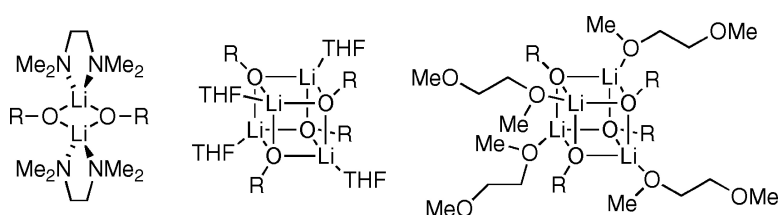


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Lithium Enolates of Simple Ketones: Structure Determination Using the Method of Continuous Variation

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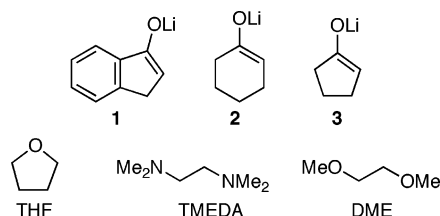
Abstract: The method of continuous variation in conjunction with ^6Li NMR spectroscopy was used to characterize lithium enolates derived from 1-indanone, cyclohexanone, and cyclopentanone in solution. The strategy relies on forming ensembles of homo- and heteroaggregated enolates. The enolates form exclusively chelated dimers in N,N,N',N' -tetramethylethylenediamine and cubic tetramers in tetrahydrofuran and 1,2-dimethoxyethane.

Introduction

Lithium enolates are used pervasively throughout organic synthesis.¹ A comprehensive survey of scaled procedures used by Pfizer Process over two decades shows that 68% of all C–C bond formations are carbanion-based and 44% of these involve enolates.^{2,3} Even a casual survey of synthesis papers emanating from academic labs reinforces the notion that lithium enolates are indispensable.¹ It may seem puzzling, therefore, that structure–reactivity relationships in enolates—the influence of solvation and aggregation on reactivity—are poorly understood when compared with other commonly used classes of organolithiums such as alkylolithiums and lithium amides.^{4–8} The primary contributions have come from Jackman and co-workers,^{4a,d,5} Streitwieser and co-workers,⁶ and several research groups focusing on methacrylate ester polymerizations.⁷ The limited progress toward understanding lithium enolates is glaringly simple: Despite extensive crystallographic determinations of lithium enolates,⁹ there are few methods for determining

enolate structures in solution, and none are general (vide infra). Without an understanding of solution structure, detailed mechanistic studies are not possible.^{10–12}

In the study described below, we characterize simple ketone enolates **1–3** coordinated by N,N,N',N' -tetramethylethylenediamine (TMEDA), tetrahydrofuran (THF), and 1,2-dimethoxyethane (DME). The strategy relies on the method of continuous variation in which ensembles of homo- and heteroaggregated enolates are monitored by ^6Li NMR spectroscopy. The results illustrate how ligands influence the structures of enolates. Of greater importance, however, is that the strategy promises to be general.



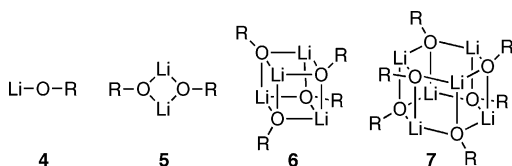
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Background

Structures of Lithium Enolates in Solution. On the basis of analogy with the crystal structures of lithium enolates and related organolithiums,^{9,13} one might surmise that **1–3** form monomers, dimers, tetramers, or hexamers (**4–7**) in solution.

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Such a claim, however, is wrought with risk. Although crystal structures offer important views of lithium enolates, one cannot infer from crystal structures the dominance or even the existence of these forms in solution: *solution aggregation numbers must be determined independently*.¹⁴ Unfortunately, the structures of lithium enolates in solution are not easily examined using NMR spectroscopy because of the high inherent symmetries of 4–7 and opaque Li–O connectivities arising from the absence of scalar Li–O coupling. Consequently, structural organolithium chemists have turned to indirect methods for probing the aggregation of lithium enolates in solution. Progress reported to date is limited and easily summarized.



Colligative measurements are often used to study aggregation behavior¹⁵ and have been used to examine lithium enolates and

related O-lithiated species on several occasions.¹⁶ Unfortunately, such measurements are sensitive to potentially undetectable impurities and offer dangerously simple answers when complex equilibria might be involved. In our opinion, they are of marginal use unless corroborated by an independent spectroscopic method.

Streitwieser and co-workers monitored mixed-aggregate equilibria derived from lithium enolate–carbanion mixtures to study the aggregation of enolates in ethereal solvents.⁶ Their methods are rigorous, but a reliance on UV spectroscopy and ultrahigh dilution has restricted their studies to enolates derived from aromatic ketones and esters. Jackman and co-workers used ¹³C spin–lattice relaxation times, colligative measurements, and ⁷Li quadrupolar splitting constants to conclude that lithium phenylsilybutyrate and several related hindered aromatic enolates are dimers or tetramers.^{5,17} More recently, Noyori and co-workers reported that the addition of hexamethylphosphoramide (HMPA) to lithium cyclopentenolate (3) affords the enolate dimer.¹⁸ Subsequently, Reich concluded that the addition of HMPA to 3 in THF causes serial ligand substitution of a tetramer to the exclusion of detectable deaggregation.¹⁹ Noyori appears to have been misled by a flawed colligative measurement of lithium cyclopentenolate in THF reported years earlier.^{16c} (We concur with Reich; vide infra). Jacobsen and co-workers used a combination of methods (including a serial solvation akin to Reich's approach) to show that lithium pinacolate forms a very

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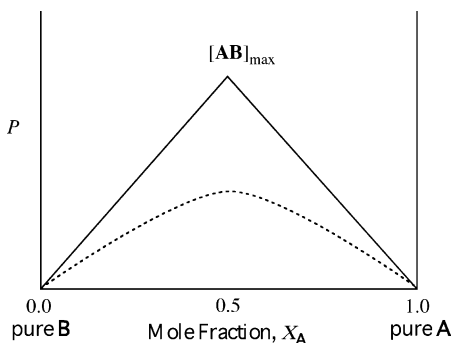
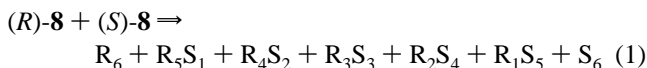
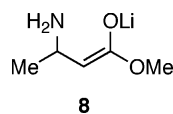


Figure 1. Representative Job plot showing a physical property, P , of complex \mathbf{AB} as a function of mole fraction (X_A) of component \mathbf{A} . $[\mathbf{AB}]_{\max}$ corresponds to the maximum concentration of complex \mathbf{AB} . The solid line (—) illustrates $K_{\text{eq}} \gg 1$. The dotted curve (- -) illustrates $K_{\text{eq}} \approx 1$.

odd trisolvated tetramer in pyridine/cyclohexane solution.²⁰ Hindered ester enolates central to methacrylate ester polymerizations have been shown to aggregate in solution. A combination of colligative and spectroscopic measurements provide a strong circumstantial case supporting dimers and tetramers.⁷

We began studying lithium enolates as part of a collaboration with Sanofi-Aventis to examine the structure and reactivity of enolate **8**.²¹ Mixtures of antipodes (*R*)-**8** and (*S*)-**8** afforded an ensemble of aggregates (eq 1) that could be monitored by ⁶Li NMR spectroscopy. Both the number of heteroaggregates and their dependencies on relative proportions of (*R*)-**8** and (*S*)-**8** proved highly characteristic of hexamers and inconsistent with monomers, dimers, and tetramers.



Method of Continuous Variation. The protocol used to characterize **8** and adapted to characterize **1–3** formally falls under the rubric of the method of continuous variation²² (also called the method of Job²³), which has found widespread applications in chemistry and biochemistry.²⁴ A brief digression may be instructive.

In its simplest and most prevalent usage, the method of continuous variation identifies the stoichiometry of a single complex (or aggregate) in solution. Imagine species \mathbf{A} and \mathbf{B} form an \mathbf{AB} complex (eq 2). Plotting a physical property (P) that reflects the concentration of \mathbf{AB} versus mole fraction of \mathbf{A} (X_A) affords what is often called a Job plot (Figure 1). The stoichiometry of the complex is gleaned from the position of the maximum ($[\mathbf{AB}]_{\max}$) along the x axis; an \mathbf{AB} complex affords

$[\mathbf{AB}]_{\max}$ at $X_A = 0.5$. If, however, \mathbf{AB}_2 or $\mathbf{A}_2\mathbf{B}$ complexes are formed, the maxima appear at $X_A = 0.33$ and 0.67 , respectively. The magnitude of the equilibrium constant (K_{eq}) is reflected in the shape of the curve: A sharp apex (solid line in Figure 1) results from $K_{\text{eq}} \gg 1$, whereas the curve (dotted line) is emblematic of $K_{\text{eq}} \approx 1$.



Ensembles of Aggregates. The method of continuous variation can, in principle, be extended to complex systems in which an ensemble of $\mathbf{A}_m\mathbf{B}_n$ aggregates is observed, and indeed, some progress has been made. There are several instances in organolithium chemistry, for example, in which investigators studied heteroaggregation with the expressed purpose of demonstrating that homoaggregation is probable.²⁵ The earliest report appears to be that of Brown and co-workers in which they demonstrated a penchant for tetramer formation by showing that mixtures of methyllithium and lithium chloride afford mixed tetramers.²⁶ Brown considered the influence of proportions on the distribution of aggregates, but the studies were largely qualitative. Günther and co-workers used mixtures of deuterated and undeuterated organolithiums to cleverly circumvent potentially costly and tedious ¹³C labeling of organolithiums.²⁷ The study of sodium alkoxides by Gagne and co-workers is probably most germane to the study described below.²⁸ ¹H NMR spectroscopy was used to probe ensembles of sodium alkoxide tetramers, with the symmetries of the mixed tetramers playing a significant role. A similar strategy was used by Chabanel and co-workers to investigate the structures of lithium thiocyanates using infrared spectroscopy.²⁹

During studies of enolate **8**, we provided a general solution to the problem of monitoring and quantitating large ensembles of aggregates. We illustrate the method using the generic ensemble described by eq 3:



Table 1 summarizes the predicted number of spectroscopically distinct structural forms observed for monomers, cyclic dimers, cubic tetramers, and hexagonal hexamers derived from $\mathbf{A}_n/\mathbf{B}_n$ mixtures. Because of their importance in this paper, we have included a graphical description of dimers and tetramers in Chart 1; magnetically inequivalent ⁶Li nuclei within each aggregate are denoted with black and gray spheres. Both the number and spectral complexity of the aggregates within the ensembles

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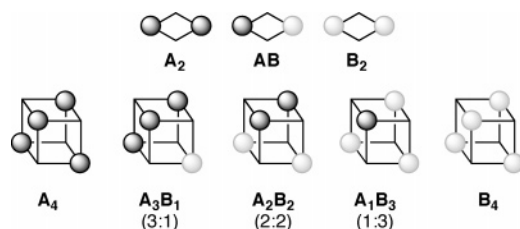
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Table 1. Spectroscopically Distinguishable Aggregates in Binary Mixtures of Lithium Enolates **A** and **B**

$A_n B_n$ aggregates (ratio of ^6Li resonances)			
monomer	dimer	tetramer	hexamer
A	A ₂	A ₄	A ₆
B	AB (1:1)	A ₃ B ₁ (3:1)	A ₅ B ₁ (1:2:2:1)
	B ₂	A ₂ B ₂ (2:2)	A ₄ B ₂ (2:2:2; 1:2:2:1; 2:4) ^a
		A ₁ B ₃ (1:3)	A ₃ B ₃ (3:3; 3:3; 1:1:1:1:1:1) ^a
	B ₄	A ₂ B ₄ (2:2:2; 1:2:2:1; 2:4) ^a	A ₁ B ₅ (1:2:2:1)
		B ₆	

^a Three positional isomers.

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

increase markedly with aggregate size. An ensemble of tetramers derived from a mixture of **A**₄ and **B**₄ contains a substantial number of aggregates (five) and an even larger number of discrete resonances (eight). Hexamers manifest enormous spectral complexity due to the proliferation of aggregate stoichiometries and the existence of positional isomers.

The populations of homo- and heteroaggregates in Table 1 are described *quantitatively* by eqs 4–6 where the experimentally measured components are mole fraction of **A** (X_A) and relative NMR resonance integrations (I_n). The model includes provisions for nonstatistical distributions (differing relative stabilities) and forms the foundation for the studies of dimeric and tetrameric enolates ($N = 2$ and 4) described in the next section.

$$X_A = \frac{\sum_{n=0}^N n[A_n B_{N-n}]}{\sum_{n=0}^N N[A_n B_{N-n}]} \quad I_n = \frac{[A_n B_{N-n}]}{\sum_{j=0}^N [A_j B_{N-j}]} \quad (4)$$

$$[A_n B_{N-n}] = C \frac{N!}{n!(N-n)!} \phi_n \exp\left(\frac{n\mu_A + (N-n)\mu_B}{kT}\right) \quad (5)$$

$$\phi_n = \left\langle \exp\left(\frac{-g_{n,p}}{kT}\right) \right\rangle_p \quad (6)$$

where μ_A and μ_B = chemical potentials of **A** and **B**; g_p = free energy of assembly of aggregates with n subunits of **A** arranged in permutation, p ; C = a constant³⁰; X_A = mole fraction of enolate **A**; I_n = relative integration of aggregate n ³¹; n =

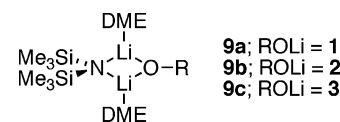
(30) We assume that the solution is ideal. For a given species, $A_n B_{N-n}$, C is the concentration at which the activity is equal to 1.^{21b}

(31) The relative integration (I_n) was previously referred as aggregate mole fraction (X_n , ref 21). We have changed it to avoid using two, distinctly different mole fraction terms and to include provisions for mixtures of aggregates which are not of the same aggregation number.

aggregate label bearing n subunits of **A**; N = aggregation number; and ϕ_n = a measure of relative stability of aggregate n .

Results

General Methods. Ensembles of homo- and heteroaggregates derived from binary mixtures of lithium enolates (prepared from [^6Li]LiHMDS) (HMDS = hexamethyldisilazide) present challenges associated with spectral dispersion and resolution. Resolution is optimal when the chemical shift separation of the homoaggregates is large. To this end, a markedly downfield ^6Li resonance renders indanone-derived enolate **1** central to the strategy. The line widths and resolution were optimized by adjusting the probe temperature although the origins of the temperature dependencies were not obvious. Spectra were also recorded using [^6Li , ^{15}N]LiHMDS³² to detect LiHMDS–lithium enolate mixed dimers;³³ only DME-solvated mixed dimers **9** (of unknown DME hapticity) were detected.³⁴ Enolates **1**–**3** are structurally homogeneous in TMEDA, THF, and DME as shown by ^6Li NMR spectroscopy.³⁵ Studies using mixtures of **1** and **2** as well as **1** and **3** provided analogous results for all solvents, although cyclopentanone-derived enolate **3** is prone to form impurities. Mixtures of **1** and **2** are presented emblematically. All raw data as well as additional NMR spectra and Job plots are provided in the Supporting Information.



TMEDA. TMEDA-solvated enolates offer the simplest illustration of how the method of continuous variation is used to ascertain aggregate structures. ^6Li NMR spectra of mixtures of enolates **1** and **2** reveal the resonances of the homo- and heteroaggregated enolates (Figure 2, LiHMDS monomer³⁶ resonance not shown), consistent with an ensemble of dimers (Table 1 and Chart 1). Plotting relative integrations of the three enolate aggregates versus mole fraction of enolate **2** (X_2) affords the Job plot in Figure 3. The curves represent a parametric fit to the data according to eqs 7 and 8. (The ϕ_n expressions in eq 8 derive from eqs 4–6.) The experimental data correlate with a nearly statistical distribution of homo- and heterodimers as illustrated in Figure 4. The aggregate proportions are invariant over a 10-fold range of absolute enolate concentration (0.05–0.50 M), supporting a shared aggregation number for the three species.

$$\frac{1}{2}A_2 + \frac{1}{2}B_2 \xrightleftharpoons{K_1} AB \quad (7)$$

$$K_1 = 2\phi_1/(\phi_0^{1/2}\phi_2^{1/2}) \quad (8)$$

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(34) A LiHMDS–lithium enolate mixed dimer chelated by two DME ligands has been reported. Williard, P. G.; Hintze, M. J. *J. Am. Chem. Soc.* **1990**, *112*, 8602.

(35) (a) A crystal structure of enolate **3** solvated by THF showing a cubic tetramer has been reported: Amstutz, R.; Schweizer, W. B.; Seebach, D.; Dunitz, J. D. *Helv. Chim. Acta* **1981**, *64*, 2617. (b) Crystal structures of enolate **1** solvated by 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU) showing a cubic tetramer and by TMEDA showing a doubly chelated dimer are archived in the Supporting Information.

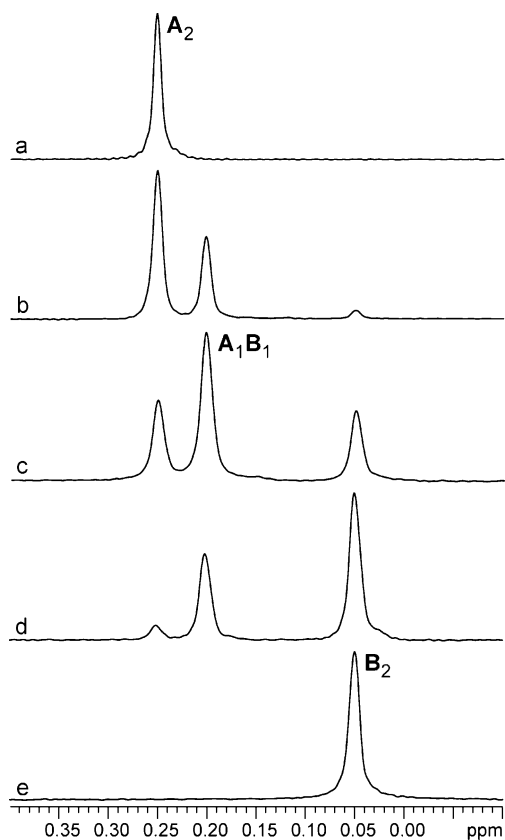


Figure 2. ^6Li NMR spectra of 0.10 M mixtures of $[\text{}^6\text{Li}]\text{I}$ (A) and $[\text{}^6\text{Li}]\text{II}$ (B) in 1.0 M TMEDA/toluene at $-90\text{ }^\circ\text{C}$. Key: (a) $X_2 = 0.0$; (b) $X_2 = 0.23$; (c) $X_2 = 0.52$; (d) $X_2 = 0.79$; (e) $X_2 = 1.0$.

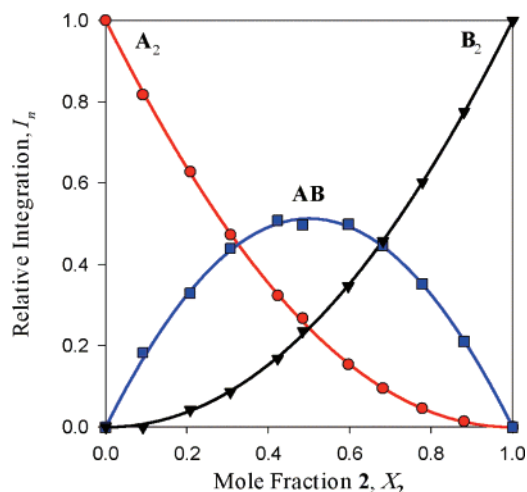


Figure 3. Job plot showing the relative integrations versus mole fraction of **2** for 0.10 M mixtures of enolates $[\text{}^6\text{Li}]\text{I}$ (A) and $[\text{}^6\text{Li}]\text{II}$ (B) in 1.0 M TMEDA/toluene at $-90\text{ }^\circ\text{C}$. From eqs 4–6: $\phi_0 = 0.95$; $\phi_1 = 1.0$; $\phi_2 = 0.95$.

Minor deviations of the intended mole fraction from the actual mole fraction can arise from experimental error, nonquantitative enolization, selective formation of mixed aggregates with LiHMDS, or formation of byproducts. Accordingly, we *measure* the mole fraction by simply integrating the ^6Li resonances. A Job plot using measured mole fraction shows a marginal improvement in the parametric fit. We believe, however, that

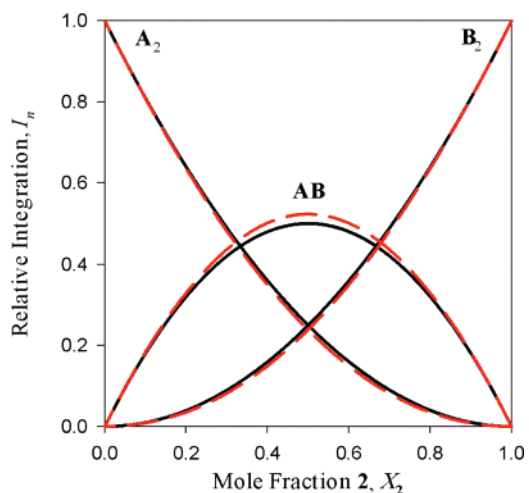


Figure 4. Best-fit curves from the Job plot in Figure 3 (dashed lines) overlaid with that expected from a statistical distribution of dimers (solid lines).

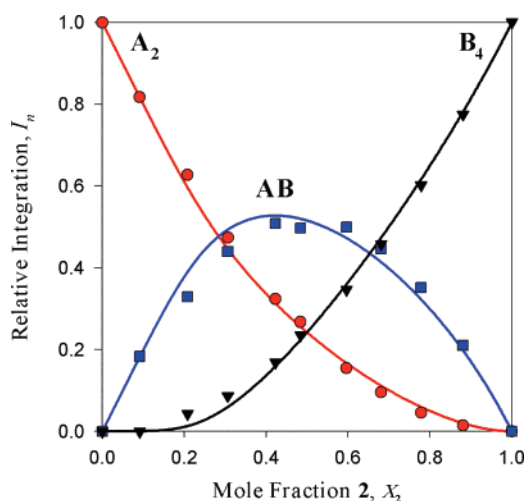


Figure 5. Job plot showing the relative integrations versus mole fraction of **2** fit to an ensemble of $\text{A}_2\text{-AB-B}_4$ (Supporting Information) of 0.10 M mixtures of enolates $[\text{}^6\text{Li}]\text{I}$ (A) and $[\text{}^6\text{Li}]\text{II}$ (B) in 1.0 M TMEDA/toluene at $-90\text{ }^\circ\text{C}$.

the measured mole fraction is more accurate than the intended mole fraction. We belabor this seemingly trivial point because measuring the mole fraction becomes important in some circumstances (*vide infra*).

The combination of aggregate count and symmetries as well as the parametric fit attest to the existence of an ensemble of dimers. Is it possible, however, that one of the homoaggregates might *not* be a dimer? Can we distinguish an all-dimer ensemble ($\text{A}_2\text{-AB-B}_2$) from, for example, an $\text{A}_2\text{-AB-B}_4$ ensemble wherein one of the homoaggregates is a tetramer? The fit in Figure 5 to the $\text{A}_2\text{-AB-B}_4$ model is inferior to the fit to the $\text{A}_2\text{-AB-B}_2$ model in Figure 4, with the offset of the maximum in the AB curve being readily apparent. The relative qualities of the fits in Figures 4 and 5 are easily visualized by plotting the sum of the absolute value of the residuals versus mole fraction (Figure 6) showing substantially larger deviations from the $\text{A}_2\text{-AB-B}_4$ model. These analyses are carried out routinely and included as Supporting Information. The Supporting Information also includes a considerable number of simulations (hypothetical cases) examining how incorrect models would deviate from the experimental data.

(36) Lucht, B. L.; Bernstein, M. P.; Remenar, J. F.; Collum, D. B. *J. Am. Chem. Soc.* **1996**, *118*, 10707.

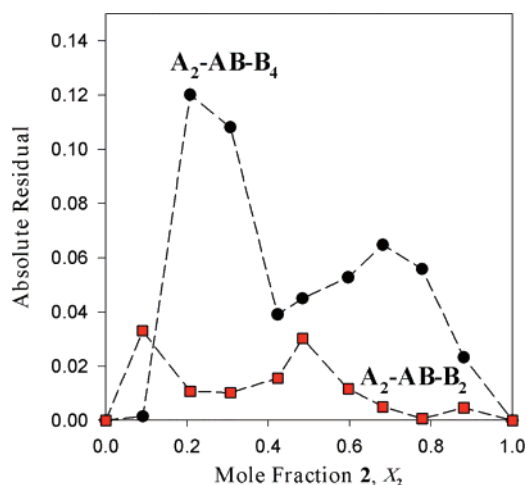
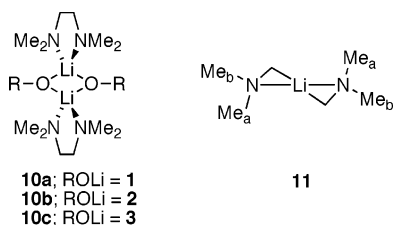


Figure 6. Absolute residuals versus mole fraction of **2** for the fits of mixtures of enolates $[\text{Li}]1$ (**A**) and $[\text{Li}]2$ (**B**) in 1.0 M TMEDA/toluene at -90°C to models based on $\text{A}_2\text{-AB-B}_4$ (●) and $\text{A}_2\text{-AB-B}_2$ (■, red). The rms of the sum of the squares of the residuals is 0.005 for the fit to $\text{A}_2\text{-AB-B}_2$ and 0.03 for the fit to $\text{A}_2\text{-AB-B}_4$.

TMEDA-solvated dimers were shown to be doubly chelated (**10**) by ^{13}C NMR spectroscopy. Spectra recorded on 0.10 M solution of **1** containing 2.0 equiv of TMEDA reveal free and bound TMEDA in equal proportions as discrete resonances. (Free and η^1 -bound TMEDA would rapidly exchange, resulting in time averaging of the resonances.³⁷) Further cooling to -90°C shows decoalescences of the methyl resonances that are highly characteristic of a half-chair conformer (**11**) in slow conformational exchange.^{38,39} The analogous decoalescences of enolates **2** and **3** were less convincing.



THF. Enolates **1–3** in THF solution are shown to form tetramers **12**. By example, ^6Li NMR spectra of mixtures of enolates **1** and **2** (Figure 7) reveal the resonances of the two homoaggregates along with three heteroaggregates displaying highly characteristic pairs of resonances in 3:1, 2:2, and 1:3 proportions (Table 1 and Chart 1). Plotting relative integrations of the five aggregates versus measured mole fraction of enolate **2** (X_2) affords the Job plot in Figure 8. The curves result from a parametric fit to the data according to eqs 9–14.²¹ (The ϕ_n expressions in eqs 12–14 derive from eqs 4–6.) The aggregate ratios are invariant over a 10-fold range of absolute enolate concentrations, confirming that the five species are of the same aggregation number. A fit to an ensemble comprising four tetramers with one homoaggregated dimer reveals an inferior fit (Supporting Information). Superimposing the parametric fit

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(39) ^6Li NMR spectra recorded on mixtures of **1** and **3** in Me_2NEt , a nonchelating analogue of TMEDA, display a distribution of resonances characteristic of an ensemble of tetramers.

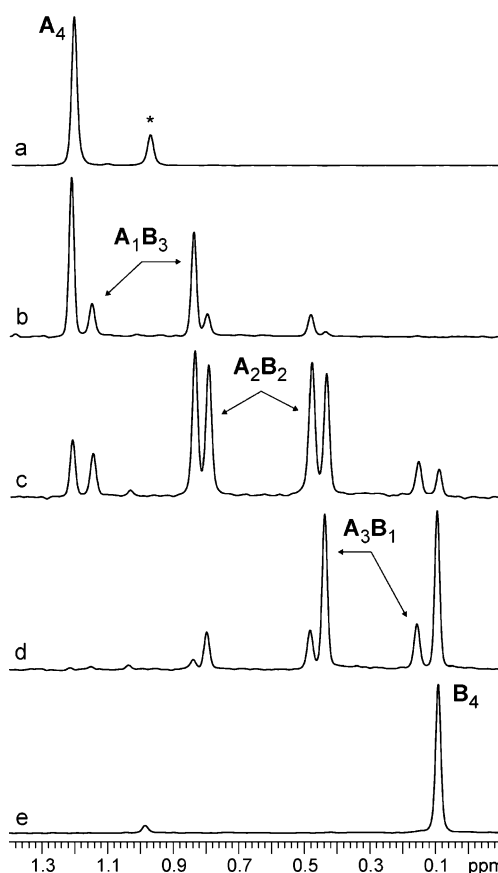
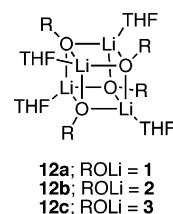
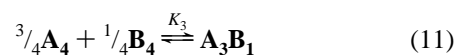
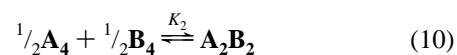
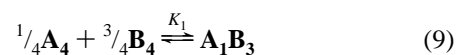


Figure 7. ^6Li NMR spectra of 0.20 M mixtures of $[\text{Li}]1$ (**A**) and $[\text{Li}]2$ (**B**) in 2.0 M THF/toluene at -30°C . Key: (a) $X_2 = 0.0$; (b) $X_2 = 0.19$; (c) $X_2 = 0.48$; (d) $X_2 = 0.78$; (e) $X_2 = 1.0$. The * denotes the LiHMDS dimer.



in Figure 8 with the results anticipated for a statistical distribution of aggregates reveals a high correlation (Figure 9).



$$K_1 = 4\phi_1/(\phi_0^{3/4}\phi_4^{1/4}) \quad (12)$$

$$K_2 = 6\phi_2/(\phi_0^{1/2}\phi_4^{1/2}) \quad (13)$$

$$K_3 = 4\phi_3/(\phi_0^{1/4}\phi_4^{3/4}) \quad (14)$$

DME. The structural studies of enolates **1–3** in DME proved challenging because of an apparent sensitivity of the enolates (or enolizations). Enolizations using 1.0 equiv of LiHMDS produced considerable impurities. Excess LiHMDS provided enolates cleanly but afforded appreciable concentrations of

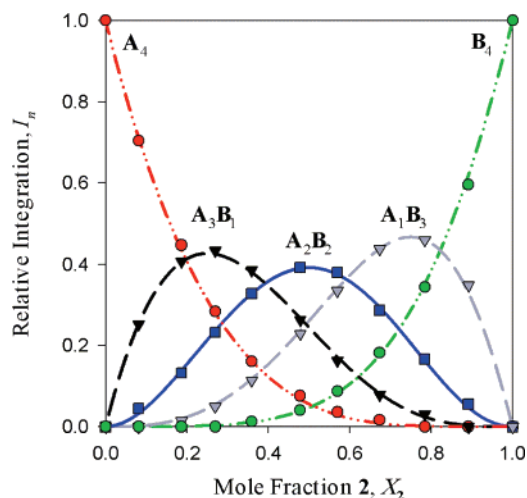


Figure 8. Job plot showing the relative integrations versus mole fraction of **2** in 0.20 M mixtures of enolates $[\text{}^6\text{Li}]\mathbf{1}$ (A) and $[\text{}^6\text{Li}]\mathbf{2}$ (B) in 2.0 M THF/toluene at $-30\text{ }^\circ\text{C}$. From eqs 4–6: $\phi_0 = 0.83$; $\phi_1 = 0.94$; $\phi_2 = 1.11$; $\phi_3 = 1.24$; $\phi_4 = 1.0$.

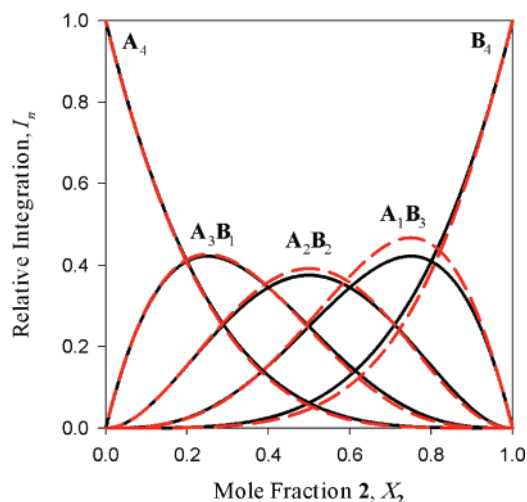


Figure 9. Best-fit curves from the Job plot in Figure 8 (dashed lines) overlaid with those expected from a statistical distribution of tetramers (solid lines).

mixed dimers **9**,^{21c,33,34} which caused resolution problems. Enolate mixtures generated from 1.1 equiv of LiHMDS offered the best compromise. ^6Li NMR spectra recorded on mixtures of **1** and **2** as well as **1** and **3** afford resonances characteristic of an ensemble of tetramers (Figure 10a). The resulting Job plots (necessarily using measured mole fraction because of the LiHMDS–lithium enolate mixed aggregates and other minor impurities) are fully consistent with nearly statistical distributions (Figure 11). Thus, the enolates form cubic tetramers **13**, presumably bearing nonchelated (η^1) DME ligands.⁴⁰ Chelated dimers of general structure **14** were not observed.

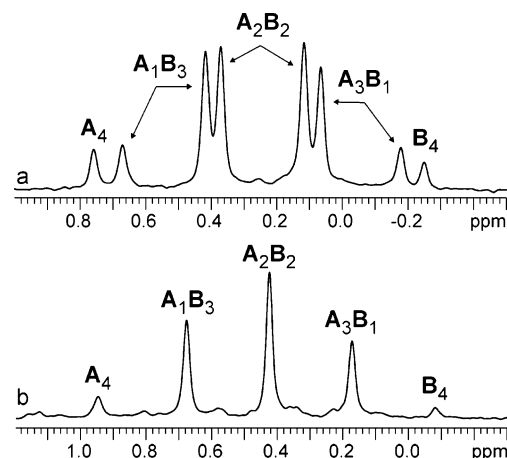
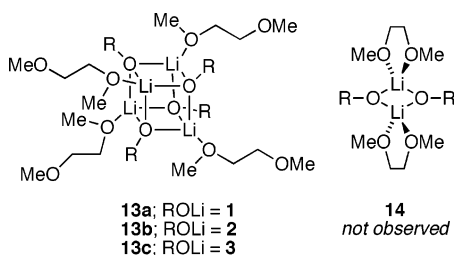


Figure 10. ^6Li NMR spectra of 0.20 M equimolar mixture of $[\text{}^6\text{Li}]\mathbf{1}$ (A) and $[\text{}^6\text{Li}]\mathbf{2}$ (B) in 2.0 M DME/toluene. Key: (a) $-105\text{ }^\circ\text{C}$; (b) $-30\text{ }^\circ\text{C}$.

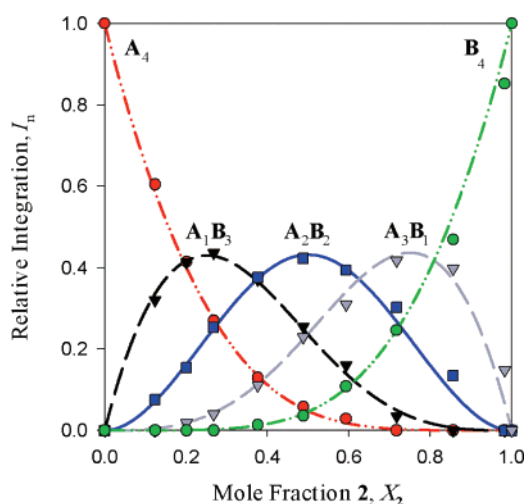
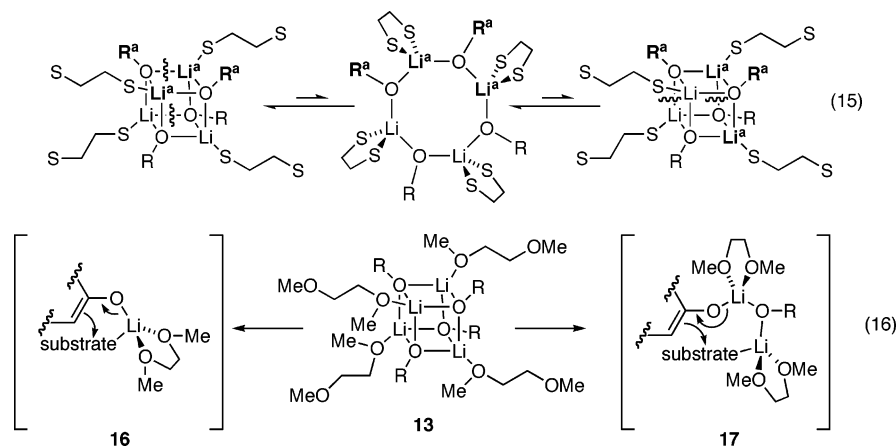


Figure 11. Job plot showing the relative integrations versus mole fraction of **2** in 0.20 M mixtures of enolates **1** and **2** in 2.4 M DME/toluene at $-105\text{ }^\circ\text{C}$. From eqs 4–6: $\phi_0 = 0.70$; $\phi_1 = 0.99$; $\phi_2 = 1.26$; $\phi_3 = 1.29$; $\phi_4 = 1.0$.

During efforts to optimize the resolution of the ^6Li resonances, we discovered a rapid *intraaggregate* exchange for DME-solvated enolates—the exchange of ^6Li nuclei within each

- (40) (a) Hilmersson, G.; Davidsson, O. *J. Org. Chem.* **1995**, *60*, 7660. (b) Remenar, J. F.; Lucht, B. L.; Collum, D. B. *J. Am. Chem. Soc.* **1997**, *119*, 5567. (c) Williard, P. G.; Nichols, M. A. *J. Am. Chem. Soc.* **1993**, *115*, 1568. (d) Barnett, N. D. R.; Mulvey, R. E.; Clegg, W.; O'Neil, P. A. *J. Am. Chem. Soc.* **1993**, *115*, 1573. (e) Black, S. J.; Hibbs, D. E.; Hursthouse, M. B.; Jones, C.; Steed, J. W. *J. Chem. Soc., Chem. Commun.* **1998**, 2199. (f) Bruce, S.; Hibbs, D. E.; Jones, C.; Steed, J. W.; Thomas, R. C.; Williams, T. C. *New J. Chem.* **2003**, *27*, 466. (g) Hahn, F. E.; Keck, M.; Raymond, K. N. *Inorg. Chem.* **1995**, *34*, 1402. (h) Henderson, K. W.; Dorigo, A. E.; Liu, Q.-Y.; Williard, P. G. *J. Am. Chem. Soc.* **1997**, *119*, 11855. (i) Deacon, G. B.; Feng, T.; Hockless, D. C. R.; Junk, P. C. J.; Skelton, B. W.; Smith, M. K.; White, A. H. *Inorg. Chim. Acta* **2007**, *360* 1364. (j) McGeary, M. J.; Coan, P. S.; Foltling, K.; Streib, W. E.; Caulton, K. G. *Inorg. Chem.* **1991**, *30*, 1723. (k) Coan, P. S.; Streib, W. E.; Caulton, K. G. *Inorg. Chem.* **1991**, *30*, 5019. (l) McGeary, M. J.; Cayton, R. H.; Foltling, K.; Huffman, J. C.; Caulton, K. G. *Polyhedron* **1992**, *11*, 1369. (m) Bochkarev, M. N.; Fedushkin, I. L.; Fagin, A. A.; Petrovskaya, T. V.; Ziller, J. W.; Broomhall-Dillard, R. N. R.; Evans, W. J. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 133. (n) Cosgriff, J. E.; Deacon, G. B.; Fallon, G. D.; Gatehouse, B. M.; Schumann, H.; Weimann, R. *Chem. Ber.* **1996**, *129* 953. (o) Deacon, G. B.; Delbridge, E. E.; Fallon, G. D.; Jones, C.; Hibbs, D. E.; Hursthouse, M. B.; Skelton, B. W.; White, A. H. *Organometallics* **2000**, *19*, 1713. (p) Link, H.; Fenske, D. *Z. Anorg. Allg. Chem.* **1999**, *625*, 1878. (q) Bonomo, L.; Solari, E.; Scopelliti, R.; Latronico, M.; Floriani, C. *J. Chem. Soc., Chem. Commun.* **1999**, 2229. (r) Rosa, P.; Mezailles, N.; Ricard, L.; Le Floch, P. *Angew. Chem., Int. Ed.* **2000**, *39* 1823. (s) Iravani, E.; Neumuller, B. *Organometallics* **2005**, *24*, 842. (t) Also see ref 36.



aggregate⁴¹—that was *not* observed for their THF-solvated counterparts. Warming the probe causes the pairs of resonances corresponding to each heteroaggregate to coalesce to a single ⁶Li resonance—five resonances total (cf. parts a and b of Figure 10). A Job plot determined at $-30\text{ }^{\circ}\text{C}$ in the limit of fast intraaggregate exchange is essentially indistinguishable from the Job plot in the slow exchange limit. The absence of a temperature dependence is notable (*vide infra*). A highly speculative mechanism accounting for the facile exchange via a transient cyclic tetramer is provided (eq 15).

The dynamic phenomenon represented by eq 15 is unique to the DME-solvated enolates and has potentially broader implications. Ligands that readily bind in chelated or nonchelated forms are said to be hemilabile.⁴² When a transition state is stabilized by chelation whereas the ground state is not, the selective stabilization can afford marked rate accelerations (up to 10 000-fold).⁴³ We suspect, therefore, that reactions of DME-solvated enolates with the standard electrophiles are accelerated by such hemilability (eq 16).

Solvent Swapping. The unexpected absence of DME-chelated dimers prompted us to turn to a simple control experiment that shows whether a change in solvent is accompanied by a change in aggregation.⁴⁴ The experiment requires a measurable ⁶Li chemical shift difference in the two limiting forms. It is based on the rapid solvent–solvent exchange (ligand substitution) and much slower aggregate–aggregate exchange.⁴⁵ By recording a series of spectra in which one coordinating solvent is incrementally replaced by a second, either of two limiting behaviors is observed: (1) If the two 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 12a); (2) if the observable forms in the two solvents differ by aggregation number, incremental solvent swap causes one aggregate to disappear and the other to appear (Figure 12b).

Indanone-derived enolate **1** provides high chemical shift dispersion and offers an excellent illustration of the technique. Substitution of THF with DME reveals only a time-averaged change in chemical shift (Figure 13a), supporting the assignment of enolate **1** as tetramers in both solvents. Conversely, incrementally replacing THF with TMEDA reveals the replacement of one resonance with the other, characteristic of an aggregate exchange (Figure 13b) and supporting the assignments as fundamentally different aggregated forms.⁴⁶ Similarly, replacing TMEDA with DME showed discrete resonances (behavior as in Figure 12b) consistent with a solvent-dependent change in aggregation number. Moreover, DME only reluctantly converts TMEDA-solvated dimer **10a** to DME-solvated tetramer **13a**; $\approx 30:1$ DME/TMEDA affords equal populations of the two aggregates.⁴⁷

Discussion

Determining the structure of organolithium species in solution has never been easy, but the problems presented by ketone enolates and related O-lithiated species are acute. Ascertaining the aggregation number invariably reduces to a problem of breaking symmetry.²⁵ In the case of N-lithiated and C-lithiated species, this is most conveniently achieved by observing ¹⁵N–⁶Li and ¹³C–⁶Li scalar coupling.^{27a,48} For O-lithiated species, ¹⁷O–⁶Li coupling is of no practical value.⁴⁹ We used the method of continuous variation^{21–25} to characterize enolates **1–3** in TMEDA, THF, and DME. The discussion begins with a synopsis of the method, which is followed by a description of the results. Our primary concern at present, however, is on developing a general solution to the problem. Accordingly, in a third section we critique the method by emphasizing subtleties that may impact future applications.

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(45) Monodentate 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, O. *Angew. Chem., Int. Ed.* **2000**, *39*, 1467. (b) Sikorski, W. H.; Reich, H. J. *J. Am. Chem. Soc.* **2001**, *123*, 6527. (c) See ref 48.

(46) In the event that TMEDA- and THF-solvated dimers coexist, the ⁶Li resonances would undergo very rapid exchange even at low temperatures. See ref 36.

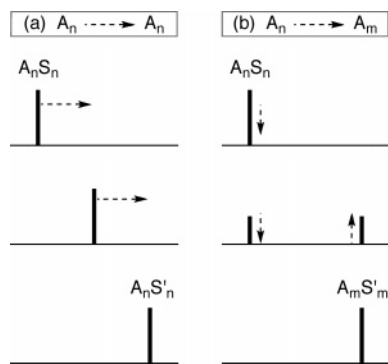


Figure 12. ^6Li NMR spectra anticipated if replacing solvent S by S' causes (a) only exchange of solvent on a common enolate aggregate (A_n) and (b) an aggregation change (A_m for A_n).

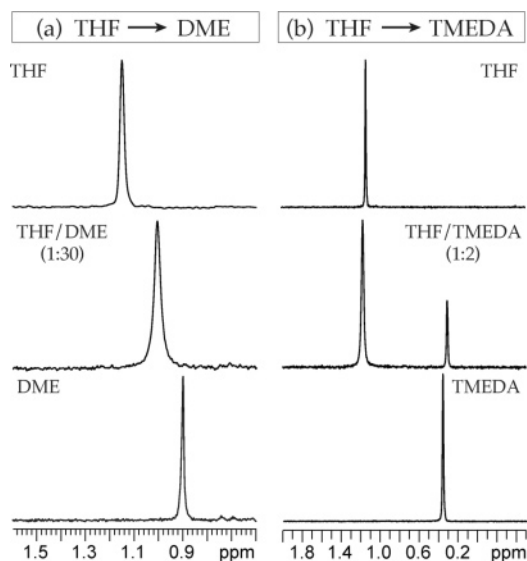
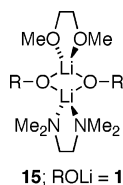


Figure 13. Selected ^6Li NMR spectra from solvent swap experiments using 0.10 M $[^6\text{Li}]\mathbf{1}$ with 3.0 M total ligand/toluene at -90°C . (a) Solvent swap between THF and DME. The mixed solvate is observed at a 1:30 ratio of the two solvents. (b) Solvent swap between THF and TMEDA. Both aggregation states are observed at a solvent ratio of 1:2.

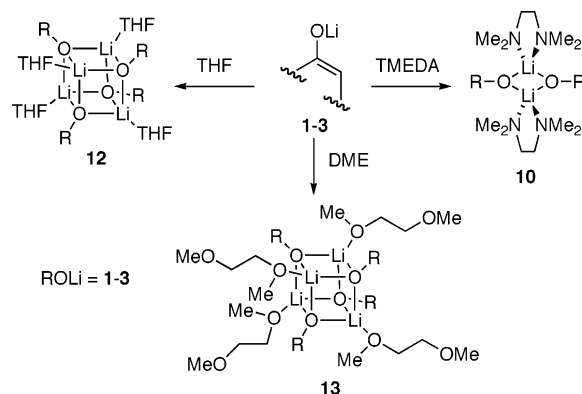
The Method of Continuous Variation. We determined the structures of lithium enolates by generating an ensemble of heteroaggregated enolates from two homoaggregated enolates (A_n and B_n) as described generically in eq 3. Two key observations using ^6Li NMR spectroscopy—the numbers of aggregates and the symmetries of the heteroaggregates—are highly diagnostic of the standard structural forms (4–7) as described in Table 1 and Chart 1. Plotting relative aggregate

- (47) At low total solvent concentration (2.0 equiv per lithium), traces of TMEDA/DME mixed-solvated dimer **15** are observed as a 1:1 pair of ^6Li resonances $< -115^\circ\text{C}$. At high total solvent concentration (30 equiv per lithium), we observe a time-averaged chemical shift that depends markedly on TMEDA/DME proportions, which is also consistent with mixed solvation.⁴⁴



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 (49) The rapid relaxation of the highly quadrupolar ^{17}O nucleus would preclude observing ^6Li – ^{17}O coupling.

Scheme 1



integrations versus mole fraction in binary enolate mixtures affords a Job plot as exemplified by Figures 3 and 8. The curves in Figures 3 and 8 correspond to best fits to models based on eqs 4–6. The results for enolates **1–3** are summarized in Scheme 1 and discussed with some literature context as follows.

Lithium Enolate Structures. TMEDA, one of the most prevalent ligands in organolithium chemistry,⁵⁰ has been shown to provide monomers, dimers, tetramers, and other more obscure structural forms.^{9,13} Although TMEDA shows a penchant for chelation, η^1 (nonchelated) TMEDA occasionally arises.⁵¹ Crystal structures of lithium enolates reveal a distinct preference for TMEDA-chelated dimers.^{9,52,53} We find that enolates **1–3** afford TMEDA-chelated dimers **10** as the only detectable forms in solution. The homo- and heteroaggregates are distributed statistically. Chelation was confirmed by ^{13}C NMR spectroscopy.

A large crystallographic database stemming from seminal studies by Seebach and co-workers suggests that THF-solvated lithium enolates and related O-lithiated species can exist in a number of aggregation states, but THF-solvated tetramers of general structure **12** are the most prevalent.⁹ Cyclopentanone-derived enolate **3**, for example, was one of the first two enolates characterized crystallographically, and it was shown to be tetrameric.^{35a} Structural studies of **3** in solution are controversial. Seebach^{16c} and Noyori¹⁸ endorse a model based on mixtures of dimers and tetramers whereas Reich concludes only tetramers exist.¹⁹ We concur with Reich; enolates **1–3** form tetramers as the only observable forms in THF.

It may be tempting to assume that DME is simply an oxygen analogue of TMEDA. One could imagine that the lower Lewis

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 (52) TMEDA-solvated enolates that are not dimers: Henderson, K. W.; Dorigo, A. E.; Williard, P. G.; Bernstein, P. R. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1322.
 (53) A solvent-free hexameric imidate crystallizes from solutions containing TMEDA: Maetzke, T.; Seebach, D. *Organometallics* **1990**, *9*, 3032.

basicity of ethers versus amines is offset by the lower steric demands of the ethers.^{54,55} With that said, considerable evidence suggests that DME is not always a strongly chelating ligand.^{43,56} DME binds to lithium in either η^1 (nonchelating)⁴⁰ or η^2 (chelating)^{9,13} capacities, depending on the steric environment. With respect to ketone enolates, there is a striking paucity of representation in the crystallographic literature.^{34,57} We were, however, somewhat surprised to find that enolates **1–3** afford tetramers **13** to the exclusion of the corresponding chelated dimers.

Homoaggregates from Heteroaggregates. The Job plots and affiliated parametric fits are fully consistent with the assignments summarized above. We remind the reader, however, that the primary goal is to exploit an ensemble of *heteroaggregates* to provide insights into the structures of the *homoaggregates*. One might question whether the linkage between the heteroaggregates and homoaggregates is strong. As a simple example, could a mixture of homoaggregated dimer and homoaggregated tetramer (eq 17) masquerade as an ensemble of dimers? The accumulated evidence that makes such a scenario unlikely is summarized as follows.



(1) The quality of the fits to the dimer and tetramer models are excellent. If an ensemble contains aggregates of differing overall aggregation numbers (as in eq 17), the Job plot would *not* be centrosymmetric and would appear so only by coincidence. The nearly statistical distribution of homo- and heteroaggregates certainly supports a shared aggregation number.⁵⁸

(2) A mixture of homo- and heteroaggregates of differing aggregation numbers would change with absolute enolate concentration; control experiments detect no such concentration dependencies. We hasten to add, however, that the concentration dependencies are technically difficult experiments.

(3) To the extent that a rogue homoaggregate of unique aggregation number results from an enthalpic effect, the equilibrium would be temperature-dependent. We detected no

such temperature dependencies. By example, mixtures of DME-solvated enolates **1** and **2** afforded Job plots at -30 and -105 °C that were indistinguishable.

(4) Chelation of TMEDA in dimers **10a–c** detected by ¹³C NMR spectroscopy convincingly excludes tetrasolvated tetramers, which would demand nonchelated TMEDA ligands.

(5) As illustrated in Figures 12 and 13, replacing one solvent incrementally with another offers a simple test of whether the change in coordinated solvent also causes a change in the aggregation number. Such “solvent swapping” experiments were fully congruent with the assignments.

(6) An ongoing study encompassing a wide array of ketone-, ester-, and carboxamide-derived enolates is allowing us to pair widely disparate enolates to form ensembles. The redundancy ensures that no single enolate is inordinately and anomalously influencing the outcome, and no surprises have appeared yet.⁵⁹

Conclusion

The studies described above can be distilled to a single concept: Ensembles of homo- and heteroaggregates—the number of discrete aggregates in the ensembles, their characteristic symmetries, and the resulting Job plots—offer a view of spectroscopically opaque homoaggregates. The strategy should apply to a diverse range of lithium enolates in a variety of solvents, and, indeed, this is being pursued. We believe, however, that exploiting ensembles to probe aggregation phenomena could be useful in a much broader context.

Experimental Section

Reagents and Solvents. Substrates are commercially available. TMEDA was recrystallized as the hydrochloride salt prior to distillation.⁶⁰ TMEDA, THF, and DME were distilled from solutions containing sodium benzophenone ketyl. Hydrocarbon solvents were distilled from blue solutions containing sodium benzophenone ketyl with approximately 1% tetraglyme to dissolve the ketyl. [⁶Li]LiHMDS and [⁶Li, ¹⁵N]LiHMDS were prepared and recrystallized as described previously.³² Air- and moisture-sensitive materials were manipulated under argon using standard glovebox, vacuum line, and syringe techniques. Samples for spectroscopic studies were prepared as described in the Supporting Information.

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Supporting Information Available: Experimental procedures, raw data, and Job plots. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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 (57) We can find no examples of crystallographically characterized homoaggregated lithium enolates solvated by DME. There are examples of the isostructural lithium aryloxides displaying a tendency to form doubly chelated dimers. See, for example: Cole, M. L.; Junk, P. C.; Proctor, K. M.; Scott, J. L.; Strauss, C. R. *Dalton Trans.* **2006**, 3338. Also, see 40e,f.
 (58) A *nonstatistical* distribution does *not* necessarily attest to differentially aggregated forms. In the case of sterically crowded aggregates, significant departure from statistical behavior (showing up as an unusual preference for heteroaggregation, for example) would not be surprising.