Communication

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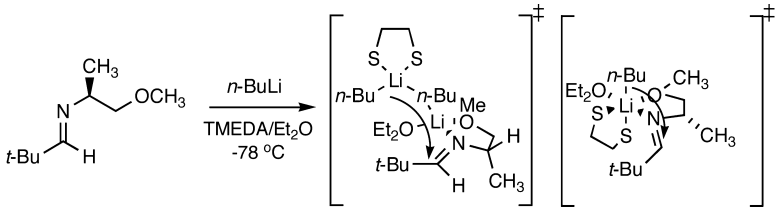

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Addition of *n*-Butyllithium to an Aldimine: Role of Chelation, Aggregation, and Cooperative Solvation

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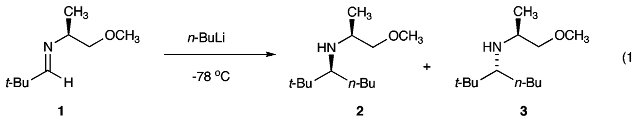
N,N,N′,N′-Tetramethylethylenediamine (TMEDA) has played a central role in organolithium chemistry.[1] Although its rise to prominence occurred in the context of anionic polymerizations,[2] synthetic organic chemists were quick to exploit TMEDA to accelerate and control a wide range of reactions.[3] TMEDA has also profoundly shaped conventional wisdom about how solvation influences aggregation and reactivity.

Approximately a decade ago we published a polemical review suggesting that TMEDA may not be a universally strong ligand for lithium and that much of the folklore surrounding TMEDA may be ill founded.[4] Among a large number of assertions, we suggested that both competitive and cooperative solvation in TMEDA/THF mixtures might be important, but the data were too meager for definitive conclusions. In passing, we implied that TMEDA/Et_2O mixtures were much less likely to present such complications.

We describe herein the investigations of 1,2-additions of *n*-BuLi to functionalized imines shown in eq 1.[5−7] The putative advantages offered by TMEDA are challenged at the outset, given that TMEDA attenuates the rates and stereoselectivities. Rate studies reveal a complex mechanistic scenario in which *four* independent mechanisms are detected. Cooperative solvation by Et_2O and TMEDA is prominent in both monomer- and dimer-based pathways.



(1)

Solvent[7]	k_{rel}	2:3
TMEDA/toluene	1.0	7:1
TMEDA/Et_2O	20	80:1
Et_2O	500	170:1

n-BuLi in TMEDA/toluene is exclusively $[(n\text{-BuLi})_2(\eta^2\text{-TMEDA})_2]$ (**4**) at all accessible *n*-BuLi and TMEDA concentrations.[8,9] The rates of the 1,2-addition of *n*-BuLi[10] to imine **1**[5] (eq 1) were investigated by monitoring the loss of **1** (exclusively uncomplexed; 1667 cm^{-1}) using in situ IR spectroscopy[11] as described for analogous *N*-isopropylaldimines.[8b] Approximately 1000-fold higher rates for **1** when compared to the isostructural *N*-isopropyl analogues in TMEDA/toluene (as well as in all TMEDA/Et_2O combinations described below) attest to the importance of chelation.

A plot of k_{obsd} versus TMEDA concentration[12] displays an inverse-first-order dependence with a nonzero asymptotic limit ($k_{obsd} = k'[\text{TMEDA}]^{-1.0\pm0.1} + k''[\text{TMEDA}]^0$) characteristic of parallel dissociative and nondissociative pathways (Figure 1 inset).[13] Plots of k_{obsd} versus *n*-BuLi concentration[12] at low and high TMEDA concentrations reveal first-order and half-order dependencies, respectively. Thus, the 1,2-addition is dominated by a dimer-based pathway—$[(n\text{-BuLi})_2(\text{TMEDA})(\mathbf{1})]^\ddagger$—at low TMEDA concentration and the more sluggish monomer-based pathway—$[(n\text{-BuLi})(\text{TMEDA})(\mathbf{1})]^\ddagger$—at high TMEDA concentration. We offer transition structures **5** and **6** as reasonable depictions, although we could depict **5** as an open dimer instead (vide infra).[16,17] The five-coordinate lithium of **6** may seem strange at first glance, but evidence of high-coordinate lithium has been accruing.[14,15]

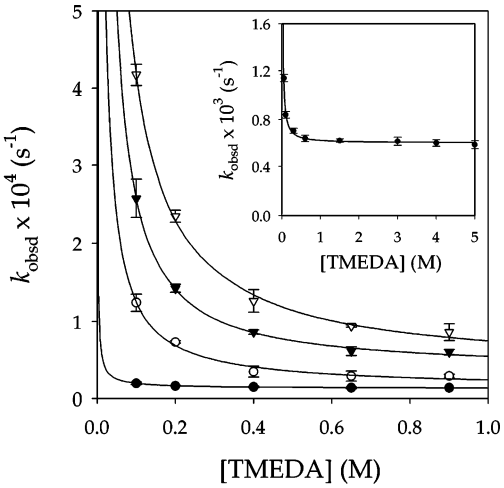
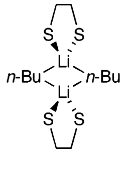
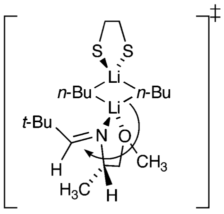


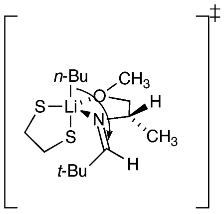
Figure 1. Plot of k_{obsd} vs TMEDA concentration for the 1,2-addition of *n*-BuLi (0.10 M) to imine **1** (0.007 M) in toluene cosolvent at −78 °C with variable Et_2O concentrations (▽, 6.0 M Et_2O; ▼, 4.0 M Et_2O; ○, 2.0 M Et_2O; ●, 0.0 M Et_2O). The curves depict unweighted least-squares fits to $k_{obsd} = a[\text{TMEDA}]^n + b$. The inset shows the dependence of k_{obsd} on TMEDA concentration (no Et_2O) at −55 °C.



4; S = NMe_2



5; S = NMe_2



6; S = NMe_2

Analogous rate studies in TMEDA/Et_2O/toluene mixtures afford surprising results. Plots of k_{obsd} versus TMEDA concentration at several Et_2O concentrations[18] display inverse-first- and zeroth-order dependencies (Figure 1), suggesting that dimer- and monomer-based pathways are still operative. Indeed, approximate first-order and half-order dependencies on the *n*-BuLi concentration are measured at low and high TMEDA concentrations, respectively. Nonetheless, the rates are markedly sensitive to the Et_2O concentration, as evidenced in Figure 1. Reprocessing the data in Figure 1 as plots of k_{obsd} versus Et_2O concentration (Figure 2) shows that the addition is first-order in Et_2O concentration at both low and high TMEDA concentrations. Thus, the rate data implicate the dominance by [(*n*-

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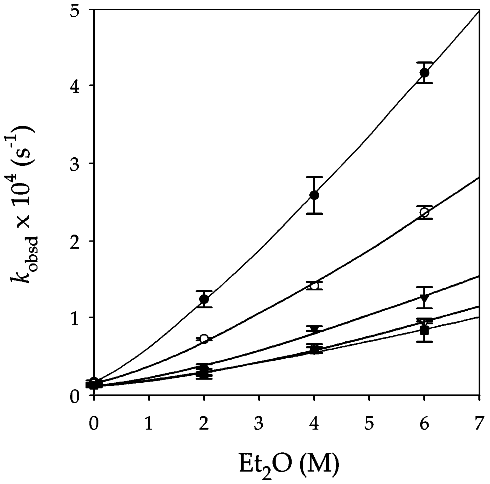
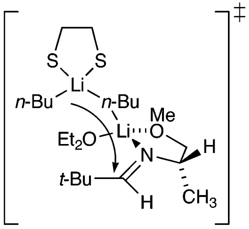
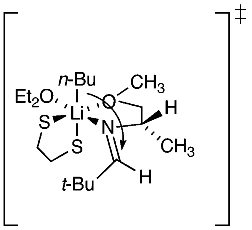


Figure 2. Plot of k_{obsd} vs Et_2O concentration for the 1,2-addition of *n*-BuLi (0.10 M) to imine **1** (0.007 M) in toluene cosolvent at −78 °C with TMEDA (●, 0.10 M TMEDA; ○, 0.20 M TMEDA; ▼, 0.40 M TMEDA; ▽, 0.65 M TMEDA; ■, 0.90 M TMEDA). The curves depict unweighted least-squares fits to $k_{obsd} = a[Et_2O]^n + b$.

BuLi)$_2$(TMEDA)(Et_2O)(**1**)]‡ at low TMEDA concentration and [(*n*-BuLi)(TMEDA)(Et_2O)(**1**)]‡ at high TMEDA concentration. Given the strong evidence of chelation by the substrate and the stoichiometries defined by the rate law, we propose transition structures **7** and **8**.



7; S = NMe_2



8; S = NMe_2

Although there are plausible isomers of dimer-based transition structure **7**, the open dimer motif of **7** is consistent with crystallographic, spectroscopic, computational, and kinetic data,[16,17] and the four-coordinate lithiums seem reasonable. By contrast, the congestion accompanying the high-coordinate lithium in **8** is likely to generate some consternation. It is possible that TMEDA ligands are not chelated. Nonetheless, we are not acutely troubled by six-coordinate (octahedral) lithium.[15]

The monomer- and dimer-based 1,2-additions to **1** contrast with analogous additions to simple imines in which exclusively monomer-based pathways are involved.[8b] The most surprising conclusion, however, is that Et_2O and TMEDA function *cooperatively* in the rate-limiting transition structures.[19] Is cooperative solvation common when mixtures of TMEDA and ethereal solvents are used? Our hunch is yes: Preliminary results on the addition of *n*-BuLi/TMEDA to simple *N*-isopropylimines show a first-order dependence on Et_2O concentration. The stereoselectivities (**2**:**3**) affiliated with the four competing pathways are crudely estimated as follows: **5**, 4:1; **6**, 15:1; **7**, 200:1; **8**, 30:1. Clearly, Et_2O markedly enhances the rates and stereoselectivities of both the dimer- and the monomer-based 1,2-additions. One should remain cognizant of this complexity when optimizing and rationalizing solvent-dependent selectivities.

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

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(12) *n*-BuLi concentration refers to the total concentration (normality). TMEDA concentration refers to the concentrations of the free (uncomplexed) ligand.
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