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GENERAL REMARKS ON STRUCTURAL, PHYSICAL, AND CHEMICAL PROPERTIES OF FLUORINATED COMPOUNDS

This chapter deals with modifications of the physical and chemical properties of an organic molecule, which are induced by the replacement of hydrogen atoms by fluorines. These changes in the physicochemical properties play an important role in the behavior of the molecule when it is put into a biological environment.

Compounds with a few fluorine atoms (arbitrarily, from a single F to a C_2F_5 group) are called "lightly fluorinated" molecules and are the focus of bioorganic and medicinal chemistry. In these compounds, the presence of fluorine atoms severely modifies their chemical reactivity, but it has only a modest influence on their physical properties. In contrast, the physical characteristics of "highly fluorinated" (perfluorinated) molecules are strongly affected with regard to their "hydrogenated analogues." Despite their important applications in the biomedicinal field (e.g., biocompatible materials and polymers, surfactants, gas carriers), such compounds are only marginally considered in this book. However, some physicochemical aspects of perfluorinated molecules are introduced in this chapter to better comprehend the properties of lightly fluorinated molecules.

Bioorganic and Medicinal Chemistry of Fluorine, by Jean-Pierre Bégué and Danièle Bonnet-Delpon

1.1 STRUCTURAL EFFECTS

Most of the effects induced by the presence of fluorine atoms in a molecule come from both the structure and the fundamental atomic properties of the fluorine atom (Table 1.1). Because of its electronic structure $1s^2\ 2s^2\ 2p^5$, fluorine has very specific properties, as indicated by the extreme values of the atomic parameters given in Table 1.1.[1–3]

The very high ionization potential[1] and the low polarizability[2] of the fluorine atom imply that fluorinated compounds have only weak intermolecular interactions. Thus, perfluoroalkylated compounds have very weak surface energies, dielectric constants, and refracting indexes.

The very high electronegativity of fluorine[3], its small size, the excellent overlap of the 2s or 2p orbitals with the corresponding orbitals of carbon, and the presence of three lone pairs of electrons mean that a fluorine atom borne by a carbon atom is always, on an inductive level, an electron-withdrawing substituent. Bonds are always strongly polarized from the sp^3 carbon (δ^+) to the fluorine (δ^-). These features associated with the low polarizability of the fluorine atom, implies that the C—F bond has a relatively important ionic character and a stronger energy than the bond between carbon and the other halogens.

The dipolar nature of the C—F bond in lightly fluorinated molecules gives a polar character to these molecules[4]. Consequently, their physico-chemical properties can be quite different from those of hydrocarbon compounds and from those of the corresponding perfluorinated compounds.

In brief, the effects of fluorination on the molecular properties stem from the combination of the atomic properties of the fluorine atom: strong electronegativity, small size, excellent overlap of the 2s or 2p orbitals with the corresponding orbitals of carbon, and very strong bond with carbon.

Table 1.1 Atomic parameters of fluorine atom[1,2,3]

Atom	Ionization Potential (kcal/mol)	Electron Affinity (kcal/mol)	Atom Polarizability (Å^3)	Van Der Waals Radii (Å)	Pauling's Electronegativity χ_p
H	313.6	17.7	0.667	1.20	2.20
F	401.8	79.5	0.557	1.47	3.98
Cl	299.0	83.3	2.18	1.75	3.16
Br	272.4	72.6	3.05	1.85	2.96
I	241.2	70.6	4.7	1.98	2.66
C	240.5	29.0	1.76	1.70	2.55
N	335.1	− 6.2	1.10	1.55	3.04
O	314.0	33.8	0.82	1.52	3.44

1.2 PHYSICAL PROPERTIES

1.2.1 Boiling Point

Highly fluorinated molecules have a nonpolar character and an extremely low polarizability, inducing only weak intra- and intermolecular interactions. As a consequence, perfluorocarbons behave almost like ideal liquids: they are very compressible and have very high vapor pressure. For example, the physical properties of perfluorohexane, heptafluorohexane, and hexane are reported in Table 1.2.[1] The effect of the polar character of the hemifluorinated compound (heptafluorohexane) on the dielectric constant value is remarkable.

Except in some rare cases, the boiling points[1] of perfluorinated compounds, functionalized or not, are always lower than those of their hydrogenated analogues Table 1.3). Conversely to what is observed with the halogenated analogues, branching has only a minor effect on the boiling point. Indeed, perfluoroisopentane has a boiling point (bp) close to that of *n*-fluoropentane, while the bp of isopentane is much less than that of *n*-pentane.

The bp of a perfluoroalkane is only 25–30 °C higher than that of the rare gas with the same molecular weight. This illustrates the "perfect" fluid character of these compounds, resulting from the low intermolecular interactions.

While the boiling points of chloro- and bromomethanes always increase according to the number of halogen atoms, this correlation does not exist in the case of fluoromethanes. The bp increases from CH_4 to CH_2F_2 and then decreases until CF_4 (Table 1.4).[1] Indeed, a parallelism exists between boiling points and dipolar moments. A partially fluorinated compound will exhibit nonnegligible intermolecular interactions according to the importance of the dipolar moment (Table 1.5).[1]

Fluorinated compounds, even the lightly fluorinated ones, have a high vapor pressure with respect to those of their hydrogenated analogues. Fluorinated molecules are often volatile, even when the boiling point is relatively high. Consequently, careful

Table 1.2 Comparative physical properties of *n*-hexanes (perfluorinated, hemifluorinated, and non fluorinated hexanes)[1]

Property	C_6F_{14}	$CF_3(CF_2)_2(CH_2)_3H$	C_6H_{14}
Boiling point (°C)	57	64	69
Heat of vaporization ΔH_v (kcal/mol)	6.7	7.9	6.9
Critical temperature T_c (°C)	174	200	235
Density, d^{25} (g·cm^3)	1.672	1.265	0.655
Viscosity, η^{25} (cP)	0.66	0.48	0.29
Surface tension, γ^{25} (dyn/cm^{-2})	11.4	14.3	17.9
Compressibility, β (10^{-6} atm^{-1})	254	198	150
Refractive index, $n_D{}^{25}$	1.252	1.292	1.372
Dielectric constant, ε	1.69	5.99	1.89

Table 1.3 Effect of fluorination on boiling points[1]

bp (°C)	"F"	29.3	30.1	29.5
	"H"	36.1	27.9	9.5
bp (°C)	"F"	144		53
	"H"	174		81
bp (°C)	"F"	56		54
	"H"	90		69
bp (°C)	"F"	111		98
	"H"	142		122
bp (°C)	"F"	75		72
	"H"	143.5		123.7
bp (°C)	"F"	81		
	"H"	82		

	bp (°C)
CF_3-COOH	78
CH_3-COOH	118
CCl_3-CF_3	43
CCl_3-CH_3	75

	bp (°C)
F	85
CF_3	105
	112

Table 1.4 Boiling points of halomethanes[1]

Compound	bp (°C)	Compound	bp (°C)	Compound	bp (°C)
CH_4	−161	CH_4	−161	CH_4	−161
CH_3F	−78.6	CH_3Cl	−24.2	CH_3Br	3.6
CH_2F_2	−51.6	CH_2Cl_2	40.1	CH_2Br_2	98.2
CHF_3	−82.2	$CHCl_3$	61.3	$CHBr_3$	149.5
CF_4	−128	CCl_4	98.2	CBr_4	189.5

Table 1.5 Dipole moments (μ) and boiling points of fluoromethanes and fluoroethanes[1]

Parameter	CH_4	CH_3F	CH_2F_2	CHF_3	CF_4	CH_3CH_3	CH_3CF_3	CF_3CF_3
μ (D)	0	1.85	1.97	1.65	0	0	2.32	0
bp (°C)	−161	−78	−52	−82	−128	−89	−47	−78

handling of fluorinated compounds is required during isolation to avoid possible accidental inhalation of these toxic substances.

1.2.2 Surface Tension and Activity

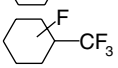
The surface tension γ measures the molecular forces that oppose the extension of the area of a liquid dropped on a surface. A perfluoroalkane always has a surface tension lower than that of the corresponding alkane (Table 1.6).[1,5,6] Perfluoroalkanes are able to wet any kind of surface. Perfluoroamines and -ethers also have low surface tensions (15–16 dyn/cm^2).[1]

Fluorinated surfactants lower the surface tension of water more strongly than their nonfluorinated analogues. Fluorinated surfactants reduce the superficial pressure of water from 72 to 15–20 dyn/cm^2 while a nonfluorinated agent only decreases the value to 25–35 dyn/cm^2 (Table 1.6).

Perfluorocarbons bearing a polar hydrophilic head are very active surfactants.[4b] Indeed, the presence of fluorine atoms strongly lowers the critical micelle concentration (CMC) of an amphiphilic compound. Moreover, fluorination generally has important effects on micellization phenomena, especially on the size and shape of formed micelles.

Hemifluorinated compounds $F(CF_2)_m—(CH_2)_nH$ often have a particular behavior. Because of their strong polarity, these compounds are able to form micelles in fluorocarbon as well as in hydrocarbon media.[5]

Table 1.6 Surface tension γ (dyn·/cm^2) and CMC (mM) values of perfluorinated compounds[1,5,6]

Compound	γ (dyn/cm^2)	Compound	γ (dyn/cm^2)	CMC (mM)
$CH_3—(CH_2)_4—CH_3$	17.9	$CF_3—(CF_2)_6—CO_2H$	15.2	2.8
$CH_3—(CH_2)_4—CH_2F$	19.8	$CHF_2—(CF_2)_6—CO_2H$	21.8	
$CH_3—(CH_2)_4—CF_3$	17.9	$CF_3—(CF_2)_7—CO_2NH_4$	14.8	6.7
$CF_3—(CF_2)_4—CHF_2$	12.6	$CF_3[OCF_2CF(CF_3)]OCF_2—CO_2NH_4$	17.5	7.0
$CF_3—(CF_2)_4—CF_3$	11.4	$C_8F_{17}CH_2[(C_2H_4O)_3CH_3]_2$	19	0.012
	23.3			
	15.4			

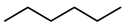
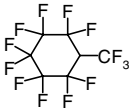
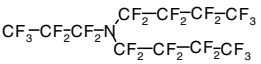
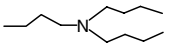
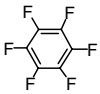
1.2.3 Polarity-Solubility

Paradoxically, fluorinated compounds are found among the least polar compounds (perfluorocarbons) as well as among the most polar ones (fluorinated alcohols), according to the empirical scale of Middleton (P_s). Some representative examples of fluorinated solvents and related hydrogenated compounds are given in Table 1.7.[7] Perfluorocarbon compounds, almost apolar, are nonmiscible with both water and hydrocarbon compounds. They are able to dissolve only compounds with very low cohesive energies, such as gases and highly fluorinated molecules.

This very specific ability of perfluorinated compounds to dissolve gases has found an application in oxygen carrier liquids (short-time blood substitutes). A perfluorocarbon dissolves three times more oxygen than the corresponding hydrocarbon, and ten times more than water. This property can be explained by the presence of large cavities in the liquid and by the weak intermolecular interactions of the medium, and not by specific interactions.

Replacing some of the fluorine atoms by hydrogen atoms increases the polarity.[4a] Hydrofluorocarbons are more polar than the corresponding perfluorocarbons. They can also be even more polar than their hydrocarbon analogues.[8]

Table 1.7 Middleton polarity index (P_s) of fluorinated and nonfluorinated compounds[7]

Compound	P_s	Compound	P_s
CF_3–CF_2–CF_2–CF_2–CF_2–CF_3	0.00		2.56
	0.46		3.34
	0.68		3.93
CF_2Cl—$CFCl_2$	3.22	$CHCl_2$—$CHCl_2$	9.23
$CFCl_3$	3.72	$CHCl_3$	4.64
CF_3Cl_3	3.22	CH_3Cl_3	7.03
	4.53		6.96
CF_3—COOEt	6.00	CH_3—COOEt	6.96
	7.86		8.94
CF_3—CH_2OH	10.2	CH_3—CH_2OH	8
CF_3—CHOH—CF_3	11.1	CH_3—CHOH—CH_3	7.85
		H—COOH/H_2O_2 50%	10.64

1.2.4 Lipophilicity

Lipophilicity is of prime importance in the design of drugs. Indeed, it controls many parameters such as absorption, biological barrier passage (and consequently transport into organs and cells), and also interaction with the macromolecular target (cf. Chapter 3).

In the case of fluorinated molecules, it is important to differentiate the lipophilic character from the hydrophobic character. Both these characters are in tune for nonfluorinated molecules, but they diverge when the number of fluorine atoms increases in a molecule. It is generally recognized that fluorination induces an increase in the lipophilicity. However, this has only been demonstrated for aromatic compounds, and more specifically when fluorine atoms are in the α position of atoms, or groups bearing π electrons (Table 1.8).[4a] Conversely, the presence of fluorine atoms in an aliphatic molecule provokes a decrease in the lipophilicity, while it can enhance the hydrophobicity. This phenomenon is so important that highly fluorinated molecules are not soluble in organic solvents or in water and constitute a third phase.

The confusion between these two characteristics is common in medicinal chemistry. It comes from the usual empirical measurement of the lipophilicity, which is the logarithm of the partition coefficient between 1-octanol and water (log P). This parameter gives a representative overview of a compound absorbed by a lipidic membrane, an essential datum in medicinal chemistry. It is often considered that the higher the log P value is, the more lipophilic the compound is. Actually, the log P value is only a measurement of relative solubility. Considering that the solubility of a fluorinated substance decreases more in water than in octanol, this measurement leads one to think that fluorinated compounds are more "lipophilic." Actually, this represents the relative lack of affinity of fluorinated compounds for both phases.

Table 1.8 shows some Hansch–Leo π values for aromatic compounds ($\pi = \log P_{C_6H_5X} - \log P_{C_6H_5X}$ for substituted benzenes).[9] Note that the effects of fluorination can be relatively important (e.g., C_6H_5—SO_2CF_3 is ~150 times more lipophilic than C_6H_5—SO_2CH_3).

Table 1.8 Hydrophobic Hansch–Leo π values (log $P_{C_6H_5X}$—log $P_{C_6H_6}$)[9]

Substituent	π (log P_X – log P_H)	Substituent	π (log P_X – log P_H)
F	0.14	SCH_3	0.61
Cl	0.71	SCF_3	1.44
NO_2	–0.27	SO_2CH_3	–1.63
CH_3	0.56	SO_2CF_3	0.55
CF_3	0.88	$NHSO_2CH_3$	–1.18
CH_3CH_2	1.02	$NHSO_2CF_3$	0.92
CF_3CF_2	1.89	CH_3–C=O	0.02
OH	–0.67	CF_3—C=O	0.55
OCH_3	–0.02	CH_3—CO—NH—	–1.27
OCF_3	1.04	CF_3—CO—NH—	0.08

Table 1.9 Octanol–water partition (log *P*) of aliphatic compounds[9,10]

Compound	log *P*	Compound	log *P*	
CH_3—CH_3	1.81	CH_3—$CHCl_2$	1.78	
		CH_3CHF_2	0.75	
$CH_3(CH_2)_3CH_3$	3.11	$CH_3(CH_2)_3CH_2F$	2.33	
Compound	log *P*	Compound	log *P*	Δlog *P*
CH_3CH_2OH	−0.32	CF_3CH_2OH	0.36	0.68
CH_3—CH_2CH_2OH	0.34	CF_3—CH_2CH_2OH	0.39	0.05
CH_3—$CH_2CH_2CH_2OH$	0.88	CF_3—$CH_2CH_2CH_2OH$	0.90	0.02
CH_3-$CH_2CH_2CH_2CH_2OH$	1.40	CF_3—$CH_2CH_2CH_2CH_2OH$	1.15	−0.04
CH_3—$CH_2CH_2CH_2CH_2CH_2OH$	1.64	CF_3—$CH_2CH_2CH_2CH_2CH_2OH$	1.36	−0.28

For aliphatic molecules, the data are rarer. Nevertheless, partial fluorination lowers the log *P* value, conversely to aromatic molecules. For alcohols, the situation is more complex: the log *P* value is dependent on the position of fluorine atoms and on the chain length (Table 1.9).[9, 10]

The log *P* value strongly depends on the solvent system chosen as a reference (e.g., cyclohexane/water versus octanol/water), since associations and hydrogen bonds are highly depending on the nature of the solvent. This is highlighted in the case of functionalized fluorinated molecules, where fluorination strongly modifies hydrogen bonding (Table 1.10).[9]

Trifluoromethyl ketones, which are enzyme inhibitors, constitute an interesting example: the log *P* value depends on the equilibrium between hydrate, hemiketal, and ketone and the equilibrium is itself less important than the solvent. The solubility of each of these forms also depends on the solvent's nature. For these reasons, the observed log *P* values are often difficult to interpret.

Table 1.10 Solvent effects on solvent–water partition[9]

Compound	log *P* (octanol/water)	log *P* (cyclohexane/water)
C_6H_5—OH	1.48	−1.00
C_6F_5—OH	3.23	−0.52
Compound	Log *P* (octanol/water)	Log *P* (hexane/water)
CH_3CO—CH_2—CO—CH_3	0.26	0.02
CH_3CO—CH_2—CO—CF_3	0.29	−0.50
Compound	log *P* (Et_2O/water)	log *P* (benzene/water)
CH_3—COOH	−0.36	−1.74
CF_3—COOH	−0.27	−1.89

1.3 EFFECTS ON ELECTRONIC PROPERTIES AND REACTIVITY

In a molecule, fluorine atoms influence bond energies, electronic distribution, acidity, hydrogen bonds, steric interactions, and the stability of intermediate entities in a transformation. These factors, which have great influence on chemical reactivity, are examined.

1.3.1 Effects of Fluorination on Bond Energies and Reactivity

The C—F bond is the strongest bond that a carbon atom can form with another atom. For example, the C—F bond is 25 kcal/mol stronger than the C—Cl bond. Moreover, the strength of the C—F bond increases with the number of fluorine atoms borne by the carbon, conversely to what occurs with the other halogens (Table 1.11).[8, 11] α-Fluorination does not have much influence on the C—H bonds, but it increases the strength of the C—F, C—O, and C—C bonds. For example, in the bis(trifluoromethyl) ether CF_3—O—CF_3, the C—O bond is 22 kcal/mol stronger than that of dimethyl ether. The C—C bond of trifluoroethane is more than 10 kcal/mol stronger than that of ethane, and also stronger than that of hexafluoroethane (Table 1.11). Strengthening of the C—F bonds by fluorination explains the great stability of the CF_3 groups. In contrast, β-fluorination strongly increases the C—H bond strengths (Table 1.12).[8] The C—H bond in $(CF_3)_2$C—H is 15 kcal/mol stronger than in $(CH_3)_2$C—H. However, β-fluorination has little effect on C—F bonds.

This strengthening of C—F, C—H, and C—O bonds, through α- or β-fluorination, gives fluoroalkyl compounds a significantly greater chemical, thermal, and enzymatic

Table 1.11 Bond dissociation energy of methanes, ethanes, and halogenoethers[8,11]

	$D°$(C—X) (kcal/mol)							
Compound	H	F	Cl	Br	CH_3	CF_3	OCF_3	OCH_3
CH_3—X		108.3	82.9	69.6	88.8	101.2		83.2
CH_2X_2		119.5	81.0	64				
CHX_3		127.5	77.7	62				
CX_4	104.3	130.5	72.9	56.2				
CF_3—X	106.7	130.5	87.1	70.6	101.2	98.7	105.2	

Table 1.12 C—X bond dissociation energies of halogenoethanes[8]

	$D°$(C—X) (kcal/mol)			
X	CH_3CH_2—X	CH_3CF_2—X	CF_3CH_2—X	CF_3CF_2—X
H	100.1	99.5	106.7	102.7
F	107.9	124.8	109.4	126.8
Cl	83.7	—	—	82.7
Br	69.5	68.6	—	68.7
I	55.3	52.1	56.3	52.3

inertness compared to their nonfluorinated analogues. Highly fluorinated, or perfluorinated, polymers exhibit very high thermal and chemical stabilities, which justify their use in the field of biocompatible materials, volatile anesthetics, and artificial blood.

The C—F bond strength renders the aliphatic fluorides much less reactive than the corresponding chlorides in S_N1 or S_N2 reactions (from 10^{-2} to 10^{-6}). In fluoroalkenes, the C—F bond is also strong: the more fluorine atoms there are, the stronger the π double bond is. In general, the reactivity of these double bonds decreases with electrophiles while it increases with nucleophiles.

1.3.2 Effects of Fluorination on the Electronic Repartition of a Molecule

Due to the inductive effect, fluorine is always an electron-withdrawing substituent. Nevertheless, it can be electron-donating through resonance. Fluoroalkyl groups always behave as electron-withdrawing substituents. The bond polarization is given in Figure 1.1.

When bonded to an unsaturated carbon atom or to an arene, the fluorine atom exerts an inductive electron-withdrawing effect ($\sigma_I > 0$) and an electron-donating effect through resonance ($\sigma_R < 0$), both being very superior to the effects of the other halogens (Figure 1.1).[12] The values of the Hammet parameters σ_I and σ_R of some fluorinated substituents are reported in Table 1.13.[1,13,14,17]

The effect of fluorination on the reactivity of the ketone carbonyl group is important. Applications in enzymology are given in Chapters 3 and 7. Nucleophiles such as water, alcohols, and, amines add easily to fluoroaldehydes and fluoroketones, providing stable adducts (e.g., hydrates, hemiketals). Trifluoroacetaldehyde (fluoral) is commercialized only under its stable forms: hydrate and hemiketal. The great electrophilicity of the carbonyl is commonly attributed to an increase in the positive charge of the carbonyl (charge control). However, *ab initio* calculations on

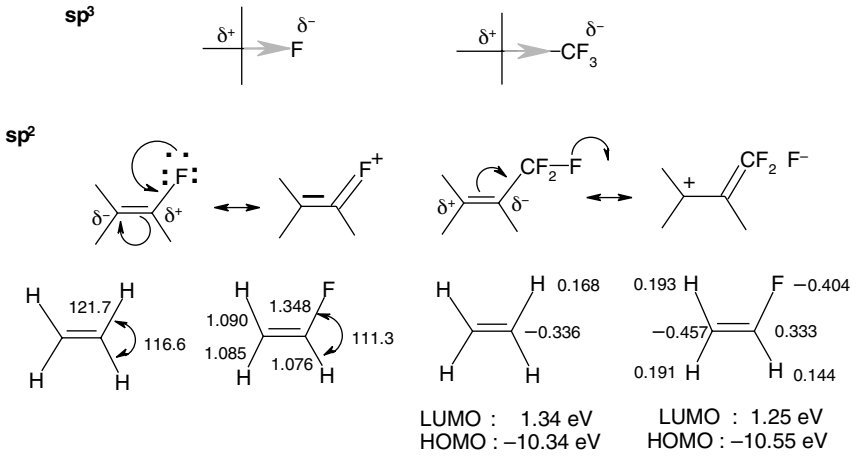


Figure 1.1 Fluorination electronic effects.[12]

Table 1.13 Hammet's electronic constants of fluorinated substituents[1,13,14,17]

Substituent	σ	$\sigma_{inductive}$	$\sigma_{resonance}$	Substituent	σ	$\sigma_{inductive}$	$\sigma_{resonance}$
F	3.10	0.52	−0.46	CH_3O		0.29	−0.43
Cl		0.47	−0.24	CF_3O		0.39	−0.18
Br		0.44	−0.22	CH_3S		0.23	−0.16
NO_2		0.56	0.22	CF_3S	2.73	0.42	0.02
OH		0.29	−0.43	$CH_3\ SO_2$		0.48	0.16
CH_3		0.04	−0.15	$CF_3\ SO_2$	4.41	0.73	0.31
CH_2F-	1.17			$CH_3\ SO_2NH$		0.42	−0.21
CHF_2-	2.0			CF_3SO_2NH		0.49	−0.10
CF_3	2.60	0.42	0.10	$(CF_3SO_2)_2\ N$		0.70	0.10
CH_3CH_2		0.05	−0.11	C_6H_5	0.60	0.08	−0.1
CF_3CH_2	0.90	0.14	−0.05	$F-C_6H_4-$	0.63		
CF_3CF_2		0.41	0.11	$CF_3-C_6H_4-$	0.96		
$CF_3-CF_2-CF_2-$	2.83			C_6F_5	1.50	0.25	0.02
				C_6H_5-CO-	2.20		
				CN		0.56	0.08

fluoroacetaldehydes have shown that the charge on the carbonyl does not vary significantly, while the length of the C=O bond and the negative charge of the oxygen atom are lowered by the fluorination (Figure 1.2).[15] Different type of computational studies show that the electrophilicity may result from a significant lowering of the carbonyl's LUMO (orbital control) (Figure 1.3).[15,16]

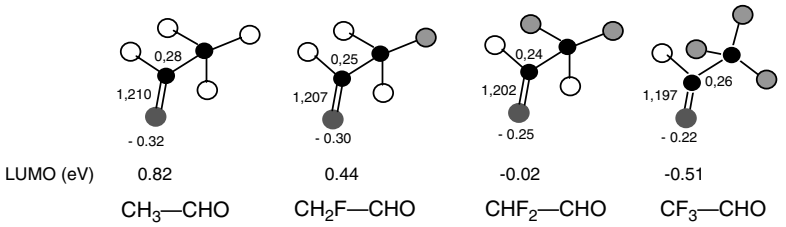


Figure 1.2 Fluoroacetaldehydes: length of C=O bond and electronic repartition.[15]

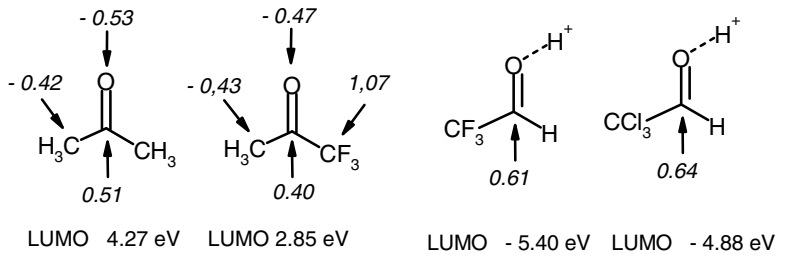


Figure 1.3 Calculated charge density (HF-31G**) and LUMO energy of acetone and acetaldehydes.[16]

1.3.3 Acidity, Basicity, and Hydrogen Bond

1.3.3.1 Acidity Fluoroalkyl groups are strong electron-withdrawing substituents; consequently, the acidity of neighboring hydrogen atoms is greatly increased (Table 1.14).[8,17–20] pK_a of carboxylic acids, alcohols, and imides are reported in Table 1.15 and Figure 1.4. In the same manner, fluorination largely lowers the basicity of amines: perfluorinated secondary amines are not able to afford hydrochlorides, and perfluorinated tertiary amines show a behavior close to that of perfluorocarbon compounds. This inertness is essential for their applications (biocompatible emulsions).[1]

1.3.3.2 Hydrogen Bond In spite of its strong electronegativity and its lone pairs of electrons, fluorine is a poor acceptor of hydrogen bond. This is due to the low polarization of its S and P electrons.[1] The calculation of the strength of the hydrogen bond C—F···H—O shows that it is approximately two times weaker than the —O···H—X (~2.4 kcal/mol).[21]

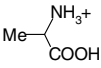
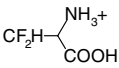
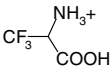
Most of the examples of H···F bonds reported in the literature concern intramolecular hydrogen bonds (fluoroalcohols, fluorophenols, and fluoroanilines) (Figure 1.5).[1] At this point, it is important to recall that the criterion to determine the existence of hydrogen bond with F is an interatomic distance between 2.0 and 2.3 Å, equal to or less than the sum of the atomic radii.

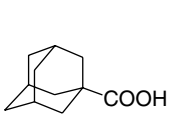
Hydrogen bonds between fluorinated substrates and biological macromolecules have been postulated in some enzyme–substrate complexes. However, it is rather difficult to determine if these hydrogen bonds really exist: other factors may stabilize the conformation corresponding to the short H···F interatomic distance observed. Indeed, this conformation can be favored by other factors (e.g., other stronger hydrogen bonds, gauche effect), without participation of an H···F interaction to stabilize the supramolecular structure.[22] The existence and possible

Table 1.14 pK_a and ΔG_{acid} calculated values of fluorinated compounds[8,17]

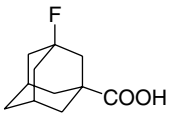
Compound	pK_a	Compound	pK_a
CHF_3	30.5	CH_3—COOMe	24
$CHCl_3$	24.4	CH_2F—COOEt	21
CF_3—CHF_2	28.2	CHF_2—COOEt	25
CF_3—$CHCl_2$	24.4	$CH_2(NO_2)_2$	3.63
$(CF_3)_3CH$	21	$CHF(NO_2)_2$	7.70
Compound	ΔG_{acid} (kcal/mol)	Compound	ΔG_{acid} (kcal/mol)
$(C_6H_5)_3CH$	352.8	$CH_2(CN)_2$	328.3
$(C_6F_5)_2CHC_6H_5$	328.4	CH $(CN)_3$	293
$(C_6F_5)_3CH$	317.6	$C_6H_5CH_2CN$	344.1
$(CF_3)_2CH_2$	343.9	$C_6F_5CH_2CN$	327.6
$(CF_3)_3CH$	326.8	$(C_6F_5)_2CHCN$	312.4

Table 1.15 pK_a, pK_b, α_2^H and β_2^H values of fluorinated compounds[17, 18]

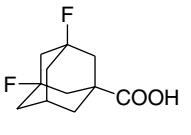
Acidity	pK_a	α_2^H	β_2^H	Acidity	pK_a	α_2^H	β_2^H
CH_3—COOH	4.76	0.550	0.42	CH_3CH_2OH	15.9	0.33	0.44
CH_2I—COOH	3.2			CF_3CH_2OH	12.4	0.57	0.18
CH_2Br—COOH	2.9			$CH_3CHOHCH_3$	16.1	0.32	0.47
CH_2Cl—COOH	2.9			$CF_3CHOHCF_3$	9.3	0.771	0.03
CH_2F—COOH	2.6			$(CH_3)_3$—COH	19.0	0.32	0.49
CF_2H—COOH	1.3			$(CF_3)_3C$-OH	5.4	0.862	
CF_3—COOH	0.5	0.951		C_6H_5—OH	10.0	0.596	0.22
C_6H_5—COOH	4.21	0.588	0.42	C_6F_5—OH	5.5	0.763	0.02
C_6F_5—COOH	1.75	0.889		Succinimide	9.6	0.493	
	2.4	2.3	1.2	F_4–succinimide	2.1	0.86	
	2.3			Basicity	pK_a		β_2^H
	1.3			$CH_3CH_2NH_2$	10.7		0.70
CH_3COOCH_3	28.2			$CF_3CH_2NH_2$	5.9		0.36
CH_2FCO_2Me	21			$C_6H_5NH_2$	4.3		0.38
CHF_2CO_2Me	25			$C_6F_5NH_2$	0.36		
				CH_3COCH_3			0.48
				CF_3COCF_3			0.24



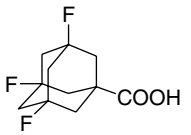
pK_a 4.8
log P 3.36



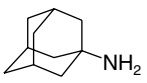
pK_a 4.2
log P 2.55



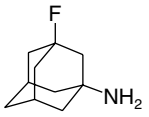
pK_a 3.8
log P 2.16



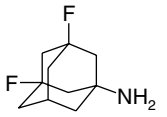
pK_a 3.2
log P 2.50



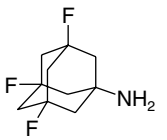
pK_a 10.9
log P 2.47



pK_a 9.4
log P 1.48



pK_a 8.4
log P 0.98



pK_a 7.4
log P 0.88

Figure 1.4 Fluorination impact on pK_a and log P of substituted adamantane.[20]

role of an H···F bond in the interactions between fluorinated substrates and biological macromolecules still remain an open question (cf. Chapter 3).

Conversely, numerous examples of coordination between a metallic ion and fluorine atoms borne by carbons can be found in the literature.[1,19, 23–27] However, the demonstration of this interaction is often indirect and is based either on theoretical calculations or on data linked to the reactivity or the stereochemistry (Figure 1.5).

If the fluorine atom itself is only slightly involved in hydrogen bonds, its inductive effect plays a very important role in the ability of neighboring functional groups to give or to accept hydrogen bonds. The presence of fluorine atoms enhances the ability of a neighboring function to donate a hydrogen bond (α_2^H) (acidity) and lowers its ability to accept hydrogen bond (β_2^H) (basicity) (Table 1.15). Thus, fluorinated alcohols are powerful donors of hydrogen bonds, but, conversely to nonfluorinated alcohols, they

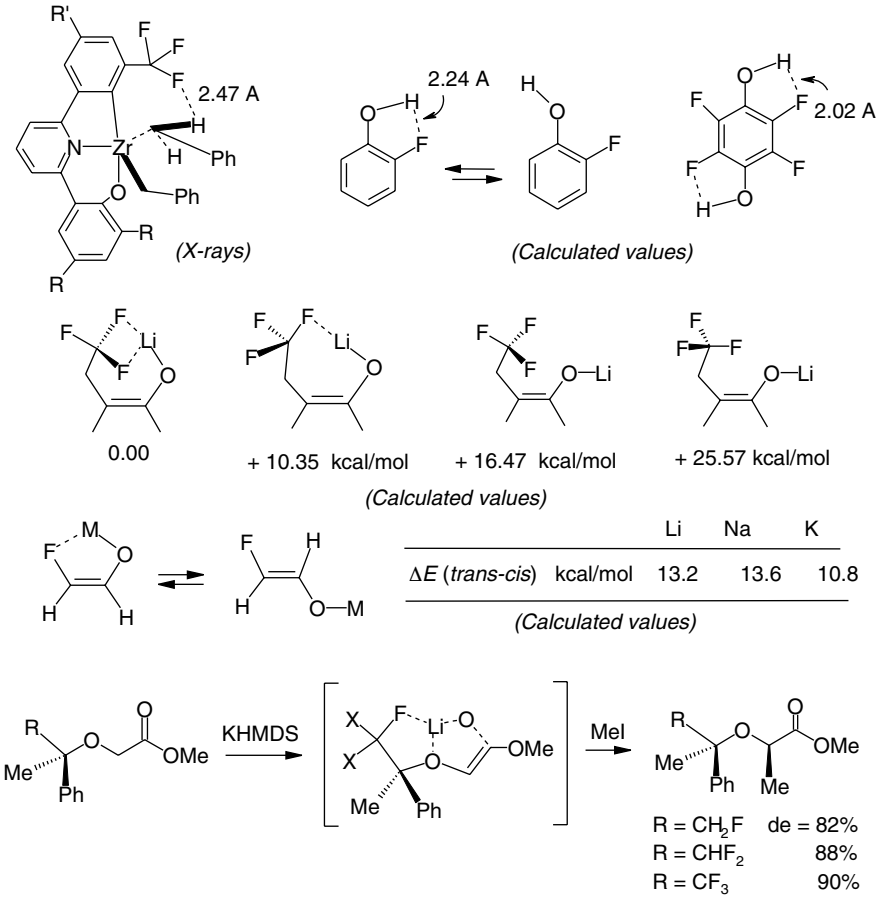


Figure 1.5 Typical examples of F···H and F···metal bonds.[1, 23–25, 30]

Table 1.16 Van der Waals radius (r_v) and bond length[1]

X	Electronegativity	r_v (Å)	Bond Length C—X (Å)
H	2.2	1.20	1.09
F	4.0	1.47	1.39
Cl	3.0	1.75	1.77
O	3.5	1.52	1.43
N	1.70	1.55	—
C		1.70	1.54

are extremely poor acceptors. Since they are poor nucleophiles, they are very useful polar solvents in organic synthesis.[28] Hydrofluorocarbon molecules can also be hydrogen bond donors, as fluorine atoms enhance the acidity of neighboring hydrogens.[29] It will be shown later that hydrogen bonds play an important role in the anesthetic properties of fluorocompounds (cf. Chapter 3).

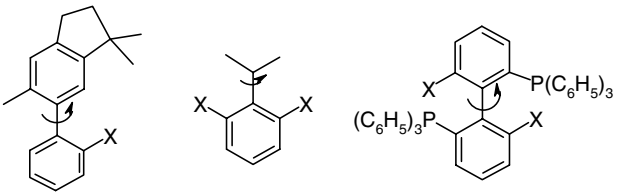
1.3.4 Steric Effects

Whereas the van der Waals radius of the fluorine atom is the smallest one after that of hydrogen, its volume is actually closer to that of oxygen (Table 1.16).[1] Note that if the volume is an intrinsic property, steric effects are dependent on the observed phenomena. They frequently appear in dynamic processes. This allows comparison of steric parameters of various groups, fluorinated or not. These parameters show that the CF_3 group is at least as bulky as an isopropyl or isobutyl group (Table 1.17).[1,31,32] These data are confirmed by the values of the rotation, or of inversion barriers, of fluorinated diphenyl-type compounds (Figure 1.6).

Table 1.17 Steric parameters of fluorinated and nonfluorinated substituents[1,32]

Substituent	E_s^0	A	v
H	0.00	0.00	0.00
F	−0.46	0.15	0.27
OH	−0.55	—	—
CH_3	−1.24	1.17	0.52
$(CH_3)_2CH$	−1.76	2.1	0.76
$(CH_3)_2CHCH_2$	−2.17	—	0.98
CFH_2	—	1.59	—
CF_2H	—	1.85	—
CF_3	−2.40	2.4	0.91
C_2F_5		2.65	—
$(CH_3)_3C$	−2.78	<3.9	—

[1] E_s, Taft steric values.[9a]; A, values from the axial–equatorial conformational equilibrium in cyclohexane v, Charton steric parameters.[9b]



X	Δ *G* (kcal/mol)	Δ *G* (kcal/mol)	Δ *G* (kcal/mol)
H	10.6	2.0	22
F	14.2	6.9	> 35
CH_3	19.3	12.8	> 30
CF_3	22.2		
$CH(CH_3)_2$	22.2		

Figure 1.6 Axial rotation barrier values.[1]

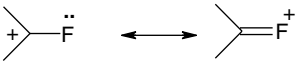
1.3.5 Fluorination Effects on the Stability of Reaction Intermediates (Carbocations, Carbanions, and Radicals)

1.3.5.1 Carbocations The effect of the presence of fluorine atoms on the stability of a carbocation is depending on whether they are borne by the α carbon or the β carbon. When the fluorine atom(s) is borne by the charged carbon, the charge is stabilized by one of the lone pair of fluorine atoms, despite the destabilizing electron-withdrawing effect. This competition between the two effects (mesomere and inductive effects) defines the stability order of fluoromethyl cations (Figure 1.7).[33, 34] Nevertheless, an alkyl group is better at stabilizing a carbocation than a fluorine atom. Mono- and difluorinated methyl carbocations are used in synthesis (Nazarov reaction and cyclialkylation).[35] Fluorinated carbocations with carborane anions can be studied in the solid state.[36]

The presence of fluorine strongly destabilizes a carbocation centered on the β carbon because only the inductive effect takes place.[34, 37] The effect on solvolysis or protonation reaction of double bonds can be very important.[18, 37] The destabilization of carbenium and alkoxycarbenium ions plays an important role in the design of enzyme inhibitors (cf. Chapter 7) and in the hydrolytic metabolism of active molecules (cf. Chapter 3).

1.3.5.2 Carbanions Although the presence of a fluorine atom in the α position has a stabilizing influence through the inductive effect, the repulsion induced by the

Back donation stabilization of fluoropropyl cation



Order of stability of fluoromethyl and fluoroethyl carbocations

$^{+}CH_3 < {}^{+}CF_3 < {}^{+}CH_2F < {}^{+}CF_2H \approx {}^{+}CH_2CH_3 << {}^{+}CF_2CH_3 \approx {}^{+}CHFCH_3$

Figure 1.7 Stability order of fluoroalkyl carbocations (gas phase).[34]

	CF_3H	$CF_3(CF_2)_5CF_2H$	$(CF_3)_2CFH$	$(CF_3)_3CH$
pK_a	30.5	30	20	11

Figure 1.8 α-and β-Fluoro carbanions.

lone electron pair is destabilizing. As a consequence, α-fluorination stabilizes carbanions less than the other halogens[39]: the acidity of haloforms decreases from bromoform (p$K_a = 22.7$) to chloroform (p$K_a = 24.4$) and to fluoroform (p$K_a = 30.5$).

Furthermore, the repulsion between the electron pairs of fluorine atoms is responsible for the pyramidal structure of the carbanion derived from fluoroform. The inversion barrier of the anion is $\sim$100 kcal/mol, while that of CH_3^- is only 2 kcal/mol. As the acidity of fluoroform is 10^{40} times higher than that of methane, the role of the pyramidal form in stabilizing the carbanion CF_3^- is essential.

On a thermodynamic level, the presence of fluorine atoms in the β position strongly stabilizes the anions (planar or not) either by inductive effect or by negative hyperconjugation (Figure 1.8).

With regard to nonfluorinated olefins, the great reactivity of fluoroolefins toward nucleophiles comes from both a higher electrophilicity of the double bond, and from the stabilization of the carbanion, resulting from the addition of the nucleophile, by β-fluorine atoms.[40]

The stabilization of a carbanion brought by α- or β-fluorine atoms is thermodynamic. Indeed, because of the great reactivity of carbanions toward elimination of a fluoride ion, they may have short lifetimes: α-fluorinated carbanions easily undergo α-elimination processes to carbenes, while β-fluorinated carbanions undergo β-elimination reactions.

The α-elimination process is a very fast and effective reaction of trifluoromethyl carbanions (Figure 1.9).[41] Consequently, the corresponding organometallic species (Li, Mg) cannot be used in organic synthesis. When the carbon-metal bond is close to a covalent bond, the anionic species is more stable, but has almost no reactivity toward electrophiles. Zinc, and especially silicon, derivatives constitute the best compromises.[42] When the fluoroalkyl chain is longer, organometallics are more stable and can be used in synthesis (Figure 1.10).[43]

The β-elimination reactions are also very frequent and they are typical of the chemistry of fluorinated compounds. They play an important role in synthesis and also

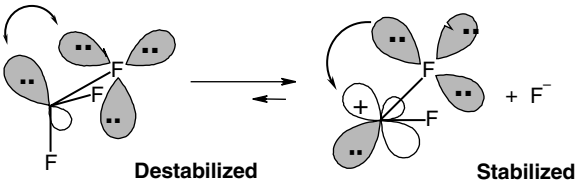


Figure 1.9 Stabilizing and destabilizing interactions of CF_3^- anion and CF_2 carbene.

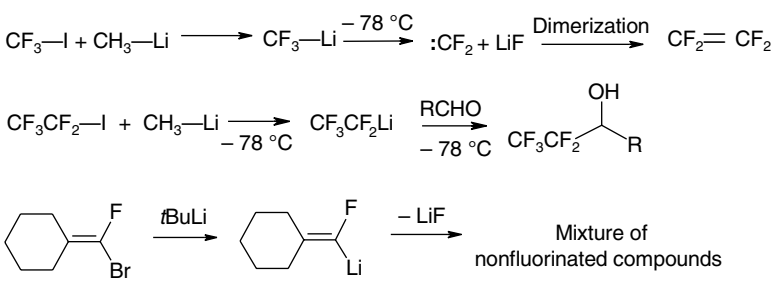


Figure 1.10 α-Elimination process of fluoride anion.[44]

in the design of irreversible enzyme inhibitors (mechanism-based inhibitors). The development of a negative charge on the β-position of a fluorine atom may induce the loss of a fluoride ion through an $E1_{CB}$ or a concerted mechanism.

Along the same line, the reactions of vinyl fluorides with nucleophiles often involve addition–elimination processes. The addition reaction generates a carbanion, and this latter induces the loss of a fluoride. As the loss of a fluoride ion is irreversible, the equilibrium is displaced toward the formation of the carbanion and, consequently, the reaction is very efficient. These reactions are often concerted ones (Figure 1.11).

In contrast to α-elimination, β-elimination processes are very common in reactions involving fluoroalkyl compounds and perfluoroolefins (Figure 1.11).

1.3.5.3 Effects on S_N1 and S_N2 Substitution Reactions The difficulty in performing S_N1 or S_N2 substitution reactions on the α, β, or even γ positions of CF_3 or fluoroalkyl groups is an important and typical feature of the reactivity of fluoro compounds.

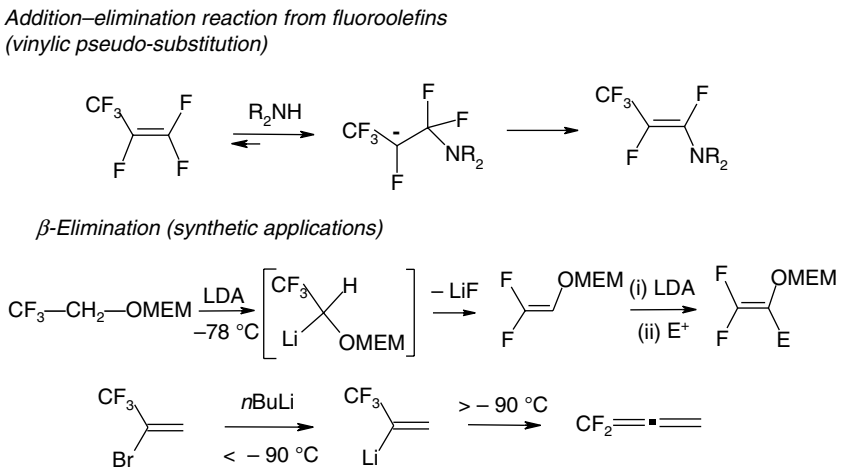


Figure 1.11 β-Elimination reactions with fluorinated compounds.[44–46]

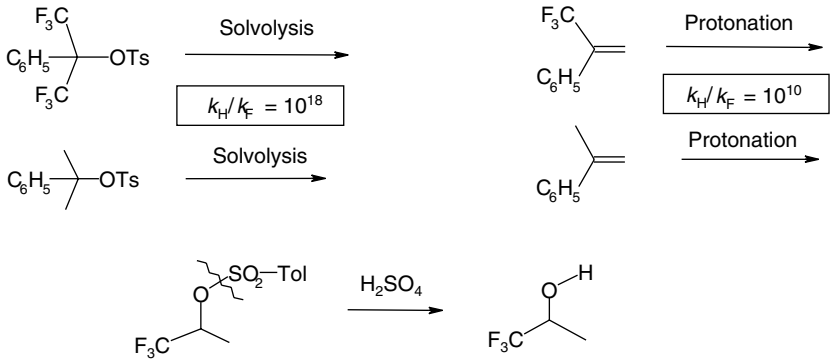


Figure 1.12 CF_3 effect on S_N1 type reactions of tosylates and on protonation of fluoroolefins.[38, 48]

Generally, an electron-withdrawing group strengthens the bond that is susceptible to cleavage during the substitution reaction. Moreover, a fluoroalkyl group strongly destabilizes a carbenium ion in the α position. As a consequence, the presence of a fluoroalkyl group makes S_N1 substitution reactions very difficult to achieve (Figure 1.12).[38, 47] The solvolysis reactions of tosylates are much slower than those of nonfluorinated tosylate analogues.[38] It has been demonstrated that the hydrolysis of the tosylate of trifluoropropanol in a concentrated sulfuric acid medium does not occur at the expected C—O bond but at the O—S bond (Figure 1.12).[48]

The inductive effect is *a priori* unfavorable for an S_N2 substitution. Moreover, the strengthening of the C—X bond disfavors its cleavage. Furthermore, the electronic as well as the steric repulsion phenomena inhibit the attack of the nucleophile. An important decreased rate is observed in the S_N2 reactions on carbons bearing a fluoroalkyl or CF_3 group (Figure 1.13).

It is important to note that the substitution of trifluoromethyl and perfluoroalkyl halides goes through a specific process. The displacement of the halogen atom never occurs via the usual S_N1 or S_N2 processes; rather it occurs either via a halophilic attack and a monoelectronic transfer ($S_{NR}1$)[13, 49] or via an α-elimination of a fluoride ion and a process involving a carbene.

1.3.5.4 Free Radicals The inductive effect of fluorine atoms destabilizes radicals.[50] For electronic reasons, fluorination has an important impact on

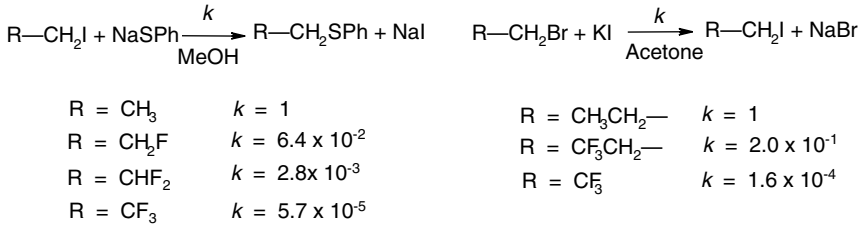


Figure 1.13 CF_3 effect on S_N2 reaction.[1]

Table 1.18 Inversion barrier of methyl and fluoromethyl radicals and dissociation energy of C—H bond of fluoromethanes[51]

Radical	CH_3	CH_2F	CHF_2	CF_3
Inversion barrier (kcal/mol)	—	~1	7	25
Dissociation energy of C—H bond (kcal/mol)	105 ± 0.2	101 ± 2	103 ± 2	107 ± 1

the structure of α-fluorinated radicals.[50] While the methyl radical is planar, the pyramidal character increases with the number of fluorine atoms. Like the CF_3^- carbanion, the $CF_3^\bullet$ radical is pyramidal. Since the inversion barrier is low, stabilization of the $CH_2F^\bullet$ and the $CHF_2^\bullet$ radicals can occur through resonance (Table 1.18).

The β-fluorinated radicals, such as the α-trifluoromethyl ones, are also destabilized due to the inductive effect. The dissociation energy grows from CH_3CH_2—H (97.7 kcal/mol) to CF_3CH_2—H (102.0 kcal/mol).[50, 52]

However, in radical reactions, the stability of radicals plays only a minor role with respect to polar and steric effects. The addition of fluoroalkyl radicals is mainly governed by orbital factors, and the polar effects play a major role in the processes.[50] The trifluoromethyl radical, which is a model of the electrophilic radical, reacts 10 times faster with ethylene than with tetrafluoroethylene, which is more electron poor. In contrast, the methyl radical reacts 10 times faster with tetrafluoroethylene than with ethylene.[50] Data on the relative speeds of addition of fluorinated radicals onto styrene and methylstyrene are collected in Table 1.19.[53] The addition of fluoroalkyl radicals onto electron-rich olefins is of great importance from a synthetic point of view. The abstraction of hydrogen by the fluoroalkyl radical is also governed by polar effects. Another important difference with regard to hydrocarbon radicals is the fact that dismutation reactions and fluorine atom migrations are rare. One of the consequences, for example, is, the formation of fluoro-polymers with very high molecular weights during radical polymerization.

Table 1.19 Absolute rate constants of addition of fluoroalkyl radical to styrene and methylstyrene[53]

	$k_{addition}/10^6\ M^{-1}\ s^{-1}$	
Radical	$C_6H_5C{=}CH_2$	$C_6H_5C(CH_3){=}CH_2$
$CH_3CH_2CH_2CH_2CH_2^\bullet$	0.12	0.06
$CH_3CH_2CH_2CF_2CH_2^\bullet$	0.52	0.98
$CH_3CH_2CH_2CH_2CHF^\bullet$	0.46	
$CH_3CH_2CH_2CH_2CF_2^\bullet$	2.7	3.3
$CF_3^\bullet$	53	87
$CF_3CF_2CF_2^\bullet$	43	78

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