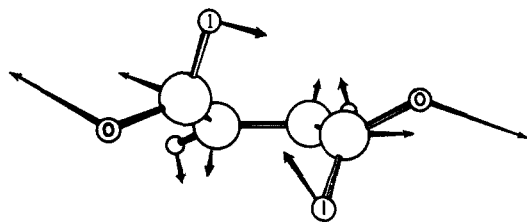
The thermal isomerization of cyclobutene to butadiene, the prototypical electrocyclic reaction first subjected to orbital symmetry based theoretical scrutiny,<sup>1-3</sup> involves a conrotatory process, a distortion from planarity in the carbon skeleton, and sundry rehybridizations; it still attracts substantial calculational attention.<sup>4</sup>

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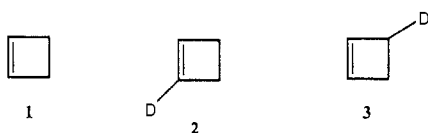


**Figure 1.** ORTEP drawing of the MP2/6-31G\* transition structure. The letters I and O label the hydrogens described in the text as "inner" and "outer", respectively. Arrows show motion in the normal mode of imaginary frequency.

Details of transition-state structures and thus of reaction mechanisms for pericyclic reactions may be probed experimentally through determinations of primary and secondary deuterium kinetic isotope effects.<sup>5-8</sup> This approach, however, has not been fully exploited, for stereochemical subtleties have usually been neglected. In the cyclobutene to butadiene conversion, for instance, the cis and trans isomers of [3,4-<sup>2</sup>H<sub>2</sub>]cyclobutene were found to undergo electrocyclic ring openings at nearly equal rates, with  $k_{\text{H}}/k_{\text{D}} = 1.22$  and 1.21, respectively, at 139.5 °C.<sup>9</sup> It was inferred, then, that  $k_{\text{H}}/k_{\text{D}} = 1.10$  per deuterium and that the cis or trans disposition of deuterium atoms could be excluded as a major factor in determining  $k_{\text{H}}/k_{\text{D}}$ .<sup>9</sup>

Yet, in view of the C<sub>2</sub> symmetry of the transition state structure for the isomerization of cyclobutene, one may anticipate that the substitution of deuterium for the cyclobutene C3-H rotating in, or for the C3-H rotating out, could well be associated with different  $k_{\text{H}}/k_{\text{D}}$  effects,<sup>8</sup> though enantiotopic in the ground state, these methylene hydrogens are diastereotopic in the transition state structure and hence no longer equivalent.

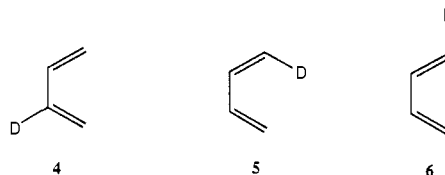
This possibility has now been addressed experimentally by preparing and following the gas-phase isomerizations of cyclobutene (1), [1-<sup>2</sup>H]cyclobutene (2), and [3-<sup>2</sup>H]cyclobutene (3).



1-Deuteriocyclobutene (2) was obtained from cyclobutanone<sup>10</sup> through LiAlD<sub>4</sub> reduction, conversion of the resultant alcohol to its tosylate ester, and elimination<sup>11</sup> of *p*-toluenesulfonic acid with potassium *tert*-butoxide in DMSO. A 1:4 mixture of 2:3 was made from cyclopropanecarboxaldehyde, via LiAlD<sub>4</sub> reduction, an acid-catalyzed isomerization<sup>10</sup> to yield isomeric 2-deuteriocyclobutanols, the corresponding crystalline 2-naphthalenesulfonates, and an elimination using potassium *tert*-butoxide/DMSO.

The competitive isomerizations of 1 and 2 at 140.0 °C in the gas phase were followed by GC/MS: the concentration ratio [1]/[2] remained 0.868 ± 0.005 over 336 min (six analyses, 2.6 half-lives), so the  $k_{\text{H}}/k_{\text{D}}$  effect at C1 is negligible. The competitive first-order isomerizations of 2 and 3 were followed by <sup>2</sup>H NMR<sup>12</sup> over 304 min (six analyses, more than two half-lives); the rate

constants derived were  $k(2 \text{ to } 4) = 8.93 \times 10^{-5} \text{ s}^{-1}$  and  $k(3 \text{ to } (5 + 6)) = 8.17 \times 10^{-5} \text{ s}^{-1}$ . The [6]/[5] ratio in the product mixture, equivalent to the ratio of <sup>2</sup>H NMR signal intensities at δ 5.15 and 5.25 ppm,<sup>13</sup> was 0.908 ± 0.042; hence  $k_{\text{H}}/k_{\text{D}} = 1.04 \pm 0.03$  for the reaction 3 to 5 and 1.15 ± 0.03 for 3 to 6.



These kinetic results agree, within probable experimental uncertainties, with Honig's earlier study,<sup>9</sup> for the cis isomer of [3,4-<sup>2</sup>H<sub>2</sub>]cyclobutene, according to the present work, should isomerize with  $k_{\text{H}}/k_{\text{D}} = (1.04)(1.15) = 1.20$ , while the trans analogue should exhibit  $k_{\text{H}}/k_{\text{D}} = 2/(1.15^{-2} + 1.04^{-2}) = 1.19$ . The observed near equality of overall  $k_{\text{H}}/k_{\text{D}}$  values for the isomerizations of [3,4-<sup>2</sup>H<sub>2</sub>]cyclobutene isomers may obscure but does not conflict with the diastereotopically distinct  $k_{\text{H}}/k_{\text{D}}$  effects now discovered.

SCF/3-21G, SCF/6-31G\*, and MP2/6-31G\* computations of the structure of cyclobutene and the conrotatory transition state structure were carried out on a SCS 40 computer with the CADPAC program.<sup>14</sup> Vibrational frequencies were computed for these systems and their isotopomers with ab initio force constants scaled by a factor of 0.8. These frequencies were used to compute "semiclassical" kinetic isotope effects to which Bell's tunnel correction was applied<sup>8</sup> to give, in the MP2/6-31G\* approximation,  $k_{\text{H}}/k_{\text{D}} = 1.05$  for the reaction of 3 to 5 and 1.12 for 3 to 6, in fair agreement with the experimental observations above.

Correlations between hybridization changes and secondary  $k_{\text{H}}/k_{\text{D}}$  values,<sup>15</sup> and the observed diastereotopically distinct  $k_{\text{H}}/k_{\text{D}}$  effects, suggest that the two cyclobutene C3-H bonds may have substantially different hybridizations at the transition state. From the geometrical description of the conrotatory transition state structure provided by ab initio calculations at the MP2/6-31G\* level (Figure 1), and the relationship  $\lambda_i \lambda_j \cos \theta_{ij} = -1$ , one may conclude that the π orbital at C3 is almost pure p (97% p character), while the diastereotopically distinct C3-H bonds are of 74% (inner H) and 68% (outer H) p character. The former C3-H hybrid has experienced only about a fourth of the overall change in hybridization associated with the reaction, while the latter has realized nearly all of the overall change in hybridization. The timing of rehybridization for the diastereotopically distinct methylene hydrogens is indeed markedly different, as one might have anticipated.<sup>16</sup>

Further joint experimental and theoretical studies of isotopic effects on pericyclic reactions are in progress.

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