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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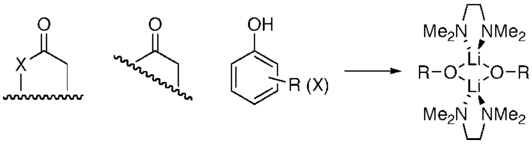

The method of continuous variation was used to characterize lithium enolates, phenolates, carboxylates, and alkoxides solvated by *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA). The method relies on characterizing an ensemble of homo- and heteroaggregates using ^{6}Li NMR spectroscopy. A combination 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 mechanistic studies is characterizing lithium enolate structures 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 variation[9] (the method of Job[10]) to show that lithium enolates of β-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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(1) (a) Green, J. R. In *Science of Synthesis*; Georg Thieme Verlag: New York, 2005; Vol. 8a, pp 427−486. (b) Schetter, B.; Mahrwald, R. *Angew. Chem., Int. Ed.* **2006**, *45*, 7506. (c) Arya, P.; Qin, H. *Tetrahedron* **2000**, *56*, 917. (d) Caine, D. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: New York, 1989; Vol. 1, p 1. Martin, S. F. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: New York, 1989; Vol. 1, p 475. (e) Plaquevent, J.-C.; Cahard, D.; Guillen, F.; Green, J. R. In *Science of Synthesis*; Georg Thieme Verlag: New York, 2005; Vol. 26, pp 463−511. (f) *Comprehensive Organic Functional Group Transformations II*; Katritzky, A., Taylor, R., Richard, J. K., Eds.; Elsevier: Oxford, U.K., 1995; pp 834−835. (g) Cativiela, C.; Diaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **2007**, *18*, 569. (h) Dugger, R. W.; Ragan, J. A.; Ripin, D. H. B. *Org. Process Res. Dev.* **2005**, *9*, 253. (i) Farina, V.; Reeves, J. T.; Senanayake, C. H.; Song, J. J. *Chem. Rev.* **2006**, *106*, 2734. (j) Wu, G.; Huang, M. *Chem. Rev.* **2006**, *106*, 2596.

(2) Representative examples and leading references to structural and rate studies: (a) Jackman, L. M.; Lange, B. C. *Tetrahedron* **1977**, *33*, 2737. (b) Jackman, L. M.; Bortiatynski, J. *Adv. Carbanion Chem.* **1992**, *1*, 45. (c) Jackman, L. M.; Chen, X. *J. Am. Chem. Soc.* **1997**, *119*, 8681. (d) Wang, D. Z.; Kim, Y.-J.; Streitwieser, A. *J. Am. Chem. Soc.* **2000**, *122*, 10754. (e) Kim, Y.-J.; Streitwieser, A. *Org. Lett.* **2002**, *4*, 573. (f) Kim, Y.-J.; Wang, D. Z. *Org. Lett.* **2001**, *3*, 2599. (g) Zune, C.; Jerome, R. *Prog. Polym. Sci.* **1999**, *24*, 631. (h) Baskaran, D. *Prog. Polym. Sci.* **2003**, *28*, 521. (i) For an extensive bibliography of the structural and mechanistic studies of lithium enolates, see ref 3.

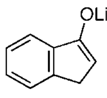
(3) Liou, L. R.; McNeil, A. J.; Ramirez, A.; Toombes, G. E. S.; Gruver, J. M.; Collum, D. B. *J. Am. Chem. Soc.* **2008**, *130*, 4859.

(4) For additional examples of and leading references to structural studies of lithium enolates in solution, see: (a) Yamataka, K.; Yamada, H.; Tomioka, H. In *The Chemistry of Organolithium Compounds*; Rappoport, Z., Marek, I., Eds.; Wiley: New York, 2004; Vol. 2, p 908. (b) Zabicky, J. In *The Chemistry of Organolithium Compounds*; Rappoport, Z., Marek, I., Eds.; Wiley: New York, 2004; Vol. 2, p 376. (c) Pospisil, P. J.; Wilson, S. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1992**, *114*, 7585. (d) Biddle, M. M.; Reich, H. J. *J. Org. Chem.* **2006**, *71*, 4031.

(5) Edwards, J. O.; Greene, E. F.; Ross, J. The rate law provides the stoichiometry of the transition structure relative to the reactant. *J. Chem. Educ.* **1968**, *45*, 381; knowing the structure of the reactant is essential. For a review describing some recent advances and details of studying organolithium reaction mechanism, see: Collum, D. B.; McNeil, A. J.; Ramirez, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 3002.

10.1021/jo801532d CCC: $40.75

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



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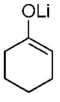

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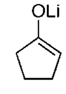

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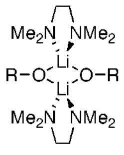

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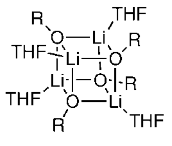

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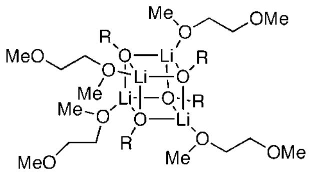

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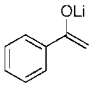
We have now significantly expanded the range of characterized TMEDA-solvated O-lithiated species.[12] All species in the following chart form cyclic dimers of general structure **4**.[6,13,14] Standard lithium alkoxides constitute the primary exception, affording higher oligomers. The protocols used to determine structure were refined.



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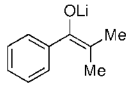

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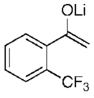

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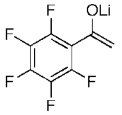

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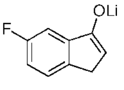

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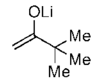

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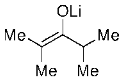

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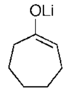

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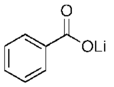

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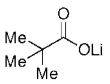

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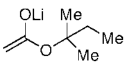

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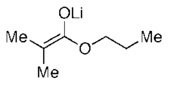

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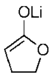

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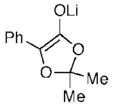

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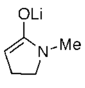

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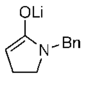

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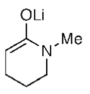

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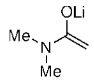

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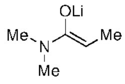

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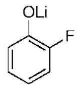

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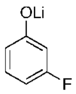

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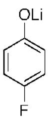

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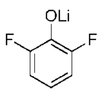

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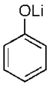

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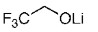

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Results and Discussion

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,[4d] and others.[18,19] An ensemble of homo- and heteroaggregated enolates (eq 1) is monitored as a function of the mole fractions of enolate subunits (**A** and **B**) using ^{6}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 **A$_2$-AB-B$_2$** model from **A$_2$-AB-B** and **A$_2$-AB-B$_4$** models (see Supporting Information).

TABLE 1. **^{6}Li NMR Chemical Shifts Relative to a 0.30 M [^{6}Li]LiCl/MeOH Standard at −90 °C in 0.24 M TMEDA/Toluene**

substrate	δ ^{6}Li	substrate	δ ^{6}Li
1	0.22	**18**	−0.33
2	−0.02	**19**	0.29
3	0.05	**20**	0.05
7	0.14	**21**	−0.24
8	−0.05	**22**	−0.14
9	−0.12	**23**	−0.26
10	−0.34	**24**[b]	−0.14
11	0.00	**25**[c]	−0.04
12	−0.27	**26**	0.30
13	−0.42	**27**	0.03
14	−0.06	**28**	0.04
15	1.12	**29**	0.32
16	0.66	**30**	0.30
17[a]	0.33	**31**	−0.13

[a] 3.0 M TMEDA/0.11 M THF in 2/1 toluene/pentane. [b] −60 °C. [c] −70 °C.

$$A_n + B_n \Rightarrow A_n + A_{n-1}B_1 + A_{n-2}B_2 + A_{n-3}B_3 + B_n \quad (1)$$

$$A_2 + B_2 \overset{K_1}{\rightleftharpoons} 2AB \quad (2)$$

Optimizing the resolution of the ^{6}Li resonances of the various aggregates is of paramount importance. Resolution is most readily achieved by pairing **A$_n$** and **B$_n$** with distinctly different ^{6}Li chemical shifts (Table 1.)[3] 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, nonquantitative enolization, selective formation of mixed aggregates with base,[6f,7,21] or formation of byproduct. (Metalations using [^{6}Li,^{15}N]LDA[22] and [^{6}Li,^{15}N]LiHMDS[23] reveal that only LDA

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(6) The crystallographic literature of lithium enolates[7] reveals a prevalence of chelated dimers for TMEDA solvates: (a) Nichols, M. A.; Leposa, C. M.; Hunter, A. D.; Zeller, M. *J. Chem. Crystallogr.* **2007**, *37*, 825. (b) Seebach, D.; Amstutz, R.; Laube, T.; Schweizer, W. B.; Dunitz, J. D. *J. Am. Chem. Soc.* **1985**, *107*, 5403. (c) Meyers, A. I.; Seefeld, M. A.; Lefker, B. A.; Blake, J. F.; Williard, P. G. *J. Am. Chem. Soc.* **1998**, *120*, 7429. (d) Boche, G.; Langlotz, I.; Marsch, M.; Harms, K. *Chem. Ber.* **1994**, *127*, 2059. (e) Hahn, E.; Maetzke, T.; Plattner, D. A.; Seebach, D. *Chem. Ber.* **1990**, *123*, 2059. (f) Henderson, K. W.; Dorigo, A. E.; Williard, P. G.; Bernste, P. R. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1322. (g) See refs 21c and 7a.

(7) (a) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1624. (b) Setzer, W. N.; Schleyer, P. v. R. *Adv. Organomet. Chem.* **1985**, *24*, 353. (c) Williard, P. G. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: New York, 1991; Vol. 1, Chapter 1.1.

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

(9) (a) Gil, V. M. S.; Oliveira, N. C. *J. Chem. Educ.* **1990**, *67*, 473. (b) Huang, C. Y. *Methods Enzymol.* **1982**, *87*, 509. (c) Hirose, K. *J. Inclusion Phenom.* **2001**, *39*, 193. (d) Likussar, W.; Boltz, D. F. *Anal. Chem.* **1971**, *43*, 1265.

(10) Job, P. *Ann. Chim.* **1928**, *9*, 113.

(11) (a) McNeil, A. J.; Toombes, G. E. S.; Gruner, S. M.; Lobkovsky, E.; Collum, D. B.; Chandramouli, S. V.; Vanasse, B. J.; Ayers, T. A. *J. Am. Chem. Soc.* **2004**, *126*, 16559. (b) McNeil, A. J.; Toombes, G. E. S.; Chandramouli, S. V.; Vanasse, B. J.; Ayers, T. A.; O'Brien, M. K.; Lobkovsky, E.; Gruner, S. M.; Marohn, J. A.; Collum, D. B. *J. Am. Chem. Soc.* **2004**, *126*, 5938. (c) McNeil, A. J.; Collum, D. B. *J. Am. Chem. Soc.* **2005**, *127*, 5655.

(12) TMEDA is one of the most prevalent ligands in organolithium chemistry. (a) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879. (b) Clayden, J. *Organolithiums: Selectivity for Synthesis*; Pergamon: New York, 2002. (c) *Polyamine-Chelated Alkali Metal Compounds*; Langer, A. W., Jr., Ed.; American Chemical Society: Washington, DC, 1974. (d) For a discussion of the effect of TMEDA on anionic polymerizations of methyl methacrylate, see: Baskaran, D.; Muller, A. H. E.; Sivaram, S. *Macromol. Chem. Phys.* **2000**, *201*, 1901.

(13) ^{6}Li NMR spectra recorded on mixtures of **1** and **3** in Me$_2$NEt, a nonchelating analog of TMEDA, display a distribution of resonances characteristic of an ensemble of tetramers.[3]

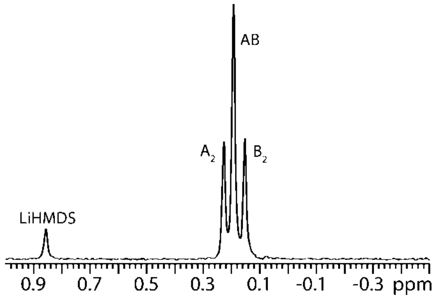

FIGURE 1. ^{6}Li NMR spectrum of an equimolar mixture (mole fraction: $X_7 = 0.5$) of [^{6}Li]**1** (**A**) and [^{6}Li]**7** (**B**) in 0.24 M TMEDA/toluene at −50 °C.

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 chart were found to be dimeric in TMEDA/toluene solution. Typical results are 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)[24] 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 enolates (**12** and **13**) were paired with their less-congested counterparts (see Figure 3). We suspected that steric interactions destabilized the congested homoaggregated dimers. Indeed, pairing hindered enolates **12** and **13** afforded a statistical distribution that fits the **A$_2$-AB-B$_2$** model.

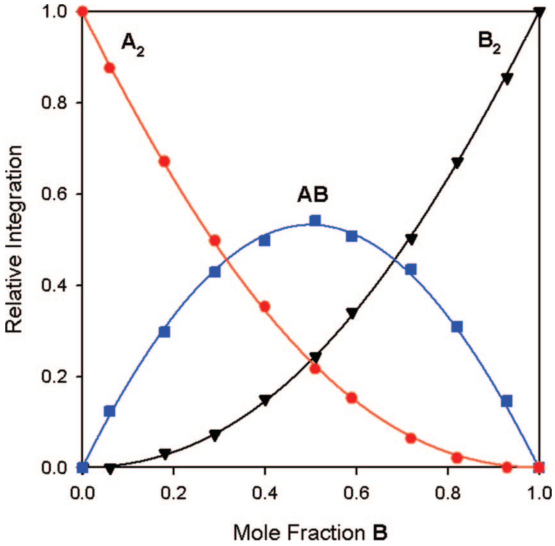

FIGURE 2. Job plot showing the relative integrations versus mole fractions of **7** for 0.10 M mixtures of enolates [^{6}Li]**1** (**A**) and [^{6}Li]**7** (**B**) in 0.24 M TMEDA/toluene at −50 °C.

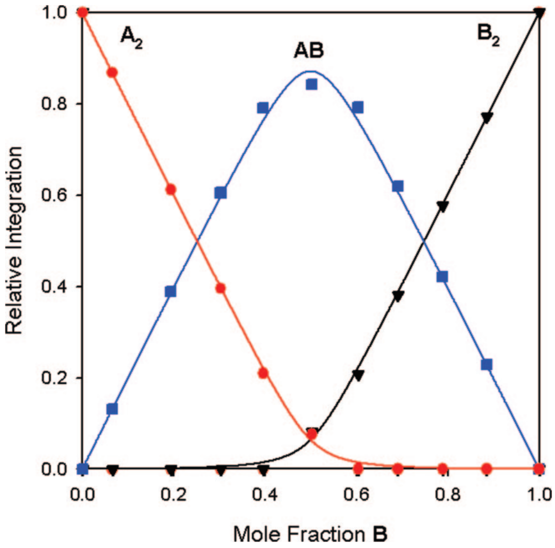

FIGURE 3. Job plot showing the relative integrations versus mole fractions of **13** for 0.10 M mixtures of enolates [^{6}Li]**1** (**A**) and [^{6}Li]**13** (**B**) in 0.24 M TMEDA/toluene at −90 °C.

Similar preferences for heteroaggregates (approaching quantitative formation of the heterodimer in some cases) resulted when lithium carboxylates **15** or **16** were paired with lithium enolates. Once again, statistical behavior returned when carboxylates **15** and **16** were paired. Although TMEDA-solvated lithium carboxylates could be represented by dimer **32**, crystallographic guidance is surprisingly absent. A lithium carbamate reported by Snaith and co-workers was found to have a ring-expanded structure (**33**).[26]

We admit being surprised that lithium carboxylates form homo- and heteroaggregates of well-defined structure. We

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

[15] (a) Goralski, P.; Chabanel, M. *Inorg. Chem.* **1987**, *26*, 2169. (b) Goralski, P.; Legoff, D.; Chabanel, M. *J. Organomet. Chem.* **1993**, *456*, 1.

[16] Kissling, R. M.; Gagne, M. R. *J. Org. Chem.* **2001**, *66*, 9005.

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[18] (a) Novak, D. P.; Brown, T. L. *J. Am. Chem. Soc.* **1972**, *94*, 3793. (b) Desjardins, S.; Flinois, K.; Oulyadi, H.; Davoust, D.; Giessner-Prettre, C.; Parisel, O.; Maddaluno, J. *Organometallics* **2003**, *22*, 4090. (c) Weingarten, H.; Van Wazer, J. R. *J. Am. Chem. Soc.* **1965**, *87*, 724.

[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 $(\text{LiX})_n$ and $(\text{LiX})_m(\text{LiX}')_n$ as a "homoaggregate" and "heteroaggregate", respectively, and reserve the term "mixed aggregate" for $(\text{LiX})_m(\text{LiY})_n$.

[21] (a) Collum, D. B. *Acc. Chem. Res.* **1993**, *26*, 227. (b) Williard, P. G.; Hintze, M. J. *J. Am. Chem. Soc.* **1990**, *112*, 8602. (c) See ref 28d.

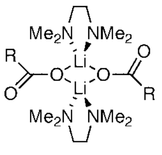
[22] Kim, Y.-J.; Bernstein, M. P.; Galiano-Roth, A. S.; Romesberg, F. E.; Fuller, D. J.; Harrison, A. T.; Collum, D. B.; Williard, P. G. *J. Org. Chem.* **1991**, *56*, 4435.

[23] Romesberg, F. E.; Bernstein, M. P.; Gilchrist, J. H.; Harrison, A. T.; Fuller, D. J.; Collum, D. B. *J. Am. Chem. Soc.* **1993**, *115*, 3475.

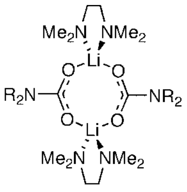
[24] The relative integration $(I_n)^3$ was previously referred to as aggregate mole fraction (X_n).[11] The change was made to avoid using two distinctly different mole fraction terms and to include provisions for mixtures of aggregates with different aggregation numbers.

[25] The mathematics underlying the parametric fits has been described in detail in refs 3 and 11.

[26] Ball, S. C.; Cragg-Hine, I.; Davidson, M. G.; Davies, R. P.; Edwards, A. J.; Lopez-Solera, I.; Raithby, P. R.; Snaith, R. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 921.



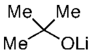
32



33

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 ^{6}Li 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]



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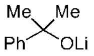

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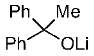

36

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 **36**[31] afforded remarkable spectral complexity (Figure 5) exceeding even that anticipated for an ensemble of tetramers (**A$_4$-A$_3$B-A$_2$B$_2$-AB$_3$-B$_4$**).[3] It seems probable, therefore, that the hindered alkoxides are hexameric (possibly only partially solvated),[32−34] as indicated by X-ray crystallography[35,36] 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 ^{6}Li 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 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]

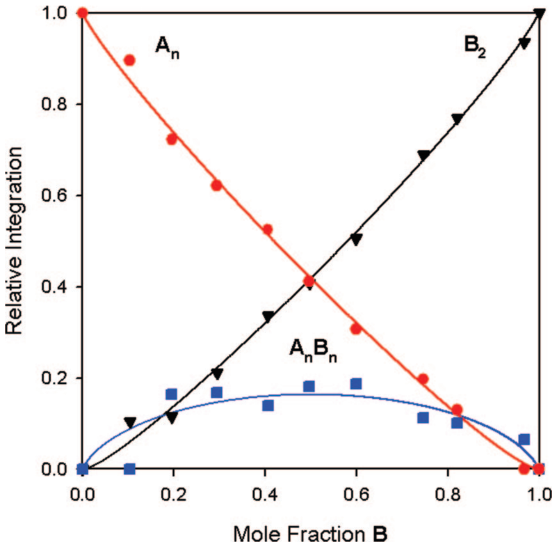

FIGURE 4. Job plot showing the relative integrations versus mole fractions of **1** for 0.10 M mixtures of alkoxide [^{6}Li]**34** (**A**) and enolate [^{6}Li]**1** (**B**) in 0.24 M TMEDA/toluene at −90 °C.

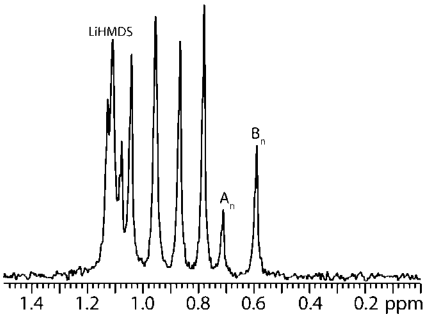

FIGURE 5. ^{6}Li NMR spectrum of a 1:1 mixture of [^{6}Li]**34** and [^{6}Li]**36** in 0.24 M TMEDA/toluene at −30 °C.

Conclusion

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

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(28) Leading references to salt effects: (a) Tchoubar, B.; Loupy, A. *Salt Effects in Organic and Organometallic Chemistry*; VCH: New York, 1992; Chapters 4, 5, and 7. (b) Seebach, D. In *Proceedings of the Robert A. Welch Foundation Conferences on Chemistry and Biochemistry*; Wiley: New York, 1984; p 93. (c) Gossage, R. A.; Jastrzebski, J. T. B. H.; van Koten, G. *Angew. Chem., Int. Ed.* **2005**, *44*, 1448. (d) Ramirez, A.; Sun, X.; Collum, D. B. *J. Am. Chem. Soc.* **2006**, *128*, 10326. (e) Also, see ref 7a.

(29) Green, J. R. In *Science of Synthesis*; Georg Thieme Verlag: New York, 2005; Vol. 8a, p 427.

(30) A mixed aryloxide/alkoxide tetramer has been characterized crystallographically. Ko, B.-T.; Lin, C.-C. *J. Am. Chem. Soc.* **2001** *123* 7973.

(31) The phenyl moieties on **35** and **36** were necessary to maximize the resolution in the ^{6}Li NMR spectrum when paired with *t*-BuOLi (**34**).

(32) Collum, D. B. *Acc. Chem. Res.* **1992**, *25*, 448.

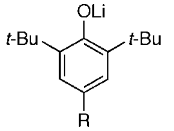
(33) A solvent-free hexameric imidate crystallizes from solutions containing TMEDA: Maetzke, T.; Seebach, D. *Organometallics* **1990**, *9*, 3032.

(34) For early discussions of steric effects on solvation and aggregation, see: (a) Settle, F. A.; Haggerty, M.; Eastham, J. F. *J. Am. Chem. Soc.* **1964**, *86*, 2076. (b) Lewis, H. L.; Brown, T. L. *J. Am. Chem. Soc.* **1970**, *92*, 4664. (c) Brown, T. L.; Gerteis, R. L.; Rafus, D. A.; Ladd, J. A. *J. Am. Chem. Soc.* **1964**, *86*, 2135.

(35) Unsolvated *t*-BuOLi (**34**) is octameric in the solid state. Allan, J. F.; Nassar, R.; Specht, E.; Beatty, A.; Calin, N.; Henderson, K. W. *J. Am. Chem. Soc.* **2004**, *126*, 484.

(36) Unsolvated Me$_2$PhCOLi (**35**) is hexameric in the solid state. Chisholm, M. H.; Drake, S. R.; Naiini, A. A.; Streb, W. F. *Polyhedron* **1991**, *10*, 805.

(37) (a) Kamienski, C. W.; Lewis, D. H. *J. Org. Chem.* **1965**, *30*, 3498. (b) Golovanov, I. B.; Simonov, A. P.; Priskunov, A. K.; Talalseva, T. V.; Tsareva, G. V.; Kocheshkov, K. *Dokl. Adka. Nauk. SSSR* **1963**, *149*, 835. (c) Simonov, A. P.; Shigorin, D. N.; Talalseva, T. V.; Kocheshkov, K. A. *Bull. Acad. Sci. USSR Div. Chem. Sci.* **1962**, *6*, 1056.



37; R = t-Bu
38; R = H

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 salt[39] and subsequently 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. We prepared and recrystallized $[^6Li]$LiHMDS, $[^6Li,^{15}N]$LiHMDS, $[^6Li]$LDA, and $[^6Li,^{15}N]$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.

^{6}Li 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 ^{6}LiCl/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 line shapes. 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.[3,11]

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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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