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Deuterium Kinetic Isotope Effects and Mechanism of the Thermal Isomerization of Bicyclo[4.2.0]oct-7-ene to 1,3-Cyclooctadiene

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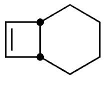
The thermal conversion of *cis*-bicyclo[4.2.0]oct-7-ene to *cis,cis*-1,3-cyclooctadiene might involve a direct disrotatory ring opening, or it might possibly take place by way of *cis,trans*-1,3-cyclooctadiene. This *cis,trans*-diene might possibly form the more stable cis,cis isomer through a [1,5] hydrogen shift or a trans-to-cis isomerization about the trans double bond. Deuterium kinetic isotope effect determinations for the isomerizations of 2,2,5,5-d_4-bicyclo[4.2.0]oct-7-ene and 7,8-d_2-bicyclo[4.2.0]-oct-7-ene rule out these two alternatives because the observed effects are much smaller than would be anticipated for these mechanisms: $k_H/k_D(d_4)$ at 250 °C is 1.17 (1.04 per D), and $k_H/k_D(d_2)$ at 238 °C is 1.20 (1.10 per D). The direct disrotatory ring opening route remains the preferred mechanism.

Introduction

cis-Bicyclo[4.2.0]oct-7-ene (**1**) was first prepared by Vogel in 1953 through a short route from cyclooctatetraene.[1] It soon became more easily accessible through the photoisomerization of *cis,cis*-1,3-cyclooctadiene (**2**),[2] a route more convenient than other options.[3]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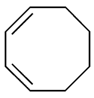
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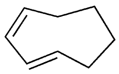
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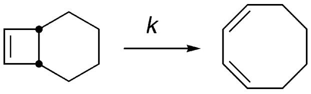
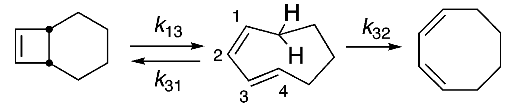
The thermal isomerization of **1** to **2** was reported in 1965,[4] and careful gas-phase kinetic work was published the following year.[5]



1 **2**

SCHEME 1. Indirect Thermal Isomerization of 1 to 2 by Way of 3



1 **3** **2**

The direct conversion of **1** to **2** could take place through a disrotatory ring opening, a mechanistic formulation favored by Branton and co-workers;[6]however, other mechanistic possibilities were recognized. Criegee and co-workers pointed out[4] that *cis,trans*-1,3-cyclooctadiene (**3**)[7] might be the primary product and reaction intermediate. Bloomfield and McConaghy suggested that the reaction path might involve the reversible formation of **3** as an intermediate followed by a rate-determining isomerization of **3** to **2** through a [1,5] hydrogen shift.[8,9] Others considered the possibility that intermediate **3** might lead to the final product **2** through rotation about the trans olefinic bond.[10,11] The reactions of Scheme 1 frame these alternatives featuring *cis,trans*-diene **3** as an intermediate along the reaction coordinate. Here, k_{32} might be

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[1] (a) Vogel, E. *Angew. Chem.* **1953**, *65*, 346−347. (b) Allinger, N. L.; Miller, M. A.; Tushaus, L. A. *J. Org. Chem.* **1963**, *28*, 2555−2557.

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

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[8] McConaghy, J. S., Jr.; Bloomfield, J. J. *Tetrahedron Lett.* **1969**, 3719−3721.

[9] Bloomfield, J. J.; McConaghy, J. S., Jr. *Tetrahedron Lett.* **1969**, 3723−3726.

[10] Padwa, A.; Koehn, W.; Masaracchia, J.; Osborn, C. L.; Trecker, D. J. *J. Am. Chem. Soc.* **1971**, *93*, 3633−3638.

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10.1021/jo040220l CCC: $27.50

associated with either a [1,5] hydrogen shift or a trans-to-cis isomerization about the C3−C4 double bond of **3**.

This mechanistic puzzle has been well recognized for decades, and yet it has remained unclarified. It is recalcitrant largely because of difficulties associated with the relative magnitudes of rate constants that may be of importance. Arrhenius parameters for the observable conversion of **1** to **2** determined by Branton, Frey, and Skinner[5] are given in eq 1. Bloomfield and McConaghy followed the isomerization of **3** to **1** over the temperature range of 64−90 °C and derived the Arrhenius parameters shown in eq 2.[9]

$$\log k = 14.13 - 43180/(2.303RT) \qquad (1)$$

$$\log k_{31} = 13.14 - 27850/(2.303RT) \qquad (2)$$

Temperature-dependent equilibrium constants for [**1**]/[**3**] from 89.8 to 170.0 °C have been obtained,[9] and together with the parameters of eq 2, they allow one to calculate $\log k_{13}$ as a function of temperature (eq 3).[12]

$$\log k_{13} = 13.3 - 33450/(2.303RT) \qquad (3)$$

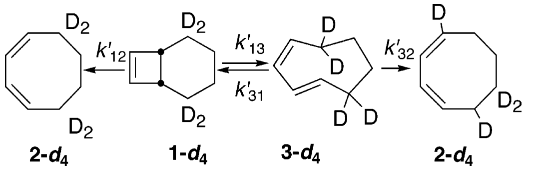
The kinetic situation relevant to the mechanistic problem is simple enough. Exact integrated mole fraction versus time expressions corresponding to Scheme 1 are well-known,[13] and when, as here, a steady-state treatment is appropriate ($k_{31} \gg k_{32}$), one has $k_{obs} = k = (k_{13}/k_{31})k_{32}$ (if $k_{12} = 0$). If the mechanism of Scheme 1 is correct, the Arrhenius equations of eqs 1−3 lead directly to one for k_{32} (eq 4).[12]

$$\log k_{32} = 14.0 - 37600/(2.303RT) \qquad (4)$$

The difficulties are posed not by kinetic complexity but rather by the relative magnitudes of k_{13}, k_{31}, k_{12}, and k_{32}. At 250 °C, for example, the Arrhenius expressions in eqs 1−4 give $k = 1.2 \times 10^{-4}$ s^{-1} for the isomerization of **1** to **2**, while the rate constant ($k_{13} + k_{31}$) for the approach to equilibrium between **1** and **3** is about 32 s^{-1}, or 2.7×10^5 times faster than $k = k_{12}$ (if $k_{32} = 0$) or $(k_{13}/k_{31})k_{32}$ (if $k_{12} = 0$). Thus, whether **1** or **3** is the starting material, the initial rate of formation of **2** will be identical, within plausible analytical limits. The kinetic question of whether **2** is formed 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[14] would, in the present instance, be extremely demanding and impractical.

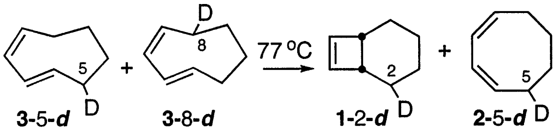
In addition, simple isotopic labeling studies dependent upon detecting just where a label that appears initially in **1** appears in thermal product **2** cannot resolve the mechanistic question. The [1,5] hydrogen shifts in diene **2** will redistribute label(s) at a rate orders of magnitude faster than the rate at which **1** gives **2** through any mechanism. At 250 °C, for example, the rate constant for one [1,5] hydrogen migration in **2** ($\log A = 10.4$, $E_a =$ 29.0 kcal/mol) is 1.9×10^{-2} s^{-1}, which is 160 times faster than k, the observed rate constant for the conversion of **1** to **2**.[15,16]

SCHEME 2. Alternatives for 2,2,5,5-d_4-Bicyclo[4.2.0]oct-7-ene (1-d_4)



The mechanistic issues formalized in Scheme 1 have long remained unresolved. 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."[12] The hydrogen shift mechanism seems "permissible, if not operative",[17] but it would require a small positive $\Delta S^{\ddagger}$, hardly an expected characteristic.[18]

The most recent contribution toward a sure mechanistic understanding of the isomerization of **1** to **2** reported that *cis,trans*-1,3-cyclooctadiene labeled with one deuterium at C5 or C8 (**3**-*d*) isomerized in a dilute CCl_4 solution at reflux (bp 77 °C) under nitrogen to give 76% of **1**-*d* and 24% of **2**-*d*. The deuterium label in **1**-*d* was found at C2, while the label in **2**-*d* was exclusively at C5. This finding seemed to rule out a mechanism for the isomerization of **3** to **2** through a [1,5] hydrogen shift. When a binary mechanistic choice was assumed, these results led to the conclusion that a trans-to-cis rotation must occur.[11] Clearly, the deuterium-labeled *cis,cis*-1,3-cyclooctadiene product did not form directly from **3**-*d* through a hydrogen shift.



The present work approached this long-standing mechanistic problem anew.[19] Distinctions among the three alternatives (a direct disrotatory **1**-to-**2** process, a **3**-to-**2** reaction involving a [1,5] hydrogen shift, and a **3**-to-**2** path through rotation about the trans double bond) were sought. These three mechanisms should be associated with distinctive deuterium kinetic isotope effects, given appropriate specific labeling of the bicyclooctene reactant.

Were the starting material labeled with deuterium atoms at C2 and C5, as in Scheme 2, the k'_{32} reaction would involve a primary deuterium kinetic isotope effect and be expected, due to relevant precedents, to be unmistakably primary. Relevant precedents are available; the [1,5] hydrogen shifts in 1,3,6-cyclooctatriene and

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

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

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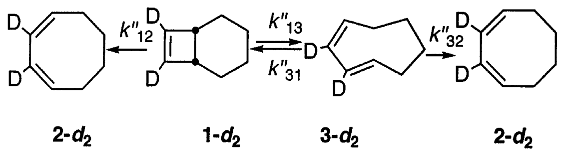
[19] A preliminary account of this work has appeared: Baldwin, J. E.; Gallagher, S. S.; Leber, P. A.; Raghavan, A. *Org. Lett.* **2004**, *6*, 1457−1460.

SCHEME 3. Alternatives for 7,8-d_2-Bicyclo[4.2.0]oct-7-ene (1-d_2)



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.[20] In the alternative rate-determining disrotatory process (k'_{12}), modest β secondary deuterium kinetic isotope effects might be seen. These kinetic 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.

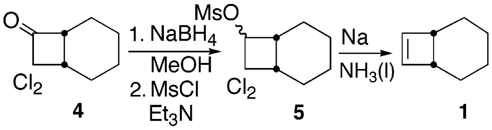
Deuterium labels at C7 and C8 of the starting material, as shown in Scheme 3, would become labels at C2 and C3 of the monocyclic *cis,trans*-diene. The label on the trans double bond in **3**-d_2 would be expected to show a substantial kinetic isotope effect if the product were formed through a k''_{32} path with a trans-to-cis isomerization about the C3−C4 double bond but not if the reaction took place through the direct k''_{12} route.

The thermal isomerizations of *trans*-1-phenylcyclohexene[21] and *trans*-1-phenyl-2-*d*-cyclohexene to the respective cis isomers are characterized by k_H/k_D effects of 2.0 at room temperature.[22] Certainly, dienes **3** and **3**-d_2 are less strained than these *trans*-cyclohexenes,[23] and a possible cis,trans-to-cis,cis thermal isomerization of **3** and **3**-d_2 would take place with a higher activation energy. There is precedent for large secondary deuterium kinetic isotope effects on thermally activated rotations about the double bond of alkenes, even at elevated temperatures. For *cis*-2-butene (d_0 and 2,3-d_2 at 300 °C), $k_H/k_D(d_2) = 1.58$ (or 1.87 when corrected for tunneling) according to MCSCF calculations; for *cis*-stilbene (d_0- and α,α'-d_2 at 287 °C), $k_H/k_D(d_2) = 1.47 \pm 0.13$, as determined experimentally.[24] Thus, a large k_H/k_D effect might be anticipated if k''_{32} were rate limiting (Scheme 3). If k''_{12} were rate limiting, the experimentally observable β secondary k_H/k_D effect would be expected to be small, reflecting possible changes in geometry or hybridization or hyperconjugation in the transition structure leading from **1**-d_2 to the cis,cis cyclic diene **2**-d_2.

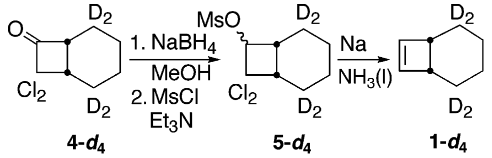
Results

Syntheses. Unlabeled *cis*-bicyclo[4.2.0]oct-7-ene (**1**) was prepared through two routes. Photoisomerization of *cis,cis*-1,3-cyclooctadiene (**2**) in heptane in the presence of acetophenone as a sensitizer, followed by preparative GC isolation, gave an authentic sample of **1**.[2,25] It was also secured from the [2 + 2] cycloadduct of cyclohexene and dichloroketene, 8,8-dichlorobicyclo[4.2.0]octan-7-one (**4**),[26] using the route outlined in Scheme 4 as a run-through for analogous sequences affording labeled analogues. When the methods of Greene and co-workers[27] and syntheses of various deuterium-labeled bicyclo[3.2.0]-hepta-2,6-dienes developed by Belfield were followed,[28] ketone **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.

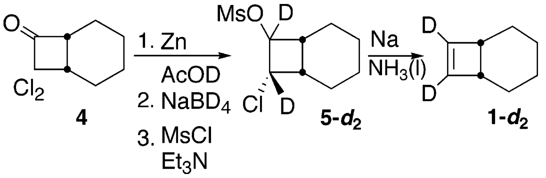
SCHEME 4. Conversion of Ketone 4 to Bicyclo[4.2.0]oct-7-ene



SCHEME 5. Preparation of 2,2,5,5-d_4-Bicyclo[4.2.0]oct-7-ene



SCHEME 6. 7,8-d_2-Bicyclo[4.2.0]oct-7-ene from Ketone 4



Starting the reaction with 3,3,6,6-d_4-cyclohexene, the cycloaddition with dichloroketene generated from trichloroacetyl chloride and zinc in ether (with sonication)[29] gave **4**-d_4 (Scheme 5). This intermediate was converted to **1**-d_4 using the three-step sequence outlined in Scheme 5. After isolation and purification of the mixture by preparative GC, the **1**-d_4 was characterized by NMR spectroscopy and mass spectrometry. 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.

A modification of the reaction sequences used in Schemes 4 and 5 led to the 7,8-d_2-labeled bicyclooctene **1**-d_2 (Scheme 6). Reduction of **4** with zinc in the presence of *O*-deuterioacetic acid gave a deuterium-labeled

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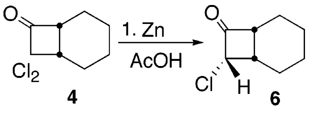
TABLE 1. Mole Percent Relative Concentration Data for Bicyclo[4.2.0]oct-7-ene (1) and 7,8-d_2-Bicyclo[4.2.0]oct-7-ene (1-d_2) at 238.2 °C as Functions of Reaction Time

time (s)	**1** (%)	time (s)	**1**-d_2 (%)
0	100.0	0	100.0
3600	81.3	3600	84.4
3600[a]	81.7[a]	6060	75.1
7200	68.6	10800	59.9
9000	60.1	14400	50.6
12600	50.3	57600	8.8
14400	43.1		
18000	38.6		
25200	27.8		
42000	8.7		
72000	1.9		

[a] Duplicate kinetic run.

monochloride, which was reduced with $NaBD_4$; the alcohols obtained were treated with methanesulfonyl chloride to afford **5**-d_2. Reduction with Na and NH_3/THF gave 7,8-d_2-bicyclo[4.2.0]oct-7-ene (**1**-d_2).

The proton NMR spectrum of the monochloroketone formed through the reduction of **4** with zinc and *O*-deuterioacetic acid showed a distinctive doublet of doublets from C8-*exo*-H at δ 4.95 (J = 2.2 and 8.8 Hz), revealing that the product included some unlabeled 8-*endo*-chlorobicyclo[4.2.0]octan-7-one (**6**).[30] Adventitious moisture apparently contaminated the AcOD that was utilized or reflected inadequately dried glassware. The relative intensities of the strong MS ions at *m*/*z* 124 ($C_8H_{10}DO^+$) and 123 ($C_8H_{11}O^+$), 78:22, provided a quantitative estimate of the d_1:d_0 product ratio.



After the reduction with $NaBD_4$ and the conversion of the alcohols obtained the mesylate esters (**5**-d_2), the esters were examined by mass spectrometry. The MS *m*/*z* 109:108 ($C_8H_9D_2^+$:$C_8H_{10}D^+$) ion intensity ratio was 79:21, suggestive of essentially quantitative incorporation of deuterium through the borodeuteride reduction. When **1**-d_2 was in hand, another estimate of the isotopic integrity of the synthetic route was obtained. Integration of the ^{1}H NMR spectrum of a GC purified sample showed δ 6.10 (vinyl H) and 2.83 (bridgehead H) relative intensities to be 0.14:1.00, consistent with 28% d_1 and 72% d_2 labeling.

Kinetic Results. Kinetic runs were conducted using a gas-phase static reactor, an associated vacuum system, and temperature-control and measurement instruments that have been detailed elsewhere.[31] The isomerizations of **1** and of **1**-d_2 were run with pentane as the bath gas and decane as an internal standard; product mixtures were analyzed by capillary GC. Cyclic dienes **2** and **2**-d_2 were the only products observed. The mole percent concentrations versus time data are given in Table 1.

Least-squares best-fit calculations provided the unimolecular rate constant for the isomerization of **1** at 238.2 ± 0.8 °C ($k = 5.47 \times 10^{-5}$ s^{-1}). The isomerizations of **1**-d_2 and **1**-d_1 at 238.2 ± 0.1 °C were modeled with [**1**-$d_2(t)$ + **1**-$d_1(t)$] $= 72 \times \exp(-k\alpha^2 t) + 28 \times \exp(-k\alpha t)$. The least-squares best-fit value of $\alpha = (k_H/k_D)^{-1}$ per deuterium was 0.912; $k_H/k_D = 1.10$ per deuterium.

The imperfect temperature control experienced during the kinetic runs with **1** was annoying but not of telling consequence, for its impact on the rate constant determination should be very small. Whatever reasonable likely errors in the derived rate constants one may postulate, the essential finding remains clear. The observed $k_H/k_D(d_2)$ ratio, 1.20 (1.10 per deuterium), falls far short of the magnitude anticipated for a trans-to-cis rotation transforming **3**-d_2 to **2**-d_2. We conclude that the k''_{32} path plays no significant role in the overall isomerization. This conclusion follows from the observed $k_H/k_D(d_2)$ and the rationale leading from reports in the literature[21-24] to an anticipated isotope effect of 2 or so for the k''_{32} reaction. If that rationale were seriously off the mark, the conclusion would be unwarranted. Further experimental and theoretical effort would be required to address this caveat.

The kinetic runs leading to an experimental definition of a $k_H/k_D(d_4)$ kinetic isotope effect were different in several respects: a different bath temperature was deliberately selected, 2,2-dimethylbutane was used as the bath gas, and both **1** and **1**-d_4 samples were run simultaneously, thus eliminating any possibility that the samples might be isomerized at different temperatures or under different reaction conditions of any sort. The original plan projected analyses based on both capillary GC and GC/MS. Analyses by GC would have given relative concentrations of [**1** + **1**-d_4] and [**2** + **2**-d_4] at various reaction times, and the ratios of the isotopomers of each structure at each reaction time would have been followed from relative ion intensities at masses characteristic of each species. In practice, GC proved to be sufficient since the unlabeled and d_4-labeled starting materials and products separated well enough to give reliable integrated intensities through flame ionization detection.[19] The retention times of the unlabeled and d_4-labeled bicyclooctene and *cis,cis*-diene isomers at 40 °C differed by 10.5 and 12.2 s, respectively. In each pair of isotopomers, the d_4-labeled sample had the shorter retention time, as determined by GC/MS.[19] Precedents for separations of deuterium-labeled and unlabeled versions of the same structure have been reported in the literature, and the labeled variants usually elute earlier.[32]

The kinetic data secured for runs starting from a 54:46 mixture of **1** and **1**-d_4 at 249.9 ± 0.1 °C in the presence of 2,2-dimethylbutane as a bath gas and cyclooctane as an internal standard are recorded in Table 2.

From these data, least-squares best-fit calculations provided overall rate constants of $k = 1.16 \times 10^{-4}$ s^{-1} and $k(d_4) = 0.99 \times 10^{-4}$ s^{-1}. The ratio $k_H/k_D(d_4) = 1.17$; $k_H/k_D = 1.04$ per deuterium. The substantial primary k_H/k_D effect anticipated for a rate-determining [1,5] hydrogen shift converting **3** to **2** and **3**-d_4 to **2**-d_4 was not observed.

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TABLE 2. Mole Percent Relative Concentration Data for 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
16041	16.8	19.0

Discussion

From the present work, it appears that the cis,trans isomer of cyclooctadiene (**3**) is not an intermediate on the mechanistic path leading from *cis*-bicyclo[4.2.0]oct-2-ene (**1**) to *cis,cis*-1,3-cyclooctadiene (**3**), for neither a direct trans-to-cis rotation taking **3**-d_2 to **2**-d_2 nor a [1,5] deuterium shift leading from **3**-d_4 to **2**-d_4 is consistent with the kinetic isotope effects observed. The k_H/k_D values found are completely consistent with expectations for β secondary deuterium kinetic isotope effects and direct reactions converting **1** to **2**, **1**-d_4 to **2**-d_4, and **1**-d_2 to **2**-d_2.

Among the roster of postulated mechanisms advanced in the literature, only the direct disrotatory electrocyclic reaction remains viable. How does it fit with related reactions shown by other bicyclic cyclobutenes?

This question played an interesting role in the early developments of orbital symmetry theory. The thermal isomerizations of monocyclic hydrocarbons based on cyclobutene substructures take place at relatively low temperatures and invariably prefer to proceed in a conrotatory fashion. However, geometrically restricted bicyclic systems, such as 6,7-dimethylbicyclo[3.2.0]hept-6-ene, isomerize much more slowly.[33] These experimental observations were an instrumental stimulus for the intellectual and pattern-recognition insights associated with Woodward and Hoffmann's breakthrough first communication on the stereochemistry of electrocyclic reactions.[34] That paper includes a clear perspective on the relevance of the reactivity differences noted for bicyclic systems restricted to disrotatory isomerizations or some other less-direct mechanism: "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. ... In [6,7-dimethylbicyclo[3.2.0]hept-6-ene], the presence of the five-membered ring makes a conrotatory process impossible, and the disrotatory opening is observed, but only slowly at 400°."[34] In the later review article and book on *The Conservation of Orbital Symmetry*, these authors emphasized that cis-fused bicyclo[*n*.2.0]alkenes similar to bicyclo[4.2.0]oct-7-ene react to give monocyclic *cis,cis*-dienes at rates dependent on reaction thermochemistry.[35] The less-strained bicyclic olefins isomerize to give *cis,cis*-diene products more slowly than similar monocyclic hydrocarbons rearrange through conrotatory ring openings. The trend was summarized as follows, giving the temperature (°C) at which the half-life for the electrocyclic isomerization is about 2 h, for $n = 1$ (bicyclo[2.1.0]-pent-2-ene), $n = 2$ (bicyclo[2.2.0]hex-2-ene), $n = 3$ (bicyclo-[3.2.0]hept-6-ene), $n = 4$ (bicyclo[4.2.0]oct-7-ene), $n = 5$ (bicyclo[5.2.0]non-8-ene), and $n = 6$ (bicyclo[6.2.0]dec-9-ene).[35]

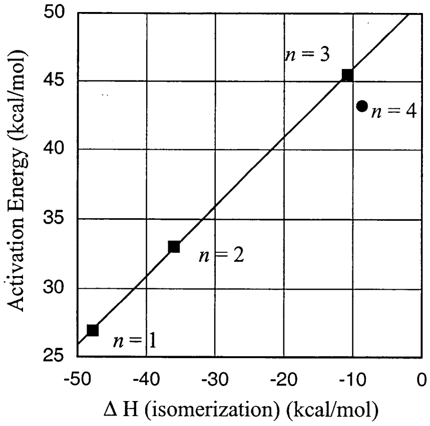

FIGURE 1. Correlation of ΔH_r for thermal isomerizations of *cis*-3,4-$(CH_2)_n$-bridged cyclobutenes, bicyclo[2.1.0]pent-2-ene ($n = 1$), bicyclo[2.2.0]hex-2-ene ($n = 2$), bicyclo[3.2.0]hept-6-ene ($n = 3$), and *cis*-bicyclo[4.2.0]oct-7-ene (**1**; $n = 4$), with E_a for the reactions. For $n = 1-3$ isomerizations (■), the linear relationship shows that more exothermic reactions have lower activation energies. For the $n = 4$ case (**1**−**2**; ●), the extrapolated E_a value (46.9 kcal/mol) and the experimentally determined E_a value (43.18 kcal/mol)[5] are noticeably distinct.

n	1	2	3	4	5	6
T (°C)	<100	195	>380	350	335	180

Careful gas-phase kinetic studies on the $n = 1-4$ systems have now been published, and this qualitative presentation of the unmistakable and clearly important influence of structure on reactivity can be revised as follows:[5,6,9,36]

n	1	2	3	4	5	6
T (°C)	50	130	270	250	235	225

When $n = 5$ or 6, the conrotatory electrocyclic process leading to an equilibrium between bicyclic cyclobutene and monocyclic *cis,trans*-diene dominates, yet the overall isomerization rates do not reflect a comparable advantage.[36,37]

Attempts to correlate overall reaction rates with the heats of reaction for these isomerizations have been made in several ways, including tabulations of E_a and ΔH_r values.[38] Using thermochemical and kinetic data better than those available to Lupton in 1968, the correlation shown in Figure 1 is obtained. The activation energies for the $n = 1-4$ bicyclo[*n*.2.0] systems are 26.9, 33.0, 45.5,

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and 43.2 kcal/mol, respectively;[36] the corresponding ΔH_r values are −47.8, −36.0, −10.8, and −8.7 kcal/mol.[39]

The linear correlation for the bicyclics with $n = 1-3$ would extrapolate to an E_a value of 46.9 kcal/mol for **1**, whereas the experimental value is 43.18 kcal/mol.[5] This difference may signal that another influence begins to contribute to the overall trend when the isomerizations become less dramatically exothermic as the starting materials become less strained (from left to right in Figure 1). However, the difference in E_a values between bicyclo[3.2.0]hept-6-ene and **1** is only 2.3 kcal/mol, and both probably occur through a common mechanism.[5] This plausibility consideration, combined with the present demonstration of a $k_H/k_D(d_4)$ ratio inconsistent with a [1,5] hydrogen shift, brings one back to the break in the linear correlation of Figure 1. One possibility is that the additional molecular flexibility in the C8 homologue relative to the smaller bicyclic cyclobutenes facilitates the disrotatory ring-opening reaction by allowing access to more geometrically favorable transition structures. This hypothesis implies that the transition structure for the disrotatory isomerization lacks C_s symmetry, a testable proposition.

With regard to the activation parameters derived for the rate constant k_{32}, are they really plausible for a [1,5] hydrogen shift reaction? The E_a value, 37.6 kcal/mol, is clearly within a reasonable range, but the preexponential factor is 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 *cis*-1,3-pentadiene, $\Delta S^\ddagger = -12$ eu, and for diene **2**, $\Delta S^\ddagger = -10$ eu. The symmetry-allowed suprafacial [1,5] hydrogen shift has a relatively low activation energy but very demanding geometric preferences in the transition region.[40]

In hindsight, 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 hydrogens 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 stereoview along the C4−C3 bond of **3**, provided by Isaksson and co-workers,[7c] or through a direct consideration of molecular models. The [1,5] hydrogen shift hypothesis does not provide an alluring dodge for avoiding a "forbidden" reaction in a mechanistic formulation; it merely transposes the forbidden event to another topology.

What of the evidence derived from experiments with a deuterium-labeled version of **3** reported by Bramham and Samuel?[11] Three groups have previously reported that **3** isomerizes at 80 °C to the bicyclic product **1** quantitatively (or nearly quantitatively).[7b,9,41] An exception was noted by Padwa and co-workers in the course of their study of the thermal bimolecular combination of **3** to form mixtures of three isomeric [2 + 2] dimers.[10] Under the reaction conditions (concentrated mixture of *cis*,*trans*-diene and diethyl phthalate as an internal standard), both bicyclooctene **1** and diene **2** were detected as minor, nondimeric products. However, the proportions of **1** and **2** were not constant over reaction time, nor were they consistent from run to run. The *cis*,*cis*-diene might well have derived from a bimolecular path involving the formation of a transient diradical derived from two molecules of **3**.[10]

In Bramham and Samuel's work,[11] the 5 (or 8)-*d*-*cis*,*trans*-1,3-cyclooctadiene was isolated by an aqueous silver nitrate extraction following the work of Cope and Bumgardner;[7a] the complex, in a mixture of ice and water, was treated with ammonia and extracted with carbon tetrachloride. The organic solution was either passed through a short column of activity I alumina or dried over magnesium sulfate and filtered to remove the residual silver complex.[42]

Were even extremely minor traces of the silver ion−*cis*,*trans*-diene complex to survive these precautions, the formation of a cis,cis product at 77 °C could be easily rationalized and the observed labeling outcome would be consistent with expectations. It is of course notoriously difficult to obviate, with certainty, the intervention of catalytically active trace impurities.[43] The absence of a cis,cis product from **3** in kinetically monitored first-order reactions[7b,9,41] is strong evidence that the direct isomerization of **3** to **2** is not kinetically competitive with the well-established **3**-to-**1** isomerization. Small amounts of catalytically active impurities could not account for the clean kinetic results for the **3**-to-**1** reaction reported from three laboratories. Given the possibility of silver ion catalysis as a contributing factor in the isomerizations reported,[11] and the present $k_H/k_D(d_2)$ determination, the case for a direct trans-to-cis isomerization from **3** to **2** does not seem persuasive.

Conclusions

The deuterium kinetic isotope effect determinations reported here are inconsistent with mechanistic formulations of the thermal isomerization of *cis*-bicyclo[4.2.0]oct-7-ene (**1**) to *cis*,*cis*-1,3-cyclooctadiene (**2**) through an indirect route involving *cis*,*trans*-1,3-cyclooctadiene (**3**). The mechanism consistent with the isotope effects that were seen, one dependent on a disrotatory ring-opening process leading from **1** to **2** directly, takes place in competition with the symmetry-allowed conrotatory isomerization leading reversibly to *cis*,*trans*-diene **3**. The activation energies for the disrotatory and conrotatory electrocyclic reactions shown by *cis*-bicyclo[4.2.0]oct-7-ene (43.2 and 33.5 kcal/mol, respectively) reflect the substantial energetic advantage of the allowed over the forbidden reaction. Yet the forbidden isomerization provides the

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mechanistically viable route for the overall reaction, while the allowed process simply forms a short-lived intermediate which does not lie along the reaction coordinate. The reversible interconversion of **1** with **3** takes place but does not lead to the reaction product, *cis*,*cis*-diene **2**.

No serious theoretical work on the isomerization of **1** to **2** appears to have been undertaken. Such an effort would be quite valuable but would require work using more than single-determinant methods. The geometry, energy, and vibrational frequencies of the transition structure would provide insights into the reaction not accessible directly through the mechanistic definition obtained in the present work. Similar calculations for the disrotatory isomerization of *cis*-bicyclo[3.2.0]hept-6-ene to *cis*,*cis*-1,3-cycloheptadiene could well provide a rationale for the 2.3 kcal/mol difference in E_a values for the disrotatory ring-opening isomerizations of **1** and bicyclo[3.2.0]hept-6-ene or the 3.7 kcal/mol energetic preference relative to the extrapolated value obtained from the correlation of Figure 1. One may reasonably imagine that differences in geometrical flexibility along the reaction coordinate enjoyed by the larger bicyclic system provide the advantage, but the findings of appropriate computational work will be necessary before the issues may be resolved.

Experimental Section

Bicyclo[4.2.0]oct-7-ene (1) was prepared by the photoisomerization of *cis*,*cis*-1,3-cyclooctadiene using acetophenone as the sensitizer, heptane as the solvent, a 450-W medium-pressure mercury lamp, and an immersion apparatus.[2] After an unexceptional workup and isolation was completed, a sample of **1** was purified and isolated through preparative GC on a 1-m 10% SE-30 column at 60 °C. Sample homogeneity was confirmed using a fused silica 0.2-mm i.d., 25-m cross-linked 5% phenyl methyl siloxane capillary GC column. The recorded NMR spectra matched those reported in the literature:[24] ^{1}H NMR δ 6.10 (s, 2H), 2.83 (m, 2H), 1.30−1.75 (m, 8H); ^{13}C NMR δ 140.5 (C7, C8), 41.5 (C1, C6), 24.9 (C2, C5), 18.8 (C3, C4).

8,8-Dichlorobicyclo[4.2.0]octan-7-one (4).[26] To a mixture of zinc (6.53 g, 0.1 mol), cyclohexene (5.0 mL, 0.05 mol), and 125 mL of anhydrous ether placed in a sonication bath[29] maintained at 15−20 °C was added over a 90-min period a solution of 13 g (0.072 mol) of trichloroacetyl chloride in 63 mL of ether. Sonication of the reaction mixture at 15 °C was continued for another 6.5 h. The mixture was quenched with wet ether and filtered through a sintered glass funnel; the zinc was rinsed with wet ether, and the total filtrate was washed with water (2 × 20 mL), $NaHCO_3$(aq) (5 × 20 mL), and brine (20 mL). The ethereal solution was dried (Na_2SO_4), filtered, and concentrated to yield 7.33 g (78%) of dichloroketone **4**: ^{1}H NMR δ 3.86 (m, 1H), 2.90 (m, 1H), 2.03 (m, 2H), 1.54 (m, 3H), 1.33 (m, 1H), 1.18 (m, 2H); ^{13}C NMR δ 196.7, 87.86, 52.67, 43.2, 25.56, 21.54, 21.21, 20.67; MS (*m*/*z*) 68 (base), 122, weak 192 (M^+, $C_8H_{10}{}^{35}Cl_2O$). The 192:194:196 intensity ratio was 100:65:10.

Bicyclo[4.2.0]oct-7-ene (1) from 8,8-Dichlorobicyclo[4.2.0]octan-7-one (4).[27,28] A three-step route from dichloroketone **4** to bicyclooctene **1** (reduction with $NaBH_4$ to give a mixture of alcohols, reaction of these alcohols with MsCl and Et_3N in CH_2Cl_2 to afford the corresponding mixture of mesylate esters, and finally reduction with Na in NH_3/THF, following the detailed protocols used by Belfield) gave olefin **1**, identical with an authentic sample: ^{13}C NMR δ 140.5, 41.4, 24.8, 18.8.

2,2,5,5-d_4-Bicyclo[4.2.0]oct-7-ene (1-d_4) from 2,2,5,5-d_4-8,8-Dichlorobicyclo[4.2.0]octan-7-one (4-d_4). A sample of 0.60 g of 3,3,6,6-d_4-cyclohexene (98 atom % D) was combined with zinc and trichloroacetyl chloride in ether under the sonication conditions detailed above for the unlabeled cycloaddition to provide **1**-d_4: ^{1}H NMR δ 6.12 (s, 2H), 2.83 (s, 2H), 1.56 (m, 2H), 1.35 (m, 2H); ^{13}C NMR δ 140.5 (C7, C8), 41.3 (C1, C6), 18.6 (C3, C4); ^{2}H NMR δ 1.67 (br s, 2D), 1.49 (br s, 2D).

8-*endo*-Chloro-8-*d*-bicyclo[4.2.0]octan-7-one. Ketone **4** (768 mg, 4 mmol), dissolved in 5 mL of CH_3COOD (99% D), was added to 262 mg of zinc dust (4 mmol). The suspension was stirred at room temperature periodically monitored by GC. After 3 h, 32 mg of zinc (0.5 mmol) was added. After another 30 min, the starting material was consumed. The reaction mixture was filtered, and the solid was washed with several small portions of ether. The filtrate was washed with 1 N $NaHCO_3$, water, and brine; it was then dried over $MgSO_4$ and filtered. Concentration provided 445 mg of the 8-*endo*-chloro compound (70% yield) as a pale-yellow liquid. Analysis by capillary GC revealed one isomer. The ^{1}H NMR spectrum of the ketone showed residual C8−H absorptions at δ 4.95 as a doublet of doublets (J = 2.2 and 8.8 Hz).[30] The intensities of the strong MS ions at *m*/*z* 124 ($C_8H_{10}DO^+$) and 123 ($C_8H_{11}O^+$) were in the ratio of 78:22.

7-Methylsulfonyl-8-chloro-7,8-d_2-bicyclo[4.2.0]octane (5-d_2). The ketone prepared immediately above (400 mg, 2.5 mmol) and 5 mL of CH_3OD were placed in a 25-mL three-necked flask fitted with a magnetic stirrer and solid addition device. The solution was cooled to 0 °C; $NaBD_4$ (925 mg, 25 mmol) was added in small portions over 1 h. The reaction mixture was allowed to warm to room temperature and was stirred for 21 h; it was then cooled to 0 °C and diluted with a cold mixture of 10 mL of 1 N HCl and 20 mL of ether. The layers were separated, and the aqueous phase was extracted three times with ether. The combined ethereal material was washed with water, 1 N HCl, water, saturated $NaHCO_3$, water, and brine; it was then dried over $MgSO_4$ and filtered. Concentration afforded 327 mg (80% yield) of crude 7-hydroxy-8-chloro-7,8-d_2-bicyclo[4.2.0]octanes as a colorless liquid.

To a solution of 300 mg of these alcohols (1.85 mmol) in 20 mL of CH_2Cl_2 in a 50-mL flask cooled to 0 °C was added 1.0 mL of triethylamine (7.4 mmol). Methanesulfonyl chloride (0.5 mL, 6.13 mmol) was placed in an addition funnel and added slowly over 1 h. The reaction mixture was allowed to warm slowly to room temperature, stirred for 7 h, and then cooled to 0 °C. A mixture of 5 mL of cold water and 5 mL of CH_2Cl_2 was added. The mixture was stirred for 30 min; cold 1 N HCl was added, and the layers were separated. The aqueous phase was extracted three times with CH_2Cl_2. The combined organic material was washed with cold 1 N HCl, cold water, saturated Na_2CO_3, cold water, and brine; it was dried ($MgSO_4$), filtered, and concentrated to afford 260 mg (60% yield) of crude mesylates **5**-d_2 as a dark-orange liquid. The MS *m*/*z* 109:108 ($C_8H_9D_2{}^+$/$C_8H_{10}D^+$) ion intensity ratio was 79:21.

7,8-d_2-Bicyclo[4.2.0]oct-7-ene (1-d_2). Ammonia (100 mL) was condensed at −78 °C in a 250-mL three-necked flask fitted with a magnetic stirrer, a dry ice/acetone condenser, and an addition funnel. Sodium (1.0 g, 43 mmol) was added in small pieces, producing a deep-blue color, and the solution temperature was maintained at −78 °C. A solution of 400 mg of crude monochloromesylates **5**-d_2 (260 mg, 1.66 mmol) in 20 mL of dry THF was placed in the addition funnel and added to the Na/NH_3 reaction mixture over 30 min. The reaction mixture was allowed to warm to −35 °C and stirred for 3.5 h. Then, NH_4Cl was added until the blue color was gone. The dry ice/acetone condenser and the addition funnel were replaced with two cold-water condensers with attached oil bubblers. The reaction mixture was allowed to warm to 0 °C. Water (10 mL) was added to dissolve the remaining salts, and then 30 mL of pentane was added. The layers were separated, and the aqueous phase was extracted three times with pentane. The combined organic material was washed with water, 1 N HCl, water, $NaHCO_3$(aq), water, and brine. It was dried over

$MgSO_4$, filtered, and concentrated to provide 20 mg (11%) of **1**-d_2. Integration of the ^1H NMR spectrum of a GC-purified sample showed relative intensities for absorptions at δ 6.10 (vinyl H) and 2.83 ppm (bridgehead H) of 0.14:1.00 (86% average d_2 labeling or 28% d_1 and 72% d_2).

Thermolysis reactions in the gas phase were conducted in a static reactor with pentane or 2,2-dimethylbutane as a bath gas and cyclooctane as an internal standard. The apparatus, associated instrumentation, and methods used for the kinetic runs have been detailed elsewhere. The time-dependent decays of bicyclooctenes as cyclooctadienes were formed are summarized in Tables 1 and 2.

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