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Lithium Hexamethyldisilazide/Triethylamine-Mediated Ketone Enolization: Remarkable Rate Accelerations Stemming from a Dimer-Based Mechanism

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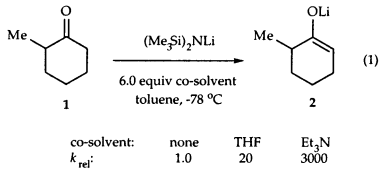
The long-held belief that strongly coordinating solvents necessarily accelerate organolithium reactions due to intervening deaggregations is not altogether logical.[1] We illustrate the point with a truism: High reaction rates stem from *selective* stabilization of the rate-limiting transition structures *relative* to the reactants. It follows that reaction rates should be maximized in solvents showing little or no affinity for the reactants and a high affinity for the transition structure(s). It is unclear why strongly coordinating solvents would be so discriminating. Nevertheless, a preoccupation with highly Lewis basic solvents has practical consequences. For example, whereas solvents perceived to be strongly coordinating are prominent in organolithium chemistry,[1] poorly coordinating[2] trialkylamines have been abandoned by all but a few polymer chemists.[3−5] The lithium hexamethyldisilazide (LiHMDS)-mediated enolization illustrated in eq 1 suggests that trialkylamines deserve further evaluation. The rate studies described herein reveal that the acceleration imparted by Et_3N stems from a dimer-based mechanism (Scheme 1). In contrast, the slower enolization in THF appears to derive from a monomer-based mechanism.[6,7]



The highly solvent-dependent enolization is best understood in the context of the low reactivity of LiHMDS in neat toluene. Treatment of freshly recrystallized LiHMDS[8] (0.05−0.30 M) in toluene with low concentrations of ketone **1** (0.004 M; IR: 1722 cm^{-1}) affords LiHMDS-ketone complex **3** (1707 cm^{-1}) quantitatively.[9] Complex **3** was fully characterized using [^{6}Li,^{15}N]LiHMDS and well-established ^{6}Li and ^{15}N NMR spectroscopies.[10,11] Using in situ IR spectroscopy to follow the loss of **3** and its 2,6,6-trideuterated analogue (**3-*d*$_3$**) reveals first-order decays and a large kinetic isotope effect ($k_{obsd(H)}/k_{obsd(D)} = 10 \pm 1$ at −40 °C).[12] In conjunction with a first-order dependence on [**3**], a zeroth-order dependence on [LiHMDS] indicates that enolization proceeds via a dimer-based transition structure such as **5** (Scheme 1).[13,14]

Enolization of ketone **1** by LiHMDS/Et_3N mixtures also proceeds via a dimer-based mechanism. The conversion of complex **3** at low [Et_3N] to **4** at elevated [Et_3N] is accompanied by a characteristic downfield shift[15] of the ^{6}Li resonance corresponding to the Et_3N-solvated ^{6}Li nucleus (Figure 1).[16] The ^{6}Li spectrum also includes the primary product, mixed dimer **7**.[11,17] IR spectroscopy reveals that the ketone remains complexed to the lithium of **4** even at high [Et_3N]. Monitoring the enolization using IR spectroscopy reveals a first-order loss of **4** and a substantial isotope effect ($k_{obsd(H)}/k_{obsd(D)} = 5 \pm 1$ at −78 °C). A plot of k_{obsd} versus [Et_3N] (Figure 2) displays saturation kinetics consistent with recalcitrant conversion of **3** to **4**. A zeroth-order dependence on [Et_3N] and [LiHMDS] (at high [Et_3N]), in conjunction with the first-order loss of **4**, indicates that dimer **4** reacts via a monosolvated-dimer-based transition

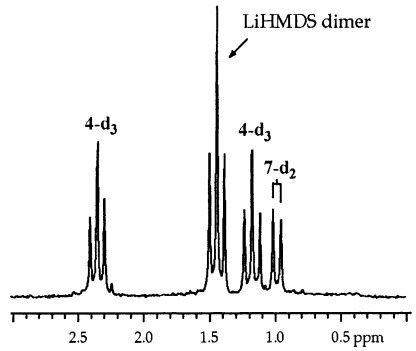


Figure 1. ^{6}Li NMR spectrum of [^{6}Li,^{15}N]LiHMDS (0.10 M in pentane) at −120 °C showing complexation by ketone **1-*d*$_3$** (0.2 equiv) and Et_3N (3.0 equiv).

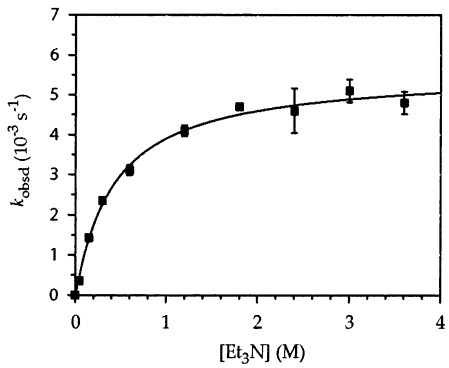
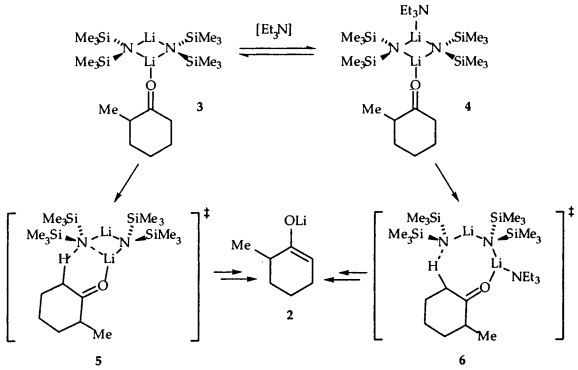


Figure 2. Plot of k_{obsd} versus [Et_3N] in toluene for the enolization of **1-*d*$_3$** (0.004 M) by LiHMDS (0.10 M) at −78 °C. The curve depicts the results of an unweighted least-squares fit to $k_{obsd} = a[Et_3N]/(1 + b[Et_3N])$.

Scheme 1



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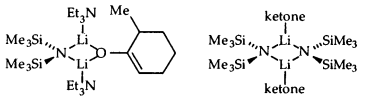
structure.



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The spectroscopic and rate studies are consistent with dimer-based transition structures, $[\{(Me_3Si)_2NLi\}_2(\mathbf{1})]^{\ddagger}$ and $[\{(Me_3Si)_2NLi\}_2(\mathbf{1})(Et_3N)]^{\ddagger}$; previous computational studies offer structural details depicted in Scheme 1, including evidence of the terminal solvation in **6**.[14b] The large Et_3N-mediated rate acceleration appears to derive from severe steric effects affiliated with solvation in the reactant that are alleviated in the transition structure. The promotion of open dimer-based enolizations by sterically hindered ligands was foreshadowed by semiempirical calculations[14] and is supported by ongoing investigations of other LiHMDS/R_3N combinations.[7]

Enolizations under more synthetically relevant conditions reveal some interesting subtleties. For example, enolization using 1.0 equiv of LiHMDS/Et_3N (1:5) is approximately 80 times slower than enolization under pseudo-first-order conditions. The inhibition observed at the *outset* of the reaction cannot derive from autoinhibition by mixed dimer **7** − the mixed dimer appears only as the reaction proceeds[18] − but rather from the formation of doubly complexed dimer **8** and the accompanying loss of steric acceleration. Indeed, enolizations using 2.0 equiv of LiHMDS/Et_3N (1:5) − conditions affording appreciable concentrations of mono-complexed dimer **4** and mixed dimer **7** (the product of enolization) − are nearly as fast as the enolizations under pseudo-first-order conditions. Although it may seem counterintuitive, organolithium reactions can be inhibited by either the substrate[19] or the product.[18]

In conclusion, the marked rate accelerations stemming from poorly coordinating solvents and aggregate-based pathways do not follow conventional wisdom. It may seem odd that a rate acceleration affiliated with a poorly coordinating solvent does *not* derive from a pathway involving a desolvation step. Nonetheless, these observations are fully consistent with the simple notion that solvent-dependent rate accelerations, whether by weakly or strongly coordinating ligands, derive from *selective* stabilization of the transition state *relative* to the ground state. On a practical note, the possible synthetic (and economic) importance of LiHMDS/Et_3N and the more generic RLi/R_3N mixtures in hydrocarbons warrants further investigation.[20]

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

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