

On the Structure of Lithium 2,2,6,6-Tetramethylpiperidide (LiTMP) and Lithium Diisopropylamide (LDA) in the Presence of Hexamethylphosphoramide (HMPA): Structure-Dependent Distribution of Cyclic and Open Dimers, Ion Triplets, and Monomers

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Abstract: Isotopically labeled samples of lithium diisopropylamide (LDA) and lithium 2,2,6,6-tetramethylpiperidide (LiTMP) in THF/pentane containing varying quantities of hexamethylphosphoramide (HMPA) have been subjected to ^6Li , ^{15}N , and ^{31}P NMR spectroscopy at low temperatures. The LDA dimer serially solvates through a monosolvated and disolvated form as evidenced by both ^6Li - ^{15}N and ^6Li - ^{31}P coupling patterns. No evidence of further solvation or deaggregation is observed. LiTMP is shown in previous work to exist as a 90:10 dimer-monomer equilibrium. In the presence of HMPA, the monomer solvates in two discrete steps, although evidence of the specific solvation states is indirect. The dimer undergoes parallel solvation via a mono- and disolvate with 0.0-1.0 equiv of added HMPA. A disolvated open dimer is also observed. At elevated HMPA concentrations, anionic ion triplets of general structure $[\text{R}_2\text{NLiNR}_2]^-/\text{LiS}_n$ bearing both 3 and 4 HMPA ligands on the Li^+ gegenion are readily observed and fully characterized. In addition, indirect evidence of a tetrasolvated closed dimer is also reported. Arguments refuting HMPA as a deaggregating agent are briefly presented. Further evidence against the existence of solvated lithium dialkylamide trimers and a discussion of the possible roles of anionic ion triplets in organolithium chemistry are included.

Introduction

Hexamethylphosphoramide (HMPA; **1**) has been shown to dramatically enhance the rates of a wide variety of organolithium reactions.¹ The general consensus appears to be that HMPA dissociates aggregates to highly reactive monomers, ion pairs, or free ions.^{2,3} Nevertheless, the effects of HMPA on organolithium solution structures and the detailed mechanism(s) by which HMPA modifies reactivity and selectivity have remained obscure for the most part. The first truly illuminating results were reported by Jackman and co-workers.⁴ They found that excess HMPA converts dimeric lithium anilides to predominantly monomers and low concentrations of anionic ion triplets.⁵⁻⁷ More recently, Reich⁸

(1) Effects of HMPA on the chemistry of lithium amides: Fataftah, Z. A.; Kopka, I. E.; Rathke, M. W. *J. Am. Chem. Soc.* **1980**, *102*, 3959. Fraser, R. R.; Mansour, T. S. *Tetrahedron Lett.* **1986**, *27*, 331. Kodomari, M.; Sawa, S.; Morozumi, K.; Ohkita, T. *Nippon Kagaku Kaishi* **1976**, 301. Cuvigny, T.; Larcheveque, M.; Normant, H. *Liebigs Ann. Chem.* **1975**, 719. Reisdorf, D.; Normant, H. *Organomet. Chem. Synth.* **1972**, *1*, 375. Hosomi, A.; Araki, Y.; Sakurai, H. *J. Am. Chem. Soc.* **1982**, *104*, 2081. Cregge, R. J.; Hermann, J. L.; Lee, C. S.; Richman, J. E.; Schlessinger, R. H. *Tetrahedron Lett.* **1973**, 2425. Shirai, R.; Tanaka, M.; Koga, K. *J. Am. Chem. Soc.* **1986**, *108*, 543. Tsushima, K.; Araki, K.; Murai, A. *Chem. Lett.* **1989**, 1313. Tanaka, Y.; Tsujimoto, K.; Ohashi, M. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 788. See also ref 14. Eude, D. van; Cravador, A.; Krief, A. *J. Organomet. Chem.* **1979**, *177*, 1. Rathke, M. W.; Sullivan, D. *Tetrahedron Lett.* **1986**, *27*, 1249.

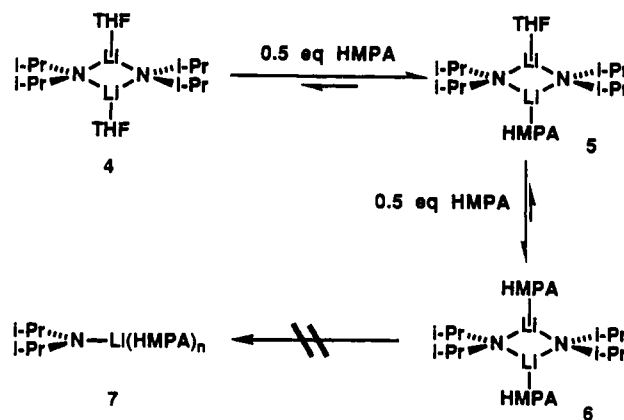
(2) See for example: Newcomb, M.; Varick, T. R.; Goh, S.-H. *J. Am. Chem. Soc.* **1990**, *112*, 5186.

(3) Seebach and co-workers have suggested that HMPA may activate aggregates without intervening deaggregations by inserting into an aggregate site normally occupied by the anionic fragment: Seebach, D.; Amstutz, R.; Dunitz, J. D. *Helv. Chim. Acta* **1981**, *64*, 2622.

(4) Jackman, L. M.; Scarmoutzos, L. M.; Porter, W. *J. Am. Chem. Soc.* **1987**, *109*, 6524. Jackman, L. M.; Scarmoutzos, L. M.; Smith, B. D.; Williard, P. G. *J. Am. Chem. Soc.* **1988**, *110*, 6058.

(5) The terms "ion triplet", "ion triple", "triple ion", and "triplet ion" have been used interchangeably to describe clusters of three ions. The clusters can be either anionic (e.g., $[\text{R}^-\text{M}^+\text{R}^-]$), neutral (e.g., $[\text{R}^-\text{M}^+\text{R}^-]$), or cationic (e.g., $[\text{M}^+\text{R}^-\text{M}^+]$). Throughout this manuscript we will refer only to the anionic forms and use only the ion triplet nomenclature.

Scheme I



and Snaith⁹ documented the first examples of two-bond Li-P coupling in HMPA-Li solvates, providing a view of lithium ion solvation with unprecedented clarity.^{10,11} Snaith demonstrated

(6) Leading references to anionic ion triplets: Galiano-Roth, A. S.; Collum, D. B. *J. Am. Chem. Soc.* **1988**, 3546.

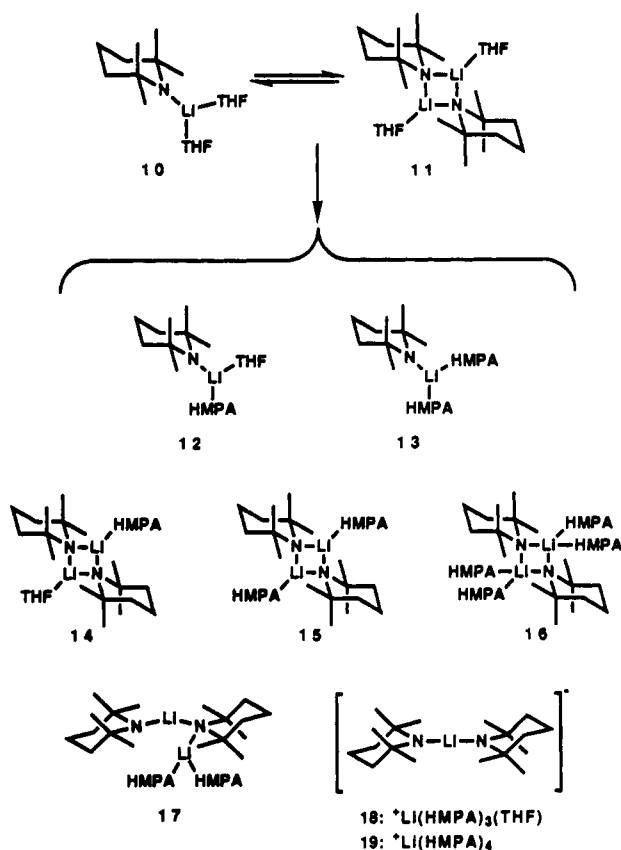
(7) For an excellent review of how aggregation and mixed aggregation affect organolithium structure and reactivity, see: Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1624. For a comprehensive review of the structures of N-lithiated species, see: Gregory, K.; Schleyer, P. v. R.; Snaith, R. *Adv. Organomet. Chem.*, in press.

(8) Reich, H. J.; Gree, D. P. *J. Am. Chem. Soc.* **1989**, *111*, 8729. Reich, H. J.; Green, D. P.; Phillips, N. H. *J. Am. Chem. Soc.* **1989**, *111*, 3444. Reich, H. J.; Borst, J. P. *J. Am. Chem. Soc.* **1991**, *113*, 1835.

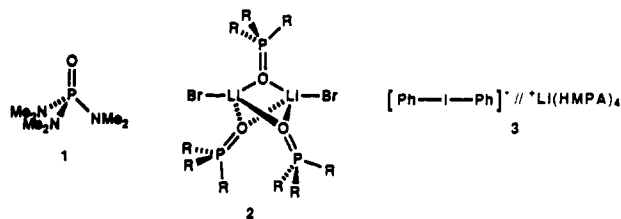
(9) Barr, D.; Doyle, M. J.; Mulvey, R. E.; Raithby, P. R.; Reed, D.; Snaith, R.; Wright, D. S. *J. Chem. Soc., Chem. Commun.* **1989**, 318.

(10) For studies of solvation of N-lithiated species, see: Kallman, N.; Collum, D. B. *J. Am. Chem. Soc.* **1987**, *109*, 7466. Depue, J. S.; Collum, D. B. *J. Am. Chem. Soc.* **1988**, *109*, 5518. Jackman, L. M.; Scarmoutzos, L. M.; DeBrosse, C. W. *J. Am. Chem. Soc.* **1987**, *109*, 5355. Wanat, R. A.; Collum, D. B.; Van Duyne, G.; Clardy, J.; DePue, R. T. *J. Am. Chem. Soc.* **1986**, *108*, 3416.

Scheme II



that the curious bridged dimer 2 observed crystallographically retains its integrity in solution.⁸ Reich and co-workers unequivocally demonstrated that HMPA deaggregates dimeric phenyllithium to a monomer $[PhLi(HMPA)]_n$.⁸ Reich's full characterization of tetrasolvated iodinate 3 and ensuing kinetic analysis of metal-halogen exchange constitutes one of the few clear structure-reactivity correlations in organolithium chemistry.⁷ More recently, Denmark exploited the observable two-bond 6Li - ^{31}P coupling in phosphorus-stabilized carbanions to demonstrate the dimeric structure.¹² Their use of ^{31}P decoupling is also notable.



We describe herein 6Li , ^{15}N , and ^{31}P NMR spectroscopic studies of isotopically enriched lithium diisopropylamide ($[^6Li]LDA$ and

Table I. NMR Spectroscopic Data of $[^6Li]LDA$ and $[^6Li,^{15}N]LDA$ Solvates^a

compd	equiv of HMPA ^b	6Li δ (m, J_{N-Li} , J_{P-Li})	^{15}N δ (m, J_{N-Li})	^{31}P δ (m, J_{P-Li})
4	0.0	1.86 (t, 5.0, -)	75.2 (quint, 5.0)	
5	0.5	1.96 (t, 5.5, -) 1.48 (q, 4.2, 4.2)	72.0 (quint, 4.9)	26.4 (t, 4.3)
6	2.0	1.55 (q, 4.4, 4.3)	74.1 (quint, 4.7)	26.3 (t, 4.3)

^aSpectra were recorded at -125 °C. The $[LDA] = 0.13$ M in a 2:1 THF/pentane cosolvent. Coupling constants were measured after resolution enhancement: s = singlet, t = triplet, q = quartet, quint = quintet, br = broad multiplet. Chemical shifts are recorded (in hertz) relative to external standards as described in the Experimental Section. ^bEquivalents of HMPA in the NMR sample from which the tabulated data derive.

Table II. NMR Spectroscopic Data of $[^6Li]LiTMP$ and $[^6Li,^{15}N]LiTMP$ Solvates^a

compd	equiv of HMPA ^b	6Li δ (m, J_{N-Li} , J_{P-Li}) ^c	^{15}N δ (m, J_{N-Li})	^{31}P δ (m, J_{P-Li})
10	0.0	0.48 (d, 8.5, -)	93.5 (t, 8.5)	
11	0.0	1.48 (t, 4.8, -)	79.7 (quint, 5.0)	
12	1.0	0.93 (d, 9.0, <i>d</i>)	91.4 (d, 9.0)	28.1 (s, v br)
13	4.0	0.73 (d, 8.5, <i>d</i>)	90.9 (d, 8.5)	<i>f</i>
14	0.5	1.55 (t, 5.1, -) 1.06 (q, 4.9, 4.6)	79.8 (quint, 5.0)	26.4 (t, 4.3)
15	1.0	1.12 (q, 4.3, 3.8)	78.6 (quint, 4.3)	26.2 (t, 3.7)
16	4.0	0.80 (t, 3.5, <i>d</i>)	78.8 (quint, 3.5)	<i>f</i>
17	1.5	1.65 (dd, 5.1, 8.4, -)	89.1 (t, 8.4)	<i>g</i>
18	1.5	0.75 (e, -, 3.8) 2.48 (t, 9.9, -) -0.54 (q, -, 3.5)	80.0 (q, 5.2) 100.4 (t, 9.9)	<i>g</i>
19	4.0	2.49 (t, 9.9, -) -0.54 (quint, -, 2.9)	101.2 (t, 10.0)	<i>h</i> <i>h</i>

^aSpectra were recorded at -115 °C. The $[LiTMP] = 0.13$ M in a 2:1 THF/pentane cosolvent. Coupling constants were measured after resolution enhancement: s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, br = broad multiplet. Chemical shifts are recorded (in hertz) relative to external standards as described in the Experimental Section. ^bEquivalents of HMPA in the NMR sample from which the tabulated data derive. ^cDistinction of Li-N from Li-P was made by comparison of $[^6Li]LiTMP$ and $[^6Li,^{15}N]LiTMP$. ^dCoupling not observed by 6Li NMR spectroscopy although indirect evidence clearly supports the existence of one (or more) HMPA ligands. ^eAlthough severe resonance overlaps prevented a direct multiplicity determination, indirect evidence cited in the text is consistent with a quartet arising from coupling to one ^{15}N and two ^{31}P nuclei. ^fFeatureless mounds in the ^{31}P NMR spectra resulted from rapid solvent exchange. ^gDespite chemical exchange processes precluding a detailed analysis, triplets at δ 27.2 (br) and 27.09 ppm appear to correlate with 17 and 18. ^hIn the limit of high $[HMPA]$, a broad ^{31}P triplet that may correspond to ion triplet 19 is observed at δ 27.1 ppm along with broad mounds resulting from rapid exchange processes.

$[^6Li,^{15}N]LDA$) and lithium 2,2,6,6-tetramethylpiperidide ($[^6Li]LiTMP$ and $[^6Li,^{15}N]LiTMP$).¹³ We will show that LDA serially forms dimers 5 and 6, but does not deaggregate to monomer 7 (Scheme I). Further, addition of 0.0–5.0 equiv of HMPA to the LiTMP monomer-dimer mixture has minimal effects on the absolute aggregation state, while producing a bewildering array of structural forms (Scheme II). Monomer 13, tetrasolvated dimer 16, and ion triplet 19 are the observable structures in the limit of high HMPA concentrations.

Results

In all of the structures, the numbers of THF solvents depicted are based exclusively on analogy with studies described elsewhere¹⁰ as well as with the directly determined HMPA solvation numbers. Terms such as "monosolvate" and "disolvate" are used colloquially to describe only the number of HMPA ligands. All stereochemical

(11) For other examples of the determination of organolithium solvation states in solution, see: Brown, T. L.; Gerteis, R. L.; Rafus, D. A.; Ladd, J. A. *J. Am. Chem. Soc.* 1964, 86, 2135. Lewis, H. L.; Brown, T. L. *J. Am. Chem. Soc.* 1970, 92, 4664. Quirk, R. P.; Kester, D. E. *J. Organomet. Chem.* 1977, 127, 111. Bartlett, P. D.; Goebel, C. V.; Weber, W. P. *J. Am. Chem. Soc.* 1969, 91, 7425. Cheema, Z. K.; Gibson, G. W.; Eastham, J. F. *J. Am. Chem. Soc.* 1963, 85, 3517. Eastham, J. F.; Gibson, G. W. *J. Am. Chem. Soc.* 1963, 85, 2171. Waack, R.; Doran, M. A.; Stevenson, P. E. *J. Am. Chem. Soc.* 1966, 88, 2109. Bauer, W.; Klusener, P. A. A.; Harder, S.; Kanters, J. A.; Duisenberg, A. J. M.; Brandsma, L.; Schleyer, P. v. R. *Organometallics* 1988, 7, 552. Harder, S.; Boersma, J.; Brandsma, L.; Kanters, J. A.; Bauer, W.; Pi, R.; Schleyer, P. v. R.; Schölnhorn, H.; Thewalt, U. *Organometallics* 1989, 8, 1688. Bauer, W.; Schleyer, P. v. R. *J. Am. Chem. Soc.* 1989, 111, 7191. Fraenkel, G.; Chow, A.; Winchester, W. R. *J. Am. Chem. Soc.* 1990, 112, 1382. Quirk, R. P.; McFay, D. J. *Polym. Sci., Polym. Chem. Ed.* 1981, 19, 1445. Wehman, E.; Jastrzebski, J. T. B. H.; Ernsting, J.-M.; Grove, J. M.; van Koten, G. *J. Organomet. Chem.* 1988, 353, 145.

(12) Denmark, S. E.; Miller, P. C.; Wilson, S. R. *J. Am. Chem. Soc.* 1991, 113, 1468.

(13) For leading references to $^6Li/^{15}N$ double labeling studies of N-lithiated species, see ref 15.

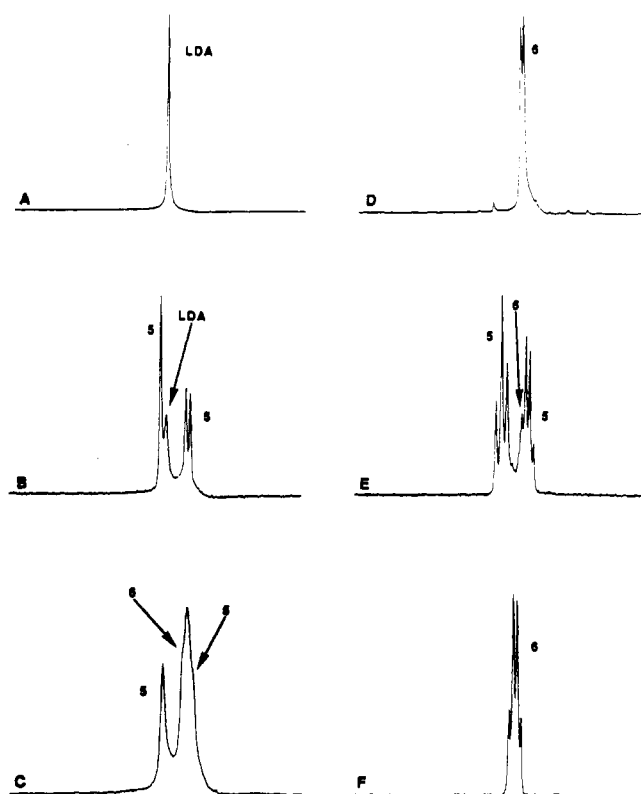


Figure 1. ^6Li NMR spectra of 0.13 M LDA in 2:1 THF/pentane at -125°C : (A) ^6Li LDA with no added HMPA; (B) ^6Li LDA with 0.5 equiv of HMPA/Li; (C) ^6Li LDA with 0.8 equiv of HMPA/Li; (D) ^6Li LDA with 2.0 equiv of HMPA/Li; (E) $^6\text{Li},^{15}\text{N}$ LDA with 0.5 equiv of HMPA/Li; (F) $^6\text{Li},^{15}\text{N}$ LDA with 2.0 equiv of HMPA/Li.

and spectroscopic studies were carried out using analytically pure lithium amides. Suspecting (albeit incorrectly) that some of the observable species were the result of solvent decomposition,¹⁴ samples have all been prepared at 77 K under helium atmosphere; all resonances described prove to be fully reproducible irrespective of the specific sample of lithium amide or date of preparation. Overall, the NMR samples were either freshly prepared or stored at 77 K (-70°C for LDA samples) wherein decomposition was shown to be undetectable. The NMR spectral data are summarized in Tables I and II. The detailed NMR description found in the Results is followed by a summary of the results at the start of the Discussion.

LDA-HMPA Solvates. Previous studies demonstrated that LDA exists exclusively as a cyclic oligomer.^{15,16} Additional data further support disolvated dimer 4 rather than higher oligomers and higher solvates, although that conclusion remains marginally speculative. Increments of up to 0.5 equiv of HMPA (per Li) to ^6Li LDA¹⁸ cause the appearance of mixed solvated dimer 5 at the expense of 4. Dimer 5 displays a singlet and doublet ($^2J_{\text{Li-P}} = 4.3\text{ Hz}$) in a 1:1 ratio in the ^6Li NMR spectra (Figure 1) and a triplet in the ^{31}P NMR spectra (Table I; supplementary material). The ^{15}N NMR spectrum derived from $^6\text{Li},^{15}\text{N}$ LDA

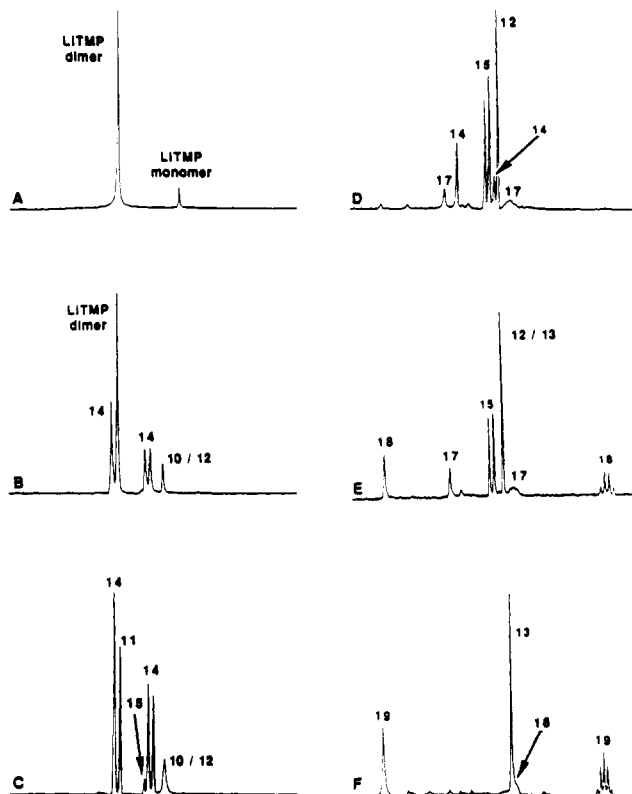


Figure 2. ^6Li NMR spectra of 0.13 M ^6Li LiTMP in 2:1 THF/pentane at -115°C : (A) no added HMPA; (B) 0.3 equiv of HMPA/Li; (C) 0.5 equiv of HMPA/Li; (D) 0.8 equiv of HMPA/Li; (E) 1.0 equiv of HMPA/Li; (F) 2.0 equiv of HMPA/Li.

exhibits a solitary new quintet for 5 (Table I; supplementary material). The aforementioned doublet of 5 now appears as a quartet in the ^6Li spectrum due to ^{31}P and ^{15}N coupling, and the singlet appears as a triplet due to $^6\text{Li}-^{15}\text{N}$ coupling. Notably, the 1:1 ratio of ^6Li resonances is inconsistent with a trimeric structure, providing further evidence that solvated lithium dialkylamide trimers are not readily observable in solution.^{16,17} The coupling of the ^{31}P resonance to one neighboring ^6Li nucleus also excludes any form of bridging solvate such as 9.^{19,20}

Addition of up to 1.0 equiv of HMPA per lithium to ^6Li LDA converts mixed solvated dimer 5 to the disolvated dimer 6 as evidenced by the appearance of a new ^6Li doublet ($\delta 1.55$) and ^{31}P triplet. Analysis of $^6\text{Li},^{15}\text{N}$ LDA/HMPA shows the ^6Li resonance at $\delta 1.55$ further split by two neighboring ^{15}N nuclei with the concomitant appearance of a new quintet in the ^{15}N NMR spectrum. Although one cannot exclude cyclic trimers and higher oligomers, the analogy with 5 provides compelling support of the dimer structure. From 1.0–5.0 equiv of HMPA/Li we observe dimer 6 in the ^6Li , ^{15}N , and ^{31}P NMR spectra along with free HMPA in the ^{31}P spectra. *HMPA does not measurably deaggregate LDA.*

Overall, the cyclic oligomer structure of LDA remains intact in the presence of excess HMPA. Further, the desymmetrized mixed solvated dimer 5 provides additional evidence^{16,17} that lithium dialkylamides exist as dimers rather than higher oligomers in the presence of donor solvents. Furthermore, since coordinated THF molecules are not spectroscopically detectable, the formation of disolvated dimer 6 in the limit of high HMPA concentration rather than a tetrasolvate (e.g., 9) appears to be strong evidence

(14) Kopka, I. E.; Fataftah, Z. A.; Rathke, M. W. *J. Org. Chem.* **1987**, *52*, 448.

(15) Galiano-Roth, A. S.; Collum, D. B. *J. Am. Chem. Soc.* **1989**, *111*, 6772.

(16) Computational, crystallographic, and solution structural studies have led several groups to argue that higher oligomers are stable only in the absence of donor solvents. Armstrong, D. R.; Mulvey, R. E.; Walker, G. T.; Barr, D.; Snaith, R.; Clegg, W.; Reed, D. *J. Chem. Soc., Dalton Trans.* **1987**, 617. See also ref 17.

(17) Gilchrist, J. H.; Harrison, A. T.; Fuller, D. J.; Collum, D. B. *J. Am. Chem. Soc.* **1990**, *112*, 4069 and references cited therein.

(18) Procedures for the preparation of ^6Li and ^{15}N labeled LiTMP and LDA as analytically pure solids are described in detail elsewhere: Kim, Y. J.; Bernstein, M.; Galiano Roth, A. S.; Romesberg, F. E.; Williard, P. G.; Fuller, D. J.; Harrison, A. T.; Collum, D. B. *J. Org. Chem.* **1991**, *56*, in press. See also ref 21.

(19) Armstrong, D. R.; Barr, D.; Brooker, A. T.; Clegg, W.; Gregory, K.; Hodgson, S. M.; Snaith, R.; Wright, D. S. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 410 and references cited therein.

(20) Thermal $^6\text{Li}-^{31}\text{P}$ decoupling is achieved by warming of the probe over a few degrees. If two species differ only in their solvation state, broadening will occur when the difference in their chemical shifts is comparable in magnitude to the coupling constant. Species differing in aggregation state show little evidence of coalescence.

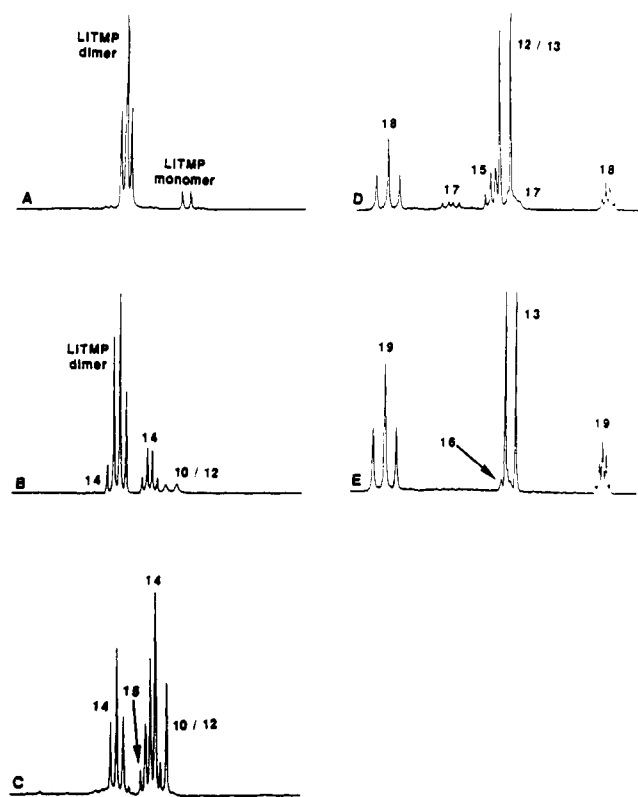
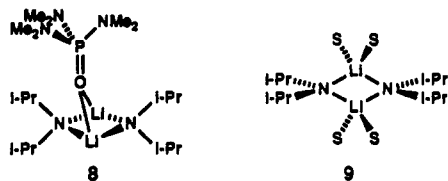


Figure 3. ^6Li NMR spectra of 0.13 M $[\text{}^6\text{Li},^{15}\text{N}]\text{LiTMP}$ in 2:1 THF/pentane at $-115\text{ }^\circ\text{C}$: (A) no added HMPA; (B) 0.3 equiv of HMPA/Li; (C) 0.8 equiv of HMPA/Li; (E) 1.5 equiv of HMPA/Li; (F) 2.0 equiv of HMPA/Li.

supporting the instability of four-coordinate lithium in highly hindered lithium dialkylamides.¹⁰ We hasten to add, however, that albeit less direct evidence of a tetrasolvated LiTMP dimer cited below contrasts with this conclusion.



LiTMP–HMPA Solvates. ^6Li and ^{15}N double labeling studies reported elsewhere²¹ confirmed the conclusion of Fox and Renaud²² that LiTMP (0.1 M in THF at $-115\text{ }^\circ\text{C}$) exists as a 1:9 mixture of monomer 10 and dimer 11. Addition of 0.3 equiv of HMPA (per Li) to $[\text{}^6\text{Li}]\text{LiTMP}$ causes the appearance of mixed solvated dimer 14 and downfield shifting of the monomer resonance (Figure 2). (At $-125\text{ }^\circ\text{C}$ the monomer broadens into the base line.) In direct analogy with LDA, the ^6Li spectrum of $[\text{}^6\text{Li}]\text{LiTMP}$ reveals two resonances in a 1:1 ratio for mixed solvated dimer 14, with one showing coupling to a single ^{31}P nucleus. The corresponding ^6Li spectrum of $[\text{}^6\text{Li},^{15}\text{N}]\text{LiTMP}$ shows that both are coupled to a common pair of chemically equivalent ^{15}N nuclei (Figure 3). The ^{15}N NMR spectrum displays the quintet of 11 along with a substantially broadened quintet that correlates with the two ^6Li resonances of 14 (Figure 4) as shown by single frequency decoupling (supplementary material). The broadening is consistent with a rapid exchange of the two inequivalent ^{15}N nuclei of 14 by a facile chair–chair flip mechanism.²³ The ^{31}P NMR spectrum shows a corresponding triplet consistent with a terminal rather than a bridging HMPA.

(21) Hall, P.; Gilchrist, J. H.; Harrison, A. T.; Fuller, D. J.; Collum, D. B. Submitted for publication.

(22) Renaud, P.; Fox, M. A. *J. Am. Chem. Soc.* **1988**, *110*, 5705.

(23) The barrier to chair–chair inversion of LiTMP–LiX mixed aggregates can be frozen on ^6Li NMR time scales below $-80\text{ }^\circ\text{C}$.²¹ The influence of a coordinated HMPA on this barrier is not known at this time.

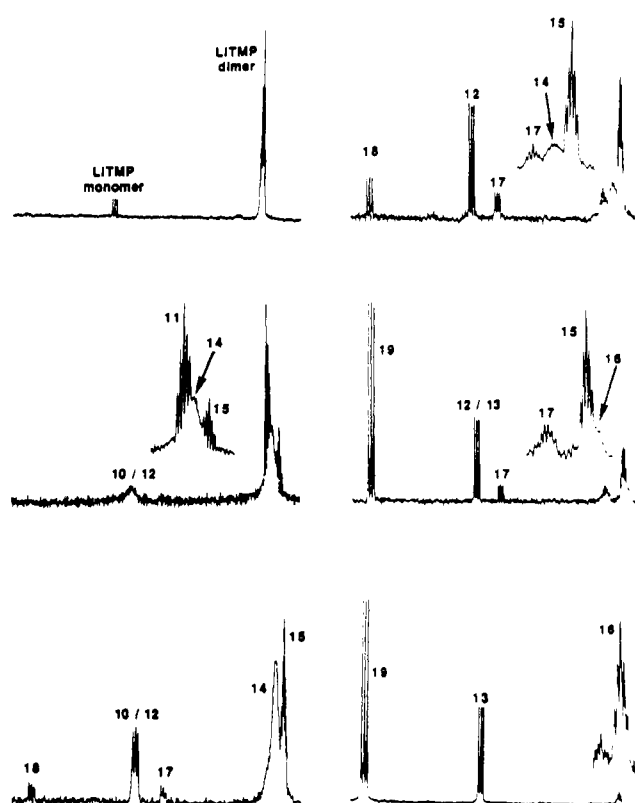


Figure 4. ^{15}N NMR spectra of 0.13 M $[\text{}^6\text{Li}]\text{LiTMP}$ in 2:1 THF/pentane at $-115\text{ }^\circ\text{C}$: (A) no added HMPA; (B) 0.5 equiv of HMPA/Li; (C) 0.8 equiv of HMPA/Li; (D) 1.0 equiv of HMPA/Li; (E) 1.5 equiv of HMPA/Li; (F) 2.0 equiv of HMPA/Li.

While the ^6Li and ^{15}N NMR spectra of doubly labeled samples show the monomer with its characteristic ^6Li – ^{15}N coupling patterns shifted substantially downfield, rapid solvent exchange precludes detection of the ^6Li – ^{31}P coupling characteristic of an HMPA solvate. (Similar phenomena have been observed by Reich in a number of instances.)⁸ The ^{31}P NMR spectrum displays a broad singlet that we ascribe to an HMPA-solvated monomer. We will eventually summarize the circumstantial evidence indicating that the monomer serially solvates to mixed solvated monomer 12 and desolvated monomer 13.

As one exceeds 0.5 equiv of HMPA/Li, a number of additional spectroscopic changes take place. The monomer resonance continues to shift downfield by a total of 0.45 ppm while sharpening to an ^{15}N -coupled doublet even at the lowest temperatures. In addition, resonances consistent with desolvated dimer 15 and open dimer 17 appear.^{24,25} The sole ^6Li resonance of 15 displays clear coupling to a single ^{31}P nucleus as well as coupling to two equivalent ^{15}N nuclei (as shown by single frequency decoupling; supplementary material). The ^{31}P spectrum shows two new resonances (each coupled to a single ^6Li nucleus) that appear to correlate with the appearance of 15 and 17. However, at intermediate and high HMPA concentrations the ^{31}P spectra become noninformative due to complex exchange processes (supplementary material).

Open dimer 17 shows characteristic connectivities and curious spectroscopic properties consistent with the presence of both monomer-like and dimer-like nuclei. In the ^6Li spectra of

(24) Related organolithium open dimers have been characterized crystallographically: Schröder, v. F. A.; Weber, H. R. *Acta Crystallogr.*, **B** **1975**, *B31*, 1745. Fenton, D. E.; Truter, M. R. *J. Chem. Soc., Dalton Trans.* **1973**, 2188. Armstrong, D. R.; Barr, D.; Clegg, W.; Hodgson, S. M.; Mulvey, R. E.; Reed, D.; Snaith, R.; Wright, D. S. *J. Am. Chem. Soc.* **1989**, *111*, 4719. Raston, C. L.; Skelton, B. W.; Whitaker, C. R.; White, A. H. *J. Chem. Soc., Dalton Trans.* **1988**, 987. Brooks, P.; Craig, D. C.; Gallagher, M. J.; Rae, A. D.; Sarroff, A. *J. Organomet. Chem.* **1987**, *323*, C1.

(25) For solution structural studies of related open dimers (contact ion paired ion triplet), see: Jackman, L. M.; Rakiewicz, E. F. *J. Am. Chem. Soc.* **1991**, *113*, 1202. Paquette, L. A.; Bauer, W.; Sivik, M. R.; Bühl, M.; Feigel, M.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1990**, *112*, 8776.

[^6Li]LiTMP, the resonances corresponding to **17** appear as a singlet and a triplet, indicating zero and two HMPA ligands, respectively. (One cannot exclude the possibility that the singlet results from rapid HMPA exchange.) In the spectra of [$^6\text{Li},^{15}\text{N}$]LiTMP, the aforementioned singlet appears as a doublet of doublets ($J_{\text{Li-N}} = 5.1$ and 8.4 Hz) indicative of coupling to two substantially different neighboring nitrogens. The doubly solvated ^6Li resonance is tentatively assigned as quartet, but it is obscured by severe resonance overlap. In the ^{15}N NMR spectrum, one observes a triplet and quintet in a 1:1 ratio. Irradiation of the triplet corresponding to the terminal nitrogen of **17** eliminates the large coupling, resulting in collapse of the ^6Li doublet of doublets to a narrowly coupled doublet. Irradiation of the quintet corresponding to the internal ^{15}N of **17** causes the doublet of doublets to collapse to a strongly coupled doublet with concomitant collapse of the partially obscured multiplet corresponding to the disolvated lithium. Thus, the terminal ^{15}N nucleus couples to the adjoining ^6Li with a large coupling constant characteristic of the monomer. In contrast, the internal ^{15}N nucleus couples to the same Li nucleus with a magnitude that mimics a cyclic dimer. The chemical shifts of the two resonances mimic those of the monomers and cyclic dimers as well.

As the HMPA content exceeds 1.0 equiv/Li the downfield shifting of the monomer resonance subsides. The mixed solvated dimer **14** is no longer observable. Dimers **15** and **17** begin to be replaced by more highly solvated aggregates. At 1.5 equiv of HMPA/Li, the monomer resonance shows a marked upfield chemical shift consistent with a second solvation state (e.g., **13** see below). The predominant aggregate is anionic ion triplet **18**. Ion triplet **18** derived from [^6Li]LiTMP displays a quartet (due to the three neighboring ^{31}P nuclei of $^+\text{Li}(\text{HMPA})_3(\text{THF})$) and a downfield shifted singlet in a 1:1 ratio. The corresponding ^6Li spectrum of [$^6\text{Li},^{15}\text{N}$]LiTMP exhibits a very strongly coupled triplet ($J_{\text{Li-N}} = 9.9$ Hz) in place of the singlet, while the quartet remains unperturbed by the ^{15}N isotopic substitution. The ^{15}N spectrum shows a strongly coupled 1:1:1 triplet shown by single frequency irradiation to correlate with the ^6Li triplet. These spectral properties are fully consistent with tri-HMPA-solvated ion triplet **18**.⁶

In excess of 2.0 equiv of HMPA/Li, the ^6Li quartet corresponding to the $^+\text{Li}(\text{HMPA})_3\text{THF}$ gegenion of the tri-HMPA-solvated ion triplet **18** is converted to a quintet indicating formation of the tetrasolvated ion triplet **19**. As the ion triplet reaches its limiting solvation state, the ^6Li resonance of the monomer ceases to shift upfield. Since the equilibrium of the monomer and ion triplet **19** bearing two HMPA molecules per Li is independent of the HMPA concentration from 2.0–5.0 equiv of HMPA, we suggest that the limiting monomer structure is disolvated monomer **13**. If so, the downfield shift of the monomer resonance followed by an upfield shift can be interpreted as a shift from purely THF solvated monomer **10** to disolvated monomer **13** through the intermediacy of downfield shifted mixed solvated dimer **12**. MNDO calculations lend support to the implicit solvation states of **10**, **12**, and **13**.²⁸

As the monomer and ion triplet approach their limiting behaviors, there appears a limited concentration (~5%) of a third species that we assign as tetrasolvated dimer **16**. The ^{15}N and ^6Li spectra of [$^6\text{Li},^{15}\text{N}$]LiTMP in the limit of high HMPA concentrations show a quintet and triplet (respectively) due to ^6Li – ^{15}N coupling consistent with a cyclic dimer structure; the ^6Li spectra derived from [^6Li]LiTMP show a corresponding singlet. Clearly, the absence of ^6Li – ^{31}P must be a result of rapid solvent exchange. The chemical shift of the ^{15}N quintet is quite characteristic of the dimer unit. Quite notably, the 3.5 Hz Li–N coupling is substantially less than the corresponding lower solvated dimers, possibly indicating distortion in the dimer core. Furthermore, the HMPA concentration dependencies clearly show that **16** is more highly solvated than tri-HMPA-solvated ion triplet **18** and of a comparable solvation state to that of tetrasolvate **19**. Thus, we suggest tetrasolvated dimer **16** is the most plausible structural assignment. The bothersome aspect of this conclusion is that we accrued no evidence of an analogous tetrasolvate for the (pre-

sumably) less hindered LDA dimer (vide supra).

Discussion

Summary. We find that treatment of LDA dimer **4** with HMPA causes sequential solvation to give mixed solvated dimer **5** and disolvated dimer **6**. Much to our surprise, despite the highly touted capabilities of HMPA to deaggregate organolithium derivatives, we find no evidence of deaggregation or even further solvation; *disolvated dimer 6 is the only observable form of LDA in the limit of excess HMPA.*

The solution structures of LiTMP in THF containing 0.1–5.0 equiv of HMPA are best described in three categories:

(1) The monomeric form serially solvates through at least two different solvation states as evidenced by a significant downfield shift (0.0–1.0 equiv of added HMPA) followed by marked upfield shift (1.0–2.0 equiv of HMPA) of the ^6Li resonance. Although rapid solvent exchange precluded direct solvation-state determination, mass action effects strongly support monosolvated **12** and disolvated monomer **13** as the observable forms.

(2) The dimer is serially solvated through monosolvated dimer **14** and disolvated dimer **15** in complete analogy to LDA. The cyclic dimers seem to almost disappear from view at intermediate HMPA concentrations, only to reappear in the limit of high HMPA concentration as the tetrasolvate **16**. Once again, direct solvation state determination of **16** was precluded by rapid solvent exchange. Nevertheless, mass action effects show an isomeric relationship of **16** to the fully characterized tetrasolvated ion triplet **19** mentioned in (3).

(3) At approximately 1.0–1.5 equiv of added HMPA (per Li), disolvated open dimer **17** can be readily detected and characterized by the ^6Li – ^{15}N and ^6Li – ^{31}P coupling patterns.²⁴ Although it is isomeric to disolvated dimer **15**, it might be more appropriately described as a contact ion paired ion triplet.^{15,25,26} As the HMPA concentrations exceed 1.0 equiv per Li, **17** gives way to tri- and tetrasolvated ion triplets **18** and **19**. The exceedingly large Li–N coupling of the ion triplets seems to indicate a very tightly bound anionic fragment. In the limit of high HMPA concentration, monomer **13**, dimer **16**, and ion triplet **19** are the only observable species and appear to exist in an HMPA concentration independent equilibrium over albeit a limited accessible concentration range.

Effects of HMPA on Lithium Amide Aggregation. The absence of LDA monomer at high HMPA concentrations renders the often cited deaggregating capabilities of HMPA suspect. The results for LiTMP, wherein the delicately balanced monomer–dimer equilibrium exists even in the absence of HMPA, are very revealing indeed. If one sums the concentrations of all monomers and all dimers (including the ion triplets^{26,27}), it becomes apparent that HMPA does not substantially alter the overall aggregation state. Instead, HMPA shows a far greater capacity to effect ionization (separated ion pair formation). This dichotomy was clearly noted by Jackman in a 1987 manuscript.⁴ We hasten to add that Reich has observed clear instances in which HMPA does deaggregate

(26) Fraenkel, G.; Hallden-Abberton, M. P. *J. Am. Chem. Soc.* **1981**, *103*, 5657. Bhattacharyya, D. N.; Lee, C. L.; Smid, J.; Szwarc, M. *J. Phys. Chem.* **1965**, *69*, 612. Bhattacharyya, D. N.; Smid, J.; Szwarc, M. *J. Am. Chem. Soc.* **1964**, *86*, 5024. Vinogradova, L. V.; Zgonnik, V. N.; Nikolaev, N. I.; Tsvetanov, K. B. *Eur. Polym. J.* **1979**, *15*, 545. Arnett, E. M.; Maroldo, S. G.; Schriver, G. W.; Schilling, S. L.; Troughton, E. B. *J. Am. Chem. Soc.* **1985**, *107*, 2091. Cambillau, C.; Bram, G.; Corset, J.; Riche, C. *Now. J. Chim.* **1979**, *3*, 9. Cambillau, C.; Ourevitch, M. *J. Chem. Soc., Chem. Commun.* **1981**, 996. Raban, M.; Noe, E. A.; Yamamoto, G. *J. Am. Chem. Soc.* **1977**, *99*, 6527. Olmstead, W. N.; Bordwell, F. G. *J. Org. Chem.* **1980**, *45*, 3299. Teixidor, F.; Lobet, A.; Casabe, J.; Solans, X.; Font-Altaba, M.; Aguilé, M. *Inorg. Chem.* **1985**, *24*, 2315. Tsvetanov, Ch. B.; Dotcheva, D. T. *J. Polym. Sci., Part A: Polym. Chem.* **1986**, *24*, 2253. Buttrus, N. H.; Eaborn, C.; Hitchcock, P. B.; Smith, J. D.; Stamper, J. G.; Sullivan, A. C. *J. Chem. Soc., Chem. Commun.* **1986**, 969. For a related anionic ion triplet, see Eaborn, C.; Hitchcock, P. B.; Smith, P. B.; Sullivan, A. C. *J. Chem. Soc., Chem. Commun.* **1983**, 827. Viteva, L.; Stefanovsky, Y.; Tsvetanov, C.; Gorrichon, L. *J. Phys. Org. Chem.* **1990**, *3*, 205. See also refs 4 and 6.

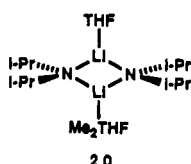
(27) Behavior of ion triplets as one rather than two fragments is a consequence of the extremely low dissociation constants of even the most stabilized ion pairs in THF: Bhattacharyya, D. N.; Lee, C. L.; Smid, J.; Szwarc, M. *J. Phys. Chem.* **1965**, *69*, 608. Wong, M. K.; Popov, A. I. *J. Inorg. Nucl. Chem.* **1972**, *34*, 3615.

lithium salts, often producing the separated ion pairs in the limit.⁸ It appears that the effects of HMPA on organolithium solution structures cannot be generalized at this time.

Comments on Ion Triplets. We mentioned the notion that the open dimer **17** is essentially a contact ion paired ion triplet. We have carried out extensive MNDO calculations on the various solvation states of monomeric, dimeric, and ion triplet forms of both LDA and LiTMP. While these will be described in detail at another time,²⁸ some of the especially pertinent results are worth mentioning. Most importantly, MNDO revealed a high propensity of LiTMP to form open dimers similar to **17** prior to its detection. MNDO calculations further suggest that the open dimers as well as the ion triplets display a 90° rotation of the piperidine rings and a substantial increase in the N–Li–N bond angle (175–180°) in order to alleviate severe steric strain found in the closed dimer structures.²⁹ Overall, these ground-state computations gave one an inescapable sense of a dynamic process, wherein the closed dimers are twisting open to form the ion triplets.

Despite the well-documented role of anionic ion triplets in electrochemistry³⁰ originating from the seminal work of Fuoss in the 1930's,³¹ in only several instances have organolithium ion triplets have been characterized or even detected.^{4,6,26} Several groups^{4,6,7} have argued that anionic ion triplets, by analogy with other main group "ate" complexes,³² should be highly reactive intermediates under ionizing conditions. Our arguments of their importance were made in the context of ion triplet cryptates of metallated hydrazones.⁶ Therefore, it was gratifying to uncover ion triplets **18** and **19** in the LiTMP/HMPA mixtures. It seems quite likely that ion triplets may be prominent reactive intermediates that have eluded detection by masquerading either as ion pairs or simple aggregates. Kinetic investigations founded upon well-characterized ground-state structures could resolve this issue.

Mixed Solvates. Possible Structure–Reactivity Correlation. The direct observation of related mixed solvated dimers **5** and **14** is interesting in several ways. Firstly, the suggestions that lithium dialkylamides in the presence of donor solvents exist as dimers (rather than trimers or higher oligomers)^{16,17} receive strong support; the spectroscopic properties of **5** and **14** are fully *inconsistent* with cyclic trimers and are only consistent with higher oligomers given some unlikely coincidences. Secondly, in a recent report on the metalation of dimethylhydrazones by LDA in mixtures of THF and 2,5-dimethyltetrahydrofuran (Me₂THF) we cited kinetic evidence that mixed solvated dimer **20** is more



reactive than either the corresponding bis(THF) or bis(Me₂THF) solvated dimers.¹⁵ Since **20** does not lend itself to complete characterization due to facile ethereal solvent exchanges, the direct observation of **5** and **14** assumes an added importance. Our interest in the possible roles of mixed solvates was heightened dramatically by studies of 3-pentanone enolization by LDA. Although the stereochemical investigations will be reported in due course, one provocative result showing a selectivity maximum at

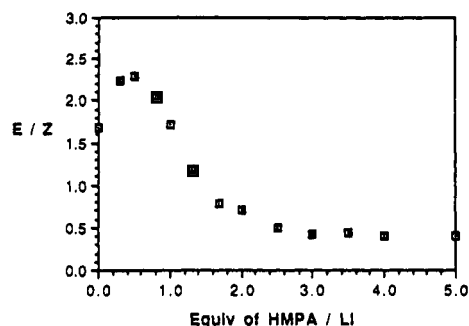
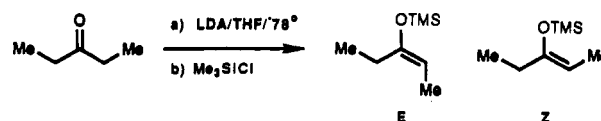


Figure 5.

precisely 0.5 equiv of HMPA per Li (1.0 equiv per Li (1.0 equiv per dimer) is illustrated in Figure 5.^{23,33} Whether this *apparent* correlation of a selectivity maximum optimal concentration of mixed solvated dimer **5** is of mechanistic significance remains to be determined. The chemistry of mixed solvates in organolithium chemistry could prove very interesting in light of analogous chemistry of mixed-ligand complexes in the transition series.

Conclusions

The conclusions drawn from this study are as follows:

(1) On the basis of two representative cases, HMPA does not dramatically shift monomer–dimer equilibria in lithium dialkylamides. HMPA does appear to readily mediate ionization of dimers to form ion triplets.

(2) The direct observation by Reich and Snaith of Li–P coupling in Li–HMPA solvates provides a very important view of the coordination sphere of lithium.

(3) The role of HMPA in organolithium chemistry is substantially more complicated than at least most of us thought, and the effects of HMPA on structure cannot be generalized yet. In fact, one might say that there are still very few fully reliable dictums in organolithium chemistry at this time.

Experimental Section

Reagents and Solvents. Tetrahydrofuran (THF) and *n*-pentane were distilled from blue or purple solutions containing sodium benzophenone ketyl under vacuum. The hydrocarbon stills contained 1% tetraglyme to dissolve the ketyl. HMPA was stirred over Na at rt for 12 h and distilled from the resulting dark green solution under vacuum. Samples were immediately sealed in ampules and opened under N₂ atmosphere prior to each use. ⁶Li metal (95.5% enriched) was obtained from Oak Ridge National Laboratory. The ethyllithium and [⁶Li]ethylithium used to prepare the lithium amides were prepared by the standard literature procedure³⁴ and were recrystallized from hexane and doubly sublimed to remove lithium halide impurities. The isotopically labeled LDA and LiTMP were prepared as analytically pure solids as described elsewhere.^{18,21} The diphenylacetic acid used to determine the solution titers³⁵ 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. ⁶Li spectra were recorded on a Varian XL-400 or Bruker AC 300 spectrometer operating at 58.84 and 44.17 MHz (respectively) and referenced to an external 0.3 M [⁶LiCl]/methanol standard at –100 °C according to the suggestion of Reich and co-workers.⁸ ¹⁵N NMR spectra were recorded on a Varian XL-400 or a Bruker AC 300 NMR spectrometer operating at 40.52 and 30.42 MHz (respectively) and referenced to an external 0.15 M [¹⁵N]aniline/THF standard set at δ 52 ppm using internal [¹⁵N]-2,2,6,6-tetramethylpiperidine at –100 °C (δ 76.12 ppm) and [¹⁵N]diisopropylamine at –100

(28) Romesberg, F. E.; Collum, D. B. Unpublished results.

(29) It should be noted that the ion triplets show inordinate destabilization using MNDO due to problems with electron correlation.

(30) Robinson, R. A.; Stokes, R. H. *Electrolyte Solutions*; Butterworths: London, 1965; Chapter 14. Beronius, P.; Linbäck, T. *Acta Chem. Scand.*, Ser. A **1978**, A32, 423. Beronius, P.; Linbäck, T. *Acta Chem. Scand.*, Ser. A **1979**, A33, 397. Saar, D.; Petrucci, S. J. *Phys. Chem.* **1986**, 90, 3326. Cachet, H.; Cyrot, A.; Fekir, M.; Lestrade, J.-C. *J. Phys. Chem.* **1979**, 83, 2419.

(31) Fuoss, R. M.; Kraus, C. A. *J. Am. Chem. Soc.* **1933**, 55, 2387.

(32) Richey, H. G., Jr.; Farkas, J., Jr. *Organometallics* **1990**, 9, 1778. Corey, E. J.; Hannon, F. J. *Tetrahedron Lett.* **1987**, 28, 5233. Corriu, *Pure Appl. Chem.* **1988**, 60, 99. Pelter, A.; Smith, K. In *Comprehensive Organic Chemistry*; Barton, D. H. R., Ollis, W. D., Eds.; Pergamon Press: New York, 1979; Vol. 3, Chapter 14. Lipshutz, B. H. *Synthesis* **1987**, 325.

(33) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, 98, 2868.

(34) Lewis, H. L.; Brown, T. L. *J. Am. Chem. Soc.* **1970**, 92, 4664. A detailed procedure for the preparation of ethyllithium is described in ref 18.

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

$^{\circ}\text{C}$ (δ 67.6 ppm) as secondary standards. ^{31}P NMR spectra were recorded on a Varian XL-400 spectrometer at 161.82 MHz and referenced to free HMPA set at δ 26.4 ppm according to Reich. NMR probe temperatures are accurate to ± 2 $^{\circ}\text{C}$. The shims were adjusted using ^1H line shape and free-induction decays rather than using the deuterium lock solvent to maximize field homogeneity. Resolution enhancements were performed by Lorentz-Gaussian multiplication of the FID prior to Fourier transformation. The hardware modifications necessary for single frequency irradiations are described elsewhere.¹⁷

The following is a representative procedure for preparing samples for NMR spectroscopic analysis. Working in an inert atmosphere glovebox [$^6\text{Li},^{15}\text{N}$]LiTMP (0.103 g, 0.70 mmol) and diphenylacetic acid (200 mg, 0.942 mmol) were added to separate serum vials containing stir fleas and capped with serum stoppers. An additional serum vial fitted with a stir flea and serum cap, the three samples prepared previously, and four NMR tubes fitted with serum stoppers were removed from the glovebox and placed under positive helium pressure with needle inlets connected to a He/vacuum double manifold. (Helium is used to prevent explosions due to gas condensation). To the vial containing the [$^6\text{Li},^{15}\text{N}$]LiTMP cooled to -78 $^{\circ}\text{C}$ was added THF (1.40 mL) down the walls with constant agitation to minimize local heating. Solutions of HMPA (1.30 M) and diphenylacetic acid (0.0942 M) were prepared by bringing the volumes to 10.0 mL with dry THF (accounting for the volume of the stir flea). The LiTMP titer was determined by adding 0.50 mL of the

LiTMP stock solution to 0.5 mL of THF in the last serum vial and titrated to a yellow-to-colorless endpoint with diphenylacetic acid in THF. The NMR tubes at 77 K were each charged with 250 μL of dry pentane, 0.098 mmol of the [$^6\text{Li},^{15}\text{N}$]LiTMP stock solution, variable quantities of the HMPA stock solution, and enough THF to result in a final volume of 750 μL . Samples were flame sealed at 77 K under reduced pressure and stored at 77 K until the spectroscopic analyses were initiated.

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Supplementary Material Available: ^{15}N NMR spectra of [$^6\text{Li},^{15}\text{N}$]LDA/HMPA, ^{31}P NMR spectra of [^6Li]LDA/HMPA and [^6Li]LiTMP/HMPA, and single frequency decouplings of [$^6\text{Li},^{15}\text{N}$]LiTMP/HMPA (5 pages). Ordering information is given on any current masthead page.

Distorted Amides as Models for Activated Peptide N-C(O) Units. 3. Synthesis, Hydrolytic Profile, and Molecular Structure of 2,3,4,5-Tetrahydro-2-oxo-1,5-propanobenzazepine

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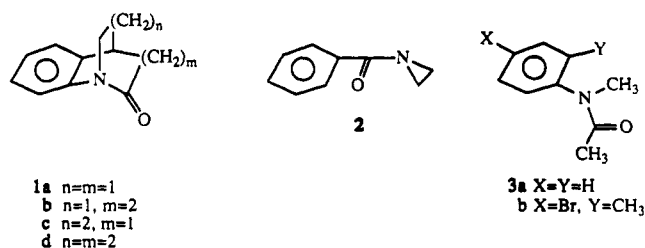
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Received December 18, 1990

Abstract: A distorted amide (2,3,4,5-tetrahydro-2-oxo-1,5-propanobenzazepine (**1d**)) was synthesized and its structure determined by X-ray diffraction. The amidic unit of **1d** is compared with that found in undistorted *p*-bromo-*N*,2-dimethylacetanilide (**3b**) and more distorted 2,3,4,5-tetrahydro-2-oxo-1,5-ethanobenzazepine (**1b**) and 3,4-dihydro-2-oxo-1,4-propanoquinoline (**1c**). The progressive distortion manifests itself in a lengthening of the N-C(O) bond, a slight shortening of the C=O bond, and a twisting about the N-C(O) unit with attendant rehybridization of the N from sp^2 to sp^3 and a slight pyramidalization of the (N)(C)C=O unit. The hydrolysis of **1d** in D_2O and H_2O is compared with those of *N*-methylacetanilide (**3a**), **1b**, **1c**, and **1a** (3,4-dihydro-2-oxo-1,4-ethanoquinoline), the most distorted anilide in the series. In passing from **3a** to **1a**, the attack of OH^- is accelerated by roughly 7 orders of magnitude, while the acid-catalyzed hydrolysis is accelerated by 11 orders of magnitude. Based on the solvent kinetic isotope effects, pH/rate profiles, and activation parameters, a unified mechanism for H_3O^+ - and OH^- -promoted hydrolysis of these anilides is proposed. The effect of varying [acetate] in catalyzing the hydrolysis of **1b** and **1c** in H_2O and D_2O as a function of pL was studied and analyzed in terms of a specific-acid/general-base process involving acetate-promoted delivery of L_2O on protonated amide.

Introduction

Structural distortion of an amide unit away from planarity has been shown to markedly alter its spectroscopic properties and kinetic reactivity toward nucleophilic attack/hydrolysis.¹⁻³ Recent work from these laboratories³ has concentrated on the relationship between hydrolytic reactivity and amidic distortions that involve (1) rotation about and lengthening of the N-C(O) bond and (2) N-pyramidalization. In these studies it was shown that both factors accelerate the attack of nucleophiles on the C=O unit of molecules such as **1a-c** and **2**. Moreover, it was demonstrated that the amidic distortion inherent in **1b** predisposes it toward attack by bifunctional nucleophiles such as β -amino alcohols^{3b-d} and diacids capable of forming cyclic anhydrides^{3e} in a way that

is reminiscent of the serine proteases and aspartate proteinases, respectively.



(1) (a) Pracejus, H. von; Kehlen, M.; Kehlen, H.; Matschiner, H. *Tetrahedron* 1965, 21, 2257. (b) Pracejus, H. von *Chem. Ber.* 1959, 92, 988. (c) Kostyanovskii, R. G.; Mikhlina, E. E.; Levkoeva, E. I.; Yakhontov, L. N. *Org. Mass. Spectrom.* 1970, 3, 1023.

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