On the Structure of Lithium 2,2,6,6-Tetramethylpiperide (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-tetramethylpiperide (LiTMP) in THF/pentane containing varying quantities of hexamethylphosphoramide (HMPA) have been subjected to $^6$Li, $^{15}$N, and $^{31}$P NMR spectroscopy at low temperatures. The LDA dimer serially solvates through a monosolvated and disolvated form as evidenced by both $^6$Li-$^{15}$N and $^6$Li-$^{31}$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 [R$_3$NLiR$_3$]$_2$ $^+$/Li$^+$, bearing both 3 and 4 HMPA ligands on the Li$^+$ cation 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. The general consensus appears to be that HMPA dissociates aggregates to highly reactive monomers, ion pairs, or free ions. 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. They found that excess HMPA converts dimeric lithium anilides to predominantly monomers and low concentrations of anionic ion triplets. More recently, Reich documented the first examples of two-bond Li-P coupling in HMPA-Li solvates, providing a view of lithium ion solvation with unprecedented clarity. Snaithe demonstrated...
that the curious bridged dimer 2 observed crystallographically retains its integrity in solution. Reich and co-workers unequivocally demonstrated that HMPA deaggregates dimeric phenylithium to a monomer [PhLi(HMPA)]

More recently, Denmark exploited the observable two-bond 3$^1$P coupling in phosphorus-stabilized carbanions to demonstrate the dimeric structure. Their use of 3$^1$P decoupling is also notable.

We describe herein 6Li, 15N, and 3$^1$P NMR spectroscopic studies of isotopically enriched lithium diisopropylamide ([6Li]$^2$LiDA and [6Li,15N]$^2$LiDA Solvates)

### Table I. NMR Spectroscopic Data of [6Li]$^2$LiDA and [6Li,15N]$^2$LiDA Solvates

<table>
<thead>
<tr>
<th>compd</th>
<th>6Li δ (m, J\textsubscript{N-Li})</th>
<th>15N δ (m, J\textsubscript{N-Li})</th>
<th>3$^1$P δ (m, J\textsubscript{P-Li})</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>0.0 1.86 (t, 5.0, -)</td>
<td>93.5 (7, 5.5)</td>
<td>26.4 (7, 4.5, 7)</td>
</tr>
<tr>
<td>5</td>
<td>0.5 1.96 (t, 5.5, -)</td>
<td>72.0 (7, 4.5)</td>
<td>26.4 (7, 4.5, 7)</td>
</tr>
<tr>
<td>6</td>
<td>2.0 1.55 (q, 4.4, 4)</td>
<td>74.1 (7, 4.7)</td>
<td>26.3 (7, 4.3)</td>
</tr>
</tbody>
</table>

*Spectra were recorded at 125 °C. The [LITMP] = 0.13 M in an 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. Equivalents of HMPA in the NMR sample from which the tabulated data derive.

### Table II. NMR Spectroscopic Data of [6Li]$^2$LiTMP and [6Li,15N]$^2$LiTMP Solvates

<table>
<thead>
<tr>
<th>compd</th>
<th>6Li δ (m, J\textsubscript{N-Li})</th>
<th>15N δ (m, J\textsubscript{N-Li})</th>
<th>3$^1$P δ (m, J\textsubscript{P-Li})</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>0.0 0.48 (d, 8.5, -)</td>
<td>93.5 (7, 5.5)</td>
<td>26.4 (7, 4.5, 7)</td>
</tr>
<tr>
<td>11</td>
<td>0.0 1.48 (t, 4.8, -)</td>
<td>79.7 (7, 5.5)</td>
<td>26.4 (7, 4.5, 7)</td>
</tr>
<tr>
<td>12</td>
<td>1.0 0.93 (d, 9.0, -)</td>
<td>91.4 (7, 5.5)</td>
<td>28.1 (7, 4.5, 7)</td>
</tr>
<tr>
<td>13</td>
<td>4.0 0.73 (d, 8.5, -)</td>
<td>90.9 (7, 5.5)</td>
<td>26.4 (7, 4.5, 7)</td>
</tr>
<tr>
<td>14</td>
<td>0.5 1.55 (t, 5.1, -)</td>
<td>79.8 (7, 5.5)</td>
<td>26.4 (7, 4.5, 7)</td>
</tr>
</tbody>
</table>

*Spectra were recorded at 0 °C. The [LITMP] = 0.13 M in an 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. Equivalents of HMPA in the NMR sample from which the tabulated data derive.

**Results**

In all of the structures, the numbers of THF solvents depicted are based exclusively on analogy with studies described elsewhere 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
Cyclic and Open Dimers, Ion Triplets, and Monomers

samples have all been prepared at observable species were the result of solvent decomposition, all resonances described prove to and spectroscopic studies were carried out using analytically pure shown to be undetectable. The NMR spectral data are sum-
marized in Tables I. Lithium amides. Suspecting (albeit incorrectly) that some of the and higher solvates, although that conclusion remains marginally of the Discussion.

LDA-HMPA Solvates. Previous studies demonstrated that LDA exists exclusively as a cyclic oligomer. Addition of extra 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 [Li]LDA cause the appearance of mixed solvated dimer 5 at the expense of 4. Dimer 5 displays a singlet and doublet of 4.3 Hz in a 1:1 ratio in the 6Li NMR spectra (Figure 1) and a triplet in the 31P NMR spectra (Table I; supplementary material). The 31P NMR spectrum derived from [Li,15N]LDA 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 31P and 15N coupling, and the singlet appears as a triplet due to 6Li-15N 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. The coupling of the 31P resonance to one neighboring 6Li nucleus also excludes any form of bridging solvate such as LDA.

Addition of up to 1.0 equiv of HMPA per lithium to [Li]LDA converts mixed solvated dimer 5 to the disolvated dimer 6 as evidenced by the appearance of a new 6Li doublet (Δ1.55) and 31P triplet. Analysis of [Li,15N]LDA/HMPA shows the 6Li resonance at Δ 1.55 further split by two neighboring 15N nuclei with the concomitant appearance of a new quintet in the 15N 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, 15N, and 31P NMR spectra along with free HMPA in the 31P spectra. HMPA does not measurably de aggregate LDA.

Overall, the cyclic oligomer structure of LDA remains intact in the presence of excess HMPA. Further, the desymmetricized mixed solvated dimer 5 provides additional evidence 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

![Figure 1](image_url)

![Figure 2](image_url)

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

\[\text{Figure 2.} \ 6Li \text{ NMR spectra of 0.13 M [Li]LITMP in 2:1 THF/pentane at } -115 \degree C. (A) no added HMPA; (B) 0.3 equiv of HMPA/Li; (C) 0.5 equiv of HMPA/Li; (D) 0.8 equiv of HMPA/Li; (E) 1.0 equiv of HMPA/Li; (E) 2.0 equiv of HMPA/Li.\]

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, E. R.; Walker, G. T.; Barr, D.; Snith, R.; Clegg, W.; Reed, D. J. Chem. Soc., Dalton Trans. 1987, 617. See also ref 17.
18 Procedures for the preparation of 6Li and 15N labeled LITMP and LDA as analytically pure solids are described in detail elsewhere: Kim, Y. J.; Bernstein, M.; Galiano Roth, A. S.; Ronesberg, 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.
20 Thermal 6Li-31P 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.
can be frozen on Li NMR time scales coordinated HMPA on this barrier is not known at this time.

The 15N NMR spectrum displays the quintet of resonances of that albeit less direct evidence of a tetrasolvated LiTMP dimer hindered lithium dialkylamides. We hasten to add, however, with a rapid exchange of the two ine uivalent 15N nuclei of the monomer broadens into the base line.) The 15N NMR spectrum displays the quintet of 11 along with a substantially broadened quintet that correlates with the two 13Li 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 15N nuclei of 14 by a facile chair–chair flip mechanism. The 31P NMR spectrum shows a corresponding triplet consistent with a terminal rather than a bridging HMPA.

Figure 3. 6Li NMR spectra of 0.13 M [6Li,15N]LiTMP in 2:1 THF/pentane at -115 °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.

While the 6Li and 15N NMR spectra of doubly labeled samples show the monomer with its characteristic 6Li-15N coupling patterns shifted substantially downfield, rapid solvent exchange precludes detection of the 6Li-31P coupling characteristic of an HMPA solvate. (Similar phenomena have been observed by Reich in a number of instances.)

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 15N-coupled doublet even at the lowest temperatures. In addition, resonances consistent with disolvated dimer 15 and open dimer 17 appear. The sole 6Li resonance of 15 displays clear coupling to a single 31P nucleus as well as coupling to two equivalent 15N nuclei (as shown by single frequency decoupling; supplementary material). The 31P 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 31P 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 6Li and 15N double labeling studies reported elsewhere confirmed the conclusion of Fox and Renaud that LiTMP (0.1 M in THF at -125 °C) exists as a 1:1 mixture of monomer 10 and dimer 11. Addition of 0.3 equiv of HMPA (per Li) to [6Li]LiTMP causes the appearance of mixed solvated dimer 14 and downfield shifting of the monomer resonance (Figure 2). (At -125 °C the monomer broadens into the base line.) In direct analogy with LDA, the 6Li spectrum of [6Li]LiTMP reveals two resonances in a 1:1 ratio for mixed solvated dimer 14, with one showing coupling to a single 31P nucleus. The corresponding 6Li spectrum of [6Li,15N]LiTMP shows that both are coupled to a common pair of chemically equivalent 15N nuclei (Figure 3). The 15N 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 15N nuclei of 14 by a facile chair–chair flip mechanism. The 31P 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.
23 The barrier to chair–chair inversion of LiTMP–LIX mixed aggregates can be frozen on 6Li NMR time scales below -80 °C. The influence of a coordinated HMPA on this barrier is not known at this time.

[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 [6Li,15N]LiTMP, the aforementioned singlet appears as a doublet of doublets (J_{6Li,15N} = 8.5 Hz and 5.2 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 13N 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 15N 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 15N nucleus couples to the adjoining 6Li with a large coupling constant characteristic of the monomer. In contrast, the internal 15N 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 15N nuclei of [Li(LiTMP)3(THF)]1−) on a doublet of doublets shifted singlet in a 1:1 ratio. The corresponding 6Li spectrum of [Li,15N]LiTMP exhibits a very strongly coupled triplet (J_{6Li,15N} = 9.9 Hz) in place of the singlet, while the quartet remains unperturbed by the 15N isotopic substitution. The 13N 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.

In excess of 2.0 equiv of HMPA/Li, the 6Li quartet corresponding to the 6Li(LiTMP)THF regenon of the tri-HMPA-solvated ion triplet 18 is converted to a quartet indicating formation of the tetrasolvated ion triplet 19. As the ion triplet reaches its limiting solvated state, the 6Li resonance of the monomer ceases to shift upfield. Since the equilibrium of the monomer to disolvated open dimer 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 intermediary of downfield shifted mixed solvated dimer 12. MNDO calculations lend support to the imlple solvation states of 10, 12, and 13.

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 13N and 6Li spectra of [Li,15N]LiTMP in the limit of high HMPA concentrations show a quartet and triplet (respectively) due to 6Li−15N coupling consistent with a cyclic dimer structure; the 6Li spectra derived from [6Li]LiTMP show a corresponding singlet. Clearly, the absence of 6Li−15N must be a result of rapid solvent exchange. The chemical shift of the 15N 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, a result 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.** 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 19 can be serially detected and characterized by the 6Li−15N and 6Li−31P coupling patterns. Although it is isomeric to disolvated dimer 15, it might be more appropriately described as a contact ion pair dimer, 15,13,15. As the HMPA concentrations exceed 1.5 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.
lithium salts, often producing the separated ion pairs in the limit. 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 solution states of monomeric, dimeric, and ion triplet forms of both LDA and LiTMP. While these will be described in detail at another time, 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. 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 electrochemistry originating from the seminal work of Fuoss in the 1930's, in only several instances have organolithium ion triplets been characterized or even detected. Several groups have argued that anionic ion triplets, by analogy with other main group "ate" complexes, 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. Therefore, it was gratifying to uncover a selectivity maximum at one provocative result showing a selectivity maximum at another time, 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. 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.

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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. 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. Li metal (95.5% enriched) was obtained from Oak Ridge National Laboratory. The ethylidinium and [Li]ethylidinium used to prepare the lithium amides were prepared by the standard literature procedure and were recrystallized from hexane and doubly sublimed to remove lithium halide impurities. The isotopically labelled LDA and LiTMP were prepared as analytically pure solids as described elsewhere. The diphénylacetic acid used to determine the solution 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 38.84 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. ¹³C 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 [⁰¹C]naphthalene/THF standard set at δ 52 ppm using internal [⁰¹C]-2,2,6,6-tetramethylpiperidine at -100 °C (δ 76.12 ppm) and [⁰¹C]disopropylamine at -100 °C.

**References.**

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

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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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 amide unit of 1d is compared with that found in undistorted p-bromo-N,N-dimethylanilide (3b) and more distorted 2,3,4,5-tetrahydro-2-oxo-1,5-ethanobenzazepine (1b) and 3,4-dihydro-2-oxo-1,4-propanoquinoline (1e). 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 of the N–C(O) bond, with attendant rehybridization of the N from sp2 to sp3 and a slight pyramidalization of the (N)(C)C=O unit. The hydrolysis of 1d in D2O and H2O is compared with those of N-methylacetanilide (3a), 1b, 1e, 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 H2O* and OH*–promoted hydrolysis of these anilides is proposed. The effect of varying [acetate] in catalyzing the hydrolysis of 1b and 1e in H2O and D2O as a function of pL was studied and analyzed in terms of a specific-acid/general-base process involving acetate-promoted delivery of L20 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 laboratories 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 N–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 alcohols4 and dicarboxylic anhydrides5 in a way that is reminiscent of the serine proteases and aspartate proteinas.