Enantioselective Synthesis

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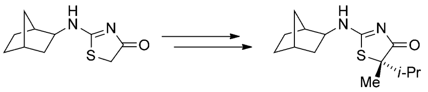
Mixed Aggregates of the Dilithiated Koga Tetraamine: NMR Spectroscopic and Computational Studies

Yun Ma, Kyle A. Mack, Jun Liang, Ivan Keresztes, David B. Collum, and Armen Zakarian**

***Abstract:** A combination of ^{1}H, ^{6}Li, ^{13}C, and ^{15}N NMR spectroscopies and density functional theory computations explores the formation of mixed aggregates by a dilithium salt of a C_2-symmetric chiral tetraamine (Koga's base). Lithium halides, acetylides, alkoxides, and monoalkylamides form isostructural trilithiated mixed aggregates with few exceptions. ^{6}Li–^{13}C and ^{6}Li–^{15}N couplings reveal heretofore undetected transannular contacts (laddering) with lithium acetylides and lithium monoalkylamides. Marked temperature-dependent ^{15}N chemical shifts seem to be associated with this laddering. Computational studies shed light on the general structures of the aggregates, their penchant for laddering, and the stereochemical consequences of aggregation.*

The C_2-symmetric dilithiated tetraamine **1**, developed by Koga and co-workers[1] as a chiral Brønsted base, has proven to be a versatile, non-covalent auxiliary for enantioselective synthesis.[2,3] Frizzle et al.[2] achieved asymmetric alkylations of simple enolates en route to steroid dehydrogenase inhibitors [Eq. (1)], and one of us (AZ)[3] developed enantioselective asymmetric alkylations and 1,4-additions of enediolates (Scheme 1).[4] The exceptional selectivities prompted a collaboration to study the structures of the putative mixed aggregates derived from dilithiated enediolates and dianion **1**.[5] Despite the potential complexity of characterizing mixtures of two dianions, mixed aggregates **2** (containing *n*-BuLi) and **3** (containing dilithium enediolate) proved structurally tractable and yielded a computationally viable and predictive stereochemical model.[5]



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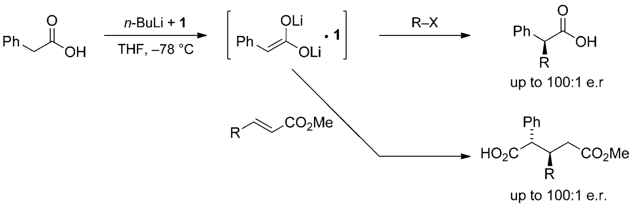
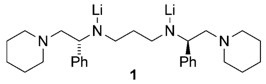


Scheme 1. Enantioselective alkylation and 1,4-addition of enediolates.



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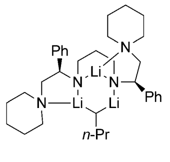

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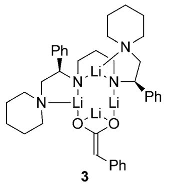

3

In instances for which highly stereoselective organolithium reactions have been traced to specific solvation and aggregation effects,[6] the control of aggregate structure appears to accompany and possibly be a prerequisite for high stereocontrol. With that hypothesis in mind, we surveyed the structures of the mixed aggregates of **1** with a variety of lithium salts (Scheme 2). Dianion **1** is a promiscuous pairing partner, yielding isostructural mixed aggregates **4** or the corresponding ladder structures **5** (distinguishable from **4** by the presence of a transannular Li–X contact).[7] Spectroscopic and computational studies revealed structural nuances, including the stereochemical consequences of aggregation.[8–10]

Mixed aggregation of **1** was examined by ^{6}Li NMR spectroscopy. We routinely used minor excesses of *n*-BuLi-derived mixed aggregate **2** to generate the new mixed aggregates from LiX precursors, which caused low concentrations of **2** to persist in most of the recorded spectra. Otherwise, the spectra were usually quite clean, as documented in the Supporting Information. The LiX salts **A**–**HH** (Scheme 2) show a three-resonance fingerprint (1:1:1) characteristic of **4** or **5**. Throughout, we refer to the mixed aggregates as **4**, **5**, or **4**/**5**, depending on the context and the confidence levels of our assignments. The default attribution is **4**. We occasionally detected minor species (possibly other mixed aggregates) that were not pursued but are documented in the supporting information.

We balanced the depth of study against the scope of the survey. Five mixed aggregates prepared from salts **A**–**E** were

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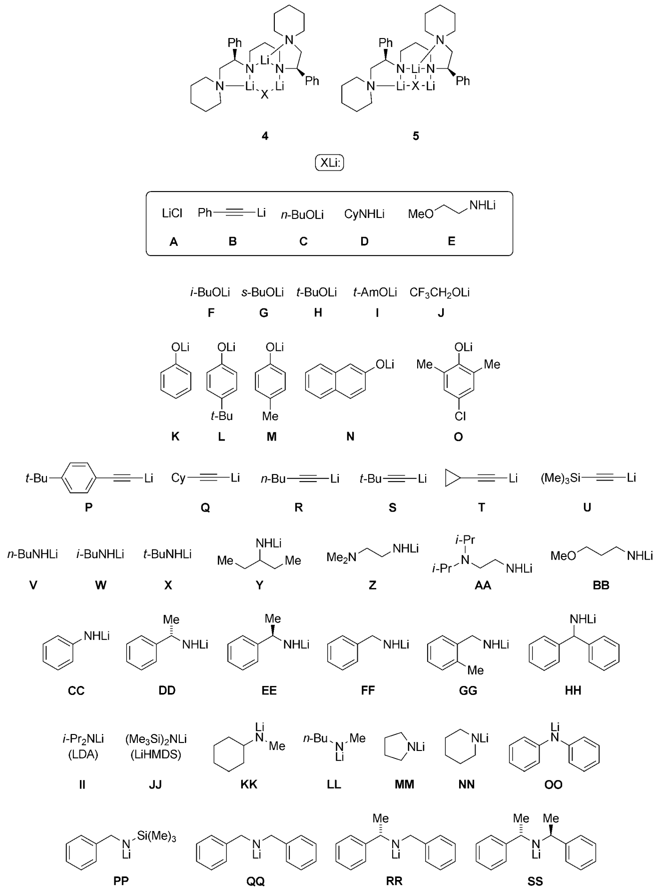


Scheme 2. Lithium salts used for mixed aggregate formation.

deemed to be of special importance because of their role in current synthesis applications or because isotopically labeled LiX offered useful spectroscopic probes. In these cases, we used the relatively precious labeled dilithium amide [^{15}N$_4$]**1**[5] to confirm the connectivities within the full aggregate structures[11] and exploited a combination of COSY, TOCSY, HSQC, HMBC, and ROESY spectroscopy to obtain three-dimensional structures. Unexpected insights into the complex interplay between solvation and laddering came from temperature- and tetrahydrofuran (THF)-concentration-dependent ^{6}Li and ^{15}N chemical shifts. Assignments for salts **F**–**HH** were based on the presence of the characteristic three-peak pattern and by analogy to the detailed studies. Dialkylamides **II**–**SS** failed to cleanly form mixed aggregates, displaying a variety of pathologies.

Density functional theory (DFT) calculations at the B3LYP/6-31G(d) level of theory[12] with single-point calculations at the MP2 level of theory examined conformational properties and solvation. The results concurred with those described in detail elsewhere[5] and are largely relegated to the Supporting Information. A few especially pertinent computational results are used throughout the text.

We begin the survey with a description of LiCl-derived mixed aggregate type **4A** (or **5A**; see Scheme 2) owing to the key role of lithium halides as alkylation byproducts. ^{6}Li and ^{15}N NMR spectra of samples of **4A** showed ^{6}Li–^{15}N coupling patterns akin to those observed for mixed aggregate **2** in a previous study (Figure 1 A).[5] Owing to slow aggregate exchanges, the samples required aging. The corresponding ^{6}Li spectrum with broadband ^{15}N decoupling revealed three resonances (1:1:1) along with the three resonances of residual **2** (Figure 1 B). Single-frequency ^{15}N decoupling readily deconvoluted the splitting (Supporting Information) and provided the gross structure as **4A** (or **5A**). A combination of COSY, TOCSY, HSQC, HMBC, and ROESY spectroscopies of **4A** in [D$_8$]THF showed a three-dimensional structure consistent with the lowest-energy computed structure of **4A** (Figure 2). Of the two possible diastereomers resulting from the chelate orientations [Eq. (2)], the observed form was the same as that noted previously.[5] The preference illustrated in Equation (2) was constant for all mixed aggregates prepared from dianion **1**.

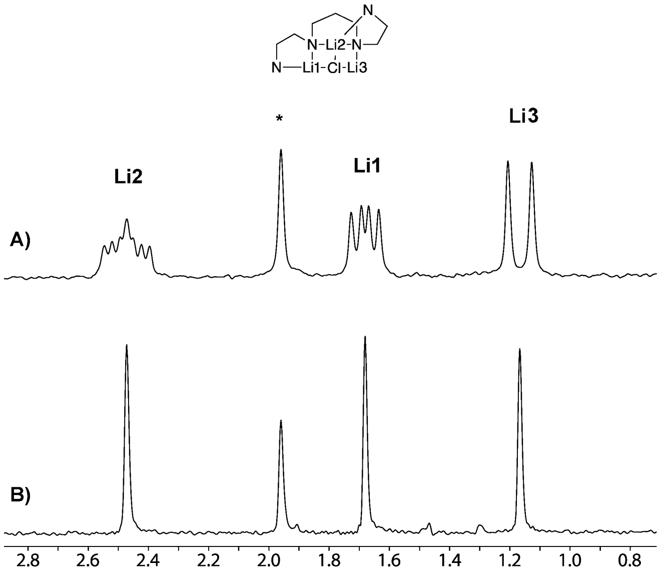


Figure 1. ^{6}Li NMR spectra of 0.10 M [^{6}Li,^{15}N]**4**/**5A** prepared from 0.10 M *n*-BuLi-derived mixed aggregate [^{6}Li,^{15}N]**2** and 0.10 M [^{6}Li]LiCl/*i*-Pr$_2$NH in neat [D$_8$]THF. The spectra were recorded at −70 °C after aging at −78 °C for 12 h: A) ^{6}Li spectrum; B) ^{6}Li{^{15}N} spectrum. LiCl/*i*-Pr$_2$NH was generated in situ from Et$_3$N·HCl and [^{6}Li]LDA (LDA = lithium diisopropylamide), with regeneration of the visible LDA by *n*-BuLi as denoted by ⋆.

Variable-temperature NMR spectroscopic studies revealed moderately temperature-dependent ^{6}Li chemical

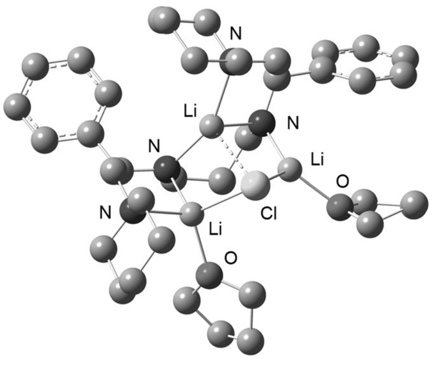
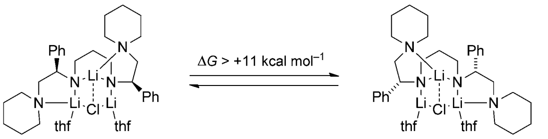


Figure 2. DFT-calculated structure of **4**/**5A**.



(2)

shifts and strikingly temperature-dependent ^{15}N chemical shifts (Figure 3). The two anionic amido ^{15}N resonances changed markedly with temperature, whereas the chelating piperidino resonances were unaffected. Given the results of studies of the lithium acetylides described in the next section, we suspect that a temperature-dependent **4A**-**5A** equilibrium with affiliated solvation number changes is operative.

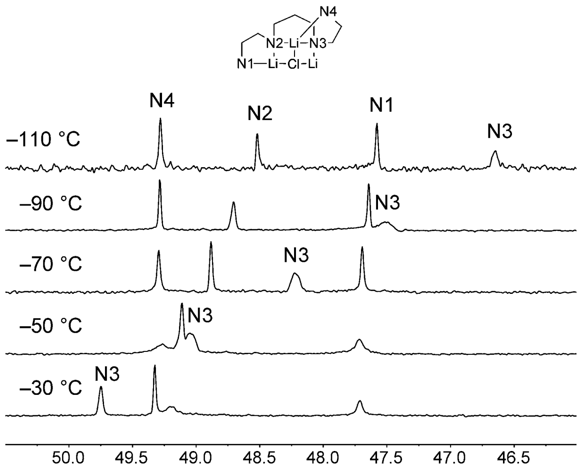
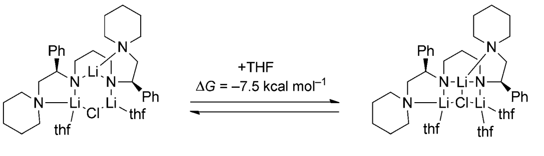


Figure 3. Variable-temperature ^{15}N NMR spectra of 0.10 M [^{6}Li,^{15}N]**4/5A** prepared from 0.10 M *n*-BuLi-derived mixed aggregate [^{6}Li,^{15}N]**2** and 0.10 M [^{6}Li]LiCl/*i*-Pr$_2$NH in neat [D$_8$]THF after aging at −78 °C for 12 h. LiCl/*i*-Pr$_2$NH was generated in situ from Et$_3$N·HCl and [^{6}Li]LDA.

Prompted by the temperature-dependent shifts and results obtained with the lithium acetylides (below), we focused the DFT computations on the relationship between laddering and solvation. We found a single minimum rather than discrete structures corresponding to **4A** and **5A**. The di- and trisolvated forms were, within the error of the computations, of equal energy [Eq. (3)]. We noticed, however, that compared with the disolvated form (2.83 Å), the trisolvate showed a shortening of the transannular Li−Cl contact (2.63 Å). Mixed aggregates bearing a single THF are much less stable, with no evidence of the Li−Cl contact. These issues become more prominent and spectroscopically tractable in the context of the lithium acetylides discussed below. It may seem counterintuitive that laddering is associated with solvation, but laddering opens up the coordination sphere on the right-hand lithium.



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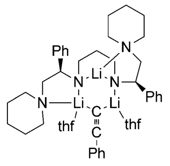
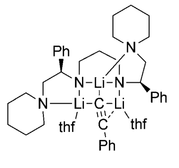
4A **5A**

Lithium acetylides brought the laddering into full view. The mixed aggregate derived from lithium phenylacetylide (**B**) showed the characteristic three resonances. Analogous spectra recorded with a ^{15}N-labeled substrate showed the expected coupling for **4B** or **5B**. Spectra obtained with [^{6}Li,^{13}C]PhCCLi showed strong ^{6}Li–^{13}C coupling, producing three ^{6}Li doublets and a ^{13}C septet consistent with ladder structure **5B**. The transannular ^{6}Li–^{13}C coupling ($J_{\text{Li-C}} = 5.2$ Hz) is comparable to the other two ($J_{\text{Li-C}} = 5.0$ and 5.3 Hz). This arrangement appears to stem from a static structure. Warming the sample, however, caused the transannular coupling to decrease monotonically ($J_{\text{Li-C}} = 3.8$ Hz at −20 °C) while the other two doublets coalesced.[13]



4B



5B

Variable-temperature NMR spectroscopic studies revealed temperature-dependent ^{6}Li and ^{15}N chemical shifts analogous to those noted for the LiCl-containing mixed aggregate (Figure 3). The two anionic amido ^{15}N resonances migrated downfield with warming, whereas the chelating piperidino resonances (N1 and N4) were unaffected. The two ^{6}Li resonances (Li1 and Li3), suggested to be THF solvated, also shifted downfield with warming to a limited extent, whereas the THF-free ^{6}Li resonance (Li2) remained invariant.

To probe the role of solvation–desolvation, we carried out two types of experiments. Monitoring chemical shift versus THF concentration by using hexane as a cosolvent showed little change in the chemical shift. Although pyridine is often a particularly useful chemical shift reagent for ^{6}Li NMR spectroscopy,[14] preliminary studies of samples containing added pyridine were complex and unhelpful.

Computational studies uncovered a single discrete structure corresponding to ladder **5B**. The acetylide showed a distinct cant toward the three-coordinate lithium bearing one THF (no chelated piperidine). Whether this result derives from a stabilizing acetylide–lithium interaction or simply avoidance of steric problems is unknown, but arguments for steric bias stem from similar canting by lithium monoalkylamides and alkoxides (see below).

A low-resolution (1.04 Å) crystal structure was obtained after all spectroscopic and computational studies were complete. Comparison of the solid-state structure with the computed lowest-energy form shows remarkable similarities, including a highly puckered ladder, a canted acetylide, and two THF ligands (Figure 4). A cursory survey of lithium acetylides **P**–**U** produced spectra suggesting analogy to lithium phenylacetylide.

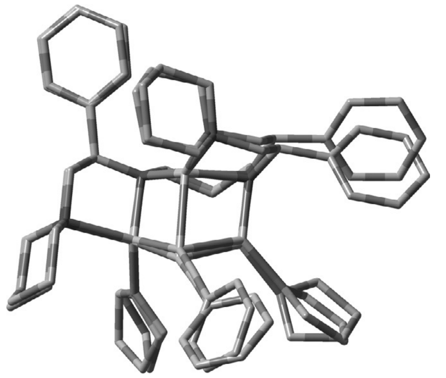


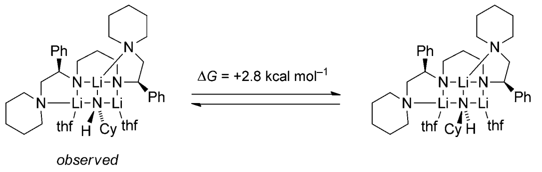
Figure 4. Overlap of DFT-computed and crystallographically characterized structures of **5B**.

We focused the studies of lithium alkoxides and related O-lithiated species on *n*-BuOLi as a potential (albeit unobserved) contaminant in *n*-BuLi. ^{6}Li NMR spectroscopy showed a three-resonance pattern characteristic of mixed aggregate **4C** or ladder **5C** along with low concentrations of *n*-BuLi-derived mixed aggregate **2** resulting from the method of preparation. [^{6}Li,^{15}N]**1** showed multiplets and coupling patterns consistent with **4C**/**5C** (Supporting Information). Two-dimensional ^{1}H and ^{13}C NMR spectroscopy showed spatial relationships more consistent with **5C**, although they did not exclude **4C**. Temperature-dependent ^{15}N resonances akin to those observed for both lithium phenylacetylide and LiCl were observed. Computations converged on disolvated ladder-type aggregate **5C** with a 2.10 Å transannular Li−O contact irrespective of the starting geometry.

A cursory examination of assorted lithium alkoxides (**F**–**J**) and lithium phenolates (**K**–**N**) showed the characteristic three-resonance pattern. The only exception was highly hindered phenolate **4O**, which incorporates into a mixed aggregate to only a limited extent.

Studies of monoalkylamides first focused on lithium cyclohexylamide (**D**). ^{6}Li and ^{15}N NMR spectroscopy using mixed aggregates prepared from [^{15}N$_4$]**1** showed the usual three resonances and associated coupling patterns. Samples prepared from [^{15}N]**D**[5] showed the expected strong coupling within the Li$_3$N$_3$ ring ($J_{\text{Li-N}} = 4.6$ and 3.7 Hz) as well as a weak transannular coupling ($J_{\text{Li-N}} = 1.1$ Hz) indicative of laddering. Whether the weak coupling attested to a long contact or a dynamic exchange between the laddered and unladdered forms could not be determined experimentally. Computations showed a single species with a long (2.87 Å) N−Li transannular contact for the lowest-energy disolvated form. (Three THF ligands would not bind.) Of the two possible orientations of the H and Cy substituents on nitrogen, the computationally most viable structure placed the N−H on the β-face and formed a ladder [Eq. (4)]. That orientation was confirmed by ^{1}H and ^{13}C NMR spectroscopy.

A complete spectroscopic analysis of mixed aggregates with both [^{15}N$_4$]**1** and [^{15}N]**E** showed the same patterns observed for lithium cyclohexylamide. In addition, spectra recorded at −100 °C showed decoalesced resonances consistent with a 2:1 mixture of two isomers presumed to be isomeric chelates. Computations showed the relative energies of two logical isomers in [Eq. (5)]. Detailed ^{1}H and ^{13}C NMR spectroscopy failed to distinguish the two.



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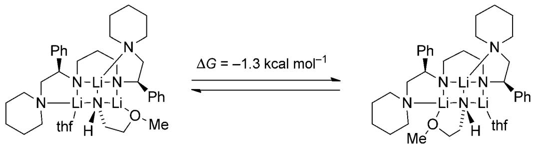
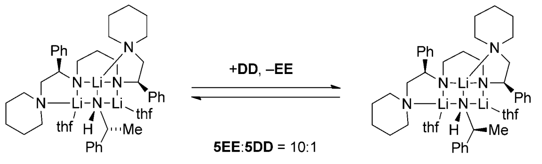


(5)

Monoalkylamides **V**–**HH** all formed discrete structures **4** or **5**. We briefly probed the stereochemical consequences of the stereogenic centers in phenethylamides **DD** and **EE**. Samples containing 1.0 equiv of each had a 10:1 preference for forming **5EE** [Eq. (6)]. This selectivity was good considering that the distinction of the two is based on subtle steric effects. One could envision schemes in which such distinctions might be used for kinetic resolutions.



(6)

5EE **5DD**

Presumably owing to steric hindrance, the dialkylamides did not cleanly form mixed aggregates of type **4** or **5**. In some cases they may have been detected, but they were part of complex mixtures that were insufficiently important to pursue further.

Mixed aggregates of dilithiated tetraamine **1** have provided interesting structural comparisons through NMR spectroscopy, DFT computational chemistry, and X-ray crystallography. The computationally and spectroscopically determined structures matched remarkably well. A crystal structure provided a pleasing correlation among the solid-state, solution, and computed structures. The results also offer a guide for exploiting mixed aggregates of Koga's base in enantioselective synthesis. A striking reversal in selectivity with subtle changes in the ligand structure[3a], namely replacing the piperidines of **1** with pyrrolidines, underscores how little we understand the influence of aggregate structure and reaction mechanism on enantioselective transformations.[14]

Acknowledgements

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