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Consequences of Correlated Solvation on the Structures and Reactivities of RLi-Diamine Complexes: 1,2-Addition and α-Lithiation Reactions of Imines by TMEDA-Solvated *n*-Butyllithium and Phenyllithium

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Abstract: ^{6}Li and ^{13}C NMR spectroscopic studies were carried out on [^{6}Li]*n*-BuLi and [^{6}Li]PhLi (RLi) in toluene-d_8 containing the following diamines: *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA), *N*,*N*,*N*′,*N*′-tetraethylethylenediamine, 1,2-dipyrrolidinoethane, 1,2-dipiperidinoethane, *N*,*N*,*N*′,*N*′-tetramethylpropanediamine, *trans*-(*R*,*R*)-*N*,*N*,*N*′,*N*′-tetramethylcyclohexanediamine, and (−)-sparteine. Dimers of general structure $(RLi)_2S_2$ (S = chelating diamine) are formed in each case. Treatment of RLi with two different diamines (S and S′) affords homosolvates $(RLi)_2S_2$ and $(RLi)_2S'_2$ along with a heterosolvate $(RLi)_2SS'$. Relative binding constants and associated free energies for the sequential solvent substitutions are obtained by competing pairs of diamines. The high relative stabilities of certain heterosolvates indicate that solvent binding to the RLi dimer can be highly correlated. Rate studies of both the 1,2-addition of RLi/TMEDA to the *N*-isopropylimine of cyclohexane carboxaldehyde and the RLi/TMEDA-mediated α-lithiation of the *N*-isopropylimine of cyclohexanone reveal monomer-based transition structures, $[(RLi)(TMEDA)(imine)]^{‡}$, in all cases. The complex relationships of solvent binding constants and relative reactivities toward 1,2-additions and α-lithiations are discussed.

Introduction

Research during the last 40 years has shown that *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) and related diamines strongly influence organolithium structures and reactivities.[1−3] The capacity of TMEDA to reduce organolithium aggregation and elicit high reactivities has had an enormous impact on much of our thinking about structure and reactivity.[4] We recently began investigating how TMEDA and related polyfunctional solvents influence some of the most commonly used organolithiums[5] with a long-term goal of ascertaining the mechanistic basis of stereo-, regio-, and chemoselectivity.[6]

In this paper, we describe structures and reactivities of organolithium−diamine combinations. ^{6}Li and ^{13}C NMR spectroscopic studies of *n*-BuLi and PhLi dimers **4** and **5** solvated by a range of diamines (**A**−**G**; Chart 1)[7−10] reveal highly solvent-dependent solvation energies and correlated solvation effects.[5b,11−13] Subsequent rate studies of the *n*-BuLi/TMEDA- and PhLi/TMEDA-mediated 1,2-additions and α-lithiations in eqs 1 and 2[14−16] afford analogous rate laws implicating monomer-based reactions. Despite the strong structural and mechanistic homologies, structure−reactivity relationships are

(1) The first report of a polyamine-modified organolithium reaction appeared in 1960: Langer, A. W., Jr. U.S. Patent 3,451,988.
(2) Beak, P. *Chem. Rev.* **1984**, *84*, 471. Beak, P.; Meyers, A. I. *Acc. Chem. Res.* **1986**, *19*, 356. Gschwend, H. W.; Rodriguez, H. R. *Org. React.* **1979**, *26*, 1. Beak, P.; Snieckus, V. *Acc. Chem. Res.* **1982**, *15*, 306. Snieckus, V. *Chem. Rev.* **1990**, *90*, 879.
(3) *Polyamine-Chelated Alkali Metal Compounds*; Langer, A. W., Jr., Ed.; American Chemical Society: Washington, 1974. Szwarc, M. *Carbanions, Living Polymers, and Electron-Transfer Processes*; Interscience: New York, 1968. Morton, M. *Anionic Polymerization: Principles and Practice*; Academic Press: New York, 1983. *Anionic Polymerization: Kinetics, Mechanism, and Synthesis*; McGrath, J. E., Ed.; American Chemical Society: Washington, 1981; Chapters 1, 2, and 29. Hsieh, H. L.; Quirk, R. P. *Anionic Polymerization: Principles and Practical Applications*; Marcel Dekker: New York, 1996.
(4) Collum, D. B. *Acc. Chem. Res.* **1992**, *25*, 448.
(5) (a) Rennels, R. A.; Maliakal, A. J.; Collum, D. B. *J. Am. Chem. Soc.* **1998**, *120*, 421. (b) Hoffmann, D.; Collum, D. B. *J. Am. Chem. Soc.* **1998**, *120*, 5810. (c) Chadwick, S. T.; Rennels, R. A.; Rutherford, J. L.; Collum, D. B. *J. Am. Chem. Soc.* **2000**, *122*, 8640. (d) Remenar, J. F.; Collum, D. B. *J. Am. Chem. Soc.* **1998**, *120*, 4081. (e) Remenar, J. F.; Lucht, B. L.; Kruglyak, D.; Collum, D. B. *J. Org. Chem.* **1997**, *62*, 5748. (f) Lucht, B. L.; Bernstein, M. P.; Remenar, J. F.; Collum, D. B. *J. Am. Chem. Soc.* **1996**, *118*, 10707.
(6) For leading references to investigations of selectivities of organolithium reactions from a mechanistic perspective, see: 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. For other recent examples, see: Arvidsson, P. I.; Davidsson, Ö. *Angew. Chem.* **2000**, *39*, 1467. Arvidsson, P. I.; Hilmersson, G.; Davidsson, Ö. *Chem.-Eur. J.* **1999**, *5*, 2348. Fressigne, C.; Corruble, A.; Valnot, J. Y.; Maddaluno, J.; Giessner-Prettre, C. *J. Organomet. Chem.* **1997**, *549*, 81. Sato, D.; Kawasaki, H.; Koga, K. *Chem. Pharm. Bull.* **1997**, *45*, 1399. Nudelman, N. S.; Schulz, H. G. *J. Chem. Soc., Perkin Trans. 2* **1999**, 2761.
(7) The assignments of $\mathbf{4_A}$ and $\mathbf{5_A}$ have been established previously.[8−10] Spectroscopic studies of *n*-BuLi solvated by a range of diamines have been communicated previously.[5b]
(8) For crystallographic studies of *n*-BuLi-TMEDA, see: (a) Nichols, M. A.; Williard, P. G. *J. Am. Chem. Soc.* **1993**, *115*, 1568. (b) Barnett, N. D. R.; Mulvey, R. E.; Clegg, W.; O'Neil, P. A. *J. Am. Chem. Soc.* **1993**, *115*, 1573. (c) Kottke, T.; Stalke, D. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 580.

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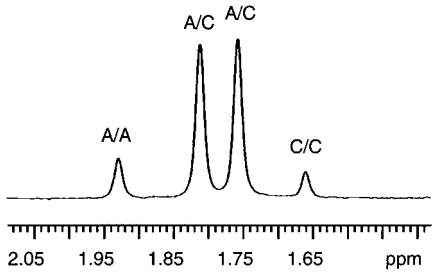
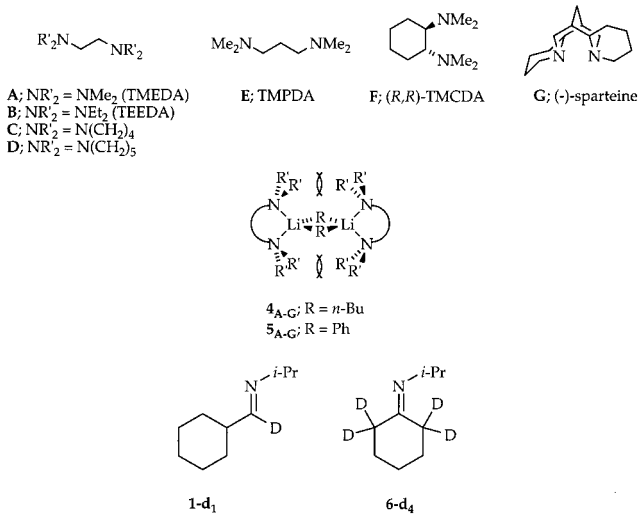


Figure 1. ^{6}Li NMR spectrum of a 0.10 M [^{6}Li]*n*-BuLi/toluene-d_8 solution containing 0.6 equiv of TMEDA (A) and 0.6 equiv of 1,2-dipyrrolidinoethane (C) at −100 °C. Labels refer to homosolvated (A/A = $\mathbf{4_A}$ and C/C = $\mathbf{4_C}$) and heterosolvated (A/C) *n*-BuLi dimer (**4**).

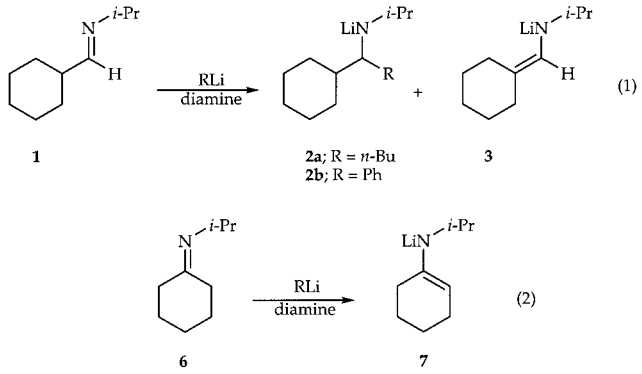
Chart 1



neither simple nor compelling. We attribute this in large part to the correlated solvation effects.[5b,11−13]

Results

NMR Spectroscopic Studies. NMR spectra and tables of spectral data of PhLi/diamine and *n*-BuLi/diamine mixtures are located in Supporting Information. The methods and strategies are illustrated and discussed below using *n*-BuLi.



^{13}C NMR spectra of toluene-d_8 solutions containing freshly recrystallized[5a,8c] [^{6}Li]*n*-BuLi (0.10 M)[17] and a diamine (**A**−**G**; 0.10−0.40 M)[17,18] at −70 °C reveal a single structural form (>20:1) in most cases.[19−21] The ^{13}C resonances corresponding to C_1 display multiplicities (quintets, $J^6_{Li-^{13}C} = 7-8$ Hz) and chemical shifts (δ 11.8−15.1 ppm) characteristic of cyclic dimers ($\mathbf{4_A}-\mathbf{4_G}$).[9] The free and coordinated diamines could be observed in the slow exchange limit using ^{13}C NMR spectroscopy in most instances.[19,21] The corresponding ^{6}Li NMR spectra display a single resonance in each case.[20,21] Samples containing excesses of two diamines display two new ^{6}Li resonances of a heterosolvate, (*n*-BuLi)$_2$SS′, along with one or both homosolvates, (*n*-BuLi)$_2$S$_2$ and (*n*-BuLi)$_2$S′$_2$ (Figure 1).[20]

In principle, the relative binding constants for a two-step solvent substitution (K_1 and K_2, eq 3) and the equilibrium constants for the complete solvent exchange (K_{tot}) could be determined for any pair of diamines by competing the two diamines for complexation to the organolithium dimer (eqs 3−6). However, the homosolvate containing two inferior

(9) For previous spectroscopic studies confirming the structure of *n*-BuLi-TMEDA ($\mathbf{4_A}$), see: Waldmüller, D.; Kotsatos, B. J.; Nichols, M. A.; Williard, P. G. *J. Am. Chem. Soc.* **1997**, *119*, 5479. Seebach, D.; Hässig, R.; Gabriel, J. *Helv. Chim. Acta* **1983**, *66*, 308. Also, see: Bauer, W.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1989**, *111*, 7191. 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: Phys. Sci.* **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.

(10) For excellent leading references to the structure and reactivity of PhLi, see: Reich, H. J.; Green, D. P.; Medina, M. A.; Goldenberg, W. S.; Gudmundsson, B. Ö.; Dykstra, R. R.; Phillips, N. H. *J. Am. Chem. Soc.* **1998**, *120*, 7201. Reich, H. J.; Goldenberg, W. S.; Gudmundsson, B. Ö.; Sanders, A. W.; Kulicke, K. J.; Simon, K.; Guzei, I. A. *J. Am. Chem. Soc.* **2001**, *123*, 8067.

(11) 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.

(12) For investigations of correlated phosphine binding to transition metals, see: Li, C.; Oliván, M.; Nolan, S.; Caulton, K. G. *Organometallics* **1997**, *16*, 4223 and references therein. Monodentate ethereal solvents display uncorrelated solvation of lithium amide dimers. Lucht, B. L.; Collum, D. B. *J. Am. Chem. Soc.* **1995**, *117*, 9863.

(13) For early discussions of steric effects on solvation and aggregation, see: Settle, F. A.; Haggerty, M.; Eastham, J. F. *J. Am. Chem. Soc.* **1964**, *86*, 2076. Lewis, H. L.; Brown, T. L. *J. Am. Chem. Soc.* **1970**, *92*, 4664. Brown, T. L.; Gerteis, R. L.; Rafus, D. A.; Ladd, J. A. *J. Am. Chem. Soc.* **1964**, *86*, 2135. For a more recent discussion and leading references, see: Lucht, B. L.; Collum, D. B. *J. Am. Chem. Soc.* **1996**, *118*, 2217.

(14) Recent 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.

(15) For examples of competitive 1,2-additions and α-lithiations of imines, see: Klusener, P. A. A.; Tip, L.; Brandsma, L. *Tetrahedron* **1991**, *47*, 2041.

(16) For leading references to the kinetics of LDA-mediated imine metalations, see ref 35.

(17) Concentrations of *n*-BuLi and PhLi refer to the total concentration (normality). Concentrations of the diamines refer to the concentrations of the free (uncomplexed) amine rather than to the total concentration.

(18) For leading bibliographies to diamines **A**−**G**, see ref 5b and f.

(19) Free and *n*-BuLi-coordinated solvent could not be completely resolved for solvents **E**, **F**, and **G**.

(20) (a) 1,2-Dipiperidinoethane (**D**) appeared to coordinate in several conformational forms corresponding to the chair−chair flip. For *n*-BuLi, the effect manifested only subtle broadening of the ^{6}Li resonances bearing coordinated **D**. In the case of PhLi, severe broadening of the resonance corresponding to dimer $\mathbf{5_D}$ implicated two or more of the *seven* possible conformational isomers. Mixed dimers (e.g., $\mathbf{5_{A/D}}$) displayed an additional resonance. In principle there are two resonances for each of *three* conformers, along with additional broadening, which provided additional support for conformational isomerism. Using 1,2-di(4-methylpiperidino)ethane, an analogue of **D** requiring an Li−N bond cleavage to achieve the equivalent of a chair−chair flip[20b] revealed the anticipated substantial spectral complexity. Detailed investigations of isomerism were precluded, however, by low solubilities of the PhLi complexes. The results underscore the complexities underlying piperidine-based solvents. (b) Lucht, B. L.; Collum, D. B. *J. Am. Chem. Soc.* **1994**, *116*, 7949.

(21) (a) Dimer $\mathbf{4_G}$ displays two resonances in a nearly 1:1 ratio, consistent with two possible orientations of sparteine. (b) On several occasions, one of the two heterosolvate ^{6}Li resonances was obscured by the resonance of the homosolvate. Adjustments of the solvent concentration confirm the location of the missing resonance, which could then be accounted for in the resonance integrations.

$$(RLi)_2S_2 + 2S' \overset{K_1}{\rightleftharpoons} (RLi)_2SS' + S + S' \overset{K_2}{\rightleftharpoons} (RLi)_2S'_2 + 2S \quad (3)$$

$$K_1 = \{[(RLi)_2SS'][S]\}/\{[(RLi)_2S_2][S']\} \quad (4)$$

$$K_2 = \{[(RLi)_2S'_2][S]\}/\{[(RLi)_2SS'][S']\} \quad (5)$$

$$K_{tot} = K_1K_2 = \{[(RLi)_2S'_2][S]^2\}/\{[(RLi)_2S_2][S']^2\} \quad (6)$$

solvents cannot always be observed, allowing only K_1 to be determined. To obtain K_2 and K_{tot}, the two solvents are competed under conditions in which the total solvent concentration is only slightly greater than the RLi concentration. The low total solvent concentration forces the coordination of *both* solvents irrespective of the relative solvent binding affinities, allowing $(RLi)_2S_2$, $(RLi)_2S'_2$, and $(RLi)_2SS'$ to be observed concomitantly and K′ to be determined from eqs 7 and 8. K_2 and K_{tot} can then be calculated using eqs 9−11. Formally, K′ is a measure of the

$$(RLi)_2S_2 + (RLi)_2S'_2 \overset{K'}{\rightleftharpoons} 2(RLi)_2SS' \quad (7)$$

$$K' = \{[(RLi)_2SS']^2\}/\{[(RLi)_2S_2][(RLi)_2S'_2]\} \quad (8)$$

$$K' = K_1/K_2 \quad (9)$$

$$K_{corr} = K'/4 \quad (10)$$

$$K_{tot} = (K_1)^2/4K_{corr} \quad (11)$$

extent that the solvation of the two sites is correlated. If only statistical factors are considered, however, $K_1 = 4K_2$ and $K' = 4$.[22] Consequently, we define a new constant, K_{corr} (eq 10), to describe *nonstatistical* preferences for heterosolvation. If no steric or electronic communication between the bound diamines occurs, $K_{corr} = 1$. Nonstatistical preferences for the hetero- or homosolvates would be reflected by $K_{corr} \neq 1$.

The key equilibrium constants, K_{corr} and K_{tot}, for the coordination of diamines to *n*-BuLi are summarized in Table 1. Values of K_{tot} are scaled relative to TMEDA (S = TMEDA, S′ = diamine). Analogous data of a more limited scope for PhLi[23] are summarized in Table 2. The substantial deviations of K_{corr} values from unity, implicating highly correlated solvation, ensure that structure−reactivity correlations will be complex.

Rate Studies of 1,2-Addition. The rates of the 1,2-addition of *n*-BuLi and PhLi to imine **1** (eq 1) were investigated by monitoring the loss of imine **1** (1667 cm^{-1}) using ReactIR spectroscopy.[24] Pseudo-first-order conditions were established by maintaining imine **1** at low concentrations (0.004−0.010 M) and the freshly recrystallized *n*-BuLi or PhLi and TMEDA at high, yet adjustable, concentrations using pentane as the cosolvent. The absence of competitive α-lithiation using *n*-BuLi was indicated by the lack of an absorbance at 1590−1610 cm^{-1}, which is characteristic of the lithiated imine.[25] The approximate 5% α-lithiation observed for PhLi/TMEDA should have little impact on the kinetics of 1,2-addition.[26] The rate equations for 1,2-additions by *n*-BuLi/TMEDA and PhLi/TMEDA are summarized in Table 3. The results for *n*-BuLi are emblematic, as described below.

Table 1. Relative Binding Constants and Free Energies of Solvation by Diamines **A**−**G** to *n*-BuLi Dimer **4**

		K_{corr}[b]						
ligand	$K_{tot}(\Delta G^\circ_{tot})$[a]	**A**	**B**	**C**	**D**	**E**	**F**	**G**
A (TMEDA)	1 (0)	1.0						
B (TEEDA)	2.2×10^{-4} (2.9)	30	1.0					
C	0.75 (0.1)	33	−[c]	1.0				
D	6.9×10^{-4} (2.5)	110	−[c]	0.9	1.0			
E (TMPDA)	1.2×10^{-3} (2.3)[d]	1.0	0.65	2.1	2.5	1.0		
F ((*R*,*R*)-TMCDA)	5.7 (−0.6)	1.1	13	20	50	1.1	1.0	
G ((−)-sparteine)	7.1×10^{-3} (1.7)	4.5	0.20	0.93	0.15	0.65	0.60	1.0

[a] Relative binding constants (K_{tot}) and binding energies (ΔG°_{tot}, kcal/mol) of diamines (S′) relative to TMEDA (S) were determined according to eqs 3−11 by competing TMEDA (**A**) against diamines **B**−**G** and are estimated to be ±10%. [b] Correlated binding constants (K_{corr}) were determined by competing combinations of ligands **A**−**G** as described in the text. [c] Complete overlap of the resonances of the homosolvates precluded determination of K_{corr}. [d] Exchange broadening was significant for *n*-BuLi/TMPDA/TMEDA. K_{tot} of TMPDA was determined by competing TMPDA (**E**) against TEEDA (**B**).

Table 2. Relative Binding Constants and Free Energies of Solvation by Diamines **A**−**G** to PhLi Dimer **5**

		K_{corr}[b]	
ligand	$K_{tot}(\Delta G^\circ_{tot})$[a]	**A**	**G**
A (TMEDA)	1 (0)	1	
B (TEEDA)	−[c]	8	2.0
C	6.1×10^{-4} (2.6)	2.3	3.3
D	−[c]	1.0	−[d]
E (TMPDA)	9×10^{-7} (4.7)	1.8	0.75
F ((*R*,*R*)-TMCDA)	3.9 (−0.46)	1.3[e]	3.8
G ((−)-sparteine)	4×10^{-4} (2.7)	48	1

[a] Relative binding constants (K_{tot}) and binding energies (ΔG°_{tot}, kcal/mol) of diamines (S′) relative to TMEDA (S) were determined according to eqs 3−11 by competing TMEDA (**A**) against diamines **B**−**G** and are estimated to be ±10%. [b] Correlated binding constants (K_{corr}) were determined by competing ligands against **A** or **G** as described in the text. [c] The poor binding affinities of **B** and **D** in competition with TMEDA caused formation of exclusively the TMEDA-solvated dimer $\mathbf{5_A}$. Competitions of **B** and **D** reveal **D** to be a substantially weaker ligand. [d] Severe broadening of peaks[20] precluded their assignment and determination of K_{corr}. [e] Overlapping resonances in the ^{6}Li NMR spectra mandated that K_{corr} be determined by ^{1}H NMR spectroscopy for the competition of ligand **F** with ligand **A**.

The loss of imine **1** follows clean first-order decay (Figure 2), affording pseudo-first-order rate constants (k_{obsd}) that are independent of the initial imine concentration. The formation of mixed aggregates (see below)[27] and other unforseen conversion dependencies were shown to not influence the rate by reestablishing the baseline at the end of a run, injecting a second aliquot of imine, and showing that the first and second rate constants are equivalent. A small inverse isotope effect determined by comparing k_{obsd} for imine **1** and imine $\mathbf{1}$-$\boldsymbol{d_1}$ (Table 3) is consistent with a rate-limiting addition to the C=N moiety.[28]

(22) 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.
(23) Reich, H. J.; Borst, J. P.; Dykstra, R. R.; Green, D. P. *J. Am. Chem. Soc.* **1993**, *115*, 8728.
(24) ASI Applied Systems, Millersville, MD 21108.
(25) Reaction of **1** with LDA afforded absorbances of lithiated imine **3** at 1590−1610 cm^{-1}.
(26) Kinetics of parallel reactions: Espenson, J. H. *Chemical Kinetics and Reaction Mechanisms*; McGraw-Hill: New York, 1995; pp 58−62.
(27) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1624. Seebach, D. *Proceedings of the Robert A. Welch Foundation Conferences on Chemistry and Biochemistry*; Wiley: New York, 1984.

Table 3. Reaction Orders and Deuterium Isotope Effects for the 1,2-Addition to Imine **1** (Eq 1) and α-Lithiation of Imine **6** (Eq 2)[a]

reagent	reaction	RLi order	TMEDA order[b]	KIE (k_H/k_D)[c]
n-BuLi/ TMEDA	1,2-addition	0.56(2)	0	0.7(1)
n-BuLi/ TMEDA	α-lithiation	0.57(4)	0	6.5(1)
PhLi/ TMEDA	1,2-addition	0.59(4)	0	0.7(1)
PhLi/ TMEDA	α-lithiation	0.61(7)	0	5.9(1)

[a] The *n*-BuLi orders were determined at −40 °C by maintaining an excess of 0.5 M TMEDA. The PhLi orders were determined in neat TMEDA (6.6 M) at 19 °C. [b] Inferred from plots of k_{obsd} versus [TMEDA] (cf., Figure 4). [c] The kinetic isotope effects (KIE; k_H/k_D) for the 1,2-additions were determined by co-injecting **1** and **1-*d*$_1$** in the same reaction vessel and monitoring their absorbances at 1665 and 1652 cm^{-1} (respectively). k_H/k_D ratios for the α-lithiations were determined by independently measuring the rate constants for **6** and **6-*d*$_4$**.

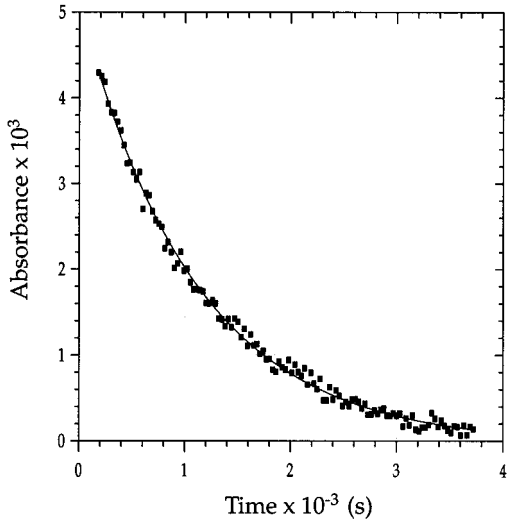


Figure 2. Loss of imine **1** (1667 cm^{-1}) at −40 °C in pentane with *n*-BuLi and TMEDA.

A plot of k_{obsd} versus [*n*-BuLi][17] shows a clean half-order dependence (Figure 3, Table 3). A corresponding plot of k_{obsd} versus [TMEDA] (Figure 4) reveals [TMEDA]-independent rates. The overall rate data are consistent with the idealized rate law described by eq 12 and monomer-based transition structures, [(RLi)(TMEDA)(**1**)]‡ (eq 13).

$$-\mathrm{d[imine]}/\mathrm{d}t = k'[\mathrm{imine}]^1[\mathrm{RLi}]^{1/2}[\mathrm{TMEDA}]^0 \quad (12)$$

$$\mathrm{imine} + {}^1/_2(\mathrm{RLi})_2(\mathrm{TMEDA})_2 \rightarrow [(\mathrm{RLi})(\mathrm{TMEDA})(\mathrm{imine})]^{‡} \quad (13)$$

Rate Studies of α-Lithiation. Using strategies analogous to those described in the previous section, detailed rate studies of the PhLi/TMEDA- and *n*-BuLi/TMEDA-mediated ketimine α-lithiation in eq 2 were carried out using ReactIR spectroscopy to monitor the loss of imine **6** (1661 cm^{-1}). Products attributable to 1,2-addition were detected by GC-MS analysis, but were minor (<10%). Substantial isotope effects determined by comparing k_{obsd} for imine **6** and imine **6-*d*$_4$** (Table 3) are consistent with a rate-limiting proton abstraction. Plots of k_{obsd} versus [RLi] show half-order dependencies (Table 3), whereas

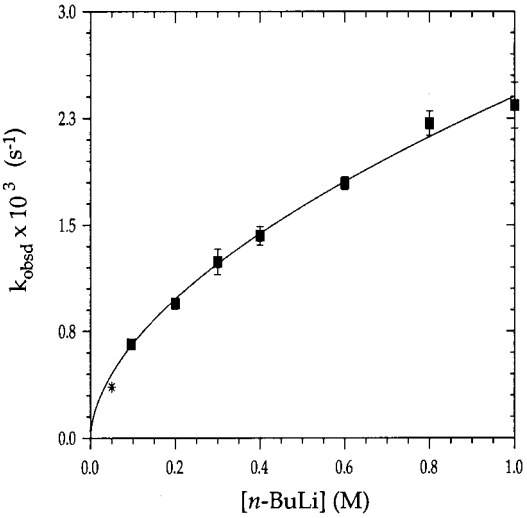


Figure 3. Plot of k_{obsd} vs [*n*-BuLi][17] for the 1,2-addition to imine **1** in TMEDA (0.5 M excess) and pentane at −40 °C. The curve depicts the result of an unweighted least-squares fit to $k_{obsd} = a[n\text{-BuLi}]^b$ ($a = 2.40(4) \times 10^{-3}$, $b = 0.56(2)$). The * was not included in the fit.

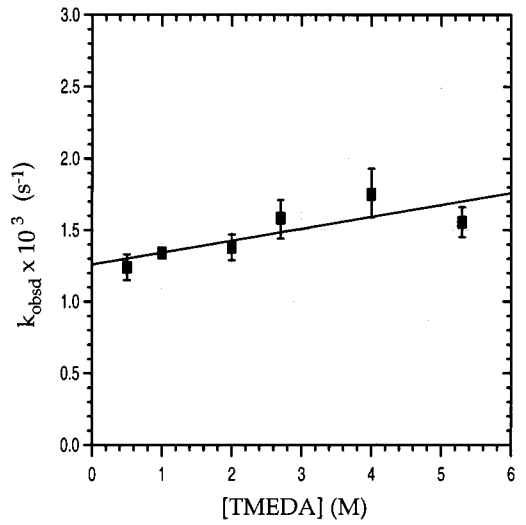


Figure 4. Plot of k_{obsd} vs [TMEDA][17] for the 1,2-addition of *n*-BuLi (0.3 M) to imine **1** in pentane at −40 °C. The curve depicts the result of an unweighted least-squares fit to $k_{obsd} = a[\mathrm{TMEDA}] + b$ ($a = 8(3) \times 10^{-5}$, $b = 1.26(9) \times 10^{-3}$).

plots of k_{obsd} versus [TMEDA] reveal essentially [TMEDA]-independent rates. In conjunction with the assignment of *n*-BuLi/TMEDA and PhLi/TMEDA as dimers $\mathbf{4_A}$ and $\mathbf{4_B}$ (respectively), the rate data are consistent with the idealized rate law described by eq 12 and monomer-based transition structures, [(RLi)(TMEDA)(**6**)]‡ (eq 13).

Relative Rate Constants. We measured the relative rate constants for 1,2-addition and α-lithiation using two independent methods. Table 4 describes the solvent-dependent selectivities for the reaction in eq 1. The high (>20:1) selectivities for *n*-BuLi are inferred from the absence of the lithiated imine **3** (detectable by the absorbance at 1590−1610 cm^{-1}).[25] In the case of PhLi, lithiated imine **3** was easily detected. The relative rate constants represent estimates obtained by integrating the area of the lithiated imine absorbance.[29] Cross-checks performed by quenching the reaction and monitoring the amine/imine ratio qualita-

(28) Carpenter, B. K. *Determination of Organic Reaction Mechanisms*; Wiley: New York, 1984.

(29) The PhLi reactions were run at slightly elevated concentrations of imine **1** (0.04 M) to improve the quantitation.

Table 4. Relative Rates of 1,2-Addition and α-Lithiation (**2:3**; Eq 1) for *n*-BuLi (−20 °C) and PhLi (19 °C) in Pentane[a]

ligand	*n*-BuLi	PhLi
A (TMEDA)	>20:1	20:1
B (TEEDA)	>20:1	20:1
C	>20:1	14:1
D	>20:1	6:1
E (TMPDA)	>20:1	20:1
F ((*R*,*R*)-TMCDA)	>20:1	2:1
G ((−)-sparteine)	>20:1	—[b]

[a] See text and Table 5 for further details. [b] PhLi/sparteine is insoluble in pentane.

Table 5. Relative Rate Constants (k_{rel}) for Diamine-Dependent 1,2-Additions (Eq 1) and α-Lithiations (Eq 2)

	n-BuLi[a]		PhLi[c]	
ligand	1,2-addition	α-lithiation	1,2-addition	α-lithiation
A (TMEDA)	15	22	5.1	15
B (TEEDA)	8.4	21	7.2	9.3[d]
C	1.0	1.9	1.0	16
D	2.7	6.5[b]	2.4	16[d]
E (TMPDA)	5.2	6.1	4.2	3.3
F ((*R*,*R*)-TMCDA)	7.9	7.9	9.8	23
G ((−)-sparteine)	4.4	16	—[e]	—[e]

[a] Measured at −20 °C with 0.1 M *n*-BuLi and 0.6 M (0.5 M excess) diamine in pentane. All *n*-BuLi values are scaled to the 1,2-addition with *n*-BuLi/**C** to maintain values greater than or equal to 1.0. [b] [**D**] = 0.4 M (excess). [c] Measured at 19 °C. Solubility problems required variations in the PhLi molarities and consequent scaling to 0.2 M assuming a half-order dependence: **A**, [PhLi] = 0.2 M; **B**, [PhLi] = 0.2 M; **C**, [PhLi] = 0.07 M; **D**, [PhLi] = 0.2 M (addition), 0.1 M (α-lithiation); **E**, [PhLi] = 0.2 M; **F**, [PhLi] = 0.1 M. The diamines were maintained at 0.5 M excess in pentane. All PhLi values are scaled to the 1,2-addition with PhLi/**C** to maintain values greater than or equal to 1.0. [d] Low concentrations of possible imine/PhLi precomplexes appear to form (1645−1655 cm^{-1}). [e] PhLi is insoluble in (−)-sparteine/pentane.

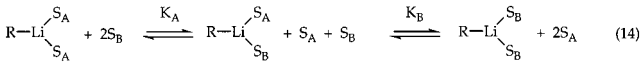
tively supported the general trends. Nonetheless, the ratios should be viewed as only approximate.

Using a distinctly different approach, we probed the solvent-dependent propensities for 1,2-addition and α-lithiation by monitoring the rate constants for the loss of imines **1** and **6** (eqs 1 and 2, respectively; Table 5). Although the results for *n*-BuLi are sound, the results for PhLi are complicated due to the competitive addition and α-lithiation of **1**,[26] solubility problems (requiring adjustments for concentration changes), and tacit evidence of substrate precomplexation for the poorly coordinating solvents.[30]

Discussion

Correlated Solvation: General Principles. The steric and electronic properties of a solvent influence the strength of the metal−solvent interactions; however, these intrinsic properties do not supersede solvent−substrate and solvent−solvent interactions. When one solvent influences the binding of another, their relative propensities to coordinate can be said to be *correlated*. The notion that solvation can be correlated is a critically important concept that has received limited attention in the organolithium literature to date.[11,31] Before discussing the chemistry of RLi-diamine complexes, it is instructive to consider four generic cases of correlated solvation.

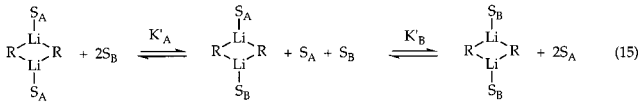
(1) Monomer Solvation. We illustrate the principle of correlated solvation using the serial substitution of the monomeric RLi in eq 14. If the two solvents are sterically and



(14)

electronically independent, the two substitutions corresponding to K_A and K_B are equally favorable except for a requisite statistical adjustment ($K_A/K_B = 4$).[22] (That is *not* to say that equimolar concentrations of S_A and S_B would afford a 1:2:1 mixture of the homo- and heterosolvates.) In the event that the three solvent−solvent interactions, S_A-S_A, S_A-S_B, and S_B-S_B, are *not* equivalent, however, the propensity of S_A or S_B to coordinate to the monomer would depend critically on the ancillary solvent ($K_A/K_B \neq 4$). Such correlated solvation influences the relative stabilities of the homo- and heterosolvates.

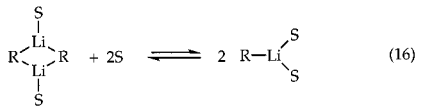
(2) Dimer Solvation. A serial solvent substitution on a dimer is illustrated in eq 15. As noted above, if the two solvents are



(15)

sterically and electronically insulated, the two solvent substitutions are equivalent except for the requisite statistical adjustment ($K'_A/K'_B = 4$).[22] Such uncorrelated solvation was observed for the ethereal solvation of lithium amide dimers.[31] If, however, the solvents interact strongly either sterically or electronically, then the propensity of any given solvent to coordinate depends on the structure of the ancillary solvent on the distal lithium. The heterosolvated dimer would display unusual stabilization or destabilization when compared to the homosolvated counterparts ($K'_A/K'_B \neq 4$).

(3) In the above examples, we used serial solvent substitutions and associated formation of mixed solvates to illustrate the principle of correlated solvation. Solvent−solvent interactions can be important in any instance in which there are two or more coordinated solvents on a complex. For example, if the solvent−solvent interactions in a dimer and monomer are different, the dimer−monomer distribution (eq 16) would display very complex solvent dependencies. Indeed, the exceptional depen-



(16)

dence of the lithium amide dimer−monomer ratios on the steric demands of the solvent was attributed to such solvent−solvent and solvent−amide interactions.[31]

(4) To the extent that solvent−solvent interactions may influence ground states and transition states to different degrees, correlated solvation would impact organolithium reactivities (as noted below.) Although the generic example illustrated in eq 17 is really a minor variant of the example in eq 16, unique substrate−solvent interactions in the transition structure not

(30) In several cases, mixtures of imine **1**, dimer **5**, and 0.5 M excess solvent displayed complex absorbances at 1645−1655 cm^{-1} distinct from the imine absorbance at 1661 cm^{-1}, consistent with limited precomplexation. Using no excess solvent yielded only a complex absorbance at 1645−1655 cm^{-1}.

(31) Lucht, B. L.; Collum, D. B. *J. Am. Chem. Soc.* **1995**, *117*, 9863. For other examples, see references cited in: Lucht, B. L.; Collum, D. B. *Acc. Chem. Res.* **1999**, *32*, 1035.

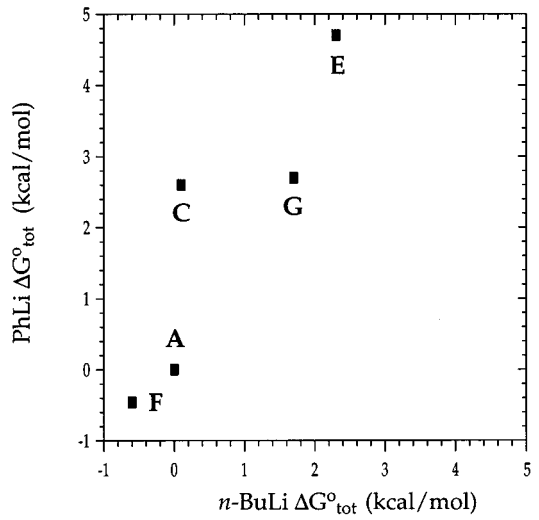
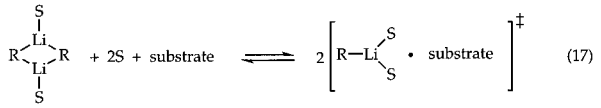


Figure 5. Plot of ΔG°_{tot} (corresponding to K_{tot}) for PhLi (eqs 3−11) vs the analogous ΔG°_{tot} for *n*-BuLi coordinated by diamines (as labeled).

found in the ground state (at least as drawn)[32] introduce added complexities. The important inference is that correlated solvation

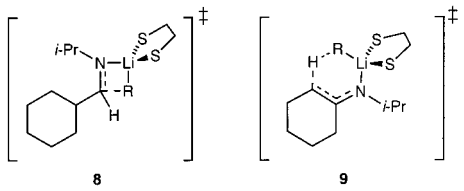


will render structure−reactivity relationships complex almost by definition.

Correlated Solvation: *n*-BuLi- and PhLi-Diamine Complexes. Investigations of *n*-BuLi and PhLi (**4** and **5**, respectively) in mixtures of diamines (**A**−**G**; eqs 3−11) revealed substantial correlated solvation. We defined a new constant, $K_{corr} = K_1/4K_2$ (eq 10), in which deviations from unity reflect the uniqueness of solvent−solvent interactions. The results from Tables 2 and 3 reveal up to a 100-fold correlated binding, attesting to the importance of solvent−solvent interactions in dimers **4** and **5**. Although stabilization of the heterosolvates appears to be fostered by bulky solvents such as *N*,*N*,*N*′,*N*′-tetraethylethylenediamine (TEEDA; **B**), anomalous stabilizations of the homosolvates found for several combinations underscore the deep-seated complexities.

It is instructive to consider what the relative binding constants *do not* reveal. Sifting through values of K_1, K_2, K_{tot}, and K_{corr} (eq 3, 7−11; Tables 1 and 2),[33] we find that compelling relationships are almost nonexistent. For example, a seemingly straightforward plot of the free energies corresponding to K_{tot} for *n*-BuLi and PhLi (Figure 5) reveals a modest trend at best. Alternatively, one might be tempted to adopt another constant, such as K_1 (eqs 3 and 4), as a measure of binding affinity.[33] Once again, however, the free energies corresponding to K_1 for *n*-BuLi and PhLi are only marginally related. The problem is not the data per se, but rather the unique transannular solvent−solvent and RLi−solvent interactions (cf. $\mathbf{4}_{\mathbf{A-G}}$ and $\mathbf{5}_{\mathbf{A-G}}$) that combine to afford highly correlated solvation effects. The strength of any metal−solvent interaction derives from an ensemble of van der Waals interactions within the coordination sphere,[34] rendering seemingly simple questions about relative solvation energies invalid. You cannot even qualitatively order the solvents from weakest to strongest, for example, because such an ordering depends critically on which ancillary diamine defines the "standard state" and whether K_1, K_2, or K_{tot} defines the measure of binding affinity.

Mechanisms of 1,2-Additions and α-Lithiations. To study the origins of the 1,2-additions and α-lithiations in eq 1, we elucidated the underlying mechanism(s). A fully comprehensive investigation of all organolithium−diamine combinations was not practical. Nonetheless, rate studies of the 1,2-addition (eq 1) and α-lithiation (eq 2) using both *n*-BuLi/TMEDA and PhLi/TMEDA revealed a notable mechanistic homology: All four reactions proceed via isomeric rate-limiting transition structures, [(RLi)(TMEDA)(imine)]‡. Transition structures **8** and **9** are plausible based on limited computational studies[35] and are well within the confines of conventional wisdom. In principle, the compelling structural homologies of the reactants and transition structures, in conjunction with the zeroth-order solvent dependencies, provided an optimal template to explore how the solvent influences reactivity. In practice, it is not that simple.



Structure−Reactivity Relationships. We plotted dozens of possible structure and reactivity relationships stemming from comparisons of (1) two organolithiums (*n*-BuLi and PhLi), (2) four solvent binding constants (K_1, K_2, K_{tot}, and K_{corr}; Tables 1 and 2), and (3) relative rate constants for 1,2-addition and α-lithiation (Tables 1 and 5). We surveyed all combinations of solvent-dependent free energies corresponding to $K_{1(PhLi)}$, $K_{2(PhLi)}$, $K_{tot(PhLi)}$, $K_{corr(PhLi)}$, $K_{1(n-BuLi)}$, $K_{2(n-BuLi)}$, $K_{tot(n-BuLi)}$, $K_{corr(n-BuLi)}$, $k_{rel(PhLi)}$, and $k_{rel(n-BuLi)}$ from Tables 1, 2, 3, and 5. We included even those that would appear to make little sense (the free energies corresponding to $K_{corr(n-BuLi)}$ vs $k_{rel(n-BuLi)}$, for example). These plots can all be reproduced from the available data. At the outset, the complexities caused by correlated solvation of the RLi dimers suggested that the structure−reactivity relationships could not possibly be simple. Moreover, putative relationships of reactivity with solvation energies of the reactants implicitly include two potentially invalid assumptions: (1) Solvation of the reactants and transition structures are necessarily related, and (2) transition structures are disproportionately stabilized by solvation when compared to the reactants. Among the many comparisons culled from the data, most afforded scatter. We mention two that afforded some semblence of a trend.

(1) It is often suggested that reactivities should increase with increasing solvation energies. Figure 6 shows that the relative activation energies for the 1,2-addition of *n*-BuLi to imine **1**, solvent-dependent to some extent, do not increase with increas-

(32) Precomplexation of the substrate would introduce solvent−substrate interactions in the ground state.
(33) K_1 and K_2 can be calculated from the values of K_{corr} and K_{tot} in Tables 2 in 3 according to eqs 9−11.
(34) For a discussion of steric effects in the context of transition metal ligation, see: Seligson, A. L.; Trogler, W. C. *J. Am. Chem. Soc.* **1991**, *113*, 2520. Choi, M.-G.; Brown, T. L. *Inorg. Chem.* **1993**, *32*, 1548.
(35) Romesberg, F. E.; Collum, D. B. *J. Am. Chem. Soc.* **1995**, *117*, 2166.

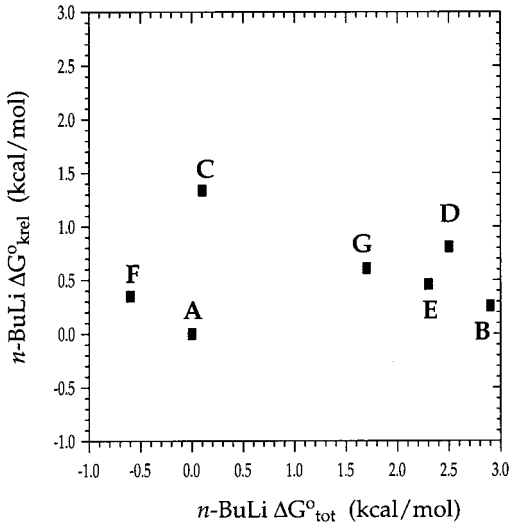


Figure 6. Plot of $\Delta G°_{krel}$ (=$-RT$ ln k_{rel}; Table 5) for the 1,2-addition of *n*-BuLi to imine **1** vs $\Delta G°_{tot}$ (corresponding to K_{tot}) for *n*-BuLi coordinated for diamines **A**−**G** (as labeled). In contrast to the values in Table 5, $\Delta G°_{krel}$ values are normalized to TMEDA.

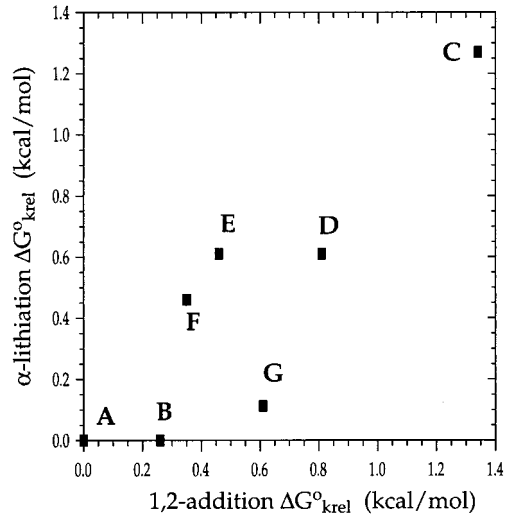


Figure 7. Plot of $\Delta G°_{krel}$ (=$-RT$ ln k_{rel}; Table 5) for the 1,2-addition of *n*-BuLi to imine **1** vs $\Delta G°_{krel}$ for the α-lithiation of imine **6** by *n*-BuLi for diamines A−G (as labeled). In contrast to the values in Table 5, the values for $\Delta G°_{krel}$ are scaled to TMEDA within each reaction type.

ing solvation energy as defined by K_{tot}.[36] Clearly, there is no evidence that stronger solvents afford higher reactivities. In fact, solvent-independent rates might be expected given that the zeroth-order dependencies on solvent concentration should cause the solvation effects in the reactants and transition structures largely to cancel. (2) One might expect parallel behaviors of *n*-BuLi and PhLi. For example, Figure 7 shows that there may be solvation effects common to the 1,2-addition and α-lithiation, but the trend is marginal at best.

The relative propensities of RLi-diamine complexes to undergo metalation and lithiation reactions via *isomeric* transition structures **8** and **9** and the importance of specific (unique) solvent−substrate and solvent−solvent interactions called for a computational study. Unfortunately, RLi-diamine dimers (**4** $_{A-G}$ and $\mathbf{5}_{A-G}$) and putative transition structures (**8** and **9**) proved too large and congested for the sterically sensitive semiempirical methods and computationally intensive Hartree−Fock ab initio methods. Simplifying the systems would strip them of the key van der Waals interactions that cause the solvent-dependencies.

Conclusion

We have previously questioned the veracity of the often-cited relationships of organolithium aggregation, solvation, and reactivity.[4] Contrary to popular opinion, strongly coordinating solvents do not necessarily promote deaggregation, elicit deaggregation, or impart high reactivities.[4,37] We describe herein the structures and reactivities of *n*-BuLi and PhLi solvated by seven structurally related diamines, $(RLi)_2(solvent)_2$ ($\mathbf{4}_{A-G}$ and $\mathbf{5}_{A-G}$). Rate studies of the 1,2-additions and α-lithiations of imines (eq 1 and 2) implicated monomer-based transition structures (such as **8** and **9**). Despite the strong structural and mechanistic homologies, however, no simple structure−reactivity relationships were culled from the plethora of relative binding and rate constants. Although this result may be unsettling to some, in retrospect it seems unreasonable to expect that simple structure−reactivity relationships could emerge from systems in which the dominant van der Waals interactions between the solvent, the organolithium, and the organic substrate are unique to each combination.

Experimental Section

Reagents and Solvents. All solvents were 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 [^{6}Li]*n*-BuLi and [^{6}Li]PhLi were prepared and purified by crystallization according to literature procedures.[5a,8c,23] *n*-BuLi used for the rate studies was purchased from Acros and recrystallized from pentane solutions.[5a,8c] The PhLi used for the rate studies was prepared and purified as noted previously.[23] The diamines were prepared and purified using literature protocols.[5f] Imine substrates and their deuterated analogues were synthesized according to generalized literature procedures.[38] The diphenylacetic acid used to check solution titers[39] was recrystallized from MeOH and sublimed at 120 °C under full vacuum. Moisture-sensitive materials were manipulated under argon or nitrogen using standard glovebox, vacuum line, and syringe techniques.

NMR Spectroscopic Analyses. Methods for preparing NMR spectroscopic samples and for recording spectra have been described in detail.[5a]

IR Spectroscopic Analyses. IR spectra were recorded using a ReactIR 1000 from ASI Applied Systems[24] fitted with a 30-bounce silicon-tipped (SiComp) probe.[40] Rate constants were usually measured in duplicate and averaged. The secondary isotope effects derived for the 1,2-addition were determined by co-injecting imines **1** and **1-*d*$_1$** and monitoring the losses of their absorbances at 1667 cm^{-1} and 1653

(36) A qualitatively similar plot is obtained when solvation energy is compared to the relative activation energies for *n*-BuLi-mediated α-lithiation of imine **6**.

(37) For three examples from our lab as well as leading references, see: (a) Sun, X.; Collum, D. B. *J. Am. Chem. Soc.* **2000**, *122*, 2452. (b) Lucht, B. L.; Collum, D. B. *J. Am. Chem. Soc.* **1995**, *117*, 9863. (c) Bernstein, M. P.; Collum, D. B. *J. Am. Chem. Soc.* **1993**, *115*, 8008.

(38) Deuterated imine **1-*d*$_1$** was prepared from cyclohexane carboxylic acid as follows: (1) $LiAlD_4$ reduction, (2) pyridinium chlorochromate/CH_2Cl_2 oxidation, and (3) *i*-$PrNH_2$ condensation. Deuterated imine **6-*d*$_4$** was prepared as described previously.[37c]

(39) Kofron, W. G.; Baclawski, L. M. *J. Org. Chem.* **1976**, *41*, 1879.

(40) The device and protocol for carrying out kinetics using a ReactIR 1000 spectrometer were described previously.[37a]

cm^{-1}, respectively, to minimize experimental error.[41] The primary isotope effects for the α-lithiations were ascertained by measuring the rate constants for **6** and **6-*d*$_4$** in separate experiments.

Acknowledgment. We thank the National Science Foundation for direct support of this work. We acknowledge Boehringer-Ingelheim for partial support of J.L.R. 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.

(41) Wang, Y.; Poirier, R. A. *J. Phys. Chem. A* **1997**, *101*, 907. Reimers, J. R.; Hall, L. E. *J. Am. Chem. Soc.* **1999**, *121*, 3730.

Supporting Information Available: ^{6}Li and ^{13}C NMR spectra of *n*-BuLi, rate data for the 1,2-additions of aldimines and α-lithiations of ketimines, and general experimental protocols (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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