Communication

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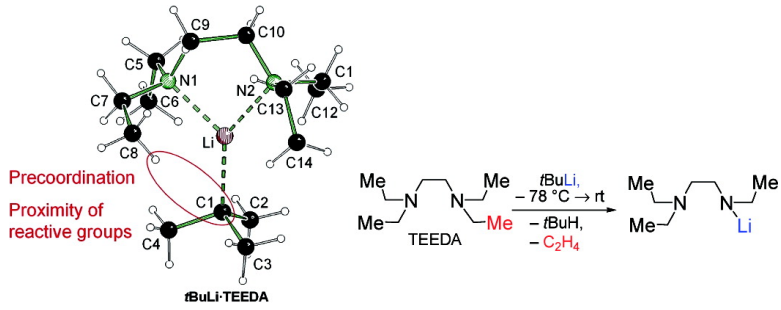

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Lithiation of TMEDA and its Higher Homologous TEEDA: Understanding Observed α- and β-Deprotonation

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The use of Lewis bases to increase the reactivity of lithium organics is an important tool in synthetic chemistry. Thereby, *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA, **1**) belongs to the most powerful and most often used Lewis bases in various types of reactions.[1] The increased reactivity is based on the deaggregation of the lithiumalkyl, which has been shown in many examples by X-ray diffraction analysis.[2] However, besides the activation property, these powerful metalating systems can easily attack solvents or lead to intramolecular lithiation of the amine, resulting in side products and loss of base. Among others, TMEDA (**1**) is known to undergo a direct α-lithiation, the regioselectivity of which depends on the used deprotonation agent.[3] Another, but less often used, Lewis base is the ethyl-substituted analogue of TMEDA, *N*,*N*,*N*′,*N*′-tetraethylethylenediamine (TEEDA, **4**). Although there is less known about this ligand, investigations show an increased reactivity of lithium bases and higher selectivities by changing from TMEDA to TEEDA.[4]

Figure 1. Lithiation of nonmetal functionalized alkyls (e.g., El = R_2N, R_2P, R_3Si).

We present herein structural and mechanistic investigations of the lithiation of TMEDA and TEEDA. Based on X-ray structures we will give an explanation for the unexpected, selective β-lithiation of TEEDA. While the deprotonation in the α-position to a nonmetal is a well-known phenomenon, e.g. of phosphorus or nitrogen compounds, the lithiation in the β-position to these elements is highly exceptional (Figure 1), as a saturated hydrocarbon unit needs to be directly lithiated by a lithiumalkyl.[3] As TEEDA with its ethyl groups bound to a heteroatom resembles diethylether, these results hint to the mechanism of the decomposition of ether, which is of central interest in organolithium chemistry.[5,2]

After intermediate warming to room temperature, α-lithiated TMEDA (**2**) crystallizes at −78 °C from *n*-pentane out of a solution of the amine and *t*BuLi (Figure 2).[6] **2** crystallizes in the tetragonal crystal system, space group $I4_1/a$ as an S_4 symmetric tetramer. Each Li atom possesses four contacts: two to the nitrogen atoms of the ligand and two to the lithiated carbon centers. The Li−C distances [2.174(2) and 2.148(2) Å] and Li−N distances [2.116(2) and 2.037(2) Å] are comparable with known lithiated methylamines.[3] TMEDA is a rare example of a methylamine, which undergoes direct α-lithiation of its methyl group.[3f,g] However, competitive lithiation of the ethylene bridge limits the yield of trapping reactions of α-lithiated TMEDA. Nevertheless, it can be used synthetically for the preparation of new ligands such as the tridentate ligand **3** (Scheme 1).

An attempt to deprotonate the methylene group of TEEDA led to a totally different result. Cooling to −78 °C of a previously

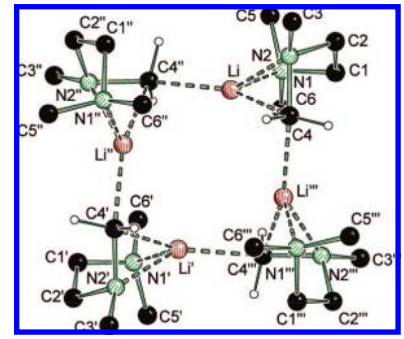
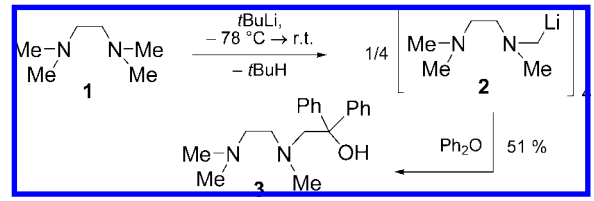
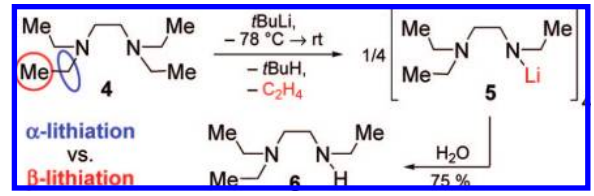


Figure 2. Molecular structure of α-lithiated TMEDA (**2**) in the crystal (several hydrogens omitted). Selected bond lengths (Å) and angles (deg): Li−C4, 2.174(2); Li‴−C4, 2.148(2); Li−N1, 2.116(2); Li−N2, 2.037(2); C4″−Li−C4, 152.30(11); Li−C4−Li‴, 88.26(11).

Scheme 1. α-Lithiation of TMEDA to the Tridentate Ligand **3**



Scheme 2. β-Lithiation of TEEDA **4** to Lithium Amide **5** and Amine **6** After Hydrolysis (75% Nonoptimized Yield)



warmed reaction mixture of TEEDA and *t*BuLi yielded crystals of the lithium amide **5** as result of the deprotonation of the β-hydrogen atom and following elimination of ethene (Scheme 2).[7] The same reaction was observed with *n*BuLi, *s*BuLi, and *i*PrLi as bases, leading to the corresponding amine, *N*,*N*,*N*′-triethylethylenediamine (**6**), after hydrolysis of **5** with water. Altogether, the deprotonation of TEEDA is an unexpected example of a direct deprotonation of a primary carbon unit by a lithiumalkyl. Such an elimination reaction generally requires activated CH bonds and polar solvents for the stabilization of intermediate species.

This different lithiation behavior of TMEDA and TEEDA prompted us to take a closer glance at the ongoing processes. Therefore, we tried to isolate an intermediate species, based on which the reaction behavior can be explained. Out of a mixture of *t*BuLi and TEEDA, monomeric *t*BuLi·TEEDA (**7**) crystallizes in the monoclinic crystal system, space group $P2_1/n$ (Figure 3). The

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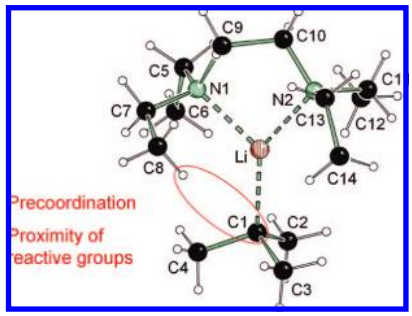

Figure 3. Molecular structure of *t*BuLi·TEEDA (**7**). Selected bond lengths (Å) and angles (deg): C1−Li, 2.101(3); Li−N1, 2.102(3); Li−N2, 2.094(3); C1−H8c, 3.28(2); C1−H6c, 3.15(2); C1−H5b, 3.95(2); C1−Li−N1, 130.99(15); C1−Li−N2, 141.14(16); N1−Li−N2, 87.79(12).

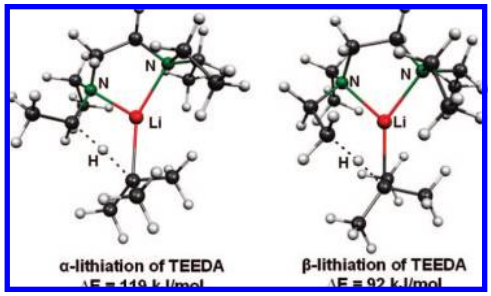

Figure 4. Transition states of the α- and *β*-lithiation of TEEDA via monomeric *t*BuLi·TEEDA (**7**), [B3LYP/6-31+G(d)].

Li−C [2.101(4) Å] and Li−N distances [2.102(3) and 2.094(3) Å] are in the range of other known monomeric lithiumalkyls and are thus shorter than those in dimeric aggregates. Beside *t*BuLi-(−)-sparteine and the adducts of *t*BuLi and *s*BuLi with (1*R*,2*R*)-*N*,*N*,*N*′,*N*′-tetramethylcyclohexane-1,2-diamine, compound **7** is one of the rare monomeric lithiated saturated hydrocarbons which generally tend to form oligomers.[2,8]

Based on the intermediate, *t*BuLi·TEEDA (**7**), DFT studies at the B3LYP/6-31+G(d) level were performed to gain insight into the lithiation processes.[9] Thereby, deprotonation via an analogous *t*BuLi·TMEDA showed a reaction barrier of only 101 kJ/mol for the α-lithiation of TMEDA, confirming the process of the deprotonation at room temperature. However, in the case of TEEDA the α-lithiation possesses a barrier of 119 kJ/mol, while the deprotonation of the *β*-hydrogen only requires 92 kJ/mol (Figure 4). These results show a significant kinetic favoritism of the *β*-lithiation over the α-lithiation of the methylene group. This is also indicated in the crystal structure of *t*BuLi·TEEDA (**7**), showing closer contacts between the carbanionic center and the *β*-hydrogens [3.15(2) to 3.42(2) Å (closest H atom at each *β*-carbon)] than to the α-hydrogens [at least 3.95(2) Å] (see Figure 3). Furthermore, the *β*-hydrogen is already directed toward the carbanionic center, while the deprotonation of the α-hydrogen requires a conformational change of the ethyl groups (Figure 4). The regioselectivity of the lithiation can thus be explained by precoordination according to the Complex Induced Proximity Effect (CIPE).[10] The phenomenon of *β*-elimination is also known for ether compounds. A. Maercker and W. Demuth showed that the decomposition of diethylether by lithiumalkyls occurs via a *β*-elimination reaction.[5] The results of the lithiation of TEEDA suggest an analogous mechanism of this reaction by precoordination of the ether to the lithiumalkyl.

In conclusion, we presented the structural and mechanistic investigation of the lithiation of TMEDA and its ethyl-substituted analogue, TEEDA (**4**). Hereby, we isolated α-lithiated TMEDA (**2**) as a tetrameric compound and monomeric *t*BuLi·TEEDA (**7**). Based on **7** the unexpected favoritism for the *β*-lithiation of TEEDA could be explained by means of DFT studies indicating a kinetic favoritism for the *β*-lithiation in comparison to the α-deprotonation. This favoritism according to the complex-induced proximity effect is also indicated by the crystal structure of intermediate **7**, showing short distances and an arrangement of the *β*-hydrogen atom toward the carbanionic center.

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Supporting Information Available: Crystallographic (CIF), experimental and computational data, complete ref 9. This material is available free of charge via the Internet at http://pubs.acs.org.

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(6) CCDC-684634 (**2**), CCDC-684636 (**5**), and CCDC-684635 (**7**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre under www.ccdc.cam.ac.uk/data_request/cif.

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