Solution Structure of Unstabilized Cyclic α-Aminoorganolithiums by ^{13}C, ^{15}N, and ^{6}Li NMR Spectroscopy

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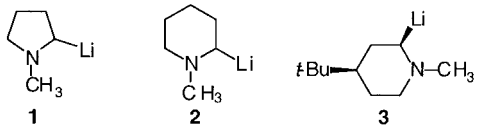
Organolithium reagents have become indispensable in the formation of carbon−carbon bonds in modern organic synthesis and chiral, nonracemic organolithium reagents are playing an increasingly important role.[1] A continuing point of interest is the structure and properties of species having a stereogenic metal-bearing carbon, since many of these species exhibit extraordinary configurational stability. Furthermore, the steric course of electrophilic substitutions[2] of configurationally stable, chiral, nonracemic organolithiums varies from complete retention to complete inversion of configuration, and various points between (summarized in ref 3). A consistent trend that explains the variabilities of these reactions has not yet emerged, so structural studies of the reactive species are of interest.

2-Lithio-*N*-methylpyrrolidines, **1**, and 2-lithio-*N*-methylpiperidines, **2** and **3**, react with carbonyls and alkyl halides in excellent yields.[3−5] These unstabilized α-aminoorganolithiums



are configurationally stable up to −40 °C.[6] They react in high yield with most carbonyl electrophiles with 100% retention of configuration at the metal-bearing carbon ($S_E2$ret) and with varying degrees of inversion ($S_E2$inv) with alkyl halides, *depending on the size of the heterocyclic ring*.[3,4] For example, piperidine **2** reacts with 3-phenyl-1-bromopropane to give 100% inversion at the anionic center; however, pyrrolidine **1** reacts with only 78−79% inversion through competing polar pathways.[3,4] With electrophiles that are easily reduced, SET processes intervene.[3] Rigid piperidine **3**, having a pseudoequatorial lithium, cannot react with inversion and undergoes SET processes in reactions with alkyl halides, whereas retentive substitution by carbonyl electrophiles is facile.[5] Organolithiums **1** and **2** are unique among chiral organolithiums that undergo $S_E2$inv reactions in that the transition state for inversion is not mesomerically stabilized.

As part of an investigation into the reasons for the extraordinary configurational stability and varying reactivity in these systems, we have used ^{6}Li, ^{15}N, and ^{13}C NMR to investigate the solution structure of these species at low temperature, and report the results herein.

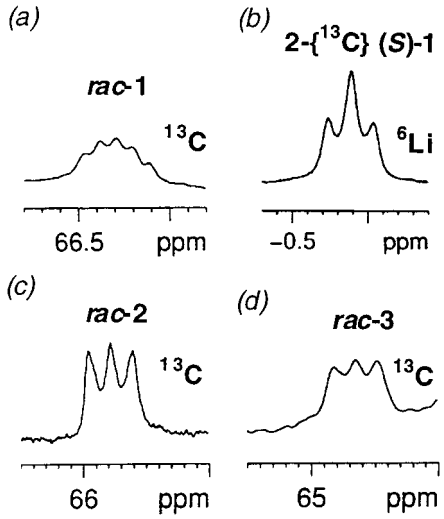


Figure 1. (a) Partial ^{13}C spectrum of {^{6}Li} *rac*-**1** (0.39M); (b) ^{6}Li spectrum of {^{13}C,^{6}Li} (*S*)-**1** (er 90:10, 0.34 M; a ∼0.05 M solution showed similar splitting); (c) partial ^{13}C spectrum of {^{6}Li} *rac*-**2** (0.43 M) ({^{6}Li} (*S*)-**2** and {^{6}Li} (*R*)-**2** (er ≥ 98:2) are similar); and (d) partial ^{13}C spectrum of {^{6}Li} *rac*-**3** (0.35 M).

All three organolithium species were prepared by Sn/Li exchange from the corresponding stannanes, as reported previously.[4−7] To avoid complications from excess butyllithium, and to ensure that the species being observed were only α-aminoorganolithiums **1**−**3**, we reacted a substoichiometric amount of {^{6}Li} BuLi[8] with each stannane. Examination of the ^{6}Li spectra of each revealed only one sharp singlet, indicating the presence of only one organolithium species at −100 °C.[9]

The aggregation state of a {^{6}Li} organolithium complex can be determined from the multiplicity of a coupled carbon signal or from the magnitude of the $^{1}J(^{13}C-^{6}Li)$ coupling constant using the empirical relationship $J = 17$ Hz/n, where n is the aggregation number.[10]

The ^{13}C NMR spectrum of {^{6}Li} *rac*-**1** shows a well-defined quintet at 66.3 ppm with a coupling constant $^{1}J(^{13}C-^{6}Li)$ of 6.8 Hz, indicating a dimeric structure (Figure 1a). Although heterochiral dimeric structures are known in the solid state, we were interested in knowing if a dimer would also form with the nonracemic organolithium. In the ^{13}C NMR spectrum of {^{6}Li} (*S*)-**1** (∼90:10) the multiplet associated with C-2 was shifted downfield into the THF-d_8 signal, obscuring the downfield portion of the multiplet, although it was clear that the species was not monomeric. An unambiguous picture was obtained by examining the ^{6}Li spectrum of (*S*)-**1** enriched with carbon-13 at C2 and C5 (see Supporting Information for synthesis details). As shown in Figure 1b, the ^{6}Li signal was a 1:2:1 triplet, clearly indicating a

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(9) All NMR spectra were recorded at −100 °C in THF-d_8. ^{13}C chemical shifts (75 MHz) were referenced to THF-d_8 (67.6 ppm); ^{6}Li spectra (44 MHz) were externally referenced to a 0.3 M solution of $^{6}LiCl$ in CD_3OD (0 ppm); ^{15}N spectra (30 MHz) were externally referenced to a 0.3 M solution of {^{15}N} aniline in C_6D_6 (50 ppm). The temperature was calibrated using the method of Reich et al.: Sikorski, W. H.; Sanders, A. W.; Reich, H. J. *Magn. Reson. Chem.* **1998**, *36*, S118. Details for the preparation of neat {^{6}Li} BuLi and for the preparation of the NMR samples can be found in the Supporting Information.

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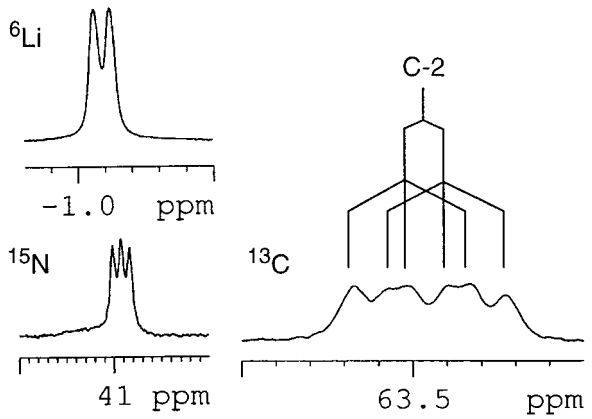


Figure 2. ^{6}Li, ^{15}N, and partial ^{13}C NMR of {^{15}N,^{6}Li} *rac*-**2** (0.44 M).

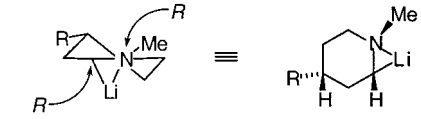
dimeric structure. The dimeric structure persisted even at 7-fold dilution. The enantiomer ratio of these samples was ~90:10, and both homochiral and heterochiral dimers could have been formed in principle. The latter could be formed in relative amounts up to 20% of the total, depending on $\Delta G°$ between the two dimers and the limiting amount of minor enantiomer. Neither the ^{13}C nor the ^{6}Li spectra showed evidence of a second species in appreciable amounts, indicating only one dimer.

Enantiomerically pure and racemic {^{6}Li} **2** exhibited 1:1:1 triplets for C-2, indicating that both exist as monomers at −100 °C ($^1J(^{13}C-^6Li)$ = 13.3 Hz), Figure 1c. *Thus, in both **1** and **2**, enantiopurity has no effect on aggregation state.* With *rac*-**1**, we cannot say conclusively whether there are homochiral or heterochiral dimers, but the absence of two signals in the 90:10 er sample suggests that homochiral dimers predominate. Conformationally rigid piperidine {^{6}Li} *rac*-**3** exhibited a 1:1:1 triplet with $^1J(^{13}C-^6Li)$ = 13.1 Hz, indicating that *rac*-**3** is also a monomer in solution at −100 °C (Figure 1d).

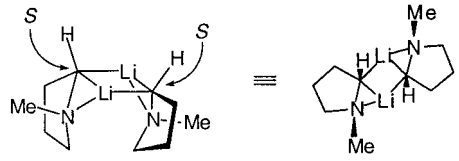
We have previously speculated that the lithium atom bridges C-2 and the nitrogen in **1** and **2**, and that this structural effect could account for the extraordinary configurational stability of these compounds.[6b] Lithium bridging of this type has been observed in α-aminoorganolithiums in the solid state.[11]

To address this issue in solution we examined {^{15}N} **2** (see Supporting Information for synthesis details). If the lithium atom bridged both C-2 and the nitrogen we should see a doublet in the ^{6}Li NMR of {^{6}Li,^{15}N} **2**, which is exactly what we found (Figure 2). The $^1J(^{15}N-^6Li)$ coupling constant was 2.7 Hz in the ^{15}N spectrum and 2.6 Hz in the ^{6}Li spectrum. The C-2 signal is a doublet of triplets in the ^{13}C NMR spectrum due to simultaneous coupling to both ^{6}Li and ^{15}N, with $^1J(^{13}C-^{15}N)$ = 8.0 Hz and the $^1J(^{13}C-^6Li)$ = 12.7 Hz. These data constitute firm evidence that lithium bridges the anionic carbon and the nitrogen of **2** and we assume a bridged species also exists in **1** and **3**.

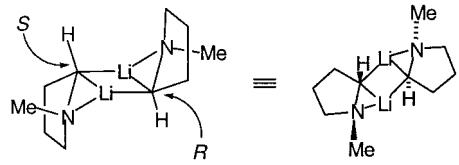
The solution structures of organolithiums **1**−**3** are shown below in both 2D and 3D projections, with any possible solvent ligating the lithiums deleted for clarity. The simplest structures are **2** and **3**, which are monomers in THF solution. Lithium bridging across both carbon and nitrogen must yield a bicyclic ring structure, and the ring fusion must be cis due to ring strain in a trans compound. The cis ring fusion determines the absolute configuration of the nitrogen, which is now stereogenic. In the dimers of (*S*)-**1**, an interesting situation arises for the assignment of a CIP descriptor, since the issue of pentavalent chirality centers is not addressed by the CIP system.[12] For simplicity, we maintain the descriptor of the monomer, since the relative configuration of the other ligands around the metal-bearing carbon is the same in both monomer and dimer. The *observed* homochiral dimer and the *possible* heterochiral dimer of **1** are shown. In both, the C2 hydrogen is again cis to the *N*-methyl. If one traces the *N*−*Li*−*C*−*N*−*Li*−*C* six-membered ring, it becomes apparent that the heterochiral dimer resembles a chair while the homochiral dimer resembles a twist-boat.



2: R = H
3: R = *t*-Bu



Homochiral dimer of *(S)*-**1**



Possible heterochiral dimer of *rac*-**1**

In summary, we find that lithiated pyrrolidines are dimers in solution whereas lithiopiperidines are monomers. Further, we provide definitive evidence of bridging across nitrogen and carbon by lithium, previously only observed in the solid state.

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Supporting Information Available: Experimental procedures for the er determination of *N*-Boc-2-(tributylstannyl)pyrrolidine by supercritical fluid chromatography (SFC), the preparation of {^{15}N} enriched piperidinostannane precursor to **2** and {^{13}C} enriched pyrrolidinostannane precursor to **1**, as well as a procedure for making neat ^{6}LiBu and for preparing the NMR samples (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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