Density Functional Theory Calculations of the Effect of Fluorine Substitution on the Cyclobutylcarbinyl to 4-Pentenyl Radical Rearrangement

John Marshall Baker and William R. Dolbier, Jr.*

Department of Chemistry, University of Florida, P.O. Box 117200, Gainesville, Florida 32611-7200

wrd@chem.ufl.edu

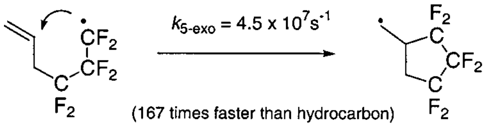
Received October 6, 2000

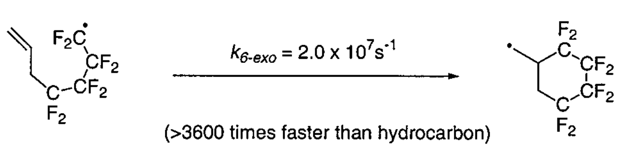
The effects of fluorine substitution on the cyclobutylcarbinyl to 4-pentenyl radical rearrangement and on the strain of cyclobutane have being studied using density functional theory, the ring-opening being modestly inhibited and the strain generally not greatly affected. Perfluorocyclobutane is predicted to have 6 kcal/mol *less* strain than cyclobutane. Cyclizations of 1,1,2,2-tetrafluoro- and 1,1,2,2,3,3-hexafluoro-4-pentenyl radicals should be significantly enhanced (~2400 times faster) relative to the parent system. The calculations are consistent with the few experimental data available.

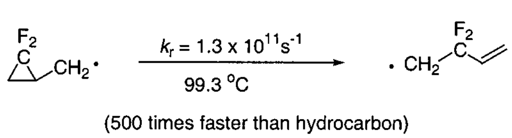
Introduction

Because of their broad potential for mechanistic and synthetic applications, radical rearrangements have long been a subject of broad interest to organic chemists. The radical rearrangements that have attracted the most attention have been the 5-exo cyclization of the 5-hexenyl radical, the ring-opening conversion of the cyclopropylcarbinyl (CPC) to the 3-butenyl radical, and somewhat to a lesser extent, the 6-exo cyclization of the 6-heptenyl radical. The efforts of many research groups have led to a reasonable understanding of the structure−activity relationships involved in determining the regiochemical and dynamic behavior of these families of radicals.

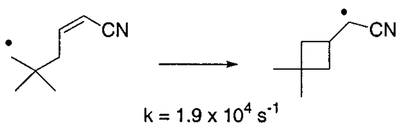
As seen by the examples below, fluorine substituents have a dramatic impact upon the reactivity of all three of these radical systems:[1−3]







In contrast to the extensive literature related to the above-mentioned radical systems, cyclobutylcarbinyl (CBC) radical ring openings and the respective reverse process, 4-exo cyclizations of 4-pentenyl radicals, have received much less attention. Kinetic studies of this exothermic ring-opening process have been confined to the parent system and a few methyl- and phenyl-substituted derivatives,[4−8] whereas 4-pentenyl cyclizations are generally observed only when a stabilized radical is formed in the process,[9−13] such as the example below where one of the few available rate constants for such a process was obtained:[14,15]



We have been interested in this system for some time from the standpoint of the impact of fluorine substituents, initially because of two papers by Piccardi and co-workers,[16,17] who reported a four-membered ring product

---

[1] Dolbier, W. R., Jr.; Rong, X. X.; Bartberger, M. D.; Koroniak, H.; Smart, B. E.; Yang, Z. Y. *J. Chem. Soc., Perkin Trans. 2* **1998**, 219−231.

[2] Tian, F.; Dolbier, W. R., Jr. *Org. Lett* **2000**, *2*, 835−837.

[3] Li, A.-R.; Shtarev, A. B.; Smart, B. E.; Yang, Z.-Y.; Lusztyk, J.; Ingold, K. U.; Bravo, A.; Dolbier, W. R., Jr. *J. Org. Chem.* **1999**, *64*, 5993−5999.

[4] Beckwith, A. L. J.; Moad, G. *J. Chem. Soc., Perkin Trans. 2* **1980**, 1083−1092.

[5] Ingold, K. U.; Maillard, B.; Walton, J. C. *J. Chem. Soc., Perkin Trans. 2* **1981**, 970−974.

[6] Walton, J. C. *J. Chem. Soc., Perkin Trans. 2* **1989**, 173−177.

[7] Choi, S.-Y.; Horner, J. H.; Newcomb, M. *J. Org. Chem.* **2000**, *65*, 4447−4449.

[8] Newcomb, M.; Horner, J. H.; Emanuel, C. J. *J. Am. Chem. Soc.* **1997**, *119*, 7147−7148.

[9] Clark, A. J.; Peacock, J. L. *Tetrahedron Lett.* **1998**, *39*, 1295−1298.

[10] D'Annibale, A.; Trogolo, C. *Tetrahedron Lett.* **2000**, *41*, 3261−3264.

[11] Ishibashi, H.; Higuchi, M.; Ohba, M.; Ikeda, M. *Tetrahedron Lett.* **1998**, *39*, 75−78.

[12] Ishibashi, H.; Nakamura, N.; Sato, S.; Takeuchi, M.; Ikeda, M. *Tetrahedron Lett.* **1991**, *32*, 1725−1728.

[13] Ogura, K.; Sumitani, N.; Kayano, A.; Iguchi, H.; Fujita, M. *Chem. Lett.* **1992**, 1487−1488.

[14] Park, S. U.; Varick, T. R.; Newcomb, M. *Tetrahedron Lett.* **1990**, *31*, 2975−2978.

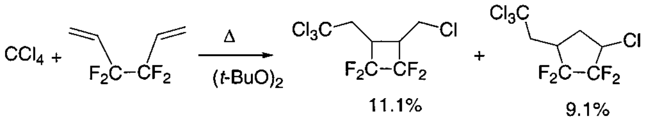
[15] Rong, X. X.; Pan, H. Q.; Dolbier, W. R., Jr.; Smart, B. E. *J. Am. Chem. Soc.* **1994**, *116*, 4521−4522.

[16] Piccardi, P.; Modena, M.; Cavalli, L. *J. Chem. Soc. C* **1971**, 3959−3966.

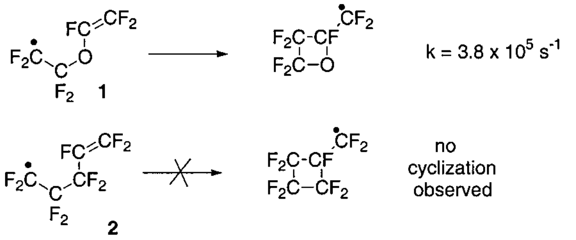
[17] Piccardi, P.; Massardo, P.; Modena, M.; Santaro, E. *J. Chem. Soc., Perkin Trans. 1* **1973**, 982.

10.1021/jo001449d CCC: $20.00

resulting from the addition of radicals to 3,3,4,4-tetrafluoro-1,5-hexadiene, i.e.:



In an early preliminary study, we were able to observe and obtain the rate constant for the cyclization of the 3-oxa-perfluoro-4-pentenyl radical, **1**, but curiously were not able to see cyclization of the non-ether, perfluoro-4-pentenyl radical, **2**.[15]

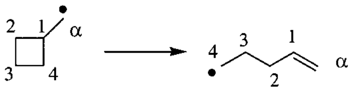


Having found the fluorinated cyclopropylcarbinyl radical system to be amenable to credible computational examination, using DFT methodology,[18] a similar systematic examination of the effect of fluorine substitution on the cyclobutylcarbinyl−4-pentenyl radical system was carried out. The aim of these calculations was to obtain useful structure−activity relationships for this radical system that would allow selection of systems that would be worthy of experimental examination.

Computational Methodology

Density functional theory calculations were performed using the Gaussian98 program package.[19] Structures and transition structures were optimized using Becke's hybrid three-parameter functional (B3LYP)[20] and the 6-31G(d) basis set.[21] Restricted and unrestricted wave functions were used for closed- and open-shell species, respectively. Using the same level of theory, vibrational frequency calculations were performed on all stationary points to identify transition structures and determine thermochemical information. Transition structures were characterized by a single imaginary frequency. Thermal energies and entropy terms were obtained using frequencies scaled by 0.9989 and 1.0015,[22] respectively, at 298.15 K and 1 atm. Thermal energy is the sum of zero-point, vibrational, rotational, and translational energies at the given temperature. In the cases of molecules with symmetry axes, the correct symmetry number term was used in computing the rotational contribution to entropy. An IRC (intrinsic reaction coordinate) calculation was performed for each transition structure to examine the reaction pathway for each elementary step. Single-point energies were calculated using B3LYP level of theory using the 6-311+G(2df,2p) basis set.[23] Calculated rate constants were derived from transition-state theory.

Table 1. Calculated Kinetic and Thermochemical Values (kcal/mol) for Ring Opening of Fluorinated Cyclobutylcarbinyl Radicals [UB3LYP/6-311+G(2df,2p)//UB3LYP/6-31G(d)]



radical	position of CF_2	$\Delta H^‡$	$\Delta S^‡$	ΔH	ΔS
3	none	11.0	−4.8	−5.6	4.5
4	4	12.5	−1.1	−1.5	5.6
4′	2	11.2	−1.9	−2.5	6.4
5	3	11.1	−3.7	−2.4	4.4
6	3 and 4	12.5	−2.0	−0.1	4.7
6′	2 and 3	11.4	−2.9	−2.7	6.1
7	2, 3, and 4	12.6	−4.4	−0.27	1.7
8	α	15.2	0.64	−1.6	8.7
9	perfluoro	15.6	+1.2	+1.2	7.6

Results and Discussion

The standard enthalpies and entropies of activation and the enthalpies and entropies of reaction for ring openings of CBC radicals with CF_2 groups at various positions were calculated (Table 1).

The parent hydrocarbon radical, **3**, has the lowest calculated standard enthalpy of activation (11.0 kcal/mol) in the series, and its ring opening is the most exothermic of the those calculated. As for the fluorinated systems, when ring opening involves cleavage of a $C-CH_2$ bond (radicals **4′**, **5**, and **6′**), little kinetic effect is predicted despite the ~2−3 kcal/mol less favorable thermodynamics of these systems. The observed thermodynamic differences in these systems derive from a complex combination of strain differences in the CBC system combined with the impact of fluorine substitution on the respective 4-pentenyl radicals. Regarding the latter, it is widely recognized that fluoroalkyl substitution destabilizes both radicals and alkenes, whereas contiguous CF_2 groups provide extra stabilization to an alkyl system.[24,25]

When CBC ring opening involves cleavage of a $C-CF_2$ bond, as is the case for radicals **4**, **6**, and **7**, a larger increase in $\Delta H^‡$ (~1.5 kcal/mol) is observed, along with still less favorable thermodynamics. This increase almost surely derives from the normal C−C bond strengthening that occurs when one or both of the carbons are bearing fluorine substituents.[25]

Impact of α-Fluorine Substitution. Fluorine substitution at the α-position, that is at the carbinyl, radical-bearing site, as in radicals **8** and **9**, leads to a more dramatic increase in their barriers to ring opening. This observed disparity between the CH_2 and the CF_2 cyclobutylcarbinyl systems can be simply attributed to the fact that, whereas $RCH_2^•$ radicals are planar π-radicals, $RCF_2^•$ radicals are pyramidal σ-radicals,[24] which when undergoing ring opening 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

---

[18] Tian, F.; Bartberger, M. D.; Dolbier, W. R. J. *J. Org. Chem.* **1999**, *64*, 540−546.

[19] Frisch, M. J. T., G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Baboul, A. G.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. Gaussian 98, Revision A.7, Gaussian, Inc., Pittsburgh, PA, 1998.

[20] Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648−5652.

[21] Hariharan, P. C.; Pople, J. A. *Theor. Chem. Acta* **1973**, *28*, 213−222.

[22] Scott, A. P.; Radom, L. *J. Phys. Chem.* **1996**, *100*, 16502−16513.

[23] Raghavachari, K.; Trucks, G. W. *J. Chem. Phys.* **1989**, *91*, 1062−1065.

[24] Dolbier, W. R., Jr. *Chem. Rev.* **1996**, *96*, 1557−1584.

[25] Bartberger, M. D.; Dolbier, W. R., Jr.; Lusztyk, J.; Ingold, K. U. *Tetrahedron* **1997**, *53*, 9857−9880.

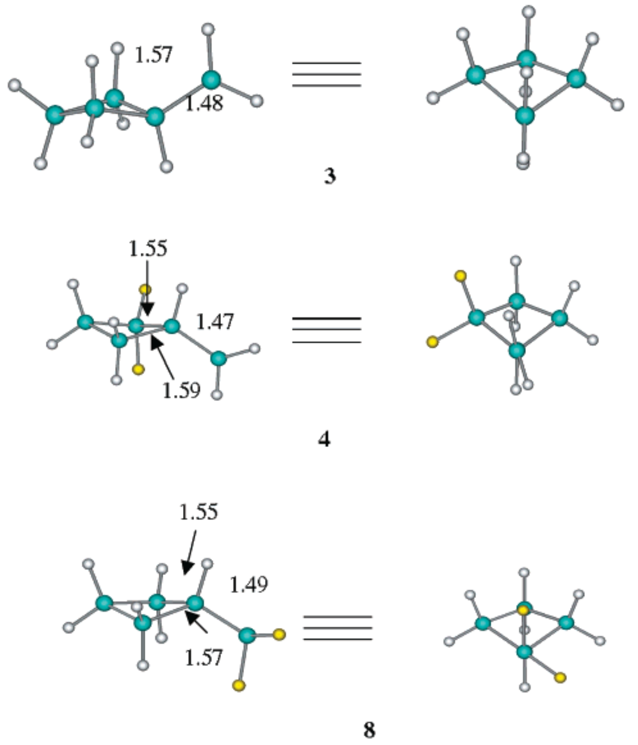
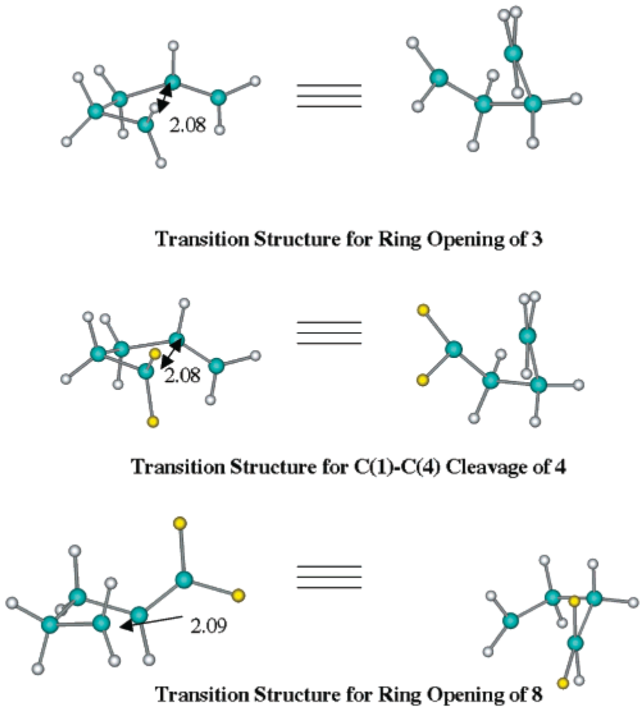


Figure 1. Structure of cyclobutylcarbinyl radicals.



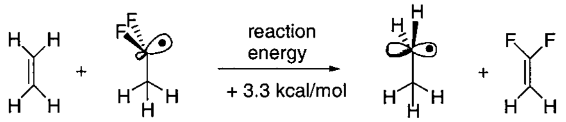
Transition Structure for Ring Opening of 3

Transition Structure for C(1)-C(4) Cleavage of 4

Transition Structure for Ring Opening of 8

Figure 2. Transition structures for CBC radical ring openings.

equation below.[18] This computed 3.3 kcal/mol reaction energy is consistent with the observed incremental differences in activation barrier for ring opening of radicals **8** and **9**.



Structures of Radicals and Transition States. The optimized structures for radicals **3**, **4**, and **8** are shown in Figure 1. Radicals **3** and **4** are planar, π radicals; however, **8** is a pyramidal, σ radical, as would be expected.[24] Ingold and co-workers have detected radical **3** experimentally using ESR techniques and concluded that the conformation of the radical center is similar to that shown in Figure 1.[5] These conformations should be favorable to ring cleavage since the SOMO can overlap effectively with the cyclobutane σ^* orbital.

Transition structures for the ring opening for selected examples are shown in Figure 2. The geometry of the α carbon is somewhat planar in these transition states, and it could therefore be rationalized that $\Delta\Delta H^{\ddagger} = 4.2$ kcal/mol between **8** and **3** is due to the extra energy required for the pyramidal radical to become planar.[18] Also, although ring openings of CPC radicals and cyclizations of 5-hexenyl radicals are recognized to have early transition states, the C−C bond breaking distance for CBC ring openings are ca. 2.1 Å, which indicates that they do not have early transition states, unlike those for the exothermic ring openings of CPC radicals and the cyclizations of 5-hexenyl radicals.

For cleavage to occur, the SOMO for the radical must overlap with the σ^* for the C−C cyclobutane bond. Fluorine substituents on carbon are known to increase the bond strength of the C(α)−C(β) bond. Therefore, it is not surprising that C−C bonds bearing hydrogen have lower enthalpies of activation since they have the weaker bond with a lower lying σ^*. Perhaps surprising is the fact that, whereas fluorine substituents on a cyclopropane ring significantly lower the E_a for any reaction involving cleavage of the cyclopropane ring, fluorine substituents on the cyclobutane ring appear to *increase* the enthalpy of activation for *every* radical listed in Table 1.

Ring Strain. The major driving force for both the cyclopropylcarbinyl and cyclobutylcarbinyl ring-opening rearrangements is the release of ring strain. Measured heats of combustion have shown that cyclopropane and cyclobutane have nearly the same strain energies, 27.5 and 26.5 kcal/mol, respectively.[26] Fluorine substituents are recognized to have a profound effect on the ring strain of cyclopropane, increasing by 5−7 kcal/mol per fluorine.[18] The use of appropriate isodesmic reactions can provide quantitative insight regarding molecular thermodynamic issues. Isodesmic reactions a−d (Chart 1) were designed to determine the effect of ring strain by fluorine substituents on cyclobutane, assuming that fluorine substituents on a cyclohexane ring do not give rise to strain. Perfluorocyclohexane has previously been suggested as a reasonable model for strain estimates of small ring perfluorocycloalkanes.[27]

Whereas two and four fluorine atoms are seen to increase ring cyclobutane's strain slightly, by 0.9 and 2.0 kcal/mol, respectively, the introduction of additional fluorine atoms actually gives rise to a *decrease* in the ring strain, with the ring strain of *perfluoro*cyclobutane being 5.9 kcal/mol less than that of cyclobutane.[27,28]

Rate Constant Comparisons for 4-*exo*-Pentenyl Cyclizations. From the data given in Table 1, the

---

[26] Schleyer, P. v. R.; Williams, J. E.; Blanchard, K. R. *J. Am. Chem. Soc.* **1970**, *92*, 2377−2386.

[27] Smart, B. E. In *Molecular Structure and Energetics*; Liebman, J. F., Greenberg, A., Eds.; VCH Publishers: Deerfield Beach, FL, 1986; Vol. III, pp 182−183.

Chart 1. Isodesmic Equations

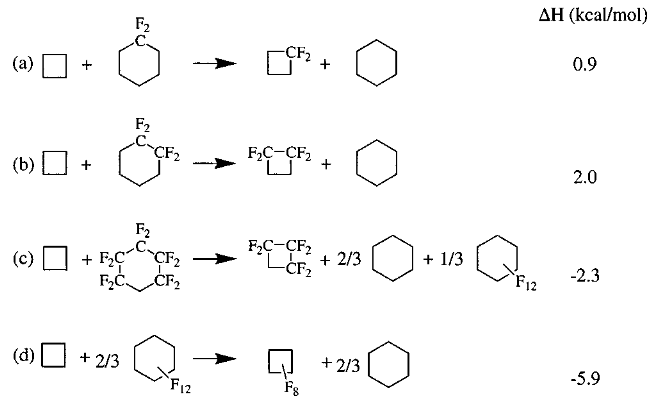
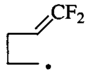
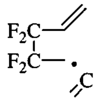
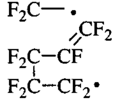
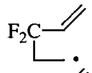
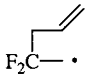
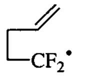
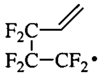
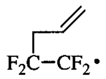
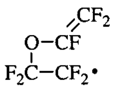


Table 2. Kinetic and Thermodynamic Parameters and Relative Rates for Cyclization of Fluorinated 4-Pentenyl Radicals at 25 °C

	$\Delta H^\ddagger$	$\Delta S^\ddagger$	k_{rel}
	16.6	-9.2	1[a]
	16.8	-8.0	1
	14.2	-9.0	65
	14.3	-6.4	175
	13.7	-8.2	208
	13.5	-8.1	309
	14.0	-6.6	280
	12.9	-6.0	2463
	12.6	-6.7	2689
	7.1	-5.5	6.1 x 10^7

[a] $k_{25} = 4.4 \times 10^{-2}$ s^{-1}.

standard enthalpies of activation for each of the 4-*exo cyclizations* can be determined, and fluorine is seen to have a greater impact on the cyclizations than on the ring openings (when compared to the hydrocarbon system). For example, the $\Delta\Delta H^\ddagger$ between **3** and **6** for their C(1)–C(4) bond cleavages is 1.5 kcal/mol (higher for **6**), whereas the $\Delta\Delta H^\ddagger$ for the reverse process is +4.0 kcal/mol (*lower* for fluorinated **6**). The calculated relative rate constants for each of the 4-*exo* cyclizations are shown below in Table 2.

Table 3. Calculated and Experimental Cyclization Rate Constants for Radicals 1 and 2 at 30 °C

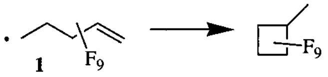
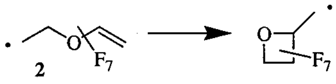
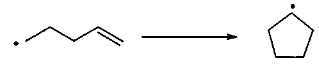
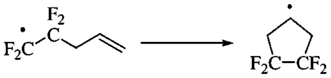
	k_{calc} x 10^5s^{-1}	k_{obs} x 10^5s^{-1}
 1	0.00113	----
 2	33.4	3.8

Table 4. Calculated Kinetic and Thermodynamic Parameters for 5-*endo*-Pentenyl Cyclizations

	$\Delta H^\ddagger$	$\Delta S^\ddagger$	ΔH^o	ΔS^o
	17.1	-9.9	-15.3	-11.5
	15.6	-7.88	-20.3	-9.7

Comparison with Experimental Rate Constants. Examination of the experimental rate constants for those systems for which such data are available indicates a good correlation with our computational results.

The calculated $\Delta H^\ddagger$ and $\Delta S^\ddagger$ for ring opening of parent, hydrocarbon radical **3** of 11.0 kcal/mol and −4.76 cal/(mol K), respectively, predicts a unimolecular rate constant for ring opening of 5.0 × 10^3 s^{-1} at 25 °C, which is no doubt fortuitously identical to the experimental value of 5 × 10^3 s^{-1}.[4−6,29]

It will be remembered that, in our preliminary study, we were able to observe and measure the rate constant for the cyclization of the 3-oxaperfluoro-4-pentenyl radical, **1**, but not that of the perfluoro-4-pentenyl radical, **2**. The computed kinetic and thermodynamic parameters for the two systems, given in Table 3, are consistent with these experimental observations.

Since, among the new radicals examined computationally, the 1,1,2,2-tetrafluoro-4-pentenyl radical has the largest cyclization rate constant, this system might be worthy of experimental examination. Therefore its potentially competitive 5-endo cyclization was also examined, although, being disfavored by Baldwin's rules, few such cyclizations have been observed to occur.[30] The data are presented in Table 4.

The 5-endo cyclization of the 1,1,2,2-tetrafluoro-4-pentenyl radical has a slightly lower enthalpy of activation than that of its hydrocarbon counterpart ($\Delta\Delta H^\ddagger$ = 1.5 kcal/mol), and its cyclization is also more exothermic by 5.0 kcal/mol. Nevertheless, a comparison of the enthalpies of activation for the competitive 4-*exo* and 5-endo cyclizations shows the 4-exo process to be favored by 3.0 kcal/mol. Therefore, little 5-endo cyclization should be observed.

Conclusion

The effects of fluorine substituents on the cyclobutylcarbinyl−4-pentenyl radical rearrangement have being studied using density functional theory. Fluorine has a greater influence on the 4-exo cyclization than it does for

---

[28] Smart has previously estimated the ring strains of some fluorinated cyclobutanes, using available thermochemical data, and he noted that the lack of thermal reactivity of fluorinated cyclobutanes, relative to the hydrocarbon, is most consistent with a decrease in their ring strain.[26]

[29] Newcomb, M. *Tetrahedron* **1993**, *49*, 1151−1176.

[30] Bogen, S.; Gulea, M.; Fensterbank, L.; Malacria, M. *J. Org. Chem.* **1999**, *64*, 4920−4925 and references therein.

the ring opening. In general, fluorine retards the ring opening and increases the rate of the 4-exo cyclization. The computational results are consistent with a combination of factors being responsible for these effects. The effect of fluorine substituents on cyclobutane ring strain is an important influence, as is the normal C−C bond-strengthening effects of fluorine substituents in hydrofluorocarbon systems.

Since 4-exo cyclizations of 4-pentenyl and related radicals are not commonly observed, both the 1,1,2,2-tetrafluoro- and 1,1,2,2,3,3-hexafluoro-4-pentenyl radicals would be interesting systems to examine experimentally.

Acknowledgment. Support of this research in part by the National Science Foundation is gratefully acknowledged. Insightful discussions with Dr. Bruce Smart of DuPont CR&D are also acknowledged with thanks.

Supporting Information Available: Molecular geometries, energies, thermal energies, and entropies for radical species and of the molecules used in ring strain calculations; transition structures for the radical rearrangements; symbols are identified and equations given. This material is available free of charge via the Internet at http://pubs.acs.org.

JO001449D