# Synthesis of Perfluoroadamantane Compounds by Direct Fluorination

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*F*-1,3-Dimethyladamantane, *F*-1,3,5,7-tetramethyladamantane, and *F*-1-adamantamine have been prepared by the controlled direct fluorination of 1,3-difluoro-5,7-dimethyladamantane, 1,3-dimethyl-5,7-bis(trifluoromethyl)-adamantane, and 1-adamantamine.

We have explored over the past few years the synthesis of structurally unusual perfluorinated organic compounds.[1] In such systems unusual steric and electronic effects are often observed as the last few protons are replaced with fluorine. In two previous studies electronic factors very significantly decreased the tendency of fluorine to react with the last few protons. The direct fluorination of adamantane yields 1-hydropentandecafluoroadamantane[1,2] rather than perfluoroadamantane with the last bridgehead proton becoming extremely unreactive toward fluorine. The synthesis of perfluoro-*m*-carborane[3] by direct fluorination proceeds very slowly due to the reduced reactivity of the C–H protons toward fluorine. Steric factors appeared to hinder the removal of the last few protons in the synthesis of perfluoro-2,2,4,4-tetramethylpentane.[4]

The direct fluorination of 1-adamantamine poses two interesting problems. The first is the preservation of the C–N bond during fluorination. The second is whether the three bridgehead protons can be removed and replaced with fluorine as the $NH_2$ group is converted to an $NF_2$ group. The presence of the $NF_2$ group might change the electronic density profile in the cage and allow complete fluorination. The direct fluorination of 1,3-difluoro-5,7-dimethyladamantane presents only the possible steric problem of fluorinating the methylene group between the two methyl groups. No bridgehead protons need to be removed since the other two bridgehead positions are already fluorine substituted. During the fluorination of 1,3-dimethyl-5,7-bis(trifluoromethyl)adamantane, all the methylene protons might possibly be sterically protected.

## Experimental Section

Mass spectra were taken on a Bell and Howell CEC 21-491 mass spectrometer operating at 70 eV. NMR data was collected on a Varian A 56/60 spectrometer operating at 56.4 MHz for $^{19}F$. Sample purification was obtained on a Bendix Model 2300 gas chromatograph using $\frac{3}{8}$ in. × 24 ft copper columns packed with either 10% fluorosilicon QF1-0065 or 10% SE-30 on Chromosorb P. Infrared data was collected on a Beckman IR-20A infrared spectrophotometer. Elemental analysis was done by Schwarzkopf Microanalytical Laboratory.

**Fluorination of 1-Adamantamine.** Two boats, each containing 1.0 g of 1-adamantamine (from Aldrich Chemical Co.), were placed in a nickel reactor for the reaction to occur at room temperature. A glass trap was placed downstream from the NaF scrubber. Dry ice was used to trap any volatile material. The fluorination conditions are given in Chart I.

The volatile material in the dry ice trap was transferred into a glass storage tube. The sample in the boat was removed and stored in a glass vessel. The material had a slightly tacky consistency.

The volatile material in the glass trap was transferred to a glass vessel to which $CCl_4$ was added. The fluorinated material was only very slightly soluble. Upon warming the $CCl_4$ solution, more of the material dissolved. The material was injected warm into the gas chromatograph. Using the SE-30 column for purification, 380 mg of *F*-1-adamantamine was obtained. This corresponds to a 6.3% yield.

*F*-1-adamantamine (pure as determined by GC) melts in a sealed capillary at 182.5–184 °C. The infrared spectrum consists of stretches at 1350 (w), 1321 (sh), 1310 (s), 1300 (s), 1260 (m), 1241 (w), 1205 (w), 1165 (vw), 1109 (vw), 1079 (vw), 1041 (m), 1010 (m), 990 (s), 945 (m), 890 (w), 841 (m), 805 (s), 790 (w), 780 (w), 775 (w), 730 (vw), and 659 (m) $cm^{-1}$. The $^{19}F$ NMR in $CCl_4$ shows chemical shifts of −113.9, +36.3, +44.9, and +144.4 ppm upfield relative to external TFA, with a relative integration of 2.2:6:6:3.2.

**Chart I**

| $F_2$ flow, $cm^3$/min | He flow, $cm^3$/min | time, h |
|---|---|---|
| 1.0 | 60 | 24 |
| 1.0 | 30 | 24 |
| 1.0 | 15 | 24 |
| 3.0 | 15 | 24 |
| 5.0 | 15 | 24 |
| 5.0 | 0 | 24 |
| 0.0 | 30 | 22 |
| 0.0 | 60 | 26 |
| Removed sample in boat, reground sample, and placed back in boat for fluorination | | |
| 2.0 | 30 | 24 |
| 2.0 | 15 | 24 |
| 2.0 | 0 | 96 |
| 2.0 | 30 | 24 |
| 0.0 | 30 | 24 |
| Removed sample in boat, reground sample, and placed back in boat for fluorination | | |
| 2.0 | 30 | 24 |
| 2.0 | 15 | 24 |
| 2.0 | 0 | 168 |
| 0.0 | 60 | 168 |

The mass spectrum displayed a parent peak at *m/e* 457 and a P–F at *m/e* 438. The complete spectrum, with relative intensities, consists of *m/e* at 69 (100.0), 100 (1.7), 131 (33.8), 143 (3.0), 155 (10.9), 181 (23.4), 186 (15.1), 236 (22.7), 245 (9.6), 267 (6.9), 286 (3.9), 293 (0.9), 305 (2.1), 317 (4.9), 336 (0.9), 355 (2.6), 405 (9.4), 421 (0.5), 438 (4.7), 457 (6.5).

Elemental analyses confirmed the identity of $C_{10}F_{17}N$. Calcd: C, 26.26; F, 26.19; N, 3.06. Found: C, 26.19; F, 69.86; N, 2.97. Analysis for hydrogen showed 0%.

**Fluorination of 1,3-Difluoro-5,7-dimethyl(adamantane).** The reactor system used to perform the fluorinations was modified to an expanded version of the cryogenic zone reactor described previously.[2,3] The inlet consisted of a heated oil evaporator. After the cryogenic zone reactor, the material passed through a sodium fluoride tube into a hot-surface reactor. The hot-surface reaction chamber consisted of a nickel tube 18 in. long and 1.5 in. wide, tightly packed with fluorinated copper turnings. It was wrapped with asbestos insulated electrical heating tape and thermally insulated with 0.25 in. of glass wool. The tube was then wrapped externally with asbestos cloth. Heating was controlled with a variac. A thermometer was placed under the wrapping so that the bulb was in contact with the metal casing but not in direct contact with the heating tape and protruded so that temperatures above 30 °C could be read. Another sodium fluoride scrubber followed this reactor. The final products were collected in a glass trap cooled to −78 °C with a dry ice/isopropyl alcohol bath.

For subambient temperatures, the zones of the cryogenic reactor were cooled with dry ice in isopropyl alcohol. This was siphoned out and replaced with mineral oil heated with an immersion heater during the supraambient reaction stage.

A 0.405-g (0.230 mmol) sample of 1,3-difluoro-5,7-dimethyladamantane[5] was injected into the oil evaporator heated to 65 °C and flushed into the first zone of the cryogenic reactor with a helium flow of 75 $cm^3$/min with zones 2 and 3 cooled to −78 °C. After 18 h of helium passage, zones 1 and 2 were cooled to −78 °C and the fluorine flow was initiated at a rate of 0.5 $cm^3$/min, mixed, and diluted in a 60 $cm^3$/min flow of helium. The conditions for the reaction are summa-

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**Table I**

| He flow, $cm^3$/min | $F_2$ flow, $cm^3$/min | cryogenic zones, °C 1 | 2 | 3 | 4 | hot-surface chamber, °C | duration, days |
|---|---|---|---|---|---|---|---|
| 60 | 0.5 | −78 | −78 | RT | RT | 45 | 1.5 |
| 30 | 0.5 | RT | −78 | −78 | RT | 45 | 1 |
| 30 | 1.0 | RT | −78 | −78 | RT | 45 | 2 |
| 15 | 1.0 | RT | −78 | −78 | −78 | 60 | 1 |
| 15 | 1.5 | RT | RT | −78 | −78 | 60 | 2 |
| 3 | 1.5 | RT | RT | RT | −78 | 60 | 1 |
| 3 | 2.0 | RT | RT | RT | −78 | 60 | 1 |
| 3 | 2.0 | RT | RT | RT | RT | 75 | 3 |
| 40 | 2.0 | +60 | +60 | RT | RT | 75 | 1 |
| 40 | 2.0 | +60 | +60 | +60 | RT | 75 | 1 |
| 10 | 2.5 | +60 | +60 | +60 | +60 | 75 | 2 |
| 80 | 0 | +60 | +60 | +60 | +60 | 75 | 2 |

rized in Table I. Attempts to decrease the total time required for the reaction resulted in charring of the compound or incomplete fluorination, dramatically decreasing the yield.

After the reaction was completed, the line was purged for 2 days with 80 $cm^3$/min of helium flowing through the heated reaction chambers, with the collection trap cooled to −196 °C with liquid nitrogen. The trap was then removed from the line, and the raw products were fractionated through −23, −45, −95, and 196 °C traps on a vacuum line. The contents of the −23 °C trap were a colorless oily liquid at room temperature, which were injected directly into the gas chromatograph, where the components were separated and isolated using the fluorosilicone column; 0.309 g (0.059 mmol) of perfluoro-1,3-dimethyladamantane were obtained in this manner, resulting in a yield of 26%.

Perfluoro-1,3-dimethyladamantane melts in a sealed capillary at 67–68.5 °C. The vapor phase infrared spectrum (10 cm path) consists of stretches at 1329 (sh), 1310 (vs), 1251 (w), 1235 (w), 1205 (w), 1180 (s), 1165 (w), 1015 (s), 965 (s), 879 (s), 820 (m), 740 (m), 686 (m), 640 (w), and 621 (m) $cm^{-1}$. $^{19}F$ NMR in $CH_2Cl_2$ displays chemical shifts at −20.7, +23.0, +35.4, +44.6, and +142.1 ppm (upfield relative to external TFA) with a relative integration of 6:2:8:2:2 (see Figure 1).

The mass spectrum revealed a small parent peak at *m/e* 524 with a larger P–F at 505. The couple spectrum, with relative intensities, consists of *m/e* at 31 (10.0), 69 (100.0), 100 (4.7), 131 (13.6), 150 (3.4), 169 (10.1), 181 (14.3), 219 (0.6), 231 (3.2), 243 (1.4), 255 (3.0), 269 (1.6), 281 (2.1), 331 (2.0), 343 (1.0), 381 (1.0), 393 (1.0), 455 (0.4), 481 (0.2), 505 (1.6), and 524 (0.07).

Elemental analysis confirmed the identity of $C_{12}F_{20}$. Calcd: C, 27.48; F, 72.52. Found: C, 27.37; F, 72.80 (H, 0.00).

**Fluorination of 1,3-Dimethyl-5,7-bis(trifluoromethyl)adamantane.** Perfluorotetramethyladamantane was obtained by direct fluorination in a manner similar to perfluorodimethyladamantane. A 0.289-g sample of bis(trifluoromethyl)dimethyladamantane[6] was placed in a nickel boat inside a bucket reactor, cooled with ice to 0 °C. The ice water was removed and replaced with mineral oil for temperatures above 25 °C. The outlet of the bucket reactor was through a NaF scrubber and into a hot surface reactor, heated with resistance tape and variac. The final trap was cooled to −78 °C and the reaction run under the conditions in Chart II.

The material in the −78 °C trap was fractionated on a vacuum line.

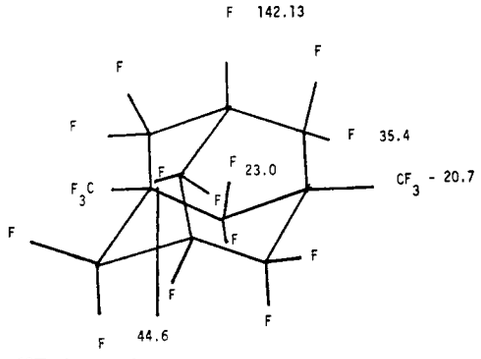


**Figure 1.** $^{19}F$ chemical shift assignment for *F*-1,3-dimethyladamantane; numbers are ppm with respect to external TFA.

**Chart II**

| He flow, $cm^3$/min | $F_2$ flow, $cm^3$/min | bucket temp, °C | HSR temp, °C | time, days |
|---|---|---|---|---|
| 60 | 0.5 | 0 | 50 | 1 |
| 60 | 1.0 | 0 | 60 | 0.5 |
| 30 | 1.5 | 0 | 60 | 2 |
| 15 | 2.0 | 0 | 65 | 2 |
| 8 | 2.5 | RT | 65 | 1 |
| 8 | 2.5 | 60 | 75 | 1 |
| 1.5 | 3.0 | 70 | 75 | 1 |
| 0 | 3.0 | 80 | 85 | 3 |
| 60 | 0 | 90 | 90 | 2 |

Only material stopping in the −23 °C trap proved to be of interest. The material was a white powder of very low volatility. The powder was dissolved in hot $CCl_4$. The hot $CCl_4$ solution was injected in 400–500-μL portions into a 10% SE-30 column described previously. The program used was: 90 °C isothermal for 20 min, then increased at 6.5 °C/min to 135 °C for 15 min. Perfluorotetramethyladamantane had a reaction time of approximately 26.5 min. A 0.025-g sample was recovered giving an overall yield of 4.2%. Perfluorotetramethyladamantane crystallizes very rapidly from cold $CCl_4$ but dissolves at 70 °C. Thus, the $^{19}NMR$ spectrum was run in a sealed tube at 70 °C. It consisted of two equal, sharp peaks at −24.4 and +19.7 ppm upfield from TFA.

The melting point of perfluorotetramethyladamantane is extremely sensitive to impurities.[1] Impure material obtained by the above chromatographic separation (mp 118–119 °C) was repeatedly run through the same column at isothermal 85 °C, increasing the retention time to almost 40 min. After one run the compound emerged with a melting point of 135.5–136 °C, and after subsequent runs a melting point of 137–138 °C was obtained, which did not increase or sharpen after subsequent purification. (All melting points were taken in a sealed, evacuated capillary.) This property may prove useful in preparing a liquid, high molecular weight fluorocarbon blood substitute.

Infrared and mass spectra were relatively concise as compared to the other perfluoroalkyladamantanes. The infrared spectrum, taken in the solid phase as a KBr pellet, consisted of stretches at 1300 (vs), 1265 (sh), 1245 (m), 1230 (m), 1220 (m), 1179 (w), 1170 (m), 1150 (m), 1000 (m), 815 (m), 685 (m), 619 (m), and 550 (w) $cm^{-1}$. The mass spectrum reveals a P–F peak but no parent peak was observed. The complete spectrum, with relative intensities, consists of *m/e* at 69 (100.0), 131 (2.2), 181 (19.0), 268 (1.0), 355 (0.8), 405 (0.6), 517 (0.5), 555 (0.5), and 605 (1.5).

Anal. Calcd for $C_{14}F_{24}$: C, 26.92; F, 73.08. Found: C, 26.87; F, 73.20 (H, 0.00).

## Discussion

The fluorination of adamantane previously produced only monohydropentadecafluoroadamantane as the highest fluorinated adamantane compound.[2] It was difficult to explain why no perfluoroadamantane was produced despite very vigorous reaction conditions. The fluorination of 1-adamantamine was attempted to see if this bridgehead phenomena was a general one, i.e., that on all adamantane compounds one bridgehead proton would remain unfluorinated.

Although the yield of *F*-1-adamantamine is relatively low, the isolation of the compound demonstrates two things. The first is that a C–N bond can be preserved as a $NH_2$ group is converted to a $NF_2$ group. With the $NF_2$ moiety intact and the other three bridgehead positions containing fluorine, we have prepared a completely fluorine-containing adamantane-type compound. Therefore, it appears that alteration of certain electronic factors in the adamantane structure can lead to highly fluorinated adamantane compounds.

Two other major products are produced in the fluorination of 1-adamantamine. 1-Monohydropentadecafluoroadamantane is the major product, comprising about 25% of the total products. The formation of 1-monohydropentadecafluoroadamantane probably occurs with cleavage of the C–N bond before all of the bridgehead protons have been replaced with fluorine.

Cleaving of the C–N bond by fluorine results in a partially

fluorinated adamantane specie, with fluorine replacing the amine group bridgehead, but at least one other bridgehead must have a proton on it for C–N cleavage to occur. The abundance of monohydropentadecafluoroadamantane strongly supports this. It is interesting to note that the C–N bond will not be cleaved by fluorine if all other bridgehead positions have already been fluorinated; otherwise, perfluoroadamantane should have been isolated with the products.

The other major product is a ring-cleavage product of adamantane. $^{19}F$ NMR indicates that the compound is a perfluorodimethyl-substituted cyclooctane compound.

As hydrogens are replaced by fluorine, the remaining protons become increasingly acidic and the resultant tendency toward carbanion formation may lead to carbon–carbon bond cleavage, especially at the bridgehead positions. To minimize the disintegration at bridgehead sites the fluorination of 1,3-difluoro-5,7-dimethyladamantane was undertaken. All bridgeheads were substituted (two fluorine substitutions, two methyl substitutions). Nevertheless, significant thermal decomposition in the hot surface reactor was observed. In the conventional zone reactor, a low degree of perfluorination was found; monohydro and polyhydro compounds were the major products, with only a small degree of decomposition into small chain fluorocarbons. While the heated reactor increased the yield of the perfluoro product from less than 2% to nearly 30%, the remaining 70% consisted principally of fragmentation products. More gentle heating decreased the fragmentation, but did not activate the reaction with the sterically protected protons of the number 2 carbon atom.

The perfluorination of 1,3-difluoro-5,7-dimethyladamantane indicates that the methylene protons between the two $CF_3$ groups were not as sterically hindered as one might have suspected.

The preparation of *F*-1,3,5,7-tetramethyladamantane indicates that the methylene protons can be fluorinated. In a comparison with the yield of *F*-1,3-dimethyladamantane one might speculate either that the methylene protons are more sterically hindered in 1,3-dimethyl-5,7-bis(trifluoromethyl)-adamantane than in 1,3-difluoro-5,7-dimethyladamantane or that some electronic factor inhibits attack on the methylene protons when the neighboring methyl groups are partially or completely substituted. To help elucidate the contributing factors, we are presently examining other substituted adamantane compounds. New highly fluorinated systems of unusual structure should result.

The fluorine NMR spectra were used to identify the groups on the substituted adamantane compounds. Figure 1 shows the assigned chemical shifts to the various groups on *F*-1,3-dimethyladamantane. The assignment of +23.0 for the $CF_2$ group between the two $CF_3$ groups is in agreement with the chemical shift for the analogous group on *F*-1,3,5,7-tetramethyladamantane and *F*-2,2,4,4-tetramethylpentane.[7]

All three perfluoro compounds reported here are readily sublimable crystalline solids. The melting point of *F*-1-adamantamine is quite high, indicating good thermal stability of the material.

With increasing interest in high molecular weight fluorocarbons of high symmetry for potential artificial blood substitutes convenient synthetic methods are of value. Direct fluorination has proven to be an extremely useful technique for the synthesis of a highly fluorinated system of unusual structures.

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**Registry No.**—*F*-1,3-Dimethyladamantane, 36481-20-6; *F*-1,3,5,7-tetramethyladamantane, 67700-17-8; *F*-1-adamantamine, 67700-18-9; 1,3-difluoro-5,7-dimethyladamantane, 60389-56-2; 1,3-dimethyl-5,7-bis(trifluoromethyl)adamantane, 40556-52-3; 1-adamantamine, 768-94-5.

## References and Notes

(1) This project grew out of our collaborative effort on the synthesis of potential fluorocarbon substitutes with R. E. Moore of Sun Tech Inc. Work at Sun Tech Inc. closely related to this study appears in the preceding paper: Robert E. Moore and Gary L. Driscoll, *J. Org. Chem.*, preceding paper in this issue.
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