Variations in the Mechanisms of Direct Metallation of Cyclic and Acyclic Aminals

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The development of preparative protocols for direct a-metallation of amines is a challenging but worthwhile task, due to the importance of such reagents for synthesis. Because of the electron-density accumulation on the adjacent nitrogen atom and carbanionic function, these systems are regarded as non-stabilised or even destabilised carbanions.[1] Alternative multi-step approaches to a-metallated amines via transmetallation,[2] reactions of iminium salts with low-valent metal halides,[3] C−S or C−Te bond cleavage[4] or activation of amines by BF$_3$ adduct formation[5] involve enormous preparative effort and are inefficient due to loss of substance.

Despite substantial progress in the few last years, the number of amine systems directly accessible to deprotonation is still easy to overlook. n-Butyllithium mono-lithiates $N,N',N''$-trimethyl-1,4,7-triazacyclononane[^6] at one methyl group; N-methylpiperidine is deprotonated at the CH$_3$ group using Schlosser/C$_2$H$_5$ base;[^7] the deprotonation of Me$_2$N(CH$_2$)$_2$NMe$_2$ (TMEDA) was described by two groups, but never occurs in large yield;[^8] MeN[(CH$_2$)$_2$NMe]$_2$ (PMDTA) can be lithiated, but again in limited yield,[^9] and the chiral diamine ((R,R)-tetramethyl-1,2-diaminocyclohexane ((R,R)-TMCDA) was found to undergo direct metallation—again at its terminal CH$_3$ group.[10] The latter three examples are important due to the fact that the substrates are widely applied as auxiliary bases in alkyllithium chemistry, without the intention of metallating these.

Generating a carbanion adjacent to two nitrogen atoms seemed even more difficult. However, we recently found that aminal units incorporated in saturated six-membered rings are selectively lithiated at the endocyclic NCH$_2$N position. The reaction of 1,3,5-trimethyl-1,3,5-triazacyclohexane (TMTAC) with nBuLi and even better with tBuLi in hexane proceeds smoothly giving a product consisting of a dimer of lithiated TMTAC linked into chains alternating with TMTAC, {[MeN(CH$_2$)$_2$(NMe)$_2$]CHLi$_2$·TMTAC}$_2$.[11][12] Later we found that conducting the reaction for a longer time at low temperatures leads to the completely lithiated compound. A similar result was found for 1,3-dimethyl-1,3-diazacycloclohexane (DMDAC), which is also lithiated at the NCH$_2$N position by tBuLi. These compounds have been shown to be applicable as Corey–Seebach lithiated dithiane analogous reagents,[12] but with the advantage of heavy-metal free workup procedures.[11] Even a system that has two diazacyclohexane units joined via a methylene group H$_2$C(CH$_2$)$_3$NMe$_2$ can be doubly deprotonated in high yields to give a dimer of H$_2$C[NCH(Li)N(Me)](CH$_2$)$_3$.[13]

These results are in contrast to reports by Karsch, in which open-chain aminals of the type RMeNCH$_2$NMeR can be simultaneously lithiated at both methyl groups by treatment with BuLi (Scheme 1).[^14] Obviously there are different mechanisms involved.

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Scheme 1. Principles of different regioselectivities in the lithiation reactions of cyclic and acyclic aminals (adduct formation and aggregation of adducts ignored).
Just recently, Strohmann and Gessner have been able to crystallise a \( \text{tBuLi} \) adduct of TMTAC, in which its three N atoms bind three Li ions. These are linked by tert-butyl carbanions.[15] They explained the regioselectivity by the proximity of one of the NCH\(_2\)N protons to the carbanion, according to the CIPE concept (complex-induced proximity effect).[16]

Repeating the metallation reaction of DMDAC under different conditions, we found now that the products of this reaction depend on the concentrations of reagents. With lower concentrations of \( \text{tBuLi} \) and longer reaction times the product is a dimer of lithium allylmethylamide complexed by two units of DMDAC (Scheme 2, experiments described in the Supporting Information). This means an obvious degradation of the ring system, which can be mechanistically rationalised by metallation of the non-nitrogen bound methylene group opposite to the aminal unit, followed by alkene extrusion (yielding the allyl group) and cleavage of the aminal system under formation of the amide (see Scheme 3).

![Scheme 2. Lithiation of DMDAC.](image1)

The identity of 1 has been proven by NMR and IR spectroscopy and a structure determination by X-ray diffraction.[17] The \(^1\)H and \(^13\)C NMR spectra show the presence of the DMDAC unit and in particular signals for the unsaturated allyl group at \( \delta = 5.14, 5.35 \) and \( 6.14 \) ppm in the \(^1\)H NMR spectrum and \( \delta = 111 \) and 145 ppm in the \(^13\)C NMR spectrum. An absorption at 1634 cm\(^{-1}\) in the IR spectrum also identifies the allyl function.

The crystal structure (Figure 1) displays the centrosymmetric dimeric nature of 1. The Li-N distances to the anionic amide N atoms N(3) and N(3a) are shorter (2.010(3) and 1.984(3) Å) than to those of the DMDAC unit, N(1) and N(2) (2.255(3) and 2.206(2) Å). The Li-N\(_2\) rhombus is far from a square geometry and characterised by N-Li-N angles of 104.3(1)° and Li-N-Li angles of 75.7(1)°. Diagnostic for the double bond C(9)=C(10) is the distance of 1.301(3) Å.

In \([D_8]\)THF solution the lithiated CH group of 2 causes resonances at \( \delta = 2.26 \) ppm in the \(^1\)H NMR spectrum and at \( \delta = 80.1 \) ppm in the \(^13\)C NMR spectrum. The spectra show two sets of signals for the rest of the ring structures according to lithiated and free DMDAP in solution. A \(^7\)Li NMR resonance at \( \delta = 0.26 \) ppm is in the same range as that of lithiated TMTAC (\( \delta = 0.02 \) ppm).

The solid product 2 contains an endless array of dimers (Figure 2) of the lithiated product linked by non-reacted DMDAP units (Figure 3). The lithium atoms have close contacts to five neighbouring atoms: to two nitrogen atoms, N(1) and N(2) (2.073(2), 2.128(2) Å) of one deprotonated DMDAP unit, to the carbanion C(1a) of a second deprotonated DMDAP unit with a bond length of 2.173(2) Å and to a neutral DMDAP unit via N(4) (2.123(2) Å); the distance to the carbanion C(1) (2.185(2) Å) is longer, but is probably a non-bonding contact in terms of electron density.[13] As in 1, the Li-C\(_2\) rhombus is far from square geometry with larger C-Li-C (105.2(1)°) and smaller Li-C-Li angles (74.8(1)°).

Logical application of Strohmann’s model for lithiation of TMTAC (pre-coordination of one \( \text{tBuLi} \) unit per N atom) to...
the compounds containing only two nitrogen atoms leads to the assumption of the formation of the pre-coordination complexes \([\text{DMDAP} \cdot 2\text{tBuLi}] (4)\) and \([\text{DMDAC} \cdot 2\text{tBuLi}] (5)\) and \([\text{Me}_2\text{NCH}_2\text{NMe}_2 \cdot 2\text{tBuLi}] (6)\). On these model structures we first performed geometry optimisations at the B3LYP level, followed by vibrational calculations to identify such modes of vibrations, which can point to possible reaction coordinates by bringing carbanions and protons to be abstracted close together and therefore defining reaction coordinates. Scheme 5 shows schematic representations of low-frequency vibrational modes, which bring the carbanions close to the protons to be abstracted; they represent the initial movements of the hydrogen atoms along the reaction paths. Figure 4 contains the structures of these adducts, of the transition states of proton abstraction and the products. The geometries were calculated at the HF/6-31++G** level of theory. The given energies were obtained with single-point DFT calculations (B3LYP/6-31++G**) (more details on the calculations and an assessment of their reliability are provided in the Supporting Information). Note that the products represent just first-step products ignoring further (re)aggregation reactions.

A low-frequency mode at 54 cm\(^{-1}\) for 4 allows the positions of the aminal hydrogen atom to come close to the carbanionic centre. The transition state with an energy of 90.6 kJ mol\(^{-1}\) is a realistic value for such a reaction.\(^{[15]}\) Further vibrational modes bringing the other hydrogen atoms closer to the carbanionic centres, were not found. This clearly explains the formation of a sole lithiated product in the deprotonation of DMDAP.

For 5 there is one low-frequency mode at 74 cm\(^{-1}\) (swinging movement of the whole six-membered ring) which allows both, the aminal hydrogen atom and one of the non-nitrogen bound methylene groups each to approach one of the two carbanionic centres. The two transition states are different in energy; the aminal proton abstraction process is associated with a lower barrier of 88 kJ mol\(^{-1}\), while the alternative position requires overcoming a barrier of 105.5 kJ mol\(^{-1}\). This explains the preferred abstraction of the aminal proton in DMDAC under double-stoichiometric concentrations of tBuLi. The observed deprotonation of the alternative position under lower concentrations, however, cannot be explained in this way and the possibility that this process occurs as a follow-up reaction of the lithiated aminal structure as a base to deprotonate the alternative position in a later step, cannot be excluded.

The most interesting results of the calculations were those for complex 6. For this pre-coordination complex two potentially reaction-determining low-frequency modes are found. One, at 129 cm\(^{-1}\), is associated with a movement of an aminal proton towards a carbanion, but this is accompanied by a simultaneous movement of two methyl groups at either ends of the aminal towards each other, leading to some repulsion. The mode at lower frequency (54 cm\(^{-1}\)) allows a terminal methyl group to move towards the other carbanion so that this comes close to a hydrogen atom. The energies of the transition states for abstraction of these two protons, CH\(_2\)- and CH\(_3\)-proton, are different, but only by about 5 kJ mol\(^{-1}\), favouring the proton abstraction from the terminal methyl group.

However, it was also interesting to note the large change in the orientation of the lithium atoms required to reach the transition state for the deprotonation of the methylene unit.
This motion roughly corresponds to a normal mode with a frequency of 317 cm\(^{-1}\) (HF value), which is too high to be considered a large amplitude motion. The greater reactivity at methyl groups may therefore also be the result of a relatively simple pathway (in terms of atom motions required) from the pre-complex to the transition state than simply seen on the basis of transition state energies.

This is inline with the experimental observation. Also from the thermodynamic point of view, this product is lower in energy than the one with deprotonated aminal site, but care is suggested not to overinterpret these results, as the final aggregation will of course be different and will have a substantial influence on the total thermodynamics.

In this context it has also to be added that such calculations can give only rough estimates, as proton abstractions involve a substantial influence of hydrogen tunnelling, lowering the barriers in a way very difficult to predict by means of calculations. Also entropy effects of different aggregates can play an important role, which is neglected in the present considerations. Whilst, these calculations represent some likely, but of course not all possible aggregation forms of \(t\)BuLi towards these aminal molecules, the results are consistent with the observed different reactivities of open-chain and ring-type aminals. In summary, it is the ring closure, which prevents the exocyclic methyl groups in the ring-type aminals from exerting the movement towards the carbanion in the pre-coordination complex. This hindrance is absent in the open-chain aminal and therefore leads to a different regioselectively of lithiation.

The results show that only the sum of information of various reaction systems and a systematic comparison of the molecular dynamics properties of certain common structural features may allow the prediction of reaction products in such deprotonation reactions. Still, the structural diversity occurring in hydrogen abstraction reactions with lithium alkyls is too large to enable one to predict exactly the outcome of such reactions. However, the
now rapidly growing information on aggregation motifs and mechanisms will sharpen our predictive tools for future reactions. The combination of experiment and quantum-chemical calculations plays a very fruitful role in this context.

Experimental Section

Lithium allyl(methyl)amine-DMDAC-adduct (1): A solution of DMDAC (1.4 mL, 1.14 g, 10 mmol) in hexane (10 mL) was added dropwise slowly to a solution of tBuLi (1.5 mL in pentane, 6.7 mL, 10 mmol) at −78°C. The reaction mixture was stirred overnight and allowed to reach ambient temperature. It was filtered through celite and washed several times with hexane. The remaining solution was concentrated and stored at −26°C. Colourless crystals, suitable for X-ray determination, were obtained after four weeks. Yield: 1.27 g (66%). 1H NMR (500 MHz, CD2Cl2): δ = 1.58 (br, 2H, CH2CH2CH2), 2.04 (s, 6H, NCH3), 2.11 (br, 4H, CH2CH2CH2), 2.70 (br, 2H, NCH2N), 3.07 (s, 3H, NCH3), 3.81 (d, 1JHM = 3.8 Hz, 2H, NCH2CH2), 5.14 (d, 1JHM = 17.3 Hz, 1H, CHC-trans-H), 5.35 (d, 1JHM = 10.0 Hz, 1H, CHC-cis-H), 6.35 ppm (m, 1H, CH2CH2CH2); 13C NMR (100 MHz, CD2Cl2): δ = 23.37 (CH2CH2CH2), 42.96 (NCH3), 46 (br, LNCH3), 54.32 (CH2CH2CH2), 79.39 (NCH3), 65 (br, LNCH3), 111 (br, CH2CH2CH2); 13C NMR (155 MHz, CD2Cl2): δ = 1.57 ppm; IR: v ≈ 2942 (ν(CH3)), 2788 (ν(N–NCH3)), 1634 (ν-v(C–C–N)), 1472 (ν(CH3)), 1389 cm−1 (ν(N–N)).

Bis[2,5-dimethyl-2,5-diaza-cyclopentene-1-yl]lithium (1,3-dimethyl-1,3-diaza-cyclopentane) adduct (2): A solution of DMDAP (6.63 g, 63.2 mmol) in pentane (40 mL) was slowly added to a hexane solution of tBuLi (1.6 mL, 39.5 mL, 63.2 mmol) with rigorous stirring at −78°C. The reaction mixture was stirred overnight and allowed to reach ambient temperature. A white precipitate formed. The mixture was filtered; the solids was washed with pentane (3 × 10 mL) and dried under vacuum. The precipitate was crystallised. The precipitate mixture was filtered; the solid was washed with pentane (3 × 10 mL) and dried under vacuum. The precipitate was crystallised. The precipitate mixture was filtered. The solids was washed with pentane (3 × 10 mL) and dried under vacuum. The precipitate was crystallised. The precipitate mixture was filtered. The solids was washed with pentane (3 × 10 mL) and dried under vacuum.

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