Lithium 2,2,6,6-Tetramethylpiperidide and Lithium 2,2,4,6,6-Pentamethylpiperidide: Influence of TMEDA and Related Chelating Ligands on the Solution Structures. Characterization of Higher Cyclic Oligomers, Cyclic Dimers, Open Dimers, and Monomers

Julius F. Remenar, Brett L. Lucht, Dmitriy Kruglyak, Floyd E. Romesberg, James H. Gilchirst, and David B. Collum*

Department of Chemistry, Baker Laboratory, Cornell University, Ithaca, New York 14853-1301

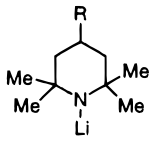
Received March 21, 1997

Spectroscopic investigations of 2,2,6,6-tetramethylpiperidide (LiTMP) and the conformationally locked (but otherwise isostructural) lithium 2,2,4,6,6-pentamethylpiperidide (LiPMP) are described. ^{6}Li and ^{15}N NMR spectroscopic studies of [^{6}Li]LiPMP and [^{6}Li,^{15}N]LiPMP in hydrocarbon solution reveal a mixture comprised of four isomeric cyclic tetramers (C_{4h}, D_{2h}, C_{2v}, and C_s) and one isomeric cyclic trimer (C_{3h}). These results are compared with the aggregation numbers and conformational preferences of lithium 2,2,6,6-tetramethylpiperidide (LiTMP) in the solid state studied by Lappert and co-workers. In the presence of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA), [^{6}Li,^{15}N]LiPMP affords monomer and open dimer to the exclusion of solvated cyclic dimer. The open dimer undergoes a degenerate intramolecular rearrangement. Spectroscopic studies in TMEDA/THF mixtures reveal an unexpected competitive solvation and implicate the observable THF-solvated cyclic dimer to possess one THF per Li. Dimethylethylamine (a monodentate analog of TMEDA) and *N*,*N*,*N*′,*N*′-tetramethylpropylenediamine (a six-membered ring chelating analog of TMEDA) are inferior as ligands for LiPMP. Investigations of LiPMP in the presence of other bidentate ligands reveal related monomers and open dimers whose proportions depend upon ligand structure and concentration. The relative binding constants and binding energies to the LiPMP monomer are reported. Ligands studied include the following: *N*,*N*,*N*′,*N*′-tetraethylethylenediamine, *N*,*N*-diethyl-*N*′,*N*′-dimethylethylenediamine, *N*,*N*′-diethyl-*N*,*N*′-dimethylethylenediamine, *N*-ethyl-*N*,*N*′,*N*′-trimethylethylenediamine, 1,2-dipyrrolidinoethane, 1,2-dipiperidinoethane, 1-(dimethylamino)-2-pyrrolidinoethane, 1-(dimethylamino)-2-methoxyethane, 1-(dimethylamino)-2-ethoxyethane, 1-azetidino-2-methoxyethane, 1-methoxy-2-pyrrolidinoethane, 1-methoxy-2-piperidinoethane, 1-ethoxy-2-pyrrolidinoethane, *trans*-*N*,*N*,*N*′,*N*′-tetramethylcyclohexanediamine, *trans*-1-(dimethylamino)-2-methoxycyclohexane, and sparteine.

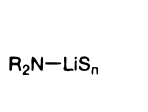
Introduction

Lithium 2,2,6,6-tetramethylpiperidide (LiTMP, **1**) plays a central role in organic chemistry as a reactive and highly selective base.[1] LiTMP also provides interesting opportunities for studying lithium salt aggregation.[2−10] In addition to a delicately balanced equilibrium of monomers and dimers (**3** and **4**, respectively),[2,3] LiTMP can form larger cyclic oligomers,[4] open dimers (**5**),[6,7] triple ions (**6**),[6] and assorted mixed aggregates with lithium halides and lithium enolates.[3,8−10]

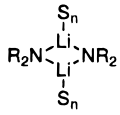
Having studied LiTMP on several occasions in the past, we were drawn back to LiTMP by two separate interests.



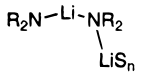
1; R = H
2; R = Me



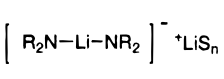
3



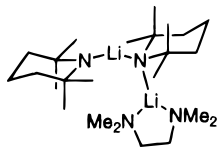
4



5



6



7

The first involves a preoccupation with how *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) and related polydentate ligands influence the structures and stabilities of lithium amide and organolithium aggregates.[11,12] The investigation of LiTMP solvated by polydentate ligands is an extension of related investigations of lithium hexamethyldisilazide (LiHMDS)[13] and lithium diisopropylamide (LDA).[14] The second, more specific, interest is to understand the stabilities and reactivities of lithium amide open dimers (**5**). Lithium amide open dimers were first invoked in 1988 by Schlosser and co-workers in the context of dehydrohalogenations by lithium diisopropylamide (LDA).[15] More recent computational,[16] spectroscopic,[6] crystallographic,[7] and kinetic studies[17] have

⊗ Abstract published in *Advance ACS Abstracts,* July 15, 1997.

(1) Hall, P. L.; Gilchrist, J. H. *J. Am. Chem. Soc.* **1991**, *113*, 9571. Fataftah, Z. A.; Kopka, I. E.; Rathke, M. W. *J. Am. Chem. Soc.* **1980**, *102*, 3959. Snieckus, V. *Chem. Rev.* **1990**, *90*, 879. Olofson, R. A.; Dougherty, C. M. *J. Am. Chem. Soc.* **1973**, *95*, 582. Fraser, R. R.; Mansour, T. S. *J. Org. Chem.* **1984**, *49*, 3442.

(2) Renaud, P.; Fox, M. A. *J. Am. Chem. Soc.* **1988**, *110*, 5702.

(3) Hall, P. L.; Gilchrist, J. H.; Harrison, A. T.; Fuller, D. J.; Collum, D. B. *J. Am. Chem. Soc.* **1991**, *113*, 9575.

(4) Lappert, M. F.; Slade, M. J.; Singh, A.; Atwood, J. L.; Rogers, R. D.; Shakir, R. *J. Am. Chem. Soc.* **1983**, *105*, 302.

(5) Lucht, B. L.; Collum, D. B. *J. Am. Chem. Soc.* **1994**, *116*, 7949.

(6) Romesberg, F. E.; Gilchrist, J. H.; Harrison, A. T.; Fuller, D. J.; Collum, D. B. *J. Am. Chem. Soc.* **1991**, *113*, 5751.

(7) Williard, P. G.; Liu, Q.-Y. *J. Am. Chem. Soc.* **1993**, *115*, 3380. For related structures see: Stalke, D.; Klingebiel, U.; Sheldrick, G. M. *J. Organomet. Chem.* **1988**, *344*, 37. Dipple, K.; Klingebiel, U.; Kottke, T.; Pauer, F.; Sheldrick, G. M.; Stalke, D. *Chem. Ber.* **1990**, *123*, 237.

(8) Henderson, K. W.; Dorigo, A. E.;Liu, Q.-Y.; Williard, P. G.; Schleyer, P. v. R.; Bernstein, P. R. *J. Am. Chem. Soc.* **1996**, *118*, 1339.

S0022-3263(97)00520-3 CCC: $14.00

shown open dimers to be observable species and important reactive intermediates.[7,16,18] Open dimers contain vacant coordination sites for substrate precomplexation and a potentially basic lone pair on nitrogen.[16] Our interests in bidentate ligands, open dimers, and LiTMP were brought into a common focus by the crystal structure determination of open dimer **7** reported by Williard and Liu.[7] The stabilization of open dimers by chelating ligands has received additional support.[16,17]

We are interested in determining the structures of LiTMP solvated by polydentate ligands. However, the failure to completely freeze out the chair−chair interconversion of the piperidine ring on NMR spectroscopic time scales ($\Delta G°_{act} = 7-9$ kcal/mol)[3] prompted us to use lithium 2,2,4,6,6-pentamethylpiperidide (LiPMP, **2**) as a surrogate for LiTMP.[3] Previous structural investigations revealed that LiPMP and LiTMP are completely interchangeable with two important exceptions: (1) LiPMP cannot undergo a chair−chair flip. The equivalent isomerization in LiPMP corresponds to a considerably less facile diastereomer interconversion requiring N−Li bond cleavage and an inversion at nitrogen (eq 1). This allows us to study and exploit the stereoisomerism well within the slow exchange limit. (2) LiPMP is substantially more hydrocarbon-soluble than LiTMP, making studies in the absence of ligands or at low ligand concentrations more feasible.

The spectroscopic studies described herein reveal LiPMP and, by inference, LiTMP in hydrocarbons to be a mixture of stereoisomers of cyclic oligomers (Chart 1, **8**−**13**) as communicated previously.[5] The primary focus of this paper is to describe the structures of LiPMP monomers and open dimers (**14A**−**R** and **15A**−**R**) coordinated by a wide variety of bidentate ligands (Chart 2). We will also provide relative energies for binding to the LiPMP monomer.

Chart 1

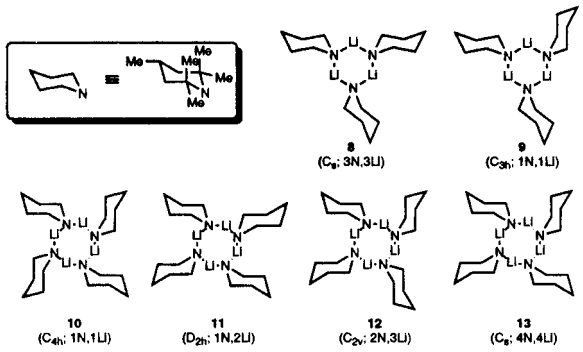
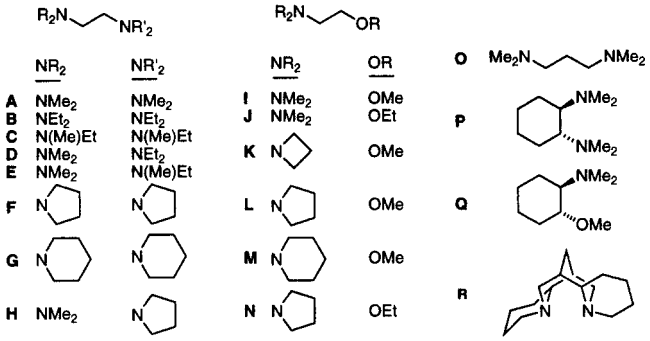
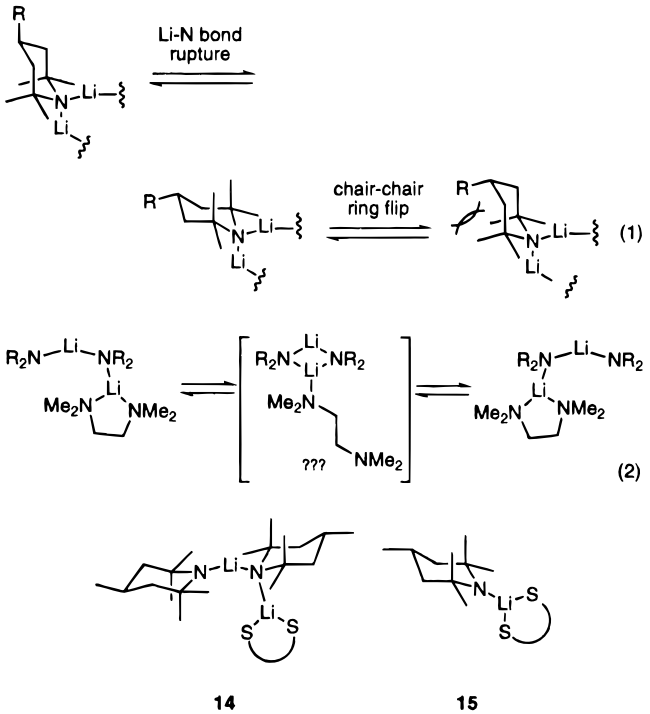


Chart 2





Results

LiTMP and LiPMP in Hydrocarbons. ^{6}Li and ^{15}N NMR spectroscopic studies of 0.10 M [^{6}Li,^{15}N]LiTMP[3] in pentane at −40 °C reveal two species (~4:1), each displaying 1:2:1 ^{6}Li triplets and 1:2:3:2:1 ^{15}N quintets characteristic of cyclic oligomers (Figure 1A,B).[10,19] The predominant form was shown by concentration depend-

(9) For other spectroscopic and mechanistic investigations of LiTMP, see: Ashby, E. C.; Park, B.; Patil, G. S.; Gadru, K.; Gurumurthy, R. *J. Org. Chem.* **1993**, *58*, 424−37. Grimm, D. T.; Bartmess, J. E. *J. Am. Chem. Soc.* **1992**, *114*, 1227. Arnett, E. M.; Moe, K. D. *J. Am. Chem. Soc.* **1991**, *113*, 7068. Xie, L.; Saunders, W. H., Jr. *J. Am. Chem. Soc.* **1991**, *113*, 3123. Miah, M. A. J.; Fraser, R. R. *J. Bangladesh Chem. Soc.* **1989** *2*, 77. Tobia, D.; Rickborn, B. *J. Org. Chem.* **1989**, *54*, 777. Podraza, K. F.; Bassfield, R. L. *J. Org. Chem.* **1988**, *53*, 2643. Kahn, J. D.; Haag, A.; Schleyer, P. v. R. *J. Phys. Chem.* **1988**, *92*, 212. Ahlbrecht, H.; Schneider, G. *Tetrahedron* **1986**, *42*, 4729. Fraser, R. R.; Mansour, T. S. *Tetrahedron Lett.* **1986**, *27*, 331. Kopka, I. E.; Fataftah, Z. A.; Rathke, M. W. *J. Org. Chem.* **1987** *52*, 448−50. Mansour, T. S.; Wong, T. C.; Kaiser, E. M. *J. Chem. Soc., Perkin Trans. 2* **1985**, 2045. Fraser, R. R.; Mansour, T. S.; Savard, S. *J. Org. Chem.* **1985**, *50*, 3232. Fraser, R. R.; Bresse, M.; Mansour, T. S. *J. Am. Chem. Soc.* **1983**, *105*, 7790. Fraser, R. R.; Baignee, A.; Bresse, M.; Hata, K. *Tetrahedron Lett.* **1982**, *23*, 4195. Tuschka, T.; Naito, K.; Rickborn, B. *J. Org. Chem.* **1983**, *48*, 70. Reich, H. J.; Willis, W. W., Jr. *J. Org. Chem.* **1980**, *45*, 5227.

(10) Reviews of lithium dialkylamides: (a) Collum, D. B. *Acc. Chem. Res.* **1992**, *25*, 227. (b) Gregory, K; Schleyer, P. v. R.; Snaith, R. *Adv. Inorg. Chem.* **1991**, *37*, 47. (c) Mulvey, R. E. *Chem. Soc. Rev.* **1991**, *20*, 167. (d) Caubere, P. In *Reviews of Heteroatom Chemistry*; MYU: Tokyo, 1991; Vol. 4, pp 78−139. Cox, P. J.; Simpkins, N. S. *Tetrahedron: Asymmetry* **1991**, *2*, 1.

(11) Collum, D. B. *Acc. Chem. Res.* **1992**, *25*, 448.

(12) For extensive leading references to the chelate effect in organolithium chemistry, see ref 11.

(13) Lucht, B. L.; Bernstein, M. P.; Remenar, J. F. *J. Am. Chem. Soc.* **1996**, *118*, 10707.

(14) Remenar, J. F.; Lucht, B. L.; Collum, D. B. *J. Am. Chem. Soc.* **1997**, *119*, 5567.

(15) Matsuda, H.; Hamatani, T.; Matsubara, S.; Schlosser, M. *Tetrahedron* **1988**, *44*, 2865.

(16) Romesberg, F. E.; Collum, D. B. *J. Am. Chem. Soc.* **1992**, *114*, 2112. Romesberg, F. E.; Collum, D. B. *J. Am. Chem. Soc.* **1994**, *116*, 9187. Romesberg, F. E.; Collum, D. B. *J. Am. Chem. Soc.* **1995**, *117*, 2166. Pratt, L. M.; Khan, I. M. *Tetrahedron: Asymmetry* **1995**, *6*, 2165. Pratt, L. M.; Hogen-Esch, T. E.; Khan, I. M. *Tetrahedron* **1995**, *51*, 5955. Koch, R.; Wiedel, Anders, E. *J. Org. Chem.* **1996**, *61*, 2523. Also see ref 7.

(17) Bernstein, M. P.; Collum, D. B. *J. Am. Chem. Soc.* **1993**, *115*, 789. Bernstein, M. P.; Collum, D. B. *J. Am. Chem. Soc.* **1993**, *115*, 8008. Remenar, J. F.; Collum, D. B. Unpublished results.

(18) Petasis, N. A.; Teets, K. A. *J. Am. Chem. Soc.* **1992**, *114*, 10328. Shimano, M.; Meyers, A. I. *J. Org. Chem.* **1996**, *61*, 5714.

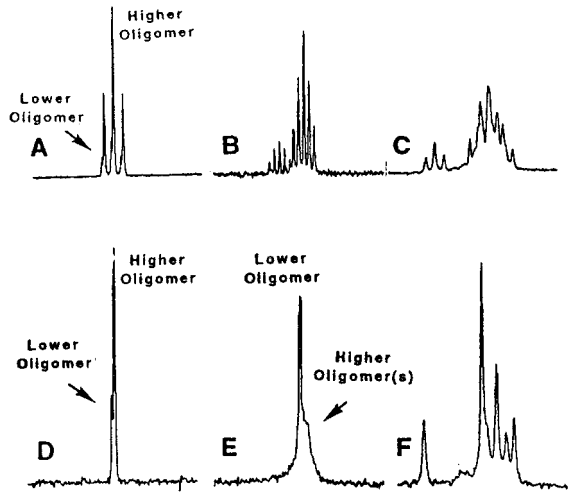


Figure 1. (A) ^{6}Li NMR spectrum of 0.10 M [^{6}Li,^{15}N]LiTMP in pentane at −40 °C; (B) ^{15}N NMR spectrum of 0.10 M [^{6}Li,^{15}N]LiTMP in pentane at −40 °C; (C) ^{6}Li NMR spectrum of 0.10 M [^{6}Li,^{15}N]LiTMP in pentane at −120 °C; (D) ^{6}Li NMR spectrum of 0.11 M [^{6}Li]LiTMP in pentane at −50 °C; (E) ^{6}Li NMR spectrum of 0.11 M [^{6}Li]LiTMP in pentane at −75 °C; (F) ^{6}Li NMR spectrum of 0.11 M [^{6}Li]LiTMP in pentane at −100 °C.

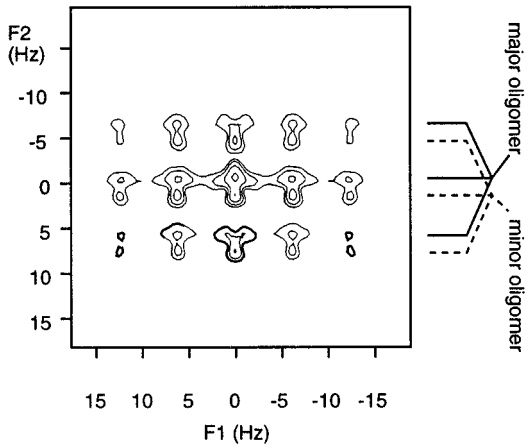


Figure 2. ^{6}Li-detected ^{15}N zero-quantum NMR spectrum of 0.05 M [^{6}Li,^{15}N]LiTMP in pentane at −50 °C. A total of 64 t_1 increments were acquired with 16 transients/increment over 150 min. Data were processed in the phase-sensitive mode. Digital resolution in f_1 prior to zero filling is 1.8 Hz.

encies to be a higher aggregate. The inverse-detected ^{15}N homonuclear zero-quantum NMR spectrum[20] recorded at −50 °C shows splitting in f_1 (Figure 2), revealing that both cyclic oligomers are larger than dimers. Neither loss of coupling resulting from *intermolecular* site exchanges nor an increase in multiplicity resulting from rapid *intramolecular* Li−Li site exchanges[21] was observed upon warming the sample to 20 °C. In fact, the exchanges were shown to be slow on laboratory time scales by mixing solutions of [^{6}Li]LiTMP and [^{6}Li,^{15}N]LiTMP. ^{6}Li doublets characteristic of ^{14}N−^{6}Li−^{15}N subunits appear

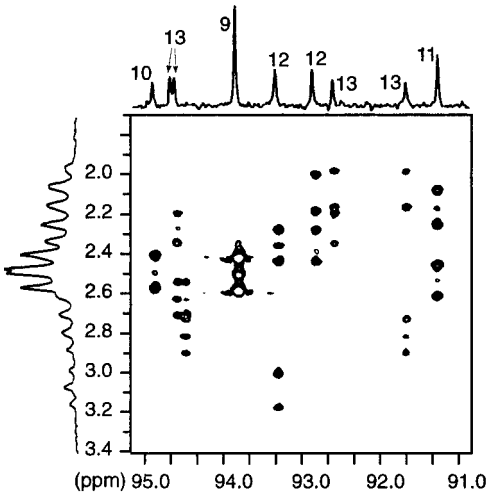


Figure 3. ^{6}Li−^{15}N HMQC spectrum of 0.1 M [^{6}Li,^{15}N]LiPMP in pentane at −100 °C. A total of 256 t_1 increments were acquired with 32 transients/increment over 480 min. The left-hand and upper traces are the corresponding one-dimensional ^{6}Li and ^{15}N{^{1}H,^{6}Li}NMR spectra, respectively. The spectrum was recorded on a Varian Unity 500 spectrometer equipped with a custom-built three-channel probe designed to accommodate lithium and nitrogen pulses with concurrent proton decoupling. The spectrometer operates at 73.56 and 50.65 MHz for ^{6}Li and ^{15}N (respectively). Data were processed in the phase-sensitive mode. Digital resolution in f_1 prior to zero filling is 2.0 Hz.

only upon *heating to 70 °C*. Upon decreasing the probe temperature to −120 °C, the ^{6}Li resonance corresponding to the larger of the two oligomers of [^{6}Li,^{15}N]LiPMP resolves into a number of overlapping ^{6}Li triplets (Figure 1C), consistent with the appearance of several (but not necessarily all) chair−chair conformers in slow exchange. In contrast, the ^{6}Li resonance corresponding to the smaller of the two cyclic oligomers remains sharp over the entire temperature range (Figure 1D−F), suggestive of a single, symmetric conformer.

Since the ^{15}N zero-quantum NMR spectrum of LiTMP recorded under conditions of rapid conformer exchange showed that neither of the two cyclic oligomers are dimers, we suspected that the two aggregation states correspond to cyclic trimers and tetramers. If so, there are six possible chemically distinct solution structures (**8**−**13**; methyls are omitted for clarity). However, since it was not clear whether the slow exchange limit had been fully attained, we turned to [^{6}Li,^{15}N]LiPMP. The ^{6}Li and ^{15}N NMR spectra of [^{6}Li,^{15}N]LiPMP in pentane show complex patterns up to ≥70 °C. The isomers were assigned from a ^{6}Li−^{15}N heteronuclear multiple quantum correlation (HMQC) spectrum of [^{6}Li,^{15}N]LiPMP (Figure 3).[22] The center lines of the triplets correspond to nonselected orders of coherence and are almost entirely canceled by the phase cycle. The number of ^{6}Li and ^{15}N resonances and the resonance correlations allow us to assign the structures depicted in Chart 1 (Table 1). The four tetramers are in nearly equal proportions *and are uniquely distinguished by the number of ^{6}Li and ^{15}N resonances*. In fact, the observation of four distinct isomers secures the tetramer assignment. The C_{4h} tetramer **10** and C_{3h} trimer **9** both display single ^{6}Li and ^{15}N resonances yet can be readily distinguished since the tetramethyl analog of **10** is related to the other three

(19) The spins of ^{6}Li and ^{15}N are 1 and 1/2, respectively: *NMR of Newly Accessible Nuclei*; Laszlo, P., Ed.; Academic Press: New York, 1983. Günther, H. *Encyclopedia of NMR*; Wiley: New York, 1996; Vol. 5, pp 2807−2828.

(20) Gilchrist, J. H.; Collum, D. B. *J. Am. Chem. Soc.* **1992**, *114*, 794.

(21) Bywater, S.; Lachance, P.; Worsfold, D. J. *J. Phys. Chem.* **1975**, *79*, 2148. Fraenkel, G.; Henrichs, M.; Hewitt, J. M.; Su, B. M.; Geckle, M. J. *J. Am. Chem. Soc.* **1980**, *102*, 3345. Thomas, R. D.; Clarke, M. T.; Jensen, R. M.; Young, T. C. *Organometallics* **1986**, *5*, 1851.

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

Table 1. ^{6}Li and ^{15}N NMR Spectroscopic Data of [^{6}Li,^{15}N]LiPMP[a]

compd	^{6}Li δ (m, J_{N-Li})	^{15}N δ (m, J_{N-Li})
9	2.74 (t, 6.2)	93.75 (quint, 6.2)
10	2.71 (t, 6.2)	95.35 (quint, 6.2)
11	2.41 (t, 6.7)	89.82 (quint, 6.3)
	2.77 (t, 6.0)	
12	2.32 (t, 7.0)	92.26 (quint, 6.6)
	2.60 (t, 6.1)	92.96 (quint, 6.3)
	3.33 (t, 6.6)	
13	2.31 (t, 7.0)	90.45 (quint, 6.4)
	2.51 (t, 5.8)	91.86 (quint, 6.0)
	2.87 (t, 6.3)	95.00 (quint, 6.3)
	3.05 (t, 6.2)	94.92 (quint, 6.6)

[a] Spectra were recorded on 0.1 M solutions of [^{6}Li,^{15}N]LiPMP in pentane at −100 °C. The chemical shifts are reported in ppm relative to 0.3 M ^{6}LiCl/MeOH at −100 °C (0.0 ppm) and [^{15}N]aniline (52 ppm). The coupling constants are reported in Hz.

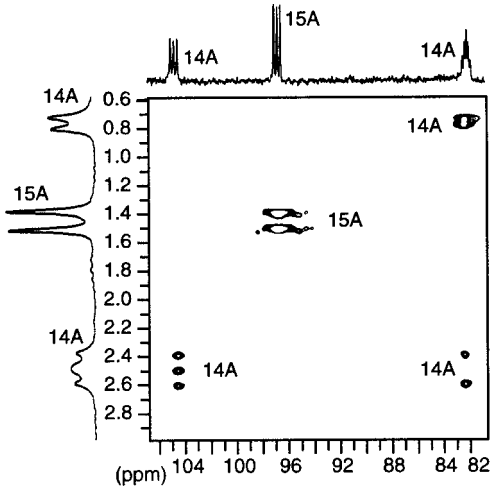


Figure 4. ^{6}Li−^{15}N HMQC NMR spectrum of a sample containing 0.10 M [^{6}Li,^{15}N]LiPMP and 0.75 equiv of TMEDA at −105 °C in 2:1 toluene:pentane. The top and left hand traces are the corresponding ^{15}N {^{1}H} and ^{6}Li NMR spectra.

tetramers by a facile conformational exchange noted for in TMP. Furthermore, **9** is at a lower aggregation state as shown by the concentration-dependent intensities but is *not* a dimer as shown by the zero-quantum NMR spectroscopic experiment noted above.[23] The C_s trimer **8** is not detectable.

LiPMP−TMEDA and Related Solvates: NMR Spectroscopy. We illustrate the results of our investigations of bidentate ligands using TMEDA (**A**). Spectra recorded at −105 °C on a 0.05 M 2:1 toluene−pentane solution of [^{6}Li,^{15}N]LiPMP containing 0.75 equiv of TMEDA reveal a mixture of open dimer **14A** and monomer **15A** to the exclusion of the unsolvated cyclic oligomers (Figure 4, Table 2). The monomer becomes the sole observable species at >10 equiv of TMEDA. A ^{6}Li doublet and ^{15}N triplet are readily ascribable to **15A**. Similarly, the $Li_a-N_b-Li_c-N_d$ connectivity of open dimer **14A** can be gleaned from the multiplicities and resonance correlations available from ^{6}Li,^{15}N-HMQC spectroscopy[22] and single frequency decouplings.[24] Li_a appears as a doublet due to coupling to N_b, while Li_c appears as a doublet-of-doublets arising from coupling to N_b and N_d. As noted previously for a structurally related bis(HMPA)-solvated open dimer,[6] the number of lithium nuclei adjoining the ^{15}N nuclei dictates the magnitude of the ^{6}Li−^{15}N coupling.[25] ^{6}Li−^{15}N coupling to the terminal nitrogen (N_d-Li_c) is large (J_{Li-N} = 9.9 Hz), whereas both couplings to the bridging nitrogen (Li_a-N_b and Li_c-N_b) are small (J_{Li-N} = 6.2 and 6.9 Hz). Upon warming the probe from −105 to −95 °C, the ^{6}Li doublet corresponding to Li_a becomes a triplet accompanied by a 50% reduction in the coupling constant (rendering it dimer-like), and the Li_c doublet-of-doublets becomes a triplet consistent with an *intramolecular* degenerate isomerization (eq 2). However, the retention of two discrete lithium resonances does not imply that the degenerate exchange fails to interconvert Li_a and Li_c; the coalescence of the Li_a and Li_c resonances is expected to occur at substantially higher temperatures than the coupling changes due to the substantial frequency separation.

Assignment of **14A** and **15A** as chelates is based on comparisons of TMEDA with dimethylethylamine (Me_2NEt; DMEA)—an isostructural trialkylamine lacking the capacity to chelate.[26] In stark contrast to TMEDA, DMEA shows a marked resistance to ligate LiPMP; unsolvated LiPMP oligomers and the DMEA-solvated monomer[27] are observable in *neat* DMEA.[28]

We investigated a number of diamines and related amino ethers (Chart 2) structurally related to TMEDA to gain further insight into the factors influencing metal−ligand interactions in general and chelate stability in particular. Addition of <1.0 equiv of ligand affords mixtures of unsolvated oligomers, open dimers, and monomers, while excess ligand promotes monomer formation (Table 3). The ^{6}Li and ^{15}N NMR spectral data for a variety of monomers and open dimers are listed in Table 2. Unfortunately, the ^{6}Li and ^{15}N resonances of the open dimers are broadened by a facile exchange process in most instances. Consequently, the ^{15}N spectra were recorded with ^{6}Li broadband decoupling, and the coupling constants are not listed. Nevertheless, we are confident in the assignments because of the highly characteristic ^{6}Li and ^{15}N chemical shifts and 1:1 peak intensities. In addition, single frequency irradiations of the ^{15}N resonances cause the appropriate ^{6}Li resonances to sharpen.

LiPMP−Diamine and Related Solvates: Relative Binding Energies. As a result of our interest in the lore surrounding TMEDA as a ligand for lithium,[11] we explored the competitive solvation of LiPMP by TMEDA in equimolar competition with THF. Spectroscopic studies of lithium hexamethyldisilazide (LiHMDS)[13] and lithium diisopropylamide (LDA)[14] led us to believe that TMEDA would *not* successfully compete with THF for coordination to LiPMP. Nonetheless, treatment of [^{6}Li,^{15}N]LiPMP with 2.0 equiv (per lithium) each of THF and TMEDA affords an approximate equimolar mixture of TMEDA-solvated monomer **15A** and the previously

(23) The ^{15}N homonuclear zero-quantum NMR spectrum is carried out using [^{6}Li,^{15}N]LiTMP in the limit of rapid conformer exchange since the spectra of [^{6}Li,^{15}N]LiPMP in the limit of slow diastereomer exchange limit are inordinately complex.

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

(25) For theoretical investigations of ^{6}Li-^{15}N coupling, see: Koizumi, T.; Morihashi, K.; Kikuchi, O. *Bull. Chem. Soc. Jpn.* **1996**, *69*, 305.

(26) Bernstein, M. P.; Romesberg, F. E.; Fuller, D. J.; Harrison, A. T.; Collum, D. B.; Liu, Q.-Y.; Williard, P. G. *J. Am. Chem. Soc.* **1992**, *114*, 5100.

(27) The traces of [^{6}Li,^{15}N]LiPMP solvated by DMEA monomer appear as a ^{6}Li doublet at 1.63 ppm ($^{1}J_{Li-N}$ = 9.3 Hz).

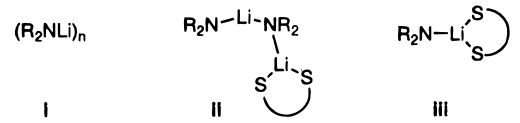
(28) We did not investigate restricted rotation about the R_2N--Li bond of LiPMP in detail. However, several unsymmetrical ligands afforded a doubling of the monomer ^{6}Li doublet consistent with two orientations. For example, 5.0 equiv of sparteine (**R**) affords a 1:1 mixture of two monomers along with approximately 80% unsolvated oligomers.

Table 2. ^{6}Li and ^{15}N Chemical Shifts of LiPMP Monomers and Open Dimers[a]

compd	^{6}Li δ (J_{Li-N})	^{15}N δ (J_{Li-N})[b]	compd	^{6}Li δ (J_{Li-N})	^{15}N δ (J_{Li-N})[b]
14A	0.87 (d, 6.2)	82.1 (t, 10.4)	**14Q**	0.75 (br d, 5.8)	81.6
	2.53 (dd, 6.9, 9.9)	104.2 (q, 6.3)		2.73 (br t, 7.2)	102.8
14C	0.74 (d, 6.2)	81.9	**15A**	1.54 (d, 9.9)	96.4 (t, 9.9)
	c	103.5	**15B**	1.29 (d, 9.6)	92.4 (t, 9.5)
14D	0.67 (d, 6.3)	82.6	**15C**	1.34 (d, 9.5)	92.5 (t, 9.9)
	c	*d*	**15D**	1.32 (d, 9.8)	95.7 (t, 9.6)
14E	0.81 (d, 5.9)	81.9	**15E**	1.46 (d, 9.8)	95.4 (t, 9.8)
	2.52 (dd, 5.3, 9.9)	104.0	**15F**	1.15 (d, 9.6)	94.8 (t, 9.7)
14H	0.71 (br d, 6.4)	81.7	**15G**	1.24 (d, 9.6)	92.1 (t, 9.6)
	2.44 (br)	102.2	**15H**	1.31 (d, 8.8)	96.2 (t, 9.1)
14I	0.62 (br)	81.4	**15I**	1.28	97.1
	2.69 (br)	103.4	**15J**	1.22 (d, 9.8)	94.8
14J	0.58 (br)	80.7	**15K**	1.56 (d, 10.2)	97.3
	2.73 (br t, 7.9)	103.7	**15L**	1.17 (d, 10.0)	96.7 (t, 9.9)
14K	0.78 (br)	81.5	**15M**	1.24 (d, 9.8)	95.8 (t, 10.0)
	2.79 (t, 7.5)	103.0	**15N**	1.03 (d, 9.8)	92.7 (t, 10.0)
14L	0.33 (br)	80.3	15O	1.60 (d, 9.9)	93.2 (t, 9.5)
	2.74 (br)	101.8	**15P**	1.59 (d, 10.0)	96.6 (t, 10.0)
14N	0.40 (d, 6.3)	80.3	**15Q**	1.51 (d, 9.8)	97.8 (t, 10.2)
	2.73 (br)	102.7	**15R**	1.58 (d, 9.8)	94.4 (t, 9.8)
14P	0.86 (d, 6.4)	82.8		1.63 (d, 9.8)	94.9 (t, 9.8)
	2.51 (dd)	102.9			

[a] Spectra were as 0.1 M solutions of [^{6}Li,^{15}N]LiPMP in 2:1 toluene:pentane at −100 °C with 0.5−5.0 equiv of added ligand. The chemical shifts are reported in ppm relative to 0.3 M ^{6}LiCl/MeOH at −100 °C (0.0 ppm) and [^{15}N]aniline (52 ppm). The coupling constants are reported in Hz. [b] For those cases in which broadening precluded observation of a multiplet, the chemical shifts are reported with ^{6}Li broadband decoupling. [c] The internal lithium of the open dimer is buried under the unsolvated oligomer resonances. [d] The multiplet was too small to be observed.

Table 3. Ratios of Unsolvated Oligomers (i), Open Dimers (ii), and Monomers (iii) for 2:1 Pentane:Toluene Solutions of LiPMP (0.1 M) at −100 °C Containing Chelating Ligand



I II III

ligand structure	ligand (equiv)	% **i**[a]	**ii**:**iii**[b]	ligand structure	ligand (equiv)	% **i**[a]	**ii**:**iii**[b]
A	0.75	<2	1:1	**J**			
	5.0	<2	1:8	**K**	0.75	<2	3:1
B	5.0	75	1:>100		1.5	<2	1:1
	20	20	1:>100	**L**	0.75	17	1:1
C	0.75	37	1:6		2.0	<2	1:>25
	2.0	14	1:25	**M**	0.75	39	1:>100
D	0.75	56	1:12		2.0	30	1:>100
	2.0	23	1:50	**N**	0.75	34	1:6
E	0.75	25	1:3		1.1	<2	1:>100
	2.0	<2	1:8	**O**	5	82	1:>100
F	0.75	25	1:>100		20	32	1:>100
	2.0	<2	1:>100	**P**	0.75	<2	1:4
G	5	78	1:>100		2.0	<2	1:>100
	20	75	1:>100	**Q**	0.75	25	1:4
H	0.75	28	1:10		2.0	<2	1:>100
	2.0	<2	1:>100				
I	0.75	<2	3:1[c]				
	1.0	<2	1.8:1				
	2.0	<2	1:>1.5[e]				

[a] Corresponds to percent of total ^{6}Li resonance integration. [b] Molar ratio. [c] Some decomposition occurs. [d] Substantial decomposition occurs. [e] Partially obscured by decomposition.

characterized THF-solvated dimer **16**.[29] Moreover, if the concentrations of TMEDA and THF are increased 5-fold while maintaining the 1:1 proportions, the ratio of **15A** and **16** remains constant, suggesting that **15A** and **16** are at equivalent per-lithium solvation numbers. One solvent per lithium (as drawn) is fully consistent with previous investigations of lithium amides.[29]

(29) Galiano-Roth, A. S.; Collum, D. B. *J. Am. Chem. Soc.* **1989**, *111*, 6772. See also: Lucht, B. L.; Collum, D. B. *J. Am. Chem. Soc.* **1995**, *117*, 9863.

Table 4. Relative Binding Constants (K_{rel}) and Free Energies ($\Delta G°_{rel}$) for Coordination of Bidentate Ligands to LiPMP Determined According to Eqs 3 and 4[a,b]

ligand	K_{rel}	$\Delta G°_{rel}$ (kcal/mol)
A	1.0[a]	0.0[a]
B	<0.05	>1.1
C	0.83	0.06
D	0.28	0.43
E	0.92	0.03
F	11	~0.84
G	<0.05	>1.1
H	2.6	−0.33
I−**K**	*c*	*c*
L	0.25	0.47
M	0.19	0.56
N	0.60	0.20
O	<0.05	>1.1
P	53	−1.4
Q	4.3	−0.53
R	<0.05	>1.1

[a] The concentrations of the lithium salts were determined by integration of the resonances in samples containing 0.1 M [^{6}Li]-LiPMP and chelating ligand (2−10 equiv per lithium) in 2:1 toluene−pentane at −90 °C. [b] The values of K_{rel} and $\Delta G°_{rel}$ are reported relative to TMEDA with estimated errors of ±10%. [c] The measurement was precluded by ligand decomposition.

Relative binding energies were determined by competing the diamines against THF (eq 3 and 4) as described previously.[13,14] The relative equilibrium constants (K_{rel}) and free energies ($\Delta G°_{rel}$) defined by eq 5 and 6 are listed in Table 4.

Discussion

Unsolvated LiTMP and LiPMP Cyclic Oligomers. The chair conformers of the LiTMP and LiPMP piperidine rings cause the aggregates to display unusual structural complexities. We found, for example, that LiTMP and LiPMP (**1** and **2**, respectively) exist in hydrocarbon solutions as a mixture containing one of two possible trimers (**9**) and all four possible stereoisomeric tetramers **10**−**13** (Chart 1). The unique combinations of resonance numbers and Li−N connectivities in each

$$\text{1/2 } (\text{LiPMP})_2(\text{THF})_2 + \text{L} \underset{}{\overset{K_{eq(L)}}{\rightleftharpoons}} \text{LiPMP·L} + \text{THF} \qquad (3)$$

16 A-R 15A-R

$$K_{eq} = [15][\text{THF}]/[16]^{1/2}[\text{L}] \qquad (4)$$

$$\text{LiPMP·TMEDA} + \text{L} \underset{}{\overset{K_{rel}\ (\Delta G^{\circ}_{rel})}{\rightleftharpoons}} \text{LiPMP·L} + \text{TMEDA} \qquad (5)$$

15A 15B-R

$$K_{rel} = K_{eq(L)}/K_{eq(TMEDA)} \qquad (6)$$

of the four tetrameric isomers made the structural assignments possible. The existence of all four isomeric tetramers posed some challenges yet provided a unique spectroscopic fingerprint and compelling support for the aggregation state assignment.

Crystallographic studies by Lappert and co-workers[4] show LiTMP to be the C_{4h} tetramer analogous to **10**, clearly foreshadowing the detection of tetramers in solution. However, the spectroscopic studies also show that the conformational preference derives entirely from lattice effects. This serves as a reminder to be cautious when incorporating subtle conformational preferences observed crystallographically into mechanistic discussions.

Characterization of Solvated Monomers and Open Dimers. Treatment of [^{6}Li,^{15}N]LiPMP with a variety of chelating ligands (Chart 2) affords ligand-dependent mixtures of unsolvated cyclic oligomers (**9**−**13**), open dimers (**14**), and monomers (**15**). Although the broadening of the ^{15}N multiplets caused some of the assignments to be more tentative than usual, those cases that could be definitively assigned leave us confident that all assignments are correct. Open dimers appear to be important reactive intermediates in the chemistry of lithium amides.[6,7,16−18] In fact, lithium amide open dimers have been detected crystallographically, spectroscopically, or kinetically in several instances.[6,7,17] However, we have relied inordinately on computational studies for our insights into their stabilities.[16] The detection of LiPMP open dimers of general structure **14** confirms that they are stabilized by bidentate ligands.

Monomer vs. Open Dimer Stabilities. Although the data in Table 3 must be interpreted cautiously and qualitatively, they offer some insights into the general tendency of chelating ligands to solvate LiPMP. For example, a ligand's penchant for binding can be inferred from the percentage of unsolvated oligomers (**i**; see Table 3). The ligands can be grouped as those showing (1) a high affinity for LiPMP (**A**, **I**, **K**, and **P**); (2) a measurable reluctance to solvate LiPMP (**C** and **D**); or (3) a marked reluctance to solvate LiPMP (**B** and **O**). In general, however, quantitative investigations of ligand binding to the LiPMP monomer described in the following section provide more useful measures of metal−ligand bond strengths.

We measured the open dimer:monomer ratios (Table 3) to better understand the factors that influence the *relative* monomer and open dimer stabilities. MNDO computations[30] predicted that bulky ligands would stabilize the monomer relative to the open dimer. Inspection of the data in Table 3 suggests that this may be true, although some clarification is required. If the open dimer (**ii**) is substantially less stable than the monomer (**iii**), 0.75 equiv of ligand would afford monomer and unsolvated oligomer (**i**) (≥25%) to the exclusion of open dimer. This behavior is exemplified by ligands **B**, **F**, **G**, **M**, and **O**. Similarly, if the open dimer is very stable compared to the monomer, we would observe exclusively open dimer, and 0.25 equiv of ligand would remain free in solution. No ligands display this behavior. The intermediate cases are more difficult to interpret. If the *dominant* driving force is to maximize the number of ligand−lithium interactions, then addition of 0.75 equiv of ligand to LiPMP will necessarily yield monomer. If, in addition, the open dimer is stable relative to the monomer, the maximum attainable open dimer:monomer ratio is 1:2. A ratio of <1:2 indicates that the monomer and unsolvated oligomers are forming preferentially, and the open dimer should not be observed much beyond 1.0 equiv of ligand. This behavior is found for ligands **C**−**E**. If exploiting all available ligand is not a dominant driving force, then addition of 0.75 equiv of ligand can cause free ligand to remain in solution, and the open dimer: monomer ratio can exceed 1:2. This implicates a degree of open dimer stability. In such a case, open dimer would be observable at >1.0 equiv of ligand per LDA. This behavior is observed for ligands **A**, **I**, and **L**.

Overall, there appears to be a general tendency of ligand bulk to destabilize open dimers relative to monomers as well as destabilize both solvated forms relative to the unsolvated oligomers. For example, the replacement of the *N*-methyl groups on TMEDA with ethyl groups (**B**, **C**, **D**, and **E**) shows a decreased tendency to form open dimer with increasing substitution. Other sterically hindered ligands such as **G** and **R** that are reluctant to bind LiPMP also afford monomers as the only observable solvated forms.

Ligand-Dependent Binding Constants. Quantitative insights into the ligand-dependent binding to the LiPMP monomer were obtained by measuring the concentrations of the THF-solvated dimer (**16**) and ligand-solvated monomer (**15**) in THF/ligand mixtures (eq 3). Relative binding constants (K_{rel}) and free energies (ΔG°_{rel}) determined according to eq 4 are listed in Table 4. The results are consistent with those obtained from LiHMDS[13] and LDA[14] as follows: (1) TMCDA (**P**) is the best ligand, while **D** and **M**, which contain bulky diethylamino and piperidino groups, are poor. (2) Alkoxy groups do not appear to be particularly stabilizing compared to dimethylamino groups, despite the lower steric requirements of the alkoxy groups. This is consistent with the higher azaphilicity than oxaphilicity of lithium amide monomers (but not dimers) noted previously.[31] (3) Six-membered chelates are unfavorable as evidenced by the failure of TMPDA (**O**) to completely saturate LiPMP even when in large excess (50 equiv).

The ability of the bidentate ligands to compete with THF (eq 3) was not expected on the basis of studies with the sterically less congested LiHMDS and LDA. We infer from this result that the increased steric demand of the LiPMP fragment is disproportionately greater in the THF-solvated dimer than in the chelated monomer. It is also surprising that ligand **N**, which contains an ethoxy group, binds more strongly than the methoxy analog **L**. We do not have a reason to question the validity of this data nor do we have a plausible explanation.

(30) Remenar, J. F.; Romesberg, F. E.; Cajthaml, C. E.; Collum, D. B. Unpublished results.

(31) Lucht, B. L.; Collum, D. B. *J. Am. Chem. Soc.* **1996**, *118*, 2217.

Summary and Conclusions

Structural studies of the highly hindered LiPMP (**2**) serving as a conformationally locked surrogate of LiTMP (**1**) reveal mixtures of trimers and tetramers in hydrocarbons and mixtures of unsolvated oligomers, open dimers, and monomers in the presence of bidentate ligands. These results are generally consistent with crystallographic studies of LiTMP reported by Lappert[4] and Williard.[7] Some insights into the ligand-dependent stabilization of the monomer and open dimer were obtained. Although the need to understand monomers and open dimers is underscored by their potential importance as reactive intermediates,[6,7,15−18] the data are difficult to interpret. Quantitative determinations of ligand binding constants on the LiPMP monomer display a general correlation with those obtained for LiHMDS. Similar binding affinities for LiHMDS, LDA, and LiPMP were observed; however, some differences serve to remind us of the specificity of substrate−ligand interactions. In our opinion, the binding constants will prove to be the most enduring results by providing thermochemical foundations for studies of lithium amide structure−reactivity relationships.

Experimental Section

Reagents and Solvents. All amines 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. ^{6}Li metal (95.5% enriched) was obtained from Oak Ridge National Laboratory. The [^{6}Li]ethyllithium used to prepare the [^{6}Li]-LiPMP was prepared and purified by the standard literature procedure.[32] [^{6}Li,^{15}N]LiPMP was prepared as an analytically pure solid as described previously.[3] The ligands were purchased or prepared using protocols described previously.[13,14] The diphenylacetic acid used to check solution titers[33] was recrystallized from methanol and sublimed at 120 °C under full vacuum. Air- and moisture-sensitive materials were manipulated under argon or nitrogen using standard glovebox, vacuum line, and syringe techniques.

NMR Spectroscopic Analyses. Samples for spectroscopic analyses were prepared using a sample preparation protocol described in detail elsewhere.[3] 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 and 58.84 MHz (respectively). The ^{6}Li and ^{15}N resonances are referenced to 0.3 M [^{6}Li]LiCl/MeOH at −100 °C (0.0 ppm) and neat Me_2NEt at −100 °C (25.7 ppm), respectively. The ^{6}Li−^{15}N HMQC spectra[22] were recorded on the Varian Unity 500 spectrometer equipped with a custom-built three-channel probe designed to accommodate lithium and nitrogen pulses with concurrent proton decoupling. The HMQC pulse sequence[34] was obtained through Varian. 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 the pulse sequence described previously.[35] Broadband ^{1}H decoupling was used during all periods of the experiment. Data were processed in the phase-sensitive mode with exponential line broadening in f_1 and Lorentz-Gaussian resolution enhancement in f_2.

Acknowledgment. We thank the National Institutes of Health for direct support of this work and for a predoctoral training grant to B.L.L. We also acknowledge the National Science Foundation Instrumentation Program (CHE 7904825 and PCM 8018643), the National Institutes of Health (RR02002), and IBM for support of the Cornell Nuclear Magnetic Resonance Facility.

Supporting Information Available: ^{6}Li and ^{15}N NMR spectra of LiPMP (21 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead for ordering information.

JO970520L

(32) Kim, Y.-J.; Bernstein, M. P.; Galiano-Roth, A. S.; Romesberg, F. E.; Williard, P. G.; Fuller, D. J.; Harrison, A. T.; Collum, D. B. *J. Org. Chem.* **1991**, *56*, 4435.

(33) Kofron, W. G.; Baclawski, L. M. *J. Org. Chem.* **1976**, *41*, 1879.

(34) Bax, A.; Griffey, R. H.; Hawkins, B. L. *J. Magn. Reson.*, **1983**, *55*, 301. Summers, M. F.; Marzilli, L. G.; Bax, A. *J. Am. Chem. Soc.* **1986**, *108*, 4285.

(35) Bodenhausen, G.; Ruben, D. J. *Chem. Phys. Lett.* **1980**, *69*, 185. Müller, L. *J. Am. Chem. Soc.* **1979**, *101*, 4481.