SYNTHESIS OF 14C-LABLED PERFLUORODECANOIC AND PERFLUORODEODECANIC ACIDS; PURIFICATION OF PERFLUORODEODECANIC 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 14C-labeling in C1 position. The carboxyl labeled materials were prepared in 88% and 53% yield by carboxylation of perfluorohexylithium and perfluoromethylithium at 100°C. An efficient chemical method for purification of PFOA was also developed. Treatment of commercial PFOA with refluxing potassium hydroxide solution resulted in removal of the mono and diisotopic impurities to give >99% pure PFOA.

Key Words: Perfluorinated Acids, Perfluoromethyl 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). 14C-labeled materials would be useful in these studies but are not commercially available.

Johncock prepared unlabeled PFOA in low yield by carboxylation of the unstable perfluorooctylithium at -90°C (4,5). We anticipated several problems in applying this procedure to the synthesis of the 14C-labeled material. Johncock’s procedure was run on a fairly large scale (10 mmol) with excess CO2. This would not be desirable when working with 14CO2. In addition, the all glass vacuum line apparatus, normally used for 14CO2 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 CO2 as the limiting reagent.

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Commerically available PFDA (Alrich Chemical Company) has been found to contain impurities of mono- and disubstituted perfluorodecanoic acids by GC mass spectrometry (7). Since it was extremely important for the toxicological studies to have PFDA of high purity and the monosubstituteor PFDA was to be synthesized from PFDA, we devised a chemical purification of the commercially available material which served to remove the proto 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 perfluorocyclohexane 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 carboxylation of phenyllithium that greater than 90% of the CO$_2$ was trapped.

Figure 1. Apparatus for Preparation of Labeled Perfluorocarboxylic Acids
Preparation of the Fluorinated Acids. Since perfluorinated lithium reagents are known to be unstable (9), it was necessary to prepare perfluorophenyl lithium by lithium-iodide exchange at -100°C and to trap the lithium reagent with CO₂ at this temperature.

\[
\text{CF}_3\text{CF}_2\text{Li} + \text{CO}_2 \rightarrow \text{CF}_3\text{CF}_2\text{CO}_2\text{Li}
\]

A series of experiments established the necessary criteria for optimum yield:
1) The CO₂ 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 50% whereas use of ether-pentane reduced the yield slightly. 3) Low halide methyllithium was used for the exchange since any unreacted reagent would produce 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 CH₃Li:RicCO₂ was 1:2.6:0.5. The 2:1 ratio of iodide to CH₃Li results in the formation of the perfluorolithium reagent in the presence of the perfluorolate 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 CO₂ was added subsequently; another in which the CO₂ 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 CO₂ did not improve the yield. Under these experimental conditions, it was possible to obtain reproducibly 95% yields of these carboxyl labeled acids on a 0.5 mmol scale with no loss of the specific activity of the starting Ba[¹⁴C]CO₂.

Preparation of Perfluorononyl Iodide. Perfluorononyl iodide, the required precursor of perfluorononyllithium, was synthesized using the Hundt-Becker reaction which had been applied to lower perfluorinated homologs (9).

\[
\text{CF}_3\text{CF}_2\text{CO}_2\text{Li} + \text{I}_2 \rightarrow \text{CF}_3\text{CF}_2\text{ICO}_2\text{Li} + \text{LiI}
\]

Purification of Perfluorodecanoic Acid. Since it had been reported by George and Anderson (7) and confirmed by us (Figure 2) that the impurities in commerci-
cis PFOA were mono- and diprotiofluorodecanoic 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 proto acids into small fragments easily separated by crystallization.

\[
\text{CF}_2\text{CF}_2\text{CF}_2\text{CO}_2^- + \text{OH}^- \rightarrow \text{CF}_2\text{CF}_2\text{CF}_2\text{CO}_2\text{OH}^- + \text{OH}^- 
\]
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 14% 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. 1106 M3) and purified as described below. Perfluorohexyl iodide was from SOM Specialty Chemicals and found to be 98% pure by GC analysis. BeF<sub>2</sub>CO<sub>2</sub> was obtained from American with a specific activity of 5.7 mCi/mmol. Methyl lithium 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 6600D or 3215). 1H NMR spectra were taken at 100.3 MHz using CF<sub>3</sub>COOH as internal reference at -76.6 ppm (negative shifts are upfield from CF<sub>3</sub>CO<sub>2</sub>). 13C NMR spectra were taken at 25 MHz using CDCl<sub>3</sub> or CF<sub>3</sub>CO<sub>2</sub>H as internal reference at -81.0 ppm (negative shifts are upfield from CF<sub>3</sub>CO<sub>2</sub>H).

**Perfluorocrotonic Acid.** In a 25-ml flask equipped with magnetic stirring bar and attached drying tube containing Drierite, was placed 99 mg (0.8 mmol) of BeF<sub>2</sub>CO<sub>2</sub> (5.7 mCi/mmol). A pressure-equalizing addition funnel containing 1 ml of concentrated sulfuric acid was capped with a septum and
attached to the flask. The drying tube was capped with a septum and attenuated
via a steel cannula to the two-necked 100-ml reaction flask equipped with mag-
netic stirrer (Figure 1). The system was purged with N\textsubscript{2} for 20 min and then
placed under slight positive N\textsubscript{2} pressure. To the reaction flask was added 20 ml
of ether (freshly distilled from sodium benzenophene ketyl) followed by 0.480 ml
(2.0 mmol) of perfluoroethyl iodide. The iodide in ether solution was cooled
to -105° in an ether-liquid N\textsubscript{2} bath. To this well-stirred solution, 0.95 ml of
CH\textsubscript{2}Cl\textsubscript{2} solution (1.10 M in ether, 0.058 M halide) was added slowly by syringe.
After this addition, the reaction flask was cooled to -196°C (frozen) in a
liquid N\textsubscript{2} bath ( Dewar flask). The system was purged with N\textsubscript{2} and sulfuric acid
was added dropwise to the Ba\textsuperscript{14}CO\textsubscript{3} with stirring. Nitrogen purging was done for
40 min to ensure that all \textsuperscript{14}CO\textsubscript{2} was swept into the reaction flask and condensed.
The CO\textsubscript{2} generating flask was heated briefly with a heat gun to liberate all the
CO\textsubscript{2}. The system was placed under positive N\textsubscript{2} pressure and the reaction flask
was allowed to warm to 100°C in an ether-liquid N\textsubscript{2} bath. The solution melted
and stirring began. At this point the N\textsubscript{2} pressure was removed, and the flask
was stoppered and allowed to warm to -75°C over approximately 20 min. Positive
N\textsubscript{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\textsubscript{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\textsubscript{2}SO\textsubscript{4}. An oil separated which
upon swirling and cooling formed crystals. The crystals were filtered to yield
0.104 gm (48.0%) of PFDA with specific activity 4.93 Ci/mmol. This material was
recrystallized from ether-pentane to yield 0.097 gm (29%) of material with spe-
cific activity 5.50 Ci/mmol. The mother liquors from each crystallization were
mixed with 0.20 gm of cold PFDA and crystallized to yield 0.432 gm (0.100 mCi/
mmol) and 0.327 gm (0.195 mCi/mmol), respectively. \textsuperscript{19F NMR (acetone-d\textsubscript{6}) of
unlabeled material:} a=91.2 (tt, J=7.5, 2.8 Hz, 3F), -139.3 (tt, J=9.5, 2.1 Hz,

*These yields were calculated using the formula weight for PFDA as 432 which
includes a molecule of d\textsubscript{2}O as shown by \textsuperscript{19F 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 Perfluorooctane Acid Methyl Ester. To 30 mg of PFOA or PFDA in 1 ml of ether, a solution of diazomethane (CH2N2) in ether was added dropwise until the yellow color persisted. The excess CH2N2 was removed by blowing a stream of H2 over the solution. The ether was removed on a rotary evaporator taking care to remove the flask before significant evaporation of the ether occurred. NMR (acetone-d6): PFOA ester: δ1.5 (t, J=7.7 Hz, 3F), -119.3 (tt, J=8.3, 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: δ1.3 (t, J=8.8 Hz, 3F), -118.7 (broad s, 2F), -121.8 (broad s, 4F), -127.8 (broad s, 2F), -129.9 (broad s, 2F), -126.2 (broad s, 2F).

Purification of Perfluorooctane Acid. To a 2-l, round bottom flask equipped with magnetic stirring bar, condenser and containing 11 of water was added 50 g (98 mmol) of PFOA (Aldrich lot no. 1105M4, 85.45 pure by gas chromatographic analysis of the methyl ester, Figure 2) and 56 g 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 subsided. 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 PFOA was added to 2 l of HzO. To this slurry was added 100 ml (1.8 mol) of concentrated H3PO4 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, 10X 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 PFOA 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 14.3 g of 99% pure acid, mp 87-88°C (Figure 2).
The solid material, by all indications, appeared to be potassium perfluorodecaneate. This salt was treated again in 500 ml of H2O with 50 ml of conc. H2SO4, cooled, filtered and dried to yield an additional 25 gm of perfluorodecanoic acid which was likewise recrystallized from ether-pentane to yield 20.7 gm. Total yield was 37.0 gm, 74%.

**Silver perfluorodecaneate.** To a 21 Erlenmeyer flask containing 110 ml of H2O, was added purified PFBA (15.3 gm, 30 mmol). The slurry was stirred and warmed to 50-60°C while silver oxide (3.82 gm, 16.6 mmol) was added. The mixture 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, 60 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 perfluorodecaneate.

**Perfluoropyranyl Iodide.** Silver perfluorodecaneate (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 6 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 (0.9 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 30.6 gm of a white solid which completely turned brown on standing. The solid was distilled on a Kugelrohr at 23-34°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. 2F NMR (CDCl3): -60.0 (t, J = 15.1 Hz, 2F), -61.7 (t, J = 9.1 Hz, 3F), -113.6 (broad s, 2F), -121.6 (broad s, 2F), -122.6 (broad s, 6F), -123.8 (broad s, 2F) -126.9 (broad s, 2F). The iodide can be crystallized from pentane at -78°C.

**Perfluorodecanoic-13C-l Acid.** Done in a way similar to the synthesis of
perfluorooctanoic-1\textsuperscript{14}C-1 acid using 112 mg of Ba\textsuperscript{4}Hg\textsubscript{2} (5.71 mCi/mmol). The yield of crystals after acidification with H\textsubscript{2}O\textsubscript{2} was 0.142 gm (94%)\textsuperscript{**}, 4.53 mCi/mmol. After crystallization from ether-pentane, the yield was 0.076 gm (79%)\textsuperscript{**}, 5.12 mCi/mmol. The mother liquors from each crystallization were treated with 0.90 gm of caustic FDA and crystallized to yield 0.430 gm (0.170 mCi/mmol) and 0.408 gm (0.279 mCi/mmol), respectively. \textsuperscript{19}F NMR (d\textsubscript{4}-acetone): -81.3 (t, J = 20.3 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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REFERENCES


**These yields were calculated using the formula weight for FDA as 532 which includes a molecule of H\textsubscript{2}O as shown by \textsuperscript{1}H NMR.