# Lithium Diisopropylamide Solvated by Monodentate and Bidentate Ligands: Solution Structures and Ligand Binding Constants

**Julius F. Remenar, Brett L. Lucht, and David B. Collum***

*Contribution from the Department of Chemistry, Baker Laboratory, Cornell University, Ithaca, New York 14853-1301*

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**Abstract:** $^{6}$Li and $^{15}$N NMR spectroscopic studies of lithium diisopropylamide ([$^{6}$Li]LDA and [$^{6}$Li,$^{15}$N]LDA) in toluene/pentane solutions containing a variety of mono- and polydentate ligands are reported. LDA forms exclusively dimers in the presence of *n*-BuOMe, $Et_2O$, *t*-BuOMe, THF, 2-methyltetrahydrofuran, 2,2-dimethyltetrahydrofuran, tetrahydropyran, dimethoxyethane, *N*,*N*,*N*′,*N*′-tetramethylethylenediamine, and $MeOCH_2CH_2NR_2$ ($NR_2$ = $NMe_2$, $NEt_2$, pyrrolidino). Addition of 1,2-dipyrrolidinoethane and (2-pyrrolidinoethyl)dimethylamine provides monomer−dimer mixtures. Treatment of LDA with *trans*-*N*,*N*,*N*′,*N*′-tetramethylcyclohexanediamine (TMCDA) or *trans*-1-(dimethylamino)-2-isopropoxycyclohexane in hydrocarbons afford exclusively monomers. Sparteine binds only reluctantly, giving a mixture of unsolvated oligomers and monomer. Competitions of the ethereal ligands vs TMCDA afford binding constants and associated free energies for dimer solvation which are correlated with those obtained previously for lithium hexamethyldisilazide.

## Introduction

Despite the importance of organolithium reagents in organic chemistry,[1] our understanding of precisely how ligand structure affects lithium ion coordination is still limited.[2] Ligand-dependent reactivities, selectivities, and other empirical observations are often suggested to reflect ligand binding constants without adequate justification. We submit that an understanding of reactivities requires a knowledge of (1) the reactant structures and stabilities, (2) the aggregation and solvation events leading up to the rate limiting transition structure, and (3) the influence of organolithium reagent, solvent, and substrate on the stabilities of the transition structures. Computational studies of the possible transition structures become more important once structure and rate studies establish the transition structure stoichiometry.

We describe a two-part investigation of lithium diisopropylamide (LDA).[3] In this paper we will present NMR spectroscopic investigations of LDA in the presence of a variety of monodentate and bidentate ligands.[4−7] While ethereal ligands provide dimeric LDA, several diamines afford the first examples of monomeric LDA. We will show how a strongly coordinating diamine—*trans*-*N*,*N*,*N*′,*N*′-tetramethyl-1,2-cyclohexanediamine—can be used to determine the relative binding constants of the ethereal ligands on the LDA dimer fragment. This investigation of mono- and polydentate ligands is a logical extension of previous investigations of lithium amide solvation and aggregation. It also provides important structural and thermochemical foundations for detailed rate studies of LDA-mediated dehydrohalogenations described in the second portion of the study.[8]

[⊗] Abstract published in *Advance ACS Abstracts,* May 1, 1997.

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S0002-7863(97)00029-2 CCC: $14.00 

**Chart 1**

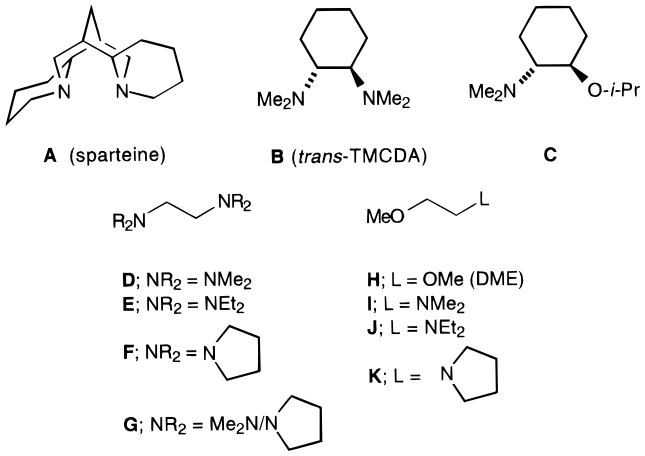



**Table 1.** $^{6}$Li and $^{15}$N NMR Spectroscopic Data[a]

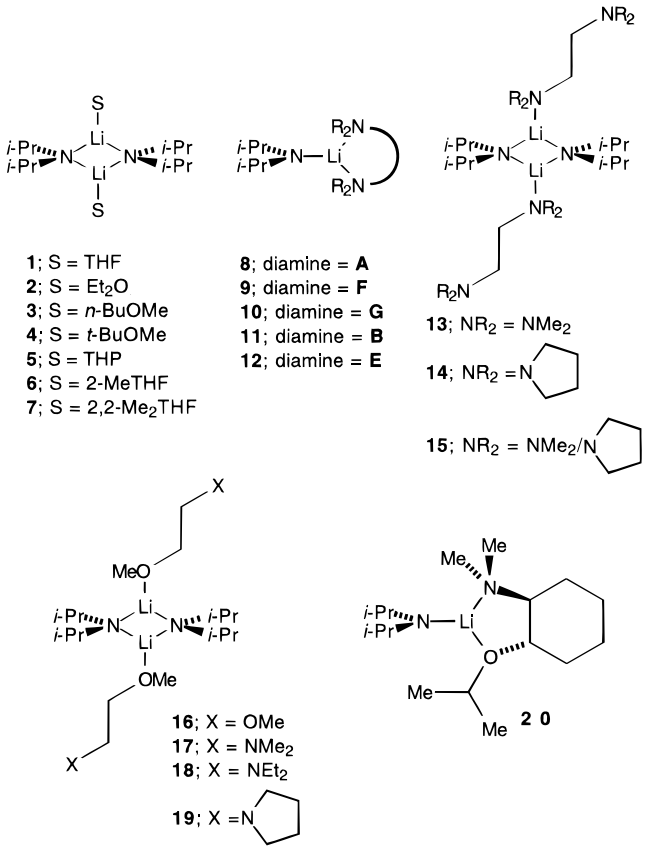
| compd | $\delta$ $^{6}$Li (mult)[b] | $\delta$ $^{15}$N (mult)[b] | $J_{Li-N}$ (Hz) |
|---|---|---|---|
| 1 | 1.98 (t) | 74.6 (q) | 5.1 |
| 2 | 1.88 (t) | 73.2 (q) | 5.1 |
| 3 | 1.84 (t) | 74.0 (q) | 5.2 |
| 4 | 1.51 (t) | 69.1 (q) | 5.2 |
| 5 | 1.89 (t) | 74.2 (q) | 5.1 |
| 6 | 1.93 (t) | 73.9 (q) | 5.0 |
| 7 | 1.76 (t) | 72.1 (q) | 5.1 |
| 8 | 1.62 (d) | 93.7 (t) | 9.7 |
| 9 | 1.35 (d) | 94.3 (t) | 10.1 |
| 10 | 1.49 (d) | 95.1 (t) | 9.9 |
| 11 | 1.66 (d) | 96.3 (t) | 10.1 |
| 12 | 1.47 (d)[c] | 92.1 (t)[c] | 9.6[c] |
| 13 | 2.03 (t) | 73.4 (q) | 4.6 |
| 14 | 1.76 (t) | 71.2[d] | 4.9 |
| 15 | 1.83 (t) | 70.9[d] | 5.0 |
| 16 | 1.54 (t) | 72.3 (q) | 5.0 |
| 17 | 1.26 (t) | 70.0 (q) | 4.3 |
| 18 | 1.77 (t) | 74.6 (q) | 5.0 |
| 19 | 1.48 (t) | 72.3 (−)[d] | 5.0 |
| 20 | 1.63 (d) | 94.2 (t) | 9.5 |

[a] Samples contain 0.10 M [$^{6}$Li,$^{15}$N]LDA in 2:1 toluene−pentane solution with variable (2−20 equiv) amounts of ligand at −90 °C. [b] Chemical shifts are reported in ppm relative to 0.3 M $^{6}$LiCl/MeOH at −100 °C (0.0 ppm) and neat $Me_2NEt$ (25.7 ppm). All *J* values are reported in hertz. Multiplicities are listed as d = doublet, t = triplet, q = quartet, and br m = broad multiplet. [c] Spectra recorded in neat TMEDA at −55 °C as described previously.[4a] [d] The small $^{15}$N resonance could only be observed with $^{6}$Li broad-band decoupling.

## Results

Mixtures of LDA and potentially chelating ligands (Chart 1)[9,10] were studied with use of variable-temperature $^{6}$Li and $^{15}$N NMR spectroscopy.[7c] The spectra were recorded on 0.1 M solutions of [$^{6}$Li,$^{15}$N]LDA[4b,f] with 2:1 toluene−pentane mixtures. The Li−N connectivities stem directly from the spin 1 $^{6}$Li and spin $^{1}/_{2}$ $^{15}$N coupling patterns (Table 1). Figure 1 includes $^{6}$Li and $^{15}$N NMR spectra displaying representative multiplets. All other spectra are located in Supporting Information. The experimental protocols are similar to those described in greater detail elsewhere.[11]

**LDA Solution Structures.** Addition of 1.0 equiv of THF, $Et_2O$, *n*-BuOMe, *t*-BuOMe, THP, 2-MeTHF, and 2,2-$Me_2$THF to 0.1 M solutions of [$^{6}$Li,$^{15}$N]LDA in 2:1 toluene−pentane affords exclusively dimers **1**−**7**. NMR spectra display $^{6}$Li triplets and $^{15}$N quintets characteristic of cyclic dimers (Table 1).[7c] Although free and bound ethereal ligands could not be observed in the slow exchange limit down to −125 °C,[12] compelling spectroscopic,[10] kinetic,[4a,d,6c] and computational[4a,c,6a,6d] evidence indicates that the dimers are disolvated.




Hydrocarbon solutions of [$^{6}$Li,$^{15}$N]LDA containing chelating diamines and related polydentate ligands (Chart 1)[9] form a variety of structures depending upon the choice of ligand. TMEDA (**D**) had been shown previously to afford exclusively disolvated dimer **13**.[4a] Sparteine (**A**) displays a reluctance to solvate LDA, affording LDA monomer **8** along with substantial concentrations of unsolvated oligomers characterized previously.[4b] Monomer **8** becomes the sole observable form only upon addition of >10 equiv of sparteine. Treatment of [$^{6}$Li,$^{15}$N]LDA in 2:1 toluene−pentane at −125 °C with 2.0 equiv of dipyrrolidinoethane (**F**) affords a mixture of dimer **14** and monomer **9** (1:5) along with low concentrations of unsolvated oligomers. Similarly, ethylenediamine **G** containing a dimethylamino and a pyrrolidino group affords dimer **15** and monomer **10** (25:1). In each case, increasing the ligand concentration does *not* change the monomer−dimer proportions, consistent with equivalent per-lithium solvation numbers. *N*,*N*,*N*′,*N*′-Tetraethylethylenediamine (**E**) is the poorest ligand; treatment of LDA with 5 equiv of **E** affords approximately 30% monomer **12** and 70% unsolvated LDA.

We investigated DME (**H**) and related amino ethers **I**, **J**, and **K**, several of which will assume a central role in the following paper. Treating [$^{6}$Li,$^{15}$N]LDA with 2.0 equiv of **H**, **I**, **J**, or **K**

(8) Remenar, J. F.; Collum, D. B. *J. Am. Chem. Soc.* **1997**, *119*, 5573.
(9) For extensive bibliographies to each of the ligands depicted in Chart 1, see ref 10a.
(10) (a) Lucht, B. L.; Bernstein, M. P.; Remenar, J. F.; Collum, D. B. *J. Am. Chem. Soc.* **1996**, *118*, 10707. (b) Lucht, B. L.; Collum, D. B. *J. Am. Chem. Soc.* **1996**, *118*, 2217. (c) Lucht, B. L.; Collum, D. B. *J. Am. Chem. Soc.* **1995**, *117*, 9863. (d) Lucht, B. L.; Collum, D. B. *J. Am. Chem. Soc.* **1994**, *116*, 6009.
(11) Hall, P.; Gilchrist, J. H.; Harrison, A. T.; Fuller, D. J.; Collum, D. B. *J. Am. Chem. Soc.* **1991**, *113*, 9575.
(12) Addition of <1.0 equiv of ethers per lithium affords a complex series of partially solvated oligomers in the slow exchange limit. Remenar, J. F. Unpublished.

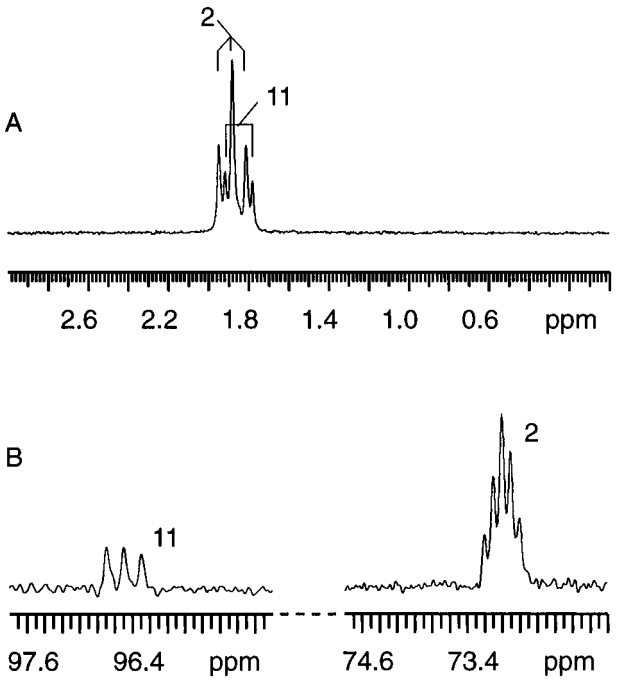



**Figure 1.** Representative $^{6}$Li and $^{15}$N NMR spectra (A and B, respectively) showing coupling of spin 1 $^{6}$Li and spin $^{1}/_{2}$ $^{15}$N. The spectra were recorded on a sample containing 0.10 M [$^{6}$Li,$^{15}$N]LDA in 2:1 toluene−pentane with 2 equiv of TMCDA and 20 equiv of $Et_2O$ at −90 °C.

affords exclusively disolvated dimers **16**−**19** (respectively). The assignments as $\eta^1$ (non-chelated), oxygen-coordinated ligands are based on previous investigations of LiHMDS[10] as well as the binding constant determinations described below. The preference for oxygen rather than nitrogen coordination results from the substantial steric demands of the trialkylamino groups.[4a,6a,10b,13,14] Amino ether **C** affords exclusively monomer **20**.[15] We note parenthetically that the ligands of **16**−**19** cause high exchange rates when compared to simple monodentate ligands as evidenced by the low probe temperatures required to observe $^{6}$Li−$^{15}$N coupling.

**Relative Ethereal Ligand Binding Constants.** The task of determining ethereal ligand binding constants is notoriously difficult.[16] For example, we could not observe free and LDA-bound ethereal ligands in the slow exchange limit, precluding direct methods. Instead, we employed a protocol for measuring

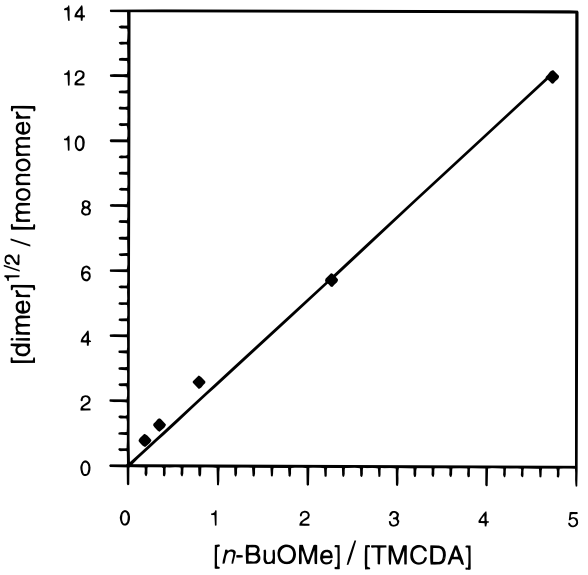
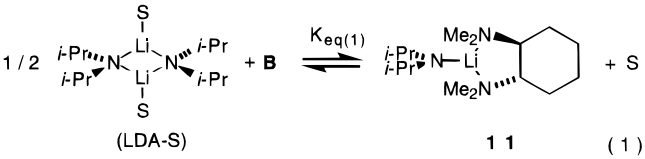



**Figure 2.** Representative plot used to determine the relative binding contant, $K_{eq}$, of ethereal ligands to the LDA dimer. The function represents a linear least-squares fit to eq 2.

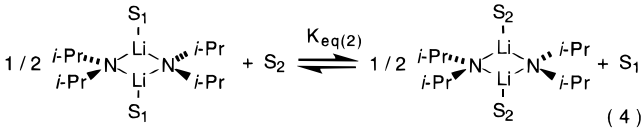
relative binding through competition of ethereal ligands with *trans*-TMCDA, **B** (eqs 1 and 2).[10] Defining $K_{eq(2)}$ according to




(1)

$$[\text{LDA-S}]^{1/2}/[\mathbf{11}] = [\text{S}]/\{K_{eq(1)}[\mathbf{B}]\} \quad (2)$$

$$K_{eq(2)} = (K_{eq(1)} \text{ for } S_1)/(K_{eq(1)} \text{ for } S_2) \quad (3)$$




(4)

$$K_{eq(2)} = \{[\text{LDA-S}_2]^{1/2}[S_1]\}/\{[\text{LDA-S}_1]^{1/2}[S_2]\} \quad (5)$$

eq 3, the relative dimer solvation energies (eqs 4 and 5) can be calculated. A plot of [LDA-S]$^{1/2}$/[**11**] vs [S]/[**B**] affords a line of slope $1/K_{eq(1)}$; an example is shown in Figure 2. The binding constants for ethereal solvation of the dimers and affiliated free energies are compiled in Table 2.[17,18] Despite concerns that mixed solvated monomers[19] containing both ether and diamine ligands might skew the results, previous investigations of LiHMDS showed that the relative binding free energies

(13) For a discussion of steric effects of amines in the context of transition metal ligation see: Seligson, A. L.; Trogler, W. C. *J. Am. Chem. Soc.* **1991**, *113*, 2520. Choi, M.-G.; Brown, T. L. *Inorg. Chem.* **1993**, *32*, 1548. Widenhoefer, R. A.; Buchwald, S. L. *Organometallics* **1996**, *15*, 3534.

(14) For early studies revealing poor coordination of trialkylamines to organolithium aggregates, see: 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.

(15) The methoxy analog of ligand **C** appears to be base labile, affording mixtures of some form of mixed dimer manifesting a $^{6}$Li doublet with a small (4.6 Hz), dimer-like coupling constant along with cyclic dimer to the exclusion of monomer.

(16) Lewis, H. L.; Brown, T. L. *J. Am. Chem. Soc.* **1970**, *92*, 4664. Sergutin, V. M.; Zgonnik, V. N.; Kalninsh, K. K. *J. Organomet. Chem.* **1979**, *170*, 151. Quirk, R. P.; Kester, D. E. *J. Organomet. Chem.* **1977**, *127*, 111. Xu, W. Y.; Smid, J. *J. Am. Chem. Soc.* **1984**, *106*, 3790. Chan, L.-L.; Wong, K. H.; Smid, J. *J. Am. Chem. Soc.* **1970**, *92*, 1955. Chan, L.-L.; Smid, J. *J. Am. Chem. Soc.* **1967**, *89*, 4547. Smetana, A. J.; Popov, A. I. *J. Solution Chem.* **1980**, *9*, 183. Gerhard, A.; Cobranchi, D. P.; Garland, B. A.; Highley, A. M.; Huang, Y.-H.; Konya, G.; Zahl, A.; van Eldik, R.; Petrucci, S.; Eyring, E. M. *J. Phys. Chem.* **1994**, *98*, 7923. Spencer, J. N.; Mihalick, J. E.; Nicholson, T. J.; Cortina, P. A.; Rinehimer, J. L.; Smith, J. E.; Ke, X.; He, Q.; Daniels, S. E. *J. Phys. Chem.* **1993**, *97*, 10509. Also, see ref 3.

(17) Whereas a 1:2 toluene−pentane mixture affords a 6:1 mixture of dimer **14** and monomer **9**, a 2:1 toluene−pentane mixture affords a 2:1 mixture of **14** and **9**. A similar hydrocarbon dependence of the LiHMDS monomer−dimer equilibrium in the presence of monodentate trialkylamines[10b] and chelating amines[10a] was traced to the stabilization of the *disolvated* monomer by toluene.[18]

(18) Wu, S.; Lee, S.; Beak, P. *J. Am. Chem. Soc.* **1996**, *118*, 715. Dougherty, D. A. *Science* **1996**, *271*, 163. Mills, N. S.; Ruud, C. C. *J. Chem. Soc., Perkin Trans. 2* **1996**, 2035. Pitchumani, K.; Ramamurthy, V. *Tetrahedron Lett.* **1996**, *37*, 5297. For leading references to $^{+}$Li−arene solvates, see: Siemeling, U.; Redecker, T.; Neumann, B.; Stammler, H.-G. *J. Am. Chem. Soc.* **1994**, *116*, 5507.

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

**Table 2.** Binding Constants and Affiliated Free Energies for LDA Dimer Solvation by Ethereal Ligands

| ligand | $K_{eq(1)}$[a] | $K_{eq(2)}$[b] | $\Delta G°$ (kcal/mol)[c] |
|---|---|---|---|
| THF | 0.012 | 1.0 | 0.0 |
| THP | 0.016 | 1.3 | 0.11 |
| 2-MeTHF | 0.045 | 3.8 | 0.52 |
| **I** | 0.124 | 10 | 0.90 |
| **H** (DME) | 0.163 | 14 | 1.0 |
| 2,2-$Me_2$THF | 0.224 | 19 | 1.1 |
| **K** | 0.3 | 25 | 1.2 |
| **J** | 0.34 | 28 | 1.3 |
| *n*-BuOMe | 0.39 | 33 | 1.3 |
| $Et_2O$ | 2.17 | 180 | 2.0 |
| *t*-BuOMe | 2.53 | 210 | 2.0 |

[a] Equilibrium constants were calculated from $^6$Li NMR integrations from samples containing 0.10 M [$^6$Li]LDA in 2:1 toluene−pentane and 2−20 equiv each of ethereal ligands and TMCDA (**B**) at −80 °C ($\sigma \approx +10\%$). The values of $K_{eq(1)}$ were calculated according to eqs 1 and 2 with an estimated $\sigma$ of +10%. [b] The values of $K_{eq(2)}$ were calculated according to eqs 4 and 5 with an estimated $\sigma$ of + 10% and are normalized relative to THF. [c] The values of $\Delta G°$ were calculated from $K_{eq(2)}$ and are reported on a per-*lithium* basis. The positive values of $\Delta G°$ indicate that THF is the most strongly coordinated ethereal ligand.

determined by this method concur with those determined by direct competition.[10] Moreover, increasing the ethereal solvent concentrations shifts the equilibrium toward the dimer, consistent with an ethereal solvation of the dimer but not the monomer.

During structural investigations of LDA in diamine/ether mixtures, we noted an unusual temperature dependence in which the ether-solvated dimers are favored at low temperature while the TMCDA-solvated monomer (**11**) is favored at higher temperature. Thus, monomer **11** is entropically favored while the ether-solvated dimers are enthalpically favored. This sharply contrasts with aggregate equilibria in ethers alone, in which the lower aggregates are enthalpically favored and the higher aggregates are entropically favored.[20] We believe that the difference stems from the relatively low solvation numbers of chelated monomers. In ethereal solvents, deaggregation is disfavored by the large negative translational entropy accompanying the coordination of additional solvents, yet is enthalpically favored by the additional lithium−solvent contacts. In the diamine-chelated, three-coordinate monomer **11**, the low ligand/Li ratio eliminates the adverse translational entropy *and* attenuates the solvation enthalpy.

## Discussion

Qualitative studies of LDA solvated by an assortment of diamines reveal solvent-dependent mixtures of dimers, monomers, and unsolvated oligomers (Table 1). The variable aggregation states precluded systematic investigations of monomer solvation energies.[10] We did note, however, an 11-fold greater monomer affinity of *trans-N,N,N′,N′*-tetramethylcyclohexanediamine (TMCDA, **B**) than dipyrrolidinoethane (**F**). Other comparisons lead to a qualitative sense of monomer binding affinities. For example, sparteine (**A**) affords low concentrations of monomer **8** along with substantial concentrations of unsolvated oligomers, suggesting that sparteine is a poor monomer ligand relative to **B** and **F**. Similar investigations of LiHMDS,[10] LiTMP,[21] and phenyllithium[22] suggest that sparteine complexation is highly sensitive to steric congestion.

**Origins of Deaggregation.** The previous discussion lacks any connotation that formation of solvated monomer relative to *solvated* dimer is indicative of the monomer−ligand interaction energy. One might be tempted, for example, to infer from the formation of predominantly monomer by dipyrrolidinoethane (**F**) and dimer by TMEDA[4a] that dipyrrolidinoethane is a better monomer ligand. However, sparteine is an even weaker monomer ligand than **F** as evidenced by the *substantial* concentrations required to consume the unsolvated LDA oligomers. Yet sparteine affords monomer **11** rather than dimer as the sole observable solvated form.

A complete description of solvent-dependent deaggregation *must* include the influence of solvent on both the monomer *and* dimer stabilities.[23] Deaggregation of LDA (or any organolithium aggregate) will be maximized for those ligands that coordinate strongly to the LDA monomer and coordinate weakly (or not at all) to the dimer. Thus, sparteine affords monomer rather than dimer due, at least in part, to its complete failure to stabilize the dimer. Similarly, the failures of DME (**H**) and bidentate amino ethers **I**, **J**, and **K** to deaggregate LDA result as much from the relatively strong dimer solvation by the unhindered $\eta^1$ methoxy groups as from the weak monomer chelation by the amino ether chelate.[24] This point is further underscored by amino ether **C** bearing a hindered isopropoxy group. While ligand **C** affords exclusively monomer **20**, the corresponding methoxy analog affords solvated dimer (and some decomposition), yet *no detectable monomer*.[15] Since it is unlikely that the isopropoxy group is intrinsically monomer stabilizing when compared to a methoxy group, the isopropoxy moiety must disproportionately destabilize the dimer.

**Ethereal Solvation of LDA Dimers: Relative Binding Constants.** Any effort to understand solvation effects within organolithium chemistry must address solvation effects in the organolithium reactant *and* transition structure. However, quantitative determinations of lithium ion solvation energies are notoriously elusive.[16] In the rare instance where free and bound solvent can be observed in the slow exchange limit, the relative binding energies can be obtained by direct competition of the ligands. Such a method afforded relative binding energies of a wide range of ethereal solvents on LiHMDS dimers and chelating amines on LiHMDS monomers.[10c] However, the solvent exchanges on solvated LDA dimers are too fast.[12] Accordingly, we turned to the less direct method. By comparing ethereal solvation of the LDA dimers with TMCDA solvation of the monomer (eqs 1 and 2), the relative ethereal solvation energies can be determined (eqs 3−5). *This method does not rely upon slow ligand exchange on NMR time scales*; simple integration of the monomer−dimer proportions (along with the free ligand concentrations) affords the relative ether binding constants. Inspection of the results summarized in Table 2 reveals the expected decrease in solvation energy with increasing steric demand. Furthermore, dimers **16**−**19** show binding energies that are comparable to that of *n*-BuOMe, reinforcing the assignment of **16**−**19** as methoxy-bound, non-chelated forms. This conclusion will assume an added importance in LDA-mediated dehydrobrominations described in the following paper.

We can now take an important first step toward addressing a persistent and fundamental question: Do lithium−solvent interaction energies correlate for different organolithiums? A plot of ether binding energies for LDA and LiHMDS determined previously is shown in Figure 3. In general, there appears to

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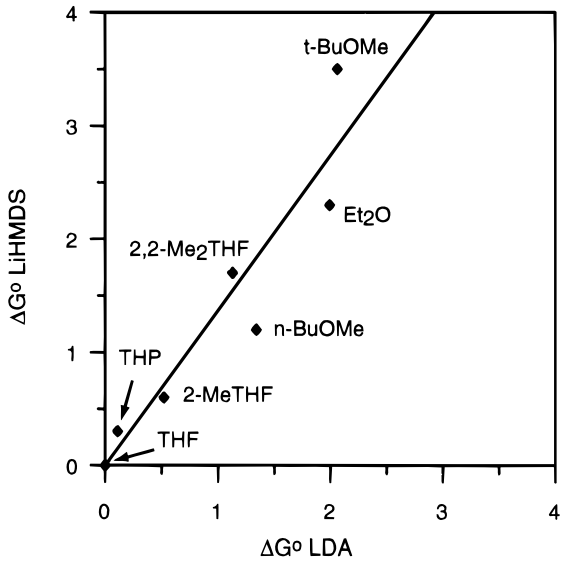


**Figure 3.** Plot of relative free energies of solvation for LDA dimer vs LiHMDS dimer (determined previously).[10a] The values of $\Delta G°$ were calculated relative to THF (in kcal/mol).

be a modest correlation.[25] Binding to LiHMDS is generally more sterically demanding; however, it is difficult to fully assess the error deriving from distinctly different methods carried out by different experimentalists.

## Summary and Conclusions

We have shown for the first time that LDA can be deaggregated by a select group of polyamines. The qualitative investigations of ligand-dependent aggregation further illustrate that both aggregate and monomer solvation are important determinants.[23] Quantitative studies of dimer solvation by monodentate ethereal ligands as well as $\eta^1$-oxygen-bound amino ethers provide basic information about lithium amide dimer solvation. The dimer solvation energies will prove generally important as we attempt to unravel the complex relationships of solvation, aggregation, and reactivity of lithium amides. Of more immediate consequence, dimers **3**, **16**, **17**, **18**, and **19** are related by nearly thermoneutral ligand substitution. The firmly established reactant stabilities will allow us to explore how chelation stabilizes the transition structures for LDA-mediated dehydrohalogenations. These studies are described in the following paper.

## Experimental Section

**Reagents and Solvents.** All monodentate ethers, ligands, and hydrocarbons were distilled by vacuum transfer from blue or purple solutions containing sodium benzophenone ketyl. The hydrocarbon stills contained 1% tetraglyme to dissolve the ketyl. Ligands **A**, **D**, and **H** are available from Aldrich. Ligands **B**, **C**, **E**, **F**, **G**, **I**, **J**, and **K** were prepared as described below.[9,10a] $^6$Li metal (95.5% enriched) was obtained from Oak Ridge National Laboratory. The [$^6$Li]ethyllithium used to prepare the [$^6$Li]LDA was prepared and purified by the standard literature procedure.[4b] [$^6$Li,$^{15}$N]LDA was prepared and isolated as an analytically pure solid as described previously.[4b,f] The diphenylacetic acid used to check solution titers[26] was recrystallized from methanol and sublimed at 120 °C under full vacuum. Air- and moisture-sensitive materials were manipulated under argon or nitrogen with use of standard glovebox, vacuum line, and syringe techniques.

**NMR Spectroscopic Analyses.** Samples for spectroscopic analyses were prepared and sealed *in vacuo* following a sample preparation protocol described in detail elsewhere.[11] Standard $^6$Li, $^{15}$N, and $^{13}$C NMR spectra were recorded 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.

***N,N,N′N′*-Tetramethyl-*trans*-1,2-cyclohexanediamine (TMCDA, B).** TMCDA was prepared from commercially available *trans*-1,2-cyclohexanediamine with use of the Eschweiler-Clark methylation of amines as follows: *trans*-1,2-Cyclohexanediamine (100 mL, 0.82 mol) was cooled to 0 °C in a 2-L round-bottom flask containing a stir bar. Following dropwise addition of 88% aqueous formic acid (300 mL, 5.8 mol, 1.7 equiv), 37% aqueous formaldehyde (360 mL, 4.4 mol, 1.4 equiv) was added. Gradual heating to 60 °C initiates rapid gas evolution. The reaction was allowed to proceed without further heating until gas evolution subsided and was then heated to 80 °C for 24 h. The reaction mixture was cooled, acidified with 20% aqueous HCl, and extracted three times with 100-mL portions of ether. The aqueous layer was stirred in a salt/ice bath and brought to pH 12 by dropwise addition of 40% aqueous NaOH without allowing the internal temperature to exceed 25 °C. Following separation of the resulting amine/aqueous layers, the aqueous layer was further extracted three times with 100-mL portions of ether. The combined organic layers were dried over KOH pellets with stirring. Fractional distillation under aspirator vacuum provided TMCDA >98% pure by GC. Further purification was achieved by forming the bis-HCl salt from aqueous HCl, drying under full vacuum, and recrystallizing from methanol/water mixtures. The free base was liberated by distillation from KOH pellets. Further drying was effected by adding additional KOH pellets (typically 5−10% by weight). Two layers sometimes form if the amine is particularly wet. The amine is decanted and distilled from Na/benzophenone (bp 85−87 °C) to provide 80 g (47% yield) of TMCDA >99.9% pure by GC. $^1$H NMR ($CDCl_3$) $\delta$ 1.11 (br m, 4H), 1.74 (br m, 2H), 1.84 (br m, 2H), 2.27 (s, 12H), 2.38 (br m, 2H). $^{13}C\{^1H\}$ NMR ($CDCl_3$) $\delta$ 21.7, 24.5, 38.9, 62.7.

***trans*-*N,N*-Dimethyl-2-isopropoxycyclohexylamine (C).** To a 500-mL round-bottom flask fitted with a dry ice condenser was added cyclohexene oxide (100 mL, 1.0 mol) and 40% aqueous dimethylamine (200 mL, 1.6 mol). The mixture was refluxed with stirring for 5 h. Cooling afforded two distinct layers. Separation of the layers and fractional distillation of the organic layer under aspirator pressure (bp 78−80 °C) provided 110 g (77% yield) of *trans*-2-(*N,N*-dimethylamino)cyclohexanol, which was further dried by distillation from $CaH_2$. $^1$H NMR ($CDCl_3$) $\delta$ 1.10 (m, 1H), 1.23 (m, 3H), 1.71 (m, 1H), 1.78 (m, 2H), 2.10 (m, 1H), 2.17 (m, 1H), 2.26 (s, 6H), 3.32 (m, 1H), 3.94 (br s, 1H). $^{13}C\{^1H\}$ NMR ($CDCl_3$) $\delta$ 20.1, 23.9, 25.1, 33.0, 39.9, 69.1, 69.3. A 250-mL round-bottom flask with a magnetic stir bar was charged with *trans*-2-(*N,N*-dimethylamino)cyclohexanol (5 g, 0.035 mol) and a solution of triphenylphosphine (10.0 g, 0.038 mol) in 25-mL of dry THF. The mixture was cooled to 25 °C and a solution of $CBr_4$ (12.5 g, 0.038 mol) in 10 mL of THF was added dropwise. The precipitate (presumably the aziridinium salt) was filtered and dried under full vacuum at 60 °C for 2 h. To a solution of 1.7 g of solid in 10 mL of dry 2-propanol was added sodium metal (1.0 g, 1.2 mol). After the initial reaction had subsided, the contents were heated to reflux until all of the sodium dissolved. The solution was cooled to 0 °C, charged with 10 mL of water, acidified with aqueous 10% aqueous HCl, and extracted with three 25 mL portions of ether. The combined aqueous layers were basicified with KOH pellets and extracted with ether. The ether layer was dried over KOH pellets and the solvent removed *in vacuo*. Following addition of 10 mL of anhydrous ether, the ethereal solution was treated with calcium hydride followed by potassium hydride to scavenge any remaining alcohols. Following removal of the ether, the product was distilled under full vacuum to yield 309 mg of **C** shown to be pure by GC. $^1$H NMR ($CDCl_3$) $\delta$ 1.15 (d, $J$ = 6.2 Hz, 3H), 1.16 (d, $J$ = 6.2 Hz, 3H), 1.22 (m, 5H), 1.66 (m, 2H), 1.76 (m, 1H), 2.04 (m, 1H), 2.37 (s, 6H), 3.33 (m, 1H), 3.75 (septet, $J$ =

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6.2 Hz, 1H). $^{13}C\{^1H\}$ NMR ($CDCl_3$) $\delta$ 22.5, 23.7, 24.2, 24.7, 25.9, 31.8, 41.4, 66.9, 68.9, 76.0.

***N,N*-Dimethyl-2-methoxyethylamine (I)** was prepared by the same procedure as TMCDA (**B**) from commercially available 2-methoxyethylamine. Following the aqueous workup, the material was dried, dissolved in three times its volume of 10% 2-propanol−THF, and acidified with HCl gas. Additional 2-propanol was added at reflux as necessary to dissolve all of the salt. After crystallization and filtration, the salt was dried under full vacuum at 60 °C for 2 h to ensure complete removal of THF. Ligand **H** was liberated by vacuum transfer from KOH (40% yield). $^1H$ NMR ($CDCl_3$) $\delta$ 2.25 (s, 6H), 2.47 (t, $J = 5.6$ Hz, 2H), 3.34 (s, 3H), 3.45 (t, $J = 5.7$Hz, 2H). $^{13}C\{^1H\}$ NMR ($CDCl_3$) $\delta$ 44.5, 57.4, 57.6, 69.3.

**1-Methoxy-2-pyrrolidinoethane (K).** Ligands **F**, **G**, **J**, and **K** were prepared following very similar procedures; the preparation of **K** is representative. To a 100-mL round-bottom flask fitted with a stir bar and reflux condenser was added 2-(chloromethoxy)ethane (10.4 g, 0.11 mol), pyrrolidine (10.2 g, 0.14 mol), water (10 mL), and $K_2CO_3$ (10.0 g, 0.07 mol). After refluxing overnight, the organic layer was separated and dried over KOH pellets. Toluene (10 mL) was added and the solution was distilled, collecting fractions up to 115 °C. The product was then distilled under aspirator vacuum, dried over $CaH_2$, and redistilled. Treating the distillate in 30 mL of approximately 4:1 THF−2-propanol with gaseous HCl afforded the HCl salt as a white precipitate, which was recrystallized directly from the THF−2-propanol. The amine was liberated from the salt by treatment with excess KOH pellets and fractionally distilled at aspirator pressure (bp 53−55 °C), affording 3.6 g (25% overall yield) of pure product. $^1H$ NMR ($CDCl_3$) $\delta$ 1.78 (br m, 4H), 2.54 (br m, 4H), 2.66 (t, $J = 5.8$ Hz, 2H), 3.36 (s, 3H), 3.50 (t, $J = 5.8$ Hz, 2H). $^{13}C\{^1H\}$ NMR ($CDCl_3$) $\delta$ 22.8, 53.9, 55.1, 58.2, 71.0.

**1,2-Dipyrrolidinoethane (F)** was prepared from 1,2-dichloroethane following the procedure desribed above. Recrystallization of the HCl salt from methanol−water followed by liberation of the amine by distillation from KOH pellets (bp 120−124 °C) afforded amine **F** in 26% overall yield. $^1H$ NMR ($CDCl_3$) $\delta$ 1.77 (br m, 8H), 2.52 (br m, 8H), 2.62 (s, 4H). $^{13}C\{^1H\}$ NMR ($CDCl_3$) $\delta$ 22.7, 53.8, 54.9.

***N,N*-Dimethyl-2-pyrrolidinoethylamine (G)** was prepared from commercially available *N,N*-dimethyl-2-chloroethylamine hydrochloride and pyrrolidine. After recrystallizing the amine hydrochloride from methanol−water, amine **G** was liberated by vacuum transfer from KOH pellets in 33% overall yield. $^1H$ NMR ($CDCl_3$) $\delta$ 1.77 (br m, 4H), 2.25 (s, 6H), 2.43 (t, $J = 7.0$ Hz, 2H), 2.51 (br m, 4H), 2.57 (t, $J = 7.0$ Hz, 2H). $^{13}C\{^1H\}$ NMR ($CDCl_3$) $\delta$ 22.6, 45.1, 53.7, 58.0.

***N,N*-Diethyl-2-methoxyethylamine (J)** was prepared from $Et_2NH$ and 1,2-dichloroethane and recrystallized from THF−2-propanol. Liberation of the amine by vacuum transfer from KOH pellets afforded amine **J** in 35% overall yield. $^1H$ NMR ($CDCl_3$) $\delta$ 1.03 (t, $J = 7.4$ Hz, 6H), 2.56 (quartet, $J = 7.4$ Hz, 4H), 2.63 (t, $J = 6.2$ Hz, 2H), 3.33 (s, 3H), 3.45 (t, $J = 6.2$ Hz, 2H). $^{13}C\{^1H\}$ NMR ($CDCl_3$) $\delta$ 10.8, 46.7, 51.5, 57.8, 70.4.

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**Supporting Information Available:** $^6Li$ and $^{15}N$ NMR spectra of LDA (24 pages). See any current masthead for ordering and Internet access instructions.

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