Structural models for lithium intermediates during carboxamide-directed metallations

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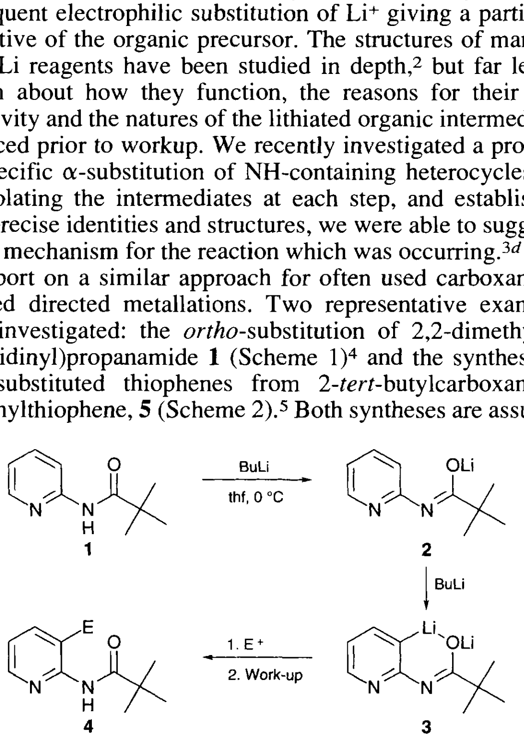
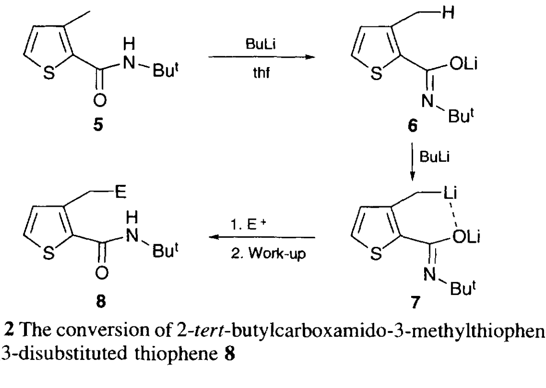
Structural models for Li intermediates during metallations of two different organic precursors having –NH–C=O units are isolated and structurally characterised, and shown to be complexed mono- and di-meric azaenolates with (–N=C–OLi·xB)$_n$ (B = Lewis base) groupings; contrary to earlier assumptions, the structures imply that the N- (rather than the O-) centres of these species would direct second lithiations to nearby C–H bonds although it has proved impossible thus far to detect the proposed dilithiated systems.

Many organic syntheses utilise lithium reagents to effect key deprotonation steps.[1] In this they are often very specific, subsequent electrophilic substitution of Li$^+$ giving a particular derivative of the organic precursor. The structures of many of these Li reagents have been studied in depth,[2] but far less is known about how they function, the reasons for their high selectivity and the natures of the lithiated organic intermediates produced prior to workup. We recently investigated a protocol for specific α-substitution of NH-containing heterocycles.[3a–c] By isolating the intermediates at each step, and establishing their precise identities and structures, we were able to suggest a viable mechanism for the reaction which was occurring.[3d] Here we report on a similar approach for often used carboxamide-induced directed metallations. Two representative examples were investigated: the *ortho*-substitution of 2,2-dimethyl-*N*-(2-pyridinyl)propanamide **1** (Scheme 1)[4] and the synthesis of 2,3-disubstituted thiophenes from 2-*tert*-butylcarboxamido-3-methylthiophene, **5** (Scheme 2).[5] Both syntheses are assumed to involve initially the formation of the Li azaenolates **2** and **6**. Further lithiation is then held to afford specifically the dilithio derivatives **3** and **7**. In both prior studies it was suggested that this regiospecificity is due to the second equivalent of Li reagent being directed towards the proton to be abstracted by a 'coordination only' mechanism involving the azaenolate O atom.[4,5] However, to our knowledge, the Li species of types **2**, **3**, **6** and **7** have not been isolated, identified and structurally examined. By studying structural models for these key intermediates we have been able to gain more insight into the mechanisms of these reactions.



Scheme 1 The conversion of 2,2-dimethyl-*N*-(2-pyridinyl)propanamide **1** into the *ortho*-substituted product **4**



Scheme 2 The conversion of 2-*tert*-butylcarboxamido-3-methylthiophene **5** into a 2,3-disubstituted thiophene **8**

Treatment of **1** in thf with Bu^{n}Li affords a solution from which a yellow microcrystalline material was isolated and identified as (**2**·thf)$_n$. Cryoscopic relative molecular mass (CRMM) measurements on C_6H_6 solutions of (**2**·thf)$_n$ show the association state (n) to be monomeric at low concentrations (n = 1.04 ± 0.03 at 0.023 mol dm^{-3}) and in a monomer–oligomer equilibrium at higher concentrations (n = 1.13 ± 0.02 at 0.045 mol dm^{-3}). Unfortunately it proved impossible to get X-ray quality crystals of this complex. However, by introducing 1 equiv. of hmpa [O=P(NMe$_2$)$_3$] into the reaction mixture, X-ray quality crystals of (**2**·hmpa)$_n$ were obtained. The complex is a dimer (n = 2) in the solid state,† with a central (OLi)$_2$ ring (Fig. 1). Each Li is bonded to two azaenolate oxygens [mean Li–O 1.928(4) Å], one hmpa O [Li–O 1.891(4) Å] and a pyridine N [Li–N 2.049(4) Å]. As was suggested (Scheme 1)[4] the amide group has indeed been deprotonated to give an azaenolate moiety. Its C atom is planar (sum of bond angles, 359.9°) and it has a *Z* configuration about the C–N bond which is slightly longer [1.311(2) Å] than expected for a double bond. Commensurate with this the C–O bond length of 1.274(2) Å is shorter than those of typical Li enolates (1.32 Å),[2d] Al azaenolate (1.33 Å),[6] and imino esters (1.34 Å).‡ It is also shorter than the C–O bonds in Li *N*-isopropylbenzamide (1.299–1.330 Å within the hexameric/octameric aggregates; mean 1.31 Å), the only previously published solid-state structure of a Li azaenolate derived from a carboxylic acid

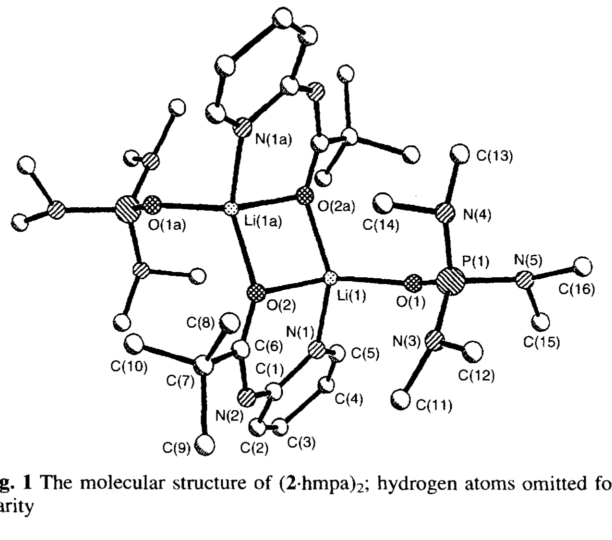


Fig. 1 The molecular structure of (**2**·hmpa)$_2$; hydrogen atoms omitted for clarity

amide.[7] However the key structural feature with respect to the reaction mechanism is that the *ortho* proton, abstracted in the second lithiation step of the reaction, is very distant from the azaenolate O. Hence the presumption that the regioselectivity of the reaction is due to this oxygen directing this second lithiation may be incorrect. It is far more feasible that such direction is being carried out by the azaenolate N atom, which is positioned next to the *ortho* proton. In proposing this new mechanism we are assuming that the orientation of the pyridine ring in solution will be similar to that in the solid state. It seems likely that (**2**·hmpa)$_n$ will, like (**2**·thf)$_n$, exist in a monomer–dimer equilibrium in solution; within a monomer the Li–N(py) interaction is likely to be even stronger than in the dimer. In addition and in any case, the nitrogen lone pair would be more available than those of the O due to steric constraints imposed by the coordinated ligands around the Li ion.

Treatment of **5** in thf with Bu^{n}Li affords a solution from which pale yellow crystals were isolated and identified as (**6**·thf)$_n$. Attempts to obtain a solid-state structure failed. However we were able also to prepare the pmdeta [MeN(CH$_2$CH$_2$NMe$_2$)$_2$] adduct **6**·pmdeta. This is a monomer in the solid state (Fig. 2),† the Li atom bonding to the three N atoms of pmdeta [mean Li–N 2.122(3) Å] and to the azaenolate O [Li–O, 1.772(3) Å]. As with (**2**·hmpa)$_2$ the azaenolate moiety possesses a *Z* configuration about the C–N double bond [1.301(2) Å] and the C atom is planar (sum of bond angles, 360.0°), but the C–O bond length (1.287 Å) is slightly longer. However the most striking structural feature is that the azaenolate oxygen, which was suggested to direct a second lithiation (Scheme 2),[5] is orientated in the opposite direction to the thiophene methyl group (which is where the second lithiation occurs). This is presumably due to steric repulsions between the pmdeta and the Me group. It must be stressed that the solution structure in thf could involve the thiophene ring being orientated differently than in the solid state. However it still seems far more feasible that, once more, the second lithiation is being directed by the azaenolate N and not by O which will always be nearby one or more Lewis base molecules binding to the Li. This illustrates an important and critical point about many proposed organic reaction mechanisms involving Li species: they usually assume that such species are monomers (frequently not the case) and that the Li is uncomplexed (not the case in polar solvents). Visual addition of a Lewis base onto Li in **2** (Scheme 1) and **6** (Scheme 2) serves at once to make the earlier proposed mechanisms unlikely.

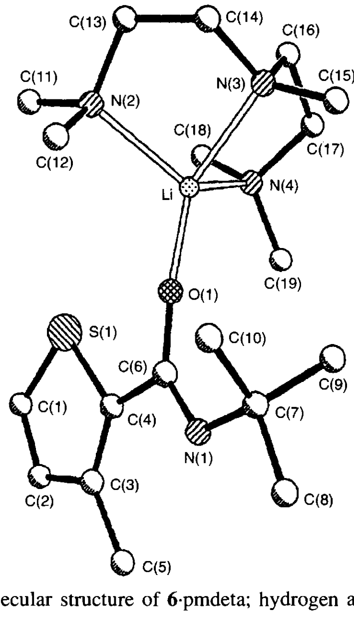


Fig. 2 The molecular structure of **6**·pmdeta; hydrogen atoms omitted for clarity

We then attempted to synthesise the proposed dilithiated intermediates **3** and **7**. However despite using varying solvent and donor systems, and different quantities of different organolithium reagents, it proved impossible to isolate any such dilithiated complexes. It has also proved impossible to detect any dilithiation spectroscopically. For example, in a typical experiment, a 2 equiv. excess LiNPr$^i_2$ (LDA) was added at 25 °C to a (CD$_3$)$_2$SO solution of the monolithiated amide in a NMR tube. A subsequent ^{1}H NMR spectrum indicated that the monolithiated amide and the unreacted LDA were the only two species present. This beckons the question of whether dilithiated species do actually exist as intermediates in two-step reactions whereby the monolithiated molecules first undergo directed second lithiation, treatment with the electrophile then leading to substitution at this position. It seems likely that for substitution to occur both the lithiating reagent and the electrophilic reagent must be present at the same time, implying that these two steps are interdependent. Explanations must be speculative, but include (*i*) the dilithiate is formed but only in trace amounts, and the equilibrium (monolithio derivative) $\rightleftharpoons$ (dilithio derivative) is driven forwards by a fast reaction between the dilithiated species and the electrophile; (*ii*) the lithiating reagent joins with the monolithio derivative to form a QUAsi DiAnion Complex.[8] This QUADAC could then behave like a dianionic species. We are investigating these possibilities.

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Footnotes

† *Crystal data*: for (**2**·hmpa)$_2$: C$_{16}$H$_{31}$LiN$_5$O$_2$P, M = 363.37, orthorhombic, space group *Pbca*, a = 16.093(3), b = 11.929(2), c = 21.209(4) Å, U = 4071.6(13) Å^3, T = 153(2) K, Z = 8, D_c = 1.186 Mg m^{-3}, $F(000)$ = 1568, λ(Mo-Kα) = 0.71073 Å, μ(Mo-Kα) = 0.153 mm^{-1}. R_1 = 0.0337 for 2273 reflections with $I > 2\sigma(I)$ and wR_2 = 0.0967 for all data. For **6**·pmdeta: C$_{19}$H$_{37}$LiN$_4$OS, M = 376.53, orthorhombic, space group *Pna*2$_1$, a = 17.338(3), b = 12.147(2), c = 10.736(2) Å, U = 2261.1(7) Å^3, T = 153(2) K, Z = 4, D_c = 1.106 Mg m^{-3}, $F(000)$ = 824, λ(Mo-Kα) = 0.71073 Å, μ(Mo-Kα) = 0.157 mm^{-1}. R_1 = 0.0376 for 4596 reflections with $I > 2\sigma(I)$ and wR_2 = 0.102 for all data. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). See Information for Authors, Issue No. 1. Any request to the CCDC for this material should quote the full literature citation and the reference number 182/139.

‡ Mean value of 18 structures from the Cambridge Structural Database, Cambridge Crystallographic Data Centre.

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