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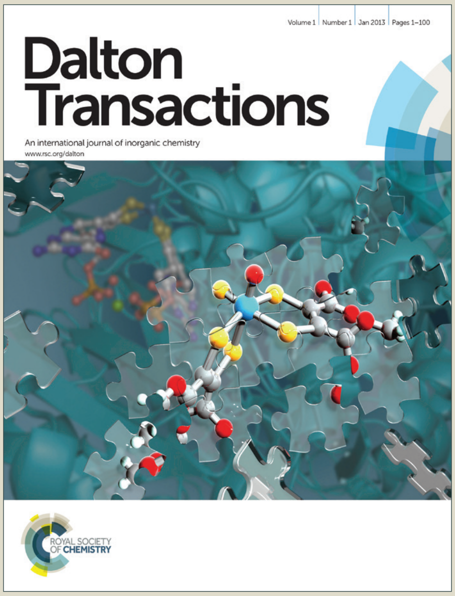

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ARTICLE

Ring lithiation of 1,8-bis(dimethylamino)naphthalene: another side of the 'proton sponge coin'

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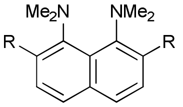
It has been found that 1,8-bis(dimethylamino)naphthalene (DMAN), unlike *N,N*-dimethylaniline, undergoes ring metallation in *n*-BuLi–TMEDA–Et_2O system with low selectivity and in poor total yield. The situation is significantly improved in *t*-BuLi–TMEDA–*n*-hexane system when 3- and 4-lithium derivatives become the only reaction products in good yield. The formation of 3-Li-DMAN is especially fortunate since no method of direct meta-functionalization of DMAN has been known to date. The relative stability and structure of DMAN lithium derivatives have been examined with the help of X-ray and multinuclear NMR measurements as well as DFT calculations.

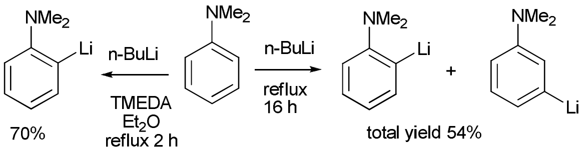
Introduction

For quite a long time, *ortho*-substituted derivatives of 1,8-bis(dimethylamino)naphthalene (proton sponge or briefly DMAN) attract great interest (see ref.[1] for reviews). Primarily, this originated from a notion that an existence of the so-called 'buttressing effect' in such compounds might strongly increase their basicity due to an extra repulsion of the *peri*-NMe_2 groups as they become closer to each other.[2] In several instances (e.g., compounds **2** and **3**)[3,4] this idea really paid off well, but in many others, e.g. **4**, failed.[5] Nevertheless, the interest to such compounds remains stable due to some other theoretical[6] and even applied[7] reasons.



1 (R = H)
2 (R = OMe)
3 (R = O^-)
4 (R = $SiMe_3$)

Traditionally, *ortho*-substituted derivatives of DMAN were synthesized by multistep procedures from the appropriate naphthalene derivatives (see e.g. ref.[8]). However, during the past decade, the situation was considerably improved because a highly selective method of DMAN *ortho*-bromination was elaborated.[7,9] This had opened a way to easy preparation (via halogen-lithium exchange) of 2-lithium and 2,7-dilithium-DMANs and therefore to a great variety of other *ortho*-derivatives of DMAN.[2,6,7] In order to further simplify the synthesis of *ortho*-substituted proton sponges and, in particular, to avoid the halogenation step, in the present work we investigated the direct lithiation of DMAN. We were counting on successful results obtained earlier for lithiation of *N,N*-dimethylaniline (DMA). Thus, it was shown that on treatment of DMA with *n*-butyllithium in Et_2O or hexane independently on temperature only C(2)–H and C(3)–H bonds were lithiated in a ~7:2 ratio.[10] However, other authors had later demonstrated that the selectivity of this process can be sharply increased in the presence of *N,N,N',N'*-tetramethylethylenediamine (TMEDA) when 2-lithium-*N,N*-dimethylaniline became the only reaction product in good yield (Scheme 1).[11] We hoped that under similar conditions DMAN will behave the same way.



Scheme 1 DMA lithiation with *n*-BuLi

DMAN lithiation

We have conducted a large series of experiments, in which 1,8-bis(dimethylamino)naphthalene was subjected to the action of *n*-butyllithium or *tert*-butyllithium either with or without TMEDA at varying solvents and temperatures (Tables 1–3, Scheme 2). To establish the ratio of thus formed lithium derivatives **5a–d**, the crude reaction mixture was usually quenched with *N,N*-dimethylformamide (DMF) to give easily identified proton sponge aldehydes **6a–d**.

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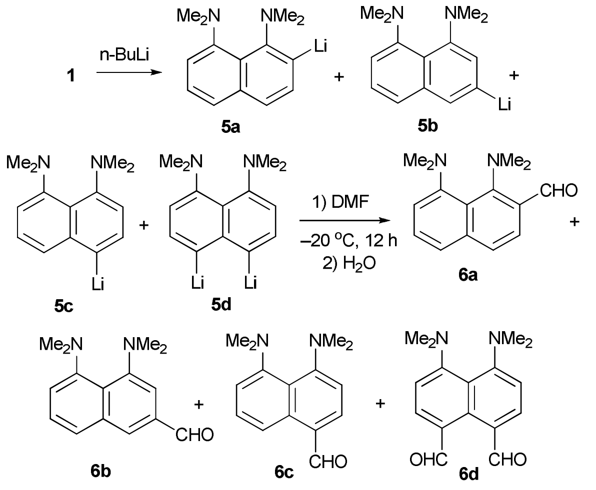
† Electronic supplementary information (ESI) available: CIF file and a table giving crystallographic data for complex ($\mathbf{5a}\cdot Et_2O)_2$; some computational details; a text file of all computed molecule Cartesian coordinates in .xyz format for convenient visualization; ^1H and ^{13}C NMR spectra for compounds **6b**, **8** and **9**. CCDC 1023357 for compound **5a**. DOI: 10.1039/C5DT02482J

First of all, it was found that unlike DMA, the metallation of DMAN is much less selective. Usually in the ^{1}H NMR spectra of the crude reaction mixture (after addition of DMF), four 'aldehyde' peaks were clearly distinguished at δ = 10.24, 10.03, 10.05 and 9.90 ppm (Figure 1). By comparison with the ^{1}H NMR spectra of the pure authentic aldehydes they were assigned to 2-, 3- and 4-monoaldehydes **6a–c** and 4,5-dialdehyde **6d**, respectively. Previously unknown 3-aldehyde **6b** was isolated in the individual state and characterized by a standard set of spectral measurements (see Experimental part). The detection in the final reaction mixtures of appreciable quantity of dialdehyde **6d**, at first sight, looks unexpected. However, this is consistent with the fact of highly selective lithiation of 1-lithiumnaphthalene to give 1,8-dilithiumnaphthalene and is suggested to be caused by the so-called agostic interactions.[12]



Scheme 2 DMAN interaction with *n*-BuLi

The second point to be discussed is that the metallation of DMAN practically does not occur in neat Et_2O (Table 1, run 1)[13] and slowly starts only on addition of TMEDA (runs 2 and 4). This can be explained by a combination of two factors: 1) pronounced tendency of *n*-BuLi to aggregation[14] and 2) a weakened CH-acidity of DMAN caused by the strong *+M*-effect of the *peri*-NMe_2 groups.[15] Room temperature (20–25 °C) is optimal for metallation; there are no signs of reaction at –20 °C (run 7), while heating or increasing the reaction time decrease the total yield of the metallation products up to 100% recovery of DMAN (runs 5, 6). The increasing amount of *n*-BuLi and TMEDA enhances the total yield to 37%, leaving the products ratio almost the same (run 3). Thirdly, the total yield of metallation products is rather modest and a large percentage of DMAN is usually recovered. In the control experiments, we have established that this stems from the expectedly high basicity of the lithium derivatives of DMAN, in particular **5a**. As a result, the lithium compounds are subjected to protolysis by diethyl ether (or Et_3N in run 8) thus being converted into initial diamine **1**. To gain more convincing evidence of the high basicity of lithium derivatives **5a–d**, we obtained one of them (**5a**) independently by treating *ortho*-bromide **7** with *n*-BuLi in Et_2O both with and without TMEDA (Table 2). The halogen-metal exchange easily occurs already at –20 °C in the absence of TMEDA (Table 2, run 1). However, the 2-lithium derivative has a relatively short lifetime due to its protolysis and accompanying Wurtz-Fittig conversion into 2-*n*-butyl-1,8-bis(dimethylamino)naphthalene (**8**) (Table 2, runs 2 and 3).[16] Both these side reactions are strongly accelerated at increasing temperature and adding TMEDA (runs 4, 5). In fact, compound **5a** is completely destroyed in Et_2O in the presence of TMEDA after storage at 20–25 °C for 24 h.

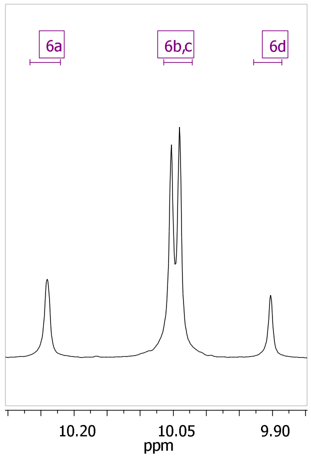


Fig. 1 The aldehyde groups region in the ^{1}H NMR spectrum ($CDCl_3$) of the reaction mixture after its quenching with DMF (Table 1, run 3).

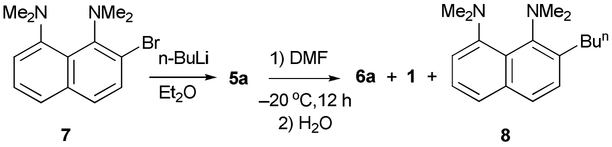
Next, the replacement of diethyl ether as a solvent for metallation of DMAN by less acidic hexane led to a substantial increase (up to 71%) of the *C*-lithium derivatives total yield (Table 3), although about 30% of the unchanged DMAN still remained in the reaction mixture after 200 h. Since metallation in hexane occurs only in the presence of TMEDA, one can assume that just TMEDA is responsible for the partial protolysis of the DMAN lithium derivatives. The relatively modest degree of the protolysis in this case can be explained by weaker CH acidity of TMEDA as compared with Et_2O.[14a] Finally, one of the most important findings made by us is that the product ratio at metallation of DMAN in hexane is rather dramatically changed depending on the incubation time. Thus, in the first measurement made after 72 h, all four aldehydes **6a–d** were detected in the reaction mixture with 10, 18, 6 and 8% yield, respectively (Table 3, run 1). However, with increasing the incubation time the percentage of 2-aldehyde and 4,5-dialdehyde was gradually decreased and after 220 h the reaction mixture (quenched with DMF) contained only 3- and 4-monoaldehydes in 44 and 27% yield, respectively (runs 7 and 8). This clearly indicates on the existence of kinetic and thermodynamic control in the metallation of DMAN in the hexane–TMEDA mixture.

Table 1 Influence of the reaction conditions on DMAN lithiation with *n*-BuLi

Run	Solvent	*n*-BuLi, eq.	TMEDA, eq.	Time, h	*T*, °C	Compounds detected in the final reaction mixture, %					
						1	**6a**	**6b**	**6c**	**6d**	**∑6a–d**
1	Et_2O	1	0	24	25	100	0	0	0	0	0
2	Et_2O	1	1	24	25	92	2	3	3	<1	8
3	Et_2O	4	4	24	25	63	10	15	10	2	37
4	Et_2O	1	1	6	25	96	1	2	1	<1	4
5	Et_2O	1	1	122	25	100	0	0	0	0	0
6	Et_2O	1	1	24	35	100	0	0	0	0	0
7	Et_2O	1	1	24	–20	100	0	0	0	0	0
8	Et_3N	1	1	24	25	100	0	0	0	0	0
9	Hexane	1	1	24	25	76	6	10	3	5	24

Apparently, in the beginning due to the combined action of the DOM effect (directed *ortho*-metallation)[17] and the above mentioned agostic interactions, the appreciable amounts of 2-lithium- **5a** and 4,5-dilithium **5d** derivatives are formed along with **5b** and **5c**. However, gradually the first two compounds undergo transformation into their more stable counterparts **5b** and **5c**, of which **5b** is clearly more stable. The relative instability of **5a** and **5d** may result from several reasons.

Table 2 Experiments showing instability of **5a** in Et_2O



Run	TMEDA, eq.	*T*, °C	Time, h	Products,[a] %		
				1	**6a**	**8**
1	0	–20	0.05	5	95	0
2	0	–20	0.3	16	84	0
3	0	–20	24	16	78	6
4	0	25	24	26	44	30
5	1	25	24	46	<1	54

[a] *After treating the reaction mixture with DMF*

Table 3 Dependence of DMAN lithiation in hexane on incubation time (4 eq. *n*-BuLi, 4 eq. TMEDA, 25 °C)

Run	Time, h	Products,[a] %					
		1	**6a**	**6b**	**6c**	**6d**	**∑6a–d**
1	72	58	10	18	6	8	42
2	96	55	9	21	9	6	45
3	120	53	6	23	12	6	47
4	144	48	8	25	13	6	52
5	168	40	4	30	20	6	60
6	192	34	2	39	22	3	64
7	216	31	0	42	25	2	69
8	264	29	0	44	27	0	71

[a] *After treating the reaction mixture with DMF*

Thus, in molecule **5a**, the repulsion of three juxtaposed lone electron pairs might be rather severe, in contrast to the parent DMAN and isomeric **5b** and **5c** where only two electron pairs are involved in the repulsion. As for dilithium derivative **5d**, its destabilization may be caused by a generally high π-excessity of the DMAN molecule,[1b] which might greatly increase due to appearance of the additional pair of the anionic centres. One cannot also disregard the strong deformation of the naphthalene ring in **5d** caused by coordination of each lithium atom with both *peri*-positions (see below).

We then found that the metallation of DMAN with *tert*-butyllithium in hexane in the presence of TMEDA occurs considerably faster and under milder conditions as compared with *n*-BuLi. This is in accordance with the higher nucleophilicity of the *tert*-butyl anion.[14a] However, the most remarkable fact is that no 2-lithium and 4,5-dilithium derivatives are formed at all when using *t*-BuLi (Table 4, Figure 2). Evidently, the greater bulkiness of this reagent directs the DMAN metallation into the sterically more available 3 and 4 positions thus preventing the second *peri*-metallation.

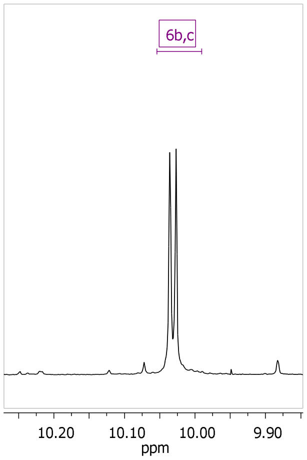


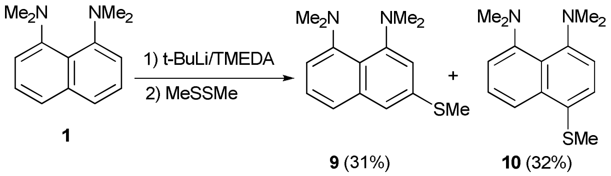
Fig. 2 The aldehyde groups region in the ^1H NMR spectrum ($CDCl_3$) of the reaction mixture in hexane after its quenching with DMF (Table 4, run 4).

We consider the formation of 3-lithium derivative **5b** an especially remarkable circumstance. The matter is that it opens the route to the synthesis of almost unknown 3-substituted derivatives of DMAN, which cannot be obtained, for example, in the reactions of DMAN with electrophiles and other reagents.[1b] Along with this, we obtained in quite appreciable yield (in addition to *meta*-aldehyde **6b**) 3-methylthio- **9** and 4-methylthio **10** derivatives of DMAN by treatment the mixture of **5b** and **5c** with dimethyldisulfide (Scheme 3).

Table 4 DMAN lithiation with 4 eq. *tert*-BuLi in hexane

Run	TMEDA, eq.	Time, h	*T*, °C	Products,[a] %		
				1	**6b**	**6c**
1	0	24	25	100	0	0
2	4	24	–20	52	22	26
3	4	24	25	35	32	32
4	4	96	–20	24	38	38

[a] *After treating the reaction mixture with DMF*



Scheme 3 DMAN Interaction with *t*-BuLi

Structural studies

X-ray measurements. During the preparation of 2-lithium derivative of DMAN from bromide **7** via halogen-lithium exchange we have noticed that **5a** is precipitated from the ether solution as yellow crystals in the form of thin plates. This allowed us to carry out their X-ray study. It was established that compound **5a**, like other lithiumnaphthalenes,[18,19] exists in the solid as a nearly symmetric dimer with the four-coordinated lithium atoms (Figure 3). Along with the C(2) and C(2′) atoms of the two aromatic rings, the lithium atoms form a rhombic structure with the following parameters: ∠Li–C–Li [67.1(3)°], ∠C–Li–C [112.9(3)°], C–Li (2.20/2.22 Å). Two other ligands for each lithium atom are the molecule of diethyl ether and the *out*-inverted 1-NMe$_2$ group with the O…Li and N…Li distances equal to 1.952(8) and 2.111(8) Å, respectively.[20] The angle between the average naphthalene ring plane and the rhombus plane (C–Li)$_2$ is 64.4(2)°.

NMR studies and solution behaviour. It seems interesting to clarify whether the dimeric structure of **5a** is also valid in solution. With this in mind we carried out the variable temperature ^{1}H, ^{7}Li and ^{13}C{^{1}H} NMR experiments with **5a** dissolved in non-deuterated THF (this technique is known as No-D spectroscopy).[19a,b] The ^{1}H and ^{13}C{^{1}H} spectra revealed the presence in the solution of small amounts (about 10% each) of DMAN and bromide **7** (Figures 4, 5). Fortunately, their signals where not overlapped with these of **5a** and could be easily singled out by comparison with the spectra of the authentic samples. Besides, the temperature lowering led to a considerable increase of the solution viscosity that resulted in almost complete disappearance of the admixture signals. As seen from Figure 4, the proton spectra of **5a** demonstrate a typical proton sponge pattern in the aromatic region and low temperature sensitivity. The only exception is a doublet at δ = 7.65 ppm, whose considerable low-field shift as well as a resemblance with the similar peak in the ^{1}H NMR spectrum of phenyllithium[22] allow to assign it to the H-3 proton deshielded by the neighbouring C–Li bond. The high-field signal at δ = 6.51 ppm on the basis of common regularities of ^{1}H NMR spectra of proton sponges[1b] can be assigned to the H-7 hydrogen. As expected, the carbanionic nature of 2-Li-DMAN causes noticeable shielding of other H-atoms including those of NMe$_2$ groups. Perhaps, an appearance of the latter is especially informative from the structural point of view (Figure 4). At –5 °C (the highest temperature employed) the NMe$_2$ groups display two close peaks at δ 2.7 ppm. Normally, such chemical shift is typical for the proton sponge NMe$_2$ groups whose methyls are turned outward and axes of electron pairs are directed inward of the internitrogen space (*in,in* conformation).[21,23]

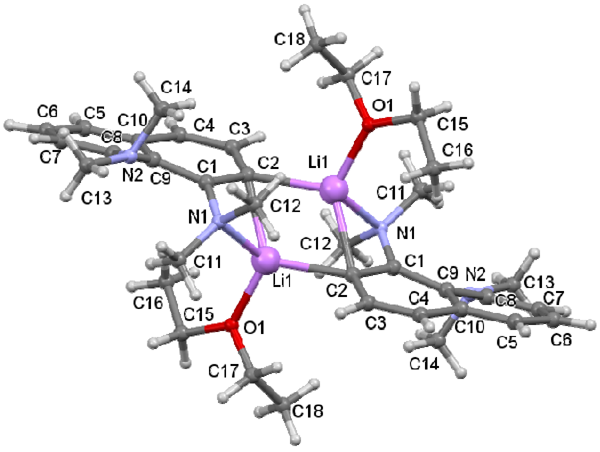


Fig. 3 Molecular structure of (**5a**·Et$_2$O)$_2$

However, on cooling the signals of two NMe$_2$ groups are gradually separated due to moving one of them into the high field region. This pattern is usually the case when 8-NMe$_2$ group is additionally pyramidalized under pressure of its 1-NMe$_2$ counterpart which undergoes nitrogen inversion due to coordination with an appropriate *ortho*-substituent.[23,24] From this, one can assume that at –5 °C, a fast equilibrium takes place mostly between structures of type **11a** and **11b** in which NMe$_2$ groups retain the *in,in* conformation incapable to coordination with the 2-lithium atom (Scheme 4). Probably, at further cooling, due to a slowing down diffusion and dynamic processes, the coordination of Li with the 1-NMe$_2$ group becomes energetically more probable and structures **11c** and **11d** with the inverted nitrogen atoms come into play. Since no doubling of signals of aromatic protons occurs (see for example ref.[6]) the coalescence temperature is not yet reached even at –90 °C, *i.e.* equilibriums between forms **11a–d** still remains rapid in the NMR time-scale. Such viewpoint is also consistent with the lithium NMR spectra (Figure 6), which demonstrate shifting the ^{7}Li signal to a higher field as the temperature decreases. This can reflect a stronger electron donation of the 1-NMe$_2$ group to the Li atom as compared with the oxygen atom of THF.

Further information was obtained from ^{13}C NMR spectrum of **5a** registered at –90 °C (Figure 5). In the aromatic region it contains ten intensive peaks of the naphthalene carbon atoms together with small impurity peaks belonging to the proton sponge **1** and 2-bromide **7**. The broaden low-field signal at δ = 172.4 ppm is the most important one. It can be unambiguously assigned to the carbon atom of the C–Li bond. This follows both from the absence of any likely peaks in the ^{13}C NMR spectrum of DMAN[1b] and its similarity with that of 1-dimethylamino-8-lithiumnaphthalene (δ = 185.5 ppm).[19b]

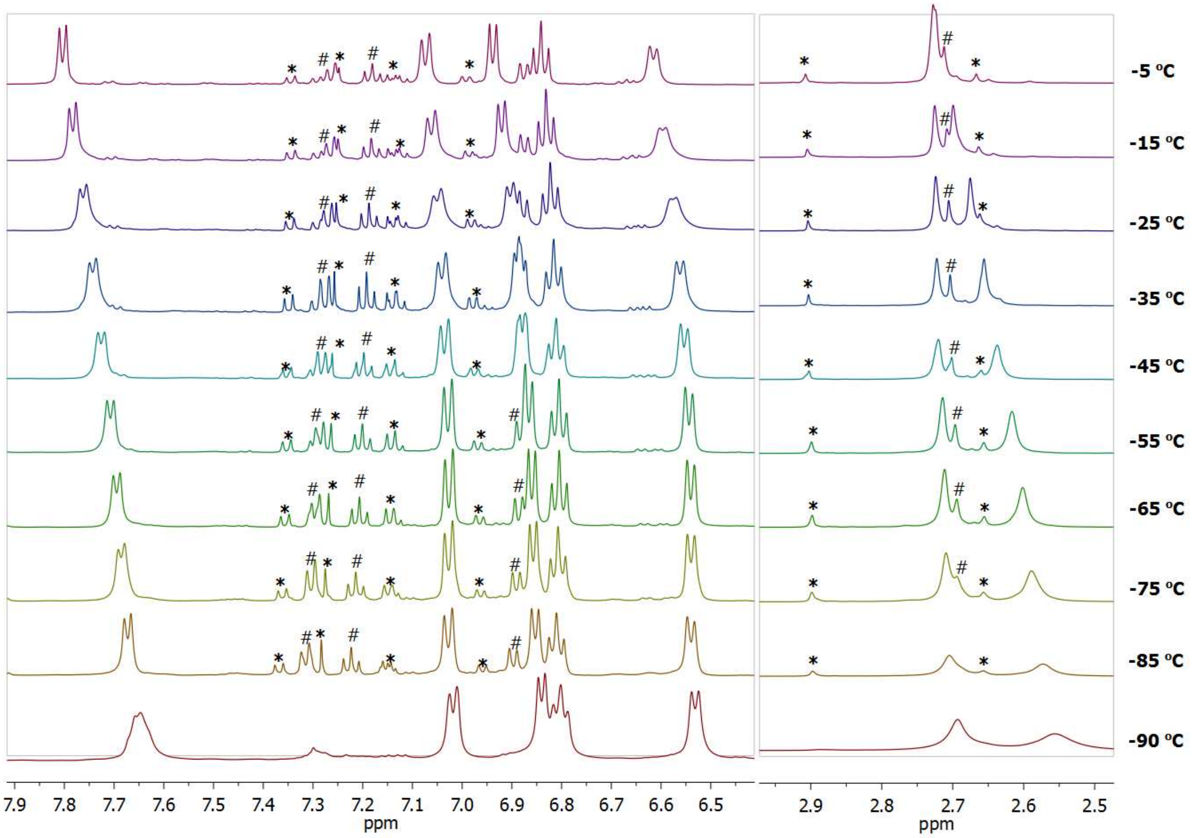


Fig. 4 Fragments of the ^{1}H No-D temperature depending NMR spectrum of 2-Li-DMAN **5a** (THF, 500 MHz). Admixture signals of **1** and **7** are marked with # and *, respectively.

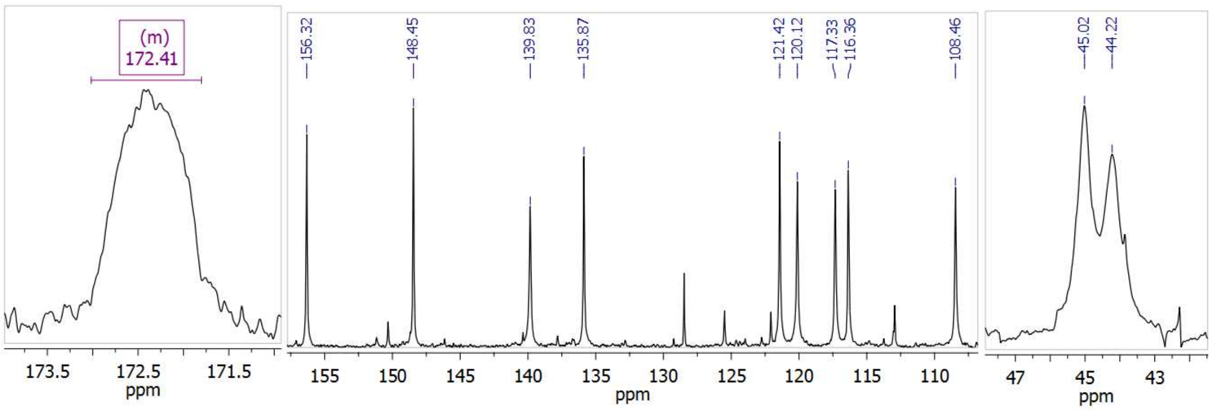
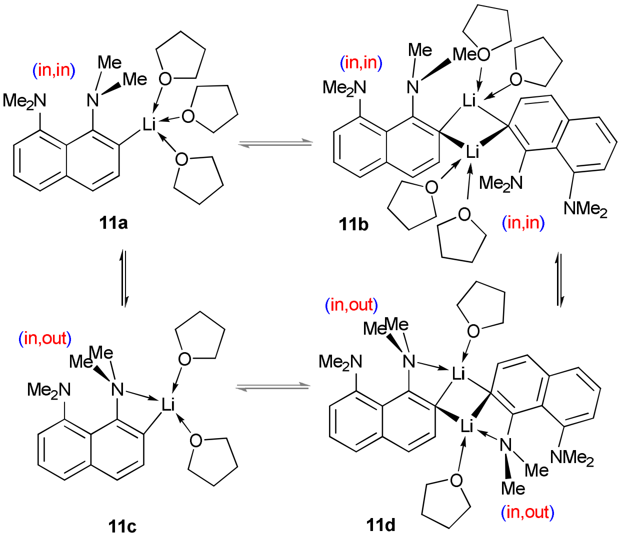


Fig. 5 Fragments of the ^{13}C No-D NMR spectrum of 2-Li-DMAN **5a** at –90 °C (THF, 126 MHz).



Scheme 4 Postulated aggregates of 2-Li-DMAN **5a** in THF solution

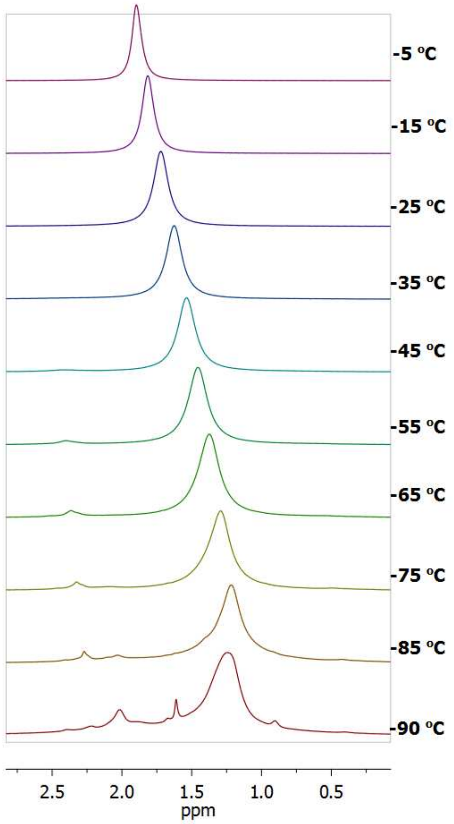
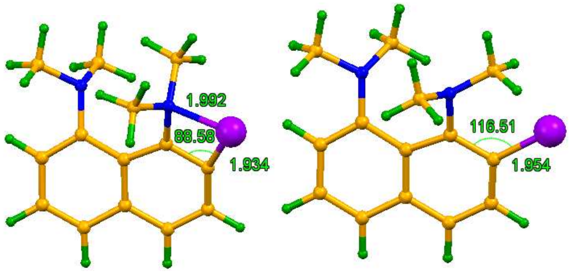


Fig. 6 ^{7}Li temperature depending No-D NMR spectrum of 2-Li-DMAN **5a** (THF, 194 MHz).

A considerable high-field shift of this signal for **5a** can be attributed to the +*M*-effect of *peri*-NMe_2 groups. If the dimeric structure of **5a** retains in solution, the signal at 172.4 ppm should appear as septet[19b] due to the spin-spin coupling of the C(2) and C(2') carbon atoms simultaneously with two ^{7}Li nuclei each of which has nuclear spin I = 3/2 (92.4% natural abundance).[25] Although the peak at 172.4 ppm is rather poorly resolved, we think that its appearance taken in combination with the above discussed NMR ^{1}H and ^{7}Li data also serve in favour of the rapid equilibria between structures **11a–d**. Apparently, at –90 °C a contribution of dimeric form **11d** considerably increases. Indirectly, this can be judged by the peak width near the base line which is equal to 154 Hz (Figure 5). Since a value of $J_{7Li\text{-}13C}$ is commonly equal to 20.5 Hz[19a,b] the spectral width of this signal is much better adapted for a septet rather than a quartet signal. Thus, with a reasonable extent of probability one can affirm that the dimeric structure **11d** prevails in solution at low temperature while at the higher temperature the equilibrium shifts to the monomeric form **11a**. Some contribution of intermediate forms like **11b** and **11c** should not be discounted as well.

Theoretical background. To get some more information on the properties of DMAN lithium derivatives, we have conducted the DFT calculations by B3LYP method with the 6-311+G(d,p) and 6-311G(d,p) basis sets. The results obtained using both sets are in good agreement. The calculations of the vibrations and zero-point energies (ZPE) are also accomplished. We were particularly interested in two issues: 1) what are the structures of lithium compounds in the gas phase and how they change on solvation and 2) what is the driving force for the transformation of 2-lithium- and 4,5-dilithium-DMANs into their 3- and 4-lithium counterparts in hexane. Regarding the first issue, the calculations unambiguously demonstrate that in the gas phase the structure of 2-Li-DMAN with the *out*-inverted 1-NMe_2 group is the most beneficial obviously due to the formation of the N→Li coordination bond (Figure 7).



E = –660.875583 a.u. E = –660.866515 a.u.

ΔE = 4.31 kcal/mol

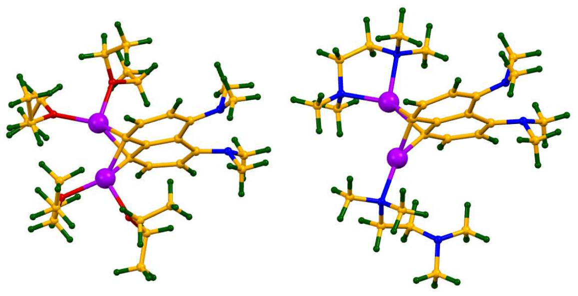
Fig. 7 Calculated geometries (selected bond lengths and distances in Å, angles in deg) for the *in,out*- and *in,in*-conformers of 2-Li-DMAN **5a** [B3LYP/6-311+G(d,p)].

In general, the difference in stability of the non-solvated **5a**(*in,out*) and **5a**(*in,in*) forms varies in the range of 4–6 kcal/mol (depending on the theoretical basis) in favour of the former. A relatively small "outness" of the 1-NMe_2 group in **5a**(*in,out*) ($\sum N_1 = 346^{o}$) is typical for proton sponges with such geometry.[23] This is caused by the fact that translocation of methyls of the 1-NMe$_2$ group into the internitrogen space meets the resistance from the 8-NMe$_2$ group, strongly increasing the N…N distance (3.09 Å for **5a** against ca. 2.80 Å for **1**). Notably, that the transition to the real dimeric structure (**5a**·Et$_2$O)$_2$ with the four-coordinated lithium atoms results in decreasing of both the 1-NMe$_2$ group "outness" (∑N$_1$ = 350^o) and the N…N distance (3.01 Å). Simultaneously, a considerable elongation of the C–Li and N–Li bonds takes place (Table 5). The tendency to elongation of the C–Li bond also appears in the DFT calculations for dimeric 3- and 4-lithium derivatives of DMAN on their coordination with TMEDA molecules (SI-2).

Table 5 Selected geometrical parameters of structure **5a**(*in*,*out*) obtained from DFT calculations [B3LYP/6-311+G(d,p)] and experimental X-ray study

Structure	Method	C–Li, Å	N–Li, Å	N…N, Å	∑N$_1$, Deg.
5a	DFT	1.934	1.992	3.093	346.1
11c≡5a·THF$_2$	DFT	2.051	2.141	3.090	347.3
5a·TMEDA	DFT	2.029	2.129	3.092	346.7
(**5a**·Et$_2$O)$_2$	X-ray	2.198(9); 2.215(9)	2.111(8)	3.011(5)	350.1(9)

The calculated gas-phase structure of 4,5-dilithium DMAN **5d** is also rather intriguing. Both lithium atoms of **5d** are located symmetrically above and below the naphthalene ring plane forming identical bonds with the C(4) and C(5) ring atoms (Figure 8, see also SI-2). This result does not dependent on the coordination saturation of the Li atoms. The only point is that while for the ether complex **5d**·(Et$_2$O)$_4$ both lithium atoms are tetracoordinated (Figure 8a), we failed to find a similar global energy minimum for the complex **5d**·(TMEDA)$_2$. The matter is that during the optimization, one of the NMe$_2$ groups of TMEDA, possibly due to steric reasons, remains unbounded with the lithium ion (Figure 8b). Anyway, the structure of **5d**·(TMEDA)$_2$ strongly reminds that of 2,2'-dilithiumbiphenyl–(TMEDA)$_2$ complex, which has been resolved by X-ray experiment.[26]



(a) (b)

Fig. 8 The calculated gas-phase structures of **5d**·(Et$_2$O)$_4$ (a) and **5d**·(TMEDA)$_2$ (b) [B3LYP/6-311+G(d,p)].

Our calculations were also rather helpful in explaining the transformation of 2-lithium- and 4,5-dilithium-DMANs into their 3- and 4-congeners in hexane. This follows from Figure 9 where total energies and their differences for the optimized structures of the Li-DMANs are depicted. To get comparable results, the structures chosen should contain an equal amount of the proton sponge residue, TMEDA and lithium atoms (SI-3). This approach for the calculation of energy parameters is grounded in the literature.[27] One can see that the lithium derivatives under consideration are clearly divided into two groups: less stable 2-lithium and 4,5-dilithium-DMANs and much more stable (nearly by 16 kcal/mol) 3- and 4-lithium DMANs. The slight difference in the energies of **5c** and **5b** obviously lies within the error of calculations and is in accordance with their close proportion on metallation of DMAN with *tert*-BuLi.

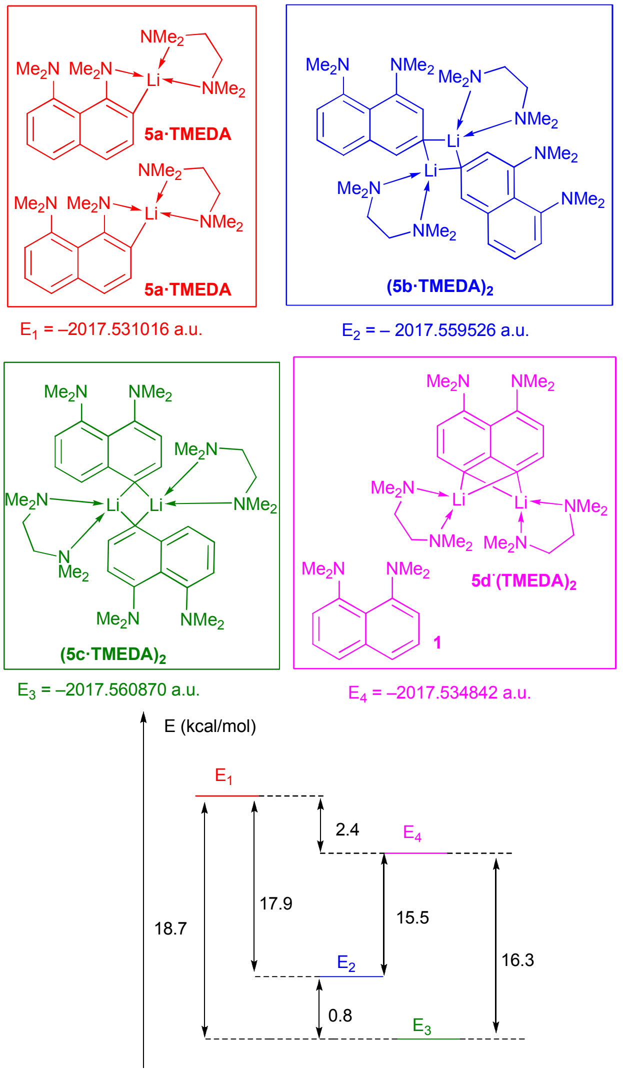


Fig. 9 Absolute (a.u.) and relative (kcal/mol) energies of Li-DMANs complexes with TMEDA [B3LYP/6-311+G(d,p)].

From the above one can conclude that on the whole the stability of lithium-DMANs and therefore the ease of their formation mostly results from their proton sponge specifics. There can be little doubt that the dominant factor here is a sharp increase of electrostatic repulsion between the nitrogen electron pairs and additionally arising carbanionic centres. Obviously, the molecule destabilization grows as a number of the latter and their proximity increases.

Conclusions

In summary, 1,8-bis(dimethylamino)naphthalene demonstrates rather poor ability to the ring metallation under ordinary conditions (*n*-BuLi, Et_2O, TMEDA) which is combined with the low selectivity of the process. Undoubtedly, this results from strong electron-donor effect of two NMe_2 groups, which lowers the ring CH-acidity. Figuratively speaking, the acidic side of the “proton sponge coin” is suppressed by its basic counterpart. Yet, using *t*-BuLi–TMEDA system in hexane allows considerable improving the situation since almost equal quantities of only 3- and 4-lithium derivatives of DMAN are formed in this case in good total yield. For the first time this opens synthetic perspectives for the *meta*-derivatization of DMAN. As to 2- and 4-lithium derivatives as well as di-lithium compounds of DMAN, they can be preferably prepared from the corresponding bromides by bromo-lithium exchange. It has also been disclosed that 2-lithium-DMAN exists in the solid and gas phase with the *out*-inverted 1-NMe_2 group while in solution it likely equilibrates between several structures. The first example of fixation of the proton sponge non-conventional *in,out* conformation via the direct coordination with the metal atom has been disclosed. Possibly our work opens a window to new and very specific kind of organometallics whose basicity supersedes that of most aryllithiums and even approaches the basicity level of alkyllithiums. Indeed, the abnormally high basicity of 2-lithium DMAN was recently applied in a new indole synthesis.[28]

Experimental

General considerations. Commercially available tetrahydrofuran and diethyl ether were distilled over sodium and benzophenone. Hexane was distilled over sodium. Liquid-state ^{1}H and $^{13}C\{^{1}H\}$ NMR experiments were performed at 250 MHz for ^{1}H, and 63 MHz for ^{13}C (Southern Federal University facilities) and 500 MHz for ^{1}H, 126 MHz for ^{13}C, and 194 MHz for ^{7}Li (Centre for Magnetic Resonance, St. Petersburg State University) using the solvent peaks as the internal reference. Mass-spectra were obtained in an electron impact mode at 70 eV. X-Ray measurements were conducted with a Bruker APEX2 diffractometer (Mo-K_{α} line, graphite monochromator, ω-scans). The quantum mechanical simulations were carried out using the Gaussian 09 suite of programs.[29a] The energy minimization was performed using DFT with the B3LYP functional.[29b] The 6-311+G(d,p) and 6-311G(d,p) basis sets were applied during the simulations.[29c–f] Harmonic frequencies calculations were performed to confirm that the obtained structures correspond to the minimum on the potential energy surface (PES) and obtaining *zero-point* Energies (ZPE) values.

Monitoring of DMAN lithiation. To investigate the influence of the experimental conditions on the proton sponge lithiation with *n*-BuLi, a solution of DMAN **1** (100 mg, 0.5 mmol) was dissolved in 1 mL of the corresponding solvent (Et_2O, *n*-hexane, or Et_3N) and placed in a glass ampoule. The required quantity of *n*-butyllithium (1.6 M solution) and dry TMEDA (optionally) were added to the reaction mixture under an argon atmosphere. The ampoule was sealed and kept under conditions shown in Tables 1 and 3. An equimolar quantity of dry *N,N*-dimethylformamide was then added to the reaction mixture at –20 °C. The reaction mass was kept additionally for 24 h at –20 °C and treated with water (5 mL). The products were extracted with Et_2O (2 × 5 mL) and the solvent was evaporated to dryness. The residue (20 mg) was dissolved in $CDCl_3$ (0.7 mL) and analyzed by ^{1}H NMR. The authentic DMAN aldehydes were prepared as described in the literature.[30,31]

DMAN lithiation with *tert*-butyllithium. Dry TMEDA (5.4 mL, 9.2 mmol) and *tert*-butyllithium 1.7 M solution in pentane (1.3 mL, 9.2 mmol) were added by syringe to a solution of DMAN 1 (500 mg, 2.3 mmol) in dry *n*-hexane (5 mL) at –20 °C under an argon atmosphere. The resulted yellow-brown suspension I was stirred for 96 h at –20 °C.

3-Formyl- and 4-formyl-1,8-bis(dimethylamino)naphthalenes 6b and 6c. Absolute *N,N*-dimethylformamide (1.1 mL, 12 mmol) was added to suspension I. The reaction mass was additionally stirred for 24 h at –20 °C and treated with water (10 mL). The products were extracted with Et_2O (2 × 25 mL), the solvent was evaporated to dryness and the residue was chromatographed on silica gel with Et_2O–*n*-hexane 1:1 mixture as the eluent. Yellow fractions with R_f = 0.5 (**6b**) and 0.2 (**6c**) were collected.

3-Formyl-1,8-bis(dimethylamino)naphthalene (**6b**): yellow-orange oil; yield 180 mg (32%). Found: C, 74.39; H, 7.45; N, 11.53. Calc. for $C_{15}H_{18}N_2O$: C, 74.35; H, 7.49; N, 11.56. UV/vis (MeCN), λ_{max} (lgε): 345 (3.51), 332 (3.46), 285 (3.97), 251 (4.60), 249 (4.65), 247 (4.66), 243 (4.63), 234 (4.70), 231 (4.69), 228 (4.70), 222 (4.66). IR (liquid film), ν_{max}/cm^{-1} 1696 (C=O). ^{1}H NMR (250 MHz, δ, $CDCl_3$): 10.03 (1H, s), 7.79 (1H, d, *J* = 1.4 Hz), 7.47 (1H, dd, *J* = 7.9, 1.0 Hz), 7.38 (1H, t, *J* = 7.7 Hz), 7.30 (1H, d, *J* = 1.5 Hz), 7.06 (1H, dd, *J* = 7.5, 1.1 Hz), 2.81 (6H, s), 2.79 (6H, s). ^{13}C NMR (63 MHz, δ, $CDCl_3$): 193.3, 152.2, 151.4, 137.5, 134.3, 129.4, 127.1, 123.7, 123.2, 116.2, 107.7, 44.6, 44.5. MS (EI), *m/z* (*I*, %): 29 (47), 30 (10), 42 (51), 43 (16), 44 (37), 45 (13), 115 (12), 126 (17), 127 (35), 128 (15), 140 (10), 154 (19), 155 (10), 167 (21), 168 (32), 169 (11), 170 (12), 182 (15), 183 (10), 196 (72), 197 (20), 198 (30), 210 (40), 211 (65), 212 (33), 227 (34), 242 (M^+, 100), 243 (17).

4-Formyl-1,8-bis(dimethylamino)naphthalene (**6c**): orange oil; yield 140 mg (25%). Characterization data were consistent with those reported in the literature.[30]

3- and 4-(methylthio)-1,8-bis(dimethylamino)naphthalenes 9 and 10. Absolute dimethyldisulfide (1.0 mL, 10 mmol) was added to suspension I. The reaction mass was stirred additionally for 24 h at –20 °C and treated with water (10 mL). The products were extracted with Et_2O (2 × 25 mL), the solvent was evaporated to dryness and the residue was chromatographed on Al_2O_3 with EtOAc–*n*-hexane 1:20 mixture as the eluent. Yellow fractions (almost colourless on adsorbent) with R_f = 0.6 (**9**) and 0.4 (**10**) were collected.

3-Methylthio-1,8-bis(dimethylamino)naphthalene (**9**): pale yellow oil with a weak "sulfide" odour; yield 192 mg (31%). Found: C, 69.23; H, 7.72; N, 10.79. Calc. for $C_{15}H_{20}N_2S$: C, 69.19; H, 7.74; N, 10.76. ^{1}H NMR (250 MHz, *δ*, $CDCl_3$): 7.20–7.30 (2H, m), 7.11 (1H, d, *J* = 1.8 Hz), 6.84 (1H, dd, *J* = 6.7, 2.0 Hz), 6.78 (1H, d, *J* = 1.8 Hz), 2.78 (6H, s), 2.76 (6H, s), 2.55 (3H, s). ^{13}C NMR (63 MHz, *δ*, $CDCl_3$): 151.0, 138.3, 135.5, 126.3, 120.8, 118.6, 117.3, 112.4, 112.3, 44.4, 44.3, 15.6. MS (EI), *m/z* (*I*, %): 12 (24), 15 (45), 16 (12), 18 (27), 27 (13), 28 (46), 29 (26), 41 (61), 42 (49), 43 (100), 44 (37), 45 (23), 47 (13), 55 (68), 56 (20), 57 (85), 58 (15), 67 (25), 69 (59), 70 (15), 71 (41), 79 (11), 81 (32), 82 (11), 83 (41), 84 (10), 85 (26), 93 (10), 95 (34), 96 (12), 97 (35), 109 (21), 111 (25), 115 (21), 123 (13), 125 (17), 127 (13), 154 (15), 167 (13), 168 (24), 169 (18), 196 (12), 201 (10), 214 (36), 215 (14), 216 (23), 228 (15), 229 (34), 230 (28), 231 (10), 245 (23), 260 (M^+, 70), 261 (15).

4-Methylthio-1,8-bis(dimethylamino)naphthalene (**10**): dark-yellow oil with a weak "sulfide" odour; yield 198 mg (32%). Characterization data were consistent with those reported in the literature.[31]

1,8-Bis(dimethylamino)-2-lithiumnaphthalene (**5a**). For No-D NMR measurements, 5a was prepared as follows: a solution of 2-bromo-1,8-bis(dimethylamino)naphthalene[7,21] (**7**) (161 mg, 0.55 mmol) in *n*-hexane (1 mL) was placed into NMR tube. *n*-BuLi (1.6 M solution in hexanes, 0.38 mL, 0.6 mmol) was added to the solution via syringe under an argon atmosphere. The solvent was removed in vacuum and the NMR tube was cooled by liquid nitrogen. Absolute THF (0.7 mL) was distilled direct into the NMR tube. The spectral measurements were performed immediately. ^{1}H NMR (500 MHz, *δ*, THF, –90 °C): 7.65 (1H, d, *J* = 5.3 Hz), 7.01 (1H, d, *J* = 7.5 Hz), 6.83 (1H, d, *J* = 6.7 Hz), 6.80 (1H, t, *J* = 7.1 Hz), 6.53 (1H, d, *J* = 6.9 Hz), 2.69 (9H, s), 2.55 (7H, s). ^{13}C NMR (126 MHz, *δ*, THF, –90 °C): 172.4 (m), 156.3, 148.5, 139.8, 135.9, 121.4, 120.1, 117.3, 116.4, 108.5, 45.0, 44.2.

For X-ray analysis of **5a**, single crystals were obtained as follows: a solution of *n*-BuLi (1.6 M, 0.2 mL, 0.32 mmol) was very slowly added to a solution of bromide 7 (100 mg, 0.34 mmol) in absolute Et_2O (1 mL) at –20 °C under an argon atmosphere. After 30 min the solution was removed via syringe and the resulted yellow crystals were immediately covered with 1 ml of Fomblin® Y to prevent the interaction with air components. When a suitable single crystal sample was chosen, it was accurately (avoiding a contact with air) transferred into the epoxy glue and then mounted onto the glass fibre attached to the goniometer head. X-Ray experiment was carried out at 120 K. Collected data were analyzed by the SAINT and SADABS programs incorporated into the APEX2 program package.[32] The structure was solved by the direct method and refined by the full-matrix least-squares procedure against F^2 in anisotropic approximation. Positions of hydrogen atoms were calculated and included in the refinement within isotropic approximation using the riding model. The refinement was carried out with the SHELXTL program.[33] The details of the data collection and crystal structure refinement are summarized in Table SI-1 (Supporting Info). CCDC 1023357 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif.

2-*n*-Butyl-1,8-bis(dimethylamino)naphthalene (8). 1.6 M solution of *n*-butyllithium (2 mL, 3.2 mmol) was added to a solution of bromide 7 (540 mg 1.8 mmol) under an argon atmosphere at room temperature. The resulted yellow suspension was treated with *n*-butylbromide (5 mL, 46.6 mmol), refluxed for 2 h and quenched with water (10 mL). The products were extracted with CH_2Cl_2 (2 × 5 mL). The solvent was removed in vacuum and the residue was chromatographed on alumina with 1:1 Et_2O–*n*-hexane mixture as the eluent. The colourless fraction (brown in iodine vapour) with R_f = 0.3 was collected. Butylnaphthalene **8** was obtained as brown oil (245 mg, 50%). Found: C, 80.00; H, 9.66; N, 10.34. Calc. for $C_{18}H_{26}N_2$: C, 79.95; H, 9.69; N, 10.36. ^{1}H NMR (250 MHz, *δ*, $CDCl_3$): 7.41 (1H, d, *J* = 8.3 Hz), 7.37 (1H, dd, *J* = 8.0, 1.1 Hz), 7.26–7.18 (2H, m), 7.03 (1H, dd, *J* = 7.4, 1.0 Hz), 2.94 (6H, s), 2.76–2.68 (8H, m), 1.64–1.50 (2H, m), 1.37 (2H, td, *J* = 14.3, 7.1 Hz), 0.93 (3H, t, *J* = 7.2 Hz). MS (EI), *m/z* (*I*, %): 29 (54), 32 (85), 39 (19), 41 (68), 42 (44), 43 (81), 44 (27), 55 (40), 56 (20), 57 (54), 58 (38), 69 (20), 70 (11), 71 (25), 77 (10), 83 (17), 85 (14), 97 (12), 115 (13), 127 (12), 149 (19), 154 (11), 167 (17), 168 (31), 169 (13), 181 (16), 182 (26), 183 (11), 196 (38), 197 (23), 211 (13), 224 (16), 225 (12), 226 (18), 239 (11), 240 (20), 241 (33), 255 (27), 270 (M^+, 100), 271 (21).

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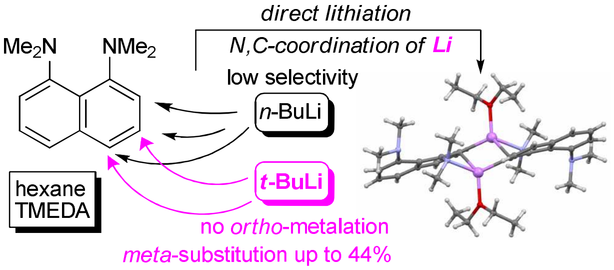

A set of X-ray, multinuclear NMR and DFT approaches was used to address a question of selectivity, relative stability and enhanced reactivity of ring lithiated 1,8-bis(dimethylamino)naphthalenes.