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Solution Structures of Lithium Enolates, Phenolates, Carboxylates, and Alkoxides in the Presence of \( N,N,N',N' \)-Tetramethylethylenediamine: A Prevalence of Cyclic Dimers

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The method of continuous variation was used to characterize lithium enolates, phenolates, carboxylates, and alkoxides solvated by \( N,N,N',N' \)-tetramethylethylenediamine (TMEDA). The method relies on characterizing an ensemble of homo- and heteroaggregates using \( ^{6}\text{Li} \) NMR spectroscopy. A combination of aggregate counts and symmetries, nearly statistical distributions, and quantitative parametric fits revealed that cyclic dimers are the dominant forms. Nonstatistical distributions favoring heteroaggregated dimers were observed when hindered enolates and carboxylates were mixed with unhindered enolates. Hindered (tertiary) alkoxides form higher aggregates (possibly hexamers), whereas hindered lithium phenolates appear to form TMEDA-solvated monomers.

Introduction

Ketone enolates are highly reactive intermediates used for a range of functionalizations in organic synthesis.1 It is no surprise, therefore, that they have also commandeered the attention of structural and mechanistic chemists.2,3 The Achilles heel of most structural and mechanistic studies is characterizing lithium enolate structures

![](image)


in solution.4–7 The problem stems from a combination of the oppressive symmetry of the possible aggregates and the absence of observable O-Li scalar coupling.8 Progress has been made by accruing data from a broad range of indirect analytical methods,2 but these methods are often specific to the substrate-solvent combination.

We recently used the method of continuous variation9 (the method of Job10) to show that lithium enolates of \( \beta \)-amino esters are hexameric.11 The generality of the method was confirmed by showing that simple enolates 1–3 are cyclic dimers (4) in

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N,N',N'-tetramethylethylenediamine (TMEDA), cubic tetramers (5) in THF, and cubic tetramers (6) in 1,2-dimethoxyethane (DME).³

![Diagram](image)

We have now significantly expanded the range of characterized TMEDA-solvated O-lithiated species.¹² All species in the following chart form cyclic dimers of general structure 4.⁵,¹³,¹⁴ Standard lithium alkoxides constitute the primary exception, affording higher oligomers. The protocols used to determine structure were refined.

Results and Discussion

Method of Continuous Variation. The general strategy for characterizing enolates and related O-lithiated species using the method of continuous variation finds its origins in studies of Chabanel,¹⁵ Gagne,¹⁶ Günther,¹⁷ Reich,⁶d and others.¹⁸,¹⁹ An ensemble of homo- and heteroaggregated enolates (eq 1) is illustrated as a function of the mole fractions of enolate subunits (A and B) using "Li NMR spectroscopy.²⁰ The number of aggregates and their symmetries reflect the aggregation state, n. As we show herein, the preponderant form of TMEDA-solvated enolates is a disolvated dimer of general structure 4, representing the simplest possible ensemble (eq 2). A high tendency toward statistical distributions and parametric fits distinguish the all-dimer A₂-AB-B₂ model from A₂-AB-B and A₂-AB₂-B₂ models (see Supporting Information).

\[ A_n + B_n \rightarrow A_n + A_{n-1}B_1 + A_{n-2}B_2 + A_{n-3}B_3 + B_n \]  

(1)

\[ A_1 + B_2 \leftrightarrow 2AB \]  

(2)

Optimizing the resolution of the "Li resonances of the various aggregates is of paramount importance. Resolution is most readily achieved by pairing Aₙ and Bₙ with distinctly different "Li chemical shifts (Table 1.)²² A second issue is that the actual mole fractions of the A and B subunits can deviate from the intended mole fractions because of experimental error, non-quantitative enolization, selective formation of mixed aggregates with base,⁶e,⁷,²¹ or formation of byproduct. (Metalations using ["Li,¹⁵N]LDA²² and ["Li,¹⁵N]LiHMDS²³ reveal that only LDA

<table>
<thead>
<tr>
<th>substrate</th>
<th>( \delta ) &quot;Li</th>
<th>substrate</th>
<th>( \delta ) &quot;Li</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.22</td>
<td>18</td>
<td>-0.33</td>
</tr>
<tr>
<td>2</td>
<td>-0.02</td>
<td>19</td>
<td>0.29</td>
</tr>
<tr>
<td>3</td>
<td>0.05</td>
<td>20</td>
<td>0.05</td>
</tr>
<tr>
<td>7</td>
<td>0.14</td>
<td>21</td>
<td>-0.24</td>
</tr>
<tr>
<td>8</td>
<td>-0.05</td>
<td>22</td>
<td>-0.14</td>
</tr>
<tr>
<td>9</td>
<td>-0.12</td>
<td>23</td>
<td>-0.26</td>
</tr>
<tr>
<td>10</td>
<td>-0.34</td>
<td>24</td>
<td>-0.14</td>
</tr>
<tr>
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<td>25</td>
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</tr>
<tr>
<td>12</td>
<td>-0.27</td>
<td>26</td>
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</tr>
<tr>
<td>13</td>
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<td>27</td>
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</tr>
<tr>
<td>14</td>
<td>-0.06</td>
<td>28</td>
<td>0.04</td>
</tr>
<tr>
<td>15</td>
<td>1.12</td>
<td>29</td>
<td>0.32</td>
</tr>
<tr>
<td>16</td>
<td>0.66</td>
<td>30</td>
<td>0.30</td>
</tr>
<tr>
<td>17a</td>
<td>0.33</td>
<td>31</td>
<td>-0.13</td>
</tr>
</tbody>
</table>

²⁰ 3.0 M TMEDA/0.11 M THF in 2/1 toluene/pentane. ²¹ -60 °C. ²² -70 °C.


(8) The rapid relaxation of the highly quadrupolar "O nucleus would preclude observing Li"-"O coupling.


(13) "Li NMR spectra recorded on mixtures of 1 and 3 in Me₆NEt, a nonchelating analog of TMEDA, display a distribution of resonances characteristic of an ensemble of tetramers.⁶
forms detectable mixed aggregates in TMEDA/toluene.\(^{21}\) Although such deviations do not impair the qualitative analysis of aggregate numbers and their symmetries, they can distort the quantitative parametric fits. Consequently, the mole fractions were measured by simply integrating the \(^6\)Li resonances. Usually, the intended and measured mole fractions are comparable, but we believe the latter are more accurate.\(^3\) One last concern pertains to deviations from statistical behavior. The parametric fits reveal that deviations from statistical behavior are usually quite small. When large deviations occur, however, the parametric fits do not readily distinguish the all-dimer \(A_2\)-AB-B\(_2\) model from the \(A_2\)-AB-B and \(A_2\)-AB-B\(_4\) models; the models become quite similar if the relative \(AB\) concentration becomes either very high or very low. Additional experiments exclude the latter two models (vide infra).

**Statistical Dimer Distributions.** All \(O\)-lithiated species in the typical results were illustrated using enolates 1 and 7. The homo- and heteroaggregated dimers were easily observed using \(^6\)Li NMR spectroscopy (Figure 1). The plot of relative aggregate integrations \((I)^{22}\) versus mole fraction \((X)\) in Figure 2 shows a nearly statistical distribution of aggregates. Inferior fits to models based on ternary ensembles \(A_2\)-AB-B and \(A_2\)-AB-B\(_4\) (evidenced by large residual deviations; Supporting Information) support the dimer assignment.\(^{25}\)

**Nonstatistical Dimer Distributions.** A nonstatistical tendency toward heteroaggregation was observed when hindered

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**FIGURE 1.** \(^6\)Li NMR spectrum of an equimolar mixture (mole fraction: \(X = 0.5\)) of \([6\text{Li}]\text{I}\) (A) and \([6\text{Li}]\text{I}^7\) (B) in 0.24 M TMEDA/toluene at \(-50\,^\circ\text{C}\).

**FIGURE 2.** Job plot showing the relative integrations versus mole fractions of 7 for 0.10 M mixtures of enolates \([6\text{Li}]\text{I}\) (A) and \([6\text{Li}]\text{I}^7\) (B) in 0.24 M TMEDA/toluene at \(-50\,^\circ\text{C}\).

**FIGURE 3.** Job plot showing the relative integrations versus mole fractions of 13 for 0.10 M mixtures of enolates \([6\text{Li}]\text{I}\) (A) and \([6\text{Li}]\text{I}^3\) (B) in 0.24 M TMEDA/toluene at \(-50\,^\circ\text{C}\).

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\(^{(14)}\) Free and bound TMEDA have been observed by \(^1\)H NMR spectroscopy for a select group of homodimers derived from 1, 2, 3, 13, 15, and 28, suggesting chelation.


\(^{(19)}\) (a) For a more recent example, see: Jacobson, M. A.; Keresztes, I.; Williard, P. G. J. Am. Chem. Soc. 2005, 127, 4965.

\(^{(20)}\) After surveying a subset of the community, we have chosen to refer to (Li\(_X\))\(_\alpha\) and (Li\(_X\))\(_\alpha\)(Li\(_X\))\(_\alpha\) as a “homoaggregate” and “heteroaggregate”, respectively, and reserve the term “mixed aggregate” for (Li\(_X\))\(_\alpha\)(Li\(_X\))\(_\alpha\).


\(^{(24)}\) The relative integration \((I)\) was previously referred to as aggregate mole fraction \((X)\).\(^{11}\) The change was made to avoid using two distinctly different mole fraction terms and to include provisions for mixtures of aggregates with different aggregate numbers.

\(^{(25)}\) The mathematics underlying the parametric fits has been described in detail in refs 3 and 11.

expected complex aggregates displaying marginal physical properties (gelling or insolubility).27 As salt effects on yields, selectivities, and reactivities continue to be reported,21,28 we are encouraged by the potential importance of carboxylates in both synthetic and mechanistic organolithium chemistry.29 There are certainly many more lithium carboxylates than lithium halides!

**Higher Oligomers.** Hindered lithium alkoxides (34–36) displayed a strong bias toward homoaggregates resulting from higher oligomers, which we believe to be hexamers. For example, tertiary alkoxides 34–36 in 0.24 M TMEDA/toluene each displayed a single 6Li resonance at −90 °C (δ 0.48, 0.71, and 0.31 ppm, respectively). Pairing tertiary alkoxides with relatively uncongested O-lithiated species afforded very low concentrations of putative heterodimers (Figure 4). It is telling that hindered alkoxides even resisted heteroaggregation with hindered enolates.30

We suspected that the reticence of alkoxides 34–36 to heteroaggregate with other O-lithiated species stemmed from a reluctance to form heterodimers of any form. Indeed, pairing t-BuOLi (34) with hindered alkoxides 35 or 3631 afforded remarkable spectral complexity (Figure 5) exceeding even that anticipated for an ensemble of tetramers (A1B1A1B1).32 It seems probable, therefore, that the hindered alkoxides are hexameric (possibly only partially solvated),32–34 as indicated by X-ray crystallography35,36 and colligative measurements for t-BuOLi in benzene.37 The large number of hexamer stoichiometries (seven) and the existence of positional isomers within hexagonal drums would result in 38 magnetically inequivalent 6Li resonances.3 The spectra appeared as though a structural assignment might be possible. Not surprisingly, however, severe overlap of resonances (as evidenced by shoulders on peaks in Figure 5) caused us to abort efforts to tease out additional insights.

We thought that hindered phenolates such as 37 might afford a monomer; we obtained insoluble material shown to contain approximately 1 equiv of TMEDA by quenching an isolated

![Figure 4](image_url)

**FIGURE 4.** Job plot showing the relative integrations versus mole fractions of 1 for 0.10 M mixtures of alkoxide [6Li]34 (A) and enolate [6Li]1 (B) in 0.24 M TMEDA/toluene at −90 °C.

![Figure 5](image_url)

**FIGURE 5.** 6Li NMR spectrum of a 1:1 mixture of [6Li]34 and [6Li]36 in 0.24 M TMEDA/toluene at −30 °C.

sample. The corresponding disubstituted phenolate 38 is soluble and forms no detectable mixed aggregates with dimeric enolate 1 or highly oligomeric alkoxide 36, suggesting that phenolates 37 and 38 are indeed TMEDA-chelated monomers. Similar studies of primary and secondary alkoxides were thwarted by insolubility and spectral complexity, possibly attributable to higher oligomers.38

**Conclusion**

Addition of TMEDA to lithium enolates, phenolates, and carboxylates affords exclusively cyclic dimers in most instances.

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(31) The phenyl moieties on 35 and 36 were necessary to maximize the resolution in the 4Li NMR spectrum when paired with t-BuOLi (34).


(33) A solvent-free hexameric imidate crystallizes from solutions containing TMEDA: Maritzko, T.; Seebach, D. Organometalics 1990, 9, 3032.


Solution Structures of TMEDA-Solvated Lithiated Species

We are encouraged by both the success and generality of the method of continuous variation in characterizing species that have traditionally proven opaque to NMR spectroscopy. Although highly functionalized lithium enolates commonly used to effect diastereo- and enantioselective carbon–carbon bond formation may present new challenges and offer a few surprises, the protocol should prove durable. More important, these results satisfy a necessary prerequisite for understanding lithium enolate structure/reactivity relationships.

Experimental Section

Reagents and Solvents. TMEDA was recrystallized as the hydrochloride salt39 and subsequently distilled from solutions containing sodium benzophenone ketyl. Hydrocarbon solvents were distilled from blue solutions containing sodium benzophenone ketyl. We prepared and recrystallized [6Li]LiHMDS, [6Li,15N]LiHMDS, [6Li]LDA, and [6Li,15N]LDA as described previously.22,23 Air- and moisture-sensitive materials were manipulated under argon using standard glovebox, vacuum line, and syringe techniques.

Spectroscopic Analysis. Individual stock solutions of the substrates and base were prepared at room temperature. An NMR tube was flame-dried on a Schlenk line and allowed to come to room temperature while under vacuum. It was then placed under argon and into a −78 °C dry ice/acetone bath. The appropriate amounts of the base followed by the substrates were added via syringe allowing about 30 s between additions. The tube was sealed under partial vacuum and immediately vortexed for approximately 10 s before being replaced into a −78 °C bath. Hindered enolates 12 and 13 required warming to 0 °C for approximately 1 h to complete the enolization. Each NMR tube had 0.10 M total substrate concentration and 0.12 M lithium amide base in 0.24 M TMEDA/toluene.

6Li NMR spectra were typically recorded at −90 °C on a 400 or 500 MHz spectrometer with a delay between scans set to >5 × T1 to ensure accurate integrations. In a few instances, adjusting the probe temperature was necessary to optimize resolution and line widths, although the origins of these temperature dependencies were not obvious. Chemical shifts are reported relative to a 0.30 M 6LiCl/MEOH standard.

NMR resonances were integrated using standard software. After weighted Fourier transform with 64,000 points and phasing, line broadening was set between 0 and 0.2, and a baseline correction was applied if appropriate. Deconvolution was performed in the absolute intensity mode, with application of a drift correction using default parameters for contributions from Lorentzian and Gaussian shape functions. For poorly resolved spectra, the resonances were indicated using the “mark” and “use mark” commands. The math underlying the parametric fits has been described in detail.31

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Supporting Information Available: Experimental procedures, raw data, plots, and table showing specific enolate pairings. This material is available free of charge via the Internet at http://pubs.acs.org.

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