

## Structure of *n*-Butyllithium in Mixtures of Ethers and Diamines: Influence of Mixed Solvation on 1,2-Additions to Imines

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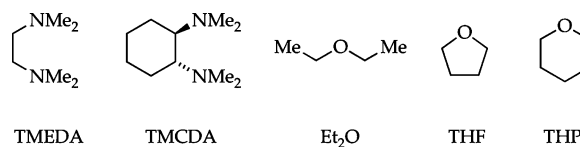
**Abstract:** *n*-BuLi in diamine/dialkyl ether mixtures forms ensembles of hetero- and homosolvated dimers. Solutions in TMEDA/THF (TMEDA = *N,N,N',N'*-tetramethylethylenediamine) are not amenable to detailed investigation because of rapid ligand exchange. TMCDA/THF mixtures (TMCDA = *trans-N,N,N',N'*-tetramethylcyclohexanediamine) afford clean assignments for a mixture of homo- and heterosolvated dimers but demonstrate poor control over structure. TMCDA/tetrahydropyran (THP) mixtures and TMEDA/Et<sub>2</sub>O mixtures afford clean structural assignments as well as excellent structural control. Rate studies of the 1,2-addition of *n*-BuLi using TMCDA/THP mixtures reveal cooperative solvation in which both THP and TMCDA coordinate to lithium at the monomer- and dimer-based transition structures. The two mechanisms are affiliated with markedly different stereochemistries of the 1,2-addition to imines. The results show strong parallels with previous investigations of 1,2-additions in TMEDA/Et<sub>2</sub>O mixtures.

### Introduction

Approximately a decade ago we challenged the conventional wisdom that *N,N,N',N'*-tetramethylethylenediamine (TMEDA) is a universally strong ligand for lithium, and we suggested that working models based on such a presumption might have fundamental flaws.<sup>1–3</sup> Along with a large number of potentially contentious assertions, we questioned whether TMEDA could compete with THF for solvation of organolithiums. More to the point, however, detailed investigations of organolithium structures and reactivities in diamine–dialkyl ether mixtures are too meager to draw definitive conclusions about the role of mixed solvation.

We describe herein a two-phase investigation of the 1,2-addition illustrated in eq 1. In the first phase, spectroscopic studies of *n*-BuLi using several diamine–dialkyl ether combinations reveal a complex distribution of structures (Chart 1) and illustrate the prominence of both homo- and heterosolvated dimers. Despite their structural complexity, several combinations provide the control of the solution structure required for detailed mechanistic studies. In the second phase, the influence of the diamines and dialkyl ethers on stereoselective 1,2-additions to chiral imines (eq 1) are examined.<sup>4</sup> In this case study, *trans-N,N,N',N'*-tetramethylcyclohexanediamine/tetrahydropyran (TMCDA/THP) mixtures serve as surrogates for TMEDA/THF

Chart 1



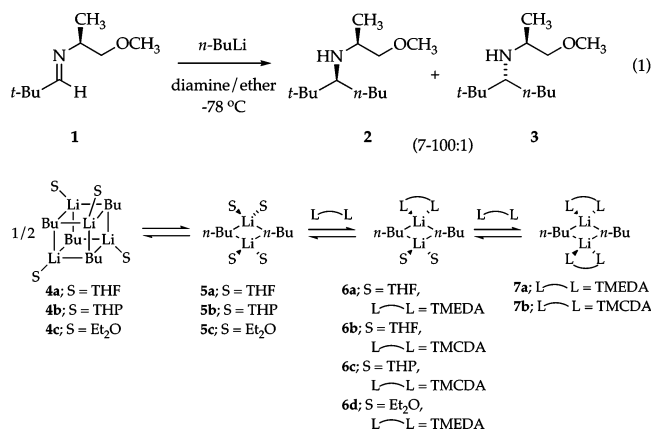
mixtures. The rate studies reveal strong parallels between TMCDA/THP and the analogous TMEDA/Et<sub>2</sub>O mixtures communicated previously.<sup>5</sup>

### Results

***n*-BuLi Structure in Solution: Background.** Previous investigations of *n*-BuLi solvated by TMEDA and TMCDA revealed chelated dimers **7a** and **7b**.<sup>6–8</sup> Moreover, TMCDA is a stronger ligand than TMEDA by  $\approx 0.5$  kcal/mol.<sup>6,9</sup> (This statement is laced with underlying complexities stemming from

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- (3) The first report of a polyamine-modified organolithium reaction appeared in 1960: Langer, A. W., Jr. U.S. Patent 3,451,988, 1960.

- (4) Reviews describing some organolithium chemistry of imines: Denmark, S. E.; Nicaise, O. J.-C. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, Y., Eds.; Springer-Verlag: Heidelberg, 1999; Chapter 26.2; Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069; Enders, D.; Reinhold, U. *Tetrahedron: Asymmetry* **1997**, *8*, 1895; Volkmann, R. A. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Chapter 1.12; Bloch, R. *Chem. Rev.* **1998**, *98*, 1407.
- (5) Qu, B.; Collum, D. B. *J. Am. Chem. Soc.* **2005**, *127*, 10820.
- (6) (a) Hoffmann, D.; Collum, D. B. *J. Am. Chem. Soc.* **1998**, *120*, 5810. (b) Rutherford, J. L.; Hoffmann, D.; Collum, D. B. *J. Am. Chem. Soc.* **2002**, *124*, 264.
- (7) For spectroscopic studies confirming the structure of *n*-BuLi-TMEDA (**7a**), see: Waldmüller, D.; Kotsatos, B. J.; Nichols, M. A.; Williard, P. G. *J. Am. Chem. Soc.* **1997**, *119*, 5479; McGarrity, J. F.; Ogle, C. A. *J. Am. Chem. Soc.* **1984**, *107*, 1805; Fraenkel, G. In *Lithium: Current Applications in Science, Medicine, and Technology*; Bach, R. O., Ed.; Wiley: New York, 1985; Baumann, W.; Oprunenko, Y.; Günther, H. Z. *Naturforsch. A* **1995**, *50*, 429; Crassous, G.; Abadie, M.; Schue, F. *Eur. Polym. J.* **1979**, *15*, 747; Saà, J. M.; Martorell, G.; Frontera, A. *J. Org. Chem.* **1996**, *61*, 5194; Also, see refs 6, 8, 11, and 17.



cooperative solvation effects; see below.)<sup>6,10</sup> *n*-BuLi in THF is assigned as a mixture of tetramer **4a** and dimer **5a**.<sup>11</sup> *n*-BuLi in THP appears to be a similar tetramer–dimer mixture (Supporting Information) with only a subtle preference for the tetramer when compared with THF. *n*-BuLi in Et<sub>2</sub>O is exclusively a higher oligomer consistent with tetramer **4c**.<sup>11,12</sup> Although it would be incorrect to infer relative binding affinities from the observed aggregation of *n*-BuLi,<sup>1,13</sup> independent evidence suggests that the binding affinities do indeed follow the order THF > THP > Et<sub>2</sub>O.<sup>9,13,14</sup> Little is known about mixed solvation of *n*-BuLi.<sup>15,16</sup> Some of the results described below were foreshadowed when Seebach and co-workers showed that the addition of TMEDA to *n*-BuLi in THF shifts the tetramer–dimer mixture toward dimer.<sup>17</sup> This shift has been inferred as evidence that TMEDA and THF are both important in *n*-BuLi/TMEDA/THF mixtures.<sup>1</sup>

**TMEDA/THF.** Reinvestigation of the structure of the *n*-BuLi dimer in TMEDA/THF mixtures provided evidence that TMEDA serially displaces THF (Chart 1). A marked TMEDA-

concentration-dependent time-averaged downfield <sup>6</sup>Li chemical shift with concomitant decrease in the tetramer-derived resonance (Figure 1A–C) indicates that TMEDA displaces THF on the dimeric form of *n*-BuLi. The incomplete conversion of tetramer to dimer with excess TMEDA shows that coordination by TMEDA is subordinate and that a recalcitrant conversion of THF-solvated dimer **5a** to TMEDA-solvated dimer **7a** might proceed via mixed-solvated dimer **6a**. Unfortunately, these details are obscured by facile ligand exchange. Other diamine/dialkyl ether combinations prove more revealing.

**TMEDA/THF.** Switching from TMEDA to the more strongly coordinating TMEDA affords lower rates of ligand exchange, allowing mixed-solvated dimer **6b** to be observed as a discrete structure along with previously characterized homosolvated dimers **5a** and **7b**.<sup>7,8,11</sup> Mixed-solvated dimer **6b** displays two <sup>6</sup>Li resonances (1:1) at <−115 °C (Figure 1D). The conversion of THF-solvated dimer **5a** to TMEDA-solvated dimer **7b** via **6b** occurs with accompanying loss of tetramer **4a**. Despite this structural transparency, TMEDA/THF is not a suitable combination of ligands for detailed rate studies because mixtures of dimer solvates are observed over large ranges of THF and TMEDA concentrations.

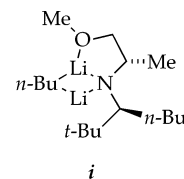
**TMEDA/THP.** Incremental additions of TMEDA to 0.10 M *n*-BuLi in 5.0 M THP/pentane also revealed dimers **5b**, **6c**, and **7b** as discrete species (Figure 1E). These results contrast with those revealed by TMEDA/THF mixtures in that mixed solvate **6c** is observed only at very low TMEDA concentrations. Thus, a slight reduction in the coordinating capacity of the ethereal solvent<sup>13,14</sup> causes TMEDA-solvated dimer **7b** to be essentially the sole observable form (>97%) over a broad range of TMEDA and THP concentrations.

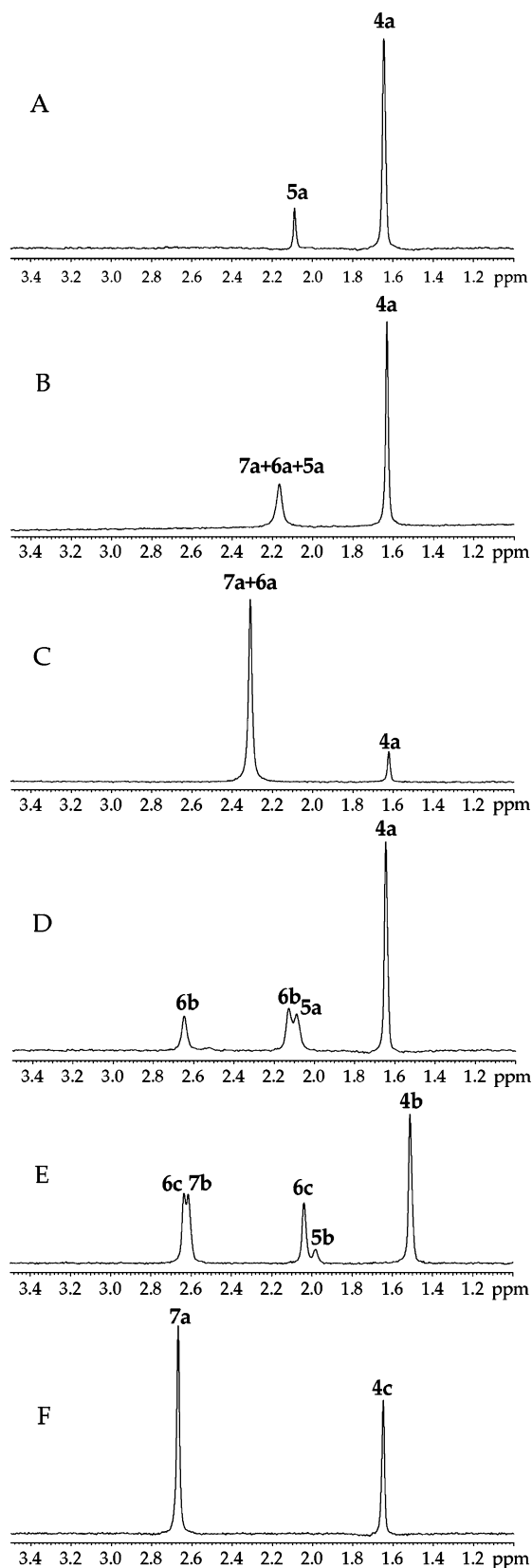
**TMEDA/Et<sub>2</sub>O.** Incremental additions of TMEDA to 0.10 M *n*-BuLi in 5.0 M Et<sub>2</sub>O/pentane resulted in the conversion of tetramer **4c** to bis-TMEDA-solvated dimer **7a** to the complete exclusion of mixed-solvated dimer (Figure 1F). TMEDA-solvated dimer **7a** is the sole observable structural form at ≥1.0 equiv of TMEDA/lithium. There is no evidence of mixed-solvated dimer **6d**.

**Rate Studies: TMEDA/THP.** The rates of the 1,2-addition of *n*-BuLi to imine **1** (eq 1) were investigated by monitoring the loss of imine **1** (1667 cm<sup>−1</sup>) using in situ IR spectroscopy.<sup>18</sup> Pseudo-first-order conditions were established by maintaining imine **1** at low concentrations (0.004–0.010 M). *n*-BuLi (recrystallized),<sup>6,19</sup> TMEDA, and THP were maintained at high, yet adjustable, concentrations using toluene as the cosolvent. The loss of imine **1** follows a clean first-order decay, affording pseudo-first-order rate constants (*k*<sub>obs</sub>) that are independent of the initial imine concentration. Formation of mixed aggregates<sup>20</sup>

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- (10) Correlated solvation of lithium salts has been addressed computationally. For examples, see: Kaufmann, E.; Gose, J.; Schleyer, P. v. R. *Organometallics* **1989**, *8*, 2577; Romesberg, F. E.; Collum, D. B. *J. Am. Chem. Soc.* **1992**, *114*, 2112.
- (11) For extensive leading references to structural studies of *n*-BuLi, see: Keresztes, I.; Williard, P. G. *J. Am. Chem. Soc.* **2000**, *122*, 10228.
- (12) Cheema, Z. W.; Gibson, G. W.; Eastham, J. F. *J. Am. Chem. Soc.* **1963**, *85*, 3517; Denisov, V. M.; Melenevskaya, E. Yu.; Zgonnik, V. N.; Kol'tsov, A. I.; Sergutin, V. M. *Izvestiya Akad. Nauk SSSR. Ser. Khim.* **1976**, *9*, 1988; Also, see ref 20.
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- (14) Lucht, B. L.; Collum, D. B. *J. Am. Chem. Soc.* **1995**, *117*, 9863; Abboud, J. L. M.; Yanez, M.; Elguero, J.; Liotard, D.; Essefar, M.; El Mouhtadi, M.; Taft, R. W. *New J. Chem.* **1992**, *16*, 739.
- (15) For examples of diamine/dialkyl ether mixed-solvated alkyllithiums, see: Strohmman, C.; Daschlein, C.; Auer, D. *J. Am. Chem. Soc.* **2006**, *128*, 704; Strohmman, C.; Strohmfeldt, K.; Schildbach, D. *J. Am. Chem. Soc.* **2003**, *125*, 13672; Bühl, M.; van Eikema Hommes, N. J. R.; Schleyer, P. v. R.; Fleischer, U.; Kutzelnigg, W. *J. Am. Chem. Soc.* **1991**, *113*, 2459; Zarges, W.; Marsch, M.; Harms, K.; Boche, G. *Chem. Ber.* **1989**, *122*, 2303; Boche, G.; Marsch, M.; Müller, A.; Harms, K. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1032; Bräuer, M.; Weston, J.; Anders, E. *J. Org. Chem.* **2000**, *65*, 1193; Gallagher, D. J.; Kerrick, S. T.; Beak, P. *J. Am. Chem. Soc.* **1992**, *114*, 5872; Ledig, B.; Marsch, M.; Harms, K.; Boche, G. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 79.
- (16) For related studies of phenyllithium in TMEDA/ethereal solvent mixtures, see: Reich, H. J.; Green, D. P.; Medina, M. A.; Goldenberg, W. S.; Gudmundsson, B. O.; Dykstra, R. R.; Phillips, N. H. *J. Am. Chem. Soc.* **1998**, *120*, 7201.
- (17) Seebach, D.; Hässig, R.; Gabriel, J. *Helv. Chim. Acta* **1983**, *66*, 308.

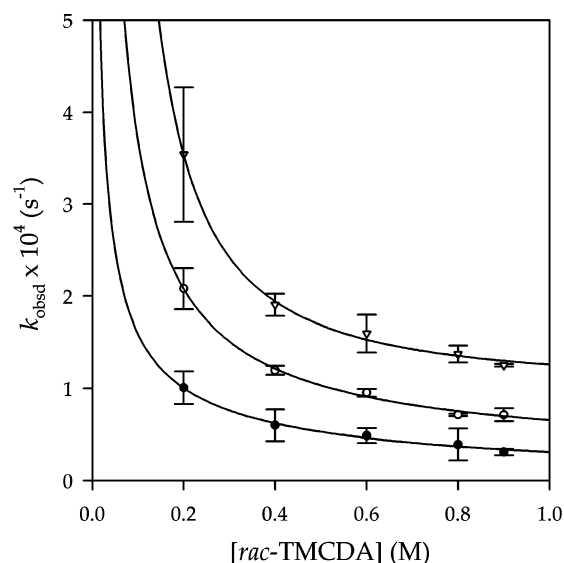
- (18) Rein, A. J.; Donahue, S. M.; Pavlosky, M. A. *Curr. Opin. Drug Discov. Dev.* **2000**, *3*, 734.
- (19) *n*-BuLi was recrystallized from pentane: Kottke, T.; Stalke, D. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 580.
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**Figure 1.**  $^6\text{Li}$  NMR spectra of  $[\text{}^6\text{Li}]\textit{n}\text{-BuLi}$  recorded on samples containing 0.10 M  $[\text{}^6\text{Li}]\textit{n}\text{-BuLi}$  in pentane at  $-115\text{ }^\circ\text{C}$ : (A) 5.0 M THF; (B) 5.0 M THF, 0.05 M TMEDA; (C) 5.0 M THF, 0.4 M TMEDA; (D) 5.0 M THF, 0.02 M *R,R*-TMEDA; (E) 5.0 M THF, 0.05 M *R,R*-TMEDA; (F) 5.0 M  $\text{Et}_2\text{O}$ , 0.05 M TMEDA.

or any other unforeseen conversion-dependent changes was shown to be inconsequential under the pseudo-first-order



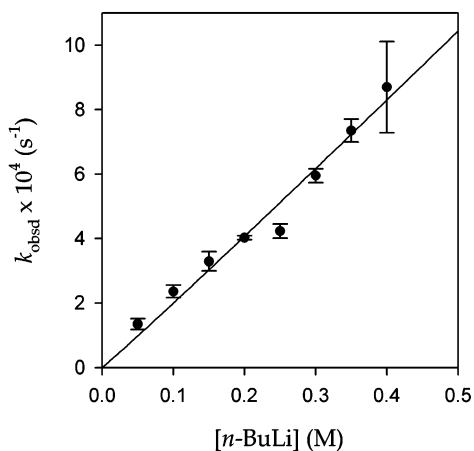
**Figure 2.** Plot of  $k_{\text{obsd}}$  vs  $[\textit{rac}\text{-TMCDA}]$  for the 1,2-addition of *n*-BuLi (0.10 M) to imine **1** (0.007 M) in toluene cosolvent at  $-78\text{ }^\circ\text{C}$  with: (A)  $\nabla$  0.80 M THF; (B)  $\circ$  0.50 M THF; (C)  $\blacksquare$  0.20 M THF. The curves depict unweighted least-squares fits to  $k_{\text{obsd}} = a[\textit{rac}\text{-TMCDA}]^n + b$ . The values of  $n$  are  $-1.4 \pm 0.2$ ,  $-0.9 \pm 0.2$ , and  $-0.7 \pm 0.3$  for curves A, B, and C, respectively.<sup>21</sup>

conditions by reestablishing the baseline at the end of a run, injecting a second aliquot of imine, and confirming that the first and second rate constants are equivalent.

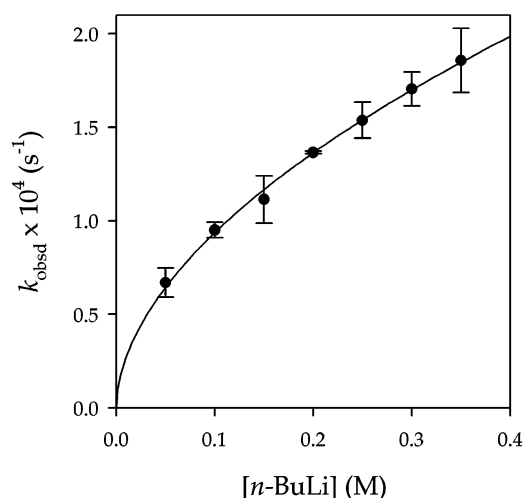
Although *n*-BuLi exists as bis-TMCDA-solvated dimer **7b** in mixtures of THF/toluene, rate studies uncovered a remarkable mechanistic complexity. A plot of  $k_{\text{obsd}}$  versus TMCDA concentration<sup>21</sup> in 0.50 M THF/toluene displays an inverse-first-order dependence with a nonzero asymptotic limit ( $k_{\text{obsd}} = k'[\text{TMCDA}]^{-1.0 \pm 0.1} + k''[\text{TMCDA}]^0$ )<sup>22</sup> characteristic of parallel dissociative and nondissociative pathways (Figure 2). Plots of  $k_{\text{obsd}}$  versus *n*-BuLi concentration<sup>21</sup> at low and high TMCDA concentrations reveal first-order and half-order dependencies, respectively (Figures 3 and 4). Thus, the 1,2-addition is dominated by a dimer-based pathway at low TMCDA concentration and by a less efficient monomer-based pathway at high TMCDA concentration. The reaction orders in THF complete the mechanistic picture. Plots of  $k_{\text{obsd}}$  versus TMCDA concentration (Figure 2, A–C) at three THF concentrations reveal that the inverse and zeroth-order TMCDA dependencies are observed over a range of THF concentrations, yet there is clearly a THF dependence. Reprocessing the data depicted in Figure 2 as plots of  $k_{\text{obsd}}$  versus THF concentration (Figure 5) reveals first-order THF dependencies at all TMCDA concentrations.

The rate data are consistent with the idealized rate law described by eqs 2 and 3 and implicate a mixed-solvated dimer-based transition structure  $[(\textit{n}\text{-BuLi})_2(\text{TMCDA})(\text{THP})(\mathbf{1})]^\ddagger$  at low TMCDA concentration and a mixed-solvated monomer-based transition structure  $[(\textit{n}\text{-BuLi})(\text{TMCDA})(\text{THP})(\mathbf{1})]^\ddagger$  at high TMCDA concentration. We offer transition structures **8** and **9** as reasonable depictions. This conclusion mirrors that derived from previous studies of TMEDA/ $\text{Et}_2\text{O}$  mixtures.<sup>5</sup> The role of open dimers, mixed solvation, chelation, and unusually high-

(21) *n*-BuLi concentration refers to the total concentration (normality). TMCDA concentration refers to the concentration of the free (uncomplexed) ligand.  
 (22) The five-point curves in Figure 2 reveal inverse first orders, but with considerable error. The cited order of  $-1.0$  derives from a more fully developed data set found in Supporting Information.



**Figure 3.** Plot of  $k_{\text{obsd}}$  vs  $[n\text{-BuLi}]$  for the 1,2-addition to imine **1** (0.007 M) in 0.15 M *rac*-TMEDA and 0.50 M THP and toluene cosolvent at  $-78$  °C. The curve depicts an unweighted least-squares fit to  $k_{\text{obsd}} = a[n\text{-BuLi}]^n$  ( $a = 2.1 \pm 0.3 \times 10^{-3}$ ,  $n = 1.03 \pm 0.10$ ).

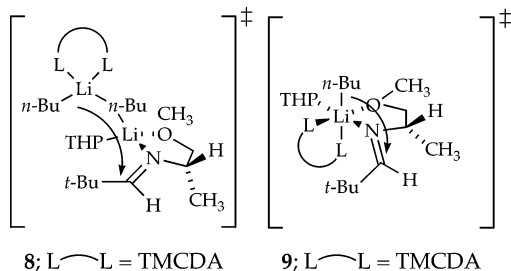


**Figure 4.** Plot of  $k_{\text{obsd}}$  vs  $[n\text{-BuLi}]$  for the 1,2-addition to imine **1** (0.007 M) in 0.60 M *rac*-TMEDA and 0.50 M THP and toluene cosolvent at  $-78$  °C. The curve depicts an unweighted least-squares fit to  $k_{\text{obsd}} = a[n\text{-BuLi}]^n$  ( $a = 3.3 \pm 0.1 \times 10^{-4}$ ,  $n = 0.54 \pm 0.02$ ).

coordinate lithium nuclei are discussed below. Interestingly, Iwao and co-workers invoked such an open dimer to explain the stereochemistry of organolithium addition to ferrocenyl-imines.<sup>23</sup>

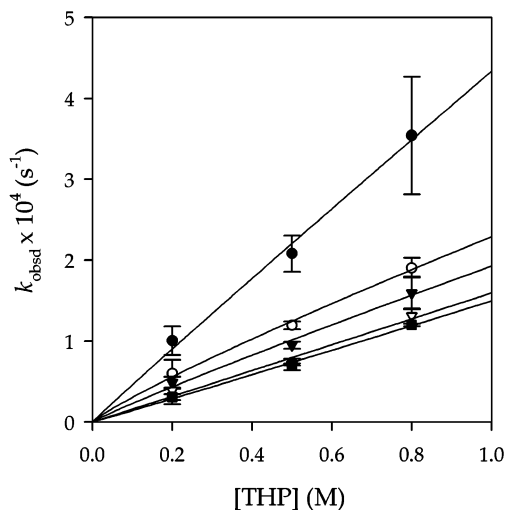
$$-d[\text{imine}]/dt = k_{\text{obsd}}[\text{imine}] \quad (2)$$

$$k_{\text{obsd}} = k'[\text{TMEDA}]^{-1}[\text{THP}]^1[\text{BuLi}]^1 + k''[\text{TMEDA}]^0[\text{THP}]^1[\text{BuLi}]^{1/2} \quad (3)$$



## Discussion

TMEDA and related diamines are often used in conjunction with ethereal cosolvents to modify the reactivity of organo-



**Figure 5.** Plot of  $k_{\text{obsd}}$  vs  $[\text{THP}]$  for the 1,2-addition of *n*-BuLi (0.10 M) to imine **1** (0.007 M) in toluene cosolvent at  $-78$  °C with: (A) ● 0.20 M *rac*-TMEDA; (B) ○ 0.40 M *rac*-TMEDA; (C) ▼ 0.60 M *rac*-TMEDA; (D) ▽ 0.80 M *rac*-TMEDA; (E) ■ 0.90 M *rac*-TMEDA. The curves depict unweighted least-squares fits to  $k_{\text{obsd}} = a[\text{THP}]^n$ . The values of  $n$  are  $1.0 \pm 0.1$ ,  $0.88 \pm 0.08$ ,  $0.9 \pm 0.1$ ,  $1.0 \pm 0.2$ , and  $1.03 \pm 0.07$  for curves A, B, C, D, and E, respectively.

lithiums.<sup>2</sup> Despite a few scattered structural studies documenting the existence of diamine/dialkyl ether mixed solvates,<sup>14–17</sup> the complexities of organolithium structure and reactivity imparted by such solvent mixtures remain largely unexplored. The results section describes NMR spectroscopic and rate studies that focus on the influence of solvent mixtures on the structure and reactivity of *n*-BuLi.

It is instructive to digress by discussing some seemingly simple concepts that underscore issues affiliated with solvent mixtures. We routinely use the term “competitive solvation” to describe a situation in which two solvents vie for a single coordination site. “Mixed solvation” connotes situations wherein two solvents bind concurrently to a single structural form, whether it is to a single lithium of a monomer or to proximate lithiums of an aggregate. The resulting solvent–solvent interactions can add complexity. We use the term “correlated solvation” to describe a situation in which one solvent influences the binding of a second.<sup>6</sup> The two solvation events are not necessarily correlated; solvation of lithium amide dimers by dialkyl ethers is emblematic.<sup>13,14</sup> Correlation can be antagonistic or antagonistic: Structural studies of *n*-BuLi in mixtures of diamines displayed nonstatistical<sup>24</sup> stabilization or destabilization of the mixed-solvated dimers, depending on the combination of diamines examined. If correlated solvation leads to a antagonistic relationship—an increased binding constant of the second solvent—one might use the term “cooperative solvation.”<sup>15</sup> Last, one must consider the role of competitive and correlated solvation in both the reactants and the rate-limiting transition structures to understand how solvent mixtures influence reactivity. In short, the structures and reactivities of organolithiums in solvent mixtures are poorly understood.

(23) Fukuda, T.; Takehara, A.; Hamiu, N.; Iwao, M. *Tetrahedron: Asymmetry* **2000**, *11*, 4083; Also, see Yamada, H.; Kawate, T.; Nishida, A.; Nakagawa, M. *J. Org. Chem.* **1999**, *64*, 8821.

(24) For the proper treatment of statistical factors, see: Benson, S. W. *J. Am. Chem. Soc.* **1958**, *80*, 5151; For additional leading references to statistical contributions in “redistribution reactions,” see: Fay, R. C.; Lowry, R. N. *Inorg. Chem.* **1974**, *13*, 1309.

**n-BuLi Structure.** Spectroscopic studies described herein reveal that both the diamine and the dialkyl ether ligands influence the structural transparency and control. *n*-BuLi in TMEDA/THF may have considerable concentrations of mixed solvate **6a**, but rapid ligand exchange precludes detailed investigation. TMEDA/THF offers structural transparency by allowing dimers **5a**, **6b**, and **7b** to be observed as discrete entities, yet the persistence of dimer mixtures over a wide range of TMEDA/THF proportions renders mechanistic studies untenable.<sup>25</sup>

Control over the coordination sphere of the dimer is achieved by attenuating the binding constant of the dialkyl ether. Thus, TMEDA/THP mixtures afford bis-TMCDA-solvated dimer **7b** over a wide range of conditions. Probably the most satisfying control is found using TMEDA/Et<sub>2</sub>O. The reduced Lewis basicity of Et<sub>2</sub>O completely precludes the formation of mixed-solvated dimer: TMEDA-solvated dimer **7a** is observed with >1.0 equiv of TMEDA at all Et<sub>2</sub>O concentrations.

**n-BuLi Reactivity.** The influence of cooperative solvation on reactivity was ascertained through studies of the 1,2-addition to imine **1** (eq 1). Analogous results were obtained using TMEDA/THP mixtures and TMEDA/Et<sub>2</sub>O; the latter was the focus of a previous communication<sup>5</sup> and is not discussed further.

In summary, rate studies of *n*-BuLi/TMCDA/THP-mediated 1,2-addition afford the idealized rate law described by eqs 2 and 3, from which we offer dimer- and monomer-based transition structures **8** and **9**. The three-dimensional depictions readily account for the stereoselectivity of the addition. The steric congestion within **8** is disturbing, and the octahedral coordination within **9** could be viewed as heretical. Nonetheless, there is some precedent for high coordinate lithium.<sup>26</sup> These concerns are heightened because structures displaying such steric congestion defy computational analysis.<sup>27</sup> It is appropriate, therefore, to critique the strengths and weaknesses of the data supporting the two hypotheses.

Our primary concern with the rate data implicating dimer-based transition structure **8** is that rates can become hypersensitive to the reaction conditions at low TMCDA concentrations wherein the rates spike with decreasing TMCDA concentration (see Figure 2). With that said, the measured orders in *n*-BuLi, TMCDA, and THP are remarkably close to the integer values consistent with **8**. Moreover, open dimers continue to be implicated by NMR spectroscopic, crystallographic, and kinetic studies.<sup>28</sup> In fact, we routinely find that inverse solvent orders are affiliated with aggregate-based pathways.<sup>29–31</sup>

One might also question the locations and hapticities of ligands in **8**. Although there is some evidence that the internal lithium of open dimers—the lithium of **8** flanked by the two *n*-butyl groups—should not be very Lewis acidic toward coordinating ligands,<sup>28b,32</sup> structural analogy with a phenyllithium triple ion<sup>33</sup> lends credence to the location of the TMCDA ligand. Are both potentially chelating moieties necessarily

chelating? Because structurally analogous *N*-isopropylimines react approximately 1000-fold slower under identical reaction conditions, it is a virtual certainty that the substrate is chelated at the rate-limiting transition structure. In principle, the TMCDA could coordinate as an  $\eta^1$ -ligand, but structural investigations of organolithiums solvated by TMCDA have offered no evidence that the  $\eta^1$  form of TMCDA is viable.<sup>34</sup> Overall, dimer-based 1,2-addition via transition structure **8**, which is favored at low TMCDA concentrations, does not seem problematic.

By contrast, in the absence of supporting data, we would have deemed monomer-based transition structure **9** as unreasonable. This determination is true even though evidence of high-coordinate lithium (including octahedral lithium) has been accruing.<sup>26</sup> Transition structure **9**, however, is strongly supported by the data. The orders in THP, TMCDA, and *n*-BuLi leave little room for equivocation over the stoichiometry of **9**. Chelation by imine **1** is supported by the profoundly lower reactivity of the isostructural *N*-isopropyl analogue under identical conditions. One could avoid invoking an octahedral lithium by assuming that TMCDA functions as a monodentate ligand or that *n*-BuLi dissociates to form an ion pair, but we find neither to be very palatable (especially the latter).<sup>35</sup>

Analogous results using TMCDA/THP and TMEDA/Et<sub>2</sub>O seem to underscore a generality in these conclusions. We infer from the data that TMEDA/THF would probably afford similar results as well; limited semiquantitative studies are in full accord.

**Stereochemistry.** Several comments about the stereochemistry of the 1,2-addition in eq 1 are warranted. Transition structures **8** and **9** are consistent with the dominant formation of diastereomeric adduct **2**. The stereoselectivity of the 1,2-addition displays a pronounced dependence on ligand concentrations and, by inference, mechanism (Figure 6). Conditions favoring dimer-based addition via **8** also promote a high (>100:1) selectivity, whereas the monomer-based addition is less selective. The selectivity does not exceed 10:1 in the absence of THP at either low or high TMCDA concentrations.<sup>5,36</sup>

A second stereochemical issue pertains to the relationship between TMCDA and the chiral imine. Previous structural studies had shown that there was no measurable cooperativity in the coordination of TMCDA ligands to the *n*-BuLi dimer:

(25) For studies of TMCDA-solvated lithium salts, see ref 9 and references therein.

(26) For leading references to high-coordinate lithium, see: Zhao, P.; Condo, A.; Keresztes, I.; Collum, D. B. *J. Am. Chem. Soc.* **2004**, *126*, 3113; For example, <sup>+</sup>Li(DME)<sub>3</sub> is a commonly observed octahedral coordination sphere: Bock, H.; Näther, C.; Havlas, Z.; John, A.; Arad, C. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 875.

(27) We routinely find that calculated structures of congested systems backed with strong experimental support are challenging to minimize and often afford distortions (elongated bonds) that may or may not represent an adequate simulation.

(28) Open dimer-based mechanisms for 1,2-additions of alkylolithiums have been investigated computationally: (a) Kaufmann, E.; Schleyer, P. v. R.; Houk, K. N.; Wu, Y.-D. *J. Am. Chem. Soc.* **1985**, *107*, 5560. (b) Nakamura, E.; Nakamura, M.; Koga, N.; Morokuma, K. *J. Am. Chem. Soc.* **1993**, *115*, 11016. Mori, S.; Kim, B. H.; Nakamura, M. *Chem. Lett.* **1997**, 1079; For additional leading references to spectroscopic, crystallographic, and kinetic evidence of open dimers, see: Zhao, P.; Collum, D. B. *J. Am. Chem. Soc.* **2003**, *125*, 14411; For calculations of monomer-based additions to a chiral hydrazone, see: Enders, D.; Diez, E.; Fernandez, R.; Martin-Zamora, E.; Munoz, J. M.; Pappalardo, R. R.; Lassaletta, J. M. *J. Org. Chem.* **1999**, *64*, 6329.

(29) Bernstein, M. P.; Collum, D. B. *J. Am. Chem. Soc.* **1993**, *115*, 8008; Remenar, J. F.; Collum, D. B. *J. Am. Chem. Soc.* **1997**, *119*, 5573; Ramirez, A.; Collum, D. B. *J. Am. Chem. Soc.* **1999**, *121*, 11114.

(30) Ramirez, A.; Candler, J.; Bashore, C. G.; Wirtz, M. C.; Coe, J. W.; Collum, D. B. *J. Am. Chem. Soc.* **2004**, *126*, 14700.

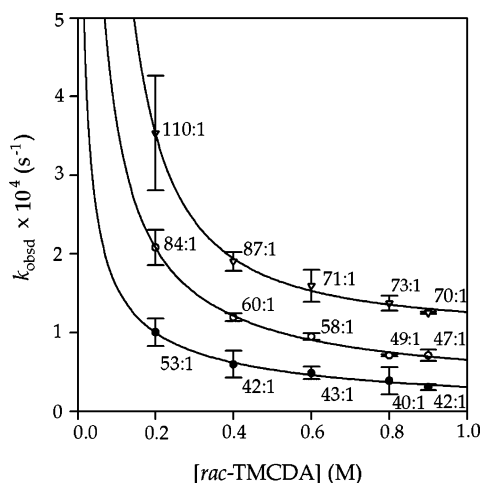
(31) For an early report of a tetramer-based reaction requiring the dissociation of a coordinating ligand, see: Bartlett, P. D.; Goebel, C. V.; Weber, W. P. *J. Am. Chem. Soc.* **1969**, *91*, 7425.

(32) Romesberg, F. E.; Collum, D. B. *J. Am. Chem. Soc.* **1992**, *114*, 2112.

(33) For a structurally related triple ion bearing a TMEDA-chelated internal lithium, see: Bildmann, U. J.; Muller, G. *Organometallics* **2001**, *20*, 1689.

(34) We suspect that the  $\eta^1$ -form of TMCDA imparts severe steric congestion (buttressing) owing to the proximity of the Li–NMe<sub>2</sub> moiety with the uncoordinated –NMe<sub>2</sub> moiety. Differences between TMEDA and TMCDA as ligands have also been attributed to the fixed bite-angle of TMCDA: Heuger, G.; Kalsow, S.; Göttlich, R. *Eur. J. Org. Chem.* **2002**, 1848.

(35) We have found in a number of computational studies that ion pair separation in such destabilized lithium salts is inordinately costly. Ramirez A.; Collum, D. B., unpublished.



**Figure 6.** Plot of  $k_{\text{obsd}}$  vs  $[\text{rac-TMCDA}]$  for the 1,2-addition of  $n\text{-BuLi}$  (0.10 M) to imine **1** (0.007 M) in toluene cosolvent at  $-78\text{ }^{\circ}\text{C}$  showing the ratio of 2/3: (A)  $\nabla$  0.80 M THP; (B)  $\circ$  0.50 M THP; (C)  $\blacksquare$  0.20 M THP.

The  $R,R$ -TMCDA and  $S,S$ -TMCDA ligands distribute statistically. Studies described herein suggest that the stereogenic centers on the ligand do not impart stereocontrol:  $R,R$ -TMCDA,  $S,S$ -TMCDA, or  $rac$ -TMCDA afford indistinguishable reaction rates and diastereoselectivities.

## Conclusion

Control over solution structure is one of the few nonnegotiable requirements for success at understanding the influence of solvation and aggregation on organolithium reactivity. Solutions of  $n\text{-BuLi}$  in TMEDA/THF afford complex mixtures of solvated

forms that are difficult to characterize fully. By contrast, TMEDA/ $\text{Et}_2\text{O}$  or TMCDA/THP afford bis-diamine-solvated dimers over a broad range of conditions. With structural assignments and control secure, we used rate studies to reveal that the diamine and dialkyl ether function cooperatively in the rate-limiting transition structures. We are left with an important unanswered question: Is cooperative solvation general? Given the plethora of reactions mediated by  $n\text{-BuLi}$  in diamine/dialkyl ether mixtures, this question should be answered.

## Experimental Section

$[\text{Li}]n\text{-BuLi}$  was purified by recrystallization.<sup>6,19</sup> *trans-R,R*-TMCDA and TMEDA were purified and dried as described.<sup>9b,37</sup> THF, THP,  $\text{Et}_2\text{O}$ , toluene, and pentane were distilled using vacuum transfer from blue or purple solutions containing sodium benzophenone ketyl. The pentane still contained 1% tetraglyme to dissolve the ketyl.  $^6\text{Li}$  NMR spectroscopy was carried using standard protocols. Air- and moisture-sensitive stock solutions of  $n\text{-BuLi}$  were prepared and manipulated under argon or nitrogen using standard glovebox, vacuum line, and syringe techniques. Rate studies using in situ IR spectroscopy were carried out as described.<sup>38</sup>

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**Supporting Information Available:** Spectroscopic, kinetic, and crystallographic data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(36) The mechanisms of dialkyl ether-free 1,2-additions by  $n\text{-BuLi}$ /TMEDA show evidence of disolvated dimer-based transition structure  $[(n\text{-BuLi})_2(\text{TMEDA})(\text{I})]^\ddagger$  at low TMEDA concentration and a monosolvated monomer-based transition structure  $[(n\text{-BuLi})(\text{TMEDA})(\text{I})]^\ddagger$ .<sup>5</sup> Preliminary data using TMCDA appear to be consistent with an analogous scenario, but detailed rate studies were not completed.

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(38) Sun, X.; Kenkre, S. L.; Remenar, J. F.; Gilchrist, J. H.; Collum, D. B. *J. Am. Chem. Soc.* **1997**, *119*, 4765.