FLUORINE COMPOUNDS, ORGANIC

1. Introduction

Fluorine is the most abundant halogen occurrence in the earth's crust, yet fewer than a dozen fluorinated organic compounds are known in Nature and usually they are found at low concentrations in exotic locations (1). Exclusive of these, all organic fluorine compounds are manmade. Of the >23 million compounds registered within the American Chemical Society (ACS) Chemical Abstracts Services (CAS), something just over 1 out of every 10 is a compound with at least one C–F bond. Most of these compounds are disclosed in patents. Fluorochemical published papers, books, and patents during the last decade represent >2% of all published documents (2) found within the CAS database. Global value of the fluorochemical business is conservatively estimated at >$5 billion/year at the producer's level.

Organic fluorine compounds were first prepared in the late nineteenth century. Pioneer work by the Belgian chemist, F. Swarts, led to observations that antimony(III) fluoride reacts with organic compounds having activated carbon–chlorine bonds to form the corresponding carbon–fluorine bonds. Preparation of fluorinated compounds was facilitated by fluorinations with antimony(III) fluoride containing an antimony(V) halide as a reaction catalyst.

It was the 1930s before the direction of organic fluorine chemistry turned commercial (3). Facing the problem of replacing methyl chloride and ammonia in household refrigerators, researchers found that dichlorodifluoromethane (CFC-12) was the best alternative as a safe, nonflammable, stable gas with low

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compressibility in the liquefied state. General Motors and Du Pont jointly lead the early application of chlorofluorocarbons (CFCs) as refrigerants.

Another impetus to expansion of this field was the advent of World War II and the development of the atomic bomb. The desired isotope of uranium, 235U, in the form of UF6 was prepared by a gaseous diffusion separation process of the mixed isotopes. UF_6 is extremely reactive and required contact with inert organic materials as process seals and greases. The wartime Manhattan Project successfully developed a family of stable materials for UF_6 service. These early materials later evolved into the current fluorochemical and fluoropolymer materials industry. A detailed description of the fluorine research performed on the Manhattan Project has been published (4).

CFC concerns arose during the 1970s about the fate of many atmospheric emissions. Chlorine atoms formed by atmospheric CFC destruction lead in turn to progressive depletion of the stratospheric ozone layer. In 1987, the formation and the global support of a multinational forum, called the Montreal Protocol on Substances That Deplete the Ozone Layer, finally led to a landmark agreement to binding reduction and phase-out targets. As a result, CFC production has been totally phased out by the end of the twentieth century (see FLUORINATED ALIPHATIC COMPOUNDS). If hydrogen atoms are introduced into the CFC structure to lower the chlorine content, the resulting hydrochlorofluorocarbon (HCFC) and hydrofluorocarbon (HFC) are more susceptible to environmental degradation in the lower atmosphere before they can reach the stratosphere. However, when a hydrogen atom is introduced into a one-carbon compound as a modified CFC, the boiling point is lowered and may be too low for the same CFC application. Therefore two- and three-carbon fluorinated compounds bearing some hydrogen are more attractive substitutes than the one-carbon modified CFCs. As hydrogen content increases, there is a countereffect of increasing flammability, which in turn limits some end-use HCFC and HFC applications.

2. Physical Properties

Substitution of fluorine for hydrogen in an organic compound has a profound influence on the compound's chemical and physical properties. Several factors that are characteristic of fluorine underlie the observed effects. Fluorine is the most electronegative of all the chemical elements while possessing a small van der Waals radius of 1.47 Å, versus 1.2 Å for hydrogen (5). Carbon–fluorine bonds are strong and possess a low degree of polarizability. Weak intermolecular forces are typical of most organic fluorine compounds due to the repulsion effects of the fluorine–fluorine interactions. These effects are illustrated by comparison

Table 1. **Boiling Points of Halomethanes**

Chlorohydrocarbon	Bp, °C	Fluorohydrocarbon	CAS Registry number	Bp, °C	Difference per F atom, °C
CH_3Cl	−24	CH_3F	[593-53-3]	−79	55
CH_2Cl_2	40	CH_2F_2	[75-10-5]	−52	46
$CHCl_3$	61	CHF_3	[75-46-7]	−82	48
CCl_4	77	CF_4	[75-73-0]	−128	51

Table 2. **Boiling Points of Hydrocarbons and Fluorocarbons**

Hydrocarbon	Bp, °C	Fluorocarbon	CAS Registry number	Bp, °C
CH_4	−161	CF_4	[75-73-0]	−128
C_2H_6	−88	C_2F_6	[76-16-4]	−78
C_3H_8	−45	C_3F_8	[76-19-7]	−38
C_4H_{10}	0.6	C_4F_{10}	[355-25-9]	−5
C_7H_{16}	98	C_7F_{16}	[355-57-9]	82
C_6H_6	80	C_6F_6	[392-56-3]	82
C_6H_{12} (cyclic)	81	C_6F_{12} (cyclic)	[355-68-0]	52

of properties of fluorocarbons to chlorocarbons and to hydrocarbons in Tables 1 and 2.

The replacement of chlorine by fluorine results in a nearly constant boiling point (bp) drop of ∼50°C for every chlorine atom that is replaced (see Table 1). In Table 2, a similar boiling point effect with hydrocarbons is apparent, even though the molecular weight of the fluorocarbon is much higher than the corresponding hydrocarbon analogue. An analogous drop in the corresponding fluorocarbon freezing point results in a widened liquid range for applications like lubricating fluids and greases. One other significant property difference, attributed to weak intermolecular forces, can be found in the very low surface tensions of fluorocarbons as compared to hydrocarbons and water (Table 3).

The low surface tension of highly fluorinated organic compounds is commercially important for their application in surfactants, antisoiling textile treatments, lubricants, and specialty wetting agents.

In contrast, the viscosities of fluorocarbons are higher than those of the corresponding hydrocarbons. This can be explained by the greater stiffness of the fluorocarbon chain arising from the large repulsive forces between molecules, and from the greater density imparted by the more massive fluorine atoms (vs, hydrogen). The fluorocarbon viscosity drops rapidly with increasing temperature and is accompanied by a simultaneous large decrease in density.

The refractive indexes and dielectric constants for the fluorocarbons are both lower than that for the corresponding hydrocarbon analogue.

Table 3. **Surface Tensions of Selected Fluids**

Compound	CAS Registry number	Surface tension, 20 °C, mN/m (= dyn/cm)
perfluoroheptane	[335-57-9]	13.6
perfluoromethylcyclohexane	[355-02-2]	15.4
perfluoro-1,4-dimethylcyclohexane	[374-77-6]	16.3
octane	[111-65-9]	21.8
benzene	[71-43-2]	28.9
methyl bromide	[74-83-9]	41.5
water	[7732-18-5]	72.8

2.1. Preparation. Various methods are briefly described for the synthesis of selected fluorinated compounds. There are many known ways to introduce fluorine into organic compounds, but hydrogen fluoride, HF [7664-39-3], is considered to be the most economical source of fluorine for many commercial applications.

Halogen Exchange. The exchange of a non-fluorine halogen atom in an organic compound for a fluorine atom is the most widely used method of fluorination. The relative ease of replacement follows the general order $I > Br > Cl$. Commonly used fluorinating agents are the fluorides of the alkali metals (especially KF) and antimony.

Antimony trifluoride, SbF_3 [7783-56-4], can be used in the following preparations (6):

$$RCOCl \xrightarrow{SbF_3} RCOF \quad (1)$$

$$C_6H_5CCl_3 \xrightarrow{SbF_3} C_6H_5CF_3 \quad (2)$$

$$R_2C = C(R) - CCl_3 \xrightarrow{SbF_3} R_2C = C(R)\text{-}CF_3 \quad (3)$$

$$RCCl_2R \xrightarrow{SbF_3} RCF_2R \quad (4)$$

$$CHCl_2OCH_2Cl \xrightarrow{SbF_3} CHF_2OCH_2F \quad (5)$$

The limitations of this reagent are several. It cannot be used to replace a single unactivated halogen atom with the exception of the chloromethyl ether (eq. 5) to form the difluoromethyl fluoromethyl ether [461-63-2]. It also cannot be used to replace a halogen attached to a carbon–carbon double bond. Fluorination of functional group compounds, eg, aldehydes, ketones, acids, esters and sulfides, produces decomposition products caused by scission of the carbon–carbon bonds.

The effectiveness of antimony fluoride is increased if it is used in conjunction with chlorine or with antimony pentachloride. The formation of either $SbCl_2F_3$ or a complex of SbF_3 and $SbCl_5$ probably accounts for the increased activity (6).

Antimony pentafluoride, SbF_5 [7783-70-2], is a highly active fluorinating agent and is generally used only to fluorinate completely halogenated compounds, since those containing hydrogen as well as halogen, usually undergo decomposition. In the case of halogenated olefins or aromatic compounds (7), addition as well as substitution occurs. Thus hexachlorobenzene forms a fluorochlorocyclohexene [27458-17-9]:

$$C_6Cl_6 \xrightarrow{SbF_5} C_6Cl_2F_8 \quad (6)$$

Potassium fluoride, KF [7789-23-3], is the most frequently used of the alkali metal fluorides, although reactivity of the alkali fluorides is in the order $CsF > RbF > KF > NaF > LiF$ (8).

The preference for KF is based on cost and availability traded off against relative reactivity. In its anhydrous form, it can be used to convert alkyl, aryl and sulfonyl halides to the fluorides. The reaction versatility makes it suitable for

halogen exchange in various functional organic compounds like alcohols, acids and esters (9). For example, 2,2-difluoroethanol [359-13-7] can be made as shown in equation (9) and methyl difluoroacetate [433-53-4] as in equation (10).

$$RX \xrightarrow{KF} RF \tag{7}$$

$$RSO_2Cl \xrightarrow{KF} RSO_2F \tag{8}$$

$$CHCl_2CH_2OH \xrightarrow{KF} CHF_2CH_2OH \tag{9}$$

$$CHCl_2CO_2CH_3 \xrightarrow{KF} CHF_2CO_2CH_3 \tag{10}$$

The preparation of fluoroaromatics by the nucleophilic reaction of fluoride ion with a ring activated mono- or polychloroaromatic, like hexachlorobenzene, has received considerable attention as the Halex reaction (10). Ring activation is achieved through the presence of one or more electron-withdrawing groups that "activate" the halogen site toward exchange with fluoride. Since KF has a low solubility in most aprotic solvents, nucleophilic fluoride exchange rates are slow, unless high surface area KF and reaction additives like crown ethers or phase-transfer catalysts are also employed.

Two KF fluorination methods were developed and include either the use of a preferred aprotic, dipolar solvent such as *N*-methylpyrrolidone (11) or no solvent (12). These methods plus findings that various fluoroaryl derivatives are effective pesticides, fungicides (13), and herbicides prompted development of a commercial process for the production of polyfluorobenzenes (10,14). The process uses a mixture of sodium and potassium fluorides or potassium fluoride alone in dimethylsulfoxide or sulfolane solvent.

Hydrogen fluoride, HF, when used alone is a comparatively ineffective exchange agent and will replace only active halogens (15), eg, acyl fluorides from acyl chlorides and benzotrifluoride [98-08-8] from benzotrichloride (eq. 11).

$$C_6H_5CCl_3 \xrightarrow{HF} C_6H_5CF_3 \tag{11}$$

When used with antimony pentachloride, the reactivity of HF is comparable to $SbCl_2F_3$ alone. Therefore a continuous fluorination exchange process is possible where antimony is the fluoride carrier from HF to the organic fluoride.

$$SbCl_5 + 3\ HF \rightarrow SbCl_2F_3 + 3\ HCl \tag{12}$$

$$SbCl_2F_3 + CHCl_3 \rightarrow SbCl_4F + CHClF_2 \tag{13}$$

$$SbCl_4F + 2\ HF \rightarrow SbCl_2F_3 + 2\ HCl \tag{14}$$

Since antimony halides serve as fluorine carriers, the actual fluorination agent is HF. This process is the principal one used in the production of CFCs and $CHClF_2$ (HCFC-22) [75-45-6] as well as many others. The application is well suited to the fluorination of one-carbon through three-carbon containing organic halides. In practice, the HF and organic halide enter by separate feeds into the process vessel. Heating under pressure, the liquid-phase reaction forms HCl and the organic fluoride. By suitable control of the feed ratios,

temperature, pressure and residence time, the degree of fluorination can be controlled. As the reaction progresses, vapors of HCl and the organic fluoride are continuously vented off for separation and recovery. Antimony salts stay in the process vessel and are periodically reactivated by treatment with chlorine to form the desired antimony(V) halide salts prior to reuse.

Heterogeneous vapor-phase fluorination of a chlorocarbon or chlorohydrocarbon with HF over a supported metal catalyst is an alternative to the liquid-phase process. Salts of chromium, nickel, cobalt, or iron on an AlF_3 support are considered viable catalysts in pellet or fluidized powder form. This process can be used to manufacture CFCs and HCFC-22, but is hampered by the formation of over-fluorinated by-products with little to no commercial value. The most effective application for vapor-phase fluorination is where all the halogens are to be replaced by fluorine, as in manufacture of 3,3,3-trifluoropropene [677-21-4] (16) for use in polyfluorosilicones.

$$CCl_3CH_2CH_2Cl \xrightarrow{HF} 4\ HCl + CF_3CH{=}CH_2 \qquad (15)$$

Another use of hydrogen fluoride, although not in halogen exchange, is the addition reaction with olefins. The addition reaction with acetylene forms 1,1-difluoroethane (HFC-152a) [75-37-6] and vinyl fluoride [75-02-5] (eq. 16), however controlled reaction conditions can alternatively lead to one or the other product as desired. Care must be exercised since HF is also an excellent olefin polymerization catalyst. Thermal cracking of HCF-152a produces vinyl fluoride and HF.

$$HC{\equiv}CH + HF \longrightarrow CH_3CHF_2 + CH_2{=}CHF \qquad (16)$$

Reaction conditions must be controlled since HF is also an excellent olefin polymerization catalyst. Controlled reaction conditions can alternatively lead to vinyl fluoride or to HFC-152a (CH_3CHF_2). The latter can be thermally cracked to form vinyl fluoride and HF.

Sulfur tetrafluoride, SF_4 [7783-60-0], replaces halogen in haloalkanes, haloalkenes, and aryl chlorides, but is only effective (even at elevated temperatures) in the presence of a Lewis acid catalyst. The reagent is most often used in the replacement of carbonyl oxygen with fluorine (17,18). Aldehydes and ketones react readily, particularly if no alpha-hydrogen atoms are present (eg, benzal fluoride [455-31-2] from benzaldehyde), but acids, esters, acid chlorides, and anhydrides are very sluggish. However, these reactions can be catalyzed by Lewis acids (HF, BF_3, etc). While highly effective in converting aryl carboxylic acids to trifluoromethylated analogues (eg, benzotrifluoride [98-08-8] from benzoic acid), SF_4 suffers from major drawbacks of high cost, high toxicity and ready hydrolysis.

$$C_6H_5CHO + SF_4 \rightarrow C_6H_5CHF_2 \qquad (17)$$

$$C_6H_5CO_2H + SF_4 \rightarrow C_6H_5CF_3 \qquad (18)$$

Halogen Fluorides. These include compounds such as IF_3, IF_5, ClF, etc, of which only a few, ClF, ClF_3, BrF_3, and IF_5 are used to some extent. They act

both as halogen exchange agents and, in the case of the monofluorides, as addition agents to unsaturated carbon–carbon bonds (19).

Replacement of Hydrogen. Three methods of substitution of a hydrogen atom by fluorine are (*1*) reaction of a C–H bond with elemental fluorine (direct fluorination), (*2*) reaction of a C–H bond with a high valence state metal fluoride like AgF_2, CoF_3, or CuF_2, and (*3*) electrochemical fluorination in which the reaction occurs at the anode of a cell containing a source of fluoride, usually HF.

Direct Fluorination. The principal disadvantage of elemental fluorine use as a fluorinating agent is the high heat of reaction. A considerable degree of carbon–carbon bond scission can occur as well as polymer formation. In order to prevent these complications, fluorine is diluted with nitrogen and the reaction zone is constructed such that good heat conductivity is possible. Low temperatures are favored to achieve maximum selectivity and yield (20). Fluorine is also effective for the fluorination of residual hydrogen in a highly fluorinated organic molecule to produce the corresponding fluorocarbon.

The fluorination reaction is best described as a radical-chain process involving fluorine atoms (21) and hydrogen abstraction as the initiation step. If the molecule contains unsaturation, addition of fluorine also takes place (19). Complete fluorination of complex molecules can be conducted using this method (see FLUORINE COMPOUNDS, ORGANIC-DIRECT FLUORINATION).

Reaction with a Metal Fluoride. A second technique for hydrogen substitution is the reaction of a higher valence metal fluoride with a hydrocarbon to form a fluorocarbon:

$$2\ CoF_2 + F_2 \rightarrow 2\ CoF_3 \quad (19)$$

$$2\ CoF_3 + RH \rightarrow RF + 2\ CoF_2 + HF \quad (20)$$

The principal advantage to this method is that the heat evolved for each carbon–fluorine bond formed, 192.5 kJ/mol (46 kcal/mol), is much less than that obtained in direct fluorination, 435.3 kJ/mol (104 kcal/mol). The reaction yields are therefore much higher and less carbon–carbon bond scission occurs.

The reactivity of the metal fluoride appears to be associated with the oxidation potential of the metal. For example, AgF replaces halogen in organic compounds, while AgF_2 replaces hydrogen.

The reaction is conducted by passing fluorine through a bed of AgCl or $CoCl_2$ at an elevated temperature to form the higher valence state fluorides. The organic reactant as vapor is then passed through the bed to realize a semicontinuous fluorination process. In general, the method is used for the preparation of fluorocarbons since any unsaturation or functionality in the reactant is usually removed. The process can also be used to fluorinate polychlorohydrocarbons, whereby replacement of both chlorine and hydrogen occurs (4). Only two metal fluorides are of practical use, AgF_2 and CoF_3. The recent use of CuF_2 at elevated temperatures shows a high selectivity for fluorination of benzene to fluorobenzene [462-06-6]. The spent CuF is easily regenerated back to CuF_2 with HF and oxygen (22) and serves as one example of environmentally "green" chemistry.

Electrochemical Fluorination. The electrochemical fluorination (ECF) of highly fluorinated organic compounds (23) involves the electrolysis of an organic reactant in liquid anhydrous HF at a voltage below that for liberation of fluorine.

The reaction is limited by temperature (usually done at 0° C) and by the solubility of the reactant in HF. Electrical conductivity is required for current to flow and the reaction to proceed. Current density is 1–2 A/dm^2 and cell voltages of 4.5–7.0 V. Fluorination takes place at the nickel anode by a stepwise, free radical process not involving the intermediate formation of elemental fluorine. Hydrogen is liberated at the cathode. Recent studies seem to confirm that reversible formation of a hypervalent nickel fluoride film at the anode surface is the actual fluorinating agent attacking chemisorbed compounds with C–H bonds. The process is used to fluorinate acyl halides, sulfonyl halides, ethers, carboxylic acids, and amines. The product is a fluorocarbon having no residual hydrogen. Olefins and carbocyclics, as well as heterocyclic compounds, become saturated. Side reactions, resulting in reduced yields, include cleavage of carbon–carbon bonds and polymer formation. The ECF yields decrease with increasing number of carbon atoms in the feed structure.

ECF is successfully used on a commercial scale to produce certain perfluoroacyl fluorides, perfluoroalkylsulfonyl fluorides, perfluoroalkyl ethers, and perfluoroalkylamines. The perfluoroacyl fluorides and perfluoroalkylsulfonyl fluorides can be hydrolyzed to form the corresponding acid and acid derivatives. Examples include perfluorooctanoyl fluoride [335-66-0], perfluorooctanoic acid [335-67-1], perfluorooctanesulfonyl fluoride [307-35-7], perfluorooctanesulfonic acid [1763-23-1], and *tris*(perfluoro-*n*-butyl)amine [311-89-7].

$$C_7H_{15}COCl \xrightarrow[HF]{ECF} C_7F_{15}COF \rightarrow C_7F_{15}CO_2H \quad (21)$$

$$C_8H_{17}SO_2Cl \xrightarrow[HF]{ECF} C_8F_{17}SO_2F \rightarrow C_8F_{17}SO_3H \quad (22)$$

$$(C_4H_9)_3N \xrightarrow[HF]{ECF} (C_4F_9)_3N \quad (23)$$

Telomer Formation. Fluorinated compounds with an active C–Br or C–I bond can add to a fluoroolefin to form addition products in high yield. The olefin most often used is tetrafluoroethylene (TFE) [116-14-3]. Telomerization involves reacting a telogen, or addition agent like $CBrF_3$ [75-63-8], CF_3I [2314-97-8], or C_2F_5I [354-64-3], with an olefin to form a longer chain addition product called telomer. The reaction is initiated by thermolysis, photolysis, free radical initiators, halogen fluorides (IF_5), certain metal complexes, and various redox chemicals. By control of the stoichiometry and reaction conditions, a simple 1:1 addition product or telomers with high fluorine content can be formed. The yield is higher than that seen with ECF production methods. The route does suffer from a distribution of adducts formed instead of one specific reaction product. The usual adducts are perfluoroalkyl iodides [25398-32-7] having up to 14 carbon atoms in the alkyl chain.

$$C_2F_5I + X\ CF_2 = CF_2 \rightarrow C_2F_5(CF_2CF_2)_xI \quad (24)$$

Often used as mixtures, the telomers are subsequently converted to commercial surfactants and stain-resistant fiber finishes through functionalizing steps using standard chemical reactions of the C–I bond.

Aromatic Ring Fluorination. The selective introduction of fluorine at specific unactivated aryl ring positions is desirable for preparation of certain fluorinated compounds requiring one or more fluorine. The formation of an aryl diazonium fluoride salt, followed by decomposition is a classical reaction (the Schiemann Reaction) for aryl fluoride preparation (24). This method has been adapted to the commercial manufacture of fluorobenzene (25), where HF is the source of the fluoride. Alternatively, the Halex reaction (10) may be utilized if there is an activated aromatic halogen to be displaced by fluoride.

$$C_6H_5NH_2 \xrightarrow{NaNO_2/HF} C_6H_5N_2^+F^- \xrightarrow{-N_2} C_6H_5F \qquad (25)$$

3. Chemical Properties and Applications

Substitution of fluorine into an organic molecule results in enhanced chemical stability. The resulting chemical reactivity of adjacent functional groups is drastically altered due to the large inductive effect of fluorine. These effects become more pronounced as the degree of fluorine substitution is increased, especially on the same carbon atom. This effect demonstrates a maximum in the fluorocarbons and their derivatives.

3.1. Fluorinated Alkanes. As the fluorine content increases, the chemical reactivity decreases until complete fluorination is achieved, after which the alkane is inert to most chemical attack, including the highly reactive element fluorine. Their lack of reactivity leads to their use in certain commercial applications where stability is valued when in contact with highly reactive chemicals.

Fluorinated Olefins. In electrophilic addition reactions, the reactivity of the unsaturated linkage is reduced by the inductive effect of fluorine. Nucleophilic additions are enhanced by this same effect. Amines, phenols, alcohols and many other nucleophiles, including fluoride ion, add to the carbon–carbon double bond of highly fluorinated olefins (26). Free radical addition of halogen halides proceeds easily using either peroxide or thermal initiation. Some halides, especially those derived from iodine, eg, ICl, react by an ionic mechanism. Fluorinated olefins also undergo free radical polymerization producing a wide range of valuable fluoropolymers.

Certain CFCs are used as raw materials to manufacture key fluorinated olefins to support polymer applications. Thermolysis of HCFC-22 affords TFE and hexafluoropropene [116-15-4] under separate processing conditions. Dechlorination of CFC-113 forms chlorotrifluoroethylene [79-38-9]. Vinylidene fluoride [75-38-7] is produced by the thermal cracking of HCFC-142b [75-68-3].

Fluorinated Aromatic Hydrocarbons. Many aromatic fluorocarbon derivatives, eg, hexafluorobenzene, octafluorotoluene [434-64-0] and perfluoronaphthalene [313-72-4] are examples of compounds that readily undergo nucleophilic ring substitution reactions with loss of one or more fluorine substituents. This is in sharp contrast to the fluorine substituents in perfluoroalkanes. Perfluoroalkyl substitution on the aromatic ring has a strong inductive effect, making the ring more susceptible to nucleophilic attack. Fluorine hyperconjugative effects are considered to be unimportant (27) in these reactivity patterns, leaving inductive effects as the primary factor to describe the substituent effect.

Fluorinated Heterocyclic Compounds. Heterocyclic compounds containing the CF_3 group are prepared by methods similar to those used in the fluorination of aliphatic compounds. The direct action of fluorine on uracil yields the cancer chemotherapy agent, 5-fluorouracil [51-21-8], as one special example of a selective fluorination on a commercial scale (28).

Fluorinated Acids. This class of compounds is characterized by the strength of the fluorocarbon acids, eg, trifluoroacetic acid [76-05-1] approaching that of mineral acids. This property results from the strong inductive effect of fluorine and is markedly less when the fluorocarbon group is moved away from the carbonyl group. Generally, their reactions are similar to organic acids and they find applications, particularly trifluoroacetic acid and its anhydride [407-25-0], as promoters in the preparation of esters and ketones and in nitration reactions.

Fluorinated Biologically Active Compounds. Many biologically active compounds are prepared from fluorobenzene, difluorobenzene, benzotrifluoride, and fluorinated steroids. The preparation of fluorinated compounds for use in medicine has increased rapidly (29,30) since the 1950s. The strong interest in these substances is based on the following considerations: (*1*) fluorine most closely resembles bioactive hydrogen analogues with respect to steric requirements at the receptor sites; (*2*) fluorine alters electronic effects, owing to its high electronegativity; (*3*) fluorine imparts improved oxidative and thermal stability to the parent molecule; (*4*) fluorine imparts lipid solubility, thereby increasing the *in vivo* absorption and transport rates across membranes.

Many fluorinated, biologically active agents have been developed and successfully used in the treatment of human diseases. The biological property of fluorinated organics has been further extended to applications in the agrochemical, veterinary and pest management fields.

Analgesics. Four examples of anti-inflammatory agents are Sulindac [38194-50-2], based on a mono fluoro indene derivative, diflunisal [22494-42-4], based on a substituted difluorobenzene, dexamethasone [50-02-2] and fluocinonide [356-12-7] based on monofluorinated and difluorinated steroids, respectively.

Antibiotic. Ciprofloxacin hydrochloride [93107-08-5] is effective prophylaxis for inhalation anthrax exposure, while enrofloxacin [93106-60-6] is useful as a veterinary antibiotic. Both compounds are based on fluoroquinolone.

Antidepressant. Fluoxetine hydrochloride is a widely used compound containing the *p*-trifluoromethylphenyl group.

Antifungal Agents. The oral antifungal Fluconazole [86386-73-4] is a heterocyclic compound containing a difluorophenyl group. Flucytosine [2022-85-7] is a mono fluorinated cytosine.

Antiviral. Trifluridine [70-00-8] is a trifluoromethyl substituted heterocyclic antiviral agent.

Appetite Depressant. Fenfluramine hydrochloride [404-82-0] is an anorexiant based on a meta-substituted benzotrifluoride.

Diruetic. The diuretic and antihypertensive agent bendroflumethiazide [73-48-3] is a benzotrifluoride-based pharmaceutical.

Inhalation Anesthetics. Examples of highly fluorinated halocarbons and ethers are halothane [151-67-7], fluroxene [406-90-6], enflurane [13838-16-9], methoxyflurane [76-38-0], sevoflurane [28523-86-6], desflurane [57041-67-5], isoflurane [26675-46-7] and pure enantiomers (31) of isoflurane as potentially

more effective anesthetic compounds than the racemic mixture. Halothane is largely replaced by isoflurane as the leading U.S. inhalation anesthetic mainly due to the increasing numbers of outpatient surgery and the resulting rapid body clearance of this anesthetic. Desflurane, enflurane and sevoflurane also enjoy global use. Methoxyflurane is used only in veterinary applications.

Tranquilizers. Fluphenazine hydrochloride [146-56-5], trifluoperazine hydrochloride [440-17-5], and triflupromazine [146-54-3] are all trifluoromethyl substituted phenothiazine chemicals useful in the management of psychotic disorders. Haloperidol [52-86-8] is a non-phenothiazine antipsychotic drug bearing a fluorophenyl substituent.

Fungicides. Flusilazole [85509-19-9] is a broad spectrum foliar fungicide containing two fluorophenyl substituents with application on cereal, fruit and vegetable crops. Flutriafol [76674-21-0] is another fluorobenzene derivative useful on small grain cereal diseases.

Herbicides. Fluometuron [2164-17-2] is a fluorophenyl substituted urea effective against grassy and broadleaf weeds in bean, grain, fruit and cotton crops. Trifluralin [1582-09-8] is a trifluoromethyl substituted dinitroaniline used as preemergence control against weeds in cotton and soybean crops. Profluralin [26399-36-0] and benfluralin [1861-40-1] are structural analogues of trifluralin. Fluorodifen [15457-05-3] is a trifluoromethyl substituted diphenyl ether used for weed control in bean and rice crops. Fluroxypyr [81406-37-3] is a fluoropyridine compound used on cereals for postemergent control of broadleaf weeds.

Insecticides. Diflubenzuron [35367-38-5] is a difluorobenzoyl urea. It inhibits insect chitin formation during larval molting. Application is with management of fruit, bean and cotton crops. Perfluoroalkylsulfonamides of carbon chain length equal to 6 or 8 show good control against fire ants.

Rodenticides. Flocoumafen [90035-08-8] is a trifluoromethylphenyl substituted anticoagulant compound useful against rats resistant to other such agents.

4. Economic Aspects

Domestic production of CFCs is now nonexistent due to environmental pressures. CFC production outside of the United States is also mostly curtailed or will be so in the third world countries during the next few years. Replacement of CFCs with HCFC and HFC production is widespread. Much of the former CFC production equipment has been successfully modified to accommodate, where possible, the new HCFC and HFC processes while saving considerable capital and associated production costs. Development of acceptable, alternative products is still ongoing due to the small HCFC ozone depletion effect and general global warming concerns. As the largest global supplier, Du Pont alone has spent well over $500 million cumulatively through 2000 to develop alternatives.

The alternatives are generally higher in price and many require retrofitting into the desired application because they are not direct “drop in” replacements. Global production of refrigerant chemicals and foam blowing agents continues to decrease due to conservation in use, elimination of emissive uses, and substitutions with non-fluorinated alternatives. Future aggregate market

growth is estimated at only 1% per annum *versus* historical values near 5%. Refrigerant chemicals are a $1 billion global enterprise. Olefinic fluorochemical production, hence the demand for both HCFC-22 and HCFC-142b as feedstock, is increasing to support the global fluoropolymer marketplace growth at 7%/annum. The global fluorochemical business is estimated at >$5 billion with about one-half of that being in the United States. The largest supplier is Du Pont with 25% of the global market share and one-third of the U.S. share. Atofina and Honeywell are close as second largest suppliers globally, while Honeywell is the second largest in the United States.

The 1991 global production for combined CFC, HCFC, and HFC chemicals, also generically called "fluorocarbons" in some reference sources, was 872,538 metric tons (t). Peak production back in 1988 reached 1,285,851 t, however, in 2001 it had dropped to only 545,896 t (32). These totals do not include captive feedstock fluorocarbons used in turn to manufacture fluoropolymers. A stable HCFC-22 production level is attributable to growing TFE demand for poly(tetrafluoroethylene) production, at its annual growth rate of 4–5%, offset by the decreasing refrigerant use. Global fluorocarbon production capacity in 2001 was split roughly as one-half in the North American area, one-third in western Europe and the remaining one-sixth in Japan.

The refrigerant CFC chemicals are replaced primarily with 1,1,1,2-tetrafluoroethane (HFC-134a) [811-97-2] at an annual global growth rate of 10–15%. Annual worldwide HFC-134a production is estimated to be >160,000 t. Europe tends to favor the low temperature refrigerant HFC-32 for air conditioning applications, while global refrigerant blends of HFC-32, HFC-125, HFC-134a, and 1,1,1-trifluoroethane (HFC-143a) [420-46-2] are sold to achieve a variety of special temperature targets. Fluorination of 2,2-dichloro-1,1,1-trifluoroethane (HCFC-123) [306-83-2] is employed to manufacture 2-chloro-1,1,1,2-tetrafluoroethane (HCFC-124) [2837-89-0], which in turn is fluorinated to 1,1,1,2,2-pentafluoroethane (HFC-125) [354-33-6].

The commercialization of HCFCs is pursued only as a stopgap measure until the ideal HFC is developed. Rigid and spray foam blowing agent applications have switched from CFCs to 1,1-dichloro-1-fluoroethane (HCFC-141b) [1717-00-6]. With a planned worldwide phase out of HCFC-141b underway, the switch to 1-chloro-1,1-difluoroethane (HCFC-142b) is well underway while further replacements, like HFC-245fa and HFC-365mfc, are still emerging.

4.1. Aliphatic Fluorocarbon Production—United States. The annual total production capacity is shown in parentheses (10^3 t) throughout each of the following detailed sections. Albemarle reportedly is offering unspecified key fluoro compounds in t quantities from its Baton Rouge, La. production site. Atofina (formerly Elf Atochem) has combined capacity (50.0) for both HCFC-141b and HCFC-142b as well as increased HFC-134a (18.1) capability at the Calvert City, Ky. facility. Their Wichita, Kan. site has HCFC-22 (34.9) capability. The Thorofare, N.J. Ausimont USA site has captive plant capacity for HCFC-142b (18.1) to support fluoropolymer manufacture. Du Pont closed its Antioch, Calif. plant. They produce HCFC-123 at Maitland, Ontario, HCFC-141b at Montague, Mich., and have capability for both HFC-152a (15.0) and HCFC-22 (100.0) at Louisville, Ky. and for HFC-152a (18.1) along with HCFC-124/HFC-134a/143a (45.4 combined) at their Corpus Christi, Tex. site. Their global HFC-134a capacity

is the world's largest with capability spread over Corpus Christi, Deepwater and Ponca City, Okla. sites. Their announced combined capacity for HFC-125 (9.1) with others at Deepwater, N.J. is through use of a multiple product process unit. They recently introduced 1,1,1,2,2,3,4,5,5,5-decafluoropentane (HFC-43-10mee) [138495-42-8] as a new nonflammable liquid for specialty solvent utility. Great Lakes Chemical Company, in a joint venture with INEOS Fluor, has agreed to produce a pharmaceutical grade 1,1,1,2,3,3,3-heptafluoropropane (HFC-227ea) [431-89-0] as aerosol propellant for an asthma inhalation drug. Their production facility at El Dorado, Ark. has a combined capacity (4.0) for HFC-32, HFC-227ea (a Halon replacement), and 3,3,3-trifluoropropene. They claim to be the largest U.S. producer of HFC-32. Honeywell (merged with former Allied-Signal) closed their Danville, Ill. plant. They produce both HCFC-141b and HCFC-142b (36.3 combined) at the El Segundo, Calif. site. The production of HCFC-22 (50.0), HFC-143a (9.1) and HFC-32 (0.9) is conducted at their Baton Rouge, La. facility. The highly flexible Geismer, La. plant has capacity to produce HCFC-124 (13.6) and HFC-125/134a (13.6). The Geismer plant also has capacity to produce 1,1,1,3,3-pentafluoropropane (HFC-245fa) [460-73-1] (18.0) and a plan was also announced to double their unspecified HFC-227ea capacity. INEOS Fluor (formerly ICI Klea) has HFC-134a (74.6) capacity with an unspecified amount of HFC-32 and HFC-125 at the Saint Gabriel, La. plant. LaRoche Industries, Inc. closed all of its fluorochemical production and mothballed its Gramercy, La. swing plant for HCFC-22 production. Solvay Fluor purchased the Ausimont fluorochemical business, but Ausimont USA retains its vinyl fluoride capability at the Thorofare, N.J. site. HCFC-141b and HCFC-142b can be used as feedstock for vinylidene fluoride manufacture.

4.2. Aliphatic Fluorocarbon Production—Europe. Atofina capacity at Pierre-Benite, France is for HCFC-22 (24.5), CFC-114/115 (7.0), HFC-125 (7.0), HFC-134a (17.0), and HCFC-141b/142b (40.0) production. The Atofina site at Zaramillo, Spain has unspecified HFC-32 and HFC-143a capability, while their site at Alonsotegui, Spain has HFC-143a (9.0) and HCFC-22 (20.0) capacity. Du Pont at their Dordrecht, Netherlands site has HCFC-22 (35.0) and HFC-134a (1.0) capability. Enichem has HFC-125 (9.0) capacity at its Porto Marghera, Italy facility, but chooses to produce HFC-134a (10.0) while recently announcing a plan for a 50% capacity increase. At Spinetta-Marengo, Italy, the Enichem capacity is directed at HCFC-22 (25.0). Fluorochemie at Frankfurt, Germany has captive HCFC-22 (15.0) capacity in turn sold to Dyneon for fluoropolymers manufacture. Honeywell is planning another HFC-245fa global production site either in Europe or in Asia, but could decide on its CFC site at Weert, Netherlands. INOES Fluor has U.K. capacity for HCF-125 and for HFC-134a (14.0 for each) plus HCFC-22 (28.0) at Runcorn. They also have a small capability to produce HFC-32 (1.0) in a second U.K. site at Widnes. Phosphoric Fertilizers Industry has a site at Thessaloniki, Greece for HCFC-22 (12.0). Rhodia Ltd. (formerly Rhone Poulenc) has capacity at Bristol, U.K. for HCFC-22 (8.0). Solvay Fluor (acquired former Hoechst fluorochemicals business) has HFC-134a (10.0) capacity at Frankfurt, and HCFC-22 (12.0) at Bad Wimpfen, both sites in Germany. The Solvay Fluor site at Vilaseca, Spain has both HFC-227ea (4.0) and HCFC-22 (10.0) capabilities. Solvay Fluor has entered into a supply agreement with Atofina to provide 1,1,1,3,3-pentafluorobutane (HFC-365mfc)

[406-58-6] (15.0) from their Tavaux, France site. This site also possesses HCFC-141b/142b (29.0) and HFC-152a (1.5) capacity.

4.3. Aliphatic Fluorocarbon Production—PacificRim/India. In Japan, Asahi Glass Company, Ltd. has HCFC-22 (18.0) capacity in addition to ability for others (2.0) at their Ichihara plant and the same situation at their Kashima plant. Central Glass Company, Ltd. has HCFC-141b capacity (8.0) and an HFC-245fa pilot plant with plans for an increase (8.0 of each) at their Kawasaki plant. Daikin Industries, Ltd. has HCFC-22 (10.0), HFC-125 (6.0), HFC-134a (5.0), HCFC-141b (10.0), and HCFC-142b (5.0) capacity at its Kashima site and HCFC-22 (25.0) and HFC-32 (4.0) at the Settsu site. Daikin also produces captive chlorotrifluoroethylene, TFE and vinyl fluoride for polymer manufacture. Du Pont-Mitsui Fluorochemicals Company, Ltd. has production capacity for HFC-134a (12.0) in Ichihara and HCFC-22 (20.0) at the Shimizu plant. INEOS Fluor has capacity to produce HFC-134a (18.0) and an unspecified amount of HFC-32 at Mihara. Showa Denko KK has combined capability (10.0) for both HFC-125 and HFC-134a at the Kawasaki site. In China, Atofina and 3F Materials Company have formed a joint venture business to produce a variety of unspecified HFC compounds (15.0). Many small Chinese companies produce fluorochemicals, but details are sketchy. It is estimated that China currently has HFC-134a operational capacity (5.0). The Shandong Dongyue Chemical Company has HCFC-22 capacity (100.0) to support both domestic refrigerant use and TFE manufacture. Zhonghao New Chemical Materials Co., Ltd. reports it has capacity to produce HCFC-22 (10.0), HCFC-142b (20.0), HFC-152a (5.0), and HFC-227ea (0.6). In Korea, Ulsan Chemical Co., Ltd. has a total capacity (23.0) for combined HCFC-22, HCFC-141b, and HCFC-142b. In Taiwan, Formosa Plastics Corp. has this same mix of fluorochemicals with identical capacities. India has an estimated collective fluorocarbon capacity (12.8) at Chemplast Sanmar Ltd., Hindustan Flurocarbons, Ltd. and Navin Fluorine Industries.

4.4. Aliphatic Fluorocarbon Production—Other. Regarding production of all other aliphatic fluorochemicals, the processes vary. The Minnesota Mining and Manufacturing Company, or 3M, manufactures specialty perfluorochemicals using mainly ECF methods at their St.Paul, Minn. and Decatur, Ala. sites. Asahi Glass, Bayer AG, Daikin Industries, Dainippon Inc., Kanto Denka Kogyo Co., Miteni, and Tokuyama Soda all reportedly either use ECF processes or have filed patents on them. Fluoroolefin telomerization technology is practiced by Asahi Glass, Du Pont, and Hoechst AG at a variety of their sites to manufacture a line of perfluorinated specialty chemicals for stain-resistant treatment, surfactant applications as well as specialty fluids. The fluoroolefins are also polymerized and copolymerized to manufacture a range of either plastic or elastomeric products. MDA Manufacturing Inc. (a Daikin and 3M joint venture) manufactures combined HCFC-22, ECF products and other unspecified fluorochemical intermediates (18.1) at the Decatur, Ala. plant site. The captive HCFC-22 production is converted both to TFE for Daikin use at their Decatur fenceline plant and to hexafluoropropene to be used by 3M at their Decatur plant. Halocarbon Products of North Augusta, S. C. manufactures a variety of monofluoro- and trifluoroacetic acids and their derivatives for direct sale.

4.5. Aromatic Fluorocarbon Production—Global. The aromatic fluorine intermediates (AFI) global market (25.0) is growing at 7%/year with a

valuation of nearly $1 billion. Global production capacity is double the market size (33). AFI consumption is segmented into the following end markets: ~45% in agrochemicals, >30% in pharmaceuticals and the rest in polymers, dyes, surfactants, and liquid-crystal applications. Most AFI production is structured around manufacture of either benzotrifluoride or fluorinated benzenes. Over the past decade, the following companies have reportedly produced various AFIs: Asahi Glass (Japan) (0.8), Du Pont (Deepwater, N.J.) (1.4), ICI Fine Chemicals (Grangemouth, U.K.) (15.9), Mallinckrodt (St. Louis, Mo.) (1.2), Miteni (Italian subsiderary of Mitsubisbi Corporation) (1.0), Riedel de Haen (subsiderary of Hoechst AG) (1.6), Rhodia Ltd. (France) (1.0); and Zeneca (U.K.) (2.5). Occidental Chemical (Niagra Falls, N.Y.) ceased production in 1999 at its new benzotrifluoride plant (20.0) after only 9 months of operation. The entire facility is available for sale. Asahi Glass has announced their development of a new continuous fluorobenzene process with an estimated 30–40% reduced cost but commercialization timing is unclear. Due to economic factors, new AFI production has gradually shifted to China and India. The following Chinese companies are listed with annual capacity for fluorobenzene and for 2,4-dichlorofluorobenzene [1435-48-9], respectively: Liaoyang High-Tech Industrial Development Corp. (Liaoning district) (1.0, 0.0); Pingquan Longwei Chemical Corp. (Hebei district), (0.6, 0.0); Xunpeng Chemical Co., Ltd. (Jiangxi district), (2.5, 2.0); Yancheng Fuyuan Chemical Co., Ltd. (Jiangsu district), (1.5, 1.2). Dongyang Weihua Chemical Co., Ltd. (Zhejiang district) has capacity for benzotrifluoride (10.0) and chlorinated benzotrifuorides (7.0). Dongyang Kangfeng Organofluorine Chemicals (Zhejiang district) cites their benzotrifluoride (1.5) and chlorinated benzotrifluoride (2.0) capacities in addition to producing combined amino and nitro functional benzotrifluorides (2.3). In India, Tanfac Industries Ltd. (Cuddalore, Tamilnadu) is producing fluorobenzene (0.12) and 2,4-dichlorobenzene (0.15) to partly address the India-wide demand (1.6) in support of fluoroquinolone drug manufacture.

5. Health and Safety Factors

The safety of fluorine compounds is possibly as varied as the numbers of compounds known that bear fluorine substituents. Most fluorine compounds are manmade and therefore not normally encountered in Nature. Aerosol or vapor inhalation is the most likely route of exposure where adverse health effects may occur. All new fluorine compounds should be handled with caution as one would do with any potentially hazardous substance until full toxicological properties are known. Existing fluorine compounds cover the range from biologically inert materials, like fluorocarbon fluids suitable for potential blood substitutes (34) (see BLOOD, ARTIFICIAL), through to biologically active materials like the very highly toxic octafluoroisobutylene [382-21-8]. The toxicity of one chemical versus another chemical is not predictable based on the number or the site of fluorine substituents. The major commercial fluorinated compounds, like the CFCs, exhibit a very low order of toxicity (35). The potential cardiotoxicity from inhalation of bronchiodilator aerosols using CFCs as propellants is well documented in the medical literature.

Many new fluorinated drug and agrochemical agents were discovered based initially on the properties that a C−F bond imparts to a molecule. Its size similarity to the C−H bond analogue allows entry into a binding site for a subsequent biological effect. The more stable linkage allows for longer term effects with slower metabolism and excretion. Some compounds possess toxic e7ffects attributable to fluoride ion toxicity and irritation of the respiratory system may be a common response, but many others demonstrate a more complex biological behavior. Long term inhalation studies with HCFC-123 as a CFC alternative have shown non-malignant tumors in male rats (36). The behavior is characteristic of this specific compound and while unexpected, it is not representative of the family of fluorinated two-carbon compounds as a whole. Many of the other members of this family show excellent safety from inhalation toxicity testing. Fluorinated inhalation anesthetics require inhalation efficacy and safety acquired only by trial and error testing. Much of the work on anesthetics heralds back to the early refrigerant development work and the safety studies that were conducted to identify this important property (37).

BIBLIOGRAPHY

"Nomenclature, Physical Properties, Reactions and Methods of Fluorination" under "Fluorine Compounds, Organic," in *ECT* 1st ed., Vol. 6, pp. 735–751, by E.T. McBee, O. R. Pierce, and W. F. Edgell, Purdue University; "Introduction" in *ECT* 2nd ed., under "Fluorine Compounds, Organic," Vol. 9, pp. 686–704, by E.T. McBee, C. J. Norton, and T. Hodgins, Purdue University; in *ECT* 3rd ed., Vol. 10, pp. 829–839, by O.R. Pierce, Dow Corning Corp.; in *ECT* 4th ed., Vol. 11, pp. 467–482, by W. X. Bajzer and Y. K. Kim, Dow Corning Corp.; "Fluorine Compounds, Organic, Introduction" in *ECT* (online), posting date: December 4, 2000, by William X. Bajzer and Yung K. Kim, Dow Corning Company.

CITED PUBLICATIONS

1. D. O'Hagan and D. B. Harper, *J. Fluorine Chem.* **100**, 1217 (1999).
2. J. Schmidt (Dow Corning Corp.), on-line search of *Chemical Abstracts Services* document database, March, 2004; H. Schofield, *J. Fluorine Chem.* **100**, 7 (1999).
3. U.S. Pat. 1,833,847 (Nov. 24, 1931), T. Midgley, Jr., A. L. Henne, and R. McNary, (to Frigidaire Corp.) and related patents.
4. C. Slesser and S. R. Schram, *Preparation, Properties and Technology of Fluorine and Organic Fluorine Compounds*, McGraw-Hill Book Co., Inc., New York, 1951.
5. A. Bondi, *J. Phys. Chem.* **68**, 441 (1964).
6. A. L. Henne, in R. Adams and co-workers, eds., *Organic Reactions*, Vol. II, John Wiley & Sons, Inc., New York, 1944, pp. 49–93.
7. E. T. McBee, P. A. Wiseman, and G. B. Bachman, *Ind. Eng. Chem.* **39**, 415 (1947).
8. N. N. Vorozhtsov and G. G. Yacobson, *Khim. Nauka Prom.* **3**, 403 (1958).
9. E. Gryszkiewicz-Trochimowski, A. Sporzynski, and J. Wnuk, *Rec. Trav. Chim.* **66**, 413 (1947).
10. J. H. Clark and co-workers, eds., *Aromatic Fluorination*, 1996, pp. 19–55.
11. J. T. Maynard, *J. Org. Chem.* **28**, 112 (1963).
12. N. N. Vorozhtsov, V. E. Platonov, and G. G. Yakobson, *Izvest. Akad. Nauk SSSR, Ser. Khim.* **8**, 1524 (1963).

13. G. C. Finger, F. H. Reed, and L. R. Tehon, *Ill. State Geol. Surv. Circ.* **199**, 1 (1955).
14. W. Prescott, *Chem. Ind. (London)* **2**, 56–63 (1978).
15. K. Wiechert, in W. Bockemuller, *Newer Methods of Preparative Organic Chemistry*, rev. ed., Interscience Publishers, Inc., New York, 1948, pp. 315–368.
16. U.S. Pat. 4,465,786 (Aug. 14, 1984), M. F. Zimmer, W. E. Smith, and D. F. Malpass, (to General Electric Co.); U.S. Pat. 4,798,818 (Jan. 17, 1989), W. X. Bajzer and co-workers (to Dow Corning Corp.).
17. G. W. Parshall, *J. Org. Chem.* **27**, 4649 (1962).
18. W. C. Smith, *Angew Chem. Int. Ed. Engl.* **1**, 467 (1962).
19. W. K. R. Musgrave, in M. Stacey and co-workers, eds., *Advances in Fluorine Chemistry*, Vol. 1, Butterworth & Co. Ltd., London, 1960, pp. 1–28.
20. W. E. Jones and E. G. Skolnik, *Chem. Rev.* **76**, 563 (1976); R. J. Lagow and J. L. Margrave, in S. J. Lippard, ed., *Progress in Inorganic Chemistry*, Vol. 26, John Wiley & Sons, Inc., New York, 1979, pp. 161–210.
21. S. T. Purrington, B. S. Kagen, and T. B. Patrick, *Chem. Rev.* **86**, 997 (1986).
22. M. A. Subramanian and co-workers, *Science* **297**, 1665 (2002).
23. J. H. Simons and co-workers, *J. Electrochem. Soc.* **95**, 47 (1949); J. Burdon and J. C. Tatlow, in Ref. 16, pp. 129–165; S. Nagase, in P. Tarrant, ed., *Fluorine Chemistry Reviews*, Vol. 1, Marcel Dekker, New York, 1967, pp. 77–106.
24. A. Roe, in R. Adams and co-workers, eds., *Organic Reactions*, Vol. V, John Wiley & Sons, Inc., New York, 1949, pp. 193–228.
25. U.S. Pat. 4,822,927 (April 18, 1989), N. J. Stepaniuk, and B. J. Lamb (to Mallinckrodt, Inc.).
26. R. D. Chambers and R. H. Mobbs, in M. Stacey and co-workers, eds., *Advances in Fluorine Chemistry*, Vol. 4, Butterworth & Co., Ltd., London, 1965, pp. 50–112.
27. D. Holtz, *Chem. Rev.* **71**, 139 (1971).
28. U.S. Pat. 3,954,758 (May 4, 1976), P. Schuman and co-workers (to PCR Inc.); U.S. Pat. 4,029,661 (June 14, 1977), R. Anderson, P. Schuman, G. Westmoreland (to PCR Inc.); U.S. Pat. 4,082,752 (April 4, 1978), S. Misaki and T. Takahara (to Daikin Kogyo Co. Ltd.).
29. R. Filler, in R. E. Banks, ed., *Organofluorine Chemicals and Their Industrial Applications*, Ellis Horwood Ltd., Chichester, U.K., 1979.
30. *AMA Drug Evaluation*, 3rd ed., Publishing Sciences Group, Inc., Littleton, Mass., 1977.
31. C. G. Huang, *Abstracts of the 203rd National Meeting of the American Chemical Society*, abstract #FLUO-018, San Francisco, April 5–10, 1992.
32. AFEAS (Alternative Fluorocarbons Environmental Acceptability Study), *Production, Sales and Emissions Statistics of Fluorocarbons Through 2001*, AFEAS online, 1333 H Street, N.W., Washington, D.C., 2002; United States International Trade Commission (USITC), *Synthetic Organic Chemicals—United States Production and Sales*, 1993, publication #2810, Washington D.C., Nov., 1994; R. Will, A. Leder, J. Riepl and A. Kishi, *Fluorocarbons* in *Chemical Economics Handbook*, Sections 543.7000 through 543.7005, SRI International, Menlo Park, Calif., April, 2001.
33. *Chem, Eng, News*, 13 (Jan. 4, 1988); 27 (Nov. 27, 1989); H. Clark, D. Wails, and T. W. Bastock, eds., *Aromatic Fluorination*, CRC Press, 1996, p. 58.
34. J. G. Riess and M. LeBlanc, in K. C. Lowe, ed., *Blood Substitutes; Preparation, Physiology and Medical Applications*, Ellis Horwood, Ltd., Chichester, U.K., 1988, pp. 94–129.
35. G. D. Clayton and F. E. Clayton, eds., *Patty*'s Industrial Hygiene and Toxicology, Vol. 2B, 3rd rev. ed., John Wiley & Sons, Inc., New York, 1981.
36. *Chem. Eng. News*, 26 (July 8, 1991); P. Zurer, *Chem. Eng. News* 21 (July 22, 1991).

37. E. R. Larsen, in P. Tarrant, ed., *Fluorine Chemistry Reviews*, Vol. 3, Marcel Dekker, 1969, pp. 1–44.

GENERAL REFERENCES

R. E. Banks, *Preparation, Properties and Industrial Applications of Organofluorine Compounds*, Ellis Horwood Ltd., Chichester, U.K., 1982.

R. E. Banks and M. G. Barbour, *Fluorocarbon and Related Chemistry*, Vols. 1–3, The Chemical Society, Burlington House, London, 1971–1976.

R. E. Banks, D. W. A. Sharp, and J. C. Tatlow, eds., *Fluorine: The First Hundred Years (1886–1986)*, Elsevier Sequoia, Lausanne, Switzerland, 1986.

R. E. Banks, B. E. Smart, and J. C. Tatlow, eds., *Organofluorine Chemistry: Principles and Commercial Applications*, Plenum Press, New York, 1994.

R. E. Banks, ed., *Organofluorine Chemicals and Their Industrial Applications*, Ellis Horwood, Ltd., Chichester, U.K., 1979.

R. D. Chambers, *Fluorine in Organic Chemistry*, John Wiley & Sons, Inc., New York, 1973.

R. D. Chambers, ed., *Organofluorine Chemistry: Fluorinated Alkenes and Reactive Intermediates*, Topics in Current Chemistry No. 192, Springer-Verlag, New York, 1997.

R. D. Chambers, ed., *Organofluorine Chemistry: Techniques and Synthons*, Topics in Current Chemistry No.193, Springer-Verlag, New York, 1997.

J. H. Clark, D. Wails, and T. W. Bastock, eds., *Aromatic Fluorination*, CRC Press, Cleveland, Ohio, 1996.

R. Filler, Y. Kobayashi, and L. M. Yagupolskii, eds., *Organofluorine Compounds in Medicinal Chemistry and Biomedical Applications, Studies in Organic Chemistry*, Vol. 48, Elsevier Science Publications BV, Amsterdam, The Netherlands, 1993.

T. Fuchigami, in P. S. Mariano, ed., *Advances in Electron Transfer Chemistry*, Vol. 6, JAI Press, Inc., Stamford, Conn., 1999, pp. 41–130.

L. German and S. Zemskov, eds., *New Fluorinating Agents In Organic Synthesis*, Springer-Verlag, New York, 1989.

M. Howe-Grant, ed., *Fluorine Chemistry: A Comprehensive Treatment*, Kirk-Othmer Encyclopedia Reprint Series, John Wiley & Sons, Inc., New York, 1995.

M. Hudlicky, *Chemistry of Organic Fluorine Compounds*, 2nd ed., Ellis Horwood, Ltd., Chichester, U.K., 1976.

M. Hudlicky, *Chemistry of Organic Fluorine Compounds: A Laboratory Manual with Comprehensive Literature Coverage*, Ellis Horwood, Chichester, U.K., 1992.

M. Hudlicky and A. E. Pavlath, eds., *Chemistry of Organic Fluorine Compounds II: A Critical Review*, ACS Monograph Series No.187, American Chemical Society Publishers, Washington, D.C., 1995.

M. Hudlicky, *Fluorine Chemistry for Organic Chemists—Problems and Solutions*, Oxford University Press, New York, 2000.

E. Kissa, *Fluorinated Surfactants: Synthesis, Properties, Applications*, Surfactant Science Series, Vol. 50, Marcel Dekker, New York, 1994.

I. L. Knunyants and G. G. Yakobson, *Synthesis of Fluoroorganic Compounds*, Springer-Verlag, New York, 1985.

C. G. Krespan and V. A. Petrov, *Chem. Rev.* **96**, 3269 (1996).

V. P. Kukhar' and V. A. Soloshonok, eds., *Fluorine-Containing Amino Acids, Synthesis and Properties*, John Wiley & Sons, Inc., New York, 1995.

J. F. Liebman, A. Greenberg, and W. R. Dolbier, Jr., eds., *Fluorine-Containing Molecules: Structure, Reactivity, Synthesis and Applications*, VCH Publishers, Inc., New York, 1988.

A. M. Lovelace, D. A. Rausch, and W. Postelnek, *Aliphatic Fluorine Compounds*, Reinhold Publishing Corp., New York, 1954.
J. Michel, ed., *Chem. Rev.* **96**, special thematic issue on Fluorine Chemistry (1996).
A. W. Miziolek and W. Tsang, eds., *Halon Replacements: Technology and Science*, ACS Symposium Series No. 611, American Chemical Society Publishers, Washington, D.C., 1995.
T. Nakajima, *Fluorine-carbon and Fluorine-carbon Materials: Chemistry, Physics, and Applications*, Marcel Dekker, New York, 1995.
I. Ojima, J. R. McCarthy, and J. T. Welch, eds., *Biomedical Frontiers of Fluorine Chemistry*, ACS Symposium Series No. 639, American Chemical Society Publishers, Washington, D.C., 1996.
G. A. Olah, R. D. Chambers, and G. K. S. Prakash, eds., *Synthetic Fluorine Chemistry*, John Wiley & Sons, Inc., New York, 1992.
A. E. Pavlath and J. E. Leffler, *Aromatic Fluorine Compounds*, Reinhold Publishing Corp., New York, 1962.
P. V. Ramachandran, ed., *Asymmetric Fluoroorganic Chemistry: Synthesis, Applications and Future Directions*, ACS Symposium Series No. 746, American Chemical Society Publisher, Washington, D.C., 2000.
J. Scheirs, ed., *Modern Fluoropolymers: High Performance Polymers for Diverse Applications*, John Wiley & Sons, Inc., New York, 1997.
G. Siegemund and co-workers, in W. Gerhartz and co-workers, eds., *Ullmann's* Encyclopedia of Industrial Chemistry, 5th rev. ed., Vol. A11, VCH Publishers, New York, 1988.
J. H. Simons, ed., *Fluorine Chemistry*, Vols. 1–5, Academic Press, Inc., New York, 1950–1964.
W. A. Sheppard and C. M. Sharts, *Organic Fluorine Chemistry*, Benjamin, Inc., New York, 1969.
P. Tarrant, ed., *Fluorine Chemistry Reviews*, Vols. 1–8, Marcel Dekker, Inc., New York, 1967–1977.
J. C. Tatlow and co-workers, eds., *Advances in Fluorine Chemistry*, Vols. 1–7, W. A. Benjamin, Inc., New York, 1960–1973.
N. Taylor, ed., *Fluorinated Carbohydrates: Chemical and Biochemical Aspects*, ACS Symposium Series No. 374, American Chemical Society Publisher, Washington, D.C., 1988.
J. S. Thrasher and S. H. Strauss, eds., *Inorganic Fluorine Chemistry: Toward the 21st Century*, ACS Symposium Series No. 555, American Chemical Society Publisher, Washington, D.C., 1994.
J. T. Welch and S. Eswarakrishnan, *Fluorine in Bioorganic Chemistry*, John Wiley & Sons, Inc., New York, 1991.
J. T. Welch, *Selective Fluorination in Organic and Bioorganic Chemistry*, ACS Symposium Series No. 456, American Chemical Society Publisher, Washington, D.C., 1991.

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