LABELLING OF FLUORINATED AROMATICS BY ISOTOPIC EXCHANGE WITH [^{18}F]FLUORIDE

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SUMMARY

The efficient and rapid nucleophilic exchange of fluorine by fluoride-^{18}F ion in aromatic rings is reported here utilizing rubidium-^{18}F-fluoride in DMSO on model compounds. Specific activities in the 3 x 10^4 Ci/mol region are readily achievable. Nucleophilic substitution is shown to be an attractive modality for fluorine-18 labeling of aromatic compounds.

Key Words: nucleophilic aromatic substitution, fluorine-18, radiopharmaceuticals.

INTRODUCTION

Interest in ^{18}F-labelled radiopharmaceuticals has been steadily growing (1), calling for efficient synthetic procedures from the available inorganic precursors. Among new [^{18}F] fluorinating agents such as ^{18}[F]F_2 (2), dioxane-H^{18}F (3), [^{18}F]trifluoromethyl hypofluorite (4), [^{18}F]diethylaminosulfur trifluoride (5) etc., introduced in the past few years, the most simple reagent [^{18}F]fluoride (available in either aqueous or anhydrous form depending on the nuclear reaction and target material used) maintains a significant role. Indeed, a number of synthetic procedures have been recently reported, based on the nucleophilic

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reactivity of $^{18}F^-$ toward aliphatic substrates containing suitable leaving groups, such as Cl, Br, I, mesyl, tosyl and methanesulphonyl groups, frequently exploiting phase-transfer techniques (6).

The preparation of aryl [^{18}F]fluorides has relied principally on the Schiemann reaction (cf. 1 a, d, f and references cited therein) and more recently on the decomposition of aryl triazenes with H^{18}F (7). The Schiemann reaction suffers the disadvantages of low yield and low specific activity aryl [^{18}F] fluorides. In comparison, the triazene decomposition gives aryl [^{18}F]fluorides at no carrier added (NCA) levels although in very low radiochemical yield. Recently XeF_2 has been used to fluorinate electron rich aromatic rings and to produce 6-[^{18}F]fluoro DOPA in low yield (8). In summary, these procedures have met with only moderate success, requiring relatively long reaction times and high temperatures, giving in many cases rather low yields and unwanted by-products and requiring elaborate purification schemes.

The need for a route of aryl [^{18}F] fluorides which would use [^{18}F] fluoride as the precursor and the results of a comprehensive kinetic study (9) on the isotopic exchange of activated fluorinated aromatics with $^{18}F^-$ in dimethyl sulfoxide (DMSO) has led to the conclusion that in many cases isotopic exchange has distinct advantages as a labeling technique over conventional procedures involving displacement of other nucleofugic groups by $^{18}F^-$ (cf. (10)). As a matter of fact, the rate constant of F-for-F displacement (k_E) can exceed by several orders of magnitude the rate constant for displacement of other groups, e.g. Br or Cl substituents by $^{18}F^-$ (k_D). This is clearly illustrated by the reaction of $^{18}F^-$ with chlorofluorobenzenes or bromofluorobenzenes, characterized (9) by k_E/k_D ratios in excess of 10^3 (9). In those systems where a <u>fast</u> isotopic exchange does occur, it becomes possible to greatly reduce the concentration of the inactive substrate without unduly prolonging the reaction time, which in turn allows a correspondingly large increase of the specific activities attainable.

The present report details the application of the isotopic exchange technique to suitably activated fluorinated aromatics, that represent useful intermediates for the synthesis of ^{18}F-labeled radiopharmaceuticals.

Choice of the exchange conditions. As expected, the rate of the isotopic exchange between $^{18}F^-$ and fluorinated aromatics has been found to critically depend on the choice of the reaction medium. As an example, the crown ether/benzene systems, successfully employed in other nucleophilic reactions (11) have been found to be inefficient in the reactions reported here.

Comparative studies have pointed to DMSO as the solvent of choice, consistent with its recognized role in nucleophilic substitution reactions (12), plus other favorable properties, including the ability to dissolve relatively large amounts of inorganic halides (13), the high boiling point, and adequate thermal stability (14). The only experimental drawback of DMSO arises from the drastic depression of the exchange rate caused by even small amounts of water. Thus the high hygroscopic nature of DMSO requires rigorous dehydration of the solvent, the reagents and the reaction vessels. Low concentration of inactive fluorides, typically below $10^{-3}M$, have been found useful in obtaining reproducible results and in eliminating adsorption of the $^{18}F^-$ activity on the surface of the glassware.

EXPERIMENTAL

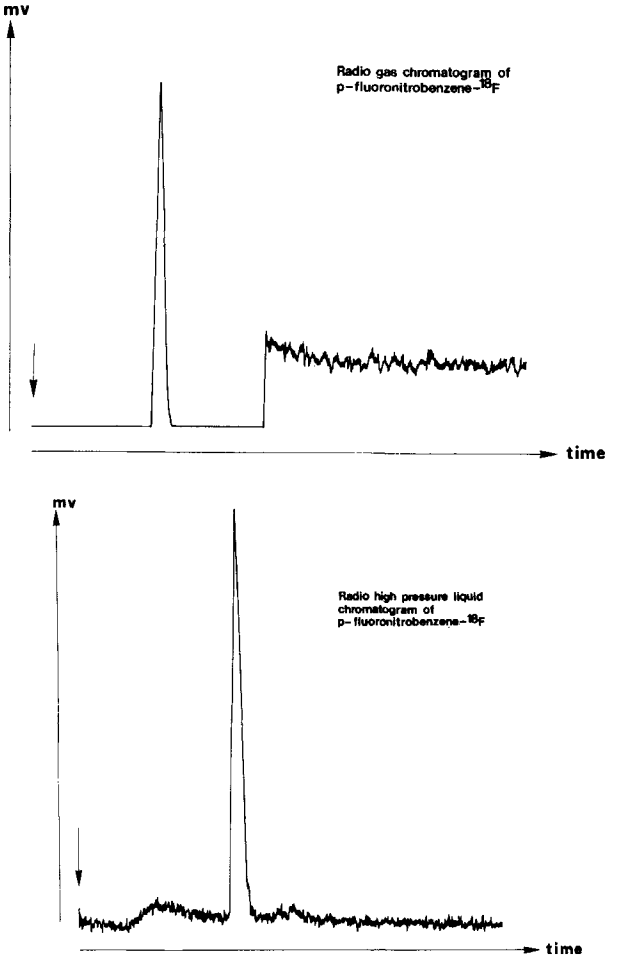
Materials. Ultrapure RbCl and 98% anhydrous KF from Alfa Products Division, Ventron Inc., were further dried by heating at 300°C under vacuum. DMSO from Matheson, Coleman and Bell Co. was stored for ca. 1 month over activated 4 Å molecular sieves (15). KCl, p-fluoronitrobenzene and p-fluorobenzonitrile were research-grade products from Aldrich Chemical Co., Inc.

Preparation of ^{18}F-F^-. The conventional wet-chemistry procedures for the preparation of labeled fluorides are not particularly suitable when an anhydrous

reagent is required. Accordingly, a convenient technique has been developed, based on the heterogeneous exchange of rubidium chloride with $[^{18}F]F_2$, yielding Cl_2 and the correspondent rubidium fluoride, a reaction previously exploited for the quantitative gas chromatographic analysis of F_2/O_2 mixtures (16). Anhydrous $^{18}F\text{-}F_2$ produced by deuteron bombardment of Ne containing a trace of F_2 (0.1 %) in the 60" cyclotron of Brookhaven National Laboratory (2) was allowed to pass through a 10-cm long, 1-mm i.d. pyrex capillary, packed with finely ground crystals of rubidium chloride. The capillary was mounted within the sensitive volume of a 7 mm x 27 mm ionization chamber from Capintec, Model CRC453X, in order to follow the accumulation of the $^{18}F^-$ activity. When the desired activity was trapped, the capillary was washed with a stream of pure Ne to remove any unreacted fluorine, and its contents were transferred into a pyrex vessel containing dry DMSO, and the calculated amount of KF which would lead to an overall (F^-) concentration of $\cong 10^{-3}$M. After vigorous stirring, the suspension was allowed to settle, and transferred with filtration into the exchange vessel. This procedure gives an $^{18}F^-$ solution remarkably free of radioactive impurities, with good yields, and typically 50 to 60% of the $^{18}F\text{-}F_2$ activity (17).

Exchange reaction and analytical procedures. The exchange was carried out using 0.5-2.0 ml of the DMSO solution to which the organic substrate (0.05 to 20 mg) had been added. The pyrex vessels were equipped with a teflon stopper and immersed in a silicone oil thermostated bath. At the end of the exchange, the reaction mixture was cooled, diluted with benzene and extracted repeatedly with a dilute aqueous solution of KF, then with water. The organic and the aqueous layers were separated and the activity in the organic phase was contained exclusively in the labeled substrate, characterized by an exceptional radiochemical purity, as quantified by radio-HPLC and radio-GLPC. The analyses were carried out with a Series 3B liquid chromatograph (Perkin Elmer Co.), connected to a model LB503 flow scintillation counter from Berthold, and with

a model 7620A Hewlett-Packard gas chromatograph connected to a flow counter (18). Typical radiochromatograms are shown in Figure 1.



RESULTS AND DISCUSSION

Table I gives the yields and the specific activities of the fluorinated aromatics labeled under different conditions. The results show that isotopic exchange on activated aromatic compounds is an efficient labeling technique, in terms of yield and attainable specific activity, provided that activated substrates and appropriate exchange conditions make the nucleophilic ^{18}F for F

TABLE I. Isotopic Exchange of Fluorinated Aromatics with $^{18}F^-$ (5 mCi) in Dimethylsulphoxide.[a]

Substrate F-⬡-S			Exchange Conditions		% Activity in the Substrate	Exchange Yield[b] %	Specific Activity (Ci/mol)	
S	mg	mol/l	minutes	°C			EOS value[c]	EOB
NO_2	66.5	$4.7.10^{-1}$	10	85°	77	77	7.7	8.2
NO_2	0.67	$9.4.10^{-3}$	140	145°	36	40	160	379
NO_2	0.67	$9.4.10^{-3}$	20	150°	42	46	388	439
NO_2	0.67	$9.4.10^{-3}$	84	145°	68	75	427	716
NO_2	0.067	$9.4.10^{-4}$	20	175°	30	62	2830	3200
CN	20.0	$8.2.10^{-2}$	240	165°	93	94	6.5	28.5
CN	2.0	$1.1.10^{-2}$	20	163°	80	88	218	247

[a] Overall F^- in the DMSO solutions $\simeq 10^{-3}$ mol/l.

[b] Ratio of the activity incorporated into the substrate to the maximum activity that can be incorporated when the isotopic exchange reaches steady state.

[c] Specific activity at the end of the exchange. [EOS = End of Synthesis]

[d] Specific activity referred to zero time. [EOB - End of Bombardment]

substitution a sufficiently fast process. The short reaction times, and the high chemical and radiochemical purity of the labeled products are obvious advantages when compared to other isotopic exchange reactions which have been described (19).

It should be emphasized that the specific activity levels attained up to ca. 3,000 Ci per mol., do not approach the ultimate potential of the method, since it appears quite feasible to increase the activity of the ^{18}F-labeled fluoride by orders of magnitude over the modest (5 mCi) level used in the present study. Nevertheless, careful inspection of Table I reveals two features typical of isotopic exchange that set an upper limit to the specific activities attainable. Decreasing the concentration of the substrate, as required to raise the specific activity of the product, decreases the reaction rate as well, which leads to an extension of the exchange time for the least activated substrates. Furhtermore, the reaction of [^{18}F] fluoride with impurities contained in the exchange medium can significantly decrease the yields at the lowest concentrations of the substrate. The most serious drawback is the maximum fraction (X_∞) of the activity which can be incorporated into the substrate when the system reaches equilibrium i.e.:

$$X_\infty = \frac{[\text{Substrate}]}{[\text{Substrate}] + [^{18}F^-]}$$

since it decreases when the concentration of the substrate becomes comparable with, or lower than the overall fluoride concentration. The latter cannot of course be indefinitely reduced, especially in regular production runs, since the specific activity of the labeled fluoride can probably not be extended beyond more than one or two orders of magnitude above the level used in the present work. Amelioration of this problem might be accomplished by utilizing ^{18}F ion from carrier free (CF) anhydrous $H^{18}F$.

However, even with the above limitations, a quite respectable specific activity (of the order of 30,000 to 50,000 Ci per mol) can be conservatively

predicted from the present data for activated substrates, which makes the labeling technique based on isotopic exchange a promising approach to a large family of synthetic intermediates.

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15. Karl Fisher titration of DMSO kept over molecular sieves gives water concentrations below 550 ppm. However the actual water content in the exchange medium can be somewhat higher, due to the hygroscopic nature of the solvent, and to the traces of moisture on the glassware, the alkali metal halides, and the $^{18}F\text{-}F_2$/Ne mixture.

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