

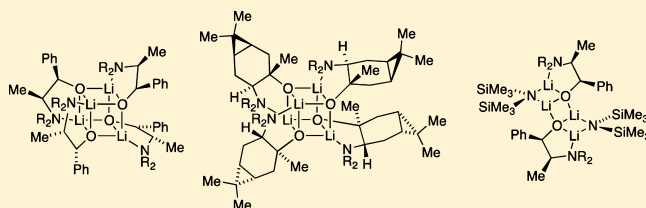
# Solution Structures of Lithium Amino Alkoxides Used in Highly Enantioselective 1,2-Additions

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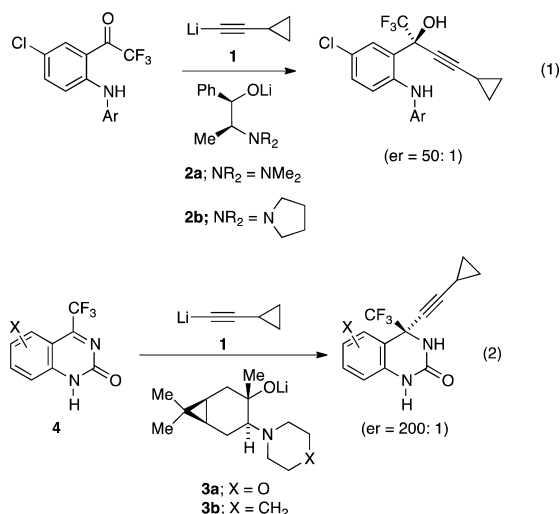
## Supporting Information

**ABSTRACT:** Lithium ephedrates and norcarane-derived lithium amino alkoxides used to effect highly enantioselective 1,2-additions on large scales have been characterized in toluene and tetrahydrofuran. The method of continuous variations in conjunction with  $^6\text{Li}$  NMR spectroscopy reveals that the lithium amino alkoxides are tetrameric. In each case, low-temperature  $^6\text{Li}$  NMR spectra show stereoisomerically pure homoaggregates displaying resonances consistent with an  $S_4$ -symmetric cubic core rather than the alternative  $D_{2d}$  core. These assignments are supported by density functional theory computations and conform to X-ray crystal structures. Slow aggregate exchanges are discussed in the context of amino alkoxides as chiral auxiliaries.



## INTRODUCTION

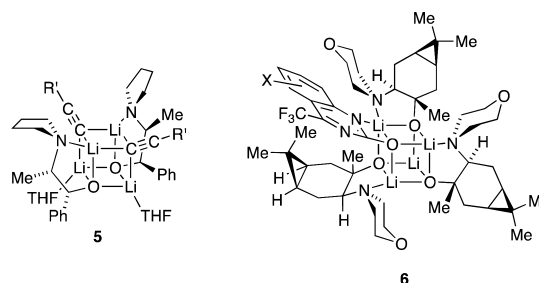
The idea of exploiting organolithium mixed aggregates to control organolithium reactivity and selectivity lurked for several decades,<sup>1</sup> but it moved to center stage in the early 1980s largely owing to contributions of Seebach and co-workers.<sup>2</sup> In a dramatic application of aggregate-based stereocontrol, the process group at Merck has shown that 2 equiv each of lithium cyclopropylacetylide **1** and lithium ephedrate **2b** effect the 1,2-addition in eq 1 in 98% enantioselectivity.<sup>3</sup> Synthesis of more



than 50 000 kg of reverse transcriptase inhibitor efavirenz (Sustiva, Stocrin) using this protocol quashed any doubt about the practicality of stoichiometric amino alkoxide auxiliaries.<sup>4</sup> Subsequently, DuPont Pharmaceuticals prepared more than 2000 kg of a second-generation reverse transcriptase inhibitor using a seemingly analogous 1,2-addition of lithium acetylide **1**

to quinazolinone **4** with an extraordinary 99.5% enantioselectivity (eq 2).<sup>5</sup> In this case, however, optimal selectivity was obtained using a 3:1 mixture of norcarane-derived amino alkoxide **3a** and **1**.

A Cornell–Merck collaboration traced the high enantioselectivity in eq 1 to the reaction of substrate with 2:2  $(\text{ROLi})_2(\text{R}'\text{Li})_2$  mixed tetramer **5**.<sup>6</sup> A subsequent Cornell–DuPont collaboration attributed the enantioselectivity in eq 2 to the external attack of acetylide on 3:1  $(\text{ROLi})_3(\text{sub})_1$  mixed tetramer **6**.<sup>7</sup> In both reactions, aging the reaction near ambient temperature before addition at low temperature was key to attaining high selectivity.



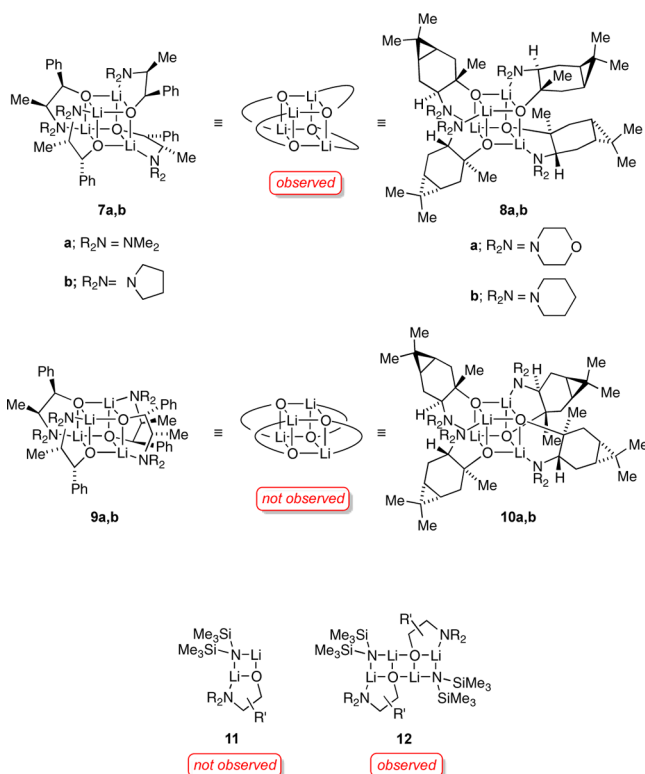
During these structural and mechanistic studies, the solution structures of the amino alkoxide homoaggregates proved elusive. The problem emanated from the difficulties associated with characterizing O-lithiated species in solution, wherein high symmetry and lack of O–Li coupling preclude direct NMR spectroscopic analysis.<sup>8</sup> Arnett and co-workers have previously reported a crystal structure of the pseudoephedrate stereoisomer of **2a** displaying an  $S_4$ -symmetric tetrameric core, but

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their efforts to determine the solution structure were less conclusive.<sup>9</sup>

Considerable inroads have now been made toward characterizing the structures of O-lithiated species in solution.<sup>8,10–12</sup> Using a combination of <sup>6</sup>Li NMR spectroscopy, the method of continuous variations (MCV),<sup>8,12,13</sup> and density functional theory computations, we show herein that amino alkoxides **2a,b** and **3a,b** form exclusively unsolvated homotetramers **7a,b** and **8a,b**.<sup>11,12,14</sup> Several intraaggregate exchanges<sup>12,15</sup> are shown to be remarkably slow. In conjunction with <sup>6</sup>Li–<sup>15</sup>N double-labeling studies, the application of MCV is extended to distinguish lithium hexamethyldisilazide–lithium amino alkoxide dimers **11** and the corresponding ladders **12**—a structural ambiguity arising from opaque O–Li linkages that has dogged us for many years.<sup>12b,17</sup>

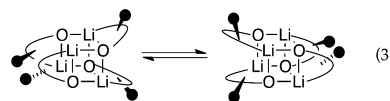


## RESULTS

**Homoaggregation.** Lithium alkoxides **2a,b** and **3a,b** were generated in toluene by treating the corresponding alcohols<sup>3e,18</sup> with 1.0 equiv of labeled lithium hexamethyldisilazide ([<sup>6</sup>Li]–LiHMDS).<sup>19</sup> To facilitate the narrative, we note at the outset that the data support cubic tetramers **7a,b** and **8a,b** bearing S<sub>4</sub>-symmetric cores.

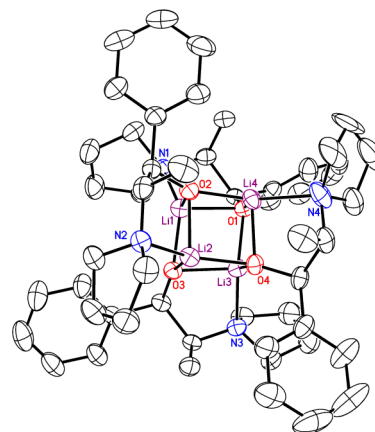
Low-temperature <sup>6</sup>Li NMR spectroscopy of all four alkoxides reveals two resonances (1:1) that coalesce above –20 °C to afford a single sharp resonance above 0 °C consistent with a single aggregate containing two magnetically inequivalent lithium nuclei. Note that cubic tetramers **7a,b** and **8a,b** would show such a pair, whereas tetramers **9a,b** and **10a,b** with D<sub>2d</sub>-symmetric cores would each display a single <sup>6</sup>Li resonance. The coalescence temperature in toluene (approximately –20 °C for all four alkoxides) is higher than that in neat THF (T<sub>coalesc</sub> ≈ –35 °C), suggesting that THF assists the exchange. We attribute these behaviors to a degenerate rearrangement of

the chelates about the cubic tetramer frameworks of **7a,b** and **8a,b** (eq 3).



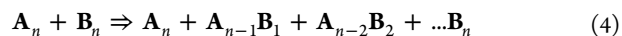
Despite the THF dependence on the rate of chelate exchange, we conclude that THF is coordinated only transiently based on a simple and powerful diagnostic probe as follows.<sup>12</sup> Pyridine strongly coordinates lithium nuclei and shifts <sup>6</sup>Li resonances markedly (0.5 to >1.0 ppm) downfield even in neat THF solutions.<sup>12c,20</sup> Amino alkoxides **2a,b** and **3a,b** showed no measurable change in chemical shift in solutions of 1.2 M pyridine/toluene compared with that in THF/toluene or toluene solutions, demonstrating that the chelates occupy all available coordination sites.

The assignment of **7a** is consistent with a crystal structure by Arnett and co-workers.<sup>9</sup> The assignment of **7b** was corroborated by an X-ray crystal structure of **5a** showing the S<sub>4</sub>-symmetric cubic tetramer core (Figure 1; Supporting Information).



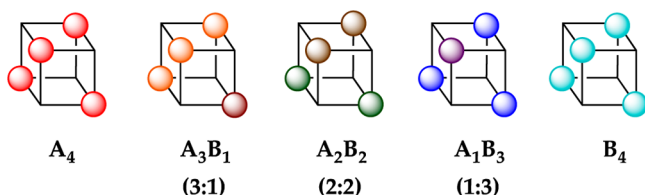
**Figure 1.** ORTEP of **5a** as fully chelated tetramer bearing an S<sub>4</sub>-symmetric cubic core.

**Heteroaggregation and MCV.** Assignment of **2a,b** and **3a,b** as tetramers **7a,b** and **8a,b** relied critically on MCV.<sup>8,12,13</sup> In this experiment, the high symmetries of the lithium alkoxides are disrupted by forming ensembles of homo- and heteroaggregates (eq 4).<sup>21,22</sup> The number and symmetries of the heteroaggregates and the dependence of the distribution on the mole fraction (X<sub>A</sub> or X<sub>B</sub>) attest to the structures of the homoaggregates, A<sub>n</sub> and B<sub>n</sub>. In most previous applications of MCV, cubic tetramers appear as a series of five homo- and heteroaggregates with the characteristic resonance counts illustrated in Chart 1.<sup>8,12</sup>

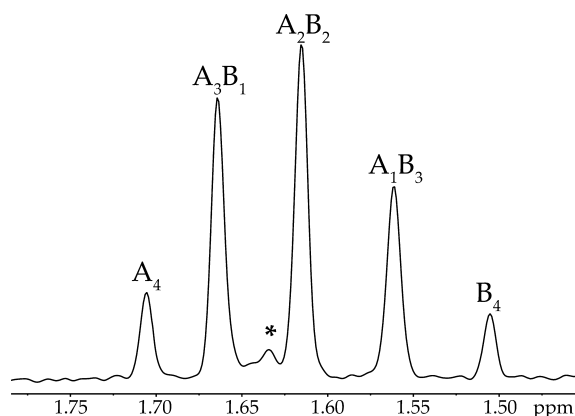


Characterization of the alkoxides as tetramers using MCV is illustrated with **2a** and **2b** emblematically. Mixtures of **2a** and **2b** in a 1:1 ratio in toluene or THF give intractable NMR spectra at low temperature. The complexity inherent to ensembles is exacerbated by the stereochemistry of chelation (discussed in detail below). On warming, however, the overlapping resonances coalesce to afford a sharp five-peak ensemble at +60 °C consistent with a tetramer ensemble—A<sub>4</sub>,

Chart 1

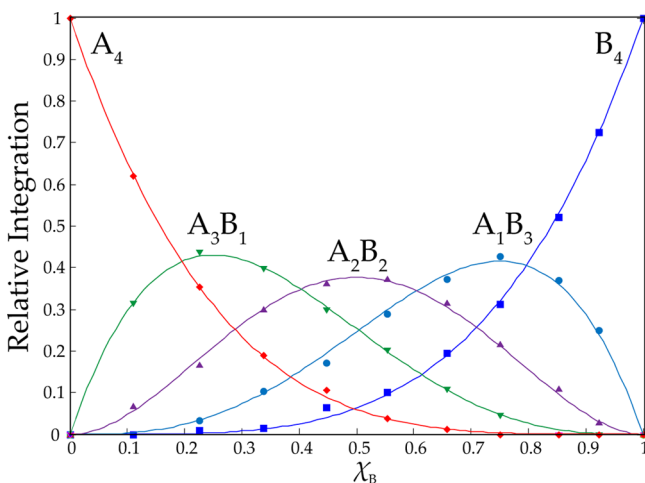


$A_3B_1$ ,  $A_2B_2$ ,  $A_1B_3$ , and  $B_4$ —with each stoichiometry appearing as a single resonance (Figure 2). The apparent *intraaggregate*



**Figure 2.**  $^6\text{Li}$  NMR spectrum of a 1:1 mixture of lithium ephedrates **2a** and **2b** in toluene recorded at +60 °C. The labels indicate the relative  $A_mB_n$  stoichiometries. The asterisk denotes an unknown impurity.

Li–Li exchange<sup>8,12,15,20a</sup> is well-precedented and has been useful in characterizing O-lithiated species, but it is usually significantly more facile. The exchange shows minor acceleration by THF relative to toluene. The aggregates were monitored in the high temperature limit with varying proportions of **2a** and **2b** and fixed total alkoxide concentration. The relative integrations of the five distinct aggregates are plotted versus measured mole fractions<sup>23</sup> ( $X_A$  or  $X_B$ ) of the two components in Figure 3. The curves result from a parametric fit as described previously.<sup>8,12</sup> The number of aggregates and

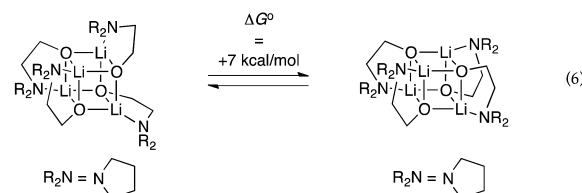
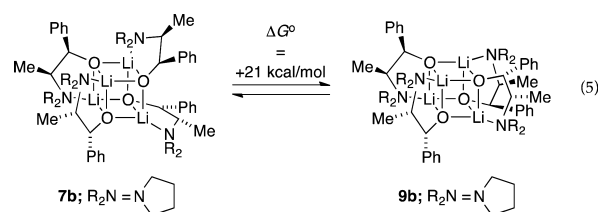


**Figure 3.** Job plot showing the relative integrations of tetrameric homo- and heteroaggregates versus measured mole fractions<sup>23</sup> of **2a** ( $X_A$ ) for 0.10 M mixtures of lithium ephedrates  $[\text{}^6\text{Li}]\text{2a}$  (**A**) and  $[\text{}^6\text{Li}]\text{2b}$  (**B**) in toluene at +60 °C.

quality of the fit confirm the tetramer assignment. In conjunction with the symmetry of the homoaggregates at low temperature and solvent-independent chemical shift, MCV completes the assignment of alkoxides **2a** and **2b** as solvent-free tetramers **7a** and **7b**.

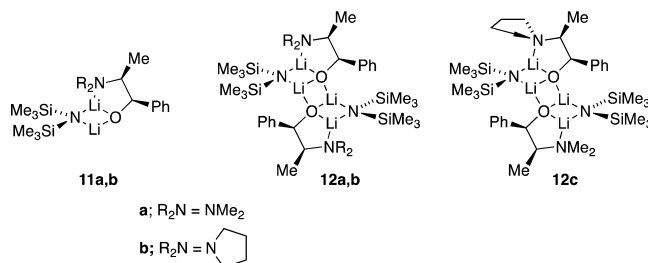
Studies of norcarane-derived alkoxides **3a** and **3b** afforded results fully analogous to those of **2a** and **2b** in every respect, supporting unsolvated cubic tetramers **8a** and **8b**. Relatively minor quantitative differences include slightly faster chelate exchanges and slightly slower intraaggregate Li–Li site exchanges.

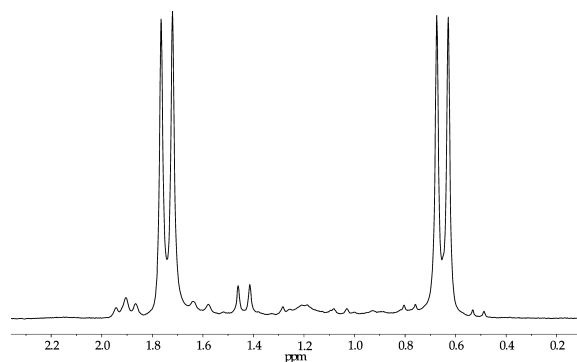
The stereochemical preference for  $S_4$  rather than  $D_{2d}$  cubic cores was examined using density functional theory computations at the B3LYP level of theory with the 6-31G(d) Pople basis set.<sup>24</sup> Free energies were calculated from MP2-derived single-point energy [6-31G(d) basis set] and a B3LYP-derived thermal correction [6-31G(d)] at 195 K and 1 atm. The 21 kcal/mol preference for the  $S_4$  form in **7b** (eq 5) is fully



consistent with the experimental data. Although we often use computations only qualitatively, this difference is *very* large for isodesmic<sup>25</sup> stereoisomers. Computations of a sterically less congested variant in which the phenyl and methyl moieties along the backbone of ephedrate **2a** were omitted show a reduced but still sizable 7 kcal/mol preference for the  $S_4$  core (eq 6).

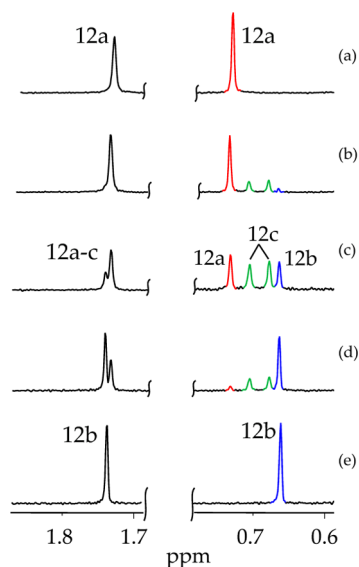
**Lithium Alkoxide–LiHMDS Mixed Aggregates.** During the studies described above, we detected lithium alkoxide–LiHMDS mixed aggregates that formed quantitatively with 1.0 equiv of excess LiHMDS.<sup>22</sup> For example, lithium ephedrate **2a** with a 1.0 equiv excess of  $[\text{}^6\text{Li}, \text{}^{15}\text{N}]\text{LiHMDS}$  displays two  $^6\text{Li}$  doublets in a 1:1 ratio ( $J_{\text{Li–N}} = 1.0$  Hz) and a single resonance appearing as a quintet in the  $^{15}\text{N}$  NMR spectrum (Figure 4). The data are consistent with the basic mixed dimer subunits **11a,b** or the corresponding ladder **12a**. Once again, the spectroscopically opaque Li–O linkages posed a problem, and MCV offered the solution.





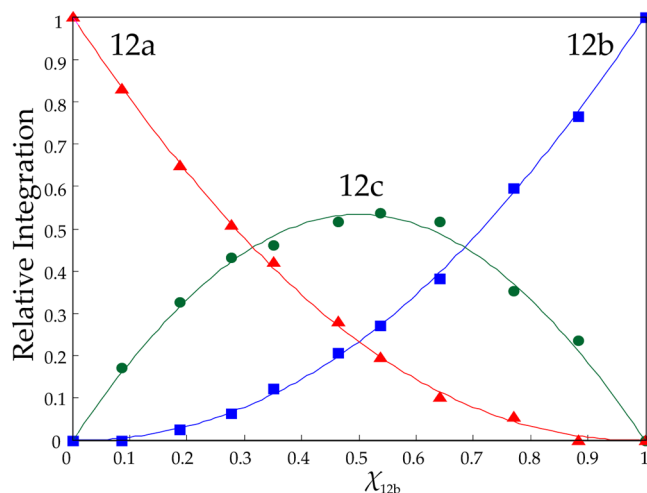
**Figure 4.**  $^6\text{Li}$  NMR spectrum recorded on a 1:1 mixture of  $[\text{}^6\text{Li}, \text{}^{15}\text{N}]\text{LiHMDS}$  (0.10 M) and lithium amino alkoxides **2a** (0.10 M total concentration) in toluene cosolvent at  $-30\text{ }^\circ\text{C}$ .

Mixtures of lithium ephedrates **2a** and **2b** in toluene at varying proportions but constant lithium alkoxide titer in the presence of 1.0 equiv of excess LiHMDS afford  $^6\text{Li}$  spectra showing the two original resonance pairs along with additional resonances consistent with mixed ladder **12c** (Figure 5). The



**Figure 5.**  $^6\text{Li}$  NMR spectra recorded on mixtures of  $[\text{}^6\text{Li}]\text{LiHMDS}$  (0.10 M) and lithium amino alkoxides **2a** and **2b** (0.10 M total concentration) in toluene cosolvent at  $-30\text{ }^\circ\text{C}$ : (a) 0.10 M  $[\text{}^6\text{Li}]\text{2b}$ ; (b) 0.080 M  $[\text{}^6\text{Li}]\text{2b}$  and 0.020 M  $[\text{}^6\text{Li}]\text{2a}$ ; (c) 0.050 M  $[\text{}^6\text{Li}]\text{2b}$  and 0.050 M  $[\text{}^6\text{Li}]\text{2a}$ ; (d) 0.020 M  $[\text{}^6\text{Li}]\text{2b}$  and 0.080 M  $[\text{}^6\text{Li}]\text{2a}$ ; and (e) 0.10 M  $[\text{}^6\text{Li}]\text{2a}$ .

downfield ensemble is not well resolved, yet the upfield resonances clearly show **12a** and **12b** along with two resonances (1:1) attributed to mixed ladder **12c**. We suspect that the well-resolved upfield resonances correspond to those bearing the dialkylamino chelates. Maintaining the total concentration of excess LiHMDS at 0.10 M and the total alkoxide titer at 0.10 M while varying proportions (mole fractions) of the two alkoxides afforded a mole fraction-dependent distribution consistent with ladders **12a**, **12b**, and **12c**. The resulting Job plot is illustrated in Figure 6. The resonance counts and quality of the fit confirm the 1:1 association of two mixed dimeric subunits and the overall ladder motif.



**Figure 6.** Job plot showing the relative integrations of mixed ladders **12a** ( $\text{A}_2$ ), **12b** ( $\text{B}_2$ ), and **12c** ( $\text{AB}$ ) versus measured mole fractions of **2b**–LiHMDS ( $X_B$ ) in mixtures containing 0.10 total amino alkoxide and 0.10 M LiHMDS at  $-30\text{ }^\circ\text{C}$ .

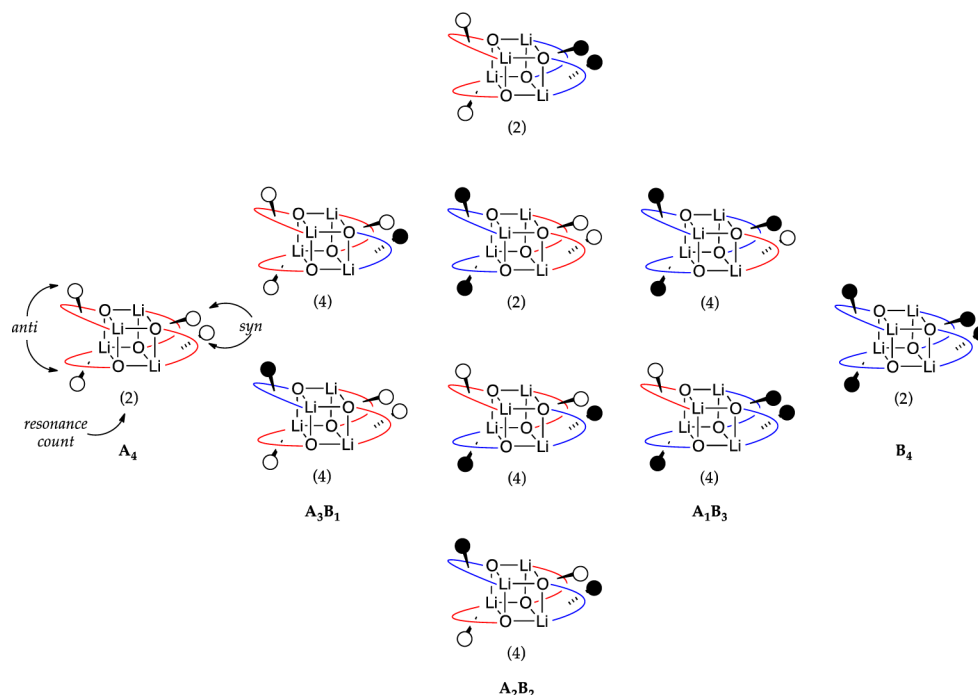
## DISCUSSION

Synthetically important lithium amino alkoxides pose an interesting challenge for structural organolithium chemists. Arnett and co-workers have shown that crystalline pseudoephedrate stereoisomer of **2a** is a cubic tetramer analogous to **9a**, but their efforts to determine the solution structure were less conclusive. Messy  $^6\text{Li}$  NMR spectra cast doubt on the colligative measurements, which are notoriously sensitive to impurities.<sup>8</sup> We previously studied amino alkoxides **2a** and **3a** using NMR spectroscopy and gleaned no useful information.<sup>6,7</sup> The current paper describes how a combination of  $^6\text{Li}$  NMR spectroscopy and MCV allowed us to characterize **2a,b** and **3a,b** as stereochemically pure cubic tetramers **7a,b** and **8a,b**. Computational studies suggest that the  $S_4$ -symmetric cubic core is inherently more stable than the  $D_{2d}$  core, a preference that is amplified by the substituents along the chelate backbone (eqs 4 and 5). During these studies, we made a number of observations and achieved some tactical developments in MCV that call for further elaboration.

In the low temperature limit, all four homoaggregates display two distinct resonances that, with warming, coalesce into a single resonance owing to facile degenerate isomerizations of the chelates (eq 3). Although this observation proved critical to complete the structural assignments, it foreshadowed severe technical problems with the use of MCV. In typical applications of MCV to characterize tetramer ensembles (eq 4), we would observe three heteroaggregates of stoichiometries—3:1, 2:2, and 1:3—displaying resonance counts and integrations reflecting the symmetries (Chart 1).<sup>12</sup> The amino alkoxides, by contrast, show a markedly increased resonance count arising from stereochemical complexity (Chart 2). The homoaggregates each show two rather than the usual one resonance. The 3:1 and 1:3 heterotetramers exist as two distinct diastereomers each displaying *eight* resonances total. There are potentially *four* diastereomeric 2:2 heterotetramers—two  $C_2$ -symmetric diastereomers displaying two resonances each and two  $C_1$ -symmetric diastereomers containing four discrete lithium resonances each. Thus, the tetramer ensemble in the slow exchange limit would include 32 resonances in total. It is not



Chart 2



shocking, therefore, that ensembles generated from **2a/2b** or **3a/3b** pairings are intractable in the low temperature limit.

Two general classes of intraaggregate exchanges would, in principle, simplify the spectra. Chelate–chelate exchange (eq 3) without further deepseated adjustments within the cubic core would reduce the complexity of Chart 2 to the simpler distribution depicted in Chart 1 and lower the <sup>6</sup>Li resonance count from 32 to 8. Intraaggregate exchange of all <sup>6</sup>Li nuclei<sup>12,15</sup> within each aggregate would lead to further symmetrization, causing the five-aggregate ensemble to appear as five discrete <sup>6</sup>Li singlets. In practice, warming the samples appeared to elicit rapid chelate exchange, but we could not readily observe all eight resonances at a single temperature owing to differential exchange rates of the different aggregates. Warming of the samples to 60–70 °C, however, elicited the hoped-for rapid intraaggregate Li–Li site exchanges. We have examined structures in the limit of rapid intraaggregate exchange before,<sup>12,20a</sup> but the temperatures required for vicinal amino alkoxides are remarkably high.

We previously noted the maxim “like aggregates with like.”<sup>12</sup> Ensembles generated from lithium alkoxides and related O-lithiated species of differing aggregation states resist heteroaggregation, affording no heteroaggregates whatsoever or an ensemble of homo- and heteroaggregates that deviates significantly from statistical data.<sup>12</sup> The most compelling assignments stem from structurally related ROLi/R’OLi pairs. At the outset, however, we thought that pairing structurally very different alkoxides would be required to obtain sufficient resolution in the <sup>6</sup>Li NMR spectra. Nonetheless, the **2a/2b** and **3a/3b** pairs differing marginally at the dialkylamino appendages provide convincing results.<sup>26</sup> More heterogeneous pairings of lithium ephedrate and norcarane-derived lithium alkoxides—**2/3** pairs—also appeared to provide tetramer ensembles, but rapid intraaggregate exchange demanded very high (>80 °C) temperatures.

Mounting evidence suggests that cubic tetramers of enolates and related O-lithiated species are far more robust (less

dynamic) than we ever suspected.<sup>27,28</sup> The effects of aging (warming–cooling cycles) and catalytically active lithium salts on aggregate equilibrations may profoundly influence stereo- and regiochemical outcomes. Both chelate–chelate and Li–Li site exchanges are observed at lower temperatures in THF than in toluene, indicating a role of THF despite apparent lack of solvation.

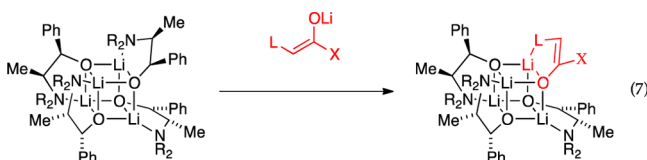
During the studies of homoaggregates we detected lithium alkoxide–LiHMDS mixed aggregates in toluene. (LiHMDS does not form mixed aggregates in THF.<sup>29</sup>) The connectivities obtained from <sup>6</sup>Li–<sup>15</sup>N double-labeling studies do not distinguish cyclic dimer **11** from ladder **12**, a distinction that has eluded us previously.<sup>17</sup> We used MCV to reveal that mixtures of LiHMDS and alkoxides afford mixed ladders (**12a–c**). The chirality of these mixed aggregates may also pique curiosity among those interested in enantioselective reactions of lithium amides.

## CONCLUSION

We have shown that cubic tetramers are a dominant form of several lithium amino alkoxides. This study and others<sup>28</sup> suggest that such tetramers composed of O-lithiated species are very robust. It is not difficult to imagine, therefore, that practitioners using lithium enolates to achieve stereocontrolled carbon–carbon bond formation have been thwarted by undetected aging and salt effects.

The importance of lithium amino alkoxides as auxiliaries in organolithium chemistry has grown markedly in the absence of any structural insights whatsoever.<sup>3–5</sup> Notably, structural studies of aggregates underlying the Merck chemistry (eq 1)<sup>6</sup> have played a direct role in the development of the protocols subsequently used at DuPont (eq 2).<sup>5,7</sup> In this context, we note a curious observation that may prove important. Inserting lithium salts into the cubic tetramers of **7a** and **8a** to form the mixed tetramers **5** and **6** central to Merck’s and DuPont’s enantioselective additions requires disruption of the chelate

orientations of the  $S_4$  core structure of homoaggregates **7a** and **8a**. We wonder: would mixed aggregates that allow three of the four chelates in the  $S_4$  core to remain intact (eq 7) offer more generalized control of the stereochemistry? Studies are, of course, ongoing.



## EXPERIMENTAL SECTION

**Reagents and Solvents.** Toluene, THF, and pyridine were distilled from blue solutions containing sodium benzophenone ketyl. The toluene contained approximately 1% tetraglyme to dissolve the ketyl.  $[^6\text{Li}]\text{LiHMDS}$  and  $[^6\text{Li},^{15}\text{N}]\text{LiHMDS}$  were prepared and recrystallized using modified literature protocols.<sup>19</sup> Air- and moisture-sensitive materials were manipulated under argon using standard glovebox, vacuum line, Schlenk, and syringe techniques. NMR samples were prepared using protocols described previously.<sup>12c</sup>  $^6\text{Li}$  NMR spectra were typically recorded on a 500 or 600 MHz spectrometer with the delay between scans set to  $>5 \times T_1$  to ensure accurate integrations. Chemical shifts are reported relative to a 0.30 M  $^6\text{LiCl}/\text{MeOH}$  standard at  $-80^\circ\text{C}$ .

## ASSOCIATED CONTENT

### Supporting Information

Spectra, additional Job plots, and authors for ref 24. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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### Notes

The authors declare no competing financial interest.

## ACKNOWLEDGMENTS

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