20-M. The *N*-iodosuccinimide was determined to have 96.5–99.5% active iodine and was used as purchased. Irradiation of reaction mixtures was effected with a G.E. Projector Spot 150-W, 130-V tungsten lamp.

Oxidation of 1-Pentanol with NIS and Irradiation. A 5-mL solution of 0.1065 g (1.210 mmol) of 1-pentanol in chlorobenzene was added to 0.2365 g (1.056 mmol) of NIS contained in a 10-mL flask. The condenser attached to the flask was ice-water cooled. The mixture was stirred and irradiated. Reaction times and percentage yields of 2-methyltetrahydrofuran were as follows: 20 min (15%), 40 min (58%), 60 min (80%), 80 min (91%), 100 min (93%), 120 min (94%). Trace amounts of pentanal (1%) and 1-iodobutane (<1%) were found. Material balance after 2 h was 99%. Succinimide was recovered in 83% yield and elemental iodine determination gave 0.443 mmol (84%).

Oxidation of 1-Pentanol with NIS in the Dark at Ambient Temperatures. A 5-mL solution of 0.1065 g (1.210 mmol) of 1-pentanol in chlorobenzene was added to 0.2822 g (1.254 mmol) of NIS contained in a 10-mL flask. The flask was covered with aluminum foil in a dark fume hood. The mixture was stirred. Reaction times and percentage yields of 2-methyltetrahydrofuran were as follows: 1 h (1%), 2.5 h (<1%), 10 h (<1%). Less than 1% yields were also found for pentanal and 1-iodobutane. A 99.5% recovery was made of the starting alcohol. Titration for positive iodine gave 1.264 mmol (101%).

Oxidation of *p*-Fluorobenzyl Alcohol with NIS and Irradiation. A 5-mL solution of 255 mg (2.03 mmol) of *p*-fluorobenzyl alcohol in benzene was added to 232 mg (1.03 mmol) of NIS is a 10-mL reaction flask. The mixture was stirred and irradiated. Reaction times and percentage yields of *p*-fluorobenzaldehyde were as follows: 12 min (69%), 35 min (70%), 1 h (76%), 2.5 h (87%). Succinimide was found in 84% and the iodine determination gave 83%. No bond-cleavage iodobenzene products were found.

Iodine Determination. The iodine produced in the oxidation of primary alcohols with NIS was determined by adding the reaction mixtures to 25 mL of a 1:1 mixture of acetic acid and water. Several drops of concentrated hydrochloric acid were added, and the iodine was titrated with a standardized solution of thiosulfate.

Succinimide Determination. Succinimide was recovered in two ways: by filtration of the cooled reaction mixtures to obtain the solvent insoluble succinimide or by extraction of the reaction solvents with water and evaporation of the water.

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Registry No. 1, 71-41-0; 2, 516-12-1; 3, 96-47-9; 5, 100-51-6; 6, 100-52-7; 13, 89-95-2; 1-butanol, 71-36-3; 3-methyl-1-butanol, 123-51-3; 2-methyl-1-propanol, 78-83-1; *p*-methylbenzyl alcohol, 589-18-4; *p*-fluorobenzyl alcohol, 459-56-3; tetrahydrofuran, 109-99-9; 3-methyltetrahydrofuran, 13423-15-9; 2-iodopropane, 75-30-9; *p*-methylbenzaldehyde, 104-87-0; *o*-methylbenzaldehyde, 529-20-4; *p*-fluorobenzaldehyde, 459-57-4.

Aerosol Direct Fluorination Synthesis of Perfluoroadamantane, the Penultimate Step

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The aerosol direct fluorination method provides a continuous process for the production of perfluorocarbons from hydrocarbons with efficient fluorine utilization and minimal fragmentation.[1] The application of this process to alkanes, ethers, cycloalkanes, ketals, and ketones has been demonstrated.[1,2] We report here the extension of the process to the synthesis of perfluoroadamantane via direct fluorination of adamantane, a feat not realized by other direct fluorination methods nor by indirect fluorination methods to any significant degree.

Due to the current interest in fluorocarbons as synthetic blood substitutes,[3] the fluorination of adamantane and substituted adamantane systems has been attempted. Moore and Driscoll, employing a CoF_3 method involving the recycling of partially fluorinated materials through a reactor, have successfully produced perfluoro-1-methyladamantane, perfluoro-1,3-dimethyladamantane, and perfluoro-1,3,5,7-tetramethyladamantane from 1-(trifluoromethyl)adamantane, 1,3-bis(trifluoromethyl)-adamantane, and 1,3-bis(trifluoromethyl)-5,7-dimethyladamantane, respectively.[4] Lagow et al. reported the successful direct fluorination of 1,3-difluoro-5,7-dimethyladamantane, 1,3-dimethyl-5,7-bis(trifluoromethyl)adamantane, and 1-adamantylamine to the perfluorinated analogues.[5]

The direct fluorination of adamantane to the perfluoro product has remained elusive however; whereas substituted adamantane systems have been successfully perfluorinated, direct fluorination of adamantane itself has previously led only to the production of 1-hydropentadecafluoroadamantane in low yields.[7] The penultimate substitution would not take place even in pure fluorine under "vigorous" conditions.[5] At the present time the only other method for the production of perfluoroadamantane, other than via the aerosol direct fluorination method presented here, appears in a recent patent application, wherein adamantane in methylcyclohexane was contacted with a CoF_3 bed at 275 °C to produce 1-hydropentadecafluoroadamantane and perfluoroadamantane (no yields given).[8]

Results and Discussion

The major product collected from the aerosol direct fluorination of adamantane was perfluoroadamantane; of the products collected, *F*-adamantane comprised 74.4% of the total by weight. Based on input of adamantane, the yield of *F*-adamantane was 28%. The aerosol system is dependent on the generation of a particulate aerosol which is ideally crystalline, of uniform size, and with little tendency to aggregate. If the conditions for producing the aerosol are ideal, percent yields based on throughputs and product percent distributions will differ by only a few percent; as molecules deviate from this ideality, the percent yields based on throughput fall due to physical losses within the aerosol generator and initial reaction stage (see ref 1). Due to the relatively low volatility of adamantane these losses are significant, resulting in significant amounts of unreacted adamantane settling throughout the reactor. The majority of material traversing the reactor, however, is seen to be upward of 70% perfluorinated, and it is likely that modifications to allow higher carrier flows through the reactor would result in a significant increase in the amounts of material reaching the collection point. The

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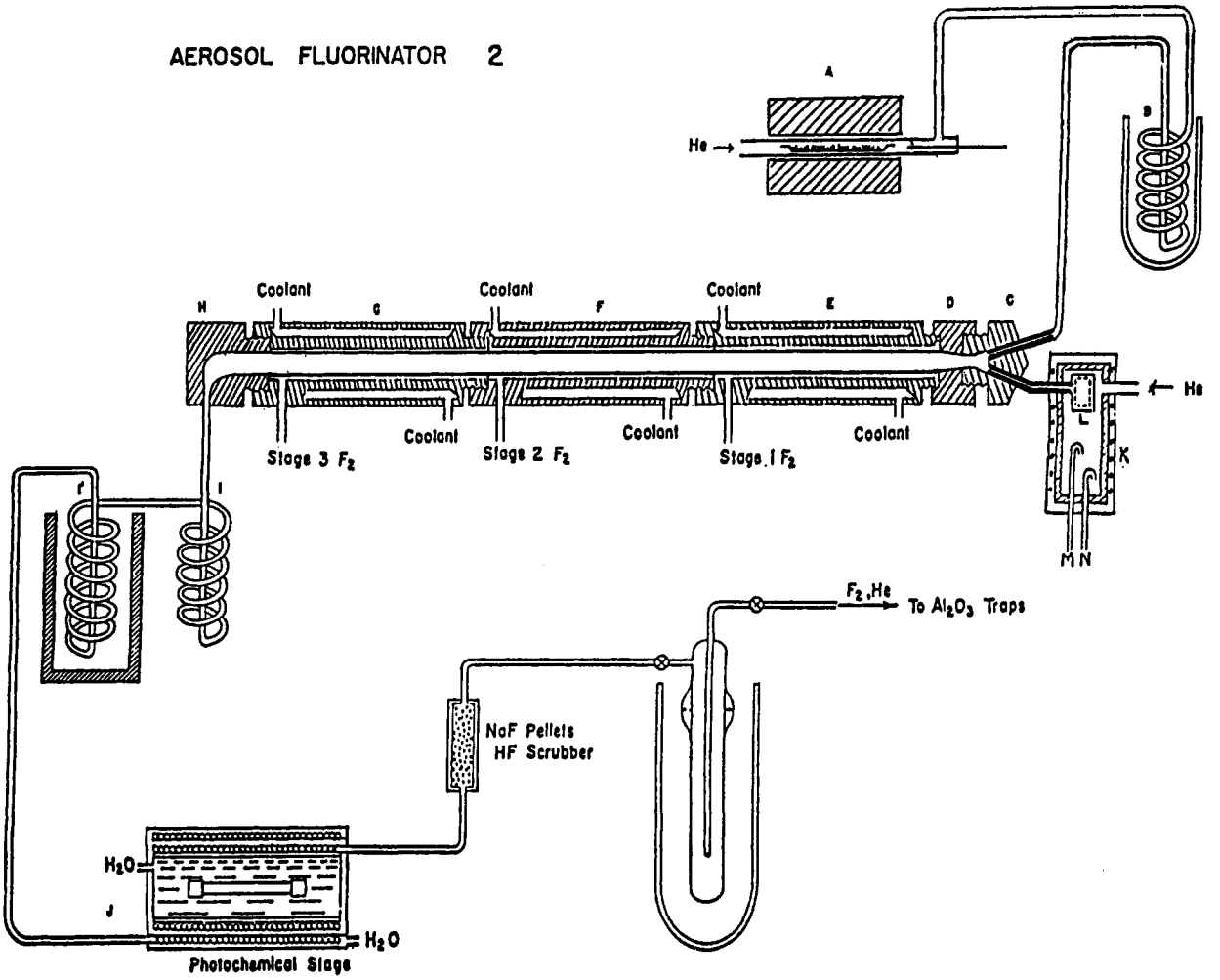

Figure 1.

difficulty of vacuum line transfers of the perfluorinated material also leads to significant losses in material isolated.

Previously, fluorinations of adamantane and its substituted derivatives have resulted in significant ring opening. Lagow et al. have attributed this tendency to the fact that "As hydrogens are replaced by fluorine, the remaining positions become increasingly acidic, and the resultant tendency toward carbanion formation may lead to carbon–carbon bond cleavage, especially at the bridge head positions."[5] This building up in positive charge, reduction in electron density, or increased acidity is likely to be the cause of the difficulty in obtaining perfluorination as well. The reluctance of fluorine to attack cations, a phenomenon reported by Bartlett, supports this conclusion.[6] Morever, Moore and Driscoll report that for the CoF_3 fluorination of 1,3-dimethyladamantane, the major products are ring-opened species.[4] In an attempt to reduce this ring opening, two bridgehead fluorines were incorporated into the molecule prior to exhaustive fluorination over CoF_3; however, fluorination of the resulting 1,3-difluoro-5,7-dimethyladamantane over CoF_3 again yielded primarily ring-opened species. Lagow was able to successfully directly fluorinate 1,3-difluoro-5,7-dimethyladamantane to the perfluoro compound, but again the majority of products (70%) consisted of ring-opened species.[5] The problem of ring opening does appear to be reduced somewhat by substitution of hydrogen and/or alkyl groups on the adamantane structure by fluorine and/or perfluoroalkyl groups prior to fluorination. Thus Lagow was able to produce *F*-1,3-dimethyladamantane (26%) and *F*-1,3,5,7-tetramethyladamantane (4.2%) from 1,3-difluoro-5,7-dimethyladamantane and 1,3-dimethyl-5,7-bis(trifluoromethyl)adamantane, respectively, while Moore and Driscoll prepared *F*-1-methyladamantane (65%), *F*-1,3-dimethyladamantane (60%), and *F*-1,3,5,7-tetramethyladamantane (10%) from 1-(trifluoromethyl)adamantane, 1,3-bis(trifluoromethyl)adamantane, and 1,3-bis(trifluoromethyl)-5,7-dimethyladamantane, respectively.[4,5]

In contrast to the above methods, aerosol fluorination of adamantane resulted in no significant amount of ring opening; the major product was the perfluorinated species, the remainder of materials being partially fluorinated adamantanes, as evidenced by mass spectral analysis of a mixture of the nonvolatile products. These results indicate the potential value of the direct aerosol method for the synthesis of perfluorinated materials that are useful as potential blood substitutes. Also the lack of problems with ring opening suggests the possibility of the production of perfluorinated alkyladamantanes directly from the hydrocarbon analogues.

Experimental Section

The basic aerosol fluorinator design and a basic description of the process are presented elsewhere.[1] A modified aerosol generator (Figure 1) was adapted to a sublimator loaded with solid adamantane and heated to 150 °C. The workup of products, following removal of hydrogen fluoride, consisted of vacuum-line fractionation, infrared assay of fractions, gas chromatographic separation of components by using a 7 m × $^3/_8$ in. 13% Fluorosilicone QF-1 (Analabs) stationary phase on 60–80 mesh, acid-washed Chromosorb P conditioned at 225 °C (12 h). Following gas chromatographic separation (Bendix Model 2300, subambient multicontroller), products were collected, transferred to the

vacuum line, assayed, and characterized by vapor-phase infrared spectrophotometry (PE 1330), electron-impact (70 eV) mass spectrometry (Hewlett-Packard GC/MS, 5710A GC, 5980A MS, 5934A computer), and ^1H and ^{19}F nuclear magnetic resonance (JEOL FX90Q, omniprobe) in $CDCl_3$ with 1% $CFCl_3$ as an internal standard. Elemental Analyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, NY.

Aerosol Fluorination of Adamantane. Adamantane (Aldrich, 99+%) was used as received. Adamantane (1.39 g, 11.2 mmol) was loaded into the sublimator. The main helium carrier flow (Figure 1) was set at 600 cm^3/m. This flow is directed through the nucleating particle (NaF) furnace (A) and the liquid nitrogen heat exchanger (B) and enters one side of the aerosol generator (C) where it is mixed in the aerosol generator (C) with the hydrocarbon carrier containing the adamantane vapor. The hydrocarbon carrier consists of one upper, primary (150 cm^3/m) and two lower, secondary (20 cm^3/m) helium flows entering into the sublimator (K) at the top (L) and bottom (M, N) of the sublimator body (K), respectively. The reactor modules (E–G) were cooled to −30 °C, −20 °C and ambient temperature (−10 °C) while the copper coil (I) preceding the photochemical stage (J) was heated to 100 °C. Fluorine flows into the reactor modules were 20 cm^3/m, 50 cm^3/m and zero, respectively. The photochemical lamp was ignited and the sublimator was then heated to 150 °C. After 7 h the reaction was stopped. When the reactor was opened, 1.23 g of unreacted adamantane was recovered (0.300 g, 2.2 mmol, reacted); 0.361 g of crude product was collected, dissolved in perfluoropentane, and separated on the Fluorosilicone QF-1 column (70 °C, 15 min; 30 °C/min to 180 °C), producing 0.259 g (74%) of *F*-adamantane, a 28% yield based on theoretical input. It should be noted that significant quantities of unfluorinated adamantane were found inside the reactor. Anal. Calcd for $C_{10}F_{16}$: C, 28.32; F, 71.68; H, 0.00. Found: C, 28.60; F, 71.88; H, 0.0. The fluorine-19 NMR consists of a pentet of intensity 12 at −121.20 ppm and a near symmetrical multiplet of ~13 prominent diminishing maxima of intensity 4 at −223.53 ppm relative to internal $CFCl_3$; a coupling constant of 6 Hz is a best fit.

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Registry No. Adamantane, 281-23-2; *F*-adamantane, 69064-33-1.

Supplementary Material Available: A reproduction of the ^{19}F NMR spectra and a complete characterization (EI MS, IR) (2 pages). Ordering information is given on any current masthead page.

A Convenient Synthesis of Disodium Acetyl Phosphate for Use in in Situ ATP Cofactor Regeneration[1]

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Many enzyme-catalyzed reactions useful in organic synthesis consume ATP.[3] We routinely regenerate ATP in situ by procedures in which acetyl phosphate[4,5] and phosphoenol pyruvate[6,7] are the ultimate phosphorylating agents. A number of syntheses of acetyl phosphate have been reported,[8] of which the best, a synthesis of crystalline diammonium acetyl phosphate,[5] is still less than ideally convenient. This synthesis involves several steps which require careful experimental control and which are accordingly difficult to carry out on large scale. Further, the ammonium ion (used in this preparation to confer crystallinity to the solid product) has two disadvantages. First, it reacts with acetyl phosphate in solution.[9] Second, it forms an insoluble precipitate (magnesium ammonium phosphate) under the reaction conditions. This precipitation both removes from the solution the magnesium ion which is required for activity[10] of the enzymes and occludes particles of immobilized enzyme.

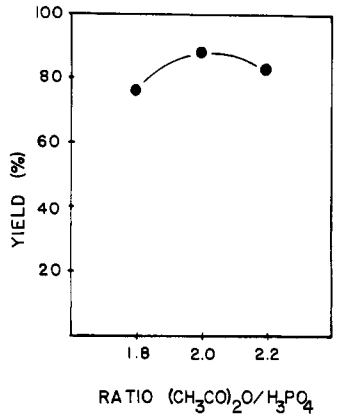

Figure 1. Yield of acetyl phosphate as a function of the molar ratio of acetic anhydride to phosphoric acid (1:1 phosphoric acid/ethyl acetate, room temperature, 25–30-min reaction time).

This manuscript describes a simple procedure for the preparation of aqueous solutions of acetyl phosphate as its sodium or potassium salt; no solid derivative of acetyl phosphate is isolated. This synthesis circumvents many of the disadvantages of previous preparations, and provides a convenient source of acetyl phosphate for use in nucleoside triphosphate cofactor regeneration.

Results

This synthesis of acetyl phosphate involves four steps: first, acylation of phosphoric acid with acetic anhydride in ethyl acetate; second, extraction of acetyl phosphate into water by treatment of the reaction mixture with cold aqueous bicarbonate solution; third, extraction of acetic acid from the resulting aqueous mixture with ethyl acetate; fourth, neutralization of the remaining aqueous solution of acetyl phosphate to pH 7 for storage and use. If one uses sodium hydroxide and sodium bicarbonate as bases, the acetyl phosphate is generated as its sodium salt.

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