SYNTHESIS OF ^{14}C-LABELED PERFLUOROOCTANOIC AND PERFLUORODECANOIC ACIDS; PURIFICATION OF PERFLUORODECANOIC ACID.

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SUMMARY

Perfluoro-n-octanoic acid (PFOA) and perfluoro-n-decanoic acid (PFDA), two widely used industrial products, have been synthesized with ^{14}C-labeling in the C-1 position. The carboxyl labeled materials were prepared in 48% and 53% yield by carbonation of perfluoroheptyllithium and perfluorononyllithium at -100°C. An efficient chemical method for purification of PFDA was also developed. Treatment of commercial PFDA with refluxing potassium hydroxide solution resulted in removal of the mono and diprotio impurities to give 99% pure PFDA.

Key Words: Perfluorinated Acids, Perfluorononyl Iodide, Perfluorolithium, Purification

INTRODUCTION

Perfluorooctanoic and -decanoic acids are representative of a series of perfluorinated acids that have been used for a variety of industrial purposes primarily due to their surfactant properties (1,2). The toxicity of these compounds is being investigated in a number of laboratories (2,3). ^{14}C-labeled materials would be useful in these studies but are not commercially available.

Johncock prepared unlabeled PFOA in low yield by carbonation of the unstable perfluoroheptyllithium at -90°C (4,5). We anticipated several problems in applying this procedure to the synthesis of the ^{14}C-labeled material. Johncock's procedure was run on a fairly large scale (10 mmol) with excess CO_2. This would not be desirable when working with [14]CO_2. In addition, the all glass vacuum line apparatus, normally used for [14]CO_2 generation (6), appeared to be poorly suited for the low-temperature-sensitive reaction required. Therefore, we optimized reaction conditions with a simplified apparatus on a 0.5 mmol scale using CO_2 as the limiting reagent.

Commercially available PFDA (Aldrich Chemical Company) has been found to
contain impurities of mono- and diprotiosubstituted perfluorodecanoic acids by
GC mass spectrometry (7). Since it was extremely important for the toxicologi-
cal studies to have PFDA of high purity and the nonyl iodide precursor to ^{14}C
PFDA was to be synthesized from PFDA, we devised a chemical purification of the
commercially available material which served to remove the protio materials.

RESULTS AND DISCUSSION

Apparatus. The $^{14}CO_2$ was generated very simply in a round bottom flask
equipped with an addition funnel and connected directly to a drying tube filled
with Drierite (Figure 1). The perfluorolithium reagent was formed in a second
round bottom flask with two long necks modified for optimum condensation of the
$^{14}CO_2$. The $^{14}CO_2$ generator and the reaction flask were connected via rubber
septa and a steel cannula. $^{14}CO_2$ was swept into the reaction flask using N_2
pressure. No vacuum pump was required. Using this apparatus (Figure 1), it was
found by carbonation of phenyllithium that greater than 90% of the CO_2 was
trapped.

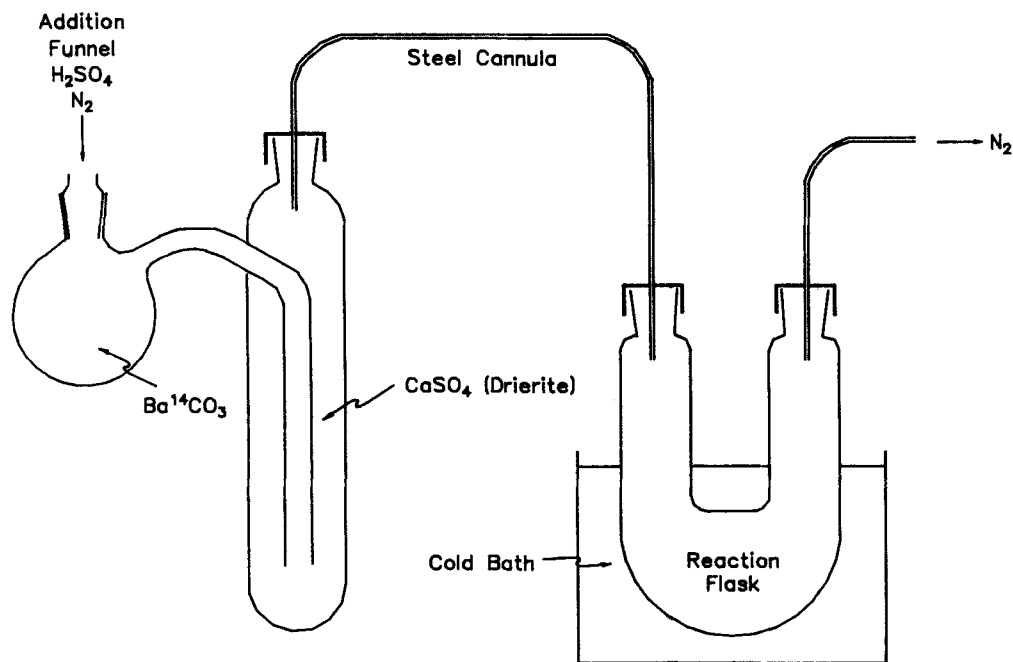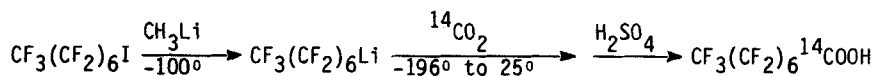Figure 1. **Apparatus for Preparation of Labelled Perfluorocarboxylic Acids**

Preparation of the Fluorinated Acids. Since perfluorinated lithium reagents are known to be unstable (5), it was necessary to prepare perfluoroheptyllithium by lithium-iodide exchange at -100°C and to trap the lithium reagent with CO_2 at this temperature.

$$CF_3(CF_2)_6I \xrightarrow[-100°]{CH_3Li} CF_3(CF_2)_6Li \xrightarrow[-196° \text{ to } 25°]{^{14}CO_2} \xrightarrow{H_2SO_4} CF_3(CF_2)_6{}^{14}COOH$$

A series of experiments established the necessary criteria for optimum yield: 1) The CO_2 had to be condensed at -196°C. Condensing it at -100°C resulted in some loss of yield. 2) The solvent of choice for this reaction was ether. Substitution of tetrahydrofuran as solvent lowered the yield to 5% whereas use of ether-pentane reduced the yield slightly. 3) Low halide methyllithium was used for the exchange since any unreacted reagent would produce acetic acid which was easily separated. n-Butyllithium and phenyllithium gave good results, but methyllithium:lithium bromide complex did not. 4) It was determined that the ideal ratio of $CH_3Li:RI:CO_2$ was 1:2:0.5. The 2:1 ratio of iodide to CH_3Li results in the formation of the perfluorolithium reagent in the presence of the perfluoroiodide which then forms a stabilized "ate" complex (8). 5) Two modes of reaction were tried. One in which the perfluorolithium reagent was pre-formed and CO_2 was added subsequently; another in which the CO_2 was present during the formation of the perfluorolithium reagent. Both modes of reaction worked equally well. 6) Finally, it was found that the use of excess CO_2 did not improve the yield. Under these experimental conditions, it was possible to obtain reproducibly 50% yields of these carboxyl labeled acids on a 0.5 mmol scale with no loss of the specific activity of the starting $Ba^{14}CO_3$.
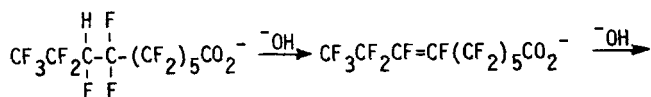
Preparation of Perfluorononyl Iodide. Perfluorononyl iodide, the required precursor of perfluorononyllithium, was synthesized using the Hunsdiecker reaction which had been applied to lower perfluorinated homologs (9).

$$CF_3(CF_2)_8COOH \xrightarrow{Ag_2O} CF_3(CF_2)_8COOAg \xrightarrow[120°]{I_2} CF_3(CF_2)_8I$$
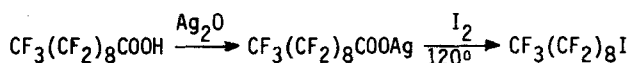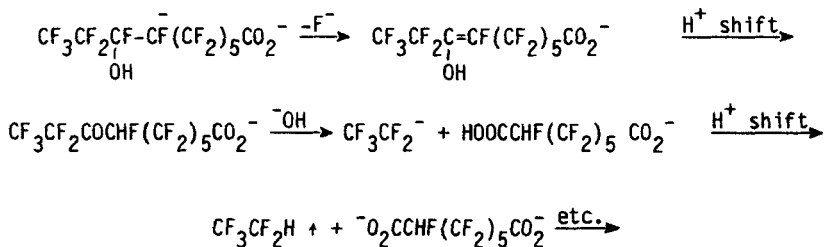
Purification of Perfluorodecanoic Acid. Since it had been reported by George and Andersen (7) and confirmed by us (Figure 2) that the impurities in commer-
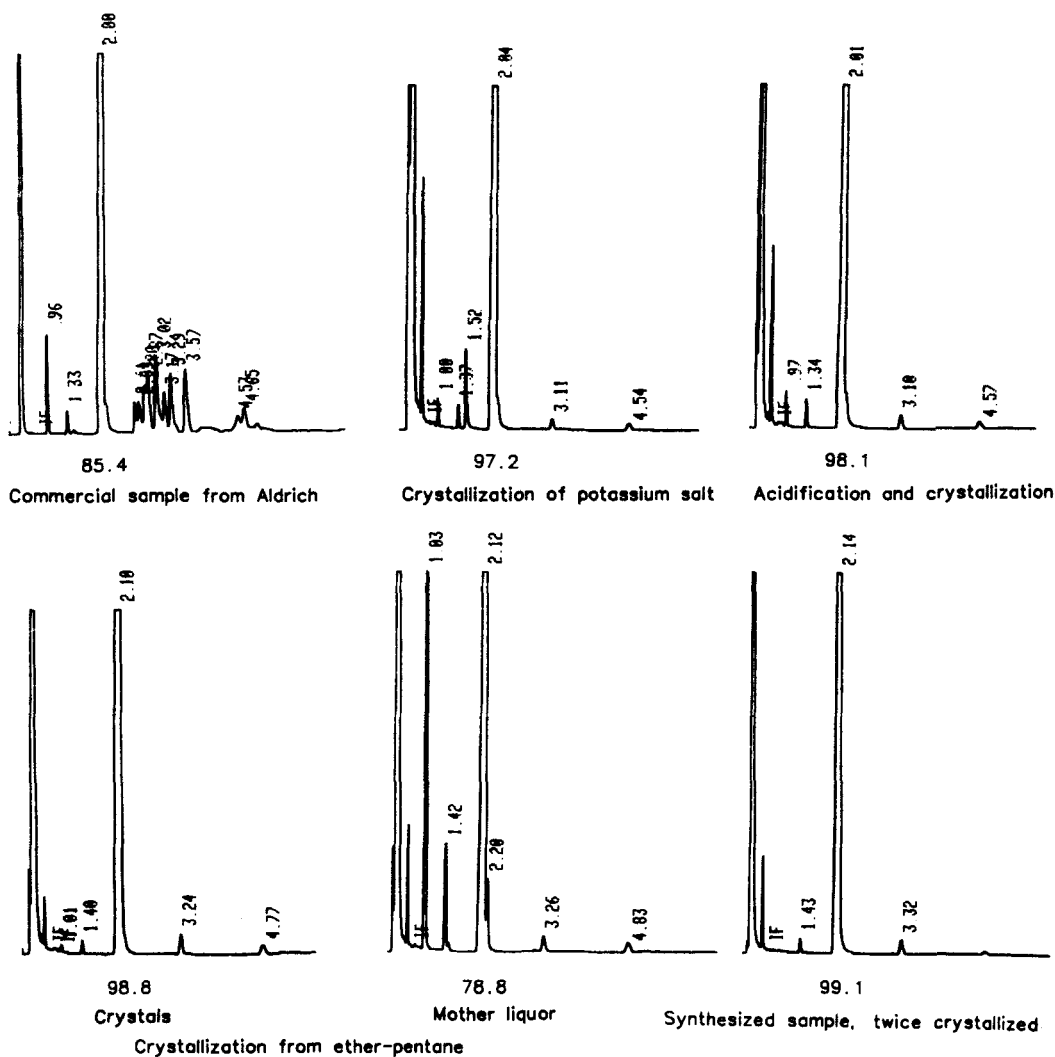
Figure 2.   Purification of CF₃(CF₂)₈COOH

cial PFDA were mono- and diprotioperfluorodecanoic acids, presumably present due
to incomplete fluorination of the hydrocarbon fatty acids, a procedure was
sought that would remove these contaminants.   Treatment with aqueous base should
initiate a series of reactions which would ultimately lead to cleavage of the
protio acids into small fragments easily separated by crystallization.

$$CF_3CF_2\overset{\displaystyle H}{\underset{\displaystyle F}{C}}\text{-}\overset{\displaystyle F}{\underset{\displaystyle F}{C}}\text{-}(CF_2)_5CO_2^- \xrightarrow{^-OH} CF_3CF_2CF{=}CF(CF_2)_5CO_2^- \xrightarrow{^-OH}$$

$$CF_3CF_2\overset{|}{\underset{OH}{C}}F\text{-}\overset{-}{C}F(CF_2)_5CO_2^- \xrightarrow{-F^-} CF_3CF_2\overset{|}{\underset{OH}{C}}{=}CF(CF_2)_5CO_2^- \xrightarrow{H^+ \text{ shift}}$$

$$CF_3CF_2COCHF(CF_2)_5CO_2^- \xrightarrow{-OH} CF_3CF_2^- + HOOCCHF(CF_2)_5 CO_2^- \xrightarrow{H^+ \text{ shift}}$$

$$CF_3CF_2H + {}^-O_2CCHF(CF_2)_5CO_2^- \xrightarrow{etc.}$$

The first step would be dehydrofluorination to give the olefin. Addition of hydroxide then leads to the ketone which could undergo the haloform reaction to give a fluorocarbon and diacid. Each fragment then contains hydrogen so each is subject to further cleavages.

In the event, refluxing the potassium salt of PFDA in 1 M potassium hydroxide solution resulted in nearly complete removal of all the impurities after crystallization of the salt (Figure 2). The salt was dried and treated with concentrated sulfuric acid to yield 74% of PFDA which was > 99% pure by GC analysis of the methyl ester.

EXPERIMENTAL SECTION

Materials. PFDA was bought from Aldrich Chemical Company (lot no. 1105 ML) and purified as described below. Perfluoroheptyl iodide was from SCM Specialty Chemicals and found to be 98% pure by GC analysis. $Ba^{14}CO_3$ was obtained from Amersham with a specific activity of 5.7 mCi/mmol. Methyllithium was purchased from Aldrich Chemical Company.

General Procedure. Gas chromatographic analysis was done on a Model 3700 Varian gas chromatograph using a 36 meter column of vitreous silica with SE-30 liquid phase. Detection was by flame ionization with 6 psi of helium as carrier gas using a 300 to 1 split ratio. Radioactivity was determined with a Packard Tricarb liquid scintillation spectrometer (Model 460CD or 3255). ^{19}F NMR spectra were taken at 188.3 MHz using CF_3COOH as internal reference at -76.5 ppm (negative shifts are upfield from $CFCl_3$).

Perfluorooctanoic-[14]C-1 Acid. In a 25-ml flask equipped with magnetic stirring bar and attached drying tube containing Drierite, was placed 99 mg (0.5 mmol) of $Ba^{14}CO_3$ (5.71 mCi/mmol). A pressure-equalizing addition funnel containing 1 ml of concentrated sulfuric acid acid was capped with a septum and

attached to the flask. The drying tube was capped with a septum and attached via a steel cannula to the two-necked 100-ml reaction flask equipped with magnetic stirrer (Figure 1). The system was purged with N_2 for 20 min and then placed under slight positive N_2 pressure. To the reaction flask was added 20 ml of ether (freshly distilled from sodium benzophenone ketyl) followed by 0.480 ml (2.0 mmol) of perfluoroheptyl iodide. The iodide in ether solution was cooled to -105° in an ether-liquid N_2 bath. To this well-stirred solution, 0.95 ml of CH_3Li solution (1.16 M in ether, 0.05M halide) was added slowly by syringe. After this addition, the reaction flask was cooled to -196°C (frozen) in a liquid N_2 bath (Dewar flask). The system was purged with N_2 and sulfuric acid was added dropwise to the $Ba^{14}CO_3$ with stirring. Nitrogen purging was done for 40 min to ensure that all $^{14}CO_2$ was swept into the reaction flask and condensed. The CO_2 generating flask was heated briefly with a heat gun to liberate all the CO_2. The system was placed under positive N_2 pressure and the reaction flask was allowed to warm to 100°C in an ether-liquid N_2 bath. The solution melted and stirring began. At this point the N_2 pressure was removed, and the flask was stoppered and allowed to warm to -75°C over approximately 20 min. Positive N_2 pressure was then applied again, the bath removed and the flask allowed to warm to room temperature. The solution was transferred to an Erlenmeyer flask and evaporated to dryness with a N_2 stream. The residue was dissolved in 5 ml of water and extracted with 5, 2, and 2 ml of pentane. The pentane layers were evaporated and found to contain mainly unreacted iodide. The aqueous layer was acidified by adding dropwise 1 ml of concentrated H_2SO_4. An oil separated which upon swirling and cooling formed crystals. The crystals were filtered to yield 0.104 gm (48%)* of PFOA with specific activity 4.93 mCi/mmol. This material was recrystallized from ether-pentane to yield 0.057 gm (26%)* of material with specific activity 5.50 mCi/mmol. The mother liquors from each crystallization were treated with 0.50 gm of cold PFOA and crystallized to yield 0.412 gm (0.100 mCi/mmol) and 0.327 gm (0.199 mCi/mmol), respectively. ^{19}F NMR (acetone-d_6) of unlabeled material: (-81.2 (tt, J=7.5, 1.8 Hz, 3F), -119.3 (tt, J=9.5, 2.1 Hz,

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*These yields were calculated using the formula weight for PFOA as 432 which
 includes a molecule of H_2O as shown by ^1H NMR.

2F), -121.9 (broad s, 2F), -122.3 (broad s, 2F), -123.1 (broad s, 2F), -123.2 (m, 2F), -126.5 (m, 2F).

Perfluorooctanoic or Perfluorodecanoic Acid Methyl Ester. To 30 mg of PFOA or PFDA in 1 ml of ether, a solution of diazomethane (CH_2N_2) in ether was added dropwise until the yellow color persisted. The excess CH_2N_2 was removed by blowing a stream of N_2 over the solution. The ether was removed on a rotary evaporator taking care to remove the flask before significant evaporation of the ester occurred ^{19}F NMR (acetone-d_6): PFOA ester; -81.5 (t, J=7.2 Hz, 3F), -119.3 (tt, J=8.5, 2.4 Hz, 2F), -122.6 (broad s, 2F), -122.8 (broad s, 2F), -123.5 (broad s, 4F), -127.0 (m, 2F). PFDA ester; -81.3 (t, J=9.8 Hz, 3F), -118.7 (broad s, 2F), -121.8 (broad s, 6F), -122.8 (broad s, 2F), -122.9 (broad s, 2F), -126.2 (broad s, 2F).

Purification of Perfluorodecanoic Acid. To a 2l, round bottom flask equipped with magnetic stirring bar, condenser and containing 1l of water was added 50 gm (98 mmol) of PFDA (Aldrich lot no. 1105ML, 85.4% pure by gas chromatographic analysis of the methyl ester, Figure 2) and 56 gm of KOH (1 mol). The flask was stirred vigorously and heated to 110°C (bath temperature). At this point much foaming occurred and it was necessary to place a 500 ml addition funnel on top of the condenser to collect the foam. After 30 min at reflux, the foaming sub-sided. The boiling was continued for 20 hr. The solution was cooled to room temperature and then in the refrigerator. The crystals were filtered, washed with 200 ml of cold water, and allowed to dry overnight at room temperature (Figure 2).

The potassium salt of PFDA was added to 2 l of H_2O. To this slurry was added 100 ml (1.8 mol) of concentrated H_2SO_4 with stirring. After stirring for 2 hr, the slurry was cooled in ice and filtered. This material was allowed to dry overnight at room temperature. To the solid, 10% ether-pentane was added and the slurry was boiled for a few minutes. More ether was added and boiling was continued to make sure all the PFDA was dissolved. The undissolved solid was filtered using a Buchner funnel and allowed to dry. The filtrate was allowed to crystallize after evaporation of most of the ether and replacement with pentane. The crystals were filtered to yield 16.3 gm of 99% pure acid, mp 87-88° (Figure 2).

The solid material, by all indications, appeared to be potassium perfluoro-decanoate. This salt was treated again in 500 ml of H_2O with 50 ml of conc. H_2SO_4, cooled, filtered and dried to yield an additional 25 gm of perfluoro-decanoic acid which was likewise recrystallized from ether-pentane to yield 20.7 gm. Total yield was 37.0 gm, 74%.

Silver perfluorodecanoate. To a 21 Erlenmeyer flask containing 1100 ml of H_2O, was added purified PFDA (15.4 gm, 30 mmol). The slurry was stirred and warmed to 50-60°C while silver oxide (3.81 gm, 16.5 mmol) was added. The mix-ture became very thick after about 30 min. Stirring was continued for a total of 3.5 hr. After cooling, the slurry was extracted with 400, 200, 200, 100 and 100 ml of ether. The ether extracts were filtered to remove any gray silver oxide and the filtrate was evaporated to dryness to yield 15.4 gm (86%) of silver perfluorodecanoate.

Perfluorononyl Iodide. Silver perfluorodecanoate (14.4 gm, 23.2 mmol) was mixed with 6.80 gm of iodine (26.8 mmol) in a mortar and pestle and the mixture was placed in a long-necked, 100-ml round bottom flask with an oval magnetic stirrer. The bulb of the flask was immersed in an oil bath at 120°C and stirred at this temperature for 8 hr. The iodine that sublimed into the neck of the flask was periodically melted down with a heat gun. The flask was cooled, and pentane (80 ml) was added and the mixture was stirred until the solid formed a finely divided slurry. To this slurry, was added sodium bisulfite (1.2 gm, 12 mmol), sodium hydroxide (0.5 gm, 12.5 mmol), and 1 ml of water. The slurry was stirred for approximately 45 min until the purple iodine color was gone. It was then filtered through celite on a sintered glass funnel and washed with pentane. The pentane was evaporated to yield 10.6 gm of a white solid which sometimes turned brown on standing. The solid was distilled on a Kugelrohr at 25-35°C, 0.6 mm to give 10.1 gm, 77%, mp 43-44°C. Analysis by capillary GC showed the iodide to be 99% pure. ^{19}F NMR ($CDCl_3$): -60.0 (t, J = 15.1 Hz, 2F), -81.7 (t, J = 9.1 Hz, 3F), -113.6 (broad s, 2F), -121.6 (broad s, 2F), -122.5 (broad s, 6F), -123.4 (broad s, 2F) -126.9 (broad s, 2F). The iodide can be crystallized from pentane at -78°C.

Perfluorodecanoic-^{14}C-1 Acid. Done in a way similar to the synthesis of

perfluorooctanoic-[14]C-1 acid using 112 mg of $Ba^{14}CO_3$ (5.71 mCi/mmol). The yield of crystals after acidification with H_2SO_4 was 0.142 gm (53%)**, 4.53 mCi/mmol. After crystallization from ether-pentane, the yield was 0.076 gm (29%)**, 5.12 mCi/mmol. The mother liquors from each crystallization were treated with 0.50 gm of cold PFDA and crystallized to yield 0.430 gm (0.170 mCi/mmol) and 0.408 gm (0.279 mCi/mmol), respectively. ^{19}F NMR (d_6-acetone): -81.3 (t, J = 10.3 Hz, 3F), 119.2 (broad t, J=11.2 Hz, 2F), -121.8 (broad s, 4F), -121.9 (broad s, 4F), -122.7 (broad s, 2F), -123.0 (broad s, 2F), -126.2 (broad s, 2F).

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**These yields were calculated using the formula weight for PFDA as 532 which includes a molecule of H_2O as shown by ^{1}H NMR.

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