Chelated Aryllithium Reagents: Ring Size and Chelating Group Effects
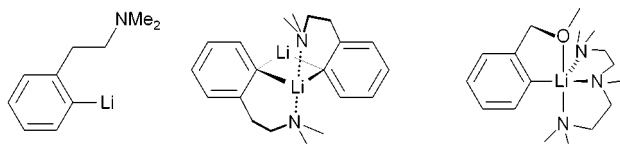
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ABSTRACT

Chelation and aggregation in phenyllithium reagents with potential 5-, 6-, and 7-ring chelating ether and amine ortho substituents have been examined utilizing variable-temperature ^6Li and ^{13}C NMR spectroscopy, ^6Li and ^{15}N isotope labeling, and the effects of solvent additives. Both ether and amine form strong 5-ring chelates; 6-ring ether chelates compete well with THF, but 6-ring amine chelates barely do, and 7-ring amine chelates do not. *o*-Methoxymethylphenyllithium (4) forms an open dimer (9) and a pentacoordinate monomer with PMDTA (10).

Chelation effects are widely used in organolithium chemistry to provide rationales for numerous stereochemical, regio-chemical, and reactivity effects and as a design element to facilitate metalations and increase structural rigidity.[1a,2a,3,4] Recent work has provided substantial insights into the consequences of chelation,[1b,2b,c,5a−e,6a,7−9] but these applications are still hampered by a lack of knowledge about the strength and even the occurrence of chelation. Although it is clear that organolithium reagents with pendant alkoxy and amino groups are often chelated under poorly solvated or solvent-free conditions (e.g., from X-ray crystal structures[10]), it is less clear whether chelating groups can compete with ethereal solvents such as THF.[5e,11]

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We have previously reported on the solution properties of several chelated alkyllithium reagents[5b−d] and the 5-ring chelate 2-(dimethylaminomethyl)phenyllithium (**1**).[5a] Here we describe work that compares the latter with its 6-and 7-ring homologues **2** and **3**, as well as with its 5-, 6- and 7-membered oxygen chelate analogues **4**, **5**, and **6** (Figure 1). Compound **1**[5a] shows unambiguous evidence of chelation
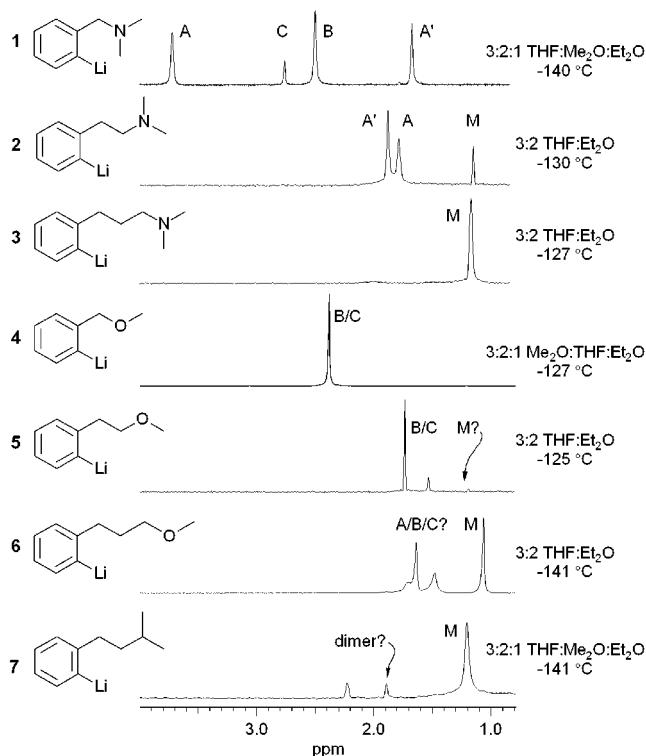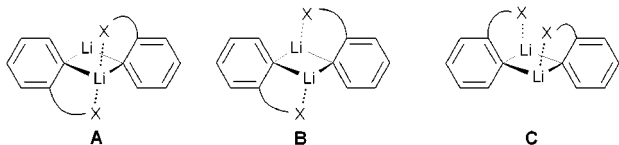
Figure 1. [6]Li NMR spectra of lithium reagents **1−7** (M = monomer, for **A/B/C** see Scheme 1).

under all conditions examined. The chelation isomers **A**, **B** and **C** were identified (Scheme 1, Figure 1). The compound

Scheme 1

shows a strong propensity to dimerize compared to models such as phenyllithium,[5f] o-tolyllithium, or **7** (Table 1). The dimers are not broken up by either TMEDA (*N,N,N′,N′*-tetramethylethylenediamine) or PMDTA (*N,N,N′,N″,N″*-pentamethyldiethylenetriamine). Both complex to **1-A** in a bidentate fashion.

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Table 1. Thermodynamic and Kinetic Data for Chelated Aryllithiums and Model Compounds

$$K_{eq} = \frac{k_{MD}}{k_{DM}} = \frac{[D]}{[M]^2} \quad \text{Eq. 1}$$

	R	K_{eq} (M^{-1})	$\Delta G°$ [a]	T (°C)	$\Delta G^{‡}$ [a]	T (°C)
	−H	40	−1.5	−75[b]	8.3[g]	−101[b]
	−CH$_3$	1.7	−0.2	−135[c]		
7	−CH$_2$CH$_2$CHMe$_2$	<0.23	≥0.6	−125[e]		
1	−CH$_2$NMe$_2$	>17 000	≤−2.6	−131[e]	>12.5[h,i]	−36[e]
2	−(CH$_2$)$_2$NMe$_2$	200	−1.3	−145[d]	9.3[j]	−103[d]
3	−(CH$_2$)$_3$NMe$_2$	<0.23	≥0.6	−130[d]		
4	−CH$_2$OMe	>15 000	≤−2.7	−133[e]	≥9.5[h]	−80[f]
5	−(CH$_2$)$_2$OMe	≥6 000	≤−2.5	−130[e]	10.5[j]	−95[e]
6	−(CH$_2$)$_3$OMe	12	−0.7	−141[e]	8.9[j]	−101[d]

[a] Free energies in kcal/mol for k_{DM}. [b] THF. [c] 4:1 THF/Et$_2$O. [d] 3:2:1 THF/Me$_2$O/Et$_2$O. [e] 3:2 THF/Et$_2$O. [f] 3:2:1 Me$_2$O/THF/Et$_2$O. [g] Reference 5f. [h] Coalescence of the 1:2:3:2:1 quintet of the C−Li carbon. [i] The rate is bimolecular. [j] Exchange of monomer and dimer signals in [6]Li NMR spectrum.

The [6]Li NMR spectra of the homologue of **1**, compound **2**, displayed three signals (Figure 2a). The two downfield
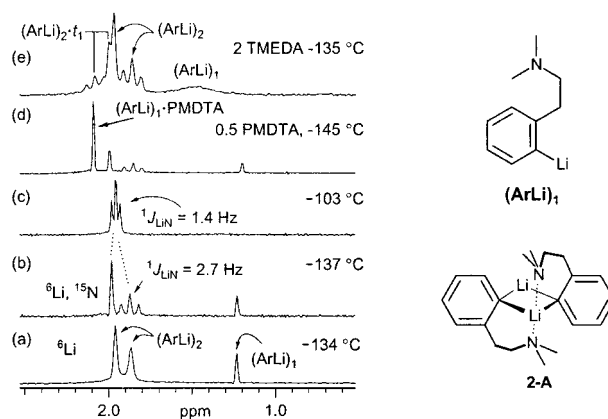
Figure 2. [6]Li NMR spectra of **2** in 3:2 THF/ether (a) and 3:2:1 THF/Me$_2$O/Et$_2$O (b and c), and in the presence of PMDTA (d) and TMEDA (e). Spectra b−e are of [15]N−[6]Li doubly labeled material (t = TMEDA).

signals were present in a 1:1 ratio at all concentrations, suggestive of a dimer of the **A** type. This assignment, and the identification of the third signal at δ 1.23 as a monomer, was supported by the concentration dependence of the signals[12] and the ^{13}C NMR properties (Table 2). Compound **2** is much less strongly chelated than **1**, but substantially more so than the model **7** (factor of >800 in K_{eq}).

A most interesting insight was obtained from examination of ^{15}N, [6]Li double-labeled **2** (Figure 2b−e). The [6]Li NMR signal at δ 1.23 for the monomer showed no sign of Li−N

(12) A plot of log[monomer] vs log[dimer] showed a slope of 2.1 ± 0.3 and intercept (log(K_{eq})) of 2.4 ± 0.6.

Table 2. Key ^{13}C NMR Chemical Shifts and C−Li Coupling of Aryllithium Reagents

	solvent	T (°C)	C-1	C-2	C-6	J_{CLi} (^{6}Li)
(PhLi)$_4$[a]	b	−106	174.0	143.8	143.8	5.1
(PhLi)$_2$[a]	c	−111	188.2	144.5	144.5	7.9[g]
(PhLi)$_1$[a]	c	−111	196.4	143.2	143.2	15.3[h]
(7)$_1$	d	−126	195.2	153.6	142.5	15.2[h]
(1)$_2$ (A)	e	−132	188.8	152.2	143.5	7.0[g]
(2)$_1$	e	−130	195.9	154.2	142.5	12[h]
(2)$_2$ (A)	e	−130	184.3	152.4	144.1	7[g]
(3)$_1$	f	−127	195.5	153.2	142.4	15[h]
(3)$_1$APMDTA	f	−127	195.8	152.5	142.2	13.3[h]
(4)$_2$	f	−127	186.1	149.7	143.1	8.1[g]
(4)$_1$APMDTA	e	−127	195.8	148.4	142.6	17[h]
(5)$_2$	f	−123	188.2	152.4	143.3	8.1[g]
(5)$_1$APMDTA	e	−147	197.0	148.0	142.1	14.8[h]
(6)$_2$	f	−118	187.9	153.0	144.2	
(6)$_1$	f	−125	195.6	152.9	142.5	15[h]

[a] Data from ref 5f. [b] Et$_2$O. [c] THF. [d] 45:25:30 THF/Me$_2$O/Et$_2$O. [e] 3:2:1 THF/Me$_2$O/ether. [f] 3:2 THF/ether. [g] 1:2:3:2:1 quintet. [h] 1:1:1 triplet.

coupling, *so the monomeric structure is unchelated*. One of the signals for the dimer, however, was split into a 1:2:1 triplet (Figure 2b), showing that *the dimer is chelated* as a type **A** structure. Thus, there is a direct relationship between chelation and aggregation.

The two dimer signals coalesced to a 1:2:1 triplet ($J_{Li−N}$ = 1.4 Hz) above −125 °C, when lithium-to-lithium migration of the dimethylamino groups became fast on the NMR time scale (Figure 2c). At higher temperatures intermolecular exchange averages the Li−N coupling as well as the monomer and dimer signals.

Taking into account the absence of other signals and the maximum ^{6}Li−^{15}N coupling possible in the monomer, we estimate that the fraction of chelated monomer is less than 15% and that of unchelated dimer is less than 2%. Thus, the association constant at −137 °C is <12 M$^{−1}$ for the unchelated monomer with unchelated dimer (undetected), and >24 000 M$^{−1}$ for the chelated monomer (undetected) with chelated dimer, a change by a factor of at least 1000.[13]

The addition of TMEDA to solutions of **2** produced TMEDA complexes of both the chelated **A**-dimer and unchelated monomer.[14] The fraction of monomer increased as TMEDA was added; K_{eq} was reduced from 200 M$^{−1}$ to 41 M$^{−1}$ at 6 equiv of TMEDA. PMDTA almost quantitatively forms a 1:1 complex with no detectable Li−N coupling in the ^{6}Li NMR spectra (Figure 2d), and with spectral properties nearly identical to the PMDTA complexes of PhLi,[15] mesityllithium,[6b,c] and **7**. Therefore, the complex is not chelated.

The next homolog, **3**, is unambiguously monomeric (^{13}C of C−Li: δ 195.5, 1:1:1 triplet, $^1J_{C−Li}$ = 15 Hz). There is at

(13) These estimates are based on the assumption that either the unchelated and chelated isomers are in fast equilibrium on the NMR time scale, or they are in slow equilibrium with the peaks in an unobscured part of the spectrum.

(14) At the low temperatures (←150 °C) required to slow intermolecular exchange of TMEDA in the monomer, the signals were sufficiently broad that a small coupling would not have been resolved.

(15) Schümann, U.; Kopf, J.; Weiss, E.; *Angew. Chem.* **1985**, *97*, 222; *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 215−216.

most a trace of dimer, and no indication of chelation in the ^{15}N,^{6}Li-labeled isotopomer, demonstrating that a 7-ring chelate does not compete with solvation by THF.

It was much harder to obtain detailed information about the solution structure of the ether analogues **4**, **5**, and **6**, since chelation could not be detected by Li coupling. Thus, we relied more on aggregation levels and interaction with cosolvents for indirect information. Compound **4** appears to be a single species in THF, giving one peak in the ^{6}Li NMR spectra and one set of peaks in the ^{13}C NMR spectra at temperatures down to −140 °C (Figure 3a). The ^{13}C chemical
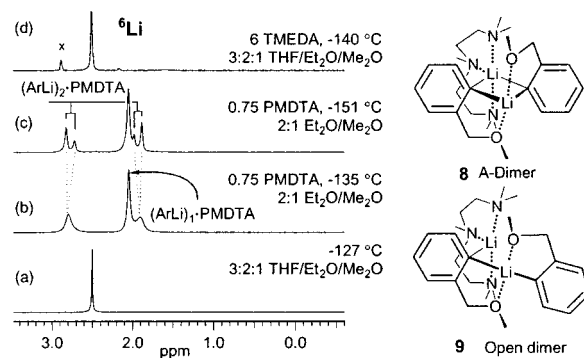

Figure 3. ^{6}Li NMR spectra of **4**: (a) in 3:2:1 THF/Me$_2$O/Et$_2$O at −127 °C; (b) with 0.75 equiv of PMDTA at −150 °C; (c) in 2:1 Et$_2$O/Me$_2$O with 0.75 equiv of PMDTA at −151 °C; (d) in 3:2:1 THF/Me$_2$O/Et$_2$O with 6 equiv of TMEDA at −140 °C.

shift of C−Li (186.1 ppm) and the carbon−lithium coupling strongly suggest a dimeric structure, although higher cyclic aggregates are possible. Our inability to detect any chelation isomers for **4** like the **A**, **B**, **C** isomers found for **1** does not mean that there is only one isomer. In fact, the absence of any diastereotopic nonequivalence in the CH$_2$OMe protons (4.70 ppm) even at −140 °C implies that equilibration is occurring among the various coordination sites much more rapidly than occurs with **1**, so lithium-to-lithium migration of methoxy is kinetically more facile than for dimethylamino groups.

There is no detectable complexation of **4** with TMEDA, so little or none of the **A** chelation isomer is present (Figure 3d). The interaction with PMDTA is complex. The spectroscopic details are only apparent at very low temperatures (Figure 3b,c). Two new species are formed as PMDTA was added. Both are examples of rare structural types in organolithium chemistry. The first to appear gives a 1:1 ratio of peaks in the ^{6}Li NMR spectra (Figure 3b). The six carbon signals are also doubled. These data suggest structures such as an **A** type dimer (**8**) or an open dimer (**9**).[16a,17] The data

(16) (a) Romesberg, F. E.; Gilchrist, J. H.; Harrison, A. T.; Fuller, D. J.; Collum, D. B. *J. Am. Chem. Soc.* **1991**, *113*, 5751. (b) Lucht, B. L.; Bernstein, M. P.; Remenar, J. F.; Collum, D. B. *J. Am. Chem. Soc.* **1996**, *118*, 10707−10718.

(17) Williard, P. G.; Liu, Q.-Y. *J. Am. Chem. Soc.* **1993**, *115*, 3380−3381.

best fits the latter, since the two signals of the ipso carbon appear at δ 193.2 (distorted 1:1:1 triplet) and δ 188.2 (coupling unresolved), quite close to the PMDTA-monomer signal at δ 195.8 and the THF-dimer signal at 186.0 ppm.

There is one additional complication in the NMR spectra of **9**. Below -145 °C, each of the two lithium signals decoalesced to a ca. 2:1 ratio of signals (Figure 3b−c). We propose that this decoalescence (with $\Delta G^{\ddagger}_{-131}$ = 7.4 kcal/mol) is the result of a dynamic conformational or configurational process which becomes slow on the NMR time scale.

The second species to appear in the PMDTA titration of **4** gives a singlet at δ 2.04 (70% at 1 equiv of PMDTA, 91% at 3 equiv). The C−Li carbon chemical shift (δ 195.8) and coupling is consistent only with a monomeric structure. The ^{13}C NMR spectroscopic behavior is different than that observed for other monomeric PMDTA complexes. For example, mesityllithium·PMDTA[6b] shows 9 signals for the PMDTA ligand at temperatures as high as -70 °C, whereas **4**·PMDTA shows broadened peaks for the bound PMDTA carbons (6 peaks visible) at -150 °C. These first coalesce to 5 signals at ca. -140 °C (symmetrization of the PMDTA ligand), and then coalesce with those of free PMDTA at ca. -110 °C. The substantially weaker complexation of PMDTA to **4** compared to the much more hindered mesityllithium (and equally or more hindered **2**, **7**, and **5**) shows that the methoxy group must be chelated, giving a rare structure with pentacoordinate lithium (**10**).
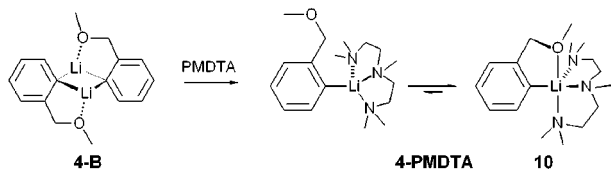
The homologue of **4**, compound **5**, behaves quite differently. Two sets of signals in a 4:1 ratio were observed in the ^{6}Li and ^{13}C NMR spectra, and this ratio was concentration independent. The two signals coalesced at -110 °C. We were unable to resolve the C−Li coupling, but the line shape and ^{13}C chemical shift (188.2 ppm) of the C−Li carbon are very similar to those observed for other dimers (Table 2). We conclude that **5** is a mixture of two dimers, probably of the **B/C** type. A small signal at δ 1.2 could correspond to a monomer (^{13}C signals were not detected). It coalesced with the dimer signals around -80 °C. If this assignment is correct, then the monomer−dimer association K_{eq} is 6000 M^{-1} at -130 °C (3:2 THF/ether), at least 4 orders of magnitude higher than the model system, and 2 orders of magnitude higher than the amine analogue **2**.

Significant concentration of **A**-dimer was not present since addition of up to 8 equiv of TMEDA to **5** gave at most a trace of a type **A** complex. PMDTA formed a monomeric complex in a nearly stoichiometric fashion, with ca. 94% conversion to a complex at 1 equiv. of PMDTA, and >98% at 2 equiv. This complex showed none of the peculiarities of **4**·PMDTA, and so we conclude that it is not chelated.

We have also examined the potentially 7-ring chelated ether **6**. The ^{6}Li (Figure 1) and ^{13}C NMR spectra at -141

°C show a monomer as a prominent species (ca 34% of total 0.24 M in 3:2 THF/ether, K_{eq} = 12). In the ^{6}Li NMR spectra three additional signals were present at -141 °C. Two of these (2:1 ratio) coalesced at -135 °C, and the two remaining signals then coalesced at -120 °C. These signals were assigned to dimers from analysis of variable concentration experiments, and from the characteristic ^{13}C line shape and chemical shifts of the C−Li carbons (187.5 and 188.0 ppm). The addition of PMDTA converted all signals in the ^{6}Li and ^{13}C NMR spectra into signals of monomeric **3**·PMDTA. Thus **6** is more aggregated and probably more strongly chelated than **7**, **2**, or **3**, but less so than **1**, **4**, or **5**.

The spectroscopic data on the series of lithium reagents provide some insights into the relative strength of the chelation as a function of ring size.[10a] Particularly instructive is the behavior with PMDTA. The PMDTA complexes of the monomers **2** to **6** must be tridentate, since TMEDA[18] only minimally increases the fraction of monomers. If we make the assumption that chelation is broken in the monomeric PMDTA complexes (probably not true for **4**·PMDTA), then the fraction of such species formed provides a qualitative measure of the strength of chelation since steric effects should be similar. The nonchelating model **7** as well as **2**, **3**, and **6** show >98% conversion to the complex with one equiv of PMDTA. Some chelation effects are evident for **5**, which forms 94% monomeric complex, and **4**, which is ca. 70% converted to monomer.[9] The strongest effect is shown by **1**, which forms little or no monomer on addition of PMDTA.[5a] The sequence of chelation strength derived from this behavior is: **1** ≫ **4** > **5** > **2**, **6**, **3**, **7**.

The strength of dimerization appears to be in the same sequence, judging from those monomer−dimer K_{eq} values which we have been able to measure or estimate directly (Table 1): **1** ≥ **4** > **5** > **2** > **6** > **3**, **7**. A similar order is also found for the kinetic stability of those dimers for which DNMR techniques could be used to measure rates (Table 1). Here we find that $\Delta G^{\ddagger}$ is in the order **1** > **5** ≥ **4** > **2** > **6** > PhLi.

In summary, for these systems amine chelation is strong in 5-membered rings, competitive with THF solvent in 6-membered rings, and absent in 7-membered rings. Ether chelation is of intermediate strength in both 5- and 6-membered rings, with the 5-membered ring chelate slightly more robust by some criteria, and the 6-ring by others.[9] The 7-ring ether is presumably weakly chelated, but the only indication is excess dimerization. There is a strong qualitative correlation between the strength of the chelation (as judged by the effect of PMDTA) and the strength of the aggregation (as judged by response to polar cosolvents, magnitude of monomer−dimer K_{eq}, and rates of monomer−dimer equilibration).

(18) PMDTA complexes monomers more strongly than does TMEDA.[6c,16b] However, in the specific case of **1**, TMEDA complexes the dimer more strongly than does PMDTA.[5a]