J. Am. Chem. Soc. 1994, 116, 1521-1527

Ab Initio Calculations on the Stereomutation of 1,1-Difluorocyclopropane. Prediction of a Substantial Preference for Coupled Disrotation of the Methylene Groups

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Received August 2, 1993[⊗]

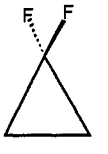
Abstract: GVB and SD-CI calculations have been performed with the 6-31G* basis set in order to explore the potential surface for the stereomutation of 1,1-difluorocyclopropane (**1**) by ring opening to 2,2-difluorotrimethylene (**2**) and 1,1-difluorotrimethylene (**3**) diradicals. The calculations predict that the presence of the geminal fluorines in **1** should (1) enhance the preference for stereomutation by coupled methylene rotations over that in cyclopropane, (2) change the preferred stereochemistry of ring opening and closure from conrotatory in the hydrocarbon to disrotatory in the fluorocarbon, (3) cause the preference for coupled rotation to be enhanced, rather than obscured, by alkyl substituents, and (4) result in the singlet lying below the triplet at the (0,0) geometry of diradical **2**. The reasons for these differences between the hydrocarbon and the fluorocarbon are traced to the strong through-bond coupling that is provided by the C–F σ^* orbitals at the (0,0) geometry of **2**. Experimental tests of the computational predictions are proposed.

It has been found experimentally that the presence of a pair of geminal fluorine substituents raises the strain energy of cyclopropane.[1] Heats of hydrogenation indicate a thermodynamic increment of 12–14 kcal/mol caused by the two fluorines in 1,1-difluorocyclopropane (**1**).[2] In good agreement with experiment, RHF calculations find that the hydrogenation energy of **1** to give 2,2-difluoropropane[3] exceeds the hydrogenation energy of cyclopropane by 11.7 kcal/mol with the 4–31G basis set[6] and 12.5 kcal/mol with 6–31G*.[7]

The additional strain introduced into cyclopropane by the presence of geminal fluorine substituents is manifested in the differences between the energies of activation for ring-opening reactions of cyclopropanes and the corresponding 1,1-difluorocyclopropanes. Kinetic studies by Dolbier and co-workers have found that substitution of two fluorines on the same ring carbon lowers the E_a for *cis–trans* isomerization of dimethylcyclopropane by 9.7 kcal/mol[8] and for the rearrangement of vinylcyclopropane to cyclopentene by 9.4 kcal/mol.[9] However, Dolbier and Fielder[10] found that geminal fluorines at a ring carbon of methylenecyclopropane lower the E_a for the rearrangement to (difluoromethylene)cyclopropane by only about 3 kcal/mol, compared to the E_a for the degenerate rearrangement of the hydrocarbon.

Whereas in the rearrangement of **1** and of 1,1-difluoro-2-vinylcyclopropane a C–C bond either proximal or distal to the fluorinated carbon can cleave, in the rearrangement of 2,2-difluoromethylenecyclopropane, the C–C bond that cleaves is proximal to the fluorinated ring carbon. Therefore, Dolbier and Fielder drew the reasonable conclusion that geminal fluorines exert only a small effect on the energy required to cleave a proximal cyclopropane ring bond but that they weaken the distal cyclopropane ring bond by 9–10 kcal/mol. This conclusion appears to have been generally accepted.[1]

A large preference for cleavage of the distal bond in **1** to form 2,2-difluorotrimethylene (**2**), rather than 1,1-difluorotrimethylene (**3**), would be consistent with the 6 kcal/mol greater thermodynamic stability of 2,2-difluoropropane, relative to 1,1-difluoropropane,[3] and with the general thermodynamic preference of electronegative atoms, such as fluorine, to be attached to the more substituted of two carbon atoms.[4,11,12] Nevertheless, Dolbier and Sellers reported the formation of significant amounts of rearrangement products that arise from the cleavage of a proximal C–C bond in 1,1-difluoro-2-vinylcyclopropanes.[9] Therefore, the preference for the formation of **2**, rather than **3**, from **1** may not be as overwhelming as the results of the Dolbier–Fielder kinetic study of the rearrangement of 2,2-difluoromethylenecyclopropane[10] might suggest.



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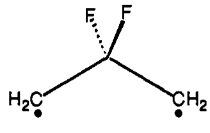

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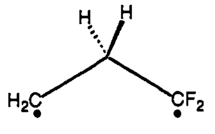

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The confluence of our interests in the effects of fluorine substituents[4,13] and in cyclopropane stereomutations[14] led us to

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[⊗] Abstract published in *Advance ACS Abstracts*, January 15, 1994.

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(2) Roth, W. R.; Kirmse, W.; Hoffmann, W.; Lennartz, H. W. *Chem. Ber.* **1982**, *115*, 2508.

(3) At the RHF/6-31G* level, 2,2-difluoropropane is computed to be 5.9 kcal/mol (7.2 kcal/mol at MP2/6-31G*) more stable than 1,1-difluoropropane.[4] This computational result agrees well with the difference of about 6 kcal/mol between the heat of formation of –129.8 kcal/mol for the former fluorocarbon[1b,5a] and an estimate of –123.7 kcal/mol for the latter.[5b]

(4) Getty, S. J.; Borden, W. T. *J. Am. Chem. Soc.* **1991**, *113*, 4334.

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(6) Greenberg, A.; Liebman, J.; Dolbier, W. R., Jr.; Medinger, K. S.; Skancke, A. *Tetrahedron* **1983**, *39*, 1533.

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(14) Getty, S. J.; Davidson, E. R.; Borden, W. T. *J. Am. Chem. Soc.* **1992**, *114*, 2085. This paper contains references to the many other calculations on cyclopropane stereomutations that have been published.

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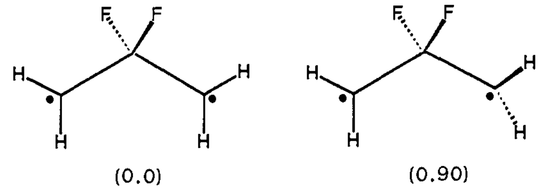
(0.0) (0.90)

Figure 1. (0,0) and (0,90) geometries of 2,2-difluorotrimethylene (**2**).

perform GVB and SD-CI calculations on the ring opening of **1**. In particular, we set out to calculate the relative energies of diradicals **2** and **3** and to determine the effect, if any, of the geminal fluorines in **2** on modifying the through-bond interaction between the radical centers in the lowest singlet state of the trimethylene diradical.[15] This paper reports the results of our investigations.

Computational Methodology

We employed computational techniques similar to those that we utilized in our previous calculations of the potential surface for stereomutation of cyclopropane.[14] All calculations were performed using the 6-31G* basis set.[16] Geometry optimization and vibrational analysis of **1** were carried out at the RHF level, while those of singlet **2** and **3** were performed at the GVB level, with one pair of electrons correlated. Triplet geometries were optimized with UHF wave functions. Vibrational analyses were used to identify optimized geometries as minima, transition states, or mountain tops, and the unscaled frequencies were used to compute zero-point energies, heat capacities, and entropies. The RHF, GVB, and UHF calculations were performed with the Gaussian88[17a] and Gaussian92[17b] packages of *ab initio* programs. Optimized geometries are available as supplementary material.[18]

In order to investigate the effects of including additional electron correlation, SD-CI calculations were performed at important geometries, possessing at least one element of symmetry.[19] The SD-CI calculations on the lowest singlet states of **2** and **3** utilized two-configuration reference wave functions, except in the case of (0,90) geometries, for which an ROHF reference wave function was employed. In order to include the effect of quadruple excitations (SDQ-CI), the Davidson correction[20] was added to the SD-CI energies. The CI calculations were performed using MELDF[21] and MOLCAS.[22]

Results

2,2-Difluorotrimethylene (2). We began by optimizing the (0,0) and (0,90) geometries[15] of **2**. As shown in Figure 1, in the former geometry, both of the terminal methylene groups are rotated by 90° from their orientation in **1**, so that they lie in the same plane as the three carbons. In the latter geometry, only one of the methylene groups is rotated into the C–C–C plane, and the H–C–H plane of the other remains perpendicular to the plane of the three carbons.

As shown in Table 1, the energy difference between (0,0) and (0,90) is 3.4 kcal/mol at the GVB level and 4.4 kcal/mol at the SDQ-CI level. These energy differences in **2** are each a factor of 3–4 larger than the corresponding energy differences between these two conformations in the unfluorinated trimethylene diradical.[14]

Another difference, not shown in the table, between the fluorocarbon and the hydrocarbon is the energy of the singlet, relative to that of the triplet, at the (0,0) geometry. At this geometry for **2**, the singlet is calculated to lie below the triplet; whereas, at the same geometry for the parent trimethylene diradical, the triplet is calculated to lie below the singlet.[23] At the GVB-ROHF and SDQ-CI levels of theory, singlet **2** is computed to lie below the triplet by respectively 3.3 and 4.5 kcal/mol at the (0,0) geometry. At the same levels of theory, our calculations find (0,0) triplet trimethylene to lie below the (0,0) singlet by respectively 0.7 and 0.8 kcal/mol.[24]

As in the case of trimethylene,[14,25] vibrational analysis of the (0,0) geometry of singlet **2** showed it to have two imaginary frequencies and thus to be a mountain top on the $C_3H_4F_2$ potential energy surface. Starting at this geometry of **2**, disrotation was found to lead back to **1** without encountering an energy barrier. However, conrotation of the methylenes by 4.3° led to a stationary point.

A vibrational analysis showed this C_2 geometry to be a true transition state. However, the vibration with the imaginary frequency corresponded not to symmetry-preserving conrotation but, instead, to symmetry-breaking disrotation. Thus, at the GVB level, this C_2 geometry is the transition state for *disrotatory* opening and closure of **1**.

Although a C_2 transition state for disrotation might seem surprising, this finding is easily understood. As in the hydrocarbon,[14] at the GVB level of theory sequential rotation of each methylene group in **2** through the C–C–C plane is apparently preferred to simultaneous rotation of both methylene groups. That is why the GVB reaction path does not pass through the (0,0) geometry. Instead, at some point along the disrotatory pathway for ring opening of **1**, it becomes energetically favorable for **2** to break C_s symmetry and to rotate just one methylene group through the plane of the three carbons, until the C_2 transition state is reached. Past the transition state, the symmetry again becomes C_1, until after the second methylene group rotates through the plane of the three carbons. The reaction path then reacquires C_s symmetry, and ring closure occurs via pure disrotation.

As shown in Table 1, the GVB energy of this transition state is essentially the same as that of the (0,0) mountain top, and at the SD-CI and SDQ-CI levels, the (0,0) geometry is actually slightly lower. It seems likely that a vibrational analysis at the CI level would find that (0,0) was a true transition state, as we suggested might be the case for the (0,0) geometry of the hydrocarbon.[14]

A second stationary point of C_2 symmetry was located at a geometry for **2** in which the terminal methylenes are each pyramidalized by 20.7° [26] and rotated from the (0,0) geometry

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(18) See the Supplementary Material Available paragraph.

(19) An SD-CI calculation on a diradical that has no element of symmetry is much larger than one on a diradical that has at least one element of symmetry. In the former case, not only are there no matrix elements that are zero by symmetry but it is necessary to use three, rather than two, reference configurations, because three configurations are needed to provide a minimal description of such a diradical.

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(24) The (0,0) geometries of the triplet states of both trimethylene and **2** are mountain tops on their respective potential energy surfaces. Yamaguchi and Schaefer[25] have found C_2 and C_s minima for triplet trimethylene, which lie respectively 0.4 and 0.3 kcal/mol below the (0,0) geometry. They find the (0,90) triplet geometry to be 0.2 kcal/mol lower than (0,0). Since we find that the triplet (0,90) geometry of **2** is 0.9 kcal/mol below (0,0), the minima on the surface for triplet **2** are probably a little more than 1 kcal/mol below the energy of the (0,0) geometry.

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Table 1: Electronic and Zero-Point Energies, Heat Capacities, Heats of Formation, Entropies, and Free Energies Calculated for the Stationary Points on the Singlet Potential Surface for Stereomutation of 1,1-Difluorocyclopropane (**1**)[a]

species	*E* (GVB)	*E* (SD-CI)	*E* (SDQ-CI)[b]	ZPE	C_v^{600}	ΔH^{600}	ΔS^{600}	ΔG^{600}
1	0[c]	0[d]	0[e]	0[f]	0[g]	0[h]	0[i]	0[j]
2 (0,0)	33.1	47.7	50.8	–5.7[k]	–0.3[k]	44.9[k]	2.9[k]	43.2[k]
(0,90)	36.5	52.0	55.2	–6.1[k]	–0.2[k]	49.0[k]	5.3[k]	45.8[k]
dis TS	33.1	47.8	51.0	–5.4	1.6	46.6	8.1[l]	41.7
con TS	35.5	51.5	54.9	–5.2	1.5	50.6	7.0[l]	46.4
Monorot TS	36.5	52.0[m]	55.2[m]	–5.8	1.7	50.4	11.4[l]	43.6
3 (0,90)	37.0	52.1	55.0	–4.2[k]	–2.0[k]	49.6[k]	4.7[k]	46.8[k]
Monorot TS	36.8	52.1[m]	55.0[m]	–3.6	–0.2	51.3	7.9[l]	46.5

[a] Energies are in kcal/mol; heat capacities and entropies are in cal/(mol·K); all thermodynamic quantities were computed at 600 K; SDQ-CI/6-31G* energies were used for computing ΔH and ΔG. [b] SD-CI plus Davidson correction for quadruple excitations.[20] [c] *E* (RHF) = –314.7645 hartrees. [d] *E* (SD-CI) = –315.4070 hartrees. [e] *E* (SDQ-CI) = –315.4941 hartrees. [f] ZPE = 44.6 kcal/mol. [g] C_v^{600} = 26.7 cal/(mol·K). [h] $\Delta H^{600} = E\,(\text{SD-CI}) + \text{ZPE} + \Delta C_v^{600} \times 600$ K. [i] ΔS^{600} = 82.4 cal/(mol·K). [j] $\Delta G^{600} = \Delta H^{600} - \Delta S^{600} \times 600$ K. [k] Mountain top—the existence of two imaginary frequencies is reflected in the lower values of ZPE, C_v, and ΔS than those for the nearby transition state. [l] *R* ln 2 added for the existence of two enantomeric transition states. [m] SD(Q)-CI energy of the nearby (0,90) geometry.

by 42.7°. A vibrational analysis showed that this C_2 geometry is also a transition state, but the vibration with the imaginary frequency is for symmetry-preserving conrotation. Also unlike the first C_2 stationary point, this one is significantly higher in energy than the (0,0) geometry, by 2.4 kcal/mol at the GVB level and by 4.1 kcal/mol at the SDQ-CI level. Consequently, unlike disrotatory closure, conrotatory closure of (0,0) **2** to **1** would encounter an energy barrier of several kilocalories/mole.

As in the hydrocarbon,[14,25] the (0,90) geometry of **2** was also found to have two vibrations with imaginary frequencies and thus to be a mountain top. One of these vibrations consists largely of pyramidalization of the CH_2 group that lies in the C–C–C plane, and the other is comprised principally of rotation of this CH_2 group. Both modes destroy the plane of symmetry in the (0,90) C_s geometry; therefore, the search for a nearby transition state had to be performed in C_1 symmetry.

The transition state for rotation of one methylene group in **2** was located close to the (0,90) geometry. The energy of this monorotatory transition state was found at the GVB level to be essentially the same as that of the (0,90) geometry and 3.4 kcal/mol above that of (0,0). Because of the similarity of the geometry and GVB energy of this transition state to those of (0,90), an SD-CI calculation was not performed at this C_1 transition state.[19]

1,1-Difluorotrimethylene (3). Unlike CH_2 radical centers, CF_2 radical centers are found, both computationally[4,13,27] and experimentally,[28] to prefer highly pyramidalized geometries. Therefore, it seemed unlikely that there would be a strong through-bond interaction of the pyramidalized CF_2 radical center with the CH_2 radical center in singlet **3**. Consequently, we did not expect to find any unusual stability associated with the (0,0) geometry of singlet **3**.

GVB calculations confirmed that the CF_2 group prefers to remain highly pyramidalized at this geometry of **3**. Even with the CF_2 group pyramidalized, this geometry is calculated to be about 0.4 kcal/mol higher in energy than the (0,90) geometry of **3** in which the pyramidalized CF_2 group is orthogonal to the C–C–C plane and the terminal CH_2 group lies in this plane. As shown in Table 1, the GVB energy of this optimized (0,90) geometry of **3** was found to be 3.9 kcal/mol higher than that of the (0,0) geometry of singlet **2** but only 0.5 kcal/mol higher than that of the (0,90) geometry of **2**. At the SDQ-CI level, the (0,90) geometries of **2** and **3** are calculated to differ in energy by only 0.2 kcal/mol.

As in the case of the (0,90) geometry of singlet **2**, this (0,90) geometry of **3** has two imaginary frequencies and, thus, is not the actual transition state for methylene group rotation. The actual C_1 transition state for monorotation in **3** was located, and its GVB energy was found to be 0.2 kcal/mol lower than that of the nearby (0,90) geometry. Once again, the similarity of these two geometries and the very small energy difference between them at the GVB level led us to forego performing an SD-CI calculation at the C_1 transition state geometry.[19]

$\Delta H^{\ddagger}$ for Coupled Methylene Rotation in 1. As shown in Table 1, the energy for ring opening of **1**, *via* coupled disrotation of both methylene groups, is calculated to require 33.1 kcal/mol, when the energy of **1** is calculated at the SCF level and that of **2** is computed with a GVB wave function. Providing correlation for the three strained σ bonds in **1** increases this energy difference to 47.8 kcal/mol at the SD-CI level and to 51.0 kcal/mol with SDQ-CI. The GVB, SD-CI, and SDQ-CI/6-31G* energies required for coupled methylene rotation in cyclopropane were previously found to be respectively 43.5, 59.6, and 62.0 kcal/mol.[14] Thus, the two fluorines in **1** are calculated to lower the energy required for coupled methylene rotation by 10.4, 11.8, and 11.0 kcal/mol at these three levels of theory.

In order to compare our calculations with experiment, the energies required for ring opening must be converted to enthalpies by correcting for the differences in zero-point energies and heat capacities. The zero-point energies (ZPEs), heat capacities at 600 K (C_v^{600}), and enthalpies at this temperature are given in Table 1. Around 600 K, where Dolbier and Enoch studied stereomutation of 1,1-difluoro-2,3-dimethylcyclopropane,[8] the differences in zero-point energies and heat capacities convert the SDQ-CI energy for ring opening of **1** to a value of $\Delta H^{\ddagger}$ = 46.6 kcal/mol. The corresponding value calculated for coupled rotation of the methylene groups in cyclopropane is $\Delta H^{\ddagger}$ = 56.5 kcal/mol.[29] Thus, the two fluorines in **1** are computed to lower $\Delta H^{\ddagger}$ for coupled methylene rotation by 9.9 kcal/mol.

This energy lowering is almost exactly the same as the effect, found by Dolbier and Enoch, of geminal fluorines on reducing E_a for stereomutation of dimethylcyclopropane.[8] However, it should be noted that Dolbier and Enoch measured the E_a for one-center epimerization of 1,1-difluoro-2,3-dimethylcyclopropane. Their experiment was not designed to detect coupled rotation. Therefore, the proper comparison of our calculations with their experiments involves the transition state for one-center epimerization of **1**.

$\Delta H^{\ddagger}$ for One-Center Epimerization of 1. As noted above, the SDQ-CI energy of the (0,90) geometry of **2** should provide a very good approximation to that of the transition state for rotation of

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(29) The value of $\Delta H^{\ddagger}$ = 58.2 kcal/mol for *single* rotation was given in ref 14. It was calculated at 749 K, but using values of C_v^{298}, rather than C_v^{749}, and it was based on the SD-CI energy difference of 61.0 kcal/mol between cyclopropane and the transition state. At 749 K the value of C_v = 26.5 cal/(mol·K) for the transition state is much closer to the value of C_v = 26.1 cal/(mol·K) for cyclopropane, so that the correct value of $\Delta H^{\ddagger}$ for single rotation in cyclopropane, based on SD-CI energies, is $\Delta H^{\ddagger}$ = 55.7 kcal/mol. However, on the basis of an SDQ-CI energy difference of 63.4 kcal/mol between cyclopropane and the transition state for monorotatory opening, $\Delta H^{\ddagger}$ = 58.1 kcal/mol. The values of $\Delta H^{\ddagger}$ for single and coupled methylene rotation differ by 1.6 cal/mol, 0.2 kcal/mol more than the energies of the two transition states.

one methylene group in **2**. After corrections for the differences in zero-point energies and heat capacities between the monorotatory transition state and **1**, $\Delta H^{\ddagger} = 50.4$ kcal/mol is obtained. This value of $\Delta H^{\ddagger}$ for rotation of one methylene group in 1,1-difluorocyclopropane is 7.7 kcal/mol lower than the value of $\Delta H^{\ddagger} = 58.1$ kcal/mol,[29] calculated for the same process in cyclopropane.

This calculated difference can be compared with the experimental value of $\Delta E_a = 9.7$ kcal/mol for the effect of geminal fluorines on reducing the energy of activation for one-centered epimerization of dimethylcyclopropane.[8] The calculated value of $\Delta H^{\ddagger} = 50.4$ kcal/mol for rotation of one methylene group in **2** is, as would be expected, slightly higher than the value of $\Delta H^{\ddagger} = 48.5$ kcal/mol that was measured by Dolbier and Enoch for epimerization of the dimethyl-substituted derivative of **1**.

However, passage across the transition state for monorotation in **2** is not the only pathway for effecting one-center epimerization of **1**. As discussed for the parent hydrocarbon, both by us[14] and by Schaefer and co-workers,[30] conrotatory opening, followed by disrotatory closure, or *vice versa*, also effects one-center epimerization of **1**. At the SDQ-CI level, the conrotatory transition state actually lies 0.3 kcal/mol below that for monorotation in **2**, but the 0.6 kcal/mol larger zero-point energy of the former results in the latter having a slightly smaller value of $\Delta H^{\ddagger}$.

Another possible mode for one-center epimerization of **1** is cleavage of a C–C bond proximal to the CF_2 group and rotation of the terminal methylene group in **3**. On the basis of our SDQ-CI calculations at the (0,90) geometries of **2** and **3**, the transition states for rotation of one methylene group in **2** and in **3** are expected to have almost exactly the same energies. The former transition state has the lower zero-point energy by 2.2 kcal/mol, at least in part, because the force constant for CH_2 pyramidalization/depyramidalization in **2** is much lower than that for the same type of mode for CF_2 in **3**. Although the higher heat capacity of the former transition state partially offsets the effect of its lower ZPE, the transition state for rotation of one methylene group is computed to have a value of $\Delta H^{\ddagger}$ that is 0.9 kcal/mol lower in **2** than in **3**.

Effect of $\Delta\Delta S^{\ddagger}$ on $\Delta\Delta G^{\ddagger}$. At 600 K the effects of entropy on the relative free energies of the transition states for stereomutation of **1** cannot be ignored. At this temperature, the 3.3 cal/(mol·K) greater entropy of the monorotatory transition state reduces the 3.8 kcal/mol enthalpic advantage of the conrotatory transition state to a free energy difference of only 1.9 kcal/mol. The latter corresponds to a predicted difference in rates of a factor of about 4.9 at 600 K.

Part of the entropic advantage of monorotation over disrotation is that the monorotatory transition state is "floppier" and thus has lower frequency vibrations than the disrotatory transition state. In addition, the latter possesses an axis of symmetry, which reduces its rotational entropy by $R \ln 2$, relative to that of the former, which has no axis of symmetry. The difference in symmetry between the two transition states favors monorotation over disrotation by a factor of 2 in rate.

The physical reason for this factor of 2 is that, on a purely statistical basis, monorotation of *either* methylene group is as probable as disrotation; so, overall, monorotation is twice as probable as disrotation. In a derivative of **1**, with a substituent, X, at C_2 and another, Y, at C_3, there would be no symmetry factor favoring monorotation over disrotation. However, rotation at C_2 would be distinguishable, at least in principle, from rotation at C_3, so there would be two different rate constants for monorotation, each contributing to the overall rate constant for monorotation. Even when X = Y, it is customary to define the overall rate constant for monorotation as $2k_{\text{mono}}$, where k_{mono} is the rate constant for rotation of a single methylene group.[31,32] Thus, our calculations on **1** predict that $k_{\text{dis}} = 4.9(2k_{\text{mono}}) = 9.8k_{\text{mono}}$.

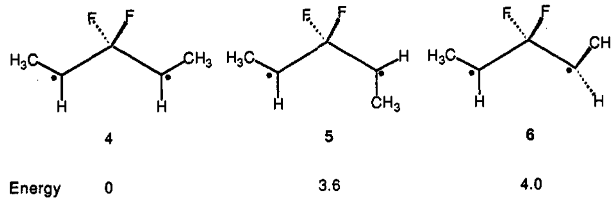

Figure 2. GVB/6-31G* energies (kcal/mol) of conformations **5** and **6** of 3,3-difluoropentane-2,4-diyl, relative to that (–392.7931 hartrees) of **4**.

Effect of Methyl Group Substituents. In order to test experimentally our computational prediction that disrotation should be favored over monorotation in the stereomutation of **1**, substituents would have to be introduced as stereochemical markers. In our calculations on cyclopropane, we found that methyl substituents cause the small preference for coupled rotation almost to disappear. Thus, when a methyl group was placed at each terminal carbon of trimethylene in the sterically least demanding fashion, the GVB preference for (0,0) over (0,90) was reduced from 0.75 kcal/mol in trimethylene to 0.16 kcal/mol in pentane-2,4-diyl.[33] This computational finding explains why the small preference for coupled methylene rotation that has been reported for cyclopropane-1,2-d_2[32,34] disappears when substituents, other than deuteria, are used as stereochemical markers in cyclopropane stereomutations.[35]

In order to investigate the effect of alkyl substituents on the much stronger preference in **2**, than in cyclopropane, for the (0,0) over the (0,90) geometry, we performed GVB calculations on three geometries of 3,3-difluoropentane-2,4-diyl. As shown in Figure 2, these geometries were (0,0) with *transoid* conformations about both the C_2–C_3 and C_3–C_4 single bonds (**4**), (0,0) with one *transoid* and one *cisoid* conformation (**5**), and (0,90) with a *transoid* conformation about the C_2–C_3 single bond (**6**). As summarized in Figure 2, the (0,90) geometry (**6**) is 4.0 kcal/mol higher in energy than the preferred (0,0) geometry (**4**). Thus, methyl substitution in the fluorocarbon actually increases the energetic preference for (0,0) over (0,90) by 0.6 kcal/mol at the GVB level. In contrast, as noted above, in the hydrocarbon, methyl substitution decreases the preference for (0,0) over (0,90) by about the same amount of energy.

Discussion

The computational results summarized in the previous section predict several differences between the stereomutation of 1,1-difluorocyclopropane (**1**) and that of cyclopropane. First, the calculated difference of 4.2 kcal/mol between the SDQ-CI energies of the transition states for coupled versus single methylene rotations in **1** is a factor of 3 larger than that of 1.4 kcal/mol between the corresponding transition states for the stereomutation of cyclopropane.[14]

In the stereomutation of cyclopropane at 700 K, the SDQ-CI energy difference between the transition states for conrotation

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(30) Yamaguchi, Y.; Schaefer, H. F., III; Baldwin, J. E. *Chem. Phys. Lett.* **1991**, *185*, 143.

(31) In Schemes I and II of ref 14, the rate constant, k_1, for single methylene rotation is multiplied by an additional factor of 2, to account for the fact that cleavage of either of two bonds in cyclopropane allows single methylene rotation. As stated in footnote 13 of ref 14, our definition of k_1 differs from that of Berson and co-workers[32] by this factor of 2. There is also a typographical error in our Scheme I; *all* the rate constants for conversion of *meso*-**1** to (+)-**1** and (–)-**1** should be divided by 2.

(32) Berson, J. A.; Pedersen, L. D. *J. Am. Chem. Soc.* **1975**, *97*, 238. Berson, J. A.; Pedersen, L. D.; Carpenter, B. K. *J. Am. Chem. Soc.* **1976**, *98*, 122.

(33) See footnote 28 of ref 14.

(34) It should be noted, however, that no preference for coupled methylene rotation has been found in cyclopropane-1,2,3-d_3: Cianciosi, S. J.; Ragunathan, N.; Freeman, T. B.; Nafie, L. A.; Baldwin, J. E. *J. Am. Chem. Soc.* **1991**, *113*, 1864. The rationalization, proposed by Baldwin, of the difference between the results obtained with cyclopropane-d_2 and cyclopropane-d_3 is not supported by the results of isotope-effect calculations.[14]

(35) Review: Berson, J. A. In *Rearrangements in Ground and Excited States*; de Mayo, P., Ed.; Academic Press: New York, 1980; Vol. 1, pp 311–390.

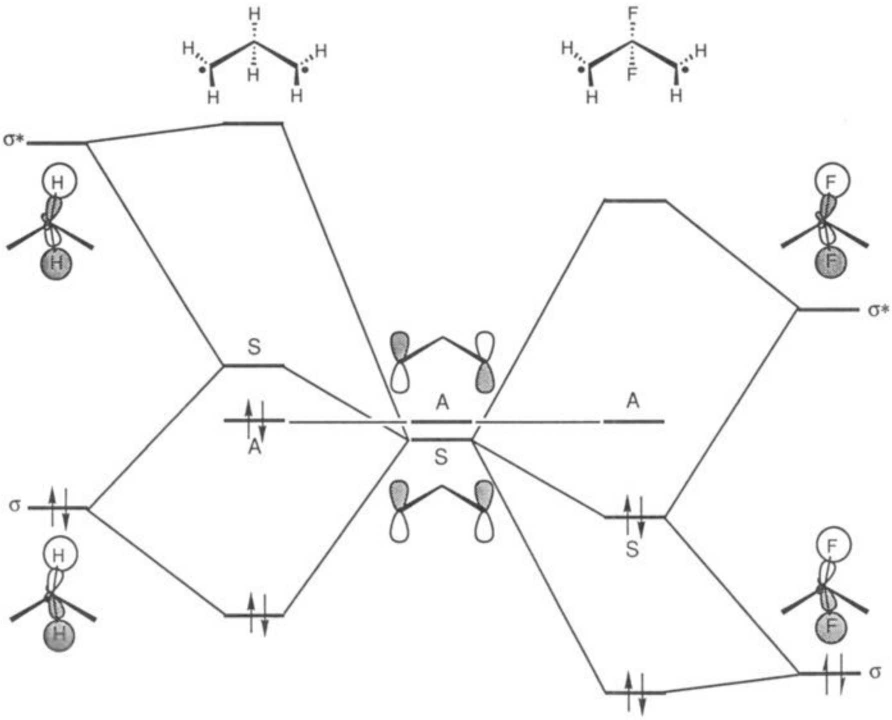

Figure 3. Comparison of the orbital interaction diagrams for the (0,0) geometries of trimethylene and **2**.

and rotation of a single methylene group translates into a calculated ratio of rate constants of $k_{con}/k_{mono} = \exp(1.7/1.4) = 3.4$. This calculated ratio is somewhat smaller than the lower limit of 5.7 found in Berson's experiments on cyclopropane-1,2-d_2.[32,34] In the ring opening of **1** at 600 K, the predicted ratio of rate constants is 9.8. This ratio, although smaller than the ratio of 33.0 that would be calculated from the 4.2 kcal/mol difference in the SDQ-CI energies, is still almost a factor of 3 larger than the ratio calculated for the stereomutation of cyclopropane.

A second predicted difference between the stereomutation of **1** and that of cyclopropane is the favored stereochemistry for coupled methylene rotation. In **1** it is predicted to be disrotatory; whereas, opening and closure of cyclopropane is predicted to prefer to be conrotatory.[14,15] In **1** conrotation leads to a transition state that is 3.9 kcal/mol higher in energy than the transition state for disrotation. In cyclopropane disrotation leads to a transition state that is higher than that for conrotation, but by only 1.5 kcal/mol.[14]

The preference for disrotatory opening and closure of **1** is readily traced to the wave function for the (0,0) geometry of **2**. The dominant configuration is the one in which the b_1 nonbonding (NB)MO is doubly occupied.[36] This NBMO consists largely of the in-phase, symmetric (S)[15] combination of p-π orbitals on the terminal methylenes. In the GVB wave function, the square of the coefficient of the configuration in which the b_1 NBMO is doubly occupied is a factor of 1.88 larger than that of the second configuration, in which the a_2 NBMO [the antisymmetric (A)[15] combination of p-π orbitals on the terminal methylenes] is doubly occupied. In contrast, at the (0,0) geometry of trimethylene, the ratio of these two coefficients in the GVB wave function is 1/1.20 = 0.83.[14]

As first pointed out by Hoffmann,[15] selective occupancy of the A NBMO in (0,0) trimethylene is what favors conrotatory opening and closure of cyclopropane. The fact that at the (0,0) geometry of **2** the occupation number of 1.31 in the S NBMO is larger than the occupation number of 1.09 in the A NBMO at the same geometry of trimethylene[14] accounts for our finding that the energetic preference for disrotatory opening and closure of **1** is calculated to be larger than that for conrotatory opening and closure of cyclopropane.

The reason for the strong preference for occupancy of the S NBMO at the (0,0) geometry of **2** can be understood by comparing the orbital interaction diagram for this diradical with that used by Hoffmann[15] to explain the preference for the occupancy of the A NBMO in (0,0) trimethylene. Figure 3 shows this comparison. In each diradical, the S combination of p-π AOs at the terminal methylene groups mixes with the b_1 symmetry combinations of both the σ and σ* C–X (X = H or F) orbitals at the central carbon. The difference between the two diradicals lies in which interaction is dominant—the mixing of the p-π AOs at the terminal methylenes with the σ or with the σ* orbitals of the adjacent C–X bonds.

As illustrated in Figure 3, in the (0,0) trimethylene diradical, the dominant interaction of the S combination of p-π AOs at the terminal methylene groups is with the filled, C–H bonding, b_1 orbital.[15] This leads to the destabilization of the S NBMO and the selective occupancy of the A NBMO. However, the ratio of the occupation numbers of the A and S NBMOs of 1.09/.91 = 1.20 deviates from unity by only 20%, indicating that the preference for the occupation of *A* is not very large.

The much greater electronegativity of fluorine, compared to hydrogen, makes the energy of both the σ and σ* C–F orbitals in **2** much lower than those of the σ and σ* C–H orbitals in the hydrocarbon. In addition, the electronegativity of fluorine, relative to carbon, polarizes the C–F bonds, so that the largest coefficients are on the fluorines in the bonding C–F MOs but on carbon in the antibonding C–F MOs. In **2** both of these effects serve to make dominant the interaction of the S combination of p-π AOs at the terminal methylene groups with the unfilled, C–F antibonding, b_1 orbital. As shown in Figure 3, this interaction stabilizes the S NBMO, relative to A in **2**; and as a result, S has the greater occupation number.

The ratio of the occupation numbers of 1.31/0.69 = 1.88 in

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(36) Our finding of a greater occupancy of the b_1 (S) than the a_2 (A) NBMO in **2** and a concomitant preference of **1** for undergoing disrotatory ring opening and closure was presaged by the results of extended Hückel calculations on 2,2-difluorocyclopentane-1,3-diyl: Chestnut, D. B.; Ferguson, S.; Smith, L. D.; Porter, N. A. *Tetrahedron Lett.* **1972**, *13*, 3713. These calculations found that, unlike the case in the hydrocarbon diradical, in the fluorocarbon diradical the S NBMO lies lower than the A NBMO. As a result, there was no barrier to ring closure calculated for the lowest singlet state of the fluorocarbon diradical.

2 deviates from unity by 88%. The much greater deviation of the ratio of occupation numbers from unity in the (0,0) fluorocarbon, than in the (0,0) hydrocarbon, confirms what is already apparent from comparison of the energy differences between the (0,0) and (0,90) geometries of the two diradicals—mixing of the S combination of p-π AOs at the terminal carbons with the C–F antibonding b_1 orbital is much the more dominant interaction in **2** than mixing with the C–H bonding b_1 orbital is in (0,0) trimethylene. Consequently, as shown schematically in Figure 3, the stabilization of S, relative to A, in **2** is larger in magnitude than the destabilization of S, relative to A, in trimethylene.

Figure 3 has a simple, but useful, physical interpretation. In (0,0) trimethylene, part of the hyperconjugative stabilization that is provided by the σ and σ^* orbitals of the C–H bonds at the central carbon involves some net electron donation to the terminal methylene groups. In contrast, at the same geometry of **2**, the C–F bonds act as net electron acceptors.[6,37] Our computational results show that the ability of the CF_2 group in **2** to accept electron density from the terminal methylene groups is significantly greater than the electron-donating ability of the central CH_2 group in trimethylene.

This interpretation of Figure 3 provides a ready explanation for a third predicted difference between the stereomutation of **1** and that of cyclopropane—addition of methyl groups to the terminal carbons nearly destroys the preference for (0,0) over (0,90) in trimethylene,[33] but it actually enhances the preference for (0,0) over (0,90) in **2**. The C–H bonds of a methyl group, like the C–H bonds of the central methylene group in trimethylene, make methyl a π-donating substituent. Therefore, in pentane-2,4-diyl, the terminal methyl groups compete with the central methylene to donate electron density to the radical centers at C_2 and C_4. Thus, the importance of π donation from the central methylene group to these two radical centers at the (0,0) geometry is diminished by methyl substituents. In contrast, at the (0,0) geometry of 3,3-difluoropentane-2,4-diyl (**4**), π electron donation from the terminal methyls to C_2 and C_4 acts synergistically with the ability of the central CF_2 group to accept π electron density from these two carbons.

The prediction that, unlike the case in cyclopropane stereomutations, the strong preference for coupled methylene rotations in the ring opening of **1** should survive the substitution of alkyl groups should not be difficult to test experimentally. An optically active 2,3-dialkyl-1,1-difluorocyclopropane could be pyrolyzed and the relative rates of enantiomerization (racemization) and diastereomerization (*cis–trans* isomerization) measured. However, if, as predicted, disrotation is the favored mode of ring opening and closure, the ratios of these two rates should be quite different, starting from the *cis* and *trans* diastereomers.

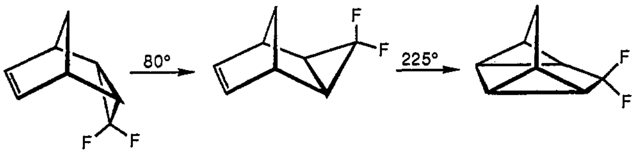
Only the *cis* diastereomer can undergo disrotation *via* a transition state analogous to **4** in Figure 2. Disrotatory opening and closure of the *trans* diastereomer would have to proceed *via* a transition state analogous to **5**, in which one alkyl group is rotated "inward". Since we calculate that the energy of **5** is almost the same as that of the (0,90) geometry (**6**),[41] the rate constants for racemization and diastereomerization should be much more nearly the same in the *trans* diastereomer than in the *cis* diastereomer. In the *cis* diastereomer, the rate constant for racemization by disrotation is expected to be considerably larger than that for formation of the *trans* isomer by monorotation.

In the highly unlikely event that conrotation, rather than disrotation, were actually preferred in stereomutation of **1**, diastereomerization would compete with enantiomerization in the *cis*, but not in the *trans*, isomer of an optically active 2,3-dialkyl-1,1-difluorocyclopropane. Therefore, pyrolysis of both diastereomers and measurement of the rate constants for enantiomerization and diastereomerization should provide a test of the predicted preference for both coupled rotation and also its stereochemistry. We have begun such an experimental test of the prediction that disrotation is the preferred path for stereomutation of **1**.

We believe that such a test is important, since the only experiments on the stereomutation of cyclopropane in which there is a strong indication of a preference for coupled rotations are those with cyclopropane-d_2.[32,34] As Berson has pointed out,[32,35] these experiments provide no information about whether the coupled rotation is, as predicted,[14,15] conrotatory. Therefore, there remains untested (and currently untestable) the disturbing possibility that methylene rotation in cyclopropane-d_2 is coupled, but disrotatory. Alternatively, conrotation and disrotation could be competitive, provided that, perhaps for dynamical reasons,[43] opening in one mode were followed by closure in the same mode.

Although there is currently no experimental evidence that disrotation is the preferred path for stereomutation of a geminal difluorocyclopropane, there are data which show that disrotatory ring opening is not difficult. Jefford and co-workers have found that **7** is transformed to **8** with a half-life of about 9 h at 80 °C.[44]

Interestingly, formation of **9** requires much higher temperatures. This latter result is consistent with our finding that the S NBMO at the (0,0) geometry of **2** has a substantially higher occupation number than the A NBMO. A substantially greater occupancy of the S NBMO would make intramolecular cycloaddition of the diradical, formed by opening the difluorocyclopropane ring in **7** or **8**, to the double bond "forbidden" by orbital symmetry.[44,45]



7 8 9

Another computational prediction, which, at least in principle, should be amenable to an experimental test, is that at the (0,0) geometry of **2** the ground state should be a singlet. This prediction for **2** contrasts with that for trimethylene, which is computed to have a triplet ground state at the (0,0) geometry.[22] The detection of the triplet state of cyclopentane-1,3-diyl and derivatives thereof[46,47] provides experimental evidence that the latter prediction is correct. Our computational prediction that, like the (0,0) geometry of **2**, 2,2-difluorocyclopentane-1,3-diyl has a singlet ground state[48] awaits experimental verification.[49]

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[37] The ability of C–F bonds to act as electron-pair acceptors has been established in fluorinated carbanions,[38] in molecules containing a π-donating heteroatom that is attached to the same carbon as a fluorine,[39] and in 3,3-difluorocyclopropene.[3,40]

(38) Dixon, D. A.; Fukunaga, T.; Smart, B. E. *J. Am. Chem. Soc.* **1993**, *115*, 1744 and references therein.

(39) See, for example: Rahman, M. M.; Lemal, D. M.; Dailey, W. P. *J. Am. Chem. Soc.* **1988**, *110*, 1964 and references cited therein.

(40) Ramaprasad, K. R.; Laurie, V. W.; Craig, N. C. *J. Chem. Phys.* **1976**, *64*, 4832.

(41) The energetic penalty for rotating one methyl group "inward" in **2** is much larger than that which we calculate for trimethylene, and we believe that this difference also has its origin in the difference between the relative energies of the S and A NBMOs in the two diradicals.[42]

(42) Getty, S. J.; Hrovat, D. A.; Xu, J. D.; Barker, S. A.; Borden, W. T. *Discuss. Faraday Soc.*, in press.

(43) For an interesting discussion of the possible role of dynamics in unimolecular organic reactions, see: Carpenter, B. K. *Acc. Chem. Res.* **1992**, *25*, 520.

(44) Jefford, C. W.; Mareda, J.; Gehret, J.-C. E.; Kabengele, nT.; Graham, W. D.; Burger, U. *J. Am. Chem. Soc.* **1976**, *98*, 2585.

(45) Woodward, R. B.; Hoffmann, R. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 781.

(46) (a) Buchwalter, S. L.; Closs, G. L. *J. Am. Chem. Soc.* **1975**, *97*, 3857. (b) Buchwalter, S. L.; Closs, G. L. *J. Am. Chem. Soc.* **1979**, *101*, 4688. (c) Coms, F. D.; Dougherty, D. A. *Tetrahedron Lett.* **1988**, *29*, 3753.

(47) Calculations predict a triplet ground state for cyclopentane-1,3-diyl: Conrad, M.; Pitzer, R.; Schaefer, H. F., III. *J. Am. Chem. Soc.* **1979**, *101*, 2245. Sherrill, C. D.; Seidl, E. T.; Schaefer, H. F., III. *J. Phys. Chem.* **1992**, *96*, 3712.

(48) Xu, J. D.; Hrovat, D. A.; Borden, W. T. Submitted for publication.

Conclusions

Our calculations predict that the presence of the geminal fluorines in cyclopropane **1** should (1) enhance the preference for stereomutation by coupled methylene rotations over that in the hydrocarbon, (2) change the preferred stereochemistry of ring opening and closure from conrotatory to disrotatory, (3) allow the preference for coupled rotation to be enhanced, rather than obscured, by alkyl substituents, and (4) cause the singlet to lie below the triplet at the (0,0) geometry of **2**. Experiments to test the first three of these predictions are underway, and we are trying also to subject the fourth prediction to experimental verification.[50]

Acknowledgment. We thank the National Science Foundation for support of this research and for a grant that allowed the purchase of the Convex C-2 computer and IBM RISC/6000 workstations, on which many of these calculations were performed. We also thank the San Diego Supercomputer Center for a generous allocation of computer time.

Supplementary Material Available: Tables listing optimized geometries and energies for **1**, for all the stationary points found on the potential surfaces of **2** and **3**, and for **4**–**6** (6 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(49) Demonstrating that 2,2-difluorocyclopentane-1,3-diyl has a singlet ground state will be a much more formidable task than demonstrating that the unfluorinated diradical has a triplet ground state.[46] Unlike the case in the hydrocarbon, where disrotatory ring closure of the singlet diradical is calculated to encounter an energy barrier, making the diradical an energy minimum on the singlet potential surface,[47] in the fluorocarbon disrotatory ring closure of the singlet diradical is computed to occur without activation, making the diradical a transition state on the singlet potential energy surface.[48]

(50) Lewis, S. B.; Borden, W. T. *Tetrahedron Lett.*, in press.