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

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Abstract

The method of continuous variation (MCV) in conjunction with ^6Li NMR spectroscopy was used 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 relative solvation energies 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 in tetrahydrofuran (THF) solution.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 Gagne¹⁹ in which the aggregation number (*n*) of enolates **A_n** and **B_n** can be extracted from characteristic ensembles (eq 1). Using ^6Li NMR spectroscopy with the aid of parametric fitting we have characterized more than 100 lithium enolate-solvent combinations to date.^{20,21}

$$\mathbf{A}_n + \mathbf{B}_n \Rightarrow \mathbf{A}_n + \mathbf{A}_{n-1}\mathbf{B}_1 + \mathbf{A}_{n-2}\mathbf{B}_2 + \dots \mathbf{B}_n \quad (1)$$

Taking a cue from early studies by Jackman and coworkers,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

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Supporting Information: Raw data and Job plots (xx pages). This material is available free of charge via the Internet at <http://pubs.acs.org>.

ensembles that are well-resolved in ^6Li spectra.²¹ The solvent-dependent formation of dimers, trimers, and tetramers (**5–7**) reveals relationships of solvation and aggregation that may seem counterintuitive.

Results

The assigned aggregation states with 5.0 equivalents per lithium of each solvent in toluene cosolvent are summarized in Table 1. 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 archived in supporting information.

MCV

Lithium phenolates **1–4** were characterized using the Method of Continuous Variation^{13,14} (MCV).¹² The output is often called a Job plot in which a physical property (P) is plotted against the mole fraction of **A** or **B** (X_A or X_B) in mixtures in which the total concentrations of **A** and **B** remain constant. In its simplest and most prevalent uses, MCV identifies 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 $A_m B_n$ 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 ^6Li nuclei within each aggregate are denoted with colored spheres. The number of aggregates within the ensembles and the affiliated spectral complexity increase markedly with aggregate size. An ensemble of tetramers, for example, contains five aggregates displaying up to a total of eight discrete resonances.

^6Li NMR Spectroscopy

Ensembles of homo- and heteroaggregates²³ derived from binary mixtures of lithium phenolates were prepared using [^6Li] lithium hexamethyldisilazide [^6Li]LiHMDS.²⁴ (The hexamethyldisilazane byproduct has no measurable Lewis basicity.^{4d}) Resolution is optimal when the chemical shift separation of the homoaggregates is large, a factor that contributed to our choice of lithium phenolates **1–4**. Figure 1a and 1b offer examples of spectra for ensembles of cyclic dimers and tetramers, respectively. The line widths and resolution were optimized by adjusting the probe temperature, although 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 inexplicably enhanced interaggregate exchange. We occasionally observed the aggregates in the limit of 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, fast *intra*aggregate exchange 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 such as hexamers 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 *measured* mole fraction of the lithium phenolate subunits (X_A or X_B) afforded Job plots for dimers, trimers, and tetramers shown emblematically in Figures 3–5. We always use the so-called measured mole fraction—the mole fraction within only the ensemble of interest—rather than the overall mole fraction of lithium phenolates added to the samples because it eliminates the distorting effects of impurities and enables concurrent analysis of several ensembles (Figure 6). The curves represent parametric fits using methods detailed elsewhere.^{3,20a} Although the fitting protocols measure deviation from statistical, the aggregate distributions almost always approximate statistical. 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 aggregate structure and solvation under the rubric of “solvent swapping.”^{20a,21} Solvent swaps are multipurpose and can take several of the forms described below. They provide insights into lithium phenolate solvation albeit with occasional complications.

A solvent swap requires a measurable ^6Li chemical shift difference for a single lithium phenolate solvated by two solvents. It is based on rapid solvent-solvent exchange (ligand substitution)²⁶ and much slower aggregate-aggregate exchange. Several behaviors can be observed by recording incrementally replacing one solvent by a second or by holding one solvent concentration fixed and varying the other (Figure 7).

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—dimer versus tetramer, for example—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 measured²⁷ provided that mixed-solvated dimers or mixed-solvated tetramers do not intervene (*vide infra*).^{28–30}

(2)

- b. If the two observable forms in the two coordinating solvents differ only in ligating solvent, 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 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—three $\text{A}_4\text{S}_m\text{S}'_{4-m}$ tetramer-based mixed solvates, for example. Nevertheless, the magnitude of the shift gives a qualitative sense of the relative capacity to solvate the tetramer.

(3)

- c. The useful 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 4). 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 tetramers³⁶ can intervene even in cooperation with strongly coordinating monodentate ligands (*vide infra*).

(4)

The results described below derived from combinations of the solvent swapping strategies. In most cases the strategy will be self-evident; all data are archived in supporting information. Our initial goal to quantitatively measure solvation of lithium phenolates was thwarted by sporadic technical problems and intervening mixed solvation. Consequently, the discussion is largely about qualitative effects (and selective examples at that) but they are revealing nonetheless.

Aprotic Solvents

Mixtures of **1** and **2** in Et₂O show exclusively tetramers. Solutions of lithium phenolate **1** in neat Et₂O with as little as 2.0 equiv of TMEDA (see eq 2) contain exclusively TMEDA-solvated dimer **5a**. Although this outcome does not attest to the relative binding constants of Et₂O and TMEDA because of the unknowable energy of aggregation, ether is poorly coordinating³⁷ compared with other solvents (except the highly hindered *i*-Pr₂NH). 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 observed when the solvents are used separately, suggesting the absence of mixed solvation (see 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 Et₂O in an experiment akin to that represented by eq 3 (Figure 7b) shows much stronger binding of pyridine than of Et₂O on a per-molar basis.

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, accompanying substantial downfield shifting of the dimer implicates mixed-solvated dimer **5b** (eq 4; S = pyridine).

Dipolar Aprotic Solvents

Highly dipolar solvents in toluene cosolvent (Table 1, entries 5–9) display a strong tendency to form tetramers for all four lithium phenolates **1–4**, which is contrary to the often-cited belief that dipolar solvents promote deaggregation.³⁸ Addition of 1.0 equiv of the dipolar solvents to TMEDA-solvated dimer **5a** elicits quantitative conversion to the corresponding tetramers (eq 2), indicating that dipolar solvents bind more strongly than do pyridine (as well as *n*-PrNH₂ and pyrrolidine; *vide infra*). Despite concerns that the dipolar ligands might catalyze facile exchanges, intraaggregate exchange is slow at low temperatures. Even the hindered 2,6-dimethylphenolates **3** and **4**, which display a penchant to deaggregate in THF²¹ afford tetramers when solvated by most of the highly dipolar ligands. Inexplicably high interaggregate exchange rates for *N,N'*-dimethyl-*N,N'*-trimethyleneurea (DMPU) precluded

studies of **3** and **4**. Acetonitrile mimicked the carbonyl-based dipolar ligands in promoting tetramers, although high interaggregate exchange rates precluded detailed studies. Attempts to measure the relative binding constants of the dipolar ligands were largely unsuccessful.^{39,40}

Mixtures of the 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 intraaggregate exchange rates depended markedly on the stoichiometry of the mixed tetramers. We turned to an alternative strategy to examine DMSO solvates.

Previous studies have shown that ¹⁹F 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 ¹⁹F 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 intraaggregate 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).

Protic Amines

We examined mono- and dialkylamines spanning a range of steric demands. *n*-PrNH₂/toluene solutions of **1** and **2** afford tetramers consistent with anticipated⁴¹ 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*-PrNH₂/toluene solutions contain only dimers. One could imagine highly stabilized tetrasolvated dimers, yet we observed dimers with as little as 1.0 equiv of *i*-BuNH₂. This dimer preference may be general, but high exchange rates for *t*-BuNH₂ and *s*-BuNH₂ precluded analysis. Further studies are needed 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 Et₂NH, 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 divergent steric demands of unhindered phenolates **1** and **2**.

The capacity of **2** solvated by piperidine to participate in two ensembles with equal facility affording statistical distributions in both cases is the first instance of such promiscuity reported to date. In previous studies, the rule of thumb “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}

The highly hindered *i*-Pr₂NH, 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. 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 consistent with at least partial solvation by *i*-Pr₂NH, 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*-Pr₂NH.

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**, although *n*-butanol shows an odd tendency to afford re-solved tetramer ensembles only using Et₂O as cosolvent, which suggested a co-operative solvation effect. Solvent swaps competing the alcohols with TMEDA (eq 2) show the anticipated qualitative drop in binding with increasing steric demands: 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 Variations (MCV).^{3,20,21} The underlying theme of this paper, however, is less about the role of MCV in determining aggregation states of lithium phenolates—a topic covered in previous studies²¹—and more about the merits of relatively nonbasic and stable lithium phenolates for the study of lithium ion solvation using 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 are moderately polar (pyridine, Et₂O, and TMEDA; Table 1, entries 1–3), highly dipolar (Table 1, entries 5–9), and protic (amines and alcohols; entries 10–21). In addition to investigation of solvent-dependent aggregation states (Table 1), solvent swapping experiments using binary solvent mixtures represented by eqs 2–4 shed light on relative binding energies, relationships of solvation and aggregation, and mixed solvation. 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 affiliated deep-seated structural changes. Occasionally, an additional (lower) aggregate also appears.

Nonpolar solvents established a foundation for the study. Et₂O 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 THF²⁸ and readily promotes tetramers with the particular advantage of causing marked (≈ 1.0 ppm) downfield ⁶Li shifts used that are useful both diagnostically and to maximize resolution. These three solvents have routinely been used as benchmarks in investigations of the 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 quite similarly to one another. The seemingly paradoxical tendency to afford tetramers despite a reputation for

deaggregating lithium salts is consistent with previous studies showing that a lack of deaggregation⁴⁸ and even 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 varying results, possibly because of their enormous range of structural diversity and steric demands. At one extreme, monoalkylamines are comparable to the dipolar ligands, although we noted a greater penchant of 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 pyrrolidine⁴³ and pyrrolidine-based chelates³³ have shown similarly strong ligation. At the other extreme, diisopropylamine appears to bind, but it is a poorly coordinating ligand at best. This additional data in conjunction with other studies⁴³ showing poor coordination of *i*-Pr₂NH contrasts with provocative and still somewhat baffling evidence that *i*-Pr₂NH 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 of binding constant with X = O and NH: the binding is independent of X.⁴³ One can see similar trends with lithium phenolates, although the correlation is unlikely to be as strong. We presume, for example, that serial solvation of the four sites of a tetramer is non-statistical, especially for sterically demanding ligands.

Studies of the alcohols were clearly the most disappointing given their prevalence in 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 of the alcoholic proton in the catalysis of inter- and intraaggregate exchanges.⁵¹ 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 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 that 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}

In routine cases such as incrementally swapping pyridine, it is possible that one homosolvated tetramer may be replaced by another (eq 3). 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, however, that they distribute statistically. Reich notes nonstatistical replacements of ethereal solvents by increments of hexamethylphosphoramide.^{10b} Jacobsen noted a 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.

(5)

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 coordination of both solvents (eq 6). We expected lithium naphtholate **3** containing 0.50 equiv of *n*-PrNH₂ and 0.50 equiv of TMEDA—one solvent molecule per lithium—to provide a mixture of homosolvated dimer **5a** and tetramer **7a** (see eq 2) but only tetramer forms, suggesting cooperativity in tetramer **7f**. The η^1 -bound TMEDA is inferred but well preceded.³⁶ If so, cooperativity—a nonstatistical preference for mixed solvation—is strongly indicated.

(6)

Conclusion

Our efforts to untangle organolithium chemistry often yield both insights into organolithium chemistry and tactical advances—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 varying steric demands show a large range of binding affinity, resulting in highly amine-dependent distributions of 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 studying the coordination chemistry (solvation) of enolates, phenolates, and related O-lithiated species. Studies 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 exceptional chemical shifts caused by coordination, which not only improve resolution but also confirm the very existence (or absence) of the pyridine-lithium contacts.

Confirming the presence or absence of solvent-lithium contacts 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 ^6Li NMR spectroscopy,²¹ underscoring the potential importance of alternative nuclei in 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 ke-tyl. Alcohols and all solvents containing carbonyls were distilled from 3 or 4 Å molecular sieves. $[\text{}^6\text{Li}]\text{LiHMDS}$ was prepared and recrystallized as described previously.²⁴ Air- and moisture-sensitive materials were manipulated under argon using standard glove box, vacuum line, and syringe techniques.

NMR Spectroscopy

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 return to room temperature. It was then backfilled with argon and placed in a -78°C dry ice/acetone bath. The appropriate amounts of $[\text{}^6\text{Li}]\text{LiHMDS}$ 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.

^6Li 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 $>5 \times T_1$ to ensure accurate integrations. Chemical shifts are reported relative to a 0.30 M $^6\text{LiCl}/\text{MeOH}$ 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 set between 0 and 0.3, 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. The mathematics underlying the parametric fits have been described in detail.^{3,20a}

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

^6Li NMR spectra recorded as approximate 1:1 mixtures of lithium phenolates in toluene cosolvent: (a) dimers of $[\text{}^6\text{Li}]\mathbf{3}$ (A) and $[\text{}^6\text{Li}]\mathbf{4}$ (B) in 0.50 M TMEDA (-80°C); (b) tetramers of $[\text{}^6\text{Li}]\mathbf{2}$ (A) and $[\text{}^6\text{Li}]\mathbf{1}$ (B) in 0.50 M propylamine with slow intraaggregate exchange (-80°C); (c) trimers of $[\text{}^6\text{Li}]\mathbf{3}$ (A) and $[\text{}^6\text{Li}]\mathbf{4}$ (B) in 0.50 M Et_2O with rapid intraaggregate exchange (-80°C); and (d) tetramers of $[\text{}^6\text{Li}]\mathbf{2}$ (A) and $[\text{}^6\text{Li}]\mathbf{1}$ (B) in 0.50 M pyridine in ether cosolvent with rapid intraaggregate exchange (22°C).

Figure 2. ^6Li NMR spectra recorded of $[\text{}^6\text{Li}]\text{2}$ (A) and $[\text{}^6\text{Li}]\text{1}$ (B) in solutions 0.50 M isobutylamine in toluene at $-80\text{ }^\circ\text{C}$.

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

Figure 4.

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

Figure 5.

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

Figure 6.

^6Li NMR spectrum of 0.50 M dimethylsulfoxide (DMSO)/toluene solutions containing approximate 1:1 mixtures of $[\text{}^6\text{Li}]\mathbf{3}$ and $[\text{}^6\text{Li}]\mathbf{4}$ recorded at $-90\text{ }^\circ\text{C}$ showing trimeric and tetrameric ensembles of homo- and heteroaggregates. The tetramer is at the limit of slow intraaggregate exchange whereas the trimer is undergoing rapid intraaggregate exchange. An ensemble appears upon warming to $-50\text{ }^\circ\text{C}$ and shows characteristics of dimers.

Figure 7.

Expected ^6Li NMR when replacing solvent S by S' : (a) elicits only a change in aggregation state (A_n for A_m), (b) causes solvent substitution on a common aggregate (A_m), or (c) causes an aggregation state change (A_n for A_m) and concurrent partial exchange of solvent on A_m to form a mixed solvate.

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 $-80\text{ }^\circ\text{C}$. **A**₄ is absent because it is NMR silent.

Chart 1.
Dimer, trimer, and tetramer mixtures showing magnetically inequivalent lithium sites.

Chart 2.

Table 1

Solvent-dependent aggregation states and ^6Li NMR chemical shifts for homoaggregates of **1–4** at -60 to -110 °C (see supporting information). Assignments are based on pairings of **1–2** and **3–4**.

Entry	Solvent ²²	Aggregate (δ ppm)	1	2	3	4
1	TMEDA	dimer (0.01)	dimer (0.23)	dimer (0.03)	dimer (0.03)	dimer (0.20)
2	Et_2O	tetramer (0.21)	tetramer (1.35)	trimer (1.06)	trimer (0.69)	trimer (0.69)
3	MeCN	tetramer (0.42)	tetramer (1.50)	tetramer (0.92)	tetramer (0.55)	tetramer (0.55)
4	pyridine	tetramer (2.00)	tetramer (3.10)	dimer (2.15)	dimer (1.94)	dimer (1.94)
5	DMA	tetramer (1.17)	tetramer (2.02)	tetramer (1.33)	tetramer (1.04)	tetramer (1.04)
6	DMF	tetramer (1.24)	tetramer (2.16)	.. ^a	.. ^a	.. ^a
7	DMSO	tetramer (0.60)	tetramer (1.62)	tetramer (1.28)	trimer (0.53)	trimer (0.53)
8	DMPU	tetramer (0.87)	tetramer (1.93)	.. ^b (0.92)	.. ^b (0.70)	.. ^b (0.70)
9	NMP	tetramer (1.13)	tetramer (2.03)	tetramer (1.47)	tetramer (1.16)	tetramer (1.16)
10	PrNH_2	tetramer (0.87)	tetramer (2.07)	dimer (0.49)	dimer (0.25)	dimer (0.25)
11	piperidine	tetramer ^b (0.75)	trimer ^c (1.80)	dimer ^d (0.36)	dimer (0.08)	dimer (0.08)
12	pyrrolidine	tetramer (0.70)	tetramer (1.96)	dimer ^d (0.59)	dimer (0.32)	dimer (0.32)
13	<i>i</i> -BuNH ₂	tetramer (0.91)	tetramer (2.22)	dimer (0.71)	dimer (0.44)	dimer (0.44)
14	<i>s</i> -BuNH ₂	tetramer (0.87)	tetramer (2.09)	.. ^b (0.13)	.. ^b (0.22)	.. ^b (0.22)
15	<i>t</i> -BuNH ₂	tetramer (0.78)	tetramer (1.96)	.. ^b (1.08)	.. ^b (0.88)	.. ^b (0.88)
16	(<i>i</i> -Pr) ₂ NH	.. ^e (1.07)	trimer ^c (1.28)	dimer (1.07)	dimer (0.84)	dimer (0.84)
17	Et_2NH	tetramer (0.55)	tetramer (1.79)	trimer (0.82)	trimer (0.42)	trimer (0.42)
18	<i>n</i> -Pr ₂ NH	tetramer (0.49)	tetramer (1.78)	trimer (0.81)	trimer (0.42)	trimer (0.42)
19	<i>t</i> -BuOH	tetramer (0.50)	tetramer (1.56)	.. ^b	.. ^b	.. ^b

Entry	Solvent ²²	Aggregate (δ ppm)
20	<i>n</i> -BuOH	tetramer (0.90) ^g --f --
21	<i>s</i> -BuOH	tetramer (1.73) --b (0.13) --b (-0.23)

^a Insoluble.

^b Could not be resolved.

^c With 4-chloro-1-naphthol.

^d Appears to be only tetrameric by ⁶Li NMR spectroscopy, whereas ¹⁹F NMR spectroscopy shows both the trimer and tetramer.

^d A major peak was left unassigned.

^e Fails to mix aggregate with **2** and **8**.

^f Temperature routinely at -80 °C; for exceptions see supporting information.

^g Resolves only with Et₂O as cosolvent.