Preparation of Dialkylamino-Substituted Benzenes and Naphthalenes by Nucleophilic Replacement of Fluorine in the Corresponding Perfluoroaromatic Compounds

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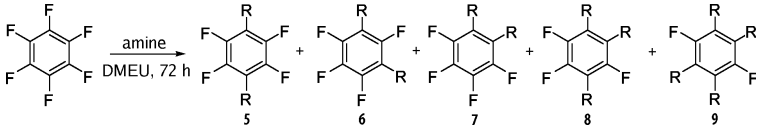
The reactions between hexafluorobenzene (HFB) and octafluoronaphthalene (OFN) with secondary aliphatic amines (pyrrolidine, dimethylamine and piperidine) and lithium amides (pyrrolidide, dimethylamide and piperidide) have been investigated both experimentally and (in part) theoretically. With amines HFB, depending on the selected conditions, gives either di-substituted products or a complex mixture of di-, tri- and tetrasubstituted compounds. Under similar conditions OFN produces almost exclusively the 2,3,6,7-tetrasubstituted compound. Interaction of HFB with the more nucleophilic lithium amides results in the replacement of four fluorines giving 1,2,4,5-tetrasubstituted difluorobenzenes, while OFN under similar conditions with lithium pyrrolidide produces an inseparable mixture of 1,2,4,5,6,8-hexa- and 1,2,3,4,5,6,8-hepta-substituted derivatives. With lithium dimethylamide, it is possible to substitute six (in dioxane) or seven (in THF) fluorines in OFN. Lithium piperidide in all employed solvents reacts with OFN to give only the 1,2,4,5,6,8-hexasubstituted derivative. Theoretical calculations indicate that with lithium dimethylamide the third fluorine is substituted at position 1, whereas with dimethylamine it is position 3. The basicities of selected hexa- and heptakis(dialkylamino)naphthalenes have been measured; they are all stronger bases than 1,8-bis(dimethylamino)naphthalene, although by less than expected.

Key words: Hexafluorobenzene, Octafluoronaphthalene, Nucleophilic Substitution, Dialkylamino-Substituted Arenes, Basicity

Introduction

It is possible to replace hydrogen by fluorine in a wide range of hydrocarbons without major structural changes [1]. The resulting fluorocarbon systems usually show high thermal stability and have volatilities similar to those of the corresponding hydrocarbon. Because fluorine is so electronegative there are of course major differences in the chemistry of hydro- and fluorocarbons; in particular whereas aromatic hydrocarbons (*e. g.*, benzene) tend to undergo electrophilic substitution (with hydrogen formally leaving as a proton) the reactions of aromatic perfluorocarbons are dominated by nucleophilic substitution. Perfluoroaromatic compounds readily undergo nucleophilic replacement of fluorines, often giving rise to highly substituted derivatives [2, 3].

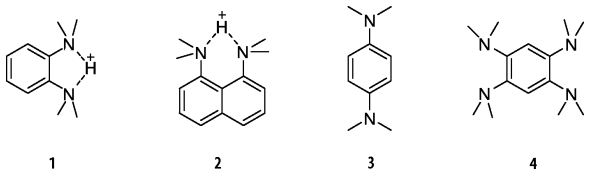
Although a great many papers have been published in this field, much remains to be done. For example, there is only limited data available concerning nucleophilic substitution by secondary amines. It is generally known that with HFB in excess secondary amine, 1,4-disubstitution typically take place [4, 5], whereas with OFN 2,6-disubstitution occurs [6]. With *N*-lithium amides, Koppang has shown that interaction of HFB with different lithium anilides allows preparation of mono-, 1,2- or 1,4-di- and 1,2,4,5-tetrasubstituted derivatives, depending on the conditions [7, 8]. We are aware of only one report on the replacement of more than one fluorine in OFN; reaction with lithium amides gave an inseparable mixture of 2,6- and 2,7-dialkylaminosubstituted derivatives (with relative abundance 2 : 1) [9]. Attempts to prepare more highly substituted products have appar-



Amine	R	T, °C	Reaction mass composition, %				
			5	**6**	**7**	**8**	**9**
Dimethylamine	$N(CH_3)_2$	95	94	5	1	0	0
Dimethylamine	$N(CH_3)_2$	190	16	2	0	69	12
Pyrrolidine	pyrrolidin-1-yl	95	84	9	7	0	0
Pyrrolidine	pyrrolidin-1-yl	190	15	2	1	66	14
Piperidine	piperidin-1-yl	95	87	8	5	0	0
Piperidine	piperidin-1-yl	190	42	0	0	53	5

Scheme 1.

ently not been reported. However, such polyamines, especially those able to form intramolecular hydrogen bonds (IHB) of types **1** and **2**, continue to attract interest as non-nucleophilic basic catalysts for organic transformations, models for studying IHB, and simulators of proton transfer reaction in living cells [10]. Furthermore, their defluorinated analogues (for example types **3** and **4** below) – due to the ease of one-electron oxidation, and the stability of the resulting radical-cations – find application both in the synthesis of magnetic and conductive materials [11] and as color developing agents in the manufacture of photographic materials [12].



Previously, the Russian authors have published in part results on nucleophilic substitution in OFN using secondary amines [13] and secondary lithium amides [14]; in this paper all collected data are presented and analyzed, and supplemented with the reactions of HFB under the same conditions.

Results and Discussion

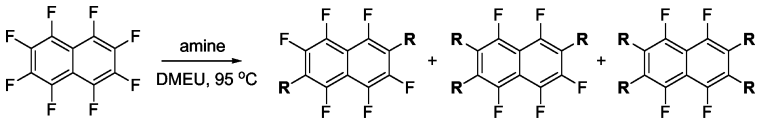
In the present work, dimethylamine, pyrrolidine, piperidine and their *N*-lithium derivatives, generated *in situ* from the corresponding amines *via* treatment with *n*-buthyl lithium, have been selected as the nitrogen nucleophiles. They differ from each other in both nucleophilicity and steric requirements and allow us to model most reaction situations and predict the behavior of other amines.

Action of neutral amines on HFB and OFN

Standard reaction conditions include: 95 °C, 1,3-dimethylimidazolidin-2-one [dimethyl(ethylene)urea, DMEU] as solvent and a 4-fold excess of amine. At lower temperatures, as well as lower amine concentrations, monosubstitution is the main reaction pathway. Selection of the reaction conditions was based on preliminary experiments in which several dipolar aprotic solvents [including dimethylformamide (DMF), hexamethylphosphoric triamide (HMPTA) and dimethyl sulphoxide (DMSO)] were tested. In particular, DMF was rejected at an early stage of this work due to its decomposition, even at low temperatures, to form dimethylamine, which competes with the starting amine in nucleophilic substitution. HMPTA was rejected mainly because of its carcinogenicity and difficulties removing this solvent from the reaction products. DMSO would seem to be a good alternative for the more expensive DMEU, but its main disadvantage is thermal lability at elevated temperatures and slightly lower yields in comparison with DMEU.

HFB under standard conditions even after 24 h produces mainly 1,4-disubstituted products of type **5** (Scheme 1), along with minor amounts of 1,3- (**6**) and 1,2- (**7**) isomers. The product composition and structures were determined by a combination of GC/MS, and ^{1}H and ^{19}F NMR. Thus, for example, compounds **6** show the following characteristic ^{19}F NMR signals: an unresolved multiplet at about $\delta = -140$ ppm (2-F), a doublet at -159 ppm (4,6-F, $^3J = 21$ Hz) and a triplet of doublets at -169 ppm (5-F, $^3J = 21$ Hz, $^5J = 2$ Hz). These ^{19}F signals resemble those observed earlier for products obtained by nucleophilic substitution in pentafluoroanilines [4].

Extending the reaction time for up to 7 days had no effect on the substitution pattern, and only with pyrrolidine were trace amounts of trisubstituted prod-



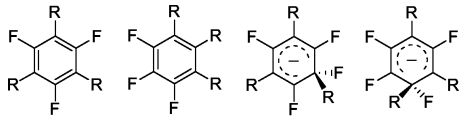
14 **15** **16**

Amine	R	Time, days	Reaction mass composition, %		
			14	**15**	**16**
Dimethylamine	$N(CH_3)_2$	3	2	75	23
Dimethylamine	$N(CH_3)_2$	7	0	0	100
Pyrrolidine	pyrrolidin-1-yl	3	0.3	79.5	20.2
Pyrrolidine	pyrrolidin-1-yl	7	0	0	100
Piperidine	piperidin-1-yl	3	3	82	15
Piperidine	piperidin-1-yl	7	0	63	37

Scheme 2 .

ucts **8** formed; the corresponding ^{19}F NMR spectrum contains three signals: a doublet near $\delta = -137$ ppm (3-F, $^5J = 8$ Hz), a doublet at -153 ppm (5-F, $^3J = 19$ Hz) and a doublet of doublets at -154 ppm (6-F, $^3J = 18$ Hz, $^5J = 8$ Hz).

Increasing the temperature to 190 °C has a significant effect on the course of the reaction, leading in the case of dimethylamine and pyrrolidine, after 72 h, to a complex mixture of di- **5**–**7**, tri- **8** and tetrasubstituted **9** products (Scheme 1). Piperidine produces mainly di- and trisubstitututed derivatives, with small amounts of the 1,2,4,5-product **9**. Unfortunately, we could not isolate trisubstituted derivatives of type **8** from the products, due to their very close mobility on common sorbents to diamines **5**. The absence of compounds of type **10** and **11** in the product mix can be explained on the basis of the well-established rule that the substitution site must have a maximum number of activating *meta*- and *ortho*-fluorines [15]. Thus only intermediate **13**, and not **12**, is produced on reaction of **6** with amines.

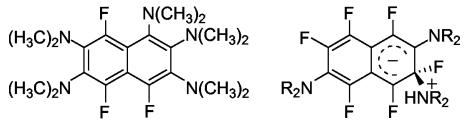


10 **11** **12** **13**

Prolonged heating (up to 7 days) does not have a major effect on the product distribution, increasing somewhat the abundance of compounds **8** and **9**.

OFN, having more sites for fluorine substitution along with a larger π-system, already after 3 days produces a mixture of di- **14**, tri- **15**, and tetrasubstituted **16** derivatives (Scheme 2). The characteristic feature is substitution of β-fluorines exclusively. Triamines **15** show the following set of ^{19}F NMR signals: a doublet of doublets at $\delta = -133$ ppm (4-F, $J_{peri} = 69$ Hz, $^5J = 15$ Hz), a doublet of doublets at -134 ppm (5-F, $J_{peri} = 68$ Hz, $^5J = 17$ Hz), a doublet of doublets at -135 ppm (1-F, $J_{peri} = 67$ Hz, $^5J = 16$ Hz), a doublet at -148 ppm (7-F, $^3J = 16$ Hz) and a doublet of multiplets at -152 (8-F, $J_{peri} = 67$ Hz). The fluorines in compounds of type **16** give a singlet at about -135 ppm (compare with the above-mentioned spectral data and [16]).

Compounds **16** become essentially the sole products in the reaction with dimethylamine and pyrrolidine at the end of 7 days. However, even under these conditions piperidine gave a mixture of **15** and **16**, and in order to make the latter the main product, increasing the temperature to 190 °C was required. The substitution pattern for the two other amines at this temperature essentially does not change, although the product yields are lower. With dimethylamine about 20% of the pentasubstituted product **17** was detected, its ^{19}F NMR spectra contained a characteristic *peri*-coupling constant of about 80 Hz in agreement with the proposed structure.



17 **18**

The exclusive β-substitution observed in the reaction of OFN is again a result of maximizing the number of activating *meta*- and *ortho*-fluorines: following substitution of two amino groups, only intermediate **18** has the maximum number of activating fluorines. Their influence is so strong that they overcome the steric hindrance associated with the introduction of a relatively bulky substituent *ortho* to an existing one.

One possible way to increase the number of substituting amino groups, as was demonstrated previously for pentafluoroaniline [3] and heptafluoroaminonaphthalene [5] derivatives, is the conversion of com-

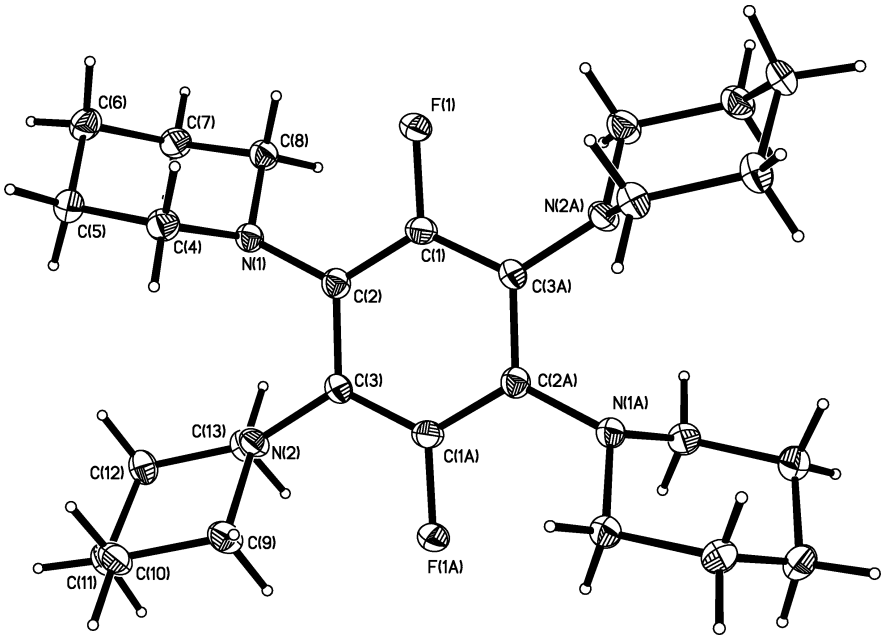


Fig. 1. The solid-state structure of 3,6-difluoro-1,2,4,5-tetrakis(piperidin-1-yl)benzene. Selected bond lengths (Å) and angles (°): C(1)-C(3A) 1.400(2), C(3A)-C(2A) 1.410(2), F(1)-C(1) 1.366(2), N(1)-C(2) 1.432(2), N(2)-C(3) 1.419(2), C(1)-C(2)-C(3) 117.5(2), C(2)-C(3)-C(1A) 117.3(2), C(3)-C(1A)-C(2A) 125.0(2), N(1)-C(2)-C(1) 123.8(2), N(1)-C(2)-C(3) 118.6(2), N(2)-C(3)-C(2) 119.1(2), N(2)-C(3)-C(1A) 123.4(2), F(1)-C(1)-C(2) 117.5(2), F(1)-C(1)-C(3A) 117.1(2), C(8)-N(1)-C(2)-C(1) 37.5(3), C(4)-N(1)-C(2)-C(3) 80.8(2), C(13)-N(2)-C(3)-C(2) 76.5(2), C(9)-N(2)-C(3)-C(1A) 36.2(3).

pounds **5** and **16** into more electron deficient *N*-oxides. However, in acidic media (H_2O_2/acetic or formic acid [3, 5]) even at low temperatures, only oxidation with tarring of all reaction mass takes place. On the other hand, in neutral conditions (H_2O_2 in methanol, similar to [17]; *t*-butyl hydroperoxide in the presence of transition metals [18]; H_2O_2-urea adduct/phthalic anhydride system [19]) the starting compounds remain unchanged even after prolonged reaction times.

The relative reaction rates and product distributions allows the nucleophilicity order for amines to be established: pyrrolidine > dimethylamine > piperidine. This sequence is in agreement with data for other nucleophilic substitution reactions [20].

Reaction with lithium dialkylamides

The amides were prepared *in situ* by reaction of *n*-butyl lithium with amines at −10 °C. We used two equivalents of amide for each fluorine atom with reactions carried out at 20 °C for a period of 24 h.

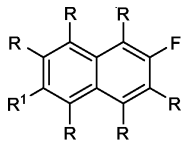
Tetrasubstituted derivatives **9** were the main products in the case of HFB, with overall yields ranging from 80 to 90%. Whereas in THF and refluxing diethyl ether only compound **9** formed, the same reaction in dioxane leads to a mixture of tri- (**8**) and tetrasubstituted (**9**) products; for example, with lithium piperidide the ratio was 42 : 58. Lithium dimethylamide was an exception giving in diethyl ether a mixture of **5**, **8** and **9**. This probably arises due to the lower solubility of dimethylamide in ether in comparison with lithium piperidide and pyrrolidide. The addition of excess amide or "disaggregating" agents, such as *N,N,N',N'*-tetramethylethylenediamine (TMEDA) and HMPTA, to THF solutions does not increase the number of fluorines replaced.

Confirmation of the functional group arrangement in tetrasubstituted benzenes was confirmed by X-ray analysis for the product of the reaction between HFB and lithium piperidide, namely 3,6-difluoro-1,2,4,5-tetrakis(piperidin-1-yl)benzene (Fig. 1). Its distinctive feature, along with considerable twisting (by 60°) of the piperidino groups relative to the benzene ring (*c.f.* 55° for 1,4,5,8-tetrafluoro-2,3,6,7-tetrakis(piperidin-1-yl)naphthalene), is the significant deviation of fluorines from the least-squares plane of the aromatic ring, 0.22 Å in comparison with 0.054 Å in a similar naphthalene derivative of type **16** [13]. Despite the presence

of sterically demanding substitutents, the benzene ring is almost planar; atoms C(1) and C(1A) (Fig. 1) deviate from the least-squares plane by only around 0.5°, showing some tendency to adopt a boat form.

With OFN, the addition of HMPTA to ethereal solvents is necessary in order to prevent contamination with less substituted derivatives. The nature of the solvent, along with nucleophile strength, are the major factors determining the number of fluorines substituted.

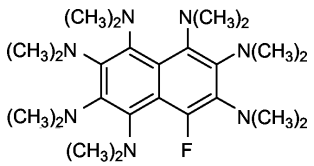
Reaction with lithium piperidide in all solvents used leads to the formation of the hexasubstituted product **19** exclusively; its structure was confirmed by X-ray analysis [14].



19 R = piperidin-1-yl, R^1 = F
20 R = $N(CH_3)_2$, R^1 = F
21 R = R^1 = $N(CH_3)_2$
22 R = pyrrolidin-1-yl, R^1 = F
23 R = R^1 = pyrrolidin-1-yl

Lithium dimethylamide give compound **20** only in dioxane; in THF the substitution pattern changes, leading to the heptasubstituted derivative **21**. With the more nucleophilic lithium pyrrolidide reaction in dioxane produced an inseparable mixture of **22** and **23** (45 and 55%, respectively), while in THF only **23** formed.

All efforts to achieve octasubstitution, by varying the reaction conditions and the concentration of amide, were unsuccessful.



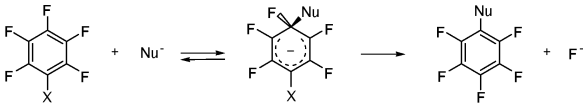
24

Attempts to substitute the remaining fluorines in tetrakis(dialkylamino)naphthalenes **16** were also made. Neither lithium piperidide nor pyrrolidide gave any new products, possibly due to repulsion between the amino groups in the corresponding σ-complexes. With lithium dimethylamide in THF, the amine **24** is formed in about 42% yield. Its ^{19}F NMR spectrum showed a number of complicated multiplets, indicating a "through space" interaction with the methyl protons of the *peri*-dimethylamino group [21].

In general reaction of OFN with neutral amines results primarily in the tetrasubstituted product **16** whereas reaction with lithium amides readily gives the hexasubstituted product **19** and even heptasubstituted products such as **21** and **23**. Why do the substitution patterns differ?

Despite the fact that we have not identified the products of mono- and disubstitution in the reaction of OFN with lithium amides, the course of nucleophilic substitution begins similarly to that with neutral amines, with initial replacement of fluorine at position 2 and then positions 6 or 7. This assumption is based on previous observations of the reaction of OFN and lithium diisopropylamide [9]. Thereafter, the substitution pattern differs, as with neutral amines positions 2, 3, 6 and 7 are substituted (see **16**), whereas with amides fluorines at positions 3 and 7 are typically *not* substituted in the final product, although all other fluorines are (see **19**). Thus the difference in substitution seems to occur during replacement of the third fluorine.

The mechanism of nucleophilic aromatic substitution (S_NAr) is generally held to proceed *via* a two-stage process involving the covalent addition of a nucleophile to a substituted (or unsubstituted) carbon ring atom, followed by departure of the leaving group (fluoride in this case) to form the substituted product (Scheme 3). The usually negatively charged intermediate, containing both the nucleophile and the leaving group, is known as a Meisenheimer complex [22], and is the anionic equivalent of the Wheland intermediate in electrophilic substitution [23]. The negative charge in the Meisenheimer complex is delocalized into the aromatic π-system which, like the Wheland intermediate, can be considered as a resonance hybrid of multiple canonical forms.



Scheme 3.

The American authors have presented a simple model for determining the principal site for nucleophilic substitution in aromatic perfluorocarbons [24] based on the relative stabilities of the various Meisenheimer complexes as calculated *via* density functional theory (using the hybrid B3LYP functional [25] with the modest 6-31G* Gaussian basis set [26], denoted B3LYP/6-31G*). Basically all possible Meisenheimer complexes for a given aromatic perfluorocarbon are calculated, using the fluoride ion as a model nucleophile, with the lowest energy complex determining the substitution site. This is essentially a purely

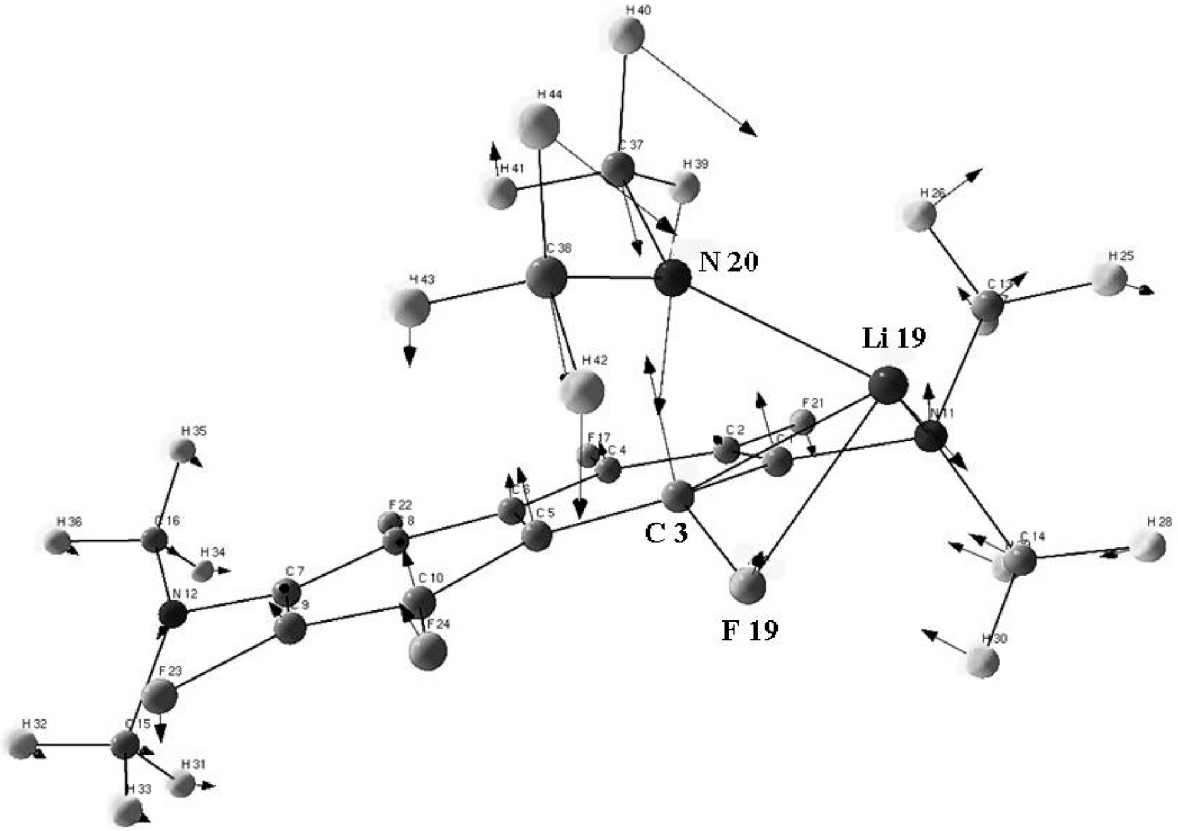


Fig. 2. Transition state for reaction of **14** with lithium dimethylamide showing nucleophilic substitution at position 1. The arrows indicate the atomic displacements in the imaginary mode. The lithium atom is "coordinated" to one of the ring fluorines and the nitrogen atom of the $N(CH_3)_2$ group at position 2; this brings the nitrogen atom of the dimethylamide (N 20) over the ring carbon at position 1, facilitating the attack. As can be seen a bond is forming between this nitrogen (arrow down) and the ring carbon atom (C 3, arrow up). The N-C distance in the transition state is 2.20 Å.

thermodynamic argument, *i. e.*, the thermodynamically most stable Meisenheimer complex is the one most likely to form, and the substitution pattern follows directly from that.

Despite its simplicity, and the fact that it cannot possibly account for all the different nucleophiles, solvents and reaction conditions found experimentally, this model proved to be remarkably reliable, successfully predicting the principal substitution site in 16 different aromatic perfluorocarbons, including OFN [24].

The general consensus among experimentalists appears to be that for strong nucleophiles the rate-limiting step in nucleophilic substitution reactions is Meisenheimer complex formation, whereas for weak nucleophiles (such as amines) the rate-limiting step is decomposition of the Meisenheimer complex into the products [2, 27]. The simple model presented in ref. [24] ought to be applicable to the latter case, as any initially formed Meisenheimer complex can decompose several times back into the reactants *before* forming products, which favors formation of the most thermodynamically stable complex. On the other hand, if the Meisenheimer complex decomposes readily to products, then the thermodynamics is of much less importance and the quantity that really needs to be computed is the barrier height. In this situation, one would not expect the model in ref. [24] to work at all.

We have carried out B3LYP/6-31G* calculations on all distinct Meisenheimer complexes derived from **14** using dimethylamine as the nucleophile ($R = N(CH_3)_2$). All calculations used the PQS program [28]. Such calculations are clearly in the spirit of the model in ref. [24]. The lowest energy Meisenheimer complex corresponds to substitution at posi-

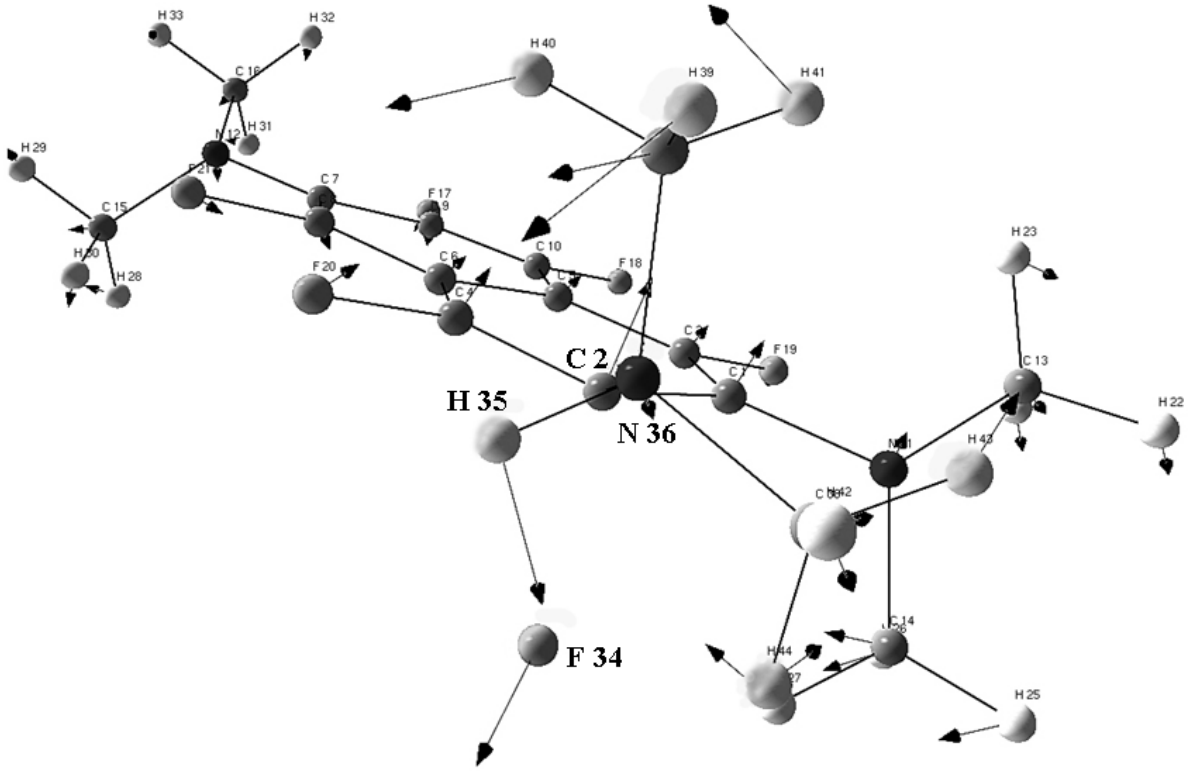


Fig. 3. Transition state for decomposition of the Meisenheimer complex derived from **14** by attachment of dimethylamine at position 3. The arrows indicate the atomic displacements in the imaginary mode. The hydrogen atom directly attached to the nitrogen in the dimethylamine ligand is leaving (arrow down) and forming a bond with the leaving fluorine atom formerly attached to the ring carbon at position 3. The ring carbon – leaving fluorine atom distance in the transition state is 1.97 Å. According to Weinhold's NBO analysis [29], this fluorine is well on the way to being a fluoride ion, with a calculated atomic charge of $-0.64|e|$.

tion 3, exactly as found experimentally. Additionally we have located transition states for the reaction of $LiN(CH_3)_2$ with **14**, with substitution at positions 1, 3 and 4. We have not incorporated any solvent effects, and thus the transition states we have located formally correspond to reaction in the gas phase. Nevertheless, the lowest energy transition state corresponds to nucleophilic attack at position 1, *not* position 3 which is actually the least favorable. The estimated barrier height for attack at position 1 is only 7.4 kcal/mol, indicating – as is found experimentally – that lithium dimethylamide is very reactive. All transition states were verified as such by vibrational analysis. A schematic of the transition structure for 1-substitution with arrows showing the atomic displacements in the imaginary mode is shown in Fig. 2. The transitions states for 3- and 4-substitution are similar.

Additionally we have calculated transition states for the loss of HF from the various Meisenheimer complexes in the reactions with dimethylamine. As expected, computed barrier heights are noticeably greater than those for the reaction with amide, being around 35 kcal/mol (gas phase), but the lowest barrier is for loss of HF from position 3. Note that in addition to the corresponding Meisenheimer complex being the most stable energetically, the 3-substituted product is also the most stable of the possible products. The transition state for loss of HF from position 3 is shown in Fig. 3.

Basicity of hexa- and heptakis(dialkylamino)fluoronaphthalenes

The basicity of the poly(dialkylamino)naphthalenes **19**–**24** is of particular interest, inasmuch as compounds producing IHB of type **2** following protonation are currently among the most intensively studied of all organic bases [10]. These derivatives furthermore contain strongly electron donating β-amino groups, which should significantly increase the resulting basicity.

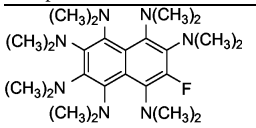
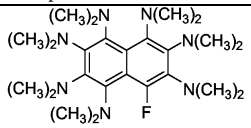
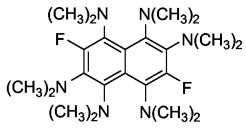
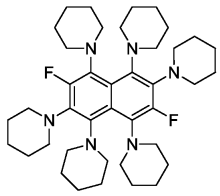
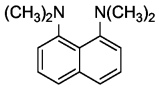
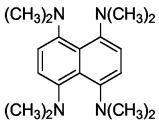
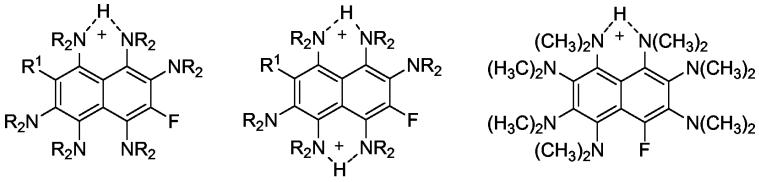
Compound	pKa[a]	Compound	pKa[a]
 **21**	12.9 ± 0.3 (7.6 ± 0.1)	 **24**	13.9 ± 0.4
 **20**	12.2 ± 0.3 (8.2 ± 0.2)	 **19**	11.2 ± 0.2 (6.9 ± 0.1)
 **25**	9.9 ± 0.1[b]	 **26**	12.7 ± 0.3 (8.2 ± 0.2)

Table 1. pKa Values for some poly(dialkylamino)naphthalenes in 80% aq. dioxane (at 25 °C).

[a] pKa^1 values, along with pKa^2 in parentheses; [b] pKa in water is 12.1 [30].



NR_2 = $N(CH_3)_2$ or piperidino; R^1 = F or $N(CH_3)_2$

27 **28** **29**

Since the pyrrolidino substituted products **22** and **23** readily oxidize upon exposure to air, we measured the basicity for piperidino **19** and dimethylamino **20**, **21**, **24** substituted derivatives. pKa values were determined in 80% aq. dioxane along with values for the parent compounds **25** and **26** (Table 1).

During our measurements derivatives **19** – **21** gave mono- **27** and then diprotonated **28** salts, while hexaamine **24** gave only the monocation **29**. As can be seen from Table 1, all compounds synthesized, except the piperidino substituted compound **19**, are stronger bases than **25** and **26**, although the increase in basicity is not as great as we anticipated based on the number of animo groups. This is most likely due to the strongly strained structures of compounds **19** – **24** and their protonated cations, which lead to IHB destabilization and accordingly decrease the basicity.

Conclusions

A series of dialkylaminosubstituted benzenes and naphthalenes have been synthesized by nucleophilic substitution in the corresponding perfluoroaromatic compounds using secondary amines and secondary lithium amides. With hexafluorobenzene (HFB) the same substitution pattern is observed with both amines and amides, but with octafluoronapthalene (OFN) the subsitution pattern differs after the first two fluorines have been replaced. Theoretical calculations indicate that with lithium dimethylamide the third fluorine is substituted at position 1, whereas with dimethylamine it is position 3. The maximum number of fluorines that can be replaced under our reaction conditions is four for HFB and six (with lithium piperidide) or seven (with dimethylamide and pyrrolidide) for OFN. The hexa- and heptasubstituted naphthalenes are stronger bases than the parent 1,8-bis(dimethylamino)naphthalene **25**, although the increase in basicity is smaller than expected.

Experimental Section

Hexafluorobenzene, octafluoronaphthalene, pyrrolidine and DMEU were purchased from Lancaster; HMPTA and

1.6 M *n*-butyl lithium in hexane from Fluka. ^{1}H and ^{19}F NMR spectra were recorded on a Varian Unity-300 spectrometer with $(CH_3)_4Si$ as the internal standard for ^{1}H and $CFCl_3$ for ^{19}F. GC/MS were performed on Perkin Elmer PE-5MS RX apparatus. A 25 m fused silica (methylphenylsilicone) capillary column was used with UHP grade helium as the carrier gas. pKa values were measured by potentiometric titration of corresponding conjugated acids with 0.1 M aq KOH in 80% aqueous dioxane according to the method described in ref. [31]. 0.05 M aq KCl was used as stock electrolyte. Hydrogen ion activity was measured using an electric cell containing glass and Ag/AgCl (reference) electrodes.

General procedure for the reaction of HFB and OFN with neutral amines

A solution of the perfluoroaromatic (0.1 mmol), amine (4 equivalents per each fluorine atom) and DMEU (2 ml) in a sealed tube was heated at the desired temperature for the selected time (see below). The reaction mixture was then poured into water (30 ml) and the products were extracted with hexane (chloroform for the less soluble piperidino substituted derivatives) (4×5 ml). The organic phase was washed with water (4×20 ml), dried over Na_2SO_4, evaporated to dryness and crystallized from an appropriate solvent.

2,3,5,6-Tetrafluoro-1,4-bis(dimethylamino)benzene

Optimal conditions: 95 °C, 24 h; yield 79%; colourless needles with m. p. 38 – 39 °C (purified by vacuum sublimation) (lit.: 38.5 °C [4]). – ^{1}H NMR (300 MHz, $CDCl_3$): $\delta =$ 2.87 (12 H, s, N(CH_3)$_2$). – ^{19}F NMR (272 MHz, $CDCl_3$): $\delta = -154.59$ (s). – $C_{10}H_{12}F_4N_2$ (236.2): calcd. C 50.85, H 5.1, N 11.9; found C 50.7, H 5.3, N 11.8.

2,3,5,6-Tetrafluoro-1,4-bis(pyrrolidin-1-yl)benzene

Optimal conditions: 95 °C, 24 h; yield 78%; colourless needles with m. p. 94 – 95 °C (from MeOH) (lit.: 88 °C [4]). – ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.90$ (8 H, m, CH_2CH_2), 3.40 (8 H, m, N(CH_2)$_2$). – ^{19}F NMR (272 MHz, $CDCl_3$): $\delta = -156.89$ (s). – $C_{14}H_{16}F_4N_2$ (288.3): calcd. C 58.3, H 5.6, N 9.7; found C 58.7, H 5.3, N 9.6.

2,3,5,6-Tetrafluoro-1,4-bis(piperidin-1-yl)benzene

Optimal conditions: 95 °C, 24 h; yield 80%; colourless plates with m. p. 134 – 135 °C (from MeOH) (lit.: 130 °C [4]). – ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.90$ (12 H, m, CH_2CH_2CH_2), 3.40 (8 H, m, N(CH_2)$_2$). – ^{19}F NMR (272 MHz, $CDCl_3$): $\delta = -156.90$ (s). – $C_{16}H_{20}F_4N_2$ (316.3): calcd. C 60.75, H 6.4, N 8.9; found C 60.6, H 6.4, N 8.6.

General procedure for the reaction of HFB and OFN with lithium amides

To the amine (2 equivalents per each fluorine atom) in anhydrous THF (or other solvent, 3 ml) 1.6 M *n*-BuLi in hexane (2 equivalents per each fluorine atom) were added dropwise at −10 °C under argon. The reaction mixture was stirred at −10 °C for 20 min and then a solution of the perfluoroaromatic (0.1 mmol) in THF (or other solvent, 2 ml) was added. The solution was allowed to warm up to room temperature, stirred for 24 h and then quenched with MeOH (1 ml). The reaction mixture was then poured into 30% aq. KOH (15 ml) and the products were extracted with hexane (5×3 ml). The extract was washed with water (3×15 ml), dried over Na_2SO_4, evaporated to dryness and crystallized from a suitable solvent or separated by column chromatography on alumina.

3,6-Difluoro-1,2,4,5-tetrakis(dimethylamino)benzene

THF as solvent, yield 80%; colourless needles with m. p. 123 – 124 °C (from MeOH). – ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.79$ (24 H, m, N(CH_3)$_2$). – ^{19}F NMR (272 MHz, $CDCl_3$): $\delta = -137.46$ (s). – MS (EI, 70 eV): *m/z* (%) = 286 (100) $[M]^+$, 256 (14) $[M\text{-}CH_2NH_2]^+$, 225 (17) $[M\text{-}2CH_2NH_2]^+$, 58 (39) $[C_3H_8N]^+$, 44 (71) $[C_2H_6N]^+$. – $C_{14}H_{24}F_2N_4$ (286.4): calcd. C 58.7, H 8.45, N 19.6; found C 59.0, H 8.3, N 19.8.

3,6-Difluoro-1,2,4,5-tetrakis(pyrrolidin-1-yl)benzene

THF as solvent, yield 90%; colourless needles with m. p. 197 – 198 °C (from MeOH). – ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.86$ (16 H, m, CH_2CH_2), 3.23 (16 H, m, N(CH_2)$_2$). – ^{19}F NMR (272 MHz, $CDCl_3$): $\delta = -137.17$ (s). – MS (EI, 70 eV): *m/z* (%) = 390 (100) $[M]^+$, 195 (16) $[M\text{-}195]^+$, 70 (55) $[C_4H_8N]^+$, 55 (20) $[C_4H_7]^+$, 41 (38) $[C_4H_7\text{-}CH_2]^+$. – $C_{22}H_{32}F_2N_4$ (390.5): calcd. C 67.7, H 8.3, N 14.35; found C 67.6, H 8.1, N 14.2.

3,6-Difluoro-1,2,4,5-tetras(piperidin-1-yl)benzene

THF as solvent, yield 79%; colourless needles with m. p. 224 – 225 °C (from MeOH). – ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.55$ (8 H, m, CH_2), 1.61 (16 H, m, CH_2CH_2), 3.03 (16 H, m, N(CH_2)$_2$). – ^{19}F NMR (272 MHz, $CDCl_3$): $\delta = -136.46$ (s). – MS (EI, 70 eV): *m/z* (%) = 446 (100) $[M]^+$, 378 (12) $[M\text{-}C_5H_8]^+$, 295 (10) $[M\text{-}C_5H_8\text{-}C_5H_9N]^+$, 83 (15) $[C_5H_9N]^+$, 43 (28) $[C_2H_5N]^+$. – $C_{26}H_{40}F_2N_4$ (446.6): calcd. C 69.9, H 9.0, N 12.5; found C 70.1, H 9.1, N 12.3.

3,6-Difluoro-1,2,4,5,7,8-hexakis(piperidin-1-yl)naphthalene

THF as solvent, yield 46%; yellow powder with m. p. 247 – 248 °C (from CH_2Cl_2). – UV/vis (*n*-hexane): $\lambda_{max}(\lg\varepsilon) = 224$ (4.46), 259 (4.43), 368 nm (4.07). –

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.59$ (36 H, m, $CH_2CH_2CH_2$), 3.03 (16 H, s, $N(CH_2)_2$), 3.16 (8 H, m, $N(CH_2)_2$). – ^{19}F NMR (272 MHz, $CDCl_3$): $\delta = -134.54$ (s). – $C_{40}H_{60}F_2N_6$ (662.9): calcd. C 72.5, H 9.1, N 12.7; found C 72.3, H 9.2, N 12.5.

7-Fluoro-1,2,3,4,5,6,8-heptakis(dimethylamino)naphthalene

THF as solvent, yield 43%; yellow needles with m. p. 148 – 149 °C (from MeOH/hexane). – UV/vis (*n*-hexane): λ_{max} ($\lg\varepsilon$) = 213 (4.54), 236 (4.50), 311 (3.41), 355 nm (shoulder). – ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.75$ (12 H, m, $N(CH_3)_2$), 2.77 (12 H, s, $N(CH_3)_2$), 2.78 (12 H, m, $N(CH_3)_2$), 2.81 (24 H, m, $N(CH_3)_2$), 2.82 (12 H, s, $N(CH_3)_2$). – ^{19}F NMR (272 MHz, $CDCl_3$): $\delta = -134.0$ (s). – MS (EI, 70 eV): *m/z* (%) = 447 (14) $[M]^+$, 389 (11) $[M\text{-}C_3H_8N]^+$, 58 (100) $[C_3H_8N]^+$. – $C_{24}H_{42}F_1N_7$ (447.6): calcd. C 64.4, H 9.5, N 21.9; found C 64.4, H 9.4, N 21.7.

7-Fluoro-1,2,3,4,5,6,8-heptakis(pyrrolidin-1-yl)naphthalene

THF as solvent, yield of crude product 45%, which readily oxidised on exposure to air and so was not characterised in detail. – ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.86$ (28 H, m, CH_2CH_2), 3.24 (28 H, m, $N(CH_2)_2$).

8-Fluoro-1,2,3,4,5,6,7-heptakis(dimethylamino)naphthalene

Obtained by reaction of 1,4,5,8-tetrafluoro-2,3,6,7-tetrakis(dimethylamino)naphthalene (0.1 mmol) with lithium dimethylamide (0.8 mmol) in THF according to the general procedure. Yield 42%; yellow crystals with m. p. 176 – 177 °C (from MeOH/hexane). – UV/vis (*n*-hexane): $\lambda_{max}(\lg\varepsilon) = 220$ (4.27), 303 (3.99), 360 nm (shoulder). – ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.77$ (12 H, m, $N(CH_3)_2$), 2.81 (24 H, s, $N(CH_3)_2$), 2.83 (12 H, m, $N(CH_3)_2$). – ^{19}F NMR (272 MHz, $CDCl_3$): $\delta = -134.5$ (m). – MS (EI, 70 eV): *m/z* (%) = 447 (30) $[M]^+$, 389 (17) $[M\text{-}C_3H_8N]^+$, 388 (12) $[M\text{-}C_3H_8N\text{-}H]^+$, 374 (12) $[M\text{-}C_3H_8N\text{-}CH_3]^+$, 58 (100) $[C_3H_8N]^+$. – $C_{24}H_{42}F_1N_7$ (447.6): calcd. C 64.4, H 9.5, N 21.9; found C 64.4, H 9.7, N 21.7.

Crystal structure determination of 3,6-difluoro-1,2,4,5-tetrakis(piperidin-1-yl)benzene

Single crystals suitable for X-ray diffraction were selected directly from the analytical sample.

Crystal data: $C_{26}H_{40}F_2N_4$, $M = 446.62$, triclinic space group $P\bar{1}$, $a = 6.5655(11)$, $b = 8.8550(15)$, $c = 10.8553(19)$ Å, $\alpha = 77.893(4)$, $\beta = 88.455(4)$, $\gamma = 79.285(4)^\circ$, $Z = 1$, $D_{calc.} = 1.223$ g cm^{-3}. Diffractometer: Bruker SMART 1000 CCD, μ(Mo-K$_\alpha$) = 0.098 mm^{-1}, graphite monochromator, crystal size $0.25 \times 0.35 \times 0.50$ mm, $T = 120(2)$ K; 4357 reflection measured, 2858 unique ($R_{int} = 0.0246$) which were used in all calculations, cut-off criterion $I > 2\sigma s(I)$, $\mu = 0.083$ mm^{-1}, solution and refinement with SHELXL-97 [32]. The final *R* and $wR(F^2)$ values were 0.0608 and 0.1182 (all data), the residual electron density was between 0.24 and -0.27 *e* Å^{-3}. Crystallographic data for the structure have been deposited with the Cambridge Crystallographic Data Centre, CCDC-272720. Copies of the data can be obtained free of charge on application to The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: int.code +(1223)336-033; e-mail for inquiry: fileserv@ccdc.cam.ac.uk).

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