Hexa- and heptasubstitution in the interaction of octafluoronaphthalene with lithium dialkylamides: a new approach to the naphthalene 'proton sponges'

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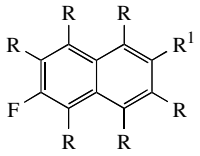
The reaction of octafluoronaphthalene with lithium dimethylamide, pyrrolidide and piperidide was performed to synthesise polykis(dialkylamino)naphthalenes with up to seven dialkylamino groups as new strongly basic naphthalene 'proton sponges'.

1,8-Bis(dimethylamino)naphthalene **1**, named as a 'proton sponge', and its derivatives attract considerable attention due to their unusual chemistry and high basicity,[1] which find wide applications in basic catalysis[2] and in the modelling of enzymatic processes.[3] Until recently, there were no attempts to prepare polykis(dialkylamino)naphthalenes containing more than four amino groups in the naphthalene core.[4] Meanwhile, beside the strained structure, these crowded compounds, especially those bearing dialkylamino groups in *peri*-positions, would possess π-donor, basic or even 'superproton sponge' properties.

To get an insight into this problem, we studied nucleophilic substitution for fluorines in octafluoronaphthalene (OFN) with lithium dialkylamides (LDAA) instead of the N-alkylation of aminonaphthalenes.[1,4]

Initially, HMPTA and 1,3-dimethylimidazolidin-2-one were used as reaction media. The LDAA were prepared *in situ* by the reactions of secondary amines (dimethylamine, pyrrolidine and piperidine) with Bu^{n}Li at –10 °C in a solvent.† Under various reaction conditions (the reaction time was up to 48 h, and the temperature varied from 20 to 95 °C), the interaction of LDAA with OFN led only to a complex mixture of partially substituted products. For example, with lithium dimethylamide in DMEU (24 h, 20 °C) the following products were detected by GC/MS: tri- (24%), tetra- (47%), penta- (8%) and hexa-substituted (< 1%) derivatives. Only with lithium piperidide at 20 °C, we isolated compound **2** (~25%) as the first hexakis-(dialkylamino) analogue of 'proton sponge' **1**. At higher temperatures (95 °C), the reaction mixtures were decomposed.



2 R = piperidino, R^1 = F
3 R = NMe$_2$, R^1 = F
4 R = R^1 = NMe$_2$
5 R = pyrrolidino, R^1 = F
6 R = R^1 = pyrrolidino

We found that, in THF or 1,4-dioxane with an addition of HMPTA (4 equiv. per fluorine atom), the course of the reaction becomes much cleaner. For lithium piperidide in either THF or dioxane, after stirring for 24 h at 20 °C, the resulting mixture contained almost solely hexaamine **2** (46%).

The interaction of OFN with lithium dimethylamide was somewhat different. While 1,2,4,5,6,8-hexakis(dimethylamino)-3,7-difluoronaphthalene **3** was formed as the main product (~40%) in dioxane at room temperature, the formation of hepta-substituted derivative **4** (43%) was observed in the case of THF under similar conditions. The same extent of substitution was found with lithium pyrrolidide: **5** (41% in dioxane) and **6** (45% in THF). Such a behaviour is probably due to difference between the dielectric constants of solvents.

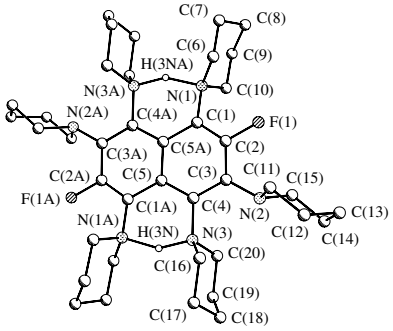


Figure 1 The X-ray structure of **2**·2HClO$_4$; view perpendicular to the central bond of the naphthalene unit (counter ions and hydrogens except those participating in H-bonding are omitted for clarity; letter A refers to equivalent positions of half the atoms). Selected bond lengths (Å) and angles (°): C(1)–C(2) 1.350(6), C(2)–F(1) 1.357(6), C(2)–C(3) 1.410(7), C(1)–N(1) 1.462(6), C(4)–N(3) 1.494(6); C(6)–N(1)–C(10) 113.7(4), N(1)–C(1)–C(5A) 119.8(4), N(1)–C(1)–C(2) 120.8(4), F(1)–C(2)–C(1) 118.6(4), N(2)–C(3)–C(4) 124.1(4), C(3)–C(4)–N(3) 117.6(5), C(16)–N(3)–C(20) 112.3(4).

The prolonged heating of LDAA with OFN in either THF or dioxane gave no products with eight dialkylamino groups in the naphthalene core. This may be explained by an increase of steric hindrances and, in part, of ring π-excessiveness as the number of dialkylamino groups was increased. We believe that the former is a major factor in the case of lithium piperidide because the corresponding heptasubstituted derivative like **4** and **6** was not detected in this case.

The structure and function arrangement in hexa- and hepta-amines, in particular, the β-location of remaining fluorines and the total displacement of α-fluorines were established by ^{1}H NMR data of their neutral and protonated forms and X-ray diffraction analysis (see below). Compounds **2**–**6** are light-yellow air-stable low-melting solids, which are easily soluble in hydrocarbons, ethers and dilute mineral acids and insoluble in dipolar aprotic solvents and alcohols.‡

We obtained X-ray diffraction data for **2** as a proton complex with HClO$_4$ (Figure 1).§ As can be seen, the salt of **2** forms a centrosymmetric dication in a similar manner as 1,4,5,8-tetrakis-

† To the amine (1.6 mmol) in anhydrous HMPTA (or another solvent, 3 ml) 1.6 M Bu^{n}Li solution in hexane (1.8 mmol) was added dropwise at –10 °C under argon. The reaction mixture was stirred at –10 °C for 20 min; then, a solution of OFN (0.1 mmol) in HMPTA (or another solvent, 2 ml) was added. After heating, the solution was additionally stirred for 24–48 h at a selected temperature (see the text) and then quenched with MeOH (1 ml). The reaction mixture was poured into 30% aq. KOH (15 ml), and products were extracted with hexane (5×3 ml). The extract was washed with water (3×15 ml), dried with Na$_2$SO$_4$, evaporated to dryness and either chromatographed on alumina or analysed by GC/MS.

‡ All new compounds gave analytical and spectroscopic data consistent with their structures. For instance, the data for 1,2,4,5,6,8-hexakis-(dimethylamino)-3,7-difluoronaphthalene **3** are as follows: lemon-yellow needles with mp 174–175 °C (from MeOH–hexane). ^{1}H NMR (300 MHz, CDCl$_3$, Me$_4$Si) δ: 2.78 (s, 12H), 2.84 (s, 12H), 2.86 (s, 12H). ^{1}H NMR [300 MHz, CD$_3$CN + HBF$_4$ (2 equiv.), Me$_4$Si] δ: 2.91 (s, 12H, NMe$_2$), 3.16 (br. s, 12H, NMe$_2$), 3.38 (d, 12H, NMe$_2$, $J_{NH,NMe}$ 3.47 Hz), 19.45 (br. s, 2H, NH). ^{19}F NMR (282 MHz, CDCl$_3$, CFCl$_3$) δ: –135.94 (s). UV [λ_{max}/nm (lg ε); *n*-hexane]: 211 (4.52), 242 (4.52), 340 (sh., 3.94), tail absorption up to 430 nm. MS, *m/z* (EI): 423 [M + 1]$^+$ (7%), 422 [M]$^+$ (30), 364 [M – 58]$^+$ (18), 349 (12), 307 (8), 58 (100).

(dimethylamino)naphthalene **7** does;[5] however, the hydrogen bridge in the dication with nitrogens 2.592 Å apart is more asymmetric (N–H, 0.95 Å; H···N, 1.73 Å; ∠NHN, 149°) than that in **7** (N–H, 1.22 Å; H···N, 1.39 Å; ∠NHN, 158°) due to the polar effect of the fluorines. Chelated protons in the ^{1}H NMR spectrum of **2**·2$HClO_4$ are strongly deshielded and appeared both at 17.8 ppm (18–21 ppm in proton sponges **3**–**6**). Despite the presence of bulky piperidino rings, the protonation takes off the steric repulsions between their electron pairs, especially for those in *peri*-positions, so the resulting salt has a virtually planar naphthalene core. All piperidino groups are in a more preferable chair conformation and almost perpendicular to the naphthalene plane with torsion angles in the range 85–88°, which explains their high ability to coordinate protons.

Similarly to hexaamine **2**, compounds **3**–**6** treated with an excess of $HClO_4$ or HBF_4 in a diethyl ether solution precipitated as diprotonated salts.¶ The basicity measurements of polyamines **2**–**6** demonstrated that, despite the presence of fluorines, all of them are at least two powers of ten more basic than **1** with pK_a1–pK_a2 difference of about 4 pK_a units (aqueous 80% dioxane, 25 °C, potentiometric titration). More specifically, for example, the pK_a is 9.89 for **1** while **3** has pK_a1 12.23 and pK_a2 8.23, and **4** has pK_a1 12.90 and pK_a2 7.63. Thus, amines **2**–**6** can be considered as new deprotonating agents since they are much stronger bases than tertiary alkylamines and stable towards oxidation and electrophiles.††

Finally, the first hexa- and heptakis(dialkylamino)naphthalenes were obtained, and the diperchlorate of 3,7-difluoro-1,2,4,5,6,8-hexakis(piperidino)naphthalene was characterised with X-ray diffraction data. The introduction of the eighth dimethylamino (pyrrolidino) groups is impossible by such a way, and the maximum number of piperidino rings per naphthalene unit is six. The new tertiary naphthylamines are considerably more basic than 1,8-bis(dimethylamino)naphthalene and prone to form dications.

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§ *Crystal data for* **2**·2$HClO_4$: $C_{40}H_{62}Cl_2F_2N_6O_8$, M = 863.86, monoclinic space group $P2_1/c$, a = 10.609(2), b = 17.486(4), c = 10.840(2) Å, β = 92.60(3)°, V = 2008.9(7) Å^3, d_{calc} = 1.428 g cm^{-3}, Z = 2, T = 163 K, Syntex P21 diffractometer, μ(MoKα) = 0.232 mm^{-1}, 6153 reflections measured, 3832 unique (R_{int} = 0.1038). The final $R_1(F)$ = 0.0741 [for 1291 reflection with $I > 2\sigma(I)$], $wR(F^2)$ was 0.1601 (all data).

Atomic coordinates, bond lengths, bond angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). These data can be obtained free of charge *via* www.ccdc.cam.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336 033; or deposit@ccdc.cam.ac.uk). Any request to the CCDC for data should quote the full literature citation and CCDC reference number 214880. For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2004.

¶ This fact, along with the strong deshielding of both of the chelated protons, proves that at least four dialkylamino groups of these amines are in 1,4,5,8-positions of the naphthalene ring. Furthermore, to resolve 3,6- and 3,7-difluoro isomers of hexaamines **3** and **5**, one should notice that the ^{1}H NMR spectra of their dications displayed only one signal for two NH protons (19.45 and 19.50 ppm, respectively), the chemical shift of which strongly depends on close environments.[1] This implies on an inversion centre in these molecules as in compound **2**.

†† Under the action of nitric acid (d 1.41) or HNO_3–H_2SO_4 and $KMnO_4$–H_2SO_4 mixtures at room temperature, compunds **2** and **3** remained unchanged.