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Structure Determination Using the Method of Continuous Variation: Lithium Phenolates Solvated by Protic and Dipolar Aprotic Ligands

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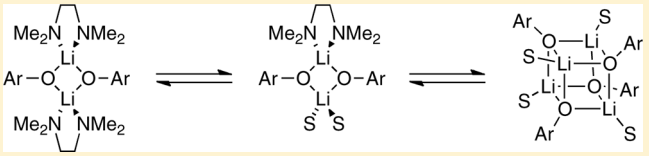
Supporting Information

ABSTRACT: The method of continuous variation (MCV) was used in conjunction with ^{6}Li NMR spectroscopy to characterize four lithium phenolates solvated by a range of solvents, including *N*,*N*,*N*′,*N*′-tetramethylethylenediamine, Et_2O, pyridine, protic amines, alcohols, and highly dipolar aprotic solvents. Dimers, trimers, and tetramers were observed, depending on the precise lithium phenolate−solvent combinations. Competition experiments (solvent swaps) provide insights into the relative propensities toward mixed solvation.



INTRODUCTION

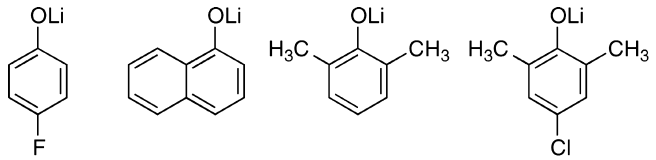
As part of a collaboration to study β-amino ester enolates used by Sanofi-Aventis to prepare the antithrombotic drug otamixaban,[1,2] we were forced to find a general solution to the problem of characterizing lithium enolates.[3] The lack of measurable Li−O scalar coupling precluded the most powerful and general NMR spectroscopic strategies used to characterize analogous Li−C and Li−N lithium salts.[4] Despite scattered reports of solution structural studies of lithium enolates and related O-lithiated species,[5−11] none of the methods manifested the right combination of reliability and generality to characterize a variety of lithium enolates in a range of solvents and temperatures. We turned to the method of continuous variation (MCV)[12−14] and a strategy founded on studies by Weingarten,[15] Chabanel,[16] Maddaluno,[17] Gunther,[18] and Gagne[19] in which the aggregation number (n) of enolates A_n and B_n can be extracted from characteristic ensembles (eq 1). Using ^{6}Li NMR spectroscopy with the aid of parametric fitting, we have characterized more than 100 lithium enolate−solvent combinations to date.[20,21]

$$A_n + B_n \rightarrow A_n + A_{n-1}B_1 + A_{n-2}B_2 + \ldots + B_n \quad (1)$$

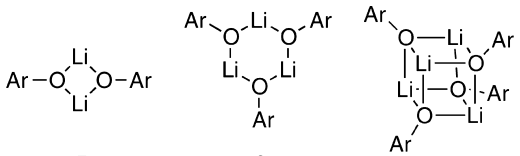
Taking a cue from early studies by Jackman and co-workers,[6] we occasionally turn to lithium phenolates as enolate models.[21] In the current study, we exploited the low basicity of lithium phenolates (**1**−**4**) to study protic and dipolar aprotic solvents that would not necessarily be compatible with more reactive lithium enolates. Lithium phenolates **1**−**4** manifest low, intermediate, and high steric demand and have been shown in previous studies to provide ensembles that are well-resolved in ^{6}Li spectra.[21] The solvent-dependent formation of dimers, trimers, and tetramers (**5**−**7**) reveals relationships between solvation and aggregation that may seem counterintuitive.

RESULTS

The assigned aggregation states with 5.0 equiv of each solvent per lithium in toluene cosolvent are summarized in Table 1.

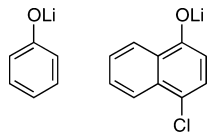


1 **2** **3** **4**



5 **6** **7**

The table headings indicate the pairings (**1**−**2** and **3**−**4**) used to make the structural assignments as dimer **5**, trimer **6**, or tetramer **7**. We occasionally used lithium phenolate **8** or lithium naphtholate **9** as pairing partners to confirm or further probe a structural assignment. The sections below delineate how we determined the solvent-dependent aggregation states and obtained insight into the relative binding efficacies of the solvents. Representative data are presented. The preponderance of spectra and affiliated Job plots are in the Supporting Information.



8 **9**

Method of Continuous Variation. Lithium phenolates **1**−**4** were characterized using the method of continuous

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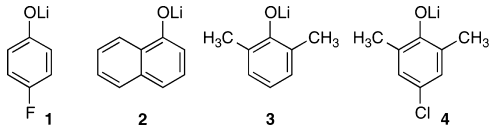
Table 1. Solvent-Dependent Aggregation States and ^{6}Li NMR Chemical Shifts for Homoaggregates of 1−4 from −60 to −110 °C (Supporting Information)[a]



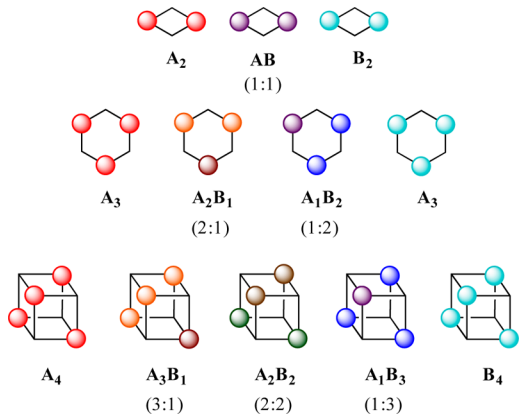
		aggregate (δ ppm)			
entry	solvent[22]	1	2	3	4
1	TMEDA	dimer (0.01)	dimer (0.23)	dimer (0.03)	dimer (−0.20)
2	Et_2O	tetramer (0.21)	trimer (1.35)	trimer (1.06)	tetramer (0.69)
3	MeCN	tetramer (0.42)	tetramer (1.50)	tetramer (0.92)	tetramer (0.55)
4	pyridine	tetramer (2.00)	tetramer (3.10)	dimer (2.15)	dimer (1.94)
5	DMA	tetramer (1.17)	tetramer (2.02)	tetramer (1.33)	tetramer (1.04)
6	DMF	tetramer (1.24)	tetramer (2.16)	[b]	[b]
7	DMSO	tetramer (0.60)	tetramer (1.62)	tetramer (1.28) trimer (0.82)	tetramer (0.53) trimer (0.53)
8	DMPU	tetramer (0.87)	tetramer (1.93)	[c] (0.92)	[c] (0.70)
9	NMP	tetramer (1.13)	tetramer (2.03)	tetramer (1.47)	tetramer (1.16)
10	$PrNH_2$	tetramer (0.87)	tetramer (2.07)	dimer (0.49)	dimer (0.25)
11	piperidine	tetramer[e] (0.75)	trimer[d] (1.80)	dimer (0.36)	dimer (0.08)
12	pyrrolidine	tetramer (0.70)	tetramer (1.96)	dimer (0.59)	dimer (0.32)
13	*i*-$BuNH_2$	tetramer (0.91)	tetramer (2.22)	dimer (0.71)	dimer (0.44)
14	*s*-$BuNH_2$	tetramer (0.87)	tetramer (2.09)	[c] (0.13)	[c] (−0.22)
15	*t*-$BuNH_2$	tetramer (0.78)	tetramer (1.96)	[c] (1.08)	[c] (0.88)
16	*i*-Pr_2NH	[f] (1.07)	trimer[d] (1.28)	dimer (1.07)	dimer (0.84)
17	Et_2NH	tetramer (0.55)	tetramer (1.79)	trimer (0.82)	trimer (0.42)
18	*n*-Pr_2NH	tetramer (0.49)	tetramer (1.78)	trimer (0.81)	trimer (0.42)
19	*t*-BuOH	tetramer (0.50)	tetramer (1.56)	[c]	[c]
20	*n*-BuOH	tetramer (0.90)[h]	tetramer (2.05)[h]	[g]	[g]
21	*s*-BuOH	tetramer (0.64)	tetramer (1.73)	[c] (0.13)	[c] (−0.23)

[a]Assignments are based on pairings of **1** with **2** and **3** with **4**. [b]Insoluble. [c]Could not be resolved. [d]With 4-chloro-1-naphthol. [e]Appears to be only tetrameric by ^{6}Li NMR spectroscopy, whereas ^{19}F NMR spectroscopy shows both the trimer and tetramer. A major peak was left unassigned. [f]Fails to form a mixed aggregate with **2** and **8**. [g]Experiment was not conducted. [h]Resolves only with Et_2O as the cosolvent.

variation (MCV).[12−14] The output is often called a Job plot, which consists of a physical property (P) plotted against the mole fraction of A or B (X_A or X_B) in mixtures where the total concentrations of A and B remain constant. In its simplest and most prevalent uses, MCV can identify the stoichiometry of a single complex (or aggregate) such as AB from the association of A and B. The stoichiometry of the complex is ascertained from the mole fraction corresponding to the maximum in the curve. In relatively rare instances, parametric fits are used to determine the equilibrium constant for complexation.[14]

MCV can be extended to an ensemble of A_mB_n aggregates (eq 1) by monitoring the concentrations of all species versus X_A or X_B.[3,20,21] Chart 1 summarizes the number of spectroscopically distinct aggregates expected for cyclic dimers, cyclic trimers, and cubic tetramers derived from A_n/B_n mixtures. Magnetically inequivalent ^{6}Li nuclei within each aggregate are denoted with colored spheres. The number of aggregates within the ensembles and the affiliated spectral complexity increase markedly with the aggregate size. An ensemble of tetramers, for example, contains five aggregates displaying a total of up to eight discrete resonances.

Chart 1. Dimer, Trimer, and Tetramer Mixtures Showing Magnetically Inequivalent Lithium Sites



^{6}Li NMR Spectroscopy. Ensembles of homo- and heteroaggregates[23] derived from binary mixtures of lithium phenolates were prepared using [^{6}Li] lithium hexamethyldisilazide [^{6}Li]LiHMDS.[24] (The hexamethyldisilazane byproduct has no measurable Lewis basicity.[4d]) The resolution is optimal when the chemical-shift separation of the homoaggregates is large, which is a factor that contributed to our choice of lithium phenolates **1**−**4**. Panels a and b of Figure 1 offer examples of spectra for ensembles of cyclic dimers and tetramers, respectively. The line widths and resolution were optimized by adjusting the probe temperature; however, the origins of the temperature dependencies were not always obvious. The stoichiometries apparent from the number of aggregates and their spectral symmetries are labeled and color coded.

For a number of lithium phenolate−solvent combinations, we found that certain proportions of two lithium phenolates result in a loss of resolution owing to an inexplicably enhanced inter-aggregate exchange. We occasionally observed the aggregates in the limit of the rapid intra-aggregate yet slow inter-aggregate exchange.[25] Under these conditions, each stoichiometry appears as a single resonance.[21] In the case of lithium phenolate trimers, for example, monitoring the ensembles at temperatures affording fast intraaggregate

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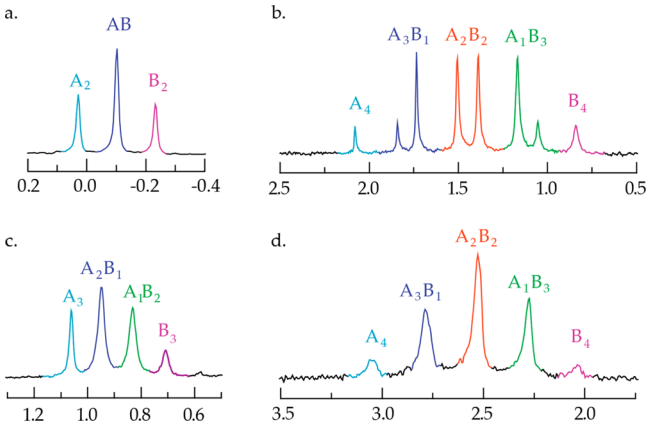

Figure 1. ^{6}Li NMR spectra recorded from ∼1:1 mixtures of lithium phenolates in toluene cosolvent. (a) Dimers of [^{6}Li]**3** (A) and [^{6}Li]**4** (B) in 0.50 M TMEDA (−80 °C), (b) tetramers of [^{6}Li]**2** (A) and [^{6}Li]**1** (B) in 0.50 M propylamine with slow intra-aggregate exchange (−80 °C), (c) trimers of [^{6}Li]**3** (A) and [^{6}Li]**4** (B) in 0.50 M Et_2O with rapid intra-aggregate exchange (−80 °C), and (d) tetramers of [^{6}Li]**2** (A) and [^{6}Li]**1** (B) in 0.50 M pyridine in ether cosolvent with rapid intra-aggregate exchange (22 °C).

exhanges was the only viable option (Figure 1c). Figure 1d shows a tetramer similar to that in Figure 1b but in the limit of rapid intra-aggregate exchange. Both limiting perspectives have merit. The symmetries are highly characteristic in the slow exchange limit, whereas the spectra are simpler and often more tractable in complex systems in the fast intra-aggregate-exchange limit.[3]

Job Plots and Parametric Fits. We monitored the homo- and heteroaggregates for various proportions of two lithium phenolates at a constant total lithium phenolate concentration (Figure 2). Plotting the relative integrations of the homo- and heteroaggregates versus the measured mole fraction of the lithium phenolate subunits (X_A or X_B) afforded Job plots for the

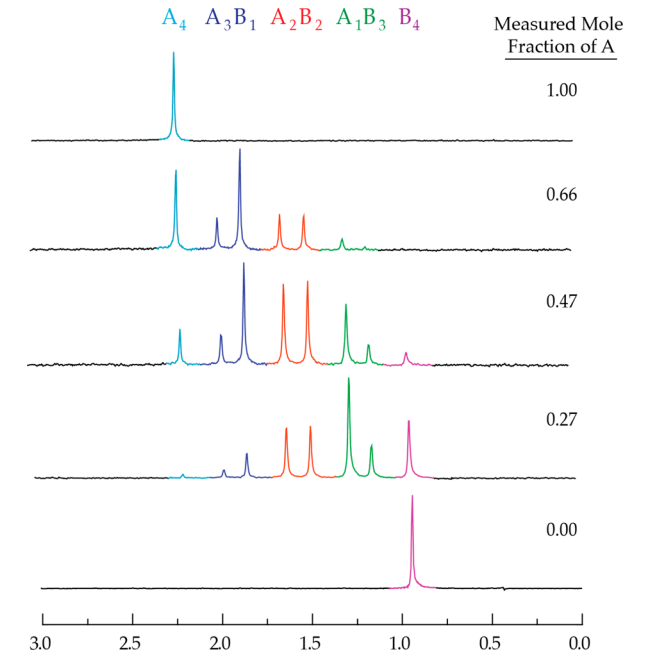

Figure 2. ^{6}Li NMR spectra recorded for [^{6}Li]**2** (A) and [^{6}Li]**1** (B) in 0.50 M isobutylamine in toluene at −80 °C.

dimers, trimers, and tetramers, which are shown emblematically in Figures 3−5. We always use the so-called measured mole

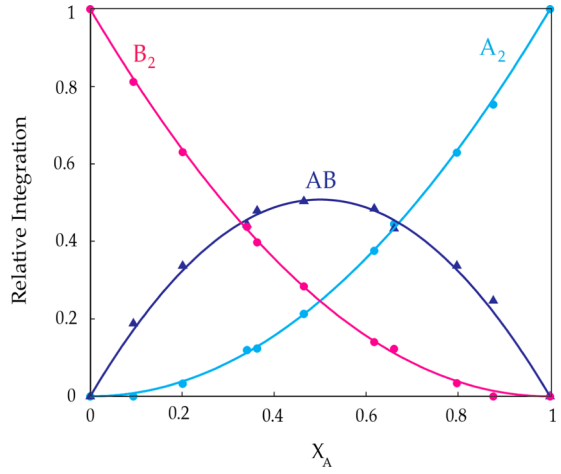

Figure 3. Job plot showing the relative integrations of dimeric homo- and heteroaggregates versus the measured mole fractions of **3** (X_A) for 0.10 M mixtures of phenolates [^{6}Li]**3** (A) and [^{6}Li]**4** (B) in 0.50 M pyridine/toluene at −80 °C.

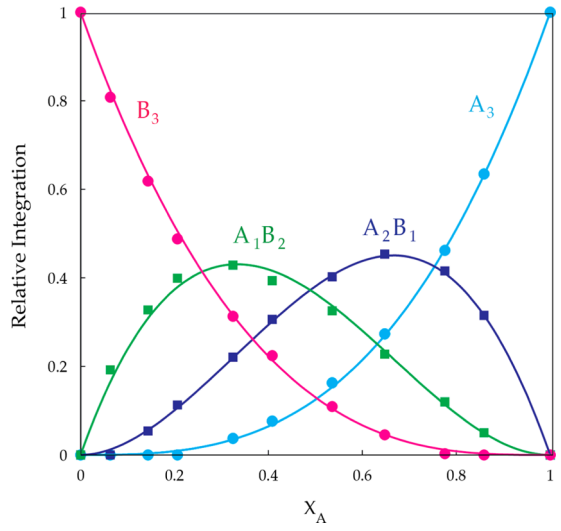

Figure 4. Job plot showing the relative integrations of trimeric homo- and heteroaggregates versus the measured mole fractions of **3** (X_A) for 0.10 M mixtures of phenolates [^{6}Li]**3** (A) and [^{6}Li]**4** (B) in 0.50 M diethyl ether/toluene at −90 °C.

fraction (the mole fraction within only the ensemble of interest) rather than the overall mole fraction of the lithium phenolates added to the samples because it eliminates the distorting effects of impurities and enables the concurrent analysis of several ensembles (Figure 6). The curves represent parametric fits using methods detailed elsewhere.[3,20a] Although the fitting protocols measure the deviation from statistical, the aggregate distributions almost always approximate statistical. The deviations from statistical, especially a resistance to form ensembles, constitute evidence of two different aggregation states. Figure 6 displays an unusual circumstance in which intra-aggregate exchange is slow for the tetramer ensemble and fast for the trimer ensemble.

Solvent Swapping and Relative Binding Constants. We have developed a number of strategies for probing

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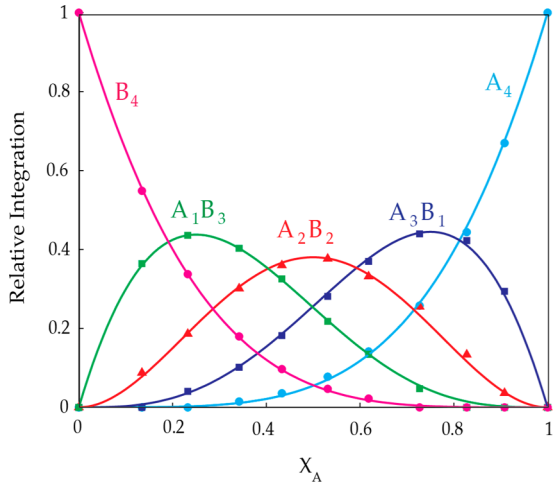


Figure 5. Job plot showing the relative integrations of tetrameric homo- and heteroaggregates versus the measured mole fractions of **2** (X_A) for 0.10 M mixtures of phenolates [^{6}Li]**2** (A) and [^{6}Li]**1** (B) in 0.50 M isobutylamine/toluene at −80 °C.

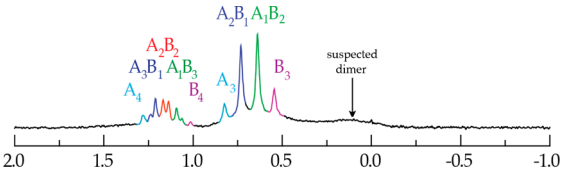


Figure 6. ^{6}Li NMR spectrum of 0.50 M dimethyl sulfoxide (DMSO)/toluene solutions containing ∼1:1 mixtures of [^{6}Li]**3** and [^{6}Li]**4** recorded at −90 °C showing the trimeric and tetrameric ensembles of homo- and heteroaggregates. The tetramer is at the limit of slow intra-aggregate exchange, whereas the trimer is undergoing rapid intra-aggregate exchange. An ensemble appears upon warming to −50 °C and shows characteristics of dimers.

aggregate structure and solvation under the rubric of solvent swapping.[20a,21] Solvent swaps are multipurpose and can take several forms described below. They provide insights into lithium phenolate solvation, albeit with occasional complications.

A solvent swap requires a measurable ^{6}Li chemical-shift difference for two distinct homosolvates of a lithium phenolate. It is based on rapid solvent−solvent exchange (ligand substitution)[26] and much slower aggregate−aggregate exchange. Several behaviors can be observed by incrementally replacing one solvent with a second or by holding one solvent concentration fixed and varying the other.

The results from the solvent-swapping experiments illustrated in Figure 7a−c are as follows:

(a) If the observable aggregates in the two solvents are different (e.g., dimer vs tetramer), then the incremental solvent swap in conjunction with slow aggregate−aggregate exchange causes one to disappear and the other to appear (Figure 7a). The coexistence of both forms in slow exchange confirms differential aggregation. With a TMEDA-solvated dimer as a benchmark (eq 2), the relative binding constants of other solvents to the lithium phenolate tetramer can be measured[27] provided that mixed-solvated dimers or mixed-solvated tetramers do not intervene (vide infra).[28−30]

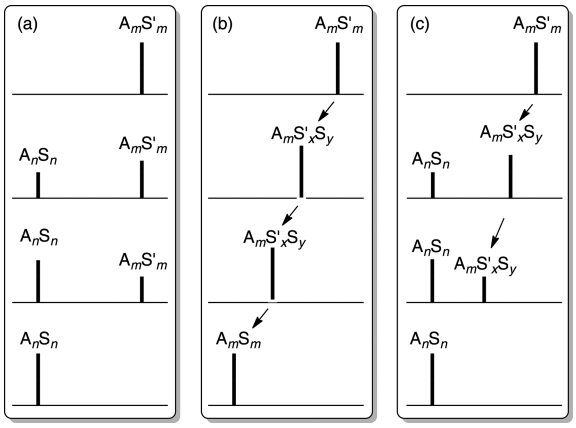
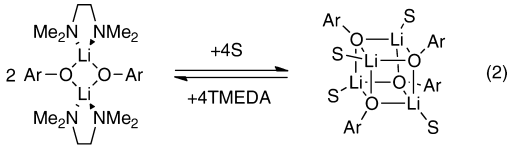


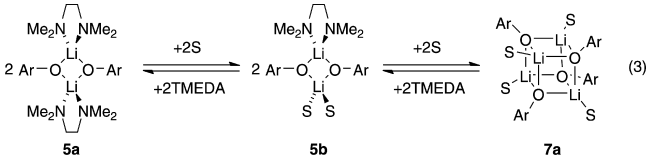
Figure 7. Expected ^{6}Li NMR when solvent *S* is replaced with *S*′. (a) Elicits only a change in the aggregation state (A_n for A_m), (b) causes solvent substitution on a common aggregate (A_m), and (c) causes an aggregation-state change (A_n for A_m) and a concurrent partial exchange of the solvent on A_m to form a mixed solvate.



5a **7a** (2)

(b) If the two observable forms in the two coordinating solvents differ only in the ligating solvent, then an incremental solvent swap in conjunction with rapid solvent exchange will cause the resonances to exchange via time averaging (Figure 7b).[26] The solvent-concentration-dependent shift confirms the common aggregation state and provides qualitative insights into the relative binding affinities. This experiment works particularly well with pyridine as one of the solvents owing to the marked (>1.0 ppm) downfield shift of pyridine solvates.[6b,31−33] Quantitation is precluded by the unknown additive effects on the chemical shift by intervening mixed solvates (e.g., three $A_4S_mS'_{4-m}$ tetramer-based mixed solvates). Nevertheless, the magnitude of the shift gives a qualitative sense of the relative capacity to solvate the tetramer.

(c) The dimer−tetramer competition in eq 2 occasionally shows evidence of mixed solvates.[34,35] The example in Figure 7c is characteristic of the occasional intervention of a mixed solvated dimer (eq 3). Strongly coordinating monodentate ligands can displace one chelated TMEDA ligand from the dimer.[28] Although TMEDA does not appear well suited to solvate tetramers, we nonetheless found evidence that η^1-TMEDA-solvated tetramers[36] can intervene even in cooperation with strongly coordinating monodentate ligands (vide infra).



5a **5b** **7a** (3)

The results described below are derived from combinations of the solvent-swapping strategies. In most cases, the strategy will be self-evident. All data are in the Supporting Information. Our initial goal of quantitatively measuring the solvation of lithium phenolates was thwarted by sporadic technical

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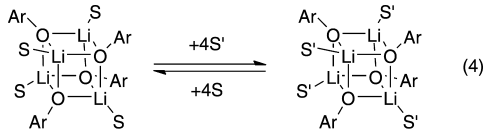
problems and intervening mixed solvation. Consequently, the discussion is largely about the qualitative effects of measuring the solvation of lithium phenolates and is based on selective examples; nonetheless, the qualitative effects are revealing.

Aprotic Solvents. Mixtures of **1** and **2** in Et_2O show exclusively tetramers. Solutions of lithium phenolate **1** in neat Et_2O with as little as 2 equiv of TMEDA (see eq 2) contain exclusively TMEDA-solvated dimer **5a**. Although this outcome does not attest to the relative binding constants of Et_2O and TMEDA because of the unknowable energy of aggregation, ether is poorly coordinating[37] compared with other solvents with the exception of highly hindered *i*-Pr_2NH. By contrast, 5 equiv of TMEDA and 5 equiv of pyridine (eq 2; S = pyridine) afforded nearly equal parts dimer and tetramer. Both resonances are at approximately the same chemical shift as that observed when the solvents are used separately, suggesting the absence of mixed solvation (Figure 7a). The dramatic downfield chemical shift imparted by pyridine is a highly characteristic and useful diagnostic probe.[6b,31] Adding pyridine incrementally in neat Et_2O in an experiment akin to that represented by eq 4 (Figure 7b) shows a much stronger binding of pyridine than that of Et_2O on a per-molar basis.



(4)

7a **7b**

Incrementally increasing the pyridine concentration in pyridine−TMEDA solutions of naphtholate **2** yields the expected replacement of the TMEDA-solvated dimer with a pyridine-solvated tetramer. However, the accompanying substantial downfield shift of the dimer implicates mixed-solvated dimer **5b** (eq 3; S = pyridine).

Dipolar Aprotic Solvents. Lithium phenolates **1**−**4** in highly dipolar solvents (Table 1, entries 5−9) display a strong tendency to form tetramers, which is contrary to the oft-cited belief that dipolar solvents promote deaggregation.[38] The addition of 1 equiv of the dipolar solvents to TMEDA-solvated dimer **5a** elicits a quantitative conversion to the corresponding tetramers (eq 2), indicating that dipolar solvents bind more strongly than does pyridine (as well as *n*-$PrNH_2$ and pyrrolidine; vide infra). Despite concerns that the dipolar ligands might catalyze facile exchanges, intra-aggregate exchange is slow at low temperatures. Even hindered 2,6-dimethylphenolates **3** and **4**, which display a penchant for deaggregating in THF,[21] afford tetramers when solvated by most of the highly dipolar ligands. Inexplicably, high inter-aggregate-exchange rates for *N*,*N*′-dimethyl-*N*,*N*′-trimethyleneurea (DMPU) precluded the study of **3** and **4**. Acetonitrile mimicked the carbonyl-based dipolar ligands in promoting tetramers; however, high inter-aggregate-exchange rates precluded detailed studies. Attempts to measure the relative binding constants of the dipolar ligands were largely unsuccessful.[39,40]

Mixtures of hindered 2,6-dimethylphenolates **3** and **4** solvated by DMSO are outliers, affording ensembles of dimers, trimers, and tetramers observed concurrently (Figure 6). DMSO-solvated mixtures of **1** and **2** also departed from the norm in that the intra-aggregate-exchange rates depended markedly on the stoichiometry of the mixed tetramers. Therefore, we turned to an alternative strategy to examine DMSO solvates.

Previous studies have shown that ^{19}F NMR spectroscopy affords superior resolution in highly fluxional ensembles,[21] but the spectral fingerprint of such ensembles is markedly different. Ensembles of **1** and **2** observed with ^{19}F NMR spectroscopy, for example, are necessarily missing the NMR-silent homonuclear tetramer of **2**. Moreover, the 1:3, 2:2, and 3:1 heterotetramers will each appear as a single resonance irrespective of the rate of intra-aggregate exchange because of the NMR-silent subunits of **2**. Mixtures of **1** and **2** in DMSO/toluene afford a well-resolved four-resonance tetramer ensemble as well as very low concentrations of what appears to be the corresponding trimer ensemble (Figure 8).

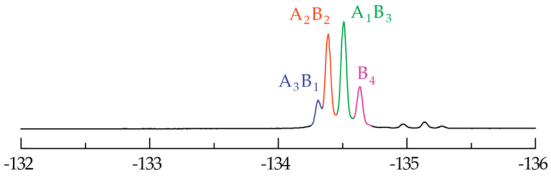


Figure 8. ^{19}F NMR spectra of a 1:1 mixture of **2** (A) and **1** (B) in toluene containing 0.50 M DMSO recorded at −80 °C. A_4 is absent because it is NMR silent.

Protic Amines. We examined mono- and dialkylamines spanning a range of steric demands. *n*-$PrNH_2$/toluene solutions of **1** and **2** afford tetramers, which is consistent with the anticipated[41] strong coordination akin to that of dipolar ligands.[42] Dipolar ligands and monoalkylamines, however, give different results with mixtures of hindered lithium phenolates **3** and **4**. Whereas dipolar ligands afford tetramers, *n*-$PrNH_2$/toluene solutions contain only dimers. One could imagine the existence of highly stabilized tetrasolvated dimers, yet we observed dimers with as little as 1 equiv of *i*-$BuNH_2$. This dimer preference may be general, but the high exchange rates for *t*-$BuNH_2$ and *s*-$BuNH_2$ precluded further studies to make definitive statements.

Pyrrolidine, the least sterically demanding dialkylamine, showed a high penchant for forming tetramers of unhindered lithium phenolates **1** and **2**. Solvent-swapping experiments showed pyrrolidine has a surprisingly high binding affinity compared to that of even pyridine.[43] Et_2NH, by contrast, affords tetramers but is a weaker ligand than pyridine. Piperidine produced conflicting results by affording a tetramer ensemble with mixtures of **1** and **2** and a trimer ensemble with mixtures of lithium naphtholates **2** and **9**, apparently resulting from the divergent steric demands of phenolates **1** and **2**.

The capacity of **2** solvated by piperidine to afford two statistical ensembles is the first instance of such promiscuity reported to date. In previous studies, the rule of thumb that "like aggregates with like" has held true.[20a,21] Hindered lithium phenolates **3** and **4** display an unexpected tendency to form trimers with unhindered dialkylamines.[6,44−46]

Hindered *i*-Pr_2NH, a ligand of some interest in the context of enolates generated from lithium diisopropylamide,[2] affords trimers from lithium naphtholates **2** and **9**, showing similarity to the less hindered piperidine. The failure to form heteroaggregates between **1** and **2** suggested that unhindered lithium phenolate **1** does not form trimers and more hindered lithium naphtholate **2** does not form tetramers. Although lithium phenolate **1** showed solubility that is consistent with at

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least partial solvation by *i*-Pr_2NH, attempts to characterize the suspected tetramer fell short. Dimethylated lithium phenolates **3** and **4** afforded trimers for most dialkylamines yet afforded exclusively dimers with *i*-Pr_2NH.

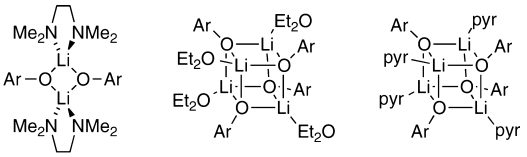
Alcohols. Alcohols generally displayed technical problems associated with high exchange rates. Methanol and ethanol, for example, failed to provide tractable results altogether. By contrast, *t*-BuOH affords tetramers with unhindered lithium phenolates **1** and **2** and intractable mixtures with hindered lithium phenolates **3** and **4**. The less demanding *n*-butanol and *s*-BuOH also afford tetramers with **1** and **2**; however, *n*-butanol shows an odd tendency to afford only resolved tetramer ensembles using Et_2O as cosolvent, which suggests a cooperative solvation effect. Solvent swaps that competed the alcohols with TMEDA (eq 2) show the anticipated qualitative drop in binding as steric demands increase: primary > secondary > tertiary.[45]

DISCUSSION

Lithium enolates, alkoxides, carboxylates, and phenolates are notoriously difficult to study in solution[3−10] owing to the absence of the single most important NMR spectroscopic probe, scalar coupling. It was in this context that we turned to the method of continuous variation (MCV).[3,20,21] The underlying theme of this Article, however, is less about the role of MCV in determining the aggregation states of lithium phenolates (a topic covered in previous studies[21]) and more about the merits of using relatively nonbasic and stable lithium phenolates for the study of lithium-ion solvation with solvents that are not easily examined with more reactive organolithiums. Lithium phenolates characterized by low steric demands (**1**), intermediate steric demands (**2**), and high steric demands (**3** and **4**) were used emblematically. The solvents used are moderately polar (pyridine, Et_2O, and TMEDA; Table 1, entries 1−3), highly dipolar (Table 1, entries 5−9), and protic (amines and alcohols; Table 1, entries 10−21). In addition to the investigation of solvent-dependent aggregation states, solvent-swapping experiments using binary solvent mixtures represented by eqs 2−4 shed light on relative binding energies, relationships between solvation and aggregation, and mixed solvation. The descriptions of metal-ion solvation as a molecular phenomenon rather than a bulk medium effect are still so elusive that even incremental gains are notable.[47] Note that the results described herein are obtained at low ligand concentrations (0.50 M); high concentrations often elicit rapid aggregate exchanges that may obscure any affiliated deep-seated structural changes.

Nonpolar solvents established a foundation for the study. Et_2O promotes tetramers and is poorly coordinating relative to most ligands. TMEDA dependably affords chelated dimers (**5a**), allowing for solvent comparisons through competition according to eq 2. Pyridine is comparable to THF[28] and readily promotes tetramers with the particular advantage of causing marked (∼1.0 ppm) downfield ^{6}Li shifts that are useful diagnostically and to maximize resolution. These three solvents were used as benchmarks in investigations of dipolar and protic solvents.

The dipolar ligands are all very strongly coordinating, as shown by the especially facile conversion of TMEDA-solvated dimers to tetramers (eq 2). Despite failed efforts to quantitate their relative binding affinities, we confirmed that they act similar to one another. The seemingly paradoxical tendency to afford tetramers despite a reputation for deaggregating lithium



5a **7c** **7d**

salts is consistent with previous studies showing that a lack of deaggregation[48] and even a promotion of aggregation[6d] are possible. DMSO is an outlier, showing a marked tendency to afford dimers, trimers, and tetramers concurrently. Overall, the dipolar ligands remind us that simple maxims about solvation and aggregation must be viewed skeptically; metal-ion and aggregate solvation are complex.

The protic amines provided the most widely varied results, possibly because of their enormous range of structural diversity and steric demands. At one extreme, the monoalkylamines are comparable to the dipolar ligands; however, we noted that there is a greater penchant for the amines to support dimers. The least-hindered dialkylamine, pyrrolidine, is also a strong ligand, exceeding pyridine in its capacity to bind. Previous studies of pyrrolidine[43] and pyrrolidine-based chelates[33] have shown similarly strong ligation. At the other extreme, *i*-Pr_2NH appears to bind, but it is a poorly coordinating ligand at best. In conjunction with other studies[43] showing poor coordination of *i*-Pr_2NH, this additional data contrasts with the provocative and still somewhat baffling evidence that *i*-Pr_2NH can influence the chemistry of lithium enolates in neat THF solution.[49] Dialkylamines also cause the unexpected appearance of lithium phenolate trimers. It would be a mistake, however, to underestimate the complexity of the steric contributions on a tetramer containing up to four ligands that could promote lower aggregates by default.

Our previous studies of LiHMDS solvated by R−X−R′ ligands in which R and R′ varied widely showed a remarkably linear correlation between the binding constants when X = O and NH; thus, the binding is independent of X.[43] One can observe similar trends with lithium phenolates, but the correlation may not be as strong. We presume, for example, that the serial solvation of the four sites of a tetramer is nonstatistical, especially for sterically demanding ligands.

The studies of the alcohols were clearly the most disappointing given their prevalence in the industrial-scale reactions of alkali metal phenolates.[50] We observed evidence that low concentrations of alcohols could support tetramers in solution, but studies of the most commonly used alcohols (methanol and ethanol) were precluded by high exchange rates. Although these high rates may simply reflect low steric demands, we cannot rule out a role for the alcoholic proton in the catalysis of inter- and intra-aggregate exchanges.[51] The somewhat more hindered cases, such as *n*-BuOH and the highly hindered *t*-BuOH, afford tetramers, but only the latter is well behaved. We reiterate that the exchange rates may be blinding us to deaggregation at the high ligand concentrations often used in synthesis.[6b]

Solvent-swapping studies using binary mixtures of coordinating solvents provided glimpses of an elusive but fascinating phenomenon collectively referred to as correlated (cooperative)[34] solvation, which has captivated our attention for some time.[28] This topic is important given the prevalence of solvent mixtures in organic chemistry. The extent to which the multiple ligands compete and cooperatively bind is relatively unexplored.[28−30]

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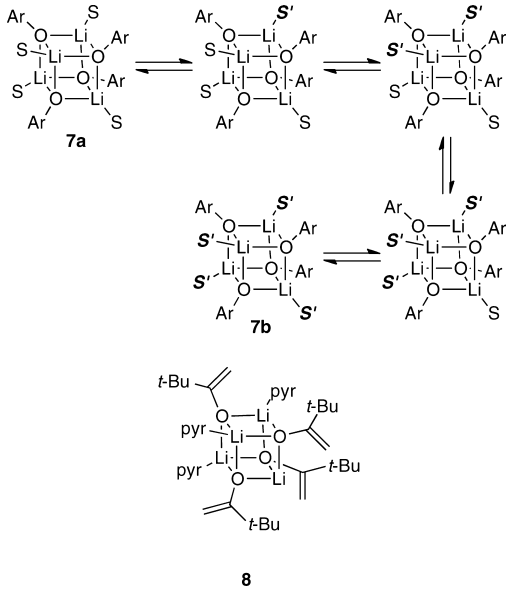
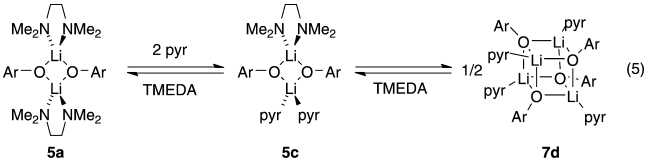
In routine cases, such as incrementally swapping pyridine, it is possible that one homosolvated tetramer may be replaced by another (eq 4). The far more likely scenario, however, is that the marked changes in chemical shift result from an ensemble of mixed-solvate tetramers (Chart 2). That is not to say,

Chart 2

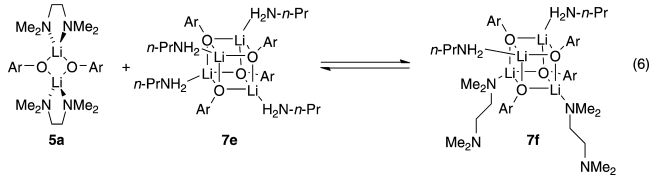


however, that they distribute statistically. Reich notes the nonstatistical replacements of ethereal solvents by increments of hexamethylphosphoramide.[10b] Jacobsen noted the surprising tendency of a hindered lithium pinacolate to favor trisolvate **8** with added pyridine.[9]

We qualitatively observed cooperative solvation on multiple occasions. Lithium naphtholate **2** in TMEDA/pyridine mixtures, for example, afforded the anticipated TMEDA-solvated dimer and pyridine-solvated tetramer, yet the dimer showed clear evidence of an intervening TMEDA/pyridine mixed-solvated dimer (eq 5). We saw no evidence that the corresponding tetramer contained any coordinated TMEDA. By contrast, lithium phenolate **1** in analogous TMEDA/pyridine mixtures showed the opposite: substantial solvent-dependent chemical shifts of the tetramer characteristic of mixed solvation occurs with no obvious changes in the dimer.



A more detailed investigation of mixed solvation is required to reveal intimate details. One possible strategy is foreshadowed by an experiment in which lithium phenolates are starved of solvent to force the coordination of both solvents (eq 6). We expected lithium naphtholate **3**, containing 0.5 equiv of *n*-$PrNH_2$ and 0.5 equiv of TMEDA (one solvent molecule per lithium) to provide a mixture of homosolvated dimer **5a** and tetramer **7a** (see eq 2); however, only tetramer forms, suggesting cooperativity in tetramer **7f**. The η^1-bound TMEDA is inferred but well precedented.[36] If so, cooperativity (a nonstatistical preference for mixed solvation) is strongly indicated.



CONCLUSIONS

Our efforts to untangle organolithium chemistry often yield both insights into organolithium chemistry and tactical advances (the expansion of our toolbox) that promise greater clarity in future studies. Several insights from the present study are noteworthy. Dipolar ligands promote aggregation, and DMSO offers evidence that it is an outlier compared with its carbonyl-based brethren. Protic amines with widely varied steric demands show a large range of binding affinity, resulting in the highly amine-dependent distributions of the aggregates. The most interesting results came from binary solvent mixtures in which evidence of mixed solvates suggest cooperative solvation.

From a tactical perspective, some promising protocols emerged for use in studying the coordination chemistry (solvation) of enolates, phenolates, and related *O*-lithiated species. The study of binary mixtures may be a fruitful direction for future studies. In particular, aggregate distributions under starved conditions in which both ligands in a binary mixture are forced to bind may reveal interesting insights into solvent–solvent (ligand–ligand) interactions within aggregates. We are using pyridine centrally in a number of projects owing to its ability to promote exceptional chemical shifts caused by coordination, which not only improve the resolution but also confirm the very existence (or absence) of the pyridine–lithium contacts, which can be difficult. We have also documented another example in which ^{19}F NMR spectroscopy was used to resolve aggregate distributions that could not be resolved by ^{6}Li NMR spectroscopy,[21] underscoring the potential importance of alternative nuclei for studies of salt aggregation and solvation using MCV.

EXPERIMENTAL SECTION

Reagents and Solvents. All phenols used are commercially available. TMEDA, Et_2O, and all amines were distilled from solutions containing sodium benzophenone ketyl. Toluene was distilled from blue solutions containing sodium benzophenone ketyl with approximately 1% tetraglyme to dissolve the ketyl. Alcohols and all solvents containing carbonyls were distilled from 3 or 4 Å molecular sieves. [^{6}Li]LiHMDS was prepared and recrystallized as described previously.[24] Air- and moisture-sensitive materials were manipulated under argon using standard glovebox, vacuum line, and syringe techniques.

NMR Spectroscopy. Individual stock solutions of substrates and bases were prepared at room temperature. An NMR tube under vacuum was flame-dried on a Schlenk line and allowed to return to room temperature. It was then backfilled with argon and placed in a −78 °C dry-ice/acetone bath. The appropriate amounts of [^{6}Li]-LiHMDS and phenol were added sequentially via syringe. The tube was sealed under partial vacuum, stored in a −86 °C freezer, and shaken prior to placement into the spectrometer. Each NMR sample contained 0.10 M total phenol and 0.11 M LiHMDS.

^{6}Li NMR spectra were typically recorded at −80 °C (unless stated otherwise) on a 500 or 600 MHz spectrometer with the delay between scans set to >5 × T1 to ensure accurate integrations. Chemical shifts are reported relative to a 0.30 M $^{6}LiCl$/MeOH standard at the reported probe temperature. The resonances were integrated using the standard software accompanying the spectrometers. After weighted Fourier transform with 64 000 points and phasing, line broadening was

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set between 0 and 0.3, and a baseline correction was applied when appropriate. Deconvolution was performed in the absolute intensity mode with the application of a drift correction using default parameters for contributions from Lorentzian and Gaussian line shapes. The mathematics underlying the parametric fits have been described in detail.[3,20a]

■ ASSOCIATED CONTENT

Supporting Information

^{6}Li and ^{19}F NMR spectra, Job plots, and solvent-swap data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(22) The abbreviations used are as follows: TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine; DMA = *N*,*N*-dimethylacetamide; DMF =

N,*N*-dimethylformamide; DMSO = dimethyl sulfoxide; DMPU = *N*,*N*′-dimethylpropyleneurea; and NMP = *N*-methylpyrrolidone.

(23) After we surveyed a subset of the community, we have chosen to refer to $(LiX)_n$ and $(LiX)_m(LiX')_n$ as a homoaggregate and heteroaggregate, respectively, and we reserved the term mixed aggregate for $(LiX)_m(LiY)_n$.

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