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Published on Web 02/20/2004

Reaction of Ketones with Lithium Hexamethyldisilazide: Competitive Enolizations and 1,2-Additions

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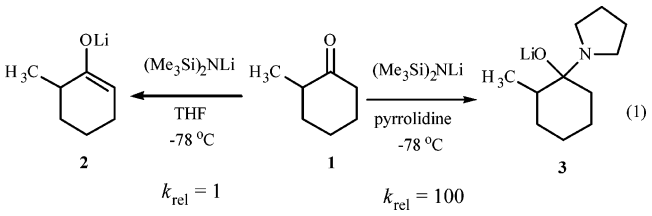
Abstract: Reaction of 2-methylcyclohexanone with lithium hexamethyldisilazide (LiHMDS, TMS_2NLi) displays highly solvent-dependent chemoselectivity. LiHMDS in THF/toluene effect enolization. Rate studies using in situ IR spectroscopy are consistent with a THF concentration-dependent monomer-based pathway. LiHMDS in pyrrolidine/toluene affords exclusively 1,2-addition of the pyrrolidine fragment to form an α-amino alkoxide-LiHMDS mixed dimer shown to be a pair of conformers by using ^6Li, ^{15}N, and ^{13}C NMR spectroscopies. Rate studies are consistent with a monomer-based transition structure $[(TMS_2NLi)(ketone)(pyrrolidine)_3]^{\ddagger}$. The partitioning between enolization and 1,2-addition is kinetically controlled.

Introduction

Recent studies have shown that lithium hexamethyldisilazide (LiHMDS) solvated by hindered ethers or hindered di- and trialkylamines mediates the enolization of 2-methylcyclohexanone via a dimer-based mechanism.[1] The amines elicit substantial accelerations relative to ethers attributable to both a steric destabilization of the reactants and an electronic stabilization of the dimer-based transition structures.

We describe herein the reaction of 2-methylcyclohexanone (**1**) with LiHMDS solvated by two sterically unhindered ligands: THF and pyrrolidine. Despite the isostructural relationship of THF and pyrrolidine, LiHMDS/THF mixtures effect clean enolization, whereas LiHMDS/pyrrolidine mixtures afford exclusively 1,2-addition of pyrrolidine (eq 1). Rate studies suggest that both reactions occur via highly solvated monomer-based transition structures. The potential implications of the 1,2-addition to organic synthesis—both positive and negative—are considered.



(1)

Results

LiHMDS/THF: Kinetics of Enolization. Addition of ketone **1** to LiHMDS in either THF or THF/hydrocarbon mixtures at −78 °C was monitored by in situ IR spectroscopy.[2] The absorbance of **1** at 1722 cm^{-1} is observed to the exclusion of absorbances in the lower frequency region of the spectrum (1710−1700 cm^{-1}),[1] showing that **1** does not measurably bind to LiHMDS.[3,4] Pseudo-first-order conditions were established by maintaining low concentrations of ketone **1** (0.004−0.01 M) and high, yet adjustable, concentrations of recrystallized[5] LiHMDS (0.05−0.40 M) and THF (0.15−12.0 M) using toluene as the cosolvent. The loss of the ketone or its less reactive deuterated analogue **1-*d*$_3$**[6] follows clean first-order decays to ≥5 half-lives. Reestablishing the IR baseline and monitoring a second injection reveals no significant change in the rate constant, showing that conversion-dependent autocatalysis or autoinhibition is unimportant under these conditions. Comparison of **1** versus **1-*d*$_3$** provided a large isotope effect (k_H/k_D = 11 ± 1), consistent with a rate-limiting proton transfer. A plot of k_{obsd} versus [THF] (Figure 1) shows a nearly first-order dependence on the THF concentration with a slight downward curvature. Superficially, this curvature is consistent with a THF concentration-dependent deaggregation manifesting incomplete first-order saturation kinetics (as illustrated by the least-squares fit). However, neither the first-order dependence nor the substantially incomplete saturation behavior are fully consistent with formation of predominantly *trisolvated* monomers in 12 M THF (eq 2).[7] We believe the relatively simple THF dependence belies a greater underlying complexity.

(1) (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.; Lucht, B. L.; Kenkre, S.; Collum, D. B. *J. Org. Chem.* **2004**, *69*, 242−249.

(2) (a) Sun, X.; Collum, D. B. *J. Am. Chem. Soc.* **2000**, *122*, 2452. (b) Review: Rein, A. J.; Donahue, S. M.; Pavlosky, M. A. *Curr. Opin. Drug Discovery Dev.* **2000**, *3*, 734.

(3) For leading references and recent examples of detectable organolithium-substrate precomplexation, see: (a) Klumpp, G. W. *Recl. Trav. Chim. Pays-Bas* **1986**, *105*, 1. (b) Andersen, D. R.; Faibish, N. C.; Beak, P. *J. Am. Chem. Soc.* **1999**, *121*, 7553. (c) Pippel, D. J.; Weisenberger, G. A.; Faibish, N. C.; Beak, P. *J. Am. Chem. Soc.* **2001**, *123*, 4919. (d) Bertini-Gross, K. M.; Beak, P. *J. Am. Chem. Soc.* **2001**, *123*, 315.

(4) For a general discussion of ketone−lithium complexation and related ketone−Lewis acid complexation, see: Shambayati, S.; Schreiber, S. L. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: New York, 1991; Vol. 1, p 283.

(5) Romesberg, F. E.; Bernstein, M. P.; Gilchrist, J. H.; Harrison, A. T.; Fuller, D. J.; Collum, D. B. *J. Am. Chem. Soc.* **1993**, *115*, 3475.

(6) Peet, N. P. *J. Labelled Compd.* **1973**, *9*, 721.

(7) Lucht, B. L.; Collum, D. B. *J. Am. Chem. Soc.* **1995**, *117*, 9863.

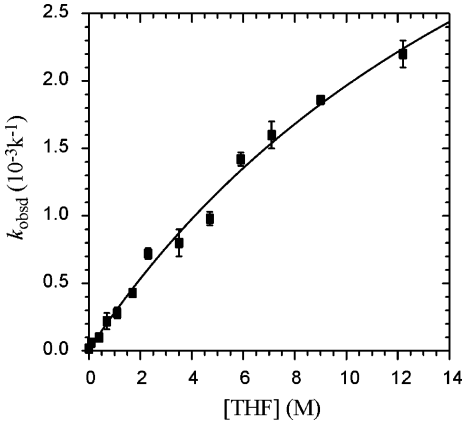
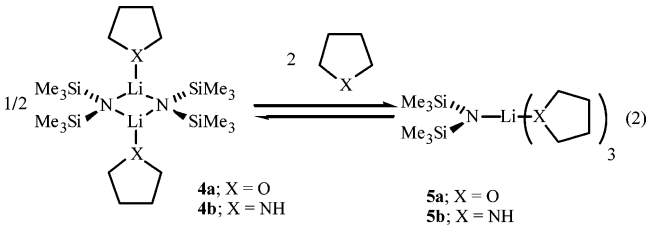


Figure 1. Plot of k_{obsd} vs [THF] in toluene for the enolization of **1** (0.004 M) by LiHMDS (0.10 M) at −78 °C. The curve depicts the results of an unweighted least-squares fit to $k_{obsd} = (a + bx)/(1 + cx)$ ($a = 1 \pm 4 \times 10^{-5}$, $b = 2.9 \pm 0.3 \times 10^{-4}$, $c = 0.05 \pm 0.01$).



A plot of k_{obsd} versus [LiHMDS] in 7.1 M THF in toluene (Figure 2) reveals a fractional order (0.61 ± 0.08).[8] A fractional order of >0.5 is consistent with a monomer-based enolization starting with the mixture of monomer and dimer (eq 2). The rate of enolization is not influenced by added hexamethyldisilazane (HMDS).

LiHMDS/Pyrrolidine: Structure of the 1,2-Adduct. Reactions of ketone **1** with LiHMDS/pyrrolidine at −78 °C under analogous pseudo-first-order conditions were monitored by in situ IR spectroscopy. The absence of ketone-LiHMDS complexation and a clean first-order loss of ketone over time are consistent with a simple mechanistic picture. A number of observations, however, suggested that ketone enolization was not occurring. The IR spectra show no absorbances in the 1610−1625 cm^{-1} region attributable to the anticipated C=C absorbance of the enolate. Attempts to trap the putative enolate with TMSCl failed completely. A small isotope effect ($k_H/k_D = 1.4 \pm 0.1$) was also troublesome (and was curiously similar to the isotope effect for the 1,2-addition of MeOH to 2,2,5,5-tetradeuteriocyclopentanone).[9] Although an equilibrium isotope effect arising from a reversible deprotonation−reprotonation facilitated by the pyrrolidine would likely be small, reaction of ketone **1-*d*$_3$** with LiHMDS/pyrrolidine followed by quenching with H_2O afforded **1-*d*$_3$** with no (<5%) loss of deuterium. Addition using *N*-d_1-pyrrolidine reveals a small ($k_H/k_D = 1.8 \pm 0.2$) solvent isotope effect.

Suspecting an intervening 1,2-addition (eq 1), we probed the reaction coordinate using NMR spectroscopy. To avoid stereochemical complexities[10] due to the 2-methyl substituent, we used 2,2,6,6-tetradeuteriocyclohexanone as a surrogate. Indeed,

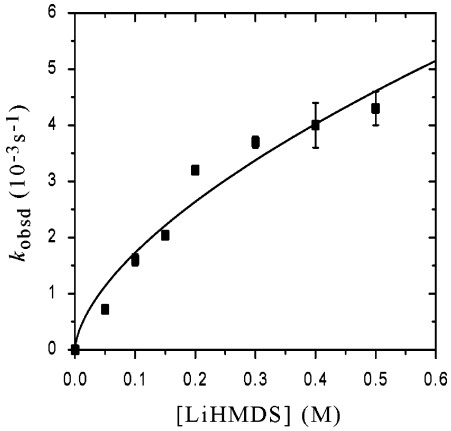
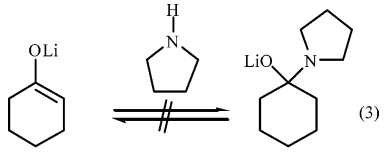


Figure 2. Plot of k_{obsd} vs [LiHMDS] in 7.1 M THF/toluene for the enolization of **1** (0.004 M) at −78 °C. The curve depicts the results of an unweighted least-squares fit to $k_{obsd} = ax^b$ ($a = 7.0 \pm 0.7 \times 10^{-3}$, $b = 0.61 \pm 0.08$).

preliminary ^{13}C NMR spectroscopic studies of a 3:10:1 mixture of LiHMDS, pyrrolidine, and cyclohexanone-d_4 revealed resonances corresponding to uncoordinated pyrrolidine along with resonances at δ 86.2 ppm (major) and 85.0 ppm (minor) consistent with the quaternary carbon (N−*C*−O) of the putative 1,2-adduct **7**.[10] The 1,2-addition in pyrrolidine and enolization in THF were shown to be irreversible (eq 3). Thus, quantitative enolization by LiHMDS/toluene[1a,b] with *subsequent* addition of pyrrolidine affords only enolate **6** displaying characteristic ^{13}C resonances at 160.0 and 89.2 ppm[11] as well as a strong IR absorbance at 1622 cm^{-1} that did not disappear on standing at −78 °C for 2 h. Similarly, ^{13}C resonances attributed to **7** generated from LiHMDS/pyrrolidine/toluene as described above show no significant change even when warmed to room temperature.



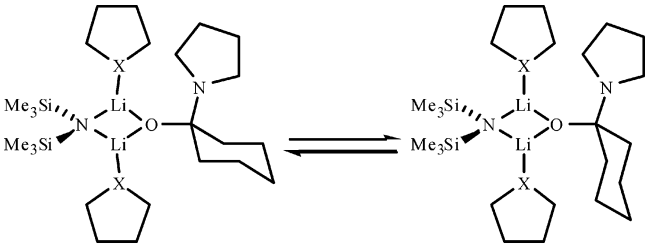
Detailed structural investigations of **7** were facilitated by the fortuitous observation that reaction of cyclohexanone with 1.0 equiv of LiHMDS (rather than excess) in pyrrolidine/toluene mixtures affords adduct **7** as a thermally stable, nearly insoluble white solid. ^{1}H NMR spectroscopy of **7** under dilute conditions in pyrrolidine/toluene-d_8 mixtures revealed the key components of **7** to the exclusion (<5%) of LiHMDS-derived resonances.The solid readily dissolves in the presence of several equivalents of [^{6}Li]LiHMDS in either pyrrolidine/cyclopentane or THF solutions due to the formation of LiHMDS/**7** mixed dimers shown to be a mixture of unchelated conformers **8** and **9** as described below (Table 1). Detailed studies used THF/toluene rather than pyrrolidine/toluene solutions due to the superior spectral quality.

(8) The concentration of the lithium amide, although expressed in units of molarity, refers to the concentration of the monomer unit (normality). The concentrations of THF and pyrrolidine are expressed as total solvent added.
(9) Jones, J. M.; Bender, M. L. *J. Am. Chem. Soc.* **1960**, *82*, 6322.
(10) The cis and trans adducts of **3** would be formed as racemates, four stereoisomers overall. If, for example, these species formed a statistical distribution of dimers, there would be a total of six spectroscopically distinct diastereomers and a much higher number of possible tetramers. By contrast, achiral adduct **7** would likely form only one dimer and two tetramers differing by the stereochemistry of chelation. Mixed dimerization with LiHMDS as described precludes much of this complexity.
(11) Kim, Y.-J.; Bernstein, M. P.; Galiano-Roth, A. S.; Romesberg, F. E.; Fuller, D. J.; Harrison, A. T.; Collum, D. B.; Williard, P. G. *J. Org. Chem.* **1991**, *56*, 4435.

Table 1. NMR Spectroscopic Data[a,b]

compd	δ ^{6}Li (mult, $J_{LiN(LiHMDS)}$)	δ ^{15}N (mult, J_{LiN}) ($^{15}N(SiMe_3)_2$)	δ ^{15}N (mult, J_{LiN})[c] (^{15}N-pyrrolidino)	δ ^{13}C (mult, J_{CN})[c] (N–*C*–O)
8a, **9a**	0.88 (d, 3.3), 0.81 (d, 3.2)	37.5 (q, 3.2), 37.7 (q, 3.2)	61.4 (s), 59.1 (s)	82.7 (s), 81.6 (s)
8b, **9b**[c]	1.35 (d, 3.4), 1.25 (- -[d])	36.8 (m, - -)	61.0 (s), 58.9 (s)	83.0 (s), 81.7 (s)
12	0.62 (d, 3.3)	37.4 (q, 3.2)	59.0 (s)	85.9 (d, 2.6)
13 or **14**[e]	0.87 (d, 3.3)	37.5 (m, - -)	58.7 (s)	82.6 (d, 2.3)
15/**16**	0.64 (d, 3.3), 0.56 (br d, 3.3)	37.5 (m, - -)	61.4 (s), 59.3 (s)	85.9 (s), 84.5 (s)

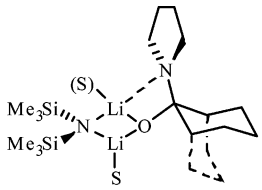
[a] Spectra were recorded in THF solutions of 0.2 M adduct/[^{6}Li,^{15}N]LiHMDS mixed aggregate and 0.4 M excess LiHMDS as listed below. Traces of free pyrrolidine (^{15}N NMR: δ 69−76 ppm; variable) were observed in all instances. Coupling constants were measured after resolution enhancement and reported in Hz. Multiplicities are denoted as follows: s = singlet, d = doublet, t = triplet, q = quintet. The chemical shifts are reported relative to 0.3 M ^{6}LiCl/MeOH at −90 °C (0.0 ppm), neat Me_2NEt at −90 °C (25.7 ppm), and neat THF at −90 °C (67.5 ppm). [b] Samples also contained [^{6}Li,^{15}N]LiHMDS dimer **4a**: ^{6}Li NMR δ 0.94 (t, 3.5), ^{15}N NMR δ 37.7 (q, 3.5); **4b**: ^{6}Li NMR δ −0.03 (d, 5.0), ^{15}N NMR δ 40.8 (t, 5.0). [c] Spectra recorded using [^{6}Li]LiHMDS adducts prepared from [^{15}N]pyrrolidine. [d] Spectra recorded using [^{6}Li]LiHMDS in 2.0 M [^{15}N]pyrrolidine/cyclopentane. [e] One isomer (see text).



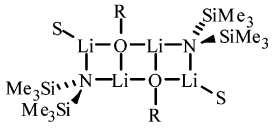
8a; X = O
8b; X = NH

9a; X = O
9b; X = NH

Mixtures of [^{6}Li]**7** and [^{6}Li,^{15}N]LiHMDS in THF/toluene display the ^{6}Li and ^{15}N resonances characteristic of LiHMDS monomer **5a** along with two ^{6}Li doublets in an *approximate* 1:1 ratio. We originally believed that the two ^{6}Li resonances stemmed from either dimer **10a** or a ladder depicted generically as **11a**. However, the ^{13}C NMR spectra display *two* quaternary carbons, and the ^{15}N NMR spectra display *two* overlapping quintets. Neither **10a** nor **11a** can account for the duplicate resonances. A ^{6}Li−^{15}N heteronuclear multiple quantum coherence (HMQC) spectrum further shows that each ^{15}N quintet is coupled to only one ^{6}Li doublet, indicating two magnetically independent mixed dimer fragments. Warming the probe revealed a coalescence of the two ^{6}Li doublets (derived from splitting by the [^{6}Li,^{15}N]LiHMDS) to a doublet between −70 and −60 °C. An activation energy of 11.0 ± 0.3 kcal/mol is consistent with the interconversion of **8a** and **9a** via a chair−chair flip.



10a; S = THF
10b; S = pyrrolidine



11a; S = THF
11b; S = pyrrolidine

Mixtures of [^{6}Li,^{15}N]**7** (prepared from [^{15}N]pyrrolidine[12]) and [^{6}Li]LiHMDS afforded spectral data that are both revealing and somewhat perplexing. Whereas two ^{15}N singlets anticipated for **8b** and **9b** were readily observed, the somewhat broad ^{13}C resonances of the two quaternary carbons display no ^{13}C−^{15}N coupling. Although this seemed odd at first, the one-bond ^{13}C−^{15}N couplings observed in the pyrrolidino α-carbon of **8a**/**9a** are only 2.9 and 3.3 Hz and difficult to discern.[13] We also observed no ^{15}N coupling in either of the two ^{6}Li resonances. A coupling constant of >2.0−3.0 Hz is expected for amine chelates.[14,15] Moreover, superposition of chelation *and* conformational isomerism of the chair could afford four ^{6}Li resonances.

Examination of three additional 1,2-adducts proved instructive. Condensation of [^{6}Li]LiHMDS/pyrrolidine with 3-pentanone (1:1) afforded an insoluble solid. Redissolving the sample with excess [^{6}Li,^{15}N]LiHMDS afforded mixed dimer **12** showing one ^{6}Li doublet, one ipso carbon resonance, and one LiHMDS-derived ^{15}N quintet. The symmetry of **12** indicates chelation is absent and suggests that the resonance duplications attributed to **8** and **9** derive from conformational isomerism rather than chelation. Also of considerable importance, samples prepared using [^{15}N]pyrrolidine displayed weak coupling to the ipso carbon (N−*C*−O; $^1J_{N-C}$ = 2.6 Hz).

The adduct derived from 4-*tert*-butylcyclohexanone affords a single stereoisomeric mixed dimer that is either **13** or **14**. The nearly thermoneutral **8**/**9** equilibrium and the highly selective preference for **13** or **14** suggests that the stereochemistry of the 1,2-addition does not correlate with the stability of the adduct. This *may* offer mechanistic insights (vide infra). A cursory examination of the adduct derived from 2-methylcyclohexanone showed far less complexity attributed to the 2-methyl moiety than originally feared.[10] Two ^{6}Li doublets can be attributed to diastereomers **15** and **16**. Severe broadening of only the ^{6}Lidoublet centered at 0.56 ppm tentatively attributed to conformational isomerism was not studied in depth.

LiHMDS/THF: Kinetics of 1,2-Addition. Rate studies of the 1,2-addition in eq 1 proved very informative. A plot of k_{obsd} versus [pyrrolidine] displays saturation kinetics (Figure 3)[16] that correlate strongly with the pyrrolidine-mediated dimer−monomer deaggregation previously studied using NMR spectroscopy

(12) Aubrecht, K. B.; Lucht, B. L.; Collum, D. B. *Organometallics* **1999**, *18*, 2981.

(13) Anomalously low $^1J(^{13}C-^{15}N)$ coupling has been discussed: (a) Yamada, S.; Nakamura, M.; Kawauchi, I. *J. Chem. Soc., Chem. Commun.* **1997**, 885. (b) Kainosho, M. *J. Am. Chem. Soc.* **1979**, *101*, 1031. (c) Tarburton, P.; Edasery, J. P.; Kingsbury, C. A.; Sopchik, A. E.; Cromwell, N. H. *J. Org. Chem.* **1979**, *44*, 2041.

(14) (a) Lucht, B. L.; Collum, D. B. *J. Am. Chem. Soc.* **1996**, *118*, 3529. (b) Waldmüller, D.; Kotsatos, B. J.; Nichols, M. A.; Williard, P. G. *J. Am. Chem. Soc.* **1997**, *119*, 5479. (c) Sato, D.; Kawasaki, H.; Shimada, I.; Arata, Y.; Okamura, K.; Date, T.; Koga, K. *J. Am. Chem. Soc.* **1992**, *114*, 761. (d) Reich, H. J.; Goldenberg, W. S.; Gudmundsson, B. O.; Sanders, A. W.; Kulicke, K. J.; Simon, K.; Guzei, I. A. *J. Am. Chem. Soc.* **2001**, *123*, 8067. (e) Johansson, A.; Davidsson, O. **2001**, *7*, 3461. See also refs 12 and 22.

(15) For a theoretical investigation of ^{6}Li−^{15}N coupling, see: Koizumi, T.; Morihashi, K.; Kikuchi, O. *Bull. Chem. Soc. Jpn.* **1996**, *69*, 305.

(16) (a) Espenson, J. H. *Chemical Kinetics and Reaction Mechanisms*, 2nd ed.; McGraw-Hill: New York, 1995; pp 86−90. (b) Dunford, H. B. *J. Chem. Educ.* **1984**, *61*, 129.

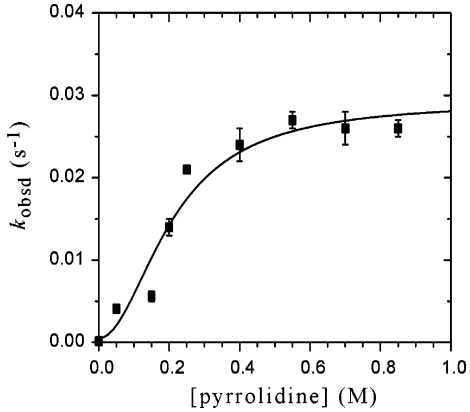


Figure 3. Plot of k_{obsd} vs [pyrrolidine] in toluene cosolvent for the 1,2-addition of pyrrolidine to **1-d_3** (0.004 M) by LiHMDS (0.10 M) at −78 °C. The curve depicts the results of an unweighted least-squares fit to $k_{obsd} = (a + bx^2)/(1 + cx^2)$ ($a = -1 \pm 2 \times 10^{-3}$, $b = 7 \pm 2 \times 10^{-1}$, $c = 23 \pm 8$).

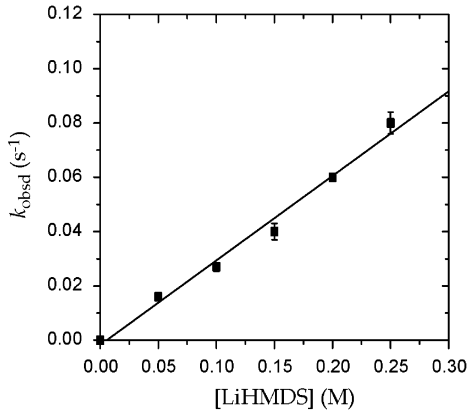
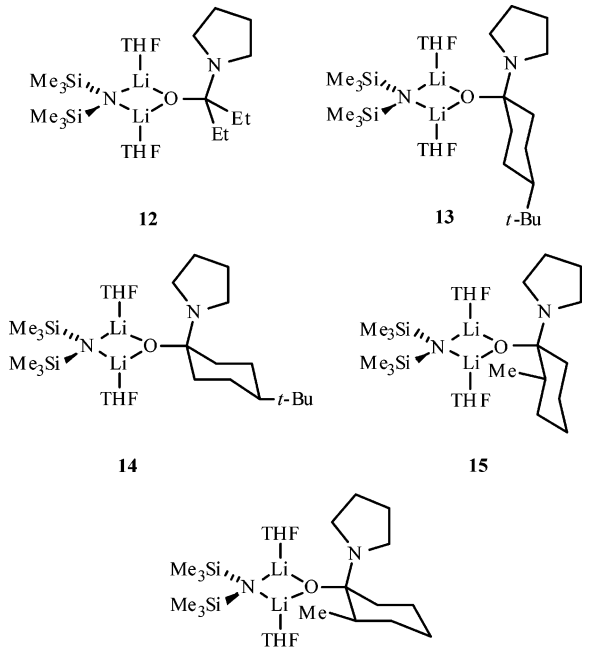


Figure 4. Plot of k_{obsd} vs [LiHMDS] in 0.55 M pyrrolidine/toluene for the 1,2-addition of pyrrolidine to **1-d_3** (0.004 M) at −78 °C. The curve depicts the results of an unweighted least-squares fit to $k_{obsd} = ax + b$ ($a = 0.31 \pm 0.02$, $b = -2 \pm 2 \times 10^{-3}$).



(eq 2).[17] The depiction of the saturation kinetics as a *second-order* dependence on the pyrrolidine concentration (exemplified by the sigmoidal shape) does *not* derive from the rate data but rather by inference from the NMR spectroscopic studies showing trisolvated monomers of general structure $TMS_2NLi(R_2NR')_3$.[17] A plot of k_{obsd} versus [LiHMDS] at high pyrrolidine concentrations affording exclusively monomer **5b** reveals a first-order dependence (Figure 4). In a control experiment, lithium pyrrolidide generated from pyrrolidine and *n*-BuLi undergoes instantaneous 1,2-addition rather than enolization.[18] However, *the rate of 1,2-addition by LiHMDS/pyrrolidine is unaffected by added TMS_2NH, indicating that a reversible, spectroscopically invisible[17] proton transfer to form low concentrations of lithium pyrrolidide and free TMS_2NH is not involved*.[19] The idealized rate law in eq 4, in conjunction with the well-defined structural assignment of LiHMDS solvated by pyrrolidine,[17] is consistent with the monomer-based mechanism described in eqs 5 and 6. Of course, the kinetics provide the stoichiometry of the rate-limiting transition structure (**17**) relative to the reactants;[20] the details of the prior steps, including the step in which the ketone enters the reaction coordinate, are conjecture.

$$-\mathrm{d}[\mathbf{1}]/\mathrm{d}t = (k_3 K_{eq}[\mathrm{LiHMDS}]_{total}[\mathrm{R_2NH}]^2)/(1 + K_{eq}[\mathrm{R_2NH}]^2) \quad (4)$$

such that $[R_2NH]$ is the total pyrrolidine concentration[8]

$$1/2(\mathrm{TMS_2NLi})_2(\mathrm{R_2NH})_2 + 2\mathrm{R_2NH} \overset{K_{eq}}{\rightleftharpoons} \underset{(\mathbf{5b})}{\mathrm{TMS_2NLi}(\mathrm{R_2NH})_3} \quad (5)$$
(**4b**)

$$\underset{(\mathbf{5b})}{\mathrm{TMS_2NLi}(\mathrm{R_2NH})_3} + \underset{(\mathbf{1})}{\mathrm{ketone}} \xrightarrow{k_1} \underset{(\mathbf{17})}{[(\mathrm{TMS_2NLi})(\mathrm{R_2NH})_3(\mathrm{ketone})]^{\ddagger}} \quad (6)$$

A cursory semiempirical (PM3) computational examination of the 1,2-addition using Me_2NH as a model for pyrrolidine afforded a 6-centered cyclic transition structure illustrated in Figure 5 and a credible (26.7 kcal/mol) activation enthalpy. We found no evidence of transannular N−Li interactions. We hasten to add that Figure 5 is included largely for its visual appeal.

Discussion

The LiHMDS/THF-mediated enolization is commonly used in synthesis.[21] The rate data for the enolization in eq 1, although undermined somewhat by the observable mixture of monomeric and dimeric LiHMDS over a range of THF concentrations, are consistent with monomer-based transition structure **18** ($n = 2$ or 3) and supported by computational data.[22] It is noteworthy that, despite the almost universal acceptance of this particular solvent-base combination for ketone enolization, enolization by

(17) Lucht, B. L.; Collum, D. B. *J. Am. Chem. Soc.* **1996**, *118*, 2217.
(18) If the saturation kinetics arose from quantitative formation of lithium pyrrolidide at high pyrrolidine concentration, the rate of the 1,2-addition by LiHMDS/pyrrolidine and *n*-BuLi/pyrrolidine would have been equivalent.
(19) Had the following reversible proton transfer been involved prior to the rate-limiting step $TMS_2NLi(R_2NH)_3 \rightleftharpoons R_2NLi(R_2NH)_2 + TMS_2NH$, an inverse first-order dependence on TMS_2NH would have been observed.
(20) Edwards, J. O.; Greene, E. F.; Ross, J. *J. Chem. Educ.* **1968**, *45*, 381.
(21) For leading references to applications of LiHMDS/THF in synthesis, see ref 1b.

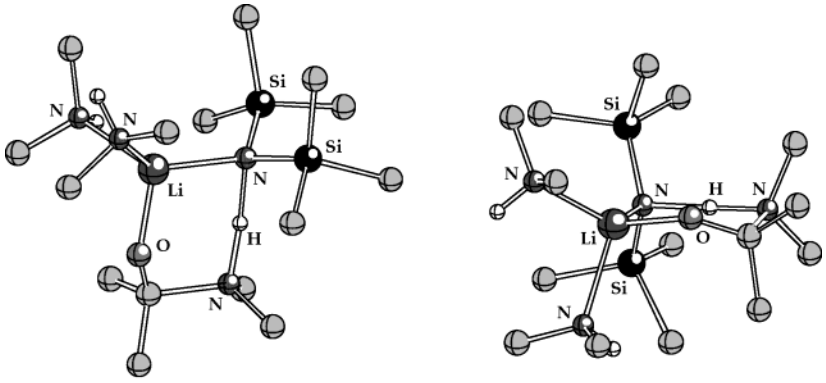
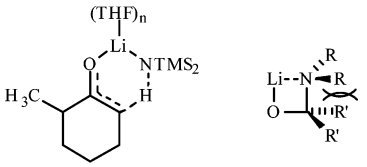


Figure 5. Transition structure $[(TMS_2NLi)(acetone)(Me_2NH)_3]^{\ddagger}$ calculated with PM3 modeling the monomer-based 1,2-addition. Methyl hydrogens are omitted for clarity. (A) View normal to approximate plane of ring. (B) View from side of ring.

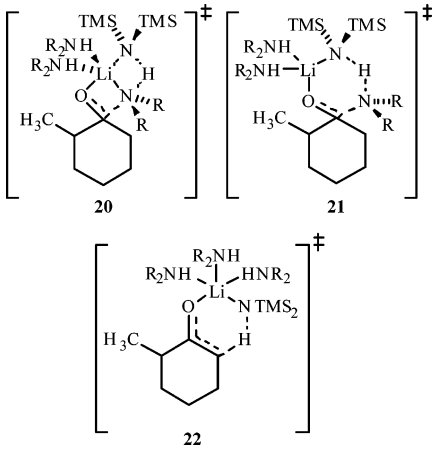
LiHMDS/THF is almost 2 orders of magnitude slower than the corresponding enolization using LiHMDS/Et_3N in toluene.[1]



18 **19**

Ketone **1** reacts with LiHMDS/pyrrolidine approximately 100 times faster than with LiHMDS/THF yet proceeds exclusively via 1,2-addition (eq 1). Structural studies reveal a pair of conformationally isomeric mixed dimers **8b** and **9b**. Detailed structural studies were carried out on the THF solvates **8a** and **9a** due to improved spectral quality. The absence of $^6Li-^{15}N$ coupling when **8a** and **9a** were prepared from ^{15}N-labeled pyrrolidine suggests that there is no chelation by the pyrrolidino group. Cursory investigations of structurally related adducts **12**−**16** (discussed in greater detail below) also show no coupling of ^6Li with the pyrrolidino nitrogen. The absence of chelation may seem odd, yet Boche and co-workers carried out computational studies on closely related 1,2-adducts and noted that chelation should be unfavorable.[23] Although Boche makes primarily electronic arguments against chelation, we believe a severe eclipsing of the two α-CH_2 substituents of the pyrroline ring with the two CH_2 substituents of the 2- and 6-carbons of the cyclohexane ring (**19**) would also be problematic. Recent investigations of chelates formed from lithium diisopropylamide (LDA) provide compelling evidence that substituents along the carbon backbone of bifunctional ligands *retard* chelation.[24]

The rate studies, in conjunction with previous spectroscopic studies,[17] reveal that the *net* 1,2-addition of lithium pyrrolidide proceeds via a monomer-based transition structure, $[(TMS_2NLi)(pyrrolidine)_3(ketone)]^{\ddagger}$ (eq 6). Importantly, the mechanism does *not* involve transiently formed lithium pyrrolidide as a discrete species, as evidenced by the zeroth-order dependence on TMS_2NH.[19] We submit transition structures **20** and **21** as plausible. Although **20** seems particularly crowded, evidence of high-coordinate lithium amides continues to accrue.[25] Nonetheless, limited semiempirical computations support **21** (Figure 5). It is certainly curious that the 1,2-addition via **21** takes precedence over enolization via isomeric transition structure **22**.



An alternative mechanism is worthy of serious consideration. The 1,2-addition of pyrrolidine could proceed by reversible addition to form **23** or **24** followed by an irreversible proton abstraction. The small isotope effect observed for the addition of LiHMDS/pyrrolidine to the α-deuterated ketones is comparable to the isotope effect observed by Bender for the 1,2-addition of MeOH to α-deuterated ketones. However, the stereochemistry of the addition offers a mixed picture. Mixtures of LiHMDS/pyrrolidine and 4-*tert*-butylcyclohexanone afford a single isomer: **13** or **14**; adduct **14** would be predicted to be the exclusive product from attack of a hindered nucleophile according to transition structure analogous to **21**.[26] In contrast, MMX calculations predict nearly equal populations of **25** and **26**. Even within the confines of the Curtin-Hammett principle, one might have expected the observed adducts derived from LiHMDS/pyrrolidine to bear some relationship to the equilibrium populations of the alcohols. Conversely, addition of LiHMDS/pyrrolidine to 2-methylcyclohexanone affords a nearly

(22) (a) McKee, M. L. *J. Am. Chem. Soc.* **1987**, *109*, 559. (b) Romesberg, F. E.; Collum, D. B. *J. Am. Chem. Soc.* **1995**, *117*, 2166. (c) Henderson, K. W.; Dorigo, A. E.; Liu, Q.-Y.; Williard, P. G.; Schleyer, P. v. R.; Bernstein, P. R. *J. Am. Chem. Soc.* **1996**, *118*, 1339. (d) Hayes, J. M.; Greer, J. C.; Mair, F. S. *New J. Chem.* **2001**, *25*, 262. (e) Bernasconi, C. F.; Wenzel, P. J. *J Am. Chem. Soc.* **1994**, *116*, 5405.

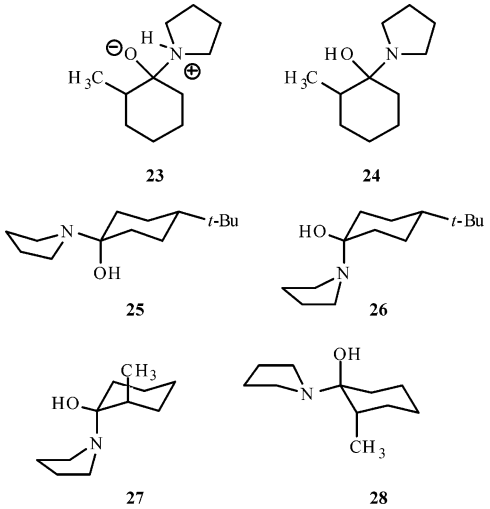
(23) Adler, M.; Marsch, M.; Nudelman, N. S.; Boche, G. *Angew. Chem., Int. Ed.* **1999**, *38*, 1261.

(24) Ramírez, A.; Lobkovsky, E.; Collum, D. B. *J. Am. Chem. Soc.* **2003**, *125*, 15376.

(25) (a) Lucht, B. L.; Bernstein, M. P.; Remenar, J. F.; Collum, D. B. *J. Am. Chem. Soc.* **1996**, *118*, 10707. (b) Depue, J. S.; Collum, D. B. *J. Am. Chem. Soc.* **1988**, *110*, 5524. (c) Ramírez, A.; Collum, D. B. Unpublished work. (d) See also ref 7.

(26) Ashby, E. C.; Laemmle, J. T. *Chem. Rev.* **1975**, *75*, 521.

equimolar mixture of two adducts; MMX calculations reveal that the lowest energy conformer of the cis adduct (**28**) is only 0.7 kcal/mol more stable than the analogous trans adduct (**27**). In this instance, a *kinetic* addition of a hindered nucleophile derived from LiHMDS/pyrrolidine to 2-methylcyclohexanone via **21** should be highly trans selective.[26]



The unanticipated and facile *net* 1,2-addition of lithium pyrrolidide intersects with many synthetic and mechanistic issues. Tetrahedral adducts analogous to **3** are key intermediates in a number of synthetically important reactions.[27] If the 1,2-addition proceeds via a lithium amide attack on the ketone (rather than a reversible addition of the amine), analogous 1,2-additions to esters—direct ester amidolyses—or other additions to C=X bonds might perhaps prove to be synthetically useful.[28,29] There is also a growing number of synthetically important reactions, however, in which 1,2-additions by protic amines[30] and protic lithium amides[31,32] to carbonyl-based electrophiles could pose problems. Enolizations of aldehydes by lithium amides, for example, fail largely due to rapid 1,2-addition.[23,33,34] Could the 1,2-additions to *ketones* occasionally intervene when protic amines or protic amides are present? It is in this context that we find the failures of some enolizations in the presence of *i*-Pr_2NH and related protic amines to be a little disturbing.[35,36] As a last cautionary note, our limited experience with protic amines and protic amides suggests that structural and mechanistic complexities are pervasive.[12,32]

Experimental Section

Reagents and Solvents. Amines and hydrocarbons were routinely 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. The LiHMDS,[17] ketone **1-*d*$_3$**,[6] and 2,2,6,6-tetradeuteriocyclohexanone[6] were prepared as described. Air- and moisture-sensitive materials were manipulated under argon or nitrogen using standard glovebox, vacuum line, and syringe techniques.

NMR Spectroscopic Analyses. Samples were prepared, and the ^{6}Li, ^{15}N, and ^{13}C NMR spectra were recorded as described elsewhere.[17] The samples of LiHMDS containing ketone **1** were prepared using a specific protocol designed to minimize rapid reaction.[1b]

IR Spectroscopic Analyses. In situ IR spectra were recorded with a 30-bounce silicon-tipped probe.[2]

Acknowledgment. We thank the National Institutes of Health for direct support of this work. We also thank DuPont Pharmaceuticals, Merck Research Laboratories, Pfizer, Aventis, R. W. Johnson, and Schering Plough for indirect support. P. Z. thanks Boehringer-Ingelheim for a fellowship. We also acknowledge the National Science Foundation Instrumentation Program (CHE 7904825 and PCM 8018643), the National Institutes of Health (RR02002), and IBM for support of the Cornell Nuclear Magnetic Resonance Facility.

Supporting Information Available: Rate data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(27) (a) Larsen, R. D.; Corley, E. G.; King, A. O.; Carroll, J. D.; Davis, P.; Verhoeven, T. R.; Reider, P. J.; Labelle, M.; Gauthier, J. Y.; Xiang, Y. B.; Zamboni, R. J. *J. Org. Chem.* **1996**, *61*, 3398. (b) Comins, D. L.; Killpack, M. O. *J. Org. Chem.* **1990**, *55*, 69. (c) Kaiser, F.; Schwink, L.; Velder, J.; Schmalz, H.-G. *J. Org. Chem.* **2002**, *67*, 9248. (d) Roschangar, F.; Brown, J. C.; Cooley, B. E.; Sharp, M. J.; Matsuoka, R. T. *Tetrahedron* **2002**, *58*, 1657. (e) Juaristi, E.; Beck, A. K.; Hansen, J.; Matt, T.; Mukhopadhyay, T.; Simson, M.; Seebach D. *Synthesis* **1993**, 1271. (f) Comins, D. L.; Brown, J. D.; Mantlo, N. B. *Tetrahedron Lett.* **1982**, *23*, 3979. (g) Hart, D. J.; Kanai, K.; Thomas, D. G.; Yang, T.-K. *J. Org. Chem.* **1983**, *48*, 289.

(28) For the direct amidolysis of methyl esters by lithium amides, see: (a) Lebegue, N.; Flouquet, N.; Berthelot, P.; Pfeiffer, B.; Renard, P. *Synth. Commun.* **2002**, *32*, 2877. (b) Koide, H.; Uemura, M. *Chirality* **2000**, *12*, 352.

(29) A seemingly related amidolysis of esters using NaHMDS/R_2NH mixtures has been reported: Riviere-Baudet, M.; Morere, A.; Dias, M. *Tetrahedron Lett.* **1992**, *33*, 6453.

(30) Eames, J.; Weerasooriya, N.; Coumbarides, G. S. *Eur. J. Org. Chem.* **2002**, 181. For additional leading references to synthetic applications of organolithiums solvated by protic amines, see ref 32.

(31) (a) Armstrong, D. R.; Carstairs, A.; Henderson, K. W. *Organometallics* **1999**, *18*, 3589. (b) Boche, G.; Ledig, B.; Marsch, M.; Harms, K. *Acta Crystallogr., Sect. E* **2001**, *57*, m570. (c) Liddle, S. T.; Clegg, W. *J. Chem. Soc., Dalton Trans.* **2001**, 3549.

(32) Leading references: (a) Rutherford, J. L.; Collum, D. B. *J. Am. Chem. Soc.* **2001**, *123*, 199. (b) Lucht, B. L.; Collum, D. B. *J. Am. Chem. Soc.* **1996**, *118*, 3529.

(33) (a) Nudelman, N. S.; García-Linares, G. E. *J. Org. Chem.* **2000**, *65*, 1629. (b) Matsumoto, T.; Hamura, T.; Kuriyama, Y.; Suzuki, K. *Tetrahedron Lett.* **1997**, *38*, 8985. (c) Armstrong, D. R.; Davies, R. P.; Raithby, P. R.; Snaith, R.; Wheatley, A. E. H. *New J. Chem.* **1999**, *23*, 499. (d) Corruble, A.; Valnot, J.-Y.; Maddaluno, J.; Duhamel, P. *J. Org. Chem.* **1998**, *63*, 8266. (e) Corruble, A.; Valnot, J.-Y.; Maddaluno, J.; Duhamel, P. *Tetrahedron: Asymmetry* **1997**, *8*, 1519. (f) Reynolds, K. A.; Finn, M. G. *J. Org. Chem.* **1997**, *62*, 2574. (g) Nudelman, N. S.; García-Linares, G. E. *J. Org. Chem.* **2000**, *65*, 1629. (h) Fressigné, C.; Maddaluno, J.; Marquez, A.; Giessner-Prettre, C. *J. Org. Chem.* **2000**, *65*, 8899. (i) Davies, J. E.; Raithby, P. R.; Snaith, R.; Wheatley, A. E. H. *J. Chem. Soc., Chem. Commun.* **1997**, 1721. (j) Armstrong, D. R.; Davies, J. E.; Davies, R. P.; Raithby, P. R.; Snaith, R.; Wheatley, A. E. H. *New J. Chem.* **1999**, *23*, 35. (k) See also ref 24.

(34) Treatment of simple aldehydes with [^{6}Li,^{15}N]LDA affords the 1,2-adduct displaying $^1J_{C-N}$ coupling: Sun, X.; Collum, D. B. Unpublished work.

(35) (a) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1624. (b) Aebi, J. D.; Seebach, D. *Helv. Chim. Acta* **1985**, *68*, 1507. (c) Laube, T.; Dunitz, J. D.; Seebach, D. *Helv. Chim. Acta* **1985**, *68*, 1373. (d) Seebach, D.; Boes, M.; Naef, R.; Schweizer, W. B. *J. Am. Chem. Soc.* **1983**, *105*, 5390.

(36) For example, see: Mohrig, J. R.; Lee, P. K.; Stein, K. A.; Mitton, M. J.; Rosenberg, R. E. *J. Org. Chem.* **1995**, *60*, 3529. For an excellent discussion and leading references, see: Vedejs, E.; Lee, N. *J. Am. Chem. Soc.* **1995**, *117*, 891.