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A Computational Study of Mixed Aggregates of Chloromethyllithium with Lithium Dialkylamides

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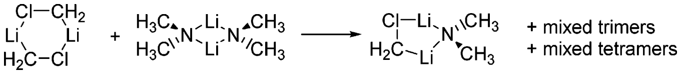

DFT calculations were performed to examine the possible formation of mixed aggregates between chloromethyllithium carbenoids and lithium dimethylamide (LiDMA). In the gas phase mixed aggregates were readily formed and consisted of mixed dimers, mixed trimers, and mixed tetramers. THF solvation disfavored the formation of mixed tetramers and resulted in less exergonic free energies of mixed dimer and mixed trimer formation.

Introduction

Lithium mixed aggregates are complexes between two different lithium compounds that may have chemical properties different from those of either component. The formation of mixed aggregates has been observed for a number of lithium systems, most often in ethereal solvents. Mixed aggregates may be formed in several ways. Lithium salts, such as lithium halides or lithium perchlorate, may be intentionally added to the reaction. Enolization reactions are sometimes performed in the presence of chlorotrimethylsilane to trap the enolate as it forms, and the lithium chloride byproduct can also form mixed aggregates with the lithium dialkylamide.[1] A slight excess of butyllithium is often used when preparing lithium dialkylamides from secondary amines, particularly hindered amines, such as tetramethylpiperidine; the result is a lithium dialkylamide−butyllithium mixed aggregate.[2,3] The exposure of alkyllithiums to small amounts of air results in the formation of lithium oxides, and these can form mixed aggregates with the remaining alkyllithium.[4−7] Lithium enolates are prepared from deprotonation of carbonyl compounds with lithium dialkylamides, and the newly formed enolate can form mixed aggregates with the remaining lithium dialkylamide.[8,9]

The changes in the chemical properties may be minor, with the reactivity of the mixed aggregate differing only slightly from that of the parent organolithium compound, or the mixed aggregate may cause major changes in the chemical reactivity. The formation of mixed aggregates is often discovered by empirical observation of how changes in the reaction conditions change the course of reactions. For example, the use of highly purified lithium reagents may yield a different product distribution than that obtained from reagents that have been exposed to small amounts of air, or from alkyllithium compounds that contain residual lithium halides. Many organic reactions are performed in the presence of lithium salts or other lithium compounds because they generate higher yields or purer products, although the mode of action remains unknown. To date, no mixed aggregates of lithium carbenoids have been reported.

The possible formation of lithium carbenoid mixed aggregates is of interest because of the potential synthetic applications of those species. Many lithium carbenoids, such as haloalkyllithiums and α-lithioethers, are unstable and difficult to study experimentally. Mixed aggregation may possibly stabilize those species. Mixed aggregates with chiral lithium amides or alkoxides have

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potential as new reagents for asymmetric synthesis. Oxiranyllithiums have properties that are intermediate between lithium carbenoids and alkyllithiums,[10−20] and these properties could be altered by mixed aggregate formation. The focus of this work is the possible formation of mixed aggregates between chloromethyllithium and lithium dimethylamide, which will serve as a model for larger systems. Mixed aggregate formation was examined in the gas phase and in THF solution.

Computational Methods

All calculations were performed using Gaussian 98 or Gaussian 03.[21] The gas-phase and solution energies reported include gas-phase internal energy, thermal corrections to the free energy (including ZPE) at 200 and 298 K, and where applicable, solvation terms. Where necessary, two or more conformations of the same structure were optimized, and the lowest energy conformer was used in subsequent calculations.

The solvation free energy change of the gas-phase organolithium molecule $(RLi)_n$ due to microsolvation by m explicit ethereal solvent ligands E (in this case, THF) is calculated by considering the process

$$(\mathrm{RLi})_n + m\mathrm{E} \rightarrow (\mathrm{RLi})_n m\mathrm{E} \tag{1}$$

The microsolvation model assumes that the free energy change accompanying this reaction adequately represents the solvation free energy $\Delta G^\circ_{\mathrm{solv}}$ of the solute $(RLi)_n$ in the solvent E, so that

$$G^\circ_T(\mathrm{solute}) = \mathrm{G}^\circ_T(\mathrm{gas}) + \Delta G^\circ_{\mathrm{solv}} \tag{2}$$

In other words, the free energy of a "supermolecule" $(RLi)_n mE$ relative to that of m solvent molecules is assumed to yield a good approximation to the free energy of the solvated molecule $(RLi)_n$ in the condensed phase. The gas-phase free energies at temperature T of the relevant species are obtained computationally as

$$G^\circ_T(\mathrm{gas}) = E_{\mathrm{en}} + \Delta G^\circ_T \tag{3}$$

where the terms on the right-hand side as well as the procedure used for calculating them are described below. The geometry of each molecule was first optimized using the B3LYP hybrid density functional method[22,23] with the MIDI! basis set,[24] and that basis set was also used for frequency calculations and to determine the ZPEs and thermal corrections to the free energies. A further refinement of the geometry and electronic energy were done at the B3LYP/6-31+G(d)[25,26] level of theory, as diffuse functions are needed for molecules that have substantial carbanion character. Basis set superposition errors (BSSE) were corrected by counterpoise corrections for unsolvated mixed aggregates, defining the fragments in each oligomer as the lithium carbenoid or lithium dimethylamide monomer units. The situation was more complex with solvated systems, as two different types of corrections were needed. When comparing the energies of disolvated and tetrasolvated species, the tetrasolvated species was counterpoise corrected, defining the fragments as the disolvated species and two THF ligands. When calculating the energies of mixed aggregate formation, each species was counterpoise corrected, including the lithium carbenoid and lithium dimethylamide dimers. Each fragment was defined as the monomer unit, as with the gas-phase calculations, and each THF solvent ligand was included as part of the nearest monomer to which it was coordinated. Thus, we have: E_{en} = the electronic energy plus nuclear repulsion of the equilibrium geometry, using B3LYP/6-31+G(d). E_0^{vib} = unscaled B3LYP/MIDI! vibrational zero point energy. ΔG°_T = B3LYP/MIDI! thermal corrections to the free energy for a standard state of 1 atm and specified temperature from the masses. This includes contributions from translational, rotational, and vibrational degrees of freedom, as well as the zero point energy.

Calculations for the free energy changes for the "reactions" (dimerizations, tetramerizations, etc.) are straightforward using the $\Delta G^\circ_T(\mathrm{gas})$ terms defined in eq 3.

The standard state of a solution is taken as 1 mol L^{-1}, and an additional correction to the free energy terms is needed to convert the standard state of an ideal gas (1 atm) to the standard state of the solution. This was incorporated by simply adding the term $RT \ln(RT)$ to each free energy term, where the numerical value of the argument of the logarithm was obtained using the pressure−volume (0.082057 L atm K^{-1} mol^{-1}) value for the gas constant. These corrections amount to 1.1120 kcal/mol at 200 K and 1.8943 kcal/mol at 298 K. These correction terms were included in all solution-phase reactions below, i.e., calculations where the microsolvation model was used.

Yet another correction is required for proper treatment of the explicit solvent molecules used in microsolvation. The traditional approach is to set the standard state of a pure liquid to be the concentration of the pure liquid itself, which then allows one to drop the concentration of the pure liquid from equilibria expressions (consider the ionic product of water, for example). However, since we have decided to adopt the standard state of 1 mol L^{-1} for all species, the free energy change for the process

$$2\mathrm{RLi{\cdot}2THF} \rightarrow (\mathrm{RLi{\cdot}THF})_2 + 2\mathrm{THF} \tag{4}$$

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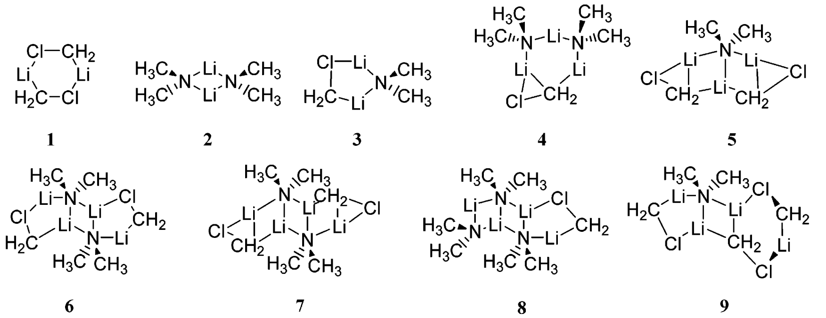
CHART 1



is given by[27]

$$\Delta G^\circ = -RT\ln\{[(\mathrm{RLi{\cdot}THF})_2]/[\mathrm{RLi{\cdot}2THF}]^2\} - 2RT\ln[\mathrm{THF}] \quad (5)$$

The molarity of the THF solvent was calculated to be 13.26 at 200 K, and 12.33 at 298 K, from its tabulated density.[28] These corrections amount to −1.0273 and −1.4883 kcal/mol per THF at 200 and 298 K, respectively.

Results and Discussion

Chloromethyllithium has been previously shown to exist primarily as a dimer.[29] Lithium dialkylamides are usually dimeric in ethereal solvents and form a variety of mixed aggregates with lithium halides and lithium enolates,[8,9] as well as a mixed dimer with alkyllithiums.[2] Therefore, geometry optimizations were performed on the chloromethyllithium (**1**) and lithium dimethylamide (LiDMA, **2**) dimers, as well as the mixed dimers, trimers, and tetramers, both in the gas phase and in THF. One mixed dimer was found (**3**); two mixed trimers, $(\mathrm{CH_2LiCl})(\mathrm{LiDMA})_2$ (**4**) and $(\mathrm{CH_2LiCl})_2(\mathrm{LiDMA})$ (**5**); and four different mixed tetramers (**6**, **7**, **8**, and **9**) (Chart 1).

The gas-phase free energies of mixed aggregate formation were calculated according to

$$^1/_2\mathbf{1} + {}^1/_2\mathbf{2} \rightarrow \mathbf{3} \quad (6)$$

$$^1/_2\mathbf{1} + \mathbf{2} \rightarrow \mathbf{4} \quad (7)$$

$$\mathbf{1} + {}^1/_2\,\mathbf{2} \rightarrow \mathbf{5} \quad (8)$$

$$\mathbf{1} + \mathbf{2} \rightarrow \mathbf{6} \quad (9)$$

$$\mathbf{1} + \mathbf{2} \rightarrow \mathbf{7} \quad (10)$$

$$^1/_2\mathbf{1} + {}^3/_2\mathbf{2} \rightarrow \mathbf{8} \quad (11)$$

$$^3/_2\mathbf{1} + {}^1/_2\mathbf{2} \rightarrow \mathbf{9} \quad (12)$$

The gas-phase free energies of dimer and trimer formation are shown in Table 1 and the tetramerization energies in Table 2. Dividing the total free energy by the number of lithium atoms in each aggregate generated the free energies per lithium, given in brackets. Comparing the free energies per lithium shows that the mixed tetramer **7** will be the major gas-phase species, but significant amounts of trimers **4** and **5** and tetramers **6** and **8** may also be present. The optimized gas phase mixed aggregate geometries are shown in Figure 1. Mixed trimer **4** adopted a cyclic structure, while mixed trimer **5** and mixed tetramers **6**−**8** optimized to ladder-like structures. Similar structures have been previously reported for other lithium dialkylamide mixed aggregates.[9,30]

TABLE 1. Gas-Phase Free Energies of Mixed Dimer and Mixed Trimer Formation (kcal/mol) [kcal/mol per Li]

T (K)	**3**	**4**	**5**
200	−0.393 [−0.196]	−10.6 [−3.53]	−10.1 [−3.37]
200 BSSE corr	−0.243 [−0.122]	−9.04 [−3.01]	−8.59 [−2.86]
298.15	−0.464 [−0.232]	−8.99 [−3.00]	−8.36 [−2.79]
298.15 BSSE corr	−0.314 [−0.157]	−7.41 [−2.47]	−6.88 [−2.29]

Basis set superposition errors (BSSEs) were almost negligible for the mixed dimer formation, as the carbenoid and lithium amide dimers were used to calculate the mixed dimer formation energies, resulting in a cancellation of errors. For mixed trimer formation, the BSSEs were about 1.5 kcal/mol, or about 0.5 kcal/mol per lithium atom. For the mixed tetramers, BSSEs ranged from 2 to 3 kcal/mol, or less than 1 kcal/mol per lithium atom.

The free energies of mixed aggregate formation were calculated in THF solution from the THF microsolvated species. In analogy to other lithium dialkylamides, LiDMA was taken to be the THF disolvate. The picture was a bit more complex with the solvation state of the chloromethyllithium carbenoid. The free energy of addition of two additional THF ligands to the chloromethyllithium disolvated dimer was calculated according to eq 12 and found to be exergonic by 2.11 kcal/mol at 200 K and endergonic by 4.25 kcal/mol at 298 K, including BSSE corrections. Because lithium carbenoid reactions are normally performed at low temperatures due to carbenoid instability at higher temperatures, the subsequent calculations used the tetrasolvated form of chloromethyllithium.

$$\mathbf{1}{\cdot}2\mathrm{THF} + 2\mathrm{THF} \rightarrow \mathbf{1}{\cdot}4\mathrm{THF} \quad (13)$$

The calculated free energies of the disolvated mixed dimer and trisolvated mixed trimer formation were obtained from eqs 14−16, respectively, and the results are given in Table 3. Compared to the gas phase, the solvated dimerization and trimerization free energies are

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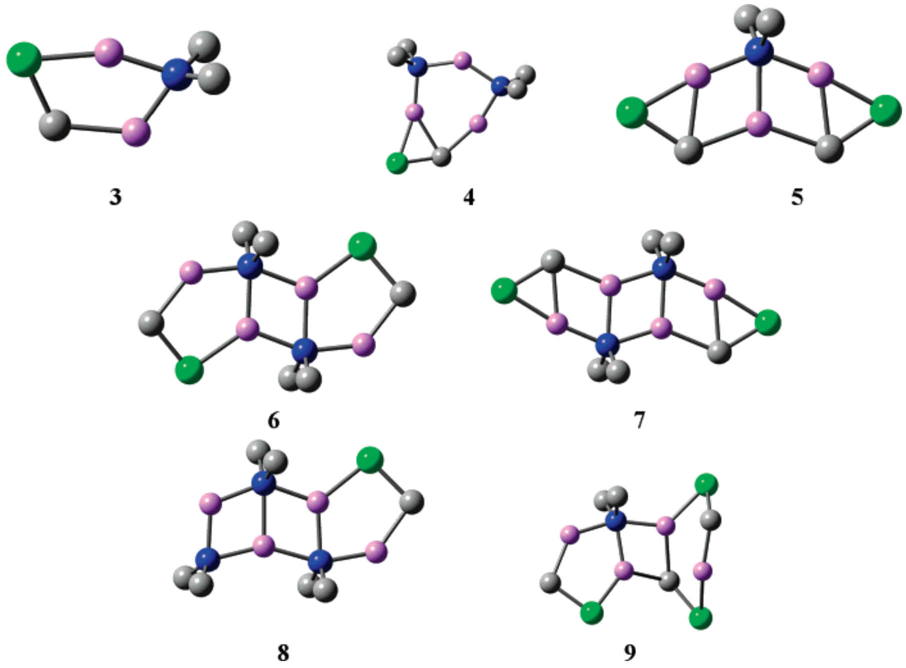


FIGURE 1. Optimized gas-phase geometries of mixed aggregates **3**−**9**. Hydrogens omitted for clarity. Key: gray, carbon; blue, nitrogen; violet, lithium; green, chlorine.

TABLE 2. Gas-Phase Free Energies of Mixed Tetramer Formation (kcal/mol) [kcal/mol per Li]

T (K)	**6**	**7**	**8**	**9**
200	−15.3 [−3.83]	−19.5 [−4.88]	−16.0 [−4.00]	−9.69 [−2.42]
200 BSSE corr	−13.3 [−3.32]	−16.6 [−4.15]	−13.7 [−3.42]	−7.48 [−1.87]
298.15	−11.8 [−2.95]	−15.9 [−3.98]	−12.7 [−3.18]	−5.92 [−1.48]
298.15 BSSE corr	−9.87 [−2.47]	−13.0 [−3.25]	−10.4 [−2.60]	−3.70 [−0.925]

TABLE 3. THF-Solvated Energies of Mixed Dimer and Mixed Trimer Formation (kcal/mol) [kcal/mol per Li]

T (K)	**3**·2THF	**4**·3THF	**5**·3THF
200	−1.39 [−0.695]	−0.361 [−0.120]	1.51 [0.503]
200 BSSE corr	−1.17 [−0.585]	−0.139 [−0.0463]	3.41 [1.14]
298.15	−4.69 [−2.34]	−3.21 [−1.07]	1.00 [0.333]
298.15 BSSE corr.	−4.47 [−2.23]	−2.98 [−0.993]	2.90 [0.967]

TABLE 4. Calculated Free Energies of Formation of Mixed Tetramer Tetrasolvates from the Disolvates (kcal/mol)

T (K)	**6**	**7**	**8**	**9**
200	4.71	0.927	N/A	−3.27
200 BSSE corr	8.33	3.99	N/A	−0.307
298.15	11.5	6.46	N/A	3.01
298.15 BSSE corr	15.1	9.52	N/A	5.98

more temperature dependent as a result of the entropy change as THF dissociate from the carbenoid during mixed aggregate formation. The calculations predict that species **3** and **4** will coexist in solution with free carbenoid and free LiDMA at 200K. At 298 K, the mixed dimer **3** and mixed trimer **4** will be the major species. The optimized geometries of the THF solvated mixed dimer and mixed trimers are shown in Figure 2.

$$ {}^{1}/_{2}\mathbf{1}\cdot 4\mathrm{THF} + {}^{1}/_{2}\mathbf{2}\cdot 2\mathrm{THF} \rightarrow \mathbf{3}\cdot 2\mathrm{THF} + \mathrm{THF} \quad (14) $$

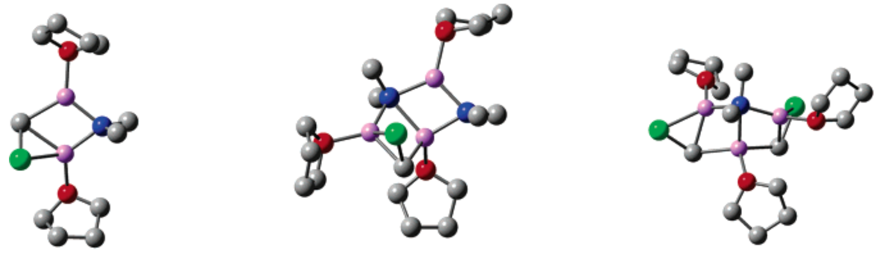
$$ {}^{1}/_{2}\mathbf{1}\cdot 4\mathrm{THF} + \mathbf{2}\cdot 2\mathrm{THF} \rightarrow \mathbf{4}\cdot 3\mathrm{THF} + \mathrm{THF} \quad (15) $$

$$ \mathbf{1}\cdot 4\mathrm{THF} + {}^{1}/_{2}\mathbf{2}\cdot 2\mathrm{THF} \rightarrow \mathbf{5}\cdot 3\mathrm{THF} + 2\mathrm{THF} \quad (16) $$

The situation is more complex with regard to mixed tetramer formation because most of the tetramers can exist either as a THF disolvate or tetrasolvate, except for **8**, which exists only as the THF disolvate. The free energies of formation of the tetramer tetrasolvates from the disolvates, according to eq 17, are shown in Table 4. Both $(CH_2LiCl)_2(LiDMA)_2$ mixed tetramers **6** and **7** were shown to exist primarily as the disolvates, especially at 298 K. The tetrasolvated mixed tetramer **8** was unstable with regard to dissociation of THF ligands. Only the sterically unhindered $(CH_2LiCl)_3(LiDMA)$ (**9**) was calculated to be more stable as the THF tetrasolvate. The disolvated forms are expected to be even more energetically favorable when bulkier lithium dialkyalmides, such as LDA, are used to form mixed aggregates. Therefore, the free energy calculations involving mixed tetramer formation were performed on the disolvated forms of **6**, **7**, and **8** and on the tetrasolvate of **9**. The optimized geometries of these species are shown in Figure 3.

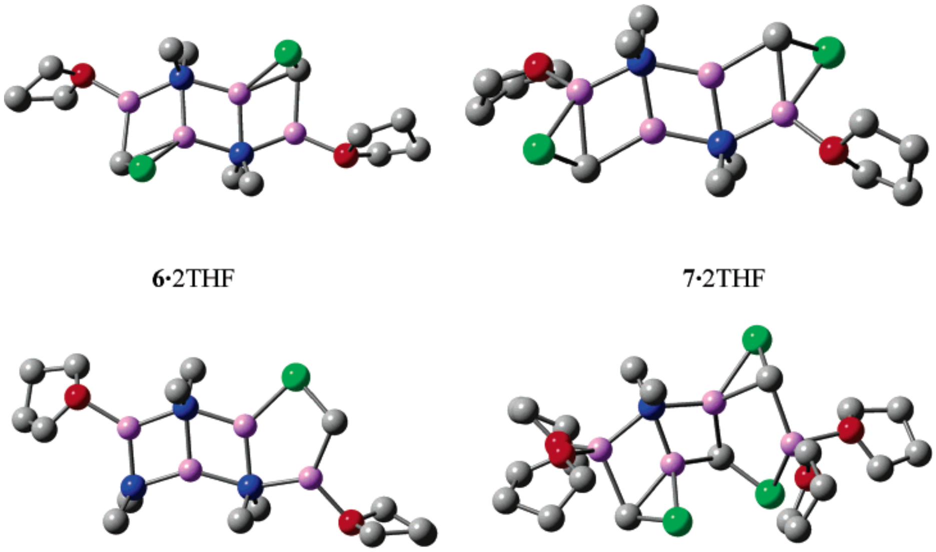
$$ \text{mixed tetramer}\cdot 2\mathrm{THF} + 2\mathrm{THF} \rightarrow \text{mixed tetramer}\cdot 4\mathrm{THF} \quad (17) $$

The free energies of mixed tetramer formation were calculated from eqs 18−21 and are listed in Table 5. At 200 K, formation of the mixed tetramers was energeti-



3·2THF **4**·3THF **5**·3THF

FIGURE 2. Optimized THF-solvated geometries of mixed aggregates **3**–**5**. Hydrogens omitted for clarity.



6·2THF **7**·2THF

8·2THF **9**·4THF

FIGURE 3. Optimized THF-solvated geometries of mixed tetramers **6**–**9**. Hydrogens omitted for clarity.

TABLE 5. THF Solvated Energies of Mixed Tetramer Formation (kcal/mol) [kcal/mol per Li]

T (K)	**6**·2THF	**7**·2THF	**8**·2THF	**9**·4THF
200	3.48 [0.870]	4.12 [1.03]	1.94 [0.485]	2.76 [0.690]
200 BSSE corr	6.38 [1.59]	6.89 [1.72]	4.89 [1.22]	5.38 [1.34]
298.15	−4.17 [−1.04]	−3.29 [−0.822]	−3.70 [−0.925]	−1.91 [−0.477]
298.15 BSSE corr	−1.28 [−0.320]	−0.519 [−0.130]	−0.749 [−0.187]	0.704 [0.176]

cally unfavorable, and formation of **6**–**8** was slightly exergonic at 298 K. Comparison of the free energy per lithium in Tables 3 and 5 shows that the mixed dimer **3** and mixed trimer **4** are likely to be the major species in THF solution at 200 K, as well as some free lithium carbenoid and LiDMA.

$$\mathbf{1}\cdot 4\mathrm{THF} + \mathbf{2}\cdot 2\mathrm{THF} \rightarrow \mathbf{6}\cdot 2\mathrm{THF} + 4\mathrm{THF} \quad (18)$$

$$\mathbf{1}\cdot 4\mathrm{THF} + \mathbf{2}\cdot 2\mathrm{THF} \rightarrow \mathbf{7}\cdot 2\mathrm{THF} + 4\mathrm{THF} \quad (19)$$

$${}^{1}/_{2}\mathbf{1}\cdot 4\mathrm{THF} + {}^{3}/_{2}\mathbf{2}\cdot 2\mathrm{THF} \rightarrow \mathbf{8}\cdot 2\mathrm{THF} + 3\mathrm{THF} \quad (20)$$

$${}^{3}/_{2}\mathbf{1}\cdot 4\mathrm{THF} + {}^{1}/_{2}\mathbf{2}\cdot 2\mathrm{THF} \rightarrow \mathbf{9}\cdot 4\mathrm{THF} + 3\mathrm{THF} \quad (21)$$

Conclusions

Lithium dimethylamide is predicted to form several different mixed aggregates with chloromethyllithium. In the gas phase, the major species will be mixed trimers and mixed tetramers. This approximates the situation in nonpolar solvents such as pentane, provided that the compounds are sufficiently soluble. In THF, the coordinating ethereal ligands change the aggregation state, disfavoring the mixed tetramers in favor of the mixed dimer and trimers. The aggregation states are predicted to be more temperature sensitive compared to the gas phase, primarily due to the entropy effects from the dissociation of coordinated THF ligands.

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Supporting Information Available: Tables of optimized geometries and energies of all reactants. This material is available free of charge via the Internet at http://pubs.acs.org.

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