Mixed Aggregates of 1-Methoxyallenyllithium with Lithium Chloride

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A combined computational and ^{13}C NMR study was used to investigate the formation of mixed aggregates of 1-methoxyallenyllithium and lithium chloride in tetrahydrofuran (THF) solution. The observed and calculated chemical shifts, as well as the calculated free energies of mixed aggregate formation (MP2/6-31+G(d)), are consistent with the formation of a mixed dimer as the major species in solution. Free energies of mixed dimer, trimer, and tetramer formation were calculated by using the B3LYP and MP2 methods and the 6-31+G(d) basis set. The two methods generated different predictions of which mixed aggregates will be formed, with B3LYP/6-31+ G(d) favoring mixed trimers and tetramers in THF solution, and MP2/6-31+G(d) favoring mixed dimers. Formation of the sterically unhindered mixed dimers is also consistent with the enhanced reactivity of these compounds in the presence of lithium chloride. The spectra are also consistent with some residual 1-methoxyallenyllithium tetramer, as well as small amounts of higher mixed aggregates. Although neither computational method is perfect, for this particular system, the calculated free energies derived using the MP2 method are in better agreement with experimental data than those derived using the B3LYP method.

Introduction

Allenyl ethers are easily deprotonated to form lithioallenes. Deprotonation typically takes place exclusively at the α carbon atom to yield carbanions that can be considered acrolein acyl carbanion equivalents.[1] The presence of the allene function in the products of nucleophilic addition of carbanions such as **1** and **2** confers reactivity due to the strain inherent in the allene, which is often advantageous for synthetic applications.[2] Our interest in **1** was initially as a reagent for the annulation of ketones to hydroxy 1,4-benzoquinones.[3] Subsequently, we discovered that **1** and **2** were exceptionally useful reagents for the allene ether version of the Nazarov cyclization.[2f,4] Lithioallene **2** was the first reagent we developed for the chiral auxiliary controlled asymmetric Nazarov cyclization.[5] Early on we had observed that the nucleophilicity of **2** was

greatly attenuated compared to **1**, and we attributed this to the presence in **2** of multiple ether functions that could effectively chelate lithium ion leading to unreactive aggregated species. Consistent with this hypothesis, we found that the nucleophilicity of **2** and of related species was restored by the addition of up to two equivalents of lithium chloride to the reaction mixture, an observation that is consistent with the known lithium chloride-induced disaggregation of carbanions.[6] This simple expedient addressed the immediate problem successfully, but it also raised questions regarding the solution phase structure of lithioallenes like **2**. A better understanding of the solution structure of these species would be useful for determining the origins of stereochemical induction in the Nazarov cyclization.[7]

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1   **2**
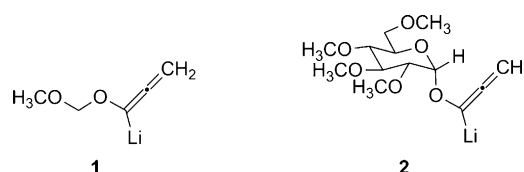
Computational Methods

All geometry optimizations, frequency calculations, and NMR chemical shift calculations were performed with the Gaussian 03 program.[8] Geometry optimizations were performed at the B3LYP/6-31+G(d) level of theory, followed by frequency calculations at the same level. The geometries were then reoptimized at the MP2/6-31+G(d). Free energy corrections were calculated at 200 K and 298.15 K from the frequency calcula-

tions and added to the electronic energies at each level of theory, in order to obtain approximate free energies of each species.

Solvent effects were modeled by placing explicit tetrahydro-furan (THF) ligands on the lithium atoms. Generally, two or three ligands per lithium are used for a monomer, one or two for a dimer, and one ligand per lithium for a higher aggregate. In some cases, fewer ligands can be accommodated on the lithium atom due to steric strain. Special care is taken to ensure consistent handling of standard states.[9, 10] Specifically, a correction term $RT\ln(c^{\circ}RT/P^{\circ})$ must be added per mole of each species in the reaction under consideration, which represents the change in free energy involved in compressing the system from standard pressure P° (or a concentration of P°/RT) used in gas-phase calculations to the standard concentration of $c^{\circ} = 1\ mol\,L^{-1}$ commonly used for solutions. This term is numerically equal to $+1.1119\ kcal\,mol^{-1}$ at 200 K and $+1.8900\ kcal\,mol^{-1}$ at 298.15 K. While it cancels from both sides when the net change in the number of moles due to reaction $\Delta n = 0$, it is a non-negligible correction in cases where $\Delta n \neq 0$. Yet another correction is required for cases where a THF ligand dissociates, as in Eq. (1), where ΔG° is given by Eq. (2).

$$\text{RLi} \cdot n\text{THF} \rightleftharpoons \text{RLi} \cdot m\text{THF} + (n-m)\text{THF} \tag{1}$$
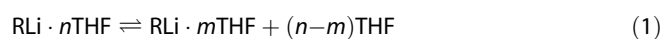
$$\Delta G^{\circ} = -RT\ln\frac{[\text{RLi} \cdot m\text{THF}]}{[\text{RLi} \cdot n\text{THF}]} - (n-m)RT\ln\frac{[\text{THF}]}{c^{\circ}} \tag{2}$$

Since the concentration of pure THF is different from the standard concentration c°, it was evaluated from its molar volume at 1 atm and 200 K or 273.15 κ using the empirical expression provided by Govender et al.,[11] and incorporated into the second term of Eq. (2). Numerically, this correction to ΔG° amounts to -1.0273 and $-1.4883\ kcal\,mol^{-1}$ per THF at 200 and 298.15 K, respectively. This approach to modeling solvation effects on organolithium compounds has been used in other studies,[12–17] and has been found to give results in agreement with available experimental evidence.

Isotropic ^{13}C NMR chemical shifts were calculated at the B3LYP/6-31+G(d) level of theory. Chemical shift calculations were performed on the MP2-optimized geometry for each species and for tetramethylsilane (TMS), and the chemical shifts of each carbon atom relative to TMS were obtained by subtraction.

Results and Discussion

We have previously reported that in the absence of lithium chloride, 1-methoxyallenyllithium exists as a dimer–tetramer equilibrium in THF.[18] The table of calculated energies of these species is reproduced in the Supporting Information. The optimized THF-solvated structures of two isomeric dimers and the tetramer are shown in Figure 1. In order to examine the tendency of this compound to form mixed aggregates with lithium chloride in the absence of the influence of solvents, the gas-phase free energies of mixed aggregate formation were
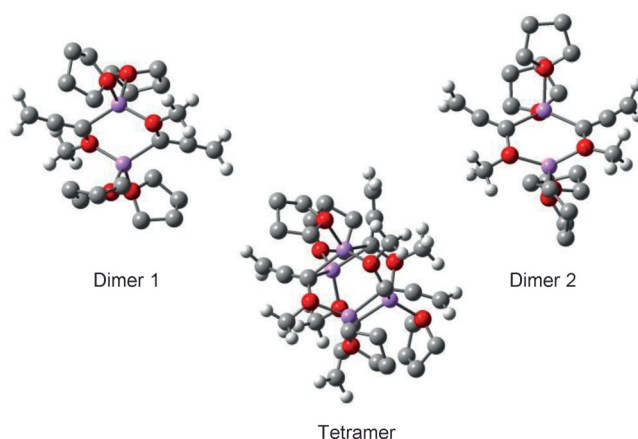
Figure 1. Optimized geometries of THF-solvated 1-methoxyallenyllithium homo-aggregates. Reproduced (adapted) with permission from ref. [18]. Copyright (2009) American Chemical Society. THF hydrogen atoms omitted for clarity. Grey: Carbon; White: Hydrogen; Red: Oxygen; Violet: Lithium.

calculated at the B3LYP/6-31+G(d) and MP2/6-31+G(d) levels of theory. The optimized geometries of the gas-phase mixed aggregates are shown in Figure 2. The calculated free energies of mixed dimer and mixed trimer formation are listed in Table 1, and those of mixed tetramer formation are in Table 2. Comparison of the two tables shows that the formation of
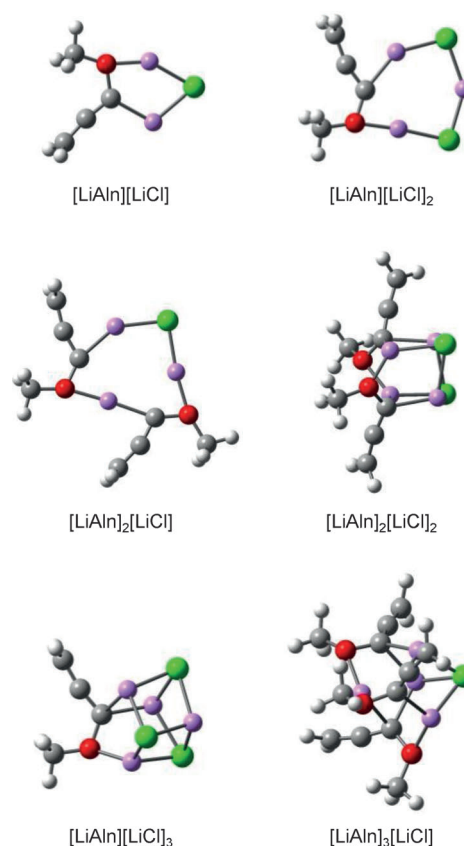
Figure 2. MP2-optimized gas-phase geometries of 1-methoxyallenyllithium (Aln) mixed aggregates with lithium chloride. Grey: Carbon; White: Hydrogen; Red: Oxygen; Violet: Lithium; Green: Chlorine.

Table 1. Free energies of gas-phase mixed dimer and mixed trimer formation of 1-methoxyallenyllithium with lithium chloride.

| Method | T [K] | Free energy [kcal mol^{-1} per Li] | | |
		[LiAln][LiCl]	[LiAln][LiCl]$_2$	[LiAln]$_2$[LiCl]
B3LYP	200	3.22	−2.73	−0.0444
B3LYP	298.15	2.75	−2.47	−0.130
MP2	200	5.27	−2.81	1.00
MP2	298.15	4.80	−2.56	0.915

Table 2. Free energies of gas-phase mixed tetramer formation of 1-methoxyallenyllithium with lithium chloride.

| Method | T [K] | Free energy [kcal mol^{-1} per Li] | | |
		[LiAln]$_2$[LiCl]$_2$	[LiAln][LiCl]$_3$	[LiAln]$_3$[LiCl]
B3LYP	200	−4.43	−6.45	−2.17
B3LYP	298.15	−3.86	−5.64	−1.88
MP2	200	−5.17	−7.75	−2.59
MP2	298.15	−4.60	−6.93	−2.30

higher mixed aggregates is most energetically favorable in the gas phase. This is consistent with previously published studies.[19–22] The free energies of gas-phase mixed aggregate formation calculated by the B3LYP and MP2 methods are in good agreement, generally within 1–2 kcal mole^{-1} of each other. Although the gas-phase calculations are valuable for comparison of different computational methods and for predicting the structures and aggregation states in non-polar solvents, the negligible solubility of lithium chloride in those solvents makes it unlikely that these mixed aggregates will be observed in solution. We therefore turned our attention to the THF-solvated structures and free energies of mixed aggregate formation.

Dimeric lithium compounds can be solvated by one or two THF ligands per lithium, while steric constraints generally limit solvation to one THF per lithium in higher aggregates. To determine which solvation state should be used for calculations involving the dimers, the free energies of tetrasolvated dimers of 1-methoxyallenyllithium, lithium chloride, and the mixed dimer were calculated from the disolvated dimers, as shown in Eq. (3). The results are shown in Table 3.

$$[LiX]_2 \cdot 2\,THF + 2\,THF \rightarrow [LiX]_2 \cdot 4\,THF \tag{3}$$
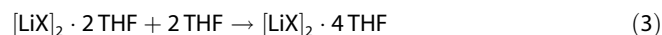
We have previously shown that the B3LYP/6-31+G(d) method predicts the disolvate to be too stable, while the MP2

Table 3. Free energies of solvation of 1-methoxyallenyllithium–lithium chloride dimers and a 1:1 mixed dimer with lithium chloride.

| Method | T [K] | Free energy [kcal mol^{-1} per Li] | | | |
		Dimer 1	Dimer 2	LiCl	Mixed dimer
B3LYP	200	−1.34	2.96	−5.91	−2.69
B3LYP	298.15	3.73	8.17	−0.248	2.34
MP2	200	−30.5	−22.2	−25.2	−25.9
MP2	298.15	−25.3	−17.0	−19.5	−20.9

calculations with the same basis set predict the tetrasolvated form to be too stable, relative to higher level calculations.[23] Due to the anion-like character of these organolithium species, the diffuse functions on the heavy atoms are necessary to adequately describe the bonding, but little advantage was gained by using even larger basis sets. Similar basis set results were obtained in calculating the dimerization energies of lithium carbenoids.[24] Taking an average of the B3LYP and MP2 solvation free energies leads to the conclusion that the tetrasolvated form of each dimer was favored, and the tetrasolvates were used in subsequent calculations.

The free energies of mixed dimer and mixed trimer formation in THF solution were calculated from the solvated homodimers of 1-methoxyallenyllithium and lithium chloride, as shown in Eq. (4)–(6). The results are shown in Table 4. The free

Table 4. Free energies of THF-solvated mixed dimer and mixed trimer formation of 1-methoxyallenyllithium with lithium chloride.

| Method | T [K] | Free energy [kcal mol^{-1} per Li] | | |
		[LiAln][LiCl]	[LiAln][LiCl]$_2$	[LiAln]$_2$[LiCl]
B3LYP	200	−0.328	0.676	−0.349
B3LYP	298.15	−0.621	−1.63	−2.67
MP2	200	−0.215	8.76	8.37
MP2	298.15	−0.507	6.45	6.05

energies of mixed tetramer formation were similarly calculated, according to Eq. (7)–(9), and the results are given in Table 5. The free energies of THF-solvated mixed tetramer formation were also calculated from the 1-methoxyallenyllithium–lithium chloride mixed dimer, according to Eq. (10)–(12), with the results presented in Table 6. Figure 3 shows the optimized geometries of the solvated mixed aggregates.

Table 5. Free energies of THF-solvated mixed tetramer formation of 1-methoxyallenyllithium with lithium chloride.
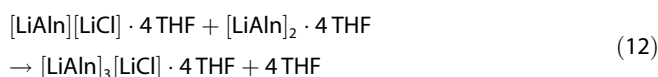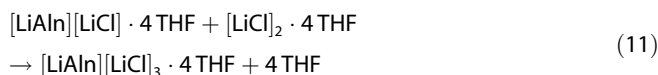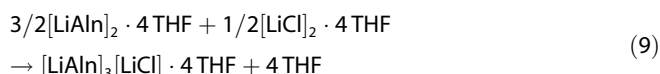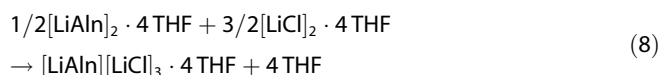
| Method | T [K] | Free energy [kcal mol^{-1} per Li] | | |
		[LiAln]$_2$[LiCl]$_2$	[LiAln][LiCl]$_3$	[LiAln]$_3$[LiCl]
B3LYP	200	−2.53	−2.27	−1.85
B3LYP	298.15	−4.26	−4.09	−3.30
MP2	200	1.86	2.17	2.47
MP2	298.15	0.126	0.343	1.02

Table 6. Free energies of THF-solvated mixed tetramer formation from the mixed dimer.

| Method | T [K] | Free energy [kcal mol^{-1}] | | |
		[LiAln]$_2$[LiCl]$_2$	[LiAln][LiCl]$_3$	[LiAln]$_3$[LiCl]
B3LYP	200	−8.83	−8.42	−6.74
B3LYP	298.15	−14.6	−15.1	−12.0
MP2	200	8.28	9.11	10.3
MP2	298.15	2.53	2.39	5.11
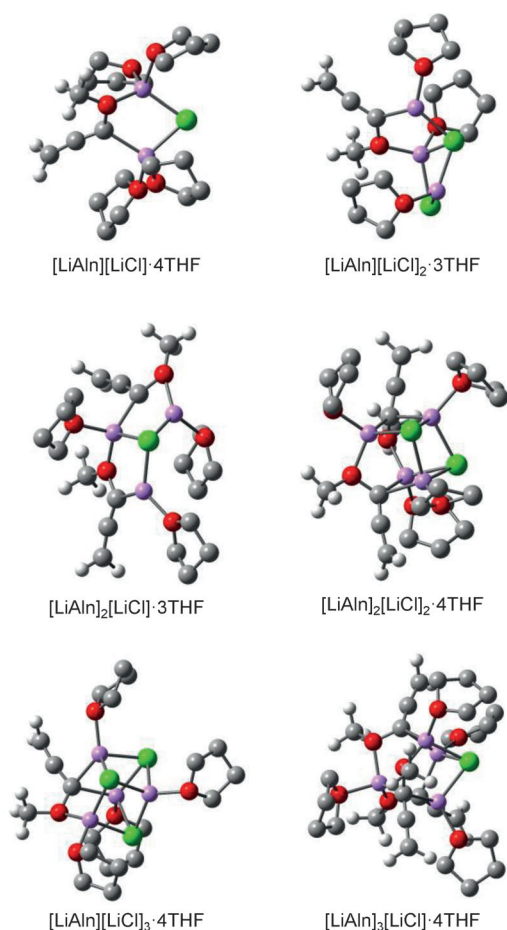
Figure 3. MP2-optimized geometries of THF-solvated 1-methoxyallenyllithium mixed aggregates with lithium chloride. Grey: Carbon; White: Hydrogen; Red: Oxygen; Violet: Lithium; Green: Chlorine.

$$\frac{1}{2}[\text{LiAln}]_2 \cdot 4\,\text{THF} + \frac{1}{2}[\text{LiCl}]_2 \cdot 4\,\text{THF}$$
$$\rightarrow [\text{LiAln}][\text{LiCl}] \cdot 4\,\text{THF} \tag{4}$$

$$\frac{1}{2}[\text{LiAln}]_2 \cdot 4\,\text{THF} + [\text{LiCl}]_2 \cdot 4\,\text{THF}$$
$$\rightarrow [\text{LiAln}][\text{LiCl}] \cdot 4\,\text{THF} + 2\,\text{THF} \tag{5}$$

$$[\text{LiAln}]_2 \cdot 4\,\text{THF} + \frac{1}{2}[\text{LiCl}]_2 \cdot 4\,\text{THF}$$
$$\rightarrow [\text{LiAln}][\text{LiCl}] \cdot 4\,\text{THF} + 2\,\text{THF} \tag{6}$$

$$[\text{LiAln}]_2 \cdot 4\,\text{THF} + [\text{LiCl}]_2 \cdot 4\,\text{THF}$$
$$\rightarrow [\text{LiAln}]_2[\text{LiCl}]_2 \cdot 4\,\text{THF} + 4\,\text{THF} \tag{7}$$

$$\frac{1}{2}[\text{LiAln}]_2 \cdot 4\,\text{THF} + \frac{3}{2}[\text{LiCl}]_2 \cdot 4\,\text{THF}$$
$$\rightarrow [\text{LiAln}][\text{LiCl}]_3 \cdot 4\,\text{THF} + 4\,\text{THF} \tag{8}$$

$$\frac{3}{2}[\text{LiAln}]_2 \cdot 4\,\text{THF} + \frac{1}{2}[\text{LiCl}]_2 \cdot 4\,\text{THF}$$
$$\rightarrow [\text{LiAln}]_3[\text{LiCl}] \cdot 4\,\text{THF} + 4\,\text{THF} \tag{9}$$

$$2[\text{LiAln}][\text{LiCl}] \cdot 4\,\text{THF}$$
$$\rightarrow [\text{LiAln}]_2[\text{LiCl}]_2 \cdot 4\,\text{THF} + 4\,\text{THF} \tag{10}$$

$$[\text{LiAln}][\text{LiCl}] \cdot 4\,\text{THF} + [\text{LiCl}]_2 \cdot 4\,\text{THF}$$
$$\rightarrow [\text{LiAln}][\text{LiCl}]_3 \cdot 4\,\text{THF} + 4\,\text{THF} \tag{11}$$

$$[\text{LiAln}][\text{LiCl}] \cdot 4\,\text{THF} + [\text{LiAln}]_2 \cdot 4\,\text{THF}$$
$$\rightarrow [\text{LiAln}]_3[\text{LiCl}] \cdot 4\,\text{THF} + 4\,\text{THF} \tag{12}$$
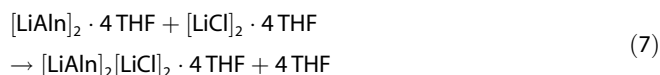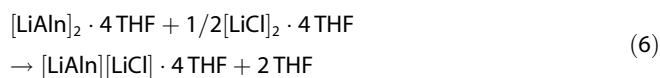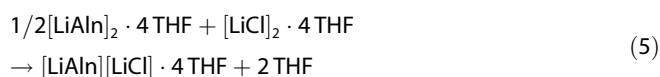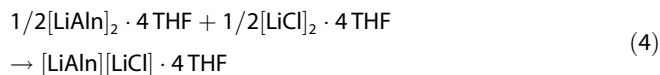
The data in Tables 4 and 5 show a significant disagreement between the B3LYP and MP2-calculated free energies of mixed aggregate formation, with the former method predicting a greater tendency toward mixed aggregate formation. The two methods differ in the inclusion of electron correlation, as B3LYP (as well as other DFT methods) includes it implicitly, while MP2 is based on perturbation theory. The MP2 calculations predict a modest tendency toward formation of the mixed dimer, with little tendency to form the mixed trimers. The data in Table 6 predicts mixed tetramers to form at the B3LYP level, but the mixed dimer was predicted to be favored at the MP2 level. The calculations predict that mixed aggregates will be formed, but since neither computational method is perfect, it isn't possible to say for certain which mixed aggregates predominate from the free energies of formation alone.

Table 7 shows the calculated ^{13}C NMR chemical shifts for the 1-methoxyallenyllithium dimers, tetramer, and its mixed aggregates with lithium chloride. The NMR spectrum of 1-methoxyallenyllithium without lithium chloride is shown in Figure 4a,

Table 7. Calculated ^{13}C NMR chemical shifts (B3LYP/6-31+G(d)) of THF-solvated 1-methoxyallenyllithium and its mixed aggregates with lithium chloride.

Aggregate	δ [ppm] (relative to TMS)			
	C1	C2	C3	Methoxy
LiAln dimer 1	153.7	193.5	67.4	57.3
LiAln dimer 2	152.0	190.9	67.2	58.3
LiAln tetramer	147.9	194.7	72.1	59.1
[LiAln][LiCl]	151.0	194.6	68.6	57.6
[LiAln][LiCl]$_2$	148.0	195.0	69.1	57.0
[LiAln]$_2$[LiCl]	144.2, 148.0	192.0, 196.5	71.8, 67.8	58.6, 58.0
[LiAln]$_2$[LiCl]$_2$	145.3	190.3	70.8	58.3
[LiAln][LiCl]$_3$	146.4	192.4	71.8	57.5
[LiAln]$_3$[LiCl]	147.6	192.7	68.6	57.8

and with 0.3 and 1.0 equivalent lithium chloride in Figures 4b and 4c, respectively. As we previously reported,[18] C1 at about 154 ppm and C2 at about 193 ppm give the most information about the aggregation state. The predominant species seen in Figure 4a is the 1-methoxyallenyllithium dimer 1, with smaller amounts of the tetramer, resonating downfield of the dimer (C1) and upfield of the dimer (C2). The small peak upfield of the C2 dimer 1 peak is consistent with a small amount of the second dimer described previously.[18]

The calculated chemical shifts of the 1-methoxyallenyllithium–lithium chloride mixed dimer are very close to those of the major homo-dimer from ref. [18] (dimer 1). The chemical shift of the mixed dimer's C2 is calculated to be slightly upfield of that of dimer 1, and a partially overlapping peak, slightly up-
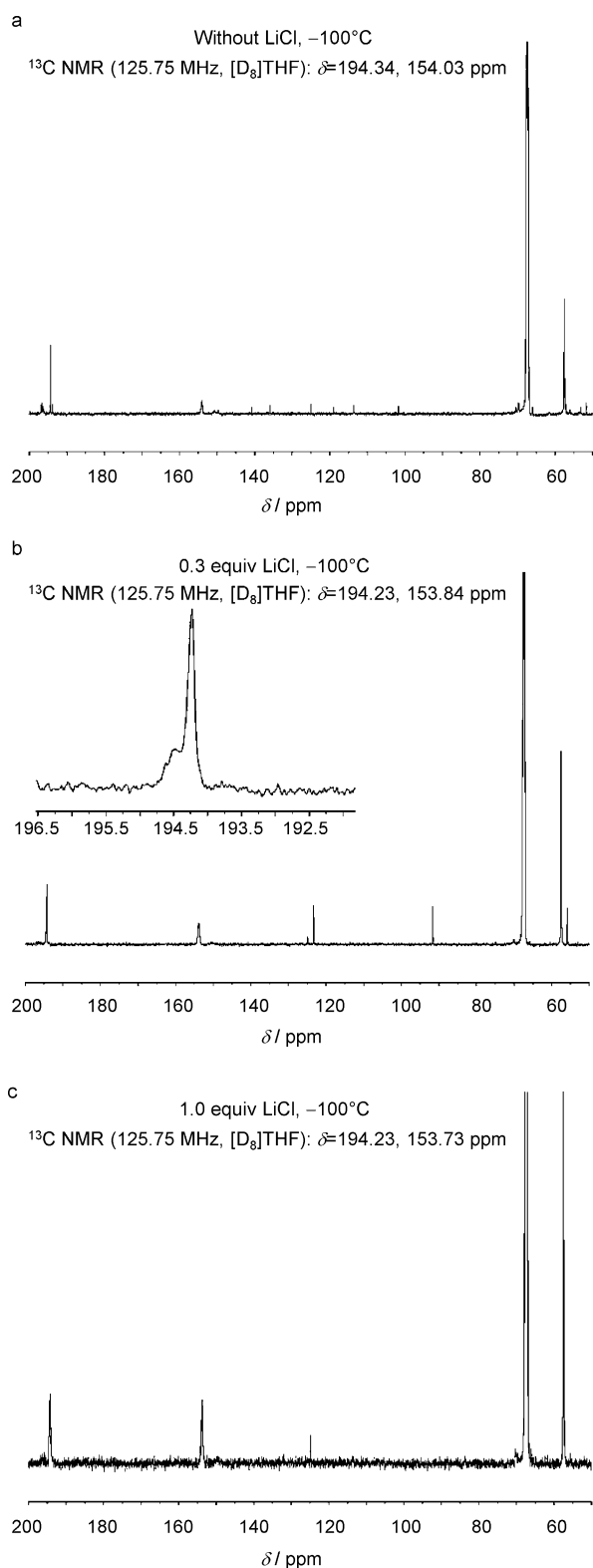
Figure 4. ^{13}C NMR spectrum of 1-methoxyallenyllithium a) without lithium chloride at $-100\,°C$. ^{13}C NMR (125.75 MHz, [D$_8$]THF): $\delta = 194.34$, 154.03 ppm; b) with 0.3 equiv lithium chloride at $-100\,°C$. ^{13}C NMR (125.75 MHz, [D$_8$]THF): $\delta = 194.23$, 153.84 ppm; c) with 1.0 equiv lithium chloride at $-100\,°C$. ^{13}C NMR (125.75 MHz, [D$_8$]THF): $\delta = 194.23$, 153.73 ppm.

field of the homo-dimer, was observed with 0.3 equivalents of lithium chloride, shown in Figure 4b. The expansion of the

region of the C2 peak clearly shows a second species. The peak corresponding to C1 was broadened from 53.8 Hz to 60.1 Hz at $^{1}/_{2}$ height with 0.3 equivalents lithium chloride, suggesting that the peaks are not fully resolved. With 1.0 equivalent lithium chloride, shown in Figure 4c, the spectrum is consistent with a single major species, and the C1 peak was narrowed to 42.8 Hz. Small peaks are visible in both spectra that may arise from small amounts of the 1-methoxyallenyllithium tetramer. Those peaks are also consistent with small amounts of higher mixed aggregates. From the relative peak sizes of C1 and C2, the relaxation time of C1 decreases with increasing lithium chloride concentration. This is further evidence of a change in the chemical environment about C1. From comparison of the observed and calculated chemical shifts, mixed trimers and tetramers are not major species in solution. Thus, the predictions of the MP2 free energies of mixed aggregate formation appear to be more reliable than B3LYP for this particular system.

Conclusions

The calculated free energies of mixed aggregate formation at the B3LYP/6-31+G(d) and MP2/6-31+G(d) levels of theory predict 1-methoxyallenyllithium to form mixed aggregates with lithium chloride. The two methods generated different predictions of which mixed aggregates will be formed, with the former favoring mixed trimers and tetramers in THF solution, and the latter favoring mixed dimers. Mixed dimer formation is consistent with the calculated and observed ^{13}C NMR chemical shifts. Formation of the sterically unhindered mixed dimers is also consistent with the enhanced reactivity of these compounds in the presence of lithium chloride, as was described in the introduction. The spectra are also consistent with some residual 1-methoxyallenyllithium tetramer, as well as small amounts of higher mixed aggregates. Although neither computational method is perfect, the MP2-calculated free energies are in better agreement with experiment than the B3LYP energies for this particular system.

Experimental Section

The ^{13}C NMR spectra in [D$_8$]THF were recorded on a Varian Unity Inova 500 (Varian, Palo Alto, USA) at 173, 193, 223, and 243 K at 125.75 MHz with a 3 s delay between pulses. Since no new features were observed at the higher temperatures, only the spectra acquired at 173 K were reported. All spectra were broadband decoupled.

Preparation of 1-methoxyallenyllithium in [D$_8$]THF: An oven-dried NMR tube was charged with methoxyallene (50 mg, 0.71 mmol) under nitrogen. [D$_8$]THF (750 µL) was added by syringe through a septum, and the solution was cooled to $-78\,°C$. A 2.46 M solution of *n*-BuLi in hexanes (0.35 mL, 1.2 equiv) was added, and the solution was left standing at $-78\,°C$ for 15 min. The total concentration of 1-methoxyallenyllithium was 0.65 M. The solution was then frozen in liquid nitrogen, and the NMR tube was flame-sealed.

Preparation of 1-methoxyallenyllithium in [D₈]THF with 0.3 equiv of LiCl: An oven-dried NMR tube was charged with methoxyallene (39 mg, 0.56 mmol) under nitrogen. LiCl in [D₈]THF (0.38 mL of a solution of 17.2 mg in 0.95 mL) was added by syringe through a septum, and the solution was cooled to −78 °C. A 2.76 M solution of n-BuLi in hexanes (0.24 mL, 1.2 equiv) was added, and the solution was left standing at −78 °C for 15 min. The total concentration of 1-methoxyallenyllithium was 0.90 M. The solution was then frozen in liquid nitrogen, and the NMR tube was flame-sealed.

Preparation of 1-methoxyallenyllithium in [D₈]THF with 1.0 equiv of LiCl: An oven dried NMR tube was charged with methoxyallene (37 mg, 0.53 mmol) under nitrogen. LiCl in [D₈]THF (0.59 mL of a solution of 36 mg in 0.95 mL) was added by syringe through a septum, and the solution was cooled to −78 °C. A 2.76 M solution of n-BuLi in hexanes (0.25 mL, 1.3 equiv) was added, and the solution was left standing at −78 °C for 15 min. The total concentration of 1-methoxyallenyllithium was 0.63 M. The solution was then frozen in liquid nitrogen, and the NMR tube was flame-sealed.

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