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Synthesis and Characterization of the First Perfluorinated Carbohydrate

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The first perfluorinated carbohydrate (sugar) has been recently synthesized by carefully controlled reactions of elemental fluorine with the carbohydrate 1,2:3,5-di-*O*-isopropylidene-D-xylofuranose. We have synthesized the compound perfluoro-1,2:3,5-di-*O*-isopropylidene-D-xylofuranose. The compound is unambiguously characterized by ^{19}F NMR and two-dimensional ^{19}F NMR.

Introduction

The first published discovery of a naturally occurring toxic fluorine-containing material, potassium fluoroacetate, is credited to Marais.[1] The biomechanism of the fluoroacetate toxicity in mammals was first elucidated by Sir Rudolph Peters. He showed that the fluoroacetate was metabolically transformed into an even more toxic fluorocitric acid isomer, a powerful inhibitor of the tricarboxylic acid cycle.[2] In nature the occurrence of a C−F bond in carbohydrates is restricted to nucleocidin, which is an antibiotic.

Interestingly, the radii of fluoride and hydroxide ions [r(F) = 133, r(OH) = 140 pm] are almost identical, and so the fluorine has the ability to replace oxygen (as hydroxide) in carbohydrates. For example, some fluorinated carbohydrates have been used as biological probes for the study of carbohydrate transport,[3] metabolisms, enzymes, and specifity.[4] A recurrent theme in biomedical studies is the rational assumption that ^{19}F and ^{18}F may replace the hydroxyl group(s) of carbohydrates with minimal perturbance to molecular structure and conformation. The change in biochemical reactivity, combined with the specific hydrogen-bonding capacity of the C−F bond, permit the use of deoxyfluorinated sugars as unique cellular and enzymatic probes.[5] In general, the reactions used to make fluorinated monosaccharides are addition reactions,[6] epoxide scission,[7] and exchange reactions.[8] Interestingly, as early as 1900, Moissan himself carried out the first reaction between elemental fluorine and glucose.[9] Without techniques available to regulate the radical chain reactions of elemental fluorine, this reaction was not successful. A perfluorinated carbohydrate has not yet been reported or attempted by other fluorination processes and is thought to be synthetically inaccessible by conventional techniques.[10] Applications of elemental fluorine as perfluorination and selective fluorination reagents for carbohydrates are under study in this laboratory.

Table 1. Fluorination Parameters for Perfluoro-1,2:3,5-di-*O*-isopropylidene-D-xylofuranose

time (h)	F_2 (mL/min)	He (mL/min)	temp (°C)
24	1	100	−90
24	1	100	−80
25	1.5	50	−80
11.5	2	50	−80
12.5	2	35	−80
12	2	20	−80
12	3	20	−80
12	4	20	−80
12	4	15	−80
10	4	10	−80
14	4	5	−80
12.5	4	0	−80
10.5	4	0	−80
12	4	0	−70
11	4	0	−60
12	4	0	−50
12	4	0	−40
12	4	0	−30
12	4	0	−20
12	4	0	−10
12	4	0	0
12	4	0	10
12	4	0	rt
24	4	0	40

Perfluoro-1,2:3,5-di-*O*-isopropylidene-D-xylofuranose has been synthesized using direct fluorination techniques, and its two-dimensional COSY ^{19}F nuclear magnetic resonance spectrum has been studied. This is a rigid molecule with interesting ^{19}F chemical shifts and complicated couplings, which will be discussed later.

Experimental Section

A well mixed powder of 5 g of starting material and 50 g of dried NaF powder was pressed through 20 mesh screen over copper turnings into a disk reactor.[11] Before the reaction started, the system was purged with helium at 200 mL/min for 2 h, then at −60 °C and 100 mL/min for 2 h as controlled by a liquid nitrogen cryogenic device. The reaction proceeded following conditions shown in Table 1. Fifteen days later,

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[1] Marais, J. S. C. *Onderstepoort J. Vet. Sci. Anim. Ind.* **1943**, *18*, 203.

[2] Taylor, N. F. *Fluorinated Carbohydrates, Chemical and Biochemical Aspects*, ACS Symposium Series 374, 2.

[3] Filler, R. *Biochemistry Involving Carbon−Fluorine Bonds*, ACS Symposium Series **1976**, *28*, 99.

[4] Ciba Foundation Symposium: *Carbon−Fluorine Compounds: Chemistry, Biochemistry and Biological Activities*; Associated Scientific Publishers: New York, 1972; pp 1−147 .

[5] Taylor, N. F. *Fluorinated Carbohydrates, Chemical and Biochemical Aspects*, ACS Symposium Series 374, ix.

[6] Dwek, R. A. CIBA Symposium, *Carbon−Fluorine Compounds: Chemistry, Biochemistry and Biological Activities*; Associated Scientific Publishers: Amsterdam, 1972; pp 239−271.

[7] Taylor, N. F.; Childs, R. F.; Brunt, R. V. *Chem. Ind.* **1964**, 1802.

[8] Foster, A. B.; Hems, R.; Webber, J. M. *Carbohydr. Res.* **1967**, *5*, 292.

[9] Moissan, H. *Le Fluorine et ses Composes*; G. Steinheil: Paris, 1900; p 244.

[10] Willis, C. J. *Coord. Chem. Rev.* **1988**, *88*, 135.

[11] Huang, H. N.; Lagow, R. J. *Bull. Soc. Chem. Fr.* **1986**, *6*, 993.

10.1021/jo9907033 CCC: $18.00

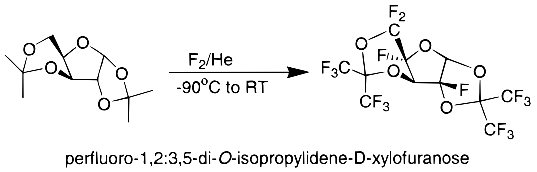

Figure 1. Fluorination of 1,2:3,5-di-O-isopropylidene-D-xylofuranose.

fluorine gas in the system was swept out with helium. The volatiles were collected into an acetone/dry ice trap. This liquid was vacuum distilled into 0, −15, −30, and −196 °C traps. Further purification of the −15 °C fraction that contained the desired product was performed by preparatory GC (15% OV-210 column, Chromosorb A 60/80, 10 ft × 0.25 in., stainless steel column, isothermal oven 100 °C, 45 mL/min flow rate of helium). The retention time was about 9.6 min. The yield was 20%. Fluorine gas was technical grade from Air Products and Chemicals. NaF powder was obtained from Fisher Scientific Company. Helium was from the Physics Department, University of Texas at Austin. Starting material and solvents were purchased from Aldrich Chemical Co. and used as received. ^{19}F NMR spectra were taken from Nicolet NT-200 or NT-360 spectrometers at ambient temperature. Samples were sealed in a coaxial tube with external Freon 11 (fluorotrichloromethane) and *d*-chloroform or *d*-acetone as references. Chemical shifts are reported in ppm upfield from CFC1$_3$. The infrared spectrum was taken from a gas cell sealed with NaC1 or KBr windows.

Results and Discussion

Perfluoro-1,2:3,5-di-*O*-isopropylidene-D-xylofuranose (Figure 1) was characterized using mass spectroscopy, ^{19}F NMR, elemental analysis, and infrared spectroscopy. Assignments of ^{19}F NMR were not possible without two-dimensional COSY work. The IR spectrum exhibited bands at 1302 (vs), 1262 (vs), 1204 (s), 1172 (s), 1117 (s), 994.5 (w), and 737.5 (w) cm^{-1}. Elemental analysis calcd: C, 23.84; F, 61.72, Found: C, 23.57; F, 61.74. MS (EI) *m/e* 485 (m − CF$_e$)$^+$; (CI) *m/e* 554 (parent)$^-$, 384 (m − C$_3$F$_6$O)$^-$, 222 (m − C$_6$F$_{12}$O$_2$)$^-$. ^{19}F NMR (CFC1$_3$, ppm) δ −80.65 (m, ~3F), −82.20 (m, ~3F), −83.10 (m, ~6F), 87.6 (doublet of pentet, J_{ij} = 150.6 Hz), −88.25 (s, ~1F), −128.25 (q, ~1F), −133.30 (s, ~1F), −134.05 (hextet, ~1F).

There are four tertiary fluorines, or chiral carbons, around the middle five-membered ring. The F−F geminal couplings of three-membered rings have been reported around 150−190 Hz,[12−14] four-membered rings about 180−230 Hz,[15] five-membered rings 230−270 Hz,[16] six-membered rings 280−305 Hz,[17−19] and seven-membered ring as 240 Hz.[20]

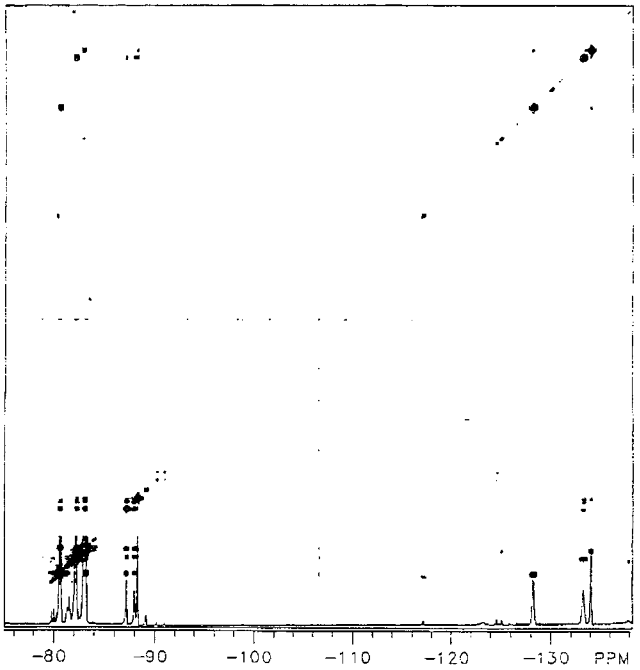

Figure 2. Two-dimensional ^{19}F spectrum of perfluoro-1,2:3,5-di-*O*-isopropylidene-D-xylofuranose.

The two-dimensional ^{19}F COSY (Figure 2) study of this molecule shows very complicated couplings as expected because fluorines not only couple through chemical bonds but also through space.[21] Ng and Sederholm[22] have suggested that F−F coupling operates by both "through bonds" and "through space" mechanisms. The major F−F coupling mechanism proceeds through the bonds and not through space. For *geminal* coupling constants both mechanisms are thought to be important; for *vicinal* coupling the through bond term is considered to be dominant. For coupling between nuclei separated by more than three bonds the spatial mechanism is invoked to explain the coupling. The chemical shifts assignments were based on symmetry, couplings, and integrations. The trifluoromethyl groups, (CF$_3$)$_a$ and (CF$_3$)$_b$, have more similar chemical environments than those of (CF$_3$)$_g$ and (CF$_3$)$_h$. The molecule does not show any fluxionality in the ^{19}F NMR time scale at ambient temperature, so F$_i$ and F$_j$ should have strong geminal couplings. Vicinal couplings are generally much weaker than geminal couplings in the case of fluorines. The resonance at −80.65 ppm couples with part of the resonance at −83.10 ppm, and hence they are assigned as (CF$_3$)$_g$ and (CF$_3$)$_h$. The resonance at −82.20 ppm couples with part of the resonance at −83.10 ppm, and hence they are assigned as (CF$_3$)$_a$ and (CF$_3$)$_b$. The resonance at −87.6 ppm (d, J_{ij} = 150.6 Hz), part of the resonance at −82.20 ppm, and part of the −83.10 ppm are F$_i$ and F$_j$, because the other doublet (F$_i$ or F$_j$) falls under resonances of −82.20 and −83.10 ppm. The resonance at −88.25 ppm is F$_e$, because it has the most unique chemical environment among all

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(12) Williamson, K. L.; Braman, B. A. *J. Am. Chem. Soc.* **1963**, *89*, 6183.

(13) Barlow, M. G.; Fields, R.; Temme, F. P. *Chem. Commun.* **1968**, 1671.

(14) Phillips, W. D. *J. Chem. Phys.* **1956**, *25*, 949.

(15) (a) Harris, R. K.; Ditchfield, R. *Spectrochim. Acta* **1968**, *24A*, 2089. (b) Harris, R. K.; Robinson, V. J. *J. Magn. Reson.* **1969**, *1*, 362. (c) Harris, R. K.; Gazzard, V. J. *Org. Magn. Reson.* **1971**, *3*, 495. (d) Newmark, R. A.; Apai, G. R.; Michael, R. O. *J. Magn. Reson.* **1969**, *1*, 418. (e) Park, J. D.; Michael, R. O.; Newmark, R. A. *J. Am. Chem. Soc.* **1969**, *91*, 5933. (f) Phillips, W. D. *J. Chem. Phys.* **1956**, *25*, 949. (g) Lambert, J. B.; Roberts, J. D. *J. Am. Chem. Soc.* **1965**, *87*, 3884.

(16) (a) Fields, R.; Green, M.; Harrison, T.; Haszeldine, R. N.; Jones, A.; Lever, A. B. P. *J. Chem. Soc. A* **1970**, 49. (b) Piccardi, P.; Modena, M.; Cavalli, L. *J. Chem. Soc. C* **1971**, 3959. (c) Piccardi, P.; Modena, M. *Chem. Commun.* **1971**, 1041.

(17) Tiers, *Proc. Chem. Soc.* **1960**, 389.

(18) Feeney, J.; Sutcliffe, L. H. *J. Chem. Soc., Faraday Trans.* **1960**, *56*, 1559.

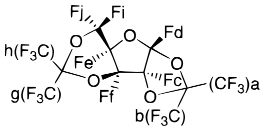
(19) Peake, A.; Thomas, L. F. *J. Chem. Soc., Faraday Trans.* **1966**, *62*, 2980.

(20) Noe, E. A.; Roberts, J. D. *J. Am. Chem. Soc.* **1965**, *93*, 7261.

(21) Emsley, W.; Feeney, J.; Sutcliffe, L. H. *High-Resolution Nuclear Magnetic Resonance Spectroscopy*; Pergamon Press Ltd. 1966; Vol. 2, Chapter 11.

(22) Ng, S.; Sederholm, C. H. *J. Chem. Phys.* **1964**, *40*, 2090.

Table 2. ^{19}F NMR Chemical Shift Assignmnts of Perfluoro-1,2:3,5-di-*O*-isopropylidene-D-xylofuranose



^{19}F NMR (δ CFCl$_3$, ppm)	
−80.65	m, ∼3F
−82.20	m, ∼3F
−83.0	m, ∼6F
−87.6	doublet of pentet, J_{ij}=150.6 Hz
−88.25	s, ∼1F
−128.25	quartet, ∼1F
−133.30	s, ∼1F
−134.05	hextet, ∼1F

	assignments
$(CF_3)_g$ and $(CF_3)_h$	−80.65 ppm and part of −83.10 ppm
$(CF_3)_a$ and $(CF_3)_b$	−82.20 ppm and part of −83.10 ppm
Fi and F_j	−87.6 ppm (d, J_{ij} = 150.6 Hz) and part of −82.20 ppm and part of −83.10 ppm
F_d	−88.25 ppm
F_c	−128.25 ppm
F_e	−133.30 pmm
F_f	−134.05 ppm

tertiary fluorines (F_c, F_e, and F_f). The resonances at −128.25, −133.30, and −134.05 ppm are F_c, F_e, and F_f, respectively. The tertiary fluorine F_f couples with F_e, F_c, and F_d and one of $(CF_3)_g$ and $(CF_3)_h$ at −83.10 ppm. The tertiary fluorine F_e couples with F_d, one of F_i and F_j at −87.6 ppm, and one of $(CF_3)_a$ and $(CF_3)_b$ at −82.20 ppm. The tertiary fluorine F_c also couples with one of $(CF_3)_g$ and $(CF_3)_h$ at −80.65 ppm. The unique tertiary fluorine F_d couples with one of F_i and F_j, that is under the resonances of −82.20 and −83.10 ppm. See Table 2 for fluorine atom labeling schemes. All spectral integrations match well with the structure.

The ketal protection groups were required because perfluorinated alcohols or alkoxides are known, with the exception of those missing α-fluorine,[23] to be highly dissociated or to undergo competing side reactions[24] at the temperature required for reaction. The main difficulty of this sugar fluorination lies in the susceptibility of the ketal linkage toward attacks by hydrogen fluoride.

Although fluorine reacts with organic molecules through free radical mechanisms,[25] it is demonstrated here that retention of absolute configuration with reasonable yield is possible using LaMar direct fluorination. Rearrangement of structures during the fluorination process using elemental fluorine has been reported by Huang[26] and Lin.[27] It is postulated, in both cases, that carbon skeletal rearrangements occurred in order to achieve more stable, radical intermediates. It is also possible that rearrangements occurred in order to release structural strains. The sugar structure studied here does not contain *tert*-butyl or *iso*-propyl groups so the relative probability of skeletal rearrangements is small. Also its structure contains rigid, fused five- and six-membered rings, so the probability of skeletal rearrangements is again smaller than those of branched chains. Although skeletal rearrangements of tertiary fluorines are likely to happen, the separation of isomers of perfluoro molecules has been successfully demonstrated by Lin and Lagow[28] using gas chromatography with appropriate stationary phases. The LaMar direct fluorination technique product has only one major component, and attempts to locate possible isomers using gas chromatography were not successful. Current analysis of two-dimensional COSY ^{19}F NMR and chemical shift assignments match well with the proposed structure.

The successful synthesis of the perfluoro-1,2:3,5-di-*O*-isopropylidene-D-xylofuranose shown in this work opens a possibility that we may find a general route for the preparation of perfluoro carbohydrates with possible retention of their absolute structures.

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[23] For example, perfluoro-*tert*-butyl alcohol.

[24] Chambers, R. D. *Fluorine in Organic Chemistry*; Wiley-Interscience: New York. 1974.

[25] Florin, R. E.; Wall, L. A. *J. Chem. Phys.* **1972**, *57*, 1791.

[26] Huang, H.-N.; Persico, D. F.; Lagow, R. J. *J. Org. Chem.* **1988**, *53*, 78.

[27] Lin, W. H.; Clark, W. D.; Lagow, R. J. *J. Org. Chem.* **1990**, *54*, 989.

[28] Lin, T. Y.; Lagow, R. J. *J. Chem. Soc.* **1991**, 12.