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ELECTROCHEMICAL PRODUCTION OF PARTIALLY FLUORINATED ORGANIC COMPOUNDS: N-METHYLMORPHOLINE FLUORINATION

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SUMMARY

The usual electrochemical fluorination of organic compounds in anhydrous HF produces completely fluorinated materials. In order to obtain partially fluorinated compounds, electrofluorination has been conducted under various conditions, including the use of solvents. None of the solvents lead to satisfactory results. Experiments have also been carried out with high concentrations of N-methylmorpholine in anhydrous HF and they have provided information about the selectivity and the mechanism of the reaction. Various partially fluorinated derivatives of N-methylmorpholine have been identified, and some of them separated from the reaction mixture.

INTRODUCTION

Some experiments for preparing partially fluorinated organic compounds *via* an electrochemical process have been carried out by Rozhkov *et al.* [1-6]. By using aprotic solvents and platinum anodes, some aromatic compounds were electrofluorinated and derivatives with one or two fluorine atoms per molecule were obtained. However, only two fluorine atoms can be introduced at the most into each molecule with acceptable yields. The use of nickel instead of platinum anodes leads, under similar conditions, to perfluorinated compounds: this seems due to adsorption on the nickel of the partially fluorinated molecules which undergo further fluorination untill all the hydrogen atoms are substituted by fluorine atoms.

Starting from the hypothesis that the use of a solvent might reduce this adsorption and hence facilitate the partial fluorination, attempts have been made to carry out electrofluorinations in HF-solvent mixtures.

N-methylmorpholine was chosen for the electrofluorination since it has three different positions where fluorination might occur and is therefore likely to give useful information about the reaction mechanism.

RESULTS AND DISCUSSION

In spite of the above statements, the experiments carried out with organic solvents have not yet given satisfactory results.

When acetonitrile was used as a solvent the process stopped after a few hours because of crusts forming on the electrodes; furthermore, the nickel anodes were considerably corroded by dissolution of nickel in the electrolytic bath. The causes of these phenomena are not yet known, but they seem to be linked to the low concentration of HF in the bath, this being insufficient to produce a deposit of a protective fluoride layer on the anodes.

With dioxan as solvent sufficient conductivity was maintained when the HF-dioxan molar ratio was higher than two and experiments have been carried out quite normally. The reaction, however, was not sufficiently selective as the solvent itself underwent electrofluorination together with the N-methylmorpholine. Therefore the reaction mixture which resulted was very complex and for this reason considerable difficulties have been met in the identification of products.

Using N,N-dimethylformamide as solvent it was not possible, either with an excess of HF, or by the addition of additives (methyl alcohol, diethylamine, KF), to obtain a bath conductivity high enough to carry out an electrolytic reaction.

Because of the difficulties encountered with solvents, it was decided to work with a large excess of N-methylmorpholine, so that it could act as a solvent as well as being the substrate. Because of its ability to bind HF molecules with precipitation of a white compound (presumably the hydrofluoride salt), the amount of N-methylmorpholine used had to be limited to about 40 % by wt of the electrolyte bath.

The electrofluorination experiments were carried out with this concentration which is very different from those usually employed in the electrofluorination of organic compounds in HF (where the organic compound concentration is seldom higher than 12 % by wt). The reaction was followed by taking aliquots after certain amounts of fluorine, calculated from the number of coulombs passed, had been introduced into the N-methylmorpholine. It was possible to identify almost all the intermediate products of partial fluorination by GLC-mass spectroscopy and NMR analysis; their structures are reported in table 1, together with their percentages in the reaction mixture.

As can be seen, the fluorine atoms are almost always introduced next to the oxygen atoms of N-methylmorpholine. Only in compound 5, which is present in lowest amount in the reaction mixture, can a fluorine atom be found adjacent to the nitrogen atom. No compound shows fluorine atoms in the methyl group, except for the perfluoro-N-methylmorpholine. Furthermore, by comparing the concentrations found for compounds 3, 4 and 5, it is clear that a second fluorine is substituted at the other position adjacent to the oxygen atom rather than the one which already contains a fluorine atom.

TABLE 1

Identified compounds and their % by wt in the reaction mixture after 1.5 mole (column I) and 2.4 mole (column II) of fluorine per mole of N-methylmorpholine have been generated

Compound	Column 1	Column 2
1) N-methylmorpholine	61.3	38.3
2) 2-fluoro-N-methylmorpholine	19.6	28.2
3) 2,6-difluoro-N-methylmorpholine	4.4	9.1
4) 2,2-difluoro-N-methylmorpholine	0.9	1.9
5) 2,5-difluoro-N-methylmorpholine	0.2	0.6
6) 2,2,6-trifluoro-N-methylmorpholine	1.6	4.4
7) 2,2,6,6-tetrafluoro-N-methylmorpholine	0.5	1.5
8) perfluoro-N-methylmorpholine	6.5	11.0

From these results it is possible to make some suggestions about the reaction mechanism. The introduction of the first fluorine atom in the N-methylmorpholine molecule can occur according to one of the two ways shown in fig. 1. As almost all the identified partially fluorinated compounds have the fluorine atoms next to the oxygen atom, the reaction evidently proceeds in the first way. It is therefore likely that the introduction of the second fluorine atom occurs by a similar mechanism, as shown in fig. 2, and so on also for the introduction of the third and the fourth fluorine atoms. Hydrogen atom substitution then continues in the positions beside the nitrogen atom and in the methyl group until the whole molecule is completely fluorinated.

It is significant that, besides the partially fluorinated intermediates, some perfluorinated N-methylmorpholine and some unchanged N-methylmorpholine are found in the reaction mixture. This shows that the reaction proceeds more rapidly in the partially fluorinated molecules. These results are unfavorable for the industrial application of this process, as it is difficult to produce one or more partially fluorinated products in good yield.

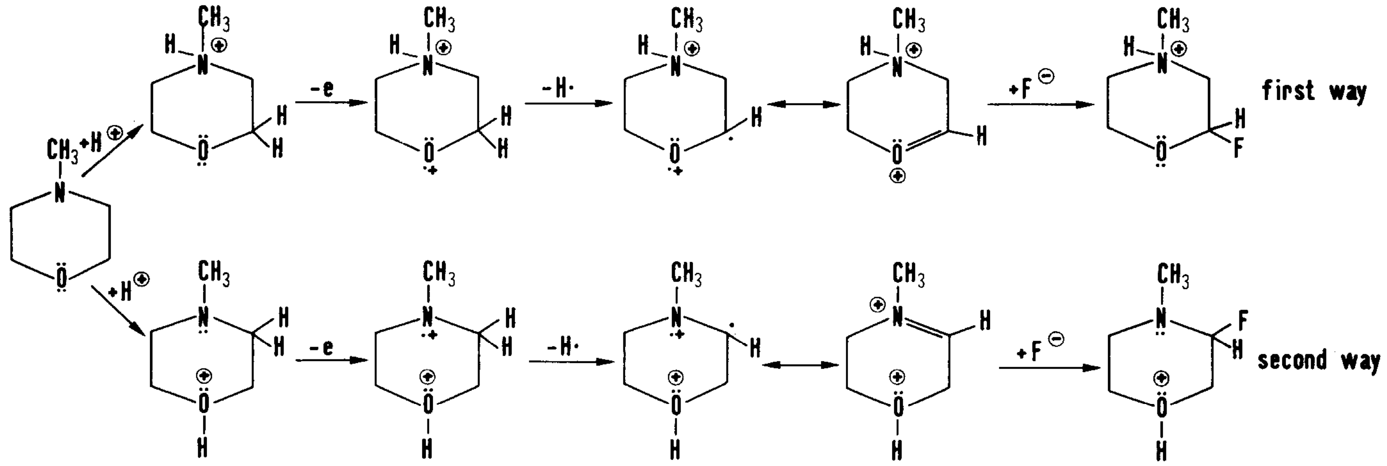

FIG. 1. Possible mechanisms for the introduction of the first fluorine atom in the N-methylmorpholine molecule.

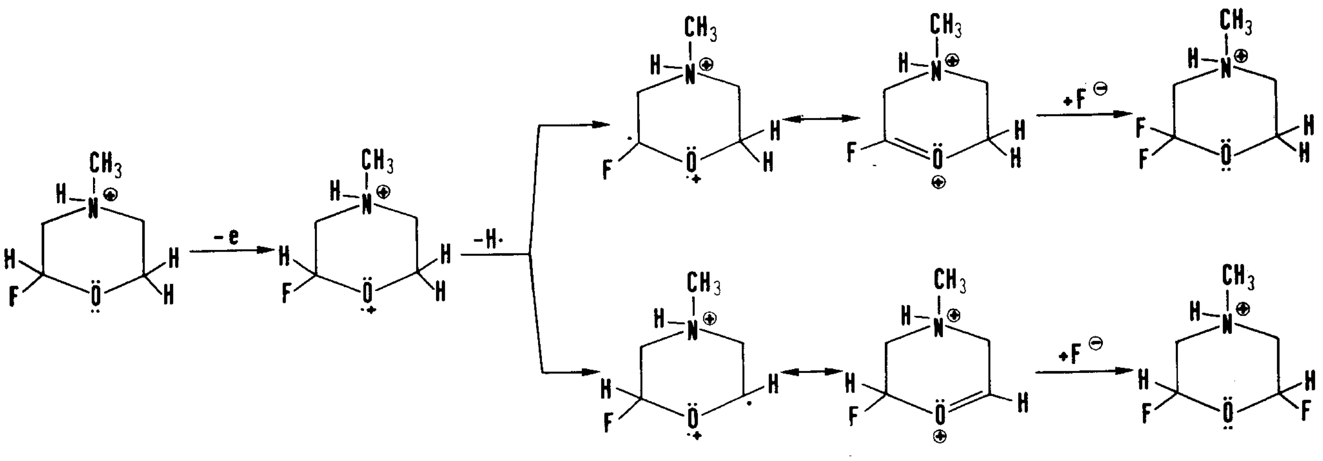

FIG. 2. Possible mechanism for the introduction of the second fluorine atom in the 2-fluoro-N-methylmorpholine molecule.

EXPERIMENTAL

The experiments have been carried out in a cylindrical electrofluorination cell with a volume (with electrodes inserted) of 2,900 ml, using iron cathodes and nickel anodes (anodic surface of 2,560 cm^2), and provided with a condenser cooled to -25 °C so that evaporated HF, and the volatile products of the reaction, could be returned to the reaction vessel. Each experiment was preceded by drying of the bath by electrolytic removal of water. The operating conditions are reported in table 2.

TABLE 2

Operating conditions for the electrofluorination of N-methylmorpholine (bath temperature 20-22 °C)

Solvent	V	mA/cm^2	Bath composition (% wt.)			
			Solvent	N-methylmorpholine	HF	Additives
acetonitrile	5.2-5.8	9-10	66-67	7-8	25-26	-
dioxan	5.9-6.2	9-12	70-71	9-10	17-18	2-3
N,N-dimethylformamide	5.3-6.0	9-11	57-58	5-6	31-32	4-5
N-methylmorpholine	5.2-5.6	8-9	-	39-40	60-61	-

The electrolytic process was followed by removing a part of the reaction mixture when the degree of fluorination required had been reached, as calculated from the following expression:

$$q = \frac{2 \cdot 19 \cdot f \cdot F \cdot M}{0.8 \cdot e} \text{ Ampere/hour}$$

where:

e = electrochemical equivalent (g/coulomb),

f = transformation factor of coulomb in Ampere/hour,

F = fluorination degree required (fluorine atoms developed per mole of organic compound),

M = moles of organic compound in the bath.

The sample withdrawn, after removal of the excess of HF by a nitrogen stream, were subjected to GLC, NMR and mass spectrometric analysis in order to identify the reaction products. Analytical data for the identified compounds are:

a) 2-fluoro-N-methylmorpholine. Mass spectrum: m/e 119 (M^{+}), m/e 99 $(M\text{-}HF)^{+}$, m/e 71 $(M\text{-}COHF)^{+\cdot}$, m/e 56 $(C_3H_6N)^{+}$, m/e 43 $(CH_2{=}N\text{-}CH_3)^{+\cdot}$ (base peak), m/e 42 $(CH_2{=}N{=}CH_2)^{+}$.

b) 2,6-difluoro-N-methylmorpholine. ^{1}H NMR spectrum (1.2 **g/l in acetone): single** peak at 1.8 δ from TMS ext.; complex doublet at 5.2 δ from TMS ext. with J(H-F)gem of 55.4 Hz. ^{19}F NMR spectrum (1.2 g/l in acetone): multiplet at 44.1 ppm from TFA ext. with J(H-F)gem of 55.4 Hz. Mass spectrum: m/e 137 (M^{+}) m/e 118 $(M\text{-}F)^{+}$, m/e 108 $(M\text{-}CHO)^{+}$, m/e 89 $(M\text{-}COHF)^{+\cdot}$, m/e 43 $(CH_2{=}N\text{-}CH_3)^{+\cdot}$ **(base** peak). Found: C, 43.5; H, 6.9; N, 10.8; F, 28.1 %. $C_5H_9F_2NO$ requires C, 43.8; H, 6.5; N, 10.2; F, 27.7 %.

c) 2,5-difluoro-N-methylmorpholine. Mass spectrum: m/e 137 (M^{+}), m/e 118 $(M\text{-}F)^{+}$, m/e 71 $(M\text{-}COF_2)^{+}$, m/e 90 $(M\text{-}COF)^{+}$, m/e 43 $(CH_2{=}N\text{-}CH_3)^{+\cdot}$ (base peak), m/e 42 $(CH_2{=}N{=}CH_2)^{+}$.

d) 2,2-difluoro-N-methylmorpholine. Mass spectrum: m/e 137 (M^{+}), m/e 118 $(M\text{-}F)^{+}$, m/e 90 $(M\text{-}COF)^{+}$, m/e 71 $(M\text{-}COF_2)^{+\cdot}$, m/e 43 $(CH_2{=}N\text{-}CH_3)^{+\bullet}$ (base peak).

e) 2,2,6-trifluoro-N-methylmorpholine. ^{1}H NMR spectrum: single peak at 2.1 δ from TMS ext.; complex doublet at 5.5 δ from TMS ext. with J(H-F)gem of 52.5 Hz. ^{19}F NMR spectrum: multiplet at 48.5 ppm from TFA ext.; complex peak at -9.2 ppm from TFA ext. Mass spectrum: m/e 155 (M^+), m/e 136 $(M-F)^+$, m/e 107 $(M-COHF)^{+\cdot}$, m/e 89 $(M-COF_2)^{+\cdot}$, m/e 43 $(CH_2=N-CH_3)^{+\cdot}$ (base peak), m/e 42 $(CH_2=N=CH_2)^+$. Found: C, 38.4; H, 5.5; N, 8.8; F, 36.5 %. $C_5H_8F_3NO$ requires C, 38.7; H, 5.2; N, 9.0; F, 36.8 %.

f) 2,2,6,6-tetrafluoro-N-methylmorpholine. ^1H NMR spectrum: single peak at 2.1 δ from TMS ext. ^{19}F NMR spectrum: triplet at -7.2 ppm from TFA ext. Mass spectrum: m/e 173 (M^+), m/e 154 $(M-F)^+$, m/e 126 $(M-COF)^+$, m/e 64 $(CH_2=CF_2)^+$, m/e 43 $(CH_2=N-CH_3)^{+\cdot}$ (base peak). Elemental analysis has not been obtained because of insufficient purity of the compound.

g) perfluoro-N-methylmorpholine. ^{19}F NMR spectrum: quintet at -24.2 ppm from TFA ext.; single peak at 9.7 ppm from TFA ext.; quartet at 17.2 ppm from TFA ext., with J(F-F) of 13.7 Hz. Found: C, 20.4; N, 4.5; F, 69.6 %. $C_5F_{11}NO$ requires C, 20.1; N, 4.7; F, 69.9 %.

CONCLUSIONS

These preliminary experiments on the electrofluorination of an organic compound in high concentrations show that the reaction is selective as the fluorination does not occur at random.

Furthermore, although it is possible to isolate the partially fluorinated intermediate compounds, even when fluorination of these molecules is preferred to fluorination of the unfluorinated starting material, it would seem that it is not possible to obtain a given partially fluorinated intermediate compound in amounts acceptable for an industrial process. The study of electrofluorination carried out under these conditions is, however, still at an early stage: research in progress will show if this industrial aim can be reached.

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