Lithium Diisopropylamide: Oligomer Structures at Low Ligand Concentrations

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Abstract: One- and two-dimensional ^{6}Li and ^{15}N NMR spectroscopic studies of lithium diisopropylamide (LDA) solvated by substoichiometric concentrations of oxetane, THF, Et_2O, and diisopropylamine are described. Partially solvated dimers and trimers are identified. Possible benefits of carrying out organolithium chemistry at low ligand concentrations are discussed.

Introduction

Spectroscopic studies of lithium amides at low ligand concentrations can provide details of lithium−ligand interactions not available when the ligand is used as the medium.[1−7] Incremental additions of coordinating solvents to lithium hexamethyldisilazide (LiHMDS), for example, offer considerable insights into the coordination chemistry of lithium amide dimers, including ligand binding constants, mechanisms of ligand substitution, and details of competitive and cooperative solvation.[2−5,7] Solvation of lithium diethylamide ($LiNEt_2$) affords a particularly clear view of ring laddering.[6,8] Lithium tetramethylpiperidide (LiTMP) solvated by sub-stoichiometric ligand concentrations provide numerous examples of mechanistically important open dimers that are not observed at higher solvent concentrations.[7]

Besides exploring the general coordination chemistry of lithium, there are practical motivations for understanding organolithium structures and reactivities at low donor solvent concentrations. Synthetic chemists often run organolithium reactions in neat coordinating solvents.[9] However, of the more than 45 rate equations determined for synthetically important LDA-mediated reactions,[10] approximately 75% display a zeroth-order dependence on the donor solvent concentration and another 20% display an *inverse* dependence. Consequently, the *majority* of LDA-mediated reactions may be effected at low ligand concentrations by using more cost-effective[11] aliphatic or aromatic hydrocarbons without sacrificing the reaction rate or efficacy. Moreover, ligands used to catalytically modify organolithium reactivity must, by definition, function at substoichiometric concentrations and should do so most effectively in the absence of other strongly coordinating ethereal ligands.[12]

Table 1. ^{6}Li and ^{15}N NMR Spectral Data[a]

structure	^{6}Li, δ (mult, J_{LiN})	^{15}N, δ (mult, J_{LiN})
2a	1.90 (t, 4.8)	70.9 (m)
	1.45 (m)	
3a	1.62 (t, 5.0)	76.0 (q, 5.2)
5a	2.82 (t, 6.8)	82.3 (m)
	1.04 (t, 4.5)	77.4 (m)
6a	2.52 (m)	75.7 (m)
	1.29 (t, 4.5)	66.0 (m)
2b	2.16 (t, 5.2)	70.0 (m)
	1.63 (m)	
3b	1.95 (t, 5.0)	74.5 (m)
5b	2.91 (m)	83.0 (m)
	1.33 (t, 4.8)	76.6 (m)
6b	2.61 (t, 6.6)	73.0 (m)
	1.54 (m)	63.7 (m)
2c	2.03 (t, 5.0)	68.6 (m)
	1.56 (m)	
3c	1.81 (t, 5.0)	73.4 (q, 5.0)
4/5c/6c[b]	2.57 (t, 6.3)[c]	81.3 (q, 6.4)[c]
	2.15 (t, 5.0)[d]	

[a] Spectra were recorded on samples containing 0.1 M total lithium concentration (normality). Coupling constants were measured after resolution enhancement. Multiplicities are denoted as follows: t = triplet, m = multiplet, q = quintet. The chemical shifts are reported relative to 0.3 M [^{6}Li]LiCl/MeOH (0.0 ppm) and neat Me_2NEt (25.7 ppm) at −90 °C. All J values are reported in hertz. THF and oxetane shifts are reported at −135 °C. Diethyl ether shifts are reported at −127 °C. [b] Peak resulting from proposed rapid ligand exchange of unsolvated and partially solvated trimers. [c] 0.25 equiv of diethyl ether. [d] 0.75 equiv of diethyl ether.

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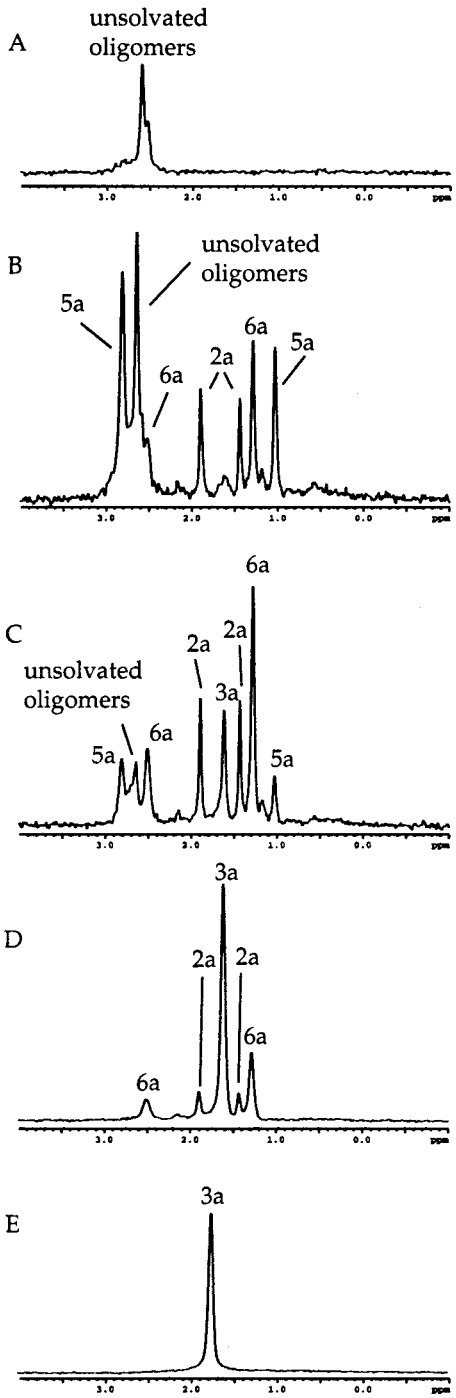


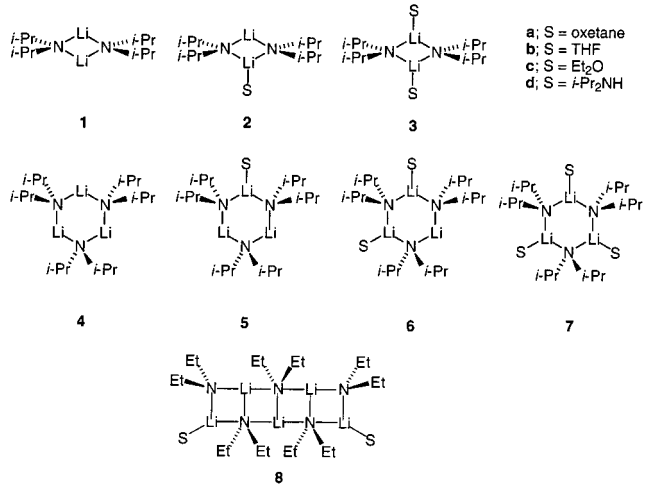
Figure 1. ^{6}Li{^{15}N} NMR spectra of 0.1 M [^{6}Li,^{15}N]LDA in 3:2 pentane:toluene at −135 °C with (A) no added ligand, (B) 0.25 equiv of oxetane, (C) 0.5 equiv of oxetane, (D) 0.75 equiv of oxetane, and (E) 1.0 equiv of oxetane.

In this study we describe the structures of the most prominent lithium amide—lithium diisopropylamide (LDA)—at low ethereal ligand concentrations. LDA contrasts with other lithium amides by revealing the serial solvation of cyclic trimers.

Results

^{6}Li and ^{15}N NMR spectra were recorded on [^{6}Li,^{15}N]LDA[13] using methods described previously.[2] The ^{6}Li−^{15}N resonance correlations critical to the structural assignments were determined by using ^{6}Li,^{15}N-heteronuclear multiple quantum correlation (HMQC) spectroscopy[14] as well as broad-band and single-frequency decouplings.[15] Table 1 summarizes the spectral data while Figures 1 and 2 illustrate selected spectra. The majority of spectra are archived as Supporting Information.

LDA/Oxetane. We investigated LDA solvation using oxetane, a strongly coordinating,[5] yet more spectroscopically tractable, analogue of THF.[6] Figure 1 illustrates representative one-dimensional spectra. The resonance coupling patterns and resonance correlations were determined by ^{6}Li,^{15}N-HMQC[14] spectroscopy (Figure 2) with support by single-frequency ^{6}Li−^{15}N decouplings.[15] Spectra recorded on 0.1 M solutions of [^{6}Li,^{15}N]LDA in 3:2 pentane:toluene without added ligands reveal the mixtures of unidentified solvent-free cyclic oligomers noted previously[16,17] (Figure 1A). Analogous solutions containing 0.25 equiv of oxetane (per Li) at −135 °C show the unsolvated LDA oligomers along with resonances corresponding to a monosolvated dimer (**2a**), a monosolvated trimer (**5a**), and a disolvated trimer (**6a**). Dimer **2a** displays two distinct ^{6}Li resonances coupled to a single ^{15}N resonance. Trimer **5a** is favored relative to **6a** at lower oxetane concentration. Trimers **5a** and **6a** each display a downfield ^{6}Li resonance corresponding to unsolvated ^{6}Li nuclei and an upfield resonance corresponding to solvated ^{6}Li nuclei.



As the oxetane concentration exceeds 0.5 equiv, disolvated dimer **3a** emerges at the expense of the lower per-lithium solvates. Dimer **3a** displays a single ^{6}Li resonance and a single ^{15}N resonance. With 0.75 equiv of oxetane, the monosolvated trimer **5a** is no longer detected, and at 1.0 equiv of oxetane

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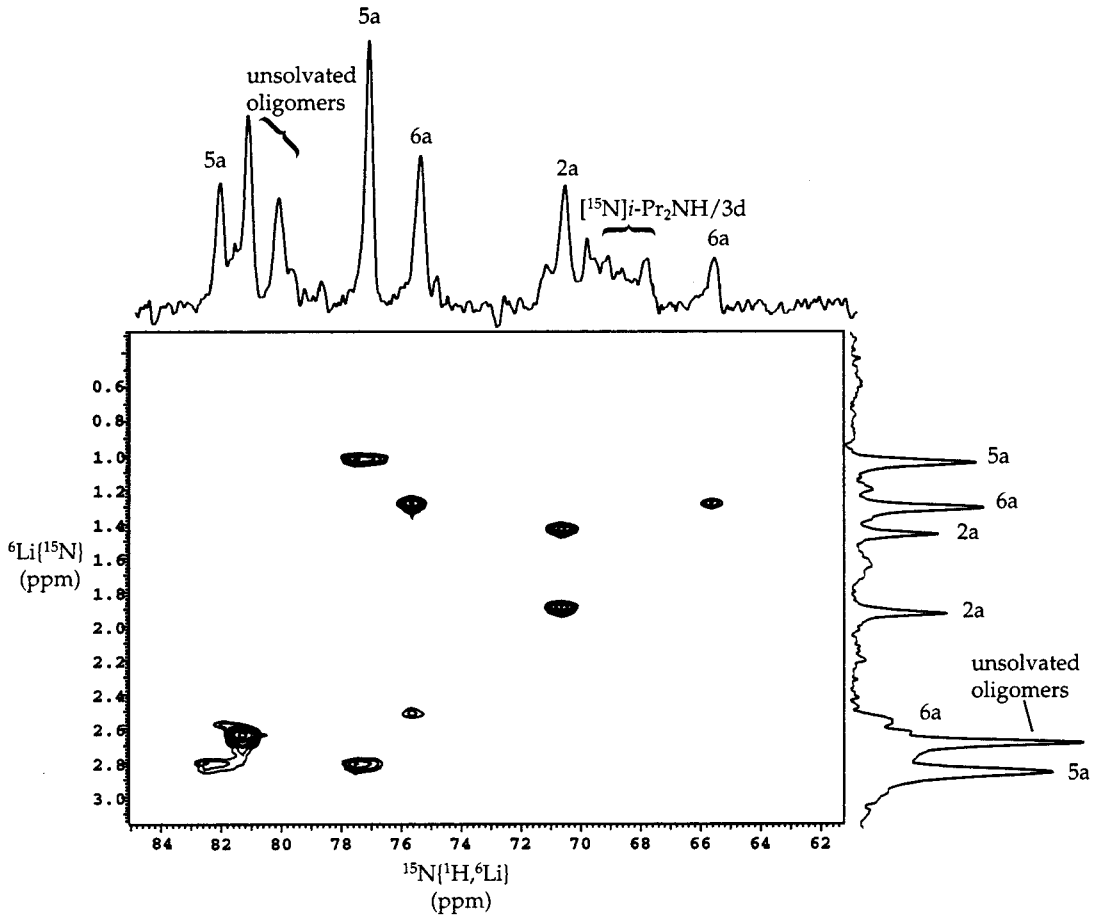

Figure 2. ^{6}Li,^{15}N HMQC spectrum of 0.1 M [^{6}Li,^{15}N]LDA in 3:2 pentane:toluene with 0.25 equiv of oxetane at −135 °C.

dimer **3a** is the only observable form. Upon addition of ≫1.0 equiv of oxetane, the ^{6}Li resonance of dimer **3a** remains unchanged, revealing the absence of deaggregation as well as confirming[18] that **3a** does not undergo further solvation.

LDA/THF. Spectra recorded on solutions of [^{6}Li,^{15}N]LDA (0.1 M) in 3:2 pentane:toluene containing low concentrations of THF at −135 °C show solvated cyclic oligomers (**2b**, **3b**, **5b**, and **6b**) similar to those found in oxetane/hydrocarbon mixtures (Table 1; Supporting Information). In contrast to the LDA/oxetane mixtures, the partially solvated trimers **5b** and **6b** are the minor species even at low concentrations of THF. At >1.0 equiv of THF, disolvated dimer **3b** is the sole observable form with rapid exchange of free and bound THF on ^{13}C NMR time scales at −135 °C.

LDA/Diethyl Ether. Spectra of [^{6}Li,^{15}N]LDA (0.1 M) in 3:2 pentane:toluene with diethyl ether recorded at −127 °C reveal dimers **2c** and **3c** as the only well-resolved solvated forms. Moreover, monosolvated dimer **2c** remains minor relative to the unsolvated and fully solvated dimers **1** and **3c** (respectively). However, the ^{6}Li resonance of the trimer shifts upfield with added ligand, suggesting rapid ligand exchange of trimers **4**, **5c**, and **6c**.

^{13}C NMR spectra of 0.1 M [^{6}Li,^{15}N]LDA with 2.0 equiv of diethyl ether reveal discrete resonances at 66.5 and 62.4 ppm corresponding to the O−CH_2 of free and bound Et_2O (respectively) at ≤−115 °C. The slower exchange when compared with THF and oxetane is consistent with the anticipated slower associative[2,5] ligand substitution.

LDA/Diisopropylamine. Investigation of LDA solvated by diisopropylamine was prompted by concerns that residual amine could cause spurious results.[19] Spectra recorded on 0.1 M solutions of [^{6}Li,^{15}N]LDA at −137 °C in 3:2 pentane:toluene with substoichiometric equivalents of diisopropylamine reveal the unsolvated oligomers. At 2.0 equiv of *i*-Pr_2NH, solvated dimer **3d** is readily apparent, although the unsolvated forms are dominant. Even at 10 equiv of diisopropylamine the unsolvated oligomers persist, indicating that the LDA dimer resists solvation by diisopropylamine. These results are consistent with previous investigations of LiHMDS, which showed that diisopropylamine is a poor ligand for lithium amide dimers.[2,3]

Discussion

Lithium amides have provided an interesting view of how solvation influences both aggregate structure[1−8] and reactivity.[9,10] By employing low donor solvent concentrations using hydrocarbon cosolvents, the donor solvent can be treated more as a ligand and less as the medium, affording a vantage point akin to that of classical coordination chemistry. Comparisons

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with related lithium salts offer insights into how the *N*-alkyl substituents influence the aggregate structures of lithium amides.

Snaith and co-workers suggested that cyclic dimers of lithium amides are more stabilized by solvation than are cyclic trimers and higher cyclic oligomers.[20] Crystallographic, computational, and NMR spectroscopic studies all seem to support the model.[1−5,8,20,21] For example, addition of 0.5 equiv of ethereal ligands to a nearly equimolar mixture of LiHMDS cyclic dimers and higher cyclic oligomers affords exclusively the partially solvated dimer (analogous to **2**) to the exclusion of the partially solvated trimers (analogous to **5** and **6**).[2] The prevalence of **5a** and **6a** in LDA/oxetane mixtures and the relatively lower concentrations of the analogous trimers in THF and Et_2O are consistent with Snaith's model. Computational studies suggested that the serial solvation of the trimer causes incrementally decreasing enthalpies per solvent,[20,21] presumably due to buttressing around the sterically congested ring. The absence of trisolvated trimers (**7a**−**c**) is also consistent with the computational predictions. The presence of partially solvated trimers for LDA, but not for LiHMDS, suggests that the *i*-Pr_2N moiety may be less sterically demanding than the $(Me_3Si)_2N$ moiety.

Lithium diethylamide offers a different view of how steric effects can influence structure.[6] Treatment of $LiNEt_2$ with substoichiometric concentrations of ethereal ligands yields a series of solvent-dependent 3-, 4-, 5-, and 6-rung ladders (e.g., **8**) resulting from transannular Li−N interactions and accompanying crowding of the *N*-alkyl moieties. The isopropyl groups of LDA appear to be sufficiently large to preclude laddering.

Structures and reactivities of lithium amides at low donor solvent concentrations could, at least in principle, be susceptible to spurious effects caused by the corresponding dialkylamines. Investigations of LiHMDS solvated by a variety of mono- and dialkylamines revealed a remarkable correlation in which the binding constants of dialkylamines are virtually identical to their dialkyl ether counterparts.[3] Therefore, it is not surprising that diisopropylamine coordinates very poorly to LDA. What we do find surprising, however, are the reports that the reactions of lithium enolates derived from LDA in THF solutions can be altered markedly by coordination of the diisopropylamine byproduct.[19] Although the empirical observations are compelling,[22] it is still difficult to understand how such low concentrations of diisopropylamine can compete with 12 M THF.

Summary and Conclusion

Comparisons of various lithium amides reveal how the complex interactions of the solvent−substituent combinations influence structure. Investigations of LDA solvated by very low concentrations of oxetane, THF, and Et_2O provide a window into the coordination chemistry of lithium amide cyclic dimers and trimers, which demonstrate behavior consistent with theoretical predictions. We show that oxetane is similar to THF[6] yet offers a better view of trimer solvation. We also find that diisopropylamine is a poor ligand for LDA, leaving unresolved the issue of how diisopropylamine can strongly influence the chemistry of enolates.

Experimental Section

Reagents and Solvents. All solvents were distilled by vacuum transfer from blue or purple solutions containing sodium benzophenone ketyl. The hydrocarbon still contained 1% tetraglyme to dissolve the ketyl. ^{6}Li metal (95.5% enriched) was obtained from Oak Ridge National Laboratory. [^{6}Li]LDA and [^{6}Li,^{15}N]LDA were prepared and isolated as described previously.[13] The [^{6}Li]*n*-BuLi used to prepare [^{6}Li]LDA and [^{6}Li,^{15}N]LDA was prepared and purified by the standard literature procedure.[23] The diphenylacetic acid used to check solution titers[24] was recrystallized from methanol and sublimed at 120 °C under full vacuum. Air- and moisture-sensitive materials were manipulated under argon or nitrogen using standard glovebox, vacuum line, and syringe techniques.

NMR Spectroscopic Analyses. Samples for spectroscopic analyses were prepared using a protocol described elsewhere.[5] Routine ^{6}Li, ^{13}C, and ^{15}N NMR spectra were recorded on a Varian XL-400 spectrometer operating at 58.84, 100.58, and 40.5 MHz (respectively). The ^{6}Li, ^{13}C, and ^{15}N spectra are referenced to 0.3 M [^{6}Li]LiCl/MeOH at −90 °C (0.0 ppm), the toluene resonance at −90 °C (20.4 ppm), and neat Me_2-NEt at −90 °C (25.7 ppm), respectively. The ^{6}Li,^{15}N-HMQC[14] spectra were recorded on a Varian Unity 500 spectrometer equipped with a custom-built 3-channel probe designed to accommodate ^{6}Li and ^{15}N pulses with concurrent proton decoupling. The probe temperatures were routinely calibrated with an internal thermocouple.

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Supporting Information Available: ^{6}Li, ^{13}C, and ^{15}N NMR spectra (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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