Variations in the solid-state, solution and theoretical structures of a laterally deprotonated aromatic tertiary amide†

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Reaction of 2-ethyl-*N,N*-diisopropyl-1-naphthamide **3** with Bu^{t}Li in tetrahydrofuran (thf) affords a laterally metallated derivative which exists as a tris(thf) solvated monomer with no Li–C interaction and an sp^2 hybridised carbanionic centre in the solid-state; NMR spectroscopy suggests that this structure is viable in solution but that Li–C bonded atropisomers are also possible and calculations corroborate these data.

The elaboration of aromatic compounds by directed metallation[1] is an established strategy in synthesis.[2] Recent total syntheses of, for example, phomactin, narciclasine, analogues of meridine and atpenin B feature key ortholithiation steps.[3] Lateral lithiation, that is metallation of alkyl groups *ortho* to a directing group,[4] is particularly valuable in the synthesis of polycyclic products, and is a key step in routes to corydalic acid methyl ester and fredericamycin.[5] The most important directors of lateral lithation are amides:[6] stereochemical aspects of the formation and reaction of laterally lithiated amides have been investigated,[7] and enantio-[8] and atroposelective lateral lithiations[9] have been reported. The directing effects of these groups have been interpreted in terms of their promotion of the "complex-induced proximity effect",[10] and evidence from kinetic isotope effects[11] has lent weight to the view that the reaction proceeds by rate-determining deprotonation of an initial substrate–organolithium complex.

It is only recently that solid-state structural evidence[12] has been provided in support of the frequently made assumption that O–Li coordination is maintained from reactive complex through to products. For tertiary benzamide **1** and naphthamide **2** directed ortholithiation has been observed despite the known sterically induced twist angle between amide and aromatic ring plane.[13] Seeking to extend this study to systems in which the arene bears potentially reactive *ortho* substituents, we now report on the structural chemistry of laterally deprotonated 2-ethyl-*N,N*-diisopropyl-1-naphthamide **3**, a chiral, atropisomeric compound in which the amide lies perpendicular to the naphthyl ring.[14] The solid-state and solution structures of the lithium derivative of **3** are probed with a view to understanding how variations therein and how interaction with external Lewis bases may influence subsequent reactivity.
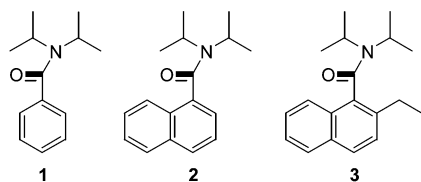
Treatment of **3** in tetrahydrofuran (thf) at −78 °C with Bu^{t}Li gave a green solution which deposited crystals† that were

identified as α-lithio-2-ethyl-*N,N*-diisopropyl-1-naphthamide–tris(thf) complex (**4**)·3thf in the solid-state.‡ It is noticeable, though, that thf is readily lost during isolation *in vacuo* (*cf.* NMR spectroscopy) which causes the product to turn from green to maroon. X-Ray crystallography reveals that (**4**)·3thf is a monomer in the solid state but that the Li$^+$ ion is not bonded to the deprotonated C$_\alpha$ centre of the 2-ethyl group (Fig. 1; the asymmetric unit contains two crystallographically independent molecules of which one will be discussed). Instead, Li$^+$ has migrated to the amide O-centre [Li1–O1 = 1.861(7) Å, Li1–O1–C11 = 137.9(3)°] where its coordination sphere is completed by thf solvation. The amide–naphthyl twist angle, known to be almost exactly perpendicular for *N,N*-diisopropyl-1-naphthamides,[12] is essentially unaffected by lithiation [C2–C1–C11–O1 = 82.5(5)°], as is the amide carbonyl bond length [C11–O1 = 1.248(4) Å]. This suggests the complete absence of overlap between naphthyl and amide group π-systems and precludes the view that an α-deprotonated structure of the type noted here might exhibit extended enolate character. The sp^2 hybridisation of deprotonated C12 [C2–C12–C13 = 125.1(5)°] means that both C12 and C13 lie in the naphthyl plane such that p-orbital overlap between C2 and C12 is maximised and a short C2···C12 bond of 1.353(7) Å is formed. Both this effect and retention of the essentially perpendicular amide contrast significantly with the recently characterized dimers of *N,N*-diisopropyl-2-lithiobenzamide–OEt$_2$ and *N,N*-diisopropyl-2-lithionaphthamide–thf, in each of which 5-membered C$_3$OLi rings resulted from intramolecular amide chelation of C$_{ortho}$-bonded and mono-ether solvated metal ions.[12]

Previous spectroscopic study of the *in situ* lithiation of **3** has suggested the formation of Li–C-bonded species by revealing the presence of non-interconverting *syn*- and *anti*-diastereoisomers in thf at −40 °C.[7] The present study reveals that the solution structure and electronic properties of the species that result from the dissolution of (**4**)·3thf are solvent dependent. Treatment with [^{2}H$_8$]thf gives a dark green solution which variable temperature ^{1}H NMR spectroscopy suggests contains one dominant species. While broad Pr^i resonances are noted at
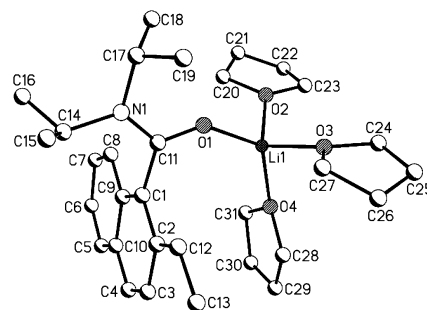
Fig. 1 Solid-state structure of (**4**)·3thf. Selected bond lengths (Å) and angles (°): Li1–O1 1.861(7), O1–C11 1.248(4), C11–N1 1.343(5), C1–C2 1.456(6), C2–C12 1.353(7), Li1–O1–C11 137.9(3), O1–C11–C1 120.2(3), O1–C11–N1 119.3(3).

+25 °C, the observation of two stereotopic Pr^i groups at −25 °C points to slow rotation about the amide C–N bond at this temperature. The remainder of the spectrum does not significantly alter over the temperature range studied and at −25 °C the deprotonated ethyl C$_\alpha$H is observed at δ 2.84 (^{1}H) and δ 68.4 (^{13}C). Two stereotopic Pr^i groups are also noted at −25 °C if dissolution is effected in [^{2}H$_8$]PhMe (a dark red solution is noted here, implying solvent dependency of the dissolved organolithiums electronic structure), as are signals attributable to the deprotonated C$_\alpha$H group (δ 2.06 and δ 58.2). However, in [^{2}H$_8$]PhMe at −48 °C all ^{1}H NMR resonances split into two in a 60 : 40 ratio such that by HMQC spectroscopy at −80 °C ^{1}H NMR quartets at δ 2.37 (0.6H) and 3.31 (0.4H) correlate with ^{13}C signals at δ 60.6 and 57.0, respectively. At the same temperature, ^{1}H NMR doublets at δ 2.21 (1.2H) and 2.18 (1.8H) correlate with ^{13}C signals at δ 14.3 and 14.1, respectively. In contrast to previous studies of the *in situ* metallation of **3**,[7] the present data suggest that upon the dissolution of (**4**)·3thf in toluene Li–C-bonded diastereoisomers form and rapidly exchange above −48 °C whilst in a large excess of thf the solid-state structure is retained.

The synthetic utility of carbanions has led to much interest in their structural properties and to the discovery that ion separation will afford naked anions in the presence of strong Lewis bases.[15] To probe this process, calculations have been undertaken for **3** and its lithium derivatives using Gaussian 98. Exploratory geometry optimisations (HF level/6-31G* basis set) were followed by a frequency calculation. Geometry was then refined using DFT procedure (B3LYP level/6-311G** basis set). Reported and deposited geometries are taken from DFT calculations while energies relate to DFT results modified by the scaled (0.91) ZPE correction from the HF study. Results indicate that the amido N-centre in the parent amide (**I**) is π-conjugated and that the amide–arene torsional angle is 98.4°. Concerning the lithium derivatives, four structure-types (**IIa**–**IId**) were probed. For each of **IIa**–**d**, mono- (**IIIa**–**d**), bis- (**IVa**–**d**) and tris- (**Va**–**d**) Me$_2$O-solvated congeners were also computed (Table 1 and ESI†). The preferred unsolvated lithiate (**IIa**) reveals Li–O and Li–C$_\alpha$ bonds of 1.866 and 2.123 Å, respectively. The formation of a 6-membered metallocycle in **IIa** has incurred a decrease in amide–arene torsion angle to 70.4°. Less stable by 7.3 kcal mol^{-1} is perimetallated **IIb**. Substitution of a C$_\alpha$H$_2$ hydrogen by lithium with *anti*-atroposelectivity with respect to C=O yields **IIc** (14.7 kcal mol^{-1} destabilised with respect to **IIa**). Least stable of the modelled unsolvated structures (by 21.9 kcal mol^{-1} relative to **IIa**), **IId** is constructed as for **IIc** but with the amide oriented as for **I**. This results in Li–N bonding.

Both Li–X (X = O, N) and Li–C links are computed to extend sequentially upon Me$_2$O solvation. The addition of a third molecule of Me$_2$O affords identical structures **Va**–**c** wherein no formal Li–C$_\alpha$ interaction exists and the metal is encapsulated by a tetraoxygen coordination sphere [amide–arene torsional angle = 83.4°, *viz.* 82.5(5)° in (**4**)·3thf]. Charge

distributions for the aromatic 1-position and ethyl C$_\alpha$ centre in **Va** (−0.32 and −0.37, respectively) are essentially unchanged relative to those in **IIa** [with the former proffering an explanation for the lack of observable nucleophile–electrophile interaction between the amide C-centre (+0.47) and the site of deprotonation].

Over all calculated structures α-metallation of the ethyl group *syn* to the amide oxygen is preferred irrespective of the presence or otherwise of etherate solvent with the energy of formation of the most stable unsolvated lithiate (**IIa**) computed (**I** + MeLi → **IIa** + MeH) to be −29.1 kcal mol^{-1}. Enthalpy of solvation (ΔE_s) for the conversion of **IIa** into **Va** decreases markedly with the sequential addition of Me$_2$O; for **IIa** + Me$_2$O → **IIIa**, **IIIa** + Me$_2$O → **IVa** and **IVa** + Me$_2$O → **Va** ΔE_s = −18.0, −9.7 and −2.4 kcal mol^{-1}, respectively. That the last of these is low is attributable to Li–C$_\alpha$ bond dislocation occurring in order to accommodate the third Me$_2$O molecule.

To conclude, (**4**)·3thf dissolves in [^{2}H$_8$]thf with retention of the solid-state structure. Contrastingly, the employment of [^{2}H$_8$]PhMe as solvent yields Li–C$_\alpha$-bonded *syn*- and *anti*-diastereoisomers, the interconversion of which can be resolved by ^{1}H NMR spectroscopy at low temperature. These data suggest that **4** exhibits strongly solvent dependent solution structures. Consistent with the observation of Li–C$_\alpha$-bonded diastereoisomers in solution, stable computed *anti*- and *syn*-atropisomers suggest a preference for Li–C$_\alpha$ interaction over Li–O(thf) bonding (except in a large excess of donor).

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Table 1 Relative energies (kcal mol^{-1}) of models n**a**–n**d** (n = **II**–**V**). Li–C bond cleavage renders **Va**–**c** identical

	a	**b**	**c**	**d**
II	0.0	7.3	14.7	21.9
III	0.0	5.4	14.5	25.3
IV	0.0	2.7	12.1	21.8
V	0.0	0.0	0.0	18.5