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COMMUNICATIONS

Experimental Characterization and Computational Study of Unique C,N-Chelated Lithium Dianions

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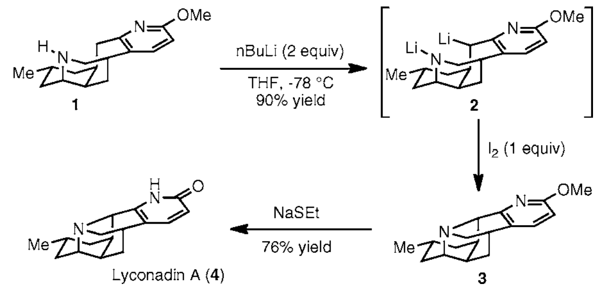
Abstract: The structure of a unique C,N-chelated dilithio dianion has been established as a solvated monomeric species using a combination of NMR and computational techniques. The highly ordered structure of the dianion may be important in its reactivity in an oxidative C−N bond-forming process.

Structural studies of lithiated anions in solution are important given the ubiquity of these intermediates in organic synthesis.[1] Despite the remarkable advances that have been made in the investigation of C-, O-, and N-lithiated species, dianionic compounds (e.g., C−Li/N−Li) have received relatively little attention.[2] During a recent total synthesis study of the *Lycopodium* alkaloid lyconadin A (**4**), (Scheme 1) Sarpong et al. discovered that amine **1** was converted to pentacycle **3** by the sequential addition of *n*-BuLi (2 equiv) and iodine (1 equiv).[3] This C−N bond-forming reaction was hypothesized to proceed via the intermediacy of a C,N-chelated lithium dianion intermediate (**2**) of ill-defined structure.

Scheme 1

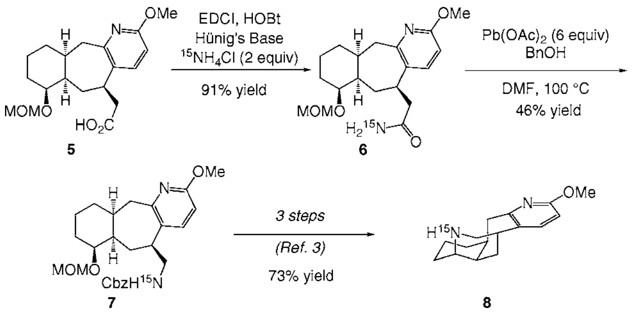


To gain insight into the solution structure of the dianion intermediates, which may enable the generalization of the C−N bond-forming sequence, we have undertaken an in-depth structural study of these unique species. In this communication, we report the synthesis of a ^{15}N-incorporated isotopomer related to **1** as well as NMR and computational studies that have resulted in the structural characterization of the affiliated lithium dianion.

Because of its ease of synthesis, desmethyl analog [^{15}N]**8** (Scheme 2), lacking a methyl group on the A-ring, was targeted for synthesis and subsequent NMR spectroscopic studies. Coupling **5**[4] with [^{15}N]NH_4Cl using standard amidation conditions[5] gave [^{15}N]**6** in 91% yield.

Hofmann rearrangement of [^{15}N]**6**, mediated by $Pb(OAc)_4$, in the presence of benzyl alcohol yielded Cbz-protected amine [^{15}N]**7**, which was converted to [^{15}N]**8** in three steps using a previously established protocol.[6]

Scheme 2



With [^{15}N]**8** in hand, we performed a series of ^{6}Li and ^{15}N NMR studies. Treatment of [^{15}N]**8** in THF-d_8 at −78 °C with [^{6}Li]*n*-BuLi (2 equiv) recrystallized from pentane[7] afforded the putative dianion. The ^{6}Li NMR spectrum of the dianion generated from [^{15}N]**8**—recorded at −90 °C (Figure 1A)—contains two distinct doublets, indicating that each lithium is bound and couples to the isotopically labeled nitrogen. The ^{15}N decoupled ^{6}Li NMR observation (Figure 1B) shows two singlets. The ^{15}N NMR spectrum, also recorded at −90 °C (Figure 1C), contains a quintet, which confirms the Li−N−Li connectivity. The structures of open dianion isomer **9** (Figure 2) and the cyclic isomer **10** are consistent with

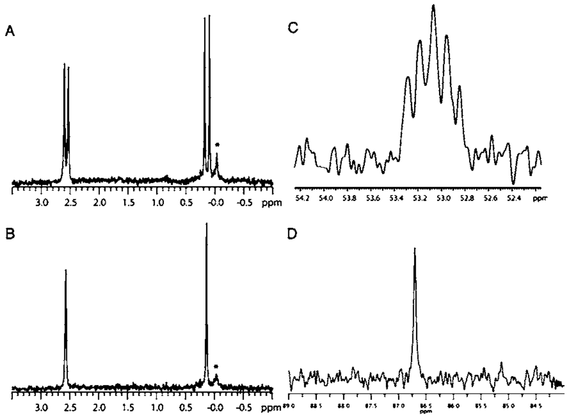


Figure 1. NMR spectra of key resonances of the dianion of [^{15}N]**8**. (A) ^{6}Li NMR spectrum of 0.05 M [^{15}N]**8** and 2.0 equiv of [^{6}Li]*n*-BuLi in THF-d_8 at −90 °C. (B) {^{15}N}^{6}Li NMR spectrum of 0.05 M [^{15}N]**8** and 2.0 equiv of [^{6}Li]*n*-BuLi in THF-d_8 at −90 °C. (C) ^{15}N NMR spectrum of 0.05 M [^{15}N]**8** and 2.0 equiv of [^{6}Li]*n*-BuLi in THF-d_8 at −90 °C. (D) ^{13}C NMR spectrum of 0.025 M **8** and 2.0 equiv of [^{6}Li]*n*-BuLi in THF-d_8 at −100 °C, expanded around the benzylic carbon resonance. *An impurity from [^{6}Li]*n*-BuLi.

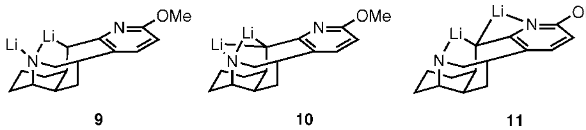


Figure 2. Possible structures for dilithio anions generated from **8**.

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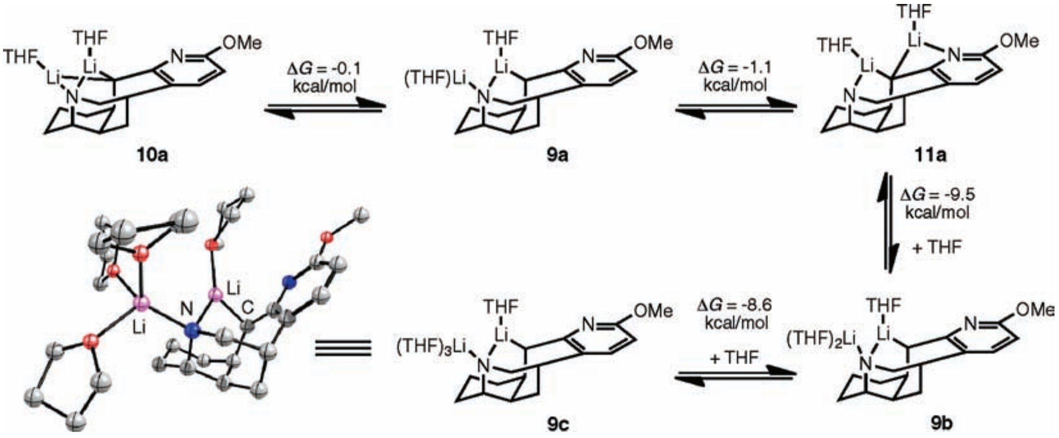
Scheme 3



the ^{6}Li and ^{15}N NMR spectral data and are well-precedented structural motifs.[2,11] Dilithio compound **11** also seems plausible but is inconsistent with the data. ^{13}C NMR spectra were recorded at −100 °C (Figure 1D) to distinguish open isomer **9** from the chelated dilithio compound **10** by ^{6}Li−^{13}C coupling. A combination of 2-D NMR techniques including ^{1}H−^{1}H gCOSY, ^{1}H−^{13}C gHMBC, and ^{1}H−^{13}C HSQC was used to identify the chemical shift of the benzylic carbon. Unfortunately, the ^{13}C spectrum shows no signs of ^{6}Li−^{13}C scalar coupling. This absence is consistent with previous observations. For example, Fraenkel et al. described difficulties observing an analogous coupling in benzyllithium that could be traced, in part, to a small $^1J(^6\text{Li}-^{13}\text{C})$ coupling.[8]

We turned to density functional theory computational studies to provide insight into the structure of the dianion intermediate. The relative free energies (ΔG, kcal/mol) of various forms of the dianion intermediate at −78 °C were calculated at the B3LYP/6-31G(d) level of theory with single-point MP2 correction.[9,10] The relative energies for the computationally most viable dilithio isomers are illustrated in Scheme 3 in monotonically increasing stability. Tetrasolvated open dianion isomer **9c** was calculated to be most stable in energy. Additional structures and their associated relative energies are reported in the Supporting Information. On the basis of these results, we conclude that open isomers of type **9** benefit from high solvation numbers.

Our studies support the existence of the C,N-chelated dilithio dianion as a monomeric species that is solvated by four molecules of solvent (see **9c**) at concentrations that are relevant to oxidative conversion to **3** (see Scheme 1).[11] Furthermore, we have amassed support for the persistence of **9c** as a highly organized dianion at low temperature. This structural organization may be critical to the oxidative C−N bond forming process. We expect that ^{15}N and ^{6}Li NMR spectroscopy in conjunction with the computational methods used to characterize dianion **9c** could be extended to the characterization of other C,N-chelated dianions. Using this combined approach, the solution structures of a range of such C,N-chelated dianions may be readily determined. These insights will serve as a starting point in our efforts to extend the scope of the oxidative C−N bond-forming reaction.

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Supporting Information Available: Experimental details and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) For full reference listing, see the Supporting Information.

(11) The computations use the Gaussian standard state of 1.0 atm. If the THF concentration is corrected to neat THF (approximately 13 M), each solvation step benefits from approximately 2.0 kcal/mol of additional stabilization at −78 °C (195 K). Pratt, L. M.; Merry, S.; Nguyen, S. C.; Quan, P.; Thanh, B. T. *Tetrahedron* **2006**, *62*, 10821–10828.

(12) The low solvation number of the internal lithium in **9c** is a property shared by all open dimers (ref 8).

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