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

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Such a claim, however, is fraught 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. 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 behavior and have been used to examine lithium enolates and related O-lithiated species on several occasions. Unfortunately, such measurements are sensitive to potentially undetectable impurities and offer dangerously simple answers when 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. 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 Li quadrupolar constants to conclude that lithium phenylisobutyrate and several related hindered aromatic enolates are dimers or tetramers. More recently, Noyori and co-workers reported that the addition of hexamethylphosphoramide (HMPA) to lithium cyclopentenolate (3) affords the enolate dimer. 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. Noyori appears to have been misled by a flawed colligative measurement of lithium cyclopentenolate in THF reported years earlier. (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 related O-lithiated species on several occasions.

odd trisolvated tetramer in pyridine/cyclohexane solution.\textsuperscript{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.\textsuperscript{7}

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

\begin{equation}
(\text{R})-8 + (\text{S})-8 \rightarrow \text{R}_6 + \text{R}_2\text{S}_1 + \text{R}_2\text{S}_2 + \text{R}_3\text{S}_3 + \text{R}_2\text{S}_4 + \text{R}_3\text{S}_5 + \text{S}_6 \quad (1)
\end{equation}

**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 variation\textsuperscript{22} (also called the method of Job\textsuperscript{23}), which has found widespread applications in chemistry and biochemistry.\textsuperscript{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 \textbf{A} and \textbf{B} form an \textbf{AB} complex (eq 2). Plotting a physical property (\textit{P}) that reflects the concentration of \textbf{AB} versus mole fraction of \textbf{A} (\textit{X}_\text{A}) affords what is often called a Job plot (Figure 1). The stoichiometry of the complex is gleaned from the position of the maximum (\textit{I}_{\text{AB}}) along the x axis; an \textbf{AB} complex affords [\textit{AB}]\text{max} at \textit{X}_\text{A} = 0.5. If, however, \textit{AB}_2 or \textit{A}_2\textit{B} complexes are formed, the maxima appear at \textit{X}_\text{A} = 0.33 and 0.67, respectively. The magnitude of the equilibrium constant (\textit{K}_{eq}) is reflected in the shape of the curve: A sharp apex (solid line in Figure 1) results from \textit{K}_{eq} \gg 1, whereas the curve (dotted line) is emblematic of \textit{K}_{eq} \approx 1.

\begin{equation}
\text{A} + \text{B} \overset{K_{eq}}{\rightleftharpoons} \text{AB} \quad (2)
\end{equation}

**Ensembles of Aggregates.** The method of continuous variation can, in principle, be extended to complex systems in which an ensemble of \textit{AB}_\textit{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.\textsuperscript{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 methylolithium and lithium chloride afford mixed tetramers.\textsuperscript{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 \textsuperscript{13}C labeling of organolithiums.\textsuperscript{27} The study of sodium alkoxides by Gagne and co-workers is probably most germane to the study described below.\textsuperscript{28} A brief digression may be instructive.

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:

\begin{equation}
\text{A}_n + \text{B}_m \rightarrow \text{A}_n + \text{A}_{n-1}\text{B}_1 + \text{A}_{n-2}\text{B}_2 + \text{A}_{n-3}\text{B}_3 + \ldots \text{B}_m \quad (3)
\end{equation}

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

\[
X_A = \frac{\sum_{n=0}^{N} n[A_nB_{N-n}]}{\sum_{n=0}^{N} [A_nB_{N-n}]} \quad I_n = \frac{[A_nB_{N-n}]}{\sum_{j=0}^{N} [A_jB_{N-j}]} \quad (4)
\]

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

\[
\phi_n = \left(\exp\left(-\frac{g_n}{kT}\right)\right)^{-1/2} \quad (6)
\]

where $\mu_A$ and $\mu_B =$ chemical potentials of $A$ and $B$; $g_n =$ free energy of assembly of aggregates with $n$ subunits of $A$ arranged in permutation; $C =$ is a constant$^{30}; X_A =$ mole fraction of enolate $A; I_n =$ relative integration of aggregate $n$.$^{31}$.$ n =$

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

<table>
<thead>
<tr>
<th>$A_nB_m$ aggregates (ratio of $^6$Li resonances)</th>
<th>dimer</th>
<th>tetramer</th>
<th>hexamer</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>A$_2$</td>
<td>A$_2$B$_1$ (3:1)</td>
<td>A$_2$B$_1$ (1:2:2:1)</td>
</tr>
<tr>
<td>B</td>
<td>AB$_1$ (1:1)</td>
<td>A$_2$B$_1$ (1:2:2:1)</td>
<td>A$_2$B$_1$ (1:2:2:1)</td>
</tr>
</tbody>
</table>

*Three positional isomers.

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

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**Results**

**General Methods.** Ensembles of homo- and heteroaggregates derived from binary mixtures of lithium enolates (prepared from $[^6$Li$],$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 $^6$Li resonance renders indane-derived enolate I 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 $[^6$Li,$^{15}$N]LiHMDS$^{35}$ to detect LiHMDS—lithium enolate mixed dimers; 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 $^6$Li 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.

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**TMEDA.** TMEDA-solvated enolates offer the simplest illustration of how the method of continuous variation is used to ascertain aggregate structures. $^6$Li NMR spectra of mixtures of enolates 1 and 2 reveal the resonances of the homo- and heteroaggregated enolates (Figure 2, LiHMDS monomer$^{36}$ 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 $\phi_n$ 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.

\[
\frac{1}{2}A_2 + \frac{1}{2}B_2 \Leftrightarrow AB \quad (7)
\]

\[
K_1 = 2\phi_1/\phi_2^{1/2} \quad (8)
\]

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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 I solvated by 1,3-dimethyl-1,4,5,6-tetrahydro-2(1H)-pyrimidone (DMPU) showing a cubic tetramer and by TMEDA showing a dodecahedrally chelated dimer are archived in the Supporting Information.
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 $^6$Li resonances. A Job plot using measured mole fraction shows a marginal improvement in the parametric fit. We believe, however, that 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 ($A_2 - AB - B_2$) from, for example, an $A_2 - AB - B_4$ ensemble wherein one of the homoaggregates is a tetramer? The fit in Figure 5 to the $A_2 - AB - B_4$ model is inferior to the fit to the $A_2 - AB - B_2$ 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 $A_2 - AB - B_4$ 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.

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 $\eta^1$-bound TMEDA would rapidly exchange, resulting in time averaging of the resonances.37) Further cooling to $-90^\circ$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, $^6$Li 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 $\phi_0$ 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 in Figure 8 with the results anticipated for a statistical distribution of aggregates reveals a high correlation (Figure 9).

\[
\begin{align*}
A_4 + 2B_2 &\rightleftharpoons A_3B_1 \\
A_4 + B_1 &\rightleftharpoons A_3B_2 \\
A_2 + 2B_1 &\rightleftharpoons A_3B_1 \\

K_1 &= 4\phi_0/\phi_1^{1/4} \phi_4^{1/4} \\
K_2 &= 6\phi_2/\phi_1^{1/2} \phi_4^{1/2} \\
K_3 &= 4\phi_1/\phi_0^{1/4} \phi_2^{3/4} \\
\end{align*}
\]

**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
mixed dimers \(^9,^{21c,33,34}\) which caused resolution problems. Enolate mixtures generated from 1.1 equiv of LiHMDS offered the best compromise. \(^6\)Li 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 \((\eta^1)\) DME ligands. \(^{40}\) Chelated dimers of general structure \(^{14}\) were not observed.

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


**Figure 8.** Job plot showing the relative integrations versus mole fraction of 2 in 0.20 M mixtures of enolates \([6\)Li]1 (A) and \([6\)Li]2 (B) in 2.0 M THF/toluene at \(-30^\circ\)C. From eqs 4–6: \(f_0 = 0.83; f_1 = 0.94; f_2 = 1.11; f_3 = 1.24; f_4 = 1.0.\)

**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).

**Figure 10.** \([6\)Li] NMR spectra of 0.20 M equimolar mixture of \([6\)Li]1 (A) and \([6\)Li]2 (B) in 2.0 M DME/toluene. Key: (a) \(-105^\circ\)C, (b) \(-30^\circ\)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 \(-105^\circ\)C. From eqs 4–6: \(f_0 = 0.70; f_1 = 0.99; f_2 = 1.26; f_3 = 1.29; f_4 = 1.0.\)
aggregate—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 \( ^6\)Li resonance—five resonances total (cf. parts a and b of Figure 10). A Job plot determined at \(-30\) °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 the DME-solvated enolates and has potentially broader implications.

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 \( ^6\)Li 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 continuous variation.\(^{21}\) In the case of N-lithiated and C-lithiated species, this is most conveniently achieved by observing \( ^1\)H—\( ^6\)Li and \( ^13\)C—\( ^6\)Li scalar coupling.\(^{27a,48}\) For O-lithiated species, \( ^17\)O—\( ^6\)Li coupling is of no practical value.\(^{49}\) We used the method of continuous variation\(^{21\,-\,23}\) 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.

Lithium Enolates of Simple Ketones

The Method of Continuous Variation. We determined the structures of lithium enolates by generating an ensemble of heteroaggregated enolates from two homoaggregated enolates (Aₙ and Bₙ) 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 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, has been shown to provide monomers, dimers, tetramers, and other more obscure structural forms. Although TMEDA shows a penchant for chelation, ⁷¹ (nonchelated) TMEDA occasionally arises. Crystal structures of lithium enolates reveal a distinct preference for TMEDA-chelated dimers. 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 ¹³C 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. Cyclopentanone-derived enolate 3, for example, was one of the first two enolates characterized crystallographically, and it was shown to be tetrameric. Structural studies of 3 in solution are controversial. Seebach and Noyori endorse a model based on mixtures of dimers and tetramers whereas Reich concludes only tetramers exist. 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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(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 °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.


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


basicity of ethers versus amines is offset by the lower steric demands of the ethers.\textsuperscript{54,55} With that said, considerable evidence suggests that DME is not always a strongly chelating ligand.\textsuperscript{45,56} DME binds to lithium in either $\eta^1$ (nonchelating)\textsuperscript{50} or $\eta^2$ (chelating)\textsuperscript{51,13} capacities, depending on the steric environment. With respect to ketone enolates, there is a striking paucity of representation in the crystallographic literature.\textsuperscript{54,57} 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.

$$A_2 + \frac{1}{2}B_4 \rightarrow 2AB \quad (17)$$

(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.\textsuperscript{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 $^{13}$C NMR spectroscopy convincingly excludes tetrascavolated 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.\textsuperscript{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.\textsuperscript{60} THF, DME, and THF 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. $[^{\text{6}}\text{Li}]\text{LiHMDS}$ and $[^{\text{6}}\text{Li},^{13}\text{C}]\text{LiHMDS}$ were prepared and recrystallized as described previously.\textsuperscript{52} 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.


\textsuperscript{57} We can find no examples of crystallographically characterized homoaggregated lithium enolates solvated by DME. There are examples of the isostructural lithium aryloides 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.

\textsuperscript{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.

\textsuperscript{59} Liu, L. R.; Gruver, J. M.; Collum, D. B., unpublished.