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Structure, Reactivity, and Chemistry of Fluoroalkyl Radicals

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I. Introduction

Within the realm of fluorinated reactive intermediates, the subject of fluorinated free radicals is particularly rich and diverse. The primary goal within this review will be to provide the reader with a thorough overview of the subject with an emphasis placed upon presenting a current perspective of the structure, reactivity, and chemistry of carbon-based, fluorine-containing free radicals in solution. The literature of the past 20 years will be covered comprehensively, with much earlier work also being included in order to put all work in historical perspective.

In contrast to closed shell molecules, free radicals are species which have an odd number of electrons. Simply speaking, all electrons in free radical species are considered to be paired up, except for one orbital which contains the single electron. The molecular orbital which describes the distribution of this odd electron is called the SOMO (singly occupied MO). In the ground state of the radical, the SOMO is also the HOMO. In a carbon-based free radical, the SOMO is generally strongly localized to a trigonal carbon atom.

Once believed to be too reactive and indiscriminate in their reactivity to be harnessed usefully for synthesis, carbon-based free radicals were largely ignored for a good 30 years subsequent to the first recognition of their widespread mechanistic importance in the late 1930s.[1,2]

There were two important exceptions to this neglect. As it became evident that free radical chain polymerization of olefins comprised perhaps the most effective pathway for the preparation of this diverse and commercially very important class of polymers,[3,4]

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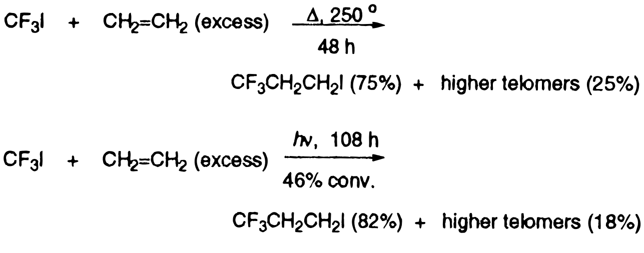
Bill Dolbier was born in Elizabeth, NJ, August 17, 1939, and he received his B.S. in Chemistry from Stetson University in 1961. He obtained his Ph.D. in organic chemistry from Cornell University in 1965, working with Mel Goldstein, and after one and a half years of postdoctoral work with Bill Doering at Yale, joined the faculty at the University of Florida in 1966. He has been at UF ever since, serving as Chairman of the Department from 1983 to 1988. Bill's research interests are physical organic in nature, and he maintains long-term interests in thermal homolytic reactions, pericyclic reactions, and secondary deuterium isotope effects. In 1975, he began applying his physical organic methodologies to the study of molecules containing fluorine, and in recent years kinetic studies of fluorinated radicals have become the main focus of his research activity. When not immersed in such activity, Bill's main interests are his wife and new son, Stephen, and a little handball.

a large amount of energy was expended and technological knowledge accumulated, mostly in industrial laboratories, related to the understanding and control of such reactions. Likewise, beginning in the mid-1940s with the work of Kharasch,[5,6] there was a large effort devoted to the understanding and synthetic utilization of carbon−carbon bond making, free radical chain reactions. The tremendous current level of interest and activity with respect to *all* aspects of the chemistry of free radicals clearly indicates that the importance of this class of reactive intermediates has finally been appropriately recognized.

Since the early days, fluorinated radicals have played a significant role in the history of free radical chemistry. It appears that the first literature report of an experiment involving the intervention of a fluorine-containing alkyl radical was a paper by Swarts in 1933 wherein he reported the Kolbe electrolysis of a solution containing trifluoroacetic acid, a reaction which led to the formation of CF_3-CF_3, among other products.[7]

However, the first significant efforts in the area of *organofluorine* free radical chemistry began shortly after Kharasch's classic work on the free radical chain addition of CCl_4 to alkenes,[5,6] when Hazeldine reported the similar chemistry of iodotrifluoromethane:[8]



$$CF_3I + CH_2{=}CH_2\ (\text{excess}) \xrightarrow[\text{48 h}]{\Delta,\ 250^\circ} CF_3CH_2CH_2I\ (75\%) + \text{higher telomers}\ (25\%)$$

$$CF_3I + CH_2{=}CH_2\ (\text{excess}) \xrightarrow[\text{46\% conv.}]{h\nu,\ 108\text{ h}} CF_3CH_2CH_2I\ (82\%) + \text{higher telomers}\ (18\%)$$

His work was followed shortly thereafter by Tarrant's studies of the peroxide-catalyzed, free radical chain addition reactions of CF_2Br_2 and polyhaloethanes, such as $CF_2Br-CFClBr$.[9−11]

It was recognized early on that fluorinated radicals had reactivities that were quite different from those of their hydrocarbon counterparts. For example, in 1961, Stefani, Herk, and Szwarc first demonstrated the electrophilicity of the $CF_3^\bullet$ radical in a study of the relative rates of addition of $CF_3^\bullet$ to various olefins.[12] They found, for example, that $CF_3^\bullet$ added to propylene and isobutylene 1.4 and 3.7 times faster than to ethylene and to tetrafluoroethylene 6.5 times slower. Since then, there has been much effort directed toward defining and understanding the differences between fluorocarbon and hydrocarbon radicals with respect to their structure, reactivity, and chemistry.

Good structure determination methods have been available for some time, and now that theoretical methods have reached a level where they can handle fluorine substituents and methods that allow *direct* measurements of the rates of radical reactions have become available, it is an appropriate time to present an up-to-date review of the rather substantial current state of knowledge of the field of fluorinated radicals. When possible, the structure, reactivity, and chemistry of fluorinated and hydrocarbon free radicals will also be compared.

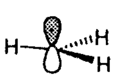
A. Influence of Fluorine as a Substituent

Substituents give rise to a perturbation of any "standard" system, whether it be a reactive intermediate, such as a radical, or a valence-satisfied molecule, and to a first approximation, the character of a substituent is considered to remain basically unaltered from one molecular environment to another. Substituent effects can be broadly divided into steric effects and polar (or electronic) effects, with electronic effects being further divided into σ inductive effects and π conjugative (resonance) effects. Although it is not a rigid rule, because of the small size of a fluorine substituent and the relatively non-sterically-demanding nature of the transition states for most types of radical reactions, the influence of fluorine substituents upon structure and reactivity of radicals is usually considered to derive largely from fluorine's electronic nature.[13] Fluorine is the most electronegative atom, and it thus exhibits a potent σ inductive electron-withdrawing effect in all situations. It is also a potentially strong π electron donor to carbon π-systems, including the semioccupied molecular orbital (SOMO) of a carbon radical, because of the good match up in size of the lone pair 2p orbitals of fluorine with those of carbon. The effectiveness of this conjugative interaction is a function of the energetic separation of the interacting orbitals, as well as of the degree of their overlap, both of which are significantly influenced by the strong inductive withdrawing nature of the fluorine substituent.

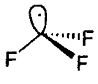
Thus, the net impact of a substituent such as fluorine, which is inductively withdrawing and π-donating, will result from a complex interplay of these disparate interactions. To make matters even more complicated, the combined influences of *multiple* fluorine substituents is not additive and cannot be readily derived from an understanding of the effect of a single fluorine substituent.

II. Structure

Fluorine substituents have a dramatic impact upon the structure of alkyl radicals. The methyl radical itself is planar; UV, IR, PES, and ESR spectroscopy, as well as the highest level of theoretical analysis, all indicate that its conformational properties are best defined as deriving from a single minimum.[14] Fluoromethyl radicals, on the other hand, are increasingly pyramidal,[15] with the trifluoromethyl radical being essentially tetrahedral[15−19] with a significant barrier to inversion.[20,21]



planar $CH_3^{\cdot}$



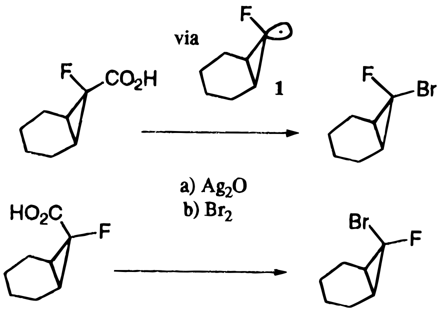
tetrahedral $CF_3^{\cdot}$

ESR spectroscopy is perhaps the best method for the unequivocal detection and observation of free radicals, and ESR ^{13}C hyperfine splitting (hfs) constants are considered to be a very useful indicator of a radical's geometry because nonplanarity introduces s character into the orbital that contains the unpaired electron. The methyl radical's $a(^{13}C)$ value of 38 G is consistent with a planar structure. Fluoromethyl radicals exhibit increased $a(^{13}C)$ values, as shown in Table 1, thus indicating increasing nonplanarity, with the trifluoromethyl radical's value of 272 G lying close to that expected for its sp^3 hybridization.[16] As also can be seen from Table 1, the α-F hfs interactions exhibited by CH_2F, CHF_2, and CF_3 are also consistent with their increasingly pyramidal nature, and Table 2 provides data for other α-fluorinated radicals which indicate their degree of bending. Direct fluorine substitution at the radical site also gives rise to large increases in the radical's barrier to inversion, with barriers of ~1, 7, and 25 kcal/mol being calculated for CH_2F, CHF_2, and CF_3, respectively.[21]

Table 1. ESR Hyperfine Splitting Constants for Fluorinated Methyl Radicals[16]

	CH_3	CH_2F	CHF_2	CF_3
$a(^{13}C)$	38.5	54.8	148.8	272
$a(^{19}F_\alpha)$		64.3	84.2	143.7
$a(H_\alpha)$	−23.0	−21.1	22.2	
g	2.0026	2.0045	2.0041	2.0026

Another indication of the propensity of a fluorine substituent to disfavor radical planarity derives from studies of α-fluorocyclopropyl radicals. Work of Ando and Walborski demonstrated that an α-fluoro substituent enhanced the configurational stability of a cyclopropyl radical such that n-Bu_3SnH reductions, Hunsdiecker reactions, and other reactions involving a geometrically stable σ-radical intermediate, such as **1** in the example given below, are virtually stereospecific.[26−28] ESR studies have moreover indicated that whereas the pyramidal carbon atom of an analogous hydrocarbon cyclopropyl radical is undergoing rapid interconversion ($k \geq 8 \times 10^7$ s^{-1}) at −108 °C, the (*Z*,*Z*)- and (*E*,*E*)-2,3-dimethyl-1-fluorocyclopropyl radicals (α-^{19}F hfs constant = 77.6 G for *E*,*E*-isomer) are static at this temperature on the ESR time scale.[29]



Such a strong influence of fluorine substituents on the geometry of a radical can be understood largely in terms of the effect of the σ inductive influence of the fluorine substituent on the thermodynamics of bonding. There is a thermodynamic advantage for the carbon orbitals used in bonding to fluorine to be relatively high in p character, as they would be in an increasingly bent radical. In such a case, the orbital containing the unpaired electron in a fluoromethyl radical would have increasing s character as the number of fluorines is increased. It has also been suggested that conjugative effects can contribute significantly to pyramidalization, but Bernardi, Epiotis, and their co-workers concede that in the case of fluorine substituents the inductive effect is primarily responsible for the observed conformational trends.[21]

From a simple MO perturbational perspective, pyramidalization of a radical $^{\bullet}CH_{3-n}X_n$ occurs when it can lead to mixing of the SOMO with the lowest occupied σ MO (LUMO). (This would lead to charge transfer and increased ionic character to the C−X bonds.) The more electronegative the substituent X is, the lower the LUMO energy, hence the lower the SOMO−LUMO gap, which results in more mixing. Being most electronegative, fluorine substituents have the strongest influence on nonplanarity.[21]

Methyl substituents also induce some bending, with ethyl, isopropyl, and *tert*-butyl radicals becoming increasingly pyramidal,[14] but in contrast to the influence of fluoro substituents, such radicals have shallow potential energy functions with very small (<1 kcal/mol) barriers to inversion.[30] (Table 2 gives the hyperfine splitting constant data for 1°, 2°, and 3° alkyl and fluoroalkyl radicals.) Placing fluoro substituents at the β-position, as in the 2-fluoroethyl radical, gives rise to conformational preferences which appear to be of minor structural consequence at the radical site.[31−33] Even the strongly electronegative trifluoromethyl substituent would appear to

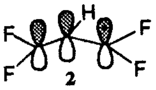
Table 2. ESR Hyperfine Splitting Constants for 1°, 2°, and 3° Alkyl and Fluorinated Alkyl Radicals[16,22−25]

	CH_3CH_2	$(CH_3)_2CH$	$(CH_3)_3C$	CH_3CF_2	CF_3CF_2	$(CF_3)_2CF$	$(CF_3)_3C$
$a(^{13}C_\alpha)$	39.1	41.3	49.5				44.3
$a(^{19}F_\alpha)$				94.0	87.6	70.3	

induce less pyramidalization than a methyl substituent. For example, the smaller $a(^{13}C)$ hfs constant exhibited by the perfluoro-*tert*-butyl radical, combined with its normal temperature dependence properties, indicate a more planar geometry than that of *tert*-butyl radical.[22,30]

With the demonstrated strong inducement by fluorine substituents to pyramidalize a radical site, the question of whether benzylic or allylic conjugation would be sufficient to make the radical site planar arises. Indeed, that seems to be the case, but as one might expect, such radicals appear to have less resonance stabilization than their hydrocarbon analogues.

In an ESR study of 1,1,3,3-difluoroallyl radicals, Krusic and co-workers were able to demonstrate that the barrier to rotation of such apparently planar radicals is substantially reduced.[34] Although allyl itself has a rotational barrier of 15 kcal/mol,[35-36] 1,1,3,3-tetrafluoroallyl, **2**, had a barrier of but 7.2 kcal/mol. The observed $a(^{19}F)$ hfs constants (42.6 and 39.7 G) were consistent with **2** being a planar system. It is likely that the lowering of the rotational barrier of **2** derives from a destabilizing interaction between the fluorine lone pairs and the doubly-occupied allyl π-MO which diminishes the net allylic resonance energy, as well as from stabilization of the transition state due to pyramidalization.



2

3

Likewise, Pittman has examined the α,α-difluorobenzyl radical (**3**) by ESR.[37] This radical also exhibited small $a(^{19}F)$ hfs (51.4 G) which is consistent with a planar or near planar radical. Because of the symmetry of the system, he could obtain no information on the radical's rotational barrier. Since there is some ambiguity in the use of α-^{19}F hfs constants as a measure of geometry because of their dependence on the radical's carbon spin density, Platonov calculated the bending dependence of the fluorinated benzylic hfs constants and has concluded that there is some pyramidal distortion of the CF_2 group in the α,α-difluorobenzyl radical.[38]

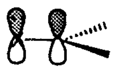
To summarize the considerable available structural data with respect to fluorine substitution, one can conclude that nonconjugated carbon radicals bearing at least two fluorine substituents will be strongly pyramidal, σ-radicals, while β-fluorine substituents appear to have little influence on the geometry of a radical. The strong σ character of CF_3, CHF_2, and perfluoro-*n*-alkyl radicals has a considerable influence on their *reactivity*.

III. Thermochemical Properties of Fluorinated Radicals

A. Radical Stabilities

The influence of fluorine substituents on the stability of alkyl radicals derives from the same complex interplay of inductive and resonance effects that affects their structure. Simple orbital interaction theory predicts that substituents of the −X: type (that is, electronegative substituents bearing lone pairs) should destabilize inductively by virture of their group electronegativities and stabilize by resonance to the extent of their ability to delocalize the odd electron.

α- and β-fluorine substituents inductively destabilize a radical. Any stabilizing influence of an α-fluorine substitutent must derive from its donating resonance interaction with the SOMO.[39] Because of the high electronegativity of fluorine, its lone pairs will be more stable (lower in energy) and thus will interact more weakly with the SOMO than would a lone pair on another second-period atom, such as an oxygen or a nitrogen. Moreover, one would expect that the requisite overlap for such delocalization would be optimal for a planar radical structure, such as **4**. Since the methyl radical becomes increasingly nonplanar with each additional fluorine substituent, one would expect that the overlap which is needed for resonance stabilization would progressively diminish, as in **5**, such that ultimately the inductive effect dominates and the trifluoromethyl radical is destabilized.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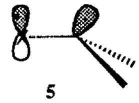
versus


5

For β-fluorine substitution, one could envision some stabilization via SOMO−C-F σ^* mixing, but apparently because the carbon radical is inately electrophilic, only C-H hyperconjugation seems to be stabilizing for a radical; thus the only significant impact of β-fluorine substituents is that of inductive destabilization.

The effect of fluorine substitution on the thermodynamic stability of a radical has been difficult to assess experimentally. Relative values of bond dissociation energies (BDEs) have traditionally been used to make assessments of radical stability. Thus, on the basis of relative C−H BDEs, $(CH_3)_3C-H$ (96.4), $(CH_3)_2CH-H$ (98.6), CH_3CH_2-H (101.1), and CH_3-H (104.8 kcal/mol),[40,41] one reaches the conclusion that the stability of hydrocarbon radicals decreases: 3° > 2° > 1° > CH_3. It is, of course, recognized that the variable degree of steric strain of the molecules within this series limits the quantitative impact of these numbers vis-a-vis radical stability.

The analogous C−H BDEs for fluorinated methanes and ethanes are given in Table 3. From these data one can reasonably conclude that a single α-fluorine substituent or two α-fluorine substituents provide small stabilization relative to a methyl radical, whereas trifluoromethyl is destabilized.

Although the experimental data for the ethanes is incomplete, it does appear that β-fluorine substitution also gives rise to radical destabilization relative

Table 3. C−H Bond Dissociation Energies of Fluorinated Methanes and Ethanes[40,41]

	CH_3-H	CH_2F-H	CHF_2-H	CF_3-H	CH_3CH_2-H	CF_3CH_2-H	CH_3CF_2-H	CF_3CF_2-H
BDE	104.8 ± 0.2	101.2 ± 2	103.2 ± 2	106.7 ± 1	101.1 ± 1	106.7 ± 1	99.5 ± 2.5	102.7 ± 0.5

Table 4. Calculated C−H Bond Dissociation Energies for Some Fluorinated Ethanes[42]

	CH_3CH_2-H	CH_2FCH_2-H	CHF_2CH_2-H	CF_3CH_2-H
BDE	97.7	99.6	101.3	102.0

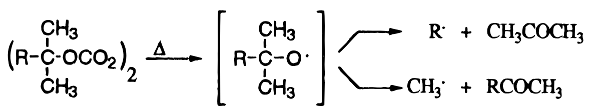
Table 5. Calculated Stabilization Energies (SE) for Substituted Methyl Radicals[43,44]

	CH_3	$(CH_3)_2$	$(CH_3)_3$	F	F_2	F_3	FCH_2	F_2CH	CF_3
SE	3.3	5.8	8.0	1.6	0.6	−4.2	1.5	0.2	−1.3

to the ethyl radical. Indeed, calculations of some missing members of the fluorinated ethyl series (Table 4) indicate that the inductive effect of even a *single β*-fluorine substituent is sufficient to destabilize an ethyl radical.[42]

Recent high-level calculations by Pasto,[43,44] Davidson,[45] and others[46−51] have given results consistent with this BDE data, as Pasto's list of stabilization energies given in Table 5 indicates.

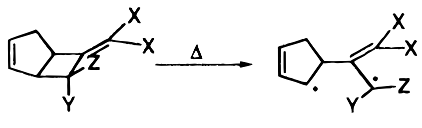
Experimental support for such an order of stability in the fluoromethyl cases derives from a study by Jiang of the radical fragmentation of the respective series of fluorinated *tert*-butoxy radicals:[52]



R = CF_3 < CH_3 < CHF_2 ~ CH_2F

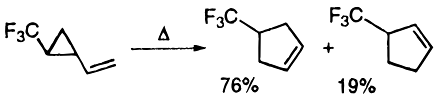
k_{rel} = 0.08 : 1 : 10.2 : 9.0

Any radical stabilization or destabilization effects deriving from fluorine substituents ought to be reflected in the experimental rates of thermal rearrangement via homolytic processes. However, in the few such systems which have been studied, one or two fluorine substituents do not seem to have a significant impact upon such rates.[53,54]

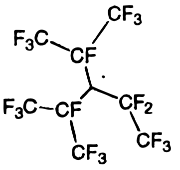


	Log A	E_a
For X=H, Y=Z =D	13.6	39.9
For X=Z=H, Y=F	13.7	39.6
For X=F, Y=Z=H	13.6	38.4

In kinetic studies where there have been trifluoromethyl groups on a C−C bond undergoing homolytic cleavage,[55−58] steric effects sometimes led to results which were difficult to interpret,[56] and other substituents were observed to influence the effect of the CF_3 group.[55,56] However, the trifluoromethyl substituent has generally been found to have minimal or even a negative effect on the rates of the rearrangements. A study of the vinylcyclopropane rearrangement of *trans*-2-(trifluoromethyl)vinylcyclopropane exemplifies the lack of significant influence of a CF_3 group on C−C bond dissociation energies and hence on carbon radical stabilities.[58] In this study McClinton found that the C_1-C_2 and C_1-C_3 bonds were cleaved competitively, and the overall rate of rearrangement was, within experimental error, identical to that of unsubstituted vinylcyclopropane.[58]



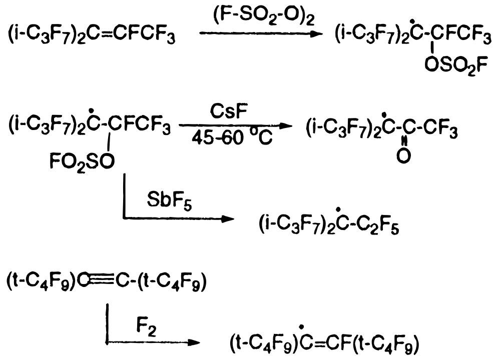
Within our discussion of the stabilities of fluorinated radicals, we have, of course, been referring to thermodynamic stabilities. In fact, most fluorinated radicals will be seen to have enhanced *kinetic* reactivity in reactions with closed shell molecules (See section IV). However, appropriate fluorine substitution can also give rise to long-lived, or persistent, radicals, the most dramatic example being Scherer's radical, **6**, which persists at room temperature, even in the presence of molecular oxygen:[59]



6

The incredible kinetic stability of Scherer's radical most likely derives from steric effects. Models indicate that the radical site is essentially buried within a protective shield of surrounding fluorine substituents.

Recently, there have been a number of other examples of stabilized perfluororadicals reported in the literature, these coming from German's group.[60−63] Included in this work, which is summarized below, are reports of the first isolable, functionalized radicals, along with some chemistry of such radicals, and the first isolable perfluoro*vinyl* radical.



B. Electronegativities, Ionization Energies, and Electron Affinities

In order to assess the contribution of polar factors to the reactivities of fluorinated radicals, one needs a measure of their electronegativities. Absolute electronegativities (χ) may be derived if one knows

Table 6. Experimental Ionization Potentials, Electron Affinities, and Absolute Electronegativities of Alkyl and Fluorinated Alkyl Radicals[67−71]

	CH_3	CH_3CH_2	$(CH_3)_2CH$	$(CH_3)_3C$	CH_2F	CHF_2	CF_3	CF_3CF_2	HCF_2CF_2	CF_3CHF
IP (eV)	9.84	8.51	7.69	6.93	9.04	8.73	9.25	9.63	9.29	9.60
EA (eV)	0.08	−0.39	−0.48	−0.30			1.84	2.1		
χ	4.96	4.06	3.61	3.32			5.55	5.87		

both the IPs and the EA values of radicals,[64] as shown:

$$\chi = \frac{\mathrm{IP} + \mathrm{EA}}{2}$$

Unfortunately, few experimental ionization potentials or electron affinities of fluorinated radicals have been reported, and the calculation of such molecular properties is fraught with difficulties, although reasonable trends can be predicted.[65,66] Table 6 provides what numbers are presently available.[67−71] Pearson has observed that the reactivity of various organic substrates, including radicals, can be correlated with their absolute electronegativies.[72] It can be seen that although trifluoromethyl and pentafluoroethyl radicals are much more electronegative than the more nucleophilic alkyl radicals, such as *tert*-butyl, methyl itself should not be much more nucleophilic than trifluoromethyl. *Nucleophilicities* of alkyl radicals increase: $CH_3 < 1° < 2° < 3°$. Although there are not sufficient IP or EA data available to substantiate the issue, the reactivity studies which are described in the next section demonstrate that the *electrophilicities* of perfluoroalkyl radicals increase: $CF_3 \approx 1° < 2° < 3°$.

IV. Reactivity of Fluorinated Radicals

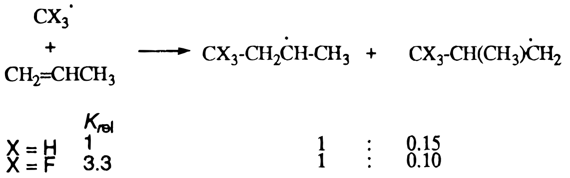
Discussions about reactivity must be carried out within the context of some reaction. For free radicals, the fundamentally most important types of reactions are those involving their addition to π-bonds, particularly their additions to alkenes, and their hydrogen abstraction reactions. Therefore, virtually all assessments of the reactivity of radicals involve studies of such reactions.

A. Alkene Addition Reactions

1. Early Studies and Insights

There has been considerable effort directed toward obtaining a fundamental understanding of the factors that govern the reactivities of carbon-centered radicals in bimolecular reactions, particularly with respect to their addition to alkenes.[73] From early liquid and gas phase studies, reactivity in such addition reactions was concluded to derive from a "complex interplay of polar, steric, and bond-strength terms",[74] which is much influenced by the nature and position of substituents on both the radical and the alkene.

Competition studies from Szwarc's group provided excellent quantitative insights into the relative affinities of methyl and trifluoromethyl radicals for a host of alkenes,[12,75,76] and from this work came the first general recognition that substituted alkyl radicals could exhibit polar characteristics ranging from nucleophilic to electrophilic. On the basis of such early work, methyl and trifluoromethyl were taken to be the prototypical nucleophilic and electrophilic radicals, respectively, characterizations which it turns out are somewhat exaggerated in both cases.



Insights which resulted from this work and that of others have been critically reviewed with a number of general conclusions being reached: (1) substituents at the carbon atom of the alkene which is *not* attacked (β-substituents) exert predominantly polar effects on the rates of addition; (2) substituents at the the carbon atom which *is* attacked (α-substituents) exert both polar and steric effects; (3) substituents at the attacking radical center exert both polar and steric effects on the rate of addition to alkenes.[77,78]

In a series of papers in the early 1980s, Sokolov's group reported relative rate studies which were similar in nature to those of the early Szwarc studies. Sokolov generated various perfluoroalkyl radicals via thermal decomposition of the respoective perfluorodiacyl peroxides in heptane containing various olefins[79] or arenes.[80] Determination of the ratio of olefin addition products to hydrogen abstraction products provided the relative rate data given in Table 7.[79]

With the recent advent of methods for direct measurement of rates of addition of radicals to alkenes in solution, such relative rate data has become for the most part obsolete, although the relative rates measured in these studies generally correlate quite well with the new data which have been derived from direct measurements.

a. Regiochemistry of Additions. Certainly, the regiochemical data deriving from the early Szwarc studies on the addition of $CF_3^{\bullet}$ to unsymmetrical alkenes remain quite valid. Indeed, Haszeldine's studies which defined the preferred mode of addition of $CF_3^{\bullet}$ to $CH_2{=}CHF$, $CH_2{=}CF_2$, $CHF{=}CF_2$, $CH_2{=}CHCH_3$, $CH_2{=}CHCF_3$, $CF_2{=}CHCH_3$, $CF_2{=}CHCF_3$, $CF_2{=}CFCF_3$, etc., provided the foundation for our present understanding of the regiochemical behavior of fluorinated radicals.[81] These data and additional, more precise data obtained in their own labs have been reviewed critically by Tedder and Walton and are partially summarized in Table 8.[74,77,78]

As concluded by Tedder and Walton, it would appear that a combination of polar and steric effects on the part of both the olefin and the trifluoromethyl

Table 7. Relative Rates of Addition of Perfluoroalkyl Radicals to Olefins vs Their Rates of Hydrogen-Atom Abstraction from Heptane at 50 °C[79]

olefin	$CF_3^\bullet$	$C_2F_5^\bullet$	$C_3F_7^\bullet$
$CH_2{=}CH_2$	132	340	290
$CH_2{=}CHF$	30	108	40
$CH_2{=}CF_2$	9	13	
$CHF{=}CF_2$	6	9	
$CF_2{=}CF_2$	8	7	<0.3
$CF_2{=}CFCF_3$		0.33	
$CF_2{=}CFOCF_3$		1.1	

Table 8. Regiochemistry of Trifluoromethyl Radical Additions to Olefins[74,77,78]

olefin	$CH_2{=}CHF$	$CH_2{=}CF_2$	$CHF{=}CF_2$	$CH_2{=}CHCl$	$CHCl{=}CF_2$
ratio	1:0.09	1:0.05	1:0.50	1:0.02	1:11.5
olefin	$CH_2{=}CHCH_3$	$CH_2{=}C(CH_3)_2$	$CH_2{=}CHCH{=}CH_2$		$CH_2{=}CHCF_3$
ratio	1:0.1	1:0.08	1:<0.01		1:0.01
olefin	$CHF{=}CHCF_3$	$CF_2{=}CHCH_3$	$CF_2{=}CHCF_3$		$CF_2{=}CFCF_3$
ratio	1:0.33	1:50	1:1.5		1:0.25

Table 9. Regioselectivities of Addition of Some Fluoroalkyl Radicals to Trifluoroethylene[82]

$$R_F^\bullet + CHF{=}CF_2 \rightarrow \underset{\alpha}{R_FCHFCF_2^\bullet} \text{ or } \underset{\beta}{{}^\bullet CHFCF_2R_F}$$

	$n\text{-}C_5F_{11}(CF_3)CF^\bullet$	$(CF_3)_2CF^\bullet$	$CF_3(CF_2)_2CF_2^\bullet$	$CF_3(CF_2)_3\mathit{CH_2}CF_2^\bullet$
$\alpha:\beta$	93:7	90:10	75:25	60:40

radical are sufficient to determine the observed regioselectivities.[78]

Recently, a quantitative study of the regiochemistry of addition of a number of different fluoroalkyl radicals to $CHF{=}CF_2$, summarized in Table 9, indicated that the observed selectivity could be correlated with the postulated relative electrophilicity of the radicals, with the conclusion being reached that the secondary $n\text{-}C_5F_{11}(CF_3)CF^\bullet$ radical was the most electrophilic.[82]

2. Factors Which Affect Radical Reactivity

Additions of carbon-centered radicals to alkenes are generally strongly exothermic since a σ-bond is formed at the expense of a π-bond (e.g., addition of methyl radical to styrene has a $\Delta H° = -38.5$ kcal/mol). Thus, according to the Hammond postulate, such reactions should have early transition states with little bond making or bond breaking being involved. This is supported by the measured activation energies for such additions, which generally lie between 3 to 8 kcal/mol,[83] as well as by theoretical calculations which indicate the involvement of unsymmetrical addition transition states that are relatively independent of the electrophilic or nucleophilic nature of the adding radical species. The calculations also indicate an approach to bonding at the α-carbon in which the radical is far removed from the β-carbon.[84−87]

Correlation of the effect of substituents on the rates of reactions with early transition states often is best accomplished in terms of perturbational molecular orbital theory, and polar effects can play a major role for such reactions.[88,89] Essentially this theory states that energy differences between the highest occupied molecular orbital (HOMO) of one reactant and the lowest unoccupied molecular orbital (LUMO) of the other reactant are decisive in determining the reaction rate: the smaller the difference in energy, the faster the predicted rate of reaction.[90,91] Since the HOMO of a free radical is the SOMO, the energy difference between the SOMO and the alkene HOMO and/or LUMO is of considerable importance in determining the rates of radical additions to alkenes.[73]

3. Absolute Rate Data

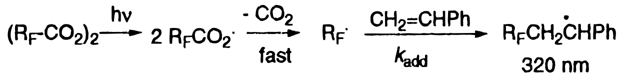
In recent years, direct, time-resolved methods have been extensively employed to obtain absolute kinetic data for a wide variety of alkyl radical reactions in the liquid phase, and there is presently a considerable body of data available for alkene addition reactions of a wide variety of radical types.[92] For example, rates of alkene addition reactions of the nucleophilic *tert*-butyl radical (with its high-lying SOMO) have been found to correlate with alkene electron affinities (EAs), which provide a measure of the alkene's LUMO energies.[93,94] The data indicate that the reactivity of such nucleophilic radicals are best understood as deriving from a dominant SOMO−LUMO interaction, leading to charge transfer interactions which stabilize the early transition state and lower both the enthalpic and entropic barriers to reaction, with consequent rate increase.

Data have also begun to appear for addition reactions of "electrophilic" radicals, ${}^\bullet CH(CN)_2$, and so-called ambiphilic radicals, ${}^\bullet CH(CO_2Et)_2$ and ${}^\bullet CH_2CO_2$-*t*-Bu, which derive their electrophilic character from π-delocalization of the carbon-centered radical onto electron-attracting substituents,[95−98] and for which the enthalpy of the addition process rather than the polar nature of the radicals may be the primary rate-determining factor.[99,100]

Fluorinated radicals, in contrast, would be expected to derive their electrophilicities virtually entirely from fluorine's inductive effect. One would expect the reactivity of perfluoro-*n*-alkyl radicals to differ significantly from that of their hydrocarbon counterparts, since the latter are electron-rich, planar π-radicals, whereas the former are electron poor, nonplanar σ-radicals.

a. Perfluoro-n-alkyl Radicals. Laser flash photolysis (LFP) studies have recently provided absolute rates of addition of perfluoro-*n*-alkyl radicals to a variety of alkenes in solution.[101,102] In these studies,

$C_2F_5^•$, $C_3F_7^•$, and n-$C_7F_{15}^•$ were generated "instantaneously" by photolysis of the respective diacyl peroxides. The initially-formed perfluoroacyloxyl radicals decarboxylated rapidly to yield the perfluoroalkyl radicals, after which the additions of these radicals to styrene, α-methylstyrene, etc., were monitored directly via observation of the growth of UV absorption due to the transient benzylic radicals.



$$(R_F\text{-}CO_2)_2 \xrightarrow{h\nu} 2\ R_FCO_2^• \xrightarrow[\text{fast}]{-CO_2} R_F^• \xrightarrow[k_{add}]{CH_2=CHPh} R_FCH_2\dot{C}HPh\ \ 320\ \text{nm}$$

The rate constants, k_{add}, obtained from the LFP experiments for addition of the perfluoro-n-alkyl radicals to the various alkenes in 1,2,2-trichloro-1,1,2-trifluoroethane (F113) are given in Table 10. It can be seen that such radicals are *much* more reactive than their hydrocarbon counterparts, particularly in additions to electron-rich alkenes, with n-$C_3F_7^•$ adding to 1-hexene 30 000 times faster and to styrene 350 times faster than an n-alkyl radical.[101,102]

Although the high electrophilicity of perfluoroalkyl radicals is probably the dominant factor giving rise to their high reactivities, there are a number of other factors which undoubtedly also contribute.

Steric effects can*not* be contributing to the observed enhanced rates since, although fluorine is a small substituent, it is certainly larger than a hydrogen atom. No doubt of some relevance is the σ-nature of perfluoro-n-alkyl radicals. Since substantial bending (14−15° from planarity) is apparently required in the transition state for alkyl radical addition to alkenes, nonplanar perfluoroalkyl radicals might therefore be expected to have an inherent energetic advantage over a (planar) alkyl radical in addition reactions.[84,110] The energy required to bend the methyl and *tert*-butyl radicals to the same extent as in their respective transition state structures for addition to ethylene has been calculated to be 1.6 and 1.5 kcal/mol, respectively.[110] In contrast, the ESR parameters for perfluoro-n-alkyl radicals, as discussed earlier, implies that their configuration at the radical center should not require further bending in order to reach their transition states for addition to alkenes.

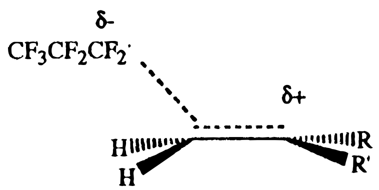


Figure 1. Typical polar transition state for addition of perfluoroalkyl radical to an electron-rich olefin.

Also of relevance is the significantly stronger (ca. 10 kcal/mol) C−C bond that forms when $R_F^•$ versus $R^•$ adds to an alkene ($CH_3{-}CH_3$, BDE = 91 versus $CF_3{-}CH_3$, BDE = 101 kcal/mol).[40] Although this greater exothermicity of the perfluoroalkyl radical addition reactions must be to some degree relevant, the relatively small, 7-fold difference in the rates of addition of n-$C_3F_7^•$ to styrene versus 1-hexene, two process which differ in exothermicity by ~14 kcal/mol, indicates that the rates of such early transition state processes *cannot* be *g*reatly affected by differences in $\Delta H°$.

The dominant factor that gives rise to the observed high reactivities of perfluoro-n-alkyl radicals, particularly in their additions to electron-rich alkenes, would appear to be the high electrophilicities of these very electron-deficient radicals.[102] A perfluoro-n-alkyl radical, which one can assume to have a low-lying SOMO, should exhibit a dominant SOMO−HOMO interaction in its additions to alkenes, and polarization of the type shown in Figure 1 will stabilize the early transition state in which little radical character has been transferred to the substrate alkene. Therefore, if steric hindrance is equivalent for a series of alkenes, the rates of addition of $R_F^•$ should correlate with the alkene IPs (which should reflect HOMO energies). As Figure 2 indicates, there is indeed a respectable correlation between log k_{add} for typical perfluoro-n-alkyl radicals and terminal alkene IPs. The styrenes all appear to be slightly more reactive than would be expected on the basis of their IPs, a result which implicates the slight intervention of enthalpy effects. However, the

Table 10. Absolute Rate Constants for the Reaction of Perfluoro-*n*-alkyl Radicals with Various Unsaturated Substrates at 298 ± 2 K, As Measured by LFP in F113[101,102]

	$k_{add}/10^6 M^{-1} s^{-1}$						
alkenes (IP)[a]	n-C_3F_7	n-C_7F_{15}	n-C_8F_{17}	C_2F_5	CF_3	RCH_2	$(CH_3)_3C$
α-methylstyrene (8.19)	78	89		94	87[b]	0.059[c]	
β-methylstyrene (8.10)	3.8	3.7		7.0	17[d]		
styrene (8.43)	43	46	46	79[d]	53[b]	0.12[e]	0.13[e]
pentafluorostyrene (9.20)	13			23[d]	26[b]	0.31[b]	
4-methylstyrene			61[h]				
4-methoxystyrene			65[h]				
4-chlorostyrene			36[h]				
4-(CF_3)styrene	29	24	25[h]				
1,4-dimethylenecyclohexane (9.12)	41					1.3×10^{-4} [f]	
1-hexene (9.14)	6.2	7.9		16		2×10^{-4} [f]	
n-$C_4F_9CH_2CH{=}CH_2$				2.5			
cyclohexene (8.94)	1.3						
$HC{\equiv}CCMe_2OH$ (10.18)	0.9						
$CH_2{=}CCl_2$ (9.79)	5.2						0.35[g]
$CH_2{=}C(CH_3)COOCH_3$ (9.70)	19						
$CH_2{=}C(CH_3)CN$			3.2[i]				
$CH_2{=}CHCN$ (10.91)	2.2	1.6	2.0[i]	3.2	4.4[d]		2.4[h]

[a] Reference 68. [b] Reference 103. [c] Reference 104. [d] Reference 105. [e] Reference 106. [f] Reference 107. [g] Reference 108. [h] Reference 109. [i] Rates obtained from competition study (ref 102).

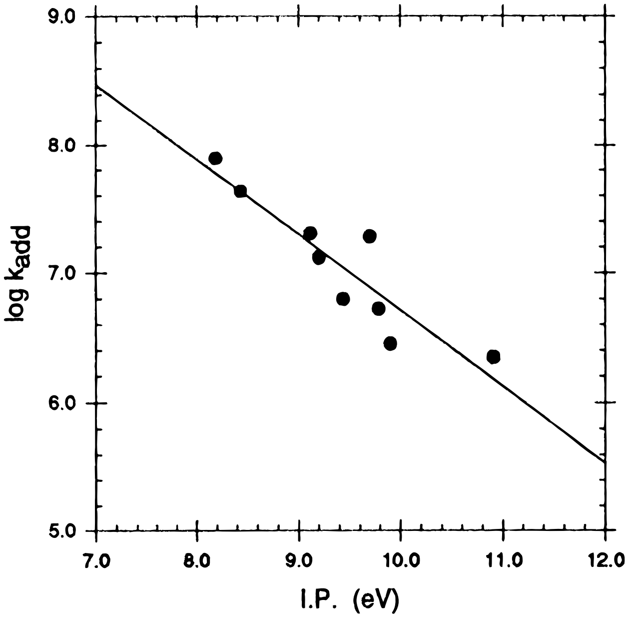


Figure 2. Plot of the log of the rate constants for addition of heptafluoro-*n*-propyl radical to some alkenes versus the ionization potentials of the alkenes.

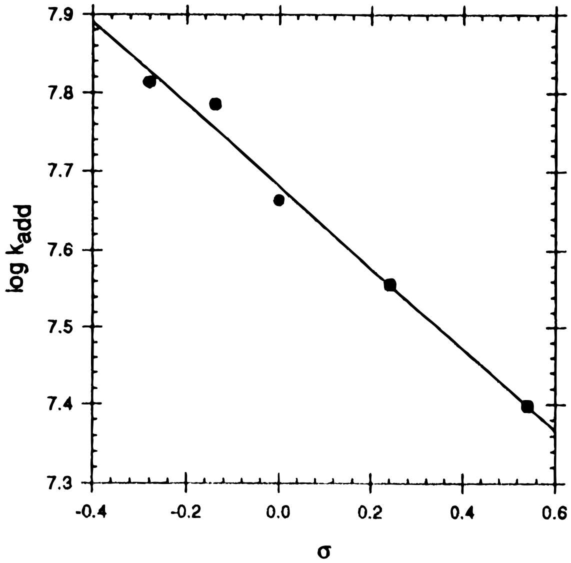


Figure 3. Plot of the log of the rate constants for addition of perfluoro-*n*-octyl radicals to some para-substituted styrenes versus Hammett σ values of the substituents.

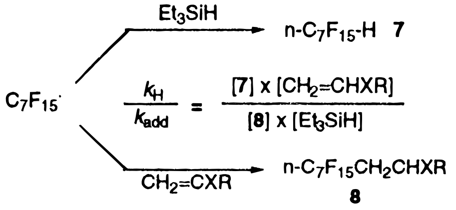
correlation expressed by Figure 2 is consistent with the electrophilic character of perfluoro-*n*-alkyl radicals. For steric reasons, the nonterminal olefins, β-methylstyrene and cyclohexene, are noticeably less reactive than might have been anticipated from their IPs.

The electrophilic character of *n*-perfluoroalkyl radicals was confirmed by a correlation of the rates of addition of the *n*-$C_8F_{17}^\bullet$ radical to a series of para-substituted styrenes with Hammett σ values, as shown in Figure 3. The ρ value is negative (−0.53), as would be expected for an electrophilic reactant.[102]

By using competition methodology, with *n*-$C_7F_{15}^\bullet$ being generated under conditions where its destruction by alkene addition and H-transfer from Et_3SiH are competitive, it was possible to obtain the rates of addition for some other, less reactive alkenes, as given in Table 11.[111] Alkenes with more fluorines on the double bond were too unreactive to be measured accurately by this method.

Table 11. Competition Rate Study of Addition of *n*-$C_7F_{15}^\bullet$ to Partially-Fluorinated Alkenes[111]

alkene	$k_{add}/10^6$ M^{-1} s^{-1}
$CH_2{=}CH(CH_2)_5CH_3$	7.5 ± 0.3
$CH_2{=}CF(CH_2)_3CH_3$	3.0 ± 0.2
$CH_2{=}CHCH_2(CF_2)_3CF_3$	1.0 ± 0.1
$CH_2{=}CH(CF_2)_3CF_3$	0.48 ± 0.05



These results are reminiscent of Szwarc, Tedder, and Walton's trifluoromethyl radical affinity data, wherein $CF_3^\bullet$ was observed to add to ethylene and the less substituted ends of fluoroethylene and 1,1-difluoroethylene with the relative rates of 1.0, 0.48, and 0.15, respectively.[12,77,78]

Finally, upon examination of the data in Table 10 one notices slight differences in reactivity for *n*-$C_3F_7^\bullet$ versus $C_2F_5^\bullet$ and $CF_3^\bullet$. Whereas *n*-$C_3F_7^\bullet$, *n*-$C_7F_{15}^\bullet$, and *n*-$C_8F_{17}^\bullet$ appear to have identical reactivities within experimental error, and, as such, the addition rates of these radicals can be considered to be of *generic* *n*-perfluoroalkyl radicals, $C_2F_5^\bullet$ and $CF_3^\bullet$ each exhibit incrementally greater reactivities than these radicals (on the average about 1.8 and 1.4 times more reactive, respectively). Such enhanced reactivities do not seem to derive from a greater electrophilicity, since the plots of log k_{add} versus alkene IP values for these two radicals lie virtually parallel to those of the generic *n*-perfluoroalkyl radicals. In all likelihood, the slightly enhanced reactivities of $C_2F_5^\bullet$ and $CF_3^\bullet$ derive from some combination of steric, pyramidalization, or enthalpic factors.

b. 2° and 3° Perfluoroalkyl Radicals. A group of perfluoroalkyl radicals which do exhibit marked increases in reactivity due to enhanced electrophilicity are the branched, 2° and 3° perfluoroalkyl radicals, specifically the perfluoro-*iso*-propyl and perfluoro-*tert*-butyl radicals.[112]

Table 12 provides the absolute rates of addition of $(CF_3)_3C^\bullet$, $(CF_3)_2CF^\bullet$, $CF_3CF_2^\bullet$, and $CF_3^\bullet$ to a group of alkenes of variable reactivity. It can be seen from the table that both the perfluoro-*iso*-propyl and perfluoro-*tert*-butyl radicals give evidence of *much greater* electrophilicity in their alkene addition reactions. For example, the latter radical reacts signifi-

Table 12. Absolute Rate Constants for the Addition of Trifluoromethyl, Pentafluoroethyl, Heptafluoroisopropyl, and Nonafluoro-*tert*-butyl Radicals to Various Olefins at 298 K in F113[105,112]

	$k_{add}/10^6$ M^{-1} s^{-1}			
olefin	CF_3	C_2F_5	$(CF_3)_2CF$	$(CF_3)_3C$
styrene	53	79	120	363
pentafluorostyrene	26	23	81	16
α-methylstyrene	87	94		589
β-methylstyrene	17	7.0	1.9	2.5
$CH_2{=}CMeCO_2Me$				3.8
$CH_2{=}CHCN$	4.4	3.2		

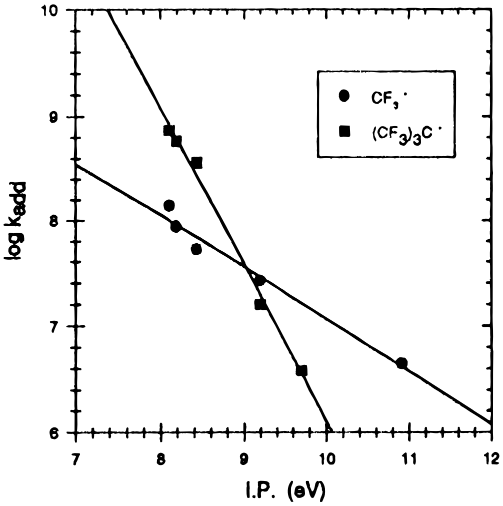


Figure 4. Plot of the log of the rate constants for addition of trifluoromethyl and perfluoro-*tert*-butyl radicals to some alkenes versus the ionization potentials of the alkenes.

cantly (6.8 times) *faster* than $CF_3^•$ with the nucleophilic α-methylstyrene (IP = 8.9 eV), but reacts significantly (1.6 times) *slower* than $CF_3^•$ with the more electrophilic pentafluorostyrene (IP = 9.2 eV). Comparative plots of all of the available rate data for alkene additions of $CF_3^•$ and $(CF_3)_3C^•$ versus alkene IP values, as seen in Figure 4, leave no doubt as to the relative electrophilicity of the two species. Moreover, the rates of addition of the very electrophilic, but *non-σ*, perfluoro-*tert*-butyl radical to the more nucleophilic alkenes, which approach diffusion-control, also leave no doubt as to the great importance of electrophilicity in giving rise to the extraordinary reactivity of *all* perfluoroalkyl radicals.

As mentioned earlier, steric effects apparently inhibit addition of virtually any radical to alkenes that are substituted at both ends of the double bond, such as *β*-methylstyrene. That being the case, one would expect that the larger the attacking radical, the greater should be its steric impact upon rate of addition. The validity of this expectation is indicated from that data in Table 12, which compares the rates of addition of various perfluoroalkyl radicals to *β*-methylstyrene with those to styrene, with the relative rate being taken as a measure of steric impact of attacking radical. It can be seen from these data that only a small steric influence is observed for $CF_3^•$, while progressively greater impact is exhibited for $C_2F_5^•$, *n*-$C_3F_7^•$, *i*-$C_3F_7^•$, and *t*-$C_4F_9^•$, with the rate of addition for the perfluoro-*tert*-butyl radical to *β*-methylstyrene being 144 times slower than that for its addition to styrene, this in spite the greater overall nucleophilicity of the former substrate as indicated by its IP.

c. Partially-Fluorinated Radicals. In order to determine whether the enhanced reactivities of perfluoroalkyl radicals could be attributed to some linear combination of the individual contributions of fluorine atoms on the α-carbon (the radical center), the *β*-carbon, and the *γ*-carbon atoms, the absolute rates of addition of a number of *partially*-fluorinated alkyl radicals to α-methylstyrene, styrene, and pentafluorostyrene were determined by LFP.[103] The data in Table 13 clearly indicated that this is not the case, that *γ*- and *β*-fluorinated *n*-alkyl radicals exhibit little enhancement, while α-difluoroalkyl radicals, although more reactive, remain very much less reactive than analogous perfluoro species. Looking at the rates of addition to styrene, it can be seen that $RCH_2CHF^•$ is 3.8 times more reactive than *n*-$C_4F_9CH_2CH_2^•$. However, the $RCH_2CF_2^•$ radical is not another 3.8 times more reactive than $RCH_2CHF^•$, but is, instead, about 6 times more reactive. That is, the second α-fluorine atom produces an extra (synergistic) enhancement in the radical's reactivity of roughly a factor of 2. Furthermore, if we continue this series of α-substitutions all the way to the $CF_3^•$ we see that this trend of unexpectedly large rate enhancements continues with the $CF_3^•$ radical being about 20 times as reactive as the $RCH_2CF_2^•$ radical. Thus $CF_3^•$ with its 441-fold rate enhancement (compared to *n*-pentyl) is about 8 times more reactive than would be expected on the basis of the incremental impact of three single F substituents. Looking at $CF_3CF_2CF_2^•$, it can be seen to exhibit a rate enhancement for addition to styrene of 358 over that of the *n*-pentyl radical, whereas on the basis of a linear combination of the effects of α-, *β*-, and *γ*-fluorine substitution, one would expect a rate enhancement of only 104. Thus, *per*fluorination of an *n*-alkyl radical system gives rise to a synergistic impact of about 3.5-fold increase in rate.

The limited data available for partially fluorinated methyl radicals are consistent with the above data in that $CH_2F^•$ and $CHF_2^•$ appear to have reactivities roughly comparable to those of $RCH_2CHF^•$ and $RCH_2CF_2^•$, respectively. For example, for their additions to pentafluorostyrene in acetonitrile: $k_{add}(CH_2F^•) = 3.5 \times 10^5\ M^{-1}\ s^{-1}$ and $k_{add}(CHF_2^•) = 5.5 \times 10^6\ M^{-1}\ s^{-1}$.[103]

The data in Table 13 also allow one to reach conclusions regarding the electrophilicity versus nucleophilicity of the partially-fluorinated radicals since the three styrene substrates have a considerable range in IP values. *β*- and to a lesser extent

Table 13. Absolute Rate Constants for Reactions of Alkyl and Fluorine-Substituted Alkyl Radicals with Three Styrenes in Freon 113 at 298 ± 2 K, As Measured by LFP[103]

	$k_{add}/10^6\ M^{-1}\ s^{-1}$		
radical	$C_6H_5CH{=}CH_2$	$C_6H_5C(CH_3){=}CH_2$	$C_6F_5CH{=}CH_2$
$CH_3CH_2CH_2CH_2CH_2^•$	0.12[a]	0.06[a,b]	0.31
$CF_3(CF_2)_3CH_2CH_2^•$	0.13	0.34	0.23
$CH_3CH_2CH_2CF_2CH_2^•$	0.52	0.98	0.39
$CH_3CH_2CH_2CH_2CHF^•$	0.46		0.70
$CH_3CH_2CH_2CH_2CF_2^•$	2.7	3.3	3.1
$CF_3^•$	53	87	26
$CF_3CF_2CF_2^•$	43	78	13

[a] From ref 104. [b] Probably too low by approximately a factor of 5.

γ-fluorine substitution would appear to have a small impact on electrophilicity, whereas a single α-fluorine substituent seems to impart slightly nucleophilic properties. α,α-Difluoro substitution appears to give rise to a radical which has neither electrophilic nor nucleophilic characteristics.[113] Two conclusions can be reached on the basis of the partially fluorinated rate studies: (1) polar effects on transition state energies are very much less important for partially fluorinated radicals than for perfluorinated radicals and (2) the effect on radical reactivity of *per*fluorination is considerably greater than the sum of its parts.

d. Solvent Effects on Rates. As would be expected for reactions with polar transition states, additions of perfluoroalkyl radicals to alkenes are faster in CH_3CN than in Freon 113 (F113) with the observed solvent effects being greater for additions to alkenes which are more electron-rich.[103,105] Table 14 provides comparisons of rates in the two solvents. For example, the rate accelerations in acetonitrile relative to F113 for additions to styrene by $CF_3^•$ and $CF_3CF_2CF_2^•$ are a factor of 3.2 and 2.5, respectively, but for additions of these two radicals to pentafluorostyrene the solvent effects are only 1.3 and 2.1. For comparison, Salikhov and Fischer have found that the rate of addition of the nucleophilic *tert*-butyl radical to (electron-deficient) acrylonitrile (IP = 10.9 eV) is also somewhat accelerated in more polar solvents, e.g., $k_{add}(CH_3CN)/k_{add}(c\text{-}C_6H_{12}) = 2.8$.[114]

Table 14. Solvent Effects on the Rates of Addition of Perfluoroalkyl Radicals to Styrene and Pentafluorostyrene at 298 ± 2 K[103,105]

	$k_{add}/10^6\ M^{-1}\ s^{-1}$			
	styrene		pentafluorostyrene	
	F113	CH_3CN	F113	CH_3CN
$CF_3^•$	53	171	26	33
$C_2F_5^•$	79	127	23	28
$n\text{-}C_3F_7^•$	43	108	13	27

B. Hydrogen Atom Abstractions

An understanding of the factors that influence the rates of hydrogen atom abstraction processes is *very* important in order to maximize the utility of radical-based processes in carbon–carbon bond-forming reactions. This is because most such reactions are chain reactions in which one of the key propagation steps involves transfer of a hydrogen atom from some hydrogen atom transfer agent, such as tri-*n*-butyltin hydride.

The rates of hydrogen atom abstractions by radicals are subject to the same factors that control rates of alkene additions.[115] Both enthalpic and polar factors are very important in determining the rates of hydrogen abstraction. Enthalpic considerations are important in that an abstraction process will be faster (a) the lower the hydrogen BDE of the molecule from which the H is abstracted and (b) the stronger the new C–H bond which is formed. For example, as indicated in Table 15, the rates of hydrogen abstraction by an alkyl radical are found to correlate very well with the BDE values of a series of related H-donors.[116]

Polar factors will be important when the "polarity" of the abstracting radical is significantly different from that of the group which comprises the H-donor. A good example is given below, wherein it is seen that although hydrogen abstraction from HCl by $CF_3^•$ is more exothermic by 2 kcal/mol than that of $CH_3^•$,[40] its E_a for H abstraction is double that of $CH_3^•$, because $CH_3^•$ provides the better match up of polarities in the abstraction transition state.[115]

$$\begin{array}{lcc} & E_a & \Delta H^\circ \\ CH_3^\cdot + HCl \longrightarrow CH_3\text{-}H + Cl^\cdot & 3.5 & -2 \\ CF_3^\cdot + HCl \longrightarrow CF_3\text{-}H + Cl^\cdot & 8.0 & -4 \end{array}$$

As in the case for alkene additions, if the SOMO of the radical is relatively high in energy, such as is the case for alkyl radicals, the principal interaction with the abstractable X–H bond will be with its unoccupied σ^* MO (one-electron–two-orbital type), and such a radical would be considered nucleophilic. If the SOMO is relatively low in energy, such as is the case for perfluoroalkyl radicals, the principal interaction with the abstractable X–H bond will be with its occupied σ MO (three-electron–two-orbital type), and the radical is considered *electrophilic.* Either way, a good match up in polarities in an H-atom transition state will give rise to beneficial transition state charge transfer interaction.[115,121,122]

1. Perfluoro-n-alkyl Radicals. Early work by Brace indicated that perfluoroalkyl radicals were pretty good abstractors of hydrogen.[123] He was able to measure the relative rates of addition and hydrogen atom abstraction for the reactions of $CF_3CF_2CF_2^•$ and $(CF_3)_2CF^•$ with cyclohexene, as shown below. (Little H abstraction was detectable in the addition of either of these radicals to 1-heptene.) H-atom abstraction from cyclohexene was found to be more competitive for the perfluoro-*iso*-propyl radical, as

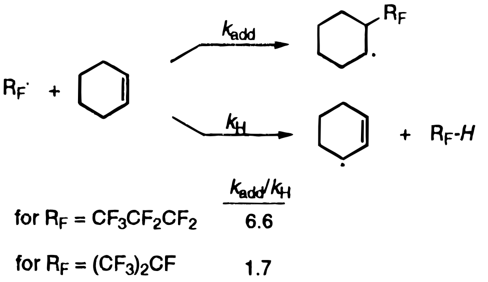


Table 15. Some Rates of Hydrogen Abstraction by a Primary Alkyl Radical[117]

	Et_3SiH	$(TMS)_2SiMeH$	$n\text{-}Bu_3GeH$	$(TMS)_3SiH$	$n\text{-}Bu_3SnH$
$k_H/10^4\ M^{-1}\ s^{-1}$	0.07	3.2	10	38	240
M–H BDE[a]	90.1[b]	85.3[b]	82.6[c]	79.0[b]	73.6[d]

[a] kcal/mol. [b] Reference 118. [c] Reference 119. [d] Reference 120.

Scheme 1

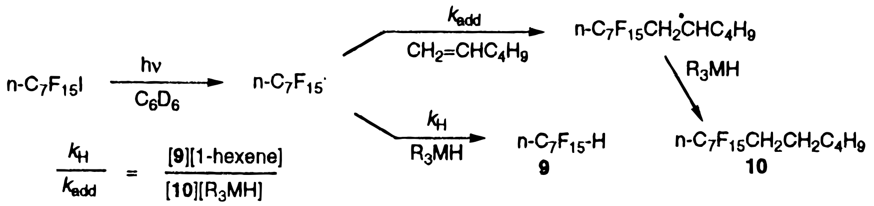


Table 16. Absolute Rate Constants for Hydrogen Abstraction by Perfluoro-*n*-heptyl Radical in C_6D_6 at 303 ± 2 K[125,126]

	Et_3SiH	$(TMS)_2SiMeH$	n-Bu_3GeH	$(TMS)_3SiH$	n-Bu_3SnH
$k_H/10^6$ M^{-1} s^{-1}	0.75	16	15	51	203

one might have expected, since the transition state for H-atom abstraction should be less sterically demanding than that for addition. Along the same lines, H-atom abstraction could not be detected in the reaction of the less sterically demanding $CF_3^•$ radical, and only a trace of CF_3CF_2H was detected in the reaction of $CF_3CF_2^•$ with cyclohexene.

Only 5 years ago, in a study of the electrochemistry of perfluoroalkyl halides, Saveant made the comment that perfluoroalkyl radicals "are much better H-atom scavengers" than alkyl radicals.[124] Therefore, there is considerable indication that highly electronegative perfluoroalkyl radicals should exhibit significantly greater reactivity toward hydrogen abstraction than their hydrocarbon counterparts.

With the availability of LFP-determined rates for addition of perfluoro-*n*-alkyl radicals to alkenes, it was possible to determine the rates of hydrogen abstraction using competition methods, of the type shown in Scheme 1.[125]

From these experiments, and using the equation above, it was possible to determine the ratios of rate constants, k_H/k_{add}, and from these ratios it was possible to obtain values for k_H since the value for k_{add} was known. As can be seen from a comparison of Tables 15 and 16, all of the silane, stannane, and germane reducing agents exhibit substantial rate enhancements in their transfer of a hydrogen atom to the perfluoro-*n*-alkyl radical in comparison to similar transfer to a hydrocarbon radical. Such rate enhancements range from a factor of 75 for the most reactive n-Bu_3SnH to 880 for the least reactive $(CH_3CH_2)_3SiH$. Like the rates of H-atom transfer to *n*-alkyl radicals, these rates also exhibit a good correlation with the H BDE values of the respective reducing agents. Interestingly, such kinetic results indicate that triethylsilane, which reduces hydrocarbon radicals so slowly as to be virtually useless as an effective chain sustaining reducing agent in alkyl radical systems, reduces perfluoro-*n*-alkyl radicals efficiently and at a rate which should make it a very useful agent for relatively slow chain processes involving fluorinated radicals.

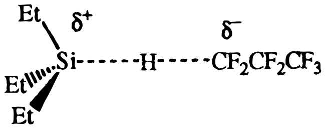


Figure 5. Favorable polar transition state for H abstraction by $R_F^•$ from Et_3SiH.

Why are perfluoroalkyl radicals so much more reactive with such H-atom donors? Certainly the observed hydrogen-atom abstractions by the perfluoro-*n*-octyl radical are more *exothermic* than those by an analogous *n*-alkyl radical (BDE values of CF_3CF_2−H and CH_3CH_2−H are 103 and 101 kcal/mol, respectively),[40] and greater rates for such processes were therefore to be expected on the basis of greater exothermicity. However, that this cannot be the entire explanation was evident from a study of the rates of hydrogen-atom abstraction from benzenethiol and its *para*-substituted derivatives. Benzenethiol is an excellent reducing agent for *alkyl* radicals ($k_H = 1.4 \times 10^8$ M^{-1} s^{-1}),[117] transferring a hydrogen atom at a rate >50 times that of n-Bu_3SnH.

In contrast, benzenethiol was found to be a relatively poor H-atom transfer agent to perfluoro-*n*-octyl radical, exhibiting a rate of 3.3×10^5 M^{-1} s^{-1} which is ~420 times *slower* than its rate of reduction of *n*-alkyl radicals.[115,116] Since the same relative exothermicities prevail for *this* reduction as for those of the other reducing agents, relative heats of reaction must not be the complete reason for observed differences in H abstraction reactivity between $R^•$ and $R_F^•$. The contrasting relative reactivities of electropositive H-atom donors such as silanes, stannanes, and germanes, and a relatively electronegative H-atom donor such as benzene thiol, undoubtedly derive from differences in how they facilitate polarity interactions in the transition states for their particular hydrogen transfers. The absolute electronegativies of *n*-alkyl and *n*-perfluoroalkyl radicals [4.00 and 5.9 (value given in section III for $C_2F_5^•$ used)] reflect their respective nucleophilic and electrophilic characters, whereas C_6H_5−$S^•$ itself has a value of 5.5, and the electronegativities of the R_3Sn, R_3Ge, and R_3Si radicals, although unknown, should lie below the value for $R_3C^•$, which is 3.3.[72] Therefore, one can see that, for H-abstractions from the silane, stannane, and germane hydrides, perfluoro-*n*-alkyl radicals should give rise to a particularly good match up of electronegativities which should lead to more highly polarized transition states for these H-transfers than for those to an alkyl radical (see Figure 5). In contrast, because of similar electronegativities, the transition state for hydrogen transfer from benzenethiol to a perfluoro-*n*-alkyl radical should have little polar character. In confirming the important role of polar effects in these hydrogen transfer processes, a good Hammett correlation was observed for the reduction of n-$C_7F_{15}I$ by a series of arenethiols.[126,127] In this study it was found that the best correlation was with

$$R_FI + p\text{-}X\text{-}C_6H_4\text{-}SH \xrightarrow[CH_2=CHC_4H_9]{h\nu} \underset{\mathbf{11}}{R_FH} + \underset{\mathbf{12}}{R_FCH_2CH_2C_4H_9}$$

$$\frac{k_H}{k_{add}} = \frac{[\mathbf{11}][\text{1-hexene}]}{[\mathbf{12}][\text{ArSH}]}$$

X =	p-CF₃	m-OCH₃	H	p-CH₃	p-OCH₃
$k_H/10^5 M^{-1}s^{-1}$ =	1.8	3.0	3.3	6.6	9.9

σ^+ values ($\rho^+ = -0.56$), which may be compared to the value of −0.30 observed in the correlation of rates of H-abstraction by *tert*-butoxyl from arenethiols.[128] In fact, it would appear that perfluoro-*n*-alkyl radical reactivity in H-atom abstraction approaches the reactivity/selectivity characteristics of the highly electronegative *tert*-butoxyl radical. For example, both n-$C_7F_{15}^\bullet$ and $(CH_3)_3C{-}O^\bullet$ abstract H from n-$Bu_3Sn{-}H$ at the same rate (2.0×10^8 M^{-1} s^{-1}).[129] However, as the data in Table 17 indicate, the differential in rates becomes quite considerable when it comes to abstraction from a C−H bond, perhaps because of the more sterically demanding nature of such H abstractions. Nevertheless, the rates of H abstraction by n-$R_F^\bullet$ are still $>10^3$ times larger than those of analogous hydrocarbon radicals.

Table 17. Comparison of Rates of H-Abstraction by Perfluoro-*n*-Alkyl and *tert*-Butoxyl Radicals[126,129]

	$k_H/10^7$ M^{-1} s^{-1}				
	n-Bu_3SnH	n-Bu_3GeH	Et_3SiH	THF	Et_3N
n-$C_7F_{15}^\bullet$	20	1.4[a]	0.075	0.061[a]	5[a]
$(CH_3)CO^\bullet$	20	9.2	0.57	8.3[b]	180[c]

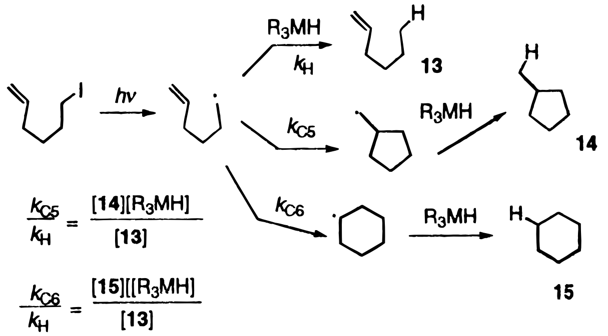
[a] Reference 130. [b] Reference 131. [c] Reference 132.

Rates of hydrogen abstraction by 2° and 3° perfluoroalkyl radicals or by partially-fluorinated radicals have not yet been determined.

C. Radical Rearrangements

In recent years, radical cyclization processes, particularly those of the 5-hexenyl system, have become very important tools within the synthetic repertoire of chemists who wish to construct five-membered rings either singly or in a tandem fashion.[117] Like other productive radical-based synthetic processes, these reactions are chain reactions in which one of the key propagation steps involves transfer of a hydrogen atom from some reducing agent, in the case of hydrocarbons usually n-Bu_3SnH or $[(CH_3)_3Si]_3SiH$. Such cyclizations have long been utilized for the purpose of gaining insight into reactivity factors which pertain to cyclization processes, but which also inevitably provide considerable insight into the chemistry of alkene addition processes. For example, our understanding of Baldwin's rules,[133]and their underlying factors,[134] was enhanced by the study of such systems, and the proposition of the "Beckwith chair" transition state provided a breakthrough in providing understanding of the regio- and stereochemistry of such cyclizations.[135−138] Much insight has also been obtained related to the influence of substituents at or near the radical site (of Thorpe−Ingold (or *gem*-dimethyl) nature[139,140] or of electronic origin).[141] Until recently, however, there had been no quantitative studies of how fluorine substituents affected the rate or regiochemistry of the cyclization process.

Once a reasonable arsenal of reducing agents with accurately determined rate constants for H-atom transfer had been acquired for perfluoro-*n*-alkyl radicals, then it became possible to take a quantitative look at *cyclizations* of fluorinated radicals. As a result, a series of perfluoroalkenyl and partially-fluorinated alkenyl radical systems have been examined for the purpose of obtaining the rates and regiochemistries of their cyclizations.[125] All of these systems were studied by means of the competition method, where cyclization was allowed to compete with direct reduction of the acyclic fluorinated radical, usually using Et_3SiH as the hydrogen-transfer agent.

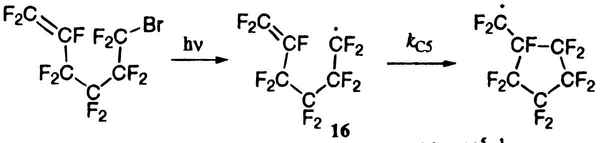


$$\frac{k_{C5}}{k_H} = \frac{[\mathbf{14}][R_3MH]}{[\mathbf{13}]}$$

$$\frac{k_{C6}}{k_H} = \frac{[\mathbf{15}][[R_3MH]}{[\mathbf{13}]}$$

1. 5-Hexenyl Radical Cyclizations

The first results from a fluorinated radical system turned out to be remarkable, namely finding that the rate, k_c, and the regiochemistry of cyclization of the *perfluoro*-5-hexenyl radical, **16**, were only slightly different from those of the parent hydrocarbon system ($k_{rel} = 2.0$), with k_{C6} being negligible for both systems. This probably was just a fortuitous result, deriving at least to some extent from the fact that polar factors must be negligible in both systems.

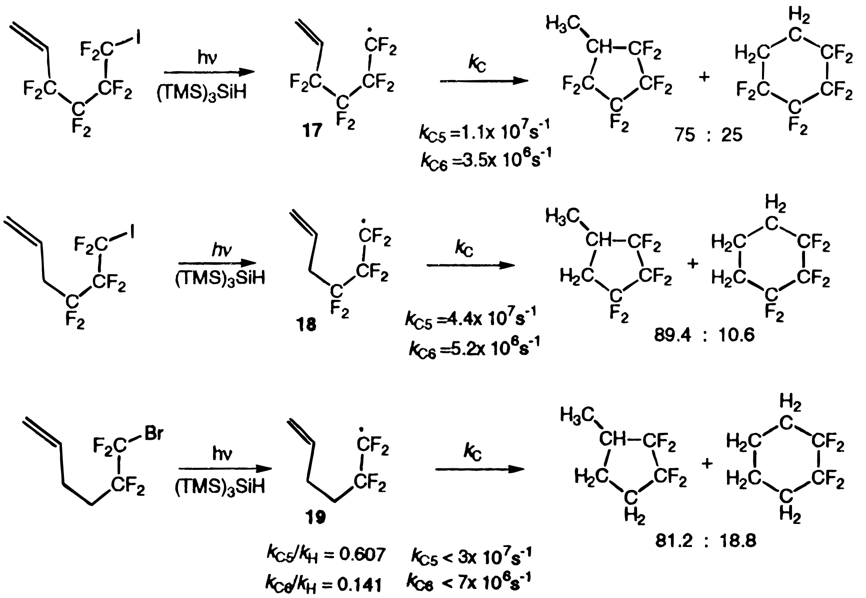


$k_{C5} = 4.9 \times 10^5 s^{-1}$

Subsequent studies of *partially*-fluorinated 5-hexenyl radical systems, however, provided substantial insight into a number of factors which are important in determining both the rate and the regiochemistry of 5-hexenyl cyclizations (Scheme 2).

It was found, for example, that significant enhancement of cyclization rate could be obtained by having a 5-hexenyl radical which combined a *perfluoro radical site* with a hydrocarbon alkene segment, as for radicals **17**−**19**. In the cases where this situation obtained, dramatic rate increases were seen, with overall 62-fold and 214-fold enhancements (compared to the parent 5-hexenyl system) being observed for octafluoro and hexafluoro radicals, **17** and **18**, respectively. (If one assumes, for the sake of argument, that k_H values for the system $RCF_2CF_2^\bullet$ would be similar to those of $R_fCF_2CF_2^\bullet$, then the overall rate enhancement of tetrafluoro radical **19** would be a factor of 166.) The large overall rate enhancements observed for these radicals are consistent with the earlier-discussed 30000-fold rate difference for n-$C_3F_7^\bullet$ versus $RCH_2CH_2^\bullet$ adding to 1-hexene.

Scheme 2



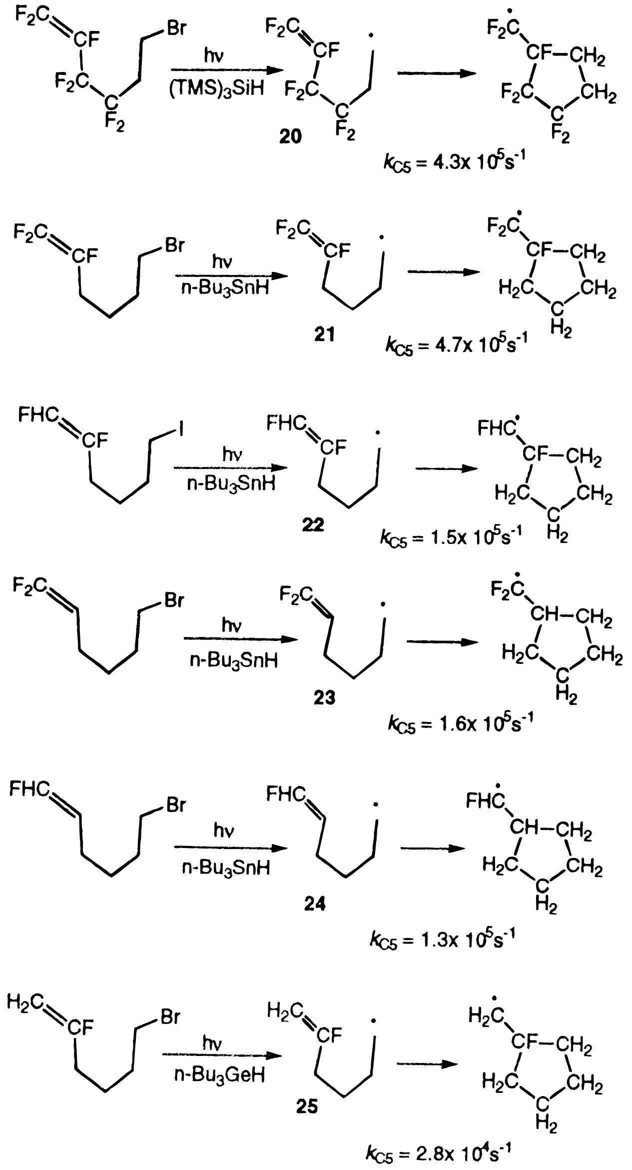
Perhaps even more remarkable was the observation that all three of these cyclizations were considerably *less regioselective* than those of either the parent or the perfluoro system, each of which strongly favored *exo* cyclization. The 25% and 10.6% *endo* cyclization exhibited by **17** and **18**, for example, meant that these *endo*-cyclizations proceeded *700 and 1040 times faster* than the *endo* cyclization of the parent hydrocarbon radical.

In marked contrast, no substantial enhancement of cyclization rate or modification of regiochemistry was observed if the mode of substitution is reversed, such as is the case for the cyclizations of radicals **20**–**25**, all of which involve the 5-hexenyl cyclizations of a 1° hydrocarbon radical sites onto partially-fluorinated alkene segments (Scheme 3).[125,130]

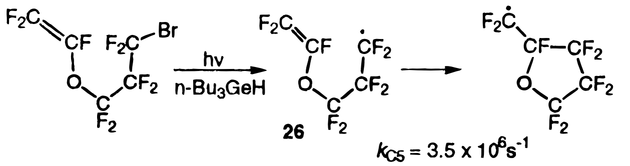
Clearly these results indicate that the degree of fluorination of the double bond has little impact upon the rate of cyclization of a 5-hexenyl radical. Although a *single* fluorine substituent at C-5 (in radical **25**) leads to a significant, 8-fold decrease in rate, mono or geminal fluorine substitution at C-6, trifluorovinyl substitution, or even the more extensive fluorine substitution of the 3,3,4,4,5,6,6-heptafluoro-5-hexenyl radical, **20**, were seen to have little effect upon the rate of cyclization.

This observed lack of kinetic impact of olefinic fluorine substituents on alkyl radical addition reactions is consistent with Tedder and Walton's early studies on methyl affinities wherein they found that methyl radical added to ethylene, and to the less substituted ends of fluoroethylene and trifluoroethylene, with relative rates of 1, 0.57, and 1.0, respectively.[143] Gas phase kinetic data also indicates a rate difference of only 4.4 for addition of methyl radical to propylene versus perfluoropropylene at 142 °C, whereas the analogous ratio for the addition of trifluoromethyl radical was 120.[77] These gas phase results are quite consistent with the contrasting cyclization results described above, where one finds the addition of the perfluoroalkyl radical to be much more sensitive to polar effects than the addition of the alkyl radical.

Scheme 3



Not unexpectedly, when one CF_2 group in the perfluoro-5-hexenyl radical is replaced by an oxygen atom, as in perfluorovinyl ether radical **26**, a 15-fold rate enhancement was observed.[125] Although no quantitative study of the analogous 4-oxa-hydrocarbon system has been reported, the *3*-oxa-5-hexenyl radical has been reported to cyclize 40 times faster than 5-hexenyl itself.[144] Such enhancement was attributed to stereoelectronic effects, i.e., the narrower C−O−C bond angle as compared with C−C−C, and the shorter C−O bond (1.41 Å as opposed to 1.54 Å for C−C), all of which were expected to favor an increased rate of 1,5-closure by comparison with the 5-hexenyl radical.



Also significant was the finding that the radical cyclizations of **20**−**25** did not vary from the dominant *exo* cyclization pattern of the parent system. This is in stark contrast with the results for the mixed *endo/exo* cyclizations of radicals **17**−**19**, each of which involve fluorocarbon radicals cyclizing on a hydrocarbon alkene segment.

It was not obvious why only radicals **17**−**19** exhibited deviant behavior with respect to the regiochemistry of cyclization. Therefore, Houk/Beckwith-type calculations[135−137] were carried out to determine the relative energies of the *endo* and *exo* cyclization transition states.[145] In these calculations, the transition state structures (both chair and boat) were optimized at the UHF/4-31G level, with some TS structures reoptimized at the UHF/6-31G* level. As can be seen in Table 18, excellent agreement was able to be obtained between the calculations and experiment. Moreover, it appears that such computative methodology should be useful in a predictive manner. For example, calculations have been carried out on the 1,1-difluoro- and the 2,2-difluoro-5-hexenyl radical systems, the former being predicted to give little (now confirmed)[145] and the latter substantial *endo* mode of cyclization! It is likely that a careful examination of these transition state structures will produce insight as to *why* there are such variations in regiochemical reactivity exhibited in this series of radical cyclizations.

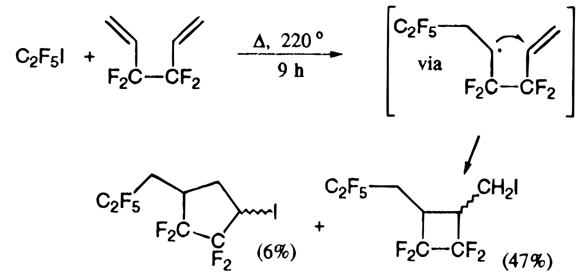
Table 18. Theoretical Calculations of Regiochemical Ratios for Fluorinated 5-Hexenyl Cyclizations[145]

radical	theory	experimental
$CF_2{=}CFCF_2CF_2CF_2CF_2^{\bullet}$ (**16**)	99.3:0.7	>98:<2[a]
$CH_2{=}CHCF_2CF_2CF_2CF_2^{\bullet}$ (**17**)	75.8:24.2	75.4:24.6[a]
$CH_2{=}CHCH_2CF_2CF_2CF_2^{\bullet}$ (**18**)	94.3:5.7	89.4:10.6[b]
$CH_2{=}CHCH_2CH_2CF_2CF_2^{\bullet}$ (**19**)	84.4:15.6	81.2:18.8[c]
$CH_2{=}CHCH_2CH_2CH_2CF_2^{\bullet}$	99.3:0.7	
$CF_2{=}CFCF_2CF_2CH_2CH_2^{\bullet}$ (**20**)	97.1:2.9	>98:<2[c]
$CH_2{=}CFCH_2CH_2CH_2CH_2^{\bullet}$ (**25**)	98.5:1.5	>98:<2[b]
$CH_2{=}CHCH_2CH_2CF_2CH_2^{\bullet}$	91.1:8.9	
$CH_2{=}CHCH_2CH_2CH_2CH_2^{\bullet}$	>99:<1	98:2[d]

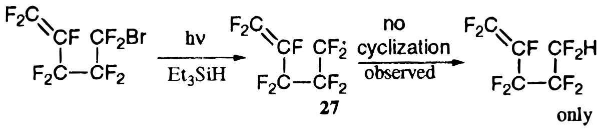
[a] Reference 125. [b] Reference 130. [c] Reference 142. [d] Reference 117.

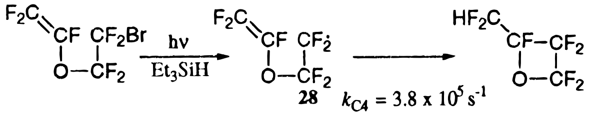
2. 4-Pentenyl Radical Cyclizations

Cyclizations to form 4-membered rings are rare in hydrocarbon systems and only occur when there is a radical stabilizing group at the terminus.[146,147] However, because fluorinated cyclobutanes appear to be less strained than their hydrocarbon counterparts,[148] cyclizations of fluorinated 4-pentenyl radicals appear to be both kinetically and thermodynamically feasible. Piccardi was the first to observe such a cyclization in the thermal addition reactions of C_2F_5I and CCl_4 to 3,3,4,4-tetrafluoro-1, 5-hexadiene, where 4-*exo-trig* 4-membered ring formation was found to be favored over 5-*endo-trig* 5-membered ring formation.[149]



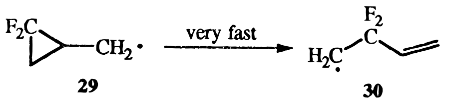
Nevertheless, in spite of this observation, it was found that the parent system, the perfluoro-4-pentenyl radical, **27**, failed to cyclize even when Et_3SiH was employed as the hydrogen atom transfer agent.[125] Either the equilibrium between **27** and the cyclized radical must be very unfavorable or the rate constant for **27**'s cyclization is less than 1 × 10^4 s^{-1} at 30 °C. Thus the lack of cyclization of **27** could be due to either thermodynamic or kinetic factors. Either way, ether analog **28** was expected to be more reactive, and indeed, **28** was found to cyclize quite efficiently with a rate constant for cyclization of 3.8 (±0.3) × 10^5 s^{-1}.[125] Only the *exo* mode of cyclization was observed, in contrast to Piccardi's results. Further studies of fluorinated 4-pentenyl and cyclobutylcarbinyl radical systems will hopefully provide eventual definitive insight into those factors which govern rates and equilibria in this system.





3. Cyclopropylcarbinyl Radical Ring Openings

The cyclopropylcarbinyl ring opening comprises a very fast clock process in the hydrocarbon system, with a rate constant of 9.4 × 10^7 s^{-1}.[117] The ring opening of the (2,2-difluorocyclopropyl)carbinyl radical, **29**, occurs with exclusive C_1−C_3 bond cleavage to produce the 2,2-difluorobut-3-enyl radical, **30**.[150]



Such a result is consistent with a wealth of data relating to the thermal isomerizations of *gem*-difluorocyclopropane systems which indicate that the cyclopropane C−C bond distal to the CF_2 group is substantially weaker toward homolytic cleavage than the proximal bonds.[151] The rate for this ring opening has not yet been determined, although it is certainly considerably faster than the already very fast ring opening of the parent, hydrocarbon system. With only 3,3-difluorobutene being observed as a product in the reduction of 2,2-difluoro-1-(bromomethyl)cyclopropane in neat n-Bu_3SnH, a minimum rate of 8×10^8 can be calculated for the cleavage of radical **29**.

There are just a few examples of such radical ring openings in the literature (see section VI), and all of them proceed with exclusive distal bond cleavage and with no observed trapping of the precursor cyclopropylcarbinyl radical.

D. Summary

In summary, perfluoroalkyl radicals exhibit extraordinary reactivity in both their alkene addition reactions and their hydrogen-abstraction processes, relative to their hydrocarbon counterparts. This reactivity can be attributed partially to the increased exothermicity of such reactions when compared to the analogous reactions of hydrocarbon radicals and partially also to the fact that perfluoro-n-alkyl radicals are σ-radicals. However the major source of the reactivity of 1°, 2°, 3° perfluoroalkyl radicals must be their high electronegativity, which gives rise to stabilizing polarization of the transition states of these radicals' addition and hydrogen-abstraction processes.

V. Chemical Sources of Perfluoroalkyl Radicals

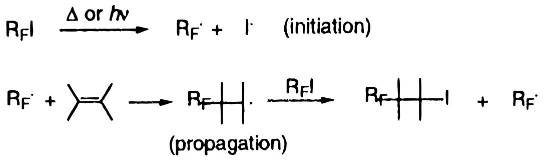
With the increasing recognition of the significance of radical chemistry in perfluoroalkylation reactions, numerous methods have been developed for the purpose of generating perfluoroalkyl radicals, including thermal and photochemical homolysis, radical initiation, and electron transfer processes.

A. Perfluoroalkyl Iodides

Perfluoroalkyl iodides comprise perhaps the most important and commonly-used source of perfluoroalkyl radicals, and all of the above techniques have been applied to perfluoroalkyl iodides for this purpose.[152−154] Most of these methods operate to initiate efficient free radical chain processes which lead to perfluoroalkylation. Numerous specific examples of the various methodologies are provided in section VI, along with references.

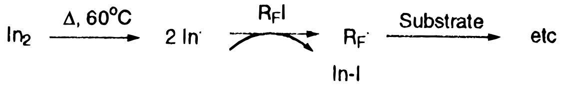
1. Thermal and Photochemically-Induced Homolysis

Simple homolysis of the C−I bond by heating or by light is the most straightforward approach and was the first used for adding perfluoroalkyl iodides to olefins. However, high temperatures are required for the thermolytic process and long photolysis times are required for the photolytic method.[11]



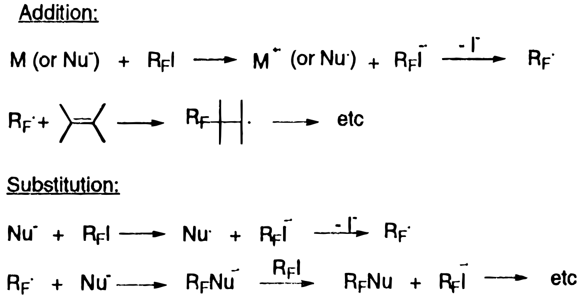
2. Use of Free Radical Initiators

The use of free radical initiators in such reactions can be very useful. They allow the reactions to be run at much lower temperatures and generally make them more efficient.[11]



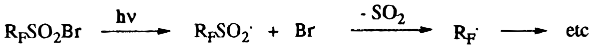
3. Chemical Reduction (SET)

The most important recent development in this area has been the use of various single-electron reductants to initiate the free radical chain process. Such reductants have been most commonly metals or anionic species, and such processes have been used either to initiate addition processes or substitution ($S_{RN}1$) processes. (See Table 20, section VI.B.5 and section VI.C for specific examples.)



B. Perfluoroalkyl Sulfonyl Halides

Perfluoroalkyl sulfonyl halides are also good photochemical sources of perfluoroalkyl radicals, and they also may be used under thermal induction, with a radical initiator, to form $R_F^•$ in a synthetically useful manner.[155] Chain transfer of a Br atom from the sulfonyl bromide seems to be more efficient than that from perfluoroalkyl iodides or bromides, but problems can be encountered with sulfonyl bromides because SO_2 expulsion is somewhat slow and sometimes competes with alkene addition of $RSO_2^•$.



C. Electrochemical Methods

Perfluoroalkyl radicals can be produced electrochemically from perfluoroalkyl iodides by cathodic reduction or from perfluoroalkanoic acids by anodic oxidation, and although there can be problems in controlling side reactions such as dimerization, such methodology can have considerable synthetic advantage (see sections VI.A and B.5)

$$R_FI + e^- \xrightarrow{redn} R_FI^{\cdot -} \xrightarrow{-I^-} R_F^\cdot \longrightarrow etc$$

$$R_FCO_2^- - e^- \xrightarrow{oxidn} R_FCO_2^\cdot \xrightarrow{-CO_2} R_F^\cdot \longrightarrow etc$$

D. Other Methods Using Perfluoroalkanoic Acids

Electron transfer from perfluoroalkanoic acids to *xenon difluoride* also was reported to give perfluoroalkyl radicals which were found to add to benzenes[156] (see section VI.B.7.)

$$2\,R_FCO_2H + XeF_2 \longrightarrow 2\,R_FCO_2^\cdot + 2\,H^+ + Xe + 2\,F^-$$

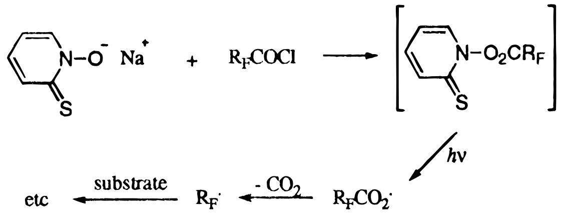
$$R_FCO_2^\cdot \xrightarrow{-CO_2} R_F^\cdot \xrightarrow{Ar\text{-}H} R_FAr$$

Perfluoroalkanoic acids also undergo *Hunsdiecker reactions* with the greatest utility for such methodology being the preparation of perfluoroalkyl iodides, bromides, and chlorides[157] (see section VI.C.3)

$$CF_3CO_2^-Ag^+ \xrightarrow{I_2} CF_3CO_2\text{-}I \longrightarrow CF_3CO_2^\cdot + I^\cdot$$

$$CF_3CO_2^\cdot \xrightarrow{-CO_2} CF_3^\cdot \xrightarrow{I_2}$$

Another way that has potential for the generation of perfluoroalkyl radicals from carboxylic acids is the use of *Barton esters*. However, unlike the situation for their hydrocarbon analogues, fluorinated thiohydroxamate esters have thus far only been able to be prepared *in situ*.[158]



E. Perfluorodiacyl Peroxides

1. Thermal and Photochemical Homolysis

Perfluoro-*n*-alkyl diacyl peroxides decompose homolytically to give perfluoroalkyl radicals under mild conditions, and radicals formed in such a manner have been used synthetically or as radical initiators for polymerizations.[159,160] Such reactions are, of course, *unimolecular* decompositions, not free radical chain processes. This fact made perfluorodiacyl peroxides ideal precursors for the laser flash photolysis studies described in section IV. Kinetics for the thermal decomposition of a number of perfluorodiacyl peroxides have been measured, and their $\Delta H^\ddagger$ values were approximately 24 kcal/mol, about 5 kcal/mol lower than for analogous hydrocarbon diacyl peroxides.[161,162] Their typical half-life is ~5 h at 20 °C, while $(HCF_2CF_2CO_2)_2$ is anomolously reactive and has a half-life of only 81 min. Although other partially-fluorinated diacyl peroxides have also been prepared, for the purpose of LFP studies,[103] other than for the case of 2,2-difluoropropionyl peroxide,[163] their thermal kinetic parameters have not yet been determined.

$$(R_FCO_2)_2 \xrightarrow{\Delta \text{ or } h\nu} 2\,R_FCO_2^\cdot \xrightarrow{CO_2} R_F^\cdot \longrightarrow etc$$

2. Electron Transfer Processes

It appears that, in the presence of electron-rich π-systems, either olefinic or aromatic, these electron-deficient diacyl peroxides undergo electron-transfer, decarboxyation, and cage recombination to give adducts in good yield.[161]

$$(R_FCO_2)_2 + ArH \longrightarrow (R_FCO_2)_2^{-\cdot} + ArH^{+\cdot} \longrightarrow$$

$$R_F^\cdot + ArH^{+\cdot} + CO_2 + R_FCO_2^- \longrightarrow R_FArH^+ \xrightarrow{-H^+} R_FAr$$

F. Perfluoroazoalkanes

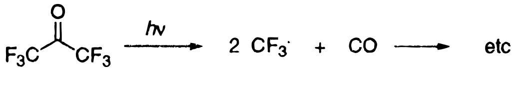
Perfluoroazoalkanes[164] have also been utilized as thermal or photochemical precursors of perfluoroalkyl radicals, with hexafluoroazomethane being the source of trifluoromethyl radicals in the early trifluoromethyl affinity studies of Szwarc.[12] However,

$$R_F\text{-}N{=}N\text{-}R_F \xrightarrow{h\nu} 2\,R_F^\cdot + N_2 \longrightarrow etc$$

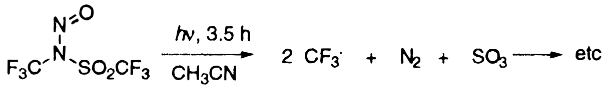
this method is generally limited by the low efficiency of photodeazetation and the high temperatures needed for thermal deazetation (half-life ≈ 1 h at 332 °C),[165] as well as by the significant intervention of cage recombination in these reactions.

G. Some Other Methods

There are other methods for perfluoroalkyl radical generation which have found occasional use, such as photolysis of hexafluoroacetone to generate trifluoromethyl radicals,[166,167] photolysis of perfluoroacyl halides,[168] Umemoto's photolysis of *N*-nitroso-*N*-(trifluoromethyl)trifluoromethanesulfonamide,[169] thermolysis of Scherer's radical,[59] photolysis of bis-



$$R_FCOCl \xrightarrow{h\nu} R_F^\cdot + {}^\cdot COCl \longrightarrow etc$$



$$(i\text{-}C_3F_7)_2\dot{C}\text{-}C_2F_5 \xrightarrow[105\,^\circ C]{\Delta} CF_3^\cdot + CF_3CF{=}C(C_2F_5)(i\text{-}C_3F_7)$$

(trifluoromethyl)tellurium,[170] thermal AIBN-induced decomposition of bis(trifluoromethyl)mercury,[171] and even an enzyme-induced addition of pentafluoroethyl iodide to alkynes.[172]

H. Formation from Radical Addition to Perfluoroolefins

In order to be complete in our discussion of methods for generation of fluorinated radicals, it must be mentioned that perfluoroalkyl radical intermediates are also formed in every reaction in which radical species such as halogen atoms, thiyl radicals, or other carbon radicals add to fluoroolefins. As will be seen in section VI.B.2, such processes are especially important in the telomerization or polymerization of fluorinated olefins.

VI. Reactions Involving Fluorinated Alkyl Radicals

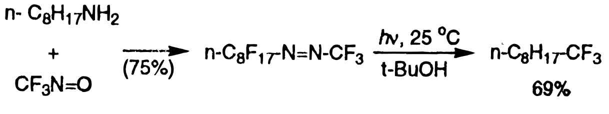
Interest in organic free radical reactions has increased in recent decades as radical-based methodology for organic synthesis has evolved, particularly with regard to carbon–carbon bond-forming reactions.[173–176] The incorporation of fluorinated alkyl groups into organic compounds also has become an area of increasing interest as the efficacious effect of such substituents upon the pharmacological properties of molecules has become recognized.[177,178]

Because perfluoroalkyl radicals are easily generated by a variety of means, because they generally have great stability with respect to unimolecular decomposition, and because they exhibit high reactivity toward diverse types of organic substrates, processes which involve intermediate free radicals are often preferred for the perfluoroalkylation of organic compounds.

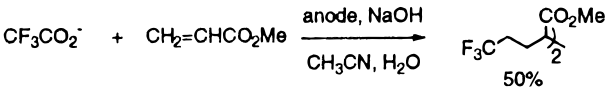
A. Disproportionation and Coupling

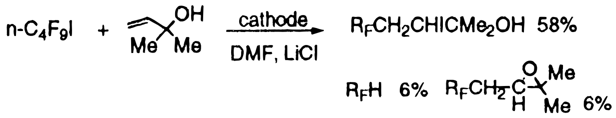
Because of the very strong β-C–F bonds of perfluoroalkyl radicals, such species do not disproportionate. Thus the only combinatorial reaction of perfluoroalkyl radicals is that of *coupling*. When two $R_F^\bullet$ radicals are generated within a solvent cage, as is the case with perfluoro azoalkane and perfluoroketone photolyses, there always results a significant amount of in-cage coupling (in the case of perfluoroazomethane this consumes about 25% of the radicals before they emerge from the cage)[12] which limits the use of such methodology in synthesis.

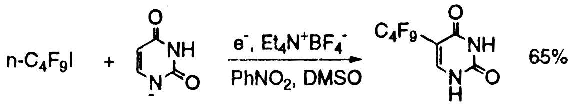
Sometimes such cage recombination can be used to advantage, such as in de Meijere's method for coupling alkyl groups to trifluoromethyl groups in which he enhances the amount of cage recombination by use of a viscous, non-H-atom donating solvent.[179]



Electrolytic generation of perfluoroalkyl radicals also can lead to coupling (Kolbe reaction), and when carried out in the presence of an addend, such as an olefin, can lead to coupling, reduction, and disproportionation-type products of the adduct radicals, as well as occasionally-decent yields of simple adducts.[180–185]







Thermal unimolecular decomposition of perfluorodiacyl peroxides seems to be less prone to cage recombination, with only 5% of coupling remaining when such decomposition is carried out in the presence of an excess of a radical scavenger such as CCl_3Br.[161] Of course, donor-induced decomposition of diacyl peroxides leads to clean chain processes with virtually no radical recombination being observed.[159]

B. Addition to Unsaturated Systems

Most useful reactions of perfluoroalkyl radicals involve efficient chain processes, and the challenge has been to find conditions where efficient propagation of the chain via chain transfer can occur. The development of such methodology has derived largely from the huge amount of work which has been devoted to studies of the addition of perfluoroalkyl radicals to unsaturated systems, particularly olefins.

Perfluoroalkyl iodides serve as the primary source of the propagating radicals in such additions, although there are situations where other precursors such as perfluoroalkyl sulfonyl bromides and diacyl peroxides may be used effectively.

1. Thermal and Photochemical, Homolytically-Induced Additions

The discovery in the late 1940's by Emeleus and Hazeldine that perfluoroalkyl iodides could be cleaved by light or heat to give perfluoroalkyl radicals certainly has proved to be historically one of the most important advances in synthetic fluorine chemistry.[186] Haszeldine was the first to recognize the potential ability of perfluoroalkyl iodides to take part in free radical chain processes which involve the intermediacy of perfluoroalkyl radicals.[8] His early studies of the thermal and photochemically-induced free radical addition of perfluoroalkyl iodides to simple olefins opened the door to a myriad of subsequent studies which were designed to control and utilize such processes for the purpose of olefin perfluoroalkylation. For his part, Haszeldine seemed most interested in defining the conditions for 1:1 adduct formation versus telomerization and in determining the orientation of addition of trifluoromethyl radicals to unsymmetrical olefins. In his studies he preferred to use thermal and photochemical homolytic initiation rather than peroxide catalysis in order to avoid side reactions deriving from such peroxide initiators.[81,187] These fundamental thermal and photochemical methodologies continue to be used and continue to evolve as useful techniques for adding perfluoroalkyl radicals to olefins and alkynes.[188]

$$CF_3I + \underset{\text{(excess)}}{CH_2{=}CH_2} \xrightarrow[48\ h]{\Delta,\ 250^\circ} CF_3CH_2CH_2I\ (75\%) + \text{higher telomers}\ (25\%)$$

$$CF_3I + \underset{\text{(excess)}}{CH_2{=}CH_2} \xrightarrow[46\%\ conv.]{h\nu,\ 108\ h} CF_3CH_2CH_2I\ (82\%) + \text{higher telomers}\ (18\%)$$

$$\underset{1\ :\ 1}{CF_3I + CF_2{=}CF_2} \xrightarrow[10\ h]{\Delta,\ 200^\circ} \text{mostly telomers}$$

$$CF_3I + CH_2{=}CHCH_3 \xrightarrow{h\nu} CF_3CH_2CHICH_3\ (98\%)$$

Indeed, the photoinitiated addition process appears to have general applicability, although it can require extensive photolysis times.[189-191] A good comprehesive review of the early work on thermal and photochemically-induced free radical addition reactions to olefins can be found in Sosnovsky's book.[11]

$$n\text{-}C_7F_{15}I + CH_2{=}CH\text{-}(CH_2)_5CH_3 \xrightarrow{h\nu} n\text{-}C_7F_{15}\text{-}CH_2CHI(CH_2)_5CH_3\ (87\%)$$

$$\underset{1\ :\ 2}{n\text{-}C_3F_7I + CH_2{=}CHCH_2OH} \xrightarrow[120\ h]{h\nu} n\text{-}C_3F_7CH_2CHICH_2OH\ (81\%)$$

$$CF_2Br_2 + CH_2{=}CHOEt \xrightarrow[10\ h]{h\nu,\ 0^\circ} BrCF_2CH_2CHBrOEt\ (83\%)$$

In a recent related piece of work, Burton's group has discovered that the use of low intensity 254 nm light enables one to obtain excellent yields of 1:1 adducts to electron-deficient olefins, such as ethyl acrylate:[192]

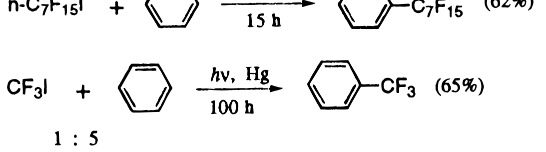
$$\underset{1\ :\ 2}{n\text{-}C_3F_7I + CH_2{=}CHCO_2Et} \xrightarrow[24\ h]{h\nu,\ 254\ nm} n\text{-}C_3F_7\text{-}CH_2CHICO_2Et\ (100\%)$$

Although, as discussed earlier in section IV, the regiochemistry for such reactions usually is such that the $R_F^\bullet$ adds to the terminal, least-highly-substituted end of the olefin, unusual regiochemistries can be observed for additions of perfluoroalkyl radicals, probably because of the intervention of polar effects.[81,193]

$$CF_3I + CF_2{=}CH\text{-}CH_3 \xrightarrow[h\nu,\ 4d,\ 100^\circ]{} CF_3CH(CH_3)CF_2I\ (70\%)$$

$$CF_3I + CF_2{=}CH\text{-}CF_3 \xrightarrow{h\nu,\ 4d,\ 100^\circ} CF_3CH(CF_3)CF_2I\ (80\%)$$

Good yields of addition to benzene and its derivatives have also been reported under both thermal and photochemical conditions:[194,195]



2. Telomerization of Fluoroolefins

It has been recognized since the time of Haszeldine's first reports that the thermal and photochemically-induced additions of perfluoroalkyl radicals to olefins were prone to lead to telomeric products due to competition between the processes of chain transfer and propagation. Indeed, extensive studies have demonstrated that the degree of telomerization is dependent upon a number of factors, including (a) the relative concentration of olefin and telogen (chain transfer agent), (b) the relative steric effect for propagation versus chain transfer, (c) reactivity factors regarding the propagating radical, (d) the reactivity of the chain transfer agent, particularly with respect to the strength of the bond which is broken in the chain transfer step, (e) reaction temperature, and (f) reaction time.

For example, Haszeldine found that, in the reaction of CF_3I with TFE, if the ratio of CF_3I:TFE is kept high, then formation of 1:1 adduct will be predominant:[196]

$$CF_3I + CF_2{=}CF_2 \xrightarrow{h\nu} CF_3(CF_2CF_2)_nI$$

ratio = 10 : 1 94% (n=1), 4%(n=2)
5 : 1 81% (n=1)
1 : 1
1 : 10 16% (n=1), 10% (n=2), 5% (n=3), 63% (n>3)
n = 10-20

Similarly thermally:

$$CF_3I + CF_2{=}CF_2 \xrightarrow[8\ h]{\Delta,\ 200^\circ} CF_3(CF_2CF_2)_nI$$

large excess of CF_3I 50% (n=1), 20% (n=2), 8% (n=3)
ratio = 1 : 2 9% (n=1), 3 % (n=1&2), 87% (n>3)

The relative efficiencies of CF_3I, C_2F_5I, n-C_3F_7I, and $(CF_3)_2CFI$ as chain transfer agents were studied within the context of the telomerization reactions of $CH_2{=}CF_2$ and TFE and it was found under almost identical conditions and a 1:1 ratio of chain transfer agent to olefin that CF_3I was the poorest and $(CF_3)_2CFI$ the best at inducing 1:1 adduct formation, a result consistent with the relative C—I bond strengths for these iodides.[197]

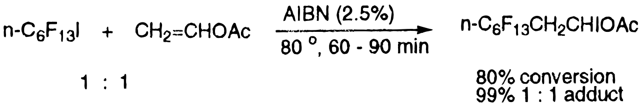
$$R_FI + CH_2{=}CF_2 \xrightarrow[17\ -\ 45\ h]{185\ -\ 200^\circ} R_F(CH_2CF_2)_nI$$

R_F = CF_3 46% (n=1), 33%(n=2), 15% (n=3), 7% (n>3)
C_2F_5 92% (n=1), 6% (n=2), 2% (n=3)
n-C_3F_7 70% (n=1), 25% (n=2), 5% (n=3)
i-C_3F_7 90% (n=1), 10% (n=2)

Moreover, higher temperature was found to lead to greater formation of telomers at the expense of 1:1 adduct.

Other similar studies have looked at additions to perfluoropropylene where 84% 1:1 adduct and 16% higher telomers were observed when a 1:1 mixture of n-C_3F_7I:C_3F_6 were heated at 200 °C for 88 h, and where again $(CF_3)_2CFI$ was found to be a better chain transfer agent than various n-R_FI's.[198,199]

In a thorough study of the effect of reactant ratio, initiator concentration, temperature, and time of reaction, it was found that the optimal reaction conditions for 1:1 adduct formation in the reaction of perfluoro-*n*-hexyl iodide to vinyl acetate are[200]



What remains to be done in this area is the tough job: to find conditions for optimization of production of telomers with various specific degrees of telomerization.

3. Polymerization of Fluoroolefins

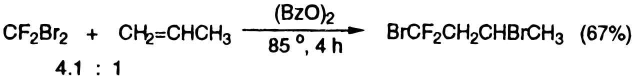
In general, fluoropolymers possess the unique combination of high thermal stability, chemical inertness, unusual surface properties, low dielectric constants and dissipation factors, low water absorptivities, excellent weatherability, and low flammabilities. Therefore there appears to be an ever-increasing market for fluoropolymers in spite of their relatively high cost.[201,202]

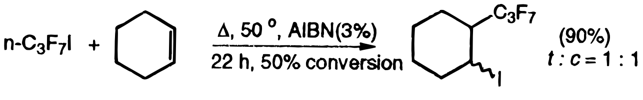
Ideal conditions for polymerization of a fluoroolefin are those where little, or better yet, *no* chain transfer occurs. Thus perfluoroalkyl iodides are not used to initiate polymerizations. Instead, non-chain-transfer agents, particularly peroxide initiators, including perfluorodiacyl peroxides and ammonium persulfate, are used effectively for this purpose.[160]

Indeed, free radical polymerization of fluoroolefins continues to be the only method which will produce high molecular weight fluoropolymers. High molecular weight homopolymers of TFE, $CFCl{=}CF_2$, CH_2CF_2, and $CH_2{=}CHF$ are prepared by current commercial processes, but homopolymers of hexafluoropropylene or longer chain fluoroolefins require extreme conditions and such polymerizations are not practiced commercially. Copolymerization of fluoroolefins has also led to a wide variety of useful fluoropolymers. Further discussion of the subject of fluoroolefin polymerization may be found elsewhere and is beyond the scope of this review.[203-205]

4. Free Radical Initiator-Induced Additions

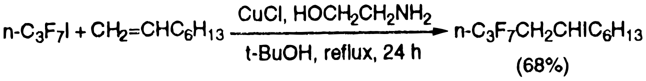
Shortly after Haszeldine's initial studies, Tarrant, Brace, and others began to use Kharasch's technique of diacyl peroxide initiation of such thermal additions.[9-11,206-209] With such inducement, these addition processes could be run at lower temperature and usually with greater efficiency. Nevertheless, such radical-induced additions can also require relatively long reaction times to attain decent conversions, apparently because of remaining difficulties in the chain transfer process. Table 19 provides a number of representative examples.

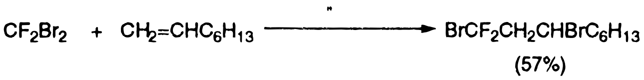




5. Reductively-Initiated Additions

It was therefore a significant breakthrough when procedures involving electron transfer initiation began to appear in the 1960s, and today reductive initiation constitutes the most commonly used method of accomplishing the addition of R_FI to olefins and alkynes.[216] Perhaps the first example of such a process was that of Kehoe and Burton in 1966.[217,218]

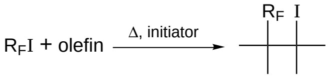




Since then, numerous other reductive systems have been discovered, all of which presumably involve as the key initiative step a single electron transfer from the reductant to the R_FI molecule. Table 20 provides representative examples of the various reductive systems which have been reported. In some cases stoichiometric amounts of a reducing agent have been used.

In the example where Me_3Al is used to promote addition,[244] the process may not involve reduction, although, as in the case of Et_3B promotion below, the reactions are observed to be enhanced by addition of $Pd(PPh_3)_4$. The mechanism may involve prior acid–base complexation of R_FI and Et_3Al, with a subsequent homolytic process leading to $R_F^•$.

Table 19. Examples of Initiator-Induced Additions to Olefins



R_FI	olefin	initiator[a]	conditions	yield, %	ref
n-$C_6F_{13}I$	$CH_2{=}CHOAc$	AIBN	80 °C, 1 h	91	209
n-C_4F_9I	$CH_2{=}$CHCH2OAc	DBP	100 °C, 45 min	90	210
$I(CF_2)_4I$	$CH_2{=}CH_2$	NBP	130 °C, 22 h	82 (1:2)	211
n-$C_6F_{13}I$	$CH_2{=}$CHCH2OAc	DBP	89 °C, 1 h	94	212
i-C_3F_7I	cyclohexene	AIBN	68 °C, 21 h	80	213
n-C_3F_7I	$CH_2{=}CHOAc$	AVN	50 °C, 7 h	96	214
n-$C_7F_{15}I$	$CH_2{=}CHCH_2CO_2Et$	AIBN	81 °C, 14 h	100	215

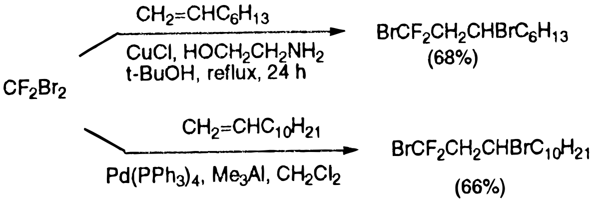
[a] AIBN = azobis(isobutyronitrile); DBP = dibenzoyl peroxide; TBP = di-*tert*-butyl peroxide; AVN = azobis(2,4-dimethylvaleronitrile).

Table 20. Representative Examples of Reductively-Induced Additions

$$\mathrm{R_FI + olefin/alkyne \xrightarrow[\text{conditions}]{\text{reductant, co-reagent}} adduct}$$

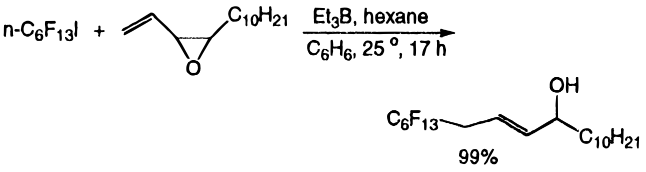
R_FI	olefin/alkyne	reductant	conditions	yield, %	ref
$Cl(CF_2)_4I$	$CH_2{=}CHC_4H_9$	Fe	DMF, 80 °C, 2 h	85	219
$Cl(CF_2)_4I$	$CH_2{=}CHC_4H_9$	Mg	DMF, 80 °C, 10 h	85	220
n-C_4F_9I	$HC{\equiv}CCMe_2OH$	Zn	CH_2Cl_2, rt, 50 min	90	221
n-$C_6F_{13}I$	$CH_2{=}CHCHMeOH$	Cu		78	222
n-C_4F_9I	$CH_2{=}CHC_6H_{13}$	Sn	H^+, Et_2O-H_2O, 30 °C	78	223
n-$C_5F_{11}I$	$CH_2{=}CMeCH_2CH_3$	Raney Ni	EtOH, 80 °C, 6 h	96	224
$Cl(CF_2)_4I$	cyclohexene	Cu	diglyme, 100 °C, 6.5 h	65	225
$CF_2{=}CFCF_2I$	$CH_2{=}CH(CH_2)_3OAc$	Cu	50 °C, 4 h	82	226
n-$C_6F_{13}I$	$CH_2{=}CHC_4H_9$	Ti	$Zn/TiCl_4$, DME, 70 °C, 4 h	85	227
n-$C_6F_{13}I$	$HC{\equiv}CC_5H_{11}$	Ti	$Zn/TiCl_4$, DME, 70 °C, 4 h	70	227
$Cl(CF_2)_4I$	$(CH_2{=}CHCH_2)_2O$	Raney Ni	EtOH, 80 °C	95	224
n-$C_6F_{13}I$	$(CH_2{=}CHCH_2CH_2)_2$	$TiCl_2Cp_2$	Fe, 65 °C, 40 h	75	228
n-$C_6F_{13}I$	$CH_2{=}CHCO_2Et$	$DyCl_3$	Zn, THF, 50 °C	74	229
n-$C_6F_{13}I$	$CH_2{=}CHCH_2OAc$	$YbCl_3$	Zn, THF, 50 °C	95	230
n-$C_8F_{17}I$	$CH_2{=}CH_2$	Ru/C	120 °C, 12 h	93	231
n-$C_8F_{17}I$	$CH_2{=}CH_2$	$Ni(CO)_2(Ph_3P)_2$	70 °C, 6 h	96	231
n-C_4F_9I	$CH_2{=}CHC_6H_{13}$	$Pd(Ph_3P)_4$	hexane	78	232
n-C_4F_9I	$HC{\equiv}CPh$	$Pd(Ph_3P)_4$	hexane	67	232
C_2F_5I	$CH_2{=}CHC_4H_9$	$Pd(Ph_3P)_4$	C_6H_6, 20 °C, 20 min	97	233
$Cl(CF_2)_4I$	$CH_2{=}CHC_5H_{11}$	$RhCl(Ph_3P)_3$	90 min, 80 °C	92	234
CF_3I	$CH_2{=}CHSiMe_3$	$Ru(CO)_{12}$	60 °C, 18 h	89	235
n-$C_8F_{15}I$	$HC{\equiv}CC_5H_{11}$	$Fe_3(CO)_{12}$	60 °C, 3 h	87	235
$Cl(CF_2)_4I$	$(CH_2{=}CHCH_2)_2O$	SmI_2	THF, 20 °C	78	236−7
n-$C_8F_{17}I$	$CH_2{=}CHC_6H_{13}$	$PhSO_2Na$	DMF, rt	73	238
C_2F_5I	$HC{\equiv}CCH_2OH$	$Na_2S_2O_4$	$NaHCO_3$, H_2O, MeCN, 0 °C, 5 h	99	239−40
$BrCF_2CF_2Br$	$HC{\equiv}CC_4H_9$	$(NH_4)_2S_2O_4$	$NaHCO_2$, DMF, 40 °C	91	241
n-C_4F_9I	$CH_2{=}CHC_4H_9$	$Na_2S_2O_4$	$NaHCO_3$, H_2O, MeCN, 0 °C, 1 h	90	242
n-C_4F_9I	$(CH_2{=}CHCH_2)_2O$	piperidine	135 °C, 3 h	65	243
CF_3I	$CH_2{=}CHCH_2Ph$	Me_3Al	CH_2Cl_2	76	244
n-C_4F_9I	$CH_2{=}CHC_5H_{11}$	Bu_4NI	135 °C, 5.5 h	82	243

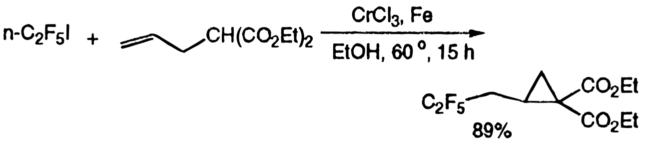
CF_2Br_2 and HCF_2I have also been utilized in reductively-induced reactions to provide 1:1 adducts:[217,244,245]



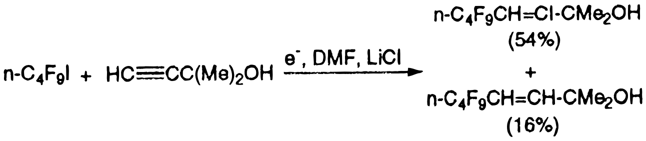
$$\mathrm{CHF_2I + CH_2{=}CHC_4H_9 \xrightarrow[\text{MeCN, H}_2\text{O, RT, 14 h}]{\text{Na}_2\text{S}_2\text{O}_4\text{/NaHCO}_3} HCF_2CH_2CHIC_4H_9}$$
(86%)

Two other examples indicate how additions of R_FI can be used to instigate more extensive chemical transformations such as an oxiranyl carbinyl radical ring-opening and cyclopropane ring formation:[242,246,247]





Controlled electrolytic methodology, as discussed earlier has also been used effectively for inducing perfluoroalkylation of olefins and alkynes, i.e.:[181]



An unusual example of addition of perfluoroalkyl iodide to isonitriles has been reported:[248]

$$\mathrm{n\text{-}C_4F_9I + n\text{-}C_4H_9N{=}C{:} \xrightarrow{Cu} n\text{-}C_4H_9\text{-}N{=}ClC_4F_9}$$ (90%)

It has been found that reductive addition of R_FI to electron-deficient alkenes can lead to good yields of *hydro*perfluoroalkylation products,[249,250] and Hu has also found conditions under which CF_2Br_2 will productively undergo reductive addition to both electron-deficient and electron-rich olefins:[251,252]

$$\mathrm{n\text{-}C_6F_{13}I + CH_2{=}CHCO_2Et \xrightarrow[\text{Zn, 20 °}]{\text{bromo(pyridine) cobaloxime(III)}} n\text{-}C_6F_{13}CH_2CH_2CO_2Et}$$
(72%)

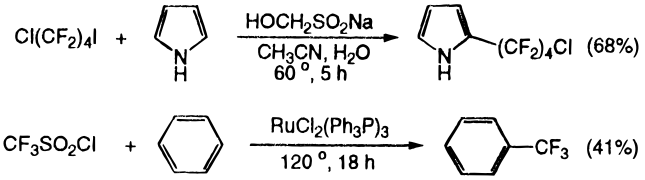
$$\mathrm{CF_2Br_2 + CH_2{=}CHCO_2Et \xrightarrow[\text{60 °, 20 h}]{\text{CrCl}_3\text{, Fe}} BrCF_2CH_2CH_2CO_2Et}$$ (72%)

When one carries out additions of R_FI using a stoichiometric amount of arenethiolates, -selenates, or -tellurates, one obtains net *perfluoroalkyl thiolation*, etc., with the tellurate being most reactive:[253,254]

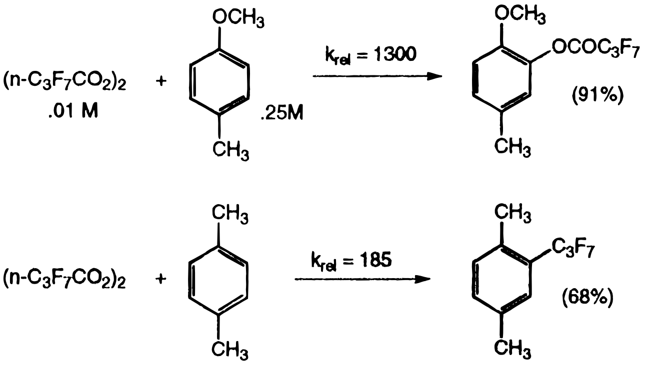
$$n\text{-}C_8F_{17}I + CH_2{=}CHC_6H_{13} \xrightarrow[\substack{RT,\ 2\ h\\ X=S,\ Se,\ Te}]{PhX^-,\ EtOH,\ Et_2O} n\text{-}C_8F_{17}CH_2CH(XPh)C_6H_{13}\ (59-81\%)$$

6. SET-Induced Additions to Aromatic Systems

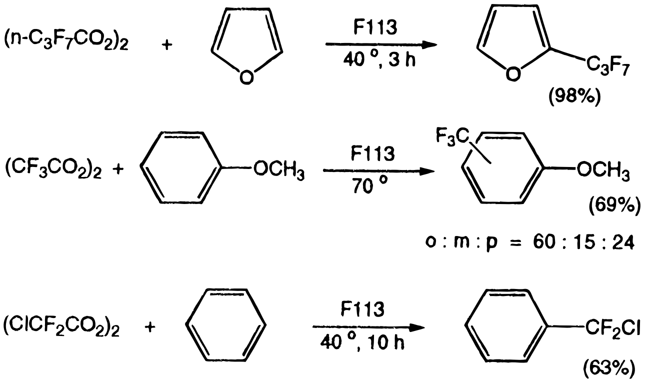
There are also a few examples of the application of the SET reductive methodology for perfluoroalkylation of *aromatics*, a reaction which although formally a substitution, mechanistically involves initial addition to the aryl substrate.[255,256]



The utilization of perfluorodiacyl peroxides for this purpose has been more widely developed. The rate of decomposition of perfluorodiacyl peroxides in the presence of electron-rich benzene derivatives is enhanced by a significant factor via a process of electron transfer.[159,257] As can be seen by the contrasting examples below,[258] highly reactive arenes are capable of trapping the perfluoroalkyl carboxyl radical before it decarboxylates to $R_F^\bullet$, a result which can diminish the synthetic utility of this process.

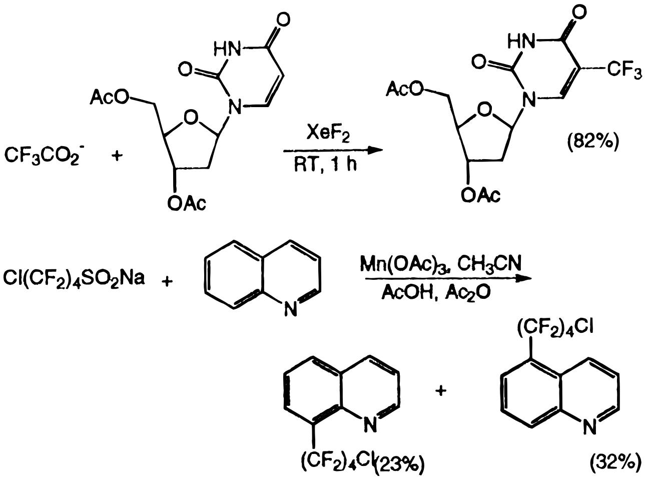


Nevertheless, there are numerous productive examples of perfluoroalkylations of benzene derivatives, heteroaromatics, and uracil derivatives using diacyl peroxides, such as $(CF_3CO_2)_2$, $(n\text{-}R_FCO_2)_2$, and $(ClCF_2CO_2)_2$, as the source of the perfluoroalkyl group.[259-263]



7. Oxidatively-Induced Additions

Kolbe-type alkylations are, of course, oxidative in nature. There are a few other oxidative processes which lead to perfluoroalkylative addition, namely oxidation of carboxylic acids with xenon difluoride and oxidation of sodium perfluoroalkyl sulfinates:[156,264]

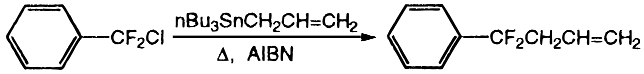


8. Other Chain Transfer Enhancing Methodologies

Although the synthetic usefulness of such reactions has not yet been widely recognized, it should be possible to carry out hydroperfluoroalkylation of olefins and alkynes very efficiently by the strategic use of an appropriate homolytic hydrogen transfer agent. The rates of hydrogen transfer for many such agents have been recently reported,[116] and both Et_3SiH and n-Bu_3GeH appear to have kinetic properties which will allow addition to compete efficiently with reduction of $R_F^\bullet$ to produce good yields of adduct.

$$n\text{-}C_7F_{15}I + CH_2{=}CHC_4H_9 \xrightarrow[C_6H_6]{Et_3SiH,\ h\nu} n\text{-}C_7F_{15}CH_2CH_2C_4H_9 + Et_3SiI + \text{some } n\text{-}C_7F_{15}H$$

Another reported way to facilitate the chain transfer process is addition of the propagating radicals to allylic stannanes.[263] Because of their efficiency, such processes as these will undoubtedly be used more frequently by synthetic chemists in the future.



C. Substitution Reactions

Perfluoroalkyl iodides are well-known for their ability to act as substrates in $S_{RN}1$ substitution reactions.[265]

1. Substitution by Thiols and Thiolates

Whereas it has been demonstrated that both malonate ions and thiolate ions can catalyze the free radical chain addition reaction of perfluoroalkyl iodides to olefins,[266,267] under appropriate conditions one can obtain products deriving from substitution in such processes. Following early work carried out photolytically in liquid ammonia, recent reports have indicated that good yields of substitution products can be obtained in polar solvents at room temperature, without irradiation.[268−273]

$$n\text{-}C_8F_{17}I + PhS^-Na^+ \xrightarrow{DMF,\ 25^\circ} n\text{-}C_8F_{17}SPh\ (92\%)$$

$$n\text{-}C_3F_7I + CH_3S^-Na^+ \xrightarrow{DMF,\ 100^\circ} n\text{-}C_3F_7SCH_3\ (73\%)$$

Perfluoro selenides and tellurides[274−276] and perfluoroalkyl sulfinates[277,278] are also synthetically accessible via similar processes:

$$CH_3Se^-Na^+ + BrCF_2CF_2Br \xrightarrow[72\ h]{NH_3,\ -78^\circ} CH_3SeCF_2CF_2SeCH_3\ (70\%)$$

$$H(CF_2)_8I + Na_2S_2O_4 \xrightarrow[CH_3CN,\ 85^\circ,\ 7\ h]{NaHCO_3,\ H_2O} H(CF_2)_8SO_2Na\ (94\%)$$

2. Substitution by Carbanions

In what has become a classic example of an $S_{RN}1$ reaction, the 2-propylnitronate anion undergoes efficient perfluoroalkylation in its reaction with perfluoroalkyl iodides:[279]

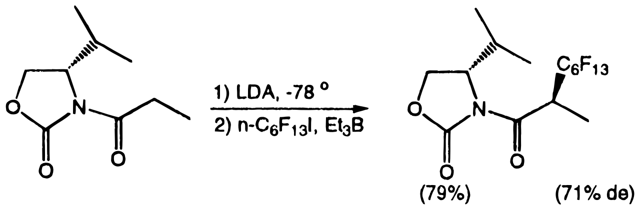
$$n\text{-}C_6F_{13}I + Na^+\ Me_2C{=}NO_2^- \xrightarrow[3\ h]{h\nu,\ DMF} n\text{-}C_6F_{13}CMe_2NO_2\ (89\%)$$

Reactions with stabilized enolate species such as malonate ions also lead to alkylation, but because of the requisite basic conditions, the initial alkylation products are subsequently converted to secondary products.[266]

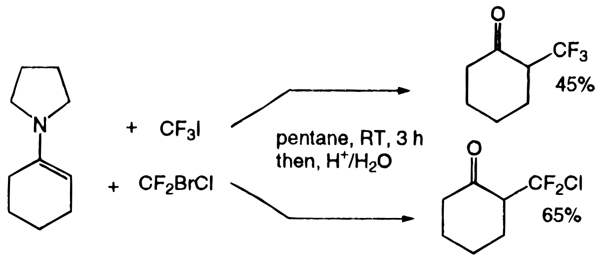
$$C_2F_5I + CH_3COCH_2COCH_3 \xrightarrow{h\nu,\ NH_3} CH_3COCH{=}C(CF_3)NH_2$$

$$[\text{via } CH_3COCH(C_2F_5)COCH_3]$$

In contrast, it has recently been found that *non-stabilized* enolates can also be perfluoroalkylated if the reaction is Et_3B-catalyzed, and if a chiral auxiliary is used, such reactions can lead to decent diastereomeric excess:[280]



Enamines are also observed to undergo reactions with perfluoroalkyl iodides which lead to overall α-perfluoroalkylation of ketones.[281]



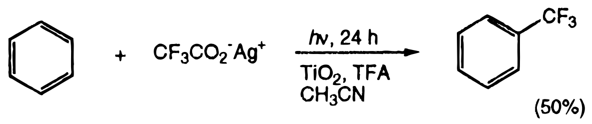
Lastly, electron transfer processes can also compete with nucleophilic acyl substitution in the reaction of perfluorodiacyl peroxides with Grignards.[282] Such a process can lead to a coupling of the Grignard with the perfluoroalkyl radical intermediate. (In contrast, benzyl lithium gives no perfluoroalkylation under the same conditions.)

$$(C_3F_7CO_2)_2 + PhCH_2MgBr \xrightarrow{Et_2O,\ F113} C_3F_7CH_2Ph\ (24\%) + C_3F_7COCH_2Ph\ (21\%)$$

3. Hunsdiecker Reactions

Hunsdiecker reactions of salts of perfluoroalkanoic acids are known primarily as perhaps the best way of making perfluoroalkyl halides,[153,283,284] but there have been other synthetic uses found for the perfluoroalkyl radicals which are formed by this decarboxylative process.[285]

$$CF_3CO_2^-Ag^+ \xrightarrow{\Delta,\ I_2\ (excess)} CF_3I\ (91\%)$$



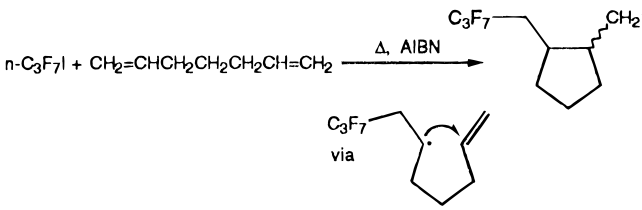
4. Reductions Involving Perfluoroalkyl Radicals

Replacement of the iodine or bromine substituent of a perfluoroalkyl iodide or bromide with hydrogen is a process which is a side reaction in most of the reductively-catalyzed perfluoroalkylation processes described earlier. If one wishes to carry out such a reaction synthetically, it may be accomplished easily by use of any of a number of hydrogen atom transfer agents such as $n\text{-}Bu_3SnH$, $n\text{-}Bu_3GeH$, $(TMS)_3SiH$, or Et_3SiH. The rate constants for each of these H-atom transfer agents have been determined, and they were presented and discussed earlier in section IV.C of this review.[126]

D. Rearrangements of Fluorinated Radicals

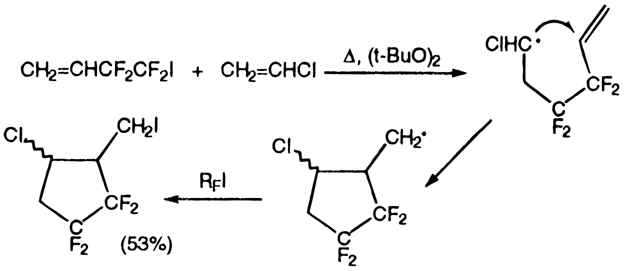
Although radicals are not nearly so prone to rearrangement as are, for example, carbocations, there are a few such "rearrangements" which have become identified as *characteristic* of carbon radicals. These include radical cyclizations, particularly the 5-hexenyl radical cyclization, and radical C−C bond cleavages, particularly the cyclopropylcarbinyl to allylcarbinyl radical rearrangement. In hydrocarbon systems, as organic synthetic chemists have learned how to control rapid chain processes, such rearrangements have become important synthetic tools.[174−176]

There are many fewer examples of perfluorofluorinated or even partially-fluorinated radicals undergoing such reactions, although Brace utilized perfluoroalkyl radicals in his early studies of hydrocarbon radical cyclization reactions; for example[286,287]



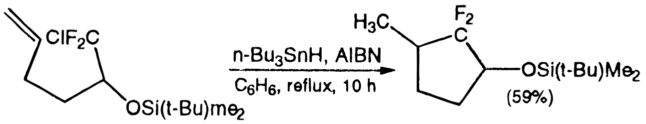
1. 5-Hexenyl Radical Cyclizations

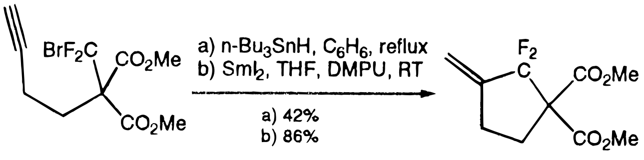
The 5-exo cyclization reactions of hydrocarbon 5-hexenyl radicals comprise the most highly studied of all cyclization processes, and such processes have been extensively and effectively exploited for synthetic purpose.[174–176] There have, however, been relatively few examples reported of comparable cyclizations of fluorinated 5-hexenyl systems. Piccardi reported an early example of cyclization of a partially-fluorinated 5-hexenyl radical system.[288]



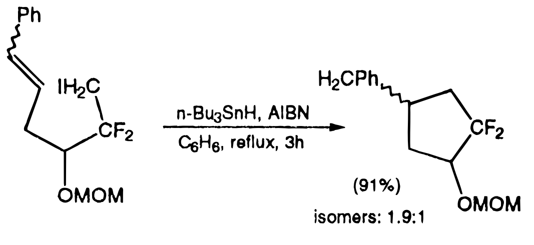
The cyclization kinetics of a number of other partially-fluorinated systems as well as for the cyclization of the parent perfluoro-5-hexenyl radical have been discussed earlier in section IV of this review.[125] Other than these examples, the only remaining reports of cyclizations of radicals with fluorine proximate to the radical center involve some examples of α,α-difluoro-, *β*,*β*-difluoro-, and α-trifluoromethyl-5-hexenyl radical systems.

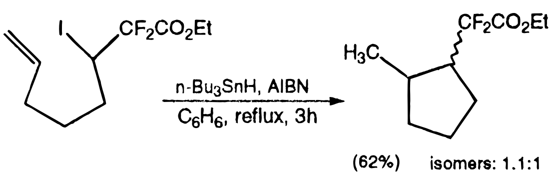
a. α,α-Difluoro Radical Systems.[113,289–291]



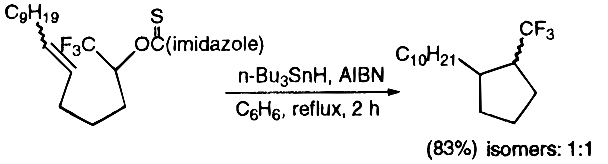


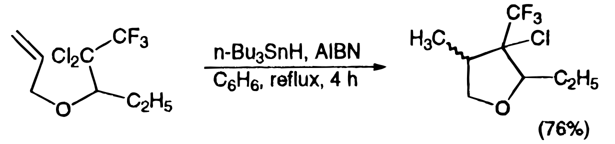
b. β,β-Difluoro Radical Systems.[292,293]





c. α-Trifluoromethyl Radical Systems.[293–295]

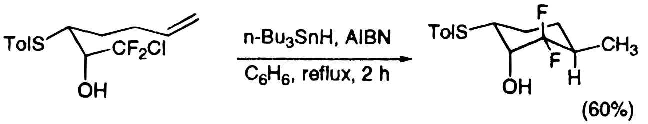


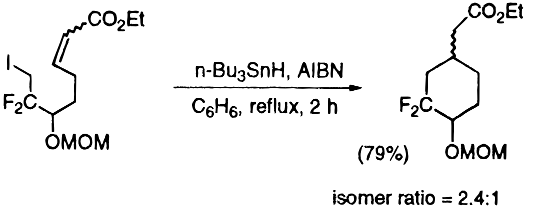


It would appear that there is considerable potential in using fluorinated 5-hexenyl radical systems to synthesize specifically fluorine-substituted cyclopentyl ring systems.

2. 6-Heptenyl Radical Cyclizations[292,296]

α,α-Difluoro- and *β*,*β*-difluoro-6-heptenyl radicals have been found to undergo *exo-trig* cyclization to form 6-membered rings in reasonable yields:

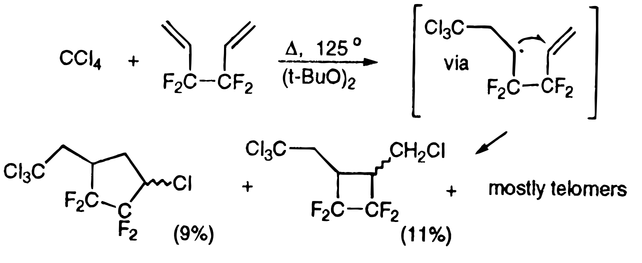




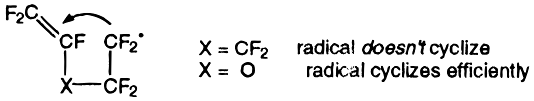
Because of the rate-enhancing effects of fluorine substitution on cyclization reactions of partially-fluorinated radical systems, it is likely that, unlike for pure hydrocarbon systems, it will be possible to utilize such processes to make 6, 7, and even larger membered rings in radical systems which have appropriate fluorine substitution.

3. 4-Pentenyl Radical Cyclizations

An interesting aspect of fluorinated 4-pentenyl radicals that distinguishes them from their hydrocarbon counterparts is their ability to cyclize to form 4-membered rings. As mentioned in section IV, Piccardi and his co-workers reported in 1971 that C_2F_5I underwent free radical addition to 3,3,4,4-tetrafluoro-1,5-hexadiene to form a 4-membered ring product.[149] Subsequently he observed similar results in the addition of CCl_4.[297]



In the kinetic studies, which were also discussed in section IV.D.3, it was found that whereas the perfluoro-4-pentenyl radical could not be induced to cyclize, the 3-oxa-perfluoro-4-pentenyl system cyclized cleanly with a rate constant of 3.8×10^5 s^{-1}, a rate which is similar to that observed for the parent 5-hexenyl radical cyclization.[125]

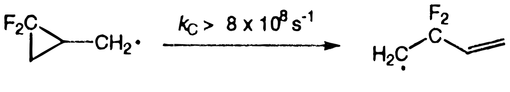


There is much yet to be learned about the factors which determine whether particular fluorinated 4-membered rings will be able to be formed via cyclization processes. Nevertheless there should be considerable synthetic utility to be found in this area.

Indeed, there will likely be considerable future research activity in the broad and potentially-fertile area of cyclizations of unsaturated fluorinated radicals.

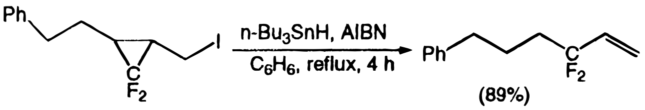
4. Cyclopropylcarbinyl Radical Rearrangements

As discussed earlier in section IV of this review, because of the incremental strain imparted by fluorine substitutents to cyclopropane systems, the rate of ring opening of the (2,2-difluorocyclopropyl)carbinyl radical is substantially enhanced with respect to the already very fast analogous hydrocarbon system.[150]

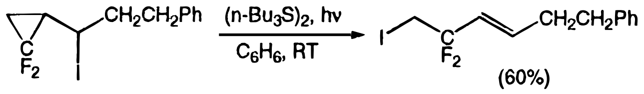


Although there are few examples, the facility of the ring opening process, as well as its regiospecificity, can be exploited for synthetic purpose:[298,299]

Reductive Ring-opening:



Iodine Atom-transfer:



VII. Conclusions

It should be evident from reading this critical review on the structure, reactivity, and chemistry of fluorinated radicals, that radicals play a very important role within the realm of organofluorine chemistry. Fluorine substituents impart unique reactivity characteristics to free radical intermediates, and knowledge of how to generate and utilize such species is very important for those synthetic chemists who wish to incorporate fluorinated alkyl groups into organic substrates. Although the present work does not comprise an all-inclusive review of work done in the area of fluorinated radicals, it has nevertheless been attempted to provide a strategic overview of each and every aspect of organofluorine radical chemistry, with the hope that all readers who have an interest in the field should be able to get their basic questions answered as well as to be stimulated to dig deeper into specific aspects of the subject via the detailed references which have been provided. I wish to acknowledge the tremendous wealth of work which has been accomplished over the last 50 years in the area of fluorinated radical chemistry which has made this review possible.

Acknowledgments

The author wishes to acknowledge with thanks the generous support of his research in the field of fluorinated radicals by the National Science Foundation.

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