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Hiscotropic Rearrangements: Hybrids of Electrocyclic and Sigmatropic Reactions

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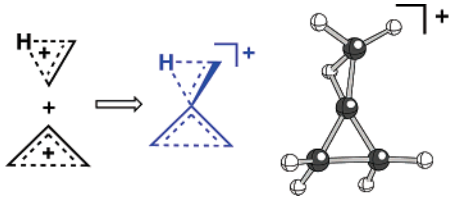
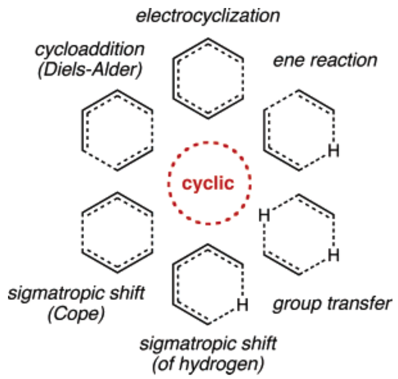


An unusual reaction manifold for cyclopropylcarbinyl cations, uncovered using B3LYP and MP2 calculations, is described. This reaction is a hybrid of a [1,2] sigmatropic hydrogen shift and a two-electron electrocyclic ring opening. These two processes occur through a single transition structure (i.e., they are concerted), although they are not synchronous. We call these reactions “hiscotropic” rearrangements. The potential energy surfaces for these reactions are often complicated, in some cases involving flat plateaus and bifurcations. Torquoselectivity occurs in some cases as a result of favorable orbital interactions between the breaking C−C and C−H bonds.

Introduction

Pericyclic reactions have a long history, rich with controversy and the excitement of reaction discovery and design.[1] On the basis of the concepts of orbital symmetry conservation, Woodward and Hoffmann constructed and described a set of guidelines for explaining and predicting the facility and stereochemistry of these types of reactions.[2] These principles, along with related concepts described by Fukui,[3] Zimmerman[4] and others,[1,5] are still employed routinely in analyzing pericyclic reaction mechanisms. The hallmark of a pericyclic reaction is the concerted, cyclic reorganization of electrons through a single delocalized, aromatic[4,6] transition state structure. Various types of pericyclic reactions have been described[2,5b] and representative examples of pericyclic transition structures are shown schematically in Chart 1 (here, six-electron reactions of hydrocarbons are shown[5d]).

CHART 1



Some of the most useful pericyclic reactions are those that occur in tandem−two or more pericyclic reactions occurring in sequence. For instance, a recent review describes many examples of cycloaddition/sigmatropic rearrangement combinations that have been applied to natural product synthesis.[7] Combinations of other pericyclic reaction types are also known. Of particular interest to us, however, are cases in which two (or more) pericyclic reactions are combined into *single-step* reactions, concerted rather than multistep combinations that

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(1) Houk, K. N.; González, J.; Li, Y. *Acc. Chem. Res.* **1995**, *28*, 81−90.

(2) (a) Woodward, R. B.; Hoffmann, R. *The Conservation of Orbital Symmetry*; Verlag Chemie: Weinheim, Germany, 1970. (b) Hoffmann, R.; Woodward, R. B. *Acc. Chem. Res.* **1968**, *1*, 17−22 and references therein. (c) Woodward, R. B.; Hoffmann, R. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 781−853.

(3) Fukui, K. *Acc. Chem. Res.* **1971**, *4*, 57−64 and references therein.

(4) Zimmerman, H. E. *Acc. Chem. Res.* **1971**, *4*, 272−280 and references therein.

(5) For leading references, see: (a) Dewar, M. J. S. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 761−776. (b) Houk, K. N.; Li, Y.; Evanseck, J. D. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 682−708. (c) Hoffmann, R.; Tantillo, D. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 5877−5882. (d) Hendrickson, J. B. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 47−76.

(6) For leading references, see: Jiao, H.; Schleyer, P. v. R. *J. Phys. Org. Chem.* **1998**, *11*, 655−662.

(7) Neuhütz, K.; Velker, J.; Neier, R. *Synthesis* **1998**, 227−255.

10.1021/jo052498z CCC: $33.50

CHART 2

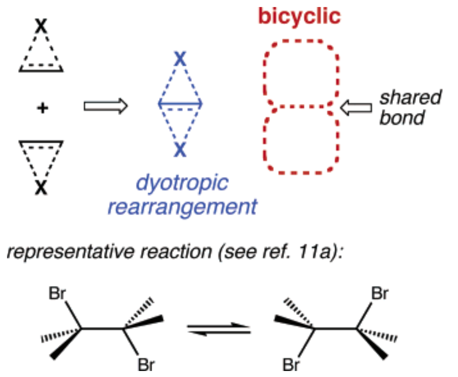


CHART 3

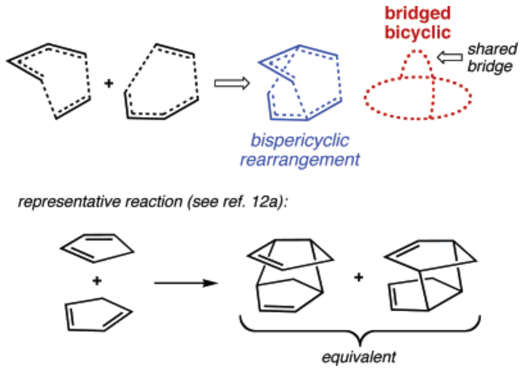
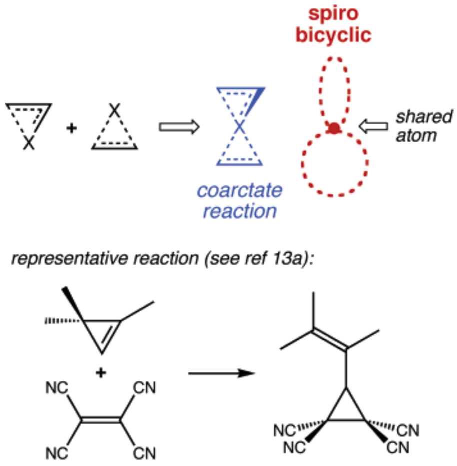


CHART 4



(even though they might no longer fit the definition of "pericyclic") can be described as fusions of multiple pericyclic processes. Such reactions are less common than "normal" pericyclic reactions (e.g., Chart 1), but they do exist.[8] For example, Reetz coined the term "dyotropic" to describe reactions in which two sigmatropic shifts occur simultaneously.[9] The transition structures for these reactions can be thought of as the transition structures for two sigmatropic shifts fused together into a single transition structure, such that they share a bond (e.g., Chart 2; here, two [1,2] shifts are combined) or are connected by an intervening π-system.[10,11] The fusion of two cycloaddition transition structures has also been described (e.g., Chart 3; here two [4 + 2] reactions are combined); these reactions have been termed "bispericyclic" and often involve complicated potential energy surfaces sporting calderas and bifurcations.[12] Herges and co-workers have published extensively on reactions with "coarctate" transition structures.[13] Some of these can also be viewed as combinations of various pericyclic reactions whose delocalized cycles share an atom or an intervening π-system (e.g., Chart 4; in this example an electrocyclization is combined with a cycloaddition [or cheletropic reaction]).

Recently, our theoretical studies[14] on possible reaction mechanisms for ladderane[15] formation led us to the discovery of a related rearrangement involving a sigmatropic shift combined with an electrocyclic ring opening. While attempting to locate the cyclopropyl cation **2** (Scheme 1) we consistently found only the ring-opened structure **3**,[16] and we were able to locate a transition structure that connected **1** and **3** directly.[17]

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[8] In a sense, the ene and group transfer reactions shown in Chart 1 can be thought of as concerted combinations of sigmatropic and cycloaddition reactions. For another related example, see: Kiefer, E. F.; Tanna, C. H. *J. Am. Chem. Soc.* **1969**, *91*, 4478−4480.

[9] (a) Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 129−130. (b) Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 130−131. (c) Reetz, M. T. *Tetrahedron* **1973**, *29*, 2189−2194. (d) Reetz, M. T. *Adv. Organomet. Chem.* **1977**, *16*, 33−65.

[10] Reetz distinguished between two types of dyotropic rearrangements: type I reactions involve the shifts of two groups in different directions such that their positions are interchanged, whereas type II reactions involve shifts without interchange of positions (here the two groups usually, but not always, migrate in the same direction).[9]

[11] Many interesting examples of dyotropic reactions have been found, including: (a) Rearrangements of vicinal dihaloalkanes: Zou, J.-W.; Yu, C.-H. *J. Phys. Chem. A* **2004**, *103*, 5649−5654 and references therein. (b) Applications in synthetic approaches to spirolactones: Li, W.; LaCour, T. G.; Fuchs, P. L. *J. Am. Chem. Soc.* **2002**, *124*, 4548−4549. (c) Organometallic rearrangements: Mobley, T. A.; Schade, C.; Bergman, R. G. *J. Am. Chem. Soc.* **1995**, *117*, 7822−7823. (d) Double alkyl shifts in carbocations: Vrcek, V.; Saunders, M.; Kronja, O. *J. Org. Chem.* **2003**, *68*, 1859−1866. (e) Stepwise possibilities: Zhang, X.; Houk, K. N.; Lin, S.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2003**, *125*, 5111−5114.

[12] For examples and leading references, see: (a) Caramella, P.; Quadrelli, P.; Toma, L. *J. Am. Chem. Soc.* **2002**, *124*, 1130−1131. (b) Quadrelli, P.; Romano, S.; Toma, L.; Caramella, P. *Tetrahedron Lett.* **2002**, *43*, 8785−8789. (c) Quadrelli, P.; Romano, S.; Toma, L.; Caramella, P. *J. Org. Chem.* **2003**, *68*, 6035−6038. (d) Leach, A. G.; Goldstein, E.; Houk, K. N. *J. Am. Chem. Soc.* **2003**, *125*, 8330−8339. (e) Limanto, J.; Khuong, K. S.; Houk, K. N.; Snapper, M. L. *J. Am. Chem. Soc.* **2003**, *125*, 16310−16321.

[13] (a) For leading references on "coarctate" transition structures, see: Herges, R. *Angew. Chem., Int.* Ed. **1994**, *33*, 255−276 and Herges, R. *J. Chem. Inf. Comput. Sci.* **1994**, *34*, 91−102. (b) A related concept involving transition structures with delocalized cycles that "cross without interacting", so-called "cruciconjugation", was described by Dewar and co-workers. See: Dewar, M. J. S.; McKee, M. L. *J. Am. Chem. Soc.* **1978**, *100*, 7499−7505. (c) Other examples of reactions that involve spiro bicyclic transition structures with orthogonal orbital arrays at their spiro centers include peracid- and dioxirane-promoted alkene epoxidations (for leading references on epoxidation transition structures, see Houk, K. N.; Liu, J.; Demello, N. C.; and Condroski, K. R. *J. Am. Chem. Soc.* **1997**, *119*, 10147−10152. Liu J.; Houk, K. N. *J. Org. Chem.* **1998**, *63*, 8565−8569. Bach, R. D.; Dmitrenko, O. *J. Phys. Chem. A* **2003**, *107*, 4300−4306) and some cyclopropanation reactions (for a recent example and leading references, see Zhao, C.; Wang, D.; Philips, D. L. *J. Am. Chem. Soc.* **2002**, *124*, 12903−12914; for a seminal report suggesting a bicyclic transition structure for the Simmons−Smith reaction, see: Simmons, H. E.; Smith, R. D. *J. Am. Chem. Soc.* **1959**, *81*, 4256−4264). (d) "Pseudopericyclic" reactions also involve orthogonal orbitals in their cyclic arrays. See, for example: Birney, D. M. *J. Am. Chem. Soc.* **2000**, *122*, 10917−10925 (a comparison with coarctate reactions with leading references). Ross, J. A.; Seiders, R. P.; Lemal, D. M. *J. Am. Chem. Soc.* **1976**, *98*, 4325−4327 (a seminal report).

[14] Nouri, D. H.; Tantillo, D. J. Unpublished results.

[15] (a) Hopf, H. *Angew. Chem., Int. Ed.* **2003**, *42*, 2822−2825. (b) Damsté, J. S. S.; Strous, M.; Rijpstra, W. I. C.; Hopmans, E. C.; Geenevasen, J. A. J.; van Duin, A. C. T.; van Niftrik, L. A.; Jetten, M. S. M. *Nature* **2002**, *419*, 708−712. (c) Kuypers, M. M. M.; Sliekers, A. O.; Lavik, G.; Schmid, M.; Jørgensen, B. B.; Kuenen, J. G.; Damsté, J. S. S.; Strous, M.; Jetten, M. S. M. *Nature* **2003**, *422*, 608−611. (d) Nouri, D. H.; Tantillo, D. J. *Curr. Org. Chem.* In press.

SCHEME 1

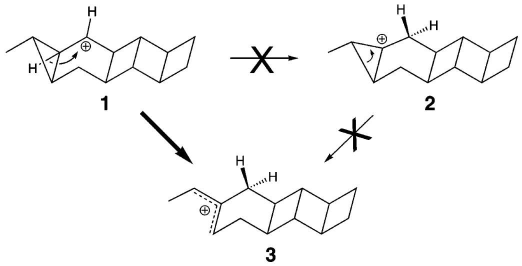
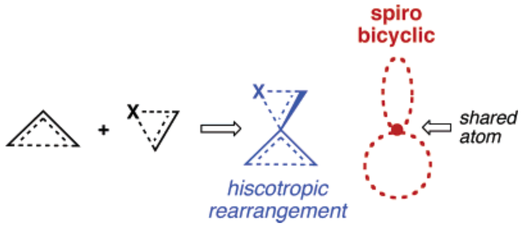
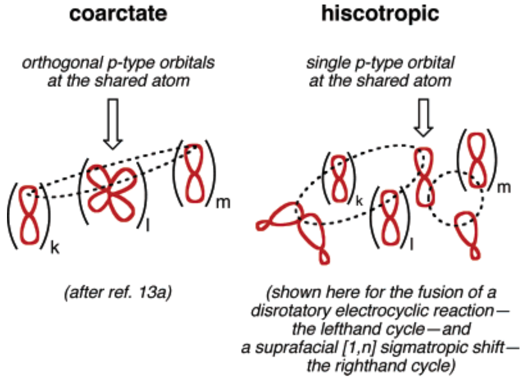


CHART 5



Although not synchronous, this reaction is concerted and therefore represents a different sort of fusion between two pericyclic transition structures: the combination of a [1,2] sigmatropic shift of hydrogen[18] and a two-electron electrocyclic ring opening (Chart 5, X = H).[16,19] We propose the name "hiscotropic" for this type of rearrangement: "hisco" from a Latin word for "open" and "tropic" being traditionally associated with rearrangements involving shifts.[20,21] Note that this type of reaction differs from the coarctate reactions described above in that the link between the two delocalized cycles involves a single p-type orbital in a hiscotropic reaction, whereas two orthogonal p-type orbitals are involved in a coarctate reaction (Chart 6).[13]

CHART 6



Thus, whereas pericyclic reactions have cyclically delocalized transition structures, dyotropic, bispericyclic, (some) coarctate, and hiscotropic reactions have bicyclically delocalized transition structures (compare Charts 1−5).[22] We now describe detailed theoretical studies on the various factors that control the rates, synchronicity, and stereoselectivity of hiscotropic reactions of the type shown in Scheme 1.[20] To the best of our knowledge, such reactions have not been proposed previously, and it is our hope that the theoretical studies described herein will both encourage and facilitate experimental studies on this intriguing class of reactions.

Methods

Geometries were optimized without symmetry constraints at the B3LYP/6-31G(d)[23] level of theory. All structures were characterized by frequency analysis, and reported energies for stationary points (except when included in IRC pictures) include zero-point energy corrections scaled by 0.9806.[24] Selected structures were also optimized using MP2/6-31G(d)[25] (see text for details), and reported energies for these structures include zero-point energy corrections scaled by 0.9661.[24] Unless otherwise noted, reported results are from our B3LYP/6-31G(d) calculations. Recent reports comparing the B3LYP and MP2 methods for computing geometries, relative energies, and electronic properties of various carbocations include those in ref 26 and papers cited therein. In general, MP2 appears

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(16) This is consistent with the previously reported difficulty in locating cyclopropyl cations as minima. For leading references on cyclopropyl cations, see: (a) Prakash, G. K. S.; Buchholz, H.; Reddy, V. P.; de Meijere, A.; Olah, G. A. *J. Am. Chem. Soc.* **1992**, *114*, 1097−1098. (b) Friedrich, E. C. *The Chemistry of the Cyclopropyl Group*; Rappoport, Z., Ed.; Wiley: New York, 1987. (c) Boche, G.; Walborsky, H. M. *Cyclopropane Derived Reactive Intermediates*; Patai, S., Rappoport, Z., Eds.; Wiley: Chichester, 1990; Chapter 3. (d) Marvell, E. N. *Thermal Electrocyclic Reactions*; Academic Press: New York, 1980; Chapter 3. (e) Radom, L.; Hariharan, P. C.; Pople, J. A.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1973**, *95*, 6531−6544. (f) For an interesting recent report, see: Kozhushkov, S. I.; Späth, T.; Kosa, M.; Apeloig, Y.; Yufit, D. S.; de Meijere, A. *Eur. J. Org. Chem.* **2003**, 4234−4242.

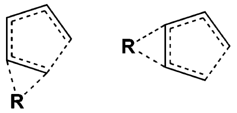
(17) This was confirmed using IRC calculations. See Methods.

(18) Cationic [1,2] hydrogen (or alkyl shifts) generally have very low activation barriers, and in some cases bridged hypercoordinate structures are actually minima rather than transition structures (so-called nonclassical ions). For leading references, see: (a) Issue 12 of *Acc. Chem. Res.* **1983**, *16*, 6. (b) Brown, H. C. (with comments by Schleyer, P. v. R.) *The Nonclassical Ion Problem*; Plenum: New York, 1977.

(19) The transition structure for this rearrangement can also be thought of as a protonated version of that for the methylenecyclopropane-to-trimethylene methane rearrangement. For a recent discussion of the protonation of pericyclic transition structures, see: ref 5c. For leading references on the methylenecyclopropane-to-trimethylene methane rearrangement, see: Lewis, S. B.; Hrovat, D. A.; Getty, S. J.; Borden, W. T. *J. Chem. Soc., Perkin Trans. 2* **1999**, 2339−2347.

(20) Combinations of other types of electrocyclic and sigmatropic reactions are, of course, possible, and studies on these will be reported in due course. If such reactions do turn out to be hiscotropic, it will likely become necessary to include numerical specifications with their names. For example, the reactions described herein could be called [1,2]/two-electron hiscotropic rearrangements.

(21) Reetz has previously mentioned the possibility of combining sigmatropic and electrocyclic reactions into a concerted proccess, but only for the systems shown below, which are significantly different from the reactions we are describing.[9c] We propose that the sorts of reactions with transition structures such as those shown below (calculations on which we will describe in a separate account;[14] for a recent computational study of a reaction of this type, see Lewis, F. D.; Sajimon, M. C.; Zuo, X.; Rubin, M.; Gevorgyan, V. *J. Org. Chem.* **2005**, *70*, 10447−10452) be termed "type I" hiscotropic reactions, whereas the sorts of reactions shown in Scheme 1 and Chart 5 be termed "type II" hiscotropic reactions. The distinction here is in the nature of the fusion between the electrocyclic and sigmatropic parts of the transition structure. Whereas in type I hiscotropic reactions these two substructures share a bond, in type II hiscotropic reactions they share only an atom, i.e., they are spiro-fused.[13] It should also be noted that Reetz did not suggest a name for the type of reactions whose transition structures are drawn below, instead including them with his dyotropic reactions, which aside from these two cases did not involve cyclizations. Note that Reetz's examples are also neutral, not cationic.



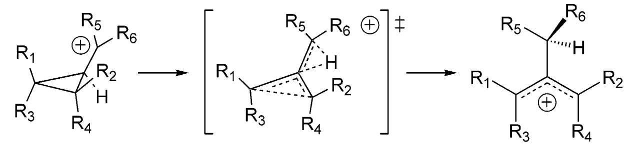
(22) Group transfer reactions of the type shown in Chart 1 are also often referred to as dyotropic reactions. It should be noted, however, that this type of reaction involves only a *single* cycle of delocalized electrons.

(23) (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648−5652. (b) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 1372−1377. (c) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785−789. (d) Stephens, P. J.; Devlin, F. J.; Chabalowski, C. F.; Frisch, M. J. *J. Phys. Chem.* **1994**, *98*, 11623−11627.

(24) Scott, A. P.; Radom, L. *J. Phys. Chem.* **1996**, *100*, 16502−16513.

(25) Møller, C.; Plesset, M. S. *Phys. Rev.* **1934**, *46*, 618−622.

SCHEME 2



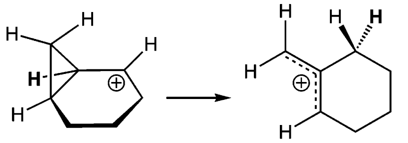
R_1 thru R_6 = H or CH_3

or

R_2/R_6 = $CH_2CH_2CH_2$, R_1, R_3, R_5 = H or CH_3, R_4 = H

(see Supporting Information for details; structures also shown in Figure 3)

SCHEME 3



4 **5**

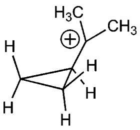
to slightly favor more delocalized cation structures compared to B3LYP, although differences between the two methods are frequently small. Both B3LYP and MP2 have been applied to the study of pericyclic reactions as well;[27] B3LYP/6-31G(d), in particular, has been shown to perform very well for such reactions. Intrinsic reaction coordinate (IRC)[28] calculations were also used to further verify the identity of transition structures. All calculations were performed with GAUSSIAN03.[29] Structural drawings were produced using Ball & Stick.[30]

Results and Discussion

Disrotation versus Conrotation. We examined a series of model systems (Scheme 2; details are available in Supporting Information) in order to explore the generality of hiscotropic rearrangements such as **1** to **3**. As a representative example, consider the **4** to **5** reaction shown in Scheme 3.[31] Here the ladderane substructure and methyl group on the cyclopropane have been removed from **1**. Like **1**, **4** rearranges to **5** via a concerted process. An IRC plot for this reaction is shown in Figure 1. The reaction is clearly concerted, although the hydrogen shift and ring opening are rather asynchronous. At the transition structure, the migrating hydrogen has traversed approximately half of the distance toward its destination. The reaction coordinate preceding the transition structure first involves a redistribution of electron density that shortens one of the cyclopropyl distances that started out quite long in the reactant (1.76 Å) due to hyperconjugation;[32] this likely contributes significantly to the magnitude of the activation barrier.[33] This is then followed by migration of the hydrogen. The reaction coordinate following the transition structure is dominated by disrotatory ring opening. Similar results were obtained using MP2 (see Supporting Information for details).[34]

The IRC plot in Figure 1 shows that the ring opening is disrotatory (**A**, Chart 7).[35] In principle, though, another disrotatory pathway (**B**) and two conrotatory pathways (**C** and **D**) are possible. The presence of the six-membered ring forces the C−H_c bond to rotate "inward", however, to avoid formation of a *trans* partial double bond in the six-membered ring of the product. This geometry-induced torquoselectivity[36] effectively prevents **B** and **D** from occurring. If the ring-opening portion of the rearrangement behaves like a "normal" two-electron electrocyclic ring opening, then orbital symmetry considerations would predict that disrotation should be favored over conrotation and path **A** should predominate.[2,16c,d] This is what we observe. In fact, we could not locate any alternative transition structures for the **4** to **5** rearrangement.[37]

Similar results were obtained for the other systems in Scheme 2 (see Supporting Information for details). Concerted asynchronous transition structures for hiscotropic rearrangements were located for all but **6**−**8** (vide infra). The activation barriers and degree of asynchronicity varied somewhat from system to system, however, as discussed below.



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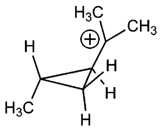

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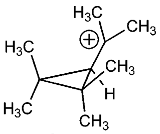

8

Orbital-Controlled Torquoselectivity. In the **4** to **5** reaction there is an additional factor that may reinforce the preference for disrotation along path **A**: a favorable orbital interaction in the preferred transition structure between the σ_{C-C} fragment

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[26] (a) Vrcek, I. V. Vrcek, V. Siehl, H.-U. *J. Phys. Chem. A* **2002**, *106*, 1604−1611. (b) Farcasiu, D.; Lukinskas, P.; Pamidighantam, S. V. *J. Phys. Chem. A* **2002**, *106*, 11672−11675. (c) Gutta, P.; Tantillo, D. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 2719−2723. (d) Siebert, M. R.; Tantillo, D. J. *J. Org. Chem.* **2006**, *71*, 645−654.

[27] For leading references, see: (a) Wiest, O.; Montiel, D. C.; Houk, K. N. *J. Phys. Chem. A* **1997**, *101*, 8378−8388. (b) Houk, K. N.; Beno, B. R.; Nendel, M.; Black, K.; Yoo, H. Y.; Wilsey, S.; Lee, J. K. *J. Mol. Struct. (THEOCHEM)* **1997**, *398*−*399*, 169−179. (c) Hrovat, D. A.; Beno, B. R.; Lange, H.; Yoo, H.-Y.; Houk, K. N.; Borden, W. T. *J. Am. Chem. Soc.* **2000**, *122*, 7456−7460. (d) Guner, V.; Khuong, K. S.; Leach, A. G.; Lee, P. S.; Bartberger, M. D.; Houk, K. N. *J. Phys. Chem. A* **2003**, *107*, 11445−11459.

[28] (a) Gonzalez, C.; Schlegel, H. B. *J. Phys. Chem.* **1990**, *94*, 5523−5527. (b) Fukui, K. *Acc. Chem. Res.* **1981**, *14*, 363−368.

[29] *GAUSSIAN03*, revision B.04; M. J. Frisch et al., Gaussian, Inc., Pittsburgh, PA, 2003 (full reference in Supporting Information).

[30] Müller, N.; Falk, A. *Ball & Stick V.3.7.6*; molecular graphics application for MacOS computers; Johannes Kepler University: Linz, 2000.

[31] (a) Other portions of the $C_7H_{11}^+$ potential energy surface have been described previously. See: Fuchs, J.-F.; Mareda, J. *J. Mol. Struct. (THEOCHEM)* **2005**, *718*, 93−104. (b) Experiments on **4** in superacid are described in: Olah, G. A.; Prakash, G. K. S.; Rawdah, T. N. *J. Org. Chem.* **1980**, *45*, 965−969.

[32] (a) Mo, Y.; Schleyer, P. v. R.; Jiao, H.; Lin, Z. *Chem. Phys. Lett.* **1997**, *280*, 439−443. (b) Olah, G. A.; Reddy, V. P.; Prakash, G. K. S. *Chem. Rev.* **1992**, *92*, 69−95.

[33] (a) In a sense, this particular example can be thought of as a hybrid of not only a hydrogen shift and an electrocyclic ring opening but also an alkene attack on a carbocation. (b) Barriers to rotation in simple cyclopropylcarbinyl cations about their $C^+−C_{cyclopropyl}$ bonds are typically ~15 kcal/mol. See, for example: Kabakoff, D. S.; Namanworth, E. *J. Am. Chem. Soc.* **1970**, *92*, 3234−3235 and ref 32. (c) Potential problems with synchronous "multibond" reactions have been discussed previously; see, for example: Dewar, M. J. S. *J. Am. Chem. Soc.* **1984**, *106*, 209−219. Dewar, M. J. S.; Jie, C. *Acc. Chem. Res.* **1992**, *25*, 537−543. Dewar, M. J. S.; Olivella, S.; Stewart, J. J. P *J. Am. Chem. Soc.* **1986**, *108*, 5771−5779 (ref 2 of this paper comments on concerted "two-stage" reactions). See also ref 1. (d) Roberts, J. D.; Mazur, R. H. *J. Am. Chem. Soc.* **1951**, *73*, 3542−3543.

[34] The relative energies (ZPE corrected) of the reactant (**4**), transition structure, and product (**5**) at the MP2/6-31G(d) level are 0.00, 39.08, and 0.93 kcal/mol.

[35] Note that curved arrows are used here not to show the movement of pairs of electrons but rather to show the sense of rotation of the groups at the ends of the breaking C−C bond.

[36] For leading references on torquoselectivity, see: Dolbier, W. R., Jr.; Koroniak H.; Houk, K. N.; Sheu, C. *Acc. Chem. Res.* **1996**, *29*, 471−477.

[37] Constrained models of the putative conrotatory transition structure for path **C** (obtained by rotating the methylene group of the breaking bond by 15−20°) were found to be 5−6 kcal/mol higher in energy than the transition structure shown in Figure 1.

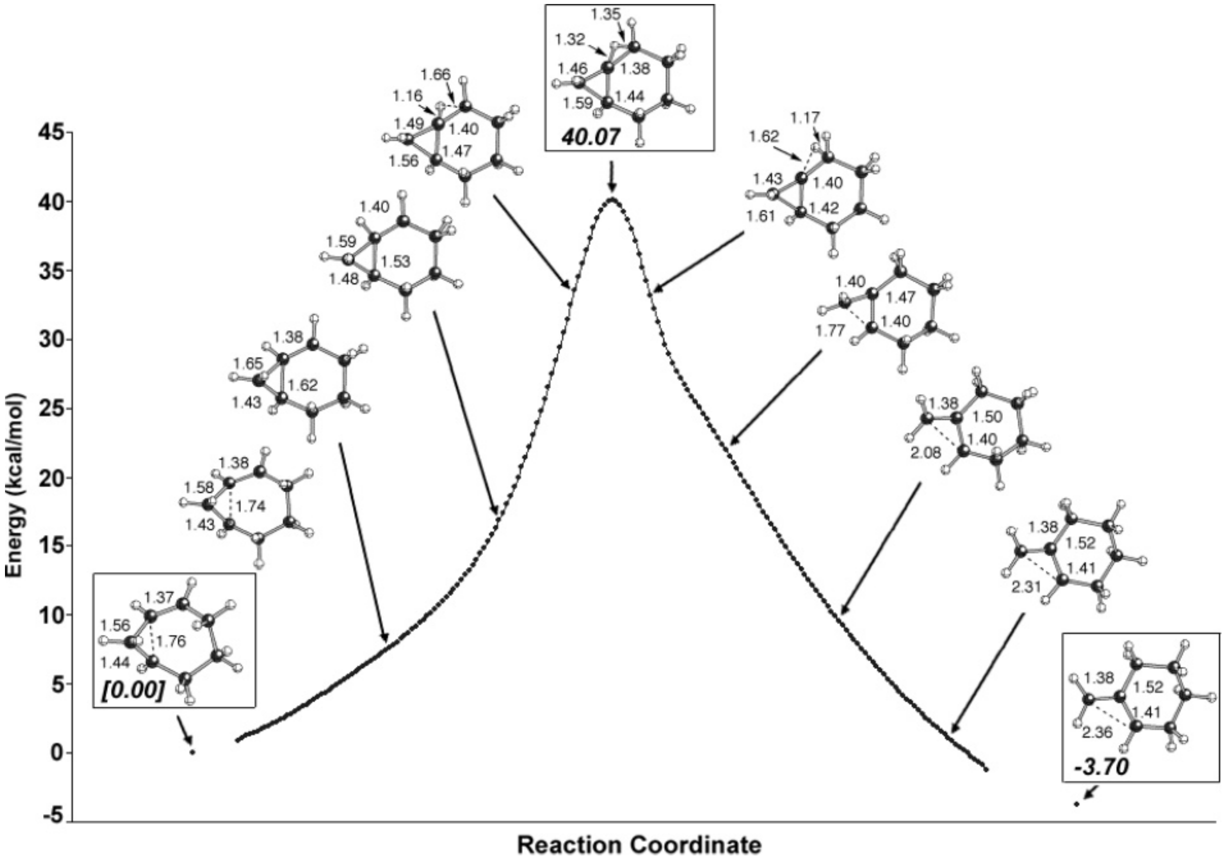
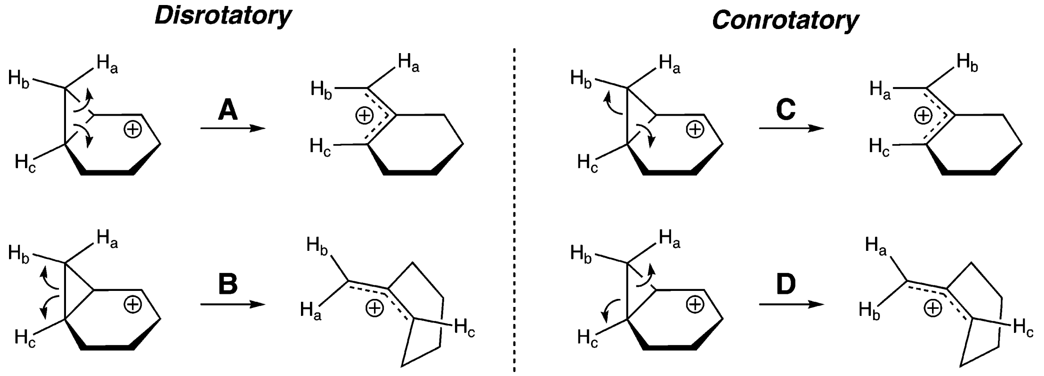


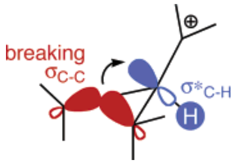
FIGURE 1. IRC (B3LYP/6-31G(d)) for rearrangement of **4**. Structures of selected points along the IRC are shown, with selected distances in Å. The top structure is the fully optimized transition structure and the leftmost and rightmost structures are the fully optimized minima that flank it (**4** and **5**). Relative energies, without zero point energy corrections, are shown in kcal/mol. The relative energies of the three stationary points with scaled (by 0.9806) zero point energy corrections included are 0.00, 36.93, and −4.65 kcal/mol, respectively.[34]

CHART 7



orbital[38] associated with the breaking C−C bond and the σ^*_{C-H} fragment orbital associated with the breaking C−H bond (Chart 8). This interaction could possibly bias the direction of ring opening even in the absence of geometric constraints (Scheme 4), since good overlap of these orbitals is only possible for disrotation of the breaking bond *away* from the C−H bond (i.e., towards the backside of the C−H bond); we refer to this sense of rotation as "dis-away".

CHART 8



To assess the proficiency of this interaction in controlling torquoselectivity,[36] we compared the energetics of dis-away and dis-towards ring-opening pathways for **9** (Scheme 2 with $R_1 = R_2 = R_3 = R_4 = R_5 = R_6 = H$) by performing a series of constrained optimizations (Figure 2).[39]

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[38] In the spirit of "portable" theories and models (Hoffmann, R. *Am. Sci.* **2003**, *91*, 9−11), our description of orbital interactions throughout this paper makes use of the language of "fragment" or "semi-delocalized" orbitals, in this case simple p orbitals and σ and σ* orbitals associated with bonds, rather than fully delocalized molecular orbitals.

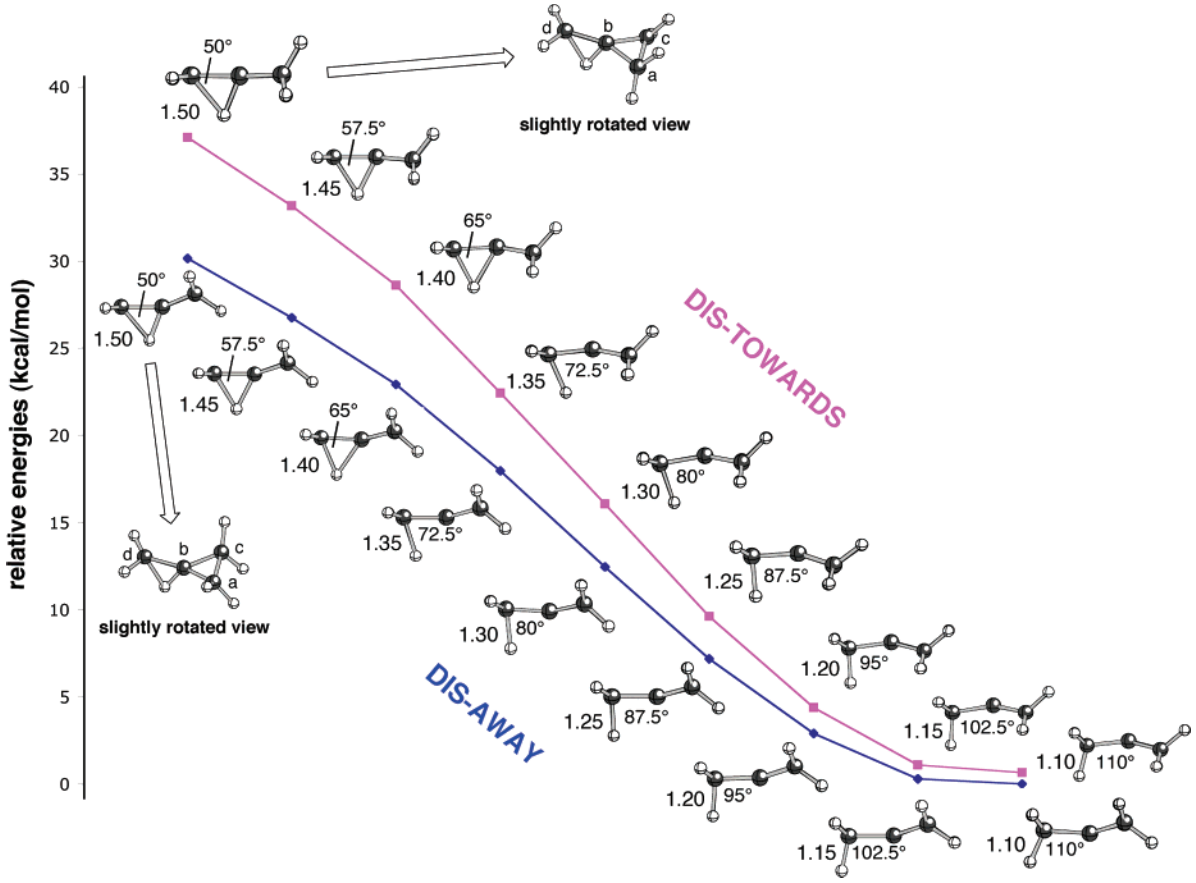
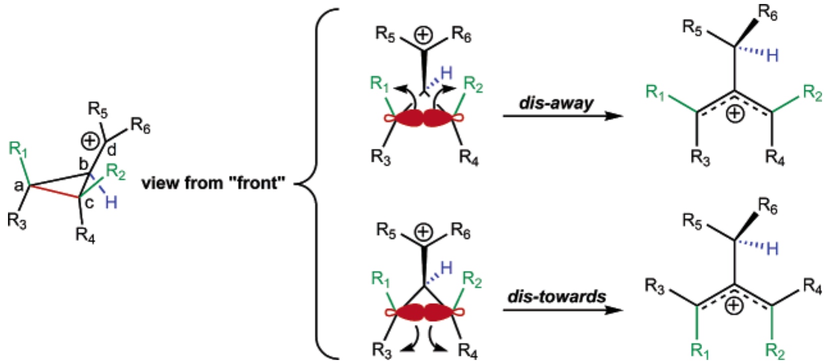


FIGURE 2. Dis-away (bottom) and dis-towards (top) structures based on **9** (B3LYP/6-31G(d); very similar results were obtained using MP2, see Supporting Information for details; side views for all structures are shown and slightly rotated views in which all atoms are visible are shown for selected structures). Systematically varied C−H distances (Å) and angles are labeled. All structures are on the same relative energy scale.

SCHEME 4



As shown in Figure 2, for all positions of the migrating hydrogen, dis-away structures are lower in energy, consistent with the presence of the orbital interaction described above. The energy difference between dis-away and dis-towards structures decreases as the hydrogen migrates away from the cyclopropane, however. This makes sense given that the further the hydrogen migrates the more the empty orbital at C_b resembles a simple p-orbital. The reduced asymmetry of this acceptor orbital allows interaction with the breaking C_a-C_c bond to occur from either the "away" or "towards" face. Note that C_b actually pyramidalizes[16c,d] as the hydrogen departs, in whichever direction will maximize this interaction. Notice also that in the dis-towards structures where the hydrogen has not migrated very much (top left) the breaking C_a-C_c bond does not bend significantly out of the plane of the other carbon atoms. Bending toward the migrating hydrogen at this point would actually bring the breaking bond near to the node of the σ^*_{C-H} orbital (see Chart

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(39) The constraints used to produce the dis-away structures (labels defined in Scheme 4): (a) the breaking C_a-C_c bond length was fixed at 1.55 Å, (b) the $R_1-C_a-C_b-C_c$ and $R_2-C_c-C_b-C_a$ dihedral angles were fixed at 76° and −76°, respectively, (c) the $R_3-C_a-C_b-C_c$ and $R_4-C_c-C_b-C_a$ dihedral angles were fixed at −141° and 141°, respectively, (d) the C_d-H distances were varied from 1.50 to 1.10 Å in 0.05 Å increments, and (e) simultaneously, the $H-C_d-C_b$ angles were varied from 50° to 110° in 7.5° increments. An analogous series of constrained optimizations was performed with the dihedral angles interchanged such that all structures had their methylene groups rotated in a dis-towards fashion (top of Figure 2).

SCHEME 5

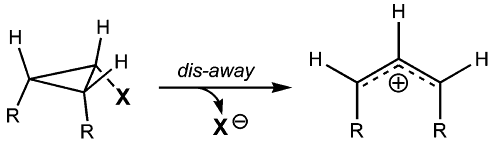
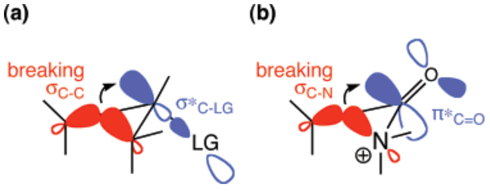


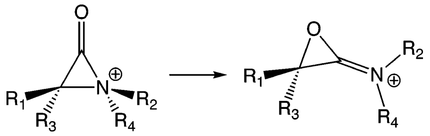
CHART 9



8); it is only when this orbital becomes more p-like that bending toward it becomes favorable. The maximum energy difference between the constrained dis-away and dis-towards structures is on the order of 5−10 kcal/mol, suggesting that the orbital interaction shown in Chart 8 has significant potential for influencing the torquoselectivity of these reactions even though $\sigma^*_{\mathrm{C-H}}$ orbitals are not particularly strong acceptors; how much influence this interaction actually has on the course of these reactions will depend on the degree of synchronicity between C−C and C−H cleavage, however (vide infra).

Analogous orbital interactions have been invoked to explain stereoselectivity in other reactions. Of particular note are the solvolytic ring openings of cyclopropyl halides and sulfonates described by the DePuy−Woodward−Hoffmann rule (Scheme 5).[16c,d,40] In these reactions a leaving group is lost while a cyclopropane ring is opened, again avoiding a discrete cyclopropyl cation. In the hiscotropic rearrangements described herein, the analogue of the leaving group (a hydride) is not lost but rather is captured straightaway by an adjacent cationic center. In both types of reaction, orbital overlap between the breaking C−C bond and the antibonding orbital of the C−X bond influences the torquoselectivity of the ring opening (Chart 9, a; compare with Chart 8). The preference for dis-away over dis-towards ring opening in the systems in Scheme 5 (based on gas-phase calculations of dis-away and dis-towards ionization transition structures for cyclopropyl bromides) has been estimated to range from ~6 to ~37 kcal/mol, depending on both the electronic properties and steric bulk of substituents.[40a,b] Previous calculations on rearrangements of *N*-protonated α-lactams (Scheme 6) also revealed a similar orbital interaction,[41] in that case between a breaking C−N bond and the π^* orbital of an adjacent carbonyl group (Chart 9, b), another example of the tendency of three-membered rings to utilize orbital interactions to control the torquoselectivity of their opening.

SCHEME 6



General Trends: Overall Energetics. Barriers for hiscotropic rearrangements of the cyclopropylcarbinyl cations shown in Scheme 2 range from 25 to 42 kcal/mol (see Supporting Information for details).[42,43] Although barriers for isolated [1,2] hydrogen shifts and cyclopropyl cation ring openings are generally very low or nonexistent,[16,18] barriers for hiscotropic rearrangements, in which these two events are intimately coupled, are fairly high.[33c] One factor contributing to the height of these barriers is the loss of hyperconjugation that occurs along the early portion of the reaction coordinate. Typical of cyclopropylcarbinyl cations,[16] all of the reactants display significant hyperconjugation between their cationic centers and cyclopropane bonds (one or both of the bonds that *do not* break in the rearrangements; see Figure 1 for an example). As discussed above, this hyperconjugation must be removed before the hydrogen shift can occur (i.e., the "empty" p-orbital must rotate into alignment with the C−H bond rather than the bonds of the cyclopropane), and thus a significant penalty must be paid before the rearrangement can proceed.[33b] It should be noted, however, that even though this obstacle must be overcome, the barriers for the hiscotropic rearrangements are comparable to those for typical DePuy−Woodward−Hoffmann-type reactions (barriers for these are generally ~25−35 kcal/mol).[16c,d,40] At first glance it might seem that a hydride ion is not nearly as good a leaving group as a halogen or sulfonate, but in the hiscotropic rearrangements its departure is readily facilitated by a nearby carbocation.

Some trends can be seen in the energetics for hiscotropic rearrangements of the cyclopropyl cations in Scheme 2 (see Figure S1). First, barriers are generally higher for the bicyclic

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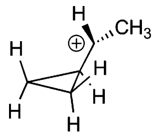
(40) For recent quantum chemical calculations on such reactions, see: (a) Faza, O. N.; López, C. S.; Álvarez, R.; de Lera, A. R. *Org. Lett.* **2004**, *6*, 905−908. (b) Faza, O. N.; López, C. S.; Álvarez, R.; de Lera, A. R. *J. Org. Chem.* **2004**, *69*, 9002−9010. Seminal reports: (d) DePuy, C. H.; Schnack, L. G.; Hausser, J. W.; Wiedemann, W. *J. Am. Chem. Soc.* **1965**, *87*, 4006. (e) DePuy, C. H.; Schnack, L. G.; Hausser, J. W. *J. Am. Chem. Soc.* **1966**, *88*, 3343−3346. (f) Woodward, R. B.; Hoffmann, R. *J. Am. Chem.* Soc. **1965**, *87*, 394−397. See also: (g) Schleyer, P. v. R.; Su, T. M.; Saunders, M.; Rosenfeld, J. C. *J. Am. Chem. Soc.* **1969**, *91*, 5174−5176. (h) Related orbital effects have been described for the stereomutation of 1,1-difluorocyclopropane and related species. See, for example: Getty, S. J.; Hrovat, D. A.; Borden, W. T. *J. Am. Chem. Soc.* **1994**, *116*, 1521−1527.

(41) Tantillo, D. J.; Houk, K. N.; Hoffman, R. V.; Tao, J. *J. Org. Chem.* **1999**, *64*, 3830−3837.

(42) (a) Barriers for the systems with secondary cations are based on reactants with the conformation shown below (i.e., the H at the cation site pointed over the face of the cyclopropane ring); conformers with the cation center rotated by ~180° were typically 1−4 kcal/mol higher in energy. See Supporting Information for details. (b) The effect of solvent on these reactions is a complicated issue (since the cations described, if examined in solution, could be formed in several ways, e.g., alkene protonation or ionization, and in such cases the conjugate base of the protonating group or the properties of the departed leaving group could be important). Nonetheless, we have performed some simple test calculations using a continuum solvation model for water (CPCM-B3LYP/6-31G(d) with UAKS radii; for details on this methodology, see: Barone, V.; Cossi, M. *J. Phys. Chem. A* **1998**, *102*, 1995−2001. Cossi, M.; Rega, N.; Scalmani, G.; Barone, V. *J. Comput. Chem.* **2003**, *24*, 669−681. Takano, Y.; Houk, K. N. *J. Chem. Theor. Comput.* **2005**, *1*, 70−77). These calculations indicate, for example, that for the **4** → **5** rearrangement bond lengths change by <0.02 Å and the activation barrier increases by ~3 kcal/mol upon inclusion of the water model. We have also checked that both **TS**$_1$ and **TS**$_2$ (Figure 5) persist in water; they do (the maximum bond length change observed is 0.04 Å), although their relative energies change by a few kcal/mol. Similar observations have been reported for other cations; see, for example: Schreiner, P. R.; Severance, D. L.; Jorgensen, W. L.; Schleyer, P. v. R.; Schaefer, H. F., III. *J. Am. Chem. Soc.* **1995**, *117*, 2663−2664.



(43) Barriers of this magnitude are not unusual for pericyclic reactions of hydrocarbons. See: Black, K. A.; Wilsey, S.; Houk, K. N. *J. Am. Chem. Soc.* **1998**, *120*, 5622−5627. See also refs 5 and 27.

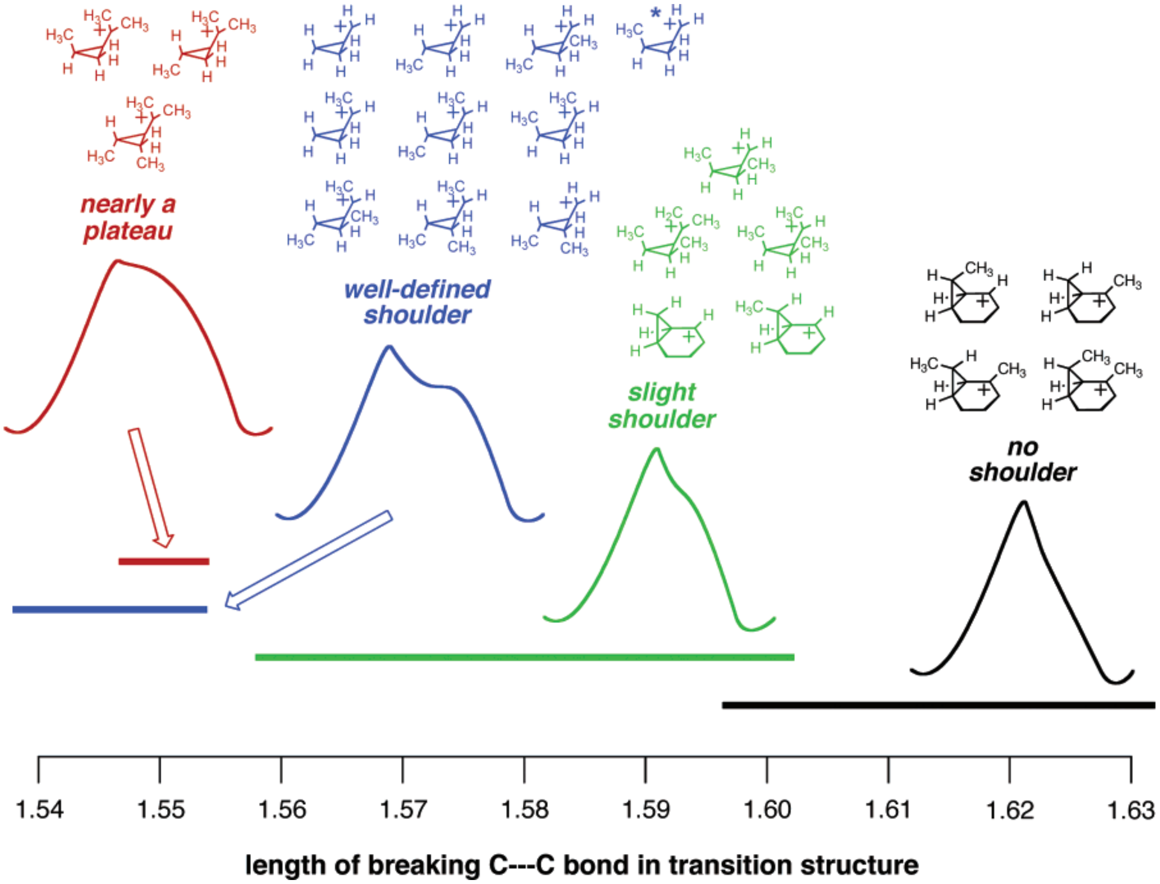


FIGURE 3. Dependence of potential energy surface shape on length of breaking C- - -C bond in transition structures for hiscotropic rearrangements of systems from Scheme 2 (and Figure S1). Solid lines show the range of bond lengths observed for each type of surface. The blue structure marked with an asterisk has a C- - -C bond length of 1.54 Å, but a reaction coordinate that is on the border between "well-defined shoulder" and "slight shoulder."

systems than for the monocyclic systems examined. Barriers are also slightly higher for migration toward primary cations than toward secondary and tertiary cations, with migration toward secondary cations having the lowest barriers. Not surprisingly, migrations toward primary cations are generally more exothermic than toward secondary cations, which are generally more exothermic/less endothermic than migrations toward tertiary cations. The effects of adding methyl substituents onto the breaking C−C bonds are less regular. Clearly, various subtle steric effects are working in concert with the electronic effects associated with varying the substitution of these cations to determine the absolute magnitudes of the barriers and reaction energies.

It should be noted that cyclopropylcarbinyl-homoallyl-bicyclobutonium interconversions provide alternative reaction pathways that will likely be easier than hiscotropic rearrangements for many simple systems.[32b,33d] We do not intend to imply that hiscotropic rearrangements will necessarily be the dominant reactions for the carbocations included in this paper. Rather, we hope to present a framework of concepts that will aid the design of systems for which these unusual reactions might be observed experimentally.

The Hazy Border between Concerted and Stepwise. The rearrangements of all but three of the cyclopropylcarbinyl cations examined (**6**−**8**) are concerted, yet ring opening and hydrogen shifting in all cases are asynchronous. The degree of asynchronicity of these two events is reflected in the shapes of the reaction coordinate for each reaction. As shown in Figure 3, we have divided the reactions into four types, depending on the presence or absence of a shoulder following the transition structure and its slope, as revealed in IRC calculations for each reaction.[44] As shown in this figure, the type of reaction coordinate observed appears to be correlated with the degree of C−C bond cleavage at the transition structure. When C−C bond breaking is relatively advanced in the transition structure (i.e., at ∼1.6 Å), little or no shoulder is observed. In these reactions, cyclopropane cleavage is most synchronous with C−H bond breaking (remember that in all cases, C−H bond breaking leads C−C bond breaking). As C−H and C−C bond breaking become more and more disconnected, the C−C distance in the transition structure is smaller and a more pronounced shoulder appears. In the extreme, the shift and ring opening are essentially separate and flat plateaus arise. No well-defined intermediates could be located for any of the cases examined, although for cyclopropylcarbinyl cations **6**−**8**, separate transition structures for hydrogen shift and ring opening connected by extremely flat plateaus were observed; a representative example, the reaction coordinate for **6**, is shown in Figure 4. It should be noted that several cases were reexamined using MP2/6-31G(d) (see Supporting Information for details), and in general, the MP2 surfaces tend to have much less prominent shoulders and plateaus.[45]

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[44] Admittedly, this categorization is somewhat subjective; nonetheless, we feel it is useful. See Supporting Information for IRC plots for all reactions.

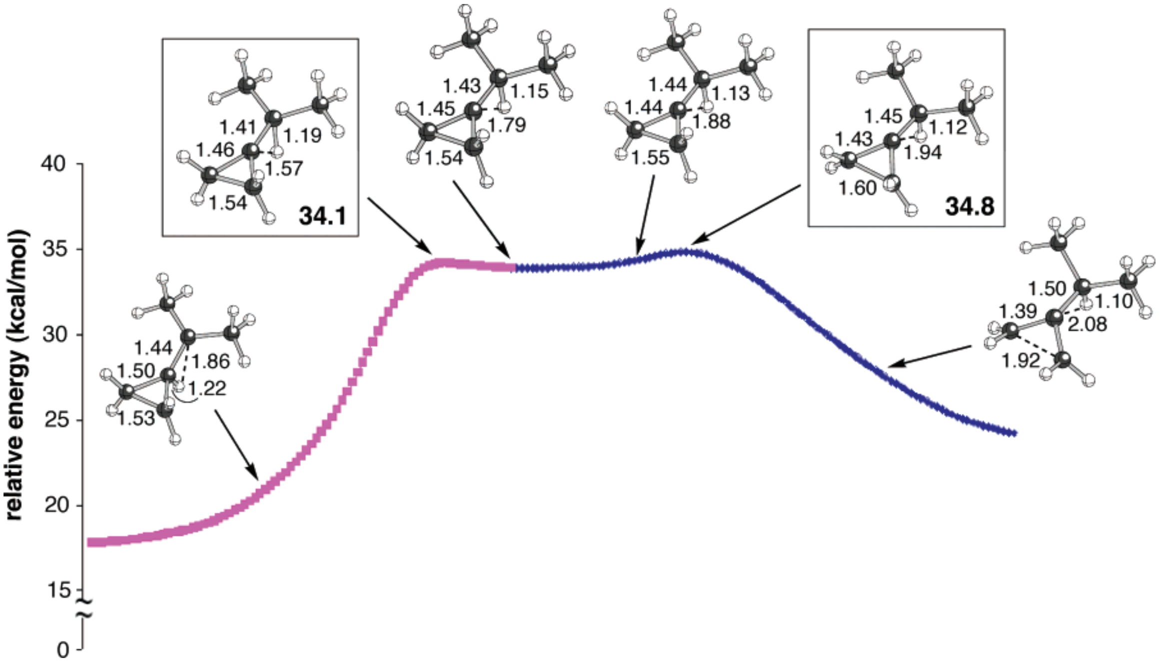
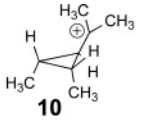


FIGURE 4. Portion of the reaction coordinate for rearrangement of **6**. This reaction coordinate was constructed by overlaying separate IRC plots generated from each transition structure (shown in boxes). No actual intermediate could be located, presumably due to the flatness of the surface in this region. The important point here is that the energy surface in this region is very flat. Selected distances are shown in Å.

Post-Transition State Stereoselectivity Determination. In the cases with well-defined shoulders/plateaus, no significant C−C bond breaking has occurred in the transition structures and consequently disrotation in one direction or the other has not begun. In fact, in such cases the plateaus following the transition structures involve structures that resemble cyclopropyl cation intermediates, but conversion of these structures to the product allyl cations is barrierless (or close to barrierless for cations **6**−**8**). We wondered then if there is any real preference for dis-towards or dis-away stereochemistry in these cases. Our IRC calculations follow a path down to one of the allyl cation products, but is the path to the other product any less favorable if both are barrierless exit channels off of a flat plateau?

For cation **6**, the IRC from the second transition structure leads to the dis-towards product (Figure 4).[46] To probe the energetics of descending from this transition structure to the dis-away product, we performed a series of constrained optimizations. Various points along the original IRC with different values for the length of the breaking C−C bond were used to construct input files. For each structure, the two methylene groups of the breaking bond were rotated from their dis-away positions to dis-towards positions, the appropriate dihedral angles were fixed to their new values, and the remainder of each structure was allowed to relax. The dis-away pathway thus created is associated with a smooth, monotonic decrease in energy, indicating that the transition structure in question does not really have any predisposition for following the dis-towards path. Analogous results were obtained for cation **7**.



10

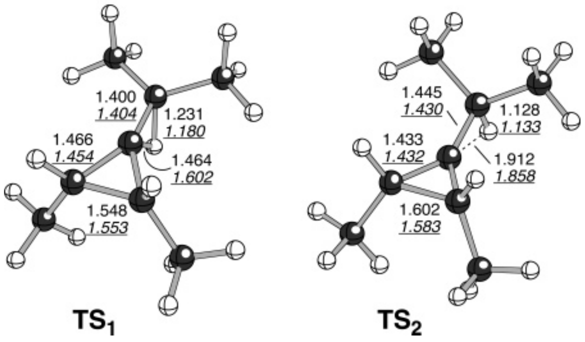


FIGURE 5. Geometries of the two transition structures involved in the rearrangement of cation **10**. Selected distances are shown in Å (B3LYP/6-31G(d) in normal type, MP2/6-31G(d) in underlined italics).[42b]

Consider also the case of cation **10**, examined carefully with both B3LYP/6-31G(d) and MP2/6-31G(d). For this cation a relatively asynchronous, and early, transition structure was found (**TS**$_1$, Figure 5), perched at the onset of a somewhat sloped plateau (see Figure 3 and Supporting Information). IRC calculations suggest that this transition structure is connected to the (sterically favored) dis-towards product cation. Interestingly, a second transition structure (**TS**$_2$), later than the first but close to it in energy, was also located; the two structures differ by 0.09 kcal/mol at B3LYP/6-31G(d) and 2.49 kcal/mol at MP2/6-31G(d), the first transition structure being lower in energy at both levels.[42b] IRC calculations on **TS**$_2$ indicate that it actually connects the dis-towards and dis-away product cations. This is an unusual situation. It seems that both of these transition structures reside on the edges of a common plateau (although use of the term “transition structure” in these cases is complicated by the flatness of the surrounding surface). Passage through **TS**$_1$ can lead directly to the dis-towards product, but

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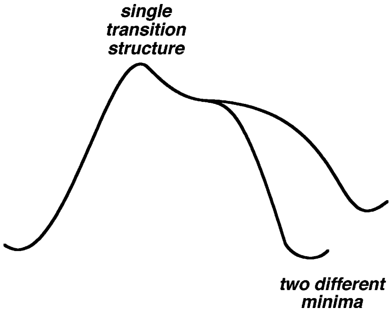
[45] This is true for **6** and **7**, but the energy surface for **8** has a prominent flat plateau at both levels of theory.

[46] Altering the step-size and coordinate system used in the IRC calculations still resulted in pathways to the same product.[47a]

CHART 10



only a slight deviation from this path leads to **TS**$_2$, which is apparently connected to both products. Again there seems to be little preference for forming one product over the other.

The observations described above indicate that perhaps a bifurcation[47] in the path from the transition structure to the allyl cation products may exist for cations such as **6**−**8** and **10** (Chart 10).[48,49] If this is so, both dis-away and dis-towards products could be formed, or one or the other could be favored based on the dynamics[50] of the system. In short, if a given reaction is extremely asynchronous and little bond breaking ($<$1.59 Å) and no disrotation has occurred at the transition structure, the reaction is not committed to any one particular stereochemical course.[51] In these cases, the orbital interaction shown in Chart 8 does not control the stereochemical outcome of the reaction since disrotation only begins after the hydrogen has migrated and left an essentially symmetrical p-orbital behind.

Conclusions and Outlook

We have described an unusual type of rearrangement reaction of cyclopropylcarbinyl cations that involves the fusion of a [1,2] sigmatropic shift and a disrotatory two-electron electrocyclic ring opening into a concerted, albeit asynchronous, process. Such reactions differ from previous examples of reactions that have been described as fusions of pericyclic processes, though, not only in the types of pericyclic reactions that are combined but also in the unusual sort of spiro bicyclic delocalization present in their transition structures.[13,21] The potential energy surfaces for these reactions can be rather complex, in some cases involving flat plateaus and little stereocontrol. In other cases, however, stereoselectivity (specifically torquoselectivity) appears to be controlled by favorable orbital interactions between the breaking C−H and C−C bonds. Comparison of these reactions with the solvolytic ring openings of cyclopropyl halides and sulfonates also highlights a connection between ionization reactions and sigmatropic shifts. Although the computed barriers for the specific hiscotropic reactions described herein are generally high, the concepts uncovered through our investigation are being used to guide the design of systems (e.g., those with different migrating groups[14]) for which hiscotropic reactions might be observed experimentally.[52]

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Supporting Information Available: Coordinates, energies, IRC plots, and full GAUSSIAN citation. This material is available free of charge via the Internet at http://pubs.acs.org.

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(47) For leading references on potential energy surface bifurcations, see: (a) Quapp, W. *J. Mol. Struct.* **2004**, *695−696*, 95−101. (b) Bakken, V.; Danovich, D.; Shail, S.; Schlegel, H. B. *J. Am. Chem. Soc.* **2001**, *123*, 130−134. (c) Castaño, O.; Frutos, L.-M.; Palmiero, R.; Notario, R.; Andrés, J.-L.; Gomperts, R.; Blancafort, L.; Robb, M. A. *Angew. Chem., Int. Ed.* **2000**, *39*, 2095−2097. (d) Merrer, D. C.; Rablen, P. R. *J. Org. Chem.* **2005**, *70*, 1630−1635. (e) Suhrada, C. P.; Selcuki, C.; Nendel, M.; Cannizzaro, C.; Houk, K. N.; Rissing, P.-J.; Baumann, D.; Hasselmann, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 3548−3552. (f) See also ref 12. (g) It is important to note that in our case no valley-ridge inflection point has been located.

(48) Related situations have been observed in bispericyclic reactions.[12]

(49) Moving backwards from the transition structure also likely involves a diverging pathway since the cationic site can rotate in two possible directions and this group is not tilted in either direction in the transition structure.[42a]

(50) (a) Carpenter, B. K. *Acc. Chem. Res.* **1992**, *25*, 520−528. (b) Carpenter, B. K. *J. Phys. Org. Chem.* **2003**, *16*, 858−868.

(51) In some geometrically constrained cyclopropyl anion ring-opening reactions it has been suggested that orbital symmetry-allowed conrotatory motion occurs before and in the transition structure and then changes to disrotatory motion further along the reaction coordinate. Perhaps the potential energy surfaces for these sorts of reactions also involve post-transition structure plateaus? For recent experimental and computational work on such reactions, see: (a) Leivers, M.; Tam, I.; Groves, K.; Leung, D.; Xie, Y.; Breslow, R. *Org. Lett.* **2003**, *5*, 3407−3409. (b) Faza, O. N.; López, C. S.; Alvarez, R.; de Lera, A. R. *Org. Lett.* **2004**, *6*, 901−904. (c) Polo, V.; Domingo, L. R.; Andrés, J. *J. Org. Chem.* **2005**, *71*, 754−762.

(52) For an interesting example of "computer-aided" discovery of new pericyclic reactions, see: Herges, R.; Hoock, C. *Science* **1992**, *255*, 711−713.