

## Structure of Lithium Hexamethyldisilazide (LiHMDS): Spectroscopic Study of Ethereal Solvation in the Slow-Exchange Limit

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Within the complex coordination chemistry of organolithium reagents, solvation is certainly one of the most important determinants—possibly the most important determinant—of aggregate structure and reactivity; it is unusual when the choice of solvent does *not* impact on structure and reactivity.<sup>1</sup> It is also true, however, that a detailed understanding of solvation has been notoriously elusive.<sup>2–5</sup> In 1989, Reich and Snaith independently discovered that ligand-exchange rates of coordinated hexamethylphosphoramide (HMPA) were sufficiently low to allow direct NMR spectroscopic distinction of coordinated and free HMPA.<sup>4</sup> This provided a view of lithium ion solvation of unparalleled clarity and importance.<sup>5</sup> Unfortunately, ethereal ligands such as THF or Et<sub>2</sub>O used as solvents throughout organolithium chemistry afford sufficiently labile metal–ligand bonds as to render solvent exchange within the lithium coordination spheres fast relative to NMR time scales.<sup>6</sup> During the course of routine structural investigations of lithium hexamethyldisilazide (LiHMDS; **1**)<sup>7,8</sup> we observed surprisingly low ligand substitution rates even for THF and Et<sub>2</sub>O. While we do not understand *why* the limit of slow ligand exchange is readily observable with LiHMDS, it offers answers to several fundamental questions that have been eluding us for some time.

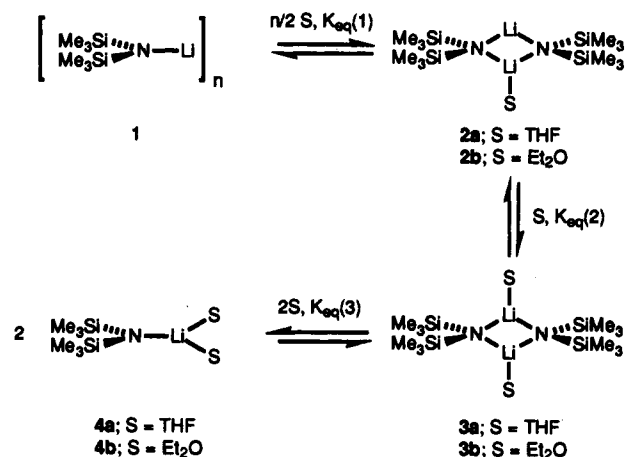
We investigated the solution structure of [<sup>6</sup>Li,<sup>15</sup>N]LiHMDS<sup>7</sup> as 0.1 M toluene-*d*<sub>8</sub> and pentane<sup>9</sup> solutions in the presence of THF and Et<sub>2</sub>O using <sup>6</sup>Li, <sup>15</sup>N, and <sup>13</sup>C NMR spectroscopy. The spectral data are summarized in Table 1. Since the results for THF and Et<sub>2</sub>O are very similar, our description consolidates the two independent cases and refers to THF and Et<sub>2</sub>O generically as “ligand”. The implicit resonance correlations were established

Table 1. NMR Spectroscopic Data of [<sup>6</sup>Li,<sup>15</sup>N]LiHMDS Solvates<sup>a</sup>

	<sup>6</sup> Li δ (m, J <sub>N-Li</sub> )	<sup>15</sup> N δ (m, J <sub>N-Li</sub> )	<sup>13</sup> C (THF)	<sup>13</sup> C (Et <sub>2</sub> O)
THF			67.6 25.6	
Et <sub>2</sub> O				66.1 15.7
<b>2a</b>	1.42 (t, 3.5) 1.78 (t, 3.9)	42.0 (q, 3.9)	68.2 24.7	
<b>2b</b>	1.03 (t, 3.4) <sup>b</sup> 1.79 (t, 3.6) <sup>b</sup>	42.2 (q, 3.5) <sup>b</sup>		62.5 13.3
<b>3a</b>	1.42 (t, 3.5)	38.2 (q, 3.5)	68.3 24.9	
<b>3b</b>	1.21 (t, 3.4)	40.2 (q, 3.4)		60.4 12.4
<b>4a</b>	0.24 (d, 5.0)	41.2 (t, 5.0)		
<b>4b</b>	1.02 (d, 5.9)	48.8 (t, 6.1)		
<b>6</b>	1.37 (t, 3.3) <sup>b</sup> 1.23 (t, 3.4) <sup>b</sup>	39.9 (q, 3.4) <sup>b</sup>	68.4 24.8	61.3 12.9

<sup>a</sup> Spectra were recorded on 0.1 M solutions of LiHMDS at –100 °C in either pentane (<sup>6</sup>Li and <sup>15</sup>N) or toluene-*d*<sub>8</sub> (<sup>13</sup>C). Coupling constants were measured after resolution enhancement: d = doublet, t = triplet, q = quintet. The chemical shifts are reported relative to 0.3 M <sup>6</sup>LiCl/MeOH at –100 °C (0.0 ppm) and [<sup>15</sup>N]aniline (52 ppm). All *J* values are reported in hertz. <sup>b</sup> Recorded at –120 °C.

by single-frequency <sup>15</sup>N decoupling experiments<sup>10</sup> or <sup>6</sup>Li,<sup>15</sup>N-heteronuclear multiple quantum correlation (HMQC) spectroscopy.<sup>11</sup>



LiHMDS in pentane was shown previously to exist as a mixture of unsolvated dimer and higher cyclic oligomer (**1**).<sup>7</sup> Addition of 0.5 equiv of ligand/Li affords monosolvated dimers (**2**) along with low concentrations of disolvated dimers (**3**) and the two unsolvated oligomers.<sup>12</sup> Each monosolvate displays a pair of <sup>6</sup>Li triplets coupled to a solitary <sup>15</sup>N quintet. The minor disolvated dimers each display a single <sup>6</sup>Li triplet coupled to a single <sup>15</sup>N quintet.<sup>13</sup> <sup>13</sup>C NMR spectra show resonances corresponding to two different forms of coordinated ligand (in proportions consistent with mixtures of **2** and **3**) to the exclusion of resonances corresponding to uncoordinated ligand. The coexistence of all three solvation states indicates that the first and second solvation steps are nearly equal energy ( $K_{\text{eq}}(1) \approx K_{\text{eq}}(2)$ ). Addition of 1.0 equiv of ligand/Li causes disolvated dimers (**3**) to be the only species observable in the <sup>6</sup>Li and <sup>15</sup>N NMR spectra. The

(10) Gilchrist, J. H.; Harrison, A. T.; Fuller, D. J.; Collum, D. B. *J. Am. Chem. Soc.* 1990, 112, 4069.

(11) Gilchrist, J. H.; Harrison, A. T.; Fuller, D. J.; Collum, D. B. *Magn. Reson. Chem.* 1992, 30, 855.

(12) Structurally analogous LiHMDS dimers monosolvated by fluorobenzenes have been characterized crystallographically: Williard, P. G.; Liu, Q.-Y. *J. Org. Chem.* 1994, 59, 1596.

(13) The assignment of **3a** and **3b** as dimers rather than higher oligomers was confirmed by <sup>15</sup>N zero-quantum NMR spectroscopy (supplementary material): Gilchrist, J. H.; Collum, D. B. *J. Am. Chem. Soc.* 1992, 114, 794.

(1) Seebach, D. *Angew. Chem., Int. Ed. Engl.* 1988, 27, 1624. *Ions and Ion Pairs in Organic Reactions*; Szwarc, M., Ed.; Wiley: New York, 1972; Vols. 1, 2. Bauer, W.; Schleyer, P. v. R. *Adv. Carbanion Chem.* 1992, 1, 89.

(2) Leading references to studies of organolithium solvation: Jackman, L. M.; Bortiatynski, J. *Adv. Carbanion Chem.* 1992, 1, 45–87. Collum, D. B. *Acc. Chem. Res.* 1992, 25, 448. Bernstein, M. P.; Collum, D. B. *J. Am. Chem. Soc.* 1993, 115, 8008.

(3) Kaufmann, E.; Gose, J.; Schleyer, P. v. R. *Organometallics* 1989, 8, 2577 and references cited therein.

(4) Reich, H. J.; Green, D. P. *J. Am. Chem. Soc.* 1989, 111, 8729. Barr, D.; Doyle, M. J.; Mulvey, R. E.; Raithby, P. R.; Reed, D.; Snaith, R.; Wright, D. S. *J. Chem. Soc., Chem. Commun.* 1989, 318.

(5) Reich, H. J.; Borst, J. P.; Dykstra, R. R.; Green, D. P. *J. Am. Chem. Soc.* 1993, 115, 8728 and references cited therein.

(6) Exchange of free and coordinated multidentate ethereal solvents has been observed. See, for example: Fraenkel, G.; Cabral, J. A. *J. Am. Chem. Soc.* 1993, 115, 1551. Izatt, R. M.; Bradshaw, J. S.; Nielsen, S. A.; Lamb, J. D.; Christensen, J. J.; Sen, D. *Chem. Rev.* 1985, 85, 271. Klumpp, G. W. *Recl. Trav. Chim. Pays-Bas* 1986, 105, 1.

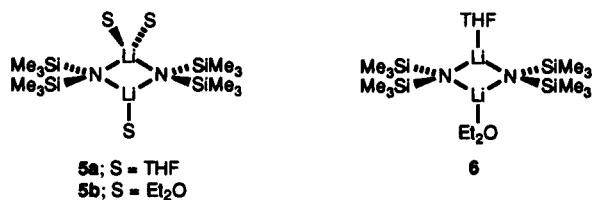
(7) Romesberg, F. E.; Bernstein, M. P.; Fuller, D. J.; Harrison, A. T.; Collum, D. B. *J. Am. Chem. Soc.* 1993, 115, 3475. For the seminal investigations of LiHMDS, see: Kimura, B. Y.; Brown, T. L. *J. Organomet. Chem.* 1971, 26, 57.

(8) Reviews of structural studies of *N*-lithiated species: Gregory, K.; Schleyer, P. v. R.; Snaith, R. *Adv. Inorg. Chem.* 1991, 37, 47. Mulvey, R. E. *Chem. Soc. Rev.* 1991, 20, 167. Collum, D. B. *Acc. Chem. Res.* 1993, 26, 227.

(9) The <sup>13</sup>C NMR spectroscopy mandated toluene-*d*<sub>8</sub>, while the low coalescence temperatures observed by <sup>6</sup>Li NMR spectroscopy required pentane to avoid sample freezing.

corresponding  $^{13}\text{C}$  NMR spectra contain the resonances of the disolvated dimers to the exclusion of those for the monosolvated dimers or free ligand. As the added ligand concentration exceeds 1.0 equiv/Li,  $^{13}\text{C}$  resonances corresponding to uncoordinated ligand appear without any other detectable spectral changes. The distinct discontinuity at 1.0 equiv/Li demonstrates a marked preference for disolvated (rather than more highly solvated) dimers. Upon incrementally progressing to neat ethereal solvent, we observe the appearance of  $^6\text{Li}$  doublets and  $^{15}\text{N}$  triplets characteristic of monomers (4). The monomer 4a becomes the major species in neat THF, while 4b remains minor in neat  $\text{Et}_2\text{O}$ .<sup>7</sup> We suspect from semiempirical computational studies and other indirect evidence that the monomers and dimers are disolvated,<sup>14</sup> but we are unable to obtain experimental verification.

Having attained the slow solvent exchange limit, we were poised to address some basic questions pertaining to solvation. For example, we were interested in ascertaining whether ligand substitution proceeds by a dissociative mechanism *via* monosolvated dimers (2) or an associative mechanism *via* trisolvated dimers (5).<sup>15</sup> Variable temperature  $^{13}\text{C}$  NMR spectroscopy of LiHMDS (0.1 M) in toluene- $d_8$  containing 2.0 equiv of ligand/Li revealed coalescences of free and coordinated ligands ( $-47 \pm 3^\circ\text{C}$  for THF;  $-76 \pm 3^\circ\text{C}$  for  $\text{Et}_2\text{O}$ ) corresponding to the following activation free energies for ligand exchange:  $\Delta G^\ddagger_{226\text{K}}(\text{THF}) = 10.8 \pm 0.2$  kcal/mol;  $\Delta G^\ddagger_{197\text{K}}(\text{Et}_2\text{O}) = 8.6 \pm 0.2$  kcal/mol.<sup>16,17</sup> The observed coalescence temperatures and calculated free energies were found to be invariant over a 20-fold range in free ligand concentration (0.02–0.4 M), indicating that *ligand exchange in the disolvated dimers proceeds by a dissociative process via monosolvated dimers.*



The activation energies for ligand dissociation *appear* to correlate with metal–ligand bond strengths. More to the point, however, we were in a position to directly measure the relative metal–ligand bond strengths. Solutions of 0.1 M [ $^6\text{Li}, ^{15}\text{N}$ ]-

LiHMDS in toluene- $d_8$  containing 2.0 equiv/Li each of THF and  $\text{Et}_2\text{O}$  contain exclusively THF-solvated dimer 3a.  $^6\text{Li}$  and  $^{15}\text{N}$  NMR spectra recorded on LiHMDS solutions containing 0.5 equiv/Li of THF and 5.0 equiv/Li of  $\text{Et}_2\text{O}$  display resonances corresponding to dimers 3a and 3b along with new  $^6\text{Li}$ ,  $^{15}\text{N}$ , and  $^{13}\text{C}$  resonances consistent with mixed solvate 6. The approximate 1:2:1 mixture of 3a/6/3b indicates that, despite the differential solvation energies of THF and  $\text{Et}_2\text{O}$ , there is no anomalous cooperativity in the solvation energies of mixed solvate 6.<sup>18</sup> The  $^{13}\text{C}$  resonances of coordinated ligands on 3a and 6 as well as free THF and free  $\text{Et}_2\text{O}$  could be integrated (173 K) and the four concentrations fitted to eq 2 to obtain  $K_{\text{eq}} = 9.7 \pm 0.5 \times 10^2$  corresponding to  $\Delta G^\circ_{173\text{K}} = -2.3 \pm 0.2$  kcal/mol.



$$K_{\text{eq}}(4) = \frac{[3\text{a}][\text{Et}_2\text{O}]}{[6][\text{THF}]} \quad (2)$$

To the best of our knowledge this represents the first instance in which exchange of simple ethereal solvents has been frozen out on NMR time scales. The consequent demonstration of dissociative ligand substitution and the direct measurement of relative solvation energies provide fundamental insight into the coordination chemistry of lithium underlying macroscopically observable structure–reactivity relationships. Demonstration that solvation of the two lithium sites on the LiHMDS dimer are nearly independent processes sheds light on issues of cooperative solvation relevant to mixed solvent systems as well as substrate precomplexation. Moreover, the activation barriers for ligand exchange could be sufficiently large to render solvent dissociation rate limiting in fast substrate metalations.

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**Supplementary Material Available:**  $^6\text{Li}$ ,  $^{13}\text{C}$ , and  $^{15}\text{N}$  NMR spectra of LiHMDS with added THF or  $\text{Et}_2\text{O}$  (6 pages). This material is contained in many 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.

(14) Romesberg, F. E.; Collum, D. B., *J. Am. Chem. Soc.* **1992**, *114*, 2112.

(15) Seebach, D.; Bauer, W.; Hansen, J.; Laube, T.; Schweizer, W. B.; Dunitz, J. D., *J. Chem. Soc., Chem. Commun.* **1984**, 853. Depue, J. S.; Collum, D. B., *J. Am. Chem. Soc.* **1988**, *110*, 5518. Williard, P. G.; Nichols, M. A., *J. Am. Chem. Soc.* **1991**, *113*, 9671. Williard, P. G.; Liu, Q.-Y. Unpublished.

(16) Application of DNMR (Stempfle, W.; Klein, J.; Hoffmann, E. G. QCPE Program No. 450) afforded activation energies scaled to  $-100^\circ\text{C}$  that varied only slightly. Unfortunately, we have reason to question their validity and must defer reporting additional details to a later time.

(17) Enthalpies of alkyl lithium solvation by THF have been shown through calorimetric measurements to be approximately 7–10 kcal/mol per Li. Quirk, R. P.; McFay, D., *J. Polym. Sci., Polym. Chem. Ed.* **1981**, *19*, 1445. Quirk, R. P.; Kester, D. E.; Delaney, R. D., *J. Organomet. Chem.* **1973**, *59*, 45. See also: Arnett, E. M.; Fisher, F. J.; Nichols, M. A.; Ribeiro, A. A., *J. Am. Chem. Soc.* **1990**, *112*, 801.

(18) Similarly, solutions of LiHMDS containing 0.5 equiv of  $\text{Et}_2\text{O}$  and 0.5 equiv of THF show an approximate 1:2:1 mixture of 3a/6/3b.