Synthesis of Unusual Perfluorocarbon Ethers and Amines Containing Bulky Fluorocarbon Groups: New Biomedical Materials

Hsu-Nan Huang, Daniel F. Persico, and Richard J. Lagow*

Department of Chemistry, The University of Texas at Austin, Austin, Texas 78712

Leland C. Clark, Jr.*

Children's Hospital Medical Center, Cincinnati, Ohio 45229

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The reactions of elemental fluorine with structurally crowded hydrocarbon ethers and amines have been studied. The perfluorinated products are currently of interest in biomedical or electronic industrial applications. The syntheses by direct fluorination of perfluoro(*tert*-butyl methyl ether), perfluoro(*tert*-butyl isobutyl ether), perfluoro(1,2-di-*tert*-butoxyethane), perfluoro(cyclohexyl neopentyl ether), perfluoro(2,2,5,5-tetramethyltetrahydrofuran), perfluoro(2,5-dimethyltetrahydrofuran), bis(perfluoroisopropyl) ether, perfluoro(2-ethyltetrahydrofuran), and perfluoro(1,2,2,6,6-pentamethylpiperidine) are reported. The skeletally rearranged byproducts perfluoro(isobutyl methyl ether), perfluoro(2,2,5-trimethyltetrahydrofuran), perfluoro(2,2,5-trimethyltetrahydropyran), 3-hydropentadecafluoro-2,2,5,5-tetramethyltetrahydrofuran, perfluoro(isopropyl propyl ether), and perfluoro(ethyl isopropyl ether) were also characterized. The ^{19}F and $^{13}C\{^{19}F\}$ (^{19}F decoupled) NMR assignments of these perfluorinated chemicals are discussed.

Introduction

In the last two decades, there has been intense interest in using perfluorochemicals (PFCS) as "artificial blood".[1] Perfluorinated ethers and amines generally form more stable PFCS-based emulsions than do perfluorinated alkanes.[2] However, previous animal studies have indicated that due to some kind of interaction with liver tissues, possibly baselike interactions, perfluorinated amines or ethers exhibit extremely long or infinite retention in the livers of most mammals.[3] Recently, a few branched perfluorinated ethers, such as bis(perfluoroisobutyl) ether, bis(perfluoroisopentyl) ether, and bis(perfluoroneopentyl) ether, have been synthesized from their hydrocarbon analogues by our unique direct fluorination process.[4] Somewhat surprisingly, these new perfluorochemicals had relatively short retention times in mammalian tissues.[4] It is our hypothesis that the branched substituted structures not only reduce the already low basicity of the perfluorinated ether but also prevent sterically their coordination to active sites. We have also found that bulky groups, such as trifluoromethyl, on carbons adjacent to ether linkages, create holes in the liquid phase which are conducive to higher oxygen solubility. On the basis of these principles, highly branched perfluorinated tertiary amines might be expected to behave similarly. Thus, the perfluorinated *tert*-butyl-like ethers and amines, a largely unknown class of compounds, were targeted for synthesis. The acid or kinetic instability of the hydrocarbon precursors or reaction intermediates make it difficult or impossible to prepare sterically crowded perfluorochemicals, such as perfluoro(*tert*-butyl alkyl ethers), perfluoro-(2,2,5,5-tetralkyltetrahydrofuran), or perfluoro(1,2,2,6,6-pentaalkylpiperidine), by the cobalt trifluoride method or the industrially important hydrogen fluoride electrochemical cell techniques.[5] The majority of perfluorinated ethers and amines are obtained by the latter process. Although perfluoro(*tert*-butyl methyl ether) was prepared by radiation of hexafluoroacetone,[6] no yield or physical data have been reported. The only previously reported preparative-scale synthesis of a *tert*-butoxy-containing perfluorinated ether, $(CF_3)_3COCF_2CF_2CF_3$, involves reaction of perfluoro-*tert*-butyl hypofluorite with hexafluoropropene,[7] an expensive and less versatile route.

Structures selected for this study illustrate well the distinct advantages of the LaMar direct fluorination techniques.[8] Many of the compounds reported here are not accessible through other routes. The preparations of these novel perfluorinated ethers and amine provide access to an unlimited number of new materials for biomedical and other studies (see Figure 1).

Experimental Section

Materials, Analyses, and Physical Measurements. 2,2,5,5-Tetramethyltetrahydrofuran, *tert*-butyl methyl ether, 1,2,2,6,6-pentamethylpiperidine, 2,5-dimethyltetrahydrofuran, 7-oxabicyclo[2,2,1]heptane, and isopropyl ether were obtained from Aldrich Chemical Co., Inc. Fluorine gas was technical grade and supplied by Air Products and Chemicals, Inc. The purity of the starting materials was checked by gas chromatography before fluorination. Neopentyl phenyl ether, *tert*-butyl isobutyl ether, and 1,2-di-*tert*-butoxyethane were prepared by following the reported procedures in the literature.[9,10] Elemental analyses were performed by Schwarzkopf Microanalytical Laboratory, Inc., Woodside, NY. Mass spectra were measured on a Bell and Howell Model 21-490 mass spectrometer at 70 eV. Room-temperature NMR spectra were taken on a Varian EM 390 spectrometer at 84.67 MHz for fluorine and 89.33 MHz for proton. $^{13}C\{^{19}F\}$ NMR spectra, and high-temperature NMR studies were done on a Bruker WH-100 instrument with a special designed probe. All the NMR spectra were run on neat liquid samples. Gas chromatography separations were made with a Bendix Model 2300 programmable gas chromatograph equipped with a cryogenic controller and thermal conductivity detector. The column used

(1) Riess, J. G.; LeBlance, M. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 621.
(2) Banks, R. E. *Preparation, Properties and Industrial Applications of Organofluorine Compounds*; Wiley: New York, 1982; pp 45–138.
(3) Clark, L. C., Jr.; Becattini, F.; Kaplan, S.; Obrock, V.; Cohen, D.; Becker, C. *Science (Washington, D.C.)* **1973**, *181*, 680.
(4) Persico, D. F.; Huang, H. N.; Clark, L. C., Jr.; Lagow, R. J. *J. Org. Chem.* **1985**, *50*, 5156.
(5) (a) Stacey, M.; Tatlow, J. C. *Adv. Fluorine Chem.* **1960**, *1*, 166. (b) Simons, J. H. *Fluorine Chemistry*; Academic: New York, 1950a, 1954b; (a) Vol. 1, p 414, (b) Vol. 2, p 1350.
(6) (a) Gordon, A. S. *J. Chem. Phys.* **1962**, *36*, 1130. (b) Chang, C.; Hanrahan, R. J. *Radiat. Phys. Chem.* **1982**, *19*, 361.
(7) Toy, M. S.; Stringham, R. S. *J. Fluorine Chem.* **1975**, *5*, 25.
(8) (a) Maraschin, N. J.; Catsikis, B. D.; Davis, L. H.; Jarrinen, G.; Lagow, R. J. *J. Am. Chem. Soc.* **1975**, *97*, 513. (b) Adcock, J. L.; Beh, R. A.; Lagow, R. J. *J. Org. Chem.* **1975**, *40*, 3271.
(9) Seyden-Penne, J.; Habert-Somny, A.; Cohen, A. M. *Bull. Soc. Chim. Fr.* **1965**, *3*, 700.
(10) Evans, T. W.; Edlund, K. R. *Ind. Eng. Chem.* **1936**, *28*, 1184.

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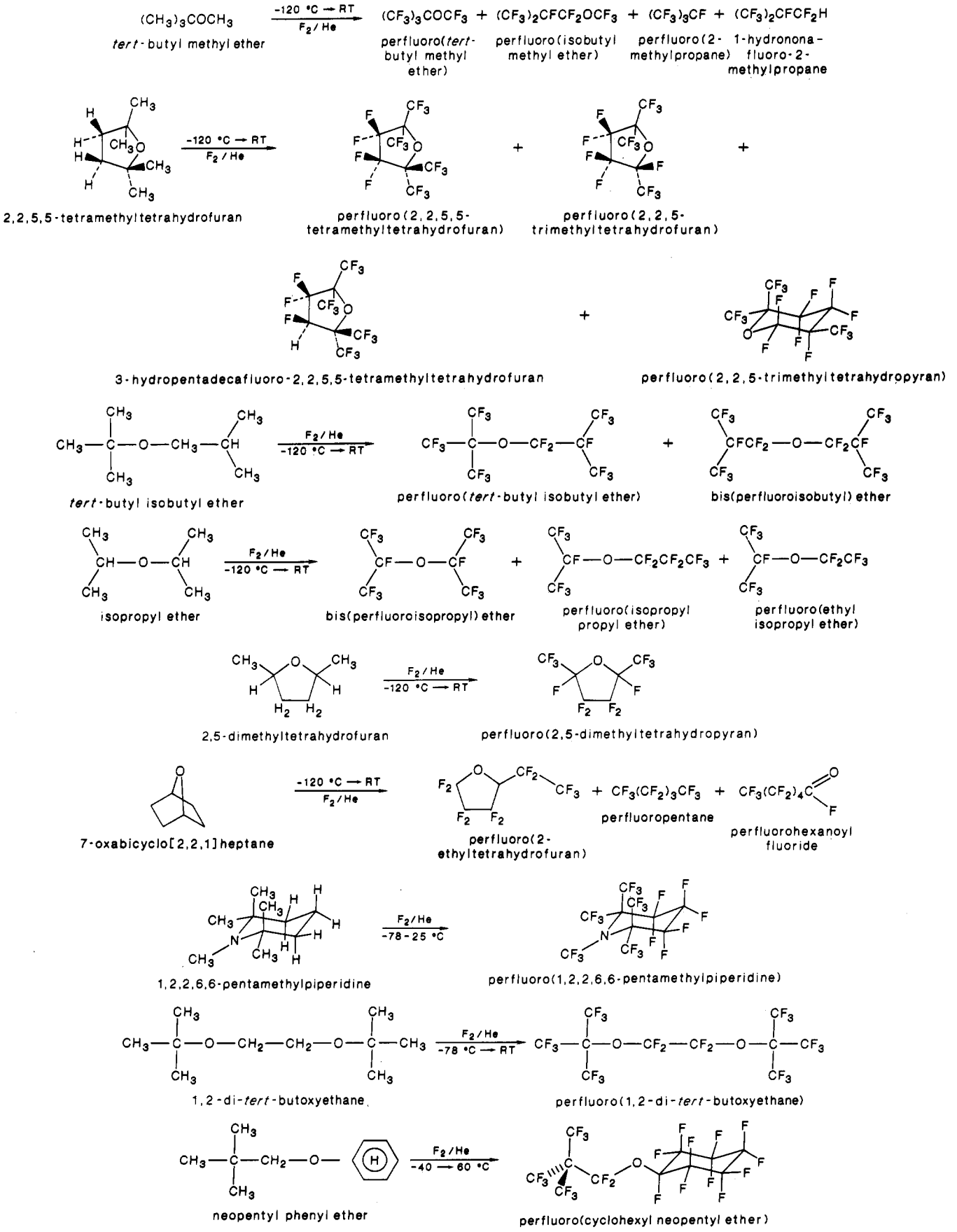


Figure 1. Direct fluorination of perfluorocarbon ethers and amines.

for checking the purity of the starting ethers was an 8 ft × $^3/_8$ in. 5% Apiezon L on Chromosorb P (60/80 mesh). The column used for separating the fluorinated products was either a 20 ft × $^3/_8$ in. 20% Fomblin Y-45 on Chromosorb P (60/80 mesh) or a 24 ft × $^1/_4$ in. 10% Fluorosilicone (QF-1-0065) on Chromosorb (60/80 mesh). The helium gas flow rate was at 60 cm^3/min. The boiling and melting points were measured in a sealed 6-mm glass tube as described previously.[11]

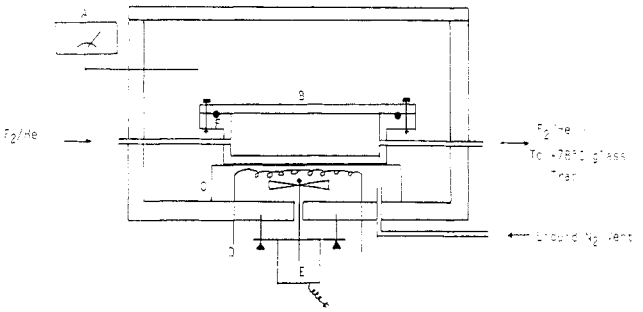


Figure 2. Cylindrical-disk fluorination reactor: (A) cryogenic temperature controller; (B) brass cylindrical-disk reactor; (C) reactor support; (D) electric heater; (E) electric fan; (F) viton O-ring.

Table I. Fluorination Conditions for *tert*-Butyl Methyl Ether

time, days	He, cm³/min	F_2, cm³/min	zones temp,[a] °C			
			1	2	3	4
1	60	1	−120	−120	−120	−120
1	30	1	−110	−110	−110	−110
1	30	2	−100	−100	−100	−100
1	10	1	−90	−90	−90	−90
1	10	2	−78	−78	−78	−78
1	10	2.5	−78	−78	−78	−78
1	0	1	−78	−78	−78	−78
1	0	1.5	−78	−78	−78	−78
1	0	2	−78	−78	−78	−78
1	0	2	amb	−78	−78	−78
1	0	2	amb	amb	−78	−78
1	0	2	amb	amb	amb	−78
1	30	2	amb	amb	amb	RT
1	30	0	amb	amb	amb	RT

[a] amb = ambient temperature; RT = room temperature.

Apparatus. A 10-in. (i.d.) × 1.5 in. tall cylindrical-disk brass reactor (see Figure 2) with two 0.25-in. pipe fittings provided as gas inlet and outlet and a Viton O-ring seal between the circular edge projections of the flanges was employed for fluorination of neopentyl phenyl ether. The inside of the reactor contained tightly packed copper turnings. This reactor was then placed in a Varian gas chromatography oven. The low-temperature reaction conditions were controlled by liquid nitrogen with a cryogenic controller, and high-temperature reaction conditions were performed by the heating elements in the oven. Other fluorinations were conducted in the previously reported four-zone cryogenic reactor.[8] In order to facilitate free flow of exit gases and prevent blockage of exit lines, the sodium fluoride trap normally used was changed into a 1.5 in. (i.d.) × 6.5 in. brass tube with $^1/_4$-in. pipe fittings on the ends.

Fluorination of *tert*-Butyl Methyl Ether. A 2 mL (1.72×10^{-2} mol) sample of *tert*-butyl methyl ether (bp 55 °C; mp −109 °C) was evaporated into a four-zone cryogenic reactor with zones 2–4 cooled to −120 °C by liquid nitrogen cryogenic control system. The evaporation coil was held at 45 °C by an oil bath, and the helium flow rate was at 100 cm³/min. Two hours after complete injections, the first zone was also cooled to −120 °C. Six hours later, fluorinations were started with the reaction conditions listed in Table I. By the same procedures, 2 mL of *tert*-butyl methyl ether were evaporated into another four-zone reactor and fluorinations were performed under the reaction conditions listed in Table II. The raw products collected in the glass trap maintained at −78 °C with dry ice/isopropyl alcohol slush were vacuum-distilled through −45, −78, −131, and −196 °C traps. The materials collected in the −45 °C trap were partially fluorinated and difficultly purified mixtures. The products left in the −131 and −78 °C traps were further purified by gas chromatography (Fomblin column) at 35 °C. The compositions of the raw products are summarized in Table III. The ratio of these volatile products

(11) Gerhardt, G. E.; Lagow, R. J. *J. Org. Chem.* **1978**, *43*, 4505.

Table II. Fluorination Conditions for *tert*-Butyl Methyl Ether

time, days	He, cm³/min	F_2, cm³/min	zone temp,[a] °C			
			1	2	3	4
1	60	1	−120	−120	−120	−120
1	30	1	−120	−120	−120	−120
1	30	2	−120	−120	−120	−120
1	10	1	−120	−120	−120	−120
1	10	2	−110	−110	−110	−110
1	0	1	−110	−110	−110	−110
1	0	1	−95	−95	−95	−95
1	0	1	−85	−85	−85	−85
1	0	1	−78	−78	−78	−78
1	0	1	amb	−78	−78	−78
1	0	1	amb	amb	−78	−78
1	0	1	amb	amb	amb	−78
1	0	1	amb	amb	amb	amb
1	30	0	amb	amb	amb	amb

[a] amb = ambient temperature.

varied as the fluorination conditions changed. The characterizations of the known compounds were done by comparing with the previously reported ^{19}F and ^1H NMR spectra.[12] It should be noted that the attempts to fluorinate *tert*-butyl methyl ether by the relatively "high" temperature fluorination conditions such as used for preparing perfluoro(1,2-dimethoxyethane) and perfluoro-1,4-dioxane[8b] resulted in degradation products.[13] With respect to the successful syntheses described here, freezing the hydrogen fluoride (mp −86 °C) liberated during the fluorination reactions is one of the critical factors. By keeping the initial reaction temperatures low and gradually increasing the concentration of fluorine, the acid-sensitive *tert*-butyl ether was converted to partially fluorinated and relatively acid-stable intermediates. Complete replacement of hydrogen was accomplished by the more vigorous fluorination conditions described in Table II.

Perfluoro(*tert*-butyl methyl ether). The mass spectrum of perfluoro(*tert*-butyl methyl ether) (bp 38 °C, mp −80 °C) contained a parent ion minus a fluorine at *m/e* 285. Other strong peaks and corresponding fragments are as follows: P − CF_3(235)$^+$, C_4F_9(219)$^+$, C_4F_8O(216)$^+$, C_4F_7O(197)$^+$, C_3F_5O(147)$^+$, C_3F_5(131)$^+$, C_3F_4O(128)$^+$, C_2F_3O(97)$^+$, and CF_3(69)$^+$ (base peak). Anal. Calcd: C, 19.74; F, 75.00. Found: C, 19.52; F, 74.76. The ^{19}F and $^{13}C\{^{19}F\}$ NMR assignments are reported in Table IV.

Perfluoro(isobutyl methyl ether). The mass spectrum of perfluoro(isobutyl methyl ether) (bp 36 °C, mp <−120 °C) contained strong peaks at *m/e* P − F(285)$^+$, C_4F_9(219)$^+$, C_4F_7O(197)$^+$, C_3F_7(169)$^+$, C_3F_6(150)$^+$, C_2F_5O(135)$^+$, C_3F_5(131)$^+$, C_3F_4O(128)$^+$, C_2F_4(100)$^+$, and CF_3(69)$^+$ (base peak). Anal. Calcd: C, 19.74; F, 75.00. Found: C, 19.57; F, 74.56. The ^{19}F and $^{13}C\{^{19}F\}$ NMR assignments are reported in Table IV.

Fluorination of 2,2,5,5-Tetramethyltetrahydrofuran. 2,2,5,5-Tetramethyltetrahydrofuran (bp 112 °C, mp −92 °C; 2 mL, 1.27×10^{-2} mol) was evaporated into a four-zone cryogenic reactor with zones 3 and 4 cooled to −120 °C. The evaporation coil was held at 100 °C, and the helium flow rate was at 100 cm³/min. Fluorinations were conducted following the reaction conditions listed in Table II. The raw products collected in the glass trap maintained at −78 °C were vacuum-distilled through −45, −78, −131, −196 °C traps and then purified by gas chromatography (Fomblin column) at 95 °C. The perfluoro(2,2,5-trimethyltetrahydropyran) and 3-hydropentadecafluoro-2,2,5,5-tetramethyltetrahydrofuran were further purified by Fluorosilicone column at 70 °C. The compositions (based on GC assay) of the raw products were 58.0% of perfluoro(2,2,5,5-tetramethyltetrahydrofuran), 27.9% of perfluoro(2,2,5-trimethyltetrahydrofuran), 6.5% of perfluoro(2,2,5-trimethyltetrahydropyran), and 4.7% of 3-hydropentadecafluoro-2,2,5,5-tetramethyltetrahydrofuran. On the basis of the weight of purified product, the overall yield of perfluoro(2,2,5,5-tetramethyltetrahydrofuran) (bp 99 °C, mp −31 °C) was 45.0%. As compared with the hydrocarbon analogue,

(12) Adcock, J. L.; Catsikis, B. D.; Thompson, J. W.; Lagow, R. J. *J. Fluorine Chem.* **1976**, *7*, 197.
(13) Huang, H. N.; Lagow, R. J., unpublished results.

Table III. Results of Fluorination of *tert*-Butyl Methyl Ether

rectn conditn	total wt. recovd, g	% composition[a] $(CF_3)_3CF$	$(CF_2H)CF(CF_3)_2$	$(CF_3)COCF_3$ (I)	$(CF_3)CFCF_2OCF_3$ (II)	unidentifd mix	ratio I/II
Table I	2.3	20.2	4.4	15.0	15.3	45.1%	0.98
Table II	3.1	18.6	6.0	32.1	11.9	31.4%	2.70

[a] The compositions were calculated on the basis of the chromatographic peak area.

the melting point of perfluoro(2,2,5,5-tetramethyltetrahydrofuran) is 61 °C higher.

Perfluoro(2,2,5,5-tetramethyltetrahydrofuran). The mass spectrum of perfluoro(2,2,5,5-tetramethyltetrahydrofuran) (bp 99 °C, mp −31 °C) contained strong peaks at *m/e* P − F(397)$^+$, P − CF_3(347)$^+$, $C_7F_{12}O$(328)$^+$, $C_7F_{11}O$(309)$^+$, C_6F_9O(259)$^+$, C_4F_7(181)$^+$, C_3F_5O(147)$^+$, C_3F_5(131)$^+$, C_3F_4O(128)$^+$, C_2F_5(119)$^+$, C_2F_4(100)$^+$, C_2F_3O(97)$^+$, C_3F_3(93)$^+$, and CF_3(69)$^+$ (base peak). Anal. Calcd: C, 23.08; F, 73.08. Found: C, 22.82; F, 72.89. The ^{19}F and $^{13}C\{^{19}F\}$ NMR assignments are reported in Table IV.

Perfluoro(2,2,5-trimethyltetrahydropyran). The mass spectrum of perfluoro(2,2,5-trimethyltetrahydropyran) (bp 107 °C) contained strong peaks at *m/e* P − F(397)$^+$, P − CF_3(347)$^+$, $C_7F_{12}O$(328)$^+$, $C_7F_{11}O$(309)$^+$, C_6F_9O(259)$^+$, C_6F_9(243)$^+$, C_4F_7(181)$^+$, C_3F_6(150)$^+$, C_3F_5(131)$^+$, C_3F_3O(109)$^+$, C_2F_4(100)$^+$, C_2F_3O(97)$^+$, and CF_3(69)$^+$ (base peak). Anal. Calcd: C, 23.08; F, 73.08. Found: C, 23.14; F, 73.20. The ^{19}F and $^{13}C\{^{19}F\}$ NMR assignments are reported in Table IV.

Perfluoro(2,2,5-trimethyltetrahydrofuran). The mass spectrum of perfluoro(2,2,5-trimethyltetrahydrofuran) (bp 70 °C) contained strong peaks at *m/e* P − F(347)$^+$, P − CF_3(297)$^+$, $C_6F_{10}O$(278)$^+$, C_6F_9O(259)$^+$, C_4F_7(181)$^+$, C_3F_7(169)$^+$, C_3F_6(150)$^+$, C_3F_5O(147)$^+$, C_3F_5(131)$^+$, C_3F_4O(128)$^+$, C_2F_5(119)$^+$, C_3F_4(112)$^+$, C_2F_4(100)$^+$, C_2F_3O(97)$^+$, C_3F_3(93)$^+$, and CF_3(69)$^+$ (base peak). Anal. Calcd: C, 22.91; F, 72.68. Found: C, 22.95; F, 72.51. The ^{19}F and $^{13}C\{^{19}F\}$ NMR assignments are reported in Table IV.

3-Hydropentadecafluoro-2,2,5,5-tetramethyltetrahydrofuran. The mass spectrum of 3-hydropentadecafluoro-2,2,5,5-tetramethyltetrahydrofuran (bp 112 °C) contained strong peaks at *m/e*: P − F(379)$^+$, P − CF_3(329)$^+$, $C_7F_{11}HO$(310)$^+$, $C_7F_{10}HO$(291)$^+$, C_5F_8H(213)$^+$, C_4F_7(181)$^+$, C_4F_6H(163)$^+$, C_3F_5O(147)$^+$, C_2F_5(119)$^+$, C_3F_4H(113)$^+$, C_2F_3O(97)$^+$, and CF_3(69)$^+$ (base peak). Anal. Calcd: C, 24.22; F, 71.60; H, 0.25. Found: C, 23.99; F, 71.62; H, 0.30. The ^{19}F and $^{13}C\{^{19}F\}$ NMR assignments are reported in Table IV.

Fluorination of *tert*-Butyl Isobutyl Ether. *tert*-Butyl isobutyl ether (bp 114 °C, mp −132 °C; 2 mL, 1.14×10^{-2} mol) was evaporated into a four-zone cryogenic reactor by the same procedures as used for 2,2,5,5-tetramethyltetrahydrofuran, and fluorinations were also done by the reaction conditions listed in Table II. The raw products collected in the glass trap maintained at −78 °C were vacuum-distilled through −45, −78, −131, and −196 °C traps. The major products (1.65 g) consisting of 7.2% of perfluoro(*tert*-butyl isobutyl ether) and 90.7% of bis (perfluoroisobutyl) ether were separated from other products by gas chromatography (Fomblin column) at 95 °C. The percentages of these unseparable structure isomers were calculated from the ^{19}F NMR spectrum. The characterizations of bis(perfluoroisobutyl) ether were done by comparing the ^{19}F and $^{13}C\{^{19}F\}$ NMR spectra with our previously reported data.[3] On the basis of the collected weight of these two isomers, the overall yield was 31.0%. The ^{19}F and $^{13}C\{^{19}F\}$ NMR assignments of perfluoro(*tert*-butyl isobutyl ether) are given in Table IV. The elemental analysis of the mixed isomers resulted in the following. Calcd: C, 21.15; F, 75.33. Found: C, 21.06; F, 75.30.

Fluorination of Isopropyl Ether. Isopropyl ether (bp 69 °C, mp −85 °C; 2 mL, 1.47×10^{-2} mol) was evaporated into a four-zone cryogenic reactor with zones 3 and 4 cooled to −110 °C. The evaporation coil was held at 60 °C, and the helium flow rate was at 100 cm^3/min. The fluorinations were done by the reaction conditions listed in Table II, and raw products were collected in the glass trap maintained at −78 °C. After vacuum distillation through −45, −78, −131, and −196 °C traps, the products were further purified by gas chromatography (Fomblin column) at 45 °C. The compositions (GC assay) of the raw products were 8.2% of perfluoro(ethyl isopropyl ether), 50.9% of bis(perfluoroisopropyl) ether, 20.6% of perfluoro(isopropyl *n*-propyl ether), and other uncharacterized products. Because of the difficult separations, the 49.2% overall yield was based on the weight of mixed bis(perfluoroisopropyl) ether and perfluoro(isopropyl *n*-propyl ether).

Perfluoro(ethyl isopropyl ether). The mass spectrum of perfluoro(ethyl isopropyl ether) (bp 54 °C, mp <−120 °C) contained strong peaks at *m/e* P − F(335)$^+$, P − CF_3(285)$^+$, C_4F_9O(235)$^+$, C_3F_7(169)$^+$, C_2F_5(119)$^+$, C_2F_4(100)$^+$, and CF_3(69)$^+$ (base peak). Anal. Calcd: F, 75.00. Found: F, 74.51. The ^{19}F and $^{13}C\{^{19}F\}$ NMR assignments are reported in Table IV.

Perfluoro(isopropyl *n*-propyl ether). The mass spectrum of perfluoro(isopropyl *n*-propyl ether) (bp 70 °C, mp <−120 °C) contained strong peaks at *m/e* P − F(285)$^+$, P − CF_3(235)$^+$, C_3F_7(169)$^+$, C_2F_5(119)$^+$, C_2F_4(100)$^+$, and CF_3(69)$^+$ (base peak). Anal. Calcd: F, 75.14. Found: F, 75.13. The ^{19}F and $^{13}C\{^{19}F\}$ NMR assignments are reported in Table IV.

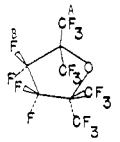
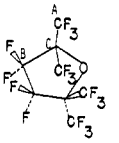
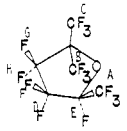
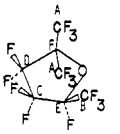
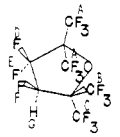
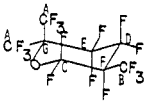
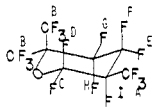
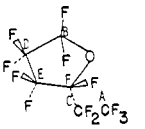
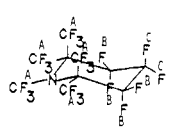
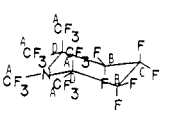
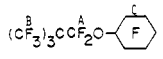
Bis(perfluoroisopropyl) Ether. Bis(perfluoroisopropyl) ether (bp 56 °C, mp −98 °C) was characterized by comparing its ^{19}F and $^{13}C\{^{19}F\}$ NMR and mass spectral data with our previously reported data.[4] Its unusual ^{19}F NMR spectrum and melting point are discussed later.

Fluorination of 2,5-Dimethyltetrahydrofuran. A mixture of *cis*- and *trans*-2,5-dimethyltetrahydrofuran (bp 90 °C, mp <−120 °C; 2 mL, 1.66×10^{-2} mol) was evaporated into a four-zone cryogenic reactor by the same conditions as used for isopropyl ether except the evaporation coil was held at 80 °C. The fluorination conditions are listed in Table II. The raw products collected in the glass trap maintained at −78 °C consisted of 69.5% of mixed *cis*- and *trans*-perfluoro(2,5-dimethyltetrahydrofuran) along with other uncharacterized products. After vacuum distillation through −45, −78, −131, and −196 °C traps and the following gas chromatographic separations (Fomblin column) at 65 °C, 2.76 g of the cis and trans mixture was obtained. The yield was 50.2%. The characterization of these mixed isomers was done by elemental analyses (C, 22.69; F, 72.11. Calcd: C, 22.78; F, 72.15) and comparing the boiling point (54 °C) and mass spectrum with the data reported by Nagase and co-workers.[14] Also, the ^{19}F NMR data matched well with Nagase's spectrum.[15] The $^{13}C\{^{19}F\}$ NMR spectrum of these mixtures contained singlet peaks at 117.6, 111.9, 111.3, 106.0, and 105.1 ppm, respectively, from external tetramethylsilane standard. Interpretations of these NMR spectra are in process.[16]

Fluorination of 7-Oxabicyclo[2.2.1]heptane. 7-Oxabicyclo[2.2.1]heptane [bp 119 °C (713 mm); 2 mL, 1.97×10^{-2}] was evaporated into a four-zone cryogenic reactor and fluorinated by the same conditions as used for 2,2,5,5-tetramethyltetrahydrofuran. The raw products collected in the glass trap maintained at −78 °C consisted of (based on GC assay) 20.0% of perfluoropentane, 15.9% of perfluorohexanoyl fluoride, 40.0% of perfluoro(2-ethyltetrahydrofuran), and other mixtures. These known products were characterized by comparison of their infrared, ^{19}F NMR, and mass spectra with reported data or authentic chemicals.[14,17] Separations were done by vacuum distillation through −45, −78, −131, and −196 °C traps and then by gas chromatographic purifications (Fomblin column) at 70 °C. The purified perfluoro(2-ethyltetrahydrofuran) weighed 1.4 g, corresponding to a 26.2% yield.

(14) Abe, T.; Nagase, S. *J. Fluorine Chem.* **1979**, *13*, 519.
(15) Private communications with Dr. S. Nagase and Dr. T. Abe.
(16) Shoulders, B. A.; Sorey, S.; Huang, H. N.; Lagow, R. J., to be published.
(17) Perfluoropentane and perfluorohexanoyl fluoride were obtained from fluorination of cyclohexanol.

Table IV. ^{19}F and $^{13}C\{^{19}F\}$ NMR of Fluorinated Products

compd	^{19}F chem shifts,[a] ppm		J,[b] Hz		compd	$^{13}C\{^{19}F\}$ chem shifts,[c] ppm	
$(CF_3)_3COCF_3$	A	−56.5 (de)[d]	A–B = B–A	6.2	$(CF_3)_3COCF_3$	A	119.9
	B	−73.2 (q)				B	119.1
						C	80.7
$(CF_3)_2CFCF_2OCF_3$	A	−57.1 (t)	C–A	9.9	$(CF_3)_2CFCF_2OCF_3$	A	119.2
	B	−74.1 (t-d)	C–B	10.7		B	119.0
	C	−79.0	D–B = B–D	5.4		C	115.9
	D	−187.0 (he)				D	88.4
	A	−74.2 (p)	A–B = B–A	7.9		A	119.5
	B	−120.5				B	115.4
						C	83.9
	A	−73.5 (he)	C–A = B–A	10.7		A	119.2
	B	−74.5	A–F	21.5		B	117.8
	C	−82.3	A–D	18.9		C	114.1
	D	−116.0 (d-q)	A–E	8.5		D	112.6
	E	−124.8 (q-m)	D–F	268.1			
	F	−127.2 (d-q)					
	G	−129.1				E	105.7
	H	−129.1				F	83.7
	A	−73.4	E–D = D–E	260.1		A	119.5
	B	−74.1				B	118.9
	C	−77.7	G–F = F–G	49.2		C	116.8
	D	−114.6	D–G = E–G	9.0		D	108.8
	E	−119.5 (d)				E	108.6
	F	−217.6 (d)				F	85.3
	^1H NMR	5.2[e] (d-t)				G	81.3
	A	−70.5	D–C = C–D	117.8	$(CF_3)_3COCF_2CF(CF_3)_2$	A	119.1
	B	−73.2	E–F = F–E	296.3		B	118.6
	C	−74.4	G–H = H–G	273.2		C	117.3
	D	−82.5				D	88.7
	E	−113.7					
	F	−120.6					
	G	−126.8					
	H	−130.2					
	I	−188.7					
$(CF_3)_3COCF_2CF(CF_3)_2$	A	−72.5 (t)	C–A	10.2	$(CF_3)_2CFOCF_2CF_3$	A	117.6
	B	−76.0				B	116.0
	C	−78.4				C	114.3
	D	−188.2				D	102.1
$(CF_3)_2CFOCF_2CF_3$	A	−84.2 (t)	D–A	2.3	$(CF_3)_2CFOCF_2CF_2CF_3$	A	117.6
	B	−89.2 (d-m)	B–A	5.4		B	117.2
	C	−90.7 (t)	D–B = B–D	21.2		C	115.7
	D	−147.5 (t)	B–C	2.2		D	106.7
						E	102.3
$(CF_3)_2CFOCF_2CF_2CF_3$	A	−83.1				A	119.2
	B	−84.1				B	117.4
	C	−132.2				C	111.6
	D	−147.3 (t)				D	108.6
						E	105.3
	A	−75.0	A–B	5.6		A	119.0
	B	−116.7				B	113.2
	C	−121.4				C	111.2
						D	90.9
$(CF_3)_3COCF_2CF_2OC(CF_3)_3$	A	−72.7 (t)	A–B = B–A	10.2	$(CF_3)_3COCF_2CF_2OC(CF_3)_3$	A	119.3
	B	−87.4 (de)				B	115.0
						C	81.1
	A	−63.8					
	B	−66.2					
	C	−135.0[f]					

[a] ^{19}F NMR chemical shifts are relative to external $CFCl_3$. [b] Only obvious coupling constants are given. [c] ^{13}C and NMR chemical shifts are relative to external $(CH_3)_4Si$. [d] de, dectet; q, quartet; t, triplet; d, doublet; he, heptet; p, pentet; m, multiplet. [e] Relative to external $(CH_3)_4Si$. [f] A broad multiplet centered at −135.0 ppm from external $CFCl_3$.

Table V. Fluorination Conditions for 1,2,2,6,6-Pentamethylpiperidine

time, days	He, cm³/min	F_2, cm³/min	zone temp,[a] °C			
			1	2	3	4
0.5	30	0	−78	−78	−78	−78
1	30	1	−78	−78	−78	−78
1	30	2	−78	−78	−78	−78
1	15	2	−78	−78	−78	−78
1	0	2	−78	−78	−78	−78
1	0	2	amb	−78	−78	−78
1	0	2	amb	amb	−78	−78
1	0	2	amb	amb	amb	−78
1	0	2	amb	amb	amb	amb
1	60	0	amb	amb	amb	amb

[a] amb = ambient temperature.

Fluorination of 1,2,2,6,6-Pentamethylpiperidine. Because of the relatively low volatility, the starting material was loaded into a four-zone reactor by a manner different from previously described. 1,2,2,6,6-Pentamethylpiperidine (bp 187 °C, mp 11 °C; 2 mL, 1.11×10^{-2} mol) was well mixed with 6 g of dry sodium fluoride powder. These "mixtures" were then suspended on the copper turnings in a four-zone reactor. Fluorination followed the reaction conditions listed in Table V, and the products were collected in the glass trap maintained at −78 °C. After vacuum distillation through −45, −78, −131, and −196 °C traps, the mixtures were further purified by gas chromatography (Fomblin column) at 150 °C. Perfluoro(1,2,2,6,6-pentamethylpiperidine) (1.1 g) corresponding to 19.5% of yield was obtained. The melting point is 98 °C lower than that of the hydrocarbon analogue.

Perfluoro(1,2,2,6,6-pentamethylpiperidine). The mass spectrum of perfluoro(1,2,2,6,6-pentamethylpiperidine) (bp 134 °C, mp −87 °C) contained strong peaks at *m/e* P − F(514)$^+$, P − CF_3(464)$^+$, C_8F_{15}(381)$^+$, C_6F_{13}(319)$^+$, C_5F_{11}(269)$^+$, C_4F_9(219)$^+$, C_4F_7(181)$^+$, C_3F_5(131)$^+$, C_2F_5(119)$^+$, C_2F_4(100)$^+$, and CF_3(69)$^+$ (base peak). Anal. Calcd: C, 22.51; F, 74.85; N, 2.63. Found: C, 22.35; F, 74.47; N, 2.38. The ^{19}F and $^{13}C\{^{19}F\}$ NMR assignments are reported in Table IV.

Fluorination of 1,2-Di-*tert*-butoxyethane. Due to the relatively low volatility of the starting material, 3 mL (1.42×10^{-2} mol) of 1,2-di-*tert*-butoxyethane (bp 171 °C, mp −52 °C) was loaded into a four-zone reactor by the same manner as used for 1,2,2,6,6-pentamethylpiperidine. The fluorination conditions are listed in Table V, and the products were collected in the glass trap maintained at −78 °C. After vacuum distillation through −45, −78, −131, and −196 °C traps, the mixtures left in the −45 and −78 °C traps were further purified by gas chromatography (Fomblin column) at 140 °C. Perfluoro(bis-1,2-*tert*-butoxyethane) (1.2 g) corresponding to 14.8% yield was obtained.

Perfluoro(1,2-di-*tert*-butoxyethane). The mass spectrum of perfluoro(1,2-di-*tert*-butoxyethane) (bp 120 °C, mp −42 °C) contained strong peaks at *m/e* P − F(551)$^+$, $C_6F_{13}O$(335)$^+$, $C_5F_{11}O$(285)$^+$, C_4F_9(219)$^+$, C_3F_5(131)$^+$, C_2F_5(119)$^+$, and CF_3(69)$^+$ (base peak). Anal. Calcd: C, 21.05; F, 73.33. Found: C, 20.81; F, 72.91. The ^{19}F and $^{13}C\{^{19}F\}$ NMR assignments are reported in Table IV.

Fluorination of Neopentyl Phenyl Ether. Due to the difficult synthesis of the hydrocarbon analogue, perfluoro(cyclohexyl neopentyl ether) was prepared from neopentyl phenyl ether [bp 78 °C (12 mm)]. A cylindrical-disk type reactor was used for fluorination mainly because of the low vapor pressure of both the starting material and fluorinated products. Neopentyl phenyl ether (1.5 g, 9.1×10^{-3} mol) was mixed well with 6 g of dry sodium fluoride powder. These "mixtures" were then suspended on the tightly packed copper turnings in the cylindrical-disk type reactor. Fluorination conditions are shown in Table VI, and the products were collected in the glass trap maintained at −78 °C. After gas chromatographic purifications (Fomblin column) at 185 °C, 0.35 g of perfluoro(cyclohexyl neopentyl ether) was obtained, corresponding to a yield of 6.0%.

Perfluoro(cyclohexyl neopentyl ether). The mass spectrum of perfluoro(cyclohexyl neopentyl ether) (bp 176 °C, mp 20 °C) contained strong peaks at *m/e* P − F(547)$^+$, C_6F_{11}(281)$^+$, C_5F_{11}(269)$^+$, C_5F_9(231)$^+$, C_4F_7(181)$^+$, C_3F_7(131)$^+$, and CF_3(69)$^+$ (base peak). Anal. Calcd: C, 23.31; F, 73.85. Found: C, 23.67; F, 73.83.

Table VI. Fluorination Conditions for Neopentyl Phenyl Ether

time, days	He, cm³/min	F_2, cm³/min	temp,[a] °C
1	20	1	−45
1	20	2	−45
1	20	2	−25
1	20	2	−10
1	20	2	0
1	0	2	0
1	0	2	RT
1	0	2	45
1	60	2	65
2	60	0	65

[a] RT = room temperature.

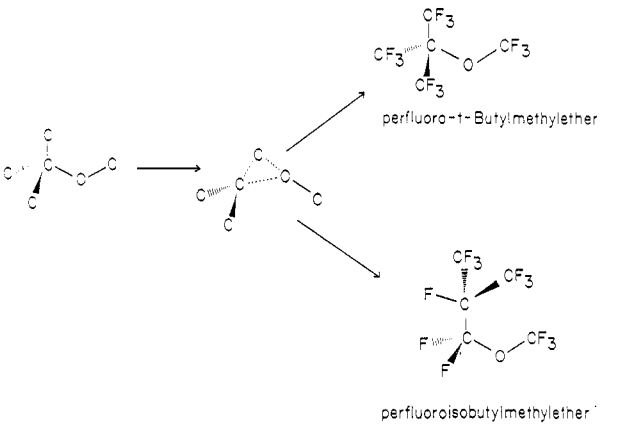


Figure 3. Skeletal rearrangement of fluorination of *tert*-butyl methyl ether.

The ^{19}F NMR assignments are reported in Table IV.

Results and Discussion

Even though the direct fluorinations of monoglyme, diglyme, and other primary aliphatic ethers are now feasible by our cryogenic fluorination process,[8b] difficulties with fluorinations of *tert*-butoxy-containing organic compounds were encountered, and the rupture of the *tert*-butyl–oxygen bond by the hydrogen fluoride liberated during the fluorination reactions was observed. Rate studies have shown that *tert*-butyl ethers decompose by acid catalysis approximately 1000 times as rapidly as primary aliphatic ethers.[18] However, the perfluoro-*tert*-butoxy group is inert to acid at room temperature.[19] The stability of the perfluoro-*tert*-butoxy group to acid is possible due to the great instability of the tertiary carbonium ion, $(CF_3)_3C^+$, as illustrated by Olah.[20] By varying the fluorination parameters, particularly the initial reaction temperatures, an acceptable yield of perfluoro(*tert*-butyl methyl ether) was obtained. With a more efficient system of hydrogen fluoride removal, one could expect to do significantly better. In addition, some acid-unstable heteroatom-containing compounds, such as tetraalkyl orthocarbonate,[21] also could be successfully fluorinated by mixing with hydrogen fluoride scavengers, such as sodium fluoride, at different temperatures. According to the generally agreed radical mechanism for the direct fluorination process,[22] the isomerized byproduct, perfluoro(isobutyl methyl ether), should result from skeletal rearrangements such as described in Figure 3. By following similar reaction approaches, perfluoro(isopropyl *n*-propyl ether) was obtained as one of the major byproducts from

(18) Norris, J. F.; Rigby, G. W. *J. Am. Chem. Soc.* **1932**, *54*, 2088.
(19) Tires, G. V. D. *J. Am. Chem. Soc.* **1955**, *77*, 4837.
(20) Olah, G. A.; Pittman, C. U., Jr. *J. Am. Chem. Soc.* **1966**, *88*, 3310.
(21) Clark, W. D.; Huang, H. N.; Lagow, R. J., to be published.
(22) Florin, R. E.; Wall, L. A. *J. Chem. Phys.* **1972**, *57*, 1791.

fluorination of isopropyl ether. Likewise, bis(perfluoroisobutyl) ether was obtained from fluorination of *tert*-butyl isobutyl ether. The 1,2-shift of the fluorinated alkoxy group does not occur in structurally analogous highly branched alkanes[8a,23] and therefore is a function of the stability of radicals and steric bulk and a characteristic of oxygen–heteroatom systems.

One of the significant problems in the electrolytic fluorinations of cyclic ethers is extensive ring-isomerization.[14] The successful preparation of perfluoro(2,2,5,5-tetramethyltetrahydrofuran) and perfluoro(2,5-dimethyltetrahydrofuran) demonstrated that the isomerizations were markedly decreased by our cryogenic fluorination process. On the other hand, the 1,2-shift was limited by the rigid ring structure. The rupture of carbon–carbon bonds adjacent (or β) to the ether linkage(s) may have been facilitated by the difficulties with sterically induced vibrational relaxation in such a bulky system. In fact, the lower degree of β cleavage occurring in fluorinations of ethers and especially ethylene glycol based diethers[8b] is another great advantage of the LaMar direct fluorination process.

According to our hypothesis, branched perfluorinated ethers and amines, e.g., perfluoro(2,2,5,5-tetramethyltetrahydrofuran), should be qualified as a "nonbasic" oxygen carrier. However, the high vapor pressure may cause physiological problems in some biomedical applications. On the other hand, this perfluorinated fluid is a good solvent for storage organs and electronic industrial applications, and higher molecular weight compounds with similar structures are being prepared. It should be noted that due to its high vapor pressure, perfluoro(2-*n*-butyltetrahydrofuran), one of the well-studied PFCS-based breathing liquids, was discarded as qualified "artificial blood".[2] Generally, in terms of vapor pressure, a promising PFCS-based "artificial blood" should have a boiling point around 140 °C. Based upon the successful fluorination results described in this manuscript, "high" boiling point and "nonbasic" perfluorinated ethers can be easily prepared from different or more alkyl-substituted hydrocarbon precursors by our direct fluorination techniques. In spite of the fact that bis(perfluoroneopentyl) ether satisfied vapor pressure and retention in mammalian tissue criteria, this *solid* perfluorinated ether does not give emulsions of sufficient stability.[24] Improved surfactants or techniques may be needed for preparing qualified PFCS-based emulsions from *solid* perfluorochemicals. Perfluoro(cyclohexyl neopentyl ether) and perfluoro(1,2-di-*tert*-butoxyethane) were prepared under the guidelines of our hypothesis and *multi*-requirements of PFSC-based "artificial blood".[2] The relatively wide *liquid* range of these new structurally crowded perfluorinated ethers is mainly caused by the irregular packing in their crystalline lattice. Testing in animals of several of these new materials for fluorocarbon blood applications is in process.[24]

The ^{19}F NMR of the compounds exhibited several interesting features. Probably because of the "direct-through-space" interactions,[25] extraordinarily long-range F–F coupling constants were observed in the ^{19}F NMR spectra of several compounds. For instance, the ^{19}F NMR spectrum of perfluoro(*tert*-butyl methyl ether) such as shown in Figure 4 consisted of a quartet (J = 6.2 Hz)

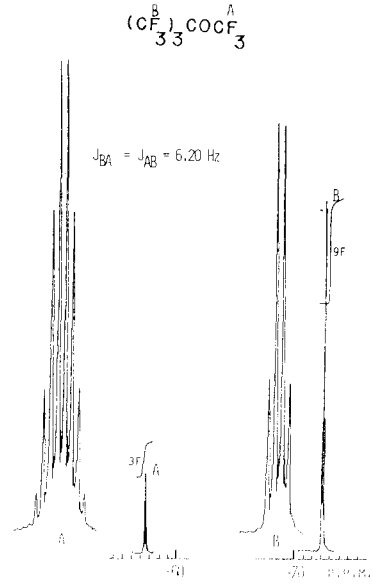


Figure 4. ^{19}F NMR of perfluoro(*tert*-butyl methyl ether).

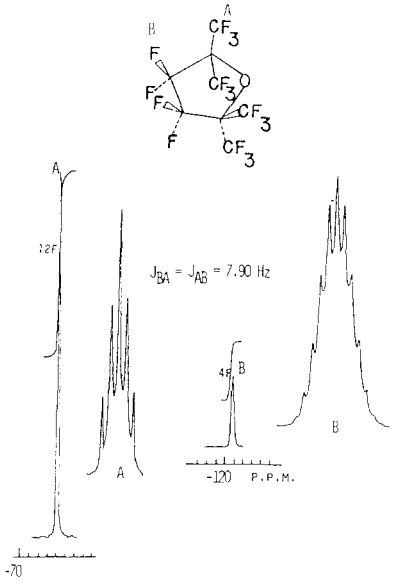


Figure 5. ^{19}F NMR of perfluoro(2,2,5,5-tetramethyltetrahydrofuran).

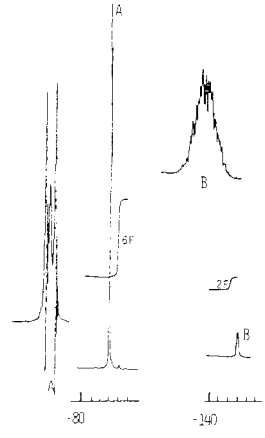


Figure 6. ^{19}F NMR of bis(perfluoroisopropyl) ether.

centered at −73.2 ppm and dectet (J = 6.2 Hz) centered at −56.5 ppm with relative intensities of 3:1. The interesting "virtual" coupling behavior[26] was found in per-

(23) (a) Shimp, L. A.; Lagow, R. J. *J. Am. Chem. Soc.* **1977**, *42*, 3437. (b) Liu, E. K. S.; Lagow, R. J. *J. Fluorine Chem.* **1979**, *13*, 71. (c) Generally speaking, we did not observe skeletal rearrangement in the direct fluorination of alkanes.

(24) Huang, H. N.; Persico, D. F.; Clark, L. C., Jr.; Lagow, R. J., to be published.

(25) Petrakis, L.; Sederholm, C. M. *J. Chem. Phys.* **1961**, *35*, 1243.

(26) Musher, J. I. *J. Chem. Phys.* **1962**, *36*, 1086.

fluoro(2,2,5,5-tetramethyltetrahydrofuran) (Figure 5) as is the case with bis(perfluoroneopentyl) ether[3,16] and other perfluorinated compounds.[26] Despite the different "through-bond" distances between trifluoromethyl and two difluoromethylene groups, it appeared that CF_3 groups were "equally" split by the four secondary fluorine atoms. On the other hand, the very complicated F–F coupling of bis(perfluoroisopropyl) ether (Figure 6) may have been due to repulsion of the intramolecular tertiary fluorine atoms; this highly branched perfluorinated ether may have a "staggered asymmetrical" structure, and the decrease in the melting point[27] could be related to this unusual structure.

Like perfluorinated ethers, perfluorinated tertiary amines are currently important materials in many electronic and medical applications.[28] Because amines dissolve well and give fair stability in anhydrous hydrogen fluoride, different classes of perfluorinated amines can be prepared from their hydrocarbon analogues by the Simons' electrochemical fluorination process.[28] In fact, this electrolytic technique is the only significant synthetic route to perfluorinated tertiary amines. However, rearrangements and degradations limit its capability to prepare highly branched perfluorinated amines. Our successful synthesis of perfluoro(1,2,2,6,6-pentamethylpiperidine) provides an improved route to perfluorinated amines. As compared with the melting point decreases observed for our novel perfluorinated fluids,[12,27] this new perfluorinated tertiary amine should be classified as an extremely structurally crowded molecule. Due to this steric advantage and the qualified physical properties, we surmise that we have obtained a promising PFSC-based "artificial blood" or "additive". Preliminary animal tests show promising results, and further studies are in process.[24] Despite the over-long retention in mammalian bodies, perfluoro(tri-*n*-propylamine) has been used as an "additive" to improve the stabilities of perfluorodecalin-based emulsions, and these "*multi*-PFSC-base" emulsions have been tested on healthy humans.[2]

Acknowledgment. We are grateful for support of this work by the Air Force Office of Scientific Research (AFOSR-82-0197). The helpful discussions with Dr. B. A. Shoulders and Mr. S. Sorey concerning the NMR interpretations and the permission to use the special $^{13}C\{^{19}F\}$ NMR probe built by Mr. O. Williams are appreciated.

Registry No. $CF_3C(CF_3)_2COCF_3$, 88995-83-9; $CF_3CF(CF_3)CF_2OCF_3$, 110719-85-2; $CF_3C(CF_3)_2COCF_2CF(CF_3)$, 88995-86-2; $[(CF_3)_2CFCF_2]_2O$, 97187-06-9; $(CF_3)_2CFOCF_2CF_3$, 56102-25-1; $[(CF_3)_2CF]_2O$, 83935-39-1; $(CF_3)_2CFOCF_2CF_2CF_3$, 83935-38-0; $[(CF_3)_3OCF_2]_2$, 110719-92-1; $(CF_3)_3CF$, 354-92-7; $(CF_3)_2CFCHF_2$, 59571-40-3; *tert*-butyl isobutyl ether, 33021-02-2; 1,2-di-*tert*-butoxyethane, 26547-47-7; perfluoro(2,2,5,5-tetramethyltetrahydrofuran), 110719-86-3; perfluoro(2,2,5-trimethyltetrahydropyran), 110719-87-4; perfluoro(2,2,5-trimethyltetrahydrofuran), 110719-88-5; 3-hydropentadecafluoro-2,2,5,5-tetramethyltetrahydrofuran, 110743-66-3; *cis*-perfluoro(2,5-dimethyltetrahydrofuran), 110719-89-6; *trans*-perfluoro(2,5-dimethyltetrahydrofuran), 110719-90-9; perfluoro(2-ethyltetrahydrofuran), 356-48-9; perfluoro(1,2,2,6-pentamethylpiperidine), 110719-91-0; perfluoro(cyclohexyl neopentyl ether), 110719-93-2; fluorine, 7782-41-4; 2,2,5,5-tetramethyltetrahydrofuran, 15045-43-9; *tert*-butyl methyl ether, 1634-04-4; 1,2,2,6,6-pentamethylpiperidine, 79-55-0; *cis*-2,5-dimethyltetrahydrofuran, 2144-41-4; 7-oxabicyclo[2.2.1]heptane, 279-49-2; isopropyl ether, 108-20-3; neopentyl phenyl ether, 2189-88-0; perfluoropentane, 678-26-2; perfluorohexanoyl fluoride, 355-38-4; *trans*-2,5-dimethyltetrahydrofuran, 2390-94-5.

(27) "Melting point drop" behavior is defined as the melting point of the perfluorinated compound lower than its hydrocarbon analogue.
(28) Danielson, R. D. *Encycl. Chem. Technol.* **1979**, *10*, 874.

Antiviral Nucleosides. A Stereospecific, Total Synthesis of 2′-Fluoro-2′-deoxy-β-D-arabinofuranosyl Nucleosides

Henry G. Howell,* Paul R. Brodfuehrer, Steven P. Brundidge, Daniel A. Benigni, and Chester Sapino, Jr.

Chemical Process Development Department, Bristol-Myers Pharmaceutical Research and Development Division, Syracuse, New York 13221-4755

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A general, total synthesis of (2′-fluoro-2′-deoxy-β-D-arabinofuranosyl)uracils **1a–d** is described. A study of the coupling reaction between 3,5-di-*O*-benzoyl-2-deoxy-2-fluoro-α-D-arabinofuranosyl bromide (**7**) and silylated pyrimidines **11a–d** has resulted in a high overall yield for the five-step stereospecific synthesis of β-nucleosides.

The severity of diseases like AIDS has intensified the interest in a variety of synthetic agents[1] that are effective against viral disease. A class of agents found to be active against DNA viruses was discovered in the late 1970s by Watanabe and Fox.[2] These compounds are (2′-fluoro-2′-deoxy-β-D-arabinofuranosyl)pyrimidines substituted in the 5 position, **1a–d** (Scheme I). As our interest in this class of biologically potent compounds developed, we began a search for efficient synthetic approaches.

Previous communications from this laboratory have described a simple preparation of 1,3,5-tri-*O*-benzoyl-α-D-ribofuranose (**4**),[3] and its conversion to 2-fluoro-2-deoxy-1,3,5-tri-*O*-benzoyl-α-D-arabinofuranose (**6**).[4] This

(1) (a) Robins, R. K. *Chem. Eng. News* January 27, **1986**, 28–40. (b) Dagooni, R. *Chem. Eng. News* December 8, **1986**, 7–14. (c) DeClerq, E. *J. Med. Chem.* **1986**, *29*, 1561.
(2) Su, T.-L.; Watanabe, K. A.; Schinazi, R. F.; Fox, J. J. *J. Med. Chem.* **1986**, *29*, 151.
(3) Howell, H. G.; Brodfuehrer, P. R.; Sapino, C. *J. Org. Chem.* **1985**, *50*, 2597.
(4) Howell, H. G.; Tann, C. H.; Brodfuehrer, P. R.; Brundidge, S. P.; Sapino, C. *J. Org. Chem.* **1985**, *50*, 3644.

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