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ORIGINAL PAPER

Production of ^{18}F by proton irradiation of C_6H_6NF and $C_6H_5NF_2$

**Emil Běták,
Renata Mikołajczak,
Joanna Staniszewska,
Stefan Mikołajewski,
Edward Rurarz,
Jolanta Wojtkowska**

Abstract. Fluorine-18 can be produced directly by the (p,pn) reaction and also indirectly by the (p,2n) reaction on the ^{19}F target. The overall cross section for both routes is 108 ± 20 mb at 22.5 ± 2.5 MeV. In this work, we obtained ^{18}F, using 25 MeV protons on 2-fluoroaniline and 2,4-difluoroaniline targets. The chemical separation yield was 46 ± 7% and 47 ± 12% for 2-fluoroaniline and 2,4-difluoroaniline, respectively. Low-current 1 h irradiations led to 90 μCi of ^{18}F produced from 2-fluoroaniline bombarded with a 70 nA beam (in good agreement with the theoretical value, 96 μCi) and to 76 μCi of ^{18}F in case of 2,4-difluoroaniline and a 33 nA beam (prediction 85 μCi). Both values are close to the thick target result reported by Dmitriev and Molin [4] for 22 MeV protons.

Key words: radiopharmaceuticals • positron emitters • radiochemistry • ^{18}F • nuclear reactions • cyclotron • production cross sections

E. Běták✉
Institute of Physics,
Slovak Academy of Sciences,
84511 Bratislava, Slovakia
and Faculty of Philosophy and Science,
Silesian University,
74601 Opava, Czech Republic,
Tel.: +421 2 5941 0573, Fax: +421 2 5477 6085,
E-mail: betak@savba.sk

R. Mikołajczak, J. Staniszewska
Institute of Atomic Energy POLATOM,
Radioisotope Centre,
05-400 Otwock/Świerk, Poland

S. Mikołajewski, E. Rurarz, J. Wojtkowska
The Andrzej Sołtan Institute for Nuclear Studies,
05-400 Otwock/Świerk, Poland

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Introduction

At present, ^{18}F is one of the most important accelerator-produced positron emitters (see, e.g. [24]) which are routinely used in the positron emission tomography (PET).

The choice of the nuclear reaction is essential for the radionuclide's purity and for the amount of radioactivity produced.

We thought it was worthwhile to investigate the feasibility of ^{18}F production at medium-sized cyclotrons. We intended to obtain ^{18}F from proton-activated monoisotopic ^{19}F, which produces ^{18}F directly by the $^{19}F(p,pn)^{18}F$ reaction, and also indirectly via ^{18}Ne ($T_{1/2}$ = 1.672 s) by the $^{19}F(p,2n)^{18}Ne \rightarrow {}^{18}F$ reaction (the half-lives quoted in this paper are taken from the tables of [30]). For both routes, 2-fluoroaniline (C_6H_6NF) is a suitable target. In the present work, the method of [23] and [22] was used to separate ^{18}F from fluoroaniline irradiated by 25 MeV protons. There is also a kind of fluoroaniline containing two fluorine atoms, namely difluoroaniline ($C_6H_5NF_2$). We irradiated this compound too and applied the same separation procedure. The proton-induced reactions on fluoroaniline and difluoroaniline targets appeared to be promising, as they benefit from the following advantages: i) satisfactory production yield, ii) simple and reliable radiochemical separation of ^{18}F from the target, iii) cheap target material, and – which is most important – iv) high radionuclide's purity.

Table 1. List of main data for proton-induced reactions on the ^{19}F, ^{12,13}C and ^{14,15}N isotopes [2, 30]. Reactions leading to stable isotopes are not included here

Reaction	Target abundance (%)	Q (MeV)	$T_{1/2}$	Decay mode
^{19}F(p,n)^{19}Ne	100	–4.02	17.22 s	EC
^{19}F(p,2n)^{18}N→^{18}F	100	–15.66	1.672 s	β^+
^{19}F(p,pn)^{18}F	100	–10.43	1.83 h	EC β^+
^{19}F(p,d)^{18}F		–8.21		
^{12}C(p,n)^{12}N	98.89	–18.12	11.00 ms	β^+
^{12}C(p,2n)^{11}N	98.89	–33.81	~10^{-20} s	
^{12}C(p,pn)^{11}C	98.89	–18.72	20.334 min	β^+
^{12}C(p,d)^{11}C		–16.50		
^{12}C(p,α)^{9}B	98.89	–7.55	≈1.4 × 10^{-18} s	
^{13}C(p,n)^{13}N	1.11	–3.00	9.965 min	β^+
^{13}C(p,2n)^{12}N	1.11	–23.07	11.00 ms	β^+
^{14}N(p,n)^{14}O	99.634	–5.93	70.641 s	β^+
^{14}N(p,2n)^{13}O	99.634	–29.10	8.58 ms	β^+
^{14}N(p,pn)^{13}N	99.634	–10.55	9.965 min	β^+
^{14}N(p,d)^{13}N		–8.33		
^{14}N(p,α)^{11}C	99.634	–2.92	20.334 min	β^+
^{15}N(p,n)^{15}O	0.366	–3.54	122.24 s	β^+
^{15}N(p,2n)^{14}O	0.366	–16.76	70.1641 s	β^+

Proton interactions with the fluoroaniline constituents

Basic information about the activities induced in C_6H_6NF and $C_6H_5NF_2$ by 25 MeV protons is summarized in Table 1. The predominant reactions in the proton energy range of interest are (p,n), (p,2n) and (p,pn) but d, t, ^{3}He and α emissions are also possible for the C, N and F target nuclei.

The radioactive nuclides produced in the (p,n) reactions on C, N and F are ^{19}Ne EC and the following short-lived β^+ emitters: ^{12}N, ^{13}N, ^{14}O and ^{15}O. Two of them, ^{13}N and ^{15}O, are used in PET. However, in our targets they are formed on very low-abundant ^{13}C and ^{15}N isotopes, thus, their expected yields must be low too.

The reaction channel (p,2n) on F, C and N produces also short-lived β^+ emitters, like ^{18}Ne, ^{12}N, ^{13}O and ^{14}O. The isotope ^{18}Ne which decays to ^{18}F with half-life of 1.67 s is important for the ^{18}F production. Two reaction channels, namely (p,pn) and (p,d), lead to the same products. Two isotopes, i.e. ^{12}C and ^{14}N, produced by this type of reactions, are stable. Two other nuclides, namely ^{11}C and ^{13}N, are the well known β^+ emitters applied in PET, and the most important is the third one: ^{18}F (see e.g. [22]).

The (p,α) reactions on fluoroaniline lead to formation of the following stable isotopes: ^{10}B, ^{12}C, ^{16}O, and of the rather unwanted ^{11}C (via the ^{14}N(p,α)^{11}C reaction). Characteristics of the theoretically possible ^{9}B and ^{11}N are not sufficiently known.

Other reactions induced by 25 MeV protons on fluoroanilines contribute also to the formation of β^+ emitters ^{11}C and ^{13}N.

If we consider the (p,xnypzα) reactions on fluoroaniline, the main possible β^+ emitters of half-lives above 15 s are ^{19}Ne, ^{14,15}O, ^{13}N and ^{11}C.

Thus, we expect five components in the decay curve of the annihilation peak. It is practical to reduce the number of components to two. This is attainable by storage of samples for suitable time after EOB (end of bombarding) to allow the short-lived nuclides ^{19}Ne, ^{15}O and ^{13}N to decay.

Experimental

Targetry and cyclotron irradiations

All irradiations were carried out using the C-30 cyclotron of the Andrzej Sołtan Institute for Nuclear Studies (Otwock/Świerk, Poland). Negative H ions were accelerated and both electrons were stripped off by the aluminum foil. The resultant proton beam was directed into a beamline which consists of two steering magnets, two quadrupole lenses, a system of slits and a small diagnostic chamber equipped with $\Delta E + E$ semiconductor Si(Li) telescope and a thick detector (also working as a spectrometer) for measuring (monitoring) proton beam intensities (see Fig. 1).

The energy of the proton beam was measured with a polyethylene foil as a proton scatterer. The elastic scattering peak from ^{12}C (constituent of the foil) and peaks corresponding to inelastically scattered protons were measured with a calibrated $\Delta E + E$ semiconductor

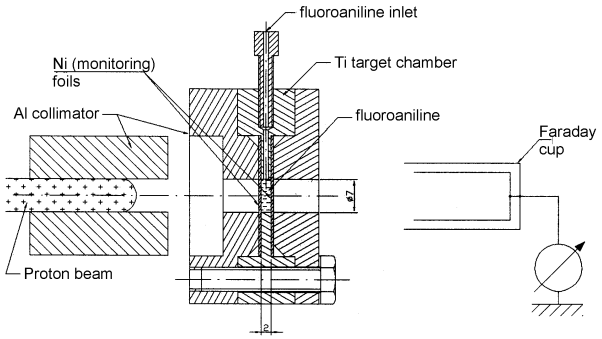

Fig. 1. Scheme of the irradiating arrangement. The 25 MeV proton beam passes through the monitoring Ni foil and then through the fluoroaniline sample and the second monitoring Ni foil, and it is stopped in the Faraday cup.

Si(Li) telescope. The proton energy after passing the cyclotron vacuum isolation foil was 25 ± 0.2 MeV.

Liquid 2-fluoroaniline and 2,4-difluoroaniline target materials were procured from Aldrich, other reagents from Merck, and the solid extraction phase Chromabond™ NO_2 column from Macherey and Nagel. Fluorine is a corrosive element, therefore inert to corrosion titanium and nickel were used as construction materials for the irradiation chamber. The defocused proton beam was directed into the irradiation chamber through a collimator of 7 mm aperture.

The thickness of the fluoroaniline layer was determined by a 2 mm titanium spacer (degradation of proton energy from 25 to 20 MeV). The front and back windows of the irradiation cell were made of nickel foils. The foils and the spacer were clamped together metal-to--metal. A hole in the base of the target chamber led to a liquid withdrawal part, and another hole in the base led to a small tunnel for filling the target irradiating cell (also as a pressure relief valve in case of volatilization of fluoroaniline).

Practically the whole entering proton beam passed through the irradiation chamber, and the total charge was collected in the Faraday cup and a calibrated current integrator. The integrated proton beam intensities were monitored also by induced activities in the front and back Ni foils. Nickel served also as a proton beam monitor due to the well known γ-ray emissions and excitation functions of the reaction products. For each irradiation, new windows were used to allow beam current determination via the monitor reactions. We were using foils with thicknesses of 5, 10 and 20 μm as windows, but the thinnest one cracked frequently and the other two caused significant energy loss of protons. Finally, most irradiations were performed with 10 μm nickel foil windows. The corresponding energy loss amounted to 0.16 MeV, so, the outgoing protons which impinged fluoroaniline (difluoroaniline) and excited the activities had the energy of 24.84 MeV. After passing a 2 mm thick fluoroaniline sample, the proton energy decreased by further 5 MeV. The energy degradation of protons going through the two Ni foils was determined basing on the stopping power and energy range [14]. They were calculated using the computer code POTAUS [26]. The protons going out of the sample with the energy of 19.84 MeV bombarded the second, monitoring Ni foil. We observed the $^{55,57}Co$, ^{57}Ni and $^{60,61}Cu$ activities in both Ni foil windows (see [1, 11, 21, 28]). For the beam current determination we used only three of them, viz. ^{55}Co, ^{57}Ni and ^{61}Cu.

Most of the charged particle beam power deposited in the target is dissipated as heat. The problem is the absorption of energy in a very small volume (0.077 cm^3) of the irradiated cell containing fluoroaniline and an effective transport of heat to the walls of the chamber. Our considerations are built on empirical data, so they may be of restricted validity.

We performed a series of irradiations with different beam currents and irradiation times in order to establish safe irradiation conditions of the sample. The target cooling was mandatory, as without it a significant loss of fluoroaniline was observed. The irradiation chamber with the nitrogen gas as a coolant was used, and a liquid nitrogen reservoir was connected to the chamber. The evolving heat was bringing the liquid nitrogen to boil and the (evaporated) nitrogen gas was used to cool the irradiation chamber. The temperature of the irradiation chamber was monitored during bombardment, using a thermocouple. The irradiation times were 60 and 110 min, and the beam currents varied in the 10–100 nA range. The beam current was stable during each irradiation.

Following the irradiation of the samples, the γ rays were detected by two HPGe (high purity germanium) spectrometers. Gamma ray spectra of the activities from fluoroaniline and monitor nickel foils were taken with a HPGe detector (Canberra, Model GX3520, carbon epoxy window, 2 keV energy resolution for 1332 keV and 1.1 keV for 122 keV) connected via a linear amplifier Tennelec TC245 to a 4096-channel computerized multichannel analyzer. The 511 keV annihilation γ quanta from the liquid 2-fluoroaniline and difluoroaniline samples were measured at the Metrological Laboratory of Radioactive Materials (MLRM, Radioisotope Centre POLATOM, Otwock/Świerk). There, the γ-ray spectra were registered with a HPGe detector (Canberra GC1520, 72 cm^3, 1.8 keV resolution at 1332 keV) connected to a spectrometric system. The data on the both spectrometric systems were processed using the GENIE-2000 code.

All liquid irradiated samples of 2-fluoroaniline and difluoroaniline were measured in glass vials. The thickness of the vial walls was carefully selected, and it was sufficient to stop more than 99% of the emitted positrons from the samples. The 511 keV peak in a γ-ray spectrum was used for the positron intensity (activity) determination. It was necessary to determine the efficiency of germanium detectors with calibrated liquid samples in glass vials (penicillin vials) for the measurements of the 2-fluoroaniline and difluoroaniline samples. All radioisotopes were in the form of 5 ml of a liquid.

Fluorine-18 activity was determined via the decay curve analysis of the 511 keV annihilation peak. The counting started 42 min after EOB to allow the short--lived products (^{13}N, $^{14,15}O$, etc.) to decay. Nuclides with the observed half-lives of 110 and 20 min were identified as ^{18}F and ^{11}C.

In our preceding work [22], the time required for chemical procedures was about 1 h after ^{18}F was produced by the $^{19}F(n,2n)^{18}F$ reaction. In order to keep a similar chemical processing time here, the chemical separation of ^{18}F started in the presence of the ^{11}C activity in the fluoroaniline sample (^{11}C remains in the target material after chemical separation of ^{18}F). Figure 2 shows the decay curves of a 2-fluoroaniline sample irradiated with 25 MeV protons. The experimentally observed activities of ^{11}C and ^{18}F can be described by $A_x = A_{0x} \exp(-\lambda_x t)$, where x stands for either ^{11}C or ^{18}F, $A_{0C} = 2.237 \times 10^5$ Bq, $A_{0F} = 3.904 \times 10^5$ Bq, $\lambda_C = 4.9630 \times 10^{-4}$ s^{-1} and $\lambda_F = 1.02684 \times 10^{-4}$ s^{-1}. In this way, we determined the "true" value of ^{18}F activity from the experimental decay curve.

Correct interpretation of results of the separation procedure requires knowledge of the activity ratio $^{18}F A/^{11}C A$ as a function of time. This ratio is also necessary for correct determination of the reaction cross section leading to formation of ^{18}F, as well as the chemical (separation) yield.

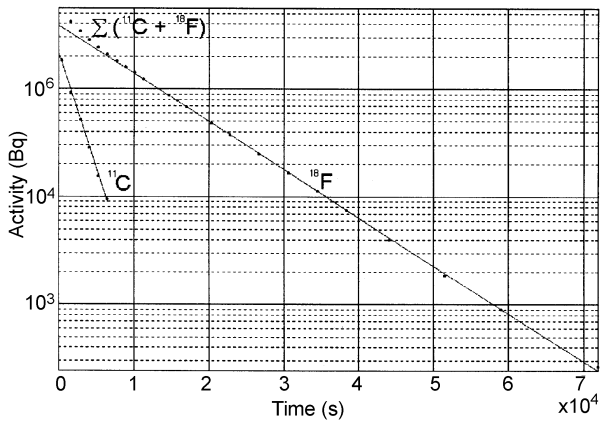

Fig. 2. Decay curve analysis of the annihilation peak from the fluoroaniline target bombarded with 25 MeV protons. Measurements started 42 min after EOB (see the text).

Chemical separation of ^{18}F from 2-fluoroaniline and 2,4-difluoroaniline

The cooling period after the end of irradiation enabled the short-living activities to die out. Then, the irradiation chamber with was transported from the cyclotron to the γ-ray spectrometr, the fluoroaniline was poured into a glass vial and its initial activity was measured. Finally, the vials were moved to the radiochemical laboratory.

For chemical processing we used the method described for the (γ,n) reaction on fluoroaniline [23] and also used for the separation of ^{18}F produced in the (n,2n) reaction on fluoroaniline [22]. We applied it assuming that formation of ^{18}F by protons in the same targets must not significantly influence the separation process.

The irradiated sample was mixed with 5 ml of fresh 2-fluoroaniline, and then we used the solvent extraction procedure. The mixture of the irradiated target and of

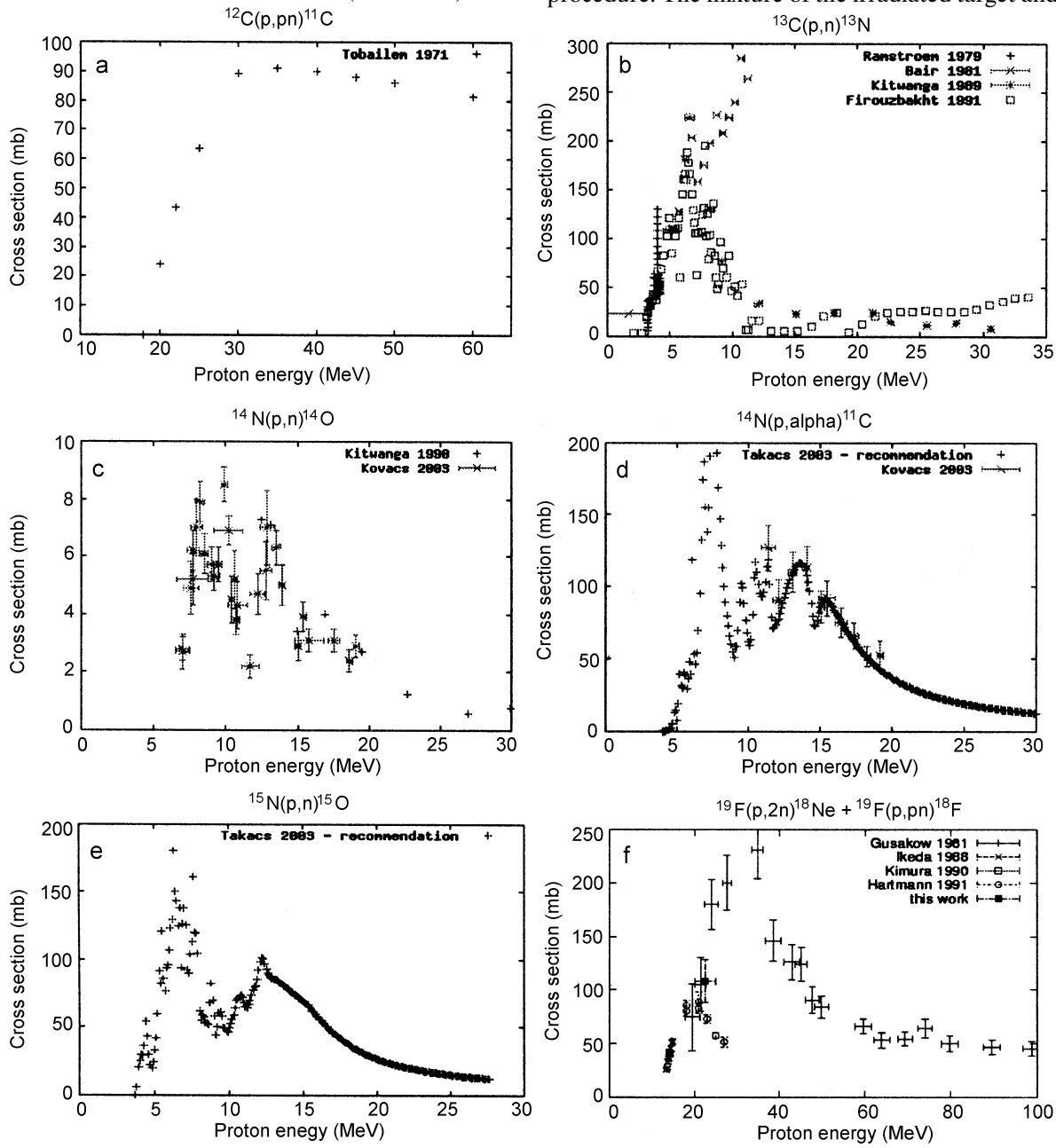

Fig. 3. Excitation functions of reactions induced by protons in the fluoroaniline components (C, N and F). The experimental data (or – in two cases – the recommended cross sections) are from [3, 6, 9, 10, 12, 16, 17, 20, 25, 27, 29, 31, 32].

the added 2-fluoroaniline was shaken with water (4 cm^3) for 1 min in order to extract fluorine ions into the water phase. Then, the mixture was centrifuged (1 min at 500 g) to separate the phases. The aqueous extract containing $^{18}F^-$ was washed with 1 ml of n-hexane and then the water phase was purified by liquid chromatography on a previously conditioned Chromabond™–NO_2 column. After loading the aqueous extract on the top of the column, the following eluents were used, subsequently: 20 cm^3 of water, 20 cm^3 of 50 mM K_2CO_3, and 20 cm^3 of 50 mM KOH, with a flow rate of about 2 cm^3/min. The eluent fractions were of 10 cm^3 each. They were collected and measured using a germanium detector. Most of the activity was in the fraction 3, with separation yield of 46 ± 7% for 2-fluoroaniline and 47 ± 12% for 2,4-difluoroaniline. The time required for all chemical procedures was 70–90 min.

Results

Excitation functions and yields

The ^{18}F production using fluorine targets was reported with non-negligible cross sections at energies exceeding 15 MeV (see [5]). Above this energy, ^{18}F can be produced by the $^{19}F(p,2n)^{18}Ne \rightarrow {}^{18}F$ reaction, in addition to the $^{19}F(p,pn)$ reaction. Therefore, the (experimental) excitation functions shown in Fig. 3 (we have not plotted the data which refer to low energies and extremely low cross sections, neither those at energies much above 100 MeV) represent a sum of the direct ^{18}F formation in the (p,pn) reaction and of the indirect formation via the ^{18}Ne decay. The $^{19}F(p,2n)^{18}Ne \rightarrow {}^{18}F$ reaction cannot be measured directly using the activation method because of the short half-life of ^{18}Ne. We used the TALYS code version 1.0 [19] to get information on the relative role of both contributing reaction channels. The cross sections of reactions on ^{19}F were calculated with allowance for the pre-equilibrium component. Two sets of the optical model parameters [15, 18] were chosen, and also the "realistic" level densities [7] in addition to the standard ones. The differences among different sets of calculations were not essential; three calculated excitation functions of the $^{19}F(p,pn)$ reactions are given in Fig. 4. The reaction leading to ^{18}F via ^{18}Ne is of very small cross sections and it represents just a tiny correction to the preceding one. In fact, only one of the curves, namely that with Goriely densities (highest cross sections for the $^{19}F(p,2n)$ reaction), is drawn for the latter reaction – the maximum is 2.4 mb at about 32 MeV, what is slightly more than one per cent of the dominant reaction. The figure also depicts the experimental results; they represent the sum of both reactions leading to ^{18}F.

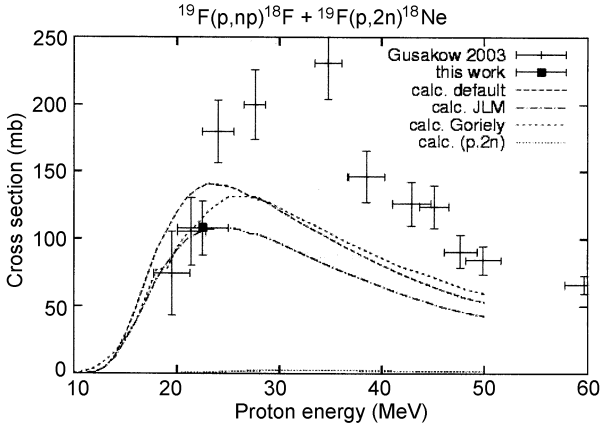

Fig. 4. Experimental excitation function for the ^{18}F formation during proton bombardment of monoisotopic ^{19}F, compared to two contributing independent excitation functions of the $^{19}F(p,pn)^{18}F$ and $^{19}F(p,2n)^{18}Ne \rightarrow {}^{18}F$ reactions.

Bombardment of fluoroaniline with 25 MeV protons produces ^{11}C, ^{13}N, $^{14,15}O$ and ^{19}F on stable isotopes of the elements composing fluoroaniline. The excitation functions for the reactions producing these nuclides are also shown in Fig. 3. The excitation functions for reactions leading to these isotopes reach maximal cross sections between 3 and 20 MeV and they have tails beyond these limits [9, 31]. Thus, the fluoroaniline target thickness must be chosen so that the outgoing proton energy exceeds 20 MeV. In the 11–20 MeV range, the (p,pn) reaction has low cross sections, so, the production of ^{18}F will be also low. For thicker targets, production of ^{18}F is low, but a lot of competing short-lived β^+ emitters can be produced in amounts significantly higher than the expected ^{18}F activity.

The targets used were not the thin ones and they did not fulfill the condition of σ = const. over the whole target thickness (equivalent of 5 MeV). We calculated the ^{18}F formation cross section using the standard activation formula. The energy of the irradiation, equal to 22.5 MeV, was taken as a midpoint in the liquid target. Our resulting cross section averaged over seven irradiations (five for 2-fluoroaniline and two for 2,4-difluoroaniline) is $\sigma = 108 \pm 20$ mb. Good agreement of our cross sections with other data (with the exception of [10]) serves as validation of our experimental method.

Thick target yield

The thick target yield Y of a nuclide produced immediately after the end of bombardment (remember that nuclides also disintegrate during their bombardment) is

$$(1) \qquad Y \propto N_t I(1-e^{\lambda t}) \int_{E_{in}}^{E_{out}} \sigma(E_x) / [dE_x / dx]^{-1} dE_x$$

where: N_t is the number of target nuclei per unit area; I is the number of incident protons per unit time; E_{in} and E_{out} are the incident proton energy and that after leaving the target, respectively; $\sigma(E_x)$ is the reaction cross section at the energy E_x, and dE_x/dx is the stopping power. The mass of fluoroaniline in the cylindrical irradiation cell is 0.088 g. Fluorine constitutes only 17.1% of the mass of 2-fluoroaniline, which in our case gives 0.015 g of ^{19}F and corresponds to 4.80×10^{20} fluorine atoms (9.19×10^{20} in the case of 2,4-difluoroaniline).

For the calculation of yield in the sample we also need the stopping powers and cross sections for the ^{18}F production. These data are presented in Table 2.

Both kinds of fluoroaniline form a uniform liquid target of a known thickness, which enables one to compare the measured yields of ^{18}F with theoretical predictions. The irradiation conditions, yield measurements, and the predicted yields of ^{18}F are listed in

Table 2. Calculated stopping powers for protons in 2-fluoroaniline and 2,4-difluoroaniline and the cross sections for ^{18}F formation in the ((p,pn) + (p,2n)) reactions on stable fluorine, from [8]

E_p (MeV)	dE_p/dx (MeV·cm^3/g) 2-fluoroaniline	dE_p/dx (MeV·cm^3/g) 2,4-difluoroaniline	σ (mb)	σ/(dE_p/dx) 2-fluoroaniline	σ/(dE_p/dx) 2,4-difluoroaniline
20	24.58	23.78	77	3.13	3.24
22.5	22.32	21.60	180	8.06	8.33
25	20.46	19.81	190	9.28	9.59

Table 3. Production yields of ^{18}F from 2-fluoroaniline and 2,4-difluoroaniline targets

Target	Target thickness (mg/cm^3)	Proton energy range (MeV)	Irradiation conditions		Yield (μCi/nA)	
			Current (nA)	Time (h)	Measured	Calculated
2-fluoroaniline	39.8	5	51.5	1	1.39	1.37
			71.6	1	1.26	
2,4-difluoroaniline	75.3	5	33.0	1	2.31	2.58
			27.0	1	2.59	

Table 3. Calculations gave the predicted thick target saturation yield of 1.37 μCi/nA for 2-fluoroaniline and 2.58 μCi/nA for 2,4-difluoroaniline. In all cases, the experimental yields are close to the predicted ones. For both fluoroaniline targets, we can see a small decrease of the yield with increasing intensity of the proton beam. In the irradiations, the diameter of the beam striking the chamber was defined by the collimator aperture as 0.7 cm. Thick target yields were determined experimentally for the ^{18}F production from 2-fluoroaniline for the irradiation time equal to the half-life of ^{18}F (1.83 h) and different currents of proton beam. The ^{18}F activities and yields were 13.6 μCi (1.39 μCi/nA), 19.3 μCi (1.44 μCi/nA) and 28.5 μCi (1.14 μCi/nA) for 9.8, 13.4 and 25 nA currents, respectively. Unnoticed evaporation (this can cause a significant loss of fluoroaniline in our open target) as well as radiolysis and bubbles may explain large discrepancies between the calculated thick target yield and the experimental values for the 1.83 h irradiations. It is worth of pointing out that the yield at 1.83 h is lower than that for the 1 h irradiation.

When we use irradiation times much longer than the half-life of ^{18}F, the activity increases as well, but this effect is not significant.

The yield can be increased when using thicker targets and higher proton energies. A great advantage of this method is that inexpensive monoisotopic natural ^{19}F in organic compounds may be used as target material, and the separation of ^{18}F is technically a simplest possible. Because of the interest in production of large quantities of ^{18}F we show that high thick target yield can be expected with higher proton energies and that the excitation function for ^{18}F production shows large cross sections. We calculated the yield for the incident energy of 60 MeV, the outgoing energy of 20 MeV, the beam current of 1 μA and the irradiation time of 1 h (at 60 MeV, we used the experimental cross sections of [8]). We assumed a cylindrical form of the target, with the base diameter of 1.128 cm and its height determined by the proton ranges in fluoroaniline at 60 and 20 MeV. The stopping power values as well as ranges of protons in both fluoro compounds were calculated using the code POTAUS. The ranges for 60 and 20 MeV are 2.87 and 0.39 cm, respectively. The difference between the ranges, equal to 2.48 cm, is the path length of the cell. The content of fluorine in 2-fluoroaniline is 17.1% and for the assumed dimensions its weight is 0.197 g, what corresponds to 1.544×10^{22} atoms. Finally, we get Y = 319 mCi/μA, what is in reasonable agreement with the result reported by [4].

This yield is sufficient to prepare PET radiopharmaceuticals for clinical use. Of course, the target system must be able to withstand the power deposited in the cell filled with fluoroaniline, and in our irradiation chamber it is equal to 40 W. This requires a much more complex target chamber construction. Similar considerations performed for the 2,4-difluoroaniline result in the calculated yield of 586 mCi/μA. Assuming the 50% chemical yield and the separation 7 time correction, this yield becomes about 70 mCi, but the price of the 2,4-difluoroaniline is about 6 × higher than that of 2-fluoroaniline.

Conclusions

Currently, essentially two methods are in use for direct production of no carrier added (NCA) ^{18}F with cyclotrons of modest proton or deuteron energy (below 16 and 14 MeV, respectively) and moderate beam currents, namely:

I. Irradiation of ^{18}O enriched water (to 95%) with protons, using the ^{18}O(p,n)^{18}F reaction. The cross section varies from 5 mb at 2.5 MeV, reaches maximum of 496 mb at 5 MeV, and decreases to 51 mb at 16 MeV. Here, 1 cm^3 (1 g) of the enriched water is needed for the ^{18}F production, and its price is 120 USD. Irradiation of 1 h with 1 μA proton beam yields 3 GBq, i.e. 80 mCi. The contamination by ^{13}N does not present a serious problem due to its significantly shorter half-life.
II. Irradiation of Ne or enriched ^{20}Ne with deuterons using reaction ^{20}Ne(d,pnα)^{18}F. The corresponding cross sections are 50 mb at 2 MeV, 226 mb at 5.5 MeV and 40 mb at 14 MeV. The target material is not expensive, and after 1 h irradiation with the deuteron beam of 1 μA at 14 MeV one can get the ^{18}F activity of 93 mCi (3.46 GBq).

Two other processes require particle accelerators with energy between 25 and 70 MeV:

1. Irradiation of natural distilled water (cheap!) by α-particles. There are two reactions to produce ^{18}F, namely $^{16}O(\alpha,d)^{18}F$ and $^{16}O(\alpha,pn)^{18}F$, with thresholds of 20.4 and 23.2 MeV, respectively. The latter reaction has a higher cross section; the cross sections of both reactions have their maxima at 35 MeV. Irradiation of water by 30 MeV alpha particles of 1 μA current during 1 h produces about 1.1 mCi of ^{18}F. Optimal production of 7 mCi/μAh is reached at 48 MeV; however, alpha beams of such energy are not routinely available with sufficient intensity.
2. A more convenient method is the proton bombardment of monoisotopic ^{19}F in fluoroorganic compounds studied here, using the $^{19}F(p,pn)^{18}F$ reaction. The target material is cheap (25 g of fluoroaniline cost 14 EUR, and the same amount of difluoroaniline 92 EUR). The experimental excitation function (threshold 11 MeV) is known in a broad proton energy range. It has a specific shape: the cross section increases rapidly up to its broad and flat maximum, and then it decreases slowly. Obviously, there are competing reactions leading to short-living β^+ emitters but, fortunately, they have maxima between 3 and 20 MeV (except reactions leading to ^{11}C). We therefore checked the applicability of separation methods. In our experiments (at unfavourable conditions) the volume of the target was rather small, and the separation of ^{18}F from fluoroaniline required addition of nonradioactive fluoroaniline, what lowered the specific activity. Another problem, which we had to address, was cooling of such a small irradiation chamber – this problem does not exist for bigger irradiation chambers. We expect that with protons of energy up to 60 MeV the ^{18}F production yield would be comparable or higher than that achieved with classical proton bombardment of pure $H_2{}^{18}O$ using medical cyclotrons of modest energies.

To our knowledge [13], more than 30 installations of medium-energy cyclotrons are available in the world, and procuring or processing of (di)fluoroaniline does not represent any problem.

Thus, one of the promising methods to produce ^{18}F ions for bio-medical purposes is the proton bombardment of 2-fluoroaniline and (more expensive) 2,4-difluoroaniline. The liquid target system requires irradiations of both fluoroorganic compounds at low intensity of the proton beam ($I_p < 100$ nA). The ^{18}F is thus produced simultaneously by two reaction channels: in the direct $^{19}F(p,pn)^{18}F$ process and indirectly, via a generator in the $^{19}F(p,2n)^{18}Ne \rightarrow {}^{18}F$ reaction. The calculated ^{18}F yields as well as those obtained experimentally are encouraging if higher proton energies ($E_p \leq 60$ MeV) would be used. The chemical procedure (extraction) is simple and rapid, and it may be adapted to remote operation.

This work indicates the feasibility of the ^{18}F production using a cheap target material and proton beam parameters corresponding to the low-energy part of the excitation function. Anyway, new investigations are necessary for protons of several dozens of MeV. The separation yield could be increased if one irradiated more massive targets with protons of higher energy than in our preliminary study. During the ^{18}F production in the $^{19}F(\gamma,n)^{18}F$ [23] and $^{19}F(n,2n)^{18}F$ [22] reactions, the irradiated volumes of 2-fluoroaniline were 5–6 cm^3 (sufficient for starting the chemical separation procedure) and the separation yields were of the order of 70%. For smaller samples used in our experiments, the determined separation yields were only about 50%.

The suggested method needs further physico-chemical studies [radiochemical and chemical purity (toxic substances), specific activity (possible radiolysis of target material exposed to proton beam irradiations), sterility and apyrogenicity], which will be a topic of a separate work.

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