# Density Functional Theory Calculations of the Effect of Fluorine Substitution on the Kinetics of Cyclopropylcarbinyl Radical Ring Openings

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DFT calculations (B3LYP/6-311+G(2df,2p)//B3LYP/6-31G(d)) indicate a dramatic impact of fluorine substituents on the structure and reactivity of the cyclopropylcarbinyl radical. Stereoelectronic influences are believed to be largely responsible for the predicted reactivity and regiospecificity of fluorinated radicals such as the 2,2-difluorocyclopropyl carbinyl radical, which has a calculated activation barrier of 1.9 kcal/mol, undergoing regiospecific $C_2-C_3$ cleavage to form the 2,2-difluoro homoallylic radical. In contrast, calculations indicate that the 2,2-difluorocyclopropylcarbinyl cation will convert regiospecifically to the 1,1-difluoro homoallylic cation.

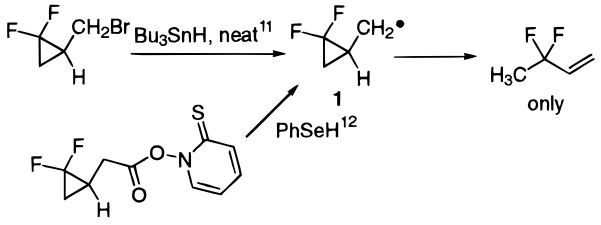
## Introduction

Knowledge of the kinetics of radical reactions is of critical importance with respect to the design of synthetic and physical organic experiments that utilize such processes.[1] A radical reaction that has attracted particular interest over the years is the cyclopropylcarbinyl−allylcarbinyl rearrangement, which, because of its speed, has found considerable use as a mechanistic probe of radical intermediacy as well as a clock for competitive, very fast radical reactions.[2] A number of cyclopropylcarbinyl radical clocks have been calibrated, generally by kinetic studies utilizing a competitive, very fast bimolecular hydrogen transfer process from benzeneselenol, but also by direct measurement using a "reporter group" approach.[3,4]

In particular, Newcomb's kinetic studies of the effect of alkyl, aryl, and alkoxy substituents appear to indicate that in these systems thermochemical (radical stabilizing) influences prevail in determining the rates of cyclopropylcarbinyl ring opening processes.[5−7] Polar influences appear to be relatively unimportant in such cases.

Newcomb's experimental results and the above conclusions have been corroborated very nicely by recent ab initio molecular orbital calculations.[8−10] In their computational work, Martinez, Schlegel, and Newcomb found good agreement between experiment and theory at the PMP2/6-31G(d) level.[8,9]

We report at this time our own calculations, carried out at the B3LYP level of theory, which provide insight into the remarkable effect of fluorine substituents on the barrier height of cyclopropylcarbinyl radical ring openings. Preliminary experimental studies have indicated an extraordinarily fast ring opening for the 2,2-difluorocyclopropylcarbinyl radical, **1**, which has yet to be trapped bimolecularly.[11−14] Very fast radical rearrangements are required to act as probes and radical clocks in studies of mechanisms of reactions, including those catalyzed by enzymes, which are believed to involve radical intermediates.




The effect of geminal fluorine substituents on cyclopropane structure, bonding and reactivity has been explored both experimentally and theoretically.[15−19] Our intent in carrying out the present calculations was to determine (a) whether such demonstrated thermochemical influences are the source of the reactivity of **1**, (b) whether polar influences play a role, and (c) what the individual and collective effects of fluorine substitution at the various positions of the cyclopropylcarbinyl radical will be on the barrier height for its rearrangement.

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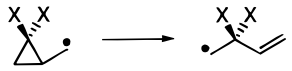
**Table 1. Calculated Barriers ($E_0$) and Standard Enthalpies of Activation ($\Delta H^{\ddagger\circ}$) for the Ring Opening of the Parent Cyclopropylcarbinyl Radical and for the 2,2-Difluorocyclopropylcarbinyl Radical[a]**



| | | UHF | | UMP2 | | PMP2 | | B3LYP | | exptl |
|---|---|---|---|---|---|---|---|---|---|---|
| radicals | X | $E_0$ | $\Delta H^{\ddagger\circ}$ | $E_0$ | $\Delta H^{\ddagger\circ}$ | $E_0$ | $\Delta H^{\ddagger\circ}$ | $E_0$ | $\Delta H^{\ddagger\circ}$ | $E_a$ |
| **2** | H | 10.5 | 10.2 | 15.3 | 15.0 | 8.1 | 7.8 | 6.7 | 6.4 | 7.0[b] |
| **1** | F | 5.2 | 4.9 | 9.1 | 8.8 | 2.9 | 2.6 | 2.2 | 1.8 | |
| differences | | 5.3 | 5.3 | 6.2 | 6.2 | 5.2 | 5.2 | 4.5 | 4.6 | |

[a] In kcal/mol, using the geometry optimized at the UHF/6-31G(d) level with ZPE calculated at UHF/6-31G(d) and scaled by factor 0.8929. [b] References 28 and 29. $\Delta H^{\ddagger\circ} = 6.4$ kcal/mol.

## Results and Discussion

**Computational Methods.** Density functional theory calculations were performed using the Gaussian 94 program package.[20] Radical reactants, products and transition structures were optimized at unrestricted Hartree−Fock (UHF)[21] and then at unrestricted Becke-style 3-Parameter (UB3LYP)[22] density functional theory (DFT) level of theory using the 6-31G(d)[23] basis set. At the same level of theory, vibrational frequencies were calculated respectively to identify transition states and ground states, and zero-point energies (ZPE) were obtained. Single-point energy[24] calculations were performed at the B3LYP level of theory using the 6-311+G(2df,2p)[25] basis set (UB3LYP/6-311+G(2df,2p)//UB3LYP/6-31G(d)). Some calculation methods that are not mentioned here will be pointed out specifically in the paper.

**Preliminary Evaluation of Methodology.** Schlegel and Newcomb sought to establish an adequate level of ab initio theory to estimate the activation barriers for ring opening reactions of cyclopropylcarbinyl radicals.[8,9] In the present study, we have repeated part of their work, performing UHF/6-31G(d) and second-order Møller−Plesset perturbation (UMP2/6-31G(d)//UHF/6-31G(d)) with spin projection[26,27] (PMP2/6-31G(d)//UHF/6-31G(d)) calculations on the parent cyclopropyl−carbinyl radical (**2**) ring opening reaction. As a comparison, DFT calculations (UB3LYP/6-31G(d)//UHF/6-31G(d)) were added to the list. The same calculations were performed for the 2, 2-difluorocyclopropylcarbinyl radical (**1**) ring opening reaction, with the reaction barriers for both the parent and the fluorinated system being given in Table 1 and the computed heats of reaction in Table 2.

**Table 2. Calculated Heats of Reaction ($\Delta H^\circ$) of the Ring Opening of the Parent Cyclopropylcarbinyl Radical and for the 2,2-Difluorocyclopropylcarbinyl Radical[a]**

| radical | X | UHF | UMP2 | PMP2 | UB3LYP | exptl |
|---|---|---|---|---|---|---|
| **2** | H | −5.2 | −0.9 | −0.0 | −2.8 | −5.4[b] |
| **1** | F | −12.8 | −5.1 | −7.9 | −9.1 | |
| difference | | 7.6 | 4.1 | 7.9 | 6.3 | |

[a] In kcal/mol, using the geometry optimized at the UHF/6-31G(d) level with ZPE calculated at UHF/6-31G(d) and scaled by a factor of 0.8929. [b] Reference 8.

Our computed barriers ($E_0$) for the parent system are very similar to Schlegel, Newcomb, and Radom's[8−10,30] Although the barriers calculated at different levels can be seen to vary by as much as 10 kcal/mol, the barrier *differences* between reaction of **1** and reaction of **2** only vary over a range of about 2 kcal/mol. A similar situation is seen for the computed heats of reaction. Such results indicate that the calculated results at different levels of theory are self-consistent. Among the levels of theory utilized here, UB3LYP gave the best results.[10] From its $\Delta H^{\ddagger\circ}$ of 6.4 kcal/mol, the $E_a$ for ring opening of **2** can be extrapolated to be 7.0 kcal/mol, which is the same as the experimental value.[8,28]

**System Calculations.** The barriers and heats of reaction for the ring opening of the cyclopropylcarbinyl radical with a $CF_2$ group at all possible positions and with all possible combinations have been computed (Table 3). With the labeling of the carbon skeletons of the computed molecules given below, the positions of fluorine substitution are indicated in the table. For example, radical **4** is the perfluorocyclopropylcarbinyl radical. The geometry of some reactant radicals and ring opening transition state of **1** are depicted in Figure 1.

Figure 1 shows the lowest energy conformations of radicals **1**, **3**, and **4**. The radical centers of **1** and **3** are planar, whereas radical **4** has a pyramidal radical center. The geminal fluorine substituents on the ring are seen

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(24) Our reported values, $E_0$, refer to the activation barrier, which is the difference between the zero point corrected electronic energies of the transition state and the reactant. Values of reaction energy ($E_{rxn}$) refer to the zero point corrected electronic energy difference between product and reactant. $\Delta H^{\ddagger\circ}$, the standard enthalpy of activation, is obtained by a thermal correction of $E_0$ to 298.15 °C, 1 atm. The Arrhenius activation energy $E_a$ can be obtained by $E_a = RT + \Delta H^{\ddagger\circ}$. The heat of reaction ($\Delta H^\circ$) refers to the difference of enthalpies between the reactant and product of a reaction at 298.15 °C, 1 atm, which is obtained from the thermal correction of $E_{rxn}$.

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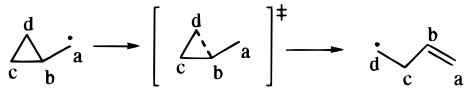
(30) Radom has recently reported that B3LYP provides a reliable level of theory for examining the cyclopropylcarbinyl radical system.[10] Comparing the current work with that of Martinez, Schlegel, and Newcomb,[8,9] a slightly more stable geometry of cyclopropylcarbinyl radical was obtained at UHF/6-31G* level of theory, whereas, at the same level of theory, the same geometries for transition-state and ring opening product were obtained. The single-point energies of product at both MP2/6-31G* and PMP2/6-31G* levels of theory differ somewhat from the data in those papers, with our data being more consistent with those in ref 10.

**Table 3. Calculated Reaction Heats and Barriers for Ring Opening of Fluorinated Cyclopropylcarbinyl Radicals[a]**




| radical | position of $CF_2$ | $E_0$ | $\Delta Hq^{\ddagger\circ}$ | $E_{rxn}$ | $\Delta H°$ |
|---|---|---|---|---|---|
| **1** | c | 1.9 | 1.6 | −10.4 | −10.1 |
| **3** | c and d | 3.8 | 3.2 | −18.4 | −18.5 |
| **5** | a and c | 4.9 | 5.0 | −9.2 | −8.6 |
| **2** | None | 6.5 | 6.2 | −4.5 | −4.1 |
| **4** | a; b; c; d | 6.5 | 6.6 | −19.3 | −19.1 |
| **1** | d | 9.0 | 8.7 | −9.8 | −9.7 |
| **6** | a | 10.2 | 10.3 | −2.6 | −1.9 |
| **5** | a and d | 10.5 | 10.6 | −11.2 | −10.9 |

[a] Calculated at UB3LYP/6-311+G(2df,2p)//UB3LYP/6-31G(d) level of theory with ZPE calculated at UB3LP/6-31G(d) and scaled by a factor of 0.9804. In kcal/mol.

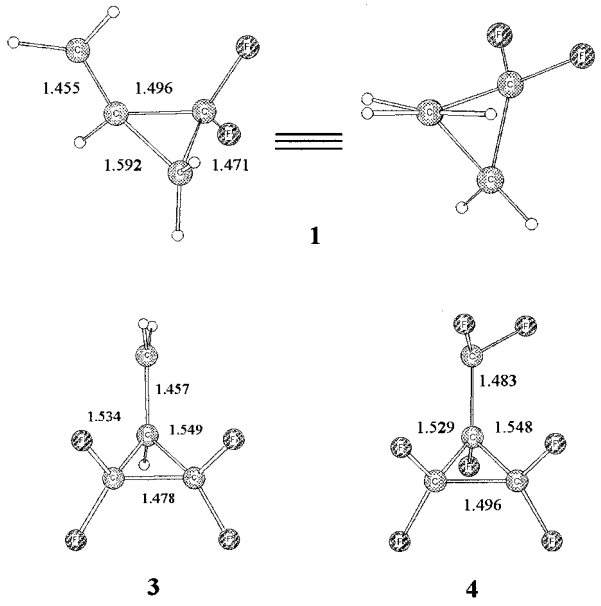



**Figure 1.** B3LYP/6-31G(d)-optimized structures of radicals **1**, **3**, and **4**. C−C bond lengths are in angstroms.

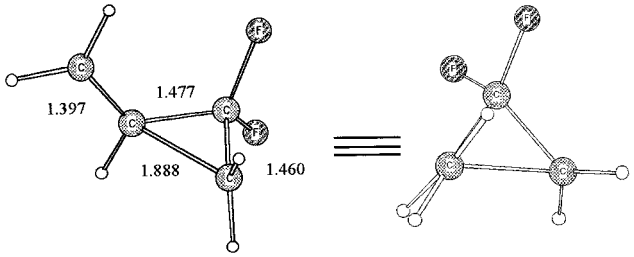


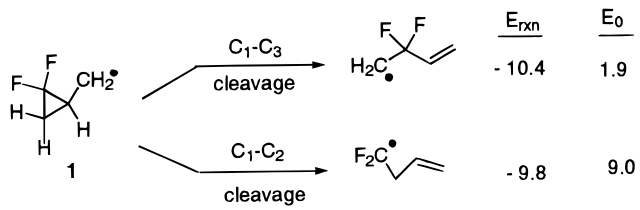

**Figure 2.** Ring opening transition-state structure of **1**.

to shorten the proximal C−C bonds and lengthen the distal C−C bonds. Our calculation predicts a length for the breaking C−C (distal to $CF_2$ group) bond of 1.888 Å for radical **1** in its ring opening transition-state structure, which indicates an early transition state (Figure 2).

The heats of reaction for ring opening of cyclopropylcarbinyl radicals **1**−**6** to some extent reflect the impact of fluorine substitution on ring strain. In 1968 Benson and O'Neal estimated, based upon kinetic data, that the ring strain of cyclopropane increases by 4−5 kcal/mol per fluorine substituent.[31] In 1982, on the basis of relative heats of hydrogenation, Roth reported that 1,1-difluorocyclopropanes are destabilized by 12−14 kcal/mol relative to their non-fluorine analogues.[32] Then, in 1997, enthalpy of combustion data reported by Ruchardt for the first time provided reliable strain-free fluorinated group equivalents that allowed one to more confidently estimate the heats of formation of strain-free fluorinated hydrocarbon systems.[33] Using the Ruchardt group equivalent values in combination with Roth's heats of hydrogenation allows one to place a value of 41.8 kcal/mol as the strain of a 1,1-difluorocyclopropane ring, which means that the incremental strain due to the geminal fluorine substituents is 14.2 kcal/mol.[34] Our own calculation performed at B3LYP/6-31G(d)//HF/6-31G(d) level of theory revealed ring strains of 28.2 kcal/mol for cyclopropane and 37.2 kcal/mol for 1,1-difluorocyclopropane. (In this calculation, cyclohexane and 1,1,4,4-tetrafluorocyclohexane were assumed to be strain-free.) Adding additional fluorine substituents certainly increases the strain of the cyclopropane system, as indicated by various kinetic criteria,[15] but there is no reliable way yet to put numbers on such strain energies.

The calculated activation barriers for rearrangements of radicals **1**−**6** are most definitely an interesting challenge to understand. They can be seen to vary widely, from a value of 1.9 kcal/mol for distal bond cleavage of **1** to a value of 10.5 kcal/mol for proximate bond cleavage of radical **5**, with there being absolutely *no* obvious correlation between such values and their respective heats of reaction!

In a result that is certainly related, when the cyclopropane ring bears but one $CF_2$ group, as in the case of radical **1**, the ring opening of the cyclopropylcarbinyl radical can take place with *two* possible regiochemistries, cleaving either the distal, $C_1-C_3$ bond, or the proximal, $C_1-C_2$ bond. Considering the fact that the reaction energies for these two competitive processes differ, for **1**, by < 1 kcal/mol, the huge difference in activation barrier for the two processes of radical **1** (7.1 kcal/mol) is quite remarkable.




The substantially lower predicted activation barriers for distal C−C bond cleavages in radicals **1**, **3**, and **5**, and the regioselectivities exhibited by radicals **1** and **5** are consistent with an abundance of experimental results that indicate a kinetic preference for homolytic cleavage of the cyclopropane bond that is distal to the geminal fluorine substituents. These phenomena are also consistent with Hoffmann's original hypothesis that fluorine substituents on cyclopropane would weaken the distal C−C bond,[17] results which have been corroborated by

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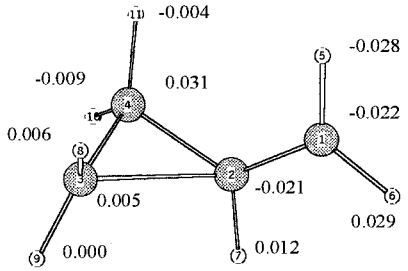
Borden's ab initio calculations indicating a 3.9 kcal/mol difference in energy between the most stable geometries of the 2,2-difluoro- and 1,1-difluorotrimethylene diradicals which would be obtained by $C_2-C_3$ and $C_1-C_2$ bond homolysis, respectively, of 1,1-difluorocyclopropane.[18] Fluorine substitution has long been recognized to stabilize saturated hydrocarbon structures, because of the impact of fluorine's electronegativity on C−C and C−H bonding.[18,35,36] The overall thermodynamic influence of a $CF_2$ group is greater when it is bound to two carbons, rather than one carbon and a hydrogen. This effect is reflected by the 3.9 kcal/mol greater heat of hydrogenation of 1,1-difluorocyclopropane to 2,2-difluoropropane than to 1,1-difluoropropane (calculated using Ruchardt's group equivalent values.)[33]

The fact remains that there is little underlying thermodynamic driving force that can be used to rationalize the above kinetic predictions.

Rates of radical processes are recognized to be influenced by four factors: thermodynamics, steric effects, polar effects, and stereoelectronic effects.[37,38] With thermodynamics and steric effects not playing a role in this series of reactions, it is tempting to try to invoke "polar" effects as the determining factor, since they have been suggested in the past as being important in cyclopropylcarbinyl rearrangements.[39] It has been suggested that the major orbital interaction in the transition state for the hydrocarbon cyclopropylcarbinyl radical rearrangement involves that between the semi-occupied orbital (at the slightly nucleophilic $CH_2^{\bullet}$ site) and the vacant $\sigma^*$ orbital of the cyclopropane C−C bond undergoing cleavage.[39] Thus, it is proposed that a fractional positive charge would be generated at the initial radical center along with a fractional negative charge at the incipient radical center, to give the transition state dipolar character.

However, in our charge distribution calculations employing CHelpG scheme (Figure 3),[40] at the ring opening transition state of hydrocarbon radical **2**, a partial negative charge (−0.022) is generated at the initial radical center, and a very small fraction of positive charge is generated at the incipient radical center, a result which indicates an "electron flow" direction which is opposite to that expected for the proposed "polar effect".[39] In the case of radical **1**, the observed charge distribution, with more negative charge on the ring $C_3H_3F_2$ part of the molecule and more positive charge on the carbinyl $CH_2$ part, is certainly consistent with the difluorocyclopropyl group being electron accepting relative to the analogous hydrocarbon group of **2**. Therefore, one might invoke this as a factor that influences the relative rate of the two ring openings. However, it is not obvious how one can use such charge distribution to rationalize the strong regiochemical preference exhibited by radical **1**.

Further calculations indicate that when one adds a methyl substituent to the carbinyl position, as in radical

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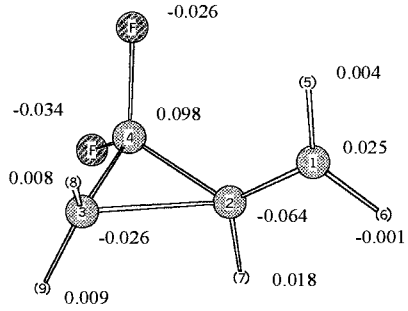
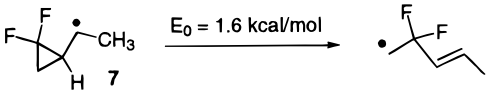


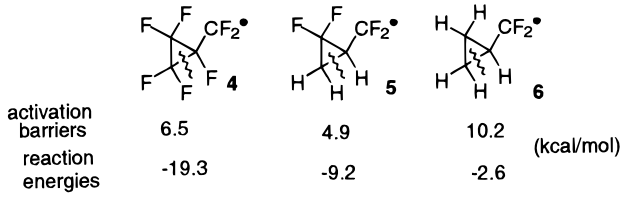

TS of 1

**Figure 3.** Charge developed in the ring opening transition state of radicals **1** and **2** relative to their radical reactants (CHelpG scheme). **The** C2−C3 bond is breaking.

**7**, the activation barrier will decrease to 1.6 kcal/mol, a result that is consistent with the carbinyl radical site of **7** being more nucleophilic than that of **1** and also is consistent with the charge distribution calculation of **1**.




Nevertheless, although such effects may play some role for radicals such as **1** and **7**, we believe that it is unlikely that polar factors are the main reason for the broad range of activation barriers found in the overall series. For example, the disparate computed barriers for the three radicals bearing fluorine substituents (i.e., **4**−**6**) at the carbinyl position are difficult to rationalize only in terms of polar effects. Therefore, in the absence of a strong computational indicator, we believe that the degree of general importance of polar effects in determining the rates and regiochemistry of cyclopropyl-carbinyl radical ring openings must remain an open question.




The differences in activation barriers for radicals **1**−**7** can, we believe, be best understood in terms of stereoelectronic effects, that is the *effectiveness of transition state overlap* between the carbinyl radical SOMO and the appropriate cyclopropane $\sigma^*$ orbital.

It can be seen in Table 4 that if one looks separately at those radical systems that have a *$CH_2$* carbinyl group

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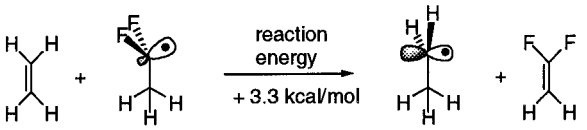
**Table 4. Bond Lengths Versus Activation Barriers for Radicals 1−6**

| radical | **1** | **2** | **3** | **1** | **6** | **4** | **5** |
|---|---|---|---|---|---|---|---|
| $C_1-C_3$ | | 1.533 | 1.549 | 1.592 | 1.529 | 1.547 | 1.571 |
| $C_1-C_2$ | 1.496 | | | | | | |
| barrier | 9.0 | 6.5 | 3.8 | 1.9 | 10.2 | 6.5 | 4.9 |

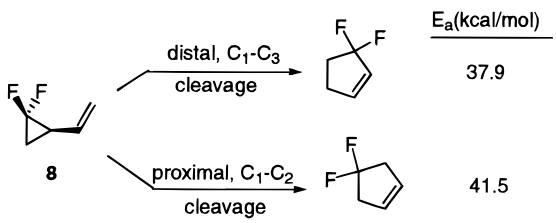
(i.e., **1**, **2**, and **3**) and those that have a $CF_2$ carbinyl group (i.e., **4**, **5**, and **6**), for each group there is an excellent correlation between the activation barriers and the ground-state bond lengths of the s bonds which are being cleaved. What this means is that, all other things being equal, longer, weaker cyclopropane bonds will have lower $\sigma^*$ orbital energies, which should lead to more effective interaction/overlap with their respective carbinyl SOMOs.

The disparity between the $CH_2$ and the $CF_2$ carbinyl systems can be simply attributed to the fact that whereas $RCH_2^{\bullet}$ radicals are planar, $\pi$-radicals, $RCF_2^{\bullet}$ radicals are pyramidal, $\sigma$-radicals,[41] which, in transforming to product, must become planar. The relative cost for conversion of a $CF_2$ carbinyl site versus a $CH_2$ carbinyl site to an olefinic site is demonstrated via the calculation of $E_{rxn}$ for the hypothetical process depicted in the equation below. This computed 3.3 kcal/mol reaction energy is consistent with the observed incremental differences in activation barrier for otherwise analogous systems **6** vs **2** (3.7 kcal/mol) and **5** vs **1** (3.0 kcal/mol).[42]



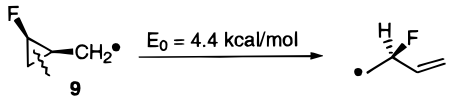

Thus, we would conclude that stereoelectronic factors probably contribute most to the activation barrier differences computed for radicals **1**−**6**.

In the only kinetic study which allows a direct comparison of distal versus proximal C−C bond cleavage, Roth found a difference of 3.6 kcal/mol for the two competitive vinylcyclopropane rearrangements of 2,2-difluorovinylcyclopropane (**8**) depicted below.[32] The smaller




difference observed by Roth for distal versus proximal cleavage of **8** than that predicted for cyclopropylcarbinyl cleavage (7.1 kcal/mol) can be understood simply by the fact that the cleavage process of **1** *is exothermic*, whereas the homolysis process of **8** is highly *endothermic*. Thus it is reasonable that stereoelectronics should play a much larger role in the early transition state of **1**, whereas thermodynamics should play a more important role in the late transition state of **8**.

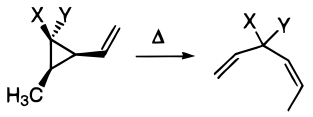
A single fluorine substituent on the cyclopropane ring appears to have about half the effect of eminal fluorine substituents with respect to cleavage of the distal, $C_1-C_3$ bond. Thus, the activation barrier of such ring opening of the *cis*-2-fluorocyclopropylcarbinyl radical (**9**) is 4.4 kcal/mol, which is 2.1 kcal/mol lower than that of the hydrocarbon system (**2**) and 2.5 kcal/mol higher than that of the *gem*-difluoro system (**1**). Likewise, the heat of reaction for distal cleavage of **9** (7.6 kcal/mol) is 3.1 kcal/mol greater than that of **2** and 2.8 kcal/mol less than that of **1**.[43]




The activation barrier for proximal, $C_1-C_2$ cleavage of **9** was calculated to be 6.7 kcal/mol, which is very close to the value for the hydrocarbon **2**. This is consistent with the fact that, unlike the situation for multiple fluorine substitution, a single fluorine substituent is known to stabilize a radical.[41,44−46]

The regiochemical preference for distal cleavage of **9** can again be rationalized on the basis of stereoelectronics, which are reflected by bond length differences. For **9**, the distal C−C bond length is 1.558 Å and the proximal C−C bond length is 1.514 Å.

Interestingly, in the only kinetic study which will allow such a comparison, the $\Delta H^{\ddagger}$ for the thermal homo-1,5-hydrogen shift rearrangement of *cis*,*cis*-2-fluoro-3-methylvinylcyclopropane (**10**) was also approximately halfway between those of the *gem*-difluoro and hydrocarbon analogues.[47−49]




X = Y = F, $\Delta H^{\ddagger}$ = 22.7 kcal/mol[46]
**10**, X = F, Y = H, $\Delta H^{\ddagger}$ = 26.7[44]
X = Y = H, $\Delta H^{\ddagger}$ = 29.9[45]

**The Importance of Rotational Barriers in Cyclopropylcarbinyl Radical Systems Having Very Low Activation Barriers.** The rotation barriers of cyclopropylcarbinyl radicals have never been considered to be large enough to affect the kinetics or regiochemistry of their ring opening processes. However, when the barriers of radical ring opening become very small, such as in the cases of radicals **1** and **7**, they can be seen to actually be lower than those expected for rotation of the carbinyl group. A potential surface scan (Figure 4) indicated that the $CH_2^{\bullet}$ group of radical **1** has a rotation barrier of 3.1 kcal/mol. No doubt, radical **7** will have an even larger rotational barrier. It is therefore likely that the rates of ring opening of radicals **1** and **7** will be faster than the rate of rotation of the carbinyl radical group. Assuming

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(42) Smart, B. E. In *Chemistry of Organic Fluorine Compounds II*; Hudlicky, M., Pavlath, A. E., Eds.; ACS Monograph 187; American Chemical Society: Washington, DC, 1995; pp 979−1010.
(43) Values for the *trans*-isomer are very similar: barriers, 4.2 kcal/mol (distal) and 6.8 kcal/mol (proximal); heat of reaction, −6.7 kcal/mol for both.
(44) Pasto, D. J.; Krasnansky, R.; Zercher, C. *J. Org. Chem.* **1987**, *52*, 3062−3072.
(45) Bordwell, F. G.; Zhang, X.-M.; Alnajjar, M. S. *J. Am. Chem. Soc.* **1992**, *114*, 7623−7629.
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(48) Ellis, R. J.; Frey, H. M. *J. Chem. Soc.* **1964**, 5578−5583.
(49) Dolbier, W. R., Jr.; Sellers, S. F. *J. Org. Chem.* **1982**, *47*, 1−4.

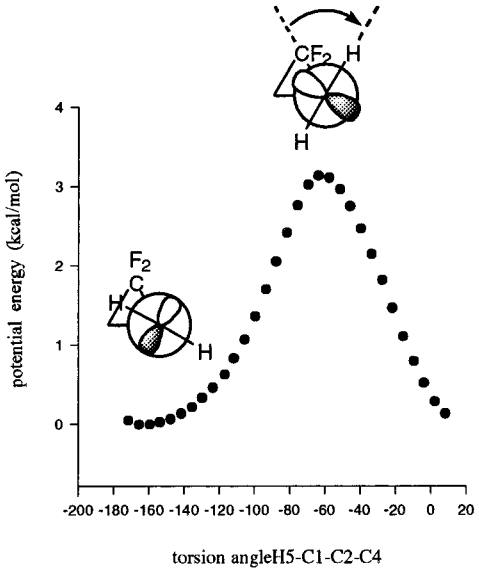
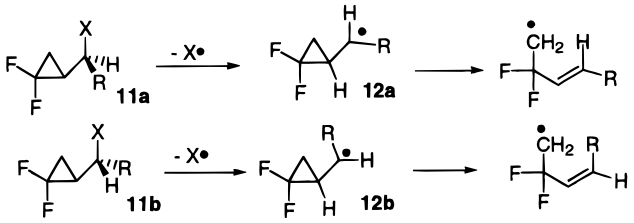



**Figure 4.** Methylene radical rotation barrier of radical (**1**) (UB3LYP/6-31G(d) without zero-point energy correction).

that a newly born cyclopropylcarbinyl radical will need to rotate to obtain the stereoelectronic orbital overlap required to ring open, we would predict that, for radicals such at **1** and **7**, conformational equilibration of the radical will *not* be attained prior to ring opening and rotation will be rate determining and product determining. That is, one could well envisage the diastereomeric radical precursors **11a** and **b**, giving rise to diastereomeric cyclopropylcarbinyl radical conformers **12a** and **b** that would, lacking conformational equilibration, lead to different ratios of diastereomeric products. This is a highly testable prediction that we are currently attempting to confirm.




**The 2,2-Difluorocyclopropylcarbinyl Cation.** As has been demonstrated by Newcomb, a radical probe is made considerably more valuable if it can, because of differences in regiochemistry, distinguish between a radical and a carbocation intermediate.[50,51] In view of the general recognition that $\beta$-fluorines destabilize carbocations much more than do α-fluorines,[42,52] we would expect the 2,2-difluorocyclopropylcarbinyl system to yield products exhibiting a different regiochemistry for a cationic intermediate versus a radical intermediate. Wishing to obtain some computational corroboration of these presumptions, we therefore carried out calculations trying to locate the 2,2-difluorocyclopropylcarbinyl cation **13** on the potential energy surface at HF/6-31G(d), MP2/6-31G(d) and B3LYP/6-31G(d)levels of theory.

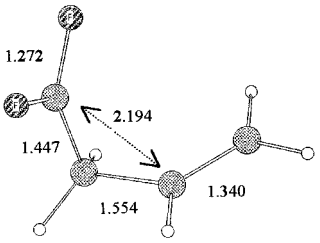
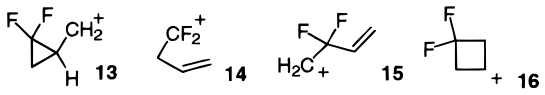


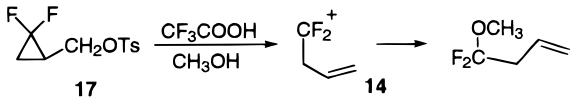

**Figure 5.** B3LYP/6-31G(d)-optimized structure of cation **14**. Distance is in angstroms.

However, in all cases, the geometry optimizations starting from the 2,2-difluorocyclopropylcarbinyl cation structure ended up with the optimized 1,1-difluoro homoallylic cation, **14**. The B3LYP/6-31G(d) optimized geometry of **14** is depicted in Figure 5. The planar geometry of the $CF_2^+$ site of **14**, and its unusually short C−F bonds (1.272 Å) are consistent with stabilization of the carbocation by its fluorine substituents. An attempt




to locate a *2,2*-difluoro homoallylic cation **15** also ended up with **14**. These results indicate that on the potential energy surface 2,2-difluorocyclopropylcarbinyl cation **13**, at least in the gas phase, is *not* a minimum, and also that there are no saddle points connecting a 2,2-difluorocyclopropylcarbinyl to a 1,1-difluoro homoallylic cation cation; thus there is no activation barrier for this transformation. Another possible cation, the 3, 3-difluorocyclobutyl cation **16**, was able to be located, but it is 17.8 kcal/mol higher in energy than cation **14**.

Therefore, considering this computational result, we predict that a solvolysis such as that of **17** depicted below, should *not* proceed via the cyclopropylcarbinyl cation intermediate, but should proceed, via synchronous ionization and cleavage of the C−C bond proximal to the $CF_2$ group, directly to the 1,1-difluoro homoallylic cation **14**. This result will lead to attachment of the nucleophile




to the fluorinated carbon, with the reaction thus exhibiting a regiochemistry different from that of the radical. There is little mention of the solvolytic chemistry of 2,2-difluorocyclopropylcarbinyl systems in the literature.[53,54] Experiments to provide definitive information regarding the rate and regiochemistry of the solvolysis of **17** are underway.

## Conclusions

In this work we have evaluated the dramatic impact of fluorine substituents on the structure and reactivity of cyclopropylcarbinyl radicals. DFT calculations (B3LYP/6-311+G(2df,2p)//B3LYP/6-31G(d)) were found to give satisfactory results with respect to predicting activation

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barriers and heats of reaction for the various fluorinated cyclopropylcarbinyl radical ring opening reactions. Stereoelectronic influences are believed to be responsible for the remarkably low barrier and highly regioselective ring opening of the distal, $C_1-C_3$ bond in the 2,2-difluorocyclopropylcarbinyl radical system.

Experimental studies of such low barrier systems should provide important insight into controversial issues related to the possibility of conformational control of rates and regiochemistry in fast cyclopropylcarbinyl radical systems and the efficacy of their use as radical clocks in very fast competitive situations.

**Acknowledgment.** Support of this research in part by the National Science Foundation is acknowledged with thanks.

**Supporting Information Available:** Tables of total energies, zero-point energies, and Cartesian coordinates for each of the calculated radicals (38 pages). This material is contained in 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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