

Modern Fluoroorganic Chemistry

Synthesis, Reactivity, Applications

Peer Kirsch



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To Annette and Alexander

“The fury of the chemical world is the element fluorine. It exists peacefully in the company with calcium in fluorspar and also in a few other compounds; but when isolated, as it recently has been, it is a rabid gas that nothing can resist.”

Scientific American, April 1888

“Fluorine leaves nobody indifferent; it inflames emotions be that affections or aversions. As a substituent, it is rarely boring, always good for a surprise, but often completely unpredictable.”

M. Schlosser, *Angew. Chem. Int. Ed.* **1998**, 37, 1496–1513

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Preface

The field of fluoroorganic chemistry has grown tremendously in recent years, and fluorochemicals have permeated nearly every aspect of our daily lives. This book is aimed at the synthetic chemist who wants to gain a deeper understanding of the fascinating implications of including the highly unusual element fluorine in organic compounds.

The idea behind this book was to introduce the reader to a wide range of synthetic methodology, based on the mechanistic background and the unique chemical and physicochemical properties of fluoroorganic compounds. There are quite some barriers to entering the field of preparative fluoroorganic chemistry, many based on unfounded prejudice. To reduce the threshold to practical engagement in fluoroorganic chemistry, I include some representative synthetic procedures which can be performed with relatively standard laboratory equipment.

To point out what can be achieved by introducing fluorine into organic molecules, a whole section of this book is dedicated to selected applications. Naturally, because of the extremely wide range of sometime highly specialized applications, this part had to be limited to examples which have gained particular importance in recent years. Of course, this selection is influenced strongly by the particular "taste" of the author.

I could not have completed this book without help and support from friends and colleagues. I would like to thank my colleagues at Merck KGaA, in particular Detlef Pauluth for his continuous support of my book project, and Matthias Bremer and Oliver Heppert for proof reading and for many good suggestions and ideas how to improve the book. The remaining errors are entirely my fault. G. K. Surya Prakash, Karl O. Christe, and David O'Hagan not only gave valuable advice but also provided me with literature. Gerd-Volker Rösenthaller, Günter Haufe, and Max Lieb introduced me to the fascinating field of fluorine chemistry. Andrew E. Feiring and Barbara Hall helped me to obtain historical photographs. Elke Maase from Wiley-VCH accompanied my work with continuous support and encouragement.

In the last 18 months I have spent most of my free time working on this book and not with my family. I would, therefore, like to dedicate this book to my wife Annette and my son Alexander.

List of Abbreviations

acac	acetylacetonate ligand	DMSO	dimethylsulfoxide
aHF	anhydrous hydrofluoric acid	DSM	dynamic scattering mode
AIBN	azobis(isobutyronitrile)	DTBP	di- <i>tert</i> -butyl peroxide
AM	active matrix	dTMP	deoxythymidine monophosphate
ASV	“Advanced Super-V”	dUMP	deoxyuridine monophosphate
ATPH	aluminum tri(2,6-bis(<i>tert</i> -butyl)-phenoxide	ECF	electrochemical fluorination
BAST	<i>N,N</i> -bis(methoxyethyl)amino sulfur trifluoride	ED	effective dose
BINOL	1,1'-bis(2-naphthol)	EPSP	5-enolpyruvylshikimate-3-phosphate
Bop-Cl	bis(2-oxo-3-oxazolidinyl)phosphinic chloride	ETFE	poly(ethylene- <i>co</i> -tetrafluoroethylene)
BSSE	basis set superposition error	FAR	α -fluorinated alkylamine reagents
BTF	benzotrifluoride	FDA	fluorodeoxyadenosine
CFC	chlorofluorocarbon	FDG	fluorodeoxyglucose
COD	cyclooctadiene	FITS	perfluoroalkyl phenyl iodonium trifluoromethylsulfonate reagents
CSA	camphor sulfonic acid	FRPSG	fluorous reversed-phase silica gel
Cso	camphor sulfonyl protecting group	FSPE	fluorous solid phase extraction
CVD	chemical vapor deposition	F-TEDA	<i>N</i> -fluoro- <i>N'</i> -chloromethyl diazoniabicyclooctane reagents
DABCO	diazabicyclooctane	GWP	global warming potential
DAST	<i>N,N</i> -diethylamino sulfur trifluoride	HFCE	hydrofluorochlorocarbon
DBH	1,3-dibromo-5,5-dimethyl hydantoin	HFC	hydrofluorocarbon
DBPO	dibenzoylperoxide	HFP	hexafluoropropene
DEAD	diethyl azodicarboxylate	HMG ⁺	hexamethyl guanidinium cation
DCC	dicyclohexyl carbodiimide	HMPA	hexamethyl phosphoric acid triamide
DEC	<i>N,N</i> -diethylcarbamoyl protecting group	IPS	in plane switching
DFI	2,2-difluoro-1,3-dimethylimidazolidine	ITO	indium tin oxide
DFT	density functional theory	LC	lethal concentration
DIP-Cl	β -chlorodiisopinocampheylborane	LCD	liquid crystal display
DMAc	<i>N,N</i> -dimethyl acetamide	LD	lethal dose
DMAP	4-(<i>N,N</i> -dimethylamino)pyridine	LDA	lithium diisopropylamide
DME	1,2-dimethoxy ethane	MCPBA	<i>m</i> -chloro perbenzoic acid
DMF	<i>N,N</i> -dimethyl formamide	MEM	methoxymethyl protecting group
		MOST	morpholino sulfur trifluoride
		MVA	multi-domain vertical alignment

NAD ⁺ /	nicotinamide adenine dinucleo-	QSAR	quantitative structure-activity
NADH	tide, oxidized/reduced form		relationship
NADP ⁺ /	nicotinamide adenine dinucleo-	SAH	S-adenosyl homocystein
NADPH	tide phosphate, oxidized/reduced		hydrolase
	form	SAM	S-adenosyl methionine
NBS	N-bromo succinimide	SBAH	sodium bis(methoxyethoxy)
NCS	N-chloro succinimide		aluminum hydride
NE	norepinephrine	scCO ₂	supercritical carbon dioxide
NFPy	N-fluoro pyridinium	SFM	super-fluorinated materials
	tetrafluoroborate	SPE	solid phase extraction
NFTh	N-fluoro benzene-1,2-	STN	super-twisted nematic
	sulfonimide	TADDOL	$\alpha,\alpha,\alpha',\alpha'$ -tetraaryl-2,2-dimethyl- 1,3-dioxolan-4,5-dimethanol
NIS	N-iodo succinimide	TAS ⁺	tris(dimethylamino)sulfonium
NLO	non-linear optics		cation
NMP	N-methyl pyrrolidone	TASF	tris(dimethylamino)sulfonium
NPSP	N-phenylselenylphthalimide		difluorotrimethylsiliconate, (Me ₂ N) ₃ S ⁺ Me ₃ SiF ₂ ⁻
OD	ornithine decarboxylase	TBAF	tetrabutylammonium fluoride
ODP	ozone-depleting potential	TBDMS	<i>tert</i> -butyldimethylsilyl protecting
PCH	phenylcyclohexane		group
PCTFE	poly(chlorotrifluoroethylene)	TBS	see TBDMS
PDA	personal digital assistant	TBTU	<i>O</i> -(benzotriazol-1-yl)- <i>N,N,N'</i> , <i>N'</i> -tetramethyluronium
PET	positron emission tomography		tetrafluoroborate
PFA	perfluoropolyether	TDAE	tetrakis(dimethylamino)ethylene
PFC	perfluorocarbon	TEMPO	2,2,6,6-tetramethylpiperidine- <i>N</i> - oxide
PFMC	perfluoro(methylcyclohexane)	TFT	thin film transistor
PFOA	perfluorooctanoic acid	THF	1. tetrahydrofuran
PFOB	perfluoro- <i>n</i> -octyl bromide		2. tetrahydrofolate coenzyme
PI	polyimide	THP	tetrahydropyranyl protecting
pip ⁺	1,1,2,2,6,6-hexamethylpiperidi-		group
	nium cation	TIPS	triisopropylsilyl protecting group
PLP	pyridoxal phosphate	TLC	thin layer chromatography
PNP	purine nucleoside phosphorylase	TMS	trimethylsilyl protecting group
PPVE	poly(heptafluoropropyl	TN	twisted nematic
	trifluorovinyl ether)	VHR	voltage holding ratio
PTC	phase transfer catalysis	ZPE	zero point energy
PTFE	poly(tetrafluoroethylene) (Teflon)		
PVDF	poly(vinylidene difluoride)		
PVPHF	poly(vinylpyridine) hydrofluoride		
QM/MM	quantum mechanics/molecular		
	mechanics		

1

Introduction

1.1

Why Organofluorine Chemistry?

Fluorine is the element of extremes, and many fluorinated organic compounds exhibit extreme and sometimes even bizarre behavior. A large number of polymers, liquid crystals, and other advanced materials owe their unique property profile to the influence of fluorinated structures.

Fluoroorganic compounds are almost completely foreign to the biosphere. No central biological processes rely on fluorinated metabolites. Many modern pharmaceuticals and agrochemicals, on the other hand, contain at least one fluorine atom, which usually has a very specific function. Perfluoroalkanes, especially, can be regarded as “orthogonal” to life – they can assume a purely physical function, for example oxygen transport, but are foreign to the living system to such an extent that they are not recognized and are completely ignored by the body.

Although fluorine itself is the most reactive of all elements, some fluoroorganic compounds have chemical inertness like that of the noble gases. They sometimes cause ecological problems not because of their reactivity but because of the lack of it, making them persistent in nature on a geological time scale.

All these points render fluoroorganic chemistry a highly unusual and fascinating field [1–13], providing surprises and intellectual stimulation in the whole range of chemistry-related sciences, including theoretical, synthetic, and biomedical chemistry and materials science.

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1.2

History

Because of the hazardous character of hydrofluoric acid and the difficult access to elemental fluorine itself, the development of organofluorine chemistry and the practical use of fluororganic compounds started relatively late in the 19th century (Table 1.1). The real breakthrough was the first synthesis of elemental fluorine by H. Moissan in 1886 [1].

Industrial application of fluorinated organic compounds started in the beginning of the 1930s with the introduction of chlorofluorocarbons (CFC) as refrigerants [2]. The major turning point in the history of industrial fluoroorganic chemistry was the beginning of the Manhattan Project for development of nuclear weapons in 1941 [3]. The Manhattan Project triggered the need for highly resistant materials, lubricants, coolants and the development of technology for handling extremely corrosive fluorinorganic compounds. The consumption of hydrofluoric acid as the main precursor of all these materials soared upward, accordingly, during the 1940s. After 1945, with the beginning of the Cold War, various defense programs provided a constant driving force for further development of the chemistry and use of organofluorine compounds. In the 1950s and 60s more civilian applications of fluorinated pharmaceuticals and materials moved into the forefront [4].

The prediction of the ozone-depleting effect of CFC in 1974 [5] and the subsequent occurrence of the ozone hole over the Antarctic in 1980 enforced a drastic reorientation of industrial fluoroorganic chemistry. With the Montreal protocol in 1987 the phasing-out of most CFC was initiated. Some of these refrigerants and cleaning chemicals could be replaced by other fluorine-containing chemicals (for example hydrofluorocarbons, HFC, and fluorinated ethers) but in general the fluorochemical industry had to refocus on other fields of application, for example fluoropolymers, fluorosurfactants, and fluorinated intermediates for pharmaceuticals and agrochemicals [4]. A major and rapidly growing market segment is fluorine-containing fine chemicals for use as intermediates in pharmaceutical and agrochemistry and in the electronics industry. Another application in which fluorochemicals have started to play an increasingly dominant role in the last

Table 1.1 Dates and historic key events in the development of fluoroorganic chemistry.

Time	Key Event
1764	First synthesis of hydrofluoric acid from fluorspar and sulfuric acid by A. S. Marggraf, repeated in 1771 by C. Scheele
1886	First synthesis of elemental fluorine by H. Moissan (Nobel Prize in 1906) by electrolysis of an HF–KF system
1890s	Beginning of halofluorocarbon chemistry by direct fluorination (H. Moissan) and Lewis acid-catalyzed halogen exchange (F. Swarts)
1920s	Access to fluoroarenes by the Balz–Schiemann reaction
1930s	Refrigerants (“Freon”, in Germany “Frigen”), fire extinguishing chemicals (“Halon”), aerosol propellants
1940s	Polymers (PTFE = “Teflon”), electrochemical fluorination (H. Simons)
1941–1954	Manhattan Project: highly resistant materials for isotope separation plants, lubricants for gas centrifuges, coolants
1950s	Fluoropharmaceuticals, agrochemicals, artificial blood substitutes, respiratory fluids, chemical weapons
1980s	Gases for plasma etching processes and cleaning fluids for the semiconductor industry
1987	The Montreal Protocol initiates the phasing-out of CFC
1990s	Fluorinated liquid crystals for active matrix liquid crystal displays (AM-LCD)
2000s	Fluorinated photoresists for the manufacture of integrated electronic circuits by 157 nm photolithography

few years is the electronics industry. Relevant compounds include plasma etching gases, cleaning fluids, specialized fluoropolymers, fluorinated photoresists for manufacturing integrated circuits by the currently emerging 157 nm photolithography, and liquid crystals for LCD application.

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1.3

The Basic Materials

Naturally occurring fluorine is composed of the pure ^{19}F isotope. Its relative abundance in the earth crust as a whole is 0.027% by weight (for comparison, Cl is 0.19% and Br $6 \times 10^{-4}\%$ by weight). Because of the extremely low solubility (solubility product 1.7×10^{-10} at 298 K) of its most important mineral, fluorspar (CaF_2), the concentration of fluoride in seawater is very low (ca. 1.4 mg L^{-1}) [1].

The most abundant natural sources of fluorine are the minerals fluorspar and cryolith (Na_3AlF_6). Fluoroapatite ($\text{Ca}_5(\text{PO}_4)_3\text{F} = "3\text{Ca}_3(\text{PO}_4)_2 \cdot \text{CaF}_2"$) is, with hydroxyapatite ($\text{Ca}_5(\text{PO}_4)_3\text{OH}$), a major component of tooth enamel, giving it its extreme mechanical strength and life-long durability.

Despite of the relatively high abundance of fluorine in the lithosphere, only very few fluoroorganic metabolites have been identified in the biosphere [2]. No central metabolic process depending essentially on fluorine is yet known. It might be speculated that the reason for this unexpected phenomenon is the poor solubility of CaF_2 , with Ca^{2+} ions being one of the central components essential for the existence of any living organism. Another reason might also be the very high hydration enthalpy of the small fluoride anion, which limits its nucleophilicity in aqueous media by requiring an energetically demanding dehydration step before any reaction as a nucleophile [2].

1.3.1

Hydrofluoric Acid

Hydrofluoric acid is the most basic common precursor of most fluorochemicals. Aqueous hydrofluoric acid is prepared by reaction of sulfuric acid with fluorspar (CaF_2). Because HF etches glass with formation of silicon tetrafluoride, it must be handled in platinum, lead, copper, Monel (a Cu–Ni alloy developed during the Manhattan Project), or plastic (e. g. polyethylene or PTFE) apparatus. The azeotrope contains 38% *w/w* HF and it is a relatively weak acid ($\text{p}K_a$ 3.18, 8% dissociation), comparable with formic acid. Other physicochemical properties of hydrofluoric acid are listed in Table 1.2.

Anhydrous hydrofluoric acid (aHF) is obtained by heating Frey's Salt ($\text{KF} \cdot \text{HF}$) as a liquid, boiling at 19.5°C . Similar to water, aHF has a liquid range of approximately 100 K and a dielectric constant ϵ of 83.5 (at 0°C). Associated by strong hy-

Table 1.2 Physicochemical properties of hydrofluoric acid [3] (the vapor pressure and density correspond to a temperature of 0°C).

<i>Property</i>	<i>Anhydrous HF</i>	<i>40% HF/H₂O</i>
Boiling point ($^\circ\text{C}$)	19.5	111.7
Melting Point ($^\circ\text{C}$)	-83.4	-44.0
HF vapor pressure (Torr)	364	21
Density (g cm^{-3})	1015	1135

drogen bonding, it forms oligomeric $(\text{HF})_n$ chains with a predominant chain length n of nine HF units. In contrast with aqueous HF, pure aHF is a very strong acid, slightly weaker than sulfuric acid. Like water, aHF undergoes autoprotolysis with an ion product $c(\text{FHF}^-) \times c(\text{HFH}^+)$ of $10^{-10.7}$ at 0°C . In combination with strong Lewis acids, for example as AsF_5 , SbF_5 , or SO_3 , anhydrous hydrofluoric acid forms some of the strongest known protic acids. The best known example is “magic acid” ($\text{FSO}_3\text{H-SbF}_5$) which can protonate and crack paraffins to give *tert*-butyl cations [3]. Apart from its use as a reagent, aHF is also an efficient and electrochemically inert solvent for a variety of inorganic and organic compounds.

The dark side of hydrofluoric acid is its toxicity and corrosiveness. Aqueous and anhydrous HF readily penetrate the skin, and, because of its locally anesthetizing effect, even in very small quantities can cause deep lesions and necroses [4, 5]. An additional health hazard is the systemic toxicity of fluoride ions, which interfere strongly with calcium metabolism. Resorption of HF by skin contact (from a contact area exceeding 160 cm^2), inhalation, or ingestion leads to hypocalcemia with very serious consequences, for example cardiac arrhythmia.

The most effective, specific antidote to HF and inorganic fluorides is calcium gluconate, which acts by precipitating fluoride ions as insoluble CaF_2 . After inhalation of HF vapor, treatment of the victim with dexamethasone aerosol is recommended, to prevent pulmonary edema. Even slight contamination with HF must always be taken seriously, and after the necessary first-aid measures a physician should be consulted as soon as possible.

It should also be kept in mind that some inorganic (e.g. CoF_3) and organic fluorinated compounds (e.g. pyridine-HF, $\text{NEt}_3 \cdot 3\text{HF}$, DAST) can hydrolyze on contact with skin and body fluids, liberating hydrofluoric acid with the same adverse consequences.

Nevertheless, when the necessary, relatively simple precautions are taken [4], hydrofluoric acid and its derivatives can be handled safely and with minimum risk to health.

1.3.2

Fluorine

Despite the ubiquitous occurrence of fluorides in nature, elemental fluorine itself proved to be quite elusive. Because of its very high redox potential (approx. +3 V, depending on the pH of aqueous systems), chemical synthesis from inorganic fluorides was impeded by the lack of a suitable oxidant. Therefore, H. Moissan's first synthesis of fluorine in 1886 by electrolysis of a solution of KF in aHF in a platinum apparatus [6, 7] was a significant scientific breakthrough, and he was awarded the Nobel Prize for chemistry in 1906 for his discovery (Figure 1.1).

Fluorine is a greenish-yellow gas, melting at -219.6°C and boiling at -188.1°C . It has a pungent smell reminiscent of a mixture of chlorine and ozone and is perceptible even at a concentration of 10 ppm. It is highly toxic and extremely corrosive, especially toward oxidizable substrates. Most organic compounds spontaneously combust or explode on contact with undiluted fluorine at ambient pres-

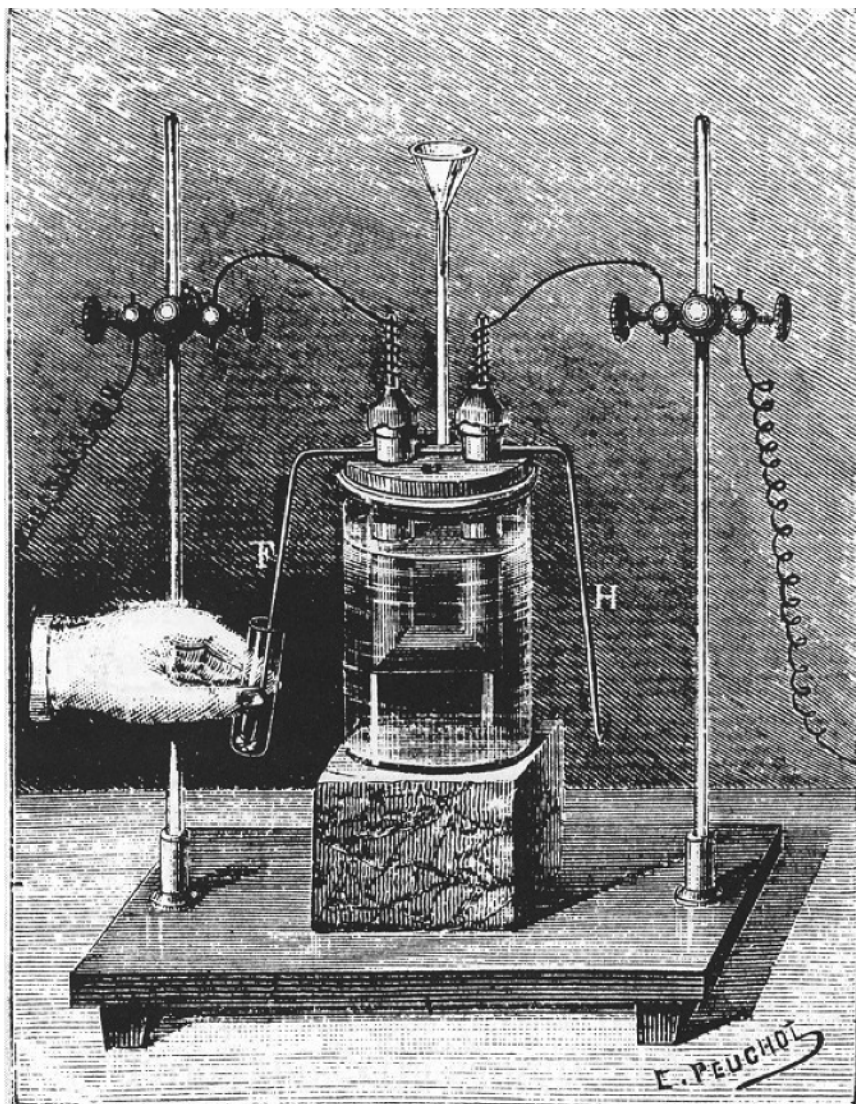


Figure 1.1 The apparatus used by H. Moissan for the first isolation of elemental fluorine by electrolysis of a HF–KF system in 1886 [6].

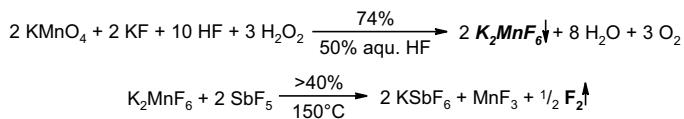
sure. Because of its high reactivity, fluorine reacts with hot platinum and gold, and even with the noble gases krypton and xenon. In contrast with hydrofluoric acid, dry fluorine gas does not etch glassware. Because of its extreme reactivity and hazardous nature, for many chemical transformations fluorine is diluted with nitrogen (typically 10% F_2 in N_2). In this form, the gas can be stored without undue risk in passivated steel pressure bottles. Reactions can be conducted either in glassware

or in fluoropolymer (PTFE or PFA) apparatus. If some elementary precautions are taken (for details see Appendix A), reactions with nitrogen-diluted fluorine can be conducted safely in an ordinarily equipped laboratory.

Fluorine owes its unparalleled reactivity, on the one hand, to the ease of its homolytic dissociation into radicals (only 37.8 kcal mol⁻¹, compared with 58.2 kcal mol⁻¹ for Cl₂) and, on the other hand, to its very high redox potentials of +3.06 V and +2.87 V, respectively, in acidic and basic aqueous media [8].

Fluorine, as the most electronegative element (electronegativity 3.98) [9], occurs in its compounds exclusively in the oxidation state -1. The high electron affinity (3.448 eV), extreme ionization energy (17.418 eV) and other unique properties of fluorine can be explained by its special location in the periodic system as the first element with p orbitals able to achieve a noble gas electron configuration (Ne) by uptake of one additional electron. For the same reason the fluoride ion is also the smallest (ion radius 133 pm) and least polarizable monoatomic anion. These very unusual characteristics are the reason fluorine or fluorine-containing non-polarizable anions can stabilize many elements in their highest and otherwise inaccessible oxidation states (e. g. IF₇, XeF₆, KrF₂, O₂⁺PtF₆⁻, N₅⁺AsF₆⁻).

A purely chemical synthesis of elemental fluorine was achieved by K. O. Christe in 1986 [10] (Scheme 1.1), just in time for the 100 year anniversary of Moissan's first electrochemical fluorine synthesis. Nevertheless, in his paper Christe remarks that all the basic know-how required for this work had already been available 50 years earlier. The key to his simple method is a displacement reaction between potassium hexafluoropermanganate [11] with the strongly fluorophilic Lewis acid antimony pentafluoride at 150 °C.



Scheme 1.1 The first “chemical” synthesis of fluorine [10].

Nowadays, industrial fluorine production is based on Moissan's original method [1]. In the so-called “middle-temperature method” a KF · 2HF melt is electrolyzed at 70–130 °C in a steel cell. The steel cell itself is used as cathode; the anodes are specially treated carbon blocks (Söderberg electrodes). The voltage used is 8–12 V per cell [12]. During the cold war the major use of elemental fluorine was in the production of uranium hexafluoride for separation of the ²³⁵U isotope. Nowadays, the production of nuclear weapons has moved into the background and a large quantity of fluorine is used for preparation of chemicals for the electronics industry (for example WF₆ for CVD (chemical vapor deposition), SF₆, NF₃, and BrF₃ as etching gases for semiconductor production, and graphite fluorides as cathode materials in primary lithium batteries) and for making polyethylene gasoline tanks inert in the automobile industry.

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1.4

The Unique Properties of Organofluorine Compounds

Fluoroorganic and, especially, perfluorinated compounds are characterized by a unique set of unusual and sometimes extreme physical and chemical properties. These are being utilized for a variety of different applications ranging from pharmaceutical chemistry to materials science [1].

1.4.1

Physical Properties

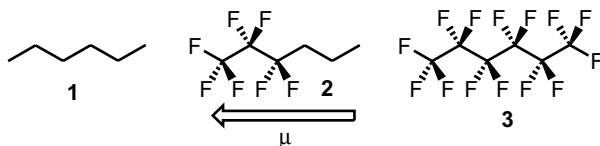
The physical properties of fluoroorganic compounds are governed by two main factors: (1) the combination of high electronegativity with moderate size, and the excellent match between the fluorine 2s or 2p orbitals with the corresponding orbitals of carbon, and (2) the resulting extremely low polarizability of fluorine [2].

Fluorine has the highest electronegativity of all the elements (3.98) [3], rendering the carbon–fluorine bond highly polar with a typical dipole moment of around 1.4 D, depending on the exact chemical environment (Table 1.3). The apparently contradictory observation that perfluorocarbons are among the most *non-polar* solvents in existence (e.g. $\epsilon = 1.69$ for C_6F_{14} (**3**) compared with 1.89 for C_6H_{14} (**1**); Table 1.4) can be explained by the fact that all local dipole moments within the same molecule cancel each other, leading in total to a non-polar compound. In semi-fluorinated compounds, for example **2**, in which some local dipole moments

Table 1.3 Comparison of the characteristics of the carbon–halogen and carbon–carbon bonds (bond lengths in pm; binding energies in kcal mol⁻¹; electronegativities from Ref. [3]; dipole moments in D; Van der Waals radii in pm from Ref. [4]; atom polarizabilities α in 10⁻²⁴ cm⁻³ from Ref. [5]).

X	H	F	Cl	Br	I	C
Bond length C–X	109	138	177	194	213	–
Binding energy C–X	98.0	115.7	77.2	64.3	50.7	~83
Electronegativity	2.20	3.98	3.16	2.96	2.66	2.55
Dipole moment, μ , C–X	(0.4)	1.41	1.46	1.38	1.19	–
Van der Waals radius	120	147	175	185	198	–
Atom polarizability, α	0.667	0.557	2.18	3.05	4.7	–

Table 1.4 Comparison of selected physicochemical properties of *n*-hexane (**1**) and its perfluorinated (**3**) and semifluorinated (**2**) analogues [2] (boiling point b. p. in °C; heat of vaporization ΔH_v in kcal mol⁻¹; critical temperature T_c in °C; density d^{25} in g cm⁻³; viscosity η^{25} in cP; surface tension γ^{25} in dyn cm⁻¹; compressibility β in 10⁻⁶ atm⁻¹; refractive index n_D^{25} ; dielectric constant ϵ).



Property	1	2	3
b. p. (°C)	69	64	57
ΔH_v (kcal mol ⁻¹)	6.9	7.9	6.7
T_c (°C)	235	200	174
d^{25} (g cm ³)	0.655	1.265	1.672
η^{25} (cP)	0.29	0.48	0.66
γ^{25} (dyn cm ⁻¹)	17.9	14.3	11.4
β (10 ⁻⁶ atm ⁻¹)	150	198	254
n_D^{25}	1.372	1.190	1.252
ϵ	1.89	5.99	1.69

are not compensated, the effects of the resulting overall dipole moment is mirrored by their physicochemical properties, especially their heats of vaporization (ΔH_v) and their dielectric constants (ϵ).

The low polarizability and the slightly larger size of fluorine compared with hydrogen (23 % larger Van der Waals radius) also have consequences for the structure and molecular dynamics of perfluorocarbons. Linear hydrocarbons have a linear zigzag conformation (Figure 1.2). Perfluorocarbons, in contrast, have a helical structure, because of the steric repulsion of the electronically “hard” fluorine substituents bound to carbon atoms in the relative 1,3-positions. Whilst the hydrocarbon backbone has some conformational flexibility, perfluorocarbons are rigid, rod-like molecules. This rigidity can be attributed to repulsive stretching by the 1,3-difluoromethylene groups.

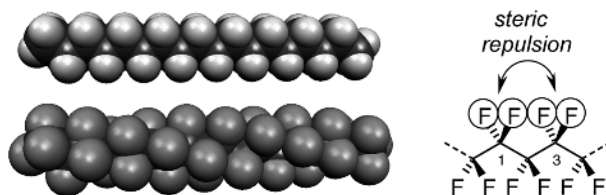


Figure 1.2 The zigzag conformation of octadecane (*above*) compared with the helical perfluorooctadecane (*below*), modeled on the PM3 level of theory [6, 7].

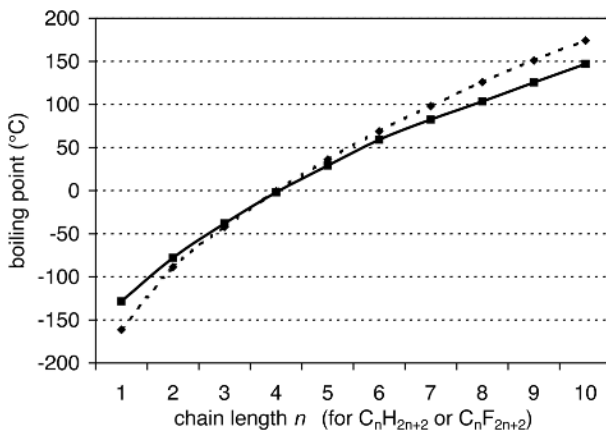


Figure 1.3 The boiling points of homologous alkanes (◆) compared with those of the corresponding perfluoroalkanes (■) [2].

Another consequence of the low polarizability of perfluorocarbons is very weak intermolecular dispersion interactions. A striking characteristic of perfluorocarbons is their very low boiling points, compared with hydrocarbons of similar molecular mass. For example, *n*-hexane and CF_4 have about the same molecular mass (M_r 86 g mol^{-1} and 88 g mol^{-1} , respectively), but the boiling point of CF_4 (b. p. -128°C) is nearly 200 K lower than for *n*-hexane (b. p. 69°C). If the homologous hydrocarbons and perfluorocarbons are compared (Figure 1.3) it is apparent they have very similar boiling points, even though the molecular mass of the perfluorocarbons is about four times higher than that of the corresponding hydrocarbons.

In contrast with typical hydrocarbon systems, branching has a negligible effect on the boiling points of perfluorocarbons (Figure 1.4).

Perfluorinated amines, ethers and ketones usually have much lower boiling points than their hydrocarbon analogues.

An interesting fact is that the boiling points of perfluorocarbons are only 25–30 K higher than those of noble gases of similar molecular mass (Kr, M_r 83.8 g mol^{-1} , b. p. -153.4°C ; Xe, M_r 131.3 g mol^{-1} , b. p. -108.1°C ; Rn, M_r 222 g mol^{-1} , b. p.

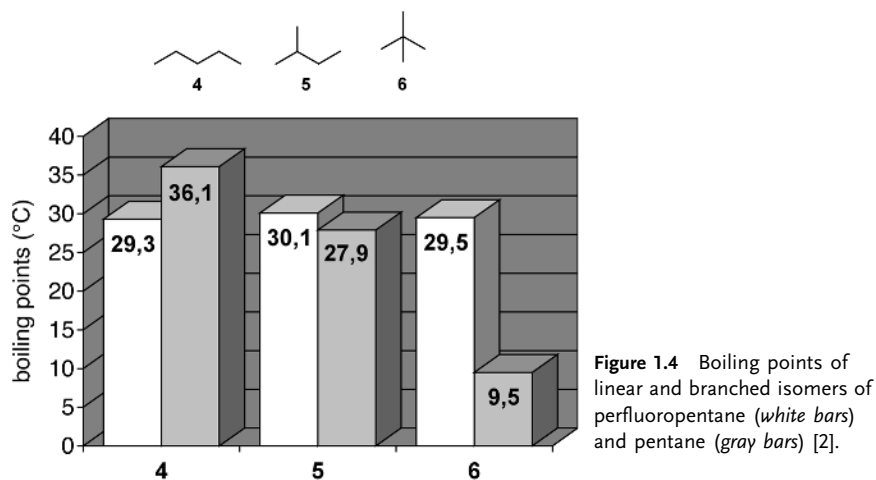


Figure 1.4 Boiling points of linear and branched isomers of perfluoropentane (white bars) and pentane (gray bars) [2].

–62.1 °C). In other aspects also, for example their limited chemical reactivity, perfluorocarbons resemble the noble gases.

Another consequence of the low polarizability of perfluorocarbons is the occurrence of large miscibility gaps in solvent systems composed of perfluorocarbons and hydrocarbons. The occurrence of a third, “fluorous”, liquid phase in addition to the “organic” and “aqueous” phases has been extensively exploited in the convenient and supposedly ecologically benign “fluorous” chemistry, which will be discussed in detail in Chapter 3.

Another very prominent characteristic resulting from their weak intermolecular interaction is the extremely low surface tension (γ) of the perfluoroalkanes. They have the lowest surface tensions of any organic liquids (an example is given in Table 1.4.) and therefore wet almost any surface [2].

Solid perfluorocarbon surfaces also have extremely low surface energies (γ_c). Thus, poly(tetrafluoroethylene) (PTFE, Teflon) has a γ_c value of 18.5 dyn cm⁻¹, which is the reason for the anti-stick and low-friction properties used for frying pans and other applications. That this effect is directly related to the fluorine content becomes obvious on comparison of the surface energies of poly(difluoroethylene) (25 dyn cm⁻¹), poly(fluoroethylene) (28 dyn cm⁻¹), and polyethylene (31 dyn cm⁻¹). If only one fluorine atom in PTFE is replaced by more polarizable chlorine, the surface energy of the resulting poly(chlorotrifluoroethylene) jumps to 31 dyn cm⁻¹, the same value as for polyethylene [8].

The decisive aspect of achieving low surface energies seems to be a surface which is densely covered by fluorine atoms. Accordingly, the lowest surface energies of any material observed are those of fluorinated graphites (C₂F)_n and (CF)_n, approximately 6 dyn cm⁻¹ [9]. Monolayers of perfluoroalkanoic acids CF₃(CF₂)_nCOOH also have surface energies ranging between 6 and 9 dyn cm⁻¹ if $n \geq 6$ [10]. The same effect is observed for alkanolic acids containing only a re-

latively short perfluorinated segment (at least $\text{CF}_3(\text{CF}_2)_6$) at the end of their alkyl chain, which is then displayed at the surface.

When a hydrophilic functional group is attached to a perfluorocarbon chain the resulting fluorosurfactants (e. g. $n\text{-C}_n\text{F}_{2n+1}\text{COOLi}$, with $n \geq 6$) can reduce the surface tension of water from 72 dyn cm^{-1} to $15\text{--}20 \text{ dyn cm}^{-1}$ compared to $25\text{--}35 \text{ dyn cm}^{-1}$ for analogous hydrocarbon surfactants [11].

Most unusual types of surfactant are the so-called diblockamphiphiles $\text{F}(\text{CF}_2)_m(\text{CH}_2)_n\text{H}$, which have both hydrocarbon and perfluorocarbon moieties. At the interface between an organic and a “fluorous” phase (e. g. a liquid perfluorocarbon) they show the behavior of typical surfactants [12], for example micelle formation.

Whereas intermolecular interactions between perfluoroalkanes are very weak, quite strong electrostatic interactions are observed for some partially fluorinated hydrocarbons (hydrofluorocarbons, HFC), because of local, non-compensated carbon–fluorine dipole moments. The most pronounced effects of this kind are observed when bonds to fluorine and hydrogen arise from the same carbon atom. In such circumstances the polarized C–H bonds can act as hydrogen-bond donors with the fluorine as the acceptor. The simplest example for this effect is difluoromethane. If the boiling points of methane and the different fluoromethanes are compared (Figure 1.5), the non-polar compounds CH_4 and CF_4 are seen to have the lowest boiling points; the more polar compounds CH_3F and CHF_3 boil at slightly higher temperatures. The maximum is for CH_2F_2 , which has the strongest molecular dipole moment and which can – at least in principle – form a three-dimensional hydrogen-bond network similar to that of water with the C–H bonds acting as the hydrogen-bond donors and C–F bonds as the acceptors (Figure 1.6.) [13].

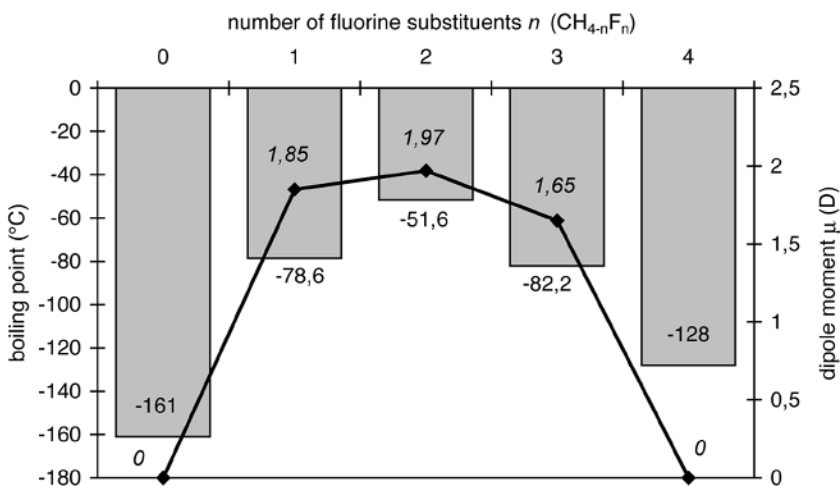


Figure 1.5 Boiling points ($^{\circ}\text{C}$; gray bars) and dipole moments μ (D; \blacklozenge , numerical values in italics) of methane and the different fluoromethanes $\text{CH}_{4-n}\text{F}_n$ [2].

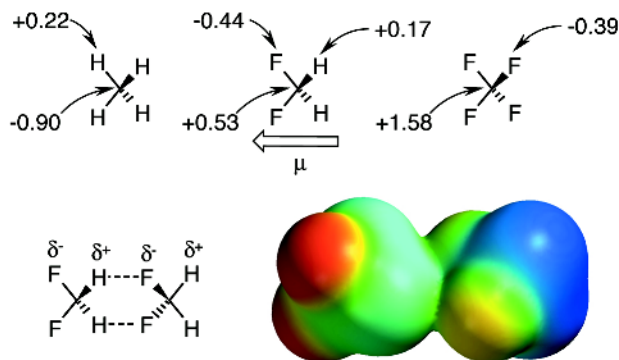


Figure 1.6 *Top*: comparison of the distribution of natural partial charges q (e) on CH_4 , CH_2F_2 , and CF_4 (MP2/6-31+G** level of theory) [14] and (*below*) the calculated structure (AM1) of a doubly hydrogen-bridged difluoromethane dimer. The electrostatic potential (red denotes negative, blue positive partial charges) is mapped on the electron isodensity surface [7].

A different type of strong electrostatic interaction is observed between arenes and perfluoroarenes (a detailed discussion of this phenomenon can be found in Ref. [15]). Benzene (m. p. 5.5°C ; b. p. 80°C) and hexafluorobenzene (m. p. 3.9°C ; b. p. 80.5°C) are known to have very similar phase-transition temperatures. In contrast, an equimolar mixture of both compounds gives a crystalline 1:1 complex melting at 23.7°C , i. e. ca. 19 K higher than the single components [16]. Different from C_6H_6 and C_6F_6 , which crystallize in a edge-to-face, fishbone pattern, $\text{C}_6\text{H}_6 \cdot \text{C}_6\text{F}_6$ co-crystals contain both components in alternating, tilted parallel, and approximately centered stacks with an inter-layer distance of ca. 3.4 \AA and a centroid-centroid distance of ca. 3.7 \AA (Figure 1.7). Neighboring stacks are slightly stabilized by additional lateral $\text{C}_{\text{aryl}}\text{-H} \cdots \text{F}$ contacts [17].

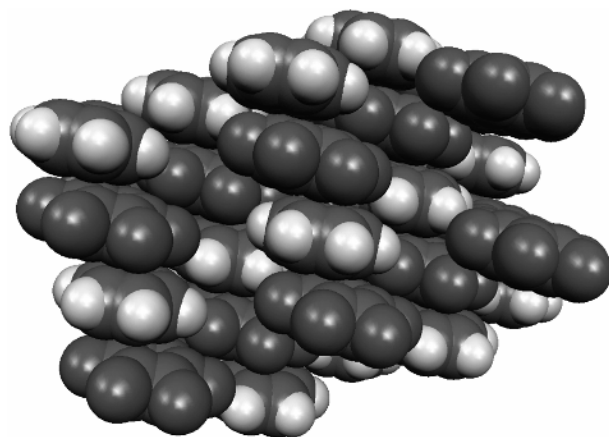


Figure 1.7 X-ray crystal structure of the benzene-hexafluorobenzene 1:1 complex, measured at 30 K in the lowest-temperature modification [17b].

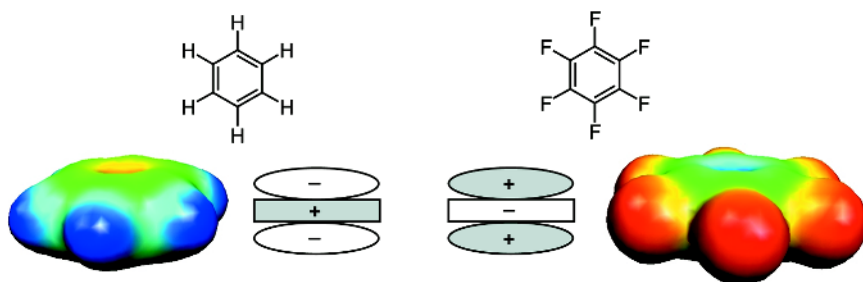


Figure 1.8 Schematic representation of the complementary quadrupole moments of benzene (*left*) ($-29.0 \times 10^{-40} \text{ C m}^{-2}$) and hexafluorobenzene (*right*) ($+31.7 \times 10^{-40} \text{ C m}^{-2}$) [14]. The color pictures show the electrostatic potentials mapped on the isodensity surfaces (B3LYP/6-31G* level of theory) [7, 14]. In benzene (*far left*) the largest negative charge density (coded in red) is located above and below the plane of the π -system. In contrast, in hexafluorobenzene, these locations carry a positive partial charge (coded in blue).

Similar structures have been observed for a variety of other arene-perfluoroarene complexes [15], indicating that this kind of interaction is a generally occurring phenomenon for this type of structure [18]. Evidence based on structural [17] and spectroscopic data [19], and on quantum chemical calculations [20] (Figure 1.8) indicates, that the observed arene-perfluoroarene interactions are mainly the consequence of strong quadrupolar electrostatic attraction [21].

The usual interactions driving “aromatic stacking forces”, for example dispersion interactions with a distance dependence of r^{-6} , seem to play an additional major role in this phenomenon. The occurrence of a charge-transfer complex between electron-rich benzene and electron-deficient hexafluorobenzene can, on the other hand, be excluded by spectroscopic data. The quadrupole moments of benzene ($-29.0 \times 10^{-40} \text{ C m}^{-2}$) and hexafluorobenzene ($+31.7 \times 10^{-40} \text{ C m}^{-2}$) have a very similar order of magnitude but with their different sign the compounds form a complementary pair, interacting with a distance dependence of r^{-5} . The directionality of the quadrupolar interaction is considered to be the main force driving preference for the sandwich-like arrangement of the complementary arenes in the solid state. Ab-initio and DFT calculations gave estimates between -3.7 and $-5.6 \text{ kcal mol}^{-1}$ (assuming an inter-planar distance of 3.6 \AA) for the interaction

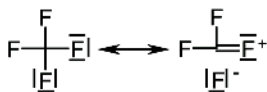


Figure 1.9 Resonance stabilization of the carbon-fluorine bond in tetrafluoromethane, and electrostatic and steric shielding against nucleophilic attack on the central carbon atom. The electrostatic potentials are mapped on the electron isodensity surface (calculation at the MP2/6-31+G* level of theory [7, 14]; red denotes negative, blue positive partial charges).

energy between a parallel, but slightly shifted heterodimer as found in the crystal structure. The interaction within the heterodimer was estimated to be between 1.5 and 3 times stronger than within the corresponding benzene or hexafluorobenzene homodimers. Another interesting result from the calculations is that the contribution of the dispersion interactions to the overall binding energy of the heterodimer is even stronger than that of the electrostatic interaction.

Electrostatic interactions resulting from the polarity of the carbon–fluorine bond play an important role in the binding of fluorinated biologically active compounds to their effectors [22] (discussed in detail in Sections 4.5 and 4.6) and for the mesophase behavior of fluorinated liquid crystals [23] (Section 4.4). The consequences of the low polarizability of perfluorinated molecular substructures have been put into commercial use for chlorofluorocarbon (CFC) refrigerants, fire fighting chemicals, lubricants, polymers with anti-stick and low-friction properties, and fluorosurfactants.

1.4.2

Chemical Properties

The most obvious characteristic of fluoroorganic compounds is the extreme stability of the carbon–fluorine bond. The stability increases with the number of fluorine substituents bound to the same carbon atom. This increase of stability is reflected in the lengths of the C–F bonds in the series CH_3F (140 pm) > CH_2F_2 (137 pm) > CHF_3 (135 pm) > CF_4 (133 pm) (calculation at the MP2/6-31+G** level of theory) [14]. The main reason for this stabilization is the nearly optimum overlap between the fluorine 2s and 2p orbitals and the corresponding orbitals of carbon; this enables the occurrence of dipolar resonance structures for multiply fluorine-substituted carbon (Figure 1.9, see p. 14). The consequences on chemical reactivity of this “self-stabilization” of multiple fluorine substituents on the same carbon atom are discussed in more detail in Section 2.1.3.

In addition to this thermodynamic stabilization, in perfluorocarbons additional kinetic stability is derived from the steric shielding of the central carbon atom by a “coating” of fluorine substituents. The three tightly bound lone electron-pairs per fluorine atom and the negative partial charges are an effective electrostatic and steric shield against any nucleophilic attack targeted against the central carbon atom.

Perfluorocarbons are, therefore, extremely inert against basic hydrolysis. PTFE, for example, can even withstand the action of molten potassium hydroxide. At high temperatures PFC are attacked by strong Lewis acids, for example aluminum chloride. In such reactions decomposition is initiated by the removal of a fluoride ion from the fluorine “protection shield”, rendering the resulting carbocation open to nucleophilic attack. Another mode of degradation of perfluorocarbons is by strong reducing agents at elevated temperatures. Thus PFC are decomposed on contact with molten alkali metals and also on contact with iron at 400–500 °C. The latter type of reaction has even been utilized for industrial synthesis of perfluoroarenes by reductive aromatization of perfluorocycloalkanes (Section 2.1.4.).

Table 1.5 Acidities (pK_a) of organic acids in comparison with their fluorinated analogues [25].

Acid	pK_a
CH ₃ COOH	4.76
CF ₃ COOH	0.52
C ₆ H ₅ COOH	4.21
C ₆ F ₅ COOH	1.75
CH ₃ CH ₂ OH	15.9
CF ₃ CH ₂ OH	12.4
(CH ₃) ₂ CHOH	16.1
(CF ₃) ₂ CHOH	9.3
(CH ₃) ₃ COH	19.0
(CF ₃) ₃ COH	5.4
C ₆ H ₅ OH	10.0
C ₆ F ₅ OH	5.5

Table 1.6 Basicities (pK_b) of organic bases in comparison with their fluorinated analogues [25].

Base	pK_b
CH ₃ CH ₂ NH ₂	3.3
CF ₃ CH ₂ NH ₂	8.1
C ₆ H ₅ NH ₂	9.4
C ₆ F ₅ NH ₂	14.36

Because of its strongly negative inductive effect, fluorine substitution tends to dramatically increase the acidity of organic acids [24, 25] (Table 1.5). For example, the acidity of trifluoroacetic acid ($pK_a = 0.52$) is four orders of magnitude higher than that of acetic acid ($pK_a = 4.76$). Even very weak acids, for example *tert*-butanol ($pK_a = 19.0$), are converted by fluorination into moderately strong acids ((CF₃)₃COH, $pK_a = 5.4$).

The inductive effect of fluorination also reduces the basicity of organic bases by approximately the same order of magnitude (Table 1.6). In contrast with basicity, the nucleophilicity of amines is influenced much less by fluorinated substituents.

Other effects of fluorine substitution in organic compounds include a strong influence on lipophilicity and the ability of fluorine to participate in hydrogen bonding either as a hydrogen-bond acceptor or as an inductive activator of a hydrogen-bond donor group. This behavior has a substantial effect on the biological activity of fluorochemicals and will be discussed in more detail in Section 4.5.

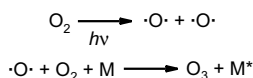
1.4.3

Ecological Impact

Despite or, better, because of their extreme chemical stability perfluorocarbons and halofluorocarbons have a dramatic impact on the global environment; this was nearly impossible to predict when the substances were first introduced into industrial mass-production and ubiquitous use.

1.4.3.1 **Ozone Depletion by Chlorofluorocarbons**

Because of their extreme stability against all kinds of aggressive chemical agent, for example radicals, perfluorocarbons and halofluorocarbons are not degraded in the lower layers of the atmosphere as are other pollutants. After several years, or even decades, they finally reach the stratosphere at altitudes of 20 to 40 km [26, 27]. In this layer, under the influence of short-wave UV irradiation, ozone is formed continuously (Scheme 1.2). This stratospheric ozone plays an essential role in preserving life on earth by absorbing the short-wavelength UV which would otherwise lead to an increase of photochemically induced mutations in most life-forms. For humans, over-exposure to short-wave UV irradiation results in a dramatically increased risk of skin cancer. Many crops and other plants also react rather sensitively towards an increase of UV exposure.



Scheme 1.2 Mechanism of the ozone formation in the stratosphere [26]. Dioxygen is photochemically split into atomic oxygen, which adds to another dioxygen molecule. The excess energy from the recombination is carried away by a collision partner (M).

Although CFC are highly stable in the lower atmospheric layers, in the stratosphere they are slowly photolyzed by the ambient short-wavelength UV radiation which also drives ozone formation. The bonds in CFC most susceptible to photolytic dissociation are the carbon–chlorine bonds; chlorine and perfluoroalkyl radicals are liberated. The chlorine radicals react with ozone with formation of oxygen and chlorooxide radicals, which are recycled back to chlorine radicals by reaction with atomic oxygen, nitrous oxide, nitric oxide, or hydroperoxy radicals (Figure 1.10). Chlorine radicals also react with stratospheric methane to give hydrochloric acid, which is rapidly re-oxidized to chlorine by hydroxyl radicals. In summary, stratospheric ozone is depleted, in a catalytic process, faster than it can be replenished by the natural, UV-driven process [27].

It has also been speculated that the concomitantly generated perfluoroalkyl radicals play a minor role in ozone depletion but, in contrast with chlorine, the trifluoromethyl radical, for example, is cleared from the atmosphere relatively quickly via its irreversible conversion to carbonyl difluoride (CF₂O) [28]. Whereas bromine

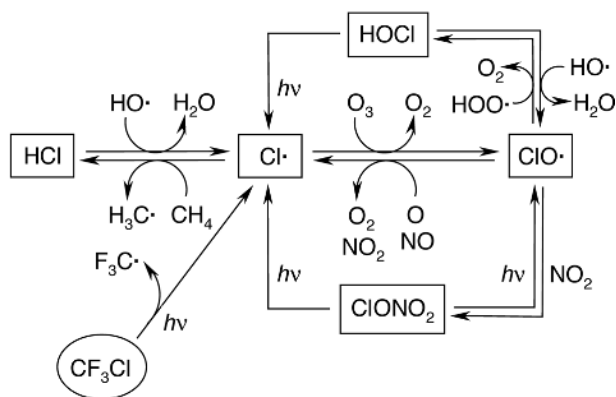


Figure 1.10 Catalytic ozone degradation by CFC in the stratosphere [26].

(arising from bromofluorocarbon-based fire-fighting chemicals, for example CF_2Br_2) has a similar effect to chlorine, fluorine radicals do not contribute very much to ozone depletion, because they are rapidly removed from the catalytic cycle by irreversible formation of highly persistent hydrofluoric acid.

When Molina and Rowland made their prediction in 1974, world production of CFCl_3 and CF_2Cl_2 was approximately 0.3 and 0.5 Mton a^{-1} , respectively; fluorocarbon production in the US was growing by 8.7% per year around 1970 [27]. Six years later, and every year since then, the predicted ozone hole was detected over Antarctica, when the chlorine concentration in the same atmospheric layer was approximately 2000 pmol mol^{-1} [29]. After this clear evidence of the deleterious effects of CFC, in 1987 this class of substance and most bromofluorocarbons were banned from further industrial use in the Montreal Protocol (ratified by the first 29 states in 1989). Because of the decade-long lifetime of stratospheric CFC, their phasing-out can be expected to show an effect no earlier than approximately 2040.

Because CFC had many essential functions in all aspects of our daily life (for example refrigerants, foaming agents, or propellants for aerosol cans), subsequent to the Montreal Protocol an intensive search for potential replacements was initiated. CFC replacements so far include hydrofluorocarbons (HFC; for example CF_3CFH_2 , marketed as HFC-134a), hydrochlorofluorocarbons (HCFC), and partially fluorinated ethers (for example CH_3OCF_3). These substances are much less stable to attack by radicals in the lower atmosphere and thus cannot reach the stratosphere where they would deplete the ozone layer [30].

1.4.3.2 Greenhouse Effect

In addition to their long atmospheric lifetime, fluorocarbons also have strong infrared absorption bands between 1000 and 1400 cm^{-1} , where the atmosphere is relatively transparent. This IR absorption is used for analytical determination of the