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REACTIONS OF PENTAFLUOROBENZENE WITH AMINO DERIVATIVES.

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SUMMARY

A metal hydrogen exchange seems to take place in pentafluorobenzene in reactions with strongly basic amino derivatives, such as lithium amide, lithium morpholide or N-lithium-N',N'-dimethylhydrazide. On the other hand a fluorine substitution in pentafluorobenzene takes place with N-lithium-p-methoxyanilide, N-lithium-N-methylanilide, N-lithiumanilide, dimethylamine, methylamine, ammonia, morpholine,and hydrazine. No reaction occurred with N,N-dimethylhydrazine, p-phenylenediamine, p-methozyaniline, N-methylaniline or aniline.

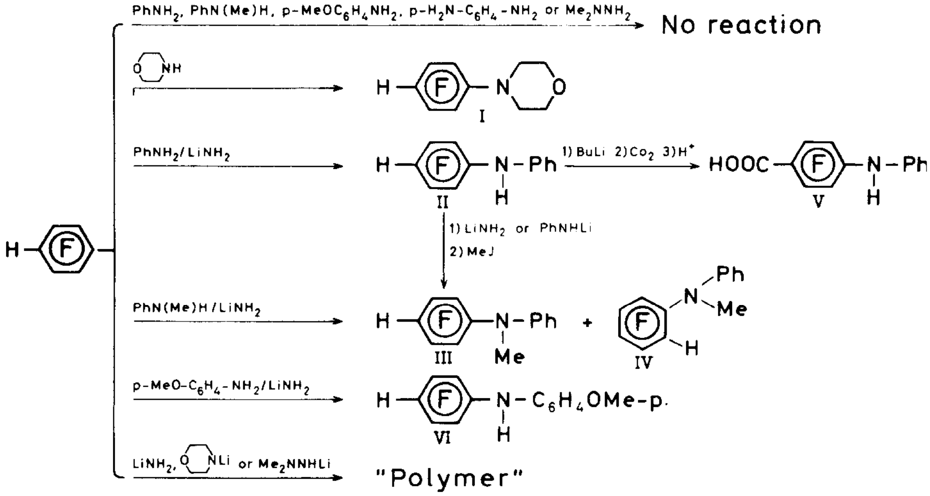
INTRODUCTION

Nucleophilic substitution of fluorine atoms in pentafluorobenzene has been described with the use of sodium-2,3,5,6-tetrafluoroanilide [1], potassium thiophenoxide [2], sodium hydrogen sulphide [2], hydrazine [3], ammonia [4], methylamine [5], dimethylamine [5], potassium hydroxide [6], and sodium methoxide [7]. Normally a substitution in the para-position to hydrogen in pentafluorobenzene occurs. Stronger bases such as lithium amide [8], Grignard [9], and lithium [9] reagents gave a metal hydrogen exchange. At higher temperatures the pentafluorophenyl lithium were "decomposed" to insoluble "polymers", most probably through a benzyne intermediate [10].

The scope of the present work was to investigate whether reactions of different amino derivatives with pentafluorobenzene could supply further information as to when a substitution or a metal hydrogen exchange in pentafluorobenzene could be anticipated.

RESULTS AND DISCUSSION

No substitution of fluorine atoms in pentafluorobenzene was obtained with aniline, N-methylaniline, p-methoxyaniline, p-phenylenediamine or N,N-dimethylhydrazine. With morpholine 2,3,5,6-tetrafluoro-4-morpholinobenzene (I) was formed. The ^{19}F NMR spectrum of I consisted of two multiplets at 10.9 and 21.5 ppm downfield to C_6F_6, which is consistent with a p-substituted tetrafluorobenzene. When lithium amide was added to pentafluorobenzene (1:1) in aniline, no reaction seemed to occur below 50°. This was not anticipated as both pentafluorobenzene and aniline react readily with lithium amide in tetrahydrofuran at 10° [8, 11]. At 50°, however, a strong exothermic reaction took place. Only one substituted compound was isolated (47%). The ^{19}F NMR spectrum of this compound consisted of two multiplets at 11.8 and 22.2 ppm downfield to C_6F_6, indicating 2,3,5,6-tetrafluoro-N-phenyl-



Scheme 1. Performed reactions.

aniline (II). Compound II neither reacted further with lithium amide (1:3) in aniline at 85°, nor with lithium anilide (1:2) in an aniline-tetrahydrofuran mixture at 70°. However, the yield of II increased (88.5 %) when pentafluorobenzene was treated with lithium anilide (1:3) at 90°. When a sample of II was reacted with lithium amide and then with methyliodide in tetrahydrofuran, 2,3,5,6-tetrafluoro-N-methyl-N-phenylaniline (III) was obtained in good yield (82.5 %). From a reaction of II with n-BuLi (1:2), and then with CO_2, p-anilino-perfluorobenzoic acid (V) was formed after hydrolysis. The yields described above for II, 47 % and 88.5 %, correspond very well with results obtained in reactions of hexafluorobenzene with sodium anilide (1:1) [12] or lithium anilide (1:2) [11], which gave pentafluoro-N-phenylaniline in 49 % and 88.5 % yields, respectively. To the reaction product of II with lithium anilide (1:1) methyl iodide was added. After hydrolysis the reaction gave compound III in 85.9 % yield together with 14.1% of unreacted II as analyzed by gaschromatography. This indicates that lithium anilide is strong enough a base to form tetra- and pentafluoro-N-lithium-N-phenylanilide readily from II and pentafluoro-N-phenylaniline, respectively. A preferred metal hydrogen exchange would then explain why a reaction of pentafluoro- or hexafluorobenzene with lithium anilide in 1:1 molar ratio only gave approximately 50 % of the wanted compounds

When pentafluorobenzene was added to a mixture of lithium amide and N-methylaniline, a strongly exothermic reaction took place at 5°. The working up afforded an oil, tetrafluoro-N-methyl-N-phenylaniline (50 %), which, by means of ^{19}F NMR and gaschromatography was shown to consist of two isomers. The ^{19}F NMR spectrum in $CDCl_3$ of the first isomer (90 %) consisted of two multiplets at 16.3 and 23.0 ppm downfield to C_6F_6, indicative of a para-compound (III). ^{19}F NMR spectrum of the other isomer (10 %) had four multiplets at 0.5, 6.7, 16.4 and 22.3 ppm downfield to C_6F_6. As fluorine in all positions seems to show ortho coupling [13], it was assumed that the compound was 2,3,4,5-tetrafluoro-N-methyl-N-phenylaniline (IV), see Fig. 1. The ortho-substituted compound (IV) may have been formed through a benzyne intermediate [14]. However, based

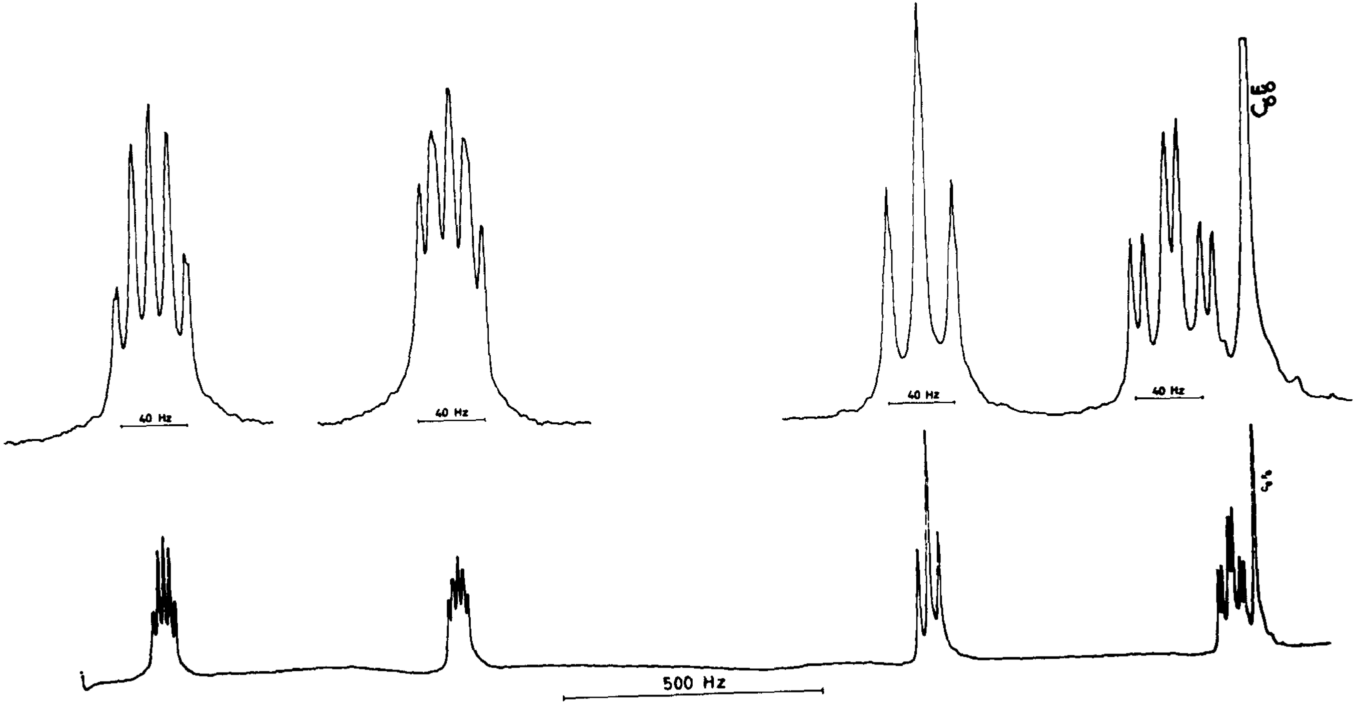
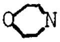


Fig. 1. The ^{19}F NMR spectrum of 2,3,4,5-tetrafluoro-N-methyl-N-phenylaniline

on the reactions with lithium anilide, it is more likely that a direct ortho-substitution occurred. o-Substitution is also known to take place with dimethylamine [5] and hydrazine [4], but not with methylamine [5] or ammonia [4].

N-lithium-p-methoxyanilide reacted with pentafluorobenzene giving a compound with a ^{19}F NMR spectrum consisting of two multiplets at 9.0 and 21.5 ppm downfield to C_6F_6. This is indicative of 2,3,5,6-tetrafluoro-N [p-methoxyphenyl]-aniline (VI).

The described amino reactants together with those previously published are arranged as follows in a series with decreasing pK_a of the corresponding acids [15, 16, 17]: $LiNH_2$[8] > ON-Li > Me_2NNHLi > p-MeO-C_6H_4-NHLi > $C_6H_5N(Me)Li$ > C_6H_5NHLi > C_6F_5Li > Me_2NH [5] > $MeNH_2$ [5] > NH_3 [4] > ON-H > H_2NNH_2 [4] > Me_2NNH_2 > p-H_2N-C_6H_4-NH_2 > p-MeO-C_6H_4-NH_2 > $C_6H_5N(Me)H$ > $C_6H_5NH_2$ From this series it will be seen that the three strongest bases together with pentafluorobenzene yielded a "polymer" as previously described for a similar reaction with lithium amide [8]. The infrared spectra of the "polymers" from the reactions of pentafluorobenzene with lithium amide, lithium morpholide and N-lithium-N',N'-dimethylhydrazide did not differ except for some minor bands. This seems to indicate that the polymers are formed through the same intermediate, viz. pentafluorophenyl lithium, which may have been obtained through a metal hydrogen exchange. The decomposition of pentafluorophenyl lithium into an insoluble "polymer" in the absence of other reactive agents, is well known [10].

The formation of a "polymer" with the stronger bases instead of the ortho-substituted compound [18], may, for lithium amide, be attributed to the heterogeneous system present. As to lithium morpholide, it has previously been demonstrated that it gave 4-bromo-N,N-dimethyl-3-morpholino-aniline with 1,4-dibromo-N,N-dimethylaniline and 3,5-dibromo-1-morpholinobenzene with 1,3,5-tribromobenzene [19], but biphenyl with o- and m-dichlorobenzene [20].

The next bases in the series, including hydrazine, gave a para-substitution in pentafluorobenzene. No products other than the starting material was isolated from attempted reactions

TABLE 1

Spectral data of substituted fluorobenzene

	^{19}F chemical shifts in $CDCl_3$ with C_6F_6 as internal standard at 94.1 MHz		^1H Chemical shifts in $CDCl_3$ with TMS as internal standard at 60 MHz			IR (cm^{-1})		
Compound	Shifts at (ppm), downfield to C_6F_6	Remarks	Shifts at δ (ppm) >NH	$-C_6F_4H$	$-CH_3$	N-H stretch	Skeletal vibrations of fluorinated ring	C-F bands
I	21.5	Multiplet		6.68			1475	1175, 1132, 1112 1100, 1065, 1025 1005, 948
	10.9	Multiplet						
II	22.2	Multiplet	5.65	6.70		3395	1520,1495 and 1465	1085, 1065 and 942
	11.8	Multiplet						
III	23.0	Multiplet		6.94	3.32		1500	1185, 1175, 1110,. 1000, 935
	16.4	Multiplet						
IV	22.3	Multiplet			3.37		1520,1490	1210, 1185, 1115, 1095, 1075, 1040, 1025 and 940
	16.3	Multiplet						
	6.7	Multiplet						
	0.5	Multiplet						
VI	21.5	Multiplet	5.54	6.57	3.73	3380	1520,1500 1485	1170, 1110, 1105 1070, 1025, 965, 945 and 912
	9.0	Multiplet						
V		-COOH >NH	One proton resonance at 7.82 in acetone d_6. One proton resonance varied with concentration. The resonances coincided when a 17% concentration was used, and both disappeared on addition of D_2O.			3400 Other characteristic IR bands: 1692 and 1635	1525,1495 and 1470	990, 915 (broad)

with the weaker bases. Attention is drawn to the observation that also bases with higher pK_a than pentafluorophenyl lithium [15] gave the para-and not the ortho-substituted compounds through a benzyne intermediate [14].

EXPERIMENTAL

All reactions were carried out under an atmosphere of dry, highly purified nitrogen. Tetrahydrofuran (THF) was dried and distilled prior to use from sodium benzophenone ketyl. n-Butyllithium was delivered from Metallgesellschaft AG (Germany). The spectral data are gathered in Table 1. IR, NMR, and MS spectra were determined employing Perkin-Elmer 457-IR, Varian 60 and 100 MHz NMR, and AEJ-MS 902 spectrometers, respectively.

Reactions attempted

Attempted reactions of pentafluorobenzene with aniline, N-methylaniline, p-methoxyaniline, p-phenylene-diamine or N,N-dimethylhydrazine were performed by adding six equivalents of the amine to one equivalent of pentafluorobenzene in petroleum (100-120°) or THF in an ampule sealed with an aluminium screw cap placed in a 100° bath for 8 to 20 h. No substituted compounds were detected in the mixture.

Reactions with lithium morpholide and N-lithium-N',N'-dimethyl hydrazide

n -BuLi (0.03 mol) was added slowly to morpholine (10 ml) or N,N-dimethyl-hydrazine (4 ml) in THF (20 ml) at -70°. The temperature was raised over 2 h to room temperature (Color Test II negative [21]) and then lowered to 0°. Pentafluorobenzene (5.04 g, 0.03 mol) was added dropwise over 30 min. After 30 min at 0° the mixture was stirred at 60° for 30 min, cooled, and hydrolyzed with 5% HCl (morpholine) or water (hydrazine). In both reactions a white insoluble material had been formed. No other products were isolated.

2,3,5,6-Tetrafluoro-4-morpholino-benzene

A mixture of morpholine (16.1 g, 0.3 mol), pentafluorobenzene (8.4 g, 0.05 mol) and light petroleum (60-80°, 15 ml) was stirred at 75° for 4 h and then at ambient temperature over night. The mixture was hydrolyzed with 10 % HCl, extracted with ether, dried and concentrated. The obtained white crystals were purified by sublimation at 90°. This gave 2.1 g (18 %) 2,3,5,6-tetrafluoro-4-morpholino-benzene (nc), m.p. 92.5-94.5° (in a sealed capillary tube). (Found: C 51.19; H 4.16; M 235. Calc. for $C_{10}H_9F_4NO$: C 51.07; H 3.86; M 235.2.)

2,3,5,6-Tetrafluoro-N-phenylaniline

1. Pentafluorobenzene (5.04 g, 0.03 mol) was added slowly to lithium anilide (0.09 mol) [11] in a mixture of THF (20 ml) and aniline (20 ml) at 0°. The mixture was then stirred at 90° for 30 min, cooled, hydrolyzed with 10 % HCl and worked up. This gave a crystalline material which was distilled under reduced pressure on to a "cold-finger" and then chromatographed on neutral Al_2O_3 (Woelm) with light petroleum (40-65°). This afforded 6.4 g (88.5 %) 2,3,5,6-tetrafluoro-N-phenylaniline (nc), m.p. 80-81.5°. (Found: C 59.80; H 3.01; M 241. Calc. for $C_{12}H_7F_4N$: C 59.57; H 2.93; M 241.2)

2. Lithium amide (2.6 g) was added over 1 h to a mixture of pentafluorobenzene (16.8 g, 0.1 mol) and aniline (31 g). When approximately 1/3 of the lithium amide had been added, the temperature of the mixture was elevated to 50°. Ammonia was slowly formed. After the addition of 2/3 of the lithium amide, a vigorous exothermic reaction suddenly took place. The mixture was cooled for 10 min and then placed on the 50° bath again, whereupon the rest of the lithium amide was added. The 50° bath was removed after 1 h, and the mixture was stirred at ambient temperature over night. Ether (50 ml) was added, and the mixture was hydrolyzed with 10 % HCl. The work-up, as

already described, gave 11.4 g (47.2 %) 2,3,5,6-tetrafluoro-N-phenylaniline, m.p. 79.5-81.5°.

p-Anilino-2,3,5,6-tetrafluorobenzoic acid

was obtained by adding n-butyllithium (0.04 mol) to N-phenyl-2,3,5,6-tetrafluoroaniline (4.8 g, 0.02 mol) dissolved in THF (100 ml) at -70° followed by CO_2-gas. The mixture was hydrolyzed with water and separated. The organic layer was washed with water and worked up to give 1.5 g recovered 2,3,5,6-tetrafluoro-N-phenylaniline. The gathered water layers were acidified with HCl and extracted three times with ether (20 ml). The ether layers were combined, dried and concentrate The afforded white crystals were sublimed at 175°/0.05 mm and gave 3.2 g (56.1 %) p-anilino-2,3,5,6-tetrafluorobenzoic acid (nc), m.p. 192-194°. (Found: C 54.64; H 2.63; M 285. Calc. for $C_{13}H_7F_4NO_2$: C 54.74; H 2.47; M 285.2).

Tetrafluoro-N-methyl-N-phenylaniline

1. Pentafluorobenzene (16.8 g, 0.1 mol) was added to a mixture of lithium amide (2.6 g) and N-methyl-aniline (31 g) at 0°. The 0° bath was removed after 15 min as no reaction seemed to occur, and the temperature was allowed to raise. After some minutes ammonia was slowly formed followed by a violent exothermic reaction. The reaction was kept under control by cooling on an ice-bath for some minutes. The mixture was stirred at ambient temperature for 1 h, ether (50 ml) was added, and the mixture was hydrolyzed with 10 % HCl. Work-up gave a black oil which was vacuum distilled. This gave 12.8 g (50.2 %) tetrafluoro-N-methyl-N-phenylaniline (128-131°/8 mm). (Found: C 61.35; H 3.58; M 255. Calc. for $C_{13}H_9F_4N$: C 61.18; H 3.56; M 255.2.) ^{19}F NMR and G.L.C. showed the presence of two compounds (9:1) in the oil. Pure samples were obtained with preparative G.L.C., which gave 2,3,5,6-tetrafluoro-N-methyl-N-phenylaniline (nc) (90 %) and 2,3,4,5-tetrafluoro-N-methyl-N-phenylaniline (nc) (10 %), m.p. 38.5-40.5°. (Found: M 255. Calc. for $C_{13}H_9F_4N$: M 255.2.)

2. THF (15 ml) was added to a mixture of lithium amide (0.52 g) and 2,3,5,6-tetrafluoro-N-phenylaniline (4.83 g, 0.02 mol) at 0°. After 2 h at ambient temperature methyl iodide (3.55 g, 0.025 mol) was added. The mixture was stirred for 1 h and then placed on a 65° bath for 1 h, cooled and hydrolyzed with 5 % HCl. The mixture was extracted with ether, washed with a $Na_2S_2O_3$-solution, dried, and concentrated. After chromatography on neutral Al_2O_3 (Woelm) with light petroleum (40-60°) and vacuum distillation, 4.2 g (82.4%) 2,3,5,6-tetrafluoro-N-methyl-N-phenylaniline (128-130°/9 mm) was identified by IR and G.L.C. with a sample from the previous reaction.

3. 2,3,5,6-Tetrafluoro-N-phenylaniline (4.83 g, 0.02 mol) dissolved in THF (15 ml) was added to a cooled mixture of lithi anilide (0.02 mol) [11] in THF (12 ml). The mixture was stirre for 1 h on a 50° bath, then cooled again, whereupon methyl iodide (2.84 g, 0.02 mol) was added. The following procedure was as in 2. G.L.C. analysis of the concentrated oil diluted with ether, gave 85.9% 2,3,5,6-tetrafluoro-N-methyl-N-phenylaniline and 14.1% 2,3,5,6-tetrafluoro-N-phenylaniline present in the dark mixture.

2,3,5,6-Tetrafluoro-N [p-methoxyphenyl]-aniline

A mixture of lithium amide (2.4 g), p-methoxyaniline (12.3 g, 0.1 mol) and THF (40 ml) was stirred for 70 min at ambient temperature, whereupon pentafluorobenzene (5.04 g, 0.03 mol) was added slowly over 1 h. After 1 h at ambient temperature and 1.5 h at 60°, the mixture was cooled, hydrolyzed with 5% HCl, extracted with ether, separated, dried, and concentrated under reduced pressure. The resulting dark solid was chromatographed on neutral Al_2O_3 (Woelm) with light petroleum (40-60°) and then slowly distilled on to a "cold-finger" under reduced pressure. This gave 6.8 g (83.5 %) 2,3,5,6-tetrafluoro-N [p-methoxyphenyl]-aniline (nc), m.p. 73.5-75.5°. (Found: C 57.62; H 3.55; M 271. Calc. for $C_{13}H_9F_4NO$: C 57.67; H 3.34; M 271.2.)

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