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Chemistry of Hexafluorobicyclo[1.1.0]butane: A Computational Study[†,1]

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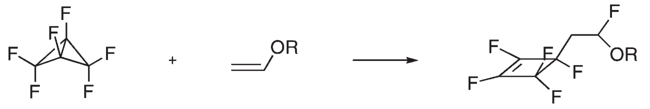
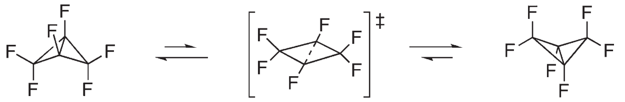


Despite its very weak central C−C bond, the yet-unknown hexafluorobicyclobutane is predicted to be quite robust. Unlike the parent hydrocarbon, which undergoes thermal rearrangement to butadiene, the perfluoro compound will yield hexafluorocyclobutene upon heating. The fluorobicyclobutane will react under mild conditions with a variety of reagents, in particular with certain alkenes in a new type of concerted transformation. This "fluorohomoene" reaction is shown to be a pseudopericyclic process, as is condensation of the bicyclobutane with water. Whereas the carbene 3-butenylidene rearranges primarily to butadiene, its perfluoro counterpart is predicted to be an efficient precursor for hexafluorobicyclobutane.

Introduction

Computational investigation of a series of fluorinated bicyclobutanes has revealed that their barrier for ring inversion falls dramatically as the number of fluorines increases. The calculated barrier for the unknown hexafluoro derivative (**1**) is extraordinarily low, $\Delta H^{\ddagger} = 3.1$ kcal/mol.[2,3] Although cleavage of the central C−C bond is not required for inversion to occur, the facile stretching of that bond shows that it is very weak. That finding raises a number of interesting questions. Does the weak bond mean that the molecule is very fragile? What is its fate when it decomposes? What kinds of reactions can it undergo that compete successfully with its self-destruction? These questions comprise the subject of the present study.



1 **1**

Methods of Calculation

Using variable-temperature NMR, we found $\Delta G^{\ddagger} = 6.8 \pm 0.2$ kcal/mol (−55 °C) for ring inversion of 1,4,5,5-tetrafluorobicyclopentane.[3] We calculated the barrier with the B3LYP functional, finding that increasing the size of the basis set lowered it, and satisfactory agreement with experiment was obtained at the B3LYP/6-311+G** level of theory ($\Delta G^{\ddagger} = 8.80$ kcal/mol at the same temperature). Thus, theory at this level was employed for the study of ring inversion in the fluorobicyclobutanes and is used throughout the current investigation as well.[4] It is noteworthy that the computed barrier for the bicyclopentane was still higher than the experimental one by 2 kcal/mol, suggesting that even the tiny barrier found for hexafluorobicyclobutane is likely to be too high.

For all of the transition states calculated, a single negative vibrational frequency was found, and intrinsic reaction coordinate calculations were carried out to ensure that they connected the assumed reactant(s) and product(s). Frequencies were not scaled. All calculations were performed without symmetry constraints, and energies were corrected for zeropoint energy differences. Atomic charges cited are electrostatic potentials.

As a check on the validity of the B3LYP/6-311+G** results, G3B3 calculations[5] were performed for the unimolecular reactions of hexafluorobicyclobutane and appear in Table 1 only.

[†] Dedicated to David W. Birney (Texas Tech), who brought the concept of pseudopericyclic reactions out of obscurity and has done far more than anyone else to develop and refine the subject.

(1) Presented in part at the 239th National Meeting of the American Chemical Society, San Francisco, CA, March 21−25, 2010.

(2) Lemal, D. M. *J. Org. Chem.* **2008**, *74*, 2413.

(3) Wei, Y.; Liu, Y.; Wong, T; Lemal, D. M. *J. Fluorine Chem.* **2006**, *127*, 688.

(4) *Jaguar, version 7.0*, Schrodinger, LLC, New York, 2007.

(5) Gaussian 09, Revision A.02 : Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; 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.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, O.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. Gaussian, Inc., Wallingford, CT, 2009.

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TABLE 1. **Energetic and Entropic Data for Unimolecular Transformations of Hexafluorobicyclobutane**[a]

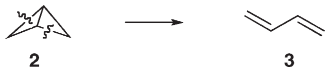
reaction	$\Delta H^{\ddagger}$	$\Delta S^{\ddagger}$	$\Delta G^{\ddagger}$	ΔH	ΔS	ΔG
1→4	33.4 (35.5)	0.4 (−2.3)	33.3 (36.2)	30.4 (32.3)	7.2 (1.2)	28.2 (32.0)
4→5	7.0 (8.8)	−5.2 (−1.8)	8.6 (9.3)	−57.1 (−55.0)	−1.0 (0.0)	−56.8 (−55.0)
1→5	37.4 (41.1)	2.0 (−0.7)	36.8 (41.3)	−26.7 (−22.7)	6.2 (1.1)	−28.6 (−23.0)
1→8	31.7 (37.4)	1.1 (−1.7)	31.4 (37.9)	−33.8 (−35.1)	0.2 (−0.7)	−33.9 (−34.9)

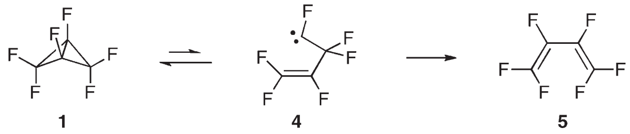
[a] All energies are in kcal/mol; entropies are in cal/mol·K; temperature is 298.15 K. Values in parentheses were obtained at the G3B3 level of theory.

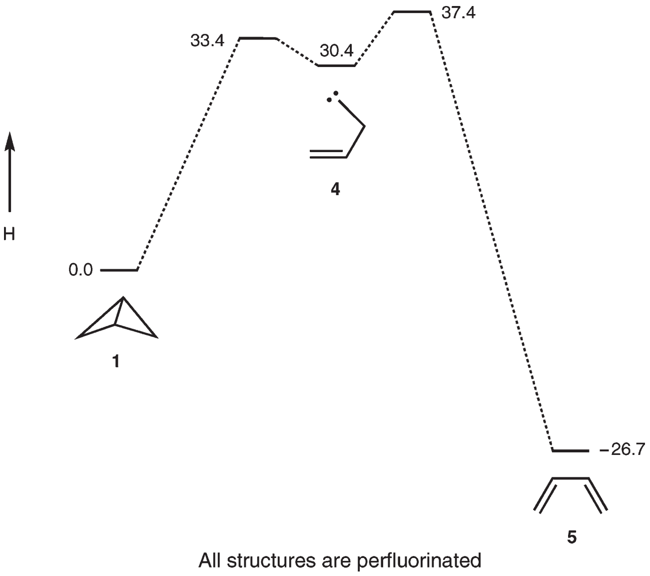
They predict higher barriers for these transformations with differences as large as several kcal/mol but do not alter the qualitative conclusions reached at the lower level of theory.

Results and Discussion

To address the question of fragility, we began by exploring the thermal chemistry of hexafluorobicyclobutane. For comparison, the parent hydrocarbon (**2**) ring opens without cleavage of the central bond to butadiene (**3**) with E_a = 40.58, log A = 14.02.[6] The stereochemistry of the process[7] is consistent with an orbital topology-allowed, four-electron Möbius transition state,[8,9] and computational studies support that interpretation.[10] In contrast, we find that the hexafluoro compound will open reversibly with cleavage of the central and a peripheral C−C bond to give the carbene hexafluoro-3-butenylidene (**4**). This species can rearrange to hexafluorobutadiene (**5**)[11] by migration of the vinyl group to the carbene center, but that requires surmounting a higher barrier than the one for reversion to the bicyclobutane. Enthalpy changes in these transformations are presented in Figure 1 and in Table 1, which also includes values of other energetic and entropic parameters.







All structures are perfluorinated

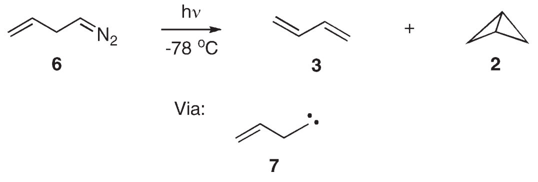
FIGURE 1. Hypothetical hexafluorobicyclobutane-to-hexafluorobutadiene pathway.

TABLE 2. **Energetic and Entropic Data for Some Bimolecular Reactions of Hexafluorobicyclobutane**[a]

reactant	$\Delta H^{\ddagger}$	$\Delta S^{\ddagger}$	$\Delta G^{\ddagger}$	ΔH	ΔS	ΔG
methyl azide	7.8	−42.4	20.5	−39.6	−50.5	−24.5
diimide	3.6	−31.3	13.0	−114.2	−4.2	−112.9
propene	12.3	−44.0	25.4	−54.1	−42.5	−41.5
isobutene	5.6	−35.9	16.3	−56.1	−35.3	−45.6

[a] All energies are in kcal/mol; entropies are in cal/mol·K; temperature is 298.15 K.

The hydrocarbon bicyclobutane (**2**) was first synthesized in our laboratory nearly a half-century ago by photolysis of allyldiazomethane (**6**), which proceeded via 3-butenylidene (**7**) to yield butadiene (**3**) and **2** in the ratio 5:1.[12] The inefficiency of this route to **2** was a consequence of the ease with which a vicinal hydrogen shifts to a carbene center. Our computational finding that **4**, the perfluorinated counterpart of carbene **7**, prefers ring closure over rearrangement to the butadiene indicates that **4** should serve as a good precursor for **1**. That is a consequence of the reluctance of fluorine to migrate to a carbene center,[13,14] which is reflected as well in the finding that rearrangement of **4** to butadiene **5** would entail shift of the trifluorovinyl group, not of fluorine, to the carbene carbon.



Bicyclobutane **1** has another option for thermal decomposition: rearrangement via opening of the central bond and 1,2-shift of a bridge fluorine to give hexafluorocyclobutene (**8**). This process is predicted to require considerably less energy than rearrangement to the butadiene (Table 1). However, given the ease of cleavage of the central C−C bond, the barrier is surprisingly high. That is further testimony to the

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[6] Frey, H. M.; Stevens, I. D. R. *Trans. Faraday Soc.* **1969**, *61*, 90. Srinivasan, R.; Levi, A. A.; Haller, I. *J. Phys. Chem.* **1965**, *69*, 1775.

[7] Wiberg, K. B.; Lavanish, J. M. *J. Am. Chem. Soc.* **1966**, *88*, 5272.

[8] Woodward, R. B.; Hoffmann, R. *The Conservation of Orbital Symmetry*; Verlag Chemie, Academic Press: New York, 1970.

[9] Zimmerman, H. E. *Acc. Chem. Res.* **1971**, *4*, 272.

[10] Mazziotti, D. A. *J. Phys. Chem. A* **2008**, *112*, 13684. Lutz, J. J.; Piecuch, P. *J. Chem. Phys.* **2008**, *128*, 154116. Kinal, A.; Piecuch, P. *J. Phys. Chem. A* **2007**, *111*, 734. Nguyen, K. A.; Gordon, M. S.; Boatz, J. A. *J. Am. Chem. Soc.* **1994**, *116*, 9241 and references cited therein.

[11] In contrast to the parent butadiene, the most stable conformation of hexafluorobutadiene is a skewed s-cis form with a dihedral angle of 47.6 ± 0.58°. Brundle, C. R.; Robin, M. B. *J. Am. Chem. Soc.* **1970**, *92*, 5550.

[12] Lemal, D. M.; Menger, F.; Clark, G. W. *J. Am. Chem. Soc.* **1963**, *85*, 2529.

[13] See, for example: O'Gara, J. E.; Dailey, W. P. *J. Am. Chem. Soc.* **1994**, *116*, 12016. Holmes, B. E.; Rakestraw, D. J. *J. Phys. Chem.* **1992**, *96*, 2210.

[14] Review: Kobrina, L. S.; Kovtonyuk, V. N. *Usp. Khim.* **1988**, *57*, 114.

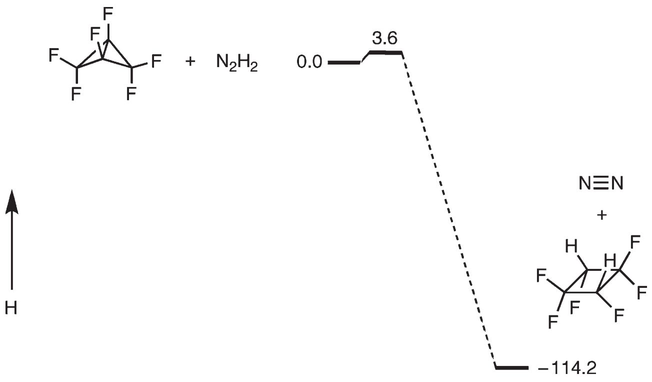


FIGURE 2. Extremely facile diimide reduction of hexafluorobicyclobutane.

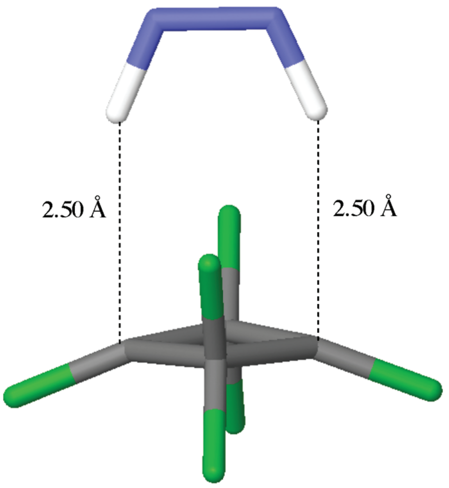
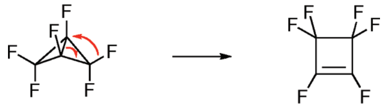


FIGURE 3. Transition structure for the reduction of **1** by diimide.

reluctance of fluorine to undergo 1,2-shifts (in neutral species[15]). The high barrier means that there will be ample opportunity for successful attack on bicyclobutane **1** by external reagents in competition with unimolecular rearrangement.



1 **8**

To begin an exploration of the intermolecular reactions of **1**, we examined a 1,3-dipolar cycloaddition. Methyl azide (**9**) will add to **1** to yield triazabicycloheptene **10**, an orbital topology-allowed process with a six-electron Hückel transition state.[8] Energetic and entropic data for this and some other bimolecular reactions examined in this study are presented in Table 2, which shows that the addition of methyl azide should be both quite exothermic and quite facile. Reduction of **1** with diimide to *cis*-1,3*H*-perfluorocyclobutane (**11**), a double-group-transfer reaction,[8] was found to have an extremely low enthalpy barrier (Figure 2). Because it will also be extraordinarily exothermic, the transition state will come very early, in accordance with the Hammond postulate.[16] This is apparent in Figure 3, where the 2.50 Å developing C−H bonds in the transition state are very long for bonds that shrink to 1.1 Å in the product. As with other reagents, attack on the bicyclobutane occurs on the concave face of the molecule.[17]

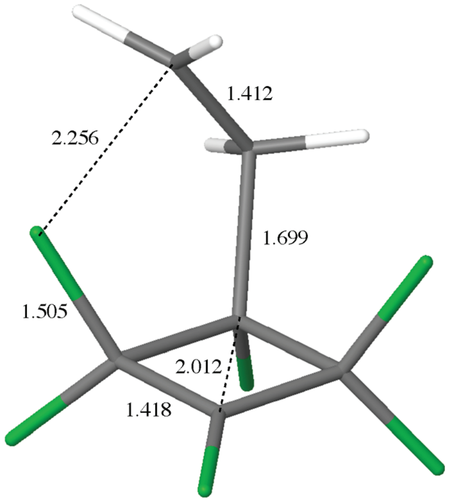
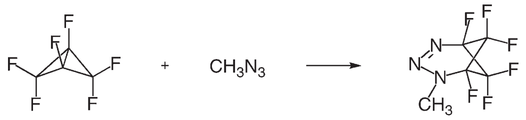


FIGURE 4. Transition structure for the fluorohomoene reaction of ethylene with **1**.



1 **9** **10**

1 **11**

To learn about an orbital topology-forbidden [2+2] process,[8] we examined the reaction of ethylene with **1**. However, ethylene found a way to avoid the forbiddenness by undergoing a type of concerted transformation that is unprecedented, a "fluorohomoene" reaction. In an ene reaction, a hydrogen is transferred between two alkenes while a C−C bond is formed between them. In the new reaction, it is a fluorine that is transferred, and "homo" is inserted in the name because a cyclopropane bond substitutes for a π bond in one of the reactants. The transition structure for the ethylene reaction, which would yield 3-(2-fluoroethyl)pentafluorocyclobutene (**12**), is shown in Figure 4 (see also Table 3). The enthalpy barrier of 23.6 kcal/mol for this process is quite low, but because it is bimolecular and therefore has a large negative entropy of activation, its calculated free energy of activation is a few kcal/mol greater than that for the unimolecular rearrangement of **1** to hexafluorocyclobutene. Thus, this reaction will probably not be realized experimentally.

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[15] Migration barriers need not be high in cations: McAllister, M.; Tidwell, T. T.; Peterson, M. R.; Csizmadia, I. G. *J. Org. Chem.* **1991**, *56*, 575.

[16] Hammond, G. S. *J. Am. Chem. Soc.* **1955**, *77*, 334.

[17] The parent bicyclobutane (**2**) is also attacked on its endo face. Pomerantz, M.; Wilke, R. N.; Gruber, G. W.; Roy, U. *J. Am. Chem. Soc.* **1972**, *94*, 2752. Pomerantz, M.; Gruber, G. W.; Wilke, R. N. *J. Am. Chem. Soc.* **1968**, *90*, 5040.

TABLE 3. Energetic and Entropic Data for Fluorine-Transfer Reactions of Hexafluorobicyclobutane[a]

reactant	$\Delta H^{\ddagger}$	$\Delta S^{\ddagger}$	$\Delta G^{\ddagger}$	ΔH	ΔS	ΔG
ethylene	23.6	−39.6	35.4	−53.3	−37.0	−42.3
vinyl alcohol	7.5	−41.1	19.7	−58.0	−41.5	−45.6
water	10.4	−39.4	22.1	−36.2	−3.2	−35.3

[a] All energies are in kcal/mol; entropies are in cal/mol·K; temperature is 298.15 K.

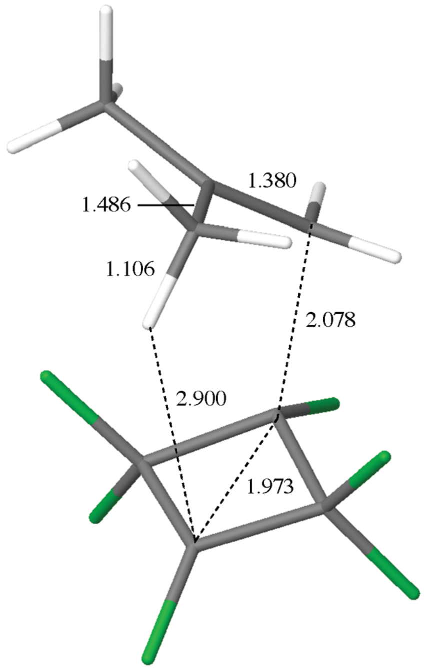
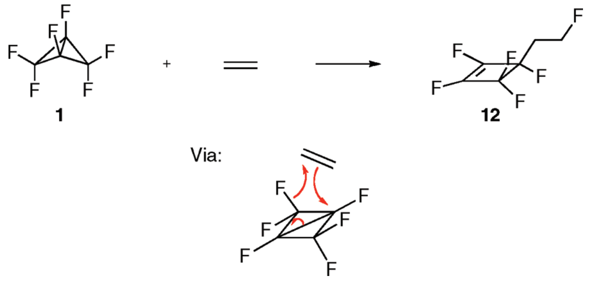


FIGURE 5. Transition structure for homoene reaction of isobutene with **1**.

To observe a fluorohomoene reaction, it will very likely be necessary to lower the barrier significantly.



1 **12**

That seemed possible with an alkene that is a better electron donor than ethylene. Propene represented a modest step in this direction, but propene was found to undergo instead a concerted homoene reaction with **1**, giving propenylcyclobutane **13**. The homoene reaction took place with isobutene as well, yielding **14**, and the barrier was much lower yet (Table 2, Figure 5).[18] Clearly, to be able to observe the fluorohomoene reaction, a donor alkene was required that had no preferred alternative pathway available.

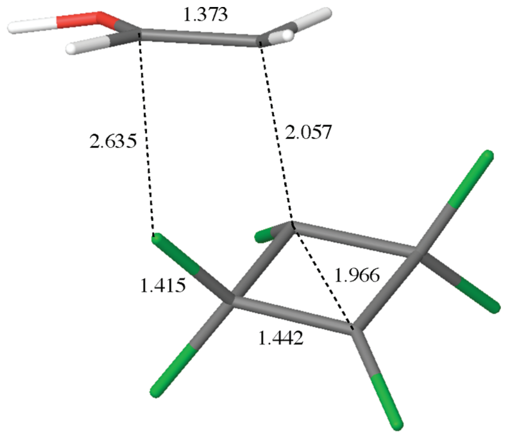
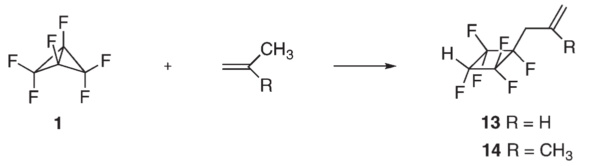
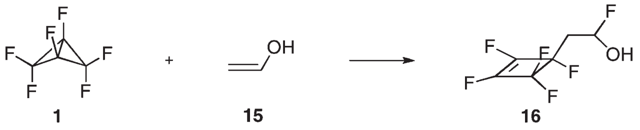


FIGURE 6. Transition structure for the fluorohomoene reaction of vinyl alcohol with **1**. The apparent C−F···C angle is misleading because of the viewing angle.



1 **13** R = H **14** R = CH_3

Vinyl alcohol (**15**), a model for vinyl ethers, appeared to be a promising choice. In fact, **15** underwent the fluorohomoene reaction with a calculated $\Delta H^{\ddagger}$ of only 7.5 kcal/mol and a $\Delta G^{\ddagger}$ of just 19.7 kcal/mol, yielding cyclobutene **16** (Figure 6, Table 3). Comparison of Figures 4 and 6 reveals that increasing the donor ability of the alkene causes the transition state to come much earlier.



1 **15** **16**

At first glance, one might think the fluorohomoene reaction is a six-electron, orbital topology-allowed reaction like the ene (or homoene) reaction,[8] but it is clear from Figure 4 that the new F−C bond is forming by overlap of the carbon p orbital with a lone pair orbital on the fluorine, not with the C−F bonding orbital. The C−F···C angle is not much larger than 90° in either of the transition states (100° for ethylene, 97° for vinyl alcohol), and when the direction of the carbon orbital is accounted for it is seen that orbital overlap with the lone pair is *greater* than if that angle were exactly 90°. Because the lone pair is orthogonal to the bonding orbital, there is a disconnection in the cyclic array of overlapping orbitals in the transition state. Thus, we believe these are single-disconnection pseudopericyclic reactions.[19−21] There are eight electrons in the cyclic orbital array, but the reactions are not forbidden to occur in concert because

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[18] Another transition structure was found for both propene and isobutene which connected the homoene with the nearly isoenergetic fluorohomoene product, and in the isobutene case it lay only 2.3 kcal/mol in enthalpy above the starting materials. No transition state was located that connected these with starting materials, e.g., forming a valley ridge pathway.

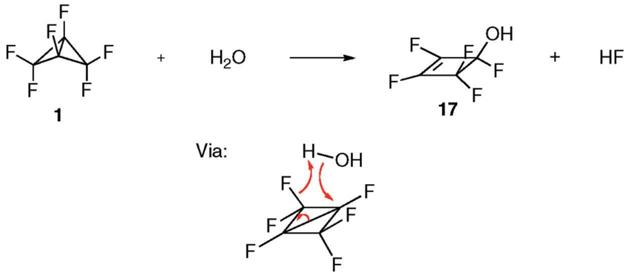
[19] Ji, H.; Xu, X.; Ham, S.; Hammad, L. A.; Birney, D. W. *J. Am. Chem. Soc.* **2009**, *131*, 528 and references therein.

[20] Birney, D. W.; Ham, S.; Unruh, G. R. *J. Am. Chem. Soc.* **1997**, *119*, 4509.

[21] Ross, J. A.; Seiders, R. P.; Lemal, D. M. *J. Am. Chem. Soc.* **1976**, *98*, 4325.

they are not subject to the Woodward–Hoffmann rules. Pseudopericyclic reactions typically have planar (or nearly planar) transition states,[20] but those discussed here represent exceptions.

Water is predicted to undergo a facile concerted condensation with **1** in which hydrogen fluoride is extruded and pentafluorocyclobut-2-enol (**17**) is formed (Table 3). This transformation is also pseudopericyclic and closely related to the fluorohomoene reactions. The C–F····H angle in the transition state is 91.2° (Figure 7), very close to the optimum angle of 90° for overlap of the hydrogen 1s orbital with the fluorine lone pair, so again there is an orbital disconnection at fluorine. Because of the involvement of an oxygen lone pair, there are 10 electrons in the cyclic orbital array with a disconnection at oxygen that is not quite complete. This condensation reaction is expected to be general for unhindered alcohols and may well occur with other compounds having a hydrogen–heteroatom bond.



The ease with which fluorine migrates in the reactions with vinyl alcohol and water is probably attributable to push–pull character in the transition state. In the former case, even though the transition state is early, 0.32 of an atomic charge has been transferred from the enol to the fluorocarbon. The migrating fluorine bears a −0.37 charge, and the target carbon a +0.26 charge. In the water transition state, 0.31 of an atomic charge has been transferred to the fluorocarbon, the migrating fluorine has a −0.34 charge, and the hydrogen it is bonding to has a charge of +0.36.

Conclusions

Hexafluorobicyclobutane (**1**) is predicted to rearrange thermally to hexafluorocyclobutene, but under conditions vigorous enough that it will react preferentially with a broad spectrum of reagents. In addition to allowed pericyclic processes, it will undergo the novel, pseudopericyclic fluorohomoene reaction. Condensation of **1** with water will also be a pseudopericyclic process. The carbene hexafluoro-3-butenylidene, unlike its hydrocarbon parent, is expected to prefer cyclization over rearrangement to the butadiene, so it should serve as an efficient precursor for the title compound. We hope to test these predictions experimentally.

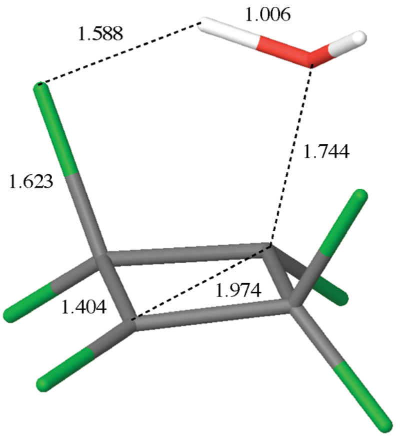


FIGURE 7. Transition structure for the condensation of water with **1**.

Acknowledgment. The author thanks the National Science Foundation for support of this work (Grant No. CHE-0653935) and Prof. Daniel Singleton for performing the G3B3 calculations.

Note added in proof: Carbene **4** has two minima that differ by rotation about the C1–C2 bond. The lower energy one lies slightly below that represented in Figure 1 and Table 1 (ΔH = −0.8 kcal/mol; ΔG = −0.9 kcal/mol, 298.15 K; B3LYP/6-311+G**).

Supporting Information Available: Total energies and Cartesian coordinates at the B3LYP/6-311+G** level of theory for hexafluorobicyclobutane, its derivatives, and all transition structures. This material is available free of charge via the Internet at http://pubs.acs.org.