

## Lithium Phenolates Solvated by Tetrahydrofuran and 1,2-Dimethoxyethane: Structure Determination Using the Method of Continuous Variation

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**Abstract:** The method of continuous variation in conjunction with  $^6\text{Li}$  NMR spectroscopy was used to characterize lithium phenolates solvated by tetrahydrofuran and 1,2-dimethoxyethane. The strategy relies on the formation of ensembles of homo- and heteroaggregated phenolates. The symmetries and concentration dependencies of the heteroaggregates attest to the aggregation numbers of the homoaggregates. The structurally diverse phenols afford substrate- and solvent-dependent combinations of lithium phenolate monomers, dimers, trimers, tetramers, and pentamers. We discuss the refinement of protocols for characterizing O-lithiated species. Computational studies examine further the substituent and solvent dependencies of aggregation.

### Introduction

Characterizing O-lithiated species in solution is particularly important because of their role in organic chemistry,<sup>1</sup> but it is a daunting task.<sup>2–7</sup> Problems stem from a combination of the high inherent symmetry of the possible aggregates and the absence of measurable Li–X scalar couplings that have in other studies proven indispensable for characterizing alkylolithiums<sup>8</sup>

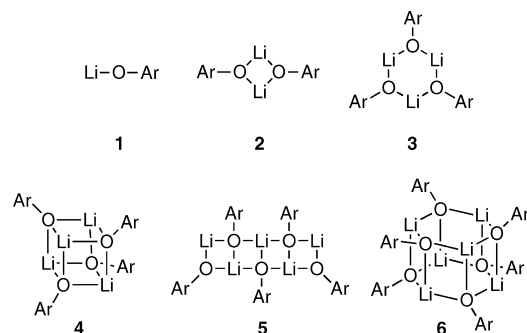
and lithium amides.<sup>9</sup> As a result, methods of characterization are indirect and often specific to the salt/solvent combination.

We have recently found the method of continuous variation<sup>10,11</sup> to be a powerful and widely applicable method for characterizing lithium enolates.<sup>6,7</sup> The strategy finds its origins in studies by Chabanel,<sup>12</sup> Gagne,<sup>13</sup> Günther,<sup>14</sup> and others.<sup>15</sup> We have now

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Chart 1



extended these studies to include a broad range of lithium phenolates (ArOLi) solvated by two commonly used ethereal solvents, tetrahydrofuran (THF) and 1,2-dimethoxyethane (DME). It is tempting to underscore the importance of alkali metal phenolates in the synthesis of pharmaceutical agents,<sup>16–18</sup> but that would be misleading because only the more reactive sodium and potassium phenolates are prominent.<sup>19</sup> In reality, we followed the lead of Jackman and co-workers<sup>5</sup> and turned to lithium phenolates as proxies for lithium enolates.<sup>20</sup> Lithium phenolates offer desirable stability as well as considerable substrate diversity that allow for a systematic study of substrate-dependent structures. An unanticipated benefit of using lithium phenolates is the remarkable substrate-dependent array of monomers, dimers, trimers, tetramers, and pentamers (Chart 1, **1–5**). (Hexamers (**6**) are noticeably absent.)<sup>21–23</sup> Such structural diversity and complexity offer opportunities for refining and stress-testing experimental protocols.

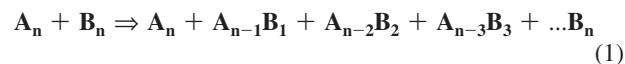
This manuscript follows two distinct themes. The results section describes strategies and tactics—a roadmap of sorts—for readers who wish to understand how the structures are assigned.

The discussion section focuses primarily on the principles of solvation and aggregation.

## Results

Table 1 summarizes the lithium phenolates studied and their resulting aggregation states and affiliated <sup>6</sup>Li chemical shifts. In lieu of a detailed description of each substrate-solvent combination, we summarize the types of experiments used to ascertain structure. Details are archived in Supporting Information. A later section illustrates how these methods can be amalgamated to assign structures to components of complex mixtures of homoaggregated phenolates.

**Ensembles of Homo- and Heteroaggregates.**<sup>24</sup> An ensemble of homo- and heteroaggregated phenolates (eq 1) was monitored as a function of the mole fractions of phenolate subunits (denoted generically as **A** and **B**) using <sup>6</sup>Li NMR spectroscopy.<sup>6,7</sup> The number of aggregates and their symmetries reflect the aggregation state, *n* (Table 2; Chart 2).<sup>13</sup> Resolution of the often large number of <sup>6</sup>Li resonances is maximized by pairing **A<sub>n</sub>** and **B<sub>n</sub>** homoaggregates with widely separated chemical shifts. (The resonance counts for pentamers and hexamers assume slow Li–Li site exchange; vide infra.) A second parameter that influences the choice of the **A<sub>n</sub>**–**B<sub>n</sub>** pair stems from the tendencies (or lack thereof) of the phenolates to form well-behaved ensembles. In short, pairs of structurally related forms (such as similarly hindered phenolates) typically provide statistical distributions<sup>7</sup> that offer compelling structural assignments. To this end, pairs of phenolates differing only in the presence or absence of a para halogen proved especially useful at times.



**Symmetries of Homo- and Heteroaggregates.** <sup>6</sup>Li NMR spectra recorded on **A<sub>n</sub>**–**B<sub>n</sub>** mixtures offer structural insights, as illustrated in Table 2 and Chart 2. When **A<sub>n</sub>** and **B<sub>n</sub>** are monomers (*n* = 1), **A**–**B** mixtures show resonances corresponding to **A** and **B** to the exclusion of additional resonances. By contrast, <sup>6</sup>Li spectra recorded on mixtures of **A<sub>2</sub>** and **B<sub>2</sub>** display resonances of the homodimers along with a single resonance corresponding to the **AB** heterodimer (Figure 1a). The **AB** resonance is typically of intermediate chemical shift consistent with Brown's "local environment" model proffered

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Table 1.  $^6\text{Li}$  NMR Chemical Shifts<sup>a</sup> and Aggregation Numbers of Lithium Phenolates in THF/Toluene and DME/Toluene

Phenolate	#	THF <sup>b</sup> ( $\delta^6\text{Li}$ )		DME <sup>c</sup> ( $\delta^6\text{Li}$ )			
		A <sub>2</sub>	A <sub>4</sub>	A <sub>2</sub>	A <sub>3</sub>	A <sub>4</sub>	A <sub>5</sub>
	7		0.75			0.49	0.63 <sup>d</sup>
	8		0.72			0.50	0.54 <sup>d</sup>
	9		0.68			0.48	0.64 <sup>d</sup>
	10		1.03			0.66	0.80 <sup>d</sup>
	11		0.47			0.27	0.31 <sup>d</sup>
	12		0.51			0.21	0.32 <sup>d</sup>
	13		0.74	0.64		0.49	
	14		0.76	0.56			
	15		0.20	0.25	0.13	0.03	<sup>e</sup>
	16	0.15 <sup>f</sup>		0.19			<sup>e</sup>
	17	0.01 <sup>f</sup>		-0.02			<sup>e</sup>
	18	0.94 <sup>g</sup>	1.69	1.01	0.55		
	19	0.82 <sup>g</sup>	1.44 <sup>h</sup>	0.87	0.39		
	20	0.87 <sup>g</sup>	1.42	0.81	0.25		
	21	-- <sup>i</sup>	-- <sup>i</sup>	0.50	0.27		
	22	-- <sup>i</sup>	-- <sup>i</sup>	0.36	0.08		

Phenolate	#	THF <sup>b</sup> ( $\delta^6\text{Li}$ )		DME <sup>c</sup> ( $\delta^6\text{Li}$ )	
		A <sub>1</sub>	A <sub>2</sub>	A <sub>1</sub>	A <sub>2</sub>
	23		-0.21 <sup>f</sup>		0.08
	24		-0.12		0.26
	25		0.15 <sup>k</sup>		0.34
	26		-0.12 <sup>k</sup>		0.14
	27		0.01		0.03
	28		-0.35		-0.72
	29		-0.58		-0.97
	30	-0.02 <sup>g</sup>	0.63	-0.52	0.32 <sup>d</sup>
	31	-- <sup>i</sup>	-- <sup>i</sup>	-0.64	
	32	-0.01 <sup>g</sup>	0.67	-0.48	0.26 <sup>d</sup>

<sup>a</sup> Chemical shifts relative to an external standard of 0.30 M  $^6\text{LiCl}$  in MeOH. <sup>b</sup> THF (1.2 M) in toluene. <sup>c</sup> DME (2.9 M) in toluene. <sup>d</sup> DME (0.22 M) in toluene. <sup>e</sup> Two minor peaks, one far upfield ( $\delta -2.6$  ppm) associated with a pentamer structure inconsistent with ladder **5**. <sup>f</sup> THF (3.0 M) in toluene. <sup>g</sup> Major species in neat THF. <sup>h</sup> Marginally soluble in 1.2 M THF/toluene. <sup>i</sup> Not characterized. <sup>j</sup> Major species. <sup>k</sup> THF (2.0 M) in toluene.

decades ago.<sup>15c,25</sup> Spectra derived from **A**<sub>4</sub>–**B**<sub>4</sub> mixtures show single resonances for **A**<sub>4</sub> and **B**<sub>4</sub> along with 3:1, 2:2, and 1:3 resonance pairs characteristic of the **A**<sub>3</sub>**B**<sub>1</sub>, **A**<sub>2</sub>**B**<sub>2</sub>, and **A**<sub>1</sub>**B**<sub>3</sub> heteroaggregates (Figure 1b). Once again, the  $^6\text{Li}$  chemical shifts are dominated by the proximate phenolates (local environment).

Trimers are rarely observed: only in DME and invariably as components of mixtures.<sup>26</sup> Although special characterization methods required by mixtures are discussed below, a few comments about the symmetries of cyclic trimer **3** versus ladder **33** are appropriate here.<sup>27</sup>

Cyclic homotrimer **3** would display a single resonance (Chart 2), whereas the corresponding ladder **33** would display a 2:1

pair of resonances provided that the exchange of lithium nuclei within the aggregates—so-called intraaggregate exchange—is slow.<sup>28</sup> In theory, **A**<sub>2</sub>**B**<sub>1</sub> and **A**<sub>1</sub>**B**<sub>2</sub> cyclic trimers would appear

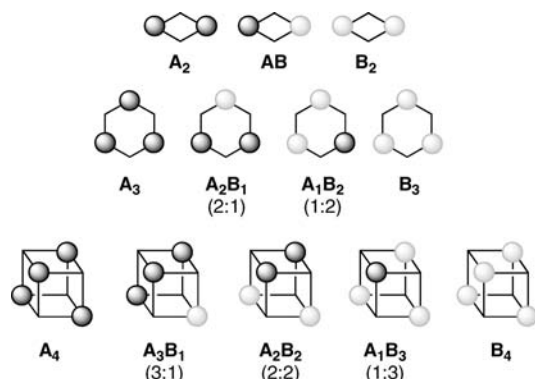
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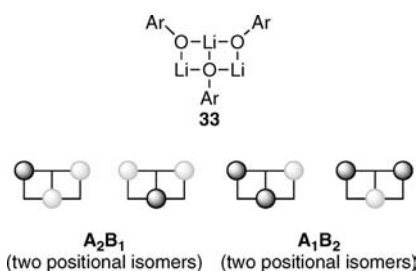
**Table 2.** Spectroscopically Distinguishable Aggregates in Binary Mixtures of Lithium Phenolates **A** and **B**

aggregation number	aggregates (ratio of $^6\text{Li}$ resonances)
monomer (1)	<b>A B</b>
dimer (2)	<b>A<sub>2</sub> AB B<sub>2</sub></b>
trimer (3)	<b>A<sub>3</sub> A<sub>2</sub>B (2:1) AB<sub>2</sub> (1:2) B<sub>3</sub></b>
tetramer (4)	<b>A<sub>4</sub> A<sub>3</sub>B<sub>1</sub> (3:1) A<sub>2</sub>B<sub>2</sub> (2:2) A<sub>1</sub>B<sub>3</sub> (1:3) B<sub>4</sub></b>
pentamer (5)	<b>A<sub>5</sub> (2:2:1)<sup>a</sup></b> <b>A<sub>4</sub>B<sub>1</sub> (3 positional isomers/13 resonances)</b> <b>A<sub>3</sub>B<sub>2</sub> (6 positional isomers/26 resonances)</b> <b>A<sub>2</sub>B<sub>3</sub> (6 positional isomers/26 resonances)</b> <b>A<sub>1</sub>B<sub>4</sub> (3 positional isomers/13 resonances)</b> <b>B<sub>5</sub> (2:2:1)<sup>a</sup></b>
hexamer (6)	<b>A<sub>6</sub></b> <b>A<sub>5</sub>B<sub>1</sub> (1:2:2:1)</b> <b>A<sub>4</sub>B<sub>2</sub> (3 positional isomers/9 resonances)</b> <b>A<sub>3</sub>B<sub>3</sub> (3 positional isomers/12 resonances)</b> <b>A<sub>2</sub>B<sub>4</sub> (3 positional isomers/9 resonances)</b> <b>A<sub>1</sub>B<sub>5</sub> (1:2:2:1)</b> <b>B<sub>6</sub></b>

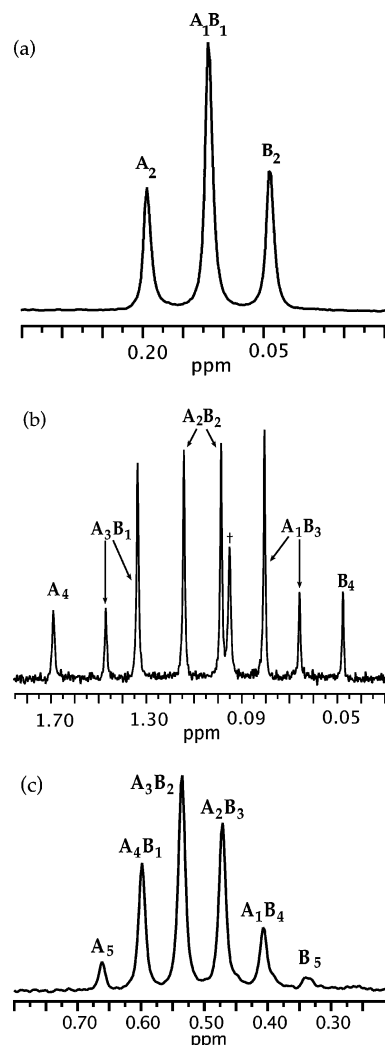
<sup>a</sup> Counts assume a pentameric ladder in slow exchange, but the observed resonances are actually time-averaged single resonances, as described in the text.

**Chart 2.** Dimer, Trimer, and Tetramer Mixtures Showing Magnetically Inequivalent Lithium Sites

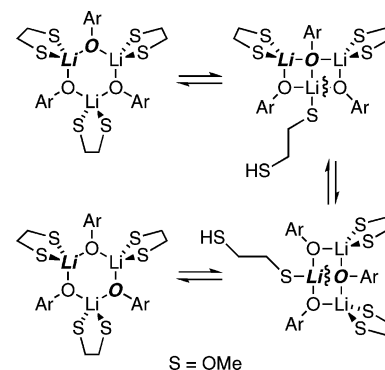
as two pairs of 2:1 resonances (four total), whereas ladder forms of **A<sub>2</sub>B<sub>1</sub>** and **A<sub>1</sub>B<sub>2</sub>** would afford, by virtue of positional isomerism (depicted below), as many as *ten* distinct resonances. In practice, single resonances observed for **A<sub>3</sub>** and **B<sub>3</sub>** homoaggregated trimers seem to implicate the cyclic trimer **3** motif. (Cyclic trimer derived from **19** appears as a single sharp resonance even when higher resolution  $^{19}\text{F}$  NMR spectroscopy is used.) **A<sub>2</sub>B<sub>1</sub>** and **A<sub>1</sub>B<sub>2</sub>** heterotrimers, however, also appear as single, sharp resonances, indicating that intraaggregate exchange is rapid on  $^6\text{Li}$  NMR time scales.<sup>28</sup> The high fluxionality, previously noted in DME-solvated lithium enolates,<sup>7</sup> is attributed to hemilability of DME as posited in Scheme 1. Thus, the cyclic and ladder motifs for trimers are indistinguishable by the apparent symmetry.



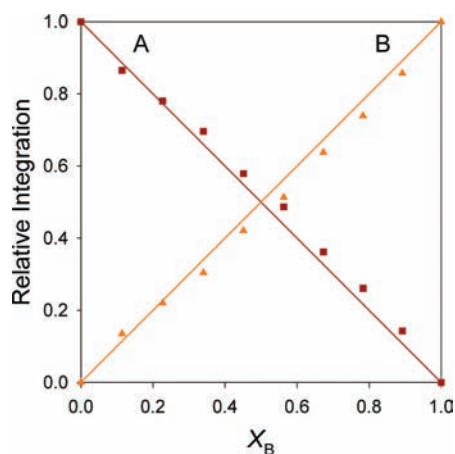
Pentamers are prevalent only at low DME concentrations (<2 equiv/Li). Homoaggregated ladder **5**,<sup>27,29</sup> the only pentameric



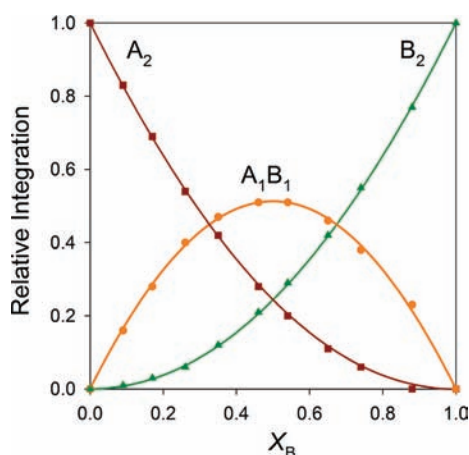
**Figure 1.**  $^6\text{Li}$  NMR spectra recorded at  $-90\text{ }^\circ\text{C}$  of toluene solutions containing approximate 1:1 mixtures of: (a)  $[\text{}^6\text{Li}]\mathbf{25}$  (**A**) and  $[\text{}^6\text{Li}]\mathbf{26}$  (**B**) in 2.0 M THF; (b)  $[\text{}^6\text{Li}]\mathbf{18}$  (**A**) and  $[\text{}^6\text{Li}]\mathbf{11}$  (**B**) in 1.20 M THF; (c)  $[\text{}^6\text{Li}]\mathbf{9}$  (**A**) and  $[\text{}^6\text{Li}]\mathbf{11}$  (**B**) in 0.22 M DME recorded at  $-30\text{ }^\circ\text{C}$ . † denotes LiHMDS dimer.

**Scheme 1**

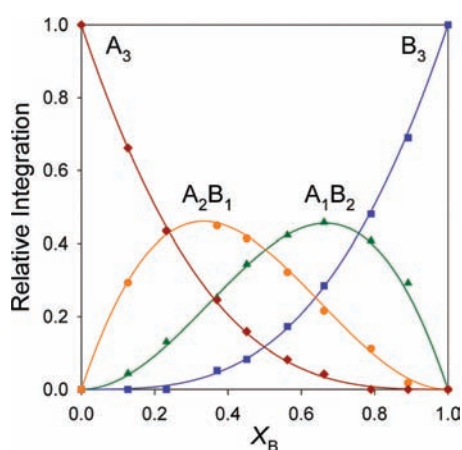
form we considered seriously, should appear as a 2:2:1 triad of resonances. In practice, however, pentamers appear as very broad downfield  $^6\text{Li}$  resonances at  $-90\text{ }^\circ\text{C}$  that sharpen to single resonances and shift markedly upfield when the probe is warmed to  $>-50\text{ }^\circ\text{C}$ . The broadness appears to derive from partially decoalesced intraaggregate exchange, and the temperature-dependent chemical shift may result from changing solvation



**Figure 2.** Job plot showing the relative integrations versus intended mole fractions of **31** ( $X_B$ ) for 0.10 M mixtures of phenolates [ $^6\text{Li}$ ]**30** (A) and [ $^6\text{Li}$ ]**31** (B) in 2.9 M DME/toluene at  $-90^\circ\text{C}$ .

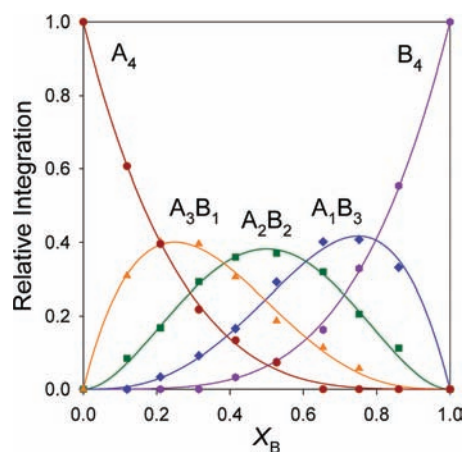


**Figure 3.** Job plot showing the relative integrations versus measured mole fractions of **29** ( $X_B$ ) for 0.10 M mixtures of phenolates [ $^6\text{Li}$ ]**28** (A) and [ $^6\text{Li}$ ]**29** (B) in 1.2 M THF/toluene at  $-90^\circ\text{C}$ .

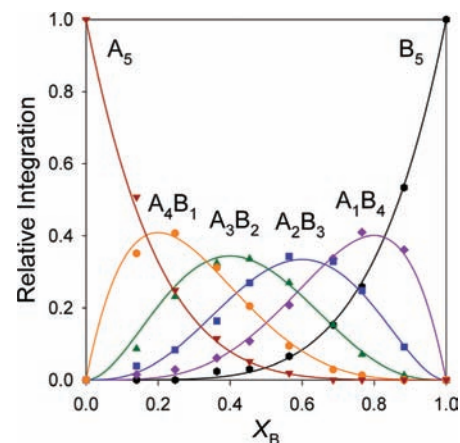


**Figure 4.** Job plot showing the relative integrations versus measured mole fractions of **20** ( $X_B$ ) for 0.10 M mixtures of phenolates [ $^6\text{Li}$ ]**18** (A) and [ $^6\text{Li}$ ]**20** (B) in 2.9 M DME/toluene at  $-90^\circ\text{C}$ .

numbers (vide infra). Poor solubilities at low DME concentrations precluded using the lower probe temperatures required to observe pentamers by  $^6\text{Li}$  NMR spectroscopy in the slow exchange limit. Fortunately,  $^{19}\text{F}$  NMR spectra of fluorinated



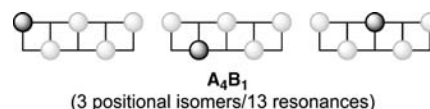
**Figure 5.** Job plot showing the relative integrations versus measured mole fractions of **11** ( $X_B$ ) for 0.10 M mixtures of phenolates [ $^6\text{Li}$ ]**9** (A) and [ $^6\text{Li}$ ]**11** (B) in 2.9 M DME/toluene at  $-90^\circ\text{C}$ .



**Figure 6.** Job plot showing the relative integrations versus measured mole fractions of **11** ( $X_B$ ) for 0.10 M mixtures of phenolates [ $^6\text{Li}$ ]**9** (A) and [ $^6\text{Li}$ ]**11** (B) in 0.22 M DME/toluene at  $-30^\circ\text{C}$ .

phenolates **11** and **12** revealed a well-resolved 2:2:1 triad in each case. Pentamer-derived Job plots (vide infra) are also compelling.

Ensembles of pentamers derived from  $\text{A}_5$ – $\text{B}_5$  mixtures could have posed serious problems because positional isomerism (illustrated emblematically for the  $\text{A}_4\text{B}_1$  form below) would afford 84 magnetically inequivalent  $^6\text{Li}$  nuclei in an  $\text{A}_5$ – $\text{B}_5$  ensemble. Indeed, spectra recorded at the lowest attainable temperatures are useless. Warming the probe above  $-50^\circ\text{C}$ , however, elicits rapid intraaggregate exchange,<sup>28</sup> causing the six stoichiometrically distinct  $\text{A}_n\text{B}_{5-n}$  pentamers to appear as six well-resolved resonances (Figure 1c). This exchange removes the inherent asymmetry of the ladders and the problems created by positional isomerism.<sup>6</sup>



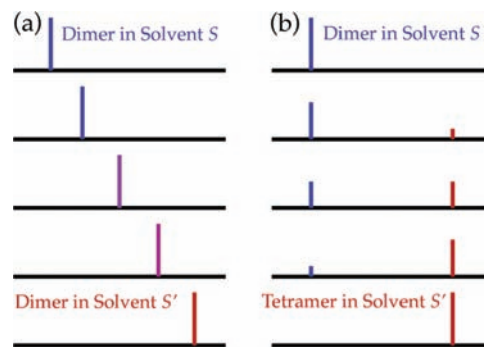
**Method of Continuous Variation.**<sup>11</sup> Plots of aggregate concentrations versus mole fractions of subunits **A** and **B**—so-called Job plots<sup>10</sup>—representing the five observed aggregation states (monomers through pentamers) are illustrated in Figures 26. The parametric fits show that all are nearly statistical

distributions; nonstatistical ensembles usually attest to deep-seated structural anomalies (vide infra). The math underlying the parametric fits has been discussed previously.<sup>6,7</sup>

The protocols used to measure aggregate concentrations for the Job plots require comment. The actual mole fractions of the **A** and **B** subunits can deviate from the intended mole fractions because of experimental error, nonquantitative lithiation, impurities, selective formation of mixed aggregates<sup>24</sup> with base (especially in DME),<sup>30,31</sup> formation of byproduct, or multiple homoaggregates (vide infra). (Some of these deviations are, admittedly, unlikely with lithium phenolates.) Although such deviations do not impair the qualitative analysis of aggregate numbers and their symmetries, they certainly distort (sometimes profoundly) the concentrations of the available **A** and **B** subunits from the intended concentrations. Consequently, the mole fractions of the **A** and **B** subunits were measured (rather than inferred from the concentrations of added phenols) by integrating the <sup>6</sup>Li resonances within an ensemble. Even in the cleanest and simplest cases wherein the intended and the measured mole fractions are comparable, we believe the latter to be more accurate. Job plots for monomers, however, must use the intended mole fraction because the measured mole fraction would necessarily afford perfect lines (no scatter).

**Deviations from Statistical Behavior.** Deviations from statistical behavior can occur for a variety of reasons. For example, a mixture of **25** and **27** in DME affords a single new resonance consistent with formation of a heterodimer, but with a non-statistical (unusually high) preference. We suspect that heteroaggregation is promoted by severe steric interactions in the homodimer of **27**.<sup>7,32</sup> When distributions deviate significantly from statistical predictions, pairing substrates that are similar is constructive. Indeed, mixtures of **25** and **26**, differing only in the absence or presence of a halogen moiety in the para position, afford statistical distributions.<sup>33</sup>

One also observes homoaggregates that resist heteroaggregation. The obvious case occurs when two monomers are paired (**30** and **31**, for example). In a more instructive example, mixtures of **11** and **14** in DME show only traces of a new species assigned by symmetry as a heterodimer. Pairing **7** and **11** shows that **11** is tetrameric (a statistical ensemble), whereas pairing **14** and **24** reveals **14** to be dimeric. Thus, heteroaggregation is precluded when the homoaggregates are of two different aggregation states. In the most potentially deceptive case, a mixture of tetrameric **9** and dimeric **16** in 2.9 M DME afforded an ensemble that could easily be confused with an all-dimer **A**<sub>2</sub>–**AB**–**B**<sub>2</sub> ensemble. The tetramer assignment of **9** was made using independent pairings and solvent swaps (vide infra).



**Figure 7.** <sup>6</sup>Li NMR spectra anticipated if replacing solvent *S* by *S'* causes: (a) only exchange of solvent on a common phenolate aggregate (**A<sub>n</sub>**), and (b) an aggregation change (**A<sub>m</sub>** for **A<sub>n</sub>**).

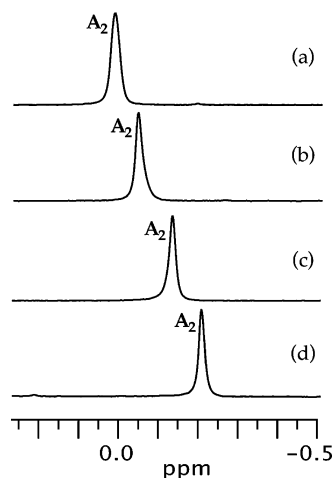
The most striking and provocative deviations from statistical behavior center around DME-solvated dimers. Pairing 2,6-diphenyl-substituted phenolate **28** with isostructural 4-bromo analog **29** affords a statistical **A**<sub>2</sub>–**AB**–**B**<sub>2</sub> ensemble; phenolate **28** in DME is clearly a dimer. Nonetheless, **28** fails to heterodimerize with seemingly similar dimeric phenolates **25** or **27**, suggesting fundamental structural differences (vide infra). Similarly, dimeric **16** and other polyhalogenated phenolates do not statistically heterodimerize with seemingly analogous dimeric hindered phenolates (such as **27**) or orthophenylated lithium phenolate **28**. There appear to be *three types of dimers*; these are discussed further below.

**Solvent Swapping.** A simple protocol can be used to show whether a change in solvent is accompanied by a change in aggregation.<sup>7,34</sup> This protocol serves as a control experiment to confirm conclusions suggested by other data and can provide structural assignments to even minor components of mixtures.

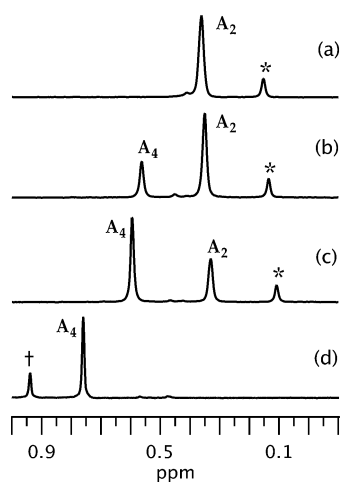
The experiment is based on the observation that solvent–solvent exchanges (ligand substitutions) occur much faster than aggregate–aggregate exchanges.<sup>35</sup> By recording a series of spectra in which one coordinating solvent is incrementally replaced (swapped) by a second, either of two limiting behaviors can be observed: (1) If the observable forms in the two coordinating solvents differ only by ligating solvent, the incremental solvent swap will cause the resonances to exchange by time-averaging (Figure 7a); (2) if the observable forms in the two solvents differ by aggregation number, an incremental solvent swap causes one aggregate to disappear and the other to appear (Figure 7b). The experiment requires a <sup>6</sup>Li chemical shift difference in the two solvents of as little as 0.05 ppm.

- (29) Although we cannot find evidence of five-rung (pentameric) ladders in the crystallographic literature, we observed them as part of nearly statistical ensembles of 3-, 4-, 5-, and 6-rung lithium diethylamide ladders: Rutherford, J. L.; Collum, D. B. *J. Am. Chem. Soc.* **1999**, *121*, 10198.
- (30) (a) Williard, P. G.; Hintze, M. J. *J. Am. Chem. Soc.* **1990**, *112*, 8602. (b) Godenschwager, P. F.; Collum, D. B. *J. Am. Chem. Soc.* **2007**, *129*, 12023.
- (31) (a) [<sup>6</sup>Li,15N]LiHMDS (ref 31b) allows us to detect mixed dimers. (b) 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.
- (32) For early discussions of steric effects on solvation and aggregation, see: Haggerty, F. A.; Settle, 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 discussion and more recent leading references, see: Zhao, P.; Collum, D. B. *J. Am. Chem. Soc.* **2003**, *125*, 14411.

- (33) In previous manuscripts we examined the efficacy of parametric fits to distinguish the all-dimer **A**<sub>2</sub>–**AB**–**B**<sub>2</sub> model from the **A**<sub>2</sub>–**AB**–**B**<sub>4</sub> or **A**<sub>2</sub>–**AB**–**B** models as well as the all tetramer **A**<sub>4</sub>–**A**<sub>3**B**–**A**<sub>2**B**<sub>2</sub>–**A**<sub>1**B**<sub>3</sub>–**B**<sub>4</sub> model from the **A**<sub>4</sub>–**A**<sub>3**B**–**A**<sub>2**B**<sub>2</sub>–**A**<sub>1**B**<sub>3</sub>–**B**<sub>4</sub> model with one homodimer (refs 6 and 7). Focusing on the dimer-dominated example emblematically, **A**<sub>2</sub>–**AB**–**B** and **A**<sub>2</sub>–**AB**–**B**<sub>4</sub> models become indistinguishable from **A**<sub>2</sub>–**AB**–**B**<sub>2</sub> by parametric fit at very low or very high relative **AB** concentration. It is ironic, therefore, that the parametric fits become less effective precisely when the deviation from statistical shows the distinction is most needed.</sub></sub></sub></sub></sub></sub>
- (34) (a) Qu, B.; Collum, D. B. *J. Am. Chem. Soc.* **2006**, *128*, 9355. (b) Bernstein, M. P.; Romesberg, F. E.; Fuller, D. J.; Harrison, A. T.; Williard, P. G.; Liu, Q. Y.; Collum, D. B. *J. Am. Chem. Soc.* **1992**, *114*, 5100.
- (35) Standard ethereal ligands have been observed coordinated to lithium ion in the slow exchange limit only rarely and only at very low temperatures. Leading references: (a) Arvidsson, P. I.; Davidsson, Ö. *Angew. Chem., Int. Ed.* **2000**, *39*, 1467. (b) Sikorski, W. H.; Reich, H. J. *J. Am. Chem. Soc.* **2001**, *123*, 6527. (c) Leading references in ref 7.



**Figure 8.**  $^6\text{Li}$  NMR spectra of 0.10 M solutions of  $[\text{}^6\text{Li}]\mathbf{23}$  (A) at  $-90\text{ }^\circ\text{C}$  in ligand/toluene showing ligands in the following proportions: (a) 100% DME; (b) 5% THF, 95% DME; (c) 28% THF, 72% DME; (d) 100% THF.

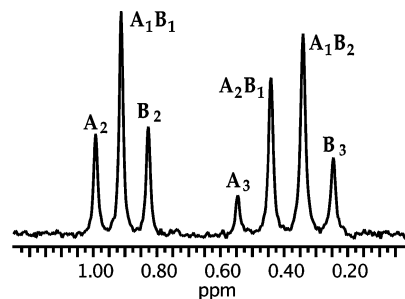


**Figure 9.**  $^6\text{Li}$  NMR spectra of 0.10 M solutions of  $[\text{}^6\text{Li}]\mathbf{14}$  (A) at  $-90\text{ }^\circ\text{C}$  in ligand/toluene showing ligands in the following proportions: (a) 100% DME; (b) 7% THF, 93% DME; (c) 16% THF, 84% DME; (d) 100% THF. \* denotes  $\text{A}\cdot\text{LiHMDS}$  mixed aggregate; † denotes excess LiHMDS.

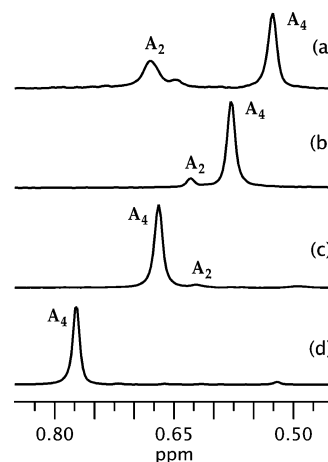
Experimental data are illustrated with DME- and THF-solvated dimers of **23** (Figure 8) and with a DME-solvated dimer and THF-solvated tetramer of **14** (Figure 9).<sup>36</sup>

**Phenolate Concentration Dependencies.** To the extent that an  $\text{A}_n\text{-B}_n$  ensemble represents a single aggregation number (all tetramers, for example), serial dilution should confirm that the proportions of aggregates within the ensemble remain unchanged. In practice, we find that the concentration range needed to provide compelling affirmation of the assignment presents technical challenges. We carry out such control experiments but consider them of minor importance relative to more compelling data supporting aggregation state assignments. Concentration changes can, however, uncover and offer insights into homoaggregate mixtures.

**Multiple Aggregation States.** Varying the absolute lithium phenolate concentration or, more consequentially, the donor solvent concentration often reveals additional homoaggregates and their *relative* solvation and aggregation numbers. Full characterization of such mixtures usually requires a combination of methods. Both qualitative and quantitative concentra-



**Figure 10.**  $^6\text{Li}$  NMR spectrum of an approximate 1:1 mixture of  $[\text{}^6\text{Li}]\mathbf{18}$  (A) and  $[\text{}^6\text{Li}]\mathbf{20}$  (B) in 2.9 M DME/toluene at  $-90\text{ }^\circ\text{C}$ .



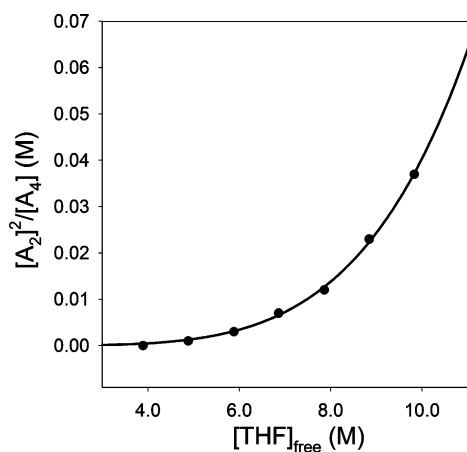
**Figure 11.**  $^6\text{Li}$  NMR spectra of 0.10 M solutions of  $[\text{}^6\text{Li}]\mathbf{13}$  (A) at  $-90\text{ }^\circ\text{C}$  in ligand/toluene showing ligands in the following proportions: (a) 100% DME; (b) 5% THF, 95% DME; (c) 16% THF, 84% DME; (d) 100% THF.

tion dependencies are discussed in the next section. First, we describe Job plots on mixtures of homoaggregates.

Mixing a previously characterized aggregate such as an  $\text{A}_2$  dimer with a  $\text{B}_m\text{-B}_n$  binary mixture in which one of the homoaggregates is a dimer typically affords a statistical  $\text{A}_2\text{-AB-B}_2$  ensemble with one homoaggregate, leaving the other homoaggregate untouched. The success of the Job plot does not demand structural homogeneity. In some instances, mixing an  $\text{A}_m\text{-A}_n$  binary mixture with an analogous  $\text{B}_m\text{-B}_n$  binary mixture affords independent  $\text{A}_m\text{-B}_m$  and  $\text{A}_n\text{-B}_n$  ensembles (Figure 10). Such multiple ensembles can be engineered by pairing structurally similar phenolates, especially those differing only in the absence or presence of a para halogen substituent.

The power of solvent swapping becomes evident when deconvoluting mixtures of homoaggregates. Combining a tetramer-dimer mixture of **13** with dimeric **27** in DME, for example, affords a statistical dimer-based ensemble, leaving the second aggregate of **13** (suspected to be tetramer) isolated. Swapping DME for THF (Figure 11) in the tetramer-dimer mixture of **13** shows that the putative tetramer time-averages with the fully characterized THF-solvated tetramer. Solvent

(36) (a) One can infer approximate relative solvent binding constants from the proportions of the two solvents required to achieve a 50% shift. In Figure 9c, for example, the average chemical shift at equimolar THF and DME suggests a preference for the THF-solvated dimer. (b) If two different aggregation states are observed from a solvent swap, one can extract relative binding constants as well: Remenar, J. F.; Lucht, B. L.; Collum, D. B. *J. Am. Chem. Soc.* **1997**, *119*, 5567.

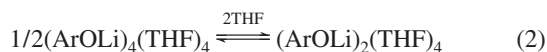


**Figure 12.** Plot of  $[A_2]^2/[A_4]$  versus  $[THF]_{free}$  in toluene as cosolvent for 0.11 M of phenolate **18** (A) at  $-90$  °C. The curve and data represent a best-fit to the model  $A_4(THF)_4 + 2n THF \rightleftharpoons 2A_2(THF)_{(n+2)}$  where  $n = 2.4 \pm 0.03$ .

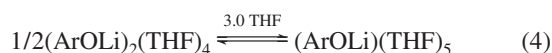
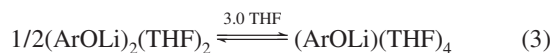
swapping can even be used to identify individual components of ternary mixtures of homoaggregates.<sup>37</sup>

#### Solvent Concentration Dependencies and Solvation Numbers.

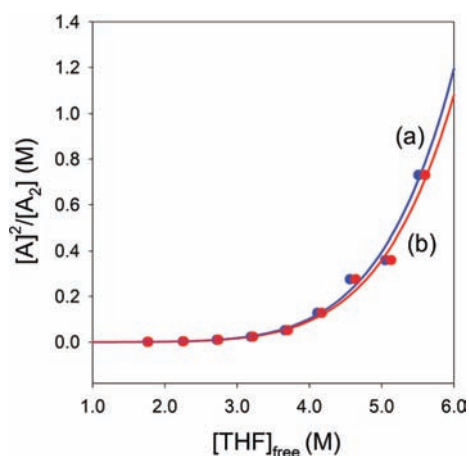
The crystallographic literature of lithium enolates and phenolates is replete with tetrasolvated tetramers.<sup>5,21</sup> If one is willing to use these as benchmarks (which we are), quantitative monitoring of tetramer-dimer ratio versus THF concentration can reveal the solvation number of the dimers. Results using lithium phenolate **18** (Figure 12; eq 2) show that the dimers are tetrasolvated.



THF-solvated monomers are only observed using acutely hindered lithium phenolates **30** and **32**. The extreme steric demand attenuates the importance of the studies because (a) the substrates are not emblematic of normal phenolates, and (b) the solvation numbers of the dimer to which the monomer assignments are anchored are not firmly established. With that said, the solvation numbers are remarkably high. Varying the THF concentrations in solutions containing monomers and dimers of **32** reveals 3.0 additional THF ligands per lithium on the monomer relative to the dimer (Figure 13), which implicates tetra- or pentasolvated monomers, depending on the solvation number of the dimer (eqs 3 and 4). We know that the dimer contains at least one solvent because of a marked shift that occurs when low concentrations of THF are added to toluene solutions of **32**.

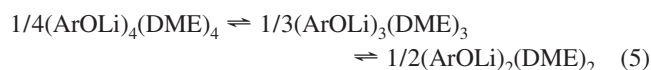


Varying the DME concentrations in solutions of structurally diverse DME solvates offers insights and surprises. DME-

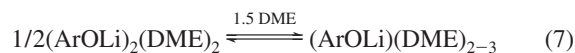
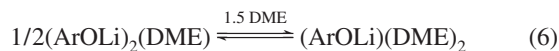


**Figure 13.** Plot of  $[A]^2/[A_2]$  versus  $[THF]_{free}$  in toluene as cosolvent for 0.11 M of phenolate **32** (A) at  $-90$  °C. (a) Blue curve represents a nonlinear least-squares fit of the data (●) to the model  $A_2THF_4 + 2n THF \rightleftharpoons 2A_1THF_{(n+2)}$  where  $n = 3.0 \pm 0.08$ . (b) Red line represents a nonlinear least-squares fit of the data (●) to the model  $A_2(THF)_2 + 2n THF \rightleftharpoons 2A_1THF_{(n+1)}$  where  $n = 3.0 \pm 0.09$ .

concentration-independent dimers, trimers, and tetramers attest to one solvent per lithium (eq 5).



Solvation numbers for DME-solvated monomers are assigned by monitoring the dimer–monomer ratio of phenolate **32**. Once again, measured solvation numbers are remarkably high, but the results are also somewhat quirky. Varying the DME concentrations shows that the monomer of **32** differs from the dimer by having 1.5 additional DME ligands per lithium on the monomer relative to the dimer. We know that the dimer is solvated by DME because of a marked shift that occurs when low concentrations of DME are added to toluene solutions of **32**. If this dimer is monosolvated—a structural motif that could result from severe buttressing—then the monomer is a disolvate (eq 6).<sup>38</sup> If the dimer is a disolvate, then the monomer solvation number is suggested to be 2.5 (eq 7). Such a fractional solvent order could stem from experimental error or a mixture of solvated forms. High solvation numbers are considered in the discussion.



The preference for DME-solvated pentamers only at very low DME concentrations attests to a low per-lithium solvation number, quite logically containing two DME ligands capping the ladder ends as chelates (see below). A significant ( $\approx 0.3$  ppm) upfield shift of the time-averaged pentamer resonance with increasing temperature, however, suggests facile desolvation<sup>39</sup>

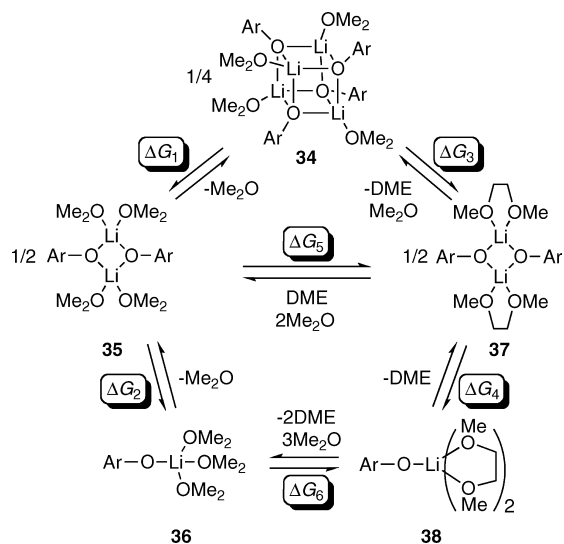
(37) Our first experience with solvent swaps occurred during studies of unsolvated lithium diisopropylamide in which addition of a weakly coordinating trialkylamine caused only one of several unsolvated cyclic oligomers to migrate to the chemical shift of the disolvated dimer (ref 34b).

(38) The crystal structure of a mixed dimer of **30** with  $Me_2AlOAr$  is unsolvated at Li with stabilizing  $Li \cdots H(t-Bu)agostic$  interactions (ref 21i).

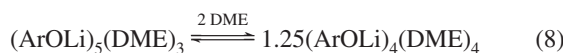
(39) The temperature-dependent change in solvation with warming is inferred to be desolvation because of the substantial negative enthalpies of solvation. For related desolvations, see refs 34 and 53.



## Scheme 2








of at least one internal lithium. Solvent concentration dependencies of pentamer-tetramer mixtures of phenolate **8** at  $-30\text{ }^{\circ}\text{C}$  are quantitatively consistent with pentamers containing an average of three DME ligands (eq 8). The concentration dependencies suggest that tetrasolvation at low temperature ( $-90\text{ }^{\circ}\text{C}$ ) is giving way to trisolvation on warming. Computations proved both supportive and instructive (vide infra).



**Density Functional Theory Computations.** Computational studies of lithium enolates, phenolates, and simple alkoxides have been reported.<sup>40,41</sup> We have carried out additional density functional theory (DFT) computations at the B3LYP/6-31G(d) level<sup>42</sup> addressing issues of particular interest to the structural studies described herein.  $\text{Me}_2\text{O}$  was used as a model for both THF and  $\eta^1$ -DME to reduce the degrees of freedom. Free energies ( $\Delta G$ ) are reported on a *per-lithium basis* in kcal/mol at  $-90\text{ }^{\circ}\text{C}$ . The results for the generic deaggregations in Scheme 2 are listed in Table 3. The solvation numbers and importance of chelation are consistent with the computational data archived in Supporting Information and seem to match experiment reasonably well. We largely refrain from detailed discussions of the absolute free energies ( $\Delta G_1 - \Delta G_6$ ), instead focusing on the influence of substituents and solvents (trends). The substituent dependencies of  $\Delta G_1 - \Delta G_6$  in Table 3 are considered in the discussion.

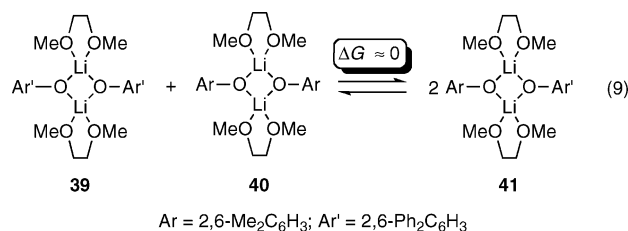
We experimentally detected what appears to be three classes of lithium phenolate dimers manifesting (1) intermediate steric demands, (2) high electron deficiency (polyfluorination), and (3) 2,6-diphenylation. Experimentally, dimers within one class

**Table 3.** Free Energies  $\Delta G_1 - \Delta G_6$  Reported in kcal/mol on a *Per-Lithium Basis*<sup>a</sup>

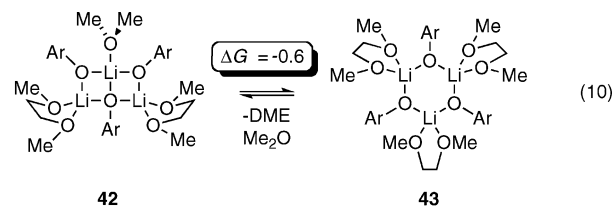
-Ar (#)	$\Delta G_1$	$\Delta G_2$	$\Delta G_3$	$\Delta G_4$	$\Delta G_5$	$\Delta G_6$
 (7)	3.67	10.43	-0.11	10.05	-3.78	-4.16
 (11)	3.79	9.86	-0.14	10.23	-3.92	-4.29
 (12)	3.27	10.59	-0.03	8.98	-3.30	-4.91
 (13)	3.80	9.25	-0.36	7.21	-3.47	-5.51
 (25)	0.21	6.75	-6.22	10.06	-6.40	-3.12

<sup>a</sup> Signs correspond to the affiliated arrows in Scheme 2.

afford decidedly nonstatistical heterodimer ensembles with phenolates from another class. We examined this finding computationally using lithium phenolates **25** and **28** (eq 9). In short, the computations showed no significant deviations of the homodimer-heterodimer equilibrium from statistical, underscoring an uncontested disagreement between theory and experiment. In this context, we re-evaluated the experimental data and stand behind it.



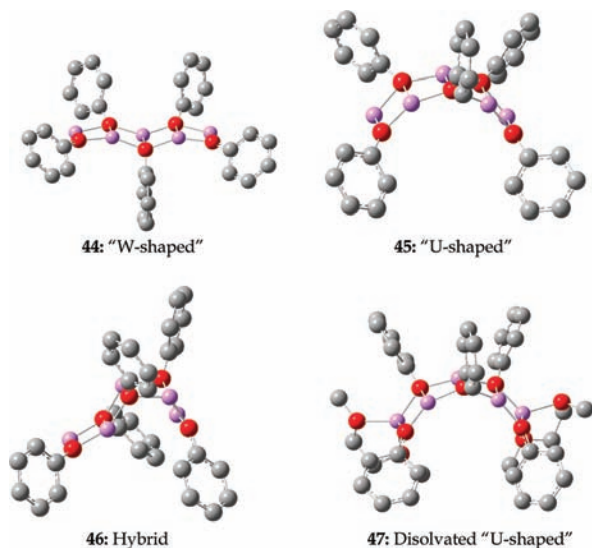
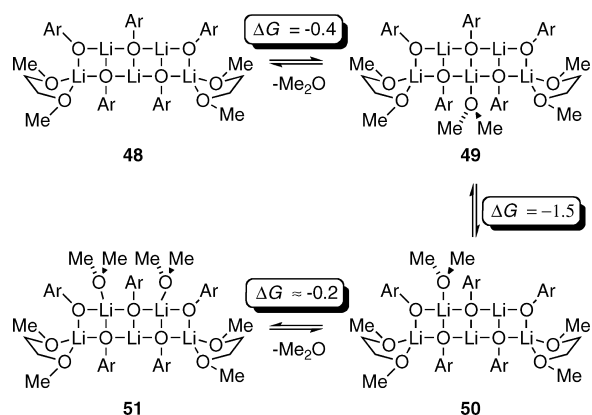
Cursory computational studies of the rarely observed DME-solvated trimers showed triply chelated cyclic form **43** to be more stable than ladder **42** bearing an  $\eta^1$  solvate. We proffered the ladder as an intermediate in the rapid intraaggregate exchange (Scheme 1).



<sup>a</sup>Energy in kcal/mol on a *per-lithium basis* at  $-90\text{ }^{\circ}\text{C}$ .

Computations evaluated the geometry and stabilities of DME-solvated pentameric ladders, suggested by experiment to be a temperature-sensitive mixture of tri- and tetrasolvates. Three geometries—W, U, and a hybrid (**44–46**)—are stable minima in their unsolvated, doubly chelated forms; the U form (**47**) is the most stable.  $\text{Me}_2\text{O}$  was used to model the solvation of the

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Scheme 3<sup>a</sup>

<sup>a</sup> All U-shaped; energies reported in kcal/mol on a per-lithium basis at  $-90\text{ }^{\circ}\text{C}$ .

internal lithiums by monodentate ( $\eta^1$ ) DME ligands (Scheme 3). Tetrasolvate **51** is calculated to be preferred at temperatures below  $-74\text{ }^{\circ}\text{C}$ , whereas trisolvate **50** is favored above  $-74\text{ }^{\circ}\text{C}$ . Thus, the computations successfully mimic the putative temperature-sensitive desolvation detected experimentally. We were also struck by the allosteric effects, phenomena we have referred to as correlated solvation.<sup>43</sup>

## Discussion

Lithium salts are centrally important in such disparate fields as organic synthesis,<sup>44</sup> polymer science,<sup>45</sup> electrochemistry,<sup>46</sup>

medicine,<sup>47</sup> and automotive lubricants.<sup>48</sup> We have been refining protocols that are based on the method of continuous variation—the method of Job—for characterizing O-lithiated species.<sup>10,11</sup> Our interest in the phenolates stems from our desire to develop and refine methods for characterizing their more synthetically important lithium enolate counterparts. Nonetheless, lithium phenolates stand on their own merits because of their stability, purity, availability, substrate flexibility, and aggregate diversity. Examination of a broad array of lithium phenolates in THF and DME solutions revealed a remarkable range of aggregates from monomers through pentamers (**1–5**) and underscored the versatility of these methods.

The problems associated with characterizing LiX species in which the X group is magnetically opaque have been long-standing and acute.<sup>49</sup> The seemingly most general and certainly most popular methods involve measuring colligative properties of solutions, which afford average molecular weights.<sup>2,4,5,19,45,49</sup> Although colligative measurements can provide valuable supporting evidence of structure, as stand-alone methods they are fraught with risk because of problems caused by undetected impurities and mixtures of structural forms. Methods that are also germane to our tactic involve quantitatively monitoring LiX–LiY mixed aggregates constituted from the LiX salt of unknown structure and an LiY salt of known structure.<sup>3,12–15,50,51</sup> In general, progress has been made—enolate studies of Streitwieser and co-workers are certainly notable<sup>3</sup>—but the strategies used are often quite specific to the LiX–solvent combination.

Of particular importance to the work described herein, Jackman and co-workers investigated the structures of lithium phenolates using a combination of methods in which <sup>7</sup>Li quadrupolar splitting constants and predicted chemical shifts of <sup>13</sup>C resonances derived from the para carbons were of paramount importance.<sup>5</sup> Obviously their method applies only to lithium phenolates and not other O-lithiated species. They also focused on a smaller and different subset of lithium phenolates as well as a number of solvents not described herein. Their emphasis on enthalpic and entropic differences in aggregates to ascertain relative solvation numbers appears to be challenging at best. But the congruence of our results and conclusions and those of Jackman and co-workers are notable despite the use of distinctly different approaches.

**Methods.** Our strategy for characterizing lithium phenolates entails breaking the high inherent symmetry (spectral simplicity) of (ROLi)<sub>n</sub> aggregates by mixing two homoaggregates (**A<sub>n</sub>** and **B<sub>n</sub>**) and generating ensembles containing both homo- and heteroaggregates (eq 1).<sup>6,7</sup> The numbers and symmetries of the heteroaggregates, as shown by <sup>6</sup>Li NMR spectroscopy, offer

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- (51) Diffusion-ordered NMR spectroscopy (DOSY) shows considerable potential to examine the structures of LiX salts: Li, D.; Keresztes, I.; Hopson, R.; Williard, P. G. *Acc. Chem. Res.* **2009**, *42*, 270.

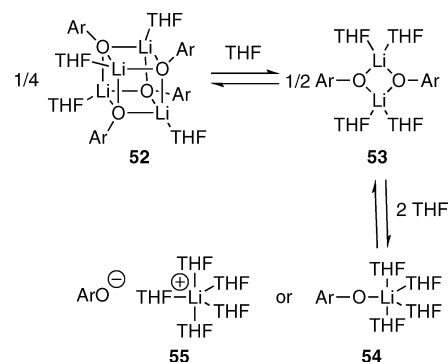
considerable insights into the structures of the homoaggregates (Table 2; Chart 2). By systematically varying the mole fractions of the **A** and **B** subunits, we can use parametric fits to afford the Job plots illustrated emblematically in Figures 2–6. Statistical distributions observed for structurally similar phenolates (some varying by as little as a para halogen substituent) confirm the structural assignments, whereas marked deviations from statistical usually foreshadow different aggregation numbers for **A<sub>m</sub>** and **B<sub>n</sub>**. Once **A<sub>n</sub>** is characterized in one solvent (such as DME) and an aggregate of unknown aggregation number is generated in a different solvent (THF), one can trivially ascertain if the aggregation number differs in the two solvents by a simple experiment illustrated in Figures 7–9 in which DME is incrementally replaced (swapped) by THF. Lithium phenolates distinguished only by the coordinated ligands display a single time-averaged <sup>6</sup>Li resonance, whereas phenolates of differing aggregation number appear as discrete resonances.

Varying the solvent and phenolate concentrations often reveals additional homoaggregates and provides qualitative insight into their relative aggregation and solvation numbers. In some instances, combining **A<sub>m</sub>**–**A<sub>n</sub>** mixtures with **B<sub>m</sub>**–**B<sub>n</sub>** mixtures afford two fully separate **A<sub>m</sub>**–**B<sub>m</sub>** and **A<sub>n</sub>**–**B<sub>n</sub>** ensembles that are easily and independently quantified. In other cases, solvent swaps reveal the structures of homoaggregates irrespective of the total number of homoaggregates. In fact, one of the more satisfying outcomes is that essentially any mixture can be characterized provided that discrete resonances are observed. One cannot, however, overstate the importance of using complementary methods as well as multiple combinations of aggregates. Overdetermination of structure is important.

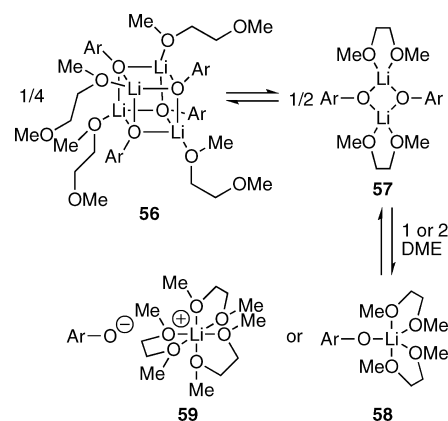
**Solvent Effects.** THF and DME were used to examine the influence of mono- and bifunctional ligands on lithium phenolate aggregation. THF affords tetrameric, dimeric, and monomeric lithium phenolates depending on solvent and substrate concentrations and on the aryl substituents (discussed below). By contrast, DME affords five aggregation states, a diversity that may stem in part from its capacity to serve as either a monodentate or bidentate (chelating) ligand.<sup>52</sup> The occurrence of cyclic trimers (**3**) and pentameric ladders (**5**) uniquely in DME suggests that chelation is mandatory. Stabilization by chelation is supported by computational studies (Scheme 2; Table 3). Qualitative data from the solvent swaps suggest that the computations may, however, overestimate the relative stability of the DME-solvated dimers (**37**).<sup>36</sup>

THF solvation numbers were assigned by monitoring how the tetramer, dimer, and monomer concentrations varied with THF concentration (Scheme 4). The tetramer and dimer numbers enjoy full computational support. The monomer solvation numbers, by contrast, are a little more difficult to interpret because only the extraordinarily hindered 2,6-di-*tert*-butyl derivatives afford monomers. Certainly phenolate **30** is not representative of phenolates in general. The data, however, support *tetra-* or *pentasolvates* **54** and **55**, respectively. Tetrasolvated monomer (Me<sub>3</sub>Si)<sub>2</sub>NLi(THF)<sub>4</sub>,<sup>54</sup> as well as other

Scheme 4



Scheme 5



evidence of high-coordinate lithium, support the tetrasolvate **54**.<sup>53–57</sup> Putative pentasolvate **55** is supported by crystallographically characterized <sup>+</sup>Li(THF)<sub>5</sub> and <sup>+</sup>Li(THF)<sub>6</sub> cations.<sup>54</sup> Nonetheless, such high solvation numbers were unanticipated and certainly are inconsistent with conventional wisdom.

Analogous studies of DME-solvated aggregates afford results comparable to those found with THF (Scheme 5). Equivalent per-lithium solvation numbers of the tetramers (**56**) and dimers (**57**) are consistent with  $\eta^1$  and  $\eta^2$ -coordinated DME, respectively. The  $\eta^1$ -DME ligands on **56** may seem a little odd on first inspection, but their presence is supported by analogy to crystallographic and solution structural studies of other DME-solvated organolithiums.<sup>58</sup> Chelation in dimer **57** has ample crystallographic and computational support, requiring no further comment.<sup>21</sup>

Once again, the monomers give us pause because of the extraordinary steric demands of phenolate **30** required to observe

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them. Moreover, the solvation numbers of the monomers are measured *relative* to the dimers, but we are not fully confident that such hindered dimers are doubly solvated. Consequently, doubly chelated monomer **58** and ion-paired monomer **59** are both consistent with the data. Five-coordinate  $\text{LiX}(\eta^2\text{-DME})_2$  complexes support the proposed structure of monomer **58**,<sup>55,56</sup> and the well-precedented  $+\text{Li}(\eta^2\text{-DME})_3$  cation supports that of **59**.<sup>57</sup> There is a significant argument against **59**: A mixture of putative ion pairs derived from lithium phenolates **30** and **31** show two distinct lithium cations. The origin of such a slow gegenion exchange is unclear. Regardless of the details, the high solvation numbers are surprising.

Trimers are observed only in DME, for a limited number of phenolates, and never as major components. The per-lithium solvation number of DME-solvated trimers is the same as those of dimers and tetramers (one per lithium). Rapid  $^6\text{Li}$  intraaggregate exchange (speculatively presented in Scheme 1) precluded distinction of a ladder versus a cyclic form of the trimers; computational studies support the cyclic form (eq 10). Based on analogy with other lithium derivatives (lithium amides in particular) in which solvated trimers appear to be sterically more problematic than their cyclic dimer counterparts, we suspect the low steric demands of DME chelates may be important.<sup>59</sup>

The exotic and unanticipated pentameric ladders are prevalent at low DME concentrations. Rapid intraaggregate exchange obscures their asymmetry using  $^6\text{Li}$  NMR spectroscopy, but 2:2:1 triads of resonances were observed using  $^{19}\text{F}$  NMR spectroscopy on two fluorinated substrates. At the outset, the low per-lithium solvation number suggested that the ends of the ladders are capped by chelating DME ligands. Concentration and temperature dependencies evidence weak solvation of *one* of the internal lithiums. Computations support a ladder capped by chelating DME ligands and indicate a marked preference

for U-shaped rather than W-shaped ladders (**45** and **44**, respectively). Moreover, the computations support partial solvation of the internal lithiums (Scheme 3). It is not obvious, however, why pentameric ladders are the only observable ladder forms (assuming, of course, that the trimers are cyclic). Although U-shaped (concave) hexameric ladders would be sterically problematic, tetrameric ladders seem plausible at low DME concentration but are not observed.<sup>60</sup>

**Electronic Effects.** Lithium phenolates are ideally suited for examining the influence of electronic effects on aggregation. Monohalogenated phenolates **11–13** are unperturbed enough to elicit measurable aggregation state changes. By contrast, computations of multiply halogenated phenolates **14–17** clearly show that halogens promote deaggregation (Table 1).<sup>61</sup> Moreover, spectroscopic studies comparing phenolate **15** and **16** under similar conditions shows that the meta fluoro moieties promote deaggregation more so than para moieties do. There are parallels with the  $\text{p}K_{\text{AS}}$  of 3- and 4-phenols.<sup>62</sup> The meta substituent and its W relationship to the anionic phenolate oxygen appears optimally oriented to influence aggregation. Computational studies comparing monofluorinated lithium phenolates with the parent phenolate **7** show that ortho > meta > para at promoting deaggregations. (Apparent Li–F contacts in THF-solvates obscure insights into the electronic effects of ortho fluoro moieties).

**Steric Effects.** Considerable empirical evidence suggests that high steric demands promote deaggregations of lithium salts because of the severe van der Waals interactions within the aggregates.<sup>32</sup> Phenolates **18–32** are sterically demanding to some extent, and all show a greater penchant for forming dimers than do simple phenolates. Only the most severely congested phenolates buttressed by two *tert*-butyl groups (**30–32**) afford monomers. Computations comparing parent phenolate **7** and 2,6-dimethyl phenolate **25** (Table 3) confirm that congestion promotes dimers relative to tetramers and monomers relative to dimers.

**Like Aggregates with Like.** It seems self-evident—a truism—that  $\text{LiX}$  salts are most likely to modify the reactivity and selectivity of organolithium reactions if they form mixed aggregates.<sup>24,44</sup> One of the most interesting and potentially important observations, therefore, is that heteroaggregation is promoted by pairing species that are similar.

**A<sub>4</sub>** and **B<sub>4</sub>** mixtures usually afford ensembles of tetramers that are nearly statistical. The same is true for other analogous **A<sub>n</sub>–B<sub>n</sub>** pairs. By contrast, **A<sub>4</sub>** tetramers and **B<sub>2</sub>** dimers resist heteroaggregation. It seems logical in retrospect that a homoaggregate would resist heteroaggregation if it meant forfeiting a preferred aggregation number. For this reason, we place great importance on statistical ensembles. Of course, there are exceptions. We observed that **A<sub>4</sub>–B<sub>2</sub>** mixtures derived from **9** and **16** (respectively) in THF afford no heterotetramers but do afford heterodimers. Homoaggregates that are on the cusp of shifting aggregation number are likely to be more promiscuous at heteroaggregation.

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(60) Tetrameric ladders are suggested to be of nearly equal stability when compared with the corresponding pentamers (both U-shaped; energy in kcal/mol on a per-lithium basis at  $-90^\circ\text{C}$ ).

(61) The tendency for electron-withdrawing groups to promote deaggregation was noted by spectroscopic studies of Jackman and coworkers (ref 5) and has previously been suggested based on combination of computations and crystal structures Henderson and coworkers (ref 40b).

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**Not all Dimers are Alike.** There appear to be three albeit loosely defined classes of dimers: (1) sterically congested lithium phenolates (**18–27**), (2) highly electron-deficient lithium phenolates (**14–17**), and (3) 2,6-diphenylated lithium phenolates (**28** and **29**). Pairs chosen from two different classes tend to form nonstatistical ensembles (sometimes markedly so). Classes 1 and 2 form heteroaggregates that are prone to deviate from statistical distributions in both directions. 2,6-Diphenylated substrates **28** and **29** present the most vexing category.<sup>63</sup> They seem to have steric demands akin to dimeric phenolates **25–27** and electronic properties that *could* be similar to polyfluorinated derivatives **14–17**, yet the 2,6-diphenylated phenolates form heterodimers only with each other, not with class 1 or 2 dimers. It was somewhat disappointing and even somewhat disconcerting that computational studies failed to mimic these results, affording statistical distributions (eq 9).

## Conclusions

There may be a niche market for insights into the structures of lithium phenolates. The work described herein, however, has broader implications. Characterizing lithium salts with an NMR-inactive gegenion has been a long-standing problem of considerable importance. The strategies and tactics described in this manuscript appear to offer general solutions, especially for O-lithiated species.<sup>6,7</sup> It became increasingly apparent as the work progressed that the view of substrate-dependent aggregation provided by lithium phenolates may be unique.<sup>5</sup> Those interested in understanding the solution structures of lithium halides have a very limited choice.<sup>49</sup> Similarly, we have studied lithium amides for almost 25 years,<sup>39</sup> yet we have examined in detail less than a dozen variations of the dialkylamido moiety, which is hardly systematic. The breadth and number of alkylolithiums studied to date is impressive,<sup>8</sup> but an RLi dependence is difficult to systematize. By contrast, lithium phenolates allow for a reasonably systematic study of how changing X in LiX salts influences aggregation state.

Our interest in lithium phenolates as vehicles for studying salt effects in solution has been piqued and will persist. The advantages and synergies of studying several solvents concurrently became evident in these studies and, in conjunction with Jackman's early studies,<sup>5</sup> should gain momentum with each additional solvent. The low basicity of lithium phenolates should

allow us to study metal ion solvation by a very broad range of solvents, including many that are incompatible with more reactive organolithium derivatives.

## Experimental Section

**Reagents and Solvents.** DME, THF, and toluene were distilled from solutions containing sodium benzophenone ketyl. The toluene stills contained approximately 1% tetraglyme to dissolve the ketyl. We prepared and recrystallized [<sup>6</sup>Li]LiHMDS and [<sup>6</sup>Li,<sup>15</sup>N]LiHMDS as described previously.<sup>31</sup> Air- and moisture-sensitive materials were manipulated under argon using standard glovebox, vacuum line, and syringe techniques. The precursor to **29** was prepared using standard halogenation procedures.<sup>64</sup>

**Spectroscopic Analysis.** Individual stock solutions of substrates and base were prepared at room temperature. An NMR tube under vacuum was flame-dried on a Schlenk line and allowed to come to room temperature. It was then backfilled with argon and placed in a  $-78\text{ }^{\circ}\text{C}$  dry ice/acetone bath. The appropriate amounts of the base and substrate were added sequentially via syringe. The tube was sealed under partial vacuum, vortexed for approximately 10 s at room temperature, and cooled to  $-78\text{ }^{\circ}\text{C}$ . Each NMR sample contained 0.10 M total phenolate and 0.11 M LiHMDS.

<sup>6</sup>Li NMR spectra were typically recorded at  $-90\text{ }^{\circ}\text{C}$  (unless stated otherwise) on a 400 or 500 MHz spectrometer with a delay between scans set to  $>5 \times T_1$  to ensure accurate integrations. Chemical shifts are reported relative to a 0.30 M <sup>6</sup>LiCl/MeOH standard at the reported probe temperature. The resonances were integrated using standard software accompanying the spectrometers. After weighted Fourier transform with 64,000 points and phasing, line broadening was set between 0 and 0.2, and a baseline correction was applied when appropriate. Deconvolution was performed in the absolute intensity mode, with application of a drift correction using default parameters for contributions from Lorentzian and Gaussian line shapes. For poorly resolved spectra, the resonances were indicated using the mark and use-mark commands. The math underlying the parametric fits has been described in detail.<sup>6,7a</sup>

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**Supporting Information Available:** NMR and computational data, experimental protocols, and a complete list of authors for ref 42. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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