

## Mixed Aggregates Containing *n*-Butyl-, *sec*-Butyl-, or *tert*-Butyllithium and a Chiral Lithium Amide Derived from *N*-Isopropyl-*O*-methyl Valinol

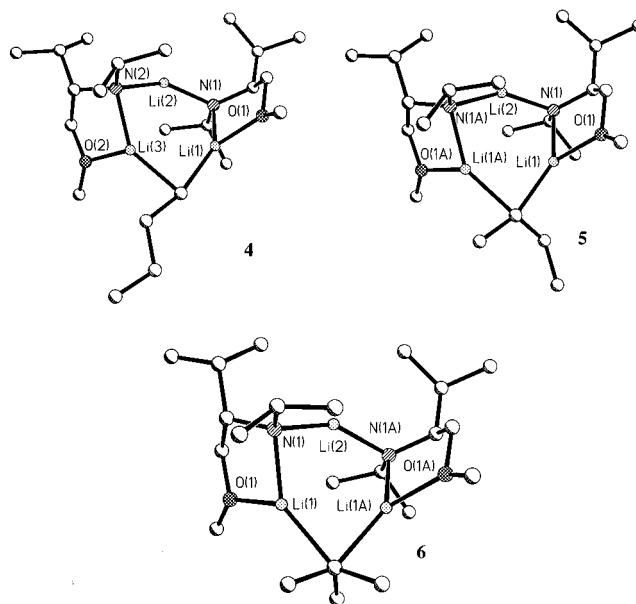
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Received July 9, 1997

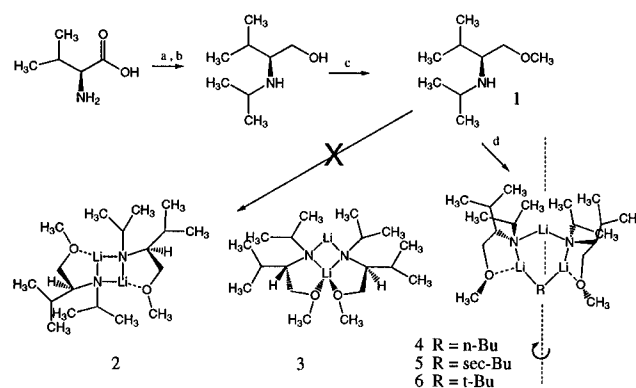
Commercially available alkyllithium reagents play a major role in many chemical reactions spanning the range from small scale synthetic applications up to large scale industrial processes. This is due to their reactivity as both strong bases and as nucleophiles. They remain reagents of choice in synthetic organic chemistry for generation of a wide variety of carbanions, amide anions derived from primary and secondary amines, and alkoxides. Consequently, it is not surprising that much effort has been expended in characterizing the structure of these important reagents both in solution<sup>1</sup> and in the solid state.<sup>2</sup> Within the past few years several different forms of *n*-butyllithium have been characterized by X-ray diffraction analysis. Extant *n*-BuLi structures include the following: an unsolvated hexamer;<sup>2a</sup> tetrameric aggregates solvated by 4 equiv of THF,<sup>2b</sup> by 4 equiv of DME, or by 1 equiv of TMEDA;<sup>2b,c</sup> and a dimer solvated by 2 equiv of TMEDA.<sup>2b</sup> Three additional structures of mixed aggregates containing *n*-butyllithium/lithium *tert*-butoxide,<sup>2d</sup> *n*-butyllithium/2,6-bis(dimethylamino)methyl-3,5-dimethylbenzyl lithium,<sup>2e</sup> and *n*-butyllithium/lithium diphenyl amide/aryl lithium<sup>2f</sup> are also known. Only a relatively few *t*-BuLi containing structures have been characterized crystallographically and to date there are no *sec*-BuLi crystal structures.<sup>3</sup> We have isolated and characterized chiral complexes of three of the most commonly utilized, commercially available alkyllithium reagents, *n*-BuLi, *sec*-BuLi, and *t*-BuLi.

Chiral amide bases have been utilized in various synthetic transformations.<sup>4</sup> Upon reaction of *N*-isopropyl-*O*-methyl valinol (**1**) with a slight excess of *n*-BuLi as outlined in Scheme 1, we expected to generate either dimeric chiral amide base **2** or **3**. Compounds **2** and **3** are analogous to the alkoxysilyl aggregates described by Veith<sup>6</sup> and to the phenyl glycidol derived amide characterized in solution by Hilmersson and Davidsson.<sup>7</sup> Either **2** or **3** were anticipated as chiral analogs of the synthetic reagent lithium diisopropyl amide previously



**Figure 1.** Crystal structures **4–6** of the 2:1 complexes of lithium amide derived from *N*-isopropyl-*O*-methyl valinol (**1**) and (a) *n*-butyllithium, or (b) *sec*-butyllithium, or (c) *tert*-butyllithium.

### Scheme 1<sup>a</sup>



<sup>a</sup> (a) acetone, Na(CN)BH<sub>3</sub>, MeOH; (b) LiAlH<sub>4</sub>, THF, 0 °C; (c) NaH, CH<sub>3</sub>I, THF; (d) 2.5 M *n*-BuLi in hexane, -40 °C

characterized as a dimer.<sup>8</sup> Instead of isolating either **2** or **3**, we crystallized and characterized a new *n*-butyllithium containing aggregate **4** depicted both in Scheme 1 and in Figure 1. Aggregate **4** consists of 1 equiv *n*-BuLi and 2 equiv of the lithium amide base derived from chiral secondary amine **1**. After determining the stoichiometry and the structure of the complex **4** crystallographically, we have found it relatively easy to repeat the procedure and to increase the yield of crystalline material to above 40% by adding the stoichiometrically appropriate amount of *n*-BuLi to the amine **1**.<sup>9</sup> In addition to the *n*-butyl derivative **4**, we are also able to prepare crystalline samples and to obtain structures of similar aggregates **5** and **6** derived from both *sec*-butyllithium and from *tert*-butyllithium, respectively.<sup>10</sup> These are depicted in Figure 1.

The alkyllithium/lithium amide aggregate **4** depicted in Scheme 1 possesses a noncrystallographic 2-fold axis of symmetry if the alkyl group is not considered. All three aggregates **4–6** depicted in Figure 2 display this 2-fold rotation symmetry. In fact the complexes **5** and **6** of the *sec*-butyl and the *tert*-butyl derivatives crystallized in the uncommon (for small molecules) chiral, tetragonal space group *P*4<sub>3</sub>2<sub>1</sub>2 in a manner which imposes an exact 2-fold rotation symmetry for the aggregate as roughly depicted for **4** in Scheme 1. Although the *sec*-butyl and *tert*-butyl groups in **5** and **6** do not possess

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2-fold rotation axis symmetry, refinement of the crystallographic data indicated disorder in the final model of the alkyl groups of **5** and **6** which incorporate 2-fold rotation axial symmetry.<sup>11</sup>

Several excellent reviews of enantioselective additions of organometallic reagents to carbonyl compounds have been published.<sup>12</sup> Most examples cited report the use of uncharged chiral ligands or of chiral lithium alkoxides complexed with organometallic reagents to induce enantioselectivity.<sup>13</sup> Several examples of the use of alkyllithium/sparteine reagents are also noteworthy for their stereoselectivity.<sup>14</sup> Particularly relevant

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(9) Crystallizations are optimized to produce diffraction quality samples and not necessarily to obtain maximum yields.

(10) X-ray diffraction data were recorded at –40 °C on a Siemens four-circle diffractometer with a SMART CCD detector. The structures solved routinely with SHELX direct methods and were refined utilizing full matrix least squares on  $F^2$ . Crystallographic parameters for each compound are summarized as follows. (a) Compound **4** crystallized from heptane solution in the monoclinic space group  $P2_1$  with unit cell parameters,  $a = 18.206(3)$  Å,  $b = 8.869(10)$  Å,  $c = 18.555(3)$  Å,  $a = \gamma = 90^\circ$ , and  $\beta = 113.35(10)^\circ$ . Of the diffraction data (12 249 reflections) recorded, a total of 7164 independent reflections with  $R_{\text{int}} = 0.029$  were utilized in refinement of 536 parameters. The final model resulted in the following statistical parameters: GOOF = 1.016,  $R(\text{all data}) = 0.046$  and  $wR2(\text{all data}) = 0.1158$ . (b) Compound **5** crystallized from heptane solution in the tetragonal space group  $P4_32_12$  with unit cell parameters,  $a = b = 8.810(10)$  Å,  $c = 34.620(10)$  Å,  $a = \beta = \gamma = 90^\circ$ . Of the diffraction data (12 376 reflections) recorded, a total of 1943 independent reflections with  $R_{\text{int}} = 0.0495$  were utilized in refinement of 146 parameters. The final model resulted in the following statistical parameters: GOOF = 1.159,  $R(\text{all data}) = 0.056$  and  $wR2(\text{all data}) = 0.143$ . (c) Compound **6** crystallized from pentane solution in the monoclinic space group  $P4_32_12$  with unit cell parameters,  $a = b = 8.971(10)$  Å,  $c = 33.758(8)$  Å,  $a = \beta = \gamma = 90^\circ$ . Of the diffraction data (12 138 reflections) recorded, a total of 1914 independent reflections with  $R_{\text{int}} = 0.071$  were utilized in refinement of 146 parameters. The final model resulted in the following statistical parameters: GOOF = 1.026,  $R(\text{all data}) = 0.068$  and  $wR2(\text{all data}) = 0.146$ .

to our structural results is the observation by Hogeveen and Eleveld of enantioselective addition of *n*-BuLi to benzaldehyde in the presence of chiral lithium amides in a variety of solvents.<sup>15</sup> It is noteworthy that the ratio of *n*-BuLi to chiral amide ligand utilized by Hogeveen was 2.7:4 and not 1:1. It is also noteworthy that the best selectivity in this study (90% ee) was observed with a chiral Li amide ligand derived from an *O*-methyl- $\alpha$ -amino alcohol which closely resembles **1**. While we are not yet willing to conclude that complexes with structures similar to **4–6** are responsible for Hogeveen's results, the reagent stoichiometry and the ligand similarity indicate that this is certainly not unreasonable.

A different structure was assigned by Hilmersson and Davidsson to the complex between a chiral lithium amide and *n*-BuLi in diethyl ether solution. These investigators conclude that a 1:1 complex of the chiral lithium amide/*n*-BuLi coexists with *n*-BuLi tetramer in solution from their NMR studies.<sup>16</sup> We are currently investigating the relationship between our chiral 2:1 amide/alkyllithium complexes and the 1:1 complexes reported by these authors as well as the stereoselectivity in carbonyl additions of the alkyl group from the complexes **4–6** which we have characterized.

**Acknowledgment.** This work was supported by the National Institutes of Health through grant GM-35982. The X-ray diffraction equipment was originally purchased with assistance from the National Science Foundation and upgraded with assistance from the National Institutes of Health. We thank Prof. Gene B. Carpenter for helpful discussions concerning the interpretation of the X-ray diffraction data. This paper is dedicated to Professor Dieter Seebach on the occasion of his 60th birthday.

**Supporting Information Available:** Tables of crystallographic data, atomic numbering schemes, thermal ellipsoid plots, atomic position and thermal parameters, and bond lengths and bond angles for complexes **4–6** (24 pages). See any current masthead page for ordering and Internet access instructions.

JA972277D

(11) The crystallographic 2-fold rotation symmetry requirement is satisfied for the *sec*-butyl complex **5** by a model with the carbanionic carbon atom located on the symmetry axis, the *sec*-butyl group adopts an *s*-cis conformation and partial occupancy/exchange of the methyl and ethyl groups about the carbanionic center and for the *tert*-butyl complex **6** by a model with the carbanionic center located on the symmetry axis and a disorder by a rotation of the *tert*-butyl group by 60° around the symmetry axis. Only one of the two occupied sites in both **5** and **6** is depicted in Figure 1 for clarity. The largest peaks and holes in the final electron density maps of **5** and **6** are less than 0.13 eÅ<sup>-3</sup>.

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