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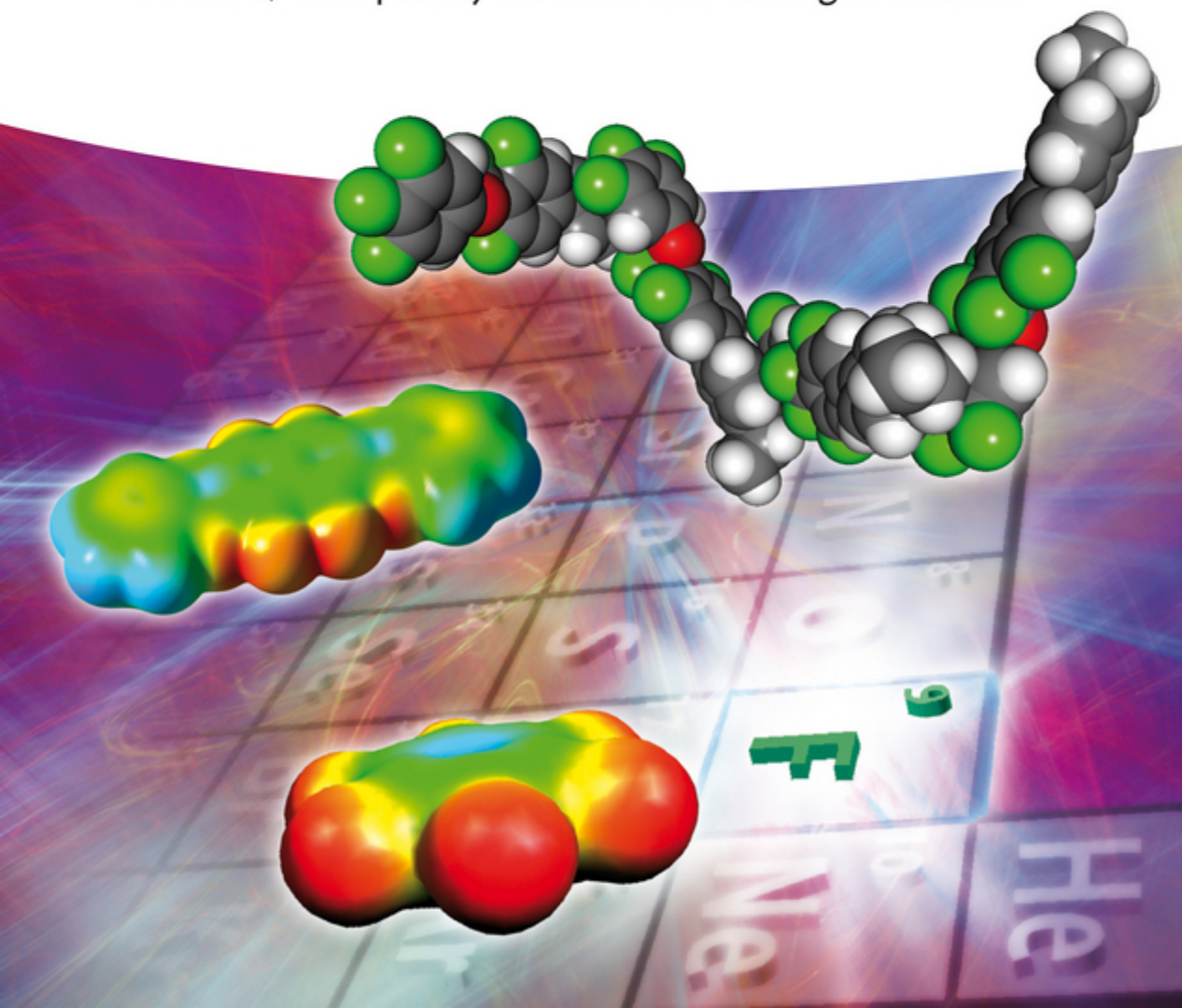
Peer Kirsch

Modern Fluoroorganic Chemistry

Synthesis, Reactivity, Applications

Second, Completely Revised and Enlarged Edition



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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.

Contents

Preface to the Second Edition

Within the few years since the first edition, the landscape of fluorine chemistry has changed dramatically: it is no longer the domain of a highly specialized (and often quite courageous) community, but the field has attracted the attention of mainstream organic and bioorganic chemists. The value of fluorine substitution in bioactive compounds and other functional materials has been widely recognized beyond the boundaries of the traditional fluorine chemistry community. Consequently, the variety of available synthetic methodology has exploded. A review with a reasonable degree of completeness has become impossible, and even the selection of the most significant developments is a very difficult task.

The scope of this book is not to offer a complete review of available methods, but to provide an introduction and a representative overview over the rapidly evolving field for the interested newcomer. It should be used as an entry point for a detailed in-depth study, but it is not intended as a stand-alone encyclopedia of fluorine chemistry. Therefore, there are many omissions, and the selection of the most interesting new developments has often been a matter of taste of the author.

The focus of the second edition is application fields where fluorine is essential for function, and also the chemistry needed to access such compounds. This applies not only to the material sciences but of course also to the biomedical field. On the synthetic side, the most remarkable new development is a huge variety of transition metal-catalyzed methods for the introduction of fluorine and fluorinated groups.

From the conceptual side, the author's choice of the most important new developments has been covered. From the application side, two new areas have been added: fluorinated dyes as one of the first areas of the industrial application of fluorine chemistry was recognized as a gap in the previous edition. In the last 10 years, the field of organic electronics has developed tremendously, and also here fluorine chemistry has found a very specific range of applications. A short review of the role and function of fluorine chemistry in this rapidly developing field has been added.

The author would like to thank the friends and colleagues who have provided their help and valuable input during the update of the text. In particular,

Matthias Bremer, Alois Haas, Ingo Krossing, David O'Hagan, Gerd Röschenthaler, Georg Schulz, Peter and Marina Wanczek, John Welch, and Yurii Yagupolskii supported my project with information and critical discussions. From Wiley-VCH, Anne Brennführer and Lesley Belfit provided me with steady support and encouragement. Most of all, I owe my gratitude to my wife Annette and my son Alexander, who received much less attention than they deserved and who provided an environment where I could make the time for writing a book on top of many other things.

Seeheim-Jugenheim *Peer Kirsch*
January 2013

Preface to the First Edition

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 Röschenthaler, 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.

Darmstadt
May 2004

Peer Kirsch

Abbreviations

acac	Acetylacetonate ligand
aHF	Anhydrous hydrofluoric acid
AIBN	Azobis(isobutyronitrile)
AM	Active matrix
ASV	''Advanced super-V''
ATPH	Aluminum tri[2,6-bis(*tert*-butyl)phenoxide]
BAST	*N*,*N*-Bis(methoxyethyl)amino sulfur trifluoride
BINOL	1,1′-Bi-2-naphthol
Boc	*tert*-Butoxycarbonyl protecting group
Bop-Cl	Bis(2-oxo-3-oxazolidinyl)phosphinic chloride
BSSE	Basis set superposition error
BTF	Benzotrifluoride
CFC	Chlorofluorocarbon
COD	Cyclooctadiene
CSA	Camphorsulfonic acid
Cso	Camphorsulfonyl protecting group
CVD	Chemical vapor deposition
cVHP	Chicken villin headpiece subdomain
DABCO	Diazabicyclooctane
DAM	Di(*p*-anisyl)methyl protecting group
DAST	*N*,*N*-Diethylamino sulfur trifluoride
DBH	1,3-Dibromo-5,5-dimethylhydantoin
DBPO	Dibenzoyl peroxide
DEAD	Diethyl azodicarboxylate
DCC	Dicyclohexylcarbodiimide
DCEH	Dicarboxyethoxyhydrazine
DEC	*N*,*N*-Diethylcarbamoyl protecting group
DFI	2,2-Difluoro-1,3-dimethylimidazolidine
DFT	Density functional theory
DIP-Cl	β-Chlorodiisopinocampheylborane
DMAc	*N*,*N*-Dimethylacetamide
DMAP	4-(*N*,*N*-Dimethylamino)pyridine
DME	1,2-Dimethoxyethane
DMF	*N*,*N*-Dimethylformamide
DMS	Dimethyl sulfide
DMSO	Dimethyl sulfoxide
DSM	Dynamic scattering mode

DTBP	Di-*tert*-butyl peroxide
dTMP	Deoxythymidine monophosphate
dUMP	Deoxyuridine monophosphate
ECF	Electrochemical fluorination
ED	Effective dose
EPSP	5-Enolpyruvylshikimate-3-phosphate
ETFE	Poly(ethylene-*co*-tetrafluoroethylene)
FAR	α-Fluorinated alkylamine reagents
FDA	Fluorodeoxyadenosine
FDG	Fluorodeoxyglucose
FET	Field effect transistor
FFS	Fringe field switching
FITS	Perfluoroalkyl phenyl iodonium trifluoromethylsulfonate reagents
FRPSG	Fluorous reversed-phase silica gel
FSPE	Fluorous solid-phase extraction
F-TEDA	*N*-Fluoro-*N*′-chloromethyldiazoniabicyclooctane reagents
GWP	Global warming potential
HFCF	Hydrofluorocarbon
HFC	Hydrofluorocarbon
HFP	Hexafluoropropene
HMG^+	Hexamethylguanidinium cation
HMPA	Hexamethylphosphoric acid triamide
HSAB	Hard and soft acids and bases (Pearson concept)
IPS	In-plane switching
ITO	Indium tin oxide
LC	1. Liquid crystal 2. Lethal concentration
LCD	Liquid crystal display
LD	Lethal dose
LDA	Lithium diisopropylamide
MCPBA	*m*-Chloroperbenzoic acid
MEM	Methoxyethoxymethyl protecting group
MOM	Methoxymethyl protecting group
MOST	Morpholino sulfur trifluoride
MVA	Multi-domain vertical alignment
NAD^+/NADH	Nicotinamide adenine dinucleotide, oxidized/reduced form
$NADP^+$/NADPH	Nicotinamide adenine dinucleotide phosphate, oxidized/reduced form
NBS	*N*-Bromosuccinimide
NCS	*N*-Chlorosuccinimide
NE	Norepinephrine
NFPy	*N*-Fluoropyridinium tetrafluoroborate
NFTh	*N*-Fluoro-*o*-benzenedisulfonimide
NIS	*N*-Iodosuccinimide
NLO	Nonlinear optics
NMP	*N*-Methylpyrrolidone
NPSP	*N*-Phenylselenylphthalimide

OD	Ornithine decarboxylase
ODP	Ozone-depleting potential
OFET	Organic field effect transistor
OLED	Organic light-emitting diode
OPV	Organic photovoltaics
OTFT	Organic thin-film transistor
PCH	Phenylcyclohexane
PCTFE	Polychlorotrifluoroethylene
PDA	Personal digital assistant
PET	1. Positron emission tomography 2. Poly(ethylene terephthlate)
PFA	Perfluoropolyether
PFC	Perfluorocarbon
PFMC	Perfluoro(methylcyclohexane)
PFOA	Perfluorooctanoic acid
PFOB	Perfluoro-*n*-octyl bromide
PFOS	Perfluorooctylsulfonic acid
phen	Phenanthroline
PI	Polyimide
PIDA	Phenyliodonium diacetate
pip^+	1,1,2,2,6,6-Hexamethylpiperidinium cation
PLP	Pyridoxal phosphate
PNP	Purine nucleoside phosphorylase
PPVE	Poly(heptafluoropropyl trifluorovinyl ether)
PTC	Phase transfer catalysis
PTFE	Polytetrafluoroethylene (Teflon^{TM})
PVDF	Poly(vinylidene difluoride)
PVPHF	Poly(vinylpyridine) hydrofluoride
P3DT	Poly(3-dodecylthiophene)
QM/MM	Quantum mechanics/molecular mechanics
QSAR	Quantitative structure–activity relationships
SAH	*S*-Adenosylhomocysteine hydrolase
SAM	1. *S*-Adenosylmethionine 2. Self-assembled monolayer
SBAH	Sodium bis(methoxyethoxy)aluminum hydride
$scCO_2$	Supercritical carbon dioxide
SFC	Supercritical fluid chromatography
SET	Single electrton transfer
SFM	Superfluorinated material
SPE	Solid-phase extraction
STN	Super-twisted nematic
TADDOL	α,α,α′,α′-Tetraaryl-2,2-dimethyl-1,3-dioxolane-4,5-dimethanol
TAS^+	Tris(dimethylamino)sulfonium cation
TASF	Tris(dimethylamino)sulfonium difluorotrimethylsiliconate, $(Me_2N)_3S^+$ $Me_3SiF_2^-$
TBAF	Tetrabutylammonium fluoride
TBDMS	*tert*-Butyldimethylsilyl protecting group
TBS	See TBDMS

TBTU	*O*-(Benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate
TDAE	Tetrakis(dimethylamino)ethylene
TEMPO	2,2,6,6-Tetramethylpiperidine-*N*-oxide
TFT	Thin film transistor
THF	1. Tetrahydrofuran 2. Tetrahydrofolate coenzyme
THP	Tetrahydropyranyl protecting group
TIPS	Triisopropylsilyl protecting group
TLC	Thin-layer chromatography
TMS	Trimethylsilyl protecting group
TN	Twisted nematic
TPP	Triphenylphosphine
TPPO	Triphenylphosphine oxide
TR	Trypanothione reductase
VHR	Voltage holding ratio
ZPE	Zero point energy

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 [1–14], providing surprises and intellectual stimulation in the whole range of chemistry-related sciences, including theoretical, synthetic, and biomedical chemistry and materials science.

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 fluoroorganic compounds started relatively late in the nineteenth century (Table 1.1). The real breakthrough was the first synthesis of elemental fluorine by Henri Moissan in 1886 [15], but the first defined fluoroorganic compound,

Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications, Second Edition. Peer Kirsch.

Table 1.1 Dates and historical 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
1863	Synthesis of benzoyl fluoride as the first fluoroorganic compound by A. Borodin
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. Fluorinated dyes with enhanced color fastness.
1940s	Polymers (PTFE = Teflon), electrochemical fluorination (H. Simons)
1941–1954	Manhattan Project: highly resistant materials for isotope separation plants, lubricants for gas centrifuges, and coolants
1950s	Fluoropharmaceuticals, agrochemicals, artificial blood substitutes, respiratory fluids, and chemical weapons
1980s	Gases for plasma etching processes and cleaning fluids for the semiconductor industry
1987	The Montreal Protocol initiates the phasing-out of CFCs
1990s	Fluorinated liquid crystals for active matrix liquid crystal displays (AM-LCDs)
2000s	Fluorinated photoresists for the manufacture of integrated electronic circuits by 157 nm photolithography

benzoyl fluoride, had already been prepared and described by the Russian chemist, physician, and composer Alexander Borodin in 1863 [16].

Industrial application of fluorinated organic compounds started at the beginning of the 1930s with the introduction of chlorofluorocarbons (CFCs) as refrigerants [17]. 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 [18]. The Manhattan Project triggered the need for highly resistant materials, lubricants, and coolants and the development of technology for handling extremely corrosive fluoroinorganic compounds. The consumption of hydrofluoric acid as the main precursor of all these materials soared, 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 1960s, more civilian applications of fluorinated pharmaceuticals and materials moved to the forefront [19].

The prediction of the ozone-depleting effect of CFCs in 1974 [20] and the subsequent occurrence of the hole in the ozone layer over the Antarctic in 1980 enforced a drastic reorientation of industrial fluoroorganic chemistry. With the Montreal Protocol in 1987, the phasing-out of most CFCs was initiated. Some of the refrigerants and cleaning chemicals could be replaced by other fluorine-containing

chemicals (for example, hydrofluorocarbons, HFCs 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 [19]. A major and rapidly growing market segment is fluorine-containing fine chemicals for use as intermediates in pharmaceuticals and agrochemistry. Another application in which fluorochemicals have started to play an increasingly dominant role in the last 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 application in liquid crystal displays (LCDs).

1.3 The Basic Materials

Naturally occurring fluorine is composed of the pure $^{19}_{9}F$ isotope. Its relative abundance in the Earth's crust as a whole is 0.027% by weight (for comparison, that of Cl is 0.19% and that of Br is 6×10^{-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 (about 1.4 mg l^{-1}) [21].

The most abundant natural sources of fluorine are the minerals fluorspar and cryolite (Na_3AlF_6). Fluorapatite [$Ca_5(PO_4)_3F$ = "$3Ca_3(PO_4)_2{\cdot}CaF_2$"] is, with hydroxyapatite [$Ca_5(PO_4)_3OH$], a major component of tooth enamel, giving it its extreme mechanical strength and life-long durability. Minor quantities of hydrogen fluoride, fluorocarbons, and even polytetrafluoroethylene (PTFE) are released by volcanoes [22]. Even elemental fluorine (F_2) occurs in Nature, as an inclusion in fluorspar (about 0.46 mg of F_2 per gram of CaF_2). The so-called "stinkspar" or "antozonite," which has been irradiated with γ-radiation from uranium ore, releases a pungent smell on rubbing or crushing [23].

Despite the relatively high abundance of fluorine in the lithosphere, only very few fluoroorganic metabolites have been identified in the biosphere [24]. 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 [24].

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

Table 1.2 Physicochemical properties of hydrofluoric acid [25] (the vapor pressure and density correspond to a temperature of 0 °C).

Property	Anhydrous HF	40% HF–H_2O
Boiling point (°C)	19.5	111.7
Melting point (°C)	−83.4	−44.0
HF vapor pressure (Torr)	364	21
Density (g cm^{-3})	1.015	1.135

(CaF_2). Because HF etches glass with the 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 (pK_a 3.18, 8% dissociation), comparable to formic acid. Other physicochemical properties of hydrofluoric acid are listed in Table 1.2.

Anhydrous hydrofluoric acid (aHF) is obtained by heating Fremi's salt (KF·HF) as a liquid, boiling at 19.5 °C. Similarly to water, aHF has a liquid range of ∼100 °C and a dielectric constant ε of 83.5 (at 0 °C). Associated by strong hydrogen bonding, it forms oligomeric $(HF)_n$ chains with a predominant chain length n of 6–7 HF units [25b]. 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 $c(FHF^-) \times c(HFH^+)$ of $10^{-10.7}$ at 0 °C. In combination with strong Lewis acids, for example, as AsF_5, SbF_5, or SO_3, aHF forms some of the strongest known protic acids. The best known example is "magic acid" (FSO_3H–SbF_5), which can protonate and crack paraffins to give *tert*-butyl cations [25]. 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, it can cause deep lesions and necroses [26, 27]. 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 patient 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, NEt_3·3HF, *N*,*N*-diethylamino sulfur

trifluoride (DAST)) can hydrolyze on contact with the skin and body fluids, liberating hydrofluoric acid with the same adverse consequences.

Nevertheless, when the necessary, relatively simple precautions are taken [26], 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 (approximately +3 V, depending on the pH of aqueous systems), chemical synthesis from inorganic fluorides was impeded by the lack of a suitable oxidant. Therefore, Moissan's first synthesis of fluorine in 1886 by electrolysis of a solution of KF in aHF in a platinum apparatus [28, 29] was a significant scientific breakthrough, and he was awarded the Nobel Prize for Chemistry in 1906 for his discovery (Figure 1.1).

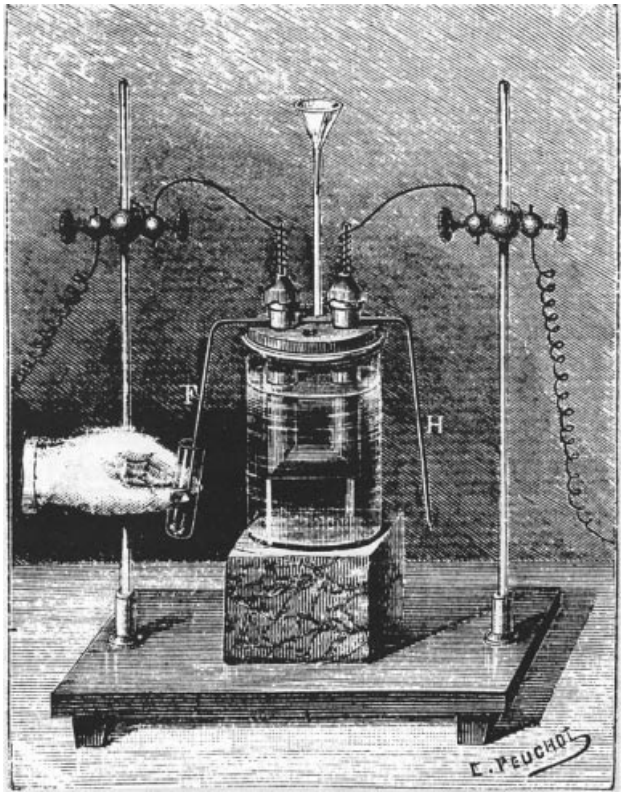


Figure 1.1 The apparatus used by Moissan for the first isolation of elemental fluorine by electrolysis of an HF–KF system in 1886 [28].

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 towards oxidizable substrates. Most organic compounds spontaneously combust or explode on contact with undiluted fluorine at ambient pressure. Because of its high reactivity, fluorine reacts with hot platinum and gold, and even with the noble gases krypton and xenon. In contrast to 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 perfluoropolyether (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 Cl_2) and, on the other hand, to its very high redox potentials of +3.06 and +2.87 V in acidic and basic aqueous media, respectively [30].

Fluorine, as the most electronegative element (electronegativity 3.98) [31], 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 anion. These very unusual characteristics are the reason why fluorine or fluorine-containing nonpolarizable anions can stabilize many elements in their highest and otherwise inaccessible oxidation states (e.g., IF_7, XeF_6, KrF_2, $O_2^+PtF_6^-$, $N_5^+AsF_6^-$).

A purely chemical synthesis of elemental fluorine was achieved by K. O. Christe in 1986 [32] (Scheme 1.1), just in time for the 100th anniversary of Moissan's first electrochemical fluorine synthesis. Nevertheless, in his paper Christe remarked 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 [33] and the strongly fluorophilic Lewis acid antimony pentafluoride at 150 °C.

$$2\,KMnO_4 + 2\,KF + 10\,HF + 3\,H_2O_2 \xrightarrow[50\%\ aq.\ HF]{74\%} 2\,\boldsymbol{K_2MnF_6}\downarrow + 8\,H_2O + 3\,O_2$$

$$K_2MnF_6 + 2\,SbF_5 \xrightarrow[150\ ^\circ C]{>40\%} 2\,KSbF_6 + MnF_3 + \tfrac{1}{2}\,\boldsymbol{F_2}\uparrow$$

Scheme 1.1 The first "chemical" synthesis of fluorine [32].

Nowadays, industrial fluorine production is based on Moissan's original method [21]. 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 the cathode; the anodes are specially treated carbon blocks (Söderberg electrodes). The voltage used is 8–12 V per cell [34]. During the Cold War, the major use of elemental fluorine was in the production of uranium hexafluoride for separation of the ^{235}U isotope. Nowadays, the production of nuclear weapons has moved into the background and large quantities of fluorine are used for preparation of chemicals for the electronics industry [for example, WF_6 for CVD (chemical vapor deposition), SF_6, NF_3, and BrF_3 as etching gases for semiconductor production, and graphite fluorides as cathode materials in primary lithium batteries] and for making inert polyethylene gasoline tanks in the automobile industry.

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 utilized in a variety of different applications ranging from pharmaceutical chemistry to materials science [35].

1.4.1 Physical Properties

The physical properties of fluoroorganic compounds are governed by two main factors: (i) 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 (ii) the resulting extremely low polarizability of fluorine [36].

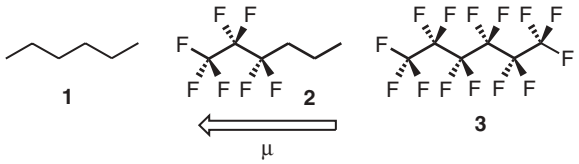
Fluorine has the highest electronegativity of all the elements (3.98) [31], rendering the carbon–fluorine bond highly polar with a typical dipole moment of around 1.4 D, depending on the exact chemical environment (Table 1.3). The apparently contradictory observation that perfluorocarbons (PFCs) are among the most *nonpolar* solvents in existence [e.g., $\varepsilon = 1.69$ 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 nonpolar compound. In semifluorinated compounds, for example, **2**, in which some local dipole moments are not compensated, the effects of the resulting overall dipole moment are 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 PFCs. Linear hydrocarbons have a linear zigzag conformation (Figure 1.2). PFCs, in contrast, have a helical structure, because of the steric repulsion of the electronically "hard" fluorine substituents

Table 1.3 Comparison of the characteristics of carbon–halogen and carbon–carbon bonds (electronegativities from Ref. [31]; van der Waals radii from Ref. [37]; atom polarizabilities from Ref. [38]).

Property	X					
	H	F	Cl	Br	I	C
Bond length C–X (pm)	109	138	177	194	213	—
Binding energy C–X (kcal mol^{-1})	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 C–X, μ (D)	(0.4)	1.41	1.46	1.38	1.19	—
van der Waals radius (pm)	120	147	175	185	198	—
Atom polarizability, α (10^{-24} cm^{-3})	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**) analogs [36].



Property	1	2	3
B.p. (°C)	69	64	57
Heat of vaporization, ΔH_v (kcal mol^{-1})	6.9	7.9	6.7
Critical temperature, T_c (°C)	235	200	174
Density, d^{25} (g cm^{-3})	0.655	1.265	1.672
Viscosity, η^{25} (cP)	0.29	0.48	0.66
Surface tension, γ^{25} (dyn cm^{-1})	17.9	14.3	11.4
Compressibility, β (10^{-6} atm^{-1})	150	198	254
Refractive index, n_D^{25}	1.372	1.190	1.252
Dielectric constant, ε	1.89	5.99	1.69

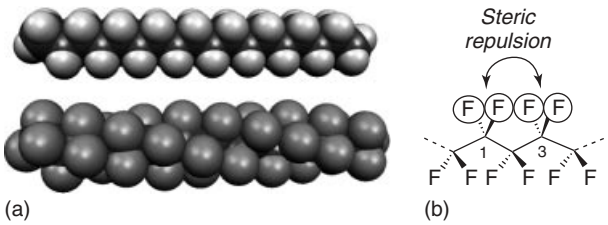


Figure 1.2 The zigzag conformation of octadecane (a) compared with the helical perfluorooctadecane (b), modeled at the PM3 level of theory [39, 40].