

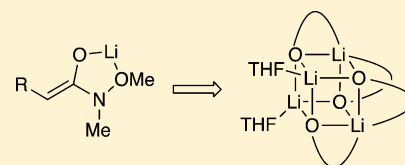
# Lithium Enolates Derived from Weinreb Amides: Insights into Five-Membered Chelate Rings

Michael J. Houghton and David B. Collum\*

Department of Chemistry and Chemical Biology, Baker Laboratory, Cornell University, Ithaca, New York 14853-1301, United States

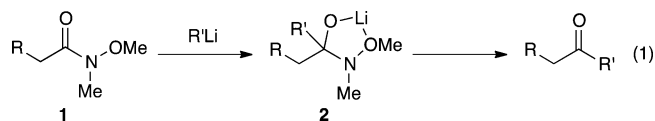
**S** Supporting Information

**ABSTRACT:** Enolization of *O*-methyl hydroxamic acids (Weinreb amides) in tetrahydrofuran solution with lithium diisopropylamide affords predominantly tetrameric enolates. Aryl substituents on the enolates promote deaggregation. The aggregation states are assigned by using the method of continuous variation in conjunction with  $^6\text{Li}$  NMR spectroscopy. Decoalescence of the tetramer resonance below  $-100\text{ }^\circ\text{C}$  shows considerable spectral complexity attributed to isomerism of the methoxy-based chelates. Density functional theory calculations were used to examine the consequences of the bite angle of five-membered chelates in cubic tetramers and resulting solvation numbers that were higher than anticipated.



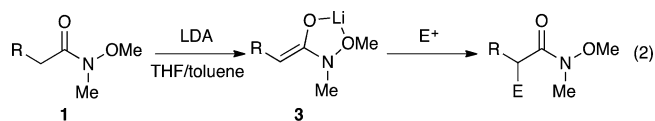
## INTRODUCTION

In 1981, Nahm and Weinreb<sup>1,2</sup> reported that *O*-methyl hydroxamic acids of general structure **1** undergo highly selective nucleophilic addition to give ketones (eq 1). The



observed monoadditions, which contrasted with the double additions observed for the corresponding esters, were attributed to chelate-stabilized tetrahedral intermediate **2**, although the mechanism proved far more complex than many surmised.<sup>3</sup>

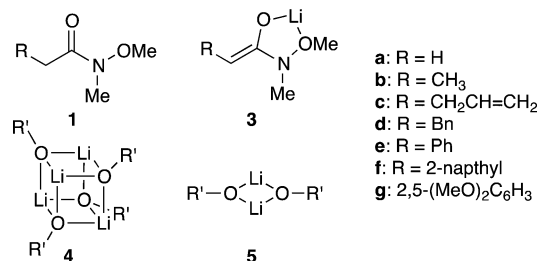
Weinreb amides are also precursors to propionate ester enolate equivalents, so-called Weinreb enolates.<sup>4–7</sup> The potentially advantageous features of reactions with these compounds include the anticipated high *Z*-selective enolization characteristic of carboxamides<sup>8</sup> and the synthetic utility of the Weinreb amides (eq 2). Several strange observations are



included in the reports. Demethoxylation occasionally affords *N*-methyl carboxamides.<sup>7,9</sup> Davis and co-workers,<sup>5</sup> incredulously, metalated and functionalized a Weinreb amide by using lithium diisopropylamide (LDA) in the presence of 5 equiv of water. In general, applications of Weinreb enolates are rare,<sup>5–7</sup> and we can find no structural or mechanistic studies.<sup>10,11</sup>

We have explored the structure of Weinreb enolates **3a–g** in tetrahydrofuran (THF)/toluene mixtures. These enolates routinely form tetramers and dimers depicted generically as **4** and **5**, respectively. Spectroscopic and computational studies

suggest an unusual role of cooperative solvation by external THF ligands and the chelating methoxy moieties. The coordination chemistry within lithium-based cubic tetramers appears to be more complex than we anticipated and is reshaping our thinking about both cubic tetramers and the influence of chelate ring size on structure and reactivity.<sup>12,13</sup>

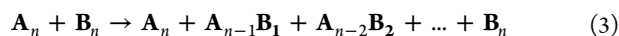


## RESULTS

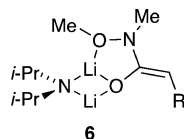
Enolates were generated in situ with recrystallized LDA ( $[\text{}^6\text{Li}]\text{LDA}$  or  $[\text{}^6\text{Li}, \text{}^{15}\text{N}]\text{LDA}$ ) prepared as described.<sup>14</sup> Aging for several hours at  $-78\text{ }^\circ\text{C}$  was required to fully equilibrate the enolate aggregates.<sup>15</sup> Structures were determined using a combination of  $^6\text{Li}$  NMR spectroscopy, the method of continuous variation (MCV),<sup>15–17</sup> and density functional theory (DFT) calculations.<sup>11,18</sup> Using MCV to characterize highly symmetric enolate aggregates entails mixing two structurally similar enolates, **A<sub>n</sub>** and **B<sub>m</sub>**, to generate an ensemble of homo- and heteroaggregates (eq 3).<sup>19</sup> The numbers and symmetries of the heteroaggregates reveal the aggregation state, *n*, which is confirmed by plotting the relative concentrations versus measured mole fraction<sup>20</sup> ( $X_{\text{A}}$  or  $X_{\text{B}}$ ) to afford a Job plot (exemplified by Figures 2 and 4).<sup>17</sup>

Received: August 22, 2016

Published: October 17, 2016

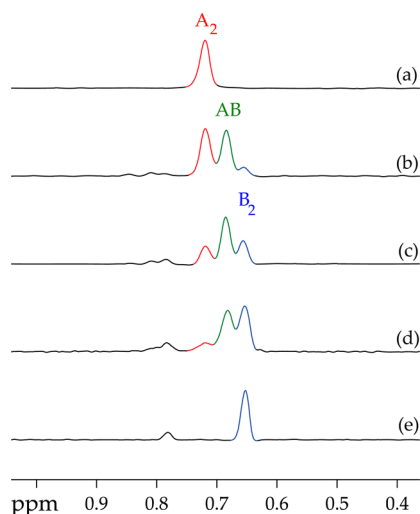


**Enolate–LDA Mixed Dimers.** The general approach to characterizing Weinreb enolates is illustrated emblematically with **3b** as follows. Enolization of propionamide **1b** with 1.1 equiv of [<sup>6</sup>Li]LDA in neat THF resulted in a single resonance in <sup>6</sup>Li NMR spectra obtained at –80 °C. NOESY revealed exclusively Z enolate. Analogous samples in 1.0–12 M THF/toluene solutions all contained the same aggregate. Enolization with [<sup>6</sup>Li,<sup>15</sup>N]LDA<sup>14</sup> showed no <sup>6</sup>Li–<sup>15</sup>N coupling, confirming that the species was a homoaggregated lithium enolate. Enolization with excess LDA, however, afforded mixed aggregates<sup>19</sup> displaying a single <sup>6</sup>Li resonance at –80 °C. By example, the mixed aggregate derived from **3e** prepared using [<sup>6</sup>Li,<sup>15</sup>N]LDA displayed a <sup>6</sup>Li 1:1 doublet and a 1:2:3:2:1 <sup>15</sup>N quintet ( $J_{Li-N} = 5.3$  Hz) consistent with mixed dimer **6**.<sup>21</sup> The two anticipated distinct <sup>6</sup>Li resonances emblematic of the chelate were not observable in 1.0 M THF/hexane at –120 °C. However, broadening consistent with decoalescence was significant.

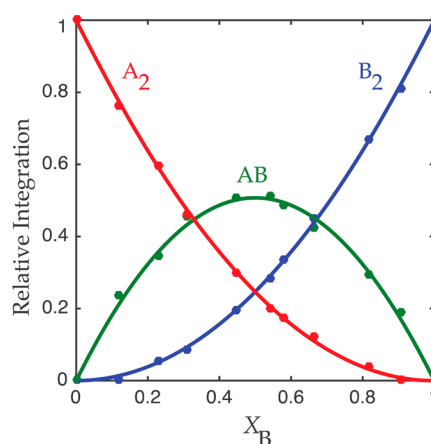


**Dimers.** Enolates **3e–g** with aromatic rings conjugated to the enolates exist as mixtures of two homoaggregates at low THF concentrations and exclusively as the lower aggregate at the elevated THF concentrations. Using MCV, we found that the sole species in THF were dimers. Thus, spectra recorded on **3e–3g** mixtures in neat THF showed the two homoaggregates along with a single heteroaggregate (Figure 1) consistent with an ensemble of dimers and afforded the Job plot in Figure 2.

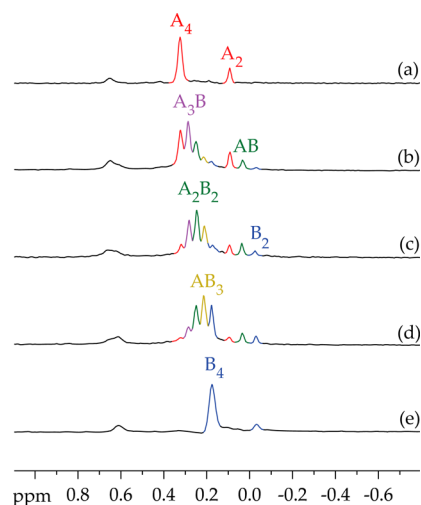
**Dimer–Tetramer Mixtures.** Enolates **3c** and **3d** in THF at –80 °C each existed as major and minor homoaggregates shown to be tetramers and dimers, respectively (Figure 3a,e). The minor species disappeared at low THF and high enolate concentrations, consistent with aggregates that are at a higher solvation state and lower aggregation state compared with the



**Figure 1.** <sup>6</sup>Li NMR spectra of 0.10 M solutions of [<sup>6</sup>Li]**3f** (A) and [<sup>6</sup>Li]**3e** (B) in 1.0 M pyridine and THF at –80 °C with 0.13 M [<sup>6</sup>Li]LDA. The measured<sup>20</sup> mole fractions B in (a)–(e) are 0.00, 0.31, 0.54, 0.81, and 1.00, respectively.



**Figure 2.** Job plot showing the relative integrations versus the measured<sup>20</sup> mole fraction of **3** for 0.10 M mixtures of [<sup>6</sup>Li]**3f** (A) and [<sup>6</sup>Li]**3e** (B) in 1.0 M pyridine and THF at –80 °C (see Figure 1).

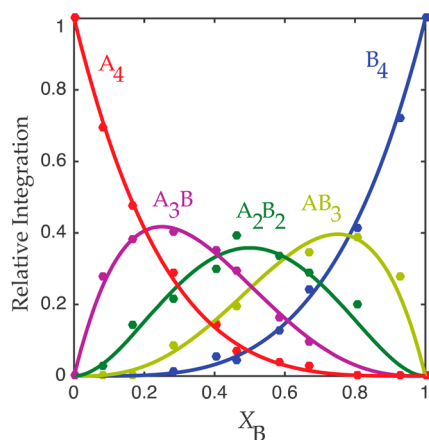


**Figure 3.** <sup>6</sup>Li NMR spectra of 0.10 M solutions of [<sup>6</sup>Li]**3d** (A) and [<sup>6</sup>Li]**3c** (B) in 0.13 M THF at –80 °C with 0.13 M [<sup>6</sup>Li]LDA. The measured mole fractions of B within the tetramer ensembles in (a)–(e) are 0.00, 0.28, 0.46, 0.67, and 1.00, respectively. For the dimers, the measured<sup>20</sup> mole fractions of B in (a)–(e) are 0.00, 0.27, 0.44, 0.61, and 1.00, respectively.

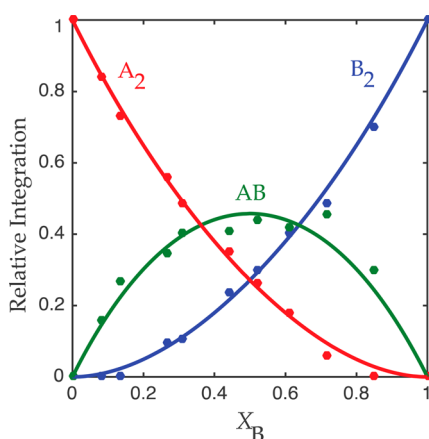
major forms. The two aggregation states were assigned with MCV in a single series of experiments as follows.

Mixtures of enolate **3c** and **3d** in THF at –80 °C showed the resonances of the two dominant homoaggregates along with 3:1, 2:2, and 1:3 heteroaggregate resonances characteristic of an ensemble of tetramers in rapid intraaggregate lithium exchange<sup>15c</sup> (Figure 3). Monitoring of the relative concentrations of the five aggregates versus measured mole fraction<sup>20</sup> afforded a Job plot (Figure 4) displaying a nearly statistical distribution of homo- and heterotetramers. The tetrameric forms of **3a–3e** were characterized with MCV analogously (Supporting Information).

The displayed ensembles of minor (lower) aggregates were consistent with dimers, affording the Job plot shown in Figure 5. We hasten to add that characterizing ensembles of aggregates from such complex mixtures (even mixtures with unknown impurities) is made possible by using the measured<sup>20</sup> rather than intended mole fraction.

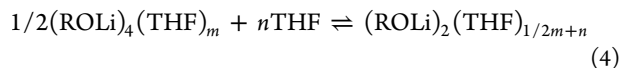


**Figure 4.** Job plot showing relative integration versus measured<sup>20</sup> mole fraction of tetramer for 0.10 M mixtures of [<sup>6</sup>Li]3d (A) and [<sup>6</sup>Li]3c (B) in 0.13 M THF at  $-80\text{ }^{\circ}\text{C}$  (see Figure 3).

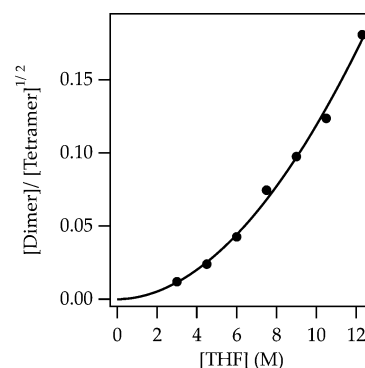


**Figure 5.** Job plot showing relative integration versus the measured<sup>20</sup> mole fraction of dimer for 0.10 M mixtures of [<sup>6</sup>Li]3d (A) and [<sup>6</sup>Li]3c (B) in 12.2 M THF at  $-80\text{ }^{\circ}\text{C}$  (see Figure 3).

**Dimer and Tetramer Solvation.** We began with a simplistic view of the role of THF. We imagined that the tetramers existed as either  $D_{2d}$  or  $S_4$  core structures (7 and 8, respectively) and were unsolvated by THF owing to the saturation of the cube by the chelating methoxy groups. Monitoring the tetramer–dimer ratio versus THF concentration for enolate 3d (eq 4) and fit according to eq 5 afforded a relative solvation number,  $n$ , of  $1.94 \pm 0.09$  (Figure 6). If we presume that the tetramer is unsolvated ( $m = 0$ )—an assumption brought into serious question below—then the dimer favored at high THF concentration is consistent with disolvate 9 (Chart 1). Dimer 10 could also exist undetected if the chelates are in the rapid-exchange limit.<sup>22</sup> Thus, 7–10 are potentially consistent with the spectroscopic data presented so far; however, the results of two experiments undermined our fundamental underlying presumptions and, thus, the assigned solvation states.

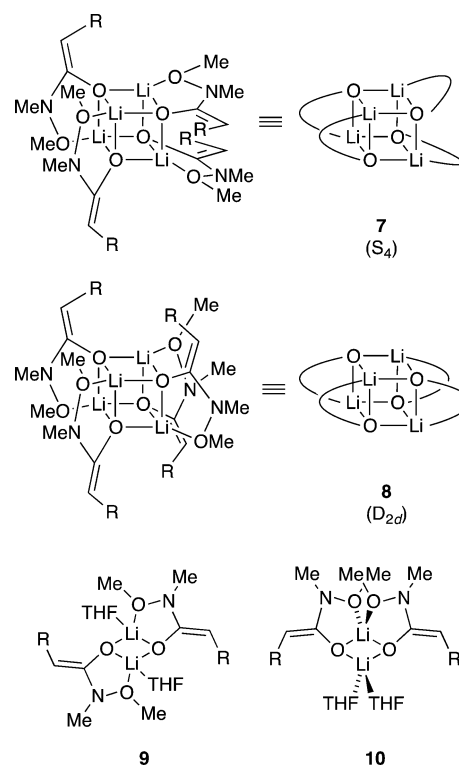


$$K_{\text{eq}}[\text{THF}]^n = \frac{[(\text{ROLi})_2(\text{THF})_{1/2m+n}]}{[(\text{ROLi})_4(\text{THF})_m]^{1/2}} \quad (5)$$



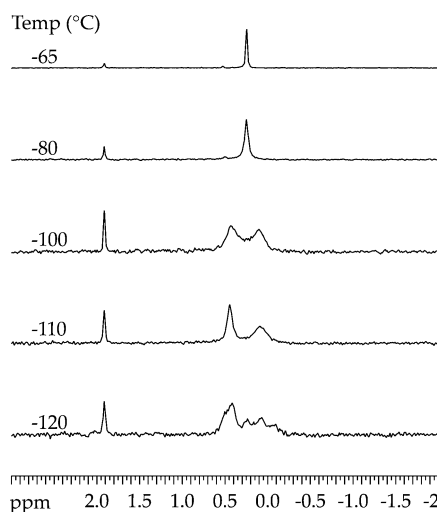
**Figure 6.** Plot of  $[\text{dimer}]/[\text{tetramer}]^{1/2}$  of 3d versus  $[\text{THF}]$  in toluene. The curve depicts an unweighted least-squares fit to  $y = K_{\text{eq}}[\text{THF}]^n$  [ $K_{\text{eq}} = (1.4 \pm 0.3) \times 10^{-3}$ ;  $n = 1.94 \pm 0.09$ ].

**Chart 1**



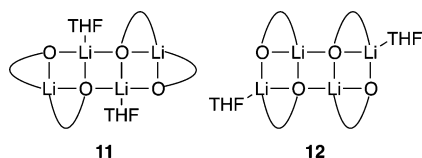
Incrementally adding pyridine as a chemical shift reagent to THF/hexane solutions of organolithiums qualitatively probes the absence or presence of coordinating solvent. Resonances corresponding to lithiums bearing substitutionally labile THF ligands shift markedly downfield, whereas unsolvated lithiums do not move appreciably.<sup>15a,23</sup> More highly solvated forms (often the lower aggregates) also increase in intensity relative to that of the lesser-solvated forms owing to mass action. In the event, incremental addition of pyridine markedly shifted the <sup>6</sup>Li resonances of dimers and tetramers. Thus, the tetramers were solvated by external ligands. It is tempting to assume that the chelates must be cleaved by THF, but we present a more nuanced model in the discussion.

Another critical observation was that cooling solutions of tetrameric enolates from  $-80\text{ }^{\circ}\text{C}$  to below  $-100\text{ }^{\circ}\text{C}$  caused broadening in all cases. In several instances (3c and 3d), decoalescence clearly yielded a pair of resonances that further decoalesced to complex envelopes of resonances (Figure 7).

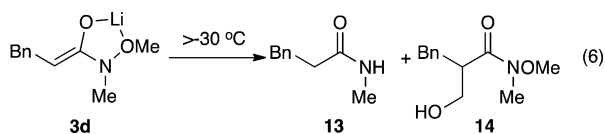


**Figure 7.**  ${}^6\text{Li}$  NMR spectra of 0.10 M solutions of  $[\text{}^6\text{Li}]\mathbf{3d}$  in 0.50 M THF/toluene recorded at various temperatures.

Presumably owing to the slowed exchange of the chelates, the structure of the tetramers appeared to be much more complex than that suggested by **7** or **8**. We cannot rigorously exclude ladders such as **11**, **12**, and a few others as the source of this complexity, but asymmetry is often readily observed owing to slow site-site exchange in ladders.<sup>24</sup> Moreover, they are all substantially (>6 kcal/mol) less stable than isomeric cubic tetramers in which chelation and external solvation are cooperative (*vide infra*).



**Demethoxylation.** Warming solutions of Weinreb enolates (typically to temperatures above  $-30\text{ }^\circ\text{C}$ ) provided evidence of demethoxylation and a formaldehyde aldol adduct (eq 6), both of which have been mentioned previously.<sup>7,9,25</sup> We know little about the mechanism.



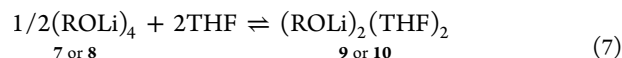
## DISCUSSION

Weinreb enolates (**3**) have found limited use in organic synthesis.<sup>5–7</sup> Evidence of an odd demethoxylation (eq 6) might preclude some applications,<sup>7,9</sup> but this outcome becomes

significant only at elevated temperatures (above  $-30\text{ }^\circ\text{C}$ ). Possible advantages of Weinreb enolates relative to propionate ester enolates include total selectivity for *Z* enolate geometry<sup>8</sup> and formation of Weinreb amide products poised for further transformation (eq 1). With this untapped potential in mind, we studied the aggregation and solvation of Weinreb enolates. Experimental data prompted DFT calculations of chelation and solvation that led us in unexpected directions. Despite uncontested evidence that five-membered rings are the preferred chelate ring size for lithium,<sup>12,13</sup> the impact of chain length on reactivity and selectivity may be less straightforward than we realized.

**Aggregation.** Weinreb enolates bearing small, saturated substituents such as **3a** and **3b** are predominantly tetrameric even in neat THF (Chart 1), whereas enolates **3e–g**, which are conjugated to aromatic rings, are susceptible to deaggregation owing to anion stabilization.<sup>10b</sup> Spectral data do not distinguish  $D_{2d}$  tetramer **8** from  $S_4$  tetramer **7**: both should display a single  ${}^6\text{Li}$  resonance and have ample precedent in the structural organolithium literature.<sup>15c,26,27</sup> We cannot exclude a fluxional stereochemical mixture; the facility of chelate exchange was suggested by the observed high symmetry of LDA mixed aggregate **6**.

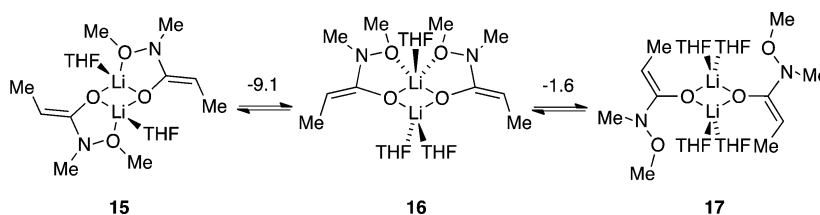
**Solvation and Chelation: An Orthodox Model.** We were predisposed to endorse the tetramer–dimer relationship in eq 7. The relative solvation numbers (eq 4) were ascertained by quantitating the THF concentration dependence (Figure 6). Stereoisomeric tetramer **7** or **8** and dimer **9** or **10** (Chart 1) are fully consistent with the data. Dimer **10** would require a facile chelate exchange, which is plausible.



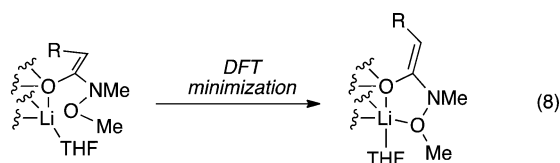
Two observations disavowed us of such an orthodox structural model during studies of solvation: (1) using pyridine as a chemical shift reagent shows that *both dimers and tetramers are solvated*, and (2) tetramers show unusual spectral complexity at temperatures below  $-100\text{ }^\circ\text{C}$ . In the discussion that follows, we rely heavily on DFT calculations to develop a markedly different view of chelation and solvation that might reach beyond the specific examples presented by Weinreb enolates.

**Solvation and Chelation: Dimers.** The computed serial solvation of dimers and their affiliated free energies ( $-80\text{ }^\circ\text{C}$ ) afforded the three lowest-energy forms of each stoichiometry shown in Scheme 1. We were moderately surprised that displacing the chelate by THF to afford tetrasolvated dimer **17** is favorable. Inspection of **15** and **16** (with a graphical interface) reveals potentially destabilizing chelate distortions as annotated. Such distortions might have been missed (or dismissed) if not for the investigations of tetramers discussed below.

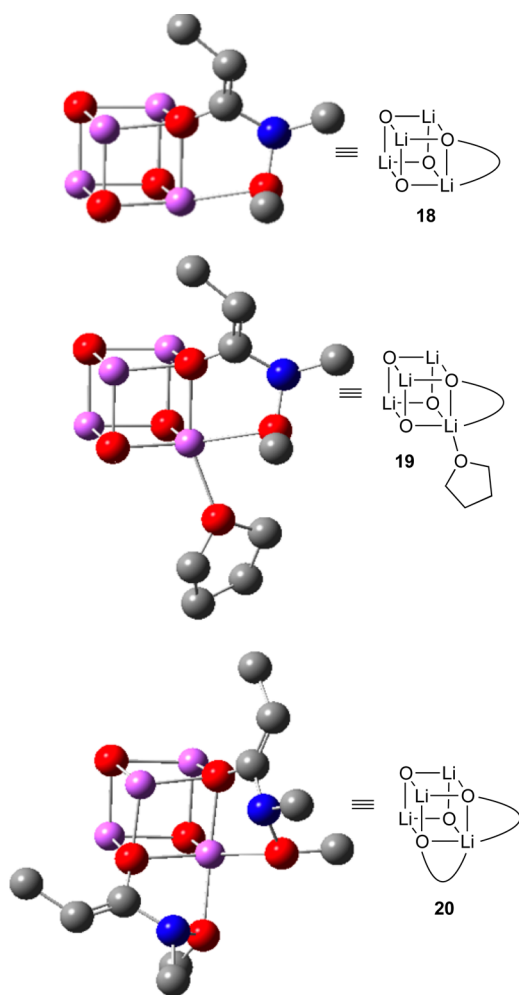
**Scheme 1**



**Solvation and Chelation: Tetramers.** DFT calculations suggest disruption of the tetramer chelates by THF is not favorable for interesting and unexpected reasons. Starting with uncomplexed methoxy moieties, minimizations converge on structures in which the methoxy moieties reassociate to lithium *without loss of THF* (eq 8). We can find only a few particularly idiosyncratic examples of five-coordinated lithium nuclei within organolithium cubes.<sup>28</sup>



There is a subtle structural feature to five-membered-ring chelates on tetrameric cubes that we had never noticed: *the internal ligand cannot reach the true corner of a cubic tetramer* (Figure 8). A partial structure of a computed tetramer (18) shows that the small bite angle forces the geometry around the chelated lithium to approximate a trigonal bipyramid. Crystal structures of analogous tetrameric chelates show this same motif.<sup>15,26,27</sup> The critical observation is that *five-membered-ring chelates with relatively small methoxy ligands*

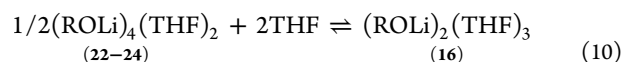
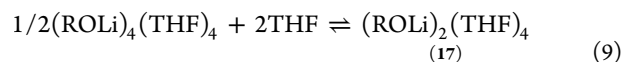


**Figure 8.** DFT computed partial structures of cubic tetramers showing an open coordination site (18), THF saturated lithium (19), and doubly chelated saturated lithium (20).

allow for cooperative solvation by THF (19) and geminal chelation (20).<sup>29,30</sup>

The computed cubic structural forms in Chart 2 include the simplest  $S_4$  from  $D_{2d}$  tetramers (7 and 8) and other forms containing various combinations of four- and five-coordinate lithium nuclei deriving from geminal chelation and cooperative chelation–THF solvation. The indicated resonance counts (in parentheses) correspond to the number of magnetically inequivalent lithiums assuming slow solvent and chelate exchange. Slow solvent exchanges on lithium are rare (except hexamethylphosphoramide<sup>10b</sup>); only recently<sup>15</sup> we observed slow exchange on cubic tetramers. However, the structures in Chart 2 underscore the possible origins of spectral complexity in Figure 7, and the calculated stabilities, even if viewed as crude approximations, also illustrate the stabilization stemming from five-coordinate lithium. In fact, the solvation energies are remarkably similar to those routinely observed when the corner of a simple cubic tetramer is solvated to afford four-coordinate lithium. Given the greatest stabilization for tri-THF solvate 26, our failure to detect tetra-THF solvated analogues of 7 or 8 is notable. Although five-coordinate lithiums could, in theory, closely approximate a trigonal bipyramid, the distortions from that geometry are considerable.<sup>32,33</sup>

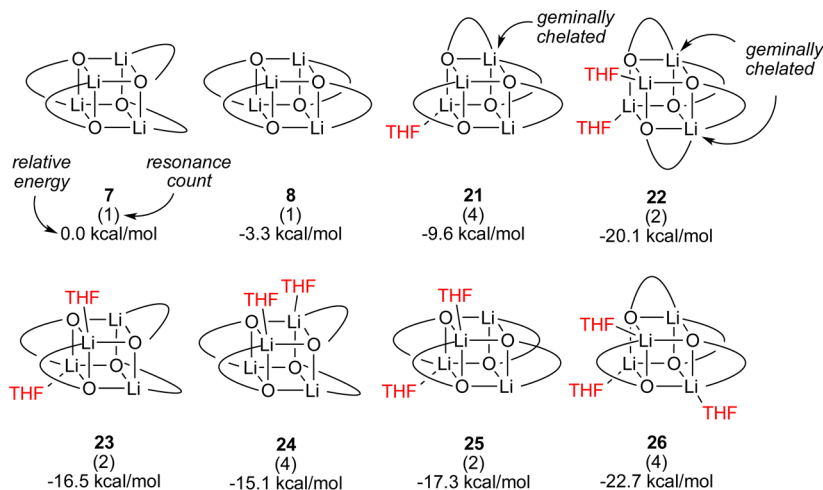
**Dimer/Tetramer Relative Solvation Revisited.** Let us revisit investigations of the tetramer/dimer proportions in various THF concentrations (Figure 6) that implicated the orthodox tetramer/dimer equilibrium in eq 7. Additional possibilities that are mathematically consistent with the measured relative solvation numbers are illustrated in eqs 9 and 10. (We exclude those requiring noninteger solvation numbers.) Equation 9 is what might be expected if all chelates are disrupted. Computational evidence for such a tetra-THF solvated tetramer, whether chelated or not, is lacking. By contrast, the model in eq 10 is consistent with computationally viable (although not *most viable*) disolvated tetramers 22–24 in exchange with the computationally viable trisolvated dimer 16 (Scheme 1). The model in eq 10 is unorthodox, arguably a paradigm shift.



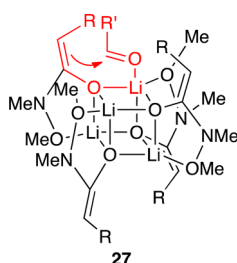
**Possible Mechanistic Consequences.** Provided that tetramers can, under some circumstances, react directly without deaggregating,<sup>34,35</sup> the possibility of high-coordinate lithium nuclei in tetrameric cubes offers a vehicle with which a substrate could enter the coordination sphere without disrupting the structurally organizing chelates. Could an aldol condensation proceed via some fleeting complex such as 27? It is curious that the aldehyde in 27 is *not* complexed to the lithium chelated by the enolate undergoing the 1,2-addition: 27 exemplifies a uniquely aggregate-based mechanism.

These implications contrast markedly with recent studies of tetrameric oxazolidinone-derived enolates (Evans enolates) in which a *six-membered chelate* capable of saturating the lithium nuclei closer to the idealized tetrahedral angle was shown to have no penchant for accepting additional coordinating solvent.<sup>15a</sup> Unusual solvation numbers in the tetrameric enolates, if undetected, would wreak havoc on kinetics-derived mechanistic models owing to the incorrectly assigned reactant.

Chart 2



\*Energies implicitly include THFs to balance equations.



## CONCLUSIONS

Weinreb enolates are sufficiently robust for additional applications in synthesis. The most important results described herein were obtained when experimental and computational data suggested that seemingly simple cubic tetramers may attain unusually high coordination numbers.<sup>15,32</sup>

After years of studying structures and mechanisms of dimeric lithium amides and dimeric carbanions, we are finding that contending with *four* subunits in tetrameric enolates is quite challenging. The relative reactivities of tetramers, dimers, and monomers are becoming well-defined through studies under nonequilibrium conditions by Reich and co-workers<sup>10b</sup> and under equilibrium conditions by Streitwieser and co-workers.<sup>11</sup> There is only spartan evidence that enolate aggregates react without intervening deaggregation.<sup>35,36</sup> Evaluations of the detailed coordination chemistry of the cubic tetramers comprise a crucial niche in the elucidation of tetramer reactivity.

## EXPERIMENTAL SECTION

**Reagents and Solvents.** THF and toluene were distilled from solutions containing sodium benzophenone ketyl. Toluene stills contained approximately 1% tetraglyme to dissolve the ketyl. [<sup>6</sup>Li]LDA and [<sup>6</sup>Li,<sup>15</sup>N]LDA were prepared as described previously.<sup>14</sup> Solutions of LDA were titrated for an active base with a literature method.<sup>37</sup> Air- and moisture-sensitive materials were manipulated under argon with standard glovebox, vacuum line, and syringe techniques. Substrates are all known and prepared using standard literature procedures.<sup>38</sup>

**NMR Spectroscopy.** Individual stock solutions of substrates and LDA were prepared at room temperature. An NMR tube under vacuum was flame-dried on a Schlenk line and allowed to return to room temperature, backfilled with argon, and placed in a  $-78\text{ }^{\circ}\text{C}$  dry

ice/acetone bath. The appropriate amounts of Weinreb amide and LDA (1.1 equiv) were added sequentially via syringe. The tube was sealed under partial vacuum and vortexed three times on a vortex mixer for 5 s with cooling between each treatment. Equilibrated samples were stored in a freezer at  $-86\text{ }^{\circ}\text{C}$ . Each sample routinely contained 0.10 M total enolate with a 0.030 M excess of LDA. Mixed dimers (**8**) generated from excess [<sup>6</sup>Li,<sup>15</sup>N]LDA were characterized by using <sup>6</sup>Li and <sup>15</sup>N NMR spectroscopy.<sup>21</sup> Standard <sup>6</sup>Li, <sup>13</sup>C, and <sup>15</sup>N NMR spectra were recorded on a 500 MHz spectrometer at 73.57, 125.79, and 50.66 MHz, respectively. <sup>6</sup>Li, <sup>13</sup>C, and <sup>15</sup>N resonances were referenced to 0.30 M [<sup>6</sup>Li]LiCl/MeOH at  $-80\text{ }^{\circ}\text{C}$  (0.0 ppm), the CH<sub>2</sub>O resonance of THF at  $-90\text{ }^{\circ}\text{C}$  (67.57 ppm), and neat Me<sub>2</sub>NiEt at  $-90\text{ }^{\circ}\text{C}$  (25.7 ppm).

**2-Benzyl-3-hydroxy-N-methoxy-N-methylpropanamide (14).** *N*-Methoxy-*N*-methyl-3-phenylpropanamide (0.050 g, 0.259 mmol) was dissolved in THF and added dropwise to a solution of lithium diisopropyl amide (0.0357 g, 0.337 mmol) at  $-78\text{ }^{\circ}\text{C}$ . The solution was allowed to warm to rt and was stirred for an additional 30 min. The reaction was quenched with pH 7 phosphate buffer and extracted with EtOAc (3×). The combined organic layer was washed with brine (1×), dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated under reduced pressure. The resulting mixture was purified by chromatography (SiO<sub>2</sub>, 100% ether) to give a 1:2 inseparable mixture of 2-benzyl-3-hydroxy-*N*-methoxy-*N*-methylpropanamide (**14**) and *N*-methyl-3-phenylpropanamide (**13**) as a clear oil after flash chromatography (0.0135 g, 23%). <sup>1</sup>H NMR (599 MHz, Chloroform-*d*)  $\delta$  7.25 (m, 2H), 7.17 (m, 3H), 3.73 (m, 2H), 3.48 (s, 3H), 3.26 (m, 1H), 3.14 (s, 3H), 2.96 (dd, *J* = 13.4, 7.4 Hz, 1H), 2.90 (s, 1H), 2.83 (dd, *J* = 13.4, 7.6 Hz, 1H); <sup>13</sup>C NMR (151 MHz, Chloroform-*d*)  $\delta$  175.6, 139.3, 129.2, 128.5, 126.5, 63.0, 61.5, 45.0, 34.4, 31.9.

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02067.

Spectroscopic, kinetic, and computational data and authors for ref 18 (PDF)

## AUTHOR INFORMATION

### Corresponding Author

\*E-mail: dbc6@cornell.edu.

### Notes

The authors declare no competing financial interest.

## ACKNOWLEDGMENTS

We thank the National Institutes of Health (GM077167) for support.

## REFERENCES

- (1) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815.
- (2) (a) Singh, J.; Satyamurthi, N.; Aidhen, I. S. *J. Prakt. Chem.* **2000**, *342*, 340. (b) Weinreb, S. M.; Folmer, J. J.; Ward, T. R.; Georg, G. I. *N,O-Dimethylhydroxylamine*. In *e-EROS Encyclopedia of Reagents for Organic Synthesis*; John Wiley & Sons: New York, 2006. (c) Sibi, M. P. *Org. Prep. Proced. Int.* **1993**, *25*, 15.
- (3) Qu, B.; Collum, D. B. *J. Org. Chem.* **2006**, *71*, 7117.
- (4) Reviews of enolates in synthesis: (a) Green, J. R. *Science of Synthesis*; Georg Thieme Verlag: New York, 2005; Vol. *8a*, pp 427–486. (b) Schetter, B.; Mahrwald, R. *Angew. Chem., Int. Ed.* **2006**, *45*, 7506. (c) Farina, V.; Reeves, J. T.; Senanayake, C. H.; Song, J. J. *Chem. Rev.* **2006**, *106*, 2734. (d) Wu, G.; Huang, M. *Chem. Rev.* **2006**, *106*, 2596. (e) Braun, M. *Helv. Chim. Acta* **2015**, *98*, 1.
- (5) (a) De la Campa, R.; Florez, J. *Chem. - Eur. J.* **2015**, *21*, 1854. (b) Davis, F. A.; Xu, P. *J. Org. Chem.* **2011**, *76*, 3329. (c) Davis, F. A.; Theddu, N. *J. Org. Chem.* **2010**, *75*, 3814. (d) Davies, S. G.; Goodwin, C. J.; Hepworth, D.; Roberts, P. M.; Thomson, J. E. *J. Org. Chem.* **2010**, *75*, 1214. (e) Davis, F. A.; Song, M.; Qiu, H.; Chai, J. *Org. Biomol. Chem.* **2009**, *7*, 5067. (f) Davis, F. A.; Song, M. *Org. Lett.* **2007**, *9*, 2413. (g) Kaur, P.; Nguyen, T.; Li, G. *Eur. J. Org. Chem.* **2009**, *6*, 912. (h) Farr, R. N. 3-Substituted Isoxazolidines as Chiral Auxillary Agents. U.S. 6020497A1. February, 1, 2000. (i) Abiko, A.; Liu, J. F.; Wang, G.; Masamune, S. *Tetrahedron Lett.* **1997**, *38*, 3261. (j) Abiko, A.; Moriya, O.; Filla, S. A.; Masamune, S. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 793. (k) Palomo, C.; Aizpurua, J. M.; Aurrekoetxea, N.; Lopez, M. C. *Tetrahedron Lett.* **1991**, *32*, 2525. (l) Sato, K.; Sekiguchi, T.; Ishihara, T.; Konno, T.; Yamanaka, H. *J. Org. Chem.* **2004**, *69*, 5041.
- (6) Davis, F. A.; Prasad, K. R.; Nolt, M. B.; Wu, Y. *Org. Lett.* **2003**, *5*, 925.
- (7) (a) Hirner, S.; Kirchner, D. K.; Somfai, P. *Eur. J. Org. Chem.* **2008**, *33*, 5583. (b) Hirner, S.; Somfai, P. *J. Org. Chem.* **2009**, *74*, 7798.
- (8) Kolonko, K. J.; Guzei, I. A.; Reich, H. J. *J. Org. Chem.* **2010**, *75*, 6163.
- (9) Sibi, M. P.; Sharma, R.; Paulson, K. L. *Tetrahedron Lett.* **1992**, *33*, 1941.
- (10) (a) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1624. (b) Reich, H. J. *Chem. Rev.* **2013**, *113*, 7130. (c) Harrison-Marchand, A.; Mongin, F. *Chem. Rev.* **2013**, *113*, 7470.
- (11) For leading references to theoretical studies of O-lithiated species, see: (a) Khartabil, H. K.; Gros, P. C.; Fort, Y.; Ruiz-Lopez, M. F. *J. Org. Chem.* **2008**, *73*, 9393. (b) Streitwieser, A. *J. Mol. Model.* **2006**, *12*, 673. (c) Pratt, L. M.; Streitwieser, A. *J. Org. Chem.* **2003**, *68*, 2830. (d) Pratt, L. M.; Nguyen, S. C.; Thanh, B. T. *J. Org. Chem.* **2008**, *73*, 6086.
- (12) Ramirez, A.; Lobkovsky, E.; Collum, D. B. *J. Am. Chem. Soc.* **2003**, *125*, 15376 and references cited therein.
- (13) Stabilization of five-membered chelates for a number of metals has been attributed to an enthalpy effect associated with greater distortion induced in the complex upon closure for a six-membered ring: (a) Munataka, M.; Kitagawa, S.; Yagi, F. *Inorg. Chem.* **1986**, *25*, 964. (b) Dobson, G. R.; Dobson, C. B.; Mansour, S. E. *Inorg. Chem.* **1985**, *24*, 2179. (c) Bisi-Castellani, C.; Maresca, L.; Natile, G. *Inorg. Chim. Acta* **1984**, *89*, 157. (d) Tobe, M. L.; Schwab, A. P.; Romeo, R. *Inorg. Chem.* **1982**, *21*, 1185. (e) Reisner, G. M.; Bernal, I.; Dobson, G. R. *J. Organomet. Chem.* **1978**, *157*, 23. (f) Knebel, W. J.; Angelici, R. J. *Inorg. Chem.* **1974**, *13*, 627. (g) Dudev, T.; Lim, C. *J. Am. Chem. Soc.* **1998**, *120*, 4450.
- (14) (a) Ma, Y.; Hoepker, A. C.; Gupta, L.; Faggini, M. F.; Collum, D. B. *J. Am. Chem. Soc.* **2010**, *132*, 15610. (b) Romesberg, F. E.; Gilchrist, J. H.; Harrison, A. T.; Fuller, D. J.; Collum, D. B. *J. Am. Chem. Soc.* **1991**, *113*, 5751.
- (15) (a) Tallmadge, E. H.; Collum, D. B. *J. Am. Chem. Soc.* **2015**, *137*, 13087. (b) Bruneau, A. M.; Collum, D. B. *J. Am. Chem. Soc.* **2014**, *136*, 2885. (c) Jin, K. J.; Collum, D. B. *J. Am. Chem. Soc.* **2015**, *137*, 14446.
- (16) Renny, J. S.; Tomasevich, L. L.; Tallmadge, E. H.; Collum, D. B. *Angew. Chem., Int. Ed.* **2013**, *52*, 11998.
- (17) Job, P. *Ann. Chim.* **1928**, *9*, 113.
- (18) Frisch, M. J. et al. *GaussianVersion 3.09*, revision A.1; Gaussian, Inc.: Wallingford, CT, **2009**.
- (19) We surveyed a subset of the community and have chosen to refer to  $(LiX)_n$  and  $(LiX)_m(LiX')_n$  as a “homoaggregate” and “heteroaggregate”, respectively, and reserve the term “mixed aggregate” for  $(LiX)_m(LiY)_n$ .
- (20) The measured mole fraction—the mole fraction within only the ensemble of interest—rather intended mole fraction of the enolates added to the samples eliminates the distorting effects of impurities.
- (21) Collum, D. B. *Acc. Chem. Res.* **1993**, *26*, 227.
- (22) For examples and leading references, see ref 10b.
- (23) (a) Reich, H. J.; Kulicke, K. J. *J. Am. Chem. Soc.* **1996**, *118*, 273. (b) Jackman, L. M.; Chen, X. *J. Am. Chem. Soc.* **1997**, *119*, 8681. (c) Jackman, L. M.; Petrei, M. M.; Smith, B. D. *J. Am. Chem. Soc.* **1991**, *113*, 3451. (d) Jackman, L. M.; DeBrosse, C. W. *J. Am. Chem. Soc.* **1983**, *105*, 4177. (e) Dean, R. K.; Reckling, A. M.; Chen, H.; Dawe, L. N.; Schneider, C. M.; Kozak, C. M. *Dalton Trans.* **2013**, *42*, 3504. (f) Boyle, T. J.; Pedrotty, D. M.; Alam, T. M.; Vick, S. C.; Rodriguez, M. A. *Inorg. Chem.* **2000**, *39*, 5133.
- (24) For (ROLi)<sub>n</sub>-type ladders characterized crystallographically, see: (a) Davies, J. E.; Raithby, P. R.; Snaith, R.; Wheatley, A. E. H. *Chem. Commun.* **1997**, *18*, 1721. (b) Armstrong, D. R.; Davies, J. E.; Davies, R. P.; Raithby, P. R.; Snaith, R.; Wheatley, A. E. H. *New J. Chem.* **1999**, *23*, 35. (c) Huang, B. H.; Ko, B. T.; Athar, T.; Lin, C. C. *Inorg. Chem.* **2006**, *45*, 7348. (d) Armstrong, D. R.; Davies, R. P.; Linton, D. J.; Schooler, P.; Shields, G. P.; Snaith, R.; Wheatley, A. E. H. *J. Chem. Soc., Dalton Trans.* **2000**, *23*, 4304. (e) Andrews, P. C.; Bull, S. D.; Koutsaplis, M. *New J. Chem.* **2010**, *34*, 1678. (f) Cousins, D. M.; Davidson, M. G.; Garcia-Vivó, D.; Mahon, M. F. *Dalton Trans.* **2010**, *39*, 8203. (g) Pink, M.; Zahn, G.; Sieler, J. *Z. Anorg. Allg. Chem.* **1994**, *620*, 749. (h) For an example of an (ArOLi)<sub>5</sub> five-rung ladder in solution, see: De Vries, T. S.; Goswami, A.; Liou, L. R.; Gruver, J. M.; Jayne, E.; Collum, D. B. *J. Am. Chem. Soc.* **2009**, *131*, 13142.
- (25) Propionamide **14** was isolated as an oil in a 1:2 mixture with N-methyl-3-phenylpropanamide that was inseparable by normal phase chromatography.
- (26) Selected examples: (a) Davies, R. P.; Wheatley, A. E. H.; Rothenberger, A. *J. Organomet. Chem.* **2006**, *691*, 3938. (b) Armbruster, F.; Armbruster, N.; Klingebiel, U.; Noltemeyer, M.; Schmatz, S. Z. *Naturforsch., B: J. Chem. Sci.* **2006**, *61*, 1261. (c) Graser, M.; Kopačka, H.; Wurst, K.; Müller, T.; Bildstein, B. *Inorg. Chim. Acta* **2013**, *401*, 38.
- (27) (a) Niemeyer, J.; Kehr, G.; Frohlich, R.; Erker, G. *Dalton Trans.* **2009**, 3731. (b) Williard, P. G.; Tata, J. R.; Schlessinger, R. H.; Adams, A. D.; Iwanowicz, E. J. *J. Am. Chem. Soc.* **1988**, *110*, 7901. (c) Jones, C.; Junk, P. C.; Leary, S. G.; Smithies, N. A. *J. Chem. Soc., Dalton Trans.* **2000**, 3186. (d) Müller, G.; Brand, J. Z. *Anorg. Allg. Chem.* **2005**, *631*, 2820. (e) Rajeswaran, M.; Begley, W. J.; Olson, L. P.; Huo, S. *Polyhedron* **2007**, *26*, 3653. (f) Kathirgamanathan, P.; Surendrakumar, S.; Antipan-Lara, J.; Ravichandran, S.; Chan, Y. F.; Arkley, V.; Ganeshamurugan, S.; Kumaravel, M.; Paramswara, G.; Partheepan, A.; Reddy, V. R.; Bailey, D.; Blake, A. J. *J. Mater. Chem.* **2012**, *22*, 6104.
- (28) (a) Deacon, G. B.; Feng, T.; Hockless, D. C. R.; Junk, P. C.; Skelton, B. W.; Smith, M. K.; White, A. H. *Inorg. Chim. Acta* **2007**, *360*, 1364. (b) Uhl, W.; Halvagar, M. R.; Layh, M. *Chem. Commun.* **2009**, *28*, 4269. (c) Janas, Z.; Nerkowski, T.; Kober, E.; Jerzykiewicz, L. B.; Lis, T. *Dalton Trans.* **2012**, *41*, 442. (d) Cousins, D. W.; Davidson, M. G.; Garcia-Vivo, D. *Chem. Commun.* **2013**, *49*, 11809. (e) Khanjin, N. A.; Menger, F. M. *J. Org. Chem.* **1997**, *62*, 8923.
- (29) The restricted bite angle may also account for the penchant of such chelated salts to form hexamers with chelates wrapped around the hexagonal faces: (a) Cosham, S. D.; Johnson, A. L.; Jordan, L.; Mahon, M. F.; Molloy, K. C. *Main Group Met. Chem.* **2012**, *35*, 153. (b) Iwasaki, M.; Narita, T.; Umino, Y. *J. Organomet. Chem.* **2011**, *696*,

2763. (c) McNeil, A. J.; Toombes, G. E. S.; Chandramouli, S. V.; Vanasse, B. J.; Ayers, T. A.; O'Brien, M. K.; Lobkovsky, E.; Gruner, S. M.; Marohn, J. A.; Collum, D. B. *J. Am. Chem. Soc.* **2004**, *126*, 5938.

(d) Armstrong, D. R.; Davies, R. P.; Raithby, P. R.; Snaith, R.; Wheatley, A. E. H. *New J. Chem.* **1999**, *23*, 499.

(30) Promotion of higher solvation by chelated amines has been noted (ref 22a).

(31) For examples of trigonal bipyramidal pentacoordinated lithium amide monomers, see: Poetschke, N.; Nieger, M.; Khan, M. A.; Niecke, E.; Ashby, M. T. *Inorg. Chem.* **1997**, *36*, 4087. Kremer, T.; Hampel, F.; Knoch, F. A.; Bauer, W.; Schmidt, A.; Gabold, P.; Schütz, M.; Ellermann, J.; Schleyer, P. v. R. *Organometallics* **1996**, *15*, 4776.

(32) Selected examples of high-coordinate lithium: (a) Schenk, C.; Schnepf, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 5314. (b) Scheschkewitz, D. *Angew. Chem., Int. Ed.* **2004**, *43*, 2965. (c) Thiele, K.; Gorls, H.; Imhof, W.; Seidel, W. Z. *Anorg. Allg. Chem.* **2002**, *628*, 107. (d) Buchalski, P.; Grabowska, I.; Kaminska, E.; Suwinska, K. *Organometallics* **2008**, *27*, 2346.

(33) There is an isomer of 25 for which we cannot find a minimum computationally.

(34) For examples of reactions that are fast relative to the rates of aggregate–aggregate exchanges, see: (a) McGarrity, J. F.; Ogle, C. A. *J. Am. Chem. Soc.* **1985**, *107*, 1805. (b) Jones, A. C.; Sanders, A. W.; Bevan, M. J.; Reich, H. J. *J. Am. Chem. Soc.* **2007**, *129*, 3492. (c) 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. (d) Jones, A. C.; Sanders, A. W.; Sikorski, W. H.; Jansen, K. L.; Reich, H. J. *J. Am. Chem. Soc.* **2008**, *130*, 6060.

(35) The concept of aggregate-based reactions of enolates has been discussed: (a) Streitwieser, A.; Leung, S. S.-W.; Kim, Y.-J. *Org. Lett.* **1999**, *1*, 145. (b) Leung, S. S.-W.; Streitwieser, A. *J. Am. Chem. Soc.* **1998**, *120*, 10557. (c) Solladié-Cavallo, A.; Csaky, A. G.; Gantz, I.; Suffert, J. *J. Org. Chem.* **1994**, *59*, 5343. (d) Yen, W.; Bakthavatchalam, R.; Xian-Ming, J.; Murphy, C. K.; Davis, F. A. *Tetrahedron Lett.* **1993**, *34*, 3715. (e) Williard, P. G.; Hintze, M. J. *J. Am. Chem. Soc.* **1987**, *109*, 5539.

(36) (a) Kolonko, K. J.; Wherritt, D. J.; Reich, H. J. *J. Am. Chem. Soc.* **2011**, *133*, 16774. (b) Casey, B. M.; Flowers, R. A. *J. Am. Chem. Soc.* **2011**, *133*, 11492.

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

(38) (a) **1a**: Juncosa, J. I.; Hansen, M.; Bonner, L. A.; Cueva, J. P.; Maglathlin, R.; McCorvy, J. D.; Marona-Lewicka, D.; Lill, M. A.; Nichols, D. E. *ACS Chem. Neurosci.* **2013**, *4*, 96. (b) **1b**: Wang, H.; Denton, J. R.; Davies, H. M. L. *Org. Lett.* **2011**, *13*, 4316. (c) **1c**: Tunoori, A. R.; White, J. M.; Georg, G. I. *Org. Lett.* **2000**, *2*, 4091. (d) **1d**: Banwell, M.; Smith, J. *Synth. Commun.* **2001**, *31*, 2011. (e) **1e**: Satyamurthi, N.; Singh, J.; Aidhen, I. S. *Synthesis* **2000**, *2000*, 375. (f) **1f**: Chenard, B. L.; Butler, T. W. Preparation of neuroprotective 3-(piperidinyl-1)-chroman-4,7-diol and 1-(4-hydroxyphenyl)-2-(piperidinyl-1)-alkanol derivatives. WO 9606081A1. February, 29, 1996. (g) **1g**: Oster, T. A.; Harris, T. M. *Tetrahedron Lett.* **1983**, *24*, 1851.