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Production of ^{34m}Cl and ^{38}Cl via the (d, α) reaction on ^{36}Ar and $^{\text{nat}}\text{Ar}$ gas at 8.4 MeV

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Abstract

Production of ^{38}Cl and ^{34m}Cl via the (d, α) reaction on natural argon and ^{36}Ar reveal medical cyclotrons' ability to supply these isotopes in small quantities. ^{38}Cl provides an inexpensive developmental tool, while ^{34m}Cl is a positron emitter of interest in PET imaging. Production yields, cyclotron target development, cryo-recovery of enriched gases, and nucleophilic chemistry of a model compound are described.

Keywords

^{34m}Cl ; cryo-recovery; PET; cyclotron; MeCl

Introduction

^{34m}Cl ($\beta^+ = 57\%$, $t_{1/2}=32.8\text{m}$) is an isotope of interest to the medical community, especially in drug development. ^{34m}Cl has been suggested as a label for several D_1 agonists,¹ and techniques for electrophilic radiochlorination have also been proposed.² Converse et al. (2004) have allayed concerns about the high positron endpoint energy's affect on imaging with MicroPET phantom studies.³ However, routine use of ^{34m}Cl is limited to facilities capable of accelerating alpha particles.⁴ Proton-only accelerators can make use of reasonable yields from enriched ^{34}S targets, but must contend with the poor thermal and electrical properties of sulphur and its compounds, which reach the molten state at even limited beam currents. Following bombardments of these brittle and insoluble targets, summarized in Table 1 below, the researcher must struggle to obtain the product in a chemically useful form. DeJesus et al. (2007) summarized the difficulty of effectively producing this isotope, attempting irradiations and the radiochemistry of [^{34m}Cl]chlorodeoxyglucose with elemental ^{34}S and aluminum [^{34}S]sulfide. ¹ In their preferred separation method, solid, irradiated elemental sulphur is dissolved in heated DMSO for ultrasound-assisted solvent extraction, obtaining up to 74% yields of ^{34m}Cl for use in later chemistry with quantitative recovery of the enriched sulphur. Target development might increase the utility of ^{34m}Cl in PET research, but obvious solutions, e.g. vertical beams to contain molten sulphur targets, are equipment intensive and must deal with electrostatic dispersion of the insulating (10^{14} ohm*cm) sulphur target material.

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The utility of the $^{20}\text{Ne}(\text{d}, \alpha)^{18}\text{F}$ and $^{78}\text{Kr}(\text{d}, \alpha)^{76}\text{Br}$ reactions suggests an alternative route to $^{34\text{m}}\text{Cl}$ via the corresponding noble gas, argon.^{10,11} The excitation function and yield measurements for $^{36}\text{Ar}(\text{d}, \alpha)^{34\text{m}}\text{Cl}$ near 8.4 MeV, the nominal deuteron energy on a PETtrace cyclotron (General Electric, Waukesha, WI) elude a careful search of the literature. Williams and Irvine (1963) used a 15.4 MeV deuteron beam to benchmark the $^{40}\text{Ar}(\text{d}, \alpha)^{38}\text{Cl}$ reaction for downward extrapolation to 10 MeV with analytical computation. They report a cross section of approximately 18 mbarns at 11 MeV.¹² Horoshko and Shapiro (1972) used the $^{36}\text{Ar}(\text{d}, \alpha)$ reaction at 19 MeV to study the level properties of ^{34}Cl , but did not directly examine the formation of $^{34\text{m}}\text{Cl}$.¹³ Brunnader et. al. (1969) studied the excitation energies of ^{34}Cl produced from argon targets in similar detail using both protons and deuterons at 45 MeV.¹⁴ Tagishi et. al. used 16 MeV polarized deuterons on ^{36}Ar and ^{38}Ar gases to study the effects of tensor analyzing powers, reporting angular cross sections for the production of ^{34}Cl , among other isotopes.¹⁵

Experimental

Argon is composed of ^{36}Ar (0.337%), ^{38}Ar (0.063%), and ^{40}Ar (99.6%). Irradiation of argon gas in natural isotopic abundance should produce primarily ^{41}Ar ($t_{1/2}=109$ min, β^-) via proton emission and $^{38}\text{Cl}^-$ ($t_{1/2}=37.2$ min, β^-) via alpha emission. This experiment was chosen as an inexpensive surrogate to probe the potential for $^{34\text{m}}\text{Cl}$ production with deuteron irradiation. A preliminary target for the GE PETtrace incorporated a removable end-plate for the insertion and removal of 1.38 cm ID quartz tubes to trap chloride from the gas phase (target volume is 35 mL with quartz tube inside). Thick-target (115 psig) deuteron irradiations of 99.99% argon gas tested yields of ^{38}Cl and the desired $^{34\text{m}}\text{Cl}$. The target was flushed twice into a 1 L syringe to remove ^{41}Ar prior to target disassembly. Following irradiation, the target was “cooled” briefly to allow the overwhelming 511 keV gammas from ^{17}F produced via $^{16}\text{O}(\text{d}, \text{n})$ in the quartz tube to decay. The tube was then removed and gamma spectroscopy performed with an HPGE detector (2.8 MeV FWHM at 1.333 MeV, spectra shown below in Figure 1).

Using these spectra and the equation predicting approximate thick target yield at the end of saturated bombardment (EoSB),

$$A_{\text{EoSB}} = \frac{A_{\text{EoB}}}{I(1 - e^{-\lambda t})} [\text{MBq/uA}], \quad (1)$$

the measured yield of ^{38}Cl is 30 ± 4 MBq/uA (0.8 ± 0.1 mCi/uA). EoSB Yields of $^{34\text{m}}\text{Cl}$ from the naturally enriched target were calculated at 0.30 ± 0.18 MBq/uA (8 ± 5 uCi/uA). In Equation (1) above, I is beam current in uA, t is irradiation time, and A_{EoB} is the activity assayed at the end of bombardment. $^{34\text{m}}\text{Cl}$ and ^{38}Cl are produced in a ratio of approximately 1:300, mirroring the mass fraction of their feedstock argon isotopes. The production of ^{38}Cl under conditions described above therefore affords the researcher an inexpensive tool to study the transport kinetics of chloride species in the ionized argon gas phase needed for further target development.

Enriched ^{36}Ar (99.993%, 1 L at STP) was obtained from Isotopix (San Francisco, CA). Use of the expensive target material necessitates efficient cryogenic recovery of the gas after each run. The Clausius-Clapeyron relation (Equation 2 below) characterizes phase transitions of ^{36}Ar and can be used to predict vapor pressure's dependence on temperature and therefore the efficiency of cryotrapping. Where P_1 and P_2 are the pressures at temperatures T_1 and T_2 , Δh is the enthalpy of vaporization, and R is the gas constant (8.314 J/K/mol) the relation takes the integrated form:

$$\ln\left(\frac{P_1}{P_2}\right) = \frac{\Delta h}{R} \left(\frac{1}{T_2} - \frac{1}{T_1} \right) \quad (2)$$

Figure 2 plots the relation for argon in the temperature range of liquid nitrogen (-196°C), commonly used in cryotrapping procedures. The plot reveals that liquid nitrogen-cooled traps will lose a significant fraction (0.3 atm) of enriched material in the target, confirmed by the recovery of $^{\text{nat}}\text{Ar}$ gas in preliminary experiments. This was considerably improved by the use of Vacorb (Varian), which dropped residual argon pressures in the target to <1 mm Hg when cooled to -196°C . The gas manifold shown below in Figure 3 is similar to those previously described for cryogenic recovery of enriched target gases.¹⁶

During a typical ^{34}mCl production, the rotary vane pump (7) first evacuates the target and stainless lines. In the process, the target and manifold are checked for vacuum tightness using a Granville-Phillips series 275 convectron gauge (6). Gas is released from the cryotrapping reservoir (1) to the target, valves are closed, and irradiation proceeds. Vacorb (Varian), housed in a 50 mL stainless steel reservoir, is cooled by submerging the trap in liquid nitrogen, and, following the run, valves between the target and the trap are opened to recover enriched target gas in ~ 10 minutes. Gas recovery is measured using a bourdon gauge (5) and an Omegadyne PX309 pressure transducer (8). All valves are then shut, the target is vented, the target endplate removed, and the liner taken out for assay and radiochemistry. For further developmental work with less expensive target materials, ^{38}Cl may still be produced using the $^{\text{nat}}\text{Ar}$ reservoir (4).

A second target, designed both to speed removal of the quartz tube post-irradiation and to better accommodate the width of the PETtrace's deuteron beam, uses a 19 mm ID quartz tube and a welded cajon end-fitting instead of the original bolted backplate, detailed below in Figure 4. The target is 20.3 cm long and has a volume of 64 mL with 19×21 mm (ID $\times$ OD) quartz inside. The beam enters the target through a 0.001" havar foil, supported by a 2.5 cm thick aluminum grid (2.5 mm flat-to-flat EDM hexagonal holes, 0.3 mm web).¹⁷ Aluminum (99.9% pure, Goodfellow) and stainless steel foils in 0.025 mm thicknesses were also obtained for use as target liners.

Results

To determine yields of the desired nuclear reaction, the ^{36}Ar -filled cryotrap was used to load the 1.90 cm ID target, which was irradiated at an initial pressure of 68 ± 1 psig by beam currents between 5 and 20 uA for 30 minutes. The larger target better accommodated the width of the PETtrace deuteron beam, albeit at some cost in target pressure. After the run, 10 minutes of cryotrapping recovered $>99.5\%$ of target material at -196°C . The target was then vented, and the quartz insert removed for analysis as described above. To date, 18 irradiations have been completed, revealing radionuclidically clean production of ^{34}mCl as determined by HPGE gamma spectroscopy (typical spectra shown in Figure 5). EoSB yields of these experiments average 66 ± 7 MBq/uA (1.8 ± 0.2 mCi/uA) for thick-target runs. In agreement with results on natural argon, increasing the size of the quartz tube ID has resulted in an increase in yield by a factor of 2, albeit at some cost in target thickness due to the reduced pressure achievable with limited quantities of enriched ^{36}Ar gas.

As Figure 6 shows, measured EoSB yields decrease with increased beam current when using a quartz tube to trap ^{34}mCl . Initially, target thinning was suspected at higher beam currents. However, using stainless steel and aluminum foils to line the target and trap chloride during irradiations produced yields that were consistent between 1 and 40 uA of deuterons, between 15 and 120 psig target gas, and with yields measured using quartz tube liners at 5 and 10 uA.

Under these conditions, HPGE gamma spectroscopy of these foils shows EoSB production and trapping of 51.8 ± 7.4 MBq/uA (1.4 ± 0.2 mCi/uA) of ^{38}Cl and 62.8 ± 7.4 MBq (1.7 ± 0.2 mCi/uA) of $^{34\text{m}}\text{Cl}$.

In an attempt to understand these results, the stainless steel foils were also imaged with a Cyclone Storage Phosphor System (Packard, Illinois) to track activity localization at various pressures and beam currents. Linear profiles of four such images, from 1 uA runs at varying pressure, are shown below in Figure 7.

It appears as if the energy deposition of the deuteron beam at low energy near the Bragg peak heats the trapping surface, causing $^{34\text{m}}/^{38}\text{Cl}$ to preferentially trap on cooler surfaces within the target. Asymmetric density reduction in the beam volume, previously reported, creates the intensity pattern shown at different pressures by establishing an upward convective gas flow within the target.¹⁸ For pressures below predicted thick-target values, e.g. the 15 psig run shown above, heating of the trapping foil occurs primarily at the rear of the target, moving activity to the front of the liner foil. At higher pressures when the beam is stopped completely in the first few cm of the tube, density reduction and heat deposition are confined to a narrow region in the front of the target. The reduction in effective width of the Bragg peak results in a banded pattern of lower activity deposition around this region of higher temperature on the liner. Insulating quartz tubes used in initial experiments retain heat throughout irradiation, reducing their ability to trap $^{34\text{m}}/^{38}\text{Cl}$ as beam power increases. Irradiations undertaken since switching to metal foils, however, confirm the thick-target yields reported above using quartz tubes at low beam currents.

Exploratory Nucleophilic Chemistry

Syntheses of [$^{38}/^{34\text{m}}\text{Cl}$]chloromethane were used to test the reactivity of chlorine recovered from these targets. Heat-assisted washing of the quartz tube with 40–45°C water extracts >95% of the activity into solution, presumably as the chloride. QMA (Waters) columns, prepped with 0.5 mL 0.7 M K_2CO_3 followed by 3 mL water, trap >95% ($n=21$) of the activity. A mixture composed of 12 mg KHCO_3 , 40 mg Kryptofix/ $\text{K}_{2,2,2}$, 4 mL MeCN and 1 mL water elutes >95% of the trapped activity in 0.6 mL. To this is added 100 uL TEAOH and 100 uL of 1 N HCl for carrier in a sealed reaction vessel, and the solution is then azeotropically dried twice at 95°C under helium flow with additions of 0.5 mL MeCN before cooling to <70°C. Once water is removed, 1 mL MeCN and 100 uL of MeI are added and the mixture again heated to 95°C under helium flow. Produced [$^{34\text{m}}\text{Cl}$]MeCl is collected in a large syringe for injection onto a Shimadzu 8610B Gas Chromatograph running 0.5 mL/min He sweep gas through an AllTech Poropak Q column (80/100, 6' $\times$ 0.125" $\times$ 0.085" SS) at 110°C and thermal conductivity detector. Radiation is detected with a Hamamatsu E8934 phototube optically coupled to NaI scintillator crystal. Data is collected using homemade National Instruments Labview code to log the output of the radiation and TCD detectors. Figures 8 and 9 shows TCD and radiation detector traces of an injection (20 uL loop) spiked with cold CH_3Cl standard.

Radiochemical yields average 80% decay corrected to the beginning of synthesis, with as much as 340 MBq (9.2 mCi) produced in a single run.

Conclusion

This work describes the first production of radionuclidically pure $^{34\text{m}}\text{Cl}$ from enriched ^{36}Ar gas with 8.4 MeV deuterons in activities suitable for subsequent radiochemistry and small animal imaging. The (d, α) nuclear reaction sidesteps many challenges posed by previously studied target materials, and further affords the researcher an inexpensive, chemically identical surrogate in ^{38}Cl , suitable for development.

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References

- DeJesus OT, Converse AK, Nickles RJ. Development of ^{34m}Cl -labeled dopamine D_1 agonists as PET imaging agents. 17th International Symposium on Radiopharmaceutical Sciences, Aachen, Germany. J Label Comp Radiopharm 2007;50:S339. 2007.
- Zhang M-R, Kumata K, Takei M, Fukumura T, Suzuki K. How to introduce radioactive chlorine into a benzene ring using $[\text{*Cl}]\text{Cl}^-$? Applied Radiation and Isotopes 2008;66:1341–1345. [PubMed: 18508276]
- Converse AK, Nye JA, Barnhart TE, Dick DW, Avila-Rodriguez MA, Sundaresan R, Dallas CB, Nickles RJ, Kalin NH, Roberts AD. MicroPET performance in the presence of the third gamma. IEEE Nuclear Science Symposium and Medical Imaging Conference, Conference Record 2004:1797–1799.
- Takeia, Mb; Nagatsua, K.; Fukumuraa, T.; Suzuki, K. Remote control production of an aqueous solution of no-carrier-added ^{34m}Cl via the $^{32}\text{S}(\alpha, \text{pn})$ nuclear reaction. Applied Radiation and Isotopes 2007;65(9):981–986. [PubMed: 17574427]
- DeLuca PM Jr, Lawson JC, Chagnon PR, Berners ED. Angular Correlation Studies in $^{32}\text{S}(^3\text{He}, \text{py})^{34}\text{Cl}$. Nucl Physics 1971;A173:307–320.
- Abrams DN, Knaus EE, Wiebe LI, Helus F, Maier-Borst W. Production of ^{34m}Cl from a gaseous hydrogen sulfide target. International Journal of Applied Radiation and Isotopes 1984;35(11):1045–1048.
- Weinreich R, Qaim SM, Stocklin G. New excitation functions for the production of medically useful halogen radioisotopes. Journal of Labelled Compounds and Radiopharmaceuticals 1977;13:233.
- Zatolokin BV, Konstantinov IO, Krasnov NN. Thick target yields of ^{34m}Cl and ^{38}Cl produced by various charged particles on phosphorus, sulphur and chlorine targets. International Journal of Applied Radiation and Isotopes 1976;27:159–161.
- Nagatsu K, Fukumura T, Takei M, Szelecsenyi F, Kovacs Z, Suzuki K. Measurement of thick target yields of the $^{nat}\text{S}(\alpha, \text{x})^{34m}\text{Cl}$ nuclear reaction and estimation of its excitation function up to 70 MeV. Nuclear Instruments and Methods in Physics Research B 2008;266:709–713.
- Casella VR, Ido T, Wolf AP, Fowler JS, MacGregor RR, Ruth TJ. Anhydrous F-18 labeled elemental fluorine for radiopharmaceutical preparation. Journal of Nuclear Medicine 1980;21:750–757. [PubMed: 7400831]
- DeJesus OT, Friedman AM. Production of Bromine-75 via (d, α) reaction on Krypton-78 gas target. Appl Radiat Isotopes, Int J Radiat Appl Instr, Part A 1988;39:709–710.
- Williams DC, Irvine JW Jr. Nuclear excitation functions and thick target yields: $\text{Zn}+\text{d}$ and $\text{Ar}^{40}(\text{d}, \alpha)$. Physical Review 1963;130(1):265–271.
- Horoshko RN, Shapiro MH. The $^{36}\text{Ar}(\text{d}, \alpha)^{34}\text{Cl}$ reaction at 19 MeV. Nuclear Physics 1972;A180:37–48.
- Brunnader H, Hardy JC, Cerny J. ^{34}Ar and $T = 1$ states in ^{34}Cl from two-nucleon pick-up reactions. Nuclear Physics 1969;A137:487–499.
- Tagishi Y, Clegg TB, Ludwig EJ, Tonsfeldt SA, Wilkerson JF. Study of (d, α) reactions on ^{32}S , ^{36}Ar and ^{38}Ar with vector- and tensor-polarized deuterons. Nuclear Physics 1982;A377:1–14.
- Nickles RJ, Daube ME, Ruth TJ. An $^{18}\text{O}_2$ target for the production of $^{18}\text{F}_2$. International Journal of Applied Radiation Isotopes 1984;35:117.
- Roberts, AD.; Armstrong, IS.; Kay, BP.; Barnhart, TE. Improved strategies for increased $[\text{}^{18}\text{F}]\text{F}^-$ yield via the $^{18}\text{O}(\text{p}, \text{n})^{18}\text{F}$ reaction with thin target windows and bodies. Presentation at the 10th Semi-Annual Workshop on Targetry and Target Chemistry; Madison, WI. 2004.
- Heselius S-J, Lindblom P, Solin O. Optical studies of the influence of an intense ion beam on high-pressure gas targets. Journal of Applied Radiation Isotopes 2002;33(8):653–659.

Figure 1.
HPGE Spectra of $^{nat}\text{Ar}(d,\alpha)$.

Figure 2. Log Plot of Argon Vapor Pressure (atm) Versus Temperature (°C). Data are generated using the integrated form of the Clausius-Clapeyron Relation.

Figure 3.

Schematic for Cryorecovery Manifold. (1) ^{36}Ar /Vacsorb cryotrapping reservoir, (2) Line to target, (3) ^{36}Ar reserve tank, (4) ^{nat}Ar tank for ^{38}Cl production, (5) Bourdon gauge, (6) Granville-Phillips convectron gauge, (7) <100 mTorr Vacuum pump, (8) Omegadyne pressure transducer.

Figure 4. Schematic of Second Target, showing 8.0 MeV deuteron end-of-range in argon gas at (1) 120 psig, 22cm, (2) 60 psig, 11 cm, and (3) 30 psig, 5.5 cm. Detailed schematics available upon request.

Figure 5.
HPGE Spectrum of $^{36}\text{Ar}(d,\alpha)^{34m}\text{Cl}$.

Figure 6.
EoSB Activity of ^{34m}Cl (MBq/uA) Trapped on Quartz Liners vs Beam Current (uA).

Figure 7.

Figure 7a: Profiles of Activity Trapped on Stainless Foil Liners at Various Initial Target Pressures ($\sqrt{n}$) vs Axial Distance (cm). Beam (1 uA, 10 min. bombardment) enters from the left.

Figure 7b: Exemplary Phosphor Image of Uncoiled Stainless Liner. The foil was irradiated for 15 minutes with 1 uA of deuterons and a starting pressure of 15 psig.

Figure 8.
Plot of TCD Output (V) vs Time for [^{34}mCl]MeCl GC Injection, Spiked with Cold MeCl Standard (Fisher).

Figure 9.
Plot of Radiation Detector Output (cts) vs Time for [^{34}mCl]MeCl GC Injection.

Table 1Previously described reactions for the production of ^{34m}Cl

Nuclear Reaction	Energy Range	Target Natural Abundance
$^{32}\text{S}, ^{31}\text{P}(\alpha, \text{xn})^{34m}\text{Cl}$	15–70 MeV 5,8,9	>95%
$^{35}\text{Cl}(\text{p}, \text{pn})^{34m}\text{Cl}$	20–30 MeV 7	75%
$^{34}\text{S}(\text{p}, \text{n})^{34m}\text{Cl}$	15–25 MeV 6,8	4.21%
$^{34}\text{S}(\text{d}, 2\text{n})^{34m}\text{Cl}$	15–25 MeV 6,8	4.21%