Solution Structure of Lithium Dicyclohexylamide (Cy₂NLi) and Related Mixed Aggregates: Comparison with Lithium Diisopropylamide

Katherine B. Aubrecht and David B. Collum*
Department of Chemistry, Baker Laboratory, Cornell University, Ithaca, New York 14853-1301

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Lithium dialkylamides are frequently used as highly reactive and selective bases for the formation of a wide range of stabilized carbanions. We have investigated the structures and reactivities of the perennial favorites—lithium tetramethylpiperidide (LiTMP), lithium hexamethyl disilazide (LiHMDS), and lithium diisopropylamide (LDA). One might expect that the fundamental relationships of solvation and aggregation would apply to other less commonly used dialkylamides as well. However, this notion was brought into question by reports of unusual properties of lithium dicyclohexylamide (Cy₂NLi). Whereas LDA exists as disolvated dimers, Cy₂NLi is insoluble in hydrocarbons, with 0.1 M solutions containing 1.0 equiv of HMPA. The spectra manifest Li triplets and ¹⁵N quinets characteristic of the cyclic dimer. Addition of 2.0 equiv of HMPA to 0.1 M solutions of [⁶Li,¹⁵N]Cy₂NLi in 2.1 THF/HMPA affords the bis(HMPA)-solvated dimer (respectively), spectroscopic and colligative studies of Cy₂NLi implicated a mixture of dimer and monomer in aromatic hydrocarbons containing 1.0 equiv of HMPA. The striking differences imparted by substituting isopropyl with cyclohexyl substituents prompted us to investigate the solution structures of Cy₂NLi. We describe herein NMR spectroscopic investigations of Cy₂NLi under a variety of circumstances suggesting that, despite significant differences in solubility, LDA and Cy₂NLi show equivalent behavior in solution.

Table 1. NMR Spectroscopic Data of [⁶Li,¹⁵N]Cy₂NLi

<table>
<thead>
<tr>
<th>compd</th>
<th>⁶Li, δ (mult, J, J)</th>
<th>¹⁵N, δ (mult, J, J)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2a</td>
<td>1.96 (t, 5.0)</td>
<td>71.3 (g, 4.9)</td>
</tr>
<tr>
<td>2b</td>
<td>1.72 (t, 4.7)</td>
<td>70.0 (g, 4.7)</td>
</tr>
<tr>
<td>2c</td>
<td>1.75 (t, 4.7)</td>
<td>74.3 (g, 4.7)</td>
</tr>
<tr>
<td>4a</td>
<td>1.32 (d, 5.1)</td>
<td>72.6 (g, 5.2)</td>
</tr>
<tr>
<td>4b</td>
<td>1.65 (d, 5.2)</td>
<td>70.2 (g, 5.1)</td>
</tr>
<tr>
<td>4c</td>
<td>0.60 (d, 5.2)</td>
<td>67.7 (g, 5.1)</td>
</tr>
<tr>
<td>5c</td>
<td>3.10 (t, 5.9)</td>
<td>70.9 (g, 5.4)</td>
</tr>
<tr>
<td>5</td>
<td>1.50 (d, 5.0)</td>
<td></td>
</tr>
</tbody>
</table>

¹⁶Li and ¹⁵N NMR spectroscopic studies were carried out on [⁶Li,¹⁵N]Cy₂NLi prepared as a white solid. The NMR spectroscopic data are summarized in Table 1. Most spectra are included as supporting information. [⁶Li,¹⁵N]Cy₂NLi is insoluble in hydrocarbons, with 0.1 M solutions available only upon addition of >3 equiv of THF per lithium. The spectra manifest Li triplets and ¹⁵N quintets (~ 5.0 Hz) characteristic of the cyclic dimer. Addition of 2.0 equiv of HMPA to 0.1 M solutions of [⁶Li,¹⁵N]Cy₂NLi in 2.1 THF/pentane affords the bis(HMPA)-solvated dimer (respectively), spectroscopic and colligative studies of Cy₂NLi implicated a mixture of dimer and monomer in aromatic hydrocarbons containing 1.0 equiv of HMPA. The striking differences imparted by substituting isopropyl with cyclohexyl substituents prompted us to investigate the solution structures of Cy₂NLi. We describe herein NMR spectroscopic investigations of Cy₂NLi under a variety of circumstances suggesting that, despite significant differences in solubility, LDA and Cy₂NLi show equivalent behavior in solution.


5. (a) Gilchrist, J. H.; Collum, D. B. J. Am. Chem. Soc. 1992, 114, 794. (b) With 0.5 equiv of HMPA, we observe two broad Li resonances at ~125 °C (0.28 Hz) suggesting the presence of a mixed solvent-dimer bearing one HMPA. The rapid exchange was confirmed by detailed investigation. (c) (i) ¹⁶Li resonance correlations were confirmed by ¹⁵N coupling of approximately 4.2 Hz). Decomposition occurs at ~80 °C, possibly due to formation of PhCH₂Li.


containing $^{6}\text{Li}, ^{15}\text{N}$Cy$_{2}$NLi and 1.1 equiv of added HMPA show 2b to the exclusion of other species (Figure 2A). If the sample is maintained at ambient temperature in a sealed NMR tube the mixed dimer soon appears (Figure 2B). Prolonged standing at room temperature causes further decomposition, resonance broadening (Figure 2C), and eventual total destruction. The decomposition appears to accelerate after a slow onset and is observably faster at elevated HMPA concentrations.

The results described above are fully consistent with the previously observed reluctance of LDA to be deaggregated by HMPA. To complete the comparison, we briefly investigated the mixed aggregation of Cy$_{2}$NLi with selected lithium salts and found complete analogy with LDA. Thus, treatment of $^{6}\text{Li}, ^{15}\text{N}$Cy$_{2}$NLi with LiCl affords 2:1 and 1:1 mixed aggregates 4b and 5. Whereas treatment with 0.5 equiv of $^{6}\text{Li}$ lithium pinacolate affords limited concentrations of the mixed dimer 4c along with the two homonuclear aggregates, treatment with 0.5 equiv of $^{6}\text{Li}$ lithium cyclohexenolate affords virtually no mixed aggregate.

In conclusion, we find no significant differences in the solution structures of Cy$_{2}$NLi and LDA; the assignment of Cy$_{2}$NLi as a monomer–dimer mixture based largely on a combination of spectroscopic and colligative measurements appears to be incorrect. Even when effected by the most careful experimentalist, colligative measurements can be very misleading. Lastly, given the high boiling point of the Cy$_{2}$NH and relatively low solubility of the Cy$_{2}$NLi, we see no apparent advantages offered by Cy$_{2}$NLi over LDA for organic synthesis applications.

**Experimental Section**

$^{15}\text{N}$Dicyclohexylamine ([15N]Cy$_{2}$NH). A nitrogen-flushed, oven-dried 250 mL round bottom flask fitted with a septum was charged sequentially with $^{15}\text{NH}_{2}\text{Cl}$ (2.0 g, 37 mmol), NaCNBH$_{3}$ (4.6 g, 73 mmol), NaOAc (4.4 g, 54 mmol), and powdered 4 Å molecular sieves (1.2 g). After the vessel was placed in an ice bath, MeOH (100 mL), AcOH (0.3 mL, 5.3 mmol), and cyclohexanone (114 mL, 110 mmol) were added. After being stirred for 23 h at room temperature, the reaction was judged to be complete by GC analysis of aliquots quenched with 3 N NaOH and extracted with ether. The pH was adjusted to pH 14 with solid NaOH pellets to hydrolyze the borate salts. After being stirred for 90 min, the solution was brought to pH 4 using AcOH and the solvent was removed in vacuo. Upon partial dissolution of the solids in 300 mL of aqueous i-PrOH followed by filtration...
and concentration of the filtrate to 25 mL, bubbling gaseous HCl through the filtrate resulted in the precipitation of crude $[^{15}N]$Cy2NH-HCl that was filtered and dried. Recrystallization from 400 mL of 3:1 THF/MeOH afforded 5.55 g (69% yield) of pure material: $^1$H NMR (D$_2$O) $\delta$ 3.1 (m, 2H), 1.5–1.9 (m, 10H), 1.2 (m, 10H); $^{13}$C($^1$H) NMR (D$_2$O) $\delta$ 48.9 (d, $J_{CN}$ = 3.8 Hz), 24.8, 20.3, 19.7. The free amine was isolated by dissolving the $[^{15}N]$Cy2NH-HCl in 3 N NaOH (80 mL), extracting once with Et$_2$O (100 mL), drying organic extracts over CaH$_2$ for 1 h, removing ether in vacuo, and vacuum distilling the amine. The Cy$_2^{15}$NH was isolated in 59% overall yield: $^1$H NMR (CDCl$_3$) $\delta$ 2.5 (m, 2H), 1.7 (m, 10H), 1.2 (m, 10H); $^{13}$C($^1$H) NMR (CDCl$_3$) $\delta$ 53.1 (d, $J_{CN}$ = 3.8 Hz), 34.4, 26.2, 25.3.

$[^{6}$Li,$^{15}$N$]$Lithium Dicyclohexylamide ($[^{6}$Li,$^{15}$N$]$Cy$_2$NLi). A 100 mL round-bottom flask was charged with doubly recrystallized $[^6$Li]ethyl lithium (230 mg, 6.56 mmol)$^1$ and degassed dry hexane (70 mL). Following warming to dissolve the ethyllithium and cooling to 0 °C, $[^{15}N]$Cy2NH (1.25 g, 6.85 mmol) was added in one portion. Lithium dicyclohexylamide precipitated as the amine was added. The suspension was stirred at rt for 3 h and then concentrated to 30 mL and placed in a −78 °C bath. Filtration afforded 1.04 g (84% yield) of a white solid displaying spectroscopic properties described in the text.

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**Supporting Information Available:** NMR spectra (6 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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