Journal of Fluorine Chemistry, 33 (1986) 361 - 375

Chapter 13

BIOLOGICALLY-ACTIVE FLUOROCHEMICALS

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Introduction

Since the mid-1950s, progress in organic fluorine chemistry has been rapidly translated into useful applications in medicine and biochemistry.

Advances in the area have been accelerated by the development of new techniques and reagents for the site-selective introduction of fluorine into organic molecules; and in some cases, synthetic methodologies have been developed specifically for the preparation of drugs [1, 2]. Nowadays, fluorine-containing medicinals feature significantly in such diverse areas as the provision of anti-cancer and anti-viral agents, anti-inflammatory and anti-parasitic agents, antibiotics and general anaesthetics, and in cardiac therapy and the treatment of mental illness. Fluorocarbon emulsions continue to show promise as blood substitutes, and several important techniques in medical diagnosis, e.g. positron emission tomography and the use of X-ray contrast agents, have profited through the use of fluorinated substances. Several books have provided useful surveys of the field in recent years [3 - 6].

Why fluorine in bioactive molecules?

The incorporation of fluorine in drug molecules as a means of increasing therapeutic efficacy is based on several considerations:

1. Fluorine, the second smallest substituent, closely mimics hydrogen with respect to steric requirements at enzyme receptor sites (van der Waals' radii: F, 1.35 Å; H, 1.2 Å).
2. The strong electron-withdrawing inductive effect of fluorine (see pp. 229, 232) can significantly influence reactivity and stability of functional groups and the reactivity of neighboring reaction centers.
3. The substitution of hydrogen by fluorine at or near a reactive site frequently causes inhibition of metabolism because of the high C—F bond energy (see footnote 2, p. 227).
4. The replacement of hydrogen by fluorine usually increases lipid solubility, thereby enhancing the rates of absorption and transport of drugs *in vivo*. The trifluoromethyl group (CF_3) is among the most lipophilic of all substituents. In many cases, this factor may be the most significant in improving pharmacological activity.

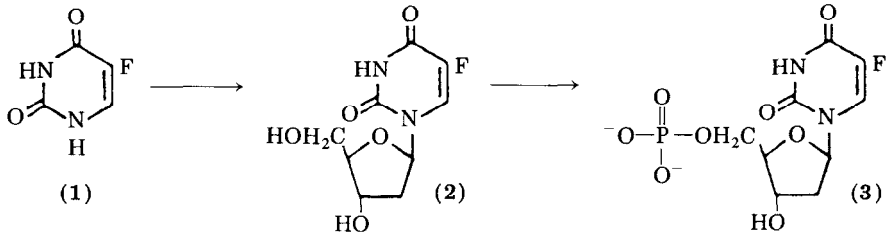
0022-1139/86/$3.50

5. Sometimes, as in the case of 5-fluorouracil (1), the presence of fluorine instead of hydrogen actually blocks an essential biochemical reaction: the fluorine behaves as a 'deceptor' group.

Anti-cancer and anti-viral agents

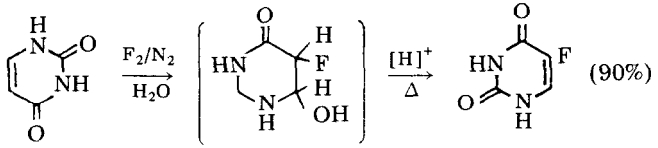
5-Fluorouracil and companions

A landmark development in cancer chemotherapy was the synthesis of nucleic acid antagonists through substitution of fluorine for hydrogen in naturally-occurring pyrimidines. In 1957, Heidelberger and his coworkers prepared 5-fluorouracil (5-FU; 1) [7] and demonstrated its significant tumor-inhibiting activity [8]. Subsequent studies revealed that 5-fluoro-2′-deoxy-β-uridine (2) is more effective and less toxic than 5-FU. Both substances are anabolized to 5-fluoro-2′-deoxyuridylate (3), a potent competitive inhibitor of thymidylate synthetase, the enzyme responsible for conversion of 2-deoxyuridylic acid to thymidylic acid, a required component of DNA. The inhibition is due to the presence of unreactive fluorine (a 'deceptor' group), instead of hydrogen, at the C-5 position, thus blocking the essential addition of formate. This enzymatic blockade inhibits tumor growth, since 5-FU and its anabolites concentrate in these cells.



(1) (2) (3)

The tedious, multistep procedure of the original synthesis of 5-FU limited its availability and kept the cost high until the direct fluorination of uracil (Scheme 13.1) was refined by the U.S. company PCR Inc. (now the SCM Corp.) [9], which provided 5-FU at a much more reasonable cost. In this process, fluorine gas diluted with nitrogen is bubbled through an aqueous solution or dispersion of uracil at 90 °C, to form 5-FU (1) and 5-fluoro-6-hydroxy-5,6-dihydrouracil monohydrate (4), which is dehydrated to 1 when

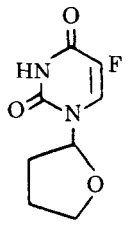


(4) (1) (90%)

Scheme 13.1. Fluorination of uracil.

heated with strong mineral acid. 5-FU yields of about 80% are obtained with a fluorine/uracil reactant molar ratio of 1.67:1.0. SCM now produce large quantities of 5-fluorouracil at a plant in Puerto Rico.

A derivative of 5-FU, N_1-tetrahydrofuranyl-5-fluorouracil (ftorafur or Futraful) (5) is a masked compound which slowly releases 5-FU *in vivo* [10]. It is less toxic than 5-FU and can be used clinically over long periods of time.



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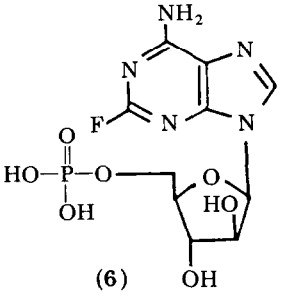
Very recently, the Taiho Pharmaceutical Company of Japan has developed an especially effective, relatively non-toxic, antitumor agent designated UFT, a combination of Futraful with uracil in a 1:4 molar ratio [11]. In clinical trials, this agent has exhibited very promising therapeutic values in the treatment of cancers of the gastrointestinal tract, lungs and breast.

Fludarabine



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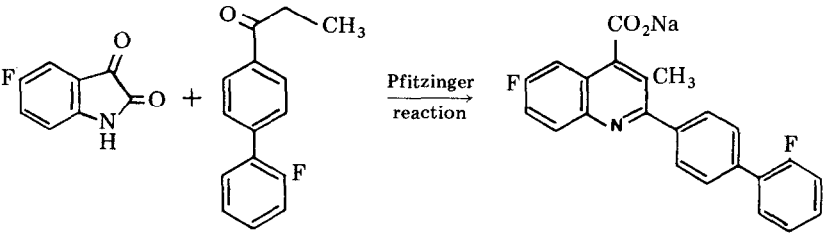
Recently, the Du Pont Company has extended the studies of Montgomery [12, 13] on fludarabine phosphate (6), a purine antimetabolite which is resistant to adenosine deaminase. Fludarabine, which exhibits moderate to good activity against murine P388 leukemia and a human lung tumor, is prepared by phosphorylation of 9-β-D-arabinofuranosyl-2-fluoroadenine [14]. Fludarabine is currently undergoing Phase II trials.

DuP-785

The novel 4-quinolinecarboxylic acid DuP-785 (7), a potentially important cancer drug [15] is being developed for clinical testing by the Du Pont Company. This compound exhibits a broad spectrum of *in vitro* and *in vivo*



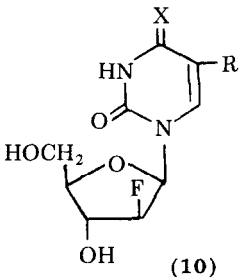
(8) (9) (7)

Scheme 13.2. Preparation of DuP-785.

activities against a variety of murine and human tumors [16]. The compound is prepared via the base-initiated reaction of 5-fluoroisatin (8) with 4-(2-fluorophenyl)propiophenone (9) (Scheme 13.2).

Fluorine-containing nucleosides as anti-viral agents

Finally, 5-substituted (2′-fluoro-β-D-arabinofuranosyl)pyrimidines (**10**) [X = O (uracil) or NH (cytosine) and R = vinyl or halogenovinyl] are very effective agents against herpes simplex viruses (HSV-1 and HSV-2) [17]. The 2′-fluoro group confers increased stability to the glycosyl linkage, which partially accounts for the greater activity than previously-used analogs against HSV-2. The 5-ethynyl analog of **10** exhibits moderate antileukemic activity.



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Inhalation anaesthetics

Important criteria for effective inhalation anaesthesia include ease of vaporization, muscle relaxation, speed of action, chemical stability toward absorbents of carbon dioxide (e.g. soda-lime) and limits of flammability in air, oxygen or oxygen–nitrous oxide mixtures [18]. Halothane, $CF_3CHClBr$ (**11**), was synthesized by Suckling [19] and introduced clinically in 1956 [20 - 22]. Its superior qualities, including non-flammability, were quickly recognized and it has become the most commonly administered anaesthetic. Halothane [Fluothane® (I.C.I.)] is prepared by several methods, such as the I.C.I. process outlined in Scheme 13.3. Fluoroxene [Fluoromar® (Air Reduc-

$$CCl_2{=}CHCl \xrightarrow[SbCl_5]{HF} (CFCl_2CH_2Cl) \longrightarrow CF_3CH_2Cl \xrightarrow[h\nu]{Br_2} \underset{(11)}{CF_3CHClBr}$$

Scheme 13.3. Synthesis of halothane.

tion)], $CF_3CH_2OCH{=}CH_2$ (12), was the first fluorinated anaesthetic investigated clinically in humans (1953), after pharmacological studies by Krantz [23]. It can be prepared from 2,2,2-trifluoroethanol in a two-step process (Scheme 13.4). Only slightly less flammable than ether, it is no longer in

$$2\,CF_3CH_2OH \xrightarrow{HC{\equiv}CH} (CF_3CH_2O)_2CHCH_3 \xrightarrow{\Delta} \underset{(12)}{CF_3CH_2OCH{=}CH_2} + CF_3CH_2OH$$

Scheme 13.4. Synthesis of fluoroxene.

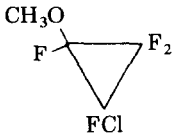
much use, largely as a result of the revelation that it possesses mutagenic properties. Several other fluoro-ethers, with much improved properties, have been introduced in recent years, including enflurane (13) and isoflurane (14). The latter behaves similarly to halothane, but is somewhat less potent. The search continues for even more effective and safer anaesthetics. The new generation includes Sevoflurane® (Travenol Labs.) (15), Synthane® (Travenol) (16), and Aliflurane® (W. R. Grace & Co.) (17).

CHF_2OCF_2CHFCl (13)

$CHF_2OCHClCF_3$ (14)

$CH_2FOCH(CF_3)_2$ (15)

$CHF_2OCHFCF_2CHF_2$ (16)



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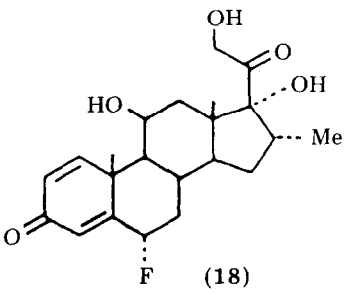
Anti-inflammatory (AI) drugs

Steroids

Fluorine-containing steroids, first introduced during the 1950s, have proved invaluable as adrenocortical and progestational agents and in androgenic hormone therapy. The greatest impact, however, has been in their use as powerful anti-inflammatory (AI) drugs. A wide variety of 9α- and 6α-fluoro-steroids, prepared by ring-opening of epoxides with hydrogen fluoride, have been developed. They are especially effective in the treatment of rheumatoid arthritis and often display markedly lower sodium retention, a major drawback of conventional steroids. Paramethasone (18) and dexamethasone (19) are two important examples.



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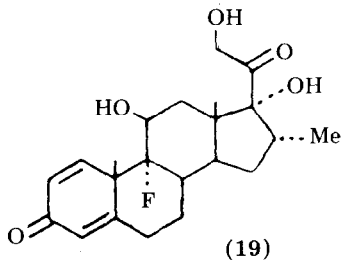

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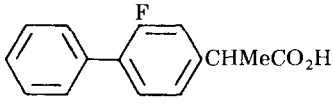
Non-steroidal anti-inflammatory drugs (NSAIDs)

Steroids are powerful drugs that must be used with great caution in many medical conditions due to their undesirable side-effects. In an effort to obviate these limitations and to minimize sodium retention, a major effort was launched in the 1960s to develop non-steroidal anti-inflammatory agents which would surpass the effectiveness of the salicylates, e.g. aspirin, and approach the potency of the steroids. Among the most effective of these drugs are several fluorine-containing compounds characterized by high analgesic and anti-inflammatory activity, namely the aralkanoic acids, flurbiprofen [Froben® (Boots)] (**20**) and sulindac [Clinoril® (Merck, Sharp and Dohme)] (**21**), and the salicylic acid analog diflunisal [Dolobid® (MSD)] (**22**),



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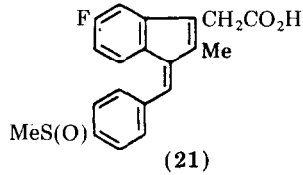
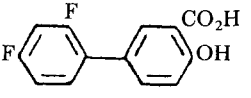


(21)

an exceptionally effective agent for the treatment of osteoarthritis and as a superior post-operative analgesic. Like aspirin, diflunisal functions by inhibiting the synthesis of prostaglandins. Very recently, workers at Du Pont have developed a new imidazole-based drug, tiflamizole (**23**), which is about eight times as potent as indomethacin, a commonly-used AI drug. Tiflamizole is currently undergoing clinical trials.



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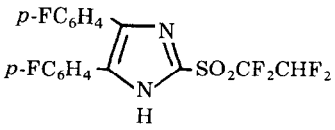

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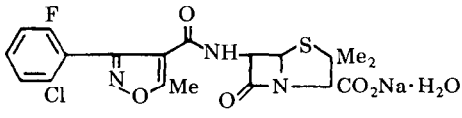
Antibiotics

Fluorine-containing compounds are being used selectively in a number of antimicrobial applications. Mention should be made of flucloxacillin (24), a narrow-spectrum antibiotic, which is stable to penicillinase. 5-Fluorocytosine (25) (flucytosine) is an orally-active antifungal agent, prepared by direct fluorination of cytosine. Fludalanine (26) exhibits wide-spectrum antibacterial activity, and mefloquine (27) is one of the most prominent antimalarial drugs.



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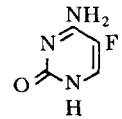

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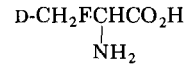

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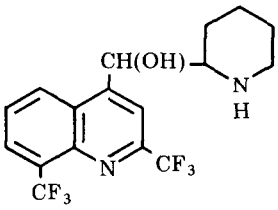

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Central nervous system (CNS) agents

The availability of psychopharmacological drugs since the 1950s has had a profound effect on the therapeutic management of mental illness and disorders of the central nervous system. Fluorine has played a remarkable rôle in the evolution of more potent and selective CNS agents. These include neuroleptics, anxiolytics, antidepressants, sedative-hypnotics, muscle relaxants and anorectics [24]. Perhaps the most important factor has been the increased lipid solubility imparted by the presence of fluorine atoms and trifluoromethyl groups, which increases the rate of absorption and transport of the drug across the blood–brain barrier into the central nervous system. Table 13.1 illustrates the wide range of fluorine-containing compounds (phenothiazines, butyrophenones, phenethylamines and 1,4-benzodiazepines) which have been effective in these applications.

Other applications

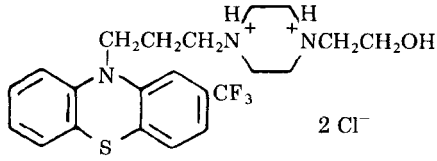
Diuretics and antihypertensive agents

Several fluorine-containing benzothiadiazines ('thiazides') have proved very useful as diuretics and antihypertensive agents. Bendroflumethiazide [Naturetin® (Squibb)] (35) is one of the more potent agents.

TABLE 13.1

Selected fluorine-containing CNS agents

Compound	Application	Compound	Application
fluphenazine hydrochloride (28)	tranquilizer and antipsychotic (management of schizophrenia)	flurazepam (32)	hypnotic, control of anxiety and tension
flupenthixol decanoate (29)	treatment of schizophrenia, antidepressant	fenfluramine (33)	anorectic (appetite depressant) for treatment of obesity
haloperidol (30)	management of schizophrenia	progabide (34)	antiepileptic drug
penfluridol (31)	antipsychotic		



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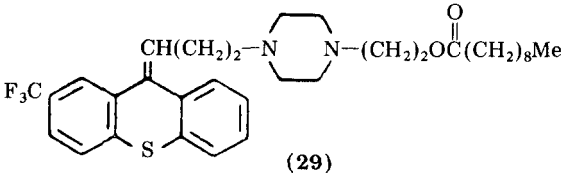

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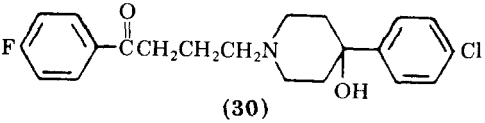

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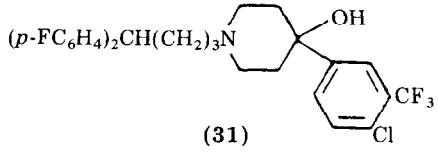

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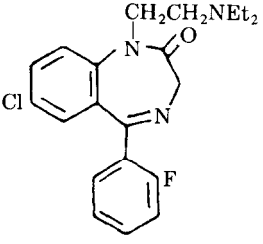

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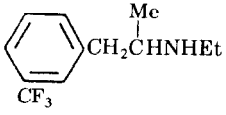

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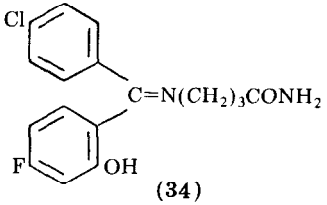

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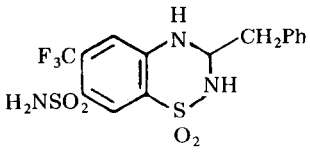

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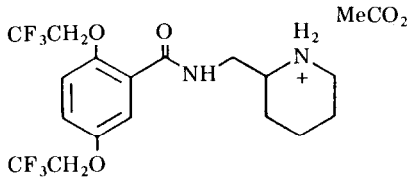
Antiarrhythmic heart drug

A fascinating story of the introduction of a major new fluorine-containing drug is the discovery and development of flecainide acetate [Tambocor® (3M)] (36), the first fluorine-containing drug for the treatment of irregular heart rhythms. In 1966, Riker Laboratories (now part of 3M) began a broad scouting program for new local anaesthetics. Among the early promising compounds that emerged were several bearing 2,2,2-trifluoroethoxy groups (OCH_2CF_3). Since local anaesthetic properties often go hand-in-hand with antiarrhythmic activity, screening for the latter began in 1968 [25]. After thorough pharmacological studies and clinical trials [26, 27], oral flecainide has now been approved for use in six European countries, Argentina and New Zealand as a very promising and potent agent for the suppression and prevention of ventricular arrhythmias, with only minor adverse effects in about 30% of patients. The two trifluoroethoxy groups on the aromatic ring and the piperidine ring in the amide side-chain are features essential to the unique properties of this drug. Flecainide, which has been found to be superior to several other established antiarrhythmic agents in terms of dose-rate, received the approval of the U.S. Food and Drug Administration in November 1985.



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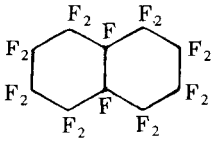
Perfluorochemicals as artificial blood substitutes

Within the past 20 years, major advances have been made in the use of perfluorochemicals (PFCs) as superior oxygen-carrying blood substitutes. The subject has been well reviewed [28 - 30] (see also p. 345). The landmark studies of Clark [31] and Geyer [32, 33] led to improved PFC-based emulsion formulations and, ultimately, to the milestone introduction of Fluosol®-DA, which was successfully infused in human volunteers at the Green Cross Corporation of Osaka, Japan, in 1978 [34].

Fluosol®-DA is a water-based emulsion normally containing 14.0% (w/v) perfluorodecalin (37), 6.0% perfluorotripropylamine (38), 2.7% Pluronic F-68 emulsifier and small quantities of yolk phospholipids, hydroxyethyl-starch, glucose and inorganic salts. Compound 37 exhibits a short organ residence period, while 38 provides favorable emulsification properties. Although Fluosol®-DA is still the only PFC emulsion available commercially, research is proceeding at an accelerated pace in at least 10 countries in an effort to identify even more effective PFC-based blood substitutes which are well-defined, reproducible, medically reliable and industrially feasible. Among the second-generation oxygen carriers being investigated are compounds 39, 40 and 41 [28]. Molecular weight has been shown to be a dominant factor in the retention of fluorochemicals in the organs.



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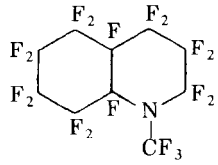
$(C_3F_7)_3N$

(38)



(39)

$(C_6F_{13})_2O$

(40)

$i\text{-}C_3F_7CH{=}CHC_6F_{13}$

(41)

Biochemical aspects

The pioneering studies on the biochemistry of fluoroacetate merit special mention. Shortly after the end of World War II, Peters and his collaborators [35, 36] demonstrated that the conversion of fluoroacetic acid, CH_2FCO_2H, to fluorocitric acid, $CHF(CO_2H)C(OH)(CO_2H)CH_2CO_2H$, via the tricarboxylic acid cycle constituted a 'lethal synthesis'. Fluorocitrate serves as a competitive inhibitor of the enzyme aconitase, thereby blocking the next step in the cycle. Later, Kun used fluorocarboxylic acids as enzymatic and metabolic probes [37]. The biochemistry and biochemical pharmacology of 5-fluorouracil (1) have been investigated in detail and recently reviewed by Santi and coworkers [38].

^{19}F NMR spectroscopy (see p. 287) is finding increasing applications in addressing a variety of biochemical studies, e.g. on drug binding to nucleic acids, fluoride-ion binding, fluorinated enzyme intermediates and enzyme complexes, such as α-chymotrypsin [39].

Medical diagnosis

X-ray contrast agents

Radiopaque fluorocarbons (RFCs), actually, fluorocarbon monobromides such as $n\text{-}C_8F_{17}Br$, either neat or in emulsified form, have been

shown to have useful, though limited, application for contrast enhancement of X-rays [40], especially in bronchography, alveolography, gastroenterography and lymphography, with some potential in tumor imaging.

Magnetic resonance imaging

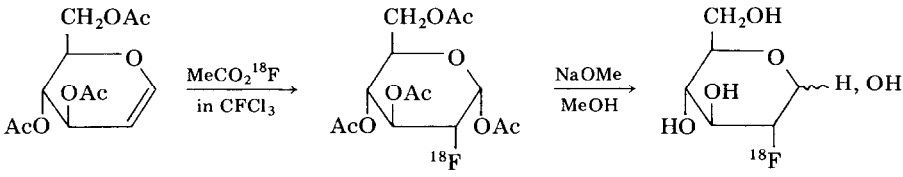
During the past few years, magnetic resonance imaging (MRI) has exploded on the medical scene as an effective, though expensive, non-invasive diagnostic technique. While most studies have involved protons, there have been a few investigations using fluorine nuclei, and it seems likely that specialized applications of ^{19}F MRI will be developed.

Fluorine in positron emission tomography

One of the most significant advances in modern medicine is positron emission tomography [PET], a non-invasive diagnostic technique for quantitative measurement of biochemical functions in live subjects. The method is especially valuable in detecting physiological abnormalities. Fluorine is playing a major rôle in this development.

Fluorine-18 (half-life, 110 min) is a positron-emitting radioisotope of fluorine (see footnote 5, p. 3) which is being increasingly used in PET [41]. It can be prepared by a variety of nuclear reactions, using either particle accelerators or reactors, and is obtained as electrophilic $[^{18}F]F_2$ or nucleophilic $[^{18}F]F^-$ forms suitable for organic synthesis.

Carrier-added, low-specific-activity ^{18}F-fluorine gas, obtained from a cyclotron target, can be immediately used as a fluorinating agent, or its reactivity and selectivity modified by conversion to ^{18}F-labeled acetyl hypofluorite, $CH_3C(O)O^{18}F$, via reaction with acetate salts (see p. 260) [42]. Both reagents add readily to olefins to yield the respective difluoro or acetoxyfluoro adducts, which are usually converted to hydroxyfluoro derivatives by hydrolysis. The most important application of these reagents is in the preparation of $[^{18}F]$2-deoxy-2-fluoro-D-glucose (42) via fluorination of the corresponding tri-O-acetylglucal (Scheme 13.5) [42 - 44]. Both $[^{18}F]F_2$ and ^{18}F-acetyl hypofluorite have been used to fluorinate suitably activated aromatic rings. Of particular interest is the fluorination of 3,4-dihydroxyphenyl-L-alanine (L-DOPA) with $[^{18}F]F_2$ in liquid HF, to produce 6-$[^{18}F]$-fluoro-L-DOPA, a radiopharmaceutical of interest in studying (*in vivo*) dopamine production in the brain [45]. Aryl $[^{18}F]$fluorides can also be



(42)

Scheme 13.5. Synthesis of $[^{18}F]$2-deoxy-2-fluoro-D-glucopyranose [43].

prepared by the reactions of $[^{18}F]F_2$ or ^{18}F-acetyl hypofluorite with aryltin [46] or arylpentafluorosilicate [47] compounds.

Fluorine-18 in the form of no-carrier-added, high-specific-activity ^{18}F-fluoride ion is receiving increasing application in ^{18}F-radiopharmaceutical syntheses. Nucleophilic displacement of suitable leaving groups (bromide, tosylate, triflate) in aliphatic compounds by ^{18}F-fluoride ion yields the corresponding ^{18}F-alkyl fluorides. Examples include the preparation of 42 [48] and the syntheses of ^{18}F-fluorinated steroidal and non-steroidal estrogens [49]. Nucleophilic substitution by ^{18}F-fluoride on activated aryl rings provides an excellent route to aryl $[^{18}F]$fluorides with high specific activity. This is now the method of choice to obtain ^{18}F-butyrophenone neuroleptics [50, 51] which are of great interest for *in vivo* studies of dopamine receptors.

A modification of Wallach's classical method (see p. 76), namely acid-catalyzed ($MeSO_3H$) decomposition of aryl piperidinyl triazenes in the presence of ^{18}F-cesium fluoride, has been used to obtain aryl $[^{18}F]$fluorides [52]. Also, applications of ^{18}F-labeled diethylaminosulfur trifluoride (DAST), an F-for-OH fluorinating agent, have been described [53], and incorporation of fluorine-18 into organic compounds by halofluorination ($Br^{18}F$, $I^{18}F$) of olefins has recently been reported [54]. Finally, reaction of XeF_2 and $^{18}F^-$ with aliphatic carboxylic acids yields carrier-added ^{18}F-fluoroalkanes by a fluorodecarboxylation mechanism (Scheme 13.6) [55].

For recent reviews of biochemical applications of radiofluorine, see refs. 56 and 58.

$$RCH_2CH_2CO_2H + XeF_2 + {}^{18}F^- \longrightarrow RCH_2CH_2\,{}^{18}F + CO_2 + HF + Xe$$

Scheme 13.6. Fluorodecarboxylation of aliphatic carboxylic acids.

Acknowledgements

The author expresses his appreciation to the SCM Corporation, E.I. Du Pont de Nemours & Company, the 3M Company and the Taiho Pharmaceutical Company (Japan) for sharing updated information. Special thanks go to Prof. Michael J. Welch of Washington University School of Medicine, St. Louis, for providing most of the material on the use of radioactive fluorine in PET studies, and to Prof. Jean G. Riess, University of Nice, for recent information on fluorocarbon blood substitutes.

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BIOGRAPHIC NOTE

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Robert Filler received a B.S. degree from City College of New York in 1943 and a Ph.D. degree from the University of Iowa (1949). He became a postdoctoral fellow under E. T. McBee at Purdue University in 1950 - 1951, and then conducted fluorine research at Wright Air Development Center before moving in 1955 to the Illinois Institute of Technology; there he became Professor of Chemistry and Departmental Chairman (1966), and subsequently the Dean of Sciences (1976). Dr. Filler has worked in the U.K. as an NIH Special Postdoctoral Fellow at the University of Cambridge (1962 - 1963) and in Israel as a visiting scientist at the Weizmann Institute (1974). He was chairman of the Division of Fluorine Chemistry of the A.C.S. in 1976, has written numerous papers and articles on fluorine chemistry, and has edited two books on biological and medicinal aspects of organofluorine compounds.