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Solution Structure of Lithium Dicyclohexylamide (Cy$_2$NLi) and Related Mixed Aggregates: Comparison with Lithium Diisopropylamide

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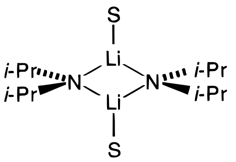
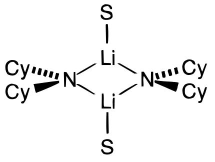
Lithium dialkylamides are frequently used as highly reactive and selective bases for the formation of a wide range of stabilized carbanions.[1] We have invested considerable energy toward understanding the structures and reactivities of the perennial favorites—lithium tetramethylpiperidide (LiTMP), lithium hexamethyldisilazide (LiHMDS), and lithium diisopropylamide (LDA).[2] 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 (Cy$_2$NLi).[3,4] Whereas LDA exists as disolvated dimers **1a** and **1b** in THF[5a] and THF−HMPA[5b] (respectively), spectroscopic and colligative studies of Cy$_2$NLi implicated a mixture of dimer and monomer in aromatic hydrocarbons containing 1.0 equiv of HMPA.[3] The striking differences imparted by substituting isopropyl with cyclohexyl substituents prompted us to investigate the solution structures of Cy$_2$NLi. We describe herein NMR spectroscopic investigations of Cy$_2$NLi under a variety of circumstances suggesting that, despite significant differences in solubility, LDA and Cy$_2$NLi show equivalent behavior in solution.



1a; S = THF
1b; S = HMPA



2a; S = THF
2b; S = HMPA

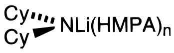


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Table 1. NMR Spectroscopic Data of [^{6}Li,^{15}N]Cy$_2$NLi[a]

compd	^{6}Li, δ (mult, J_{LiN})	^{15}N, δ (mult, J_{LiN})
2a[b]	1.96 (t, 5.0)	71.3 (q, 4.9)
2b[c]	1.72 (t, 4.7)	70.0 (q, 4.7)
2b[d]	1.75 (t, 4.7)	74.3 (q, 4.7)
4a[d]	1.32 (d, 5.1)	72.6 (q, 5.2)
4b[e]	1.65 (d, 5.2)	70.2 (q, 5.1)
4c[f]	0.60 (d, 5.2)	67.7 (q, 5.1)
5[e]	3.10 (t, 5.9) 1.50 (d, 5.0)	70.9 (q, 5.4)

[a] Spectra were recorded on 0.1 M solutions of [^{6}Li,^{15}N]Cy$_2$NLi. Coupling constants were measured after resolution enhancement. Multiplicities are denoted as d = doublet, t = triplet, q = quintet. The chemical shifts are reported in ppm relative to 0.3 M [^{6}Li]LiCl/MeOH at −90 °C (0.0 ppm) and neat Me$_2$NEt at −90 °C (25.7 ppm). [b] Recorded at −70 °C in toluene solution with 5 equiv of THF. [c] Recorded on 2:1 pentane/THF solutions at −90 °C. [d] Recorded in benzene solution at 10 °C. [e] Recorded in 1.5:1 THF/toluene at −90 °C. [f] Recorded in 3:1 THF/pentane at −115 °C.

^{6}Li and ^{15}N NMR spectroscopic studies were carried out on [^{6}Li,^{15}N]Cy$_2$NLi prepared as a white solid. The NMR spectroscopic data are summarized in Table 1. Most spectra are included as supporting information. [^{6}Li,^{15}N]Cy$_2$NLi is insoluble in hydrocarbons, with 0.1 M solutions available only upon addition of >3 equiv of THF per lithium. The spectra manifest ^{6}Li triplets and ^{15}N quintets ($^{1}J_{\text{LiN}} \approx 5.0$ Hz) characteristic of the cyclic dimers[2] (**2**). ^{15}N zero quantum NMR spectroscopy[6] confirms the observable cyclic oligomer to be a dimer rather than a higher oligomer. Addition of 2.0 equiv of HMPA to 0.1 M solutions of [^{6}Li,^{15}N]Cy$_2$NLi in 2:1 THF/pentane affords the bis(HMPA)-solvated dimer **2b**[7a] *to the exclusion of monomer* ***3***. In an effort to observe the monomer reported previously,[3] we investigated the structure of Cy$_2$NLi in the reported HMPA-benzene mixtures.[7b] The ^{6}Li spectrum recorded on solutions of [^{6}Li,^{15}N]Cy$_2$NLi (0.1 M) in benzene containing 2.0 equiv of HMPA contains a new upfield ^{6}Li doublet that appears to be the same species observed previously[3] (Figure 1A); aging the sample at 40 °C for 10 min causes an increase in the doublet intensity (Figure 1B). While the splitting is superficially consistent with the monomer attribution, the coupling constant is substantially smaller than the value of 8−11 Hz anticipated for a monomer.[2,8,9] Indeed, the ^{15}N NMR spectrum displays the 1:2:3:2:1 quintet of **2b** along with a second 1:2:3:2:1 quintet rather than the 1:1:1 triplet of a monomer (Figure 1C).[10] We assign this new species as a mixed dimer (possibly **4a**)[11] resulting from decomposition of the HMPA.[12] Benzene solutions

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[5] For ^{6}Li and ^{15}N NMR spectroscopic investigations of LDA, see: (a) Galiano-Roth, A. S.; Collum, D. B. *J. Am. Chem. Soc.* **1989**, *111*, 6772. (b) Romesberg, F. E.; Gilchrist, J. H.; Harrison, A. T.; Fuller, D. J.; Collum, D. B. *J. Am. Chem. Soc.* **1991**, *113*, 5751. (c) Galiano-Roth, A. S.; Kim, Y.-J.; Gilchrist, J. H.; Harrison, A. T.; Fuller, D. J.; Collum, D. B. *J. Am. Chem. Soc.* **1991**, *113*, 5053. (d) Kim, Y.-J.; Bernstein, M. P.; Galiano-Roth, A. S.; Romesberg, F. E.; Williard, P. G.; Fuller, D. J.; Harrison, A. T.; Collum, D. B. *J. Org. Chem.* **1991**, *56*, 4435. (e) Romesberg, F. E.; Collum, D. B. *J. Am. Chem. Soc.* **1994**, *116*, 9198. (f) Kim, Y.-J.; Bernstein, M. P.; Galiano-Roth, A. S.; Romesberg, F. E.; Williard, P. G.; Fuller, D. J.; Harrison, A. T.; Collum, D. B. *J. Org. Chem.* **1991**, *56*, 4435.

[6] Gilchrist, J. H.; Collum, D. B. *J. Am. Chem. Soc.* **1992**, *114*, 794.

[7] (a) With 0.5 equiv of HMPA, we observe two broad ^{6}Li resonances at −125 °C (δ 2.08 and 1.67 ppm) suggesting the presence of a mixed solvated dimer bearing one HMPA. The rapid exchange precluded detailed investigation. (b) Solutions of [^{6}Li,^{15}N]Cy$_2$NLi in toluene containing >1.0 equiv of HMPA contain exclusively dimer **2b** (including well-resolved ^{6}Li−^{31}P coupling of approximately 4.2 Hz). Decomposition occurs at −80 °C, possibly due to formation of PhCH$_2$Li.

[8] In fact, treatment of LDA and Cy$_2$NLi in hydrocarbons with *trans-N,N,N′,N′*-tetramethylcyclohexanediamine (TMCDA) affords the TMCDA-solvated monomers, both with coupling constants of 10.1 Hz. Remenar, J. F.; Collum, D. B. Unpublished results. Details will be reported in due course.

[9] For a theoretical investigation of ^{6}Li−^{15}N coupling, see: Koizumi, T.; Morihashi, K.; Kikuchi, O. *Bull. Chem. Soc. Jpn.* **1996**, *69*, 305.

[10] The ^{6}Li−^{15}N resonance correlations were confirmed by single frequency irradiations: Gilchrist, J. H.; Harrison, A. T.; Fuller, D. J.; Collum, D. B. *J. Am. Chem. Soc.* **1990**, *112*, 4069.

[11] Addition of Me$_2$NH to CyNLi/HMPA in benzene provided the mixed aggregate along with several other resonances, leaving us unsure of the nature of the decomposition and the resulting mixed aggregate structure.

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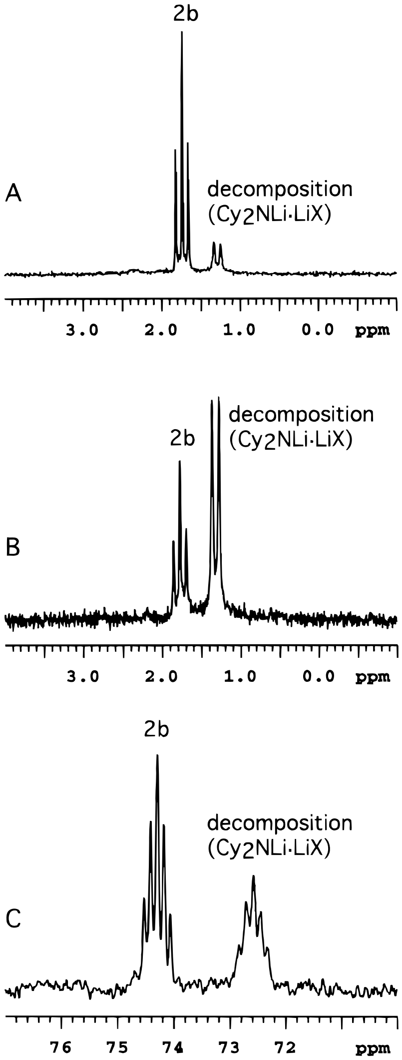
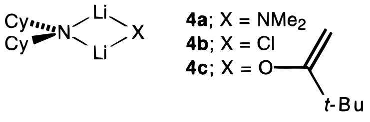
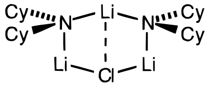


Figure 1. ^{6}Li and ^{15}N NMR spectra of 0.10 M [^{6}Li,^{15}N]Cy$_2$NLi: (A) ^{6}Li NMR spectrum with 2.0 equiv of HMPA in benzene at rt; (B) ^{6}Li NMR spectrum with 2.0 equiv of HMPA in benzene at 12 °C after aging for 10 min at 40 °C; (C) ^{15}N{^{1}H} NMR spectrum with 2.0 equiv of HMPA in benzene at 12 °C after aging for 10 min at 40 °C.

containing [^{6}Li,^{15}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.





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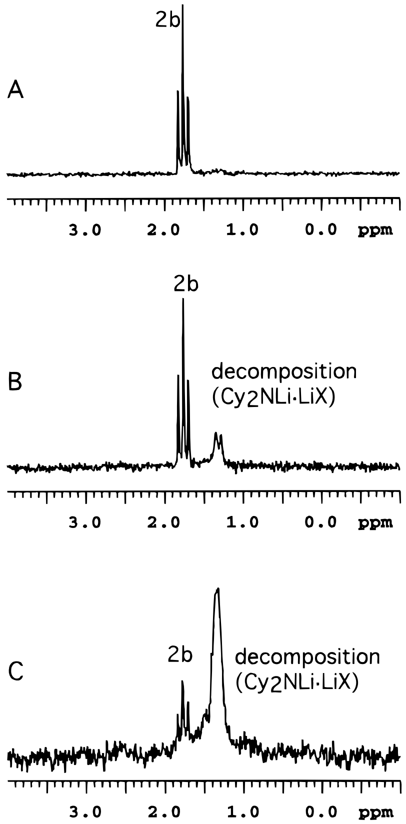

Figure 2. ^{6}Li NMR spectra of 0.10 M [^{6}Li,^{15}N]Cy$_2$NLi with 1.1 equiv of HMPA in benzene at 18 °C: (A) aged at rt for 17 min (for shimming); (B) aged at rt for 4 h; (C) aged at rt for 20 h.

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.[5c] Thus, treatment of [^{6}Li,^{15}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}Li]lithium pinacolate affords limited concentrations of the mixed dimer **4c** along with the two homonuclear aggregates, treatment with 0.5 equiv of [^{6}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}N]Dicyclohexylamine ([^{15}N]Cy$_2$NH). A nitrogen-flushed, oven-dried 250 mL round bottom flask fitted with a septum was charged sequentially with ^{15}NH$_4$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 (11.4 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

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and concentration of the filtrate to 25 mL, bubbling gaseous HCl through the filtrate resulted in the precipitation of crude [^{15}N]Cy$_2$NH·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) δ 3.1 (m, 2H), 1.5−1.9 (m, 10H), 1.2 (m, 10H); ^{13}C{^{1}H} NMR (D$_2$O) δ 48.9 (d, $J_{CN} = 3.8$ Hz), 24.8, 20.3, 19.7. The free amine was isolated by dissolving the [^{15}N]Cy$_2$NH·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$_3$) δ 2.5 (m, 2H), 1.7 (m, 10H), 1.2 (m, 10H); ^{13}C{^{1}H} NMR (CDCl$_3$) δ 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]ethyllithium (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]Cy$_2$NH (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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