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Perspective on Fluorocarbon Chemistry

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Fluorocarbons, organic molecules with carbon skeletons and fluorine “skins”, differ fundamentally from their hydrocarbon counterparts in interesting and useful ways. A selection of the myriad applications fluorocarbons and their derivatives have found in modern life is described and related to molecular properties. Salient aspects of the nature and reactivity of fluorocarbon compounds are highlighted by comparison with their more familiar hydrocarbon analogues.

A Bit of History[1a]

By the time the element fluorine was discovered by Moissan in 1886,[2a] organic chemistry had been in ferment for decades. W. H. Perkin had founded the organic chemical industry in 1857, the structural theory of Kekulé and Couper had been available since 1859, the idea of tetrahedral carbon was a dozen years old, and the combination of degradation and synthesis was establishing the structures of organic molecules at a great pace. Industry based on the organic chemistry of fluorine got its start only in 1930 following Midgely and Henne’s discovery of the excellent refrigerant properties of chlorofluorocarbons, synthesized earlier by the Belgian chemist Swarts.[1b] Plunkett’s serendipitous discovery of Teflon in 1938 at DuPont was a landmark development in organofluorine chemistry.[2b] In the early 1940s, the Manhattan Project required extremely inert materials for the separation of uranium isotopes via gas diffusion of their corrosive hexafluorides, and fluorinated materials were uniquely suited for the task.[2c] The Project gave a great impetus to fluorocarbon chemistry, which has “fluorished” ever since as an important component of the chemical industry and as a field of fundamental research.

Some Uses of Fluorocarbons[2d,3]

With fluorine “skins” covering carbon skeletons, fluorocarbons differ dramatically from their hydrocarbon counterparts in properties and chemical behavior. As a consequence, fluorocarbons and derived substances have found a great variety of uses in modern life, for many of which they are unrivaled. The selection of applications mentioned here is hardly comprehensive, but it should serve to illustrate the remarkable versatility of these materials. The thermal stability, chemical inertness, dielectric strength, water-repellency, and famous slipperiness of poly(tetrafluoroethylene) (Teflon) make it valuable for electrical insulation, nonstick coatings, Gore-Tex fabrics, uses in extreme environments (in the laboratory, industry, and space), etc.[1c] Highly fluorinated polymers have found many other applications, including such diverse items as textile and carpet finishes,[1d] fire-fighting foams,[4] lubricants for compact disks[1e] and skis,[5] antireflective coatings, and membranes for chlor-alkali production.[1f]

In the electronics industry fluorocarbons play many roles, e.g., as vapor phase soldering media, solvents for cleaning circuitry, and coolants for supercomputers.[1g] Fluoropolymers are employed as low κ dielectrics in microchip manufacture[6a−c] and as sealants and gasket materials in the processing equipment.[6d] Among a variety of other roles in this complex technology, fluorocarbons serve as etchant gases.[1g] In the quest to keep Moore’s Law[7] alive, UV photolithography on silicon[8] is in the process of being extended to 157 nm using a fluorine laser.[6e] Only fluorocarbon-rich polymers appear to be suitable as photoresists and pellicle materials at this very short wavelength.[6f−j]

In medicine, fluorocarbons serve as vascular implants,[9] inhalation anesthetics,[1h,10a] aerosol propellants,[10b] breathing liquids for immature or damaged lungs, and components in blood substitutes.[1i] Biotechnology employs fluorocarbon liquids to transport respiratory gases in cell culture systems.[10c]

Because they were so useful as refrigerants, propellants, solvents, and blowing agents, chlorofluorocarbons were produced on an enormous scale for decades, with consequent damage to the ozone layer. Since it is the chlorine in these molecules that kills the ozone, it is not surprising that their replacements are primarily other fluorocarbon derivatives.[1b,j,k] Hydrofluorocarbons are particularly desirable because they are degraded in the troposphere, thus minimizing their global warming potential.

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Recent years have witnessed the development of fluorous technology, an array of separation methods that exploit the unusual solubility properties of fluorocarbons.[10d,11] This technology offers promise for efficient catalyst recovery in industrial scale processes, for example, and facile separation of complex mixtures in the drug discovery field. In the latter application, molecules tagged with fluorocarbon "tails" of varying lengths are readily separated in order of tail length by passage through a fluorocarbon-coated silica gel column.

Fluorine is present in a large and ever increasing number of pharmaceuticals[10e] and agrochemicals,[11] typically as an occasional fluoro or trifluoromethyl substituent on a hydrocarbon-derived molecule. Devoted as it is to fluorocarbons, the present paper does not deal with this very important aspect of fluorine chemistry.

Some Characteristics of Fluorocarbons[1m]

Fluorine's distinction as the most electronegative element reflects the very tight binding of its valence electrons, which results in both low atomic polarizability and small size (van der Waals radius, 1.47 Å).[12] Because of the electronegativity difference between carbon and fluorine (2.5 vs 4.0),[13] C−F bonds are highly polar, and that contributes to their strength. The combination of very strong bonds to carbon and relatively small size makes it possible for fluorine to take the place of the hydrogens in virtually every kind of organic molecule, an ability possessed by no other element. The great strength of C−F bonds, which ranges as high as 130 kcal/mol,[14] underlies many of the applications of fluorocarbons in high temperature and/or corrosive environments. Electron withdrawal by the fluorines also strengthens the skeletal bonds in a fluorocarbon. The C−C bond in hexafluoroethane, for example, is 7 kcal/mol stronger than that in ethane.[15] Tight binding of all the valence electrons in fluorocarbon derivatives is responsible for the extreme transparency required in 157 nm photolithography and for the low refractive indices needed for antireflective coatings.

The low polarizability of the fluorine atom translates into low surface energies and thus weak cohesive forces between fluorocarbon molecules, as the interaction energy arising from London forces varies as the square of the polarizability. As a result, fluorocarbons are remarkably volatile. Perfluoro-*n*-hexane, for example, boils at 57 °C, 12 °C below *n*-hexane despite having a molecular weight roughly four times as great.[1m]

The peculiar solubility properties of fluorocarbons are another consequence of their low surface energies.[16] Though both alkanes and perfluoroalkanes are nonpolar, their mutual solubility is very low. Immiscibility of fluorocarbons with water is to be expected because the interaction energy of water molecules with themselves is so much greater than with fluorocarbon molecules, and to a lesser degree the same relationship holds between hydrocarbon and fluorocarbon molecules. Low surface energies are the reason that fluorocarbon-based textile and carpet finishes are both oil and water repellent, that fluorocarbon-based fire-fighting foams spread easily over the surface of a burning hydrocarbon liquid, that Teflon is as slippery as wet ice, and that fluorous separation technology works.

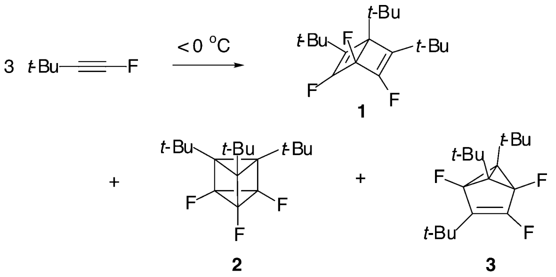
Yet another result of the weak intermolecular forces in fluorocarbon liquids is their high compressibility, which reflects the availability of interstitial space. This free volume helps to explain the high solubility of respiratory gases in fluorocarbons that make them useful as breathing liquids, blood substitutes, and components of cell culture systems.[16]

Other characteristics that enhance the value of fluorocarbons and their derivatives in many of their applications include lack of flammability and low toxicity. Fluorocarbons actually span an extremely broad range with regard to toxicity. Perfluoroisobutylene, a potent alkylating agent, is very deadly,[17] but large quantities of perfluorodecalin or perfluorooctyl bromide can be pumped into one's veins with impunity as blood substitute components. They are slowly expelled from the body unchanged.[1i,18]

Fluorocarbons vs Hydrocarbons: Contrasts in Reactivity

Comparison of the chemistry of fluorocarbons with that of their more familiar hydrocarbon counterparts will highlight what is special about fluorocarbon behavior. In addition to fluorine's extreme electronegativity, its size and lone pairs distinguish it from hydrogen and play key roles in its chemistry. While the influence of electronegativity on fluorocarbon reactivity is virtually ubiquitous, effects stemming from these other characteristics are more limited in scope. For this reason, it seems useful to divide discussion of the multifaceted chemistry of fluorocarbons into three sections: those aspects of it that depend predominantly upon electronegativity, those in which lone pair interactions are also important, and those where steric effects are prominent.

Consequences of Electronegativity. (a) The Role of Bent's Rule. This rule states that, "Atomic p character concentrates in orbitals directed toward electronegative substituents,"[19] thus allowing the more electronegative of two bonded atoms to acquire a greater share of the bonding electrons. Much of fluorocarbon reactivity follows from this generalization, and fluorine's preference for bonding to sp^3- as compared with (nominally) sp^2- or sp-hybridized carbon manifests itself in myriad ways. Regarding sp hybridization, the facile polymerization of difluoroacetylene[20] and the remarkable reactivity of *tert*-butylfluoroacetylene are cases in point. The latter compound trimerizes spontaneously below 0 °C, yielding the highly strained benzene valence isomers **1**−**3**.[21] Repulsion between fluorine lone pairs and the p orbitals of fluoroacetylenes may also contribute to their instability.[22]



The driving force toward sp^3 hybridization is evident in the polymerization of tetrafluoroethylene (TFE) to make Teflon.[23] This reaction is more exothermic by ~15 kcal/mol than polymerization of ethylene (Scheme 1).[24]

SCHEME 1

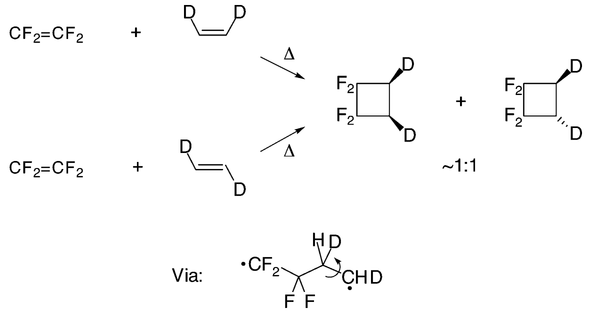
$$n\ CH_2{=}CH_2 \longrightarrow \left[CH_2{-}CH_2\right]_n \qquad \Delta H = -25.7\ \text{kcal/mol}$$

$$n\ CF_2{=}CF_2 \longrightarrow \left[CF_2{-}CF_2\right]_n \qquad \Delta H = -40.5\ \text{kcal/mol}$$

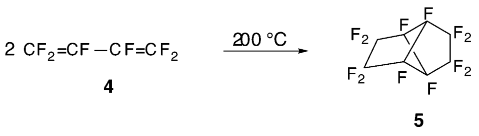
Also favoring polymerization of TFE is the enhanced strength of σ bonds between fluorinated carbons, noted above.

The same factors underlie the prominent role thermal [2 + 2] cycloadditions play in organofluorine chemistry.[25] Whereas only highly strained hydrocarbon alkenes react in this fashion, *gem*-difluoroalkenes undergo a great variety of [2 + 2] cycloadditions. They proceed stepwise, nearly always via biradical intermediates. Again, the driving force for biradical formation is provided by rehybridization of the CF_2 group(s) and formation of an unusually strong C−C bond.[26] Separate reactions of TFE with *cis*- and *trans*-dideuterioethylene both gave a roughly equimolar mixture of *cis*- and *trans*-dideuteriocyclobutanes, consistent with the intermediacy of a biradical in which stereochemical memory was lost by bond rotation before ring closure (Scheme 2).[27]

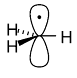
SCHEME 2



Thermal chemistry of hexafluorobutadiene (**4**) provides a further illustration of the same driving forces. An array of dimers and trimers have been identified, but after many hours at 200 °C the principal product is the tricyclic dimer **5**.[28,29] The hydrocarbon parent of **5** ring opens thermally to 1,5-cyclooctadiene, just the reverse of the final cyclization leading to the tricyclic fluorocarbon.[30]



Whereas the methyl radical (**6**) is planar, successive substitution of the hydrogens with fluorine causes increasing pyramidalization.[31] The ^{13}C hyperfine coupling constant of 272 G for the trifluoromethyl radical (**7**) reveals that it is very nearly sp^3 hybridized, another manifestation of Bent's rule. A second factor driving pyramidalization comes into play here. Stabilization of the SOMO orbital by mixing with a C−F σ^* orbital is absent in the planar configuration and increases with pyramidalization.[32] Bent's rule is presumably responsible in part for the surprising nonplanarity of tetrafluorocyclobutadiene (**8**).[33] Pyramidalization of the carbon skeleton both enhances the p character in the C−F bonds and diminishes the conjugative destabilization of this antiaromatic molecule.



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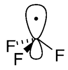

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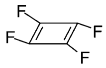

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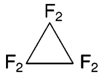
(b) Destabilization of Cyclopropanes. The strain energy of hexafluorocyclopropane (**9**) is roughly twice that of the parent hydrocarbon. Its exact magnitude is still uncertain, primarily because of the difficulty of choosing appropriate reference states.[34] The parent cyclopropane's strain energy is less than the badly distorted ring bonds would suggest for two reasons: the presence of a low lying σ orbital occupying the center of the ring (easily visualized with the Walsh model) and especially strong C−H bonds (**10**).[35] The high degree of s character in the exocyclic carbon hybrid orbitals of cyclopropane confers strength on the bonds to hydrogen but results in destabilization of the molecule when fluorines are substituted for the hydrogens.[36]



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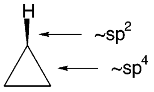

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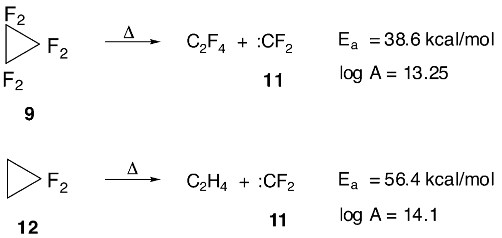
However large this effect may be, there is abundant experimental evidence for great strain in highly fluorinated cyclopropanes. Some sense of this is gained from the 18 kcal/mol difference in activation energy for extrusion of difluorocarbene (**11**) from hexafluorocyclopropane as compared with 1,1-difluorocyclopropane (**12**) (Scheme 3).[37]

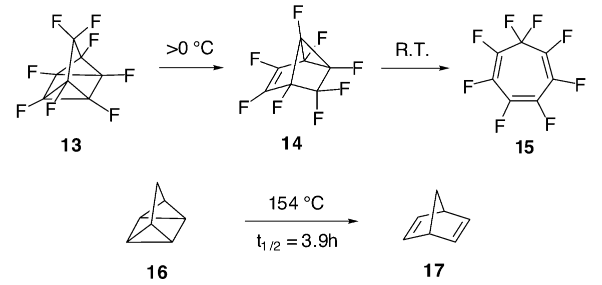
SCHEME 3



As another example, octafluoroquadricyclane (**13**) rearranges readily at temperatures above 0 °C to tricycloheptene **14**, which opens in turn at room temperature to octafluorotropilidine (**15**).[38] No octafluoronorbornadiene is observed. In sharp contrast, the parent quadricyclane (**16**) opens to norbornadiene (**17**) at a stately rate above 150 °C (Scheme 4).[39]

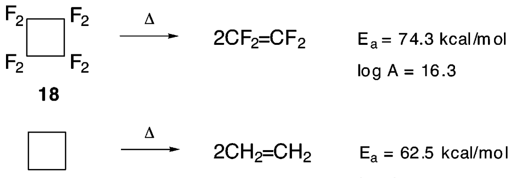
(c) Stabilization of Cyclobutanes. In contrast to hexafluorocyclopropane, octafluorocyclobutane (**18**) is believed to enjoy somewhat less ring strain than the parent hydrocarbon. Estimates of its strain energy have varied wildly,[40] but recent density functional calculations based on the (arguable) assumption that perfluorocyclohexane is strainless place the value at 5.9 kcal/mol less than that of the parent cyclobutane.[41] Attenuation of cyclobutane ring strain by fluorine has been rationalized

SCHEME 4

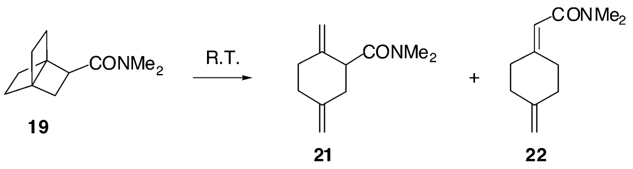


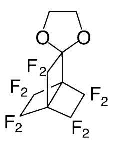
in terms of electron withdrawal from the ring. Unlike the situation in cyclopropane, part of cyclobutane's ring strain arises from repulsion between nonbonded carbons and a decrease in electron density in the ring could diminish this steric interaction.[40]

Whatever their ring strain may be, highly fluorinated cyclobutane rings are very robust by virtue of the enhanced strength of σ bonds between fluorinated carbons and the unfavorable change in hybridization required by fragmentation into two ethylenes. The best value of the activation energy for cycloreversion of octafluorocyclobutane (**18**) is 11.8 kcal/mol greater than that of cyclobutane itself.[42,43] Strengthening of the skeletal bonds as a result of electron withdrawal by the fluorines is reasonable in light of the Wolfsberg–Helmholtz approximation, which assumes that the bond integral for a pair of linked atoms is proportional to the average of their coulomb integrals.[44] Insofar as fluorines diminish electron density on a pair of bonded carbons, both their coulomb integrals and the C–C bond integral should be enhanced.



The contrast in stability between the highly strained [2.2.2]propellanes **19** and **20** is another manifestation of cyclobutane stabilization by fluorine substituents. Whereas **19** ring opens to dimethylenecyclohexanes **21** and **22** with a half-life of 28 min at 25 °C,[45] **20** is completely unchanged after 10 h at 100 °C.[46]

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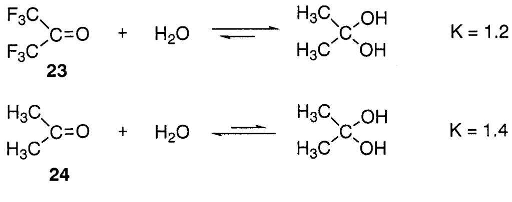
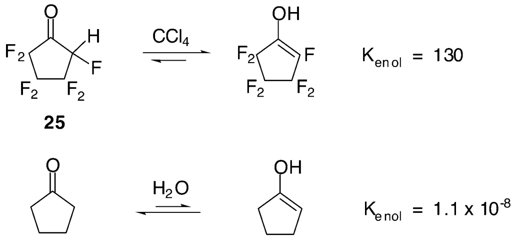
(d) Destabilization of the Carbonyl Group. Electron withdrawal by fluorines in the vicinity of a carbonyl group opposes the natural polarization that places substantial positive charge on the carbonyl carbon. This is reflected in the well-known tendency of highly fluorinated aldehydes and ketones to form stable hydrates and other tetrahedral adducts. In water at 25 °C, hydration of hexafluoroacetone (**23**) is favored over that of acetone (**24**) by a factor of a billion (Scheme 5).[47,48] Carbonyl destabilization is revealed as well in keto–enol equilibria. Typical perfluoroenols are strikingly stable kinetically, resisting ketonization in the presence of powerful acids,[49] and some cyclic ones are even thermodynamically stable relative to their ketones.[50] Perfluorocyclopenten-1-ol (**25**) is a case in point, and comparison with its hydrocarbon counterpart **26**[51] highlights the powerful effect of fluorine substitution (Scheme 6). K_{enol} for the fluorinated system would be much greater yet if it were measured in a Lewis basic solvent such as THF or acetonitrile because perfluoroenols are potent hydrogen-bond donors.[50]

SCHEME 5

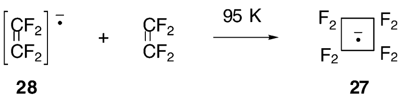


K = [hydrate]/[ketone]

SCHEME 6

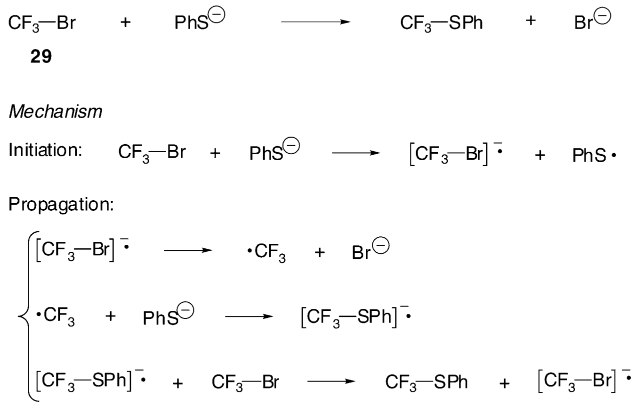


(e) Low-Lying σ* Orbitals. Electron transmission and inner-shell electron loss spectroscopies,[52] as well as electron attachment measurements,[53] have established that the LUMOs of perfluoroalkanes and -cycloalkanes lie several electron volts below those of their hydrocarbon counterparts, and in some cases, the radical anions are bound species. That of octafluorocyclobutane (**27**) has been generated with γ-radiation at 130 K in a neopentane matrix and characterized by ESR spectroscopy.[54] Interestingly, **27** has also been formed in 2-methyltetrahydrofuran at 95 K by cycloaddition of tetrafluoroethylene radical anion (**28**) to neutral tetrafluoroethylene.[55]

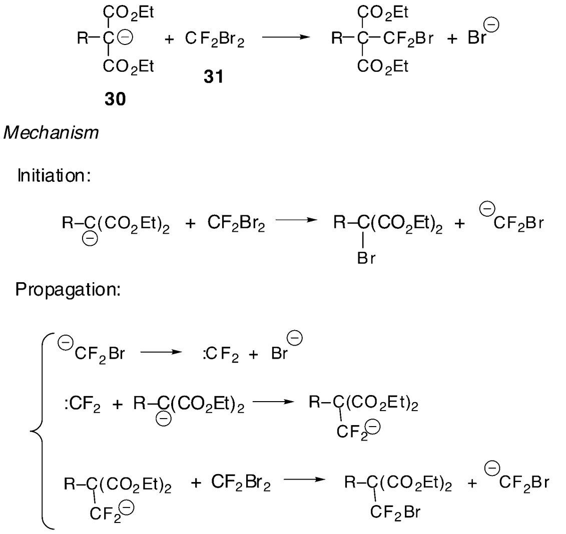


Low-lying LUMOs have a profound effect on the reactivity of many fluorocarbon derivatives. Substitution reactions on perfluoroalkyl halides illustrate this idea. Trifluoromethyl bromide (**29**), for example, does not undergo S_N2 reaction with nucleophiles like methyl bromide but often reacts via a radical ion chain mechanism ($S_{RN}1$) triggered by electron transfer into its LUMO (Scheme 7).[56] With various carbanions, nucleophilic substitution can also occur via a carbene-mediated ionic chain mechanism, as illustrated by the reaction of a malonate ion (**30**) with dibromodifluoromethane (**31**) (Scheme 8).[57,58]

SCHEME 7



SCHEME 8



Saturated fluorocarbons are amazingly robust, as they withstand high temperature and stoutly resist the onslaught of nearly all types of reagents. They have an "Achilles heel", though, for their LUMO makes them vulnerable to attack by strong electron donors. Anyone who has used a Teflon stir bar in a Birch reduction has learned that lesson. A more dramatic example is the transformation of perfluorodecalin (**32**) into octakis(phenylthio)naphthalene (**33**) by thiophenoxide ion.[59] This complex reaction is presumably initiated by electron transfer from thiophenoxide to the LUMO of perfluorodecalin, possibly photostimulated by ambient light.

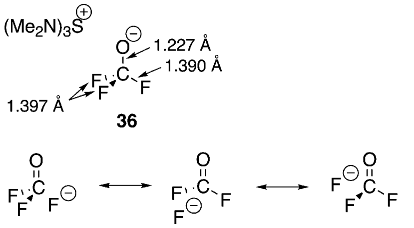
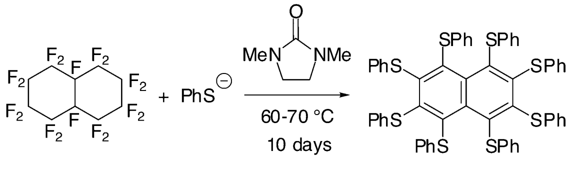
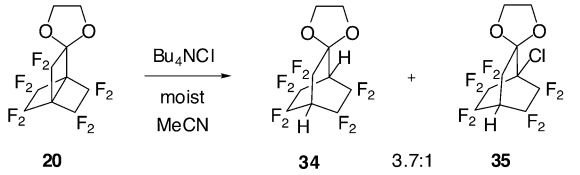


FIGURE 1. X-ray crystal structure and resonance forms for TAS trifluoromethoxide.[60]



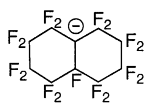
32 **33**

That propellane **20** has a low-lying LUMO is apparent from the finding that chloride ion reduces it rapidly to the dihydro compound **34** in moist acetonitrile at room temperature. Chloride ion also cleaves the same bond by nucleophilic attack, giving **35**, but this reaction channel is only about one-quarter as fast as the reduction.[46]



Low-lying σ^* orbitals make negative hyperconjugation an important phenomenon in many fluorocarbon derivatives, especially anions. The crystal structure of trifluoromethoxide ion as its tris(dimethylamino)sulfonium (TAS) salt (**36**) is a beautiful example.[60] The C−F bonds are 0.07−0.08 Å longer and the C−O bond 0.14−0.17 Å shorter than the corresponding bonds in CF_3OR molecules. In fact, the C−O bond length is only 0.06 Å longer than that in $CF_2{=}O$. This geometry testifies to the importance of charge donation from oxygen into C−F σ^* orbitals, represented in valence bond terms in Figure 1.

A variety of stable, saturated perfluorocarbanion salts such as **37** and **38** have been prepared and in many cases isolated.[61,62] They owe their stability to negative hyperconjugation, together with inductive and field effects of fluorine. To forestall elimination of fluoride from the anions, it is necessary for the positive charge of the counterion to be diffuse or hidden; hence the choice of cesium or TAS counterions. The finding that cyclopentadiene **39** is at least 18 orders of magnitude more acidic than the parent cyclopentadiene is further testimony to fluorine's ability to stabilize carbanions.[63]



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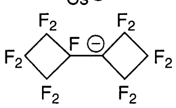

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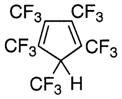

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Low-lying C−F σ^* orbitals play a role in a variety of other phenomena, e.g., conspiring with Bent's rule to weaken the π bond in highly fluorinated alkenes, to cause them to add to dienes in [2 + 2] instead of Diels−Alder fashion, and to lower rotational barriers in fluorinated allyl radicals.[32]

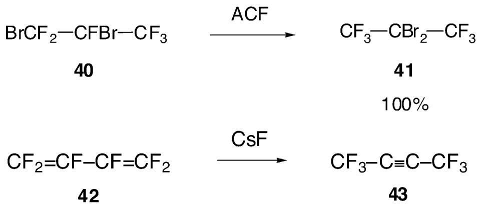
TABLE 1. C−F Bond Lengths, Bond Dissociation Energies,[a] and Atomic Charges[b] for Fluoromethanes

compd	r_{C-F} (Å)	BDE (kcal/mol)	q_C	q_F
CH_3F	1.385	109.9 ± 1	0.01	−0.23
CH_2F_2	1.357	119.5	0.40	−0.23
CHF_3	1.332	127.5	0.56	−0.21
CF_4	1.319	130.5 ± 3	0.72	−0.18

[a] Reference 14. [b] MKS electrostatic potential-derived charges at the B3LYP/6-311G* level of theory.[65,66]

(f) The *gem*-Difluoro Effect. Carbon−fluorine bonds become considerably stronger and shorter the more fluorine atoms there are bound to a carbon.[64] Calculations show that successive substitution of fluorine for hydrogen in methane results in progressively greater positive charge on the carbon while negative charges on fluorine are similar throughout the series (Table 1). Thus, the coulombic attraction of carbon for fluorine increases monotonically with the number of fluorines. Negative hyperconjugation involving fluorine lone pair donation into C−F σ* orbitals may also play a role in the mutual bond-strengthening phenomenon.[14] This effect is illustrated by the facile and quantitative aluminum chlorofluoride (ACF)-catalyzed rearrangement of halopropane **40** to its isomer **41**.[67] Another example is the highly exothermic cesium fluoride-catalyzed isomerization of hexafluorobutadiene (**42**) to hexafluoro-2-butyne (**43**),[68] but of course Bent's rule is responsible for a part of the driving force behind this transformation (Scheme 9). In contrast to fluorine, progressive substitution of any of the other halogens for the hydrogens in methane results in ever weaker C−X bonds.[14]

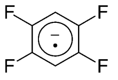
SCHEME 9



Fluorine as Schizoid Substituent. Although the Hammett substituent constant σ_p for fluorine is positive (0.15), the negative values of its Brown σ^+ (−0.08)[69] and Taft σ_R^0 (−0.31) constants[70] serve as a reminder that its ability to withdraw electrons through its σ bond to carbon can be counterbalanced by π-electron donation from a lone pair into a carbon p orbital. These countervailing tendencies are revealed with special clarity in the "perfluoro effect"; namely, the marked lowering of the energies of σ-type orbitals accompanied by little change in π-type orbital energies when fluorines are substituted on a π system.[71,72] Mixing of fluorine lone pair orbitals with adjacent π and π* orbitals tends to raise their energy, thus compensating for σ electron withdrawal. A comparison of ethylene and tetrafluoroethylene ionization potentials makes the point (Table 2). Their first ionization potentials, which involve π electrons, are virtually identical, but the second IPs differ by more than 3 eV because a σ electron is ejected. Another illustration of the selective lowering of σ-type orbitals is provided by the 1,2,4,5-tetrafluoro- (**44**), pentafluoro- (**45**), and hexafluorobenzene radical anions (**46**).[70] Whereas the SOMO of other benzene radical anions is a π* orbital, the ESR spectra of these highly fluorinated radical ions show clearly that the SOMO is a σ* orbital.

TABLE 2. Vertical Ionization Potentials of Ethylenes (eV)[71]

ethylene	first IP(π)	second IP(σ)
C_2H_4	10.6	12.85
C_2F_4	10.52	15.95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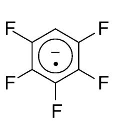
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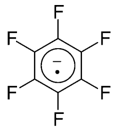
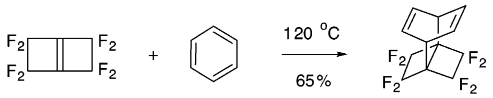
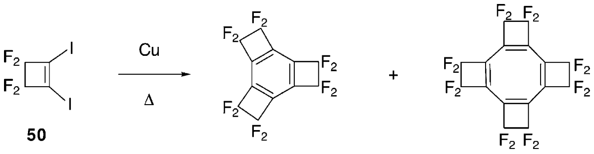

46

Unlike fluoro, perfluoroalkyl substituents have only the ability to withdraw electrons, so they drop the energy of π- as well as σ-type orbitals. Assisted by its low-lying π* LUMO, strained alkene **47** cycloadds to benzene to yield **48**.[74] To date it is the only olefinic dienophile to undergo the Diels−Alder reaction with benzene. For comparison, the hydrocarbon counterpart of **47** dimerizes and polymerizes rapidly at subambient temperatures.[75]



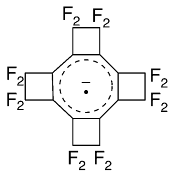
47 **48**

Deep red cyclooctatetraene **49** provides a dramatic example of the lowering of π* orbitals by perfluoroalkyl substituents. Heating 1,2-diiodotetrafluorocyclobutene (**50**) with copper yields both the benzene **51** and tetraene **49**.[76,77] Unlike the tub-shaped parent cyclooctatetraene, **49** is planar,[78] and calculations indicate that the eight-membered ring sustains a robust paramagnetic ring current as expected for an antiaromatic molecule.[79] Its two reversible reduction potentials lie at 0.79 and 0.14 V vs SCE, the first of which is >2.3 eV positive of cyclooctatetraene's.[80] Contact of a DMF solution of tetraene **49** with mercury is sufficient to generate radical anion **52**, which is stable in air. From the electrochemical data and spectra of its charge-transfer complexes with methylated benzenes and naphthalenes, the electron affinity of **49** has been estimated at 3.4 ± 0.2 eV, one of the highest values reported for a neutral organic molecule.[81] Dissolved in excess methanol, the tetraene forms an intensely blue charge transfer complex. The color quickly fades to yellow-brown, and bright yellow tetramethoxy derivative **53** is obtained.[76]



50 **51** **49**

Fluorine's schizoid character appears again in the gas-phase stability order of cations of the type $[CH_nF_{3-n}]^+$,



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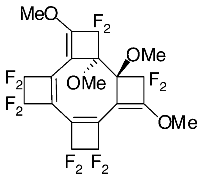
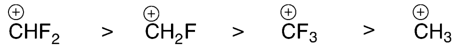


53

as determined by hydride ion affinities and adiabatic ionization potentials of the corresponding free radicals:[82]

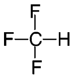


$\overset{\oplus}{C}HF_2 > \overset{\oplus}{C}H_2F > \overset{\oplus}{C}F_3 > \overset{\oplus}{C}H_3$

54

The difluoromethyl cation (**54**) represents the best compromise between destabilization of the cation by fluorine's withdrawal of σ electrons and stabilization by π electron donation.

The influence of fluorine substitution on acidity provides some interesting contrasts. As exemplified above, fluorines β to a carbanionic center invariably enhance acidity, but α substitution can either increase or diminish it. When the demand for stabilization of negative charge is great the enhancement can be dramatic, as illustrated by comparison of methane ($pK_a = 52-62$)[83] with fluoroform (**55**, $pK_a = 27$).[84] A delocalized carbanion can actually be destabilized by fluorine substitution, however. 9-Fluorofluorene (**56**) is less acidic than fluorene,[85] and fluorodinitromethane (**57**, $pK_a = 7.70$) is more than 4 orders of magnitude less acidic than dinitromethane ($pK_a = 3.57$).[86] Here, lone pair$-\pi$ repulsion in the conjugate base outweighs the charge-stabilizing effect of σ electron withdrawal.



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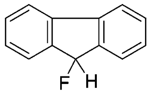

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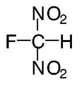
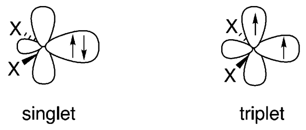


57

Whether α-fluorine increases or decreases acidity depends greatly upon the geometry of the anion. Lone pair$-\pi$ repulsion is minimized in a pyramidal ion like trifluoromethide,[31] and the p-rich hybridization of the C$-$F bond(s) facilitates electron withdrawal by fluorine. Neither factor is present in planar ions such as the conjugate bases of **56** and **57**.

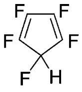
This generalization relating acidity to geometry is not infallible, however. 1,2,3,4,5-Pentafluorocyclopentadiene (**58**) is somewhat more acidic than cyclopentadiene itself ($pK_a = 13.8-15.5$ vs 15.5),[87] indicating that electron withdrawal in the conjugate base (**59**) is more significant than lone pair$-\pi$ repulsion. Anion **59** should surely be planar if the conjugate base of **56** is planar, for stabilization of the negative charge by a cyclopentadiene ring is considerably greater than by its dibenzo analogue ($pK_a = 23$).[88]

Hexafluorotropone (**60**) and its protonated form (**61**) are a conjugate acid$-$base pair of a different charge type. In this case, electron withdrawal destabilizes and lone pair donation stabilizes the ionic form. The dominance of electron withdrawal is much greater here than in anion **59**, for **61** is ~100 000 times more acidic[89] than tropone's conjugate acid (pK_a -6.2 ± 0.5 vs -1.02).[90,91] Of course, the opposing influences operate on both members of the conjugate acid$-$base pairs **58**$-$**59** and **60**$-$**61**, but in both pairs their effect should be greater on the charged species.



	:CF_2	:CCl_2	:CBr_2	:CH_2
ΔE_{ST}	-56.3 (-56.7)	-19.7	-15.6	+9.5 (+9.1)

FIGURE 2. Electronic configurations and calculated singlet$-$triplet gaps (kcal/mol) for carbenes.[94] Values in parentheses are experimental.



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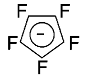

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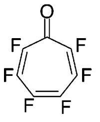

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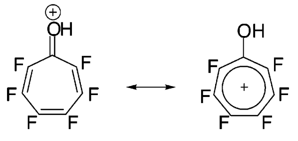
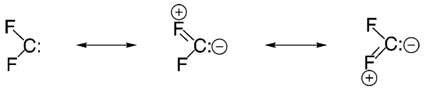


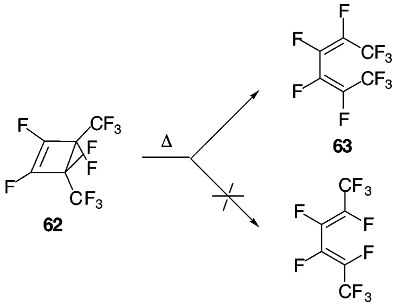
61

Like other dihalocarbenes, difluorocarbene (**11**) is electrophilic in its reactions with alkenes, but it is the most stable and least electrophilic dihalocarbene by virtue of lone pair donation to the vacant p orbital on the carbon.[22] The better match in p orbital size (and thus better overlap) between carbon and fluorine as compared with the other halogens is a key difference. At ordinary temperatures, difluorocarbene is also the most selective of the dihalocarbenes.[92] However, at elevated temperatures the selectivity order reverses, indicating a significant role for entropic effects in determining selectivity.[93] Among the dihalocarbenes, difluorocarbene has by far the largest singlet$-$triplet gap.[94,95] Here σ electron withdrawal and π donation work in synergy, not opposition. Electron withdrawal enhances the positive charge on carbon, thereby stabilizing the singlet state both by lowering the energy of the carbon lone pair orbital and by enhancing π donation into the carbon p orbital. Figure 2 shows the singlet and triplet configurations for carbenes and the singlet$-$triplet gaps for dihalocarbenes. That of methylene itself, a ground-state triplet, is included for reference.

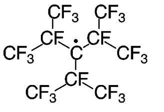


11

A final illustration of the importance of fluorine's lone pairs is provided by the counterintuitive thermal ring opening of *trans*-perfluoro-3,4-dimethylcyclobutene (**62**).[96,97] Orbital topology-allowed conrotatory pathways lead to both dienes **63** and **64**, but for steric reasons one might expect **62** to be the sole product. In fact, the cleanly torquoselective transformation gives **63**, because fluorine lone pairs both raise the energy of the transition state leading to **64** and stabilize that leading to **63**.[98] The enthalpy difference between the two dienes is a mere 1.2 kcal/mol, but the difference in activation energy for the two pathways is an astonishing 19.2 kcal/mol, and the ratio of rates at 111.5 °C is 1.9×10^9.


62 **63** **64**

The Importance of Steric Effects. The common notion that fluorine and hydrogen are virtually equal in size is a misconception, as fluorine's van der Waals radius is >20% larger (1.47 vs 1.20 Å; cf. oxygen, 1.52 Å).[12] Its effective size in a fluorocarbon is greater yet, as C−F bond lengths are about 20% longer than C−H. Thus, a CF_3 group is effectively larger than an isopropyl group; their *A* values are 2.4−2.5 and 2.21 kcal/mol[99] and their modified Taft steric values (E_s^0) are −2.40 and −1.71, respectively.[100] The perfluorotriisopropylmethyl radical (**65**) is an example *par excellence* of fluorine steric effects. This free radical is inert not only to oxygen but also to elemental fluorine.[101] Cyclophanes **66** offer another striking illustration of a fluorine steric effect. Flipping of the meta-substituted ring occurs $>10^{11}$ times faster at 25 °C when X = H than when X = F.[102]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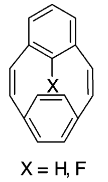
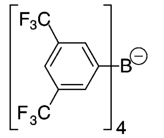

X = H, F

66


67

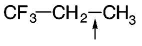
Fluorine plays a key role in many of the most weakly coordinating anions, as exemplified by BAr_F (**67**).[103] Ions such as **67** serve as counterions in active catalysts for olefin polymerization and other industrial processes. By virtue of their electron withdrawal, the eight trifluoromethyl groups in BAr_F make the ion far more resistant to oxidative or electrophilic attack than the unsubstituted tetraphenylborate ion, and they also provide steric shielding of the negative charge.

The "perfluoroalkyl effect" is defined as the stabilizing influence that perfluoroalkyl groups exert on strained carbon skeletons.[22,104] Perfluoroalkyl substituents can enhance both kinetic and thermodynamic stability. The origin of the effect is certainly steric in part, as bulky perfluoroalkyl groups can both shield a carbon skeleton from external attack and impede its rearrangement along a pathway that entails an increase in nonbonded repulsion among the substituents.

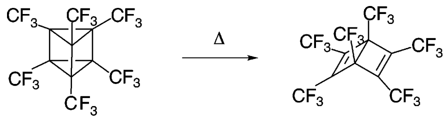
Surely the strengthening of C−C bonds by fluorine substitution also contributes importantly to the perfluoroalkyl effect. That fluorinated carbons form particularly strong C−C bonds has been commented upon, but the strengthening effect can extend beyond to an adjacent C−C bond. Thus, perfluoroalkyl-substituted carbons, not just fluorinated ones, form especially robust C−C bonds. If the reasonable approximation is made that the C−C bond in 1,1,1-trifluoroethane (**68**) and the corresponding bond in 1,1,1-trifluoropropane (**69**) are equal in strength, it turns out that the $C_2{-}C_3$ bond in **69** is ~6.5 kcal/mol stronger than the C−C bond in ethane.[105−107] The much greater thermal stability of perfluorohexamethylprismane (**70**) ($t_{1/2}$ = 29 h at 170 °C)[108] as compared with the parent prismane ($t_{1/2}$ = 11 h at 90 °C)[109] supports the conclusion that perfluoroalkyl substituents strengthen C−C bonds, for steric effects should not come into play in the formation of the Dewar isomer (**71**).

$CF_3{-}CH_3$

68


$CF_3{-}CH_2{-}CH_3$

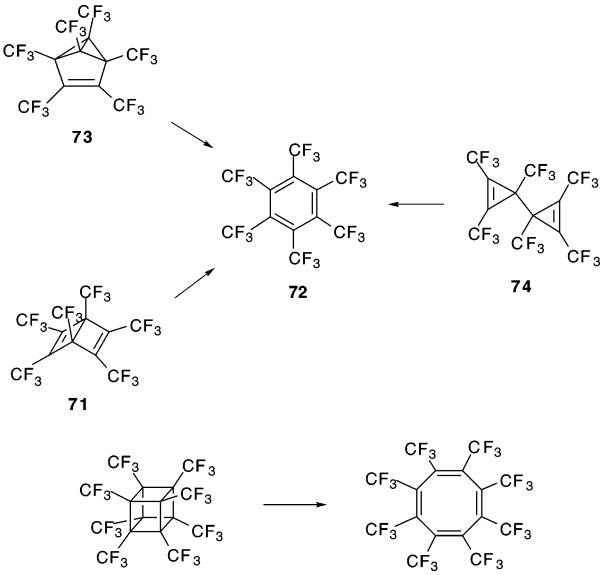
69


Δ

70 **71**

Further examples of molecules that illustrate the perfluoroalkyl effect are shown in Scheme 10. Steric effects may be expected to play a prominent role in the reactions leading to the crowded benzene **72**. Aromatization of benzvalene **73** has a half-life of 9 h and Dewar benzene **71** a half-life of 135 h at 170 °C;[108] the unsubstituted hydrocarbons happen to have the same half-life at 61.2 °C, 65 min.[110,111] For the aromatization of bicyclopropenyl **74**, $t_{1/2} \geq 2$ h at 360 °C,[112] but the parent hydrocarbon polymerizes at −10 °C.[113] Steric effects are probably less important in the ring opening of perfluorooctamethylcubane (**75**) to the tub-shaped perfluorocy-

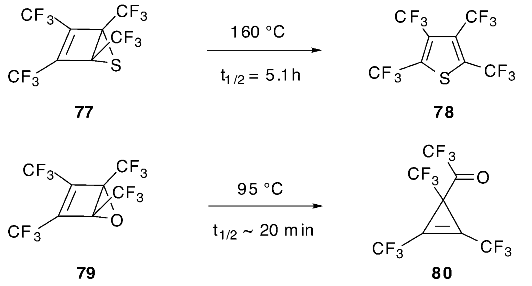
SCHEME 10

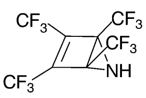

73 **72** **74** **71**

clooctatetraene (**76**),[114] which may explain why the reaction is only roughly 500 times slower at 300 °C than that of cubane itself.[115]

As illustrated by bicyclopropenyl **74**, the perfluoroalkyl effect makes it possible to synthesize and conveniently study highly strained molecules, the hydrocarbon parents of which are extremely labile or inaccessible. The Dewar heterocycles in Scheme 11 are further examples. Perfluorotetramethyl Dewar thiophene (**77**) aromatizes to the thiophene (**78**) with a half-life of 5.1 h at 160 °C.[116] By contrast, the parent Dewar thiophene is a highly labile molecule that has been observed only in cryogenic matrixes.[117] Perfluorotetramethyl Dewar furan (**79**) rearranges readily to cyclopropenyl ketone **80** at 95 °C,[118] but the parent Dewar furan rearranges in analogous fashion even at −80 °C.[119] Hydrocarbon counterparts of the stable, strained heterocycles **81**−**83** remain unknown.[120−122]

SCHEME 11





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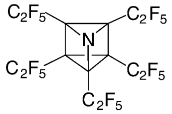

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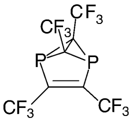
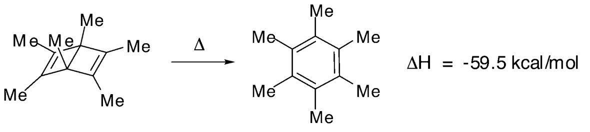


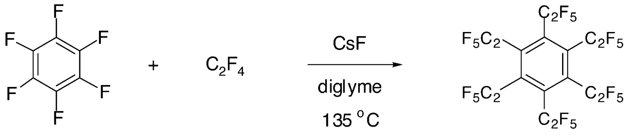
83

Release of a great deal of ring strain, together with the formation of an aromatic ring, make the ring opening of a typical Dewar benzene extremely exothermic. For the transformation of hexamethyl Dewar benzene (**84**) into hexamethylbenzene (**85**), $\Delta H = -59.5$ kcal/mol.[123]

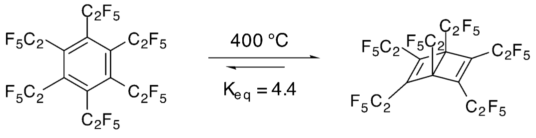


84 **85**

Perhaps the most dramatic example of the perfluoroalkyl effect is provided by perfluorohexaethyl Dewar benzene (**86**). The corresponding benzene (**87**) was synthesized by heating hexafluorobenzene (**88**) with tetrafluoroethylene and cesium fluoride.[124] Proceeding as it does via attack of a nucleophile (pentafluorethyl anion) on an electron-deficient aromatic ring with loss of an anion (fluoride), this transformation is the "polar opposite" of the Friedel−Crafts reaction. When perfluorohexaethyl benzene (**87**) vapor is subjected to low-pressure pyrolysis at 400 °C, it is transformed into its Dewar isomer **86**. This very remarkable reaction occurs because it is 50 kcal/mol less endothermic than the formation of **84** from **85** and entails a rather large increase in entropy ($\Delta H° = 9.00$ kcal/mol and $\Delta S° = 16.3$ cal/K/mol; $K_{eq} = 4.4$ at 400 °C).[125,126] The extreme crowding of the bulky pentafluoroethyl groups in the benzene is relieved when the molecule folds up into the roof-shaped Dewar structure, with an accompanying increase in degrees of freedom.



88 **87**



87 **86**

Afterword

Widely ignored in organic textbooks and courses, fluorocarbon chemistry has nonetheless contributed much to organic chemistry as a whole. It has become a gold mine of interesting structures, unusual transformations, fresh chemical insights, and products that enrich our culture. Because fluorine can take the place of hydrogen in virtually every type of organic structure, fluorocarbon chemistry is still in an early stage of development. Surely, fundamental research in the field will encounter many more surprises, and the catalog of uses for fluorocarbons will continue to expand.

Acknowledgment. The author expresses his heartfelt thanks to the able and dedicated co-workers whose names appear with his in some of the references. Thanks are also due the National Science Foundation for generous financial support and to Prof. Joel Liebman for an incisive review of the manuscript. D.M.L. apologizes to all those whose important contributions to fluorocarbon chemistry are not included in the above account, which tends to reflect his personal interests. Cover photo courtesy of Van Pelt Photographer.

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