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REVIEW

ORGANIC SYNTHESIS WITH FLUORINE-18
A CONCISE SURVEY

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SUMMARY

The published methods and results in the synthesis of ^{18}F-labelled compounds are presented after a general introduction in the field of ^{18}F-labelling. The hot atom chemistry of ^{18}F and the applications of ^{18}F in other chemistry fields are mentioned in brief.

INTRODUCTION

The established discipline of synthetic and physical organic fluorine chemistry is concerned with the isotope fluorine-19. Naturally abundant fluorine is monoisotopic as contrasted with hydrogen, carbon and many other elements that have stable isotopes which are useful in all kinds of investigations. A consultation of the Chart of the Nuclides reveals that the artificially produced isotopes of fluorine are short-lived, radioactive ones (figure 1).

F		F 17	F 18	F 19	F 20	F 21	F 22	
18.99840		66.6 s	1.8 h	natural	11.4 s	4.4 s	4.0 s	
			β^+ 97%	abundance				
		β^+	E.C. 3%	100%	β^-, γ	β^-, γ	β^-, γ	

FIGURE 1. ISOTOPES OF FLUORINE.

Considering the respective half-lifes it is obvious that organic synthesis with fluorine isotopes other than fluorine-19 deals with fluorine-18. The generally accepted value for its half-life is 109.72±0.06 minutes [1, 2]. The decay of ^{18}F to ^{18}O is quite simple: 3% of the transformations involve electron capture and 97% are by positron emission, the 511 keV annihilation radiation from which is easily detected, but ^{18}F emits no characteristic gamma radiation.

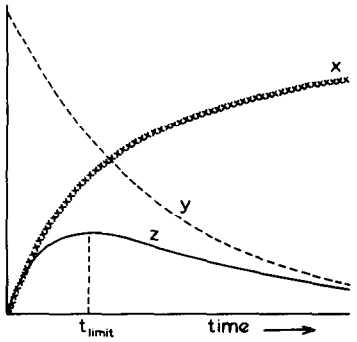
Since the discovery of ^{18}F by Snell in 1937 [3] this isotope has been used more and more as a tracer for fluorine in chemical, biological and medical studies.

Due to the short half-life ^{18}F-labelled compounds are not commercially available from stock, but the isotope ^{18}F can be produced with relative ease in both nuclear reactors and accelerators. A discussion about the nuclear reactions leading to ^{18}F is beyond the scope of this paper, the original literature is recommended [4-7]. Reactor-production of ^{18}F always leads to a solution containing $^{18}F^-$-ions, but the accelerator irradiation may yield ^{18}F-labelled F_2, NOF, HF, ClF, SF_6, SF_4, or COF_2 at the end of the bombardment [6, 8, 9].

Isotopic exchange procedures occupy a prominent place in the field of labelling organic compounds with hydrogen or halogen isotopes. ^{18}F-labelling cannot be achieved by this direct route because of the very high dissociation energy of the C-F bond (465 kJ/mol; cf. 215 kJ/mol for the C-I bond).

Most conventional methods of fluorination involve large molar excesses of the fluorinating agent and long reaction times. It is evident that these methods cannot be readily adapted to the production of ^{18}F-labelled compounds because, as a result, the radiochemical yields would be extremely low.

The short two hour half-life of ^{18}F means that the ^{18}F-chemist has no more than one (long) working day for the experiment. After six half-lifes only 1-2% of the starting activity is left. The chemist must choose and develop rapid reactions, rapid separation and purification methods and must seek ways of accelerating useful reactions. The discrepancy between the reaction times required in the synthesis of fluoro-compounds on the one hand and the 110 min half-life of ^{18}F on the other hand forces chemists to modify existing procedures or to devise new syntheses.



x = product formation.
y = decay curve of ^{18}F.
z = incorporation of ^{18}F in the labelled product.

FIGURE 2 : Kinetic relation between incorporation and decay of fluorine-18.

The formation of the desired ^{18}F-labelled fluoro-compound during the chemical reaction competes with the radioactive decay of ^{18}F (see figure 2). Reaction times longer than t_{limit} only lead to less net activity in the product.

The drawbacks just mentioned apply to a smaller degree in (in)organic isotope exchange studies [10-12] or analytical investigations with the help of fluorine-18 [13,14].

METHODS FOR THE INCORPORATION OF FLUORINE-18 IN ORGANIC COMPOUNDS

All compounds with a C-^{18}F bond which appeared in the literature up to August 1977 are compiled in the following three tables. One should notice that fluorinated amino acids and other physiologically active compounds are overrepresented. This stems from the fact that ^{18}F properties are very suitable for radiopharmaceutical research. A review article on the preparation, pharmacology and design of ^{18}F-labelled organic compounds of biomedical interest recently appeared in the literature [15].

Table I lists the ^{18}F-labelled compounds, prepared via a nucleophilic action of the $^{18}F^-$-ion. Displacement of a halogen atom or oxygen function is one of the most widely used methods of preparing fluoro-compounds. When dealing with ^{18}F one has to look for favourable conditions such as a suitable leaving group, an activated carbon-position or enhanced chemical reactivity of the $^{18}F^-$-ion.

The incorporation of ^{18}F into an aromatic system is accomplished in most cases by the Balz-Schiemann reaction. Table II gives the results. The introduction of ^{18}F is done by exchange labelling of a aryl diazonium tetrafluoroborate precursor with a solution of $^{18}F^-$-ions [32, 33, 35, 37-43] or in a heterogeneous system [34, 44]. Another method is the introduction of ^{18}F in an earlier stage, viz. the diazotisation of an aromatic amine in the presence of $LiB^{18}F_4$ [36, 38].

The incorporation of ^{18}F into an aromatic ring by the Balz-Schiemann reaction is very inefficient from a radiochemical point of view. The maximum possible (decay-corrected) radiochemical yield is only 25%.

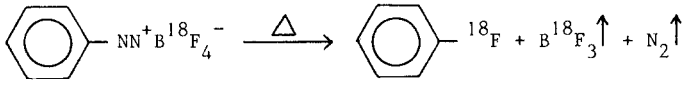


Table III presents some other ^{18}F-introducing agents and their applications. Today many sophisticated fluorine-introducing agents are available for synthesis. However, the labelling of these agents in a short period of time starting with the simple forms of ^{18}F inherent in reactor- or accelerator-production is a considerable problem.

TABLE I

INCORPORATION OF FLUORINE-18 BY NUCLEOPHILIC DISPLACEMENT

^{18}F-LABELLED COMPOUND	FLUORINATING REACTION	REFERENCES
ethyl 2-fluoroacetate*	KF + RCl	4
	(P)F + RBr	16, 17, 18
ethyl 2-fluoropropionate	KF + RBr	19
	$(C_2H_5)_4NF.2H_2O$ + RBr	20
	(P)F + RBr	21
	...	22
ethyl 2-fluorohexanoate*	(P)F + RBr	17
ethyl 2-fluorovaleriate	(P)F + RBr	18

TABLE I. (cont.'d)

^{18}F-labelled compound	fluorinating reaction	references
ethyl 2-fluorotetradecanoate*	(P)F + RBr	16, 17
monofluoroacetamide	(P)F + RBr	17
fluoro methylnitrile	(P)F + RBr	16
2-fluoroethanol**	KF + ethylene carbonate	23
	(P)F + 2-bromoethanol	16, 17, 24
3-fluoropropanol	KF + propylene carbonate	23
1-fluoropropane	F^--ion on carrier + RI	25
1-fluorohexane	$(C_2H_5)_4NF.2H_2O$ + RBr	20
	(P)F + RBr	21
CCl_3F	AgF + CCl_4	26
CCl_2F_2	AgF_2 + CCl_3F	26
benzylfluoride	$(C_2H_5)_4NF.2H_2O$ + RBr	20
	(P)F + RBr	21
acetylfluoride	(P)F + RCl	21
benzoylfluoride	(P)F + RCl	21
3-fluoro-p-menthane	KF + ROTos	23
6-deoxy-6-fluoro-α-D-galactopyranose	$(C_2H_5)_4NF.2H_2O$ + ROTos, followed by hydrolysis	27
3,5-difluoro-L-tyrosine	KF + RI_2	28
fluoro-ocytocin	KF + RI_2	28
cholesteryl fluoride	AgF + RI	29
	F^--ion + RX	30
21-fluoropregnelolone-3-acetate	KF + RI	31
21-fluoroprogesterone	KF (18-crown-6) + $ROSO_2CH_3$	31a
2,4-difluoroestrone	KF + RI_2	28
4-fluorotestosterone	KF + epoxide, $-H_2O$	28

* The corresponding salts were also obtained, ref. 16, 17.

** 2-fluoroethanol-^{18}F was also obtained by reduction of ethyl 2-fluoroacetate-^{18}F, ref. 17.

(P)F stands for polymer supported fluoride ion.

TABLE II

INCORPORATION OF FLUORINE-18 BY THE BALZ-SCHIEMANN REACTION

^{18}F-LABELLED COMPOUND	REFERENCES
fluorobenzene	32, 33
p-fluoro-benzoic acid	32, 33, 34
-anisole	32
-nitrobenzene	33
p-fluoro-biphenyl	33
o-fluoro-benzoic acid	32
-anisole	33
-chlorobenzene	32
m-fluoro-chlorobenzene	33
-acetanilide	33
2-fluoronaphtalene	33
1,3,5-tribromo-4-fluorobenzene	33
p-fluorophenylalanine*	34,35,36
o-fluorophenylalanine	36
m-fluorophenylalanine	34,36
3-fluorotyrosine	34,37
4-fluorotryptophan	22
5-fluorotryptophan	34,38
6-fluorotryptophan	34,38
6-fluorodopamine	39
5-fluoroDOPA	40,41,42
fluorohaloperidol	43

* L-p-fluorophenylalanine-^{18}F was prepared by enzyme-catalyzed resolution of a racemic precursor [44].

TABLE III

INCORPORATION OF FLUORINE-18. MISCELLANEOUS

^{18}F-LABELLED COMPOUND	FLUORINATING REACTION	REFERENCES
CH_3F	DAST* + CH_3OH	45
C_2H_5F	DAST* + C_2H_5OH	45
$HOCH_2CH_2F$	DAST* + $HOCH_2CH_2OH$	45

TABLE III. (cont.'d)

^{18}F-labelled compound	fluorinating reaction	references
2-fluorouracil	F_2 + uracil	46
5-fluorocytosine	...	8
2-fluoropurine	...	22
2-fluoroadenine	...	22
2-fluoro-2-deoxy-D-glucose	F_2 + triacetyl glucal	9
3-fluoro-3-deoxyglucose	DAST* + ROH, followed by hydrolysis	47
3-acetoxy-5-fluoro-6-hydroxy-cholestan	BF_3 + epoxide	30
3-acetoxy-5-hydroxy-6-fluoro-cholestan	BF_3 + epoxide	30

* DAST= diethylaminosulfur trifluoride

REACTIVE ^{18}F-ATOMS

The reactions taking place in the bombardment chamber of large accelerator machines are studied in a distinct specialized field of chemistry: the hot atom chemistry.

Several nuclear reactions result in recoiling ^{18}F atoms which possess kinetic energies greatly exceeding ordinary activation energies. These hot ^{18}F atoms can be thermalized by moderation through non-reactive collisional processes with inert molecules. Both hot and thermalized ^{18}F atoms show many complex reaction channels.

As we limit ourselves in this paper to glass-ware-chemistry, we draw only brief attention to the references no. 48-56 which provide easy access to the literature.

Beside all kinds of reactivity studies, hot atom chemistry is potentially useful in synthesis [48, 56]. Up to now only a few reports exist in the literature that have recorded attempts to explore its possibilities [57-61].

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