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Labelling with Reactor Produced ^{18}F—III.[1] Polymer Supported ^{18}F as a Fluorinating Agent

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A procedure is described for the preparation on a microscale of a ^{18}F-labelled anion exchange resin (Ⓟ ^{18}F). Ethyl 2-fluoropropionate-^{18}F, benzyl fluoride-^{18}F, 1-fluorohexane-^{18}F, acetyl fluoride-^{18}F and benzoyl fluoride-^{18}F were prepared by metathesis with Ⓟ ^{18}F. Radiochemically pure compounds were obtained within one half life (110 min) after end of bombardment in yields between 30% and 70%. The method proved to be suitable for labelling with carrier-free ^{18}F as well.

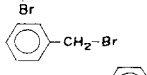
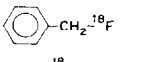
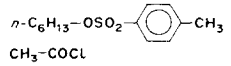
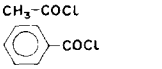
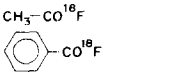
1. INTRODUCTION

REACTOR-PRODUCED ^{18}F has fewer synthetic possibilities than accelerator-produced fluorine-18. This is caused by the fact that from reactor irradiated Li_2CO_3, ^{18}F can only be obtained as a solution of F^--ions, but the accelerator irradiation may yield $^{18}F_2$, $NO^{18}F$, $H^{18}F$, $Cl^{18}F$, $S^{18}F_6$, $S^{18}F_4$ or $CO^{18}F_2$ as well.[2,3]

This restriction to F^--ions severely limits the number of fluorination reactions which can be carried out, as their incorporation into an organic molecule is only possible by nucleophilic substitution. Regarding the short half life of ^{18}F, we have to search for favourable reaction conditions like a suitable leaving group, an activated carbon-position or an enhancement of the chemical reactivity of the F^--ion. Especially during the last few years the aspect last mentioned has been exploited by the application of crown ethers[4,5] or phase-transfer catalysts.[6–8] The use of these techniques has increased the number of successful reactions with nucleophilic attack by the F^--ion.

The application of suitably modified insoluble polymers as reagents in organic synthesis is steadily growing.[9–13] An important feature of the use of a polymeric reagent is the simplified work-up procedure which is of particular interest in radiosynthetic work. If the radioactive species is attached to an insoluble polymeric support and used in a heterogeneous reaction, the distribution of the radioactivity among the

TABLE 1. Conversions with Ⓟ ^{18}F

Starting material	Spec. act. resin (cpm/μequiv)	Product	Spec. act. product (cpm/μmol)	Radiochem. yield (%)
$CH_3-\underset{Br}{CH}-COOC_2H_5$	10.8×10^4	$CH_3-\underset{^{18}F}{CH}-COOC_2H_5$	12.3×10^4	60
	15.8×10^3		22.2×10^3	30
	3.1×10^3	$n\text{-}C_6H_{13}-{}^{18}F$		
CH_3-COCl	n.d.*	$CH_3-CO^{18}F$	n.d.*	40
	n.d.*		n.d.*	40

* n.d. = not determined.

TABLE 2. Conversions with Ⓟ OAc/^{18}F

Starting material	Total act. resin (cpm)	Product	Total act. product (cpm)	Radiochem. yield (%)
$CH_3-CH(Br)-COOC_2H_5$	3.3×10^5	$CH_3-CH(^{18}F)-COOC_2H_5$	9.9×10^4	30
$n-C_6H_{13}-OSO_2-C_6H_4-CH_3$	3.5×10^5	$n-C_6H_{13}-^{18}F$	8.7×10^4	25
C_6H_5-COCl	11.9×10^5	$C_6H_5-CO^{18}F$	6.2×10^5	52

two phases gives a rapid indication of whether or not there has been any conversion.

2. METHODS AND RESULTS

The anion exchange resin in the fluoride form (Ⓟ F) or acetate form (Ⓟ OAc) is labelled with ^{18}F by rinsing with an aqueous solution of carrier-free $^{18}F^-$. After drying the, ^{18}F-labelled resin was used as the fluorine donating agent in displacement reactions using acetonitrile as a solvent. The reactions are clean and fast and do not yield radioactive byproducts. In some cases a non-radioactive elimination product is formed because of the base strength of the F^--ion. Some experimental results obtained with Ⓟ ^{18}F are summarized in Table 1.

We observed that the anion exchange resin in the acetate form could be labelled with ^{18}F almost as efficiently as the fluoride form. With Ⓟ OAc as the support of carrier-free ^{18}F we were able to prepare ^{18}F-labelled compounds without the use of carrier. The formation and yield of the desired labelled reaction products was established by radio gas chromatography.

Some experimental results with this Ⓟ OAc/^{18}F are summarized in Table 2.

3. DISCUSSION

Robinson[14–16] used ^{18}F-labelled resins for the synthesis of ^{18}F-labelled fluorocarboxylates and 2-fluoroethanol. At first we were unable to reproduce Robinson's results, until we discovered that any contact between the applied HF-solution and glass must be avoided during the preparation of the inactive anion exchange resin in the fluoride form.[17] A low concentration of H_2SiF_6 already causes competition between F^- and SiF_6^{2-} for the quaternary ammonium sites of the resin. The incorporation of SiF_6^{2-} is favoured because of its charge and size, but its fluorine is not exchangeable.

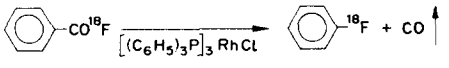
A well-defined anion exchange resin in the F^--form is obtained if all-Teflon® equipment is used. After labelling by exchange with $^{18}F^-$ and drying, we get a relatively powerful source of $^{18}F^-$-ions suitable for use in nucleophilic displacement reactions. We observed that acetonitrile with its relatively high dielectric constant is a very suitable solvent for these substitution reactions, although no doubt other solvents may produce satisfactory results as well. From the results presented in Table 1, we note that in each case the specific activity of the reaction product is higher than the specific activity of the labelled anion exchange resin. We assume that this may be the result of different accessibilities of the ammonium units of the resin. The outer surface of the resin probably has a higher specific activity than the bulk as the ^{18}F for F exchange labelling of the resin proceeds very fast. If, again, the resin surface is more involved than the bulk in the subsequent organic reaction this may result in a higher specific activity of the labelled product. From the results presented in Table 2 we note that the formation of carrier-free ^{18}F-labelled compounds is possible. As we were unable to measure the mass of the compounds, only their total activities are presented. The use of an anion exchange resin in the acetate form as a support for carrier-free ^{18}F was first mentioned by KARIM[18] who observed its ability for ^{18}F-gas phase labelling under GLC-conditions (this type of work is reviewed by ELIAS[19]). Our modification of this technique extends its applicability to compounds which can not be purified by GLC and to a variety of solvents to promote the reaction.

We observed that polymer supported fluoride is able to displace the halogen of acid halides. The formation of ^{18}F-labelled aroyl fluorides opens new perspectives for the preparation of ^{18}F-labelled aromatic rings. From a radiochemical point of view an incorporation into an aromatic ring by the Schiemann reaction is very inefficient.[20] The maximum theoretical radiochemical yield is only 25%, [reaction (A)].

(A) $C_6H_5-NN^+B^{18}F_4^- \longrightarrow C_6H_5-^{18}F + B^{18}F_3\uparrow + N_2\uparrow$

The catalytic decomposition of ^{18}F-labelled aroyl fluoride[21] is a promising alternative, theoretically up

to 100% of the ^{18}F-activity may remain in the molecule [reaction (B)].

(B) 

Investigations in this direction are under way.

The ^{18}F-labelling technique we developed may be useful for the preparation of organic compounds labelled with other radiohalogens as well.* The whole procedure, including the separation of ^{18}F from Li_2CO_3, the absorbtion of the $^{18}F^-$-ion by the anion exchange resin, the drying of the resin and, finally, the GLC purification of the reaction product, ensures the absence of any tritium in the final products.[22]

4. EXPERIMENTAL

^{18}F was produced by irradiation of quartz ampoules containing 25 mg of Li_2CO_3 (Cerac certified chemicals, purity 99.99%, 1 ppm Na) for 20 min in a thermal neutron flux of $5 \cdot 10^{13}$ neutrons/cm^2/sec. At the end of the irradiation, about 75 μCi of ^{18}F was obtained. The irradiations were performed in the High Flux Reactor of E.C.N., Petten, The Netherlands. The ^{18}F-activity was measured by counting the 511-keV annihilation radiation peak.

The capacity of the anion exchange resin in the fluoride form (Ⓟ F = Amberlyst-A26) was determined titrimetrically and radiometrically[17] to be 3.94 mequiv/g.

Identification of the products was done by conventional analytical techniques such as ^{1}H-NMR, i.r., GLC retention times, etc.

The specific activities of the labelled compounds were determined by measuring the count rate and the concentration of the fluoroderivative in an aliquot of a solution of the trapped eluate after purification by GLC. The concentration was established gaschromatographically using a reference curve.

Preparation of dry polymer supported ^{18}F (Ⓟ ^{18}F)

The irradiated Li_2CO_3 was dissolved in 2.5 ml of water and the solution was stirred for 5 min with 500 mg of Dowex 50 WX4 (H^+-form, 100/200 mesh). The resin was then separated by filtration through a sintered glass filter and rinsed with 2 ml of water. The combined aqueous phases containing carrier-free ^{18}F were brought on to a thin-walled capillary column (i.d. 1.5 mm) holding 20 mg of Ⓟ F (40/60 mesh). After the first elution more than 90% of the original ^{18}F-activity was present in the resin. Thereafter the resin was dried with methanol and diethyl ether and finally by a stream of dry nitrogen gas. The specific activity of the resin was calculated from its quantity and retained activity.

Preparation of ethyl 2-fluoropropionate-^{18}F, *benzyl fluoride-*^{18}F *and 1-fluorohexane-*^{18}F

The bottom of the capillary column was sealed and a two fold molar excess of ethyl 2-bromopropionate, benzyl bromide or *n*-hexyl tosylate was added. Dry acetonitrile was added until the totally occupied volume was about 80 μl. After cooling in liquid nitrogen, the ampoule was evacuated and sealed at about 2 cm from the bottom. The ampoule was then heated in an oil bath at a temperature of 85°C for 1 hr and crushed in a specially designed ampoule crusher (Fig. 1). This crusher is constructed in such a way that it can be used as the injector for a gaschromatograph. The products were purified on 10% w/w Carbowax 20 M on Chromosorb W/NAW and selectively trapped at the outlet of the gaschromatograph.

Preparation of acetyl fluoride-^{18}F *and benzoyl fluoride-*^{18}F

Acetyl fluoride-^{18}F and benzoyl fluoride-^{18}F were prepared by halogen exchange between the corresponding acid chlorides and the labelled ion exchange resin in the same way as described above.

Because there was no suitable GLC column available the reactions were carried out in a micro reaction flask connected to a capillary condenser instead of using a sealed capillary. The formation of the desired fluorocompounds was proved in inactive experiments. Because in no other experiment with ^{18}F-labelled resin radioactive by-products could be detected, the radiochemical yield was calculated from the total activity of the liquid phase.

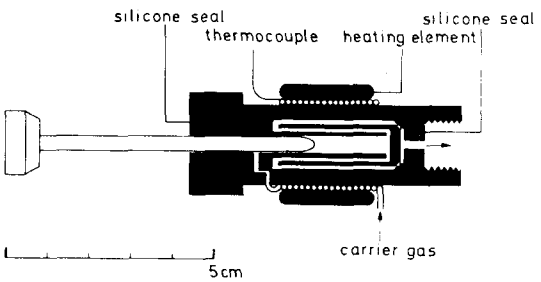


FIG. 1. The specially-designed ampoule crusher.

* After termination of the investigation described in this paper, an article by Cainelli and coworkers[9] appeared on the use of anion exchange resins in the synthesis of alkyl halides.

TABLE 3. Time table for a complete run

Procedure	Duration (min)
End of the irradiation	t_0
Decomposition of Li_2CO_3, filtering	10
Exchange labelling of the resin	20
Preparation of the sealed ampoule	8
Reaction	60
Preparative GLC	12
End of the preparation	110 min after t_0

Carrier-free experiments

The anion exchange resin, supplied in the chloride form, was converted into the hydroxyl form by treatment with 2 N NaOH and then into the acetate form by rinsing the resin with 2 N acetic acid. The labelling and drying of the resin and its use in organic displacement reactions were similar to the procedures mentioned earlier. Radio gas chromatography showed that the desired ^{18}F-labelled products were the only radioactive compounds present in the eluate.

Table 3 reflects the time consumption involved in the several reaction steps: the whole procedure takes about one half life of ^{18}F.

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