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Computational Study and Analysis of the Kinetic Isotope Effects of the Rearrangement of *cis*-Bicyclo[4.2.0]oct-7-ene to *cis,cis*-Cycloocta-1,3-diene

Carlos Silva López, Olalla Nieto Faza, and Ángel R. de Lera*

Departamento de Química Orgánica, Facultade de Química, Universidade de Vigo,
Lagoas-Marcosende, E-36310, Vigo, Galicia, Spain

qolera@uvigo.es

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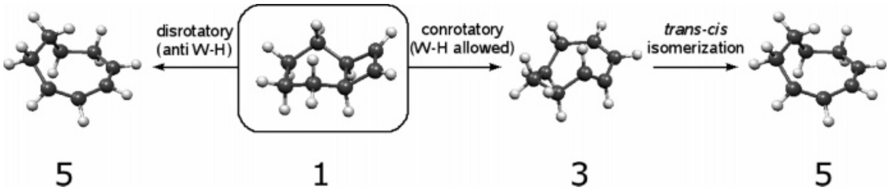
ABSTRACT



On the basis of KIE experiments, the ring opening of *cis*-bicyclo[4.2.0.]oct-7-ene has been suggested as an anti-Woodward–Hoffmann reaction candidate. We hereby report the results of a high-level computational study of the alternate reaction pathways which proves that the energy profiles show a clear preference for the conrotatory (W–H allowed) ring opening followed by double-bond isomerization. Computed KIE values for the aforementioned mechanism are in good agreement with the experimental values.

The thermal ring-opening reaction of *cis*-bicyclo[4.2.0]oct-7-ene **1** to *cis,cis*-cycloocta-1,3-diene **5** has been a mechanistic enigma for decades. Very recently, Baldwin and coworkers conducted a thorough study aimed to provide a definitive answer to such a stimulating question.[1] Three candidate mechanisms (transition-state numbering in parentheses) were considered for this rearrangement (see Figure 1):

(i) A disrotatory ring opening ($\mathbf{2}_{\mathbf{disrot}}$).

(ii) A conrotatory ring opening ($\mathbf{2}_{\mathbf{conrot}}$) to **3** followed by a $[1,5]_{\mathrm{H}}$ sigmatropic shift ($\mathbf{4}_{\mathbf{[1,5]-H}}$).

(iii) A conrotatory ring opening ($\mathbf{2}_{\mathbf{conrot}}$) to **3** followed by a double-bond isomerization ($\mathbf{4}_{\mathbf{dbi}}$).

Baldwin collected then a complete set of Arrhenius parameters of the potential steps describing the reaction and performed a number of KIE experiments devised to rule out the involvement of a $[1,5]_{\mathrm{H}}$ sigmatropic shift or a double-bond isomerization. The latter experiments seemed to confirm that none of the possible evolutions of a *cis,trans*-cycloocta-1,3-diene **3** intermediate are participating in the reaction mechanism. In this paper, however, Baldwin rec-

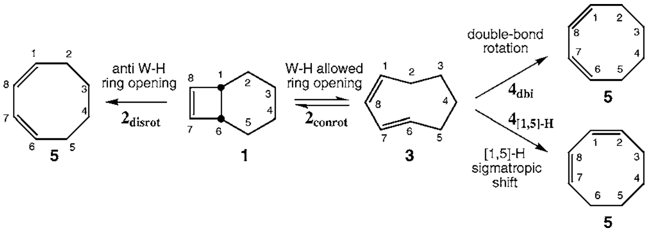


Figure 1. Mechanistic alternatives for the ring opening of *cis*-bicyclo[4.2.0]oct-7-ene **1**.

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(1) (a) Baldwin, J. E.; Gallagher, S. S.; Leber, P. A.; Raghavan, A. *Org. Lett.* **2004**, *6*, 1457. (b) Baldwin, J. E.; Gallagher, S. S.; Leber, P. A.; Raghavan, A.; Shukla, R. *J. Org. Chem.* **2004**, *69*, 7212.

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ognized the need for high-level computations to ascertain whether these conclusions are correct.

Similar electrocyclic ring openings of strained systems have been proposed as anti-Woodward–Hoffmann reactions.[2] We studied these processes and found that their reaction pathways are actually symmetry allowed, despite the opposite apparent result of the overall reaction.[3] These results have been supported and explained in further detail by Andrés and co-workers very recently.[4] Prompted by our interest in symmetry-forbidden reaction mechanisms and the relevance of this particular challenge, we theoretically addressed the mechanistic issues of the **1** to **5** isomerization.

Because of the difficulty associated with the appropriate description of biradical systems with DFT and single-determinant ab initio methods, we decided to couple DFT[5] calculations with the most robust and accurate methodology available. B3LYP and TPSS functionals were employed with the 6-31G(d) basis set to obtain optimized geometries and frequencies for all the stationary points along the three possible mechanistic pathways. Further high-level energy refinement was considered through multireference Møller–Plesset (MRMP) and coupled cluster (CC) methods. MRMP, which implies a perturbational treatment of a previous CASSCF calculation, is specifically adequate to treat diradical species and still recover a well-balanced amount of dynamic and nondynamic electron correlation.[6] The active space selected to perform the CASSCF calculations includes the four electrons involved in the electrocyclic ring opening and the corresponding antibonding orbitals, thus CASSCF-(4,4)/6-31G(d) calculations were followed by a perturbational correction to recover dynamic correlation, resulting in MRMP(4,4)/6-31G(d) energies. The coupled cluster theory is usually considered the most accurate multideterminant *black-box* approach. CC theory is particularly robust with respect to diradical character in molecules when triplet excitations are considered.[7] We therefore decided to use the CCSD(T) truncation of the CC expansion, which is often regarded as the "gold standard" of electronic structure theory,[8] as implemented in the GAMESS[9] code.

Analytical gradients are available for both DFT and CASSCF methods but not for the highly correlated CCSD-(T) and MRMP alternatives. We therefore opted for a dual-level approach. B3LYP/6-31G(d) optimized geometries and frequencies were considered,[11] and an energy refinement at the respective correlated methods was performed. This dual-level approach is usually noted MRMP/6-31G(d)//B3LYP/6-31G(d) and CCSD(T)/6-31G(d)//B3LYP/6-31G(d), respectively. All the geometry optimizations were performed with Gaussian 03.[12] All MRMP and CCSD(T) calculations were performed with the GAMESS package.

Table 1. Free-Energy Profiles (1 atm, 273 K) for the **1** to **5** Transformation (kcal/mol Relative to **1**)[a]

structure	B3LYP	TPSS	MRMP	CCSD(T)	exptl[14]
			Disrotatory Opening		
1	0.00	0.00	0.00	0.00	0.0
$\mathbf{2}_{\mathbf{disrot}}$	51.08	51.83	50.67	56.17	43.2
5	−6.68	−3.26	−6.29	−3.27	−8.7
			Conrotatory Opening and $[1,5]_{H}$ Sigmatropic Shift		
1	0.00	0.00	0.00	0.00	0.0
$\mathbf{2}_{\mathbf{conrot}}$	35.25	33.36	31.20	36.99	33.4
3	5.80	7.49	3.63	6.48	5.6
$\mathbf{4}_{\mathbf{[1,5]}}\mathbf{-H}$	**62.06**	**55.49**	**67.75**[10]	**66.45**	**43.2**
5	−6.68	−3.26	−6.29	−3.27	−8.7
			Conrotatory Opening and Double-Bond Isomerization		
1	0.00	0.00	0.00	0.00	0.0
$\mathbf{2}_{\mathbf{conrot}}$	**35.25**	33.36	31.20	36.99	33.4
3	5.80	7.49	3.63	6.48	5.6
$\mathbf{4}_{\mathbf{dbi}}$	34.68	**36.28**	**37.28**	**46.92**	**43.2**
5	−6.68	−3.26	−6.29	−3.27	−8.7

[a] Rate-limiting transition states are indicated in boldface.

Table 1 summarizes the results obtained from the computation of the energy profiles for the three potential alternative mechanistic pathways converting *cis*-bicyclo-[4.2.0]oct-7-ene **1** to *cis,cis*-cycloocta-1,3-diene **5**. In the right column, the experimental activation barriers are compared against the three mechanistic alternatives proposed. It is noteworthy how these experimental results fit reasonably well only with the last proposed mechanistic scheme (conrotatory ring opening followed by trans–cis isomerization). Notice that previous studies by Bramham and Samuel[13] (see **Ia**, Figure 2) and Baldwin and co-workers[1] (see **Ib**, Figure 2) unequivocally ruled out the $[1,5]_{H}$ shift alternative, results that are in good agreement with the computed profiles.

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(10) Active space was increased to include the C–H σ breaking bond in the sigmatropic shift.

(11) CASSCF(4,4) geometries were also computed. Only slight variations were observed between B3LYP- and CASSCF-based geometries and energies (see Supporting Information). We therefore include here only the results obtained with the more affordable density functional theory approach.

(12) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03*, revision C.02; Gaussian, Inc.: Wallingford CT, 2004.

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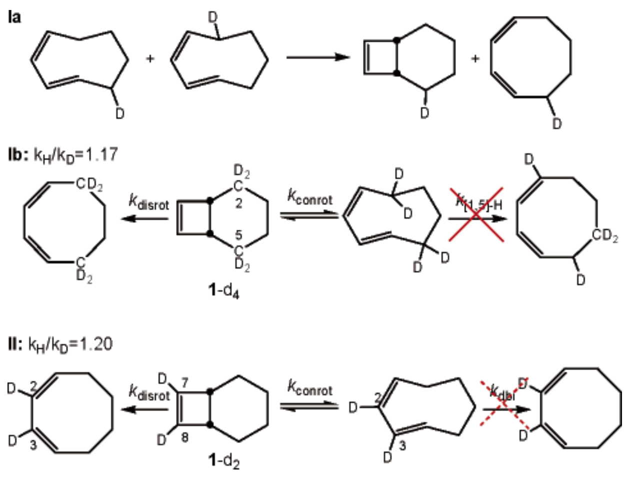

Figure 2. Experiments ruling out the sigmatropic $[1,5]_H$ shift (**Ia** and **Ib**) and, apparently, ruling out the double-bond isomerization (**II**) resorting to expected values for such kinds of transformations.

Both DFT and multideterminant methods rule out the disrotatory ring opening and the $[1,5]_H$ sigmatropic shift. B3LYP yielded however results in disagreement with the experimental Arrhenius parameters reported in earlier work.[14] Namely, B3LYP results show that the rate-limiting step is the conrotatory ring opening whereas experimental results suggest that the isomerization of the *cis*,*trans*-cycloocta-1,3-diene **3** should be the rate-limiting step (see Table 1, entries below *Conrotatory Opening and Double-Bond Isomerization*). The discrepancy is nevertheless due to only 0.57 kcal/mol. On the other hand, TPSS provides the correct rate-limiting step which might indicate that the Hartree−Fock mixing in B3LYP is worsening the results of an otherwise correct magnitude. Both multiconfigurational methodologies employed yield similar results, which are in good agreement with experimental Arrhenius parameters. Considering the fit of the computed barriers for the three reaction pathways and the fact that all the theoretical methods considered reported high-energy pathways for the disrotatory ring opening and the $[1,5]_H$ sigmatropic shift, *we conclude that the conrotatory electrocyclic ring opening followed by the double-bond isomerization of* **3** *is the most favorable pathway for the transformation of cis-bicyclo[4.2.0]oct-7-ene* **1** *to cis,cis-cycloocta-1,3-diene* **5**.

Recent work claimed however that the disrotatory (anti-Woodward−Hoffmann) electrocyclic ring opening is the only mechanistic possibility because both the sigmatropic $[1,5]_H$ shift and the double-bond isomerization can be discarded on the basis of kinetic isotope effects (see Figure 2). We therefore decided to computationally reproduce the KIE experiments, apparently ruling out the double-bond isomerization. The 7,8-d_2-*cis*-bicyclo[4.2.0]oct-7-ene reactant **1**-d_2 converts to monocyclic dienes deuterated at positions C2 and C3 after the cycloisomerization (see Figure 2). In previous work,[1] it was stated that a considerable KIE would be expected because of the deuterium label on the trans double bond, if the rate-limiting step involved a cis,trans → cis,cis isomerization through internal rotation. In fact, several experimental KIEs for cis−trans isomerizations of substrates with deuterium labels on the isomerizing alkene groups have been reported with k_H/k_D values of around 2.0 at room temperature.[15] It was also assumed that a disrotatory opening would produce a small KIE, reflecting the mild changes in the hybridization and geometry occurring at the internal positions of the cyclobutene moiety during the concerted pathway. The experimental KIE measured for **1**-d_2, $k_H/k_D(d_2)$ = 1.20, was considered too low with respect to the expected value, so the double-bond isomerization process was considered not to be involved in the reaction pathway. The KIE experiment **II** illustrated in Figure 2 was computed at both B3LYP/6-31G(d) and TPSS/6-31G(d) levels for the double-bond rotation step (Hessians are not available for MRMP and CC methods at this time), and the $k_H/k_D(d_2)$ values obtained are very low and are actually in good agreement with the experimental KIE observed by Baldwin and co-workers (see Figure 3). Furthermore, calculated KIEs at the same theory levels considering the disrotatory (anti-W−H) electrocyclic ring opening revealed that both processes would yield comparable $k_H/k_D(d_2)$ values (ca. k_H/k_D = 1.10). These results suggest that the KIE experiment devised to address whether a double-bond isomerization involved in the rate-limiting step of the of *cis*-bicyclo[4.2.0]-oct-7-ene **1** to *cis*,*cis*-cycloocta-1,3-diene **5** conversion is inconclusive.

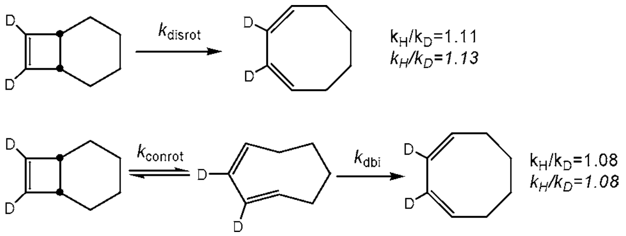

Figure 3. Kinetic isotope effects computed at the B3LYP/6-31G(d) (plain) and TPSS/6-31G(d) (italics) levels for the alternative disrotatory electrocyclic ring opening and the cis,trans → cis,cis isomerization through internal rotation of **3**.

Because of the fact that the measured KIE values seem inconclusive to ascertain which of the possible mechanisms occurs in this transformation, we considered an alternative deuterium substitution which might be suitable to distinguish both reaction paths. Computed KIE values obtained by labeling the bridgehead positions of bicyclo[4.2.0]oct-7-ene **1** with deuterium are notably different if a disrotatory ring opening or a cis,trans → cis,cis isomerization is the rate-limiting step of the rearrangement (ca. 2.5 and 2.0, respectively) (Figure 4). We suggest that this experiment would provide insightful information regarding the reaction mechanism.

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[14] See refs 1a and 1b and references therein.

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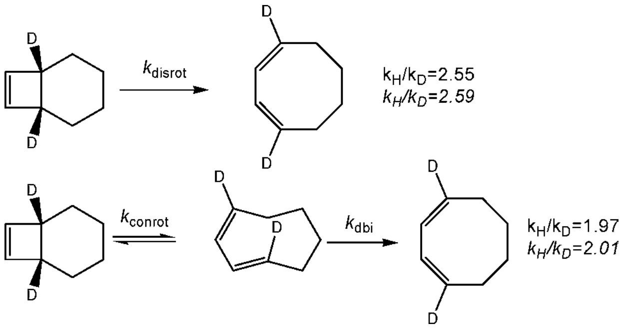

Figure 4. Kinetic isotope effects for 1,6-d_2-*cis*-bicyclo[4.2.0]oct-7-ene computed at the B3LYP/6-31G(d) (plain) and TPSS/6-31G-(d) (italics) levels for the alternative disrotatory electrocyclic ring opening and the cis,trans → cis,cis isomerization through internal rotation of **3**.

In summary, we showed that highly accurate theoretical methods support the conrotatory electrocyclic ring opening (W−H allowed) followed by double-bond isomerization as the lowest-energy alternative for the rearrangement of *cis*-bicyclo[4.2.0]oct-7-ene **1**. Computed KIE values also indicate that double-deuterium substitution of **1** at C7 and C8 is not a conclusive experiment to discard the computationally predicted conrotatory electrocyclic ring opening followed by a cis,trans → cis,cis isomerization reaction pathway. The experimental assessment of this intriguing mechanism is therefore still incomplete and subject to further studies.

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Supporting Information Available: Optimized B3LYP and CASSCF(4,4) Cartesian coordinates, and DFT, CCSD-(T), and MRMP energies. This material is available free of charge via the Internet at http://pubs.acs.org.

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