NOTE

^{18}F-LABELLING OF THIOPHENE AND N-METHYLPYRROLE.

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SUMMARY

2- and 3-[^{18}F]fluorothiophene and 2- and 3 [^{18}F]fluoro-N-methyl pyrrole have been obtained by the reaction of thiophene and N-methylpyrrole with molecular fluorine [^{18}F]-F_2 under carefully controlled conditions.

Key Words : radiofluorination; 2- and 3-[^{18}F]fluorothiophene; 2- and 3-[^{18}F]fluoro-N-methylpyrrole.

INTRODUCTION

Positron Emission Tomography (P.E.T.)[1] is a unique scientific tool for studying in vivo human metabolism and pharmacokinetics, that allows non-invasive determination of the fate of biologically active molecules labelled with positron-emitting isotopes[2].

^{18}F is extensively applied in radiopharmaceutical chemistry and nuclear medicine, owing to its convenient half-life (110 min), stable bonding to carbon, isosteric properties with OH, and a steric bulk similar to that of H. Despite the high reactivity of molecular fluorine, many radiopharmaceuticals have been synthesized by direct electrophilic fluorination with [^{18}F]-F_2 under controlled conditions[2].

In this study, two essential constituents of several physiologically active substances[3], i.e. N-methylpyrrole and thiophene, were allowed to react with elemental fluorine [^{18}F]-F_2. The reaction proved to be a route to the direct introduction of a ^{18}F atom into the ring of these two heteroaromatics, which are strongly activated towards electrophilic substitution, but react with nucleophilic reagents, such as F^-, only if their ring is activated by powerful electron-withdrawing groups.

0362–4803/90/091109–04$05.00

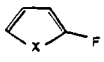
Received February 13, 1990
Revised March 27, 1990

We report here the formation of 2- and 3-[^{18}F]fluorothiophene and of 2- and 3-[^{18}F]fluoro-N-methylpyrrole, in the ratios 65 : 35 and 20 : 80 respectively, using 15μmol of [^{18}F]F_2. Similar product formation was previously observed for reactions carried out with unlabelled F_2, at a concentration of 5 mol % in He [4].

In order to reproduce in the radiochemical reactions the conditions prevailing in the "cold" fluorination, the whole [^{18}F]-F_2 content of the gas-target, i.e. about 50 μmol in Neon, was allowed to react with 100 μmol N-methylpyrrole. The products, 2- and 3-[^{18}F]fluoro-N-methylpyrrole, were obtained in a fairly constant ratio, while the amount of unknown labelled products increased with the amount of carrier F_2. The latter are probably addition products, incorporating two to four fluorine atoms per molecule.

The increased response of the radioactivity detector to these products relative to monofluorine-substituted compounds, can lead to an overestimation of their relative yields. More specifically these appear higher than those of the corresponding inactive products from reactions involving unlabelled fluorine measured by GLC and GLC-MS.

Table 1. Fluorination products from the reaction of elemental fluorine with Thiophene and N-methylpyrrole.

Reactants		Products			
		Relative Yield [a] (%)			Radiochemical Yield [b] (%)
	Fluorine			Unknown peaks	
X=N-Me	[^{18}F] -F_2 (15 μmol)	23	73	4	35 ±3
X=N-Me	[^{18}F] -F_2 (50 μmol)	17	67	16	16 ±3
X=N-Me	[^{19}F] -F_2 (50 μmol)	19	76	5	n.a.[c] [d]
X=S	[^{18}F] -F_2 (15μmol)	53	29	18	11 ±3
X=S	[^{19}F] -F_2 (50 μmol)	58	31	11	n.a.[c] [d]

(a) Standard Deviation = 5%. (b) See Experimental. (c) Not Applicable. (d) See ref. 4.

These results are interesting for two reasons. On one hand, they suggest that the fluorinating species is the same both at tracer level and at higher concentrations of fluorine. This excludes the possible role of fluorinating species resulting from the interaction of molecular fluorine with unknown and undetected impurities in the reaction system. Secondly, one may rely on the close analogy between the ^{18}F-radiolabelling conditions and those prevailing in "cold" fluorination in order to identify the labelled products using the chromatographic data established for their unlabelled counterparts. This may prove useful for the extension of the procedure to the introduction of fluorine atoms into other substituted heteroaromatics that represent models of a variety of biologically active compounds, whose application as radiopharmaceuticals does not require high specific activity.

Experimental

The fluorination of N-methylpyrrole and thiophene was carried out in the dark, at -63°C, in a $5 \cdot 10^{-2}$ M solution in 2 mL of $CHCl_3$ chosen as the solvent because of its polar and radical scavenging properties [5].

The radionuclide was generated by the nuclear reaction ^{20}Ne (d, α)^{18}F, with a specific activity in the range of 0.5- 2.0 Ci / mmol, using the Compact Cyclotron CV 28 (KFA Jülich, F.R.G.). Molecular fluorine [^{18}F] -F_2 , obtained by exchange with 50 µmol of inactive fluorine present during the irradiation in the gas target [6], was reacted with the substrate by previously described methods and devices [7].

The reaction mixture, after washing with 2M aqueous $NaHCO_3$ and drying the organic phase over $CaSO_4$, was analyzed by GLC, using two columns. The first one (a), packed with Bentone [7], was operated isothermally at 50°C with a He flow rate of 90 mL / min ; the second column (b), packed with SP 2100 / 0.1% Carbowax 1500, was operated isothermally at 50°C for the reaction products of thiophene and at 80°C for the reaction products of N-methylpyrrole, with a He flow rate of 30 mL / min.

The GLC retention times of the mono fluorination products were as follows : 2-[^{18}F]fluorothiophene 11.45' (a), 4.58' (b) ; 3-[^{18}F]fluorothiophene 13.03' (a), 6.22' (b); 2-[^{18}F]fluoro-N-methylpyrrole 8.21' (a), 5.69' (b); 3-[^{18}F]fluoro-N-methylpyrrole 12.60'(a), 8.29' (b). The gaseous effluent fractions were absorbed batchwise by small traps of charcoal [8] every 20 s, and their activity was measured with a γ scintillation detector.

Moreover, two portions of the crude reaction mixture were counted, in order to calculate the radiochemical yield of the reaction, i.e. the percentage of the radioactivity

appearing in the GLC-analyzed products relative to the amount of radioactivity in the crude product injected.

Using about 15-50 μmol of $[^{18}F]$-F_2 , the reaction was fairly clean, i.e. no tars were formed.

Acknowledgements

The author is grateful to Prof. G.Stöcklin and Dr. H.H.Coenen for valuable help carrying out the radiochemical experiments at the KFA, Jülich, and to Prof. F. Cacace and Dr. S. Fornarini for helpful discussions.

The financial support from Kernforschungsanlage Jülich, F.R.G., and the Consiglio Nazionale delle Ricerche (CNR, Roma), Progetto Strategico "Tecnologie e Metodologie Radiochimiche Avanzate" is gratefully acknowledged.

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