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The Kinetic Impact of Vinylic Fluorine Substituents on 5-Hexenyl Radical Cyclizations

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Abstract: A study of the effect of vinylic fluorine substituents on the 5-hexenyl radical cyclization indicates that substituents at the 6-position, or vicinal 5,6-difluoro substitution have little effect on the rate, whereas a 5-fluoro substituent slows down the rate by a factor of 10.8, and 5,6,6-trifluoro substitution enhances the rate by a factor of 2.3. The results are explained in terms of a combination of steric and enthalpic effects, with possible intervention of polar influences in the trifluorovinyl case. Copyright © 1996 Elsevier Science Ltd

It is commonly recognized that reactivity in radical additions to alkenes derives from a combination of steric, polar and thermodynamic factors which are dependent upon the nature of the substituents that are on both the radical and the alkene.[1,2] Radical cyclization reactions which, by their nature, have much more restricted conformational and stereoelectronic requirements,[3,4] are influenced in their own way by these same three factors, and there has been considerable effort devoted to gaining understanding of how these influences affect the rates of 5-hexenyl radical cyclizations.[5-7]

Free radical additions constitute a major class of reactions of fluoroolefins,[8,9] and free radical chain oligomerizations and polymerizations of fluoroolefins are important commercial processes.[10] Nevertheless, in spite of such interest in free radical reactions of fluoroolefins there is little quantitative data presently available dealing with the fundamental rates of radical additions to fluoroolefins.

Tedder, Walton and Low's relative rate studies on the addition of methyl radicals to fluoroolefins,[11] as summarized below, provides the most reliable of the limited data available to date on the kinetic influence of olefinic fluorine substituents on alkyl radical addition reactions, but the brevity of the Table clearly demonstrates the relative lack of information on this subject.

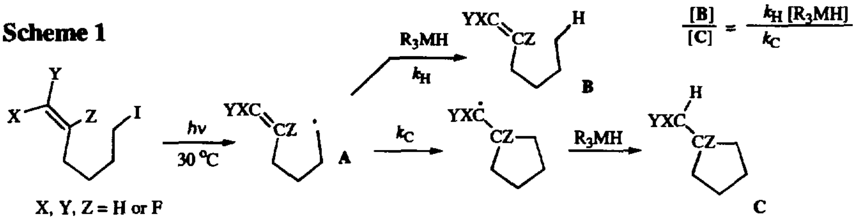
Table. Relative Rates of Addition of Methyl Radical to Some Fluoroethylenes[a,11]

	$\mathit{CH_2}$=CH$_2$	$\mathit{CH_2}$=CHF	CHF=CH$_2$	CHF=CF$_2$	$\mathit{CF_2}$=CHF
$CH_3\cdot$	1.0	0.9	0.2	1.9	3.9

[a] for addition to italicized end of olefin

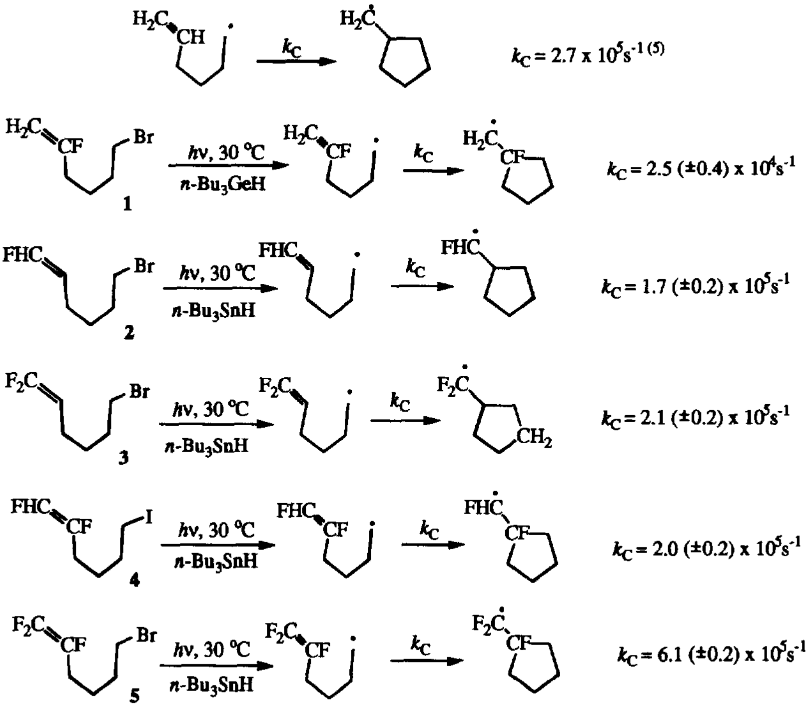
In this paper we report results from an investigation of the effect of olefinic fluorine substitution on the rates of 5-hexenyl radical cyclizations.[12] To obtain the cyclization rate constants for our series of fluorinated 5-hexenyl radical systems, **1-5**, competition studies were carried out as depicted in Scheme 1, where competitive free radical chain processes were established between unimolecular cyclization of the respective radical species **A** to eventually form **C**, and the bimolecular hydrogen atom transfer to **A** by a reductant of appropriate reactivity to form **B**.[13-16]

Scheme 1



As can be seen from the rate data given in Scheme 2 below, fluorine substitution on the double bond of the 5-hexenyl radical has remarkably little effect upon the observed rates of cyclization.

Scheme 2. Cyclization Rates at 30 °C



Only the 5-fluoro- and the 5,6,6-trifluoro-5-hexenyl radical systems exhibit any significant deviation from the cyclization rate of the parent system, with the former being slowed by a factor of 10.8 and the latter enhanced by a factor of 2.3.

Since a single fluorine substituent stabilizes an alkene,[17] much like a methyl substituent, and since *any* substituent at the 5-position should exert a detrimental steric influence on the 5-*exo* addition transition state, it is not surprising that the 5-fluoro-5-hexenyl radical cyclizes slower than the unsubstituted parent. What is somewhat surprising is that the reaction remains regiospecific, within the limits of our NMR analytical methodology (± 4%). In contrast, the 5-*methyl* system, presumably because of the steric impact of the methyl substituent, undergoes preferential 6-*endo* addition (63 %).[6]

On the other hand, the trifluorovinyl group should have a relatively reactive π-bond, as indicated by the large heat of hydrogenation of trifluoroethene (-45.7 kcal/mol, 13 kcal/mole greater than that of ethylene.)[18] Moreover, the 1,1-difluoroalkyl radical which is formed by the cyclization process should have a similar stability to that of the analogous hydrocarbon radical.[9,19] In view of the kinetic result, one must conclude that the enthalpic enhancement of the cyclization of the 5,6,6-trifluoro-5-hexenyl radical is sufficient to overcome the steric inhibition of its 5-fluoro-substituent to give rise to an overall slight enhancement. Although, polar influences could also be playing some role in the observed enhanced rate for the trifluorovinyl system, they should not be playing a significant role in most of these cyclizations, since the reported electron affinities of ethylene (-1.78 eV), fluoroethene (-1.91 eV), 1,1-difluoroethene (-2.39 eV), cis- and trans-1,2-difluoroethene (-2.18 & -1.84 eV), and 1,2,2-trifluoroethene (2.45 eV) encompass a total range of only 0.7 eV.[20] In the olefin addition reactions of the more nucleophilic *tert*-butyl radical, Fischer observed a rate variation of only ~5 for olefins with a 0.7 eV difference in EA.[21] Therefore one would not expect polar influences to be very significant for our systems.

In rationalizing the results for the other fluorine-substituted systems, the lack of significant influence of single or geminal fluorine substituents at the 6-position or of vicinal, 5,6-difluoro substituents likely derives from a canceling out of advantageous and disadvantageous effects in each case. The single 6-fluoro substituent should stabilize by approximately the same amount, both the olefin[17] and the radical which results from cyclization;[9,19] hence no resultant net effect. Geminal 6,6-difluoro substituents appear to slightly stabilize the π-system, based upon the 3.7 kcal/mol greater π-bond dissociation energy (D_π°) of $CH_2{=}CF_2$ than that of ethylene.[18] As mentioned earlier, the stability of the radical which results from cyclization should be virtually unaffected by the 1,1-difluoro substituents.[9,19] Thus geminal fluorine substituents at the terminal site should have little impact on cyclization rate. Thermodynamic data indicate that vicinal fluorination, such as in the 5,6-difluoro system, destabilizes the π-system by ~5 kcal/mol.[18] This, combined with the small stabilization of the cyclized radical, are apparently enough to offset the steric inhibition of the 5-fluoro substituent to give the observed kinetic result.

In conclusion, a systematic examination of the effect of vinylic fluorine substituents on the 5-hexenyl radical cyclization indicates that one or two substituents at the 6-position, or vicinal 5,6-difluoro substitution leads to little impact on the rates of cyclization. A 5-fluoro substituent has the greatest effect, slowing down the rate of cyclization by a factor of 10.8, whereas 5,6,6-trifluorosubstitution slightly enhances the rate. The results are rationalized largely in terms of a combination of steric and enthalpic effects, with polar influences perhaps intervening to some extent in the trifluorovinyl case.

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References and Footnotes

1. Tedder, J. M. *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 401-410.
2. Giese, B. *Angew. Chem. Int. Ed. Engl.* **1983**, *22*, 753-764.
3. Beckwith, A.L. J.; Schiesser, C. H. *Tetrahedron* **1985**, *41*, 3925-3941.
4. Spellmeyer, D. C.; Houk, K. N. *J. Org. Chem.* **1987**, *52*, 959-974.
5. Newcomb, M. *Tetrahedron* **1993**, *49*, 1151-1176.
6. Beckwith, A. L. J. *Tetrahedron* **1981**, *37*, 3073-3100.
7. Landolt-Bornstein. In *New Series, Radical Reaction Rates in Liquids*; Fischer, H., Ed.; Springer-Verlag: Berlin, 1984; Vol. 13, Parts a, b.
8. Chambers, R. D. *Fluorine in Organic Chemistry*; John Wiley and Sons, Inc.: New York, 1973; pp. 173-179.
9. Dolbier, W. R., Jr. *Chem. Rev.* **1996**, in press.
10. Feiring, A. E.; Logothetis, A. L. In *Organofluorine Chemistry Principles and Commercial Applications*; Banks, R. E.; Smart, B. E.; Tatlow, J. C. Eds.; Plenum Press: New York, 1994, pp. 339-396.
11. Low, H. C.; Tedder, J. M.; Walton, J. C. *J. Chem. Soc. Faraday Trans.* **1976**, *72*, 1707-1714.
12. Taken from the Ph. D. dissertation of Xiao X. Rong, University of Florida, 1995.
13. The values of k_H at 30 °C which were used are: *n*-Bu_3SnH, 2.7 x $10^6 M^{-1}s^{-1}$; *n*-BuGeH, 1.02 x $10^5 M^{-1}s^{-1}$.[5]
14. All competition studies were carried out at 30 °C, in C_6D_6, using photoinitiation, with combined yields of **B** and **C** in each case exceeding 90%.[15] For each compound, **1-5**, ratios of **B**/**C** were obtained for six different concentrations of R_3MH, with a plot of these ratios versus [R_3MH] providing a straight line, the slope of which was equal to k_H/k_C. Derived values of k_H/k_C for substrates **1-5** are 4.24, 15.9, 12.9, 13.5 and 4.43, respectively.
15. For further details as to experimental procedure see: Rong, X. X.; Pan, H.-Q.; Dolbier, W. R., Jr.; Smart, B. E. *J. Am. Chem. Soc.* **1994**, *116*, 4521-4522.
16. All beginning substrate halides and products of cyclization and reduction have been isolated and fully characterized by ^1H, ^{13}C and ^{19}F NMR spectroscopy, and mass spectrometry.
17. Dolbier, W. R., Jr.; Medinger, K. S. *Tetrahedron* **1982**, *38*, 2415-2419.
18. Smart, B. E. In *Molecular Structure and Energetics, Vol. 3: Studies of Organic Molecules*; Liebman, J. F.; Greenberg, A., Eds.; VCH: New York, 1986.
19. Pasto, D. J.; Krasnansky, R.; Zercher, C. *J. Org. Chem.* **1987**, *52*, 3062-3072.
20. Chiu, N. S.; Burrow, P. D.; Jordan, K. D. *Chem. Phys. Lett.* **1979**, *68*, 121-126.
21. Fischer, H. In *Substituent Effects in Radical Chemistry*; Viehe, H. G., Janousek, Z., Merenyi, R., Eds.; Reidel: Dordrecht, 1986; pp 123-142.

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