Solution and Solid-State Structures of Lithiated Phenyloxazolines

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The structures of three *ortho*-lithiated phenyloxazolines, the parent (**1**), the *para-tert*-butyl analogue (**2**), and the *para*-chloro analogue (**3**), were studied in solution. All three compounds are mixtures of monomers and dimers in THF/ether mixed solvents, with **2** the most aggregated and **3** the least. They are converted to monomers with HMPA and PMDTA. In the PMDTA complexes, the lithium appears to still be chelated to the oxazoline ring. Single-crystal X-ray structures were obtained for **1** and **2**. Both are centrosymmetric dimers of B-type (each lithium coordinated to one oxazoline ring).

Introduction

The oxazoline function has been used extensively for the protection of carboxylic acids against strong bases, as a chelating group for metals in chiral Lewis acid catalysts,[1] in the chiral complexation of organolithium[2] and other organometallic reagents,[3] and as an activating group and chiral auxiliary.[4] The latter applications have allowed the preparation of a variety of aromatic, hydroaromatic, and aliphatic organolithium reagents containing masked carboxylate functions and their use in asymmetric synthesis.[5a]

Although the structures of a variety of oxazoline-chelated metal complexes are known, there was until recently no information about organolithium reagents bearing chelating oxazolines. In this paper we report on the structures of *ortho*-lithio oxazolines **1**−**3** in solution and on **1** and **2** in the solid state. This work continues studies of a series of potentially chelated ArLi reagents with amine and ether *ortho* substituents (e.g., **4**−**7**), which showed that those which could form five- and six-membered chelating groups were chelated and consistently more highly aggregated than those with longer pendant groups (**7**) or nonchelating models (such as **8**).[6a−c]
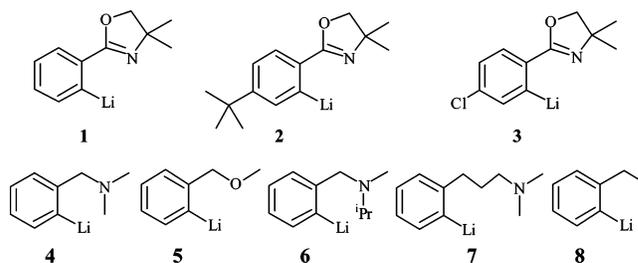
A recent publication by van Koten and co-workers[7] has shed some light on bisoxazolines of the Phebox-Li type. The reagents **9**−**11** are dimeric both in solution (toluene-d_8) and in the solid state. The dimers were not deaggregated by the addition of more polar solvents (e.g., diethyl ether, THF, and triethylamine).
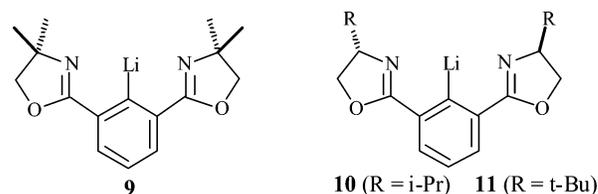
Results and Discussion

The oxazoline precursors for **1**−**3** were prepared by reaction of the appropriate acid chloride with 2-amino-2-methyl-1-propanol, followed by cyclodehydration with thionyl chloride.[5b] The oxazolines were readily *ortho*-metalated in THF using *n*-BuLi,[8] and crystals formed when the solutions were stored at

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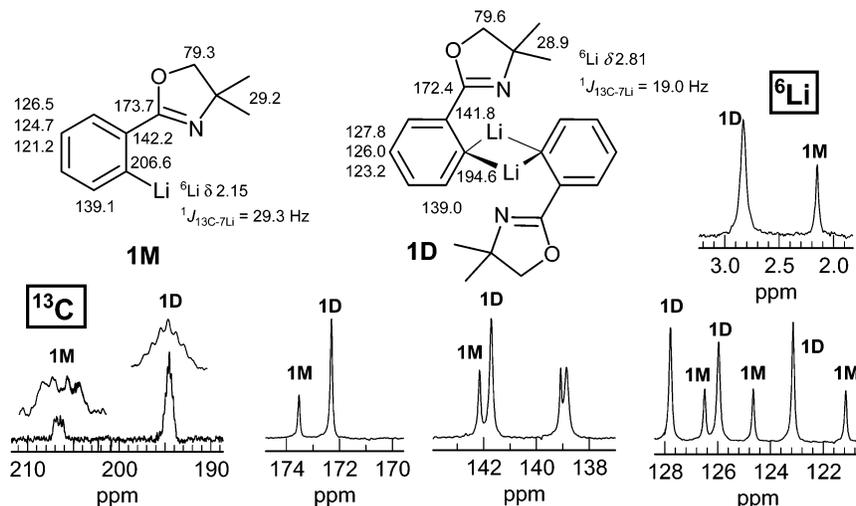
Figure 1. ^{13}C and ^6Li NMR spectra of 0.15 M **1** in 3:2 THF/Et$_2$O at -114 °C. All spectra were measured at natural abundance of lithium and carbon.

-78 °C. Both natural abundance and ^6Li-enriched samples were studied for **1** and **2**; compound **3** was studied only at natural abundance. NMR studies were performed on once or twice recrystallized materials dissolved in THF/ether mixtures or on material prepared by Li/Sn exchange of the *ortho*-trimethyl-stannyl derivatives. Such solutions were often supersaturated at the low temperatures needed for definitive NMR experiments, and slow crystallization of the reagent sometimes interfered with long-term NMR experiments, especially for the poorly soluble **1**.

[2-(4,4-Dimethyl-4,5-dihydrooxazol-2-yl)phenyl]lithium (1). In 3:2 THF/Et$_2$O at -114 °C, **1** exists as a mixture of two species (Figure 1). A signal characteristic of a monomer (1:1:1:1 quartet) was observed for the C–Li carbon in the ^{13}C NMR spectrum at δ 206.6. The poor resolution of the quartet may be due to fast quadrupole-induced relaxation of the ^7Li nucleus;[9a,b] however, the ^6Li-enriched material did not give well-resolved C–Li signals either. Also present was a significant amount of a higher aggregate that appeared as a 1:2:3:4:3:2:1 heptet at δ 194.6. The characteristic splitting pattern and coupling constant are consistent with other aryllithium dimers.[6b–e,10] A downfield shift of the *ipso* carbon on going from dimer to monomer is commonly seen with aryllithium reagents, although the one for **1**, at 12.0 ppm, is a little larger than most.[11] A variable-concentration study using ^6Li NMR spectroscopy gave a slope of 2.3 for a plot of log[dimer] versus log[monomer], which confirmed the dimer assignment. The apparent equilibrium constant, K_{MD} ([**1D**]/[**1M**]^2), was 35 M^{-1} at -114 °C. We have not included solvent molecules in K_{MD} since we do not know the number or even the identity of the coordinating ethers in this mixed solvent.

Solid-State Structure of 1. Single crystals of **1** suitable for structural determination by X-ray diffraction were obtained by slow crystallization from a THF solution. Analysis revealed a
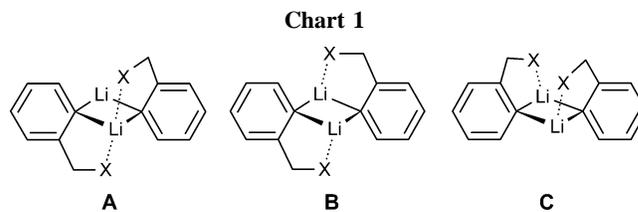
Chart 1

centrosymmetric B-type dimer structure (Chart 1) similar to that obtained for 2-(*N*-methyl-*N*-isopropylaminomethyl)phenyl-lithium (**6**)[6b] and 8-methoxy-1-naphthyllithium,[10b] with one THF molecule *endo*-coordinated to each lithium. While the overall structure type of these molecules is similar, there are some interesting differences.

The C$_2$Li$_2$ core of **1** is centrosymmetric and thus contains only two different C–Li bonds (Figure 2). One bond is part of a five-ring chelate in which the oxazoline nitrogen atom is oriented toward the lithium atom and within bonding distance (2.024(3) Å). This bond (C1–Li1) is a little longer (2.247(3) Å) than the other (C1–Li1A, 2.217(3) Å), which forms a bridge between two monomer units. It is interesting to note that the order of these bond lengths is reversed in **6**, where the longer C–Li bond (2.252(3) vs 2.186(3) Å) bridges the two monomers. The chelate structure of **1** may be considered more compact compared to that of **6** due to the smaller C–Li–N bite angle (84.95(12)° vs 86.39(10)°) and a shorter Li–N bond length (2.024(3) vs 2.139(3) Å). The coplanar position of the nitrogen atom with the phenyl ring in **1** may also play a role.

Another interesting difference between the two molecules is the angle of the planar C$_2$Li$_2$ core relative to the plane of the phenyl rings. In **6**, the C$_2$Li$_2$ core is rotated 20.84(10)° from its position perpendicular to the phenyl rings, a change that brings the chelating nitrogen closer to the lithium. In **1**, the rotation is much larger (46.88(10)°) due to the strong preference for the oxazoline ring to remain conjugated with the phenyl ring, as shown by the C1–C6–C7–N1 dihedral angle of 1.9(3)°. Because the oxazoline nitrogen cannot move from the phenyl plane, the C$_2$Li$_2$ core rotates more from the usually favored perpendicular position to bring the lithium atom in proximity with the nitrogen atom.

The dimer of **9** reported by van Koten and co-workers[7] has a structure where the two oxazoline ligands of each monomer subunit are coordinated to different lithium atoms. This structure is very similar to that observed for **1**. A comparison of the Li–N

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(11) The downfield shift in ppm in the C–Li carbon[9d] on going from dimeric to monomeric aryllithiums is for PhLi (8.2),[6d] 2-(2-dimethylami-noethyl)phenyllithium (11.6),[6c] 2-lithiothiophene (7.3),[6f] and 2-lithio-5-methylselenophene (9.0).[6f]
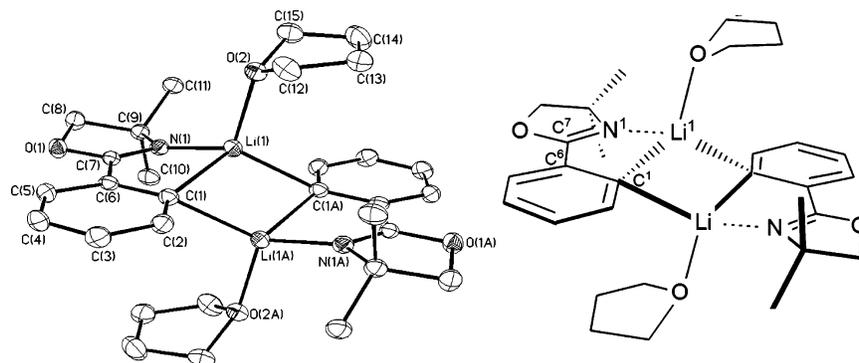
Figure 2. X-ray crystal structure of the THF-solvated, B-type dimer of **1**. Hydrogens are omitted for clarity.
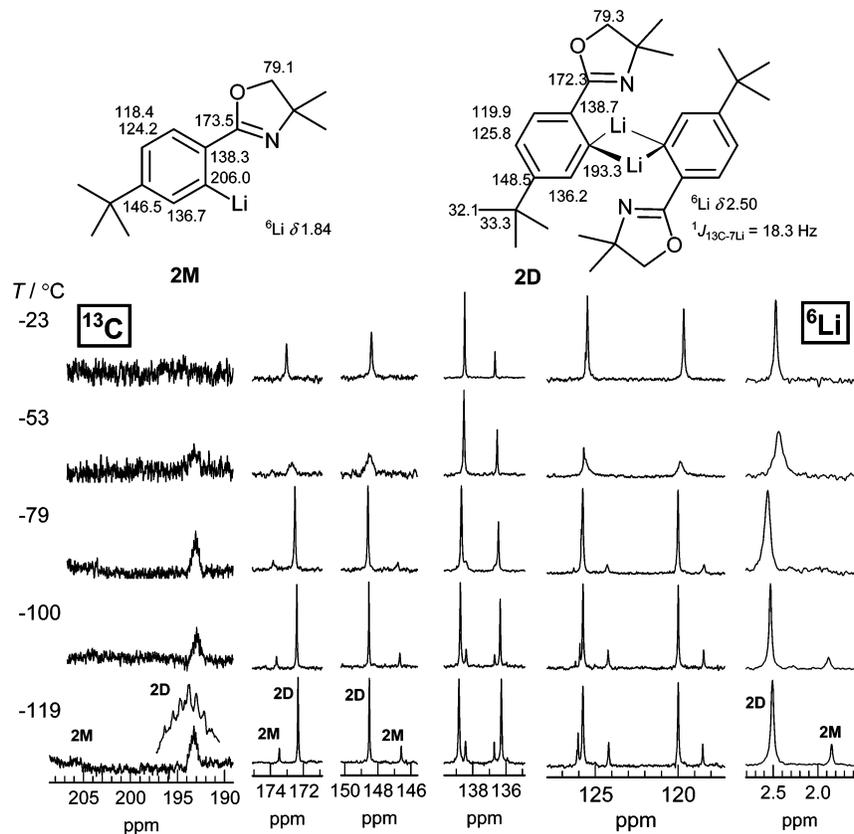

Figure 3. Variable-temperature ^{13}C and ^{6}Li NMR spectra of 0.07 M **2** in 3:2:1 THF/Me$_2$O/Et$_2$O. All spectra were measured at natural abundance lithium and carbon.

bond lengths of **1** (2.024(3) Å) and **9** (1.987(3) to 2.006(3) Å) reveals only a small difference between the two structures. The C−Li bonds of the C$_2$Li$_2$ core of **1** (2.217(3) to 2.247(3) Å) and **9** (2.247(3) to 2.299(3) Å) are also only slightly different.

Previous solution studies of five-ring ether and amine chelates have shown that nitrogen chelation is usually stronger than oxygen chelation.[6a,c,12] In the case of the oxazoline group, chelation could occur to either oxygen or nitrogen. The solid-state structures of **1** and **9** clearly show that imine chelation is favored over ether chelation, and it is reasonable to assume that imine chelation in **1** is also maintained in solution.

5-*tert*-Butyl[2-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)phenyl]-lithium (2). The low solubility of **1** in ethereal solvents made any long-term NMR spectroscopic investigation of solution structure impractical, as crystals often formed even in dilute solutions. Reagent **2** proved to be more amenable for study.

(12) Lucht, B. L.; Bernstein, M. P.; Remenar, J. F.; Collum, D. B. *J. Am. Chem. Soc.* **1996**, *118*, 10707−10718.

The ^{13}C NMR and ^{7}Li NMR spectra of **2** showed two species (Figure 3). A 1:2:3:4:3:2:1 ($^1J_{13C−7Li}$ = 18.3 Hz) heptet was visible at δ 193.3 (a 1:2:3:2:1 pentet is seen for the ^{6}Li-enriched material; see Figure 6). This chemical shift and coupling constant suggest a dimer structure since these values are very similar to those of the **1** dimer (δ 194.6 and $^1J_{13C−7Li}$ = 19.0 Hz). A second set of low-intensity signals (including a signal at δ 206.0 with unresolved lithium−carbon coupling for the *ipso* carbon) was assigned to the monomer. Although the aggregation state of this species could not be directly characterized by observation of appropriate C−Li coupling, the chemical shift difference of 12.7 ppm between the monomer and dimer C−Li signals is nearly identical to that of the better characterized monomers of **1** (12.0 ppm) and **3** (13.0 ppm). A ^{6}Li NMR variable-concentration study gave a log[dimer] versus log-[monomer] plot with a slope of 2.4. Slightly higher values than the theoretical value of 2 expected for the dimer are often seen in such experiments due to a small amount of quenching that
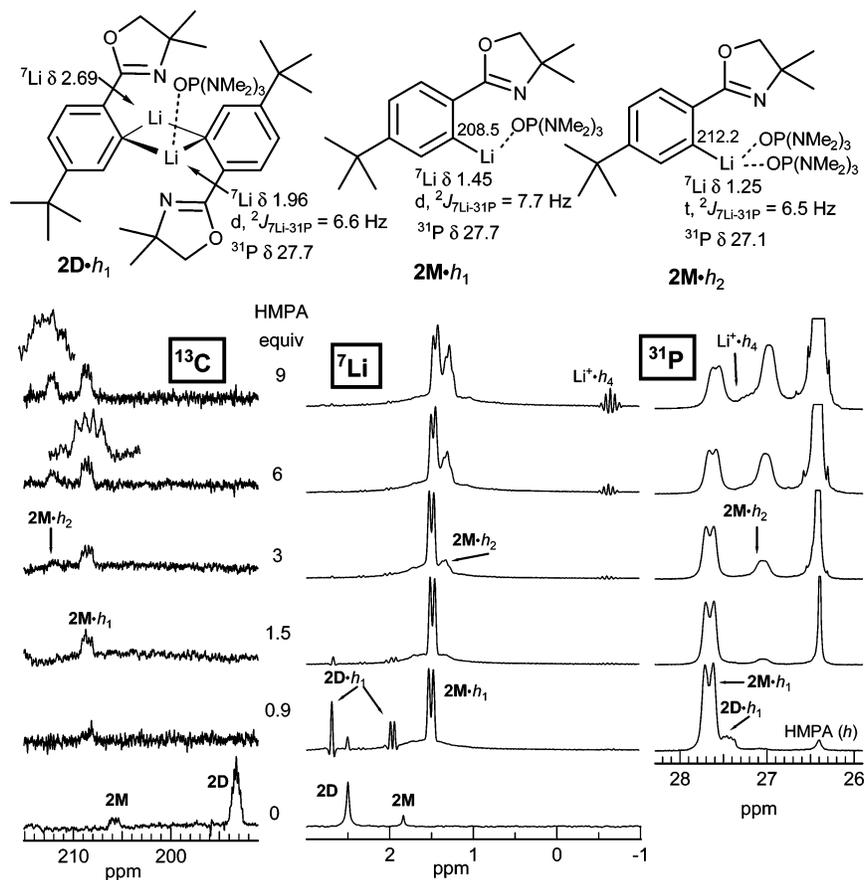
Figure 4. HMPA titration of 0.07 M **2** in 3:2:1 THF/Me$_2$O/Et$_2$O at −139 °C (h = HMPA). The ^{7}Li FIDs were processed with a Gaussian window function to provide enhanced resolution in the ^{7}Li spectra. All spectra were measured at natural abundance lithium, carbon, and phosphorus.
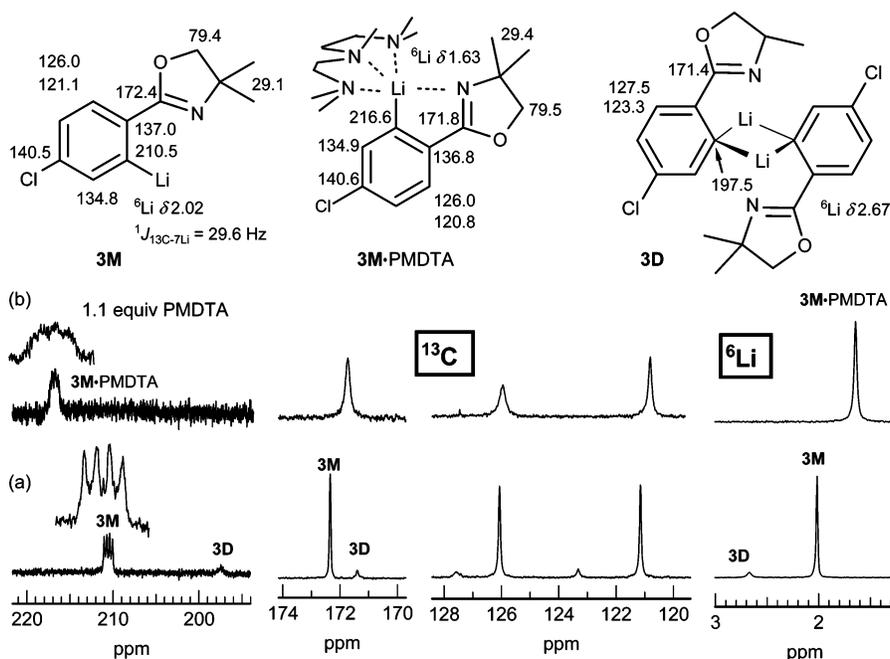

Figure 5. (a) ^{13}C and ^{6}Li NMR spectra of 0.34 M **3** in 3:2 THF/Et$_2$O at −125 °C. (b) Same sample after addition of 1.1 equiv of PMDTA. All spectra were measured at natural abundance lithium and carbon.

can occur during the serial dilutions. It is unlikely that a cyclic trimer, which would also give a heptet, was present considering that **1** is dimeric and the local structure near the carbanion has not changed. The apparent equilibrium constant K_{MD} ([**2D**]/[**2M**]^2) was determined to be 295 M^{-1} at −116 °C in 3:2:1 THF/Me$_2$O/Et$_2$O.

A variable-temperature study of **2** (Figure 3) was consistent with these assignments. At −119 °C signals for dimer and monomer (ca. 5:1 ratio) are resolved for all carbons. At −79 °C the ^{13}C NMR signals of the monomer are significantly broadened, with those at δ 136 and 139, which have the smallest $\Delta\delta$, already near coalescence. Above −79 °C, the dimer signals
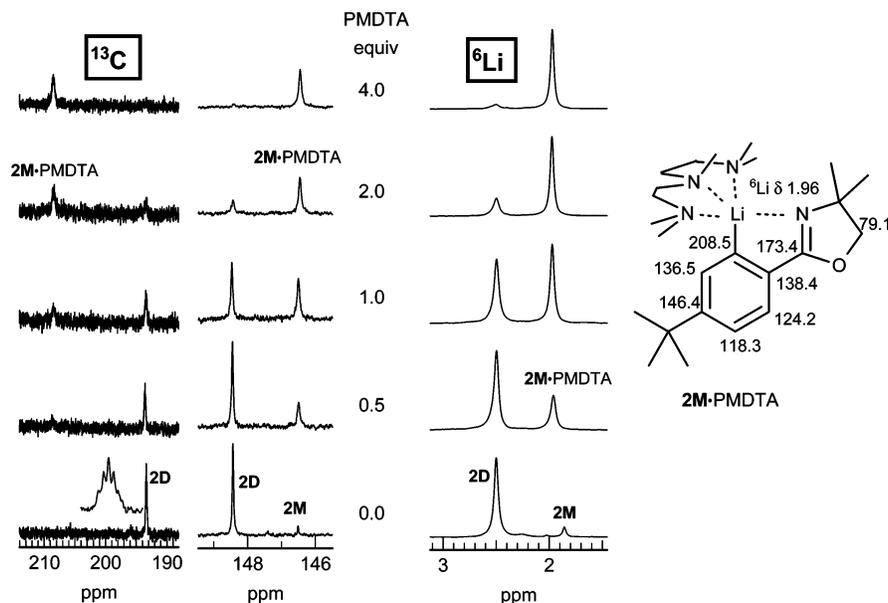
Figure 6. ^{13}C and ^6Li NMR spectra of the PMDTA titration of 0.18 M [^6Li]-**2** in 3:2 THF/Et$_2$O at -117 °C.

at δ 172.3 and 148.3 broaden as coalescence with the monomer occurs, and the signals at δ 138.7 and 136.1 sharpen as they pass through coalescence. At -23 °C, all of the ^{13}C and ^6Li NMR signals, except the C—Li signal, are coalesced due to fast monomer—dimer exchange on the NMR time scale. The low concentration of the monomer relative to the dimer made a determination of the kinetic and thermodynamic properties of the monomer—dimer exchange using DNMR line-shape simulations impractical.

Solid-State Structure of 2. Crystals of **2** suitable for X-ray crystallography were obtained from THF solution.[13] The structure of the B-type dimer that formed is quite similar to that of **1**; however, the C—Li bond lengths show the opposite trend: within the five-ring chelate the C—Li bond length (2.205(3) Å) is slightly shorter than that between the chelated monomers (2.227(3) Å). Although this might suggest that dissociation to dimer would be more favorable than for **1**, the opposite is observed: K_{MD} in **2** (295 M^{-1} at -116 °C) is larger than in **1** (35 M^{-1} at -114 °C).

Interaction of 2 with TMEDA. The TMEDA titration of [^6Li]-**2** resulted in the formation of two new species. The first was assigned as the TMEDA-solvated monomer **2M·TMEDA**. In addition to a 1:1:1 triplet ($^1J_{13C-6Li} = 11$ Hz, corresponding to $^1J_{13C-7Li} = 29$ Hz) at δ 206.8, this species gave a signal δ 138.1 in the ^{13}C NMR spectrum.[13] Both signals are close to those of the THF-solvated monomer. The THF-solvated monomer signals in both the ^{13}C and ^6Li NMR spectra disappeared after addition of 1 equiv of TMEDA. The second species showed an *ipso* carbon signal (δ 194.0) just downfield of the THF-solvated dimer, which has been tentatively assigned as the TMEDA-solvated, A-type dimer, analogous to the one formed by **4**.[6b] The two different ^6Li NMR signals expected for such a species were not identified.

Interaction of 2 with HMPA. The HMPA titration of **2** (Figure 4) was quite similar to those of other aryllithiums with similar dimer/monomer ratios (e.g., PhLi[6d]). A small amount of mono-HMPA-complexed dimer **2D·h$_1$** (identified by the singlet at δ 2.69 and a doublet, $^2J_{7Li-31P} = 6.6$ Hz, at δ 1.96 in the ^7Li NMR spectrum) is initially formed, but the predominant HMPA complexes are the HMPA-solvated monomers. First

formed was **2M·h$_1$** with a doublet in the ^7Li NMR spectrum, a distorted doublet in the ^{31}P NMR spectrum, and a 1:1:1:1 quartet in the ^{13}C NMR spectrum at δ 208.5. The $^7Li-^{31}P$ coupling is partially averaged by quadrupole-induced ^7Li relaxation,[9a,b,14] which also broadens, but does not collapse the ^7Li doublet. The $^7Li-^{13}C$ coupling is not similarly collapsed by ^7Li relaxation because $^1J_{C-Li}$ is about 4 times as large as $^2J_{P-Li}$. At higher equivalents of HMPA the bis-complex **2M·h$_2$** was visible as a distorted triplet at δ 1.25 in the ^7Li NMR spectrum and a ^{13}C signal at δ 212.2 (poorly defined 1:1:1:1 quartet). There was a small amount (ca. 3%) of Li$h_4$$^+$ present at 9 equiv of HMPA, probably due to triple ion formation (Ar$_2$Li$^-$ Li$h_4$$^+$), as seen for many ArLi reagents.[6b,f,g]

5-Chloro-[2-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)phenyl]-lithium (3). In contrast to **1** and **2**, the *para*-chloro analogue **3** is mostly monomer in 3:2 THF/Et$_2$O solution. A well-defined, 1:1:1:1 quartet is visible at δ 210.5 in the ^{13}C NMR spectrum at -125 °C (Figure 5). There is a second set of low-intensity peaks (including that of the C—Li carbon at δ 197.5) that we assigned to the dimer with an apparent equilibrium constant K_{MD}([**3D**]/[**3M**]^2) of 0.27 M^{-1} at -125 °C in 3:2 THF/Et$_2$O. The C—Li signals assigned to monomer and dimer are both shifted downfield by roughly 4 ppm relative to those of **1** and **2** as a result of the electronegative 5-chloro substituent. The small dimer peak in the ^6Li NMR spectrum at δ 2.67 is close to the dimers of **1** (δ 2.81) and **2** (δ 2.50).

Interaction of 2 and 3 with PMDTA. Nonchelated aryllithium reagents, including those with *ortho* substituents, form almost stoichiometric complexes with PMDTA (>90% complex at 1 equiv of PMDTA).[6f] The interaction can be weakened when strongly chelating groups are present, leading to substoichiometric complexation and sometimes to a greater rate of symmetrization of the complexed ligand.[6c] Both effects were seen in the PMDTA titration of [^6Li]-**2** (Figure 6). A new species was formed, which appeared to be a monomer from the chemical shift of the C—Li carbon at δ 208.5, although the C—Li coupling was not resolved to confirm this. More than 4 equiv of PMDTA was required for >90% conversion to **2M·PMDTA**. With **3**,

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(13) See Supporting Information for spectra and additional information.

(14) The 1:1:1:1 quartet of an NMR signal of a nucleus coupled to one ^7Li becomes a broad doublet at intermediate rates of T_1 relaxation:[9a,b] Bacon, J.; Gillespie, R. J.; Quail, J. W. *Can. J. Chem.* **1963**, *41*, 3063–3069.
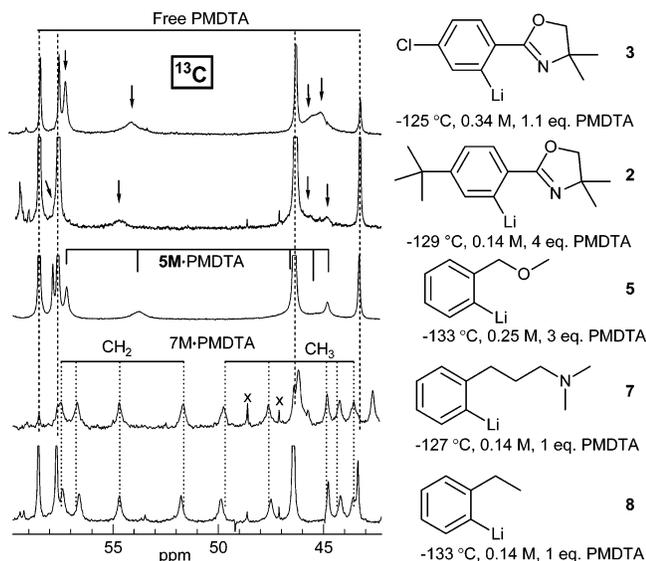
Figure 7. ^{13}C NMR spectra of various PMDTA-complexed monomers. Only the PMDTA signals are shown.

conversion to **3M·PMDTA** (C−Li signal at δ 216.6) was complete at only 1.1 equiv of PMDTA (Figure 5), as expected from the smaller monomer−dimer association constant.

Most PMDTA complexes of aryllithium reagents show nine sharp ^{13}C signals for the bound PMDTA ligand at temperatures below −120 °C (e.g., **7** and **8** in Figure 7).[6c,9c] In contrast, the PMDTA complexes of **2** and **3** show dynamically broadened ligand signals. The dynamic process is intramolecular, since the free PMDTA ligand signals are sharp in this temperature range. Such behavior was also found for **5** and ascribed to the effect of ether chelation in the PMDTA complex (pentacoordinated lithium), which weakens the strength of Li−N coordination and thus facilitates symmetrization of the ligand. We conclude that chelation is strong in **2** and **3** as well and that the PMDTA complexes contain a pentacoordinate lithium atom, with an exceptionally weakly bonded ligand.

There is one unusual feature of the lithium NMR spectra that may be related to the question of pentacoordination. In all previous monomeric ArLiAPMDTA complexes the Li chemical shift has been well downfield of the THF-solvated monomer (if present in detectable amounts), typically by 0.8 ppm. These oxazoline complexes have a different behavior. In **2** the shift of the PMDTA complex is very close to that of the monomer, whereas in **3** it is actually upfield by 0.7 ppm.[6a,c]

Conclusions

The three *ortho*-oxazoline-substituted phenyllithium reagents studied all exist as mixtures of monomer and dimer in 3:2 THF/Et$_2$O and 3:2:1 THF/Me$_2$O/Et$_2$O at low temperatures. The aggregation level is highest for the electron-donating *para-tert*-butyl-substituted reagent and lowest for the *para*-chloro. Single-crystal X-ray structures obtained for **1** and **2** show B-type dimer structures with the oxazoline nitrogen located in close proximity to the lithium atom. The oxazoline group showed evidence of strong chelation in solution, requiring 4 equiv of PMDTA to fully convert the dimer to monomer for compound **2**. The PMDTA complexes of **2** and **3** showed a very labile bound PMDTA ligand, which suggests a pentacoordinate lithium atom with oxazoline chelation maintained.

Experimental Section

General Comments. All reactions requiring a dry atmosphere were performed in glassware flame-dried or dried overnight in a 110 °C oven, sealed with septa, and flushed with dry N$_2$. Tetrahydrofuran (THF) and Et$_2$O were freshly distilled from sodium benzophenone ketyl under N$_2$. Me$_2$O was purified by condensing several milliliters in a graduated conical flask at −78 °C from a pressurized gas cylinder, adding a small portion (0.5 mL) of *n*-BuLi and distilling the dry Me$_2$O via cannula into the desired vessel at −78 °C. *N,N,N′,N′*-Tetramethylethylenediamine (TMEDA), *N,N,N′,N″,N″*-pentamethyldiethylenetriamine (PMDTA), and hexamethyl phosphoric triamide (HMPA) were distilled from CaH$_2$ under reduced pressure (if necessary) and stored over 4 Å molecular sieves under N$_2$. Common lithium reagents were handled with septum and syringe-based techniques and titrated against dry *n*-propanol in THF using 1,10-phenanthroline as indicator.[15] [^{6}Li]-*n*-BuLi was prepared according to literature methods.[16]

Low-Temperature NMR Spectroscopy. All low-temperature NMR spectra were acquired on a Bruker AVANCE spectrometer using a 10 mm broadband probe at the following frequencies: 90.556 MHz (^{13}C), 52.984 MHz (^{6}Li), 139.905 MHz (^{7}Li), and 145.785 MHz (^{31}P). All spectra were taken with the spectrometer unlocked. ^{13}C NMR spectra were referenced internally to the C−O carbon of THF (δ 67.96), Et$_2$O (δ 66.57), or Me$_2$O (δ 60.25). Exponential multiplication (LB) of 2−6 Hz was applied to ^{13}C spectra. ^{6}Li and ^{7}Li spectra were referenced externally to 0.3 M LiCl in MeOH (δ 0.00) or internally to Li$^+$(HMPA)$_4$ (δ −0.40). ^{31}P NMR spectra were referenced externally to 1.0 M PPh$_3$ in THF (δ −6.00) or internally to free HMPA (δ 26.40). Probe temperatures were measured internally with the ^{13}C chemical shift thermometer (Me$_3$Si)$_3$CH.[6h]

General Procedure for NMR Spectroscopy of Organolithium Reagents. Samples of organolithium reagents in ca. 3 mL of solvent, including 1−2 μL of ^{13}C-enriched (10%) (Me$_3$Si)$_3$CH as a shift thermometer,[6h] were prepared in thin-walled 10 mm NMR tubes that were vacuum-dried overnight, fitted with septa, and flushed with N$_2$. Silicon grease was applied to the interface between the tube and the septa before securing with Parafilm for a better seal, as well as to the top of the septa to seal needle punctures. Samples were stored at −78 °C. The spectrometer probe was cooled to <−78 °C, the sample was inserted, and the probe was shimmed on the ^{13}C FID of the THF peak. Spectra of NMR-active nuclei which usually included ^{13}C, ^{6}Li, ^{7}Li, and, when HMPA was involved, ^{31}P were measured. At this point, a cosolvent titration or variable-temperature or variable-concentration experiment could be performed. In the case of a titration experiment, for each addition the sample was ejected and placed in a −78 °C bath, the silicon grease was removed from the top of the septum, a desired amount of cosolvent was added, silicon grease was reapplied to the top of the septum, and the desired NMR spectra were measured.

Supporting Information Available: Detailed experimental procedures for the preparation of the oxazoline starting material for **1**, **2**, and **3**. Details of X-ray single-crystal structures of **1** (CCDC 619040) and **2** (CCDC 619041). This material is available free of charge via the Internet at http://pubs.acs.org.

(15) Watson, S. C.; Eastham, J. F. *J. Organomet. Chem.* **1967**, *9*, 165−168.

(16) Seebach, D.; Hässig, R.; Gabriel, J. *Helv. Chim. Acta* **1983**, *66*, 308−337.