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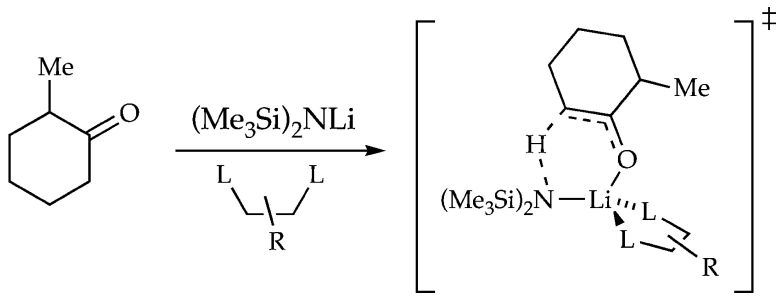

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Lithium Hexamethyldisilazide-Mediated Enolizations: Influence of Chelating Ligands and Hydrocarbon Cosolvents on the Rates and Mechanisms

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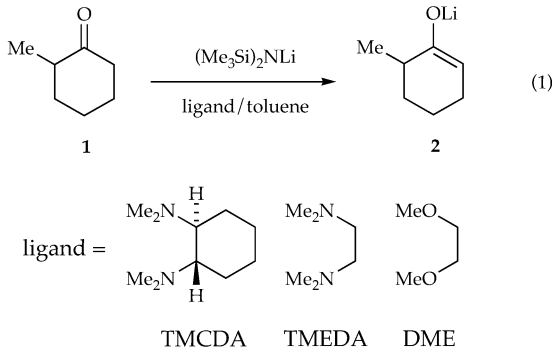
Abstract: Enolizations of 2-methylcyclohexanone by lithium hexamethyldisilazide (LiHMDS) in the presence of three chelating ligands--*trans*-*N,N,N′,N′*-tetramethylcyclohexanediamine, *N,N,N′,N′*-tetramethylethylenediamine, and dimethoxyethane--reveal an approximate 40-fold range of rates. NMR spectroscopic analyses and rate studies reveal isostructural 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.

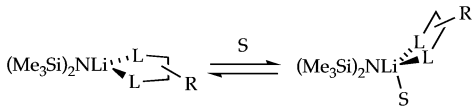
Introduction

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 preparation[3] 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]



(1)

We describe herein studies of ketone enolization mediated by LiHMDS in the presence of *trans*-*N,N,N′,N′*-tetramethylcyclohexanediamine (TMCDA),[11] *N,N,N′,N′*-tetramethylethylenediamine (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



(2)

determinant of reaction rates and mechanisms. 'S' denotes either a conventional ligating solvent or the substrate, sometimes in

(1) Eames, J. In *Science of Synthesis*; Georg Thieme Verlag: New York, 2005; Vol. 8a, pp 173−241.
(2) For selected examples in which LiHMDS is used on large scale, see: (a) Kauffman, G. S.; Harris, G. D.; Dorow, R. L.; Stone, B. R. P.; Parsons, R. L., Jr.; Pesti, J. A.; Magnus, N. A.; Fortunak, J. M.; Confalone, P. N.; Nugent, W. A. *Org. Lett.* **2000**, *2*, 3119. (b) Boys, M. L.; Cain-Janicki, K. J.; Doubleday, W. W.; Farid, P. N.; Kar, M.; Nugent, S. T.; Behling, J. R.; Pilipauskas, D. R. *Org. Process Res. Dev.* **1997**, *1*, 233. (c) Ragan, J. A.; Murry, J. A.; Castaldi, M. J.; Conrad, A. K.; Jones, B. P.; Li, B.; Makowski, T. W.; McDermott, R.; Sitter, B. J.; White, T. D.; Young, G. R. *Org. Process Res. Dev.* **2001**, *5*, 498. (d) Rico, J. G. *Tetrahedron Lett.* **1994**, *35*, 6599. DeMattei J. A.; Leanna, M. R.; Li, W.; Nichols, P. J.; Rasmussen, M. W.; Morton, H. E. *J. Org. Chem.* **2001**, *66*, 3330. (e) Kim, Y.-J.; Streitwieser, A. *Org. Lett.* **2002**, *4*, 573.
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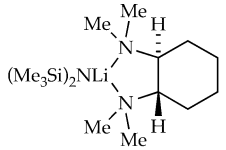
(8) (a) Zhao, P.; Collum, D. B. *J. Am. Chem. Soc.* **2003**, *125*, 4008. (b) Zhao, P.; Collum, D. B. *J. Am. Chem. Soc.* **2003**, *125*, 14411. (c) Zhao, P.; Condo, A.; Keresztes, I.; Collum, D. B. *J. Am. Chem. Soc.* **2004**, *126*, 3113. (d) Zhao, P.; Lucht, B. L.; Kenkre, S. L.; Collum, D. B. *J. Org. Chem.* **2003**, *68*, 242.

direct competition. The most peculiar observation, one foreshadowed 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, [^{6}Li,^{15}N]LiHMDS[7d] solvated by TMCDA, TMEDA, and DME afforded monomers **3**, **4**, and **5**, respectively.[7a] The high-coordinate lithium in **5** may be disturbing to some, but high coordinate lithium appears to be possible for sterically benign ligands.[7c,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), disolvated dimer **7** is observed.



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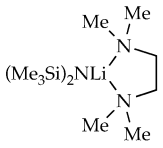

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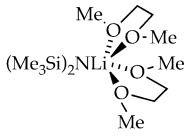

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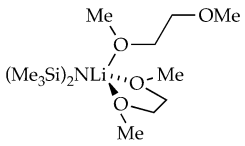

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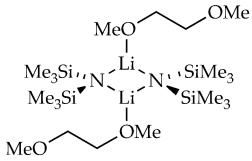

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Previous rate studies of the enolization of ketone **1** using a variety of monodentate ligands afforded widely divergent results.[8] LiHMDS/THF-mediated metalations proceed via a monomer-based transition structure (**8**).[8c] By contrast, LiHMDS/Et_3N-mediated enolizations display markedly higher rates traced to a dimer-based pathway (**9**).[8a,b] Hindered ethers also favor dimer-based metalations at rates between those found with THF and Et_3N.[8d] Attempted enolizations using LiHMDS/pyrrolidine afforded 1,2-adduct **10** rather than enolates.[8c]

Table 1. Relative Rate Constants (k_{rel}) for Enolization of Ketone **1** (eq 1)[a]

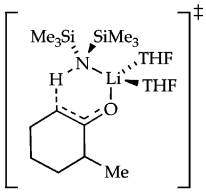
solvent	k_{rel}
TMEDA	135
DME	35
TMCDA	3
THF	1

[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]

compd	δ ^{6}Li (mult, J_{LiN})[c]	δ ^{15}N (mult, J_{LiN})[c]
3	−0.54 (*d*, 5.3)	42.1 (*t*, 5.3)
4	0.96 (*d*, 6.3)	47.2 (*t*, 6.3)
5	0.86 (*d*, 6.1)	47.6 (*t*, 6.1)
6	0.89 (*t*, 3.5)	38.4 (*q*, 3.5)
11[a]	0.82 (*d*, 5.6)	45.1 (*t*, 5.6)
11[b]	0.43 (*d*, 5.0)	42.9 (*q*, 5.0)
13	1.12 (*t*, 3.7), 1.88 (*t*, 3.2)	38.7 (*q*, 3.3)
14	2.04 (*t*, 3.1)	38.3 (*q*, 3.1)
15	−0.31 (*d*, 5.4)	42.1 (*t*, 5.5)

[a] Spectra were recorded on 0.10 M [^{6}Li,^{15}N]LiHMDS. [b] Reaction run using 3.0 M toluene/pentane, 0.050 M carbamate. [c] Coupling constants were measured after resolution enhancement and reported in Hz. Multiplicities are denoted as follows: *d* = doublet, *t* = triplet, *q* = quintet. The chemical shifts are reported relative to 0.30 M ^{6}LiCl/MeOH at −90 °C (0.0 ppm) and neat Me_2NEt at −90 °C (25.7 ppm).



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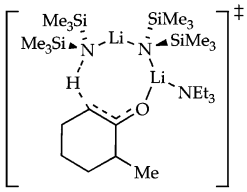

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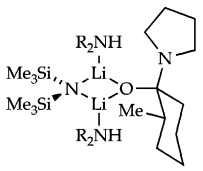

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Results

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. ^{6}Li and ^{15}N NMR spectroscopic studies were required to examine solution structures (Table 2); 2,6,6-trideuterio-2-methylcyclohexanone[18] (**1**-d_3) was used to suppress

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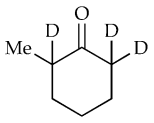
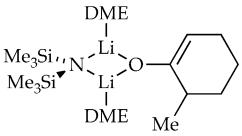
(16) (a) Ma, Y.; Ramirez, A.; Singh, K. J.; Keresztes, I.; Collum, D. B. *J. Am. Chem. Soc.* **2006**, *128*, 15399. (b) Ma, Y.; Collum, D. B. submitted for publication.
(17) For leading references to high coordinate lithium, see ref 35b.
(18) Peet, N. P. *J. Labelled Cmpd.* **1973**, *9*, 721.

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



1-d_3



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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.[8] NMR spectroscopy distinguishes monomer- and dimer-based complexes, which is critical for understanding the rate data.

Enolizations using a slight excess of [^{6}Li,^{15}N]LiHMDS[7d] were followed using ^{6}Li and ^{15}N NMR spectroscopy[6,23] as well as IR spectroscopy. LiHMDS/TMEDA- and LiHMDS/TMCDA-mediated enolizations afforded homoaggregated enolate[24] 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 Me_3SiCl/Et_3N mixtures and analysis of the resulting enol silyl ethers[26] confirmed that the enolizations were >99% regioselective.

Reaction rates were measured by monitoring the loss of ketone **1** using 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[7d] 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 half-lives in all cases. The resulting pseudo-first-order rate constants (k_{obsd}) 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

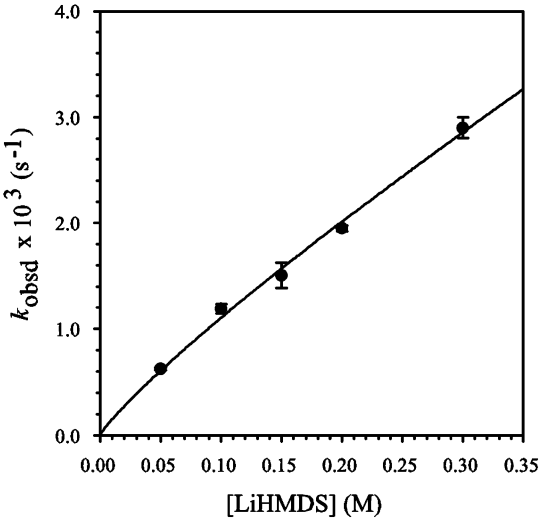
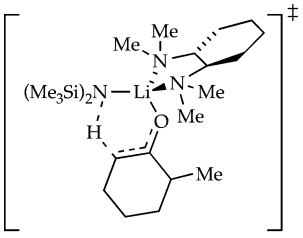


Figure 1. Plot of k_{obsd} vs [LiHMDS] in 0.40 M *trans*-TMCDA/toluene solution for the enolization of **1** (0.005 M) by LiHMDS at −55 °C. The curve depicts the unweighted least-squares fit to $k_{obsd} = a[\text{LiHMDS}]^b$, where $a = 8.0 \pm 0.5$ and $b = 0.86 \pm 0.4$.

1-d_3 provided large kinetic isotope effects ($k_H/k_D > 10$), demonstrating that proton transfers are rate limiting.[29]

TMCDA. We begin with the most straightforward case study. In situ IR spectra recorded on solutions containing **1**, LiHMDS, and TMCDA show no evidence of LiHMDS-ketone complexation under any conditions. Rate studies reveal an apparent first-order dependence on LiHMDS concentration (Figure 1), although an order of 0.86 ± 0.4 is afforded by best fit. A possible source of the deviation from 1.0 is discussed below. The enolization has a zeroth-order dependence on TMCDA concentration (Figure 2). Subtle drifts in the rates ascribed to changes in the media are not unusual.[19] The choice of hydrocarbon (toluene versus pentane) has no measurable effect on the structure of **3**; complexation is not observable using toluene or pentane as cosolvent. The enolization, however, is inhibited greater than *8-fold* by toluene (Figure 3). The rate data are consistent with the idealized rate law in eq 3 and transition structure **12**. Although toluene clearly influences the reaction rates, evidence suggests that the inhibition is *not* derived from primary shell solvation. The roles of primary versus secondary shell effects of hydrocarbon cosolvents are discussed below.

$$-\text{d}[\mathbf{1}]/\text{d}t = k[\mathbf{1}][\text{LiHMDS}][\text{TMCDA}]^0 \qquad (3)$$



12

TMEDA. In situ IR spectra recorded on mixtures of **1**-d_3, LiHMDS, and TMEDA in hydrocarbon cosolvent reveal a mixture of uncomplexed and complexed ketone (Figure 4). A marked downfield shift in the ^{6}Li resonance of monomeric LiHMDS and the absence of a dimer resonance confirm the formation of **13** rather than a dimeric LiHMDS-ketone complex.

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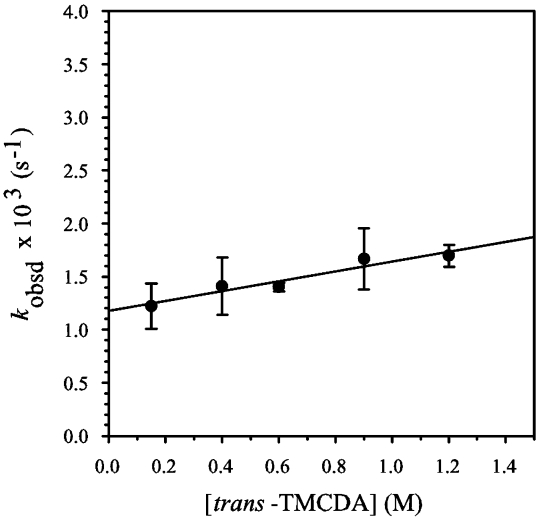


Figure 2. Plot of k_{obsd} vs [*trans*-TMCDA] in toluene cosolvent for the enolization of **1** (0.005 M) by LiHMDS (0.10 M) at −55 °C. The curve depicts the results of an unweighted least-squares fit to $k_{obsd} = a$[*trans*-TMCDA] + b, where $a = 4.6 \pm 0.1 \times 10^{-1}$, $b = 1.17 \pm 0.02$.

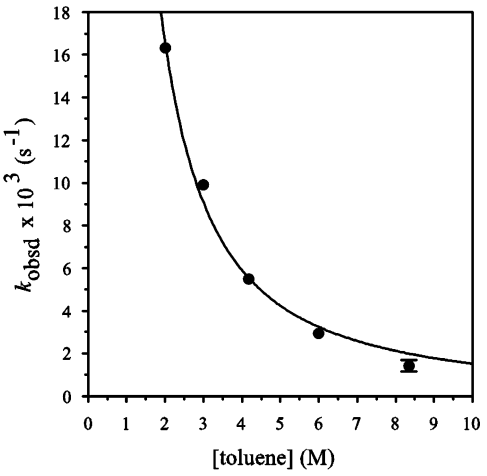
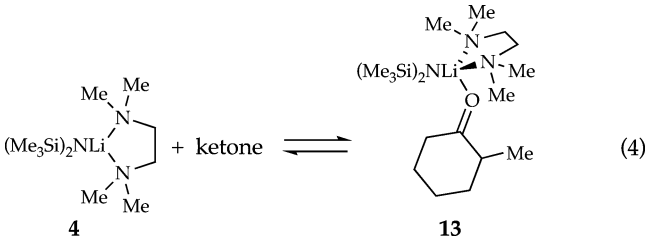


Figure 3. Plot of k_{obsd} vs [toluene] in 0.50 M TMCDA for the enolization of **1** by LiHMDS (0.10 M) in pentane cosolvent at −55 °C. The curve depicts an unweighted least-squares fit to $k_{obsd} = a$[toluene]^b, where $a = 4.6 \pm 0.4 \times 10^1$, $b = -1.4 \pm 0.1$.

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).



(4)

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.[30] 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.

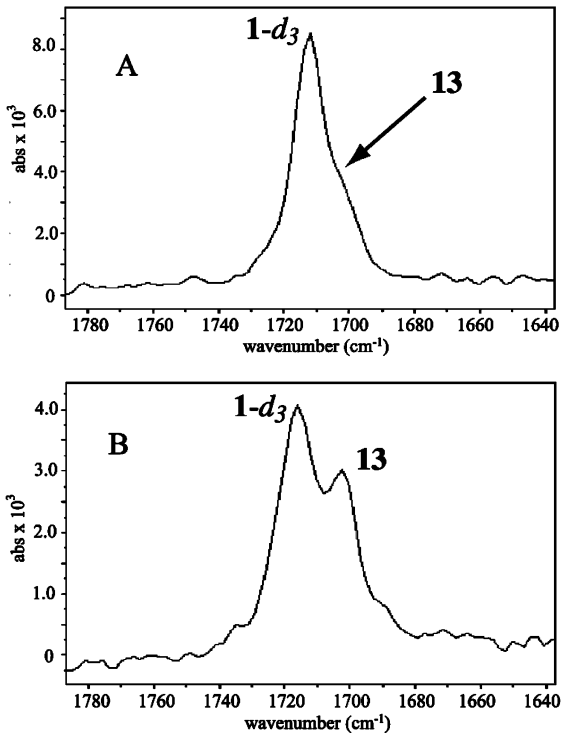


Figure 4. IR spectra showing free and LiHMDS-complexed **1**-d_3 at −60 °C with (a) LiHMDS (0.10 M), **1**-d_3 (0.005 M), in 0.50 M TMEDA/toluene solution, and (b) LiHMDS (0.10 M), **1**-d_3 (0.005 M), in 0.50 M TMEDA and 2.50 M toluene with pentane cosolvent.

^{6}Li 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 ^{6}Li resonance of the monomer in proportion to the concentration of added **15**. The ^{6}Li resonance ascribable to a discrete complex **14** appears in the upfield region typically reserved for trisolvated LiHMDS monomers bearing tetrahedral lithiums.

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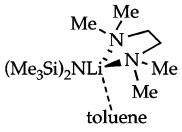

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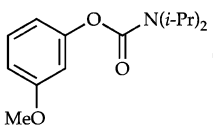

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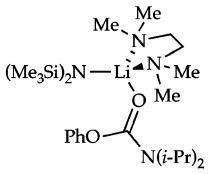


16

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 ^{6}Li chemical shifts of **4** using pentane and toluene as cosolvents are similar,[31] 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.[5,7b])

With the detection and characterization of complex **13** completed, we were poised to investigate the enolization. A plot of k_{obsd} versus TMEDA concentration reveals TMEDA-concentration-independent rates, and a plot of k_{obsd} versus LiHMDS reveals a distinct curvature (Figure 5). Downward curvatures are often emblematic of fractional orders affiliated with deaggregation,[19] 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.[32]

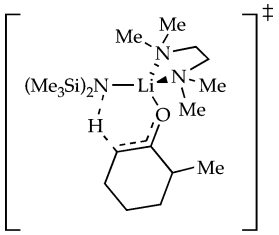
Although toluene stabilizes LiHMDS as a medium rather than as a ligand, one would still predict effects on reactivity. Indeed, a plot of k_{obsd} versus toluene concentration (Figure 6) reveals an inverse dependence, a significant inhibition by toluene. The fit shown in Figure 6 is not very good, but 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.

$$-\mathrm{d}[\mathbf{1}]/\mathrm{d}t = k[\mathbf{1}][\mathrm{LiHMDS}]/(1 + k'[\mathrm{LiHMDS}]) \quad (5)$$

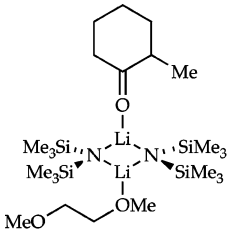
$$\underset{(\mathbf{4})}{(Me_3Si)_2NLi(TMEDA)} + \underset{(\mathbf{1})}{\text{ketone}} \rightleftharpoons \underset{(\mathbf{13})}{(Me_3Si)_2NLi(TMEDA)(ketone)} \quad (6)$$

$$\underset{(\mathbf{13})}{(Me_3Si)_2NLi(TMEDA)(ketone)} \rightarrow \underset{(\mathbf{17})}{[(Me_3Si)_2NLi(TMEDA)(ketone)]^{\ddagger}} \quad (7)$$



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.



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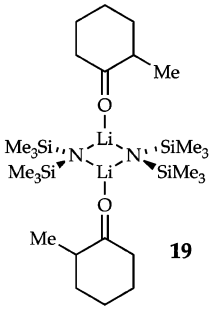

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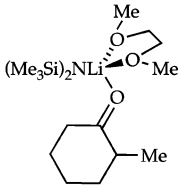


20

At 1.0 M DME, conditions are shown by IR spectroscopy to afford appreciable complexation. ^{6}Li NMR spectra of [^{6}Li,^{15}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:

$$\underset{(\mathbf{7})}{\tfrac{1}{2}[(Me_3Si)_2NLi]_2(DME)_2} + DME \rightleftharpoons \underset{(\mathbf{5})}{[(Me_3Si)_2NLi]_2(DME)_2} \quad (8)$$

(31) Small ^{6}Li chemical shift differences are often noted in saturated and aromatic hydrocarbons.

$$[(Me_3Si)_2NLi]_2(DME)_2 + \text{ketone} \rightleftharpoons [(Me_3Si)_2NLi]_2(DME)(\text{ketone}) + DME \quad (9)$$
(**7**) (**18**)

$$[(Me_3Si)_2NLi]_2(DME)(\text{ketone}) + \text{ketone} \rightleftharpoons [(Me_3Si)_2NLi]_2(\text{ketone})_2 + DME \quad (10)$$
(**18**) (**19**)

$$(Me_3Si)_2NLi(DME)_2 + \text{ketone} \rightleftharpoons (Me_3Si)_2NLi(DME)(\text{ketone}) + DME \quad (11)$$
(**5**) (**20**)

Mechanisms of Enolization:

$$[(Me_3Si)_2NLi]_2(DME)(\text{ketone}) \rightarrow [\{(Me_3Si)_2NLi\}_2(DME)(\text{ketone})]^{\ddagger} \quad (12)$$
(**18**) (**26**)

$$(Me_3Si)_2NLi(DME)(\text{ketone}) \rightarrow [(Me_3Si)_2NLi(DME)(\text{ketone})]^{\ddagger} \quad (13)$$
(**20**) (**25**)

$$2(Me_3Si)_2NLi(DME)_2 + \text{ketone} \rightarrow [\{(Me_3Si)_2NLi\}_2(DME)_4(\text{ketone})]^{\ddagger} \quad (14)$$
(**5**) (**24**)

$$(Me_3Si)_2NLi(DME)_2 + \text{ketone} \rightleftharpoons [(Me_3Si)_2NLi(DME)_2(\text{ketone})]^{\ddagger} \quad (15)$$
(**5**) (**21**, **22**, or **23**)

A plot of k_{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.[32a] 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 deaggregation, and (3) the lower reactivity observed at the *y*-intercept in Figure 7.

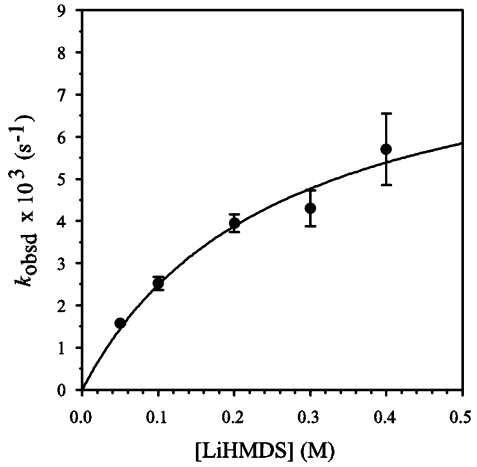


Figure 5. Plot of k_{obsd} vs [LiHMDS] in 0.40 M TMEDA/toluene solution for the enolization of **1**-d_3 by LiHMDS at −60 °C. The curve depicts the results of an unweighted least-squares fit to $k_{obsd} = a[\text{LiHMDS}]/(1 + b[\text{LiHMDS}])$, where $a = 3.4 \pm 0.6 \times 10^1$, $b = 3.9 \pm 0.1$.

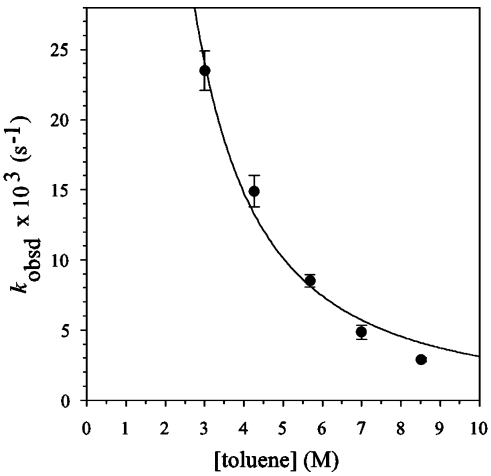


Figure 6. Plot of k_{obsd} vs [toluene] in 0.50 M TMEDA/pentane for the enolization of **1**-d_3 by LiHMDS (0.10 M) at −60 °C. The curve depicts the results of the unweighted least-squares fit to $k_{obsd} = a[\text{toluene}]^b$, where $a = 1.5 \pm 0.3 \times 10^2$ and $b = -1.6 \pm 0.1$.

The limiting rate at the lowest DME concentration, the *y*-intercept in Figure 7, corresponds to the rate starting from dimer-based complex **18** as the sole observable form of the ketone (eq 12). The implicit zeroth-order DME dependence and a measured zeroth-order LiHMDS dependence[34] are consistent with open dimer-based transition structure **26**, akin to those invoked on a number of occasions.[35]

Enolizations at the highest DME concentrations derive from monomer **5** and uncomplexed ketone **1**. The zeroth-order DME dependence is surprising given that the observable monomer **5** is highly solvated. We incorrectly surmised that the LiHMDS dependence would, nonetheless, implicate exclusively monomer-based enolization. A plot of k_{obsd} versus LiHMDS concentration (Figure 8) reveals a decidedly upward deviation from the anticipated first-order dependence that is too large to dismiss ($k_{obsd} = a[\text{LiHMDS}]^{1.35\pm0.02}$). The curvature could stem from the superposition of two mechanisms displaying first- and

(32) (a) Depue, J. S.; Collum, D. B. *J. Am. Chem. Soc.* **1988**, *110*, 5524. (b) Espenson, J. H. *Chemical Kinetics and Reaction Mechanisms*, 2nd ed.; McGraw-Hill: New York, 1995, pp 86−90. (c) Dunford, H. B. *J. Chem. Educ.* **1984**, *61*, 129.
(33) (a) Hilmersson, G.; Davidsson, O. *J. Org. Chem.* **1995**, *60*, 7660. (b) Remenar, J. F.; Lucht, B. L.; Collum, D. B. *J. Am. Chem. Soc.* **1997**, *119*, 5567. (c) See ref 7a.
(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.

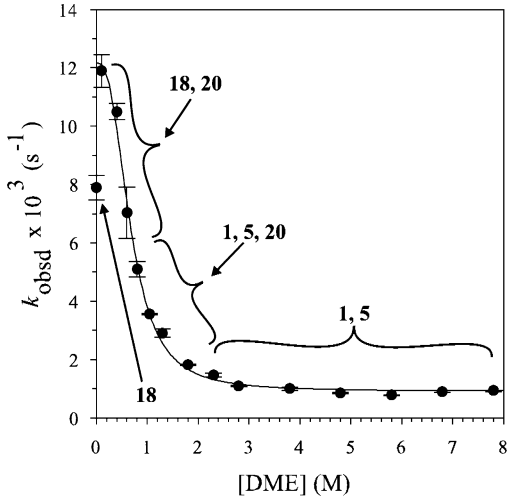


Figure 7. Plot of k_{obsd} vs [DME] in toluene cosolvent for the enolization of **1** by LiHMDS (0.10 M) at −78 °C. The labels indicate the observable structural forms. The *y*-intercept corresponds to zero *free* DME concentration. The curve depicts the results of an unweighted least-squares fit to $k_{obsd} = a[\mathrm{DME}]^b/(c + [\mathrm{DME}]^b) + d$, where $a = 1.12 \pm 0.03 \times 10^1$, $b = -2.6 \pm 0.1$, $c = 6.7 \pm 0.2 \times 10^{-1}$, $d = 9 \pm 1 \times 10^{-1}$.

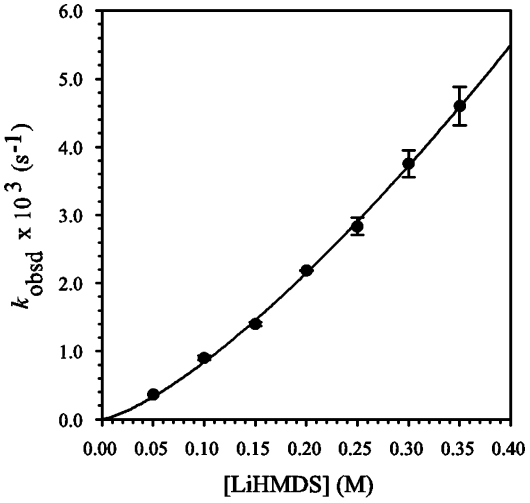


Figure 8. Plot of k_{obsd} vs [LiHMDS] in 6.8 M DME/toluene solution for the enolization of **1**-d_3 by LiHMDS at −78 °C. The curve depicts the results of an unweighted least-squares fit to $k_{obsd} = a[\mathrm{LiHMDS}]^b$, where $a = 1.90 \pm 0.07 \times 10^1$, $b = 1.35 \pm 0.02$.

second-order dependencies on LiHMDS. The first-order dependence, generically described by eq 15, implicates a monomer-based transition structure, $[\{(Me_3Si)_2NLi\}(DME)_2(\mathbf{1})]^{\ddagger}$, containing *two* DME ligands. We consider transition structures **21**−**23** plausible. The dimer-based pathway (eq 14) is consistent with transition structure $[\{(Me_3Si)_2NLi\}_2(DME)_4(\mathbf{1})]^{\ddagger}$, containing an extraordinary four DME ligands.[36] We gingerly offer triple ion **24** but with attenuated conviction. At the intermediate DME concentrations wherein a distinct inverse DME dependence can be observed (Figure 7), one could imagine the intervention of monomer-based transition structure **25**. There is very little hard evidence to support **25**, but analogy with the diamines described above seems compelling. Moreover, the maximum in the curve in Figure 7 requires an additional 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. TMCDA has been shown to be superior to TMEDA as a bidentate ligand in several instances.[7a,38] Less direct evidence suggests that TMCDA is sterically more demanding.[38b] 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 TMCDA resulting from the trans ring fusion increases its binding constant through a form of the Thorpe−Ingold effect[40,41] in which destabilizing interactions in the unbound ligand are alleviated on complexation. (An analogy to proton sponge may be instructive.[42]) 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.

(37) For leading references of rate maxima in plots of k_{obsd} versus solvent concentration, see: Collum, D. B. *Acc. Chem. Res.* **1992**, *25*, 448.

(38) (a) Remenar, J. F.; Lucht, B. L.; Collum, D. B. *J. Am. Chem. Soc.* **1997**, *119*, 5567. (b) Hoffmann, D.; Collum, D. B. *J. Am. Chem. Soc.* **1998**, *120*, 5810. (c) Remenar, J. F.; Lucht, B. L.; Kruglyak, D.; Romesberg, F. E.; Gilchrist, J. H.; Collum, D. B. *J. Org. Chem.* **1997**, *62*, 5748. (d) Also, see ref 7a.

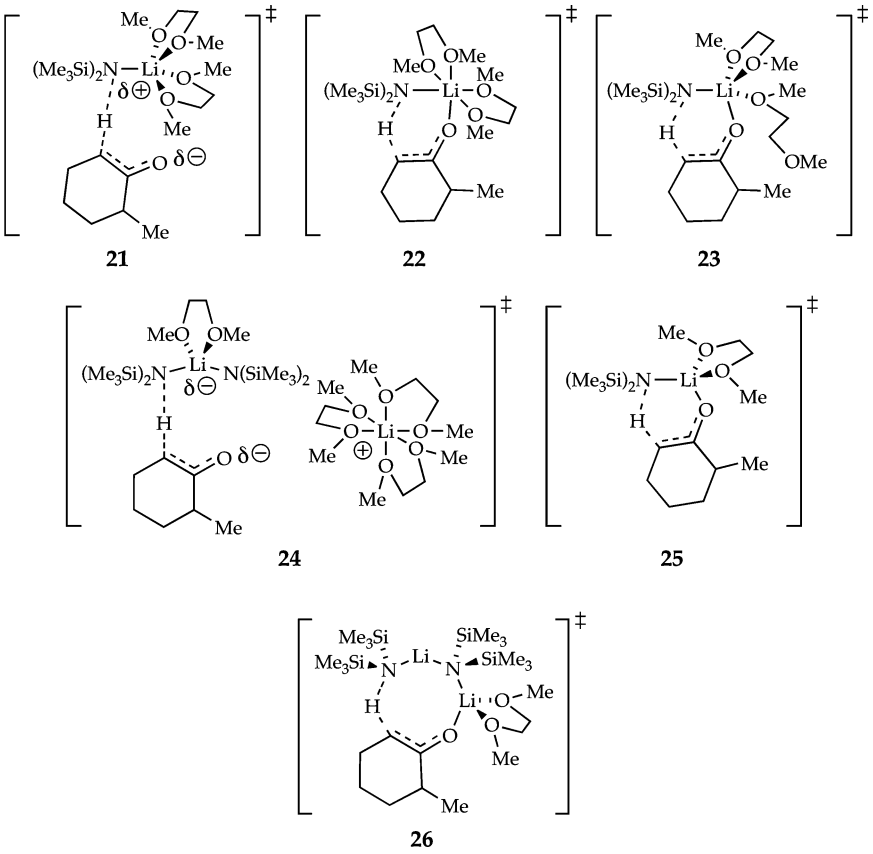
(39) Settle, F. A.; Haggerty, M.; Eastham, J. F. *J. Am. Chem. Soc.* **1964**, *86*, 2076. For additional references, see ref 8b and 33.

(40) Beesley, R. M.; Ingold, C. K.; Thorpe, J. F. *J. Chem. Soc.* **1915**, *107*, 1080. Ingold, C. K. *J. Chem. Soc.* **1921**, *119*, 305.

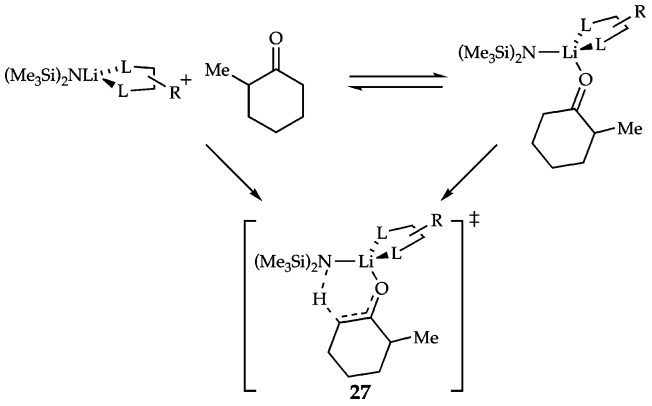
(41) For a discussion and leading references to the influence of the Thorpe−Ingold effect on chelate stability, see: Ramirez, A.; Lobkovsky, E.; Collum, D. B. *J. Am. Chem. Soc.* **2003**, *125*, 15376.

(42) *N*,*N*,*N*′,*N*′-Tetramethyl-1,8-naphthalenediamine (proton-sponge) shows a high affinity for protons that is attributed to buttressing by the two dimethylamino groups: Marshall, W. B.; Brewbaker, J. L.; Delaney, M. S. *J. Appl. Polym. Sci.* **1991**, *42*, 533. Its high basicity does not extend to lithium. See ref 7a.

Chart 1



Scheme 1



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.[5,7b,12−16] Some reactions prove to be highly sensitive to the choice of hydrocarbon cosolvent,[13] whereas others are not.[15,16] Hydrocarbon sensitivity can be observed in the presence of Lewis-basic solvents such as ethers,[12a] trialkylamines,[7b] diamines,[7a,12d,13a,c,e] and even hexamethylphosphoramide.[16,13d]

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 **15** 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 elicited 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.[7b] 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—$(Me_3Si)_2NLi(R_3N)_2$—relative to the analogous trisolvate in

toluene but not in hexane. The stabilization of $(Me_3Si)_2NLi(R_3N)_2$ also does not appear to be primary shell solvation by toluene. (The corresponding ether solvates show no such effect.[7c])

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 ± 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 $+Li(DME)_3$ and related high coordinate LiHMDS are well precedented—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.[13d,44] The octahedral cation of **24**[17] and an analogous $[R-Li-R]^-$ 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 metalations 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. TMCDA, 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. ^{6}Li metal (95.5% enriched) was obtained from Oak Ridge National Laboratory (Oak Ridge, TN). LiHMDS, [^{6}Li]LiHMDS, and [^{6}Li,^{15}N]LiHMDS were prepared and purified as described previously.[7d] Ketone **1**-d_3 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 ^{6}Li, ^{13}C, and ^{15}N NMR spectra were recorded on a 500 MHz spectrometer at 76.73, 125.79, and 50.66 MHz, respectively. The ^{6}Li, ^{13}C, and ^{15}N resonances are referenced to 0.3 M [^{6}Li]LiCl/MeOH at −90 °C (0.0 ppm), the CH_2O resonance of THF at −90 °C (67.57 ppm), and neat Me_2NEt at −90 °C (25.7 ppm), respectively.

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 mg, 1.0 mmol) in TMEDA (0.755 mL, 0.50 M) and toluene (9.08 mL) and cooled to −78 °C. After a background spectrum was recorded, ketone **1**-d_3 (50 μL, 0.050 mmol, 0.005 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.