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THE SYNTHESIS OF HIGHLY FLUORINATED ALKYLCYCLOHEXANES FOR USE AS OXYGEN CARRIERS AND THE ^{19}F AND ^{13}C NMR SPECTRA OF ALKYLCYCLOHEXANES

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SUMMARY

Perfluoroalkylcyclohexanes are promising candidates for oxygen carriers. The perfluoroalkylcyclohexane analogues and 1H-perfluoroalkylcyclohexanes of n-propylcyclohexane, i-propylcyclohexane, n-butylcyclohexane, s-butylcyclohexane, i-butylcyclohexane and t-butylcyclohexane were prepared and characterized. Their properties and NMR spectra are discussed.

INTRODUCTION

There is current interest in fluorocarbons as synthetic blood substitutes. As a satisfactory candidate, the perfluorocarbon-based emulsion must be non-toxic, chemically inert, biologically compatible, and have high oxygen-dissolving capacity, long-term stability as well as short dwelling time [1]. Highly branched molecules and cyclic compounds are expected to create more intermolecular "holes" in their liquid structures which could accommodate greater amounts of oxygen. Furthermore, branched molecules tend to form more stable water emulsions than unbranched ones [2]. Therefore, we were interested in the fluorination of branched alkylcyclohexanes Fig.1). The corresponding perfluorocarbons and 1H-perfluoroalkylcyclohexanes were isolated and characterized.

Highly branched hydrocarbons are more difficult than linear hydrocarbons to fluorinate because they are sterically crowded and vibrational relaxation from the energy released is slower. There is usually

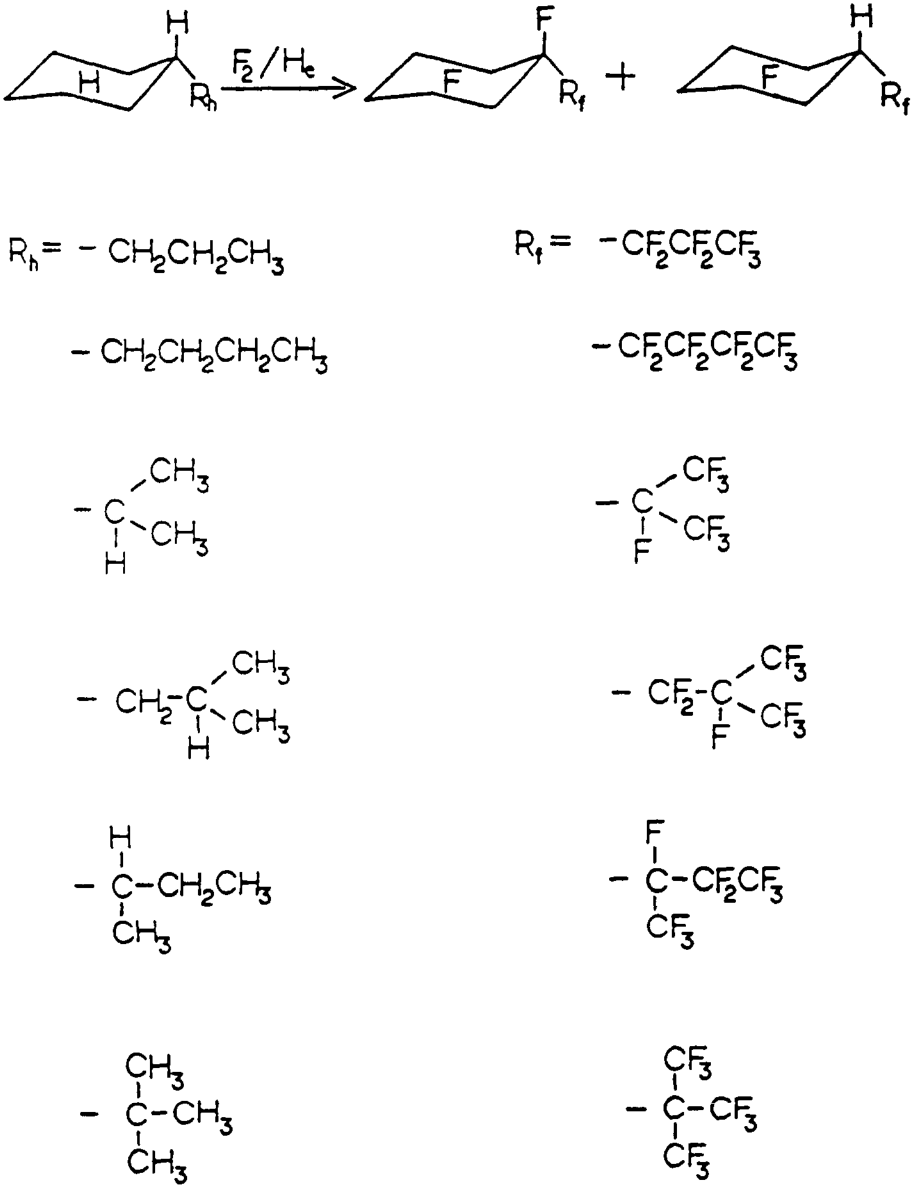


Fig.1. Fluorination of alkylcyclohexanes.

much fragmentation and rearrangement during the high-temperature cobalt trifluoride fluorination of branched molecules. Low-temperature direct fluorination technique allows good control of the exothermic reaction, and has found extensive use in fluorinating branched organic materials. Neopentane, 2,2,4,4-tetramethylpentane, 2,2,5,5-tetramethylhexane were previously fluorinated to give the fluorocarbon analogues [3-6].

Many saturated fluorocarbons have been prepared from aliphatic and aromatic hydrocarbons by fluorination with CoF_3 [7-9]. A series of perfluorinated fused ring compounds were obtained from the reaction of AgF_2 with aromatic hydrocarbons [10]. Gas-phase reaction of anthracene and decalin with elemental fluorine in the presence of gold or silver at elevated temperatures gave the corresponding fluorinated polynuclear saturated ring systems.

The fluorination of bicyclic ring compounds has been studied. CoF_3 fluorination of bicyclo[2.2.1]heptadiene gave a little perfluorobicyclo-[2.2.1]heptane and a 5.9% yield of 1H-undecafluorobicyclo[2.2.1]heptane [11]. The reaction of bicyclo[2.2.1]heptadiene and bicyclo[2.2.1]heptane with F_2 provided perfluorobicyclo[2.2.1]heptane as a predominant product in higher yield [12]. Upon direct fluorination, bicyclo[2.2.2]octane gave perfluorobicyclo[2.2.2]octane in a yield of 3.5% [6]. Using partially fluorinated functional bicyclo[2.2.2]oct-5-ene as a starting material, perfluorobicyclo[2.2.2]octane and 1H-tridecafluorobicyclo[2.2.2]octane were obtained in good yields by CoF_3 fluorination [12]. The bridgehead proton in this bicyclic system was found most difficult to fluorinate.

The electrolytic fluorination of nonfunctional hydrocarbons necessitates the addition of conductivity additives and usually produces fluorocarbons in poor yields. Attempts have been made to raise yields by introducing the CF_2 group into the molecule prior to the fluorination [13].

The reactions of saturated fluorocarbons have been reported. Perfluorobicyclohexyl undergoes homolysis with toluene, chlorine and bromine at 600-650 °C [8]. Similar reactions involving perfluoro-n-alkanes require temperature of 800-950 °C [14,15]. Hexafluoroethane reacts with chlorine or bromine at 900 °C to give chloro- and bromo- trifluoromethane, respectively.

EXPERIMENTAL

Material Source

i-propylcyclohexane	Pfaltz & Bauer, Inc.
n-propylcyclohexane	Alfa Products
n-butylcyclohexane	Aldrich Chemical Co., Inc.
i-butylcyclohexane	Alfa Products
s-butylcyclohexane	K & K Laboratories
t-butylcyclohexane	Pfaltz & Bauer, Inc.

General Fluorination

A mixture of 1 g of alkylcyclohexane and 2.5 g of powdered NaF was fluorinated in the bucket reactor. The initial temperature was controlled between -100 and -130 °C, depending on the melting points of starting substrates. All reactions were ended at 50 °C. Detailed fluorination parameters are given in Table 1. Volatile products were collected in the glass trap cooled to -78 °C. Separation was performed on a Bendix 2300 gas chromatograph equipped with a 10% Fomblin on Chromosorb P column (3/8" x 24"). Reaction yields are given in Table 2.

Perfluoroalkylcyclohexanes and 1H-perfluoroalkylcyclohexanes were identified from their nuclear magnetic resonance spectra (Tables 3, 4 and 5) and mass spectrometric information. The mass spectra showed the characteristic peak of parent ion minus one fluorine and a base peak at m/e 69 (CF_3+). The common prominent peaks observed in the spectra of perfluoroalkylcyclohexanes were m/e 331 ($C_7F_{13}+$), 281 ($C_6F_{11}+$), 243 (C_6F_9+), 231 (C_5F_9+), 219 (C_4F_9+), 181 (C_4F_7+), 131 (C_3F_5+), 119 (C_2F_5+), 100 (C_2F_4+), and the common important peaks observed on the spectra of 1H-perfluoroalkylcyclohexanes were m/e 332 ($C_7F_{13}H+$), 263 ($C_6F_{10}H+$), 243 (C_6F_9+), 225 (C_6F_8H+), 181 (C_4F_7+), 163 (C_4F_6H+), 131 (C_3F_5+), 119 (C_2F_5+), 113 (C_3F_4H+), 100 (C_2F_4+). Monohydryl fluorocarbons were also confirmed by elemental analysis (see Table 6).

RESULTS AND DISCUSSION

For the fluorination of saturated hydrocarbons, the direct fluorination technique is more effective than the cobalt trifluoride

TABLE 1

(I) Reaction Conditions for i-propyl, n-propyl, i-butylcyclohexane

Time (day)	He (cc/min)	F_2 (cc/min)	Temp. (°C)
0.5	20	1.0	-110
0.5	20	2.0	-110
0.5	20	2.0	-80
0.5	10	3.0	-80
0.5	0	1.0	-80
0.5	0	2.0	-80
1.0	0	2.0	25
1.0	0	2.0	50

(II) Reaction Conditions for n-butyl, t-butylcyclohexane

Time (day)	He (cc/min)	F_2 (cc/min)	Temp. (°C)
0.5	20	1.0	-100
0.5	20	2.0	-100
0.5	20	2.0	-80
0.5	10	3.0	-80
0.5	0	1.0	-80
0.5	0	2.0	-80
1.0	0	2.0	25
1.0	0	2.0	50

(III) Reaction Conditions for s-butylcyclohexane

Time (day)	He (cc/min)	F_2 (cc/min)	Temp. (°C)
0.5	20	1.5	-130
0.5	20	2.5	-130
0.5	20	2.5	-100
0.5	20	2.5	-80
0.5	10	3.0	-80
0.5	0	1.0	-80
0.5	0	2.0	-80
1.0	0	2.0	25
1.0	0	2.0	50

TABLE 2
Reaction yields from fluorinations [20]

Compound	Perfluorocarbons	1H-polyfluorocarbons
n-propylcyclohexane	37.20%	11.64%
i-propylcyclohexane	34.35%	8.34%
n-butylcyclohexane	35.05%	2.49%
s-butylcyclohexane	33.00%	17.10%
i-butylcyclohexane	27.60%	15.30%
t-butylcyclohexane	41.40%	7.35%

method. An additional advantage to this technique is the ability to maintain the branched carbon skeleton. It is believed that many other saturated fluorocarbons can be prepared in this manner.

The isolation of 1H-perfluoroalkylcyclohexane as the only monohydro product reflected the electropositive nature and the sterically crowded nature of the tertiary C-H bond at the C-1 position which is the most difficult to replace. A higher temperature is required to cause substitution of this tertiary hydrogen or alternatively the proton may be replaced in a second reaction step in a fluorocarbon solvent. The monohydryl perfluoroalkylcyclohexanes isolated in this experiment have not been reported before.

The remaining hydrogen in 1H-perfluoroalkylcyclohexane is fairly acidic. The most important general reaction of polyfluorocycloalkanes found has been the dehydrofluorination to give fluorocycloalkenes, which can be converted to a range of derivatives [16,17]. The reaction chemistry of the monohydrofluorocarbons are of future interest.

Table 7 shows the physical properties of fluorinated isomeric butylcyclohexanes. As one would expect, perfluoroalkylcyclohexanes have higher melting points and lower boiling points than the parent hydrocarbons. The boiling point of 1H-perfluoroalkylcyclohexane is lower than that of the corresponding perfluoroalkylcyclohexane which is somewhat unusual.

TABLE 3

Fluorine NMR data of perfluoroalkylcyclohexanes

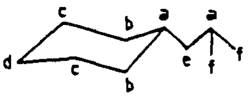
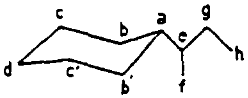
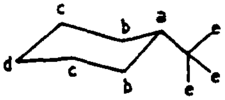
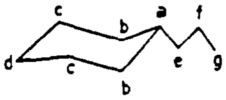
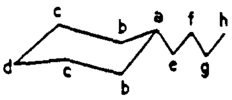
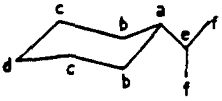
Compound	Chemical Shift (ppm)
	- 74.0 (f) - 105.0 (e) - 184.6 (a) - 117.3 (b, ax), - 122.2 (b, eq) - 125.6 (c, ax), - 147.0 (c, eq) - 126.5 (d, ax), - 143.9 (d, eq)
	- 71.3 (f) - 81.8 (h) - 116.0 (g) - 179.3 (e) - 180.0 (a)
	- 58.9 (e) - 177.7 (a) - 113.9 (b, ax), - 124.7 (b, eq) - 122.9 (c, ax), - 138.4 (c, eq) - 125.8 (d, ax), - 143.8 (d, eq)
	- 82.5 (g) - 113.8 (e) - 127.0 (f) - 186.8 (a) - 119.6 (b, ax), - 130.8 (b, eq) - 123.2 (c, ax), - 141.3 (c, eq) - 125.4 (d, ax), - 144.8 (d, eq)
	- 83.4 (h) - 112.3 (e) - 122.3 (f) - 126.0 (g) - 186.0 (a) - 120.1 (b, ax), - 131.1 (b, eq) - 123.7 (c, ax), - 141.7 (c, eq) - 125.5 (d, ax), - 144.4 (d, eq)
	- 72.9 (f) - 182.6 (e) - 183.3 (a) - 117.9 (b, ax), - 130.3 (b, eq) - 124.0 (c, ax), - 141.3 (c, eq) - 126.5 (d, ax), - 144.8 (d, eq)

TABLE 4

NMR data of 1H-perfluoroalkylcyclohexanes

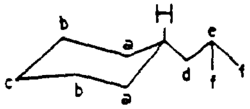
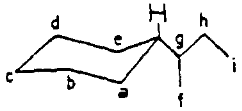
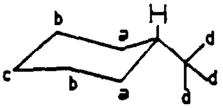
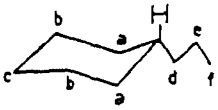
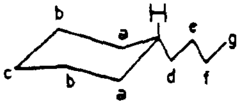
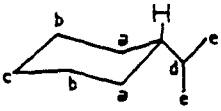
Compound	Chemical Shift (ppm)
	- 74.5 (f) - 103.4 (d) - 184.5 (e) - 117.3 (a, ax), - 122.2 (a, eq) - 125.6 (b, ax), - 147.0 (b. eq) - 126.5 (c, ax), - 143.9 (c, eq) H—3.7 septet: triplet (23.1 Hz) of triplet (11.6 Hz)
	- 73.4 (f) - 81.5 (i) - 116.3 (h) - 179.0 (g) H—3.7 triplet (J = 25.3 Hz)
	- 61.0 (d) - 112.4 (a. ax), - 116.1 (a, eq) - 124.3 (b, ax), - 144.3 (b, eq) - 126.7 (c, ax), - 143.2 (c, eq) H—3.6 triplet (J = 23.4 Hz)
	- 82.4 (f) - 113.3 (d) - 128.6 (e) - 119.6 (a. ax), - 130.8 (a, eq) - 123.2 (b, ax), - 141.3 (b, eq) - 125.4 (c. ax), - 143.8 (c, eq) H—3.5 multiplet
	- 82.8 (g) - 110.0 (d) - 124.3 (e) - 127.0 (f) - 117.8 (a. ax), - 122.0 (a, eq) - 125.7 (b. ax), - 146.9 (b, eq) - 126.8 (c, ax), - 144.3 (c, eq) H—3.6 multiplet
	- 76.3 (e) - 177.1 (d) - 115.7 (a, ax), - 120.8 (a, eq) - 126.1 (b, ax), - 147.3 (b, eq) - 127.6 (c, ax), - 144.7 (c, eq) H—3.6 triplet (J = 24.0 Hz)

TABLE 5

Comparison of ^{13}C NMR of fluoroalkylcyclohexanes and hydrocarbon alkylcyclohexanes

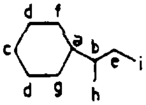
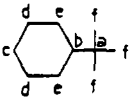
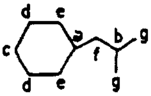
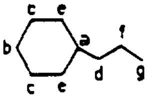
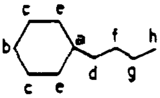
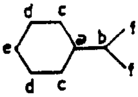
Compound	Atom	δ_C in F.C. (ppm)	δ_C in H.C. (ppm)	Δ (ppm)
	a	94.0	40.1	53.9
	b	96.8	42.8	54.0
	c	107.6	26.9	80.7
	d	108.6	27.2	81.4
	e	110.5	27.2	83.3
	f	111.1	29.1	82.0
	g	111.6	31.1	80.5
	h	118.4	15.7	102.7
	i	119.5	12.0	107.5
	a	68.2	32.6	35.6
	b	95.2	48.6	46.6
	c	107.1	26.9	80.2
	d	108.9	27.8	81.1
	e	111.5	27.8	83.7
	f	120.6	27.6	93.0
	a	91.6	35.6	56.0
	b	92.6	25.0	67.6
	c	107.8	27.0	80.8
	d	108.6	26.7	81.9
	e	110.7	34.0	76.6
	f	117.1	47.4	69.7
	g	119.5	23.0	96.5
	a	90.0	40.2	49.8
	b	107.6	27.1	80.5
	c	108.4	26.7	81.7
	d	109.3	37.7	71.6
	e	110.5	33.7	76.8
	f	114.0	20.1	93.9
	g	117.5	14.4	103.1
	a	90.0	38.1	51.9
	b	107.6	27.1	80.5
	c	108.4	26.7	81.7
	d	109.5	37.6	71.9
	e	110.6	33.8	76.8
	f	111.1	29.4	81.7
	g	114.5	23.3	91.2
	h	117.9	14.2	103.7
	a	94.1	44.4	49.7
	b	94.1	33.2	60.9
	c	110.7	30.1	80.6
	d	107.6	27.0	80.6
	e	108.6	27.0	81.6
	f	119.5	19.7	99.8

TABLE 6

Elemental analysis for monohydryl fluorocarbons

Compound	Calculated (%)	Found (%)
1H-heptadecafluoro n-propylcyclohexane	C: 25.02 F: 74.75 H: 0.23	C: 25.02 F: 74.94 H: 0.39
1H-heptadecafluoro i-propylcyclohexane	C: 25.02 F: 74.75 H: 0.23	C: 24.92 F: 75.15 H: 0.41
1H-nonadecafluoro n-butylcyclohexane	C: 24.91 F: 74.88 H: 0.21	C: 24.89 F: 74.54 H: 0.27
1H-nonadecafluoro s-butylcyclohexane	C: 24.91 F: 74.88 H: 0.21	C: 24.83 F: 75.04 H: 0.28
1H-nonadecafluoro t-butylcyclohexane	C: 24.91 F: 74.88 H: 0.21	C: 24.81 F: 75.05 H: 0.23

TABLE 7

Physical properties of fluorinated isomeric butylcyclohexanes

COMPOUND	*BOILING POINT (°C)			*MELTING POINT (°C)		
	HC	FC	1H-FC	HC	FC	1H-FC
t-butylcyclohexane	171.5	148.5	144.5	-41.2	-24	-37
s-butylcyclohexane	179.3	143.6	140.0	-110	<-110	<-116
i-butylcyclohexane	171.3	141.5	136.0	-94.8	-15.5	-25
n-butylcyclohexane	177.0	147.0	142.0	-79	-41	-60

* HC: hydrocarbon FC: perfluorocarbon

1H-FC: 1H-perfluorocarbon

Perfluoroalkylcyclohexanes have a preference for a chair conformation at room temperature, with the alkyl substitute occupying an equatorial position. Basically, a rigid conformer gives rise to three different pairs of nonequivalent geminal fluorine nuclei. Each pair of fluorines interact with each other and form an AB quartet pattern. Assignment of chemical shifts to ring fluorines was based on the assumption that axial fluorines were less shielded than equatorial fluorines [18]. Perfluoro s-butylcyclohexane gives a complicated spectrum because the s-butyl group is unsymmetric. It should be noted that perfluorocyclohexane undergoes rapid conformational interconversion and gives a single peak at room temperature; the AB pattern is observed at -50 °C and below.

Long-range coupling presumably through space was normally observed. The CF_3 groups of perfluoro t-butylcyclohexane interact with the methylene fluorine at C-2 and C-6 with different coupling constants: 26.3 Hz with equatorial fluorine and 13.5 Hz with axial fluorine. Further coupling with the tertiary methine fluorine gave a triplet of triplets of doublets (Fig.2). The rotation along the C-C bond between the bulky t-butyl group and cyclohexyl ring is highly inhibited, otherwise the CF_3 groups should be coupled equally with axial and equatorial fluorine like perfluoro methylcyclohexane which exhibits a quartet of doublets. The complexity of the CF_3 splitting pattern of perfluoro i-propylcyclohexane (Fig.3) made interpretation difficult.

The proton NMR spectra of 1H-perfluoroalkylcyclohexanes have been obtained as a multiplet, triplet or septet. A triplet resulting from the spin-coupling with two equatorial fluorines at C-2 and C-6, was observed in the cases of 1H-F-t-butylcyclohexane, 1H-F-s-butylcyclohexane, and 1H-F-i-propylcyclohexane. The spectrum of 1H-F-i-butylcyclohexane was a combination of a triplet of triplets which gave the appearance of a septet due to the coupling with equatorial fluorine and α-fluorine of the side-chain group. 1H-F-n-Butylcyclohexane and 1H-F-n-propylcyclohexane showed a multiplet arising from spin interaction with α- and β- CF_2 groups of the alkyl group as well as the nearest equatorial fluorines. The average chemical shift was 3.6 ppm.

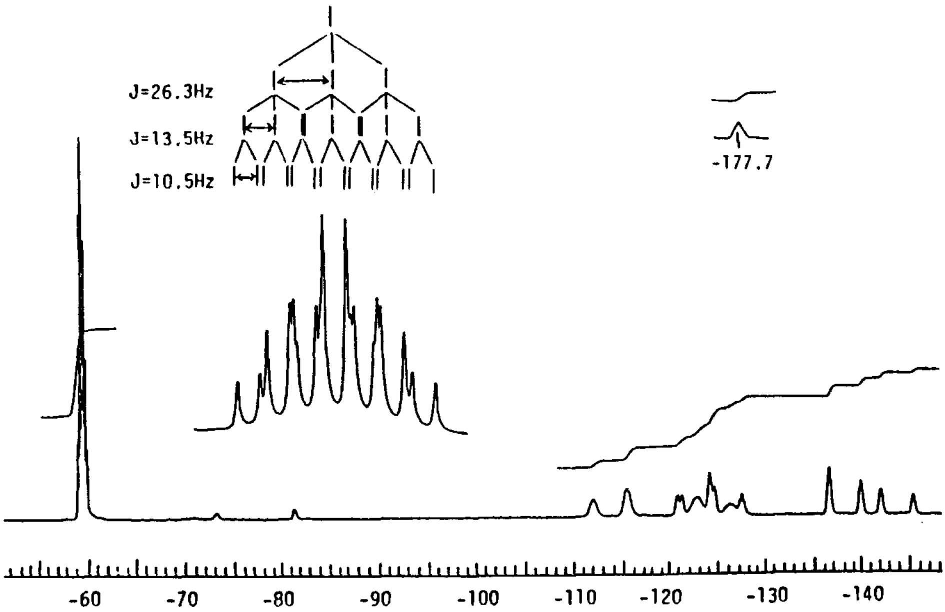


Fig.2. ^{19}F NMR spectrum of perfluoro t-butylcyclohexane.

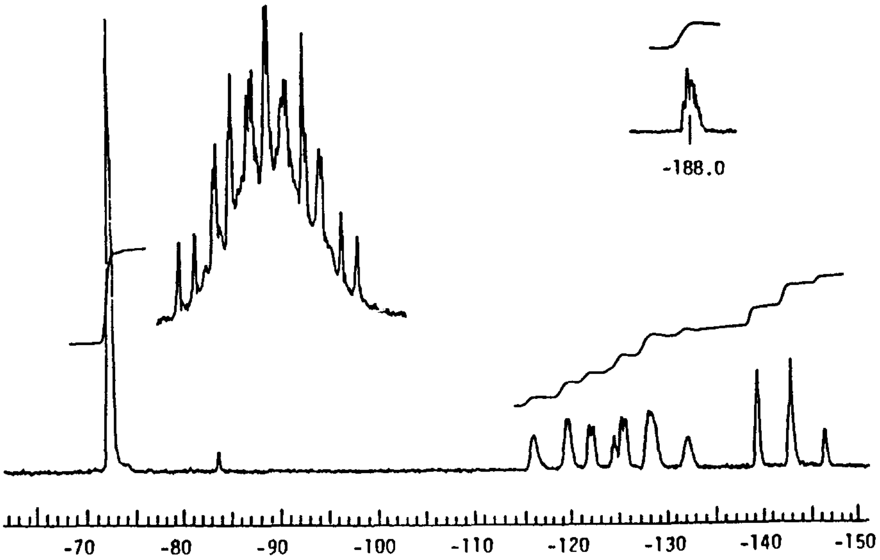


Fig.3. ^{19}F NMR spectrum of perfluoro i-propylcyclohexane.

The carbon chemical shifts of perfluorinated alkylcyclohexanes are compared with those of hydrocarbon analogues in Table 4. It appears that substitution of fluorines for hydrogens has least effect on the quaternary carbon. The carbon resonances of perfluorocarbons shift to much lower fields as compared with hydrocarbons due to the great electronegativities of fluorine nuclei. The shielding of the carbon atom depends on the number of fluorine atoms attached to it. The quaternary carbon with no surrounding fluorines has a resonance at the highest field. In general, the shielding of the carbon follows the order: 4° > 3° > 2° > 1°. This trend is opposite from that observed in hydrocarbons.

The oxygen solubility and physiological studies on animals for each of these compounds will be reported elsewhere [19].

ACKNOWLEDGEMENT

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