Mixed Aggregation of Lithium Enolates and Lithium Halides with Lithium 2,2,6,6-Tetramethylpiperidide (LiTMP)

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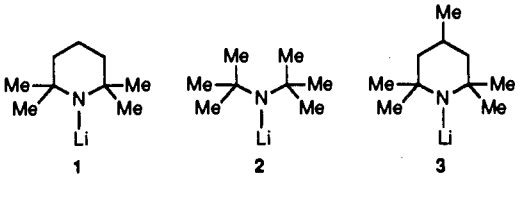
Abstract: ^{6}Li and ^{15}N NMR spectroscopic studies of [^{6}Li]-LiTMP and [^{6}Li,^{15}N]-LiTMP support an earlier suggestion that LiTMP exists as a dimer–monomer mixture in THF. In the presence of [^{6}Li]-lithium cyclohexenolate as a representative enolate, one observes mixed aggregates with 2:1, 1:1, and 2:2 LiTMP/enolate stoichiometries. Evidence of conformational isomerism is observed in the slow-exchange limit. Studies of conformationally mobile [^{6}Li]-lithium di-*tert*-butylamide and conformationally locked [^{6}Li]-lithium 2,2,4,6,6-pentamethylpiperidide shed further light on the spectroscopic consequences of the chair form of the piperidine ring system. The corresponding studies of LiTMP/LiBr mixtures reveal the predominance of a 1:1 mixed aggregate, a lower propensity to form 2:1 mixed aggregates than the analogous lithium enolate case, and no tendency whatsoever to form 2:2 mixed aggregates. LiTMP/LiCl mixtures appear to contain two conformational isomers of the 2:1 stoichiometry analogous to the LiTMP enolate case as well as a 1:1 mixed aggregate in the limit of high LiCl concentration. Severe spectral overlaps and several unassigned resonances render the LiTMP–LiCl mixed aggregate structure assignments the most tentative.

Introduction

During the evolution of structural and mechanistic organolithium chemistry, an appreciation of the importance of aggregation and mixed aggregation as determinants of reactivity and selectivity has been slow to develop. Pioneering efforts to understand the details of anionic polymerizations uncovered the existence and rate effects of alkyllithium–lithium alkoxide and alkyllithium–lithium halide mixed aggregates.[1] However, the possible consequences of mixed aggregation for a large number of commonly used reaction types remained unexplored until several seminal reviews by Seebach brought the key issues into focus.[2] There now exists a substantial number of instances wherein mixed aggregation effects are implicated.[2,3] Nevertheless, the number of cases in which the structures of mixed aggregates in solution have been studied in detail is still quite limited,[2,4,5] and the number of studies affording even approximate correlations of well-characterized mixed aggregates with changes in product selectivity or reaction rate is vanishingly small.[6]

We describe NMR spectroscopic studies of lithium tetramethylpiperidide (LiTMP, **1**). We will provide tentative structure assignments for an ensemble of LiTMP–lithium enolate and LiTMP–lithium halide mixed aggregates (Scheme I) using ^{6}Li and ^{15}N NMR spectroscopy as the primary structure probe.[7,8] Studies of conformationally mobile [^{6}Li]-lithium di-*tert*-butylamide (**2**) and conformationally locked [^{6}Li,^{15}N]-lithium 2,2,4,6,6-pentamethylpiperidide (**3**) shed further light on the spectroscopic consequences of the chair form of the piperidine ring system. While it seems likely that enolization selectivities described in the preceding paper[9] are a consequence of mixed aggregation



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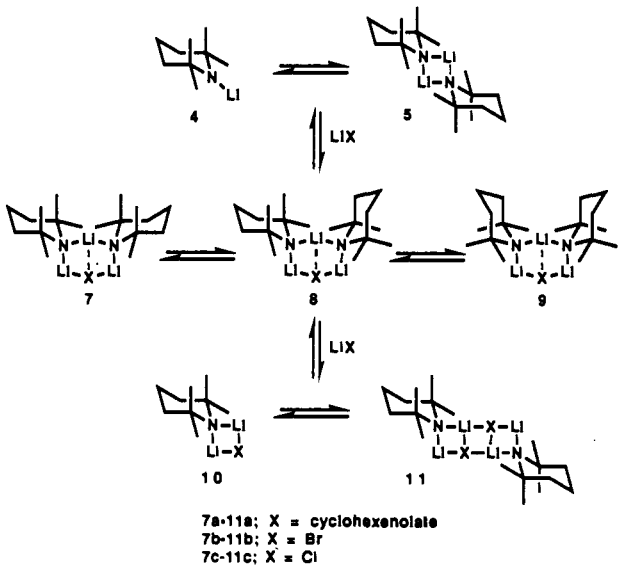
effects, we will *not* attempt to correlate structure and reactivity. Nevertheless, the results described below highlight the limitations of simplistic stereochemical models and underscore the complexity of ketone enolizations and the increasingly popular in situ TMSCl trapping protocol.[10-12]

Results

All spectroscopic studies described herein were carried out with recrystallized[13] LiTMP prepared from recrystallized, doubly sublimed ethyllithium.[14] The LiTMP stock solutions were freshly prepared and their titer checked before each experiment. The lithium halides were carefully purified and shown to contain <1% protic impurities. Except where noted, the lithium cyclohexenolate was prepared from LiTMP in hexane and isolated as a spectroscopically pure white solid as described elsewhere.[14b] Many of the nuclear magnetic resonance (NMR) spectra were reproduced 3–5 times with use of a large number of independently prepared samples of LiTMP and LiX additives. Mixtures of LiTMP and LiCl are referred to as LiTMP/LiCl. Samples enriched in ^{6}Li (95%) and ^{15}N (99%) are labeled with the appropriate prefix (e.g. [^{6}Li,^{15}N]-LiTMP/LiCl). All other mixtures are named similarly.

LiTMP and LiPMP Solution Structures. Renaud and Fox observed LiTMP in THF by ^{7}Li NMR spectroscopy; two distinct structural forms were tentatively assigned as dimer and monomer.[15] We obtained further support for the assignments using [^{6}Li,^{15}N]-LiTMP in conjunction with ^{6}Li and ^{15}N NMR spectroscopy (Figure 1 and Tables I and II).[7] The multiplicities[16] of the ^{6}Li and ^{15}N resonances are consistent with those of a mixture of monomer and cyclic aggregate.

Scheme I



A third species is observed that appears only at elevated temperatures as a quartet in the ^{6}Li spectra (Figure 1C). We suggest the apparent LiN_3 connectivity is the result of rapid *intramolecular* exchange of a species bearing three ^{15}N nuclei in total. This hypothesis is supported by analogy with alkyllithiums[17] as well as the small (2.2 Hz) coupling constant. A full structure proof has been precluded so far by (1) the absence of this species at temperatures wherein intramolecular exchange would be slow and (2) an inordinate increase in the ^{15}N T_1 values (≥120 s) at the higher temperatures. The new species does *not* appear to be a simple trimer, however, as indicated by an *increase* in its relative concentration upon 10-fold dilution. We suspect that it may contain LiOH or Li_2O units that normally are not observable in the low-temperature spectra. In any event, if one assumes all species undergo the rapid *intra*molecular site–site exchange at the elevated temperatures, then the assignment of the major aggregated form of LiTMP as a dimer rather than a trimer gains additional support.[18] See Note Added in Proof.[33]

To determine the extent that conformational isomerism of LiTMP could affect the NMR spectral complexity, we recorded the ^{13}C NMR spectra under concentrations that greatly favor the dimer (0.2 M) over the temperature range −130 to −20 °C (Tables III and IV).[19] In principle, one might see a total of four methyl resonances arising from the axial and equatorial sites in conformational isomers **5** and **12**. In practice, a pair of methyl resonances (1:1) are observed below −110 °C. Since rapid chair–chair interconversions would reult in time-averaged exchange of *all four* methyl groups, the data suggest that LiTMP exists as a single conformer. The three (rather than six) ^{13}C resonances for the ring carbons and a single ^{15}N resonance support the assignment of the methyls as axial and equatorial rather than deriving from two chemically distinct piperidine units. The free energy of activation for the chair–chair interconversion of LiTMP is comparable to that of 2,2,6,6-tetramethylpiperidine[20] (Table IV). The

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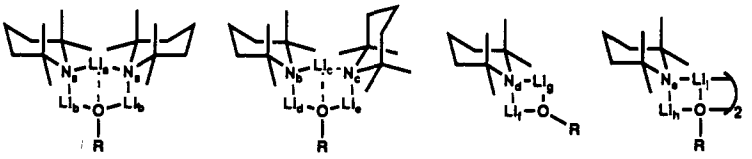
Table I. ^{6}Li NMR Spectroscopic Data of [^{6}Li,^{15}N]-LiTMP and [^{6}Li,^{15}N]-LiTMP/Lithium Cyclohexenolate Mixtures



7a **8a** **10a** **11a**

resonance	equiv of ^{6}Li enolate	temp, °C	δ, ppm	mult (*J*, Hz)[a]	T_1, s	connectivity	assign[b]
LiTMP dimer	0.0	−115	1.48	t (4.9)	1.3		**5**
LiTMP monomer	0.0	−115	0.50	d (8.5)	2.4		**4**
Li_a	0.67	−120	2.01	t (5.2)	1.3	N_a–Li_a–N_a	**7a**
Li_b	0.67	−120	0.60	d (5.5)	2.2	N_a–Li_b	**7a**
Li_c	0.67	−120	1.51	t (5.2)	1.6	N_b–Li_c–N_c	**8a**
Li_d	0.67	−120	0.29	d (5.7)	2.5	N_b–Li_d	**8a**
Li_e	0.67	−120	0.11	d (–)[c]	*c*	N_c–Li_e	**8a**
Li_f	0.67	−120	1.07	d (5.7)	2.1	N_d–Li_f	**10a**
Li_g	0.67	−120	0.11	d (4.4)	3.5	N_d–Li_g	**10a**
Li_h	1.5	−120	0.49	d (5.0)	3.4	N_e–Li_h	**11a**
Li_i	1.5	−120	0.05	d (4.8)	6.6	N_e–Li_i	**11a**
Li cyclohexenolate	1.5	−120	−0.08	s	18		**15**

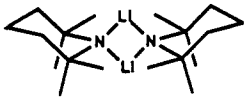
[a] s = singlet, d = doublet, t = triplet, q = quartet. The coupling constants were measured after resolution enhancement. [b] Assignment of structure **7a** rather than **9a** and the assignments of axial and equatorial lithium resonances are purely arbitrary as detailed in the text. [c] Overlap with Li_g resonance precluded a precise measurement of J_{Li-N} and T_1.

Table II. ^{15}N NMR Spectroscopic Data of [^{6}Li,^{15}N]-LiTMP and [^{6}Li,^{15}N]-LiTMP/Lithium Cyclohexenolate Mixtures

resonance	equiv of ^{6}Li enolate	temp, °C	δ, ppm	mult (*J*, Hz)[a]	connectivity	assign[b]
[^{15}N]-TMP		−115	75.6			
N of dimer	0.0	−115	79.7	quint (4.8)		**5**
N of monomer	0.0	−115	93.5	t (8.5)		**4**
N_a	0.67	−120	82.2	quint (5.7)	Li_a–N_a–Li_b	**7a**
N_b	0.67	−120	83.8	quint (5.0)[c]	Li_c–N_b–Li_d	**8a**
N_c	0.67	−120	86.1	tt (4.8, 5.4)	Li_c–N_c–Li_e	**8a**
N_d	0.67	−120	82.0	tt (4.3, 5.7)	Li_f–N_d–Li_g	**10a**
N_e	1.5	−120	83.7	quint (5.0)[c]	Li_h–N_e–Li_i	**11a**

[a] t = triplet, tt = triplet of triplets, quint = quintet. [b] Assignment of structure **7a** rather than **9a** and the assignments of inequivalent ^{15}N resonances in **8a** are purely arbitrary as detailed in the text. [c] Resonances appear to be triplet of triplets, but coupling constants are obscured by N_b and N_e overlap.

existence of a single ^{6}Li dimer resonance further argues in favor of C_{2h} conformational isomer **5** rather than the C_{2v} isomer **12**. Although it cannot be rigorously established that the slow exchange limit has been attained given the absence of definitive ^{6}Li, ^{13}C, and ^{15}N chemical shifts for *both* conformers, evidence cited below on a conformationally locked analogue renders the C_{2v} dimer **12** very unlikely.



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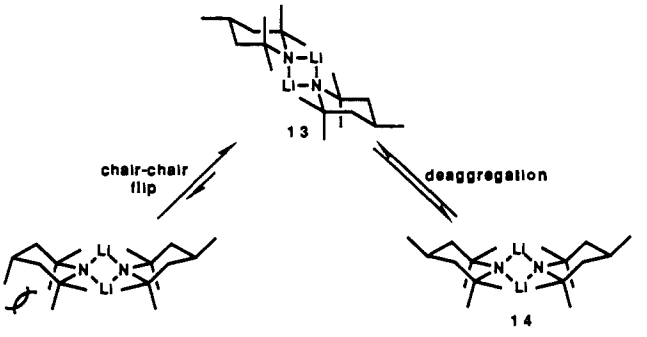
We further addressed the problem of rapid conformational exchange using lithium 2,2,4,6,6-pentamethylpiperidide (LiPMP, **3**). A relatively facile chair–chair conformational flip in LiTMP interconverts stereoisomers **5** and **12** and causes Li–Li and Me–Me site exchange. In contrast, the additional 4-methyl substituent of LiPMP precludes such a pathway, mandating the exchanges of isomers **13** and **14** (analogous to **5** and **12**) proceed via a less efficient mechanism involving N–Li bond rupture. At the same time, the remote substituent should have very little influence on the stereoisomer or monomer–dimer distributions. In the event, [^{6}Li]-LiPMP and [^{6}Li,^{15}N]-LiPMP were prepared as described in the Experimental Section and analyzed spectroscopically. In the low temperature limit (−115 °C), the ^{6}Li NMR spectrum of [^{6}Li-LiPMP] shows a dimer–monomer ratio that is indistinguishable from that of [^{6}Li]-LiTMP with chemical shifts (δ 1.50 and 0.48 ppm) that differ only slightly. The single dimer resonance is consistent with conformational isomer **13** and inconsistent with isomer **14** (Table III). Moreover, the ^{6}Li and ^{15}N NMR spectra of [^{6}Li,^{15}N]-LiPMP display a doublet of doublets (δ 1.50 ppm, J_{Li-N} = 4.5 and 5.1 Hz) and triplet of triplets (δ 76.1, J_{Li-N} = 4.7 and 5.2 Hz), respectively, as a result of differential axial and equatorial Li–N coupling (Figure 2A) in the dimer. Conformers **13** and **14** would both be expected to show a triplet-of-triplets in the ^{15}N NMR spectrum by virtue of slightly different coupling to axial and equatorial ^{6}Li nuclei. However, it is doubtful that the single ^{6}Li dimer resonance of [^{6}Li]-LiPMP could correspond to two overlapping ^{6}Li resonances of C_{2v} isomer **14** given that axial and equatorial lithium nuclei of LiTMP–LiX mixed aggregates resonate at dramatically different chemical shifts (see below). Even so, the ^{6}Li dimer resonance of [^{6}Li,^{15}N]-**14** deriving from two superimposed triplets could not give rise to the observed doublet-of-doublets (Figure 2B). Thus, the results from LiPMP exclude C_{2v} dimer **14**. They do not, however, exclude higher aggregates of C_{nh} symmetry.[33]



Solution Structures of LiTMP/Lithium Enolate Mixed Aggregates. We suspected the intervention of LiTMP–lithium enolate

Table III. ^{13}C NMR Spectroscopic Data of LiTMP and LiTMP/LiX Mixed Aggregates in THF/Hexane

compd	carbon	temp, °C	δ, ppm
LiTMP dimer (**5**)	C_1	−20	53.1
	C_2	−20	43.1
	C_3	−20	20.9
	$C_{4/5}$	−20	36.3
	C_1	−125	52.3
	C_2	−125	42.6
	C_3	−125	20.2
	C_4	−125	32.2
	C_5	−125	38.3
LiTMP·LiBr (**10b**)	C_1	−20	52.3
	C_2	−20	43.0
	C_3	−20	20.8
	$C_{4/5}$	−20	35.2
	C_1	−120	52.2
	C_2	−120	42.7
	C_3	−120	20.8
	C_4	−120	32.6
	C_5	−120	37.7
LiTMP·LiCl (**10c**)	C_1	−20	52.3
	C_2	−20	43.1
	C_3	−20	21.0
	$C_{4/5}$	−20	35.1
	C_1	−108	52.2
	C_2	−108	42.8
	C_3	−108	21.0
	C_4	−108	32.5
	C_5	−108	37.8
LiPMP dimer (**13**)	C_1	−20	54.2
	C_2	−20	52.7
	C_3	−20	26.0
	C_4	−20	33.8
	C_5	−20	39.1
	C_6	−20	24.7
	C_1	−108	54.1
	C_2	−108	52.5
	C_3	−108	25.9
	C_4	−108	33.6
	C_5	−108	38.9
	C_6	−108	24.8

Table IV. Activation Energies for the Site–Site Interconversion of LiTMP and LiTMP/LiX Mixtures[a]

sample (1:1.5)	freq	site exchange[b]	ΔG_{act}, kcal/mol	T_c,[c] °C
TMP	100.56	Me_{ax}–Me_{eq}	8.0[24]	−100[24]
LiTMP	100.56	Me_{ax}–Me_{eq}	7.0	−110
LiTMP/LiBr	100.56	Me_{ax}–Me_{eq}	9.0	−67
LiTMP/LiBr	50.30	Me_{ax}–Me_{eq}	9.0	−73
LiTMP/LiBr	58.84	Li_f–Li_g	9.1	−83
LiTMP/LiBr		Li_f–Li_g	9.1 (calcd[d])	−83
LiTMP/LiCl	100.56	Me_{ax}–Me_{eq}	9.0	−65
LiTMP/LiCl	50.30	Me_{ax}–Me_{eq}	9.1	−71
LiTMP/LiCl	58.84	Li_i–Li_j	9.2	−82
LiTMP/LiCl		Li_i–Li_j	9.3 (calcd[d])	−82

[a] Samples were recorded as 0.2 M solutions in 3:1 THF-d_8/*n*-pentane. [b] See Tables V and VII for assignments of Li resonances. The carbon multiplicities were determined by gated decoupling, while the attribution as axial and equatorial was not rigorously determined. [c] T_c corresponds to the coalescence temperature (estimated error: ±2 °C). [d] The calculated value of ΔG_{act} for Li–Li site exchange derives from measurements of the Me_{ax}–Me_{eq} site exchange on a 400 MHz spectrometer (100.56-MHz operating frequency) and a 200-MHz spectrometer (50.30-MHz operating frequency).

mixed aggregates as the source of the conversion-dependent 3-pentanone enolization selectivities.[9] Structural studies using the enolate(s) of 3-pentanone were precluded by the added complexities accompanying the *E*/*Z* mixtures. Accordingly, we turned to cyclohexanone enolate **15** as a model for *E* enolates. The results of ^6Li NMR spectroscopic studies on [^6Li]-LiTMP/**15** and

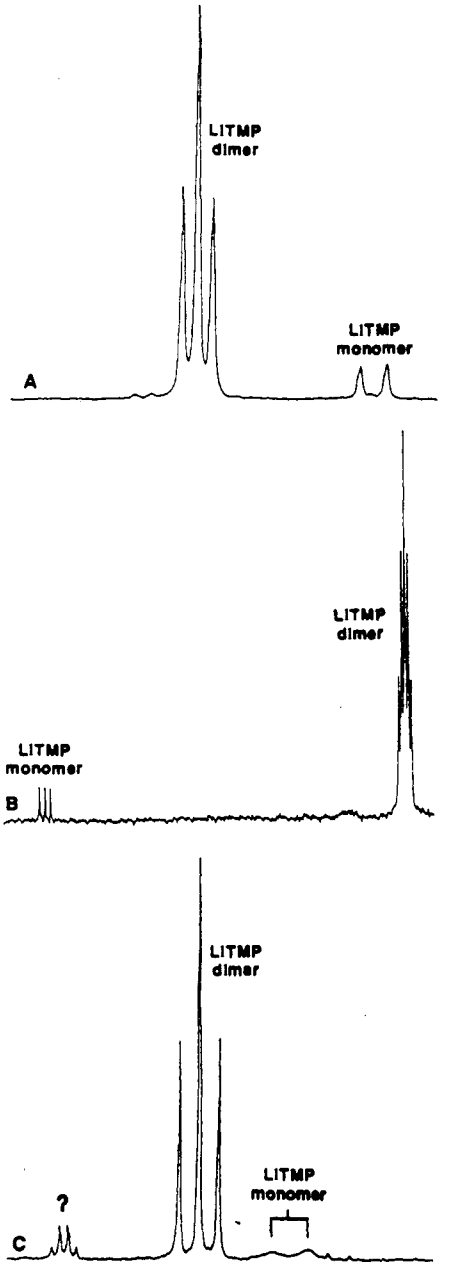
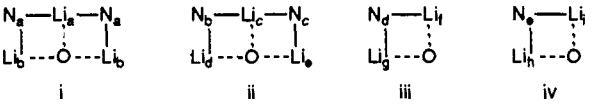
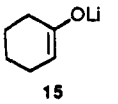


Figure 1. NMR spectra of 0.10 M [^6Li,^{15}N]-LiTMP in 3:1 THF/pentane: (A) ^6Li NMR spectrum at −115 °C; (B) ^{15}N NMR spectrum at −115 °C; (C) ^6Li NMR spectrum at −35 °C.

Chart I



[^6Li,^{15}N]-LiTMP/**15** mixtures are illustrated in Figure 3 and listed in Table I. A solitary singlet at −0.08 ppm observed in the ^6Li spectrum of enolate **15** in the absence of LiTMP is consistent with



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a number of aggregation state topologies, including that of a cubic tetramer inferred from NMR spectroscopic, colligative, and crystallographic studies.[21] By systematically changing the

(21) For a review of the solution structure and mechanistic studies of enolates and phenolates see: Jackman, L. M.; Bortiatynski In *Comprehensive Carbanion Chemistry*; in press.

Table V. ^{6}Li NMR Spectroscopic Data of [^{6}Li,^{15}N]-LiTMP/LiBr Mixtures

7b **10b**

resonance	equiv of ^{6}LiBr	temp, °C	δ, ppm	mult (J, Hz)[a]	T_1, s	connectivity	assign[b]
Li_j	0.5	−120	1.29	t (5.4)	1.3	N_f–Li_j–N_f	**7b**
Li_k	0.5	−120	0.57[c]	d (5.1)[c]	*c*	N_f–Li_k	**7b**
Li_l	1.5	−120	1.51	d (5.6)	2.4	N_g–Li_l	**10b**
Li_m	1.5	−120	0.56	d (5.1)	3.7	N_g–Li_m	**10b**
LiBr	1.5	−120	0.46	s	40		

[a] s = singlet, d = doublet, t = triplet. The coupling constants were measured after resolution enhancement. [b] Assignment of structure **7b** rather than **9b** and the assignments of axial and equatorial lithium resonances are purely arbitrary as detailed in the text. [c] Li_k is hidden under Li_m and appears by decoupling. The overlap precluded a precise measurement of J_{Li-N} and T_1.

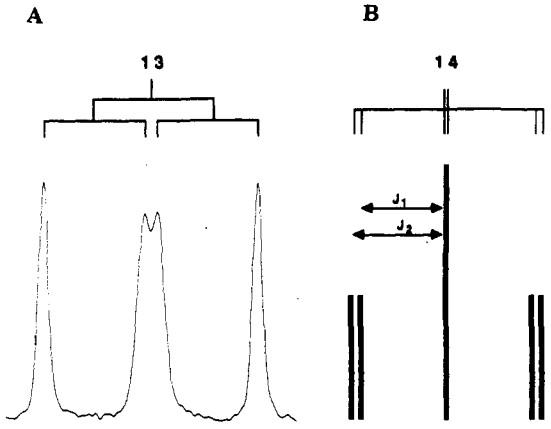


Figure 2. (A) ^{6}Li NMR spectrum of 0.10 M [^{6}Li,^{15}N]-LiPMP in 3:1 THF/pentane at −115 °C showing resonance of dimer **13**; (B) rendition of a spectrum of [^{6}Li,^{15}N]-LiPMP assuming conformer **14** with coincidental ^{6}Li chemical shifts of the inequivalent ^{6}Li nuclei.

LiTMP/**15** proportions as well as the absolute concentrations, nine mixed aggregate resonances can be observed and classified into three groups: those favored at high LiTMP/**15** ratio (labeled Li_a–Li_e), those favored at low LiTMP/**15** ratio (labeled Li_f and Li_g), and those favored at low LiTMP/**15** ratio *and* high absolute concentration (labeled Li_h and Li_i). The changes in the ^{6}Li NMR spectra occur with concomitant changes in the ^{15}N NMR spectra (Figure 4 and Table II). Single-frequency decoupling experiments[22] (Supplementary Material) afforded ^{6}Li–^{15}N resonance correlations (cf. Tables I and II) and, in turn, the partial structures i–iv illustrated in Chart I.

The concentration independence of the intensities within each of these three groups implicates either three structurally complex mixed aggregates or three groups of isomers. Evidence that the spectral complexity arises from conformational isomerism was accrued from several independent sources.

(1) The soft equilibrium even in the limit of a high enolate/LiTMP ratio prevents a detailed analysis of the conformational properties of **10a**. However, measurements of coalescence temperatures of the isostructural 1:1 LiTMP/LiX mixed aggregates **10b** and **10c** (see below) show that the Me_{ax}–Me_{eq} and the Li_{ax}–Li_{eq} site exchanges have the same activation energies within experimental error (Table IV), while the barrier to exchange between the 1:1 LiTMP/LiX mixed aggregates with free halides is substantially higher.[23]

(2) Cursory examination of *t*-Bu_2NLi/**15** by ^{6}Li NMR spectroscopy reveals a 1:1 mixed aggregate displaying only a single lithium resonance (δ 0.68 ppm), contrasting with the two (axial and equatorial) lithium resonances observed in the conformationally constrained 1:1 LiTMP/**15** mixed aggregate. The spectral simplification in this instance suggests the cyclic piperidyl ring as the source of the unexpected complexity in the spectra of LiTMP/**15** mixtures. Interestingly, as a result of the increased steric demands of the (*t*-Bu)$_2$N fragment, the 2:1 *t*-Bu_2NLi/**15** mixed aggregates do not build up to appreciable concentrations.

(3) ^{6}Li NMR spectra of mixtures of [^{6}Li]-LiPMP and enolate **15** are nearly indistinguishable from the analogous LiTMP/**15** mixtures. More specifically, the ^{6}Li spectrum of a 1:2 mixture of conformationally locked [^{6}Li]-LiPMP and enolate **15** shows two resonances (δ 1.02 and 0.15 ppm) consistent with **16a** in analogy with mixed aggregate **10a**. However, the two resonances of **16a** coalesce at substantially higher temperatures. Thus, preclusion of Li–Li site exchange by a chair–chair flip correlates well with reduced exchange rates. More detailed studies of LiPMP/LiX mixtures in progress should be especially revealing.

16a; X = cyclohexenolate
16b; X = Br
16c; X = Cl

On the basis of the concentration dependencies, multiplicities, and resonance correlations we derived the overall structure assignments summarized in Scheme I. The unsymmetric 2:1 mixed aggregate **8a** and 1:1 mixed aggregate **10a** (corresponding to connectivity fragments ii and iii) are relatively unambiguous assignments. The assignment of 2:2 mixed aggregate **11a** is based on the similarity of *its spectral properties to* ***10a*** *taken in conjunction with the concentration dependence* of the equilibrium. Similar four-rung ladder structures have been observed crystallographically.[24] Reducing the THF concentration increases the concentration of the 2:1 and 2:2 mixed aggregates at the expense of **10a** consistent with the laddering principle put forth by Snaith and co-workers.[25] This seems to suggest that the 2:1 and 2:2 mixed aggregates are at a lower per-lithium solvation state.

We hasten to add, however, that the symmetric mixed trimer corresponding to partial structure i could be either **7a** or **9a**. Similarly, we do not know which resonance of the axial/equatorial pairs Li_d/Li_e of **8a**, Li_f/Li_g of **10a**, and Li_h/Li_i of **11a** corresponds to the axial and which to the equatorial. The most important unresolved issue is whether the 2:1 mixed trimers are ladders (with the central dotted line corresponding to a discrete LiX interaction) or simple cyclic trimers.

Solution Structures of LiTMP/LiBr Mixed Aggregates. Spectroscopic analyses of [^{6}Li]-LiTMP/LiBr and [^{6}Li,^{15}N]-LiTMP/LiBr reveal a much simpler scenario. Low concentrations

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

(23) We also noted in some early studies on the LiTMP/LiCl mixed aggregates that the peak shapes and coalescences are completely independent of the donor solvent and LiTMP absolute concentrations.

(24) 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 and references cited therein.

(25) For extensive reviews of structure studies on N–Li species, see: Mulvey, R. E. *Chem. Soc. Rev.* **1991**, *20*, 167. Gregory, K.; Schleyer, P. v. R.; Snaith, R. *Adv. Organomet. Chem.* In press.

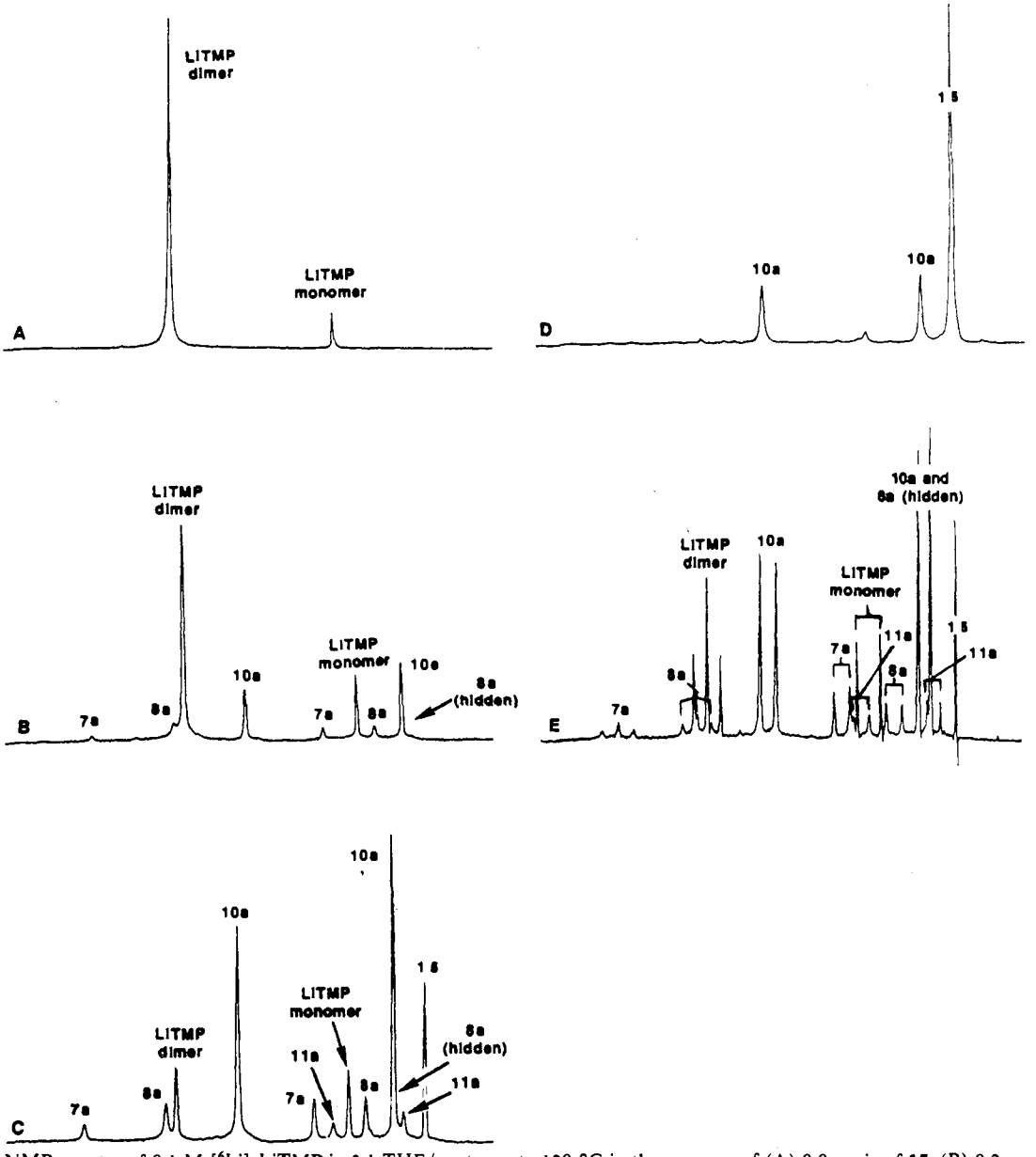


Figure 3. ^{6}Li NMR spectra of 0.1 M [^{6}Li]-LiTMP in 3:1 THF/pentane at −120 °C in the presence of (A) 0.0 equiv of **15**, (B) 0.2 equiv of **15**, and (C) 1.0 equiv of **15**. Spectrum D is at 0.02 M [^{6}Li]-LiTMP with 4 equiv of **15** prepared by adding cyclohexanone to the appropriate concentration of [^{6}Li]-LiTMP. Spectrum E is of 0.12 M with 0.7 equiv of **15** prepared by adding cyclohexanone to the appropriate concentration of [^{6}Li,^{15}N]-LiTMP. The hidden resonance of **8a** can be detected by decoupling the appropriate ^{15}N nuclei of either **8a** or **10a** (Table II).

Table VI. ^{15}N NMR Spectroscopic Data of [^{6}Li,^{15}N]-LiTMP/LiBr Mixtures

resonance	equiv of $^{6}LiBr$	temp, °C	δ, ppm	mult (J, Hz)[a]	connectivity	assign[b]
N_f	0.5	−120	86.2	quint (5.2)	Li_k–N_f–Li_j	**7b**
N_g	1.5	−120	83.1	quint (5.3)	Li_l–N_g–Li_m	**10b**

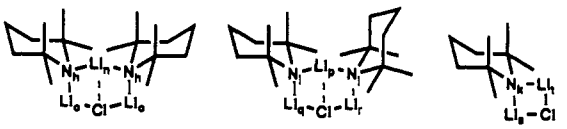
[a] quint = quintet. [b] Assignment of structure **7b** rather than **9b** is purely arbitrary as detailed in the text.

dimer **10b**. As the LiBr/LiTMP ratio exceeds 1:1, the LiTMP of a symmetric 2:1 mixed aggregate (**7b** or **9b**) are observable at low LiBr concentrations (Figures 5 and 6, Tables V and VI). However, the other symmetric and the unsymmetric 2:1 mixed aggregate (**8b**) are not detectable at any LiTMP/LiBr ratio—a result which contrasts sharply with the LiTMP/lithium enolate mixtures (vide supra) and LiTMP/LiCl mixtures (vide infra). For the most part, increments of LiBr produce monotonically increasing concentrations of 1:1 mixed aggregate **10b** showing two ^{6}Li resonances (Li_l and Li_m; 1:1) and one ^{15}N resonance (N_f). The multiplicities and atomic connectivities are consistent with mixed is consumed and only the 1:1 mixed aggregate **10b** and free LiBr are observed. As before, assignment of Li_s and Li_t as axial and equatorial lithiums of **10b** stems from (1) cursory studies of (t-Bu)$_2$NLi/LiBr showing a single mixed aggregate ^{6}Li resonance (δ 0.90 ppm) in the limit of high LiBr concentration consistent with a conformationally unlocked 1:1 dimer structure rather than a 2:2 ladder, (2) comparable activation energies for Me_{ax}–Me_{eq} and Li_l–Li_m site exchanges in **10b** (Table IV), and (3) a substantial rate decrease in the Li_{ax}–Li_{eq} site exchange for the conformationally locked LiPMP/LiBr dimer **16b**.

Solution Structures of LiTMP/LiCl Mixed Aggregates. ^{6}Li NMR spectra of [^{6}Li]-LiTMP/LiCl and [^{6}Li,^{15}N]-LiTMP/LiCl below −100 °C show a complex distribution of resonances that proved to be especially challenging to deconvolute due to severe resonance overlaps (Figure 7 and Table VII).[26] While the as-

(26) Unassigned species in the mixtures of LiTMP/LiCl totalling approximately 5% of the NMR resonance integration proved to be independent of the source of LiTMP, solvents, and LiCl. They are most clearly detected as ^{15}N multiplets shown to be centered at 85.7, 84.6, and 84.1 ppm by broad-band ^{6}Li decoupling (Figure 8b).

Table VII. ^{6}Li NMR Spectroscopic Data of 0.1 M [^{6}Li,^{15}N]-LiTMP/LiCl Mixtures in 3:1 THF/Pentane



7c **8c** **10c**

resonance	equiv of ^{6}LiCl	temp, °C	δ, ppm	mult (J, Hz)[a]	T_1, s	connectivity	assign[b]
Li_n	0.4	−115	1.40	t (5.4)	1.2	N_h–Li_n–N_h	**7c**
Li_o	0.4	−115	0.61	d (4.9)	3.7	N_h–Li_o	**7c**
Li_p	0.4	−115	1.65	t (5.1)	1.2	N_i–Li_p–N_j	**8c**
Li_q	0.4	−115	1.19	d (5.5)	2.6	N_i–Li_q	**8c**
Li_r	0.4	−115	0.61[c]	d (−)[c]	*c*	N_j–Li_r	**8c**
Li_s	1.0	−115	1.52	d (5.7)	3.1	N_k–Li_s	**10c**
Li_t	1.0	−115	0.59	d (4.8)	3.1	N_k–Li_t	**10c**
LiCl	1.0	−115	0.32	s	9.4		

[a] a_s = singlet, d = doublet, t = triplet. The coupling constants were measured after resolution enhancement. [b] Assignment of structure **7c** rather than **9c** and the assignments of axial and equatorial lithium resonances are purely arbitrary as detailed in the text. [c] Li_r is hidden under Li_o. Its existence is inferred from the collapse of N_j upon decoupling Li_o (and presumably Li_r). The overlap precluded a measurement of J_{Li-N} and T_1.

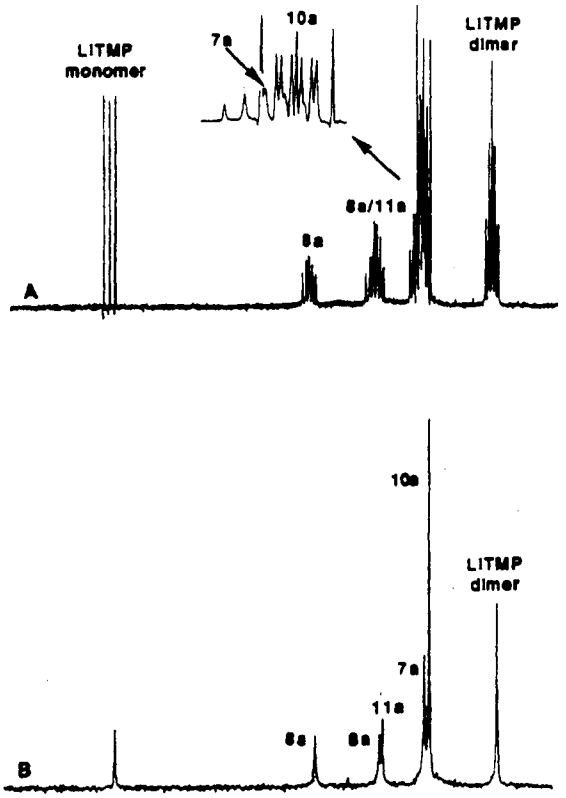


Figure 4. (A) ^{15}N NMR spectra of 0.12 M [^{6}Li,^{15}N]-LiTMP in 3:1 THF/pentane at −120 °C with 0.7 equiv of **15** prepared by adding cyclohexanone to the appropriate concentration of [^{6}Li,^{15}N]-LiTMP. (B) Broad-band ^{6}Li decoupled version of spectrum A.

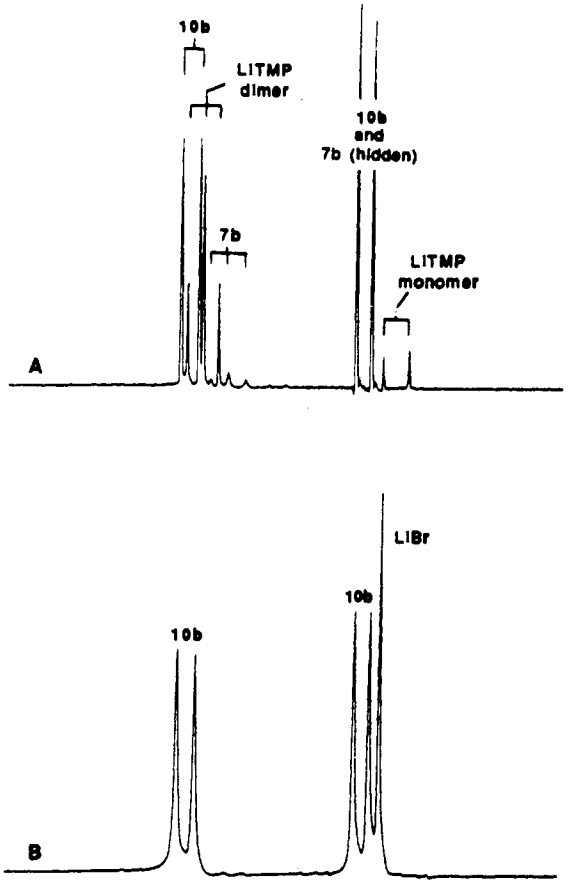


Figure 5. ^{6}Li NMR spectra of 0.1 M [^{6}Li,^{15}N]-LiTMP in 3:1 THF/pentane at −120 °C in the presence of (A) 0.5 equiv of [^{6}Li]-LiBr and (B) 1.5 equiv of [^{6}Li]-LiBr. The hidden resonance of **7b** can be detected by decoupling the appropriate ^{15}N nuclei of either **7b** or **10b** (Table II).

signments are the least rigorous of all, analogy with the enolate and LiBr cases is quite strong. Addition of 0.1 equiv of LiCl per LiTMP causes the appearance of five new resonances (labeled Li_n–Li_r). At 0.3–0.5 equiv of LiCl the intensities of Li_n–Li_r reach maxima with concomitant disappearance of the resonances corresponding to monomeric and dimeric LiTMP. At >0.3 equiv of LiCl two new resonances (Li_s and Li_t) in a 1:1 ratio begin to appear, becoming the only prominent mixed aggregate resonances in the limit of high (>1.0 equiv) LiCl content. Only resonances Li_q and Li_p display significant temperature-dependent chemical shifts. Throughout a range of LiCl, THF, and absolute concentrations the relative intensities of Li_n–Li_r remain fixed as does the 1:1 Li_s:Li_t ratio.

Selected ^{15}N NMR spectra of [^{6}Li,^{15}N]-LiTMP/LiCl are illustrated in Figure 8 and the data listed in Table VIII. The appearance of three quintets at low LiCl content (labeled N_h–N_j) coincides with the appearance of resonances Li_n–Li_r in the ^{6}Li NMR spectra. Similarly, the existence of a solitary quintet in the limit of high LiCl content (N_k) correlates with ^{6}Li resonances Li_s and Li_t. Single-frequency decoupling of ^{15}N resonances N_h–N_k provides rigorous ^{6}Li/^{15}N resonance correlations (Tables VII and VIII; decoupling are included as Supplementary Material).

From the available multiplicities, integrations, and resonance correlations emerge the connectivities listed in Tables VII and VIII. As described above, evidence that we were observing conformational isomers in the slow exchange limit includes the following: (1) Substantially simplified spectra are observed for [^{6}Li]-(t-Bu)$_2$NLi/LiCl, showing a single 2:1 mixed aggregate (δ

Table VIII. ^{15}N NMR Spectroscopic Data of [^{6}Li,^{15}N]-LiTMP/LiCl Mixtures[b,c]

resonance	equiv of $^{6}LiCl$	temp, °C	δ, ppm	mult (J, Hz)[a]	connectivity	assign[b,c]
N_h	0.3	−115	85.6	tt (5.3, 4.9)	Li_n–N_h–Li_o	**7c**
N_i	0.3	−115	86.7	quint (5.1)	Li_p–N_j–Li_r	**8c**
N_j	0.3	−115	85.6		Li_p–N_i–Li_q	**8c**
N_j	0.3	−123[d]	85.9	quint (5.2)	Li_p–N_i–Li_q	**8c**
N_i	0.3	−102[d]	84.8	quint (5.2)	Li_p–N_i–Li_q	**8c**
N_k	1.0	−115	82.6	tt (5.6, 4.8)	Li_s–N_k–Li_t	**10c**

[a] s = singlet, t = triplet, tt = triplet of triplet, quint = quintet. [b] Assignment of structure **7a** rather than **9a** and the assignments of axial and equatorial lithium resonances are purely arbitrary as detailed in the text. [c] Several minor ^{15}N resonances corresponding to approximately 5% of the total integration remained uncharacterized (ref 26).

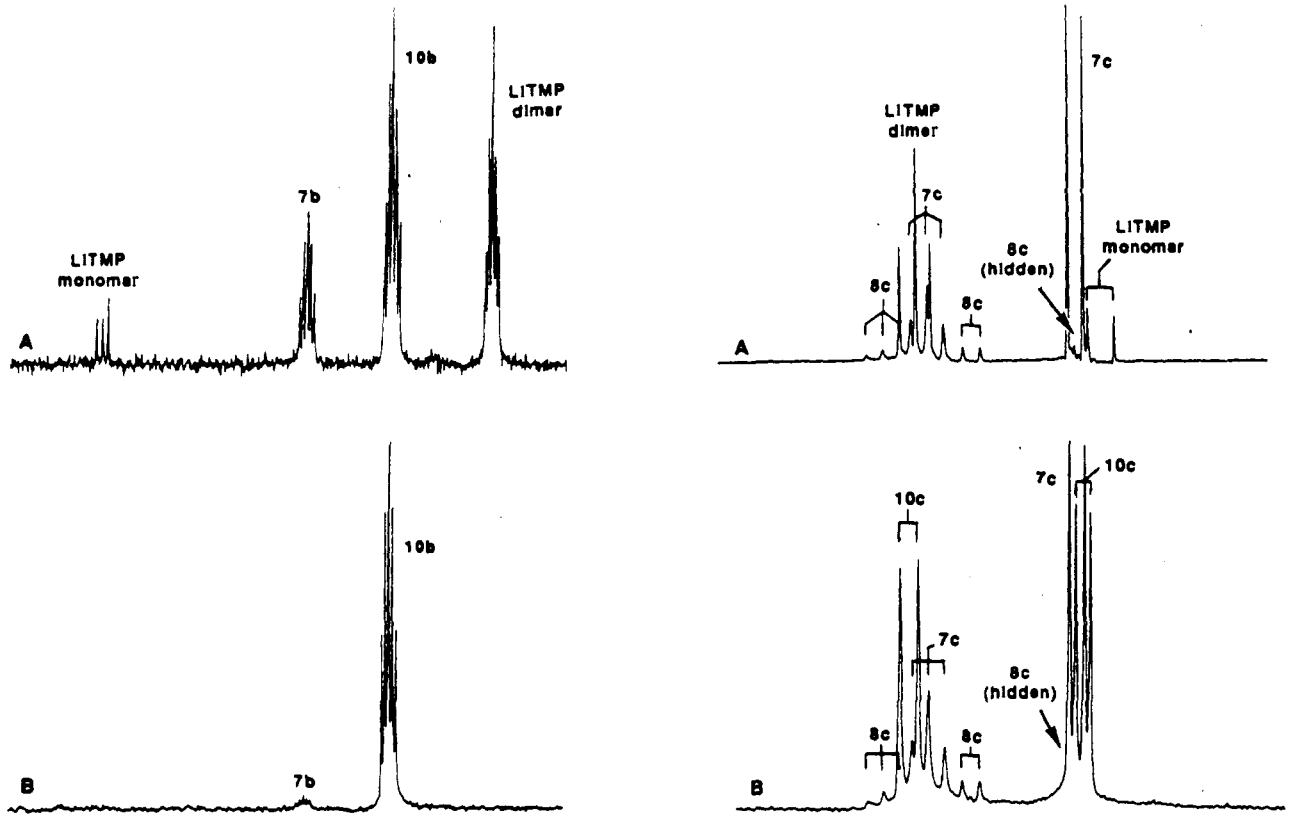


Figure 6. ^{15}N NMR spectra of 0.1 M [^{6}Li,^{15}N]-LiTMP of 3:1 THF/pentane at −120 °C in the presence of (A) 0.5 equiv of [^{6}Li]-LiBr and (B) 1.5 equiv of [^{6}Li]-LiBr.

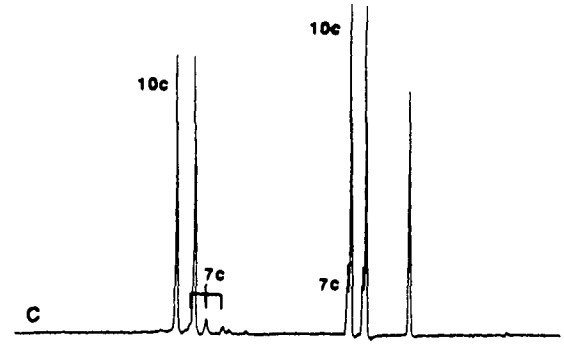


Figure 7. ^{6}Li NMR spectra of 0.1 M [^{6}Li,^{15}N]-LiTMP in 3:1 THF/pentane at −115 °C in the presence of (A) 0.3 equiv of [^{6}Li]-LiCl, (B) 0.6 equiv of [^{6}Li]-LiCl, and (C) 1.2 equiv of [^{6}Li]-LiCl. The "hidden" resonance of **8c** has not been directly observed. Its existence and location are inferred from collapse of the corresponding ^{15}N resonance of **8c** (N_i) upon irradiation at 0.6 ppm in the ^{6}Li spectrum (see Table VII).

0.64 and 1.59 ppm) and a 1:1 mixed aggregate displaying a single resonance (δ 0.95 ppm). (This also argues that the limiting structure of LiTMP/LiCl is dimer **10c** rather than ladder **11c**.) (2) Equivalent free activation energies are observed for the Me_{ax}–Me_{eq} and the Li_s–Li_t site exchanges (Table IV). (3) Substantially decreased rates of Li_{ax}–Li_{eq} site exchanges are observed in the 1:1 LiPMP/LiCl mixed aggregate **16c** (0.68 and 1.50 ppm). It should be noted once again that assignment of the symmetric 2:1 mixed aggregate as **7c** or **9c** cannot be made at this time. Secondly, ladder structures (with the central dotted line corresponding to a discrete LiX interaction) and simple cyclic trimers (with no such Li–Cl transannular interaction) cannot be distinguished.

Discussion

LiTMP Solution Structures. The assignment of LiTMP in THF as a monomer–dimer mixture by Fox and Renaud appears to be correct.[15] Unequivocally, LiTMP exists as a mixture of monomer and cyclic oligomer in THF. One normally cannot distinguish a cyclic dimer from topologically equivalent higher oligomers such as cyclic trimers or tetramers using the available NMR methods. In the past we have relied upon crystallographic, spectroscopic, and theoretical studies to tentatively conclude that the higher oligomers of lithium dialkylamides are stable only in the *absence of donor solvents*.[25] More recently, one-dimensional ^{6}Li/^{15}N single-frequency decoupling experiments on a *single* lithiated imine rigorously excluded higher cyclic oligomers as the observable solvated aggregates.[22] Spectroscopic characterization of dimeric LiTMP and LDA mixed solvates[18] strongly supports the LiTMP dimer assignment. Studies of the conformationally locked LiPMP

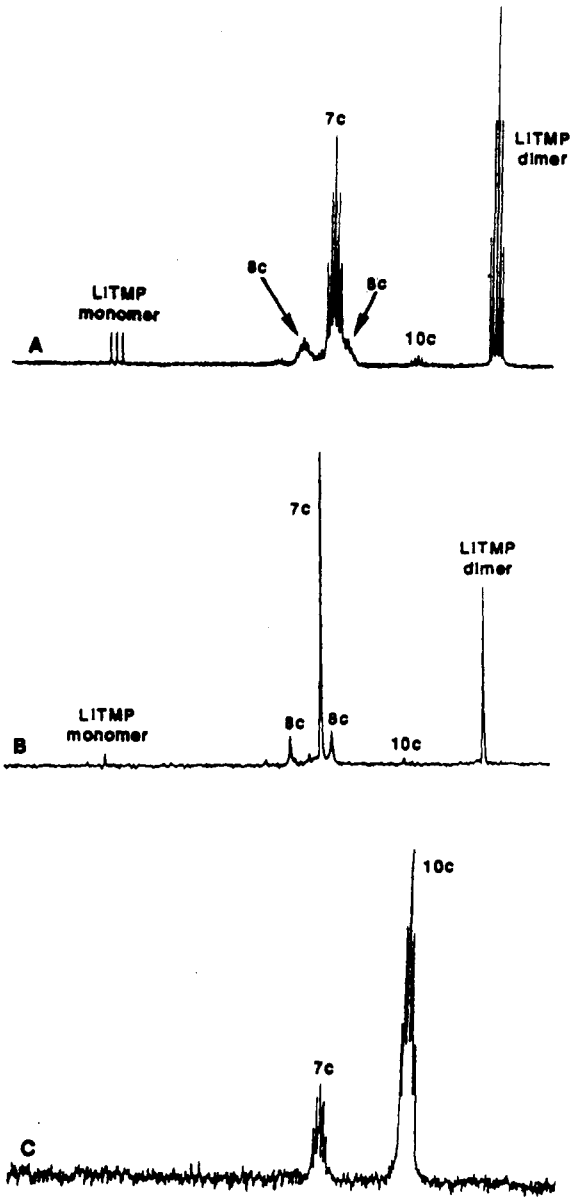


Figure 8. ^{15}N NMR spectra of 0.1 M [^{6}Li,^{15}N]-LiTMP in 3:1 THF/pentane in the presence of varying equivalents of LiCl: (A) 0.3 equiv of [^{6}Li]-LiCl (−102 °C); (B) 0.3 equiv of [^{6}Li]-LiCl (−102 °C) with broad-band ^{6}Li decoupling (30.42 rather than 40.52 MHz); and (C) 1.2 equiv of [^{6}Li]-LiCl, −115 °C.

(**17**) establish a C_{nh} symmetry consistent with assignment of the LiTMP aggregate as dimer **5**. Work is in progress to resolve the dimer vs trimer issue for a wide range of lithium amides. See Note Added in Proof.[33]

LiTMP/LiX Solution Structures. The complex ^{6}Li and ^{15}N NMR spectra arising from LiTMP–enolate and LiTMP–LiCl mixtures do not facilitate rigorous structure assignments. Nevertheless, several experiments demonstrate that the spectral complexity stems from conformational isomers surrounding the chair-like piperidine ring system; studies of conformationally mobile (t-Bu)$_2$NLi and conformationally locked LiPMP (**2**) proved especially revealing. We completed the structure assignments summarized in Scheme I. The distribution of mixed aggregates is highly gegenion-dependent. In the lithium cyclohexenolate series, all structures except one of the symmetric mixed dimers (**7a** or **9a**) can be observed. The LiBr series was far simpler, showing primarily mixed dimer **10b** and limited concentrations of a symmetric mixed trimer (**7b** or **9b**). In the LiCl series we detected unsymmetric and symmetric mixed trimers (**8c** and either **7c** or **9c**), mixed dimer **10c**, and minor concentrations (<5%) of uncharacterized species. In all three series, distinction of the symmetric 2:1 mixed aggregates (**7** vs **9**) has not been attempted. Similarly, the differentiation of the 2:1 mixed aggregates as simple cyclic mixed trimers or 3-rung ladder structures has not been achieved. While we favor the ladder structural type from analogies with crystal structures of Snaith,[25] Williard,[27] and others,[28] the suggestion is still precariously based on intuition. One point that became very clear during the course of the structural studies, however, is that the power of the ^{6}Li–^{15}N double-labeling studies for unravelling the structures of complex mixed aggregates is dramatically enhanced by $^{6}Li/^{15}N$ resonance correlations.[22] We also suggest that the conformational properties of methylated lithium piperidide derivatives, although clearly very troublesome in these early studies, may eventually provide powerful structure probes in future studies, with the conformationally locked LiPMP playing a central role.

Some comments on the high propensity of LiTMP to form mixed aggregates are warranted. We have found, for example, that the less sterically demanding lithium diisopropylamide (LDA) dimer exhibits a substantially lower propensity to form mixed aggregates than does LiTMP.[29] With highly hindered enolates, we see soft equilibria with LDA–enolate mixed dimers to the exclusion of mixed trimers. A 1:1 mixture of LDA and the sterically unhindered cyclohexanone enolate shows essentially no (<5%) mixed dimer. Thus, some feature of LiTMP appears to provide the driving force for the formation of mixed dimers, trimers, and tetramers; several indicators point to the steric demands of solvation as the culprit. If the mixed trimers (**7–9**) are ladder structures, it follows primarily from the work of Snaith[25] that this would allow the internal lithium nuclei to remain unsolvated as evidenced by a number of crystal structures of 3- and 4-rung ladders. Similarly, formation of 2:2 mixed aggregate **11a** from **10a** would result in the extrusion of solvent molecules. In this context, we underscore the THF concentration dependencies showing that dimer **10a** is more highly solvated (per Li) than the mixed aggregates **7a** (or **9a**), **8a**, and **11a**. Secondly, solution structure studies of LiTMP and LDA in the presence of hexamethylphosphoramide (HMPA) show strikingly divergent properties; LDA retains the dimer structure while the LiTMP dimer readily forms open dimers and ion triplets.[18]

Overall, mixed dimerization with sterically unhindered LiX species would provide a very efficient mechanism for decreasing the steric demands of LiTMP aggregates. Furthermore, formation of less solvated ladder structures with concomitant extrusion of solvent would provide additional steric relief.

On the Selectivity of Enolization. The previous paper demonstrated that the ketone enolizations by LiTMP in THF appear to be kinetically controlled metalations that are markedly influenced by the presence of lithium enolates, lithium chloride, or lithium bromide. It seems likely that the salt-dependent selectivities stem from the intervention of mixed aggregates in the product determining transition state(s). That is not to say, however, that we can suggest a mechanistic hypothesis. During the course of the enolizations the reaction conditions are changing continuously as a function of percent conversion; the mechanisms operating at early conversion are certainly not the same (or at least not in the same proportions) as those at the latter stages of the reaction. The primary conclusion is that any working model must at least consider the role of mixed aggregates, and the TMSCl in situ tapping protocol gaining popularity is surely not well understood at this time.[10-12]

Experimental Section

Reagents and Solvents. The general experimental procedures have been described previously.[9] Isotopically labeled ethyllithium,[14] lithium cyclohexenolate,[14b] and (t-Bu)$_2$NLi were prepared as described.[9] The

(27) A four rung LDA/enolate ladder structure has been characterized crystallographically: Williard, P. G.; Hintze, M. J. *J. Am. Chem. Soc.* **1987**, *109*, 5539.

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isotopomers of LiTMP were prepared with [^{6}Li]-ethyllithium and purified by an additional recrystallization from hexane. ^{6}Li metal (95.5% enriched) was obtained from Oak Ridge National Laboratory. [^{15}N]-NH_4Cl (99%) was obtained from Cambridge Isotope Laboratory and used without further purification.

[^{15}N]-**2,2,6,6-Tetramethylpiperidine** was prepared by modification of a literature procedure[30] as follows. A 100-mL glass bomb with a Teflon needle valve and a magnetic stir bar was charged with [^{15}N]-NH_4Cl (3.00 g, 55.1 mmol), anhydrous dibasic sodium phosphate (3.60 g, 25.3 mmol), phorone (11.9 g, 86.4 mmol), and benzene (15 mL). The contents of the vessel were frozen (to prevent premature liberation of ammonia gas) and layered with a 6.0 M solution of sodium hydroxide (12.2 mL, 73 mmol). The vessel was evacuated, sealed, and heated with stirring at 95 °C for 10 days. The aqueous layer was removed and extracted with 3 × 40 mL of methylene chloride. The extracts were combined with the initial organic phase, dried over anhydrous potassium carbonate, and filtered. Concentration in vacuo followed by treatment of the resulting light brown, low-melting solid with 2:1 toluene/hexane (400 mL) and anhydrous HCl gas afforded a precipitate. Sequential filtration, resuspension in hexane, filtration, and drying in vacuo afforded [^{15}N]-2,2,6,6-tetramethyl-4-piperidone hydrochloride (9.62 g, 91% yield based on [^{15}N]-NH_4Cl) as a beige solid of suitable purity for the next step. Mp 186–187 °C dec (authentic commercial sample mp 188–190 °C); ^{1}H NMR (D_2O) δ 0.61 (d, J_{N-H} = 2.7 Hz, 12 H), 1.84 (d, J_{N-H} = 2.0 Hz, 4 H). ^{13}C{^{1}H} NMR (D_2O) δ 208.1 (s), 59.7 (s), 49.5 (s), 27.37 (s). The free amine available from extraction could also be isolated as an off-white solid. ^{1}H NMR ($CDCl_3$) δ 1.24 (d, J_{N-H} = 2.6 Hz, 12 H), 2.26 (d, J_{N-H} = 0.8 Hz, 12 H).

[^{15}N]-2,2,6,6-Tetramethyl-4-piperidone hydrochloride (8.98 g, 46.6 mmol), triethylene glycol (50 mL), 85% hydrazine hydrate (12.0 mL, 204 mmol), and 85% KOH pellets (12.0 g, 180 mmol) were mixed and then heated to 190 °C for 7 h followed by 210 °C for 7 h. The product was steam distilled, extracted into ether, and dried over K_2CO_3. The ether was removed by simple distillation with further fractional distillation (149–150 °C; uncorrected) affording crude [^{15}N]-2,2,6,6-tetramethylpiperidine (3.54 g, 53% yield) as a colorless oil. The product was dried by fractional distillation from lithium aluminum hydride and shown to be >99% pure by GC. Yield 3.07 g (46% yield from the piperidone hydrochloride); bp = 149–150 °C; ^{1}H NMR ($CDCl_3$) δ 1.08 (d, J_{N-H} = 2.5 Hz, 12 H0, 1.24 (m, 4 H), 1.54 (m, 2 H). ^{13}C NMR ($CDCl_3$) δ 49.5 (s, quat *C*), 38.5 (t, CH_2), 31.4 (q, CH_3), 16.2 (t, CH_2).

2,2,4,6,6-Pentamethylpiperidine. The pentamethylated piperidine used to prepare lithium amide **2** was prepared as follows. A 0.47 M solution of CH_2=PPh_3 was prepared by addition of 1.63 M *n*-BuLi/hexane (144 mL, 235 mmol) to a suspension of methylenetriphenylphosphonium bromide (84 g, 235 mmol) in 300 mL of anhydrous THF. The ylide solution was added to 16.1 g (104.3 mmol) of solid 2,2,6,6-tetramethyl-4-piperidone (as free base, see above) until the yellow color of the ylide persisted. GC analysis showed a 9:1 ratio of product to starting material irrespective of reaction time and quantity of added ylide, indicating that partial enolization was occurring competitively. Accordingly, the reaction was back-titrated with enough CF_3COOH to dissipate the yellow ylide color and quench the estimated 10% enolate. Additional ylide was added until the yellow color once again persisted. Several such iterations effected complete conversion (>500:1). The reaction was quenched with a mixture of 30 g of ice and 50 mL of 5% aqueous HCl. Following 2 × 30 mL washes, the combined aqueous layers containing the amine hydrochloride were extracted with 3 × 50 mL of Et_2O, basified to pH 10 with 40% NaOH, and extracted with 3 × 60 mL of Et_2O. The Et_2O layers were treated with 8.10 mL (12.0 g, 10.5 mmol) of trifluoroacetic acid and evacuated to afford the crude trifluoroacetate salt as a white solid. Recrystallization from toluene afforded 22.65 g (81% yield) of 4-methylene-2,2,6,6-tetramethylpiperidinium trifluoroacetate as a white crystalline solid. Extractive workup followed by distillation afforded amine as a colorless liquid. ^{1}H NMR ($CDCl_3$) δ 4.84 (m, 2 H), 1.89 (m, 4 H), 1.04 (s, 12 H); ^{13}C{^{1}H} NMR ($CDCl_3$) δ 144.4 (s, *C*=CH_2), 110.0 (t, H_2C=C), 51.9 (s, CCH_3), 48.1 (t, CH_2), 31.1 (q, CH_3).

Stirring a solution of 4-methylene-2,2,6,6-tetramethylpiperidinium trifluoroacetate (11.39 g, 42.6 mmol) in 150 mL of MeOH containing PtO_2 hydrate (20 mg, 0.088 mmol) and 40 mg of activated carbon (Norit) for 3 h under 1.1 atm of H_2 resulted in complete loss of starting material as shown by GC analysis. Filtration through Celite and in vacuo removal of solvent afforded 10.67 g (93% crude yield) of white solid. Following partitioning of the solid between 30 mL of 10% NaOH and 3 × 15 mL of Et_2O, the combined organic layers were dried over K_2CO_3. Fractional distillation afforded a forerun of Et_2O followed by 4.42 g (67% yield) of 2,2,4,6,6-pentamethylpiperidine as a colorless liquid (bp = 157–160 °C). ^{1}H NMR (acetone-d_6) δ 1.80 (>20 line m, 1 H), 1.53 (dd, 2 H, J_{ax-eq} = 3.3 Hz, J_{gem} = 12.9 Hz, equatorial C*H*H), 1.14 (m, 6 H, axial CH_3), 1.05 (q, 6 H, $J_{long\ range}$ = 0.6 Hz, equatorial CH_3), 0.86 (d, 3 H, J = 6.7 Hz, 4-CH_3), 0.65 (ddq, 2 H, J_{ax-eq} = 12.1 Hz, J_{gem} = 12.8 Hz, axial C*H*H, $J_{long\ range}$ = 0.9 Hz). Note: All resonances except that at 0.86 ppm show long-range coupling that has not been fully deconvoluted at this time. ^{13}C{^{1}H} NMR ($CDCl_3$) δ 144.4 (s, *C*=CH_2), 110.0 (t, H_2C=C), 51.9 (s, CCH_3), 48.1 (t, CH_2), 31.1 (q, CH_3).

[^{15}N]-**2,2,4,6,6-Pentamethylpiperidine** was prepared by using a scaled-down procedure analogous to that described above.

[^{6}Li,^{15}N]-**Lithium 2,2,6,6-tetramethylpiperidide** (LiTMP) was prepared by elaboration of a literature procedure[13] as follows. To a magnetically stirred solution of freshly sublimed [^{6}Li]-ethyllithium (225 mg, 6.41 mmol) in pentane (40 mL) under Ar was added [^{15}N]-2,2,6,6-tetramethylpiperidine (1.24 mL, 1.04 g, 7.32 mmol) in one portion via gastight syringe. After stirring for 14 h (shorter times afforded reduced yields), the slightly turbid mixture was sequentially filtered, evacuated to $^2/_3$ the original volume, cooled to −78 °C, and filtered to collect the solids. Recrystallization from ca. 30 mL of hexane afforded [^{6}Li,^{15}N]-2,2,6,6-tetramethylpiperidide (0.52 g, 55% yield) as a white, crystalline solid. The material was shown to be pure (except for traces of amine) by ^{6}Li, ^{15}N, and ^{13}C NMR spectroscopy (Cf. Tables I–III). Titration indicated 95% of the theoretical titer.

Lithium 2,2,4,6,6-Pentamethylpiperidide ([^{6}Li]-LiPMP and [^{6}Li,^{15}N]-LiPMP). LiPMP is prepared in 40–50% recrystallized yield by an analogous procedure to that used for LiTMP. Carbon NMR data are listed in Table III. ^{6}Li NMR (3:1 THF/pentane) δ 1.50 (dd, J_{LiN} = 5.1 and 4.5 Hz, dimer), δ 0.48 (d, J_{LiN} = 8.4 Hz, monomer); ^{15}N{^{1}H} NMR δ 91.5 (t, J_{LiN} = 8.4 Hz, monomer), 78.1 (tt, J_{LiN} = 4.7 and 5.2 Hz, dimer), 74.4 (s, free amine).

[^{6}Li]-LiBr was prepared and dried[31] as follows. An argon-flushed, 1-L, 3-necked flask fitted with a mechanically rotated nichrome wire paddle was charged with 100 mL of degassed mineral oil and ^{6}Li metal (4.1 g, 680 mmol, 0.5% sodium). Upon liquefying the lithium into small droplets by vigorous stirring while heating with a flame (Caution!), the flame was removed and the mixture was cooled with an ambient temperature oil bath to solidify the lithium metal droplets. The excess oil was removed via cannula and the lithium metal was rinsed by vacuum transferring hexane and filtering. The resulting lithium sand was suspended in dry, vacuum-transferred THF (500 mL), cooled in a water bath, and treated with ethylene dibromide (64.1 g, 340 mmol). After the mixture was stirred for 2 h, the resulting suspension was diluted with THF (approx. 100 mL), filtered through Celite, and evacuated to give 48 g of crude [^{6}Li]-LiBr as a white solid. The solid was dissolved in 20 mL of water (by refluxing), and the resulting aqueous layer was extracted with xylene (2 × 10 mL), filtered, cooled to −15 °C, and filtered to remove the solid lithium bromide. After the recrystallization/filtration procedure was repeated two more times the white solid was dried in vacuo at 160 °C for 12 h, dissolved in dry (vacuum transferred) THF, filtered under argon to remove insoluble impurities, and dried in vacuo at 130 °C for 5 h to remove the THF. Yield: 4.5 g of [^{6}Li]-LiBr.

NMR Spectroscopic Analyses. ^{13}C NMR spectra were recorded on Varian XL-200 or XL-400 spectrometers operating at 50.30 and 100.56 MHz, respectively. ^{13}C chemical shifts are reported in ppm downfield of tetramethylsilane with deuterated solvent resonances as secondary standards. ^{6}Li NMR 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 ^{6}LiCl/methanol standard at −100 °C according to the suggestion of Reich and co-workers.[32] ^{15}N spectra were recorded with inverse gated ^{1}H decoupling on a Varian XL-400 or a Bruker AC 300-MHz NMR spectrometer operating at 40.52 and 30.42 MHz (respectively) and referenced to an external 0.15 M [^{15}N]-aniline/THF standard set at 50 ppm with internal [^{15}N]-2,2,6,6-tetramethylpiperidine at −115 °C (75.6 ppm) as a secondary standard. NMR probe temperatures are accurate to ±2 °C. Magnetic field inhomogeneity was adjusted by using line shape and ^{1}H free induction decays rather than the deuterium lock solvent to maximize field homogeneity. Samples requiring extended ^{15}N acquisition times included 10–15% THF-d_8 and utilized the ^{2}H lock. Other data were acquired unlocked. ^{6}Li integrations were performed on spectra acquired with 90°

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(33) **Note Added in Proof:** Recent studies using inverse-detected ^{15}N homonuclear zero-quantum NMR spectroscopy have clearly demonstrated that the cyclic oligomer of [^{6}Li,^{15}N]LiTMP observed in THF/pentane is a dimer rather than a trimer or higher oligomer. Gilchrist, J. H.; Collum, D. B. *J. Am. Chem. Soc.*, in press.

pulses on fully relaxed (>5 × T_1) samples. Resolution enhancements, where indicated, were performed by Lorentz–Gaussian multiplication of the FID prior to Fourier transformation. T_1 spin–lattice relaxation times were determined by exponential fits of data from inversion/recovery experiments. The hardware modifications necessary for single-frequency irradiations are described elsewhere.[22]

The following is a representative procedure for preparing samples for NMR spectroscopic analysis. Working in an inert atmosphere glovebox, [^{6}Li,^{15}N]-LiTMP (0.103 g, 0.70 mmol), [^{6}Ll]-LiBr (358 mg, 4.17 mmol), and diphenylacetic acid (200 mg, 0.942 mmol) were added to volumetric flasks containing stir fleas and capped with serum stoppers. An additional serum vial fitted with a stir flea and serum cap, the three samples prepared above, and four NMR tubes fitted with serum stoppers were removed from the glovebox and placed under positive nitrogen pressure with needle inlets. To the vial containing the [^{6}Li,^{15}N]-LiTMP cooled to −78 °C was added THF (1.40 mL) down the walls with constant agitation to minimize local heating. Solutions of [^{6}Li]-LiBr (0.417 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 0.17 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 at −20 °C. The NMR tubes were each charged with 190 μL of dry pentane, 100 μL of THF-d_8, 0.016 mmol of the [^{6}Li,^{15}N]-LiTMP stock solution, variable quantities of the LiBr stock solution, and enough THF to result in a final volume of 750 μL. Samples were flame sealed at −78 °C under reduced pressure and stored at −78 °C until the spectroscopic analyses were complete.

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Supplementary Material Available: Figures showing single-frequency ^{15}N decouplings of [^{6}Li,^{15}N]-LiTMP/lithium cyclohexenolate (**15**), [^{6}Li,^{15}N]-LiTMP/LiBr, and [^{6}Li,^{15}N]-LiTMP/LiCl (4 pages). Ordering information is given on any current masthead page.

Large Rate Accelerations in the Stille Reaction with Tri-2-furylphosphine and Triphenylarsine as Palladium Ligands: Mechanistic and Synthetic Implications

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Abstract: The effect of changing the palladium ligands on the rates of typical Stille cross-coupling reactions was studied. Large rate enhancements (typically 10^2–10^3 over triphenylphosphine-based catalysts) were observed with tri-2-furylphosphine (TFP) and triphenylarsine, which are recommended as the new ligands of choice in the palladium-catalyzed coupling between olefinic stannanes and electrophiles. On the basis of the evidence presented, the transmetalation, which is the rate-determining step in the catalytic cycle, is postulated to involve a π-complex between the metal and the stannane double bond. In general, ligands that readily dissociate from Pd(II) and allow ready formation of this π-complex are the ones that produce the fastest coupling rates. The utility of the new ligands is demonstrated with several synthetic examples.

Introduction

Transition-metal-catalyzed cross-coupling reactions are an extremely powerful tool in organic synthesis.[1] The choice of organometallic reagent and catalyst for a particular application is dictated by a variety of factors, including, for example, compatibility with other functional groups or protecting groups (chemoselectivity), the thermal stability of the substrate, the desire for regio- and stereospecificity, ease of operation, and economic factors. The palladium-catalyzed coupling of unsaturated halides or sulfonates with organostannanes,[2,3] now commonly referred to as the Stille reaction, is gaining the favor of the synthetic community at an impressive pace (eq 1). This is due to the growing

$$RX + R'SnR''_3 \xrightarrow{Pd(0)} RR' + XSnR''_3 \qquad (1)$$

R,R' = aryl,vinyl,allyl X = Br,I,OTf

availability of the organostannanes,[4] their stability to air and moisture, and the fact that the Stille chemistry is compatible with virtually any functional group, thereby eliminating the need for protection/deprotection strategies which are a necessity with most organometallic reactions. There is, however, a feature that may limit the usefulness of the Stille methodology: the relatively drastic conditions that must be sometimes used to induce coupling. Temperatures as high as 100 °C are not unusual, and this may reduce the yields due to thermal instability of substrates, products, or the catalyst itself.

This suggested to us that an improvement over the typical Stille conditions would be a useful development in organic synthesis, since it would help extend the range of applications of this already powerful methodology. Our interest in this chemistry was stimulated by the observation[5] that the classical Stille conditions failed when applied to a class of substrates, the 3-(triflyloxy)cephems, which are particularly sensitive to the rather harsh conditions described by Stille[6] for this type of coupling. Our observation

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