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Directed *ortho*-Lithiation: Observation of an Unexpected 1-Lithio to 3-Lithio Conversion of 1-Lithio-naphthyllithium Compounds with an *ortho*-Directing 2-(Dimethylamino)methyl Group

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Supporting Information

ABSTRACT: Regioselectivity is an important aspect in the design of organic protocols involving Directed *ortho*-Lithiation (DoL) of arenes, in particular with those arenes containing heteroatom substituents as directing groups. The DoL of 2-[(dimethylamino)methyl]naphthalene (dman) that proceeds with low regioselectivity was revisited by varying both the nature of the lithiating reagent (either *n*-BuLi or *t*-BuLi) and/or the solvent (pentane or diethyl ether); the 3-deuterated substrate, 3-Ddman, was also investigated as a substrate to compare to that of dman. The 3-lithio regioisomer exists as tetranuclear $[2\text{-}(Me_2NCH_2)C_{10}H_6Li\text{-}3]_4$, **1**, both in the solid state (X-ray) and in solution (NMR). The 1-lithio regioisomer, **2a**, is insoluble; in the presence of additional coordinating solvents (Et_2O) or ligands (dman), it exists as dinuclear $[2\text{-}(Me_2NCH_2)C_{10}H_6Li\text{-}1]_2{\cdot}L$ (coordinated L = Et_2O: **2b**, dman: **2c**) in apolar solvents. Heating solutions of **2c** in toluene-d_8 (to 90 °C) induced a surprisingly clean and quantitative 1-lithio to 3-lithio conversion of the 1-lithio-naphthalene isomer. This type of reaction is rare in organolithium chemistry and has obvious significant implications for the design of regioselective DoL protocols; this thus represents the synthetically useful protocol for the DoL of dman in a one-pot/two-step process in toluene solution. The results of the use of 3-Ddman in these reactions gives strong credence to a mechanism involving formation of the heteroleptic species $[(2\text{-}(Me_2NCH_2)C_{10}H_6\text{-}1)(2\text{-}(Me_2NCH_2)C_{10}H_6\text{-}3)Li_2]{\cdot}$[dman], **A**, as the key intermediate. Intramolecular *trans*-lithiation takes place with **A**; dman becomes selectively lithiated at its 3-position, while the formerly 1-lithio-naphthalene fragment, acting as a highly unusual *ortho*-lithiating reagent, is converted into the N-coordinated amine, dman. In this intramolecular DoL process, free dman can be considered to act as a *catalyst*.

INTRODUCTION

The lithiation of functionalized arenes, facilitated via a so-called *ortho*-directed metalation group (oDMG), is a useful method to obtain the corresponding lithiated arenes in pure form and in high yield.[1] The *ortho*-directing group plays two key roles in the lithiation process. First, it helps to precoordinate the oDMG-arene precursor, via its heteroatom, to the lithiating reagent, thereby directing the subsequent H−Li exchange process of the proton *ortho* to the oDMG. Second, by coordination of the heteroatom to the lithium atom, it directs the aryllithium species to (typically) form thermodynamically stable aggregates (dimers, trimers, etc.). The structural aspects of these functionalized aryllithium compounds, in the solid state as well as in solution, have been studied extensively.[1]

The Directed *ortho*-Lithiation (DoL) reactions are well-known as valuable tools for organic chemists.[1a−h] Moreover, the thus obtained organolithium compounds are essential starting materials for the synthesis of organometallic compounds and catalysts, notably including both organocopper and cuprate compounds, tin species (cf. Stille reaction), etc.[2a−d] Sometimes DoL reactions are found to occur with low regioselectivity or to terminate with incomplete conversion of the substrate. This situation hampers or effectively eliminates the application of this particular DoL protocol in subsequent synthetic projects. A particular interesting example is the DoL of (dimethylamino)methylbenzene and derivatives[3a−h] for which it has been shown that particular combinations of arene substrate and lithiating reagent (and solvent) might give rise to the selective formation of heteroaggregates, comprising the anticipated *ortho*-lithiated arene, the lithiating agent (usually *n*-BuLi), and the starting arene that coordinates to the aggregated organolithium unit via its heteroatom.[4,5] In fact, this type of heteroaggregate formation represents a thermodynamic sink in the DoL process and explains why incomplete lithiation is sometimes obtained and, consequently, provides the reason for the low selectivity of its subsequent reaction with (in)organic electrophiles.

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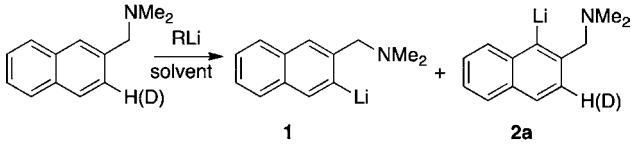
In the course of these DoL studies, we also studied the reaction of 2-[(dimethylamino)methyl]naphthalene with *n*-BuLi in diethyl ether as solvent.[6] As early as 1967, this reaction was reported to proceed with low regioselectivity affording a mixture of the respective *ortho*-derivatives, i.e., the 1- and 3-naphthyl lithium compounds (2:3 molar ratio).[1a]

In this report, we describe the synthesis and structural characterization[7] of 2-[(dimethylamino)methyl]-1-naphthyl-, 2-[(dimethylamino)methyl]-3-trimethylsilyl-1-naphthyl-, and 2-[(dimethylamino)methyl]-3-naphthyl-lithium compounds and their reactivity toward both coordinating solvents and the respective parent naphthylamines. In the course of this study, we discovered two novel aspects concerning the role of the oDMG in the DoL reaction. First, we observed that the 2-(dimethylamino)methyl-1-naphthyllithium aggregate reacts selectively with one equivalent of the parent amine, dman. The resulting dinuclear aggregate, containing one coordinated naphthalene amine substrate, is a seminal model for the key intermediate that has been proposed in the mechanism of DoL reactions. This involves the stepwise lithiation of substrate molecules that are precoordinated through their oDMG to one of the lithium atoms in the aggregated organolithium reagent. Second, and most importantly, we could establish that this type of intermediate plays a crucial role in the unexpected 1,3-lithium conversion of the 2-[(dimethylamino)methyl]-1-naphthyl- to its 3-naphthyl-lithium isomer. The mechanism for this rearrangement has been studied which resulted in the discovery of a unique methodology for the selective synthesis of the pure 3-naphthyllithium regioisomer directly from 2-[(dimethylamino)-methyl]naphthalene with *n*-BuLi in toluene as solvent.

RESULTS AND DISCUSSION

Synthetic Aspects. Earlier reports had shown that the DoL of 2-[(dimethylamino)methyl]naphthalene (dman) with *n*-BuLi (1:1 molar ratio) in diethyl ether affords the two possible regioisomers, **1** and **2a**, in a 3:2 molar ratio (see Scheme 1).[1a]

Scheme 1. Regioselectivity[a] of DoL of 2-[(Dimethylamino)methyl]naphthalene (dman) and Its 3-Deuterio-Labeled Derivative (3-Ddman) at Room Temperature[b,c]



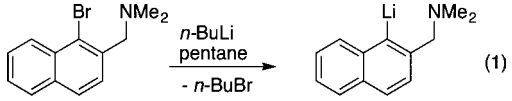
1 2a

RLi	Solvent	Conversion (%)	1 / 2a ratio
n-BuLi	diethyl ether	99 (99)	60/40 (30/70)
n-BuLi	pentane	80 (70)	75/25 (40/60)
t-BuLi	diethyl ether	99 (99)	70/30 (30/70)
t-BuLi	pentane	90 (85)	75/25 (50/50)

[a]Influence of the nature of solvent, alkyllithium reagent, and C−H vs C−D bond on the regioselectivity. [b]At room temperature no 1-lithio (**2a**) to 3-lithio (**1**) conversion occurs (vide infra). [c]Product ratios of DoL with 3-Ddman in brackets.

We have reinvestigated the lithiation of 2-[(dimethylamino)-methyl]naphthalene (dman) by varying both the nature of the lithiating reagent (either *n*-BuLi or *t*-BuLi) and the solvent (pentane: apolar; or diethyl ether: polar and potentially coordinating). Furthermore, the lithiation of the 3-deuterio-labeled 2-[(dimethylamino)methyl]naphthalene (3-Ddman) was studied under the same reaction conditions. DoL of both dman and 3-Ddman occurred almost quantitatively in diethyl ether and up to about 85% conversion in pentane. The table in Scheme 1 shows that whereas the 3-lithiated product **1** is the major regioisomer formed in the case of dman it is the 1-isomer **2a** that is the dominating product of the DoL of 3-Ddman. This result points to a kinetic isotope effect that arises from a considerable change in the barrier of activation of the DoL processes involving the 1-C−H vs the 3-C−D bonding for 3-Ddman as compared with these processes at the respective *ortho*-C−H bonds in the parent naphthalene amine: dman. It is obvious from these results that the exchange process at the 1-C−H grouping must be kinetically faster than this process at the 3-C−D grouping.

The regioisomers, **1** and **2a**, that were needed as pure starting materials in our further studies (vide infra) were obtained as follows. Reaction of dman with *t*-BuLi in a 1:1 molar ratio in pentane afforded a white suspension, which after isolation and repeated washings with pentane afforded a white crystalline solid that, according to elemental analysis and ^{1}H and ^{13}C NMR spectra (in benzene-d_6), appeared to be pure **1** (see Supporting Information S4). It must be noted that the solubility of $[2\text{-}(Me_2NCH_2)C_{10}H_6Li\text{-}3]_4$, **1**, in apolar solvents is rather low (in benzene and toluene <5 mg/mL). It is obvious that pure **2a** is not available via this protocol, but using a lithium−bromine exchange reaction, carried out in pentane (eq 1), the pure regioisomer could be afforded quantitatively (see Supporting Information S8).



2a

Regrettably, reliable ^{1}H and ^{13}C NMR spectra of **2a** could not be obtained because of its insolubility in hydrocarbon solvents such as benzene or toluene. In diethyl ether, however, **2a** appeared perfectly soluble but is actually converted into the aggregated, dinuclear lithium species **2b** possessing a $[2\text{-}(Me_2NCH_2)C_{10}H_6Li\text{-}1]_2{\cdot}OEt_2$ stoichiometry (**2b**) according to both ^{1}H and ^{13}C NMR measurements (see Supporting Information S9). The addition of 0.5 equiv of diethyl ether to a suspension of **2a** in toluene-d_8 provided likewise a clear solution of **2b**. Similarly, addition of 0.5 equiv of dman to a suspension of **2a** in toluene afforded the 2:1 adduct $[2\text{-}(Me_2NCH_2)C_{10}H_6Li\text{-}1]_2{\cdot}[C_{10}H_6(CH_2NMe_2)\text{-}2]$, **2c**. With this knowledge in mind, pure **2b** and **2c** were prepared (see Scheme 2) by adding either diethyl ether or dman, respectively, to a suspension of **2a** in hexane (see Supporting Information S9). Compounds **2b** and **2c** have comparable structural features based on a combination of ^{1}H, ^{13}C, ^{6}Li, and ^{7}Li NMR spectroscopic data. Furthermore, the molecular structure of **2c** in the solid state was determined by single-crystal X-ray crystallography (see Supporting Information S11 and vide infra). These observations are summarized schematically in Scheme 2.

The reaction of 3-trimethylsilyl-2-[(dimethylamino)methyl]-naphthalene, (3-Me_3Si)dman, with *t*-BuLi in diethyl ether was also studied as we had observed that, in the case of 3-Ddman, the regioselectivity of the DoL is steered in the direction of the 1-lithio-product. Note that in this case exclusively 1-lithiation is possible and indeed occurs quantitatively. From this reaction (see Supporting Information S10), a pale yellow crystalline material was obtained with a $[3\text{-}(SiMe_3)\text{-}2\text{-}(Me_2NCH_2)C_{10}H_5Li\text{-}1]_2{\cdot}OEt_2$ (**3**) empirical stoichiometry (^{1}H and ^{13}C NMR).[8] The structure of **3** in

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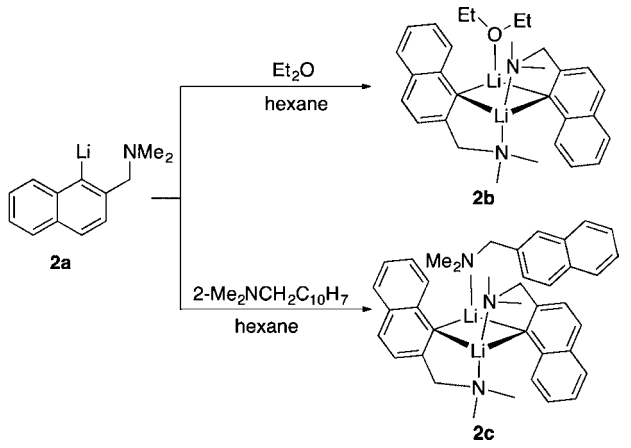
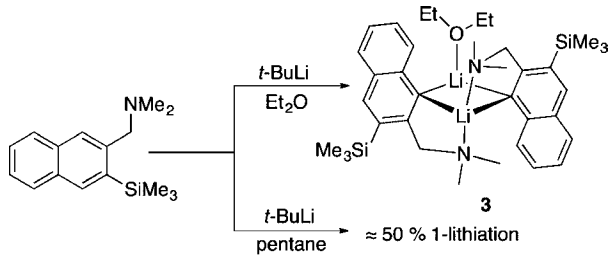
Scheme 2



Scheme 3

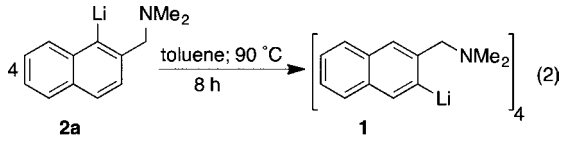


the solid (confirmed via X-ray crystal structure determination, vide infra) is schematically shown in Scheme 3.

In contrast to the quantitative DoL at the 1-position (and subsequent formation of **3** in diethyl ether), the identical reaction involving (3-Me$_3$Si)dman with *t*-BuLi in pentane, i.e., in the absence of any coordinating solvent, does not go to completion (see Scheme 3). A quench of the reaction mixture with dimethyl disulfide and subsequent GC−MS analysis of the product mixture confirmed that lithiation at the 1-position of the naphthalene skeleton had occurred but with only approximately 50% conversion. The remaining material appeared to be unreacted (3-Me$_3$Si)dman. Increasing either the reaction time, or using an excess of *t*-BuLi, did not increase the yield of lithiated product. These observations suggest the possibility of the formation of unreactive aggregates comprising the lithiating reagent, the coordinated substrate, and *ortho*-lithiated product.[4a,b]

Detailed ^{1}H, ^{13}C, ^{6}Li, and ^{7}Li NMR spectroscopic studies of solutions of tetrameric **1** and the dimeric compounds **2b**, **2c**, and **3** in *apolar* solvents (benzene or toluene) indicated that the structural features as observed for these compounds in the solid state are retained in solution. Moreover, the influence of added free ligands, either diethyl ether (for **2b** and **3**) or dman (for **2c**), on their structural features were studied. During this work, it was observed that heating solutions of [2-(Me$_2$NCH$_2$)-C$_{10}$H$_6$Li-1]$_2$·[C$_{10}$H$_6$(CH$_2$NMe$_2$)-2], **2c**, in toluene-d_8 induced a surprisingly clean and quantitative 1-lithio to 3-lithio conversion of the 1-lithio-naphthalene compound (see eq 2). We have studied this conversion, which is a rare process in organolithium chemistry,[9] in greater detail because this observation has significant implications in the design of organic protocols involving these reagents toward the sequestering of regio-pure products.

1-Lithio to 3-Lithio Conversion of 2-(Me$_2$NCH$_2$)C$_{10}$H$_6$Li-1 in Toluene. ^{1}H NMR studies of solutions of pure **2a** in toluene-d_8 at higher temperatures (up to 90 °C) showed, within a few minutes, the appearance of the resonance pattern of **1** of which the intensities increased with time. This confirms the selective and quantitative conversion of **2a** to **1** in about 8 h at 90 °C (eq 2).



Obviously, the 3-lithiated compound **1** is a thermodynamically favored product. Moreover, the lithiation reaction of 3-deuterium-labeled dman with *t*-BuLi shows a distinct kinetic isotope effect. Whereas the lithiation of dman results in a 3-lithio vs 1-lithio ratio of 3:2, vide supra, the same reaction with the 3-Ddman resulted in an almost reversed product distribution of 3:7; i.e., the 1-lithio derivative is now the predominant product. This also indicates that in the DoL process the C−H(D) bond is involved in the rate-determining step. Nevertheless, the clean conversion of the 1-lithio compound **2c** into the thermodynamically more favorable 3-lithio derivative **1** was completely unexpected (see eq 2). Note that this conversion occurred at an appreciable rate at temperatures at about 90 °C or higher indicating that this process does have a relatively high barrier of activation.

What is a likely mechanism of this unexpected, and to the best of our knowledge, unprecedented 1- to 3-lithio-conversion? At this point, it is important to note that in a solution of **1** *in toluene-d_8*, in the presence of the parent, free dman, the aggregated, tetrameric structure of **1** is stable and does not break down into amine-solvated aggregated structures; see NMR spectra (Supporting Information S27). Compound **1** requires the presence of stronger coordination solvents such as THF (or in neat THF) to facilitate the breakdown of the aggregated structure into THF-solvated dimers (see Supporting Information S5). This observation is crucial for the further interpretation of the results discussed below and the formulation of a possible mechanism for the 1- to 3-lithio conversion.

Regrettably, the reaction of the 1-lithio, **2a**, to the 3-lithio, **1**, derivative is rather nonhomogeneous and, as a consequence, is difficult to follow by NMR spectroscopy. Therefore, further studies were carried out with homogeneous solutions of the 1-lithio derivatives **2b** and **2c**, respectively, in toluene-d_8.

A clear solution of **2c** in toluene-d_8 in an NMR tube was heated in the NMR probe to +90 °C and kept at this temperature, while ^{1}H and ^{7}Li NMR spectra were recorded repeatedly over time with 5 min intervals (see Supporting Information S14) between acquisitions. Within 25 min, a quantitative conversion of **2c** to the 3-lithio-product **1** was observed (see Scheme 4). Likewise, heating of a clear solution of the diethyl ether solvate **2b** in toluene-d_8 in the NMR probe to 90 °C resulted in complete conversion of **2b** to **1** in about 100 min. It is important to note that, experimentally, it is extremely difficult to exclude any hydrolysis when dissolving solid organolithiums in an organic solvent without taking extreme precautions to exclude air and moisture. In fact, it appeared that after having dissolved pure **2b** in toluene-d_8 the resulting solution contained about 10% of dman, present in its complexed form as **2c** (see Supporting Information S35). On increasing (deliberately) the amount of free dman by adding this amine to the solution of **2b**, complete conversion to the 3-lithio-product **1** was achieved in 25 min. These observations lead us to the conclusion that the rate of

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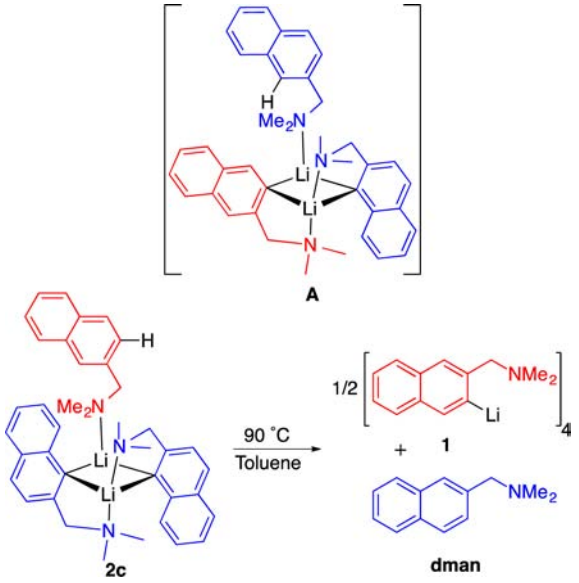
Scheme 4. Quantitative Conversion of 2c: Proposed Heteroleptic, Dimeric Intermediate "A" with the Respective Regioisomers of the Bridging Naphthyl Anions



conversion depends exclusively on the amount of dman (in either its free or complexed form).

Indications that the presence of free dman is essential indeed for the 1-lithio to 3-lithio conversion to occur became evident from an experiment in which a solution of pure **2b** had been prepared under the most extreme precautions (keeping an excess of *t*-BuLi, see Supporting Information S5) in an attempt to preclude the formation of any free dman. The resulting solution was then heated in the NMR probe similarly to +90 °C and kept at this temperature, while ^{1}H NMR spectra were recorded (15 min intervals). After 2 h, not even a trace of either free dman or the 3-lithio-product **1** could be detected in this solution. After 16 h, however, trace amounts (approximately 1%) of **1** were detectable. At this stage, a minor amount (15 μL) of dman was added to the solution while keeping the temperature at +90 °C. The ^{1}H NMR spectrum showed that the rearrangement to **1** had immediately commenced and was complete within 25 min.

The conversion of **2c** to **1** in toluene-d_8 was, furthermore, studied at two different concentrations, 136 and 20 mg/mL, respectively. It appeared that the rate of conversion in both experiments was the same (within experimental error), which provided a strong indication that the **2c** to **1** conversion occurs intramolecularly.

On the basis of these results, a mechanism for the 1-lithio to 3-lithio conversion can be proposed involving the heteroleptic species $[(2\text{-}(Me_2NCH_2)C_{10}H_6\text{-}1)(2\text{-}(Me_2NCH_2)C_{10}H_6\text{-}3)Li_2]\cdot$dman, **A**, as the key intermediate (see Scheme 4). In this mechanism, **2a** is converted by reaction with free amine into **2c** (or is formed from **2b** by displacement of the coordinating diethyl ether molecule by free dman). In the subsequent translithiation reaction, the N-coordinated dman molecule functions as a substrate and one of the two 1-lithio-naphthyl fragments as the *ortho*-lithiating agent; i.e., in the productive step[10] of this DoL process the coordinated dman molecule is selectively lithiated at its 3-position, while the formerly 1-lithio-naphthalene fragment is converted into the N-coordinated amine, dman. Actually, dman can be considered to act as a *catalyst* in this conversion. The proposed heteroleptic dimeric intermediate **A** having one 1- and one 3-naphthyl bridging anion could not be observed indicating that such a heteroleptic intermediate is likely to be thermodynamically unfavorable with respect to the disproportionation products, tetrameric **1** and homoleptic **2c**. Only **2c** and free amine were observed in the ^{1}H and ^{7}Li NMR spectra as well as the 3-lithio-product **1** that, on standing, crystallized from the toluene solution. Recall that tetrameric **1** does not react with the free amine; i.e., the overall conversion amounts to: 2 [**2c**] → $[\mathbf{1}]_4$ + 2 [free amine].

Additional evidence for such a mechanism became apparent from ^{2}H NMR studies using 3-deuterio-labeled 2-[(dimethylamino)-methyl]naphthalene (3-Ddman). Addition of 3-Ddman to a suspension of pure **2a** in toluene afforded a clear solution. Its ^{1}H NMR spectrum showed the stoichiometry of the species in solution to be $[2\text{-}(Me_2NCH_2)C_{10}H_6Li\text{-}1]_2\cdot 1.5$[3-Ddman] (i.e., 0.5 equiv excess as compared with the 2:1 stoichiometry of **2c**). The ^{2}H NMR spectrum of this solution clearly shows the 3-^{2}H resonance at 6.65 ppm of 3-Ddman. The first important observation is that no conversion to **1** is detectable upon application of heat to the sample in the spectrometer probe +90 (±0.5) °C. Only trace amounts of the 3-lithio regioisomer, **1**, are detectable after 20 min, whereas with the same reaction, but with unlabeled dman, the conversion to **1** is almost complete in 20 min at this temperature. However, when the sample **2a**/3-Ddman was heated at +100 °C, a smooth conversion to **1** started and was complete within 30 min. During the reaction, a second ^{2}H resonance appeared (assigned to 1-Ddman, 1-D-2-$(Me_2NCH_2)C_{10}H_6$) and became more intense with progress of the reaction, while the resonance of the 1-Ddman gradually shifted to lower field. This situation is in concert with the formation of an increasing amount of free amine with a concomitant decrease of the amount of the dinuclear lithium compound (with coordinated amine) (see Scheme 4). The ^{2}H NMR spectra of the quenched (H_2O) reaction mixture (after the conversion was completed) pointed to the presence of 1-Ddman and 3-Ddman in a 3:7 molar ratio. That only 30% of deuterium transfer was observed is not unexpected and is in agreement with the observation made earlier with the kinetic isotope effects of the DoL process of dman vs 3-Ddman (see Scheme 1). Actually, it is 3-Ddman that undergoes the translithiation at the initial stages of the conversion and thus forming 1-Ddman, the concentration of which increases during the progress of the reaction. It should be kept in mind, however, that a deuterium atom at the 3-position considerably enhances the barrier of activation for the DoL process at this position. Therefore, the initially formed 1-Ddman (having a ^{1}H-atom at the 3-position that is more reactive toward lithiation) is a competing substrate and becomes more important as the reaction proceeds.

The same experiment was carried out using a "catalytic amount" (~ 20%) of 3-Ddman, i.e., with a **2a**:3-Ddman molar ratio that is much lower than the 2:1 molar ratio in **2c**. It should be noted that this reaction mixture is nonhomogeneous due to the insolubility of the remaining, notably uncomplexed **2a**, vide supra. After heating to +100 °C for 35 min complete conversion to **1** is obtained. After a quench (with H_2O), its ^{2}H NMR spectrum showed the same 1-Ddman/3-Ddman molar ratio (3:7) as was observed in the "stoichiometric" DoL process.

These findings led to two further experiments that, with their outcome, fully support the proposed mechanism. First, it was found that dman undergoes regioselective and quantitative *ortho*-lithiation in the one-pot/two step reaction of dman with *t*-BuLi (1.0:0.95 molar ratio) in toluene affording exclusively

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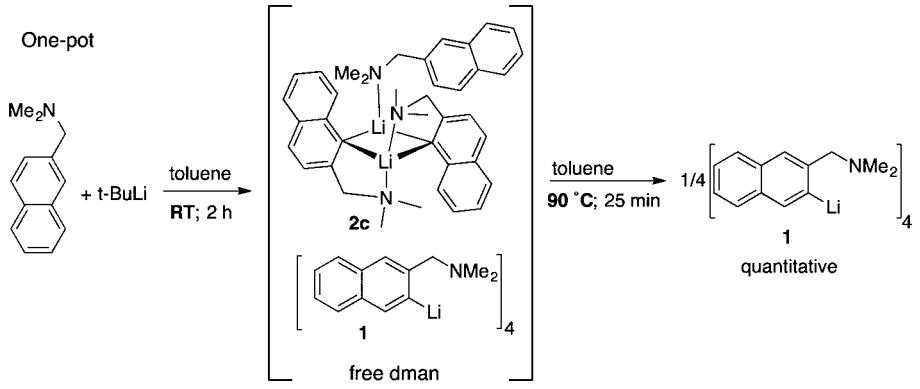
Scheme 5



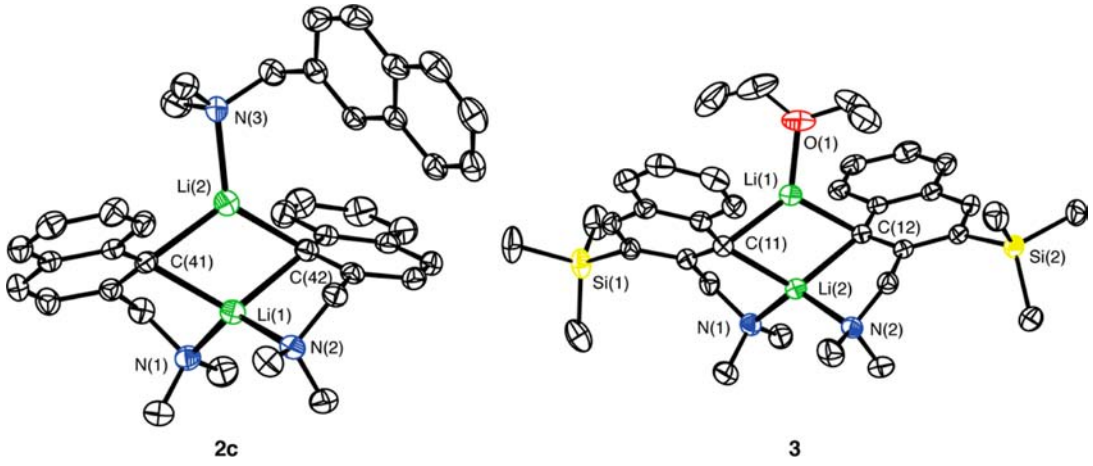
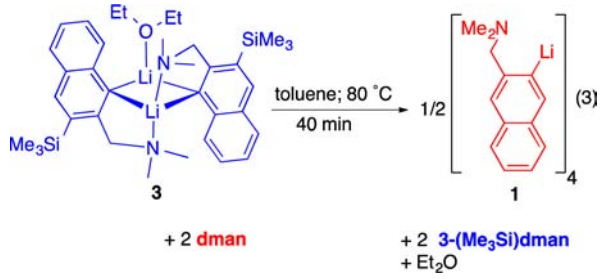


Figure 2. (A) Molecular geometry of **2c**. Relevant bond distances: C(41)−Li(1) 2.250(4), C(41)−Li(2) 2.234(4), C(42)−Li(1) 2.247(4), C(42)−Li(2) 2.207(4), N(1)−Li(1) 2.046(4), N(2)−Li(1) 2.051(4), and N(3)−Li(2) 2.076(4) Å. (B) Molecular geometry of **3**. Relevant bond distances: C(11)−Li(1) 2.156(3), C(11)−Li(2) 2.215(3), C(12)−Li(1) 2.158(3), C(12)−Li(2) 2.194(3), N(1)−Li(2) 2.051(3), N(2)−Li(2) 2.025(3), and O(1)−Li(1) 1.896(3) Å.

3-lithio-2-[(dimethylamino)methyl]naphthalene (isolated in 94% yield). In summary, the two-step procedure involves an initial reaction at room temperature (^{1}H NMR reveals the formation of **1** and **2c**), which is followed by in situ removal of the pentane (solvent for *t*-BuLi) and heating of the reaction mixture to ±90 °C (see Scheme 5).

Second, [3-Me$_3$Si-2-(Me$_2$NCH$_2$)C$_{10}$H$_5$Li-1]$_2$·(OEt$_2$), **3**, has been used successfully for regioselective DoL at the 3-position of dman (see eq 3). Reaction of two equivalents of dman with **3** in toluene-d_8 at 80 °C resulted in a quantitative and regioselective formation of **1** and 3-(Me$_3$Si)dman within 40 min.



Structural Features of the Dimeric Organolithium Aggregates 1, 2b, 2c, and 3 in the Solid State and in Solution. In this section, the structural features and solution properties of the organolithium compounds studied will be discussed. Relevant for the above-reported 1- to 3-lithio naphthalene conversion is the influence of coordinating solvents (Et$_2$O or THF) or substrates (dman) on the aggregation state of 1-lithio- and 3-lithio-2-[(dimethylamino)methyl]naphthalene, respectively.

It should be emphasized that the tetranuclear structural motif (see Supporting Information S18), as observed for **1**, is a common one for diethyl ether or THF solvated alkyl-[11] and aryllithiums[12] as well as for aryllithium compounds in which the organic moiety is a monoanionic, *C,Y*-chelating ligand (e.g., [Li$_4$(C$_6$H$_4$(CH$_2$NMe$_2$)-2)$_4$],[3a] (*R*)-[Li$_4$(C$_6$H$_4$(CH(Me)NMe$_2$)-2)$_4$][3f]) or 3-*N*- and 3-*O*-functionalized alkyllithium compounds (e.g., [Li$_4$(CH(Me)CH$_2$CH$_2$-OMe)$_4$],[13a] [Li$_4$(CH$_2$CH$_2$CH$_2$NMe$_2$)$_4$],[13b,c] and [Li$_4$(CH$_2$-CH$_2$CH$_2$OMe)$_4$])[13d] but is so far unknown for naphthyllithium compounds.

Furthermore, in earlier studies, it was shown that addition of four equivalents of THF to a toluene solution of [2-(Me$_2$NCH$_2$)-C$_6$H$_4$Li]$_4$ (the Li to THF ratio being 1:1) results in a complete breakdown of the tetrameric aggregate into dimeric species.[3a−d] For **1**, however, the situation is different; even when a large excess of THF (Li to THF ratio 1:10) is added to a solution of **1** in toluene-d_8, the ^{1}H NMR spectrum clearly reveals the resonance patterns of both tetrameric [2-(Me$_2$NCH$_2$)C$_{10}$H$_6$Li-3]$_4$, **1**, and THF-solvated [2-(Me$_2$NCH$_2$)C$_{10}$H$_6$Li-3]$_2$(THF)$_n$ species in a 3:2 molar ratio (Supporting Information S5). The slightly broadened resonances suggest that a process involving inter-aggregate exchange between tetra- and dinuclear aggregates is

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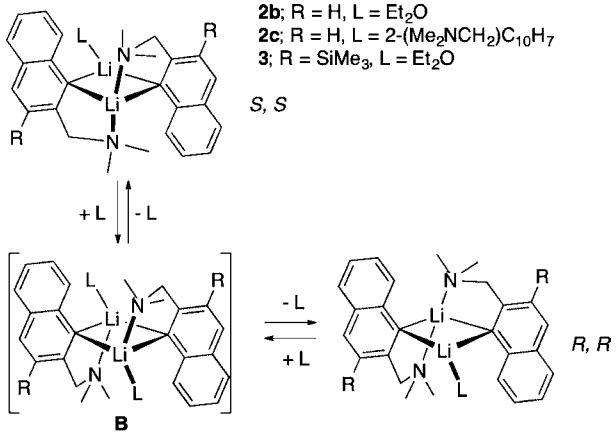
likely operative. This conclusion is further corroborated by the observation of cross peaks in the ^{1}H−^{1}H-EXSY spectrum of this equilibrium mixture between the H(4), NCH_2, and NMe_2 resonances of the tetrameric and dimeric aggregates. Addition of more THF shifts the equilibrium to the side of the THF-solvated dimers; e.g., at a Li to THF ratio of 1:60, only about 8% of the tetrameric aggregate is still present.

The strikingly similar molecular geometries of **2c** and **3** in the solid state (see Figure 2) are comprised of dimer-like structures in which two naphthalene groups are three-center two-electron bridge bonded via C_{ipso} to two lithium atoms, while the nitrogen atoms of both (dimethylamino)methyl substituents are (*intra*molecularly) coordinated to the same lithium atom. An additional ligand (dman in **2c**; Et_2O in **3**) is (*inter*molecularly) coordinated to the second lithium atom, rendering this atom three-coordinate. The trigonal-planar coordination geometry of Li(2) in **2c** and Li(1) in **3** is reflected by the sum of the bond angles around this lithium atom being 359.9(3)° for **3** and 359.0(3)° for **2c**.[14] The central C_{ipso}−Li(1)−C_{ipso}−Li(2) four-membered ring in both **2c** and **3** is essentially flat (the sum of the bond angles is 359.7(3)° for **3** and 358.5(3)° for **2c**). As a consequence, each of the coordinating nitrogen atoms approaches the lithium atom in this plane from opposite sides (N(1)−Li(1) 2.046(4) and N(2)−Li(1) 2.051(4) Å) for **2c** and (N(1)−Li(2) 2.051(3) and N(2)−Li(2) 2.025(3) Å) for **3**.[15] It should be noted that both bridging C_{ipso} atoms in **2c** and **3** are chiral centers (four different substituents are tetrahedrally arranged at C_{ipso}).[16,17] As a consequence of the two rigid five-membered chelate rings, their configuration is fixed and should be the same (either both *R* or both *S*) within one molecule. As **2c** and **3** crystallize in centro-symmetric space groups (*P*-1 and *P*bca, respectively), **2c** and **3** must exist in the solid state as enantiomeric pairs of *R*,*R*/*S*,*S* diastereoisomers.

The ^{1}H, ^{13}C, ^{6}Li, and ^{7}Li NMR spectroscopic features of **2b**, **2c**, and **3** dissolved in toluene-d_8 are quite similar. At room temperature, the spectra are rather broad, indicating that exchange processes are likely operating, whereas at −70 °C sharp spectral lines are obtained. The combined ^{1}H, ^{13}C, and ^{6}Li NMR data, as well as the results from cryoscopic measurements of **3** in benzene, support the conclusion that the respective structural features found for **2c** and **3** in the solid state are retained when **2b**, **2c**, and **3**, respectively, are dissolved in *apolar* solvents. On the basis of these results, the process depicted in Scheme 6 is proposed that is, in fact, *catalytic in diethyl ether*.[18] At the slow exchange limit, the respective C_{ipso} centers are stereogenic (four different substituents are tetrahedrally arranged at C_{ipso}). Consequently, at the slow exchange limit these naphthyllithium dimers exist in solution, as in the solid state (vide supra), as an *R*,*R*/*S*,*S* pair of diastereoisomers. The observed exchange process between the *R*,*R*- and *S*,*S*-enantiomers should involve intramolecular exchange of the coordinating nitrogen atoms (Li−N(Me_2) bond dissociation−association) with retention of the dimeric R_2Li_2-structural motif and intermolecular exchange of one diethyl ether molecule. Note that this process requires exchange of either the Et_2O molecule (**2b** and **3**, vide infra) or naphthylamine (**2c**, vide infra) between Li-centers, i.e., even the presence in solution of a catalytic amount of either Et_2O or naphthylamine, respectively, is sufficient to support this process. Moreover, coordination of the second ligand L to the dimer most likely requires prior dissociation of one of the amine groupings in the *R*,*R*- and *S*,*S*-enantiomers. Among possible intermediates is complex

Scheme 6. Proposed Exchange Process in Toluene-d_8 as Observed by ^{1}H, ^{13}C, ^{6}Li, and ^{7}Li NMR Spectroscopy for the Bis(1-naphthyllithium)·L Dimers 2b, 2c, and 3



B (see Scheme 6) in which both lithium atoms are four-coordinate.

Finally, the occurrence of exchange between dman and the dinuclear lithium intermediates (as in **A** and **B**, respectively) is corroborated by the following observations. In the ^{1}H NMR spectra of solutions of **2c** containing a slight excess of dman (L_{coord} to L_{free} ratio is 1:1.2) at −30 °C, the NCH_2 and NMe_2 resonances of the *C*,*N*-chelating 2-(Me_2NCH_2)$C_{10}H_6$-1 moieties are observed as an AB pattern and two singlets, respectively (cf. Table 1, Supporting Information S11), whereas these resonances of dman, 2-(Me_2NCH_2)$C_{10}H_7$, are extremely broad, at 2.8 and 1.9 ppm, respectively. This indicates that coordinated and free dman are undergoing exchange. At about −50 °C, decoalescence of these broad resonances begins and finally results (at −70 °C) in two different resonance patterns with a L_{coord} to L_{free} intensity ratio of 1:0.2. The most intensive resonance pattern consists of an AB pattern (NCH_2; 2.70 and 2.02 ppm) and two singlets (NMe_2; 1.89 and 0.99 ppm) assigned to the coordinated dman molecule. The other resonance pattern consists of two single lines (NCH_2; 3.33 and NMe_2; 2.14 ppm) with 1:3 intensity ratio. These latter chemical shift values correspond with those of free dman in toluene-d_8. From these observations, it may be concluded that exchange of L_{coord} (L = dman) in **2c** with L_{free} below −50 °C is slow on the NMR time scale. That exchange, however, does occur and becomes evident from the observation of clear cross-peaks in the ^{1}H−^{1}H 2D EXSY spectrum (200 ms mixing time) between the NCH_2 resonances of coordinated and free dman and the NMe_2 resonances of coordinated and free dman.

■ CONCLUSIONS

The DoL of 2-[(dimethylamino)methyl]naphthalene with either *n*-BuLi or *t*-BuLi is a known reaction that proceeds with moderate regioselectivity providing both the 3-lithio (**1**) and 1-lithio (**2a**) isomers.[1a] In the present study, we have succeeded in separating these isomers by selective crystallization and isolation of pure **1**. The pure 1-lithio-isomer (**2a**) has been prepared by a chemoselective reaction, a formal Br/Li exchange, using 1-bromo-2-[(dimethylamino)- methyl]naphthalene as the starting substrate. Isomers **1** and **2a** have a surprisingly different behavior in polar, potentially coordinating solvents. Whereas **1** exists in both toluene and diethyl ether as a stable tetranuclear Li_4-aggregate [2-(Me_2NCH_2)$C_{10}H_6$Li-3]$_4$, in contrast **2a** exists

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in diethyl ether as a dinuclear, solvated Li_2-species $[2\text{-}(Me_2NCH_2)C_{10}H_6Li\text{-}1]_2{\cdot}OEt_2$, **2b**. Another contrasting behavior that seems related to the nature of the solvent is that whereas in neat THF the aggregated structure of **1** breaks down into a mixture of three isomeric, dinuclear, THF-solvated Li_2 compounds addition of excess of THF (Li to THF ratio 1:10) to a toluene-d_8 solution of **1** yields an equilibrium mixture of both tetrameric **1** and THF-solvated $[2\text{-}(Me_2NCH_2)C_{10}H_6Li\text{-}3]_2(THF)_n$ in a 3:2 molar ratio. These observations reveal that the nature of the solvent (-mixtures) affects the relative thermodynamic stability of the various pure (**1**) and Et_2O and THF-solvated naphthyllithium aggregates. In addition, the behavior of the 1-lithio (**1**) and 3-lithio (**2a**) isomers toward the parent naphthylamine is different; again, the aggregated 3-lithio isomer **1**, dissolved in toluene, is stable in the presence of $2\text{-}(Me_2NCH_2)C_{10}H_7$, whereas **2a** forms selectively the solvated dilithium aggregate $[2\text{-}(Me_2NCH_2)C_{10}H_6Li\text{-}1]_2{\cdot}[2\text{-}(Me_2NCH_2)C_{10}H_7]$, **2c** (see Figure 2). It must be noted that the structure of **2c** in the solid state is the first demonstration of the coordination of the oDMG arene substrate to an $aryl_2Li_2$ dinuclear grouping.

These differences play an important role in the observed, selective conversion of **2a** into **1** at 80 °C (toluene). As a consequence, one is able to design the regioselective synthesis of $[2\text{-}(Me_2NCH_2)C_{10}H_6Li\text{-}3]_4$, **1**, by reacting $[3\text{-}SiMe_3\text{-}2\text{-}(CH_2NMe_2)C_{10}H_6Li\text{-}1]_2{\cdot}OEt_2$, **3**, in which the 3-position is blocked, with $2\text{-}(Me_2NCH_2)C_{10}H_7$. Formally, this latter reaction boils down to an exchange of two different aminoarenes and their respective aminoaryl-anions (see the overall equation in the abstract of this manuscript). This reaction goes to completion because, in the starting aminoaryl anion, the preferred 3-position is blocked; obviously this is not the case for the second aminoarene. It demonstrates that organolithium products can act in subsequent reactions (at elevated temperatures) again as transmetallating reagents via H−Li exchange. In the present case, the regioselectivity of the DoL is most likely due to the higher steric constraints for H−Li exchange processes occurring at the 1-position of the naphthalene ring versus those taking place at the alternative 3-position. Finally, quantitative, regioselective preparation of **1** has been achieved in a one-pot/two-step process in toluene solution, i.e., lithiation at room temperature, affording a mixture of the two regioisomers and leaving some unreacted dman, followed by heating to 90 °C.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

CIF files giving crystallographic data for **1**, **2c**, and **3** and text, tables, and figures giving experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(7) (a) The lithiation of functionalized naphthalenes is a rather unexplored area. So far, four naphthyllithium compounds have been structurally determined in the solid state by X-ray crystal structure determinations, viz., $[1\text{-}MeOC_{10}H_6Li\text{-}8(THF)]_2$,[7b] $[1\text{-}Me_2NC_{10}H_6Li\text{-}8(THF)]_2$,[7c] $[1\text{-}Me_2NC_{10}H_6Li\text{-}8(Et_2O)]_2$,[7d] and $[1\text{-}i\text{-}Pr_2NCOC_{10}H_6Li\text{-}2(THF)]_2$.[7e] (b) Betz, J.; Hampel, F.; Bauer, W. *Org. Lett.* **2000**, *2*, 3805−3807. (c) Betz, J.; Hampel, F.; Bauer, W. *J. Chem. Soc., Dalton Trans.* **2001**, 1876−1879. (d) Jastrzebski, J. T. B. H.; van Koten, G.; Goubitz, K.; Arlen, C.; Pfeffer, M. *J. Organomet. Chem.* **1983**, *246*, C75−C79. (e) Clayden, J.; Davies, R. P.; Hendy, M. A.; Snaith, R.; Wheatley, A. E. H. *Angew. Chem., Int. Ed.* **2001**, *40*, 1238−1240.

(8) (a) The lithiation of 3-trimethylsilyl-2-[(dimethylamino)methyl] naphthalene, 3-(Me_3Si)dman, has also been studied in the course of an investigation directed towards the immobilization of naphthalenethiolate copper catalysts derived from the 2-[(dimethylamino)methyl] naphthalene skeleton. In this case, the Me_3Si grouping was used to mimic the dendritic wedge of a carbosilane dendrimer.[8b,c] It is obvious that in 3-(Me_3Si)dman the 3-position is blocked for lithiation. (b) Arink, A. M.; Braam, T. W.; Keeris, R.; Jastrzebski, J. T. B. H.; Haim, C. B.; Rosset, S.; Alexakis, A.; van Koten, G. *Org. Lett.* **2004**, *6*, 1959−1962. (c) Arink, A. M.; van de Coevering, R.; Wieczorek, B.; Firet, J.; Jastrzebski, J. T. B. H.; Klein Gebbink, R. J. M.; van Koten, G. *J. Organomet. Chem.* **2004**, *689*, 3813−3819.

(9) (a) Meyers et al. reported the inter-conversion of two different lithiated species of 2-(3-methoxyphenyl)-4,5-dihydrooxazole but for which no conclusive explanation could be presented. In their reactions, Meyers used a highly polar solvent, HMPA. In these kinds of polar solvents the formation and possible role of solvent separated ion pairs (SSIPs) cannot be excluded. In the apolar solvents used in the present study, the formation of SSIPs is not likely; all species tend to be neutral and aggregated. (b) Shimano, M.; Meyers, A. I. *J. Am. Chem. Soc.* **1994**, *116*, 10815−10816.

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(14) The shorter C(11)−Li(1) (2.156(3) Å) and C(12)−Li(1) (2.159(4) Å) bond distances in **3** as compared to the longer C(11)−Li(2) (2.215(3) Å) and C(12)−Li((2) (2.194(3) Å) bond distances are not unexpected (bonding to a trigonal planar three-coordinate versus a tetrahedrally four-coordinate lithium atom). Also in **2c**, such a difference in bond distances is observed but is less pronounced (see legend to Figure 2).

(15) (a) To the best of our knowledge for only three other compounds, i.e., $[2\text{-}(Me_2NCH_2)\text{-}4,6\text{-}Me_2C_6H_2]_2Li_2(OEt_2)$,[15b] $[2\text{-}Me_3SiN{=}P(Ph)_2C_6H_4]_2Li_2(OEt_2)$,[15c] and $[2\text{-}(Me_2NC(Me)_2)C_6H_4]_2Li_2{\cdot}(OEt_2)$[15d] are the structural features encountered in this study of **2c** and **3** also found, while for a few other related compounds such an arrangement has been suggested in solution.[3c,d] (b) Belzner, J.; Schär, D.; Dehnert, U.; Noltemeyer, M. *Organometallics* **1997**, *16*, 285−288. (c) Steiner, A.; Stalke, D. *Angew. Chem., Int. Ed.* **1995**, *34*, 1752−1755. (d) Petrov, A. R.; Thomas, O.; Harms, K.; Rufanov, K. A.; Sundermeyer, J. *J. Organomet. Chem.* **2010**, *695*, 2738−2746. (e) Jantzi, K. L.; Puckett, C. L.; Guzei, I. A.; Reich, H. J. *J. Org. Chem.* **2005**, *70*, 7520−7529.

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(18) This contrasts with the observation made for 1-dimethylamino-8-lithio-naphthalene etherate[7d] which exists in the solid state as a symmetric dimer $[1\text{-}Me_2NC_{10}H_6Li\text{-}8]_2(Et_2O)_2$ but in apolar solvents (like toluene) exists in a temperature-dependent equilibrium mixture between the dimeric etherate (predominant at −70 °C) and a tetrameric aggregate $[1\text{-}Me_2NC_{10}H_6Li\text{-}8]_4$ and free diethyl ether (predominant at room temperature).