Polydentate Amine and Ether Solvates of Lithium Hexamethyldisilazide (LiHMDS): Relationship of Ligand Structure, Relative Solvation Energy, and Aggregation State

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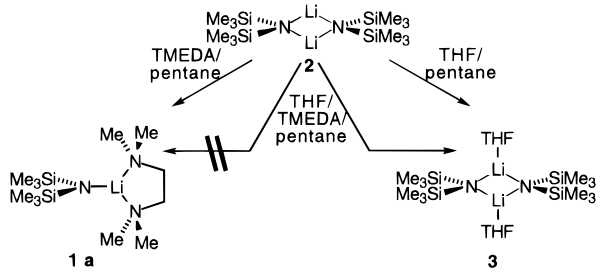
Abstract: ^{6}Li, ^{15}N, and ^{13}C NMR spectroscopic investigations of [^{6}Li,^{15}N]lithium hexamethyldisilazide ([^{6}Li,^{15}N]-LiHMDS) coordinated by 29 polyamines, polyethers, and aminoethers reveal a range of structural types including η^1-coordinated mono- and disolvated dimers, η^2-coordinated (3-coordinate) monomers, η^1,η^2-coordinated (4-coordinate) monomers, η^2,η^2-coordinated (5-coordinate) monomers, polymers (linked dimers), triple ions, and solvent-separated ion pairs. Ligand binding constants on the LiHMDS monomers shed light on chelate ring size and steric effects, aza- and oxaphilicity, mechanisms and rates of ligand substitution, and the "macrocyclic effect."

Introduction

During the course of our investigations of organolithium structure−reactivity relationships, we were drawn to lithium hexamethyldisilazide (LiHMDS, $(Me_3Si)_2NLi$) due its prominence as a selective Brönsted base in organic chemistry.[1] However, the synthetic importance of LiHMDS that piqued our interest at the onset became overshadowed by the importance of LiHMDS as a vehicle to study the basic principles of lithium ion coordination chemistry.[2−10] Several investigations of LiHMDS encouraged us to reformulate our thinking on the relationship of solvation and aggregation. For example, hexamethylphosphoramide (HMPA) readily displaces THF from LiHMDS but has only a marginal effect on the aggregation state when compared to that of THF alone.[5] In contrast, TMEDA alone readily deaggregates LiHMDS relative to THF, but fails to compete with THF when both are present (Scheme 1).[7,10−12] More recently, we observed simple (monodentate) ether and amine solvates in the limit of slow solvent exchange on NMR time scales.[6,13] This allowed us to characterize mono-, di-, and mixed solvated dimers, distinguish associative and dissociative ligand substitutions, and determine relative free energies of solvation. Investigations of the solvent-dependent dimer−monomer equilibrium revealed a complex relationship between solvation free energy, solvation number, and observable aggregation state.

Scheme 1



[⊗] Abstract published in *Advance ACS Abstracts,* October 1, 1996.

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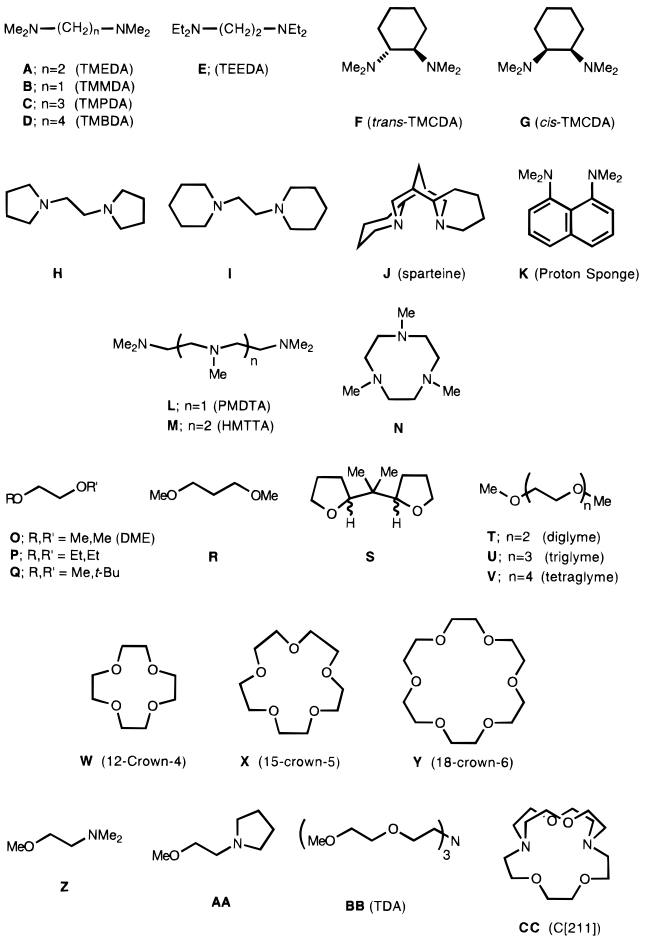
Chelating ligands have played central roles in organolithium chemistry[12,14,15] since the seminal studies of alkyllithium−polyamine complexes by Whitney and Langer in the 1960s.[14a] The perennial interest in polyamine[14] and polyether[15] ligands stems from their dramatic effects on organolithium structures and reactivities.[14,16] Nevertheless, our understanding of precisely how ligand structure affects lithium ion binding is still somewhat sketchy. Ligand-dependent reactivities, selectivities, and other empirical observations are often suggested to reflect ligand binding constants without adequate justification. Direct measures of ligand binding constants typically focus upon a restricted number and class of ligand for a given lithium salt and often suffer from ambiguities surrounding lithium salt structure and ligand stoichiometry.[12,17]

We have now extended our investigations of LiHMDS to include a number of multidentate ethers and amines (Chart 1). The Results section will emphasize ligand-dependent structural variations and provide some insight into the mechanisms of ligand substitution. The Discussion will examine insights provided by quantitative binding studies. Many of these factors may prove generalizable to other inorganic and organic lithium salts.

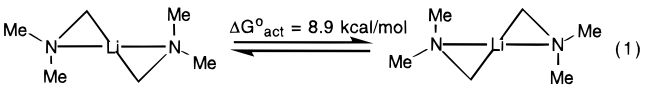
Results

Mixtures of LiHMDS and potentially chelating ligands (Chart 1) were studied using variable temperature ^{6}Li, ^{15}N, and ^{13}C NMR spectroscopies. The spectra were recorded on 0.1 M solutions of [^{6}Li,^{15}N]LiHMDS[18] using hydrocarbon cosolvents (toluene-d_8 or 2:1 pentane−toluene) unless stated explicitly otherwise. Spectral data are listed in Tables 1 and 2. Spectra are located in supporting information. The C_{2h} symmetric cyclic dimers and C_{nh} symmetric higher cyclic oligomers can be distinguished by inverse-detected ^{15}N zero-quantum NMR spectroscopy.[19] ^{6}Li−^{15}N resonance correlations can be established by single-frequency ^{15}N decoupling[20] or ^{6}Li−^{15}N heteronuclear multiple-quantum coherence (HMQC) spectroscopy.[21] The experimental protocols are similar to those described in greater detail elsewhere.[5,6]

Chart 1



LiHMDS−Polyamines. Structures. Addition of 0.5 equiv of TMEDA (per Li) to 0.1 M solutions of [^{6}Li,^{15}N]LiHMDS in toluene-d_8 affords both the previously characterized TMEDA solvated monomer **1a**[7,10,11] and unsolvated dimer **2**.[2,5] Monomer **1a** becomes the sole observable form at 1.0 equiv of TMEDA. Monomer **1a** displays a characteristic ^{6}Li doublet and ^{15}N triplet as noted previously.[7,8] In addition, the ^{13}C NMR spectrum at −100 °C contains a single, sharp TMEDA methylene resonance and two TMEDA methyl resonances. Warming the probe causes time averaging of the methyl resonances ($T_{\text{coalescence}} = -70 \pm 3$ °C, $\Delta G^\circ_{\text{act}} = 8.9 \pm 0.2$ kcal/mol) consistent with the degenerate exchange depicted in eq 1. Dynamic NMR line shape analysis afforded $\Delta H^\circ_{\text{act}} = 7.5 \pm 0.3$ kcal/mol. The kinetic parameters are similar to those affiliated with related TMEDA-lithium chelate conformer exchanges described previously.[22]



(1)

At >1.0 equiv of TMEDA the ^{13}C resonances corresponding to uncoordinated TMEDA appear along with the resonances of **1a**. The discontinuity at 1.0 equiv indicates a marked preference for monosolvated (3-coordinate) monomers. The importance of chelation is underscored by the exclusive formation of disolvated dimer in the presence of 2.0 equiv of monodentate ligands such as Me_2NEt.[6c] Addition of up to 33 equiv of TMEDA (50% by volume) causes no *detectable* structural

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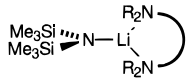
Table 1. ^{6}Li, ^{15}N, and ^{13}C NMR Spectral Data of LiHMDS−Polyamine Solvates[a]

cmpd	ligand	^{6}Li, δ (mult, J_{LiN})	^{15}N, δ (mult, J_{LiN})	^{13}C{^{1}H} (ligand)	^{13}C{^{1}H} (Me_3Si)
1a	**A**	0.76 (d, 6.3)	47.7 (t, 6.3)	54.1, 47.2, 41.5	6.7
1c	**C**	0.73 (d, 6.2)	46.4 (t, 6.2)	60.5, 45.5, 21.9	6.6
1e	**E**	0.67 (d, 6.2)	48.0 (t, 6.2)	49.0, 46.3, 45.5, 8.6	6.4
1f	**F**	0.91 (d, 6.4)	47.9 (t, 6.4)	63.9, 44.1, 35.7, 24.8, 21.4	6.9
1g	**G**	1.01 (d, 6.3)	47.7 (t, 6.4)	67.2, 55.6, 47.3, 43.4, 42.7, 42.2, 24.9, 24.4	6.9
1h	**H**	0.63 (d, 6.1)	46.6 (t, 6.1)	55.4, 52.7, 51.5, 22.4	6.4
1i	**I**	0.84 (d, 5.9)	48.6 (t, 6.0)	57.3, 54.5, 52.2, 25.1, 23.9	6.4
1j	**J**	1.01 (d, 6.2)	47.0 (t, 6.2)	66.1, 60.7, 59.2, 57.2, 53.6, 45.2, 34.4, 34.1, 29.3, 27.8, 24.7, 24.5, 24.1, 23.4, 17.7	7.1
1k	**K**	1.49 (d, 6.2)	47.1 (t, 6.4)	*b*	*b*
5	**B**	1.34 (t, 3.4)	41.2 (q, 3.4)	*b*	*b*
6	**D**	1.21 (t, 3.4)	42.1 (q, 3.3)	*b*	*b*
7	**L**	0.13 (d, 5.1)	42.3 (t, 5.2)	56.7, 55.5, 53.5, 50.0, 48.7, 48.2, 45.8, 44.0, 42.7	7.6
8[c]	**N**	0.71 (d, 5.2)	43.9 (t, 5.2)	53.1, 46.9	8.2
9[c]	**M**	0.00 (d, 5.0)	43.0 (t, 5.2)	55.6, 54.6, 52.8, 46.2, 44.3	7.6

[a] Spectra were recorded on 0.1 M toluene-d_8 solutions of LiHMDS at −100 °C (^{6}Li, ^{13}C) or −80 °C (^{15}N). Coupling constants were measured after resolution enhancement. Multiplicities (mult) are denoted as follows: d = doublet, t = triplet, and q = quintet. The chemical shifts are reported relative to 0.3 M ^{6}LiCl−MeOH at −100 °C at (0.0 ppm) and neat Me_2NEt (25.7 ppm). Chemical shifts are dependent on temperature, donor solvent concentration, and hydrocarbon cosolvent. All *J* values are reported in hertz. Some of the ligand ^{13}C resonances may be obscured by the solvent. [b] Rapid solvent exchange precluded observation of bound ligand resonances. [c] ^{13}C spectra were recorded at −40 °C.

changes, as evidenced by ^{6}Li and ^{15}N NMR spectroscopies. Nonetheless, previous structural studies of LiHMDS in the presence of monodentate amine ligands[6c] suggest that LiHMDS monomer **4** bearing η^1- and η^2-TMEDA ligands forms at elevated TMEDA concentrations.[23,24]

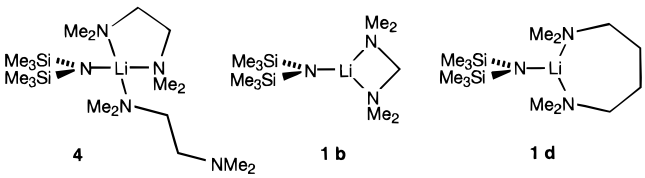
We continued studies of a selection of diamines distributed throughout the literature (**B**−**K**, Chart 1, Table 1). Most afford monomers as the sole observable form. The half-chair conformational exchange analogous to that shown in eq 1 can be observed for other vicinal diamine-bound monomers including **1e**,[25] **1h**,[26,27] and **1i**.[28]

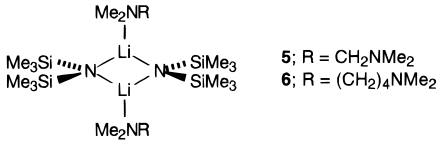


1a-k

1a-k; diamine = **A-K**

We noted a substantial chain length dependence. Addition of ≥1.0 equiv of *N*,*N*,*N*′,*N*′-tetramethylpropanediamine ($Me_2N(CH_2)_3NMe_2$, TMPDA, **C**)[29,30] affords chelated monomer **1c** with a time averaging of all methyl resonances to −110 °C. In contrast, *N*,*N*,*N*′,*N*′-tetramethylmethylenediamine ($Me_2NCH_2NMe_2$, TMMDA, **B**)[31] and *N*,*N*,*N*′,*N*′-tetramethylbutanediamine ($Me_2N(CH_2)_4NMe_2$, TMBDA, **D**)[27,32] show no measurable propensity to afford monomer beyond that expected for a monodentate ligand such as Me_2NEt.[6c] Thus, 4- and 7-membered chelates (**1b** and **1d**, respectively) are not stable relative to unchelated dimers (**5** and **6**) or unchelated monomers. Diamines **F**,[33,34] **G**,[26,36] **J**,[36] and **K**[27] also afford monomers **1f**, **1g**, **1j**, and **1k** (respectively) and will be discussed further below.





Samples of [^{6}Li,^{15}N]LiHMDS with 1.0−10 equiv of higher polyamines *N*,*N*,*N*′,*N*′′,*N*′′-pentamethyldiethylenetriamine (PM-

(23) LiHMDS-mediated ketone enolization displays an inverse first-order dependence on TMEDA concentration at high TMEDA concentrations. Lucht, B. L.; Collum, D. B. Unpublished results.

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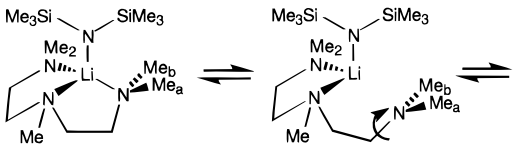
Table 2. ^{6}Li and ^{15}N NMR Spectral Data of LiHMDS−Polyether and −Aminoether Solvates[a]

cmpd	ligand	^{6}Li, δ (mult, J_{LiN})	^{15}N, δ (mult, J_{LiN})
18[d]	**O**	0.93 (t, 3.4), 1.11 (t, 3.6)	41.4 (q, 3.5)
20	**O**	1.24 (t, 3.4)	39.2 (q, 3.8)
21	**O**	0.30 (d, 5.3)	42.6 (t, 5.3)
27a	**P**	0.98 (t, 3.5)	38.2 (q, 3.5)
28a	**P**	0.60 (d, 6.1)	48.4 (t, 6.1)
27b	**R**	0.96 (t, 3.5)	38.9 (q, 3.5)
28b	**R**	0.03 (d, 5.6)	45.4 (d, 5.8)
27c	**Q**	0.97 (t, 3.6)	38.3 (q, 3.6)
28c	**Q**	0.10 (d, 5.8)	43.3 (t, 5.8)
30/31	**S**	1.32 (d, 6.4), 1.25 (d, 6.1)	47.6 (t, 6.3)
			48.2 (t, 6.1)
32a[c]	**T**	−0.14 (d, 5.2)	44.1 (t, 5.2)
32b[c]	**U**	−0.26 (d, 5.5)	44.8 (t, 5.4)
32c[c]	**V**	−0.26 (d, 5.3)	44.6 (t, 5.3)
33a[b]	**W**	−0.08 (d, 6.3)	43.6 (t, 6.3)
33b[b]	**X**	−0.66 (d, 5.4)	41.0 (t, 5.3)
33c[b]	**Y**	0.19 (d, 5.6)	43.9 (t, 5.6)
33d[c]	**BB**	−0.41 (d, 5.1)	41.6 (t, 5.0)
34a[b]	**W**	2.21 (t, 6.3), −1.39 (s)	*e*
34b[b]	**W**	2.21 (t, 6.3), −2.48 (s)	50.7 (t, 6.3)
34c[b]	**X**	2.25 (t, 6.4), −2.25 (s)	*e*
34d[b]	**X**	2.25 (t, 6.4), −2.10 (s)	49.2 (t, 6.3)
34e[b]	**Y**	2.37 (t, 6.3), −1.57 (s)	50.6 (t, 6.3)
34g[b]	**CC**	2.37 (t, 6.3), −1.24 (s)	50.2 (t, 6.3)
34h[b]	**BB**	2.42 (t, 6.1), −1.63 (s)	50.6 (t, 6.2)
38b[d]	**Z**	0.58 (t, 3.0), 1.56 (t, 4.5)	44.3 (m)
39a	**Z**	0.87 (t, 3.6)	38.6 (q, 3.5)
39b	**AA**	0.98 (t, 3.5)	38.5 (q, 3.5)
40a	**Z**	0.72 (d, 6.0)	48.2 (t, 6.1)
40b	**AA**	0.83 (d, 6.1)	47.4 (t, 6.1)
41a	**Z**	0.93 (d, 6.0)	46.6 (t, 6.0)
41b	**AA**	0.10 (d, 5.6)	44.5 (t, 5.6)
42	**CC**	0.49 (s)	46.6 (br)

[a] Spectra were recorded on 0.1 M 2:1 pentane−toluene solutions of LiHMDS at −100 °C. Coupling constants were measured after resolution enhancement. Multiplicities are denoted as follows: s = singlet, d = doublet, t = triplet, q = quintet, m = multiplet, and br = broad mound. The chemical shifts are reported relative to 0.3 M ^{6}LiCl−MeOH at −100 °C at (0.0 ppm) and neat Me_2NEt (25.7 ppm). Chemical shifts are dependent upon temperature, donor solvent concentration, and hydrocarbon cosolvent. All *J* values are reported in hertz. [b] Spectra were recorded at −60 °C in toluene−Me_4THF 2:1 to keep samples homogeneous. [c] Spectra recorded in toluene. [d] Spectra recorded at −115 °C. [e] Spectra were not recorded due to solubility problems during long acquisitions.

DTA, **L**),[37−39] *N*,*N*,*N*′,*N*′′,*N*′′′,*N*′′′-hexamethyltriethylenetetramine (HMTTA, **M**),[17,40] and *N*,*N*′,*N*′′-trimethyltriazacyclononane (TMTACN, **N**)[30,37b] display exclusively ^{6}Li doublets and ^{15}N triplets characteristic of solvated monomers. ^{13}C NMR spectra reveal free ligand at >1.0 equiv of added ligand in each case. At −40 °C, free and monomer-bound PMDTA are in slow exchange. PMDTA bound to monomer **7** appears in the ^{13}C NMR spectrum as four resonances (maximum symmetry). Two distinct processes become evident as the sample is cooled: (1) the four terminal methyl groups become two inequivalent resonances ($T_{coalescence}$ = −55 °C) consistent with combined inversion and internal rotation at nitrogen (eq 2) and (2) below −100 °C nine ligand-derived resonances



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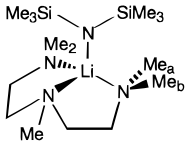
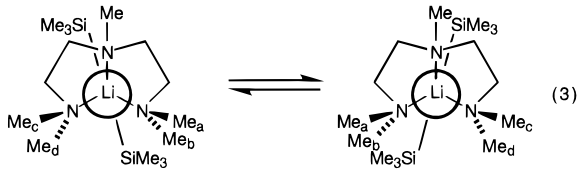
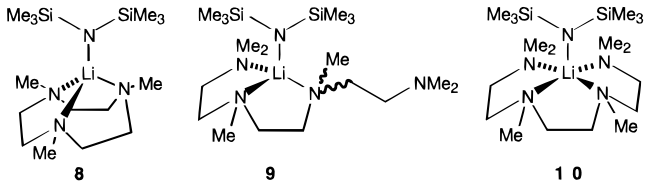


(2)

emerge, consistent with restricted rotation about the LiHMDS Li−N bond (eq 3). Similar conformational effects on alkyllithium−PMDTA complexes have been documented by Fraenkel and co-workers.[37] The high binding free energy of PMDTA relative to TMEDA (*vide infra*) and the five (rather than four) distinct methyl resonances exclude an η^2-chelated monomer[39] as the source of the asymmetry. The low-temperature ^{13}C NMR spectra recorded on the TMTACN-bound monomer **8** and HMTTA-bound monomer **9** show numerous broad ^{13}C resonances. The behavior of TMTACN-bound LiHMDS is probably the result of an analogous restricted rotation. While in the HMTTA case, the apparent coalescence could, at least in principle, arise from restricted rotation about the $(Me_3Si)_2N$−Li bond in η^4-chelated monomer **10**, the relative binding free energies of PMDTA and HMTTA described in the next section strongly implicate η^3-bound monomer **9**. The ^{13}C NMR spectroscopic behavior of **9** should be very complex because of the asymmetry and diastereoisomerism.[41]



(3)



8 **9** **10**

LiHMDS−Polyamines. Relative Binding Free Energies. Direct competition of different diamines for coordination to the LiHMDS monomer affords relative binding free energies. In a typical experiment, addition of 1.2 equiv of TMEDA and 1.2 equiv of a second ligand to toluene-d_8 solutions of [^{6}Li,^{15}N]-LiHMDS affords the TMEDA- and ligand-solvated monomers. Integration of the resonances for the free and bound diamines in the ^{13}C NMR spectra provide the concentrations necessary to determine the relative binding free energies according to eqs

(37) (a) Fraenkel, *J. Am. Chem. Soc.* **1990**, *112*, 2582. Fraenkel, *J. Am. Chem. Soc.* **1988**, *110*, 8720. (b) Fraenkel, G.; Chow, A.; Winchester, W. R. *J. Am. Chem. Soc.* **1990**, *112*, 6190. (c) Fraenkel, G.; Subramanian, S.; Chow, A. *J. Am. Chem. Soc.* **1995**, *117*, 6300.

(38) Andrews, P. C.; Armstrong, D. R.; Baker, D. R.; Mulvey, R. E.; Clegg, W.; Horsburgh, L.; O'Neil, P. A.; Reed, D. *Organometallics* **1995**, *14*, 427. Gatzke, A. L.; Green, D. P. *Macromolecules* **1994**, *27*, 2249. Reed, D.; Stalke, D.; Wright, D. S. *Angew. Chem., Int. Ed. Engl.*, **1991**, *30*, 1459. Bauer, W.; Winchester, W. R.; Schleyer, P. v. R. *Organometallics* **1987**, *6*, 2371. Armstrong, D. R.; Barr, D.; Clegg, W.; Mulvey, R. E.; Reed, D.; Snaith, R.; Wade, K. *J. Chem. Soc., Chem. Commun.* **1986**, 869. Lo, G. Y.-S.; Otterbacher, E. W.; Gatzke, A. L.; Tung, L. H. *Macromolecules* **1994**, *27*, 2233.

(39) Jutzi, P.; Schlüter, E.; Krüger, C.; Pohl, S. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 994.

(40) Assadourian, L.; Faure, R.; Gau, G. *J. Organomet. Chem.* **1985**, *280*, 153.

(41) Addition of bipyridine to LiHMDS in toluene causes blackening and loss of all ^{6}Li resonances.

Table 3. Relative LiHMDS Monomer Binding Free Energies ($\Delta G°_{solv}$) and Ligand Exchange Activation Free Energies ($\Delta G°_{act}$)[a]

solvent	$\Delta G°_{solv}$	$\Delta G°_{act}$
A (TMEDA)	0.0	10.1
C (TMPDA)	1.0	11.5
E (TEEDA)	0.3	15.2
F (*trans*-TMCDA)	−1.3	16.6
G (*cis*-TMCDA)	0.6	14.7
H	−0.6	15.7
I	−0.1	16.3
J (sparteine)	−0.5	19.1
L (PMDTA)	−2.8	14.4
M (HMTTA)	−2.2	13.9
N	−2.0	16.9
S	0.2[b]	<8.0[b]
T (Diglyme)	−0.1[b]	<8.0[b]
U (Triglyme)	−0.1[b]	<8.0[b]
V (Tetraglyme)	−0.2[b]	<8.0[b]
W (12-Crown-4)	−1.0[b]	<8.0[b]
X (15-Crown-5)	−0.9[b]	<8.0[b]
Y (18-Crown-6)	−0.1[b]	<8.0[b]
BB (TDA)	−1.5[b]	<8.0[b]

[a] $\Delta G°_{solv}$ corresponds to values determined relative to TMEDA in toluene-d_8 according to eqs 4 and 5 (±0.2 kcal/mol). $\Delta G°_{act}$ was determined according to the equation $\Delta G°_{act} = -RT \ln(kh/KT)$ where $k = 2.22*\Delta\nu$ (±0.5 kcal/mol). The resonances of free and bound ligand were monitored as a function of temperature in the ^{13}C NMR spectra using 0.1 M solvent in LiHMDS and 0.2 M in total ligand concentration. [b] High ligand exchange rates precluded integration of bound polyethers. Total ligand concentrations relative to LiHMDS were determined from ^{13}C integrations at room temperature. LiHMDS monomer binding free energies for crowns were uncertain due to the coexistence of triple ions. The upper limit for $\Delta G°_{act}$ of 8 kcal/mol was calculated assuming a $\Delta\nu$ of 25 Hz at −110 °C.

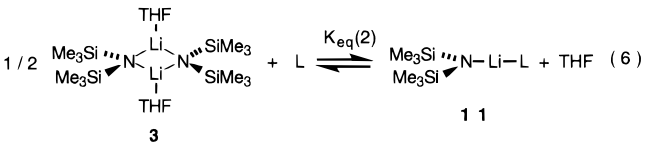
4 and 5.[6] The relative binding free energies ($\Delta G°_{solv}$) are listed

$$(Me_3Si)_2NLi{-}L_1 + L_2 \overset{K_{eq}(1)}{\rightleftharpoons} (Me_3Si)_2NLi{-}L_2 + L_1 \quad (4)$$

$$K_{eq}(1) = \{[(Me_3Si)_2NLi{-}L_2][L_1]\}/\{[(Me_3Si)_2NLi{-}L_1][L_2]\} = \exp(-\Delta G°_{solv}/RT) \quad (5)$$

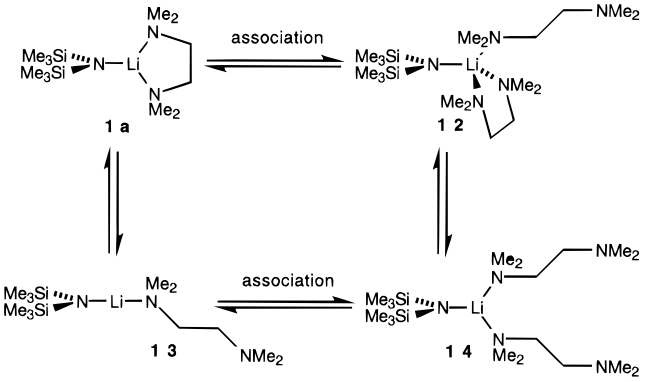
in Table 3. The more strongly coordinated ligands were more conveniently competed against *trans*-TMCDA (**F**) rather than TMEDA. Unusually weak metal−ligand bonds precluded determinations for ligands **B**,[31] **D**,[32] and **K**.[27]

We also employed an alternative protocol for determining relative monomer binding free energies through competition of polydentate ligands with THF (eqs 6 and 7), which offers the advantage of not relying upon slow ligand exchange on NMR time scales; simple integration of the monomer−dimer proportions affords the relative monomer binding free energies.



Despite concerns that mixed THF-diamine solvated monomers[42] might skew the results, the relative binding free energies concur with those determined as described above. However, using pentane in place of toluene as the cosolvent markedly lowers the monomer concentrations corresponding to a 0.7−1.1 kcal/mol decrease in monomer stability.[43] A similar hydrocarbon

Scheme 2



dependence of the LiHMDS monomer−dimer equilibrium in the presence of monodentate trialkylamines[6a] was traced to the stabilization of the *disolvated* monomer by toluene.[44]

$$K_{eq}(2) = \{[\mathbf{11}][THF]\}/\{[L][\mathbf{3}]^{1/2}\} \quad (7)$$

LiHMDS−Polyamines. Rates and Mechanisms of Ligand Substitution. The coalescence temperatures and affiliated activation free energies for exchange of free and LiHMDS-bound ligand fall into two distinct ranges (Table 3).[45] Further investigations revealed different mechanisms for sterically unhindered and sterically hindered diamines involving monomer and dimer reactive intermediates (respectively). For example, ^{13}C NMR spectroscopic analysis reveals that the exchange of free and **1a**-bound TMEDA increases markedly with increasing TMEDA concentration. Samples containing 1.2 equiv of diamine (5:1 integration ratio of bound and free ligand resonances) and samples containing 6.0 equiv of amine per Li (1:5 integration ratio of bound and free ligand resonances) show coalescence of the methylene resonances of free and bound TMEDA at −50 ± 5 °C and −80 ± 5 °C, respectively. The symmetry of the 5:1 and 1:5 intensities allows determination of concentration effects without recourse to complex line shape analyses. In a related experiment, a sample containing 0.1 M [^{6}Li,^{15}N]LiHMDS and 0.6 M TMEDA (1:5 resonance ratio) displayed the same coalescence temperature (−65 ± 5 °C) as a sample containing 0.5 M [^{6}Li,^{15}N]LiHMDS·TMEDA and 0.6 M TMEDA (5:1 resonance ratio). The dependence of the exchange rate on the free TMEDA concentration mandated a similar dependence on the LiHMDS concentration due to the overall bimolecularity; however, the comparable *magnitudes* of the TMEDA and LiHMDS concentration dependencies suggest that both are first order. (This proves to be important in light of very different results obtained for more hindered chelating ligands described below.) Analogous studies of TMPDA (**C**) reveal very similar dependencies on free ligand and LiHMDS concentrations indicating a mechanistic homology.

As illustrated in Scheme 2, an associative ligand substitution could involve (1) reversible chelate ring opening of **1a** to **13** followed by rate-limiting ligand association, (2) rate-limiting ligand association to give **12**, or (3) rate-limiting ring opening

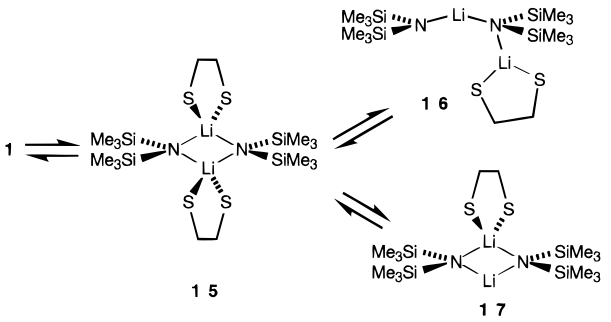
(42) Zarges, W.; Marsch, M.; Harms, K.; Boche, G. *Chem. Ber.* **1989**, *122*, 2303. Karsch, H. H.; Appelt, A.; Mueller, G. *Organometallics* **1985**, *4*, 1624.

(43) While 0.1 M pentane solutions of LiHMDS with 5.0 equiv of TMEDA and 5.0 equiv of THF contain approximately 5% TMEDA-solvated monomer (as shown in Scheme 1), the replacement of pentane with toluene affords a 60:40 dimer/monomer mixture.

(44) Kumpf, R. A.; Dougherty, D. A. *Science* **1993**, *261*, 1708. Dougherty, D. A. *Science* **1996**, *271*, 163.

(45) Under conditions where the two coalescing resonances are in 1:1 proportions, the relationship of the rate constant and coalescence temperature can be approximated as $\Delta G°_{act} = -RT \ln(k_{obs}h/kT_{coalescence})$ such that $k_{obs} = 2.22\Delta\nu$.

Scheme 3



of **12** to give **14** (or vice versa). The rate behavior is not consistent with a rate-limiting unimolecular conversion of **1a** to **13**. We suspect rate-limiting conversion of **1a** to **12** for two reasons: (1) rate studies of ketone enolization by LiHMDS/TMEDA[23] and spectroscopic studies of LiHMDS in the presence of trialkylamines[6a] suggest that **12** is formed observably at high TMEDA concentrations and (2) TMPDA (**C**) exchanges substantially more slowly despite the lower TMPDA chelate stability (noted below).

Bulky ligands exchange much more slowly than unbulky ligands (ΔG°_{act} = 15−19 kcal/mol) and show concentration dependencies indicating a different mechanism. For example, experiments akin to those described above showed that exchange rates of ligands **E** and **F** are *independent* of free ligand concentration and *dependent* upon LiHMDS concentration. We exclude a simple unimolecular rate-limiting step since the coalescence temperature would be *independent of both the LiHMDS and diamine concentration*.[46] The [LiHMDS] dependence and the absence of a [ligand] dependence requires a *rate-limiting association of two LiHMDS·diamine fragments*; some hypotheses are summarized in Scheme 3.

Loss of ^{6}Li−^{15}N coupling, which typically occurs from 0 to 50 °C, is sensitive to the concentration of *all* species: $(Me_3Si)_2NH$, solvated LiHMDS dimer, unsolvated LiHMDS oligomer, free polyamine ligand, and toluene (vs pentane). Extensive investigations using several polyamines provided little useful information due to the overall complexity and resulting hypersensitivity to the reaction conditions.

Previous investigations of monodentate ligand substitution on LiHMDS dimer revealed a dominance of a dissociative mechanism with a consequent strong correlation of binding free energies and activation free energies for exchange.[6a] The chelating ligands afford a very different result. For example, dipyrrolidinoethane (**H**) binds better than TMEDA, yet the associative ligand substitution is strongly retarded. Apparently, the associative substitution is limited by the capacity of the diamine to bind as a *monodentate* ligand in the congested environment of 4-coordinate lithium. It is interesting that the increased steric hindrance of TEEDA relative to TMEDA has little effect on the binding to LiHMDS, yet strongly retards the rate of butadiene polymerization.[25] The rate reduction may derive from the steric demand of the butadiene pre-coordination by the bound diamine. There is no correlation of ligand binding free energy (*vide infra*) and ligand exchange activation free energy (Figure 1).

LiHMDS−Polyethers. Structures. The results of spectroscopic studies of LiHMDS−dimethoxyethane (DME, **O**) solvates are not fully consonant with conventional wisdom (Scheme 4, Table 2). Addition of 0.25 equiv of DME to [^{6}Li,^{15}N]-LiHMDS affords **18** comprised of two LiHMDS units linked

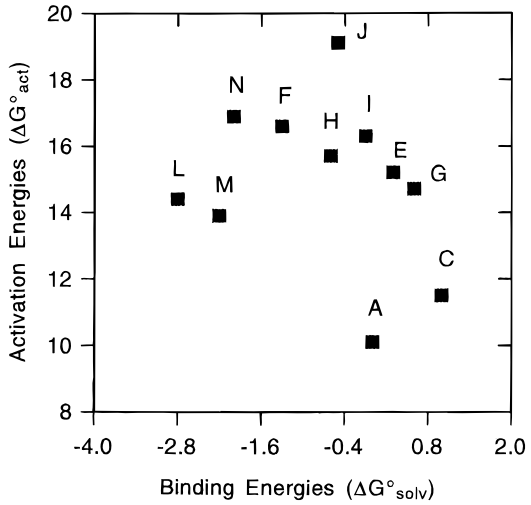
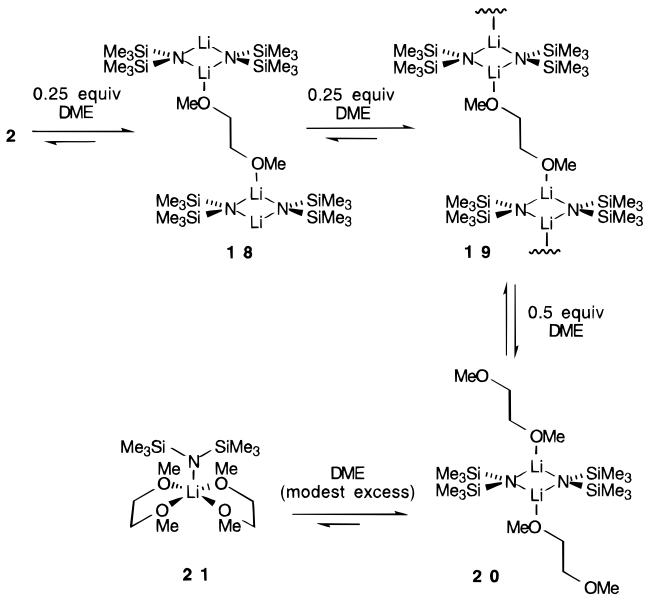


Figure 1. Plot of LiHMDS monomer binding energies (ΔG°_{solv}) vs activation free energies for ligand exchange on the LiHMDS monomer (ΔG°_{act}) as described in the text and listed in Table 3. Structures of the chelating ligands are in Chart 1.

Scheme 4



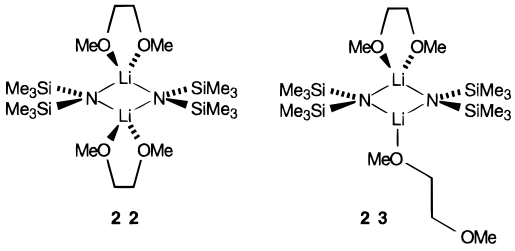
by a single DME ligand. Dimer **18** manifests two ^{6}Li triplets in a 1:1 ratio and an ^{15}N quintet in addition to the resonances corresponding to unsolvated LiHMDS.[5] The ^{13}C NMR spectrum contains a single TMS resonance and two resonances corresponding to a symmetric DME ligand. As the DME:LiHMDS stoichiometry approaches 0.5, the LiHMDS−DME complex becomes completely insoluble, presumably due to formation of polymer **19** characterized crystallographically by Williard and co-workers.[4,47] At >0.5 equiv of DME, the samples become homogeneous again, and a broad ^{6}Li triplet and ^{15}N quintet sharpen by 1.0 equiv, consistent with a deoligomerization. The ^{13}C NMR spectrum at 1.0 equiv of DME per Li reveals a single pair of DME resonances. One might infer the existence of chelated dimer **22** bearing *symmetrically coordinated* DME ligands; however, additional evidence supports dimer **20** bearing *unsymmetrical* η^1-DME ligands with resonance averaging by rapid intramolecular exchange (possibly via a transient chelated intermediate such as **23**).[4] This conclusion is based primarily upon computational

(46) For a detailed discussion of ligand substitution on metal ions, see: Lincoln, S. F.; Merbach, A. E. *Adv. Inorg. Chem.* **1995**, *42*, 1.

(47) NMR spectroscopic evidence of η^1-DME has been reported by Hilmersson and Davidsson.[13a]

studies showing LiHMDS dimers bearing chelated DME ligands to be very unstable[4] and competition studies using protocols described previously[6] showing that DME and *n*-BuOMe—a nonchelating isostructural analog of DME— display virtually identical propensities to bind to the LiHMDS dimer. Of course, it is possible that rapidly exchanging η^1- and η^2-coordinated DME ligands are of equal stability by coincidence. Nonetheless, Ockham's razor[48] argues against such a scenario, as do studies of the solvent-dependent dimer−monomer equilibrium (below).

Incremental additions of up to 10 equiv of DME cause the appearance and eventual dominance of a ^{6}Li doublet and ^{15}N triplet characteristic of a solvated monomer. The ^{13}C NMR spectra recorded in toluene-d_8 at −100 °C reveal resonances corresponding to dimer **20** along with a new set of DME and Me_3Si resonances corresponding to DME-solvated monomer in fast exchange with free DME. Inordinately rapid ligand exchange on the LiHMDS monomer was noted in previous studies of the monodentate ether solvates.[6] Since 0.1 M solutions of [^{6}Li,^{15}N]LiHMDS in neat *n*-BuOMe contain 98−99% disolvated dimer,[6] the pronounced chelate effect for DME is evident. Moreover, the DME concentration-dependent monomer−dimer ratios reveal the monomer to be at a higher per lithium solvation number than the dimer (i.e., >1.0 DME per monomer). The monomer appears to be either **21** or **24**.[49]

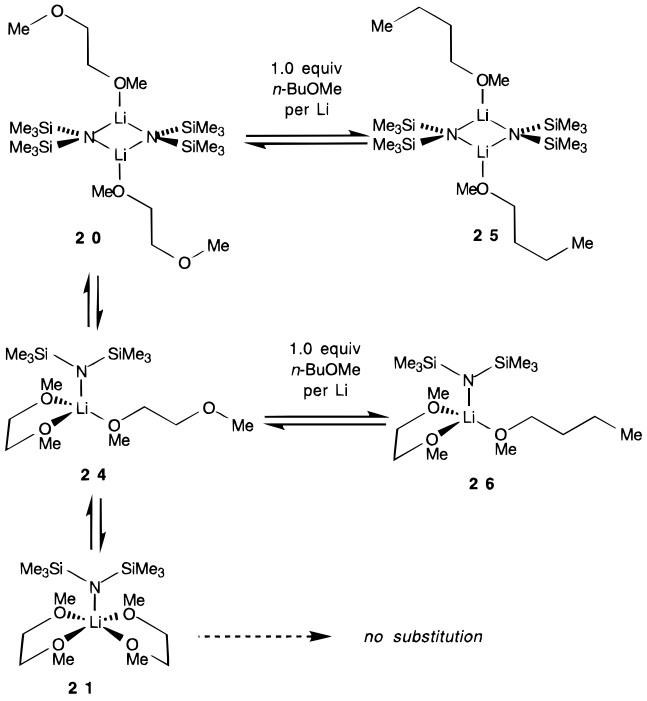


The distinction between the η^2, η^2-chelated monomer **21** and the η^1, η^2-chelated monomer **24** was made using mixtures of DME and *n*-BuOMe (Scheme 5) as follows:

(1) In the event of an equilibrium between dimer **20** and η^1, η^2-chelate **24**, *n*-BuOMe substitution of the η^1-DME ligands on **20** and **24** to give **25** and **26** (respectively) will be nearly thermoneutral and impart no net stabilization to either the monomer or the dimer. Since **20** and **24** both contain one η^1-DME ligand per lithium, replacing toluene by *n*-BuOMe while holding the DME concentration constant should have little effect on the dimer−monomer equilibrium. (Actually, one would predict a slight increase in the monomer concentration due to the slight increase in the free DME concentration.)

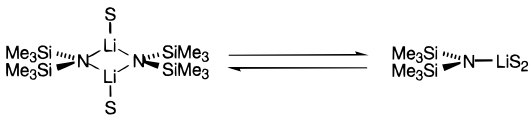
(2) In contrast, thermoneutral substitution of *n*-BuOMe for the η^1-DME ligand on **20** with no analogous thermoneutral substitution available to **21** would cause a net dimer stabilization by replacing toluene with *n*-BuOMe.[50] This prediction is counterintuitive in that simple models of solvation would not predict promotion of the higher aggregate by a potentially ligating cosolvent.

Scheme 5



Whereas treatment of [^{6}Li,^{15}N]LiHMDS with 5 equiv of DME in toluene affords a 1:9 dimer−monomer mixture, analogous treatment with 5 equiv of DME and 50 equiv of *n*-BuOMe affords a 3:2 dimer−monomer mixture. The relative stabilization of the dimer by added *n*-BuOMe supports bis-η^2-chelated monomer **21** as the dominant DME-solvated monomer.

Incremental additions of diethoxyethane (**P**)[51] to [^{6}Li,^{15}N]-LiHMDS reveal evidence of polymer (analogous to **19**) at <1.0 equiv per lithium and an equilibrium mixture of dimer **27a** and monomer **28a** at >1.0 equiv of ligand per lithium. The solvent concentration dependence of the dimer−monomer equilibrium indicates that the monomer **28a** contains at least two ligands. The high propensity to form monomer (relative to diethyl ether[6]) indicates that chelation is important. However, the monomer becomes the limiting structure only upon addition of substantial concentrations (> 20 equiv) of **P**. Similarly, considerable concentrations (>40 equiv per Li) of dimethoxypropane (**R**)[52] are required to convert the dimer **28b** to monomer. The extra CH_2 spacer of dimethoxypropane with regard to DME causes an increased stability of the polymer as well as a decreased stability of the monomer as evidenced by solubility problems with up to 4 equiv of ligand.



27a; S = η^1-$EtOCH_2CH_2OEt$ (**P**)
27b; S = η^1-$MeOCH_2CH_2CH_2OMe$ (**R**)
27c; S = η^1-$MeOCH_2CH_2O$-*t*-Bu (**Q**)

28a; S = $EtOCH_2CH_2OEt$ (**P**)
28b; S = $MeOCH_2CH_2CH_2OMe$ (**R**)
28c; S = $MeOCH_2CH_2O$-*t*-Bu (**Q**)

The bulky *tert*-butyl group of *t*-$BuOCH_2CH_2OMe$ (**Q**)[53] precludes polymer formation, affording dimer **27c** at <1.0 equiv. The *tert*-butyl group does not entirely prevent chelation,

(48) Hoffmann, R.; Minkin, V. I.; Carpenter, B. K. *Bull. Soc. Chim. Fr.* **1996**, *133*, 117.

(49) For example, +Li(DME)$_3$ is octahedral: Niecke, E.; Nieger, M.; Wendroth, P. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 353. Nieke, E.; Nieger, M.; Wenderoth, P. *J. Am. Chem. Soc.* **1993**, *115*, 6989. Schumann, H.; Janiak, C.; Pickardt, J. *J. Organomet. Chem.* **1988**, *349*, 117. Bock, H.; Näther, C.; Havlas, Z.; John, A.; Arad, C. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 875.

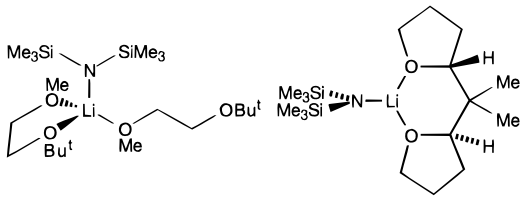
(50) Hammes, G. G. *Principles of Chemical Kinetics*; Academic Press: New York, 1978; p 14. Casado, J.; Lopez-Quintela, M. A.; Lorenzo-Barral, F. M. *J. Chem. Educ.* **1986**, *63*, 450.

(51) *Chem. Abstr.* **1990**, *112*, 102 150.

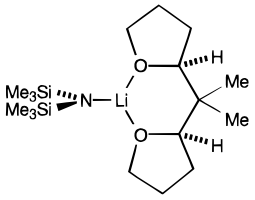
(52) Foos, J. S.; Stolki, T. S.; Beebe, X. *J. Electrochem. Soc.* **1989**, *136*, 2748. *Chem. Abstr.* **1984**, *100*, 158 027.

(53) Hellermann, W.; Nordsiek, K. H.; Wolpers, J.; Sunder-Plassmann, P. *Chem. Abstr.* **1988**, *109*, 39 247.

however. Monomer **28c** is dominant (80%) in solutions of neat **Q** whereas neat *n*-BuOMe affords virtually no monomer.[6b,54] In contrast to the results with DME, substituting *n*-BuOMe for the toluene in solutions of [^{6}Li,^{15}N]LiHMDS in *t*-BuOCH$_2$CH$_2$-OMe−toluene results in a slight increase in the concentration of the monomer, suggesting that *t*-BuOCH$_2$CH$_2$OMe-solvated monomer **28c** is more precisely depicted as the η^1, η^2-chelate **29**.



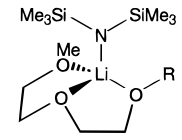
29 **30**



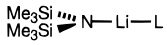
31

We were drawn to the mixture of *d,l*- and *meso*-2,2-(2-tetrahydrofuryl)propane (**S**) bearing two THF moieties due to its importance in anionic polymerization.[55] At <1.0 equiv of **S** per LiHMDS we observe diastereomeric monomers **30** and **31** as well as unsolvated dimer **2** to the exclusion of other solvated dimers. At >1.0 equiv, rapid ligand exchange causes time averaging of the two monomers in the ^{6}Li NMR spectra.

NMR spectroscopic analysis of [^{6}Li,^{15}N]LiHMDS containing <1.0 equiv of diglyme (**T**)[17,56] in toluene-d_8 is precluded by solubility problems, presumably due to formation of polymers similar to **19**. Samples with 1.0 equiv contain exclusively monomer. Addition of 1.0−10 equiv of diglyme causes no observable changes in the ^{6}Li and ^{15}N NMR spectra and affords time-averaged ^{13}C resonances of free and bound diglyme. The enhanced deaggregation compared to DME indicates that stabilization via η^3-chelated monomer **32a** is important. Triglyme (**U**)[17,56] and tetraglyme (**V**)[17,56] afford **32b** and **32c**, analogously. A tri- rather than tetradentate metal−ligand interaction is implicated by the nearly equal binding free energies for di-, tri-, and tetraglyme (*vide infra)*.



32a; R = Me
32b; R = CH_2CH_2OMe
32c; R = $(CH_2CH_2O)_2Me$



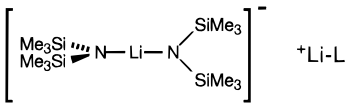
33a; L = 12-crown-4
33b; L = 15-crown-5
33c; L = 18-crown-6
33d; L = TDA (**BB**)

(54) Addition of low concentrations of ligand **Q** (1.0 equiv) to LiHMDS affords appreciable concentrations of monomer in toluene but not in pentane. No such effects are observed at any DME concentration, suggesting that DME-solvated 3-coordinate monomer is not stable.

(55) *Chem. Abstr.* **1984**, *100*, 192 532.

(56) Petersen, G.; Jacobsson, P.; Torell, L. M. *Electrochim. Acta* **1992**, *37*, 1495. Makrlik, E.; Halova, J.; Vanura, P. *Collect. Czech. Chem. Commun.* **1992**, *57*, 276. Tsvetanov, Kh.; Petrova, E.; Dimov, D.; Panaitov, I.; Smid, J. *J. Solution Chem.* **1990**, *19*, 425. Zhang, H.; Dearden, D. V. *J. Am. Chem. Soc.* **1992**, *114*, 2754.

Crown ethers[15,30,57−59] revealed a somewhat unexpected behavior than their corresponding acyclic polyether counterparts. A solution of LiHMDS and 0.5 equiv of 12-crown-4 (**W**) in 1:2 (v/v) 2,2,5,5-tetramethyltetrahydrofuran−toluene (to maintain solubility) affords triple ion **34a** to the exclusion of either monomer or cyclic dimer.[60] Triple ion **34a** manifests a ^{6}Li singlet and ^{6}Li triplet with a characteristically large Li−N coupling constant analogous to triple ions observed in THF−pentane−HMPA mixtures.[5,60] The ^{15}N NMR spectrum shows the anticipated 1:1:1 triplet. The 1:2 ligand−LiHMDS stoichiometry requires that the lithium cation of **34a** contain only one 12-crown-4. At ≥1:1 ligand−LiHMDS stoichiometry, we observe monomer **33a**—characterized crystallographically by Power and co-workers[9a]— along with triple ion **34b** (≈30%). The ^{6}Li resonance corresponding to the Li$^+$ counterion of **34b** is shifted upfield by >1.0 ppm relative to the counterion at the lower ligand−LiHMDS stoichiometry, consistent with the coordination of a second crown. Moreover, the monomer−triple ion ratio becomes insensitive[61] to the crown concentration beyond 1.0 equiv per Li. This is consistent with both the monomer and triple ion bearing a 1:1 ligand−lithium stoichiometry. The ^{13}C NMR spectra recorded on solutions of [^{6}Li]LiHMDS in toluene-d_8 containing >1.0 equiv of 12-crown-4 reveal only time-averaged free and bound ligand resonances.



34a; $^+$Li-L = $^+$Li(12-crown-4) **34e**; $^+$Li-L = $^+$Li(18-crown-6)
34b; $^+$Li-L = $^+$Li(12-crown-4)$_2$ **34f**; $^+$Li-L = $^+$Li(18-crown-6)$_2$
34c; $^+$Li-L = $^+$Li(15-crown-5) **34g**; L = $^+$Li(C[211]) (**CC**)
34d; $^+$Li-L = $^+$Li(15-crown-5)$_2$ **34h**; L = $^+$Li(TDA) (**BB**)

While Li$^+$(12-crown-4)$_2$ sandwiches of general structure **35** are known,[62] it was not at all obvious at the onset that the ionization to give **34a** could be supported by a single 12-crown-4. The ionic radius of Li$^+$ is estimated to be approximately 10−20% larger than the 12-crown-4 cavity,[15,58,63] forcing the lithium cation of **34a** above the crown plane. It is likely that

(57) Underiner, G.; Tan, R. P.; Powell, D. R.; West, R. *J. Am. Chem. Soc.* **1991**, *113*, 8437. Iwachido, T.; Shibuya, K.; Nakamura, N.; Motomizu, S. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 4169. Zavada, J.; Pechanec, V.; Kocian, O. *Collect. Czech. Chem. Commun.* **1983**, *48*, 2509.

(58) For leading references to computational studies of crown ether complexation, see: Hay, B. P.; Rustad, J. R. *J. Am. Chem. Soc.* **1994**, *116*, 6316. Glendening, E. D.; Feller, D.; Thompson, M. A. *J. Am. Chem. Soc.* **1994**, *116*, 10657. Also, see: ref 30.

(59) Chu, I.-H.; Zhang, H.; Dearden, D. V. *J. Am. Chem. Soc.* **1993**, *115*, 5736. Dearden, D. V.; Zhang, H.; Chu, I.-H.; Wong, P.; Chen, Q. *Pure Appl. Chem.* **1993**, *65*, 423. Maleknia, S.; Brodbelt, J. *J. Am. Chem. Soc.* **1992**, *114*, 4295.

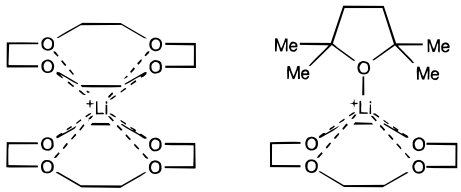
(60) For leading references to triple ions, see: Romesberg, F. E.; Collum, D. B. *J. Am. Chem. Soc.* **1994**, *116*, 9187. Also, see: Reich, H. J.; Holladay, J. E.; Mason, J. D.; Sikorski, W. H. *J. Am. Chem. Soc.* **1995**, *117*, 12137. Lappert, M. F. unpublished case

(61) While the triple ion−monomer proportions do not change upon addition of 1.0−10 equiv of 15−crown-5, addition of 1.0−10 equiv of 12-crown-4 shows a very slight shift favoring the monomer. This may arise from a soft equilibrium between triple ion **34a** and **34b** due to crown−crown interactions in **34b**.[58]

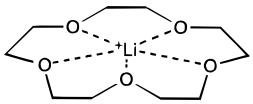
(62) For an example of a triple ion bearing a +Li(12-crown-4)$_2$ counterion, see: Zaegel, F.; Gallucci, J. C.; Meunier, P.; Gautheron, B.; Sivik, M. R.; Paquette, L. A. *J. Am. Chem. Soc.* **1994**, *116*, 6466.

(63) MNDO calculations reveal no evidence of a minimum for an inclusive Li$^+$(12-crown-4) complex. If one is created through enforcing O−Li−O bond angles of 90°, the free energy is >10 kcal/mol less stable than the relaxed (exclusive) complex.

the lithium cation of **34a** is capped by one or more Me_4THF ligands (e.g., **36**).[64]



35 **36**



37

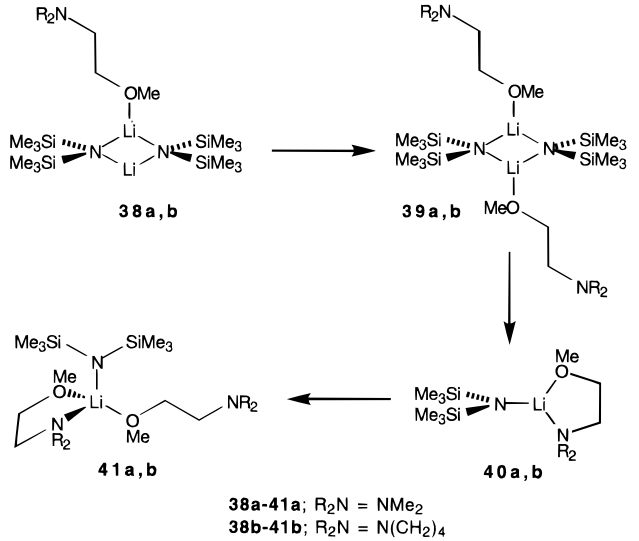
Addition of 0.5 equiv of 15-crown-5 (**X**) again affords exclusively triple ion **34c**, presumably containing the inclusive $^+$Li(15-crown-5)[65] counterion **37**. Addition of 1.0 equiv of 15-crown-5 affords a monomer−triple ion mixture that remains invariant with up to 10 equiv. The concentration independence implicates triple ion **34d** bearing the $^+$Li(15-crown-5)$_2$ sandwich counterion (although there is no marked chemical shift change as found for the 12-crown-4 case).

Addition of 0.5 equiv of 18-crown-6 (**Y**) affords exclusively triple ion **34e** while 1.0 equiv affords a 1:1 mixture of monomer−triple ion. In contrast to both 12-crown-4 and 15-crown-5, excess 18-crown-6 (>5.0 equiv per lithium) affords exclusively monomer. This suggests that **34f** with the $^+$Li(18-crown-6)$_2$ counterion is not particularly stable. However, we cannot exclude the possibility that the 18-crown-6 is sufficiently flexible to afford a disolvated monomer akin to DME-solvated monomer **21**; $^+$Li(η^2-18-crown-6) has been observed crystallographically.[66]

LiHMDS−Polyethers. Relative Binding Constants. The high polyether and crown ether exchange rates precluded observation of free and LiHMDS-bound crown in the slow-exchange limit. Fortunately, their binding constants could be determined by competing the crown ethers and polyethers against the kinetically more inert TMEDA- and *trans*-TMCDA-solvated monomers (**1a** and **1f**) as in eqs 4 and 5 (or against the THF solvated dimer as in eqs 6 and 7). The relative concentrations of polyether- and diamine-solvated monomers and consequent relative binding free energies were determined by ^{6}Li NMR spectroscopy according to eqs 4 and 5. The total concentrations of polyamine, polyether, and LiHMDS were determined by integrating the ^{13}C resonances of the ligand and silyl groups at ambient temperature. The results are listed in Table 3. The solvation free energies listed in Table 3 cannot be compared to the energies of those cases where disolvated monomers are formed because of the standard state dependence. In these latter cases, the relative propensities to promote monomer formation are as follows: **O** > **P** > **R** > **Q**.

Aminoethers. Aminoethers **Z**[28,29] and **AA**[28,29] manifest properties that underscore their hybrid character (Scheme 6). For example, $Me_2NCH_2CH_2OMe$ (**Z**) affords monosolvated dimer **38a**, disolvated dimer **39a**, and chelated monomer **40a** in the slow-exchange limit at <1.0 equiv of ligand per Li.[67] Monomer promotion with increasing ligand concentration indicates that a monomer such as **41a** containing two ligands

Scheme 6

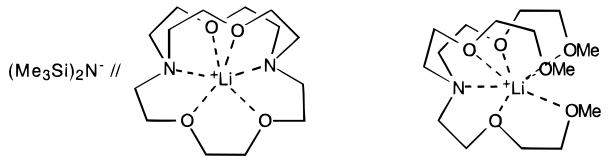


38a,b **39a,b** **40a,b** **41a,b**

38a-41a; R_2N = NMe_2
38b-41b; R_2N = $N(CH_2)_4$

forms. These properties are similar to those exemplified by DME. However, observation of monomer at <1.0 equiv per Li is more akin to TMEDA. Once again we noted a pronounced hydrocarbon dependence wherein the 3-coordinate monomers **40a,b** are stabilized substantially more in toluene than in pentane.

The low basicity makes LiHMDS compatible with the moderately base-labile[68,69] lithium-selective cryptand C[211] (**CC**). Addition of 0.5 equiv of **CC** to [^{6}Li,^{15}N]LiHMDS in 2:1 THF−pentane solution affords triple ion **34g** quantitatively. Additional C[211] causes the ^{6}Li resonance corresponding to the $^+$Li(C[211]) cation to increase at the expense of the resonance corresponding to the [$R_2N-Li-NR_2$] anionic fragment (70:30 ratio at 2.0 equiv of C[211]); a broad ^{15}N resonance appears concomitantly. The concentration dependencies and spectroscopic properties are consistent with formation of ion pair **42**.[70]



42 **43**

Tris[2-(2-methoxyethoxy)ethyl]amine (TDA, **BB**), sparingly employed as a phase transfer catalyst,[71] seemed promising as an inexpensive alternative to the crowns and cryptands. Treatment of [^{6}Li,^{15}N]LiHMDS with 0.5 equiv of TDA per lithium affords exclusively triple ion **34h**, presumably bearing some form of encapsulated counterion such as **43**. At >0.5 equiv of TDA, monomer **33d** appears and becomes the sole observable form of LiHMDS at 2.0 equiv of TDA per lithium. While

(64) Me_4THF appreciably coordinates to the LiHMDS dimer.[6b]

(65) Stark, P. C.; Huff, M.; Babaian, E. A.; Barden, L. M.; Hrncir, D. C.; Bott, S. G.; Atwood, J. L. *J. Inclusion Phenom.* **1987**, *5*, 683.

(66) Dye, J. L.; Huang, R. H. *Pure Appl. Chem.* **1993**, *65*, 435.

(67) The spectroscopic properties are fully consistent with monosolvated cyclic dimers **38a,b**. However, in these particular cases, the disparate coupling constants and chemical shifts are suggestive of open dimer **16** in rapid (degenerate) exchange. Such an exchange has been observed for chelated LiTMP open dimers.[73]

(68) A mixture of lithium diisopropylamide and C[211] decompose at low temperature.[69]

(69) Galiano-Roth, A. S.; Collum, D. B. *J. Am. Chem. Soc.* **1988**, *110*, 3546.

(70) Moras, D.; Weiss, R. *Acta Crystallogr., Sect. B* **1973**, *B29*, 400.

(71) Miller, J. M.; Brown, S. J.; Theberge, R.; Clark, J. H. J. *Chem. Soc., Dalton Trans.* **1986**, 2525. Cambie, R. C.; Janssen, S. J.; Rutledge, P. S.; Woodgate, P. D. *J. Organomet. Chem.* **1991**, *420*, 387. *Chem. Abstr.* **1989**, *110*, 215 192.

promotion of monomer relative to triple ion at high TDA concentrations is logical based upon stoichiometries of 0.5 and 1.0 ligands per lithium (respectively), it had not occurred to us at the onset that increasing the concentration of a polydentate ligand would retard ionization.

Discussion

The high thermal stability of LiHMDS, an unusual penchant toward slow ligand exchange, and the structural transparency offered by ^{6}Li−^{15}N doubly labeled LiHMDS in conjunction with ^{6}Li, ^{15}N, and ^{13}C NMR spectroscopies combine to provide a unique view of lithium ion solvation by a host of chelating ligands shown in Chart 1. In the Results section we provided detailed descriptions of ligand-dependent LiHMDS structures and limited investigations of the mechanisms of ligand exchange. However, the primary goal of the studies described above was to ascertain how ligand structure influences the LiHMDS monomer binding free energy. This will be the primary focus of the Discussion.

LiHMDS−Diamine Complexes. Treatment of LiHMDS with low concentrations (1.0−5.0 equiv) of various diamines (**A**−**K**, Chart 1) affords the LiHMDS monomer of general chelated structure **1** to the exclusion of solvated dimer or more highly solvated monomer. Relative ligand binding constants (Table 3) determined by direct competition (eqs 4 and 5) or indirectly by competition with the THF-solvated LiHMDS dimer (eqs 6 and 7) reveal a number of trends. Most apparently, varying the chain length shows a distinct preference for 5- vs 6-membered rings and no tendency to form 4- or 7-membered chelates. A similar preference was convincingly documented by the groups of Klumpp[14b] and Reich.[13c]

A comparison of TMEDA (**A**) and the more sterically congested TEEDA (**E**) display little difference in binding affinity. Apparently, LiHMDS is not sufficiently hindered to attain what Brown[72] refers to as the "minimum steric threshold" required to detect differences in ligand bulk. This contrasts with diamine solvates of lithium 2,2,6,6-tetramethylpiperidide (LiTMP) in which TEEDA shows a strongly reduced binding affinity relative to TMEDA.[73,74] The results from TMEDA and TEEDA suggest that the relatively strong binding of pyrrolidine-based diamine **H** is due to electronic rather than steric differences. Interestingly, pyrrolidine ($(CH_2)_4NH$) shows a high affinity for the LiHMDS dimer compared to that of other dialkylamines.[6a]

Two chiral chelating ligands, sparteine (**J**)[36] and *trans*-*N*,*N*,*N*′,*N*′-tetramethyl-1,2-cyclohexanediamine (*trans*-TMCDA, **F**),[33] bind more strongly than TMEDA. The high affinity of sparteine is especially interesting in light of its steric demand and importance in organic synthesis. In contrast to *trans*-TMCDA, *cis*-TMCDA (**G**) is a poor ligand. The preferential binding of the *trans* derivative is fully consistent with similar assertions of Langer and Whitney.[75] Proton sponge (**K**)[27], a diamine known for its high Brönsted basicity, shows very low affinity for LiHMDS monomer, affording substantial concentrations of unsolvated oligomer even with excess ligand.

It seems possible that all but the most bulky organolithium monomers may display only minimal sensitivity to the steric demands of a chelating diamine. Nevertheless, the capacity of diamines to cause deaggregation will still be sensitive to ligand bulk since solvation of dimers and other higher oligomers is sensitive to ligand bulk.[6,76] One might also be tempted to infer that ligand substitution (and accompanying changes in reactivity in general) might correlate with chelating ligand binding affinity. However, due to the apparent existence of at least two discrete ligand exchange mechanisms as well as a dominance of associative rather than dissociative processes in both mechanisms, no such correlation exists (Figure 1).

We noted a dependence of diamine binding on the hydrocarbon cosolvent. Competitions of TMEDA and *trans*-TMCDA with THF afford THF-solvated LiHMDS dimer and diamine-coordinated monomer (eq 6). While the relative binding constants using toluene cosolvent concur with those derived from the more direct competition (also in toluene), we noted a significantly lower (≈1.0 kcal/mol) monomer stability in pentane. An analogous hydrocarbon dependence on LiHMDS monomer−dimer mixture in the presence of simple (monodentate) trialkylamines was ascribed to the stabilization of 3-coordinate monomers by the substantial quadrupole[44] of the toluene.[6a] We are beginning to suspect this hydrocarbon effect may be general and of some consequence to reactivity. Beak and co-workers reported a 5-fold increased enantioselectivity of *sec*-BuLi/sparteine-mediated metalations upon changing from pentane to toluene cosolvent.[77]

LiHMDS−Polyamine Complexes. Treatment of LiHMDS with *N*,*N*,*N*′,*N*″,*N*″-pentamethyldiethylenetriamine (PMDTA, **L**) affords the 4-coordinate monomer **7** showing restricted rotation about the Li−N bond akin to that observed by Fraenkel and co-workers for PMDTA-solvated aryl- and alkyllithiums.[37] Coordination by all three amino groups is evidenced by the substantially larger binding free energy relative to simple diamines. The corresponding tetramine (**M**, HMTTA) offers no advantages over PMDTA. In fact, the added steric bulk of the pendant (uncoordinated) side chain in monomer **9** compared to the steric bulk of a methyl moiety in **7** causes HMTTA to be a weaker ligand. It is somewhat surprising that the cyclic triamine TMTACN (**N**) is inferior to PMDTA as a ligand for the LiHMDS monomer. The limited consequences of the "macrocyclic effect"[78] on LiHMDS monomer−ligand complex stability is also manifested by the crown ethers as described below.

LiHMDS−Polyether Complexes. The LiHMDS−polyether complexes show a much greater structural diversity than the polyamines. Complexation of LiHMDS by diethers such as DME (**O**) afford complex equilibria containing η^1-solvated dimers and chelated monomers as illustrated in Scheme 4. The reluctance of DME to afford chelated LiHMDS dimers is supported by both crystallographic and computational studies of Williard and co-workers.[4] The stability of 5-coordinate monomer **21** is consistent with crystallographic studies showing that DME can promote high-coordinate lithium[49] and spectroscopic investigations showing that LiHMDS monomer may exist as a 5-coordinate tetrasolvate in THF or oxetane.[6b] Diglyme, triglyme, and tetraglyme (**T**, **U**, and **V**, respectively) afford exclusively monomer at ≥1.0 equiv of polyether per lithium.

(72) For a discussion of steric effects of amines in the context of transition metal ligation, see: Choi, M.-G.; Brown, T. L. *Inorg. Chem.* **1993**, *32*, 1548. Also, see: Seligson, A. L.; Trogler, W. C. *J. Am. Chem. Soc.* **1991**, *113*, 2520.

(73) Remenar, J. F.; Lucht, B. L.; Collum, D. B. Unpublished results.

(74) Attempts to investigate unhindered protic diamines afford complex mixed aggregation and solvation phenomena: Lucht, B. L.; Collum, D. B. *J. Am. Chem. Soc.* **1996**, *118*, 3529.

(75) See p 144 of ref 14a.

(76) Settle, F. A.; Haggerty, M.; Eastham, J. F. *J. Am. Chem. Soc.* **1964**, *86*, 2076. Lewis, H. L.; Brown, T. L. *J. Am. Chem. Soc.* **1970**, *92*, 4664. Brown, T. L.; Gerteis, R. L.; Rafus, D. A.; Ladd, J. A. *J. Am. Chem. Soc.* **1964**, *86*, 2135. Quirk, R. P.; Kester, D. E. *J. Organomet. Chem.* **1977**, *127*, 111. Romesberg, F. E.; Collum, D. B. *J. Am. Chem. Soc.* **1992**, *114*, 2112.

(77) Wu, S.; Lee, S.; Beak, P. *J. Am. Chem. Soc.* **1996**, *118*, 715.

(78) Cabbiness, D. K.; Margerum, D. W. *J. Am. Chem. Soc.* **1969**, *91*, 6540. For leading references to recent studies, see: Chen, Q.; Cannell, K.; Nicoll, J.; Dearden, D. V. *J. Am. Chem. Soc.* **1996**, *118*, 6335.

The relative LiHMDS monomer binding free energies of polyethers (Table 3) are generally lower than the binding free energies of their polyamine counterparts. For example, diglyme is a considerably weaker ligand than PMDTA. This corroborates the findings of Klumpp[14b] and Reich[13c] that monomeric organolithium derivatives with internal ligands form stronger chelates with pendant amines than ethers. While this may appear to be self-evident from the higher Brönsted basicity of amines, LiHMDS monomers and dimers solvated by monodentate ethers and amines reveal a relatively high azaphilicity on the monomers, but not on the dimers.[6a]

The equivalent binding free energies of di-, tri-, and tetraglyme suggest that only three oxygens coordinate to the lithium cation. This was noted in previous studies of acyclic polyethers.[17] Unfortunately, we could not obtain a valid relative binding free energy for DME due to the tendency to form doubly chelated monomer **21**. The ditetrahydrofuran ligand **S** (an isomeric mixture) shows a strong penchant toward coordination to the LiHMDS monomer, affording diastereomers **30** and **31**. The high lithium ion affinity of **S** (despite the 6-membered ring) and the consequent importance of **S** in anionic polymerization[55] may derive from the Thorpe−Ingold (gem dimethyl) effect.[79]

LiHMDS−crown ether solution structures and affiliated crown ether binding constants prove to be interesting. Additions of 0.5 equiv of 12-crown-4 (**W**), 15-crown-5 (**X**), and 18-crown-6 (**Y**) to LiHMDS afford triple ions **34a**,**c**,**e** bearing a single crown per lithium cation (0.5 equiv per total Li). This is not surprising for 15-crown-5 and 18-crown-6 since the complexation of lithium ion can be inclusive (e.g., **37**);[15] however, the small cavity of 12-crown-4 seems to require an exclusive (out-of-plane) lithium cation with additional coordination by the ethereal cosolvent (**36**).[58] At elevated crown concentrations, LiHMDS−crown monomer complexes are formed along with triple ions. The concentration dependencies indicate that 12-crown-4 and 15-crown-5 afford triple ions **34b** and **34d** (respectively) bearing $^{+}$Li(crown)$_2$ sandwich cations (e.g., **35**). In contrast, triple ion **34f** bearing two 18-crown-6 ligands are not stable. The *lower* concentrations of species exhibiting ion pair separation at higher crown ether concentrations may explain a reported inverse correlation of conductivity with crown ether concentration.[80] Quantitative studies indicate that the "macrocyclic effect"[78]—the enhanced binding of the crowns compared to the acyclic polyglymes—adds only 0.7−0.9 kcal/mol of stabilization to the LiHMDS monomer. Overall, the structural variations observed for the different crown ethers underscore the potential dangers of using empirical observations (such as conductivity) to determine crown binding affinities and highlight the merits of the gas phase binding studies.[59]

LiHMDS−Aminoether Complexes. Vicinal aminoethers (**Z** and **AA**) manifest properties intermediate to those of the corresponding diamines and diethers. On the one hand, they afford η^1-solvated LiHMDS dimers at low concentration (<1.0 equiv per Li) and more highly solvated monomers (e.g., **41**) at elevated ligand concentrations akin to DME. On the other hand, observable LiHMDS monomer at low ligand concentrations (<1.0 equiv per Li) is more characteristic of the diamines.

The results from crown ethers instigated brief investigations of the aminoether-based cryptand C[211] (**CC**). Indeed, triple ion **34g** is the preferred form with the simple ion pair **42** appearing only at elevated cryptand concentrations. Previous studies of lithiated hydrazones uncovered a similar reluctance of the anionic triple ion fragments to forfeit the Li$^+$ to the C[211] ligand.[69] The corresponding acyclic aminoether ligand TDA (**BB**) gives interesting results from several perspectives. TDA contrasts with the polyglymes and functions more like a crown or cryptand by affording substantial concentrations of triple ion **34h**. Once again we observed that higher ligand concentrations and accompanying monomer formation retard ion pair separation. Most importantly, TDA affords crown- and cryptand-like solvation at <10% the cost of the crowns and <0.1% the cost of C[211].

Conclusion

Some of the specific conclusions arising from an investigation of LiHMDS solvated by 29 different chelating ligands are as follows:

(1) Treatment of LiHMDS with bidentate ligands affords η^1-coordinated mono- and disolvated dimers, η^2-coordinated (3-coordinate) monomers, η^1,η^2-coordinated (4-coordinate) monomers, and η^2,η^2-coordinated (5-coordinate) monomers, depending on the choice of ligand and concentration. Polydentate ligands afford additional structures including triple ions and solvent-separated ion pairs.

(2) LiHMDS monomer solvation by diamines shows a limited sensitivity to ligand steric demand, a marked preference for 5-membered chelates, and a previously noted sensitivity to choice of hydrocarbon cosolvent.

(3) The LiHMDS monomer displays a higher azaphilicity than oxaphilicity.

(4) Diamine exchange proceeds by either of two mechanisms: (i) ligand association to give more highly solvated LiHMDS monomer intermediates or (ii) LiHMDS monomer association to give dimer intermediates. Irrespective of mechanism, the ligand exchange rates do not correlate with chelate stability.

(5) LiHMDS−crown ether complexes are only slightly more stable than the corresponding LiHMDS−polyether complexes; the macrocyclic effect appears to be marginal for the LiHMDS monomer. The macrocyclic effect plays prominently in the solvation of lithium cation to the extent that crowns and cryptands readily afford triple ions, whereas the acyclic polyamines and polyethers do not. Overall, the capacity of a chelating ligand to coordinate the LiHMDS monomer and solvent-separated lithium cation do not correlate.

(6) Ionization of LiHMDS due to formation of triple ions at low crown concentrations is *retarded* at elevated crown ether concentrations due to promotion of LiHMDS monomers.

(7) The polydentate aminoether TDA affords a highly economical alternative to the substantially more expensive crown ethers and cryptands.

(8) Very few polydentate ligands are competitive with neat THF for coordination to LiHMDS.

In principle, a better understanding of lithium ion solvation in general and chelation in particular could find application in the development of new asymmetric reagents for organic synthesis, improved syntheses of elastomers via anionic polymerization, superior electrolytes for rechargeable lithium batteries, and even neurologically important pharmaceuticals. It is questionable, however, whether the plethora of ligand-dependent empirical observations can afford substantial insights in the absence of detailed structural information. The structural diversity that can be easily observed in LiHMDS underscores the ambiguities affiliated with less structurally transparent systems. We have certainly not resolved all structural details of the LiHMDS coordination sphere. However, the insights gained from the LiHMDS structural studies and monomer binding free energies may prove to be transferrable to other

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systems. Of course, during efforts to choose or design ligands for lithium ion solvation one must first ascertain whether desired properties will be best attained through ligands that are strongly binding or weakly binding.

Experimental Section

Reagents and Solvents. The majority of ligands in Chart 1 were obtained from Aldrich. 2,2-(2-tetrahydrofuryl)propane (**S**) was obtained from TCI. Ligands **H**,[81] **I**,[81] **R**,[82] **Z**,[81] and **AA**[81] were prepared according to literature procedures. All solvents and the more volatile ligands were distilled from blue or purple solutions containing sodium benzophenone ketyl. The higher boiling ligands (**J**, **L**, **M**, **T**−**Y**, and **BB**) were distilled from sodium metal without added benzophenone. Ligands **K**, **N**, and **CC** were used without further purification. The hydrocarbon stills contained 1% tetraglyme to dissolve the ketyl. ^{6}Li metal (95.5% enriched) was obtained from Oak Ridge National Laboratory. The [^{6}Li]ethyllithium used to prepare the [^{6}Li]LiHMDS and [^{6}Li,^{15}N]LiHMDS were prepared and purified as described.[83] Air and moisture sensitive materials were manipulated under argon or nitrogen using standard glove box, vacuum line, and syringe techniques.

NMR Spectroscopic Analyses. Samples for spectroscopic analyses were prepared using a sample preparation protocol described in detail elsewhere.[84] Standard ^{6}Li, ^{15}N, and ^{13}C NMR spectra were recorded on a Varian XL-400 spectrometer operating at 58.84, 40.52, and 100.58 MHz (respectively) or on a Varian Unity 500 spectrometer operating at 73.57, 58.84, and 125.76 MHz (respectively). The ^{6}Li, ^{15}N, and ^{13}C resonances are referenced to 0.3 M [^{6}Li]LiCl/MeOH at −100 °C (0.0 ppm), neat Me_2NEt at −100 °C (25.7 ppm), and the toluene methyl resonance at −100 °C (20.4 ppm), respectively. The ^{6}Li−^{15}N HMQC spectra[21] were recorded on the Varian Unity 500 spectrometer equipped with a custom-built 3-channel probe designed to accommodate lithium and nitrogen pulses with concurrent proton decoupling. The ^{6}Li-detected ^{15}N zero-quantum NMR spectra were recorded using the same spectrometer configuration as for the ^{6}Li−^{15}N HMQC experiments with a pulse sequence described previously.[19]

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Supporting Information Available: NMR spectra (29 pages). See any current masthead page for ordering and Internet access instructions.

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