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ON THE ELECTROCHEMICAL FLUORINATION OF AMINOETHERS TO GIVE PERFLUOROAMINOETHERS: POSSIBLE CANDIDATES FOR BLOOD SUBSTITUTES

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SUMMARY

Aminoethers, $ROC_2H_4\overline{NCH_2CH_2OCH_2CH_2}$ (R = C_6H_5, C_6F_5, C_2H_5), $C_6F_5OC_2H_4N[CH_2]_5$, were electrofluorinated in anhydrous hydrogen fluoride, the corresponding saturated perfluoroaminoethers being the largest individual substances in each case. One of them, F-[4-(2-cyclohexyloxyethyl)morpholine], has promising properties as a blood substitute.

INTRODUCTION

In developing blood substitutes we are interested in perfluoro compounds whose molecules include oxygen atoms and cyclic structures. These structural elements should increase emulsion stability as well as excretion rate of the respective perfluoro compounds [1]. Moore et al. have demonstrated that a route to such compounds is the electrochemical fluorination (ECF) of aminoethers, which mostly proceeds smoothly and gives moderate or good yields [2]. In general, it is supposed that

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by using fluorinated starting compounds the ECF yield will be improved. This is supported by, e.g., the findings of Sander and Blöchl [3], who studied the ECF of alkanes, and corresponds also with the results of the ECF of aminoethers having fluorinated alkyl groups [4]. Likewise, ECF of N,N-dimethylpentafluoroaniline gave a higher yield than that of its H-analogue [5]. But fluorinated starting compounds are not in every case advantageous for ECF. Thus, e.g., the ECF results for 1-dipropylamino-F-1-propene and 1-dipropylamino-2-hydryl-F-propane were quite similar to that for tripropylamine [6], and there are even partially fluorinated trialkylamines which yield no perfluorotrialkylamines [7, 8]. Knowing all these results it was interesting to see whether ECF of such types of aminoethers we are interested in could be improved by using fluoroaromatic starting compounds, and whether the corresponding perfluorinated aminoethers are suitable candidates for blood substitutes.

RESULTS AND DISCUSSION

The compounds submitted to ECF and the results of these experiments are shown in Tables 1 and 2. In general, ECF of the aminoethers results in 3 groups of products, namely crude liquid perfluorocarbon materials, gaseous fluorinated cleavage products, and partially fluorinated HF-soluble products. This corresponds well with results for trialkylamines [7]. Another similarity to trialkylamines exists in that the starting compounds disappear rapidly as electrolysis proceeds [8]. This can be seen in case of compounds 1 and 3 by the decrease of the ^{19}F-NMR signals of the perfluoroaromatic ring. Fig. 1 shows that compound 1 was not further detectable in the HF solution after 30 % of the theoretically needed amount of current has been passed through the cell. During this time no perfluorinated products were formed, other than gaseous cleavage products. These observations are inconsistent with a 'zipper-like' mechanism of perfluorination [8].

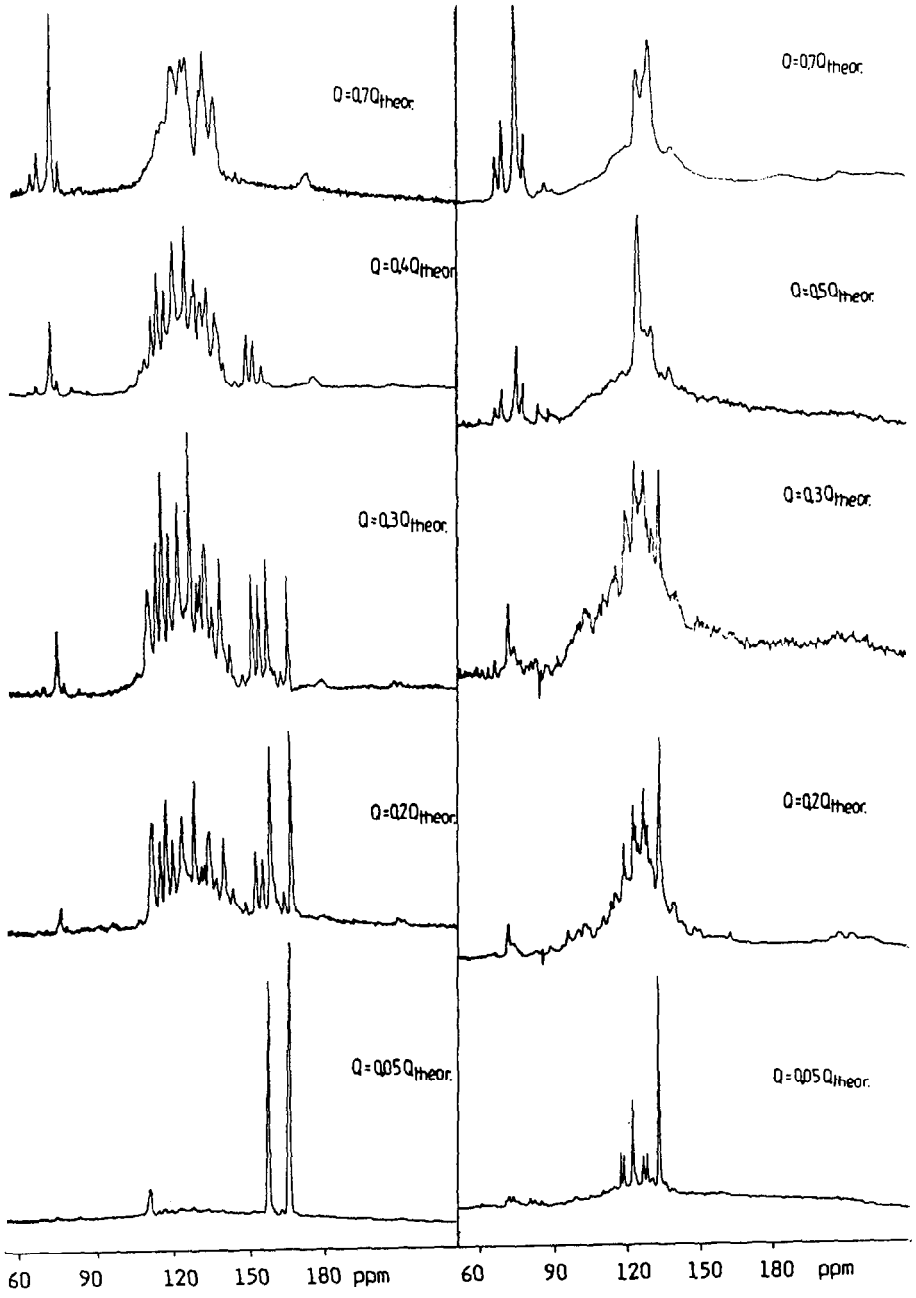
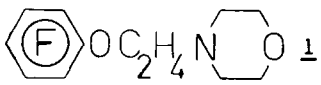
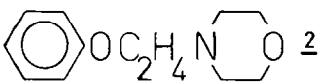
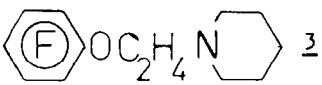
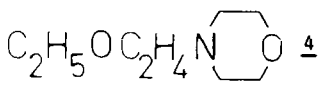


Fig. 1. ^{19}F-NMR spectra of the organics from the HF in the course of ECF. Left: compound 1. Right: compound 2.

TABLE 1

Electrochemical fluorination of aminoethers.
Product distribution among perfluorocarbons (PFC), gaseous fluorination products (gas phase) and partially fluorinated, HF-soluble products (HF-phase)

Aminoether	Average yield [%][a]			Experimental example				
	PFC	gas phase	HF-phase	initial amount [g]	electric current [Ah]; [%][b]	PFC [g][c] [%][d]	gas phase [l]; [ml NF_3][e] [%][f]	HF-phase [g]; [%F][g] [%][h]
 1	25-30	30-45	30-40	38	75.6; 73.5	22.5 28	33; 305 42	21; 64.4 30
 2	5	5-30	60-95	69.4	270; 75	1 0.5	99; 600 8.7	102; 38.4 90.8
 3	40-50	30-40	10-25	63	190; 75	60.5 42.8	77; 435 36	24; 63.4 21.2
 4	20-30	40-65	5-30	62.3	473; 132	48 26.3	175; 2445 64.8	8.4; 36 8.9

a means of at least 3 experiments, yields in mole % of the starting compound

b current applied; also given as percentage of the current theoretically needed for complete perfluorination

c total yield of crude liquid PFC

d mole % of the starting compound; all liquids products taken as 5, 8 or 10, respectively (see Table 2)

e total amount of gases in l (H_2 and others) and total amount of NF_3 in ml

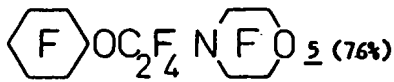
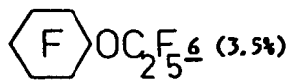
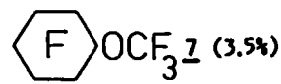
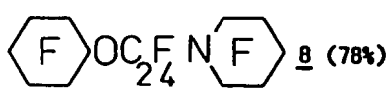
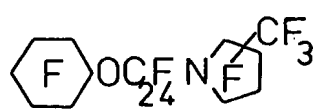
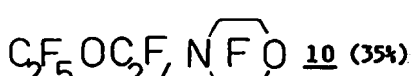
f mole %, this value is the difference between the sum of "d" and "h" and 100 %

g total amount of organic material dissolved in the HF and its relative F-content

h mole %; all compounds were taken as partially fluorinated starting compounds with unchanged C-skeleton

TABLE 2

Liquid perfluorination products from ECF of aminoethers

Aminoether	Perfluoro products (relative amounts according to GLC)
1	 5 (76%)  6 (3.5%)  7 (3.5%)
2	5 (74%)
3	 8 (78%)  9 (15%) 6 (1%) 7 (1%)
4	 10 (35%)

Perfluoroaminoethers

As Table 1 shows, there are differences between the aminoethers tested concerning the respective yields of crude perfluorocarbons. ECF of compound 1 results in good yields of the corresponding perfluoro compound 5 together with the ethers 6 and 7 (Table 2). But, surprisingly, compound 2, which differs from 1 only in having a H-aromatic ring instead of the F-aromatic one, yields very little perfluoroether. Most of the aminoether 2 remains partially fluorinated in the HF. Such a great difference in product yield between the compounds 1 and 2 could not be expected, neither from the results which Plashkin et al. [5] have observed in the aniline system nor from the yields reported by Moore et al. [2] for different aminoethers. Also, the difference cannot be explained by assuming a higher stability of the F-aromatic ring towards C-C-cleavage during ECF. If this is the reason, one should find much more perfluorinated cleavage products, liquid or gaseous ones, during the ECF of compound 2 in comparison with compound 1. But this is not the case. ECF of compound 3 results in a yield of crude perfluorinated products which is even higher than that of compound 1 (~45 % vs. ~30 %). This is obviously due to the piperidino ring in compound 3 (instead of morpholino in 1), but such an increase in yield is not the rule [2]. The result obtained with compound 4 shows that in case of compounds 1 and 3 the fluoroaromatic groups are not absolutely responsible for enhanced yields, but their presence overcomes the difficulties linked with H-aromatic nuclei.

Formation of partially fluorinated compounds

All aminoethers tested yield different amounts of partially fluorinated HF-soluble compounds ('HF-phase'), which remain dissolved in the HF when the formation of crude perfluorinated target products ceases. At that time the amount of gaseous fluorination products, such as NF_3, CF_4, C_2F_6 and (ECF of 1, 2, 4) $C_2F_5OC_2F_5$, increases considerably (up to 10 fold). If, however, new starting compound is added to the cell, the amount of gaseous products immediately decreases. Thus it is obvious that every electrofluorination reaction is linked with the formation of fluorinated gaseous fragments (in fact, they

can be detected soon after beginning an ECF experiment), but these compounds are the dominating or perhaps the only products of the electrofluorination of the "HF-phases". The qualitative composition of the gaseous compounds remains nearly constant throughout the ECF experiment. The compounds forming the HF-phase are obviously by-products. However, the rapid disappearance of the starting compound in the course of ECF (Fig. 1) indicates that real intermediates are formed too, i.e. partially fluorinated compounds which become easily perfluorinated, yielding the crude target product. Which of these 2 types of partially fluorinated compounds are predominantly formed depends on the starting compound. Thus compound 2 yields much more HF-phase than compound 1 or 3, emphasizing the special role of the H-aromatic ring in this respect. In case of compound 4 there are also partially fluorinated by-products formed. Continuing electrolysis consumes these by-products, but then only gaseous cleavage products are formed.

It appears that the nature of the partially fluorinated HF-soluble compounds, formed as intermediates or as by-products during ECF, is the clue to the pathway of the ECF process [7, 8]. These two types of compounds can only differ in their respective distribution of F-atoms within their molecules. The nature of the by-products, the HF-phase, remains unknown, because their complexity makes identification difficult [8]. However, some general conclusions can be drawn from their ^{19}F-NMR spectra, especially from the development of the signals as electrolysis proceeds as exemplified for compound 1 in Fig. 1. A broad, unresolved group of signals in the region from δ ($CFCl_3$) 115 to 140 ppm appears, while the signals of the pentafluorophenyl group disappear. Somewhat later, signals appear at lower field, from 62 to 74 ppm. Likewise, ECF of compound 2 causes the development of the ^{19}F-signals (none due to pentafluorophenyl). The signals at 115 to 140 ppm differ somewhat from those of compound 1, but at the end of the ECF experiment the ^{19}F-spectrum of the HF-phase of compound 2 resembles that of compound 1. The ECF of compound 3 also results in the development of a very broad signal at 112 to 140 ppm which finally looks like that from compound 1, while the fluoroaromatic signals disappear. However, unlike compounds 1,

2 and 4 the HF-phase of compound 3 shows no signals at low field, besides a very small one at 71 ppm. The ^{19}F-NMR spectrum of the HF-phase from compound 4 differs from the others in the low intensity of the signals at 120 to 140 ppm in comparison with the signals at 71 and 74 ppm. There are further small signals at 54, 63, 65 and from 83 to 92 ppm.

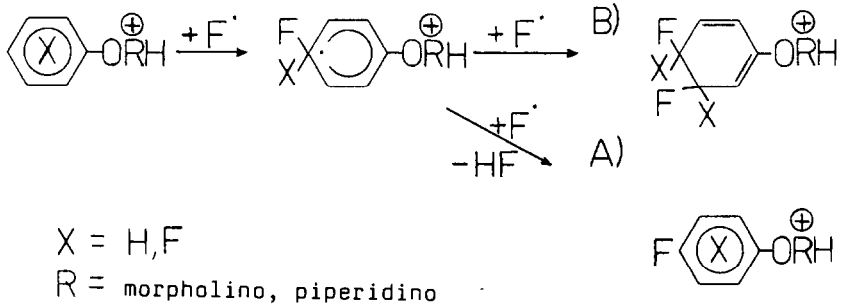
The signals at 62 to 74 ppm of the HF-phases of the compounds 1, 2 and 4 are more likely to arise from $-O-CF_2-CH_2-$ of partially fluorinated morpholines [9] than of the bridging group, since these signals are almost absent in case of compound 3. The dominating signals at 112 to 140 ppm (compounds 1, 2 and 3) can be assigned to $-CF_2-$ of the carbocycle, and also to 2,6-difluoromorpholine [9]. The former is more likely for the following reasons. Firstly, in case of compound 4, where there is no carbocycle at all, such signals are weak. Secondly, these signals occur at the very beginning of the ECF, at the same time as the pentafluorophenyl signals begin to disappear. The pentafluoroaromatic system can only disappear with the formation of CF_2-groups.

The ^{19}F-NMR spectra give no evidence of the presence of compounds bearing a perfluorinated morpholine cycle (HF-phases of compounds 1, 2 and 4), but perfluorocyclohexyl cannot be excluded, since its signals would be in the region from 120 to 140 ppm.

Investigations of dibutylmethylamine ECF have led to the conclusion [8] that compounds bearing the structural element $-CF_2-CH_2-N\langle$, or possibly even $-CF_2-CH_2-$, can be quite resistant to electrochemical perfluorination; the structures either survive or undergo extensive cleavage. On the basis of these results, ECF might come to an end or might be slowed down if within the morpholine cycle the structure $-O-CF_2-CH_2-N$ is formed. The occurrence of such a structure in the HF-phases of the compounds 1, 2 and 4 is very likely, according to their ^{19}F-NMR spectra and corresponding to the literature [9]. But this cannot explain why compound 2 yields much less crude perfluoroether than compound 1 (Table 1). To explain these and other experimental facts a reliable ECF-theory is needed which accounts for the perfluorinated products, including gaseous splitting products, as well as partially fluorinated products.

Unfortunately, the latter have been neglected up to now. However, a low yield of perfluorinated target product is not linked in every case with a high production of gaseous splitting products or of polymerization products. A considerable part of the starting compound can be consumed by the formation of partially fluorinated products, as in case of compound 2.

The NMR-data shown in Fig. 1 suggest that the ECF of compound 1 starts with an attack at the fluoroaromatic ring. Since the positively charged molecules in the vicinity of the anode (even adsorbed to it) are probably predominantly orientated so that the positively charged part of the molecules (e.g. the morpholine ring) is kept away from the anode, the other part of the molecule (e.g. the fluoroaromatic ring) is likely to be fluorinated at first. On the other hand, a radical attack at the molecule, by F· or more likely by F-H-F· radicals, should also preferably start at the aromatic system because of its greater ability to stabilize the new radical formed. Possible reaction pathways for the primary steps of the fluorination of the aromatic rings are given in Scheme 1.



Scheme 1.

In principle, for X = H, both routes are possible, but for X = F only B (Scheme 1). Since in the ECF of compound 2 no pentafluoroaromatic compounds could be detected by ^{19}F-NMR, A is unlikely even for X = H or there is only a partial H-F-exchange followed by way B. Route B (Scheme 1) results in olefines, whose properties should for X = F or X = H considerably differ from each other, obviously also regarding their perfluorination.

F-Aminoethers as candidates for blood substitution

There are different criteria for the selection of perfluorocarbons for blood substitutes. The most important properties are the stability of the PFC-in-water-emulsion and the rate of excretion of the PFC from the living body. PFCs having oxygen atoms and ring structures as part of their molecules are promising candidates for blood substitutes [1]. Besides these criteria it is important that the PFC can easily be produced. Of the aminoethers this paper is concerned with, compound 5, perfluoro[4-(2-cyclohexyloxyethyl)morpholine], fulfils most of the criteria. It has two oxygen atoms and two rings in the molecule, and it can be produced in reasonable yield. Therefore it was thoroughly tested, some results of these tests are:

Toxicity (i.p. in mice): LD_{50} = >56 g/kg
Oxygen solubility: 51.7 % (v/v) at 25 °C
Vapour pressure: 6.1 mmHg at 37 °C
Density: 1.859 g/cm³
Critical solubility temperature (CST in n-hexane): 44.2 °C
Emulsion stability (with surfactant Pluronic F 68 in water): >1 year

Compound 5 is promising for use in blood substitutes.

EXPERIMENTAL

Synthesis of the starting aminoethers

An excess of 1,2-dibromoethane was reacted with phenol (for compound 2), or pentafluorophenol (1 and 3), or ethanol (4), respectively, according to Williamson's ether synthesis. The ether obtained was then reacted with morpholine (compounds 1, 2 or 4) or with piperidine (for compound 3). The respective aminoether was isolated and purified by distillation and its structure confirmed by ^{1}H-NMR and/or ^{19}F-NMR. All were known compounds.

Electrochemical fluorination

The electrofluorination experiments were carried out in a 450 cm³ PTFE cell with nickel anodes (4 dm²) and cathodes at

about 19 °C, 5 - 6.5 V, and 5 - 10 A. The cell was fitted with a reflux condenser, maintained at -20 °C, and with cooling traps to condense volatile products. The fluorination experiments were started with about 10 % concentration of the respective aminoethers, additional portions were added during electrolysis, up to the amount given in Table 1.Liquid, HF insoluble fluorination products ('crude PFCs') were drained off, washed with water and $NaHCO_3$ solution, refluxed for 12 hours with C_2H_5OH/KOH, again washed with water, and distilled off. By this procedure 10 to 30 % of the crude PFC were lost. After a final fractional distillation (100 theoretical plates) the perfluoro products shown in Table 2 were identified by ^{19}F-NMR and/or by MS, or without distillation by GC/MS.

Besides the liquid perfluorination products, the amounts of gaseous fluorination products ('gas phase', Table 1) and of incompletely fluorinated products remaining dissolved in the HF ('HF-phase', Table 1) were also determined. The gases were washed with 5 N KOH, collected and the NF_3 content determined by GC. After electrolysis the amount of remaining HF-phase was determined according to [7] by alkaline treatment of the HF. Total weights and fluorine contents of the isolated organic material were determined.

The yields given in Table 1 are calculated on the basis of simplifying assumptions. PFCs: All the crude products were regarded as the respective perfluorinated target products, and the molar yields were calculated the usual way. HF-phases: The HF-phases were regarded as the respective partially fluorinated aminoether with unchanged carbon skeleton. The mean molar weights (MW_{HF}) were calculated by the relationship

$MW_{HF} = MW \times 100/(100-\%F)$

with MW = molar weight of the starting compound, and %F = difference between the fluorine content of the HF-phase and that of the starting compound. From the total amount and MW_{HF}, the molar yield was calculated.

Analytical investigations

The ^{19}F-NMR spectra were recorded at 57 MHz on a FKS 176/178 spectrometer, on a VARIAN spectrometer at 84.25 MHz, on a VARIAN spectrometer at 282 MHz, or on a BRUKER spectro-

meter at 376 MHz, respectively, in each case with TFA as external reference. The values are given relative to $CFCl_3$ ($\delta_{CFCl_3} = \delta_{TFA} + 76.5$), values upfield to $CFCl_3$ being designated positive.

Gas chromatography was carried out on a CHROMATRON GCHF 18.3 machine with packed columns (10 % FS 16 on N-AW-DMCS, 3.7 mm; for NF_3 determination packed with Porapak Q).

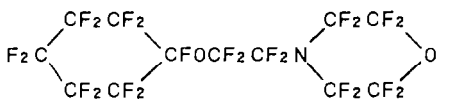
Mass spectra were recorded with a FINNIGAN MAT 212 (double focus) et EI = 70 eV. GC/MS was done with a FINNIGAN MAT GC/MS system 5100 (quadrupol), GC = 50 m SE 30, EI = 90 eV.

Organically bound fluorine was determined by the Wickboldt-method [10] using fluoride sensitive electrodes.

Perfluorinated products (Table 2)

Besides the liquid perfluorination products discussed below, there were in every electrofluorination run perfluorinated gaseous products such as NF_3, CF_4, C_2F_6 and sometimes $(C_2F_5)_2O$, the identities of which were confirmed by comparison with authentic GC-samples or by MS.

Compound 5: b.p. 185.8 °C. Analysis: Found: C, 22.65; F, 69.9; N, 2.40 %. $C_{12}F_{23}NO_2$ requires C, 22.97; F, 69.69; N, 2.23 %.

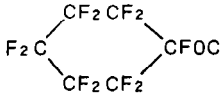


a,b c,d e,f g h i j k

^{19}F-NMR (ppm): a 126.3, b 138.6, c 125.4, d 137.8, e 123, f 135.5, g 140, h 84, i 94, j 91.5 (tt), k 86.6; J_{ab} 292 Hz, J_{cd} 291 Hz, J_{ef} 285 Hz, J_{ij} 18 Hz, J_{hj} 8 Hz

MS: 608 $[M-19]^+$, 330 $[CF_2CF_2\overline{NCF_2CF_2OCF_2CF_2}]^+$, 280 $[CF_2\overline{NCF_2CF_2OCF_2CF_2}]^+$, 119 $[C_2F_5]^+$ (base peak)

Compound 6: b.p. 96 °C. Analysis: Found: F, 73.2 %. $C_8F_{16}O$ requires F, 73.08 %.

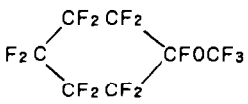


a,b c,d e,f g h i

^{19}F-NMR (ppm): a 128.5, b 138.5, c 128, d 138, e 126, f 136, g 143.5, h 86.7 (m), i 88.5

MS: 416 $[M]^+$, 397 $[M-19]^+$, 347 $[M-CF_3]^+$ 281 $[C_6F_{11}]^+$, 119 $[C_2F_5]^+$, (base peak)

Compound 7: b.p. 80.3 °C. Analysis: Found: F, 72.4 %.
$C_7F_{14}O$ requires F, 72.68 %.



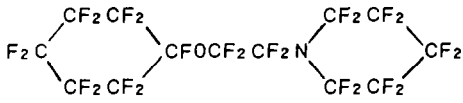
a,b c,d e,f g h

^{19}F-NMR (ppm): a 128, b 140.6, c 127.4, d 139.4, e 125.3, f 137.2, g 143.1, h 55.4

MS: 347 $[M-19]^+$, 281 $[C_6F_{11}]^+$, 69 $[CF_3]^+$ (base peak)

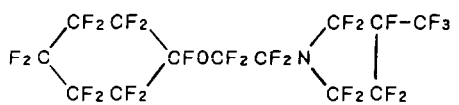
Compound 8: Compounds 8 and 9 form a mixture (about 5 to 1) we could not separate by distillation. The NMR data were obtained from the mixture.

^{19}F-NMR (ppm): a to g 122.2 to 142.7, h 85.7, i 95.2 (p), j 92.0 (m), k 133.2, l 135.5, MS: 642 $[M-19]^+$,
364 $[CF_2CF_2\overline{N(CF_2)_4CF_2}]^+$,
314 $[CF_2\overline{N(CF_2)_4CF_2}]^+$,
226 $[C_5F_8N]^+$, 176 $[C_4F_6N]^+$,
119 $[C_2F_5]^+$ (base peak),
114 $[C_2F_4N]^+$



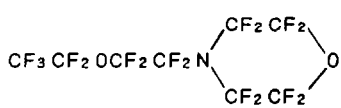
a,b c,d e,f g h i j k l

Compound 9: ^{19}F-NMR (ppm) (from a mixture with 8); a to g 122.2 to 142.7, h 85.7, i 95.2, j 92.0, k 133.2, m 184.5, n 74.1
MS: 642 $[M-19]^+$,
592 $[M-CF_3]^+$, 364, 314, 226, 119 (base peak)



a,b c,d e,f g h i j k

Compound 10: b.p. 129-134 °C. Analysis:Found: F, 69.1 %. $C_8F_{17}NO_2$ requires F, 69.46 %. ^{19}F-NMR (ppm): a 81.5, b 86, c 88.5, d 96, e 92.5, f 87.5; MS: 446 $[M-19]^+$,
330 $[CF_2CF_2\overline{NCF_2CF_2OCF_2CF_2}]^+$,
308 $[OCCF_2\overline{NCF_2CF_2OCF_2CF_2}]^+$,
280 $[CF_2\overline{NCF_2CF_2OCF_2CF_2}]^+$,
192 $[C_4F_8NO]^+$,
185 $[CF_3CF_2OCF_2]^+$,
119 $[C_2F_5]^+$ (base peak)



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