

## Synthesis of [<sup>15</sup>N,<sup>15</sup>N']-N,N,N',N'-Tetramethylethylenediamine and Its Use in Solvation Studies of [<sup>6</sup>Li]-*n*-Butyllithium

Delia Waldmüller,<sup>†</sup> Barbara J. Kotsatos,<sup>‡</sup>  
Michael A. Nichols,<sup>\*,‡</sup> and Paul G. Williard<sup>\*,†</sup>

Department of Chemistry, Brown University  
Providence, Rhode Island 02912-9000  
Department of Chemistry, John Carroll University  
University Heights, Ohio 44118

Received February 21, 1997

*N,N,N',N'*-Tetramethylethylenediamine (TMEDA) is widely used as a ligand or cosolvent in organic syntheses, particularly when organolithium reagents are involved.<sup>1</sup> TMEDA has been shown to improve product yields, alter product distributions and increase reaction rates primarily through solvation and chelation of the lithium cations.<sup>1a</sup> In order to elucidate the exact mechanisms by which these reactions take place, methods which permit the direct observation of the solvation of organolithium bases such as lithium amides and alkyllithium compounds must be developed and employed. While <sup>6</sup>Li, <sup>15</sup>N, <sup>13</sup>C, and <sup>31</sup>P NMR techniques have been used to directly determine the aggregation states of lithium amides<sup>1a,b,2</sup> and alkyllithium compounds<sup>1c,3</sup> and their solvation by hexamethylphosphoramide (HMPA),<sup>4</sup> relatively few NMR studies have been reported using an [<sup>15</sup>N]-labeled ligand, either covalently attached to the organolithium compound<sup>2f,4a</sup> or as a free ligand in solution,<sup>5</sup> to directly observe solvation of the lithium cation. Herein, we report the synthesis

<sup>†</sup> Brown University.

<sup>‡</sup> John Carroll University.

\* Author to whom all correspondence should be sent: M. A. Nichols, John Carroll University.

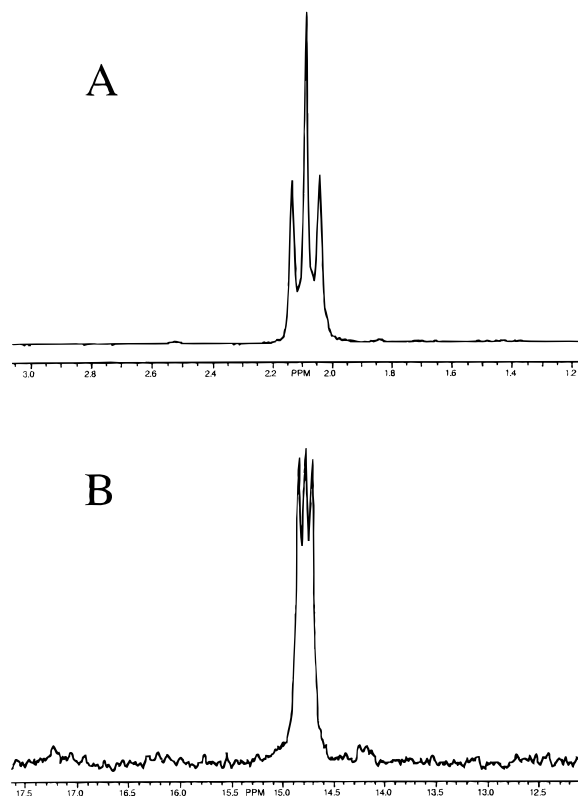
(1) (a) For leading references and a historical discussion of TMEDA's use in organolithium chemistry, see: Collum, D. B. *Acc. Chem. Res.* **1992**, *25*, 448–54. (b) Lucht, B. L.; Bernstein, M. P.; Remenar, J. E.; Collum, D. B. *J. Am. Chem. Soc.* **1996**, *118*, 10707–18 and references therein. (c) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1624 and references therein. (d) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879.

(2) (a) Collum, D. B. *Acc. Chem. Res.* **1993**, *26*, 227–234 and references therein. (b) Wanat, R. A.; Collum, D. B.; Van Duyne, G.; Clardy, J.; DePue, R. T. *J. Am. Chem. Soc.* **1986**, *108*, 3415. (c) Jackman, L. M.; Scarmoutzos, L. M. *J. Am. Chem. Soc.* **1987**, *109*, 5348–55. (d) Sugawara, K.; Shindo, M.; Noguchi, H.; Koga, K. *Tetrahedron Lett.* **1996**, *37*, 7377–80. (e) Hilmersson, G.; Davidsson, O. *J. Org. Chem.* **1995**, *60*, 7660–9. (f) Sato, D.; Kawasaki, H.; Shimada, I.; Arata, Y.; Okamura, K.; Date, T.; Koga, K. *J. Am. Chem. Soc.* **1992**, *114*, 761–3.

(3) (a) Bauer, W. *J. Am. Chem. Soc.* **1996**, *118*, 5450–5. (b) For leading references to this group's work, see: Bauer, W.; Schleyer, P. v. R. In *Advances in Carbanion Chemistry*; Snieckus, V., Ed.; JAI: New York, 1992; p 89. (c) For leading references to this group's work, see: Guenther, H.; Eppers, O.; Hausmann, H.; Huels, D.; Mons, H.-E.; Klein, K.-D.; Maercker, A. *Helv. Chim. Acta* **1995**, *78*, 1913–32. (d) For leading references to this group's work, see: DeLong, G. T.; Pannell, D. K.; Clarke, M. T.; Thomas, R. D. *J. Am. Chem. Soc.* **1993**, *115*, 7013–7014. (e) For leading references to this group's work, see: Fraenkel, G.; Martin, K. V. *J. Am. Chem. Soc.* **1995**, *117*, 10336. (f) Seebach, D.; Gabriel, J.; Hassig, R. *Helv. Chim. Acta* **1984**, *67*, 1083–99. (g) Seebach, D.; Hassig, R.; Gabriel, J. *Helv. Chim. Acta* **1983**, *66*, 308–37. (h) Gunther, M.; Moskau, D.; Bast, P.; Schmalz, D. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1212.

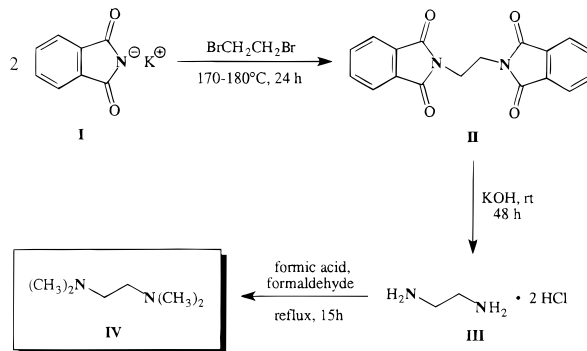
(4) (a) Reich, H. J.; Gudmundsson, B. O. *J. Am. Chem. Soc.* **1996**, *118*, 6074–5. (b) Reich, H. J.; Borst, J. P.; Dykstra, R. R.; Green, D. P. *J. Am. Chem. Soc.* **1993**, *115*, 8728–41. (c) Jackman, L. M.; Chen, X. *J. Am. Chem. Soc.* **1992**, *114*, 403–11. (d) Riech, H. J.; Borst, J. P. *J. Am. Chem. Soc.* **1991**, *113*, 1835–7. (e) Riech, H. J.; Green, D. P. *J. Am. Chem. Soc.* **1989**, *111*, 8729–31. (f) Romesberg, F. E.; Bernstein, M. P.; Gilchrist, J. H.; Harrison, A. T.; Fuller, D. J.; Collum, D. B. *J. Am. Chem. Soc.* **1993**, *115*, 3475–83. (g) Romesberg, F. E.; Gilchrist, J. H.; Harrison, A. T.; Fuller, D. J.; Collum, D. B. *J. Am. Chem. Soc.* **1991**, *113*, 5751–7. (h) Barr, D.; Doyle, M. J.; Mulvey, R. E.; Raithby, P. R.; Reed, D.; Snaith, R.; Wright, D. S. *J. Chem. Soc., Chem. Commun.* **1989**, 318. (i) Raithby, P. R.; Reed, D.; Snaith, R.; Wright, D. S. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1011.

(5) (a) Lucht, B. L.; Collum, D. B. *J. Am. Chem. Soc.* **1996**, *118*, 3529–30. (b) Lucht, B. L.; Collum, D. B. *J. Am. Chem. Soc.* **1996**, *118*, 2217–25. (c) Falcone, M. A. M.S. Thesis, John Carroll University, University Heights, OH 44118, 1996.



**Figure 1.** NMR spectra for a 0.14 M [<sup>6</sup>Li]-*n*-BuLi solution in the presence of 1.1–1.2 equiv of [<sup>15</sup>N,<sup>15</sup>N']TMEDA in toluene-*d*<sub>8</sub> at –110 °C: (A) <sup>6</sup>Li NMR spectrum; (B) <sup>15</sup>N NMR spectrum. The <sup>6</sup>Li–<sup>15</sup>N coupling constant is 2.0 Hz in each spectrum. Line broadening of 0 Hz was applied to each spectrum. The <sup>6</sup>Li (44.15 MHz) and <sup>15</sup>N (30.408 MHz) NMR spectra are referenced to external 0.02 M [<sup>6</sup>Li]OCD<sub>3</sub>/CD<sub>3</sub>-OD ( $\delta = 0$  ppm) and 98% aniline/DMSO-*d*<sub>6</sub> ( $\delta = 50$  ppm) solutions, respectively.<sup>9</sup>

**Scheme 1.** The Synthesis of [<sup>15</sup>N,<sup>15</sup>N']TMEDA (**IV**) from [<sup>15</sup>N]Potassium Phthalimide (**I**) Where All Nitrogen Atoms Are [<sup>15</sup>N]-labeled (98%)<sup>9</sup>



of [<sup>15</sup>N,<sup>15</sup>N']TMEDA and its use in the solvation studies of [<sup>6</sup>Li]-*n*-butyllithium (*n*-BuLi) in toluene-*d*<sub>8</sub> at –110 °C using <sup>6</sup>Li and <sup>15</sup>N NMR.

We prepared [<sup>15</sup>N,<sup>15</sup>N']TMEDA in three steps starting from [<sup>15</sup>N]potassium phthalimide,<sup>6</sup> **I**, which was reacted with 1,2-dibromoethane at 170–180 °C for 12 h to yield [<sup>15</sup>N,<sup>15</sup>N']-diphthalimidoethane, **II** (Scheme 1).<sup>7</sup> Alkaline hydrolysis of **II** lead to [<sup>15</sup>N,<sup>15</sup>N']ethylenediamine (EDA), which was subsequently isolated as the [<sup>15</sup>N,<sup>15</sup>N']EDA·2HCl salt, **III**. The key

(6) Purchased from Aldrich Chemical Co.; 98% isotopic enrichment.

(7) Modified from the reported procedure: Salzberg, P. L.; Supniewski, J. W. *Organic Syntheses*; Wiley: New York, 1941; Collect. Vol. I, pp 119–21. Other procedures have been published, see: Soai, K.; Ookawa, A.; Kato, K. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 1671–72. Landini, D.; Rolla, F. *Synthesis* **1976**, *6*, 389–91.

step is the Eschweiler–Clarke<sup>8</sup> methylation of [<sup>15</sup>N,<sup>15</sup>N']-IV with formaldehyde in formic acid to yield the desired [<sup>15</sup>N,<sup>15</sup>N']-TMEDA, IV, in 11% overall percent yield from [<sup>15</sup>N]-I.<sup>9</sup>

Figure 1 shows the <sup>6</sup>Li NMR (A) and <sup>15</sup>N NMR (B) spectra recorded for a 0.14 M solution of [<sup>6</sup>Li]-*n*-BuLi<sup>10</sup> in the presence of 1.1–1.2 equiv of [<sup>15</sup>N,<sup>15</sup>N']TMEDA. The spectra were recorded at –110 °C in toluene-*d*<sub>8</sub>, and both spectra clearly depict triplets<sup>11</sup> having <sup>6</sup>Li–<sup>15</sup>N coupling constants of 2.0 Hz.<sup>12</sup> The splitting of the <sup>15</sup>N (1:1:1) and <sup>6</sup>Li resonances (1:2:1) leads unambiguously to the conclusion that each <sup>6</sup>Li cation is attached to two <sup>15</sup>N atoms, while each <sup>15</sup>N amine atom is attached to only one <sup>6</sup>Li cation. The coupling pattern and the observation of only one <sup>15</sup>N resonance strongly suggests that TMEDA must be chelating the <sup>6</sup>Li cations in a dimeric aggregate having a similar structure to our reported (*n*-BuLi·TMEDA)<sub>2</sub> X-ray crystal structure.<sup>13</sup> The <sup>13</sup>C NMR resonance of the α-carbon of [<sup>6</sup>Li]-*n*-BuLi was broad and was not the resolved pentuplet predicted from the <sup>6</sup>Li–<sup>13</sup>C coupling for a dimeric aggregate.<sup>11</sup> Two explanations can be proposed: long-range coupling of a TMEDA <sup>15</sup>N nucleus to the α-<sup>13</sup>C nucleus through the <sup>6</sup>Li nucleus and/or slow interaggregate exchange due to the low temperature used (–110 °C).<sup>14</sup> When an identical [<sup>6</sup>Li]-*n*-BuLi

sample in toluene-*d*<sub>8</sub> containing unlabeled TMEDA was analyzed at –110 °C, the appearance of the α-<sup>13</sup>C resonance of *n*-BuLi was identical to the one obtained using the [<sup>15</sup>N,<sup>15</sup>N']-TMEDA. Therefore, no long-range <sup>15</sup>N–<sup>13</sup>C coupling is occurring. Evidence of slow interaggregate exchange was obtained when the sample was warmed to –96 or –78 °C; the broad α-<sup>13</sup>C resonance sharpened to yield a well-resolved pentuplet having a <sup>6</sup>Li–<sup>13</sup>C coupling constant of 8.1 Hz, which is in agreement with previous <sup>13</sup>C,<sup>6</sup>Li NMR solution studies of *n*-BuLi, where dimers were observed in hydrocarbon solutions in the presence of TMEDA.<sup>3g,15</sup> The future use of [<sup>15</sup>N,<sup>15</sup>N']-TMEDA to probe solvation of other organolithium compounds will undoubtedly provide further insight into the solution structures and reactivities of important organolithium compounds and those results will be reported in due course.<sup>16</sup>

**Acknowledgment.** This work was supported by the National Institutes of Health through grant GM-35980 to P.G.W. Funding was also provided to M.A.N. through a Summer Research Fellowship from the JCU Graduate School and to B.J.K. in the form of a BP America Summer Undergraduate Research Fellowship. A Kresge Science Initiative Grant was used to purchase the NMR and GC/MS instruments at JCU.

**Supporting Information Available:** Experimental syntheses and spectral characterization data for compounds II–IV and NMR spectra from the [<sup>6</sup>Li]-*n*-BuLi·[<sup>15</sup>N,<sup>15</sup>N']TMEDA experiment (18 pages). See any current masthead page for ordering and Internet access instructions.

JA970557N

(15) Solid-state NMR (CP/MAS) studies of TMEDA and alkyl lithium compounds have been reported, see: Baumann, W.; Oprunenko, Y.; Guenther, H. Z. *Naturforsch. A* **1995**, *50*, 429.

(16) When solutions of [<sup>6</sup>Li]-*n*-BuLi containing less than 1 equiv of [<sup>15</sup>N,<sup>15</sup>N']TMEDA are analyzed using <sup>6</sup>Li and <sup>15</sup>N NMR, both spectra are extremely complicated. When 2 equiv of [<sup>15</sup>N,<sup>15</sup>N']TMEDA is present, the spectra are essentially the same as that seen in Figure 1, with some line broadening due to increased ligand exchange. The <sup>6</sup>Li triplet can be resolved using resolution enhancement. In contrast, when an excess of an [<sup>15</sup>N]monodentate ligand is added to a [<sup>6</sup>Li,<sup>15</sup>N]lithium amide, all <sup>6</sup>Li–<sup>15</sup>N coupling is lost: see ref 5b,c.

(8) (a) McElvain, S. M.; Bannister, L. W. *J. Am. Chem. Soc.* **1954**, *76*, 1126. (b) Clarke, H. T.; Gillespie, H. B.; Weisshaus, S. Z. *J. Am. Chem. Soc.* **1933**, *55*, 4571.

(9) See the Supporting Information for the synthetic details and spectral characterization of II–IV and <sup>1</sup>H, <sup>13</sup>C, <sup>6</sup>Li, and <sup>15</sup>N NMR spectra for the [<sup>6</sup>Li]-*n*-BuLi·[<sup>15</sup>N,<sup>15</sup>N']TMEDA solution in toluene-*d*<sub>8</sub> at –110 °C.

(10) Synthesized by the “sono-reflux” of 1-chlorobutane with <sup>6</sup>Li metal (obtained from Oak Ridge National Laboratories). For a similar procedure, see: Arnett, E. M.; Fisher, F. J.; Nichols, M. A.; Ribeiro, A. A. *J. Am. Chem. Soc.* **1990**, *112*, 801–8.

(11) The coupling of the <sup>6</sup>Li and <sup>15</sup>N (or <sup>13</sup>C) resonances is governed by the equation  $2nI + 1$ , where  $n = 1$  for <sup>6</sup>Li and  $1/2$  for <sup>15</sup>N (or <sup>13</sup>C). The coupling of <sup>6</sup>Li and <sup>15</sup>N has been discussed in ref 2a.

(12) Previously reported <sup>15</sup>N–<sup>6</sup>Li coupling constants for chelating and solvating amine groups range from 1.3 to 3.7 Hz. See refs 2f, 4a, and 5.

(13) Nichols, M. A.; Williard, P. G. *J. Am. Chem. Soc.* **1993**, *115*, 11568–72.

(14) We thank a reviewer for these suggestions.