The Effect of Target-Gas Purity on the Chemical Form of F-18 during ^{18}F-F_2 Production Using the Neon/Fluorine Target

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Irradiation of gas mixtures of F_2/Ne ($^{20}Ne \xrightarrow{d,\alpha} {}^{18}F$) which contained percent levels (>0.1%) of N_2, CO_2, or CF_4 resulted in the production of unacceptable levels of F-18-labeled NF_3 and CF_4 at the expense of ^{18}F-F_2. Analytical gas chromatographic methods have been devised to determine contaminant levels in the target gas as well as in the products arising from them. Commercial mixtures of 1% F_2/Ne, pure F_2, and neon have been analyzed for contaminants (N_2, O_2, CO, CO_2, and CF_4) and found to vary widely in the levels of these impurities from batch to batch. The N_2 levels in the 1% F_2/Ne mixtures varied from 0.039 to 0.49%, and the CO_2 levels from 0.028 to 0.13%. No detectable impurities were found in the neon (Research Purity), but F_2 was found to contain ~11% CF_4. Reproducibly high yields of ^{18}F-F_2 are obtained if the levels of N_2, CO_2, and CF_4 in the final target gas mixture are <0.01% and carrier F_2 is ~0.1%. Hydrocarbons and CO were not detected in our gas mixtures, but would also be expected to decrease yields of ^{18}F-F_2.

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The production of ^{18}F-F_2 of high specific activity using the $^{20}Ne(d,\alpha)^{18}F$ reaction has been of considerable interest in light of its use in the synthesis of 2-[^{18}F]fluoro-2-deoxy-D-glucose (^{18}FDG), a tracer that has been used successfully in the quantitative measurement of regional brain glucose metabolism (*1*). Moreover, its use in clinical research requires a highly reliable production method.

We have recently described a simplified system for ^{18}F-F_2 production that eliminates the need for a high-vacuum system and the handling of pure fluorine gas (*2*). This system, although manually operated, eliminated problems of direct handling of radioactive targets and allowed for the development of a remotely operated synthetic method for ^{18}FDG (*3*). A major factor in the simplification of this system was the use of a commercially available mixture of 1% fluorine in neon, which was subsequently mixed with research-grade neon to provide a target gas with the required amount of carrier $^{19}F_2$. The target, which typically contained 0.1% F_2 (~ 60 μmol), and this ^{18}F-F_2 production system have been used routinely for over a year with no difficulty to produce ^{18}FDG for human neurological studies.

Recently, however, the production of F-18 as ^{18}F-F_2 decreased rapidly with a concomitant dramatic increase in the production of F-18-labeled, chemically inert gaseous material(s)*. The serious consequences of this problem to the reliability of the production of ^{18}F-F_2 and of labeled compounds requiring its use, necessitated an investigation of the factors influencing the chemical form of F-18 produced from the $^{20}Ne(d,\alpha)^{18}F$ reaction in the presence of carrier F_2. Additionally, it was felt that erratic behavior of this target system reported by other laboratories reinforced the need for a thorough investigation of its causes. The factors needing to be identified and reported on in this paper include: (a) assay of target gases for contaminants that react with F_2, resulting in the production of large quantities of chemically inert F-18-labeled products at the expense of ^{18}F-F_2; (b) description of the analytical methods for assaying target-

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gas mixtures; (c) the identification and quantitation of the inert F-18-labeled products from the Ne/F_2 target; and (d) conditions and specifications for a reproducible and effective gaseous target composition for ^{18}F-F_2 production.

MATERIALS AND METHODS

Irradiation conditions, targetry, and gas handling system. All irradiations were performed at the BNL 60-in. (1.5-m) cyclotron. The Inconel 600 two-port target and flow-through loading system described previously were used (*2*). The 23-MeV deuteron beam from the cyclotron was degraded to 14.0 MeV before entering the target gas. Sufficient target gas (~25 atm) is used to degrade the beam below threshold unless otherwise indicated. Irradiations were carried out at constant dose and dose rate—namely, 10 μA for 10 min (theoretical F-18 yield: 50 mCi) (*4*)—with typical F-18 recoveries being 40-50% of the theoretical value. Although the Inconel target was used in these studies as a matter of convenience, production targets must have highly polished *pure nickel* surfaces wherever exposed to the F_2/Ne mixture (*2*).

The contents of the target after irradiation were analyzed by purging them through a series of traps containing KI, soda lime, and charcoal as previously described (*2*), with modifications to accommodate various sampling vessels as described in the following section. Although one can postulate other fluorine-containing compounds that would be hydrolyzed in water or would oxidize KI, we support our identification of the predominant chemical form recovered from the target as F_2 by its chemical reactivity with 3,4,6-tri-O-acetyl-D-glucal to produce the difluoro adducts (*5*). Work is in progress to develop new analytical techniques for F_2 and the minor reactive gaseous products.

Target gases. FLOURINE IS A HIGHLY TOXIC AND REACTIVE GAS. THE READER IS DIRECTED TO A SERIES OF ARTICLES (*6,7*) ON THE MANIPULATION AND HANDLING OF GASEOUS FLUORINE IN ORDER TO BECOME FULLY AWARE OF THE HAZARDS IN HANDLING THIS DANGEROUS GAS.

The various commercial F_2/Ne mixtures are identified for reference in Table 1. Undiluted F_2 (3.4 atm)[†] and undiluted Ne (Research Grade)[‡] were also obtained commercially.

Target-gas analyses. Gas chromatographic analysis of target gases (before and after irradiation) was used to identify and quantitate N_2, O_2, CO, CO_2, CH_4, and CF_4 contaminants. Samples of target gas were analyzed directly from the target, as well as after removal of fluorine, to ensure against the introduction of artifacts due to the possible reactivity of the fluorine with the column materials. Analyses were performed using an analyzer[‖] equipped with a thermal-conductivity detector and digital processor to quantitate mass peak areas. Samples of the target gas were collected in flow-through gas bulbs fitted with Burrell seals for purposes of analytical screening. Samples were withdrawn in gastight syringes and injected onto the column. Conditions were as follows (contaminant gas, column characteristics, temperature, He flow rate, retention time): for oxygen, molecular sieve 5A (60–80 mesh), 6 ft × 1/4 in., 50°, 21 cc/min, 3.0 min; for nitrogen, molecular sieve, 50°, 21 cc/min, 5.7 min; for carbon monoxide, molecular sieve, 50°, 50 cc/min, 9.4 min; for carbon dioxide, silica gel (30–60 mesh), 6 ft × 1/4 in., 75°, 31 cc/min, 10.6 min; and for carbon tetrafluoride, silica gel, 35°, 21 cc/min, 6.6 min.

When absolute values were required and when the exclusion of air from the sample was necessary, gases were collected in calibrated glass sampling loops. The loops were attached on-line to the column, the dead-volume gas swept out, and the sample passed

TABLE 1. IDENTIFICATION, SOURCE, AND PURITY ANALYSIS OF TARGET GASES

Gas	Source (date received)	Sample designation	% N_2	% O_2	% CO_2	% CF_4
1% F_2/Ne[*]	Matheson (12/77)	(A)	0.040	sh.[†]	0.068	none detected
1% F_2/Ne	Matheson (4/78)	(B)	0.046	sh.	not determined	not determined
1% F_2/Ne	Matheson (8/79)	(C)	0.039	sh.	0.028	none detected
2% F_2/Ne[‡]	Homemade	(D)	0.006	0.24	0.16	0.22
1% F_2/Ne[‡]	Homemade[‖]	(E)	0.003[**]	0.12[**]	none detected	none detected
1% F_2/Ne[§]	Matheson (1/79)	(F)	0.49	0.60	0.13	none detected
Neon[¶]	Matheson	(G)	none detected	none detected	none detected	none detected none
F_2	Air Products	(H)	not[**] determined	not determined	not determined	11.0[**]

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[*] 1% F_2/Ne mixtures were purchased in size 3F gas tanks at a pressure of 35 atm.

[†] Appeared as a shoulder on the neon peak and was too small to be integrated.

[‡] These "homemade" mixtures were prepared using Air Products F_2 (Tank H) and Matheson Research Purity neon (Tank G).

[‖] In the preparation of Tank E, the fluorine was passed through a liquid-N_2 trap to remove CF_4 and CO_2.

[§] All premixed gases were prepared with Research Purity neon except Tank F, which was inadvertently supplied with purified neon.

[¶] Research Purity neon.

[**] Not directly determined but can be estimated from analysis of D or E.

onto the column. These analyses were carried out at ambient temperatures. Conditions were (contaminant gas, column characteristics, He flow rate, retention time): for oxygen, molecular sieve 5A (60–80 mesh), 6 ft × 1/4 in., 21 cc/min, 4.1 min; for nitrogen, molecular sieve, 21 cc/min, 7.6 min; for carbon dioxide, Porapak T (80–100 mesh), 6 ft × 1/4 in., 50 cc/min, 9.6 min; for carbon tetrafluoride, Porapak Q (80–120 mesh), 20 ft × 1/4 in., 20 cc/min, 10.8 min; and for nitrogen trifluoride, Porapak Q, 20 cc/min, 12.7 min.

F-18-labeled inert gas identification, mass determination, and activity assay. A sample of the F-18-labeled inert gas mixture was prepared for mass spectral analysis by the irradiation (at 10 μA for 10 min) of a gas mixture consisting of 2.9 atm of Tank F (Table 1) diluted to 25.9 atm with neon (Tank G). The contents of the target were purged through a KI solution, a soda lime trap, and a cold (−78°C) charcoal trap. The charcoal trap containing the F-18-labeled, chemically inert gases, was evacuated while cooling at −78°C to remove the bulk of the neon, and the contents then transferred into the sample inlet of the mass spectrometer[§] by warming the charcoal. The mass spectrum was obtained at an ionization potential of 80 eV.

The fluorine-18-labeled inert gaseous compounds were also identified and the activities measured by a combination of gas chromatography and automated gas-phase effluent counting (*8*). The system consisted of a gas-liquid chromatograph, effluent counter, effluent flowmeter, and automatic data-collecting device. A description of the system and its operation is given elsewhere (*9*). A research chromatograph[§] equipped with a thermal conductivity detector was used for analysis of gas mixtures before and after irradiation. Conditions similar to those described in the literature (*10*)—20 ft × 1/4 in. o.d. copper column containing 50-80 mesh Porapak Q at 0°C, 20 cc/min He flow rate—were used to separate CF_4 (mp = −184°C, bp = −128°C) and NF_3 (mp = −207°C, bp = −129°C). For purposes of specific-activity measurements and postirradiation mass and activity analysis, mass calibration curves for CF_4 and NF_3 were prepared. Stainless steel injection loops (1/8 in. o.d.) of known volume, fitted with four-port switching valves, were filled with 0.5–2.0% of the appropriate gas, brought up to 1 atm with the high-purity neon, allowed to equilibrate, and then analyzed. Similar procedures were used for analysis of both mass and activity of target-gas mixtures after irradiation. When relative activity ratios were of interest, samples were injected directly into the GC by gas-tight syringes.

After separation of the labeled gas mixture, the radioactive effluent was monitored by a cylindrical window-type flow proportional counter, previously calibrated for flow efficiency, connected directly to the TC detector exit port of the gas chromatograph. The identity of the chemically inert but radioactive products, namely, $^{18}F\text{-}CF_4$ and $^{18}F\text{-}NF_3$, was ascertained (a) by comparison of their retention times (after correction for TC detector/counter dead volume) with the calibrated elution times for CF_4 and NF_3; and (b) in addition, carrier CF_4 and NF_3 were added to the target gas after irradiation as additional proof of product assignment. In all cases, the amount of F-18 activity as CF_4 and/or NF_3 was >95% of the volatile radioactivity as determined by (a) comparing the integrated counts in the products (corrected for flow efficiency and nuclear decay) and an aliquot counted in a NaI(Tl) detector, and (b) comparison of the activity of an aliquot trapped after passage through the GC and counter with the corrected integrated counts from the radiochromatogram.

Gamma spectroscopy. A Ge(Li) detector with preamplifier[**] and a multichannel analyzer with a built-in amplifier,[††] calibrated for both energy and efficiency using NBS standards, were used to monitor radionuclidic purity.

Purification of commercial fluorine and the preparation of fluorine–neon mixtures (D and E, Table 1). Commercial F_2 (Tank H, 0.34 atm) was diluted with neon (17 atm) to give a ~2% F_2/Ne mixture (D in Table 1) contaminated with CO_2 and CF_4. Fluorine (Tank H) was cryogenically purified by isolating 2.72 atm in a stainless steel radiator trap, cooling to −196°C to give a pressure of ~0.3 atm and opening the trap to an evacuated stainless steel cylinder. Dilution with neon produced a 1% F_2/Ne mixture (E in Table 1). The unused F_2 remaining in the vacuum line was diluted with neon and disposed of by purging through a dry soda-lime trap.

Carrier CO_2 experiment. Carbon dioxide carrier (2.1%) was added to the 1% F_2/Ne mixture (Tank C of Table 1, total pressure = 24.5 atm) and the target irradiated. The target gas was assayed for CO_2 and CF_4 before and after irradiation, and a radioassay was performed.

RESULTS AND DISCUSSION

In Table 1 the various commercial gas mixtures of 1% F_2/Ne, as well as neon and F_2, are identified. A sample of gas from each tank was submitted to quantitative gas chromatographic analysis to determine levels of N_2, O_2, CO_2, and CF_4 contaminants. The analyses, presented in Table 1, show a large variability in the levels of contaminants present, with Tanks A, B, and C having far lower levels of N_2 and CO_2 than Tank F. Also, there were large amounts of CF_4 and CO_2 contaminating the "undiluted" F_2 (Tank H). The neon (Tank G) used in these studies had no detectable contaminants. Neither CO, NF_3, CH_4, nor any other hydrocarbon, was detected in any of the samples.

The amount of $^{18}F\text{-}F_2$ recovered from the Ne/F_2 target showed a dramatic dependence on the batch of 1% F_2/Ne target gas used. Whenever $^{18}F\text{-}F_2$ recovery was low, there was a simultaneous increase in the F-18-labeled inert gaseous compounds. The recoveries of $^{18}F\text{-}F_2$ varied from 15 to 98%, depending on the levels of target-gas contaminants, the rest being F-18-labeled gaseous compound(s) (Table 2).

A mass spectrum of the "inert" component of the irradiated target gas (i.e., that which passed through the KI solution and was trapped in charcoal at −78°C) showed the presence of both CF_4 and NF_3, with fragmentation patterns in agreement with literature values (*11*). This was confirmed by comparison of GC retention times with authentic samples of CF_4 and NF_3. Gas radiochromatography also showed that CF_4 and NF_3 accounted for >95% of the total F-18-labeled inert gaseous compounds. Relative amounts of F-18-labeled NF_3 and CF_4 from various target-gas mixtures are shown in Table 2. Tetrafluorohydrazine (potentially formed by recombination of NF_2 radicals) was not detected by either mass spectral or gas chromatographic analysis.

In order to determine which target-gas contaminants are consumed by reaction with F_2, target-gas samples were analyzed before and after irradiation. N_2, O_2, CO, CO_2, CF_4, and NF_3 were analyzed by GC, and F_2 by passage through KI and titration with $Na_2S_2O_3$ (*2*). These data are presented in Table 3, and show that the formation of F-18-labeled NF_3 and CF_4 is accompanied by a decrease in N_2 and CO_2, demonstrating that N_2 and

TABLE 2. ANALYSES OF IRRADIATED GASES

Run No.	Target gas	% ^{18}F-F_2	% ^{18}F-NF_3	% ^{18}F-CF_4
1	Tank F (12.7 atm)*	29	54.1	16.9
2	Tank F (1.6 atm) Neon (24.3 atm)	29	50.7	20.3
3	Same as Run 2	20	62.2	17.8
4	Tank C (1.2 atm) Neon (24.3 atm)	98	1.8	0.2
5	Tank D (1.02 atm) Neon (25.5 atm)	15	0	85
6	Tank E (1.02 atm) Neon (25.0 atm)	93	0	7

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* Pressure represents ~90% of thick-target conditions.

CO_2 (or some radiolytic decomposition products from them) are the source of nitrogen and carbon atoms in the NF_3 and CF_4.

More specifically, the mass analysis of NF_3 produced as compared with N_2 consumed, and of CF_4 produced as compared with CO_2 consumed, showed that 37.0% of the N_2 consumed was accounted for as NF_3, and 34.0% of the CO_2 consumed was accounted for as CF_4. The fluorine balance, also performed, indicated that most (85.5%) of the F_2 consumed was present in the gases NF_3 and CF_4. As additional evidence that CO_2 (or a radiolytic product, such as CO) can serve as a carbon source for ^{18}F-CF_4 formation during irradiation, CO_2 was deliberately added to an otherwise pure 1% F_2/Ne mixture (Tank C). This resulted in 87% of the F-18 products being in the form of ^{18}F-CF_4. It should be reemphasized that Tank C consistently gave a high yield of ^{18}F-F_2 on irradiation, with very little labeled inert gas being formed. The results of this experiment are summarized in Table 4 and show that the formation of CF_4 is accompanied by a decrease in the amount of CO_2 and F_2, with approximately 2 millimoles of F_2 consumed for each millimole of CF_4 produced. Studies are currently under way to determine the amounts of other radiolysis products (such as CO and O_2) from this reaction. Note that whereas only about two-thirds of the F_2 was converted to CF_4, the ^{18}F-CF_4 accounted for 87% of the radioactivity.

TABLE 3. TARGET GAS COMPOSITION BEFORE AND AFTER IRRADIATION OF AN IMPURE COMMERCIAL GAS MIXTURE (TANK F) PLUS NEON (TANK G)*

Target-gas composition	Amount before irradiation (μmol)	Amount after irradiation (μmol)
N_2	164	90
CO_2	32.7	5.6
F_2	168.6	50.9
CF_4	none detected	9.2
NF_3	none detected	54.8
Ne	79 X 10^3	79 X 10^3

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* Target gas consisted of 5.2 atm 1% F_2/Ne premixed gas from Tank F and pressurized up to 25.0 atm with neon in a target volume of 78.3 ml. Numbers represent average values for three runs each with s.d. <10%.

Gas radiochromatography on the inert gas mixture revealed a minor (1–3%) peak having a retention time between that of N_2 and O_2 on Porapak Q. This radioisotope was isolated and subjected to gamma-ray spectroscopy. The only photon present below 1500 keV had an energy 1294 keV and this corresponds to a transition in the decay of Ar-41. This argon is probably the product of the (d,p) reaction on the Ar-40 (99.60% natural abundance) that was present as a trace contaminant in the 1% F_2/Ne (Tank F). We note that the reported half-life of Ar-41 is 1.83 hr, which is 109.8 m, the accepted half-life of F-18 (*12*).

Gas samples taken immediately after bombardment showed short-lived inert gaseous activity having a $t_{1/2}$ of <1 min. While these nuclides were not conclusively identified, they appear to be Ne-18 and Ne-19 ($t_{1/2}$ = 1.7 and 17 sec, respectively). These short-lived activities did not interfere with our studies, since analysis was not

TABLE 4. CO_2/F_2 TARGET GAS ANALYSIS BEFORE AND AFTER IRRADIATION*

Gas	Amount before irradiation (mmol)	Amount after irradiation (mmol)
CO_2†	1.76	1.30
CF_4†	none detected	0.20
F_2‡	0.62	0.25

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* See text for experimental details.
† Analyzed by gas chromatography.
‡ Analyzed by titration with sodium thiosulfate.

made before end of bombardment + 30 min.

CONCLUSION

Small quantities of N_2 and CO_2, which do not react with F_2 under normal conditions, become highly reactive with F_2 under the radiation conditions of F-18 production. The present study had as its aim the identification of factors contributing to the formation of gaseous F-18 compounds during F-18 production. A detailed study of the mechanisms of NF_3 and CF_4 formation under radiation conditions is currently under way here.

This work shows that irradiation of a 0.1% F_2/Ne mixture that contains <0.01% of N_2, CO_2, and CF_4 gives excellent yields of ^{18}F-F_2 during production conditions. This level of purity should be easily met by commercially available mixtures of 1% F_2/Ne and neon when the standards for Research Purity are maintained by the supplier. However, we suggest communication with the supplier during procurement of gases and gas mixtures for the F_2/Ne target, to emphasize the importance of eliminating contaminants. It is especially important that nitrogen contamination be minimized, since this gas cannot be as easily removed as CO_2 or CF_4. Moreover, all other sources of nitrogen and carbon (air, pump oil, etc.) in the system should be removed or avoided. The F-18-labeled gaseous compounds will, of course, depend on the contaminants in the F_2 and Ne, and it is possible that contaminants other than those we have studied may be encountered in other batches of gases. These may lead to other F-18-labeled products at the expense of ^{18}F-F_2 because of the highly efficient hot-atom and thermal reactions of fluorine atoms and ions with the contaminants and their products of radiolysis. In addition, absorbed water and water vapor must be avoided in any part of the target and gas-delivery system so that the ^{18}F-F_2 is not converted to H^{18}F. The presence of oxygen at the levels we report here does not adversely affect production. Further studies are in progress on the reaction of fluorine atoms with oxygen.

FOOTNOTES

[*] We use the term "inert gases" to refer to those compounds that did not react with water, potassium iodide, soda lime, or olefins under the conditions we describe here.

[†] Air Products Co., special order.

[‡] Matheson Gas Products Co.

[‖] Hewlett-Packard 5830A

[§] Hitachi RMU 7

[¶] Hewlett-Packard Model 7620A

[**] Princeton Gamma-Tech

[††] Canberra

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