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Thermal Disrotatory Electrocyclic Isomerization of *cis*-Bicyclo[4.2.0]oct-7-ene to *cis,cis*-1,3-Cyclooctadiene

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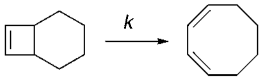
ABSTRACT

The ratio of observed rate constants, *k*/*k*′, for thermal isomerizations of *cis*-bicyclo[4.2.0]oct-7-ene and its 2,2,5,5-d_4 analogue to *cis*,*cis*-1,3-cyclooctadienes at 250 °C is 1.17, indicative of a secondary, not a primary, deuterium kinetic isotope effect. The reaction does not occur through a [1,5] hydrogen shift from the transient *cis*,*trans*-1,3-cyclooctadiene intermediate to form the observed *cis*,*cis*-diene product.

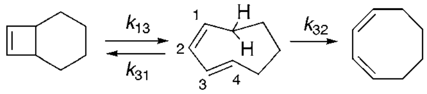
The thermal conversion of *cis*-bicyclo[4.2.0]oct-7-ene (**1**) to *cis*,*cis*-1,3-cyclooctadiene (**2**) (Scheme 1) was first reported in 1965.[1] The uncertainties associated with possible mechanisms for this transformation have been widely recognized but never resolved. They now may be laid to rest.

Scheme 1



The valence isomerization of **1** to **2** was conceded immediately to be possibly a borderline case.[1] While the observed product clearly corresponded to an overall disrotatory outcome for the electrocyclic process, it was thought not impossible, or not unthinkable, that the less stable *cis*,*trans*-1,3-cyclooctadiene (**3**) might be the primary product, one that was converted spontaneously under the thermal reaction conditions to the more stable *cis*,*cis*-diene **2**, as outlined in Scheme 2.[1]

Scheme 2



This mechanistically ambiguous conversion attracted considerable attention over the next few years. Gas-phase kinetic work on the isomerization of **1** to **2** provided reliable activation parameters for the overall reaction characterized by rate constant *k*.[2] Equilibrium constants for the bicyclic

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[1] Criegee, R.; Seebach, D.; Winter, R. E.; Börretzen, B.; Brune, H. A. *Chem. Ber*. **1965**, *98*, 2339−2352.

[2] Branton, G. R.; Frey, H. M.; Skinner, R. F. *Trans. Faraday Soc.* **1966**, *62*, 1546−1552.

10.1021/ol040022g CCC: $27.50

cyclobutene **1** and the *cis*,*trans*-diene **3**, $K_{eq} = [\mathbf{1}]/[\mathbf{3}]$, over a range of temperatures were measured, and kinetic work on the rearrangement of **3** to **1** in dilute benzene solutions at six temperatures between 64 and 90 °C defined activation parameters for k_{31}.[3] Together, the equilibrium and rate data allowed one to define activation parameters for k_{13} as well. Further, it was suggested that an isomerization of **3** to **2** might take place through a [1,5] hydrogen sigmatropic shift.[3] Thus, the apparent disrotatory opening of **1** to **2** might actually take place through a process involving first an orbital symmetry-allowed conrotatory opening of **1** to form **3**, followed in a second step by a [1,5] shift to convert **3** to **2**.

This interpretation has been much discussed and generally viewed as a real possibility, but not as an established mechanistic understanding. It was recognized that before a mechanistic choice might be made, "further experiments are necessary."[3] While the indirect mechanism from **1** to **2** by way of intermediate **3** "has much to recommend it, the possibility that the isomerization" of **1** to **2** "may proceed directly cannot be ruled out."[4] The hydrogen shift mechanism seems "permissible, if not operative",[5] but it would require a small positive $\Delta S^{\ddagger}$, hardly an expected characteristic.[6]

Just why this mechanistic conundrum has not been settled is largely dependent on two circumstances or difficulties. Neither is related to kinetic complexities, for the kinetic situation relevant to the mechanistic problem is simple. Exact integrated mole fraction versus time expressions corresponding to Scheme 2 are well-known,[7] and when, as here, a steady-state treatment is appropriate ($k_{31} \gg k_{32}$), one has $k = (k_{13}/k_{31})k_{32}$ (if $k_{12} = 0$). The first difficulty is posed not by kinetic complexity but rather by the relative magnitudes of k, k_{13}, k_{31}, k_{12}, and k_{32} (if $k_{12} = 0$).

The rate constants defined experimentally for the reactions involved (eqs 1−3), [2−4] or that would be involved if k_{32} were equal to $k(k_{31}/k_{13})$ (eq 4),[4] are such that the equilibrium between **1** and **3** will be established much faster than any appreciable amount of **2** will be formed whether $k = k_{12}$ or $k = (k_{13}/k_{31})k_{32}$.

$$\log k = 14.13 - 43\,180/(2.303RT) \tag{1}$$

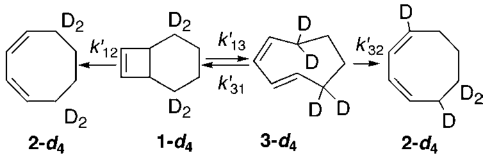
$$\log k_{31} = 13.14 - 27\,850/(2.303RT) \tag{2}$$

$$\log k_{13} = 13.3 - 33\,450/(2.303RT) \tag{3}$$

$$\log k_{32} = 14.0 - 37\,600/(2.303RT) \tag{4}$$

At 523 K (250 °C), for example, experimental data[3] may be extrapolated to give the estimates $[\mathbf{1}]/[\mathbf{3}]\mathrm{eq} = 315$, $k_{13} = 2.1 \times 10^{-1}\ \mathrm{s}^{-1}$, and $k_{31} = 32\ \mathrm{s}^{-1}$. The rate constant ($k_{13} + k_{31}$) for approach to equilibrium between **1** and **3** is about 2.6×10^{5} times faster than $k = k_{12}$ (if k_{32} is zero) or $(k_{13}/k_{31})k_{32}$ (if k_{12} is zero). Thus, whether **1** or **3** is the starting material, the initial rate of formation of **2** will be identical, within plausible analytical limits. The question of whether **2** forms from **1** or from **3** cannot be answered readily through kinetic approaches. Distinctions dependent on detecting different initial rates of product formation starting from different initial reactants[8] would, in the present instance, be extremely demanding or even altogether impractical.

Scheme 3



The second difficulty follows from the fact that simple deuterium labeling studies dependent upon detecting just where a label initially in **1** appears in thermal product **2** cannot resolve the mechanistic question. The [1,5] hydrogen shifts in diene **2** will redistribute label(s) orders of magnitude faster than the rate at which **1** gives **2** through either mechanism. At 250 °C, for example, the rate constant for a [1,5] hydrogen migration in **2** is some 200 times faster than k, the phenomenological rate constant for the conversion of **1** to **2**.[9,10]

The present work approached this refractory mechanistic problem anew. An experimental distinction between a direct disrotatory path leading from **1** to **2** in the rate-determining step and an indirect path through a rate-determining isomerization of **3** to **2** through a [1,5] hydrogen shift was sought.

The distinction was pursued through a determination of a deuterium kinetic isotope effect. Were the starting material labeled with deuterium atoms at C2 and C5, as in Scheme 3, the k_{32}/k'_{32} ratio would reflect a large primary deuterium kinetic isotope effect. Relevant precedent is available: the [1,5] hydrogen shifts in 1,3,6-cyclooctatriene and in *cis*-1,3-pentadiene are characterized by k_H/k_D values of 5.0 at 120 °C and of 5.1 at 200 °C, respectively.[11] In the alternative rate-determining disrotatory process, with $k = k_{12}$, k_{12}/k'_{12} would show only a modest secondary deuterium kinetic isotope. The distinct anticipated isotope effects would reflect structural changes at the transition state region of the potential energy surface. They would not be obscured by subsequent rapid [1,5] hydrogen shifts equilibrating all possible deuterium-labeled *cis*,*cis*-1,3-cyclooctadienes.

Unlabeled bicyclo[4.2.0]oct-7-ene was prepared through two routes. Photoisomerization of *cis*,*cis*-1,3-cyclooctadiene

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[3] (a) McConaghy, J. S.; Bloomfield, J. J. *Tetrahedron Lett.* **1969**, 3719−3721. (b) Bloomfield, J. J.; McConaghy, J. S. *Tetrahedron Lett.* **1969**, 3723−3726.

[4] Cocks, A. T.; Frey, H. M. *J. Chem. Soc. B* **1970**, 952−954.

[5] Marvell, E. N. *Thermal Electrocyclic Reactions*; Academic Press: New York, 1980; pp 171−173.

[6] Gajewski, J. J. *Hydrocarbon Thermal Isomerizations*; Academic Press: New York, 1981; pp 281−282.

[7] For example, see: McDaniel, D. H.; Smoot, C. R. *J. Phys. Chem.* **1956**, *60*, 966−969.

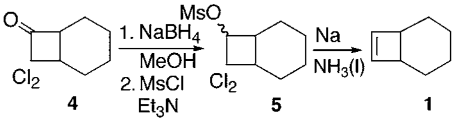
[8] Baldwin, J. E.; Kaplan, M. S. *J. Am. Chem. Soc.* **1972**, *94*, 4696−4699.

[9] Glass, D. S.; Boikess, R. S.; Winstein, S. *Tetrahedron Lett.* **1966**, 999−1008.

[10] Baldwin, J. E.; Leber, P. A.; Lee, T. W. *J. Org. Chem.* **2001**, *66*, 5269−5271

[11] (a) Kloosterziel, H.; ter Borg, A. P. *Recl. Trav. Chim. Pays-Bas* **1965**, *84*, 1305−1314. (b) Roth, W. R.; König, J. *Liebigs Ann. Chem.* **1966**, *699*, 24−32. (c) Roth, W. R. *Chimia* **1966**, *20*, 229−236.

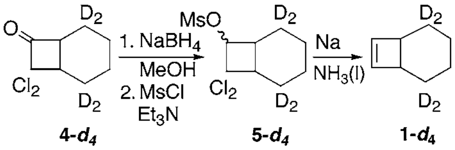
Scheme 4



in heptane in the presence of acetophenone as a sensitizer, followed by preparative GC isolation, gave an authentic sample.[12] It was also secured from cyclohexene using the route outlined in Scheme 4, as a run-through for analogous sequences affording labeled analogues. Following Greene and co-workers,[13] and syntheses of various deuterium-labeled bicyclo[3.2.0]hepta-2,6-dienes developed by Belfield,[14] the cycloadduct of dichloroketene with cyclohexene, 8,8-dichlorobicyclo[4.2.0]octan-7-one (**4**), was reduced with $NaBH_4$ and the epimeric mixture of alcohols produced was converted to the corresponding mesylates (**5**). Reduction of the mesylates with sodium in liquid ammonia afforded the bicyclic olefin **1**, identical to the authentic reference sample. The proton-decoupled carbon-13 spectrum had absorptions at δ 140.5, 41.5, 24.8, and 18.8.

Starting with 3,3,6,6-d_4-cyclohexene, the cycloaddition with dichloroketene generated from trichloroacetyl chloride and zinc in ether, with sonication,[15] gave **4-d_4** (Scheme 5).

Scheme 5



This intermediate was converted using the three-step sequence utilized in Scheme 4 by way of **5-d_4** to give **1-d_4**. Following isolation and purification by preparative GC, its identity was confirmed through its NMR and mass spectroscopic characteristics. The ^{2}H NMR spectrum showed the two types of deuterium atoms as singlets at δ 1.67 and 1.48; the broad-band proton-decoupled carbon-13 spectrum had the expected resonances at δ 140.5, 41.3, and 18.6.

Kinetic runs were conducted using a gas-phase static reactor, an associated vacuum system, and temperature control and measurement instrumentation that have been detailed elsewhere.[16] The isomerizations of **1** and of **1-d_4** were followed simultaneously, thus eliminating any possibility that different samples might be subjected to slightly different reaction conditions of any sort. Conveniently enough, it turned out that unlabeled and d_4-labeled starting materials and products separated sufficiently well on a HP Ultra 2 25 m × 0.2 mm × 0.33 μm cross-linked 5% phenyl methyl siloxane GC column so that reliable integrated peak intensities could be measured (Figure 1). The retention times of the unlabeled and d_4-labeled bicyclooctene and *cis,cis*-diene isomers at 40 °C differed by 12 s. In each pair of isotopomers, the d_4-labeled sample had the shorter retention time, as determined by GC/MS.

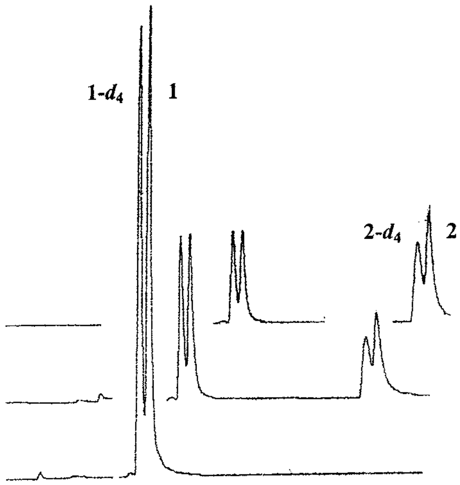


Figure 1. Capillary GC traces of a 54:46 mixture of **1** and **1-d_4** at $t = 0$ and of mixtures of **1** and **1-d_4** with thermal products **2** and **2-d_4** at $t = 2192$ and 5112 s (off-set back and to the right). The retention times from the left are 9.45, 9.65, 12.94, and 13.14 min; cyclooctane (at 15.34 min) is not shown.

The kinetic data secured for runs starting from a 54:46 mixture of **1** and **1-d_4**, 2,2-dimethylbutane as a bath gas, and cyclooctane as an internal standard are recorded in Table 1.

Table 1. Mole Percent Relative Concentration Data for *cis*-Bicyclo[4.2.0]oct-7-ene (**1**) and 2,2,5,5-d_4-Bicyclo[4.2.0]oct-7-ene (**1-d_4**) at 249.9 °C as Functions of Reaction Time

time (s)	**1** (%)	**1-d_4** (%)
0	100.0	100.0
2192	77.5	83.9
5112	53.2	60.5
9000	36.1	41.0
16 041	16.8	19.0

From these data, least-squares best-fit calculations provided overall rate constants $k = 1.16 \times 10^{-4}$ s^{-1} and $k' = 0.99 \times 10^{-4}$ s^{-1}. The k/k' ratio is 1.17. The substantial primary effect anticipated for a rate-determining [1,5] hydrogen shift converting **3** to **2** and **3-d_4** to **2-d_4** with rate constants k_{32} and k'_{32} was not observed. The measured k/k'

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[12] (a) Chappell, S. F.; Clark, R. F. *Chem. Ind. (London)* **1962**, 1198. (b) Dauben, W. G.; Cargill, R. C. *J. Org. Chem.* **1962**, *27*, 1910. (c) Srinivasan, R. *J. Am. Chem. Soc.* **1962**, *84*, 4141−4145.

[13] Greene, A. E.; Luche, M. J.; Serra. A. A. *J. Org. Chem.* **1985**, *50*, 3957−3962.

[14] Baldwin, J. E.; Belfield, K. D. *J. Org. Chem.* **1987**, *52*, 4772−4776.

[15] Mehta, G.; Rao, H. S. *Synth. Lett.* **1985**, *15*, 991−1000.

[16] (a) Baldwin, J. E.; Burrell, R. C. *J. Org. Chem.* **1999**, *64*, 3567−3571. (b) Baldwin, J. E.; Burrell, R. C. *J. Org. Chem.* **2002**, 67, 3249−3256.

value is completely consistent with expectations for a small β secondary deuterium kinetic isotope effect on direct **1**-to-**2** and **1-*d*$_4$**-to-**2-*d*$_4$** reactions.

The direct disrotatory electrocyclic isomerization of **1** to **2** (E_a = 43.2 kcal/mol) requires about 10 kcal/mol more activation energy than the conrotatory alternative taking **1** to **3** (eqs 1 and 3), a preference in accord with orbital symmetry theory. The disrotatory conversion of **1** to **2** does occur, just as *cis*-bicyclo[3.2.0]hept-6-ene isomerizes through a disrotatory process to form *cis*,*cis*-1,3-cycloheptadiene (E_a = 45.5 kcal/mol).[17] The point made by Woodward and Hoffmann is worth remembering here: "It should be emphasized that our hypothesis specifies in any case which of two types of geometrical displacements will represent a favored process, but does not exclude the operation of the other under very energetic conditions."[18]

In retrospect, might one have sensed that the [1,5] hydrogen shift mechanism was improbable? Two considerations pointing in that direction may be mentioned here, and others will be provided in a more detailed account, one that includes explicit consideration of a possible **3**-to-**2** isomerization through rotation about the trans double bond.[19,20]

Are the activation parameters derived for the rate constant k_{32} (eq 4) for the case where $k_{12} = 0$ really plausible for a [1,5] hydrogen shift reaction? The hypothetical E_a value, 37.6 kcal/mol (eq 4), is perhaps within a reasonable range, but the pre-exponential factor seems much too high. The log *A* term, 14.0, translates to $\Delta S^{\ddagger} = +2.4$ eu at 250 °C, corresponding to a "loose" transition structure, whereas [1,5] hydrogen shifts typically have substantial negative $\Delta S^{\ddagger}$ values. For diene **2** $\Delta S^{\ddagger} = -13.7$ eu[10] and for *cis*-1,3-pentadiene, $\Delta S^{\ddagger} = -7.1$ eu.[11b] Most symmetry-allowed suprafacial [1,5] hydrogen shifts have relatively low activation energies, but very demanding geometrical requirements in the transition region.[21]

Another strike against the **3**-to-**2** [1,5] hydrogen shift mechanism for the overall **1**-to-**2** isomerization follows from a careful consideration of the geometrical limitations inherent in the *cis*,*trans*-diene **3**. The most favored conformation of this highly skewed diene locates the end of the trans double bond (C4) closest to the hydrogen bonded to C8 that might be available for the shift in a disposition limiting the shift to an antarafacial outcome. This limitation is evident from a close examination of the calculationally derived stereoview along the C4−C3 bond of **3** provided by Isaksson and coworkers[22] or through a direct consideration of molecular models. The [1,5] hydrogen shift hypothesis does not provide an alluring means of avoiding a "forbidden" reaction in a mechanistic formulation. It merely transposes the forbidden event to another isomerization step. The transient intermediate *cis*,*trans*-diene **3** is undoubtedly formed reversibly from bicyclooctene **1**, but it does not lie along the reaction path leading to the *cis*,*cis*-diene **2**. As one reviewer has commented, the reversible formation of **3** from **1** "is an unproductive sideshow."

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Supporting Information Available: Selected NMR spectra, GC-MS data for **1**, **1-*d*$_4$**, **2**, and **2-*d*$_4$**, and kinetic plots. This material is available free of charge via the Internet at http://pubs.acs.org.

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[17] Branton, G. R.; Frey, H. M.; Montague, D. C.; Stevens, I. D. R. *Trans. Faraday Soc.* **1966**, *62*, 659−663.

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[21] Hess, B. A.; Baldwin, J. E. *J. Org. Chem.* **2002**, *67*, 6025−6033.

[22] Isaksson, R.; Roschester, J.; Sandström, J.; Wistrand, L.-G. *J. Am. Chem. Soc.* **1985**, *107*, 4074−4075.