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Ketone Enolization by Lithium Hexamethyldisilazide: Structural and Rate Studies of the Accelerating Effects of Trialkylamines

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Abstract: Mechanistic studies of the enolization of 2-methylcyclohexanone mediated by lithium hexamethyldisilazide (LiHMDS; TMS_2NLi) in toluene and toluene/amine mixtures are described. NMR spectroscopic studies of LiHMDS/ketone mixtures in toluene reveal the ketone-complexed cyclic dimer $(TMS_2NLi)_2$(ketone). Rate studies using in situ IR spectroscopy show the enolization proceeds via a dimer-based transition structure, $[(TMS_2NLi)_2(\text{ketone})]^{\ddagger}$. NMR spectroscopic studies of LiHMDS/ketone mixtures in the presence of relatively unhindered trialkylamines such as Me_2NEt reveal the quantitative formation of cyclic dimers of general structure $(TMS_2NLi)_2(R_3N)$(ketone). Rate studies trace a >200-fold rate acceleration to a dimer-based transition structure, $[(TMS_2NLi)_2(R_3N)(\text{ketone})]^{\ddagger}$. Amines of intermediate steric demand, such as Et_3N, are characterized by recalcitrant solvation, saturation kinetics, and exceptional (>3000-fold) accelerations traced to the aforementioned dimer-based pathway. Amines of high steric demand, such as *i*-Pr_2NEt, do not observably solvate $(TMS_2NLi)_2$(ketone) but mediate enolization via $[(TMS_2NLi)_2(R_3N)(\text{ketone})]^{\ddagger}$ with muted accelerations. The most highly hindered amines, such as *i*-Bu_3N, do not influence the LiHMDS structure or the enolization rate. Overall, surprisingly complex dependencies of the enolization rates on the structures and concentrations of the amines derive from unexpectedly simple steric effects. The consequences of aggregation, mixed aggregation, and substrate−base precomplexation are discussed.

Introduction

> I believe that, for those who seek to discover new reactions, the most insightful lessons come from trying to trace important reactivity principles back to their origins.
>
> K. Barry Sharpless, 1983[1,2]

Almost 20 years later, physical organic chemistry is in the midst of a renaissance that is fueled, oddly enough, by pharmaceutical companies and related chemical industries. As medicinal chemists generate complex drug candidates using state-of-the-art synthetic methods, the push to obtain the first few kilograms of material for early clinical trials inspires process chemists to press very complex chemistry to increasingly larger scales.[3] Inundated with real-time chromatographic, in situ spectroscopic, and calorimetric data of a quantity and quality unavailable a decade ago,[4] the process chemists are finding that the fundamental principles of reactivity gleaned during the golden age of physical organic chemistry no longer provide adequate mechanistic support.[5] Thus, in the high-stakes world of drug development, fundamental investigations of structure and mechanism are creeping toward center stage.[6]

Organolithium chemistry has benefited greatly from these evolutionary changes. The highly reactive, selective, and often sophisticated lithium-based reagents,[7] previously considered the purview of academia, are now used routinely on very large scales for complex drug synthesis.[8] Although improvements in computational, crystallographic, and spectroscopic techniques have accelerated progress in structural organolithium chemistry,[9,10] an overall understanding of reaction mechanisms and fundamental determinants of reactivity lag far behind.[11,12] In this regard, we feel that lithium hexamethyldisilazide (LiHMDS; TMS_2NLi) offers a particularly promising opportunity. The high steric demands and thermal stability make LiHMDS one of the

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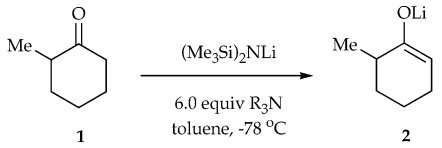
10.1021/ja030168v CCC: $25.00

most useful Bronsted bases in organic chemistry.[13] In addition, the coordination chemistry of LiHMDS solvated by a wide range of mono- and polydentate ligands has been investigated in considerable depth,[10] providing sound structural foundations on which to build an understanding of structure−reactivity relationships.

We report detailed investigations of the LiHMDS-mediated enolization of 2-methylcyclohexanone (**1**; eq 1) in the presence of a broad range of di- and trialkyl-amines (Charts 1 and 2).[14,15a] The selected relative rate constants (k_{rel}) shown in eq 1 set the tenor of this paper by highlighting a number of unusual effects.



1 **2** (1)

R_3N:	none	Me_2NEt	n-Bu_3N	n-Bu_2Ni-Bu	i-Bu_3N
k_{rel}:	1.0	200	3000	10	1.0

For example, the marked rate accelerations affiliated with the poorly coordinating[16,17] trialkylamines may be somewhat surprising given that high reactivity is often associated with strongly coordinating solvents.[11,18] (By comparison, the analogous enolization of **1** using 6.0 equiv of THF affords $k_{rel} = 20$.) The apparent inverse correlation of the enolization rate with increasing steric demand and rate maxima when amines of intermediate steric requirements are used seems especially difficult to explain.[19] The *300-fold* decline in the rate caused by replacing n-Bu_3N with n-Bu_2Ni-Bu is stunning. Other oddities not captured by the data in eq 1 are also noteworthy. We will show, for example, amine-concentration-dependent reversals in the relative reactivities that appear quite irrational by normal metrics. Spectroscopically observable LiHMDS dimer−monomer equilibria,[10,16,20,21] often ascribed to major changes in reactivity, have no effect on the enolizations.[15b]

We traced these baffling reactivities to the relatively simple dimer-based mechanism depicted in Scheme 1. From a tactical perspective, it is notable how spectroscopic and kinetic methods combine to provide insight into weak solvent−lithium interactions and other elusive phenomena. On a practical level, the rate increases caused by adding low concentrations of simple trialkylamines to LiHMDS/toluene solutions may be useful to synthetic organic chemists. A summary of the structural and rate studies is presented at the beginning of the discussion for the convenience of the reader.

Results

Structures of LiHMDS and Amine Classifications. Extensive structural studies of [^{6}Li,^{15}N]LiHMDS[22] solvated by di- and trialkylamines using a combination of one- and two-dimensional ^{6}Li and ^{15}N NMR spectroscopies provide an excellent foundation for the rate studies.[16] Although additional NMR spectroscopic studies were required to fill in some details, the methods are now well established and the results are incremental. Accordingly, some new results are simply archived in the Supporting Information. A few key observations are mentioned in the appropriate context below.

The widely varying solvent effects described in this paper derive from only a few underlying principles. Nonetheless, maintaining adequate perspective during the presentation can be daunting. Consequently, we have classified the amines into four general types to clarify the results and discussion. We summarize results from prior studies of LiHMDS in solution in the context of the amine classifications as follows.

(1) Type I. Additions of ≥1.0 equiv of relatively unhindered amines quantitatively convert a mixture of higher oligomer **7**

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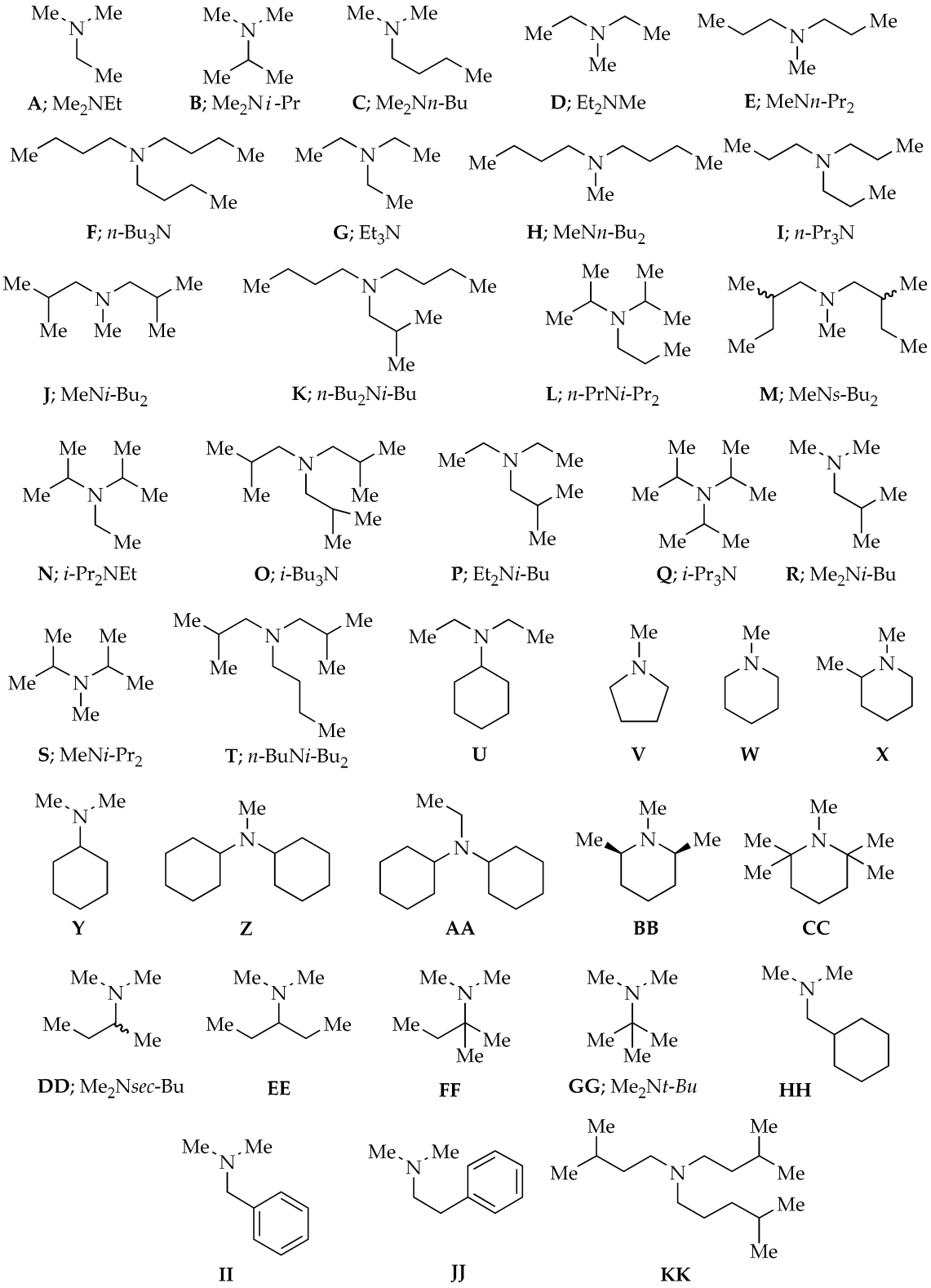
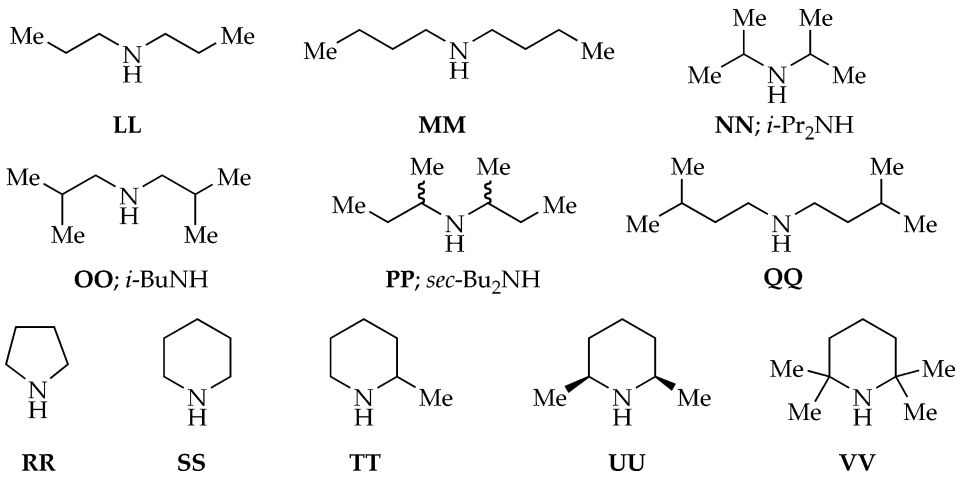
Chart 1



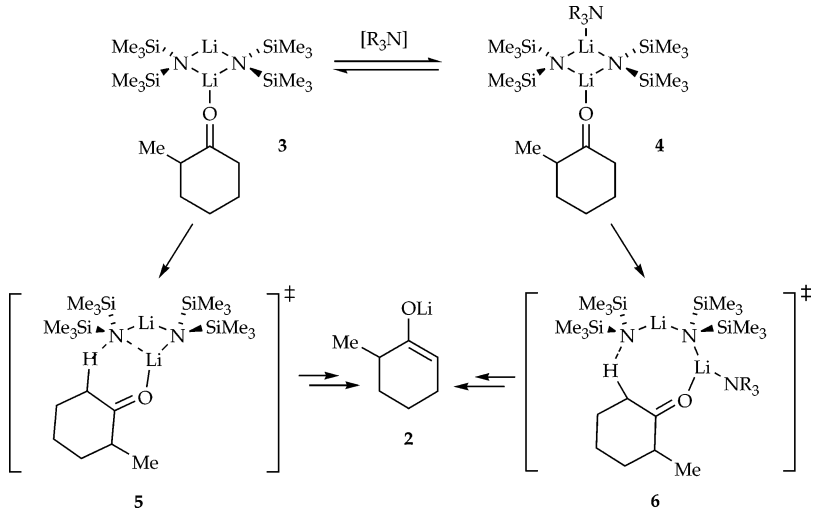
and dimer **8** to the disolvated dimer **10** (Scheme 2). Me_2NEt (**A**) undergoes slow exchange on the LiHMDS dimer observable by ^6Li and ^{13}C NMR spectroscopies,[13,23] allowing the solvation numbers to be assigned unequivocally by direct integration of the ^{13}C resonances. In more hindered Type I amines wherein solvent exchange is rapid on NMR time scales, solvation of the dimer by ≥ 1.0 equiv of amine is confirmed by the conversion of higher oligomer **7** to dimer **10**[10] and the affiliated changes in the ^6Li chemical shift of the dimer previously shown to be highly characteristic of solvation.[16,24] Although Type I

(23) Monodentate ligands have been observed coordinated to lithium ion in the slow exchange limit. Leading references: Arvidsson, P. I.; Davidsson, Ö. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 1467. Sikorski, W. H.; Reich, H. J. *J. Am. Chem. Soc.* **2001**, *123*, 6527. For numerous examples involving LiHMDS, see ref 10.

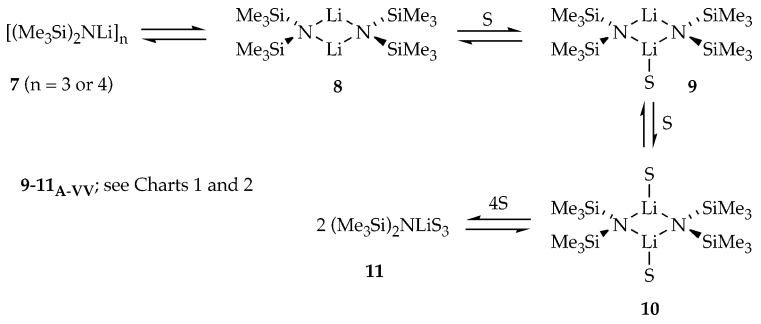
Chart 2



Scheme 1



Scheme 2



amines elicit deaggregations to monomers (**11**) at higher amine concentrations, such deaggregations will be shown to be of no mechanistic consequence.

(2) Type II. Amines of intermediate steric demand, exemplified by Et_3N, solvate dimer **8** to give dimers **9** and **10** reluctantly. Complexation of such Type II amines is detected by the loss of higher oligomer **7** as well as by the highly characteristic [R_3N]-dependent ^{6}Li chemical shift signifying formation of disolvated dimer **10** only at elevated concentrations (Figure 1). Rate studies reveal corresponding saturation kinetics (below).[25]

(3) Type III. Hindered amines, exemplified by *i*-Pr_2NEt (N) and designated as Type III, do not appreciably bind to the LiHMDS dimer, as shown by the absence of change in either

(24) Spectroscopic,[24a] crystallographic,[24b] computational,[24c,d] calorimetric,[24e] and kinetic[24f] studies have shown that LiHMDS and related hindered lithium amide dimers contain *one* ligand per lithium irrespective of the choice of ligand. (a) Romesberg, F. E.; Gilchrist, J. H.; Harrison, A. T.; Fuller, D. J.; Collum, D. B. *J. Am. Chem. Soc.* **1991**, *113*, 5751. Lucht, B. L.; Collum, D. B. *J. Am. Chem. Soc.* **1995**, *117*, 9863. (b) Williard, P. G.; Hintze, M. J. *J. Am. Chem. Soc.* **1987**, *109*, 5539. (c) Romesberg, F. E.; Collum, D. B. *J. Am. Chem. Soc.* **1992**, *114*, 2112. (d) Romesberg, F. E.; Collum, D. B. *J. Am. Chem. Soc.* **1995**, *117*, 2166. (e) Prikoszovich, W. (Novartis), personal communication. (f) Galiano-Roth, A. S.; Collum, D. B. *J. Am. Chem. Soc.* **1989**, *111*, 6772.

(25) (a) Bernstein, M. P.; Romesberg, F. E.; Fuller, D. J.; Harrison, A. T.; Williard, P. G.; Liu, Q. Y.; Collum, D. B. *J. Am. Chem. Soc.* **1992**, *114*, 5100. (b) Depue, J. S.; Collum, D. B. *J. Am. Chem. Soc.* **1988**, *110*, 5524. (c) Karlsson, A.; Hilmersson, G.; Davidsson, O.; Lowendahl, M.; Ahlberg, P. *Acta Chem. Scand.* **1999**, *53*, 693. (d) Welch, F. J. *J. Am. Chem. Soc.* **1960**, *82*, 6000.

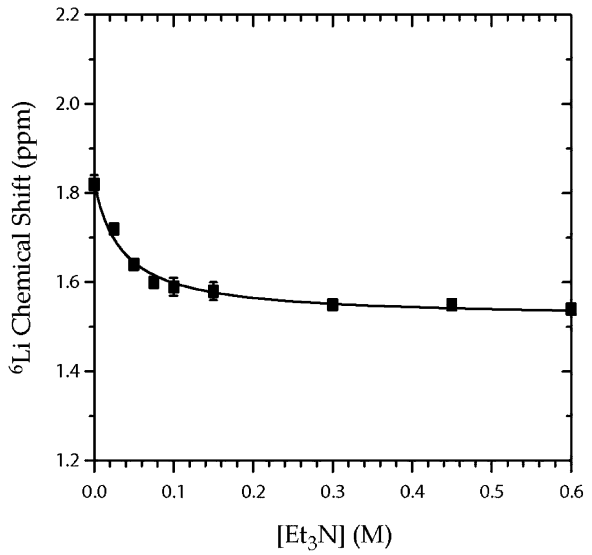


Figure 1. Plot of ^{6}Li chemical shift vs [Et$_3$N] for 0.1 M [^{6}Li,^{15}N]LiHMDS in Et$_3$N/pentane mixtures at −60 °C. The curve depicts the results of an unweighted least-squares fit to $y = ax/(1 + bx) + c$. The values of the parameters are as follows: $a = -9 \pm 1$ (ppm·M^{-1}), $b = K_{eq} = 28 \pm 3$ (M^{-1}), $c = 2 \pm 1$ (ppm).

the dimer−higher oligomer distribution or the chemical shift of the dimer ^{6}Li resonance. They do, however, bind transiently, as evidenced by [R$_3$N]-dependent enolization rates.

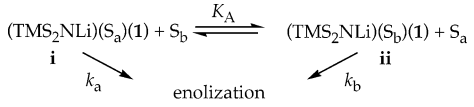
(4) Type IV. The most sterically hindered (Type IV) amines, such as *i*-Bu$_3$N (**O**), show no measurable influence on LiHMDS structure or reactivity, serving merely as hydrocarbon analogues.[26]

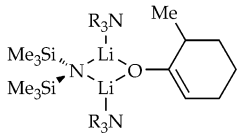
LiHMDS−Ketone Complexation. LiHMDS−ketone complexes were detected and shown to form quantitatively by in situ IR spectroscopy (vide infra).[27−30] Because accurate interpretations of the rate equations require rigorous structural assignments, it was imperative that we distinguish the dimer-based complexes of general structure (TMS$_2$NLi)$_2$(R$_3$N)(ketone) (**4**) from the monomer-based complexes of general structure (TMS$_2$NLi)(R$_3$N)$_2$(ketone) (**12**). Deuterated ketone (2,6,6-trideuterio-2-methylcyclohexanone; **1**-d_3)[31] was used to suppress the enolization.

^{6}Li NMR spectra recorded on amine-free toluene solutions of [^{6}Li,^{15}N]LiHMDS containing 0.2 equiv of ketone **1**-d_3 display the resonances of dimer **8** along with two new ^{6}Li triplets (1:1) coupled to a single new ^{15}N quintet attributed to ketone-complexed dimer **3**-d_3 (Figure 2A). Incremental increases in the ketone concentration causes **3**-d_3 to be replaced by a symmetric species displaying a ^{6}Li triplet and an ^{15}N quintet characteristic of dicomplexed dimer **13**-d_6 (Figure 2B).

NMR spectra recorded on LiHMDS/R$_3$N/**1**-d_3 mixtures in toluene reveal three behaviors.

(1) LiHMDS/Me$_2$NEt/ketone. Solutions of [^{6}Li,^{15}N]LiHMDS in toluene containing 6.0 equiv of Me$_2$NEt (Type I) and 0.2 equiv of **1**-d_3 exhibit ^{6}Li and ^{15}N multiplets characteristic of mixed solvated complex **4A**-d_3 (R$_3$N = Me$_2$NEt) along with disolvated dimer **10A** (Figure 2C). Incremental additions of 0.1−1.0 equiv of Me$_2$NEt to analogous LiHMDS/**1**-d_3 mixtures cause the unsolvated distal lithium of **3**-d_3 to shift markedly (0.5 ppm) downfield, confirming the conversion of **3**-d_3 to **4**-d_3. Alternatively, incremental additions of ketone **1**-d_3 to solutions of LiHMDS containing 6.0 equiv of Me$_2$NEt affords (sequentially) **4**-d_3 and doubly complexed dimer **13**-d_6 (Figure 2D). (The appearance of LiHMDS/lithium enolate mixed dimer **14** will be discussed below.) Higher concentrations of Me$_2$NEt cause deaggregation to monomer **11** without measurable loss of dimer complex **4**-d_3.[32]





14

(2) LiHMDS/Et$_3$N/ketone. Spectroscopic studies of [^{6}Li,^{15}N]-LiHMDS/-Et$_3$N/ketone mixtures required understanding recalcitrant solvation by Type II amines and proved technically difficult due to rapid enolization at −78 °C. Although we could observe the ketone complexation before enolization at <−100 °C, solvation of lithium amides is very temperature sensitive,[25a,33] causing even low concentrations of Et$_3$N to quantitatively solvate LiHMDS. Consequently, we were unable to investigate the conversion of ketone complex **3**-d_3 to **4**-d_3 (R$_3$N = Et$_3$N) that we anticipated from the saturation kinetics described below. Nonetheless, the saturation behavior for the conversion of unsolvated dimer (**8**) to disolvated dimer (**10**) shown in Figure 1 represents a reasonable proxy.

(3) LiHMDS/*i*-Pr$_2$NEt/ketone. Solutions of [^{6}Li,^{15}N]LiHMDS in toluene containing excess *i*-Pr$_2$NEt (a Type III amine) and 0.2 equiv of ketone **1**-d_3 display resonances of the unsolvated complex **3**-d_3 as well as those of uncomplexed dimer. The two ^{6}Li resonances of **3**-d_3 are not appreciably influenced by the concentration of the amine, consistent with the studies of LiHMDS/*i*-Pr$_2$NEt mixtures without added ketone, which show no evidence of coordination by the amine.

Kinetics: General Methods. Adding ketone **1** to LiHMDS in either hydrocarbon or hydrocarbon/amine mixtures at −78 °C and monitoring by in situ IR spectroscopy reveals that **1** (1722 cm^{-1}) is quantitatively converted to LiHMDS−ketone complexes (1706−1708 cm^{-1}).[29,30] The LiHMDS−ketone com-

(26) (Me$_3$Si)$_2$NH does not measurably bind to LiHMDS in hydrocarbons solutions.[16]
(27) Williard, P. G.; Liu, Q. Y.; Lochmann, L. *J. Am. Chem. Soc.* **1992**, *114*, 348.
(28) Sun, X.; Collum, D. B. *J. Am. Chem. Soc.* **2000**, *122*, 2452.
(29) For leading references and recent examples of detectable organolithium−substrate precomplexation, see: Klumpp, G. W. *Recl. Trav. Chim. Pays-Bas* **1986**, *105*, 1. Andersen, D. R.; Faibish, N. C.; Beak, P. *J. Am. Chem. Soc.* **1999**, *121*, 7553. For more recent examples of observable RLi−substrate precomplexation, see: Pippel, D. J.; Weisenberger, G. A.; Faibish, N. C.; Beak, P. *J. Am. Chem. Soc.* **2001**, *123*, 4919. Bertini-Gross, K. M.; Beak, P. *J. Am. Chem. Soc.* **2001**, *123*, 315.
(30) 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.
(31) Peet, N. P. *J. Label. Compound.* **1973**, *9*, 721.
(32) The promotion of aggregation by superior ligands is probably not widely appreciated, but it has been noted. Jackman, L. M.; Chen, X. *J. Am. Chem. Soc.* **1992**, *114*, 403. Also, see refs 10 and 25a.
(33) Hall, P. L.; Gilchrist, J. H.; Harrison, A. T.; Fuller, D. J.; Collum, D. B. *J. Am. Chem. Soc.* **1991**, *113*, 9575. Also, see pp 15−16 of ref 12.

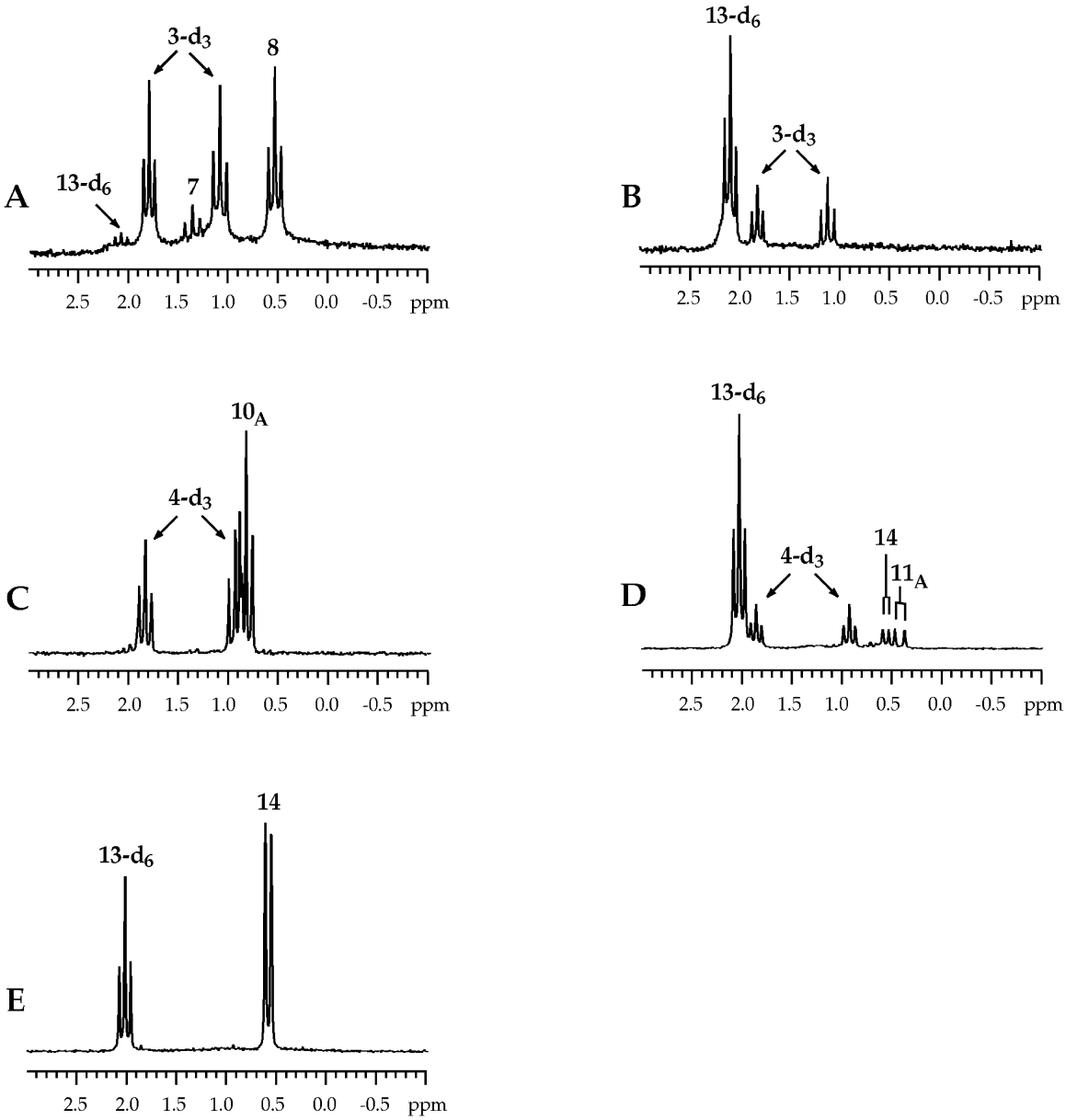


Figure 2. ^{6}Li NMR spectra showing LiHMDS showing complexation by the ketone (**1**-d_3) and Me_2NEt (**A**). Spectra were recorded on mixtures of [^{6}Li,^{15}N]LiHMDS in toluene at −100 °C with (A) 0.2 equiv of ketone; (B) 0.8 equiv of ketone; (C) 0.2 equiv of ketone and 6.0 equiv of Me_2NEt; (D) 0.8 equiv of ketone and 6.0 equiv of Me_2NEt; (E) 0.8 equiv of ketone and 12 equiv of Me_2NEt.

plexes were identified as **3** or **4** by NMR spectroscopy as described above. 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[22] LiHMDS (0.05−0.40 M) and amines (0.15−2.40 M), with toluene as the cosolvent. At these low ketone concentrations, only dimers **3** or **4**, which bear a single coordinated ketone, are formed. In all cases, the loss of the LiHMDS−ketone complexes or of their less reactive deuterated analogues **3**-d_3 or **4**-d_3 monitored by in situ IR spectroscopy display clean first-order decays to ≥5 half-lives.[34] The resulting pseudo-first-order rate constants (k_{obsd}) are independent of ketone concentration (0.004−0.04 M). 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.[35] Comparisons of **3** versus **3**-d_3, and **4** versus **4**-d_3 provided large kinetic isotope effects (see Supporting Information), confirming rate-limiting proton transfers.[36,37]

Reaction Orders in Amine. The pseudo-first-order rate constants were measured as a function of the amine concentrations at a fixed LiHMDS concentration (0.10 M) in toluene. To facilitate the discussion, we have provided a theoretical plot of the observed saturation kinetics (Figure 3).[38] The designations I, II, III, and IV refer to the amine classifications described at the start of the Results section and indicate the limiting behaviors observed experimentally. (The nonzero intercept corresponding

(34) Some of the slower reactions were monitored using the initial rates method. Espenson, J. H. *Chemical Kinetics and Reaction Mechanisms*; McGraw-Hill: New York, 1995; p 32.

(35) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1624. Sun, X.; Collum, D. B. *J. Am. Chem. Soc.* **2000**, *122*, 2459. McGarrity, J. F.; Ogle, C. A. *J. Am. Chem. Soc.* **1984**, *107*, 1810. Thompson, A.; Corley, E. G.; Huntington, M. F.; Grabowski, E. J. J.; Remenar, J. F.; Collum, D. B. *J. Am. Chem. Soc.* **1998**, *120*, 2028.

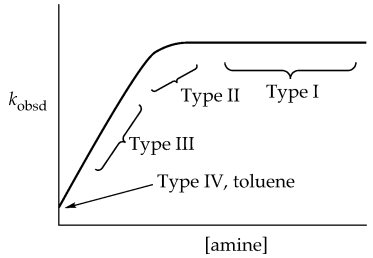


Figure 3. Idealized plot showing four limiting behaviors of saturation kinetics corresponding to amine Types I−IV.

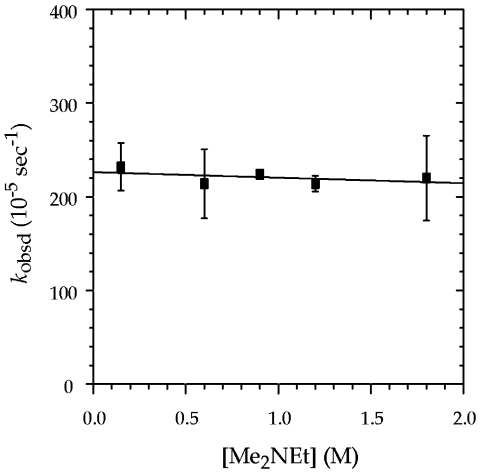


Figure 4. Plot of k_{obsd} vs [Me_2NEt] (**A**) in toluene cosolvent for the enolization of **1** (0.004 M) by LiHMDS (0.10 M) at −78 °C. The curve depicts the results of an unweighted least-squares fit to $k_{obsd} = a[Me_2NEt] + b$, where $a = 6 \pm 6 \times 10^{-5}$ ($s^{-1}\cdot M^{-1}$), $b = 2.26 \pm 0.07 \times 10^{-3}$ (s^{-1}).

to <0.1% of the *y*-axis is greatly exaggerated.) Representative data depicted in Figures 4−7 illustrate four perspectives of saturation kinetics. Additional examples are discussed below in the context of the amine-dependent relative rates.

(1) A plot of k_{obsd} versus [Me_2NEt][39] reveals a zeroth-order dependence (Figure 4), indicating that the observable amine-solvated complex **4A** neither gains nor loses a molecule of Me_2-NEt leading to the rate-limiting transition structure. This behavior is denoted as Type I in Figure 3.

(2) A plot of k_{obsd} versus [Et_3N] shows saturation kinetics (Figure 5).[38,40] At low concentrations of Et_3N, unsolvated complex **3**-d_3 is the dominant form (see above), affording a first-order [Et_3N] dependence. At high concentrations of Et_3N, fully solvated complex **4**-d_3 becomes the dominant form and a zeroth-order Et_3N dependence results. By comparison, the dramatic (up to 3000-fold) rate accelerations render a potential nonzero intercept corresponding to the basal enolization rate in amine-free toluene insignificant by comparison. This behavior is denoted as Type II in Figure 3.

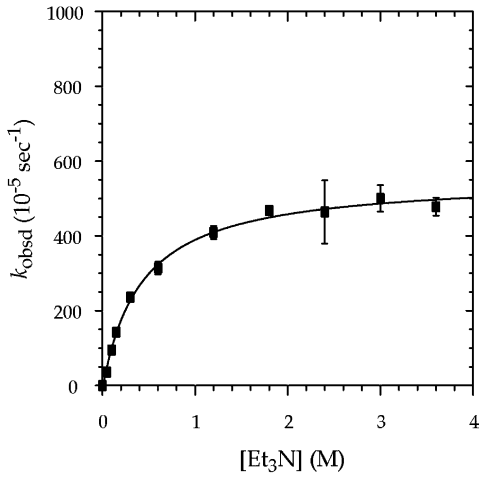


Figure 5. Plot of k_{obsd} vs [Et_3N] (**G**) in toluene cosolvent for the enolization of **1**-d_3 (0.004 M) by LiHMDS (0.10 M) at −78 °C. The curve depicts the results of an unweighted least-squares fit to $k_{obsd} = a[Et_3N]/(1 + b[Et_3N])$, where $a = k_2K_{eq} = 0.0125 \pm 0.0008$ ($s^{-1}\cdot M^{-1}$), $b = K_{eq} = 2.2 \pm 0.2$ (s^{-1}).

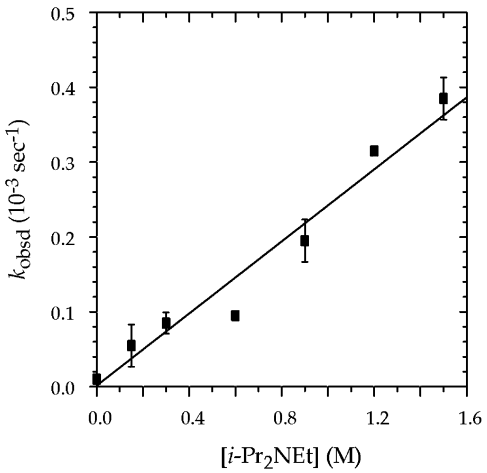


Figure 6. Plot of k_{obsd} vs [(i-Pr)$_2$NEt] (**N**) in toluene cosolvent for the enolization of **1** (0.004 M) by LiHMDS (0.10 M) at −78 °C. The curve depicts the results of an unweighted least-squares fit to $k_{obsd} = a[(i\text{-Pr})_2NEt] + b$, where $a = 2.4 \pm 0.2 \times 10^{-4}$ ($s^{-1}\cdot M^{-1}$), $b = 0 \pm 2 \times 10^{-5}$ (s^{-1}).

(3) A plot of k_{obsd} versus [i-Pr_2NEt] shows a first-order dependence (Figure 6), indicating that the observable unsolvated complex **3** is solvated transiently by a molecule of i-Pr_2NEt to afford a low, steady-state concentration of an amine-solvated **4** during enolization. A nonzero intercept corresponding to the low enolization rate of **3**-d_3 in neat toluene solution (shown in Figure 3) is undetectable outside experimental error.

(4) A plot of k_{obsd} versus [i-Bu_3N] shows no accelerating effect whatsoever compared with amine-free enolizations in toluene (Figure 7). The most sterically hindered amines do not participate at any point along the reaction coordinate. This behavior is denoted as Type IV in Figure 3.

(36) Isotope effects for LiHMDS-mediated ketone enolizations have been measured previously. Held, G.; Xie, L. F. *Microchem. J.* **1997**, *55*, 261. Xie, L. F.; Saunders: W. H. *J. Am. Chem. Soc.* **1991**, *113*, 3123. For leading references to structural and mechanistic studies of LiHMDS, see ref 16. For more recent examples, see: Higgins, P. R.; Hinde, R. J.; Grimm, D. T.; Bloor, J. E.; Bartmess, J. E. *Int. J. Mass Spectrom.* **2001**, *210/211*, 231. Davies, R. P. *Inorg. Chem. Commun.* **2000**, *3*, 13. Hartung, M.; Günther, H.; Amoureux, J.-P.; Fernandez, C. *Magn. Reson. Chem.* **1998**, *36*, S61. Armstrong, D. R.; Davies, R. P.; Dunbar, L.; Raithby, P. R.; Snaith, R.; Wheatley, A. E. H. *Phosphorus, Sulfur Silicon Relat. Elem.* **1997**, *124/125*, 51.

(37) The regioselectivity indicated in eq 1 was shown to be >20:1 by trapping with Me_3SiCl/Et_3N mixtures and comparing the crude product with authentic material by GC.[33]

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

(39) The concentration of the lithium amide, although expressed in units of molarity, refers to the concentration of the monomer unit (normality). The concentration of the amine refers to the total concentration of the amine added. In cases where the degree of binding is known either quantitative (Type I amines) or undetectable (Type III and IV amines), the concentration of the free amine is readily ascertained.

(40) Depue, J. S.; Collum, D. B. *J. Am. Chem. Soc.* **1988**, *110*, 5524. Also, see refs 25a,d.

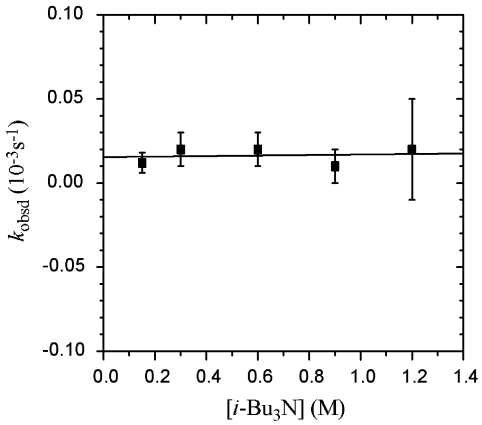


Figure 7. Plot of k_{obsd} vs [(i-Bu)$_3$N] (**O**) in toluene for the enolization of **1** (0.004 M) by LiHMDS (0.10 M) at −78 °C. The curve depicts the results of an unweighted least-squares fit to $k_{obsd} = a$[(i-Bu)$_3$N] + b, where $a = 2 \pm 7 \times 10^{-6}$ (s^{-1}·M^{-1}), $b = 1.5 \pm 0.5 \times 10^{-5}$ (s^{-1}).

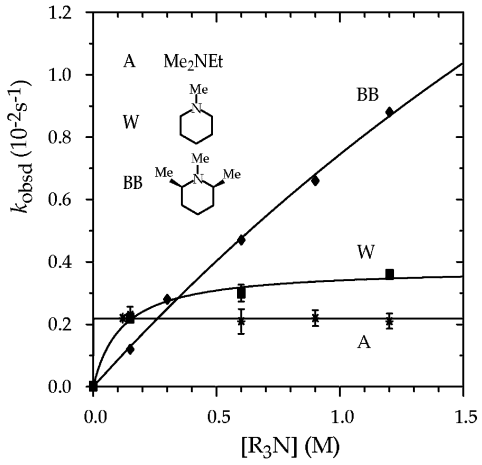


Figure 8. Plot of k_{obsd} vs [R$_3$N] in toluene cosolvent for the enolization of **1** (0.004 M) by LiHMDS (0.10 M) at −78 °C. The curves depict the results of unweighted least-squares fit to $k_{obsd} = a$[R$_3$N]/(1 + b[R$_3$N]). **BB**: $a = 3.3 \pm 0.7 \times 10^{-2}$ (s^{-1}·M^{-1}), $b = 9 \pm 2$ (M^{-1}); **W**: $a = 8.8 \pm 0.6 \times 10^{-3}$ (s^{-1}·M^{-1}), $b = 1.8 \pm 0.8 \times 10^{-1}$ (M^{-1}); **A**: $a = 1.1 \times 10^{14}$ (s^{-1}·M^{-1}), $b = 4.9 \times 10^{16}$ (M^{-1}).

The full consequence of solvation on reactivity is better understood by comparing both the qualitative trends and the relative rates. Figure 8 shows the superposition of concentration-dependent rate constants for several amines. The sensitive relationships among ligand structures, binding constants, concentration dependencies, and relative reaction rates are discussed in detail below.

Reaction Orders in LiHMDS. Plots of k_{obsd} versus [LiHMDS][39] reveal zeroth-order dependencies in all amines; Figure 9 is representative. In conjunction with the structural assignments of dimer-based complexes **3** and **4**, the [LiHMDS]-independent rates indicate the enolizations proceed via LiHMDS dimers.

Overall Rate Laws. The four limiting amine dependencies summarized by Figure 3 can be placed in the context of the mechanism depicted generically in eqs 2−4 and four limiting forms of the idealized rate law in eq 5: (1) For strongly coordinating (Type I) amines, eq 5 reduces to eq 6 and the mechanism is described by eq 4. (2) Type II amines of intermediate steric demand afford two limiting behaviors leading to fully developed saturation kinetics (eqs 3 and 4) described by eq 7. (3) Hindered (Type III) amines afford very low (steady-state) concentrations of **4**, resulting in a first-order [R$_3$N] dependence. The rate law reduces to eq 8, and the mechanism is described by eqs 2−4. (The small nonzero intercept is still difficult to detect.) (4) In the absence of added amine or in the presence of noncoordinating (Type IV) amines, eq 5 reduces to eq 9 and the mechanism is described by eq 2.

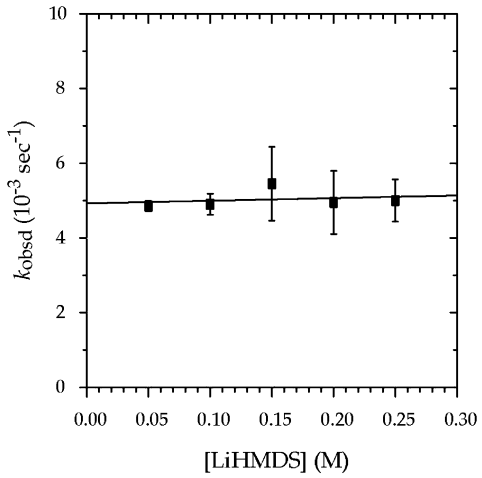


Figure 9. Plot of k_{obsd} vs [LiHMDS] in 3.0 M Et$_3$N/toluene solution for the enolization of **1**-d_3 (0.004 M) by LiHMDS at −78 °C. The curve depicts the results of an unweighted least-squares fit to $k_{obsd} = a$[LiHMDS] + b, where $a = 0 \pm 2 \times 10^{-5}$ (s^{-1}·M^{-1}), $b = 4.9 \pm 0.3 \times 10^{-3}$ (M^{-1}).

$$[(TMS_2NLi)_2(ketone)]\ (\mathbf{3}) \xrightarrow{k_1} [(TMS_2NLi)_2(ketone)]^{\ddagger}\ (\mathbf{5}) \quad (2)$$

$$[(TMS_2NLi)_2(ketone)]\ (\mathbf{3}) + R_3N \overset{K_{eq}}{\rightleftharpoons} [(TMS_2NLi)_2(R_3N)(ketone)]\ (\mathbf{4}) \quad (3)$$

$$[(TMS_2NLi)_2(R_3N)(ketone)]\ (\mathbf{4}) \xrightarrow{k_2} [(TMS_2NLi)_2(R_3N)(ketone)]^{\ddagger}\ (\mathbf{6}) \quad (4)$$

$$-d[complex]_{total}/dt = (k_1[complex]_{total} + k_2K_{eq}[R_3N][complex]_{total})/(1 + K_{eq}[R_3N]) \quad (5)$$

such that $[complex]_{total} = [\mathbf{3}] + [\mathbf{4}]$

$$-d[\mathbf{4}]/dt = k_2[\mathbf{4}] \quad (6)$$

$$-d[complex]_{total}/dt = (k_2K_{eq}[R_3N][complex]_{total})/(1 + K_{eq}[R_3N]) \quad (7)$$

$$-d[complex]_{total}/dt = (k_1 + k_2K_{eq}[R_3N])[complex]_{total} \quad (8)$$

$$-d[\mathbf{3}]/dt = k_1[\mathbf{3}] \quad (9)$$

Amine-Dependent Relative Rate Constants. The rate studies showed that the highly amine-dependent rates stem from what is essentially a single mechanism, summarized generically by eqs 2−4 (and discussed below in the context of Scheme 1). An extensive survey of the amine-dependent enolization rates is depicted in two distinctly different ways.

Table 1. Relative Rate Constants for the LiHMDS-Mediated Enolization (eq 1) in the Presence of Trialkylamines (R_3N; Chart 1) and Dialkylamines (R_2NH; Chart 2)[a]

amine	k_{rel} 0.5 equiv	k_{rel} 5.0 equiv	k_{rel} 11 equiv	ligand type
none (toluene)	1	1	1	
A; Me_2NEt	230	210	210	I
B; Me_2Ni-Pr	640	840	1000	I
C; Me_2Nn-Bu	200	270	250	I
D; $MeNEt_2$	1100	1600	1200	I
E; $MeNn$-Pr_2	1100	1300	1200	I
F; n-Bu_3N[b]	110	420	520	II
G; Et_3N[b]	140	310	410	II
H; $MeNn$-Bu_2[b]	90	100	80	I
I; n-Pr_3N[b]	50	120	160	II
J; $MeNi$-Bu_2	1	2	1	IV
K; n-Bu_2Ni-Bu	7	30	35	III
L; n-$PrNi$-Pr_2	3	10	10	III
M; $MeNsec$-Bu_2	12	54	121	III
N; i-Pr_2NEt	4	10	26	III
O; i-Bu_3N	2	2	2	IV
P; Et_2Ni-Bu[b]	130	220	290	II
Q; i-Pr_3N	2	8	20	III
R; Me_2Ni-Bu	450	670	620	I
S; $MeNi$-Pr_2	190	680	1100	III
T; n-$BuNi$-Bu_2	5	4	4	IV
U	200	900	1500	III
V	80	90	100	I
W	220	300	360	I
X[b]	60	140	130	II
Y	520	620	600	I
Z	300	1100	3000	III
AA	8	25	49	III
BB	120	470	880	III
CC	3	14	24	III
DD; Me_2Nsec-Bu	1000	1200	1200	I
EE	290	550	650	I/II
FF	300	450	600	I/II
GG; Me_2Nt-Bu[b]	40	45	46	I
HH	800	2000	2200	I/II
II; Me_2NCH_2Ph	340	300	370	I
JJ; $Me_2NCH_2CH_2Ph$	220	310	230	I
KK	1200	e	e	II
LL; n-Pr_2NH	10	c,e	e	I
MM; n-Bu_2NH	8	11[c]	e	I
NN; i-Pr_2NH	1200	1500	1400	I
OO; i-Bu_2NH	4	4	4	I
PP; s-Bu_2NH	1200	1400	1400	I
QQ	15	20	22	I
RR; pyrrolidine	(370)[d]	c,e	*e*	I
SS; piperidine	10	70[c]	*e*	I
TT; 2-methylpiperidine	7	12	*e*	I
UU; *cis*-2,6-dimethyl-piperidine	660	540	580	I
VV; 2,2,6,6-tetramethyl-piperidine[b]	110	200	420	II

[a] Enolizations were carried out with 2-methylcyclohexanone (**1**, 0.004 M) and LiHMDS (0.10 M) in toluene cosolvent at −78 °C. [b] Deuterated substrate (**1**-d_3, 0.004 M) was used to attenuate the rates. [c] Deaggregation was observed at higher ligand concentrations. [d] LiHMDS affords 1,2-addition rather than enolization. [e] Not done.

Table 1 lists the relative rate constants for each amine compared to the rate in neat toluene. Entries for 1.5, 6.0, and 12.0 equiv of amine provide qualitative insights into the concentration dependencies by showing whether the amine dependence is approximately zeroth order, first order, or an intermediate order. We found that the k_{rel}'s recorded for the most hindered amines have larger errors due to very low rates and potential intervention of trace impurities at the higher amine concentrations. Figure 10 is a somewhat unorthodox, but pedagogically useful, presentation of the relative rates. The *y*-axis corresponds to $\ln[k_{rel}]$ determined at 6.0 equiv of amine. The *x*-axis defies rigorous description but is suggested to reflect the steric demands of the amines (see below). The smoothness of the curve is an artifact of the presentation—the points were intentionally moved along the *x*-axis so as to be placed on the parabola. Placements on the left or right half of the parabola are based on whether the rate and spectroscopic data implicate strong or weak solvation. It was impractical to determine full rate laws for each amine. Nonetheless, comparisons of the data from 1.5, 6.0, and 12.0 equiv of amine[39] in conjunction with the detailed rate studies for selected cases and NMR spectroscopic studies help us assign the amines to the four general classes: (1) Relatively unhindered (Type I) amines (Table 1) elicit high, $[R_3N]$-independent rates; (2) Moderately hindered Type II amines afford concentration-dependent values of k_{rel} in which the 8-fold increases in the total amine concentration cause rate increases that are measurably less than 8-fold;[41] (3) Hindered Type III amines in which 8-fold increases in $[R_3N]$ afford approximately 8-fold increases in k_{rel}; (4) Highly hindered Type IV amines fail to elicit rate accelerations when compared with toluene.

Relative Binding Constants. The spectroscopic studies reveal a gradient of behaviors ranging from quantitative solvation of the LiHMDS to a complete resistance to solvate LiHMDS. It was important to confirm the apparent correlation of reactivity with the binding constant. Although the fully developed saturation kinetics affords a formal binding constant for Type II amines such as Et_3N or n-Bu_3N, the method was not general enough to clearly demonstrate the quantitative correlation of solvation energies and activation energies. Accordingly, to demonstrate quantitatively the relationship of binding constant and reactivity, we turned to a conceptually and operationally simple method[25a,42] derived from the method of continuous variations (Job plots).[43]

Consider the enolizations in Scheme 3 and the simple thermochemical picture in Figure 11. If only S_a or S_b is present, the two limiting observable species are variants of dimer−ketone complex **4**, denoted as **i** and **ii**, respectively. The rate constants measured in the presence of S_a and S_b provide the free energies of activation, $\Delta G^{\ddagger}(A)$ and $\Delta G^{\ddagger}(B)$, respectively. Equation 10 describes k_{obsd} in terms of mechanistic constants and solvent concentrations. Substituting for $[S_a]$ and $[S_b]$ by their mole fractions, X_a and $1 - X_a$, respectively, affords eq 11. The calculated value of K_A provides a measure of the relative free energies of the two ground states corresponding to dimers **i** and **ii** [ΔG^{o}_{GS}; Figure 11]. The estimated free energies of activation and relative ground-state free energies, in turn, provide the difference in the transition-state energies [ΔG^{o}_{TS}] to complete the thermochemical picture in Figure 11.

$$k_{obsd} = \{k_a + k_b K_A([S_b]/[S_a])\}/\{1 + K_A([S_b]/[S_a])\} \quad (10)$$

$$k_{obsd} = [k_a X_a + k_b K_A(1 - X_a)]/[X_a + K_A(1 - X_a)] \quad (11)$$

This strategy for investigating LiHMDS solvation offers both qualitative and quantitative insight. Figure 12 shows theoretical curves assuming a 10-fold relative rate difference in neat donor solvents ($k_{obsd}(S_b)/k_{obsd}(S_a) = 10$) for three relative binding

(41) An 8-fold increase in amine concentration can produce <8-fold rate increases when the following occurs: (1) the lower and higher Type II amine concentrations lie on the concentration-dependent and -independent regions of the saturation curve, respectively, and (2) the nonzero intercept for a highly hindered Type III amine is significant.

(42) Remenar, J. F.; Collum, D. B. *J. Am. Chem. Soc.* **1997**, *119*, 5573.
(43) Job, P. *Ann. Chim.* **1928**, *9*, 113. For more recent examples and leading references, see: Huang, C. Y. *Method Enzymol.* **1982**, *87*, 509. Hubbard, R. D.; Horner, S. R.; Miller, B. L. *J. Am. Chem. Soc.* **2001**, *123*, 5810. Potluri, V.; Maitra, U. *J. Org. Chem.* **2000**, *65*, 7764.

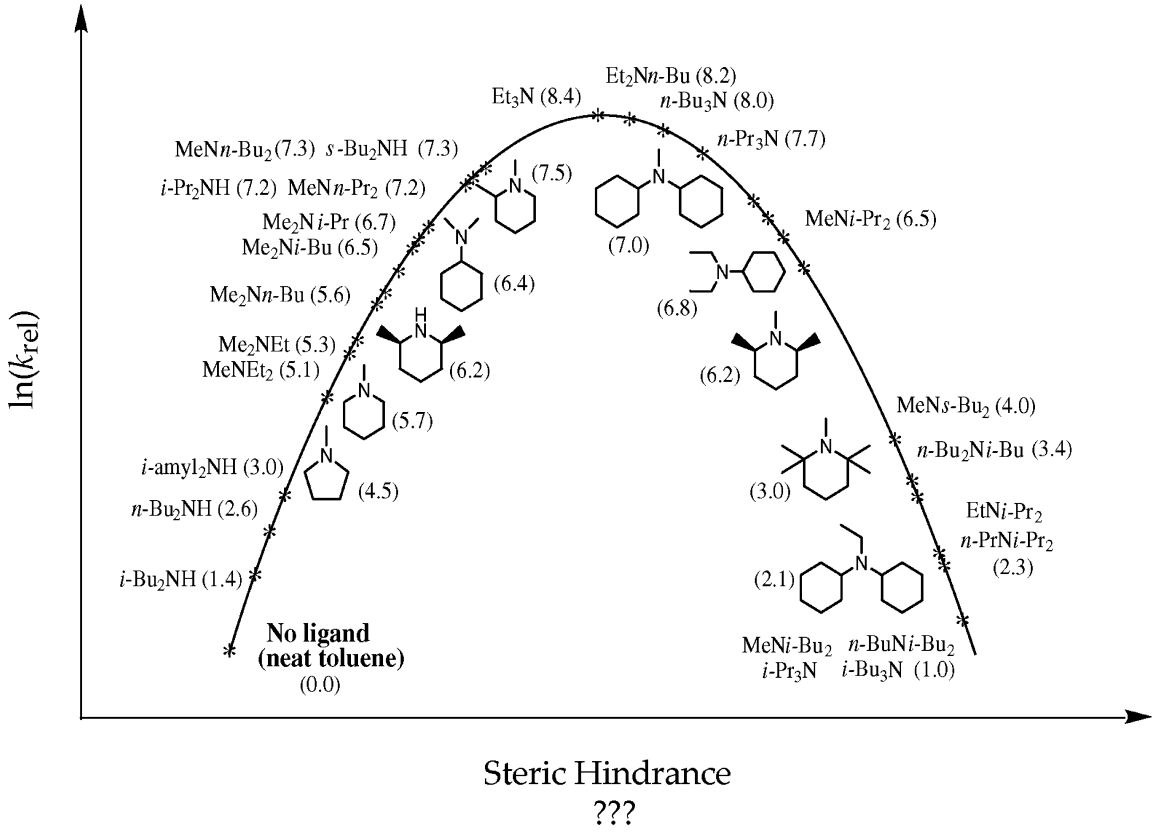
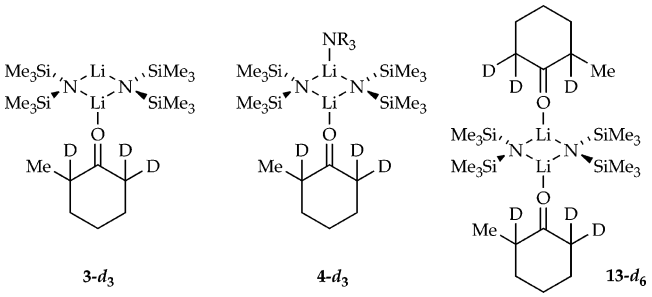


Figure 10. Rate constants for the enolization of **1** (0.004 M) by LiHMDS (0.10 M) in 0.60 M amine/toluene mixtures at −78 °C.

Scheme 3



affinities: $K_A = 10$ (curve A), 1.0 (curve B), and 0.1 (curve C). Curve A results if the superior donor solvent (S_b) affords highly reactive species (as commonly suggested). Conversely, curve C results if the superior solvent (S_a in this case) affords kinetically less reactive species. If the two ligands bind equally, the rate should change linearly with the mole fraction (curve B).

Before considering the experimental results, it is important to understand the underlying assumptions and approximations. (1) The mathematical description would become more complex than that described by eq 11 if the dominant mechanisms were not both zeroth order in donor solvent. (2) If the solvation states of **i** and **ii** are incorrect, the mathematical form of eq 11 is incorrect. For LiHMDS dimers, the assignments are based on compelling evidence.[10,24] (3) When measuring pseudo-first-order rate constants using solvent mixtures, both solvents should be in excess to avoid substantial errors in the estimates of free (as opposed to total) solvent concentration. (This measurement is probably our largest source of error.) Also, substantial errors arise when $K_A \gg 10$ or $K_A \ll 0.1$ because the highly curved

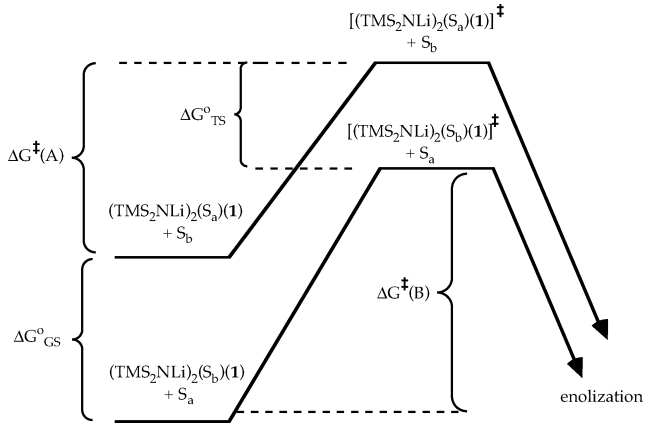


Figure 11.

portion of the function cannot be adequately sampled. We cover a broad scale of binding constants by laddering (comparing S_a to S_b, S_b to S_c, and so on). (4) The left-hand and right-hand *y*-intercepts represented in Figure 12 do not necessarily correspond to neat donor solvents. In fact, it is conceptually cleaner to maintain the total donor solvent concentration at a fixed molarity and define X_a and X_b as fractions of that fixed molarity. (5) In principle, amine structure- and concentration-dependent deaggregation of the LiHMDS could have introduced inordinate complexity to the analysis. In practice, the zeroth-order dependencies of the rate on the LiHMDS concentration render this issue moot.

Emblematic results in Figure 13 show the measured pseudo-first-order rate constants for the enolization of **1** by LiHMDS in Et_2NMe/Et_3N (**D**/**G**) mixtures plotted as a function of the mole fraction X. For this case, we define X as the fraction of

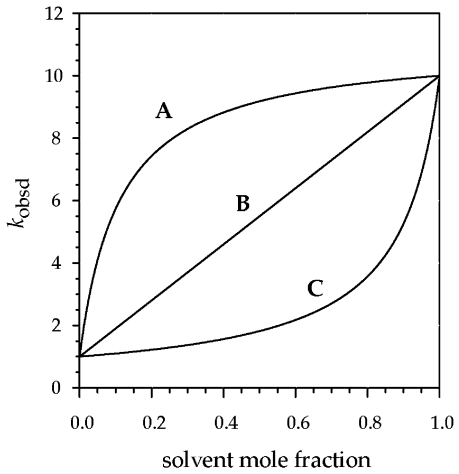


Figure 12. Theoretical plots showing k_{obsd} as a function of solvent mole fraction in a binary solvent mixture. The plots assume a 10-fold relative rate difference in neat donor solvents ($k_{obsd}(S_b)/k_{obsd}(S_a) = 10$) for three relative binding affinities: $K_A = 10$ (curve A), 1.0 (curve B), and 0.1 (curve C). The curves were built according to the equation $y = (k_a + (k_b - k_a)x)/(1 + (K_A - 1)x)$, where $k_a = 1$, $k_b = 10$.

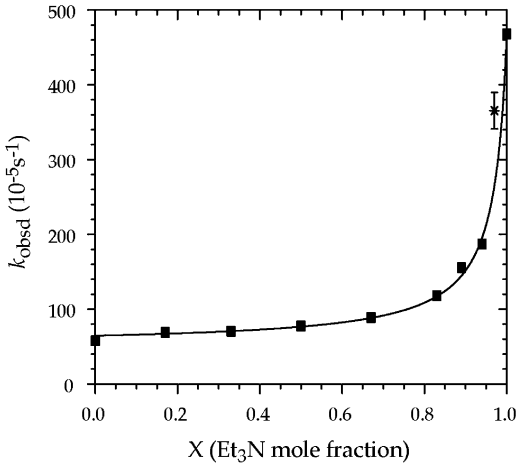


Figure 13. Plot of k_{obsd} vs Et_3N mole fraction in Et_3N/Et_2NMe/toluene mixture for the enolization of **1**-d_3 (0.004 M) by LiHMDS (0.10 M) at −78 °C. The total concentration of Et_3N and Et_2NMe is 1.8 M. The curve depicts the results of an unweighted least-squares fit to $y = (a + bx)/(1 + cx)$, where $a = 6.4 \pm 0.4 \times 10^{-4}$ (s^{-1}), $b = -5.2 \pm 0.5 \times 10^{-4}$ (s^{-1}), $c = -0.971 \pm 0.002$. K_A (Et_2NMe/Et_3N) $= 1 + c = 2.9 \pm 0.2 \times 10^{-5}$.

1.8 M total amine concentration using toluene as the cosolvent. Fitting the data to eq 11 ($S_a = Et_2NMe$ and $S_b = Et_3N$) affords $K_A(Et_2NMe/Et_3N) = 0.029 \pm 0.002$, corresponding to a ground-state free energy difference, ΔG^o_{GS}, of 1.5 ± 0.1 kcal/mol. Analogous mixtures of other Type I amines afforded ΔG^o_{GS} in Figure 11. The relative activation energies for enolization $\Delta G^{\ddagger}$(A) and $\Delta G^{\ddagger}$(B) provides ΔG^o_{TS}. A plot of ΔG^o_{GS} versus ΔG^o_{TS} (Figure 14) affords a surprisingly simple relationship described by eq 12. The results confirm that the rates correlate inversely with the energy of solvation, and the accelerations stem from greater steric effects in the reactants than in the transition structures.

$$\Delta G^o_{TS} \approx 0.6\Delta G^o_{GS} \qquad (12)$$

Substrate and Mixed Aggregation Effects. We compared enolizations using 1.0 and 2.0 equiv of LiHMDS per equivalent of ketone to ascertain whether the rate-accelerating influence of the amines could be exploited under practical conditions.

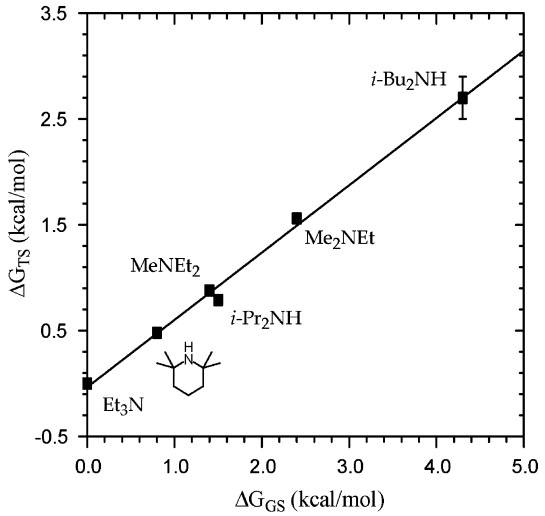


Figure 14. Plot of ΔG^o_{TS} vs ΔG^o_{GS} for selected amine ligands. Rate constants were measured in toluene cosolvent at −78 °C. The curve depicts the results of an unweighted least-squares fit to $y = ax + b$, where $a = 1.56 \pm 0.06$, $b = 0.06 \pm 0.08$ (kcal/mol).

Table 2. Enolization Rates under Non-pseudo-first-order Conditions[a]

	$10^5 \cdot k_{obsd}$ (s^{-1})			
LiHMDS equiv	none[b]	i-Pr_2NEt[c]	Me_2NEt[d]	Et_3N[e]
1.0	200	150	210	410
2.0	510	230	110	260
20	340	80	7	5

[a] Reactions were carried out with 2-methylcyclohexanone (**1**; 0.005−0.10 M) and LiHMDS (0.10 M) in toluene cosolvent. [b] $T = 40$ °C. [c] $T = -60$ °C with 1.2 M $(i\text{-Pr})_2NEt$. [d] $T = -78$ °C with 0.60 M Me_2NEt. [e] $T = -78$ °C with 1.2 M Et_3N and deuterated substrate (**1**-d_3).

Many of these studies proved confounding and in need of further investigation. A highly truncated summary, however, is instructive.

NMR spectroscopic studies following enolizations using 1:1 and 2:1 mixtures of [^{6}Li,^{15}N]LiHMDS and **1** (or **1**-d_3) in neat toluene or in toluene containing relatively hindered Type II−IV amines provide exceedingly complex mixtures of $(TMS_2NLi)_x(enolate)_y$ mixed aggregates. In contrast, enolizations using LiHMDS/Me_2NEt mixtures proceeded cleanly via mixed dimer **14** (Figure 2E).[44,45] (We suspect that the Me_2NEt may disrupt laddering that can lead to very complex mixtures.)[46] Given the structural complexity, it was surprising that analogous enolizations monitored by IR spectroscopy displayed only minor deviations from first-order decays even when followed to >3.0 half-lives (Supporting Information). In any event, the rates were approximated as first-order rate constants listed in Table 2. Rows 1 and 2 in Table 2 provide first-order rate constants using 1.0 and 2.0 equiv of LiHMDS, respectively. Row 3 offers pseudo-first-order rate constants as benchmarks. The rate constants

(44) For a crystallographically characterized mixed dimer of LiHMDS and a lithium enolate, see: Williard, P. G.; Hintze, M. J. *J. Am. Chem. Soc.* **1990**, *112*, 8602.
(45) Mixed aggregates of LiHMDS are not readily formed in the presence of strongly coordinating solvents. Romesberg, F. E.; Collum, D. B. *J. Am. Chem. Soc.* **1994**, *116*, 9198. However, mixed aggregates of LiHMDS and the lithium enolates of isobutyrophenones in THF were recently implicated during rate studies of enolization[15a] and subsequently supported by NMR spectroscopy: McNeil, A. J.; Collum, D. B. Unpublished results.
(46) For an early suggestion that steric effects are major determinants of solvation, see: Settle, F. A.; Haggerty, M.; Eastham, J. F. *J. Am. Chem. Soc.* **1964**, *86*, 2076.

across any given row are *not* comparable because different ketones (**1** and **1**-d_3) and different temperatures (−40, −60, and −78 °C) were used to modulate the rates.

The most compelling conclusion drawn from the data in Table 2 is that enolizations containing a 1:1 LiHMDS:ketone ratio are strikingly slower than analogous enolizations containing a 2:1 ratio. In fact, enolizations of 1:1 LiHMDS−ketone mixtures are not accelerated by trialkylamines. Since inhibition by mixed aggregate would only occur as the reaction proceeds, the inhibition with 1.0 equiv of ketone likely derives from the stability of bis-ketone complex **13**.[47]

Discussion

We described spectroscopic and mechanistic investigations of some seemingly complex trialkylamine-dependent rate accelerations exemplified by eq 1. Structural and rate studies traced the solvent effects to a mechanistic scenario depicted in Scheme 1 that is simple by comparison. We have taken the liberty of introducing four distinct classifications of amines (Type I−IV). The classifications are *not* intended to be used in other contexts but are included simply to facilitate and clarify the presentation. We also include the idealized plot of saturation kinetics in Figure 3 to facilitate the discussion. A summary of the results is followed by more detailed discussions.

Summary. IR and NMR spectroscopic studies revealed that mixtures of ketone **1** and excess LiHMDS in toluene afford mono-ketone complex **3** and bis-ketone complex **13**. Rate studies under pseudo-first-order conditions (affording only **3**) pointed to a dimer-based transition structure. Although we have previously invoked open dimer transition structures, the somewhat more closed variant **5** proposed by Williard and co-workers[48] seems reasonable in the absence of ancillary ligands.

Unhindered Type I amines such as Me_2NEt, although not strongly coordinating compared to standard ethereal solvents,[10,16] quantitatively solvate LiHMDS to afford disolvated dimer **10**. Similarly, LiHMDS−ketone complex **3** is quantitatively converted to the corresponding monosolvate **4**. Only the trialkylamines of general structure Me_2NR are sufficiently unhindered to display Type I behavior. In contrast, all but the most hindered dialkylamines (R_2NH) show quantitative binding characteristic of the Type I designation.[49] Rate studies show that enolization occurs by a mechanism involving a solvated dimer-based transition structure such as open dimer **6**. Placement of the amine and ketone on the terminal lithium of **6** stems from previous computational, spectroscopic, and crystallographic studies of lithium amide open dimers.[48,50,51] Steric effects are described in more detail below.

Type II amines of intermediate steric demand, exemplified by Et_3N, afford disolvated LiHMDS dimers but only at elevated amine concentrations. The spectroscopically observable saturation behavior (Figure 1) coincides with the saturation kinetics observed in the rate studies (Figure 5). The rate data are fully consistent with sluggish enolization via unsolvated dimer **5** at low Et_3N concentrations and rapid enolizations via solvated open dimer **6** at high Et_3N concentrations.

Sterically demanding Type III amines such as *i*-Pr_2NEt fail to observably coordinate to LiHMDS or ketone complex **3** but can coordinate transiently and, in turn, influence reactivity. Consequently, plots of k_{obsd} versus the concentration of Type III amines display first-order rate dependencies but not saturation behavior (Figures 3 and 6). Type III amines could, in principle, afford enolization rates that exceed those from Type II amines but often at molarities beyond the practical limit. In fact, the more hindered the Type III amine, the more muted the effect on the rate within the accessible concentration ranges.

The highly hindered Type IV amines exemplified by *i*-Bu_3N fail to coordinate to LiHMDS under any circumstances. They function as aliphatic hydrocarbons.

Steric Effects. Table 1 lists the structure- and concentration-dependent relative rate constants for the enolization facilitated by the amines in Charts 1 and 2. In the Results section we described in detail how we arrived at the ligand designations of Types I−IV. Table 1 is intractable to the casual observer; consequently, we introduced the somewhat whimsical presentation of the amine-dependent relative rate constants in Figure 10. (The liberties taken to place the rate constants on the parabola are detailed in the Results section.) The intention is to illustrate the rise and subsequent fall in rates with increasing steric demand. It is our assertion that the *x*-axis, although by no means rigorously defined or quantitative, corresponds to steric demand. There are a number of subtle consequences of the steric effects on the mechanism in Scheme 1 that warrant more detailed consideration.

The reaction rates increase markedly with what appears to be increasing steric demands for Type I and II amines. This putative inverse correlation of reactivity with solvation energy, depicted energetically in Figure 11, is a phenomenon that is *not* consistent with most conventional wisdom. A plot of ΔG^{o}_{GS} versus ΔG^{o}_{TS} (Figure 14) is surprisingly linear[16,52] and reveals that the solvation of the ground state and transition state by Type I amines is neatly described by eq 12. In essence, the acceleration enjoyed by the increasing steric demand stems from the steric relief that occurs on proceeding from dimer **4** to the rate-limiting transition structure **6**. In fact, semiempirical computational studies completed several years ago suggested that steric demands of coordinated solvents are more severe in closed dimers than in their open dimer counterparts.[24c,d] Type II amines, the most sterically demanding amines that can still be coerced to completely solvate (saturate) the LiHMDS at high concentrations, afford the highest rates of enolization.

As the steric demands of the ligands become excessive as found for *i*-Pr_2NEt and other Type III amines, a *decrease* in reaction rates with increasing steric demands of the amine stems from the reluctance of hindered amines to coordinate. The 300-fold drop in reactivity observed when a single *n*-butyl group of *n*-Bu_3N is replaced by an isobutyl group of *n*-Bu_2Ni-Bu (see eq 1 and Table 1) underscores the remarkable sensitivity of the enolization to steric effects. Moreover, it highlights the surprising

(47) Hay, D. R.; Song, Z.; Smith, S. G.; Beak, P. *J. Am. Chem. Soc.* **1988**, *110*, 8145.
(48) Haeffner, F.; Sun, C. Z.; Williard, P. G. *J. Am. Chem. Soc.* **2000**, *122*, 12542.
(49) For leading references to lithium ion coordination by protic amines, see: Aubrecht, K. B.; Lucht, B. L.; Collum, D. B. *Organometallics* **1999**, *18*, 2981.
(50) For leading references to spectroscopic, computational, crystallographic, and mechanistic studies of open dimers of lithium amides, see refs 28 and 51.
(51) Remenar, J. F.; Lucht, B. L.; Kruglyak, D.; Collum, D. B. *J. Org. Chem.* **1997**, *62*, 5748. Remenar, J. F.; Collum, D. B. *J. Am. Chem. Soc.* **1998**, *120*, 4081. Williard, P. G.; Liu, Q.-Y. *J. Am. Chem. Soc.* **1993**, *115*, 3380.
(52) Solvation of the two sites on LiHMDS are expected to be weakly correlated at best.[16] For discussions of correlated solvation, see: Rutherford, J. L.; Hoffmann, D.; Collum, D. B. *J. Am. Chem. Soc.* **2002**, *124*, 264. Hoffmann, D.; Collum, D. B. *J. Am. Chem. Soc.* **1998**, *120*, 5810.

steric demand of the isobutyl moiety detected during spectroscopic investigations of LiHMDS/amine mixtures.[16] In short, amines containing primary alkyl groups with β substituents appear to be more sterically demanding than analogous amines containing secondary alkyl groups. Authors in other disciplines have made similar observations without much comment.[53] To the extent that the relative rate constants for the enolization reflect relative steric demand, the following sizes are implicated by the kinetics: MeN*i*-Bu$_2$ (**J**) $\gg$ MeN*i*-Pr$_2$ (**S**); *i*-Bu$_2$N*n*-Bu (**T**) $\gg$ *i*-Pr$_2$N*n*-Pr (**L**). In contrast, the less demanding comparison, Me$_2$N*i*-Bu (**R**) $\approx$ Me$_2$N*i*-Pr (**B**), indicates that the impact of β substitution is restricted to severely congested systems, which is consistent with Brown's concept of a steric threshold in ligand coordination.[54] Although the exceptional steric congestion pervasive to the LiHMDS−amine solvates has thwarted our attempts to investigate these systems computationally,[55] inspection of molecular models suggests that moving a substituent from the α to the β position of the *N*-alkyl groups of the amines enhances the interaction with the trimethylsilyl groups of LiHMDS.[56]

The dependencies of the enolization rates on the structures and concentrations of the amines can afford some very strange reversals in reactivity. Although the point can be illustrated using real data (Figure 8), the theoretical analogue shown in Figure 15 may be easier to understand. The superimposed plots ln k_{rel} versus [R_3N] for Type I, II, and III amines reveal four distinct concentration ranges labeled A, B, C, and D. Each concentration range displays a unique ordering of the amine-dependent relative rates. Thus, four distinct relative reactivities can be observed by simply changing the standardized amine concentrations chosen for the comparison. We have little doubt that such reversals, had they been detected through empiricism, would have been incomprehensible.

Aggregation Effects. The enolization via dimer-based transition structure **6** requires neither a gain nor loss of a LiHMDS fragment from **4**—*the rate is independent of the LiHMDS concentration*. Consequently, the readily observable deaggregations of the free (uncomplexed) LiHMDS (Scheme 2), phenomena often associated with dramatic changes in reactivity, do not influence the rates of enolization. Although organolithium reactions are not necessarily facilitated by excess organolithium reagent (due to zeroth-order dependencies), limited investigations under non-pseudo-first-order conditions reveal that the rates do depend on the proportion of LiHMDS in fashions that, in this instance, may seem counterintuitive (see below).

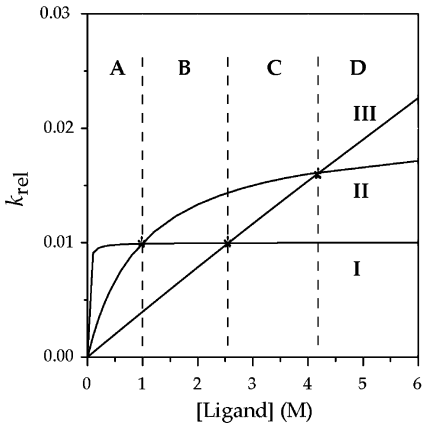


Figure 15. Theoretical plot of k_{rel} vs [Ligand]. The curves depict saturation kinetics and are built on the equation $k_{rel} = k'K_{eq}[\text{Ligand}]/(1 + K_{eq}[\text{Ligand}])$ with three parameter sets: (I) $k' = 100$, $K_{eq} = 1$; (II) $k' = 10$, $K_{eq} = 10$; (III) $k' = 1$, $K_{eq} = 100$. The resulting relative rate constants fall into four regions: (A) $k_{III} > k_{II} > k_I$; (B) $k_{II} > k_{III} > k_I$; (C) $k_{II} > k_I > k_{III}$; (D) $k_I > k_{II} > k_{III}$.

Mixed Aggregation Effects. Rate studies under pseudo-first-order conditions (>20 equiv of LiHMDS) eliminate the effects of mixed aggregation and other percent-conversion-dependent phenomena. Three fundamental determinants of reactivity explicitly excluded by the detailed rate studies are as follows: (1) A dominance of bis-ketone complex **13** would influence the rate at the outset because the ketone would serve as both the substrate and as an unhindered (inhibiting) ancillary ligand; (2) As the reaction proceeds, the ketone may become bound to the resulting enolate rather than to the LiHMDS dimer, causing a net autoinhibition; (3) Intervening LiHMDS−enolate mixed aggregates could elicit conversion-dependent changes in structure and mechanism, causing autocatalysis or autoinhibition.

To ascertain whether the amine-mediated accelerations are synthetically practical, we compared enolizations using 1.0 and 2.0 equiv of LiHMDS. Despite the intervention of mixed aggregates readily detected by ^{6}Li NMR spectroscopy, the enolizations using 2.0 equiv of LiHMDS followed clean and benign exponential decays to full conversions. Thus, the mixed aggregates intervening along the reaction coordinate had surprisingly little effect on the rates.[15] Solvent effects on reactivities R_2NLi−lithium enolate mixed aggregates have been discussed and will certainly be a topic for further investigation.

The most important observation under non-pseudo-first-order conditions is the pronounced importance of a second equiv of LiHMDS to achieve an amine-accelerated enolization (Table 2). The second equivalent of LiHMDS appears to facilitate the reaction markedly by converting the unreactive diketone complex **13** to the mixed ketone/amine solvate **4**.[52] This observation may have broadly based implications. Many organolithium reactions empirically require excess organolithium reagent to provide satisfactory yields. Although the intervention of mixed aggregates and resulting autoinhibition could be involved, one must also consider the role of the highly stabilized (unreactive) 1:1 RLi−substrate complexes.[47]

Conclusions

LiHMDS/amine-mediated ketone enolizations have provided a revealing view of how solvation and aggregation influence

(53) Brown, H. C.; Zaidlewicz, M.; Dalvi, P. V.; Narasimhan, S.; Mukhopadhyay, A. *Organometallics* **1999**, *18*, 1305. Chapman, N. B.; Dack, M. R. J.; Shorter, J. *J. Chem. Soc. B* **1971**, *5*, 834. Chapman, N. B.; Lee, J. R.; Shorter, J. *J. Chem. Soc. B* **1969**, *6*, 769. Buckley, A.; Chapman, N. B.; Dack, M. R. J.; Shorter, J.; Wall, H. M. *J. Chem. Soc. B* **1968**, *6*, 631. Sayre, L. M.; Jensen, F. R. *J. Am. Chem. Soc*. **1979**, *101*, 1900. Newman, M. S. *J. Am. Chem. Soc*. **1950**, *72*, 4783. Duthaler, R. O.; Roberts, J. D. *J. Am. Chem. Soc*. **1978**, *100*, 3882. Santry, L. J.; Azer, S.; McClelland, R. A. D. *J. Am. Chem. Soc*. **1988**, *110*, 2909. Cho, B. R.; Chung, H. S.; Pyun, S. Y. *J. Org. Chem*. **1999**, *64*, 8375. Lee, K. J.; Brown, T. L. *Inorg. Chem*. **1992**, *31*, 289. Takayama, C.; Fujita, T.; Nakajima, M. *J. Org. Chem*. **1979**, *44*, 2871. Duthaler, R. O.; Roberts, J. D. *J. Am. Chem. Soc*. **1978**, *100*, 3889. Cho, B. R.; Namgoong, S. K.; Bartsch, R. A. *J. Org. Chem*. **1986**, *51*, 1320. Also, see ref 54.

(54) Choi, M.-G.; Brown, T. L. *Inorg. Chem.* **1993**, *32*, 1548. See also: Seligson, A. L.; Trogler, W. C. *J. Am. Chem. Soc*. **1991**, *113*, 2520.

(55) Henderson, K. W.; Dorigo, A. E.; Liu, Q. Y.; Williard, P. G. *J. Am. Chem. Soc*. **1997**, *119*, 11855. Koch, R. O.; Wiedel, B.; Anders, E. *J. Org. Chem.* **1996**, *61*, 2523. Grimm, D. T.; Bartmess, J. E. *J. Am. Chem. Soc.* **1992**, *114*, 1227. 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. Henderson, K. W.; Dorigo, A. E.; Williard, P. G.; Bernstein, P. R. *Angew. Chem., Int. Ed. Engl*. **1996**, *35*, 1322. Also, see ref 22.

(56) We detect no consequences of branching at the γ-carbon.

reactivity. The rates are hypersensitive to the structure—but not necessarily the concentrations—of the amines. Despite a 3000-fold range of rates, the enolizations all proceed via dimer-based mechanisms. Such solvent-dependent rates and solvent-independent mechanisms are striking in the context of LDA-mediated ester enolizations in which solvent-*independent* rates obscured highly solvent-*dependent* mechanisms.[28] Given that such structural and mechanistic complexities appear to be the norm, the durability of organolithium chemistry's role in synthesis is not only fortunate but surprising. Congruent with the quote by Sharpless that introduced this paper, the >1000-fold rate accelerations elicited by several equivalents of simple amines may also prove useful.[57]

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, [^{6}Li]-LiHMDS, and [^{6}Li,^{15}N]LiHMDS were prepared and purified as described previously.[13] Most amines were available from commercial sources. All other amines have been described.[58] Ketone **1**-d_3 has been prepared as described previously.[31] 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.[59]

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 s intervals) at a gain of one and a resolution of four or eight. A representative reaction was carried out as follows: The IR probe was inserted through a nylon adapter and O-ring seal into an oven-dried, cylindrical flask fitted with a magnetic stir bar and T-joint. The T-joint was capped by a septum for injections and an argon line. Following evacuation under full vacuum and flushing with argon, the flask was charged with a solution of LiHMDS (170 mg, 1.0 mmol) in Me_2NEt (0.25 mL) and toluene (10.0 mL) and cooled to an internal reaction temperature of -60.0 ± 0.5 °C as determined with a thermocouple. After recording a background spectrum, ketone **1**-d_3 (5.0 μL, 0.040 mmol, 0.004 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 2.0 min were discarded. In some of the slowest cases, we used initial rates methods[34] in which the reactions were only monitored to 5% conversion.

Acknowledgment. We thank the National Institutes of Health for direct support of this work as well as Dupont Pharmaceuticals, Merck Research Laboratories, Pfizer, Aventis, R. W. Johnson, and Schering Plough for indirect support. P.Z. thanks Boehringer-Ingelheim for direct support in the form of a partial 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: NMR spectra and rate data (37 pages). This material is available free of charge via the Internet at http://pubs.acs.org. See any current masthead page for ordering information and Web access instructions.

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(57) LiHMDS/Et_3N mixtures were used inadvertently by Fukuzaki et al. when they carried out LiHMDS/toluene-mediated enolizations with a Et_3N/Me_2SiCl_2 in situ trap. Fukuzaki, T.; Kobayashi, S.; Hibi, T.; Ikuma, Y.; Ishihara, J.; Kanoh, N.; Murai, A. *Org. Lett.* **2002**, *4*, 2877.

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