Lithium Hexamethyldisilazide-Mediated Enolizations: Influence of Chelating Ligands and Hydrocarbon Cosolvents on the Rates and Mechanisms

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Abstract: Enolizations of 2-methylcyclohexanone by lithium hexamethyldisilazide (LiHMDS) in the presence of three chelating ligands—trans-N,N,N,N',N'-tetracymethylcyclohexanediame, N,N,N,N'-tetracycloethylene-diamine, and dimethoxyethane—reveal an approximate 40-fold range of rates. NMR spectroscopic analyses and rate studies reveal isostuctural transition structures based on monomeric LiHMDS for the diamines. Rate studies of LiHMDS/dimethoxyethane-mediated enolizations implicate a substantial number of monomer- and dimer-based mechanisms. The rate laws vary for the three ligands because of ligand-dependent structural differences in both the reactants and the transition structures. The importance of LiHMDS-ketone complexes and the role of hydrocarbon cosolvents are discussed.

Introduction

Lithium hexamethyldisilazide (LiHMDS) has played a prominent role in organic synthesis.1-2 It is so prevalent that it has been decades since practitioners using LiHMDS have felt compelled to cite the first reports of its preparation3 or the early applications in organic synthesis.4 LiHMDS has also served as an excellent template for the study of lithium ion solvation and solvent-dependent aggregation, beginning with the seminal studies of Kimura and Brown.5-7 Understanding how solvation and aggregation influence reactivity, to make connections between structural studies and synthetic applications, requires knowledge of reaction mechanisms that is highly limited at this time.8-10

We describe herein studies of ketone enolization mediated by LiHMDS in the presence of trans-N,N,N',N'-tetracyclohexanediamine (TMCDAs),11 N,N,N',N'-tetracycloethylene-diamine (TMEDA), and dimethoxyethane (DME). Although previous structural studies have shown that chelating ligands routinely afford monomeric LiHMDS,7a these three ligands are not interchangeable. Table 1 illustrates the solvent-dependent relative rate constants of the enolizations with 5.0 equiv of added ligand. Rate studies reveal mechanistic variations lurking beneath the surface. Mixed solvation (eq 2) is a major determinant of reaction rates and mechanisms. ‘S’ denotes either a conventional ligating solvent or the substrate, sometimes in
direct competition. The most peculiar observation, one fore-shadowed by previous structural and rate studies of lithium amides,7b,8 is that hydrocarbon cosolvents can markedly influence structures and reactivities.12–16

**Background.** In previously reported structural studies,6b-Li15N)LiHMDs24 solvated by TMFDA, TMEDA, and DME afforded monomers 3, 4, and 5, respectively.7 The high-coordinate lithium in 5 may be disturbing to some, but high coordinate lithium appears to be possible for sterically benign ligands.8,17 An alternative assignment as 6 is inconsistent with the spectroscopic data but cannot be rigorously excluded. At low DME concentrations (1.0–8.0 equiv.), dissolved dimer 7 is observed.

![结构图](image)

Previous rate studies of the enolization of ketone 1 using a variety of monodentate ligands afforded widely divergent results.8 LiHMDS/THF-mediated metallations proceed via a

### Table 1. Relative Rate Constants (k_{\text{rel}}) for Enolization of Ketone 1 (eq 1)^a

<table>
<thead>
<tr>
<th>solvent</th>
<th>k_{\text{rel}}</th>
</tr>
</thead>
<tbody>
<tr>
<td>TMEDA</td>
<td>135</td>
</tr>
<tr>
<td>DME</td>
<td>35</td>
</tr>
<tr>
<td>TMFDA</td>
<td>3</td>
</tr>
<tr>
<td>THF</td>
<td>1</td>
</tr>
</tbody>
</table>

*a Reaction run using 0.10 M LiHMDS/toluene with 5.0 equiv. of added ligand at ~78 °C.

### Table 2. NMR Spectroscopic Data^a

<table>
<thead>
<tr>
<th>compd</th>
<th>δ &quot;H (mult, J_{\text{HH}})^b</th>
<th>δ &quot;^13C (mult, J_{\text{CC}})^b</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>−0.54 (d, 5.3)</td>
<td>42.1 (t, 5.3)</td>
</tr>
<tr>
<td>4</td>
<td>0.96 (d, 6.3)</td>
<td>47.2 (t, 6.3)</td>
</tr>
<tr>
<td>5</td>
<td>0.86 (d, 6.1)</td>
<td>47.6 (t, 6.1)</td>
</tr>
<tr>
<td>6</td>
<td>0.89 (d, 3.5)</td>
<td>38.4 (q, 3.5)</td>
</tr>
<tr>
<td>11a</td>
<td>0.82 (d, 5.6)</td>
<td>45.1 (t, 5.6)</td>
</tr>
<tr>
<td>11b</td>
<td>0.43 (d, 5.0)</td>
<td>42.9 (q, 5.0)</td>
</tr>
<tr>
<td>13</td>
<td>1.12 (t, 3.7), 1.88 (t, 3.2)</td>
<td>38.7 (q, 3.3)</td>
</tr>
<tr>
<td>14</td>
<td>2.04 (t, 3.1)</td>
<td>38.5 (q, 3.1)</td>
</tr>
<tr>
<td>15</td>
<td>−0.31 (d, 5.4)</td>
<td>42.1 (t, 5.5)</td>
</tr>
</tbody>
</table>

*a Spectra were recorded on 0.10 M [Li15N)LiHMDs. * Reaction run using 3.0 M toluene/pentane, 0.050 M carbamate. * Coupling constants were measured after resolution enhancement and reported in Hz. Multiplicities are denoted as follows: d = doublet, q = quartet. The chemical shifts are reported relative to 0.40 M LiCl/MeOH at ~90 °C (0.0 ppm) and neat Me2NcEt at ~90 °C (25.7 ppm).

monomer-based transition structure (8).8c By contrast, LiHMDS/Et2N-mediated enolizations display markedly higher rates traced to a dimer-based pathway (9).8a,b Hindered ethers also favor dimer-based metatalizations at rates between those found with THF and Et2N.8d Attempted enolizations using LiHMDS/pyrrolidine afforded 1,2-adduct 10 rather than enolates.8c

### Results

Results from IR and NMR spectroscopic studies are described separately for each ligand below. These are prefaced by a few general comments and descriptions.

### General Methods.

5Li and 15N NMR spectroscopic studies were required to examine solution structures (Table 2); 2,6,6-trideoxy-2-methylcyclohexanone18 (1-\(\text{d}_{2}\)) was used to suppress

![结构图](image)


### (15) Hydrocarbons can have widely varying influences on closely related reactions (see ref 16).


### (17) For leading references to high coordinate lithium, see ref 35b.

the enolization rate. The NMR spectroscopic methods are well established, prompting us to use Supporting Information aggressively.

Complexation of substrates to organolithium reagents markedly influences the mathematical form of the rate law if and only if the complex attains appreciable concentrations.8,19–21 (Fleeting intermediates are kinetically irrelevant.) LiHMDS-ketone complexes were detected using in situ IR spectroscopy as described in detail below.22 The shifts of the carbonyl absorbance to lower frequencies on complexation were small (8–10 cm⁻¹) compared with seemingly related examples.5 NMR spectroscopy distinguishes monomer- and dimer-based complexes, which is critical for understanding the rate data.

Enolizations using a slight excess of [6Li,15N]LiHMDS were followed using 6Li and 15N NMR spectroscopy,6,23 as well as IR spectroscopy. LiHMDS/TMEDA- and LiHMDS/TMCDA-mediated enolizations afforded homoaggregated enolate24 to the exclusion of mixed aggregates. LiHMDS/DME-mediated enolization afforded mixed dimer 11 (hapticity of DME unknown; Table 2) accompanied by a commonly observed autoinhibition.25 Quenching reactions with Me3SiCl/Et3N mixtures and analysis of the resulting enol silyl ethers confirmed that the enolizations were >99% regioselective.

Reaction rates were measured by monitoring the loss of ketone I in situ IR spectroscopy.8,22 Pseudo-first-order conditions were established by maintaining low concentrations of ketone (0.004–0.010 M) and high, yet adjustable concentrations of recrystallized 2 LiHMDS (0.05–0.40 M) and bifunctional ligands (0.10–7.8 M) with toluene or pentane as the cosolvent. Clean first-order decays were observed to five halves in all cases. The resulting pseudo-first-order rate constants (kobsd) are independent of ketone concentration (0.004–0.04 M), confirming the first-order dependence on substrate. Re-establishing the IR baseline and monitoring a second aliquot revealed no significant change in the rate constants, showing that conversion-dependent autocatalysis or autoinhibition are unimportant under these conditions.25,27,28 Comparisons of 1 versus

\[ \frac{-d[1]}{dt} = k[1][\text{LiHMDS}][\text{TMCDA}]^{0} \]  

\[ (3) \]

**Figure 1.** Plot of kobsd vs [LiHMDS] in 0.40 M trans-TMCDA/toluene solution for the enolization of 1 (0.005 M) by LiHMDS at −55 °C. The curve depicts the unweighted least-squares fit to kobsd = a[LiHMDS]^b, where a = 8.0 ± 0.5 and b = 0.86 ± 0.4.

1-d3 provided large kinetic isotope effects (kH/kD > 10), demonstrating that proton transfers are rate limiting.29

**TMEDA.** In situ IR spectra recorded on mixtures of 1-d3, LiHMDS, and TMEDA in hydrocarbon cosolvent reveal a mixture of uncomplexed and complexed ketone (Figure 4). A marked downfield shift in the 6Li resonance of monomeric LiHMDS and the absence of a dimer resonance confirm the formation of 13 rather than a dimeric LiHMDS-ketone complex.
The concentration of complexed ketone is favored at high LiHMDS concentration and is independent of the TMEDA concentration as would be anticipated for the formation of complex 13. There is, however, a striking dependence on the choice of hydrocarbons: toluene favors unbound ketone, whereas pentane promotes the bound form (cf., A and B in Figure 4).

\[
\begin{align*}
\text{(MeSi)\text{NLi}} + \text{ketone} & \rightarrow \text{LiHMDS} \\
\end{align*}
\]

Stabilization of monomer 4 as a discrete toluene complex (14) is provocative. Before proceeding with rate studies we wished to examine the role of toluene using carbamate 15 as an inert surrogate of ketone 1. Carbamate 15 also displays superior resolution of the free and complexed forms. Treatment of 4 with 15 (1719 cm\(^{-1}\)) affords free 15 and monomeric complex 16 (1700 cm\(^{-1}\)). The bound form is promoted by high LiHMDS concentration and low toluene concentration, whereas the relative proportions of free and bound carbamate are independent of TMEDA concentration. The bound form is also strongly favored at low temperature, indicating that binding is enthalpically favored.

\[
\begin{align*}
\text{[toluene]} & \rightarrow [\text{toluene}] \\
\text{[TMEDA]} & \rightarrow [\text{TMEDA}] \\
\end{align*}
\]

4Li NMR spectroscopic studies are particularly revealing. Under conditions in which appreciable concentrations of bound carbamate are detectable using IR spectroscopy, only monomeric LiHMDS is observable by NMR spectroscopy; the complexed form must be monomer 16. Moreover, complexation is accompanied by a substantial (>0.8 ppm) time-averaged upfield shift in the 4Li resonance of the monomer in proportion to the concentration of added 15. The 4Li resonance ascribable to a discrete complex 14 appears in the upfield region typically reserved for trisolvated LiHMDS monomers bearing tetrahedral lithiums.

Figure 2. Plot of \(k_{\text{obsd}}\) vs \([\text{trans-TMEDA}]\) in toluene cosolvent for the enolization of 1 (0.005 M) by LiHMDS (0.10 M) at \(-55^\circ\text{C}\). The curve depicts the results of an unweighted least-squares fit to \(k_{\text{obsd}} = a[\text{trans-TMEDA}] + b\), where \(a = 4.6 \pm 0.1 \times 10^{-3}\), \(b = 1.17 \pm 0.02\).

Figure 3. Plot of \(k_{\text{obsd}}\) vs \([\text{toluene}]\) in 0.50 M TMEDA for the enolization of 1 by LiHMDS (0.10 M) in pentane cosolvent at \(-55^\circ\text{C}\). The curve depicts an unweighted least-squares fit to \(k_{\text{obsd}} = a[\text{toluene}]^b\), where \(a = 4.6 \pm 0.4 \times 10^{-1}\), \(b = -1.4 \pm 0.1\).

Figure 4. IR spectra showing free and LiHMDS-complexed 1-d\(_3\) at \(-60^\circ\text{C}\) with (a) LiHMDS (0.10 M), 1-d\(_3\) (0.005 M), in 0.50 M TMEDA/ toluene solution, and (b) LiHMDS (0.10 M), 1-d\(_3\) (0.005 M), in 0.50 M TMEDA and 2.50 M toluene with pentane cosolvent.


Toluene clearly stabilizes uncomplexed LiHMDS monomer 4. The stabilization, however, does not appear to derive from a sterically sensitive, primary shell solvation exemplified by 14 for several reasons: (1) mesitylene (1,3,5-trimethylbenzene) and toluene are interchangeable despite the greater steric demands of mesitylene; (2) the $^1$H chemical shifts of 4 using pentane and toluene as cosolvents are similar, suggesting that the toluene is not generating four-coordinate lithium; and (3) 1-hexene has no effect on the stability or chemical shift of monomer 4 compared with $n$-pentane. (In previous studies of primary shell coordination to LiHMDS dimer, 1-hexene and toluene showed similar binding properties.)

With the detection and characterization of complex 13 completed, we were poised to investigate the enolization. A plot of $k_{\text{obs}}$ versus TMEDA concentration reveals TMEDA-concentration-independent rates, and a plot of $k_{\text{obs}}$ versus LiHMDS reveals a distinct curvature (Figure 5). Downward curvatures are often emblematic of fractional orders affiliated with deaggregation, yet the absence of dimers in solution refutes this notion. The downward curvature is also consistent with partial saturation kinetics expected from the incomplete formation of complex 13 described above. The curve in Figure 5 derives from a fit to $f(x) = ax/(1 + bx)$ emblematic of saturation kinetics.

Although toluene stabilizes LiHMDS as a medium rather than as a ligand, one would still predict effects on reactivity. Indeed, a plot of $k_{\text{obs}}$ versus toluene concentration (Figure 6) reveals an inverse dependence, a significant inhibition by toluene. The fit shown in Figure 6 is not very good, but that is to be expected because a medium effect should not necessarily fit to a power function. Most important, a simple change in hydrocarbon cosolvent elicits an 8-fold change in enolization rate.

The rate data are consistent with the idealized rate law in eq 5, the generic mechanism described by eqs 6 and 7, and monomer-based transition structure 17. We omitted toluene from the rate law and mechanism because of its role as a medium rather than as a ligand. Although the LiHMDS concentration dependencies using TMEDA are quantitatively different from those using TMCDA, the putative transition structures, 12 and 17, are isostructural.

\[
-d[1]/dt = k[1][\text{LiHMDS}]/(1 + k'[\text{LiHMDS}])
\]  

(5)

\[
(\text{Me}_3\text{Si})_2\text{NLi(TMEDA)} + \text{ketone} \leftrightarrow (\text{Me}_3\text{Si})_2\text{NLi(TMEDA)ketone)}
\]  

(4)

(\text{Me}_3\text{Si})_2\text{NLi(TMEDA)ketone)} \rightarrow \tag{13}

(13)

\[
[(\text{Me}_3\text{Si})_2\text{NLi(TMEDA)ketone}]^+ \tag{17}
\]  

(17)

DME. IR spectroscopic studies of mixtures of ketone 1, LiHMDS, and DME in hydrocarbons reveal uncomplexed ketone at 1712 cm$^{-1}$ along with complexed ketone as a poorly resolved shoulder at 1706$-$1702 cm$^{-1}$. In contrast with results from TMCDA and TMEDA, neither the stability of the complex nor the rate of enolization is sensitive to the choice of hydrocarbon cosolvent. Ketone complexation is promoted at low DME concentration, indicating a requisite dissociation of a coordinated DME. No complex is observed at $>2.0$ M DME. Possible structures of the LiHMDS-ketone complex include 18$-$20. (The requisite DME dissociation excludes a monomer-ketone complex retaining two DME ligands.) Previous studies in the presence of simple trialkylamines$^{8a,b}$ show dimer-based complexes analogous to 18 and 19. 33 Monomer 20 might be expected by analogy with TMEDA. All three are characterized as follows.

At 1.0 M DME, conditions are shown by IR spectroscopy to afford appreciable complexation. $^6$Li NMR spectra of [$^1$Li,$^1^5$N]-LiHMDS and ketone 1$-$d$_3$ show monomer to the exclusion of dimer. Complex 20 is further evidenced by a slight (0.05 ppm) downfield shift of the monomer resonance (Table 2). At low DME concentrations (1.0$-$5.0 equiv per lithium), dimer-based complexes 18 and 19 become prevalent. The observable equilibria are summarized by eqs 8$-$11.

The kinetics of enolization were necessarily complex owing to the large number of species involved. We have summarized the mechanisms described generically by eqs 12$-$15 and putative transition structures under consideration in Chart 1. Describing an explicit rate law is not possible, but partial rate laws and considerable information can be gleaned as follows. 

**Observable Equilibria:**

\[
\frac{1}{2}[(\text{Me}_3\text{Si})_2\text{NLi}]_3(\text{DME})_2 + \text{DME} \leftrightarrow \tag{7}

[(\text{Me}_3\text{Si})_2\text{NLi}]_4(\text{DME})_2 \tag{5}
\]  

(31) Small $^4$Li chemical shift differences are often noted in saturated and aromatic hydrocarbons.
Mechanisms of Enolization:

\[
[(\text{Me}_3\text{Si})_2\text{NLi}]_2(\text{DME})(\text{ketone}) \rightarrow [(\text{Me}_3\text{Si})_2\text{NLi}]_2(\text{DME})(\text{ketone})]^+ \quad (12)
\]

\[
(\text{Me}_3\text{Si})_2\text{NLi}(\text{DME})(\text{ketone}) \rightarrow [(\text{Me}_3\text{Si})_2\text{NLi}]_2(\text{DME})(\text{ketone})]^+ \quad (13)
\]

\[
2(\text{Me}_3\text{Si})_2\text{NLi}(\text{DME}) + \text{ketone} \rightarrow [(\text{Me}_3\text{Si})_2\text{NLi}]_2(\text{DME})(\text{ketone})]^+ \quad (14)
\]

\[
(\text{Me}_3\text{Si})_2\text{NLi}(\text{DME}) + \text{ketone} \rightarrow [(\text{Me}_3\text{Si})_2\text{NLi}]_2(\text{DME})(\text{ketone})]^+ \quad (15)
\]

A plot of \(k_{\text{obsd}}\) versus DME concentration is illustrated in Figure 7. Spectroscopically observable structural forms are included in Figure 7 to facilitate the discussion. Starting with only 1.0 equiv of DME per lithium (no uncoordinated DME left in solution), we observe that the rate constants rise with added DME, reaching a maximum at approximately 2.0 equiv (1.0 equiv of uncoordinated) DME. This rise in rates is small but reproducible. At \(>2.0\) equiv DME, the rates decrease sigmoidally, revealing a distinct inhibition and a nonzero rate in the high DME concentration limit. The function in Figure 7 has its origins from a model describing double saturation behavior. It does not, however, include provisions for (1) appreciable concentrations of both 18 and 20 at intermediate DME concentrations (1.0–10 equiv), (2) the requisite disassociation, and (3) the lower reactivity observed at the y-intercept in Figure 7.


(34) See Supporting Information.

(35) (a) Open dimers were first proposed for the isomerization of oxiranes to allylic alcohols by mixed metal-bases: (a) Mordini, A.; Rayana, E. B.; Margot, C.; Schlosser, M. Tetrahedron 1990, 46, 2401. (b) For a bibliography of lithium amide open dimers, see Ramirez, A.; Sun, X.; Collum, D. B. J. Am. Chem. Soc. 2006, 128, 10326.
dependencies is demanding. For monomer-ketone F. enolization the complexation. W. Lucht, Collum, fusion effects transition J. could ion suspect 1). F.; the TMEDA. in the 305. LiHMDS/TMCDA/M.; a J. metric, above ligand-dependent versus Beesley, F. be Chem. structures Chem. The R. by rates Polym. support observed to a rigidity the AM. many Chem. consistent to than 15376. Soc. well (b) the excess accelerate enolizations monomer-per-lithium TMCDA imagine on the TMEDA structures and ligands 15, There excess ligands 14). The AM. DME/toluene reaction pathway that has a higher per-lithium solvation number than 26 and a lower per-lithium solvation number than 21–23.37

Discussion

A survey of LiHMDS-mediated enolizations of ketone 1 reveals that bifunctional ligands accelerate the enolization relative to THF (Table 1). The three potentially chelating ligands display ligand-dependent influences on both reactant structures and mechanisms, underscoring some of the subtleties of organolithium chemistry.

TMCDA and TMEDA. Casual survey of the literature suggests that many authors are tempted to focus on the critical rate-limiting transition structures as the essence of mechanism. By this metric, LiHMDS-mediated enolizations in the presence of TMCDA and TMEDA are mechanistically homogeneous in that both promote reaction via monomer-based transition structures 27 (Scheme 1). Do isostructural transition structures suggest that the mechanisms are equivalent? In short, no. A correct view of mechanism considers the critical transformations required to convert the reactants to the rate-limiting transition structures.

The concentration dependencies observed for LiHMDS-mediated enolizations are distinctly different for TMCDA and TMEDA because of ligand-dependent differences in the reactants rather than in the transition structures. LiHMDS/TMCDA/1 mixtures contain chelated monomer 3 (in large excess) and uncoordinated ketone 1. The reaction rates display first-order dependencies on the concentrations of ketone 1 and monomer 3 and are independent of TMCDA concentration; monomer-based transition structure 12 is implicated. By contrast, analogous LiHMDS/TMEDA/1 mixtures include excess monomer 2 as well as both free ketone 1 and monomer-ketone complex 13. Partial complexation causes partial (incomplete) saturation kinetics; the enolization rates rise (nonlinearly) with increasing LiHMDS concentration.

One might ask why TMEDA promotes formation of an LiHMDS-ketone complex, whereas TMCDA does not. TMEDA has been shown to be superior to TMEDA as a bidentate ligand in several instances.74,78 Less direct evidence suggests that TMEDA is stericly more demanding.38 This conclusion might appear to be contradictory given that steric effects are primary determinants of lithium ion solvation.39 We suspect that the rigidity of TMEDA resulting from the trans ring fusion increases its binding constant through a form of the Thorpe–Ingold effect40,41 in which destabilizing interactions in the unbound ligand are alleviated on complexation. (An analogy to proton sponge may be instructive.)52 This same rigidity could also

(36) The rate law provides the stoichiometry of the transition structure relative to that of the reactants: Edwards, J. O.; Greene, E. F.; Ross, J. J. Chem. Educ. 1968, 45, 381.
preclude the conformational adjustments necessary to allow for the coordination of ketone 1 to monomer 3. Steric demands, however, are not the entire story.

Formation of TMEDA-solvated complex 13 and the inhibition of the enolization by toluene in TMCDA/toluene and TMEDA/toluene mixtures resurrects the discussion of when and how hydrocarbon cosolvents influence organolithium structure and reactivity.  Some reactions prove to be highly sensitive to the choice of hydrocarbon cosolvent, whereas others are not. Hydrocarbon sensitivity can be observed in the presence of Lewis-basic solvents such as ethers, trialkylamines, diamines, and even hexamethylphosphoramide. The observed hydrocarbon effects on the structure and reactivity described above are easily summarized. No complexation of ketone 1 to TMCDA-solvated monomer 3 is observed in either toluene or pentane. Conversely, TMEDA-solvated complex 13 is observed in pentane but not in toluene. This cosolvent dependence, an apparent stabilization of monomer 3 by toluene, was examined in some detail using carbamate as an inert surrogate for ketone 1, and analogous results were obtained. Rate studies, however, show that the toluene stabilizes both TMCDA- and TMEDA-solvated monomers 3 and 4. Replacing 3.0 M toluene in pentane with neat toluene causes 8-fold reductions in the rates of LiHMDS/TMCDA- and LiHMDS/TMEDA-mediated enolizations.

On first inspection, the influence of toluene on the reaction rates may seem confusing. The inhibition in LiHMDS/TMEDA mixtures elicted by toluene is affiliated with the loss of observable ketone complexation. The structural change is fully consistent with simple notions of inhibition, but it is deceptive. Toluene inhibits the enolization through stabilization of the reactants. Whether this stabilization has affiliated with it the loss of observable complexation is of secondary importance.

How does toluene stabilize monomers 3 and 4 relative to rate-limiting monomer-based transition structures? Could toluene coordinate to lithium as a discrete complex as in 14? We do not believe that the data support a primary shell complex. Previous studies of primary shell solvation of LiHMDS dimer revealed distinct and logical dependencies on the structure of the cosolvent: n-hexene acted like toluene whereas mesitylene (bearing three methyl groups) was more akin to hexane. We find the opposite to be true for monomer 4; mesitylene is interchangeable with toluene, and 1-hexene is interchangeable with n-hexane. Related studies of LiHMDS/trialkylamine mixtures show a striking stabilization of the disolvated monomer—((Me₃Si)₂NLi(R₃N))₂—relative to the analogous trisolvate in...
toulene but not in hexane. The stabilization of \((\text{Me}_3\text{Si})_2\text{NLi}-(\text{R}_2\text{N})_2\) also does not appear to be primary shell solvation by toluene. (The corresponding ether solvates show no such effect.)\(^{25}\)

DME, LiHMDS/DME mixtures are structurally complex and appear to offer a diverse array of enolization mechanisms. We attribute this divergence from the corresponding LiHMDS/diamine mixtures to low steric demands and relatively facile partial and total dissociations of DME.\(^{43}\)

LiHMDS exists as unchelated dimer \(7\) at very low DME concentrations and doubly chelated monomer \(5\) at \(>0.80\) M DME.\(^{7a}\) Mixtures of ketone \(1\) and LiHMDS afford complex \(18\) at low DME concentrations, monomer-based complex \(20\) at slightly elevated DME concentrations, and no LiHMDS-ketone complex at \(>2.0\) M DME. The choice of hydrocarbon cosolvent is unimportant. The structural complexity of the reactants foreshadowed a mechanistic diversity. The DME-concentration-dependent rates illustrated in Figure 7 show a number of divergent behaviors including a rate maximum at low DME concentrations and saturation kinetics following a sigmoidal function at intermediate and high DME concentrations. The rate studies provided evidence of as many as four competing mechanisms. Transition structures \(21\)–\(26\) (compiled in Chart 1) are given serious consideration. At the lowest DME concentrations, the \(y\)-intercept of Figure 6, an open dimer-based pathway via \(26\) is implicated. We have invoked these on many occasions, and they usually arise at low-solvent concentrations.\(^{35}\)

We attribute the rate maximum in Figure 6 to the intervention of monomer-based transition structure \(25\). Despite strong analogies with the results from the diamines, the evidence for \(25\) is, at best, circumstantial.

We surmised that high DME concentrations, wherein monomer \(5\) and uncomplexed ketone \(1\) exist exclusively would offer mechanistic homogeneity as well. Nonetheless, an unusual LiHMDS order \((1.35 \pm 0.02)\) suggested the superposition of both monomer- and dimer-based enolization. Both are highly solvated. We considered monomer-based transition structures \(21\)–\(23\). They are supported by structural analogy—octahedral \(+\text{Li(DME)}\)_\(5\) and related high coordinate LiHMDS are well precedence—although such high coordination numbers certainly depart from many conventional notions of lithium ion solvation. The dimer-based reactivity appears to have an extraordinary four coordinated DME ligands; we invoke triple ion \(24\) albeit with some reservation. Triple ions of LiHMDS have been observed spectroscopically (but not in DME),\(^{7a,d}\) and we have invoked triple ion-based pathways for LDA-mediated enolizations.\(^{1,3,4,44}\)

The octahedral cation of \(24\)\(^{17}\) and an analogous \([\text{R}^-\text{Li}^-\text{R}^-]\) bearing a chelating ligand\(^{45}\) offer structural precedent.

Conclusions

Solvent-dependent rates and selectivities are legion in organolithium chemistry. It is difficult to predict, however, what structural and mechanistic oddities underlie the macroscopic observables. Solvent-dependent enolizations described herein are no exception. Two isostructural diamines cause the meta-lations to proceed through isostructural monomeric transition structures. That is not to say, however, the mechanisms are equivalent. Enolizations display ligand- and LiHMDS-concentration dependencies that derive from ligand-dependent differences in the reactants. One might have anticipated that the results for LiHMDS/DME mixtures would be analogous to those of the LiHMDS/diamine mixtures, but such a hypothesis would prove incorrect. DME elicits marked changes in both reactants and transition structures. It is easy to focus on transition structures and overlook the role of the reactants, yet both are important determinants of mechanism. It is also easy to rely on analogy despite evidence that such analogies often fail.

Experimental Section

Reagents and Solvents. TMEDA, TMEDA, DME, hexane, and toluene hydrocarbons were distilled by vacuum transfer from blue or purple solutions containing sodium benzophenone ketyl. The hydrocarbon stills contained 1% tetraglyme to dissolve the ketyl. \(\text{Li}\) metal \((95.5\%\) enriched) was obtained from Oak Ridge National Laboratory (Oak Ridge, TN). LiHMDS, \([\text{Li}]\text{LiHMDS, and }[\text{Li}]^{15}\text{N}\text{LiHMDS were prepared and purified as described previously.}\(^{24}\) Ketone \(1-d\) was also prepared as described previously.\(^{18}\) Air- and moisture-sensitive materials were manipulated under argon or nitrogen using standard glovebox, vacuum line, and syringe techniques.

NMR Spectroscopic Analyses. All NMR tubes were prepared using stock solutions and sealed under partial vacuum. Standard \(^1\text{Li, }^{13}\text{C, and }^{15}\text{N}\) spectra were recorded on a 500 MHz spectrometer at 76.73, 125.79, and 50.66 MHz, respectively. The \(^1\text{Li, }^{13}\text{C, and }^{15}\text{N}\) resonances are referenced to 0.3 M \([\text{Li}]\text{LiCl/MeOH at }\approx 0^\circ\text{C} (0.0\) ppm), the \(\text{CH}_2\text{O} \text{resonance of } \text{THF at }\approx 90^\circ\text{C} (67.57\text{ ppm})\), and neat \(\text{Me}_2\text{NET at }\approx 90^\circ\text{C} (25.7\text{ ppm})\).

IR Spectroscopic Analyses. Spectra were recorded with an in situ IR spectrometer fitted with a 30-bounce, silicon-tipped probe optimized for sensitivity. The spectra were acquired in 16 scans (30-sec intervals) at a gain of 1 and a resolution of 4 or 8. A representative reaction was carried out as follows: The IR probe was inserted through a nylon adapter and an O-ring seal into an oven-dried, cylindrical flask fitted with a magnetic stir bar and T-joint. The T-joint was capped with a septum for injections and an argon line. After evacuation under full vacuum and flushing with argon, the flask was charged with a solution of LiHMDS \((167 \text{ mg, } 1.0 \text{ mmol})\) in TMEDA \((0.755 \text{ mL, } 0.50 \text{ M})\) and toluene \((9.08 \text{ mL})\) and cooled to \(\approx 78^\circ\text{C}\). After a background spectrum was recorded, ketone \(1-d\) \((50 \text{ mL, } 0.050 \text{ mmol, } 0.005 \text{ M})\) was added neat with stirring. IR spectra were recorded over five half-lives. To account for mixing and temperature equilibration, spectra recorded in the first 1.0 min were discarded.

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Supporting Information Available: NMR spectra and rate data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(43) Hemilability of DME is well documented (see ref 41).
(44) For an attempted comprehensive bibliography of lithium-based triple ions, see ref 16a.
(45) For a structurally related triple ion bearing a TMEDA-chelated internal lithium, see: Bildmann, U. J.; Muller, G. Organometallics 2001, 20, 1689.