Aggregation and Reactivity of Phenyllithium Solutions

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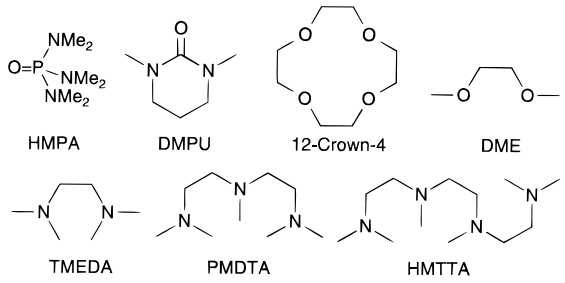
Abstract: Phenyllithium forms a mixture of tetramer and dimer in ether. Complete conversion to dimeric solvates is achieved by the addition of THF, dioxolane, DME, or TMEDA in near stoichiometric amounts. The addition of 2,5-dimethyltetrahydrofuran favors dimer, but tetramer is still detectable at 14 equiv of cosolvent. PMDTA converts PhLi to monomer in ether. In THF, PhLi is a mixture of dimer and monomer. Addition of TMEDA forms a series of complexes, but the dimer/monomer ratio is essentially unaffected. PMDTA and HMPA form monomeric PhLi stoichiometrically. HMTTA and DMPU also result in monomer formation but several equiv are required. 12-Crown-4 shows no spectroscopically detectable complexation of PhLi in THF. All of the cosolvents tested increase the reactivity of PhLi in THF in a test metalation reaction: HMPA and 12-crown-4 show the largest effects, PMDTA is intermediate, and HMTTA and TMEDA result in the least activation. In two selectivity tests, HMPA and 12-crown-4 show a substantially lower selectivity than the other cosolvents. We postulate that a contribution from a highly reactive separated ion pair (SIP) intermediate is responsible for the lower selectivity.

Introduction

The profound effects of donor solvents in altering the reactivity of organolithium reagents have been empirically useful in optimizing preparative uses of organolithium reagents, but their origin has not been well understood. We report here the results of NMR and reactivity studies on phenyllithium (PhLi) in diethyl ether (ether) and tetrahydrofuran (THF) with various donors. These studies were initiated as part of a wide-ranging investigation of the lithium-metalloid exchange reaction, in which ate complexes formed by addition of PhLi to iodobenzene,[1a,b] diphenyl telluride,[1b] tetraorganostannanes,[1c] and diphenyl mercury[1b] played a key role. The spectroscopic data obtained for these systems was uninterpretable without detailed information on the aggregation status of PhLi under the conditions of the ate complex experiments.

We selected PhLi for this role because of its ease of preparation and stability. It also has favorable solubility properties in common solvents used for organolithium reagents such as ether and THF, so pure crystalline material can be prepared and studied in solution at low temperatures. Its reactivity is sufficiently moderate (in contrast to the more aggressive alkyllithium reagents) that polar additives such as hexamethylphosphoric triamide (HMPA), *N*,*N*′-dimethylpropyleneurea (DMPU), 1,2-dimethoxyethane (DME), crown ethers, *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA), *N*,*N*,*N*′,*N*″,*N*″-pentamethyldiethylenetriamine (PMDTA), and *N*,*N*,*N*′,*N*″,*N*‴,*N*‴-hexamethyltriethylenetetraamine (HMTTA) can be used at low temperatures without excessive destruction of the PhLi by reaction with either the solvent or the additive. However, [2.2.1]-crypt cannot be used with PhLi.



Even at the time our studies began PhLi was one of the best understood of all organolithium reagents, with several X-ray crystal structures,[2,3] a variety of NMR studies (^{13}C,[4a,b,5a,6a,7] ^{6}Li,[4a,b,7] and ^{7}Li[4a,b,7,8]), and colligative property measurements[6b,9a]

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to determine aggregation state. During the time we worked on this problem, a number of additional solution[10a,11−13] and solid state[14] spectroscopic and thermochemical[15] studies of PhLi were reported. The powerful isotopic fingerprint technique was applied to PhLi in several solvents.[11a,b]

X-ray crystallographic studies have shown PhLi can be tetrameric (ether solvate),[2] trimeric (mixed aggregate with LiBr),[2] dimeric (TMEDA solvate),[3a] or monomeric (PMDTA solvate)[3b] in the solid state, depending on coordinating ligands and added salts. It is predominantly tetrameric in ether[5a,11a] and dimeric in THF,[6a,11a] THF/TMEDA,[11a] and dimethoxymethane[11b] solutions. The PMDTA solvate has a monomeric structure in THF solution.[10a,11c] Phenyllithium has also been used in several studies of organolithium reactivity.[9b,c,16] From these studies, PhLi clearly has an unusual richness of structure both in the solid state and in solution.

Results

Phenyllithium in Ether. The most reliable method for establishing aggregation, the observation of Li−C *J* coupling by ^{13}C or $^{6/7}$Li NMR spectroscopy has not previously been successful for all PhLi aggregates.[4a,b,11a] The X-ray crystal structure of the ether-solvated tetramer,[2] observation of ^{13}C *ipso* carbon signals upfield of the better established THF-solvated dimer,[4a,b] ^{7}Li quadrupolar relaxation rates,[5a] and measurements of colligative properties[6b,9a] suggested a predominantly tetrameric structure. Eppers and Günther identified PhLi tetramer and dimer on the basis of characteristic multiplet patterns of C_6H_5Li/C_6D_5Li mixtures by ^{6}Li NMR (isotopic fingerprint method).[11a]

Our experiments with Ph^{7}Li and Ph^{6}Li confirm that a mixture of tetramer and dimer are formed in ether, since we have been able to resolve the ^{1}J ^{13}C−^{6}Li coupling in both signals in the ^{13}C NMR spectra: the 1:2:3:2:1 quintet at 187.0 ppm (J_{C-Li} = 7.6 Hz) for the dimer and the apparent septet at 174.0 ppm (J_{C-Li} = 5.1 Hz) corresponding to the tetramer (Figure 1). The Günther isotopic fingerprint method showed that the PhLi tetramer was dynamic (each Li interacting with four C).[11a] Line shape simulations[17] of our tetramer signal show a better fit to the 1:3:6:7:6:3:1 septet expected for the static tetramer (C coupled to three Li) than to the 1:4:10:16:19:16:10:4:1 nonet (outer lines not resolved) expected for the dynamic tetramer (C coupled equally to four Li), but the differences are subtle and not as unambiguous as the Günther result.[11a]

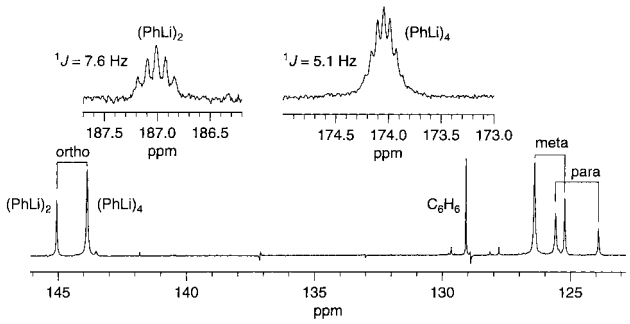


Figure 1. ^{13}C NMR spectra of 0.16 M Ph^{6}Li in ether at −106 °C.

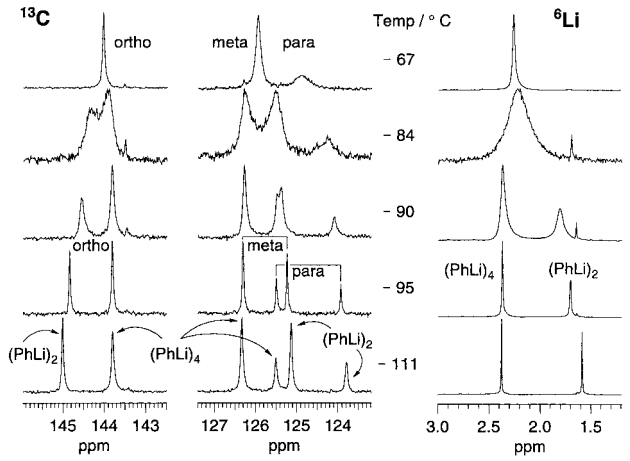
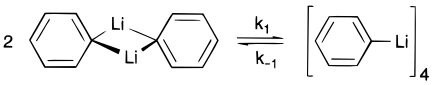


Figure 2. Variable temperature ^{13}C and ^{6}Li NMR spectra of 0.08 M Ph^{6}Li in ether.

The results of a variable concentration study support the tetramer/dimer assignment and rule out other assignments for the lower aggregate consistent with the NMR coupling data (such as a cyclic trimer). A plot of log [tetramer] vs log [dimer] (integration of ^{13}C NMR spectra) has a slope of 2.1 ± 0.1, confirming that the two species differ in aggregation state by a factor of 2.[17]



$\Delta H_1^{\ddagger}$ = 9.1 ± 0.6 kcal/mol $\Delta S_1^{\ddagger}$ = 6 ± 4 eu
$\Delta H_{-1}^{\ddagger}$ = 9.3 ± 0.6 kcal/mol $\Delta S_{-1}^{\ddagger}$ = 0 ± 4 eu
$\Delta H°$ = 0 ± 0.2 kcal/mol $\Delta S°$ = 7 ± 2 eu (Eq. 1)

Figure 2 presents variable temperature ^{13}C NMR spectra of PhLi in ether. Line shape fitting of the ortho, meta, and para carbon signals gave $\Delta G^{\ddagger}_{189\ K}$ = 10 ± 1 kcal/mol for k_1 (eq 1).[17] The line shape fitting also showed the equilibrium constant to be essentially temperature independent (K_{eq} = 34 L/mol at −84 °C).

Phenyllithium in THF. We have reported in preliminary form our low-temperature NMR studies on PhLi.[1b,d] These suggested, as did similar independent studies by Bauer, Winchester, and Schleyer[10a] and earlier kinetic[9b,c] and cryoscopic

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(17) See Supporting Information for figure, simulation, data, or additional experimental details.

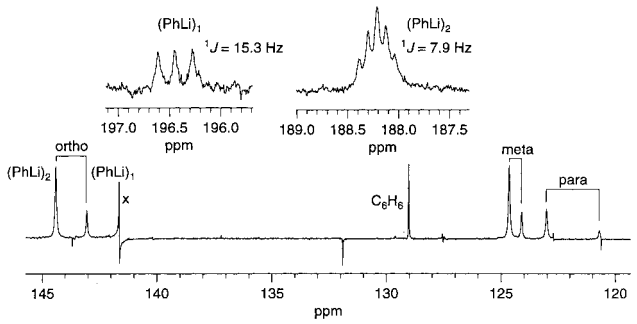


Figure 3. ^{13}C NMR spectra of 0.08 M Ph^{6}Li in THF at −111 °C.

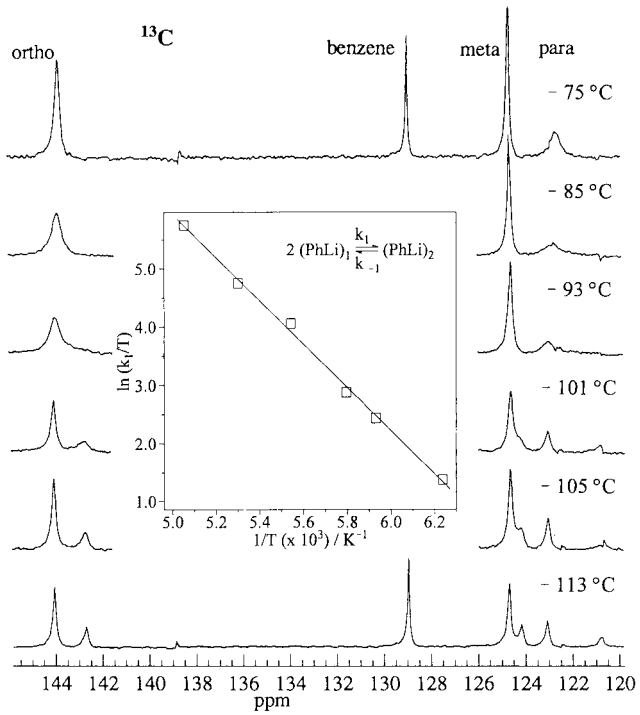


Figure 4. Variable temperature ^{13}C NMR study of 0.127 M PhLi in THF.

measurements,[6b,9a] that some monomeric PhLi is present. Figure 3 reports the first observation of ^{1}J ^{13}C−^{6}Li coupling for THF-solvated Ph^{6}Li monomer (C_1 at 196.4 ppm), which confirms this assignment. The other *ipso* carbon signal at 188.2 ppm corresponds to the dimer since a variable concentration study[17] showed that the two species differ in aggregation by a factor of 2. Although it is now clear that low aggregation states are the norm for organolithium reagents in THF,[18] this was one of earliest cases of an unhindered monomeric organolithium reagent.

Figure 4 presents variable temperature ^{13}C NMR spectra of PhLi in THF. Line shape fitting of these data (*ortho* carbons at 143.2 and 144.5 ppm) gave $\Delta G^{\ddagger}_{180\ K} = 8.0 \pm 0.2$ kcal/mol for k_1 (eq 2).[17] The line shape fitting also showed only a slight (if any) temperature dependence on the equilibrium constant ($K_{eq} = 31$ L/mol at −113 °C and 40 L/mol at −75 °C). These values are fully consistent with the cryoscopic work of Seebach and Bauer ($K_{eq} = 33$ L/mol at the freezing point of THF).[6b]

(18) Unhindered primary organolithium such as lithium acetylides, MeLi and *n*-BuLi are partially or fully tetrameric in THF. We know of no other C−Li monolithium reagents that form aggregates higher than dimers in THF or similar solvents such as Me_2O, and most are monomeric:[1k,l,4c,d,9a,10a,b] Goldstein, M. J.; Wenzel, T. T. *Helv. Chim. Acta* **1984**, *67*, 2029. Harder, S.; Brandsma, L.; Kanters, J. A.; Duisenberg, A.; van Lenthe, J. H. *J. Organomet. Chem.* **1991**, *420*, 143.

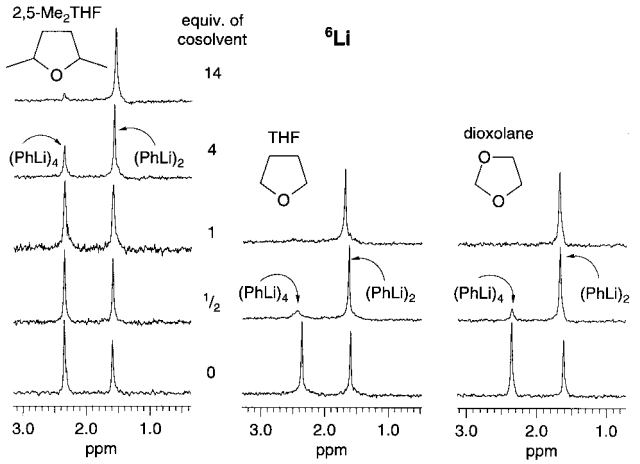
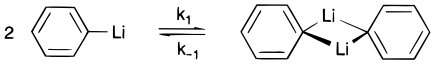


Figure 5. ^{6}Li NMR study of the effect of 2,5-dimethyltetrahydrofuran, THF, and dioxolane on 0.08 M PhLi in ether at −113 to −115 °C.



(Eq. 2)

$\Delta H_1^{\ddagger} = 7.5 \pm 0.1$ kcal/mol $\quad \Delta S_1^{\ddagger} = 2.5 \pm 1$ eu

$\Delta H_{-1}^{\ddagger} = 7.0 \pm 0.1$ kcal/mol $\quad \Delta S_{-1}^{\ddagger} = -7.4 \pm 1$ eu

$\Delta H° = 0.5 \pm 0.2$ kcal/mol $\quad \Delta S° = 10 \pm 2$ eu

Effect of Additives on Phenyllithium Solutions in Ether and THF. We have performed qualitative experiments to examine the effect of 2,5-dimethyltetrahydrofuran, THF, dioxolane, DME, TMEDA, PMDTA, HMTTA, HMPA, DMPU, and 12-crown-4 on the aggregation state of PhLi in ether and/or THF. In ether, 2,5-dimethyltetrahydrofuran is weakly complexed; THF, DME, and TMEDA are strongly complexed and convert PhLi to the dimer. HMPA and PMDTA convert PhLi to monomer in both ether and THF. DMPU and HMTTA convert PhLi to monomer in THF, but several equiv are required. 12-Crown-4 has no detectable effect in THF. With the exceptions of 2,5-dimethyltetrahydrofuran in ether and 12-crown-4 in THF, these ether−cosolvent combinations cannot be properly thought of as mixed solvents, since there is a quite specific and nearly stoichiometric interaction of the PhLi aggregates with each of the cosolvents.

THF, Dioxolane, and 2,5-Dimethyltetrahydrofuran in Ether. Figure 5 presents ^{6}Li NMR spectral data for addition of 2,5-dimethyltetrahydrofuran, THF, and dioxolane to PhLi in ether. Both THF and dioxolane interact strongly and nearly stoichiometrically with PhLi in ether. Below 1 equiv of THF some line broadening and changes in chemical shift for the tetramer signals are seen in the ^{6}Li (Figure 5) and ^{13}C NMR spectra[17] and may be ascribable to incipient decoalescence of mixed ether- and THF-solvated tetramers. Similar broadening is not seen with dioxolane.[17] Slow exchange of monodentate solvents on the NMR time scale in ethereal solvents can be seen in favorable circumstances.[1f,19a,b,d,20] It is interesting that the addition of THF to PhLi in *toluene* appears to lead to a THF-solvated tetramer.[12]

2,5-Dimethyltetrahydrofuran showed a substantially smaller effect on the aggregation state of PhLi than THF or dioxolane, with tetramer still detectable even when 14 equiv had been added (Figure 5). This is consistent with other studies which show the methyl-substituted tetrahydrofurans to be weaker coordinators than THF,[19b] presumably for steric reasons. The dipole moment of 2,5-dimethyltetrahydrofuran (1.48 D[21]) is only a little smaller than that of THF (1.75 D) and larger than that of dioxolane (1.19 D).

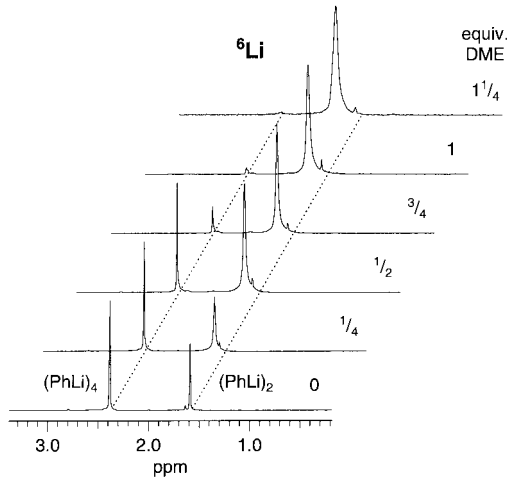


Figure 6. ^{6}Li NMR spectra of 0.08 M Ph^{6}Li in ether at −110 °C with the addition of DME.

Phenyllithium and DME. The addition of 1,2-dimethoxyethane (DME) to PhLi in ether causes partial loss of tetramer at 0.5 equiv of cosolvent and essentially complete conversion to dimer at 1 equiv (Figure 6). Thus DME, like THF, almost quantitatively displaces ether on PhLi. The addition of DME to solutions of PhLi in THF (spectra not shown) causes barely detectable changes in the aggregation of PhLi but does seem to cause increases in the rate of interconversion between monomers and dimers.

Phenyllithium and TMEDA. The complex of PhLi dimer with TMEDA has been studied in solution by ^{6}Li and ^{13}C NMR spectroscopy[11a] and in the solid state by X-ray crystallography[3a] and CP-MAS NMR.[14b] Our NMR studies reveal substantially more detail about this system.

TMEDA has different effects on PhLi aggregation in ether and THF. In ether, static mono- and bis-TMEDA dimer complexes, $(PhLi)_2{\cdot}(TMEDA)_1$ and $(PhLi)_2{\cdot}(TMEDA)_2$, are formed.[22] Their *ortho* and *para* carbon signals are resolved in the ^{13}C NMR spectrum at 0.4 equiv of TMEDA, but the ^{6}Li NMR signals are not (Figure 7). No tetrametric complexes were detected. The complexation is stoichiometric, so that at 1 equiv of TMEDA only dimer was observed. Further addition of cosolvent does not promote monomer formation (spectra not shown).

As can be seen from the spectra (Figure 7) we did not observe the second signal reported by Eppers and Günther at 2.07 ppm for PhLi-TMEDA in ether.[11a] We assign this signal to the mixed dimer PhLi·LiBr·$(TMEDA)_n$ (a signal appeared at 2.07 ppm when we added LiBr to the PhLi−TMEDA solution).

In THF solution, TMEDA also forms a series of complexes with PhLi, but the complexation is not stoichiometric. The spectra can be interpreted in terms of the static dimers $(PhLi)_2{\cdot}(TMEDA)_n$, with $n = 0$, 1, and 2, and the monomers PhLi·

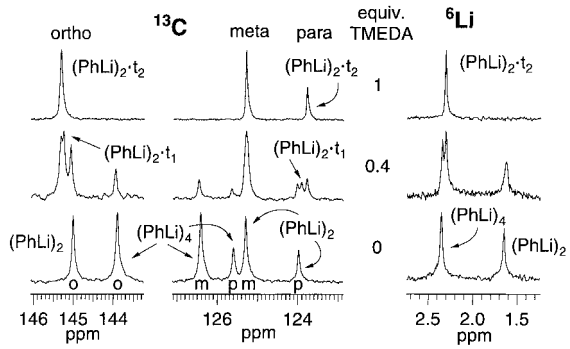
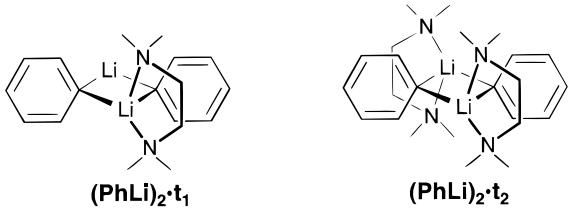


Figure 7. ^{13}C and ^{6}Li NMR spectra of 0.08 M PhLi in ether at −107 °C with the addition of TMEDA (t = TMEDA).



$(TMEDA)_n$ with $n = 0$ and 1. Figure 8 shows ^{13}C and ^{6}Li signals at key points.

The mono-TMEDA dimer $(PhLi)_2{\cdot}(TMEDA)_1$ gives two signals at 1.43 and 2.12 ppm in the ^{6}Li NMR spectra for the uncomplexed and complexed lithium cations. The former is very close to that of the THF-complexed PhLi dimer at 1.55 ppm and the latter to that of the bis complex $(PhLi)_2{\cdot}(TMEDA)_2$[3a,22] at 2.06 ppm. The small splitting in the *ortho* carbon peak at 145.3 ppm for the bis TMEDA complex may be due to slow inversion within the chelate ring, as observed for amide-TMEDA complexes.[19d] TMEDA also complexes monomeric PhLi to form PhLi·$(TMEDA)_n$ (n probably 1). The monomers did not give separate signals, rather the resonance moved steadily downfield as TMEDA was added (dotted line in Figure 8, ^{6}Li NMR). We were able to decoalesce the ^{6}Li signals for PhLi·$(TMEDA)_1$ and PhLi·$(THF/Me_2O)_n$ in a 1:1 THF/Me_2O solution with 0.5 equiv of TMEDA at temperatures below −140 °C.[17] The PhLi·$(TMEDA)_1$ signal is under that of $(PhLi)_2{\cdot}(THF/Me_2O)_n$ (1.55 ppm). Simulation of the spectra below and above the coalescence temperature (−154 and −133 °C) confirms this interpretation.

Although TMEDA has long been viewed as a powerful deaggregating solvent,[23] there are now a number of cases where complexation is weak, and only minimal changes in reactivity are seen.[19c] The data we have obtained show that in the present system TMEDA quantitatively converts tetramer to dimer in ether[22] but has little if any effect on the monomer-to-dimer ratio in solvents containing THF. This is shown by analysis of the spectra in 1:1 THF/Me_2O at 0.5 equiv of TMEDA,[17] which gave a ratio of PhLi·$(TMEDA)_1$ to PhLi·$(THF)_n$ of 0.63 and a ratio of $(PhLi)_2{\cdot}(TMEDA)_1$ to $(PhLi)_2{\cdot}(THF)_n$ of 0.53; i.e., monomer and dimer PhLi have, within experimental error, identical association constants with TMEDA. A similar conclusion is reached from integration of the ^{13}C NMR spectra in THF where PhLi·$(TMEDA)_1$ and PhLi·$(THF)_n$ are not resolved, but all of the dimer signals are well resolved from the monomer signals (Figure 8). In THF the dimer/monomer ratio is 3.1, whereas in the presence of 6.0 equiv of TMEDA (where only small amounts of $(PhLi)_2{\cdot}(THF)_n$ and PhLi·$(THF)_n$ remain) this ratio

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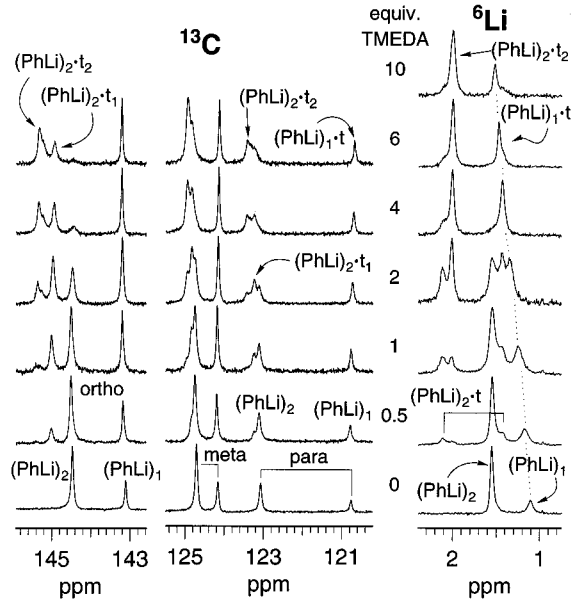


Figure 8. ^{13}C and ^{6}Li NMR spectra of a TMEDA titration of 0.08 M Ph^{6}Li in THF at −115 °C (t = TMEDA).

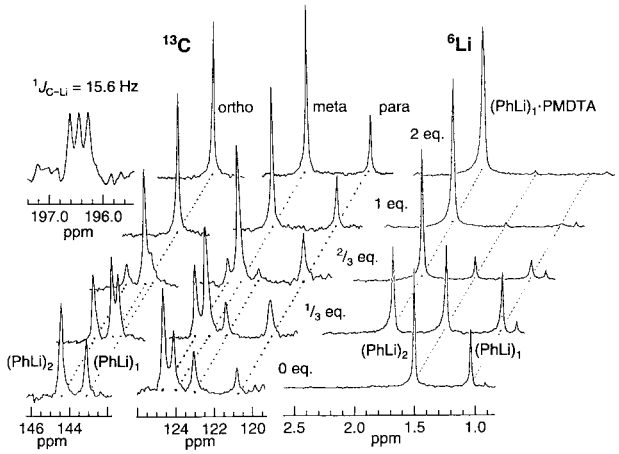


Figure 9. ^{13}C and ^{6}Li NMR spectra of PMDTA titrations of PhLi. The ^{13}C spectra are 0.08 M Ph^{6}Li at −105 °C and the ^{6}Li NMR spectra are 0.04 M Ph^{6}Li in 2:1 THF/Me_2O at −125 °C.

becomes 2.5. This difference is probably also within experimental error considering the inherent problems in integrating ^{13}C NMR spectra.

Phenyllithium and PMDTA. PMDTA converts the PhLi tetramer/dimer mixture in ether and the dimer/monomer mixture in THF to a monomer (J_{Li-C} = 16.0 Hz in ether, J_{Li-C} = 15.6 Hz in THF).[10a] An X-ray crystal structure of the monomeric complex crystallized from hexane solution has been reported.[3b] Figure 9 shows NMR studies of the titration of PhLi with PMDTA. The spectra show the interesting effect that a signal at the chemical shift of $(PhLi)_2$·$(THF)_n$ is still easily detectable even after 1 equiv of PMDTA had been added, so the strength of complexation may be rather modest. There is a caveat to this conclusion: the PhLi monomer signal can be seen only as a broadened peak at 1 equiv of PMDTA and not at all at 2 equiv, although it should have been easily detectable since it would have a larger area than the dimer signal.

Phenyllithium and HMTTA. To test the behavior of a tetradentate ligand we examined the effect of HMTTA on PhLi aggregation. This ligand is similar to, but not as effective as, PMDTA (spectra not shown). HMTTA converts PhLi in THF to monomer, but 3 equiv of cosolvent are required before the fraction of dimer is below 10%. The interesting paradox about HMTTA is that it behaves like PMDTA in deaggregating PhLi but like TMEDA in accelerating PhLi reactivity (shown in the section on **Reactivity Effects**).

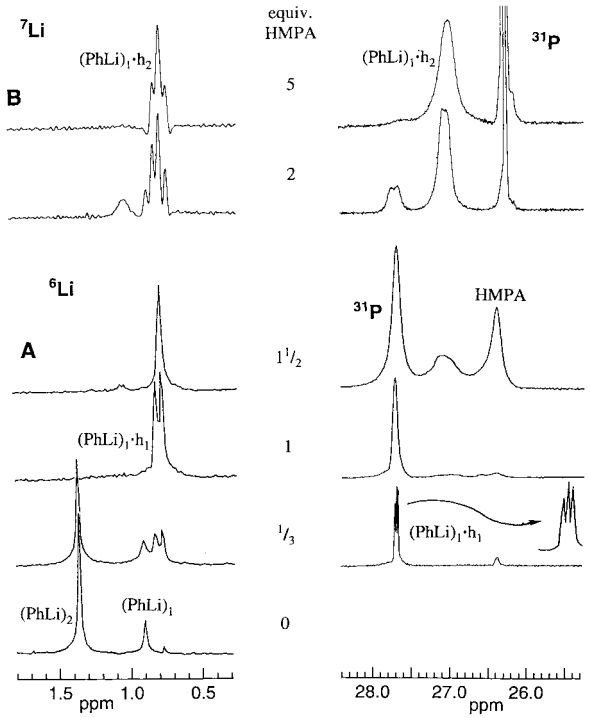


Figure 10. A. ^{6}Li and ^{31}P NMR spectra of an HMPA titration of 0.04 M PhLi in 2:1 THF/Me_2O at −125 °C. B. ^{7}Li and ^{31}P NMR spectra of 0.16 M PhLi in 42:42:16 THF/Me_2O/ether with 2 and 5 equiv of HMPA at −150 to −160 °C (h = HMPA).

Phenyllithium and HMPA. The interaction of HMPA with PhLi produces a number of species, some of which can be securely identified from chemical shift considerations and the observation of $^{2}J_{Li-P}$.[1g] The spectra are simplest in THF,[1d,g] in part because the low temperatures needed to slow ligand exchange rates and resolve some of the species cannot be achieved. We have previously reported ^{13}C, ^{7}Li, and ^{31}P NMR studies of HMPA titrations in THF.[1g,h] A single new species was stoichiometrically formed with 1 equiv of HMPA added. This species was ascribed to PhLi·$(HMPA)_1$ from observation of the $^{6}Li-^{13}C$ *ipso* carbon coupling, a 1:1:1 triplet at 199.5 ppm with $^{1}J_{Li-C}$ = 13 Hz. Free HMPA appears above 1 equiv, so the complexation is no longer stoichiometric, and the Li−P coupling is lost because of rapid exchange, presumably by an associative mechanism. Weak complexation and rapid associative exchange of HMPA has also been reported for lithium amides.[19e] In THF, no discrete signals can be seen for any $(PhLi)_2$·$(HMPA)_n$ species nor for PhLi·$(HMPA)_2$.

A clearer picture of the various PhLi−HMPA complexes was obtained in solvents containing THF and Me_2O, which permitted studies at much lower temperatures. Figure 10A shows ^{6}Li and ^{31}P NMR spectra from an HMPA titration of Ph^{6}Li in 2:1 THF/Me_2O at −125 °C. Initially, the PhLi·HMPA complex grows in, with well-resolved ^{6}Li-^{31}P coupling in both the ^{6}Li and ^{31}P NMR spectra. Above 1 equiv a new species appears in the ^{31}P NMR spectrum at 27.0 ppm. The corresponding ^{6}Li signal is a broadened singlet which was identified as PhLi·$(HMPA)_2$ in a very low-temperature HMPA titration of Ph^{7}Li in the ternary solvent system THF/Me_2O/ether 42:42:16 (Figure 10B, the exchange rate between dimer and monomer is sufficiently fast that the signals are well resolved only below −150 °C).

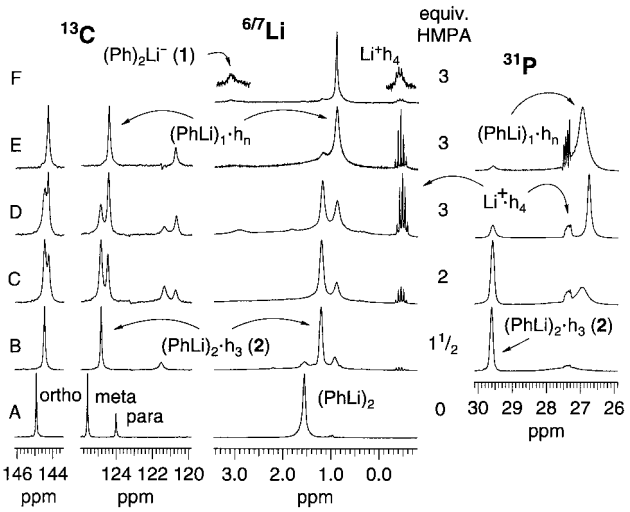
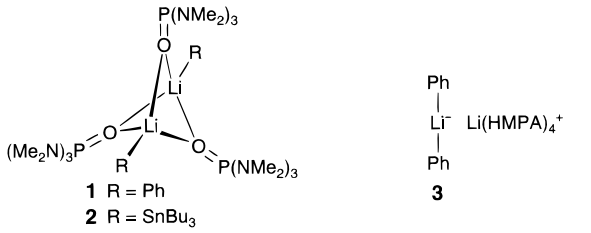


Figure 11. A−D. ^{13}C, ^{7}Li, and ^{31}P NMR spectra of 0.15 M PhLi in 9:1 ether/THF at −120 °C. E. ^{13}C, ^{7}Li, and ^{31}P NMR spectra in 10:1 THF/ether with 3 equiv of HMPA at −125 to −130 °C. F. Same as E, except ^{6}Li NMR spectrum (h = HMPA).

The first 0.25 equiv of HMPA in THF/Me_2O/ether at −150 to −160 °C (spectra not shown) results in the appearance of a doublet at 0.8 ppm for PhLi·HMPA in the ^{7}Li NMR spectrum. Several other signals appear, tentatively identified as $(PhLi)_2$·$(HMPA)_1$ (a doublet at 0.5 ppm and singlet at 1.5 ppm, which rise and fall together) and $(PhLi)_2$·$(HMPA)_2$ (doublet at 0.7 ppm). A fourth species appears as a singlet at 1.8 ppm in the ^{7}Li NMR spectrum and an associated signal at 31.2 ppm in the ^{31}P NMR spectrum. It may be the triply bridged dimer **1**, which dominates the titration in the less polar medium 9:1 THF/ether (Figure 11). The reduction in the amount of bridged dimer as more THF was added to the ethereal solution is expected; other systems such as LiBr[24] and Bu_3SnLi (**2**)[1j] form major fractions of such species in ether and show no trace of them in THF.[1g]



Above 1 equiv of HMPA, the triplet at 0.8 ppm in the ^{7}Li NMR spectrum can be assigned to PhLi·$(HMPA)_2$ (see Figure 10B). Interestingly, no tris-solvated PhLi·$(HMPA)_3$ can be detected even with a large excess of HMPA. It is possible the rapid exchange of HMPA on PhLi·$(HMPA)_2$ at temperatures above −150 °C is a consequence of an associative process which involves PhLi·$(HMPA)_3$ as a transient intermediate.

The second species which appears at high equiv of HMPA shows a small quintet at −0.4 ppm due to the separated ion $Li^+(HMPA)_4$. We assign this signal, and a singlet at 3.2 ppm, to the external and internal lithiums of the triple ion **3** (Figure 11D, E, F). The signals have areas close to 1:1 and amount to ∼14% of total PhLi. The inside Li of the triple ion is very broad in the ^{7}Li NMR spectra, probably due to quadrupolar relaxation, and can best be recognized in ^{6}Li NMR spectra. The ^{13}C signals of **3** could not be detected. On the basis of the evidence presented here, the structure **3** cannot be assigned unambiguously. However, similar signals in other aryllithium reagents which form larger fractions of triple ion (e.g., 2,6-diisopropylphenyllithium and 2,6-dimethoxyphenyllithium) have been more securely identified.[1i]

An HMPA titration of PhLi in pure ether could not be performed since insoluble material formed (probably **1**). A better behaved system was PhLi in a 9:1 ether/THF solution, where $(PhLi)_2$ was the only aggregate detectable by ^{13}C and ^{7}Li NMR. The interesting feature of the HMPA titration in Figure 11A−D was the appearance of a new species assigned as the bridged dimer **1**, in addition to the usual signal for PhLi·$(HMPA)_n$. Unfortunately, the highly diagnostic 1:3:3:1 quartet with a small $^{2}J_{Li-P}$ in the ^{7}Li NMR spectrum and associated 1:2:3:4:3:2:1 septet in the ^{31}P NMR spectrum, which were detected for the structurally analogous triply bridged dimers formed with LiBr[24] and Bu_3SnLi (**2**),[1j] could not be resolved in these spectra. However, the stoichiometry (the signal is maximized at 1.5 equiv of HMPA), the absence of the normally easily detectable Li−P coupling in the ^{7}Li NMR spectra,[1g] and the unusual downfield ^{31}P chemical shift of the coordinated HMPA (29.6 ppm, similar to that observed for **2** at 30.6 ppm) allowed assignment of structure **1** to the species formed from PhLi and HMPA.

As expected from the relatively weak complexation of PhLi in THF by both TMEDA and PMDTA, HMPA was found to quantitatively displace both of these ligands from PhLi (spectra not shown).

Phenyllithium and DMPU. *N,N′*-Dimethylpropyleneurea (DMPU) has been promoted[6c] as a safe substitute for HMPA with comparable reactivity effects on lithium reagents. Our ^{13}C NMR study of the addition of DMPU to PhLi in THF required special care since DMPU (in contrast to HMPA) reacts with PhLi at a significant rate at −78 °C.[17] The addition of 1 equiv of DMPU converts the ∼1:1 ratio of monomer to dimer seen for 0.08 M PhLi in THF to a ∼4:1 ratio. Even at 2 and 3 equiv of DMPU, dimeric PhLi is still detectable in the spectra. In comparison, only 1 equiv of HMPA is required to convert PhLi to monomer in THF. This is consistent with other studies[6c] which showed substantially (approximately a factor of 2) more DMPU than HMPA is required for the same chemical effect to be observed.

Phenyllithium and 12-Crown-4. The most unexpected result was obtained with 12-crown-4. Several X-ray structures of solvent separated carbanion ion pairs involving Li^+(12-crown-4)$_2$ have been reported, and appropriately sized crowns have a reputation as strong complexing ligands for alkali metals.[25] We were therefore surprised to find there were no intensity changes, no new signals, and no significant shift changes in the ^{13}C or ^{7}Li NMR spectra of PhLi in THF as several equiv of 12-crown-4 were added (Figure 12).[5c,19d] The absence of new peaks or chemical shift changes in the NMR spectra could simply result from an accidental coincidence of signals for the THF−Li and crown-Li signals, which would not be unreasonable. Several strong arguments can be marshaled against this explanation. First, TMEDA complexes PhLi in THF nonstoichiometrically, but the complexation is easily detectable (Figures 7 and 8). We have carried out a TMEDA titration of a 0.08 M PhLi solution in THF containing 2 equiv of 12-crown-4 and found that the ratio of the various PhLi-TMEDA species was essentially unaffected by the presence of 12-crown-4. If the crown ether were forming a strong complex, complexation by TMEDA should have been reduced or eliminated (as happens with

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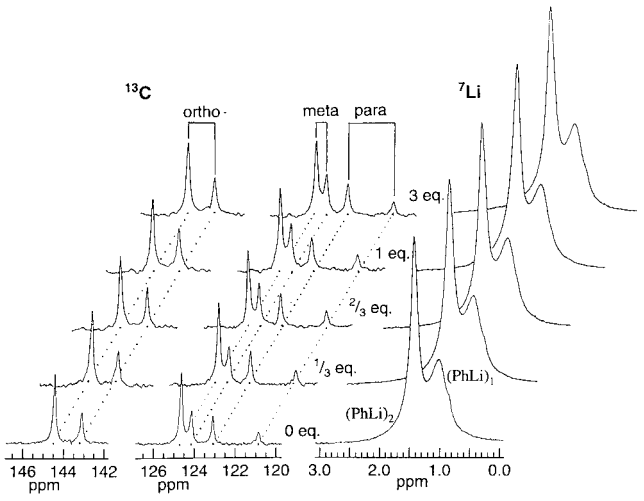
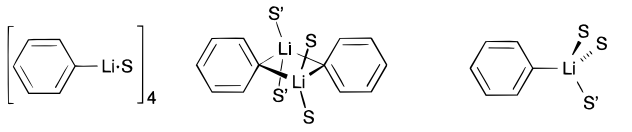


Figure 12. The effect of adding 12-crown-4 to PhLi in THF monitored by ^{13}C (0.08 M) and ^{7}Li (0.04 M) NMR spectroscopy at −105 °C.



S S'	Et_2O	Et_2O Et_2O	THF THF	THF TMEDA	TMEDA TMEDA	THF THF	THF HMPA	PMDTA
δ-i	174.0	187.0	188.2	190.7	191.8	196.4	199.5	196.5
δ-o	143.8	145.0	144.5	144.9	145.3	143.2	143.7	143.8
δ-m	126.3	125.1	124.6	124.7	124.9	124.1	124.3	124.0
δ-p	125.5	123.8	123.0	123.1	123.3	120.7	120.7	120.7
δ_{Li}	2.36	1.59	1.55	1.43 2.12	2.06	1.11	0.80	2.03

Figure 13. ^{13}C and $^{6/7}$Li NMR chemical shifts of PhLi measured between −105 and −125 °C.

HMPA). A second argument against "hidden complexation" by 12-crown-4 involves the constancy of the monomer-to-dimer ratio as crown was added. This means the complexation constants of dimer and monomer with 12-crown-4 would have to be identical, which seems highly unlikely, considering the very different steric environment around the lithium of monomer and dimer PhLi and the expected difference in complexing behavior of the monodentate THF ligand and the tetradentate 12-crown-4 ligand. (For example, the tridentate ligand PMDTA converts PhLi aggregates to monomer in an almost stoichiometric process (Figure 9).) We conclude that 12-crown-4 does not complex with PhLi in significant amounts.

^{13}C Chemical Shift Effects. The ^{13}C chemical shifts of a number of the solvates and aggregates of PhLi are summarized in Figure 13. The *ipso* carbon is the most sensitive to changes in aggregation and moves *downfield* over 25 ppm from 174.0 ppm for the ether-solvated tetramer to 199.5 ppm for the HMPA-solvated monomer. These changes are principally a consequence of magnetic mixing of the carbanion lone pair orbital with π^* orbitals.[4b] The change in chemical shift is the result of increased charge density at the carbanion carbon due to the reduction of the number of lithium cations coordinated to it and the increased solvation at lithium from better donors.[4a,b,14a] By this chemical shift criterion, the donor strength of THF and TMEDA are very similar, with TMEDA perhaps a stronger donor as judged by the 2−3 ppm further downfield shift of the *ipso* carbon in the TMEDA dimers. However, a variety of chemical shift effects operate on the *ipso* carbon, so detailed interpretation is not warranted.

The *para* carbon chemical shift moves in the opposite direction to that of the *ipso* carbon, reflecting the transmission

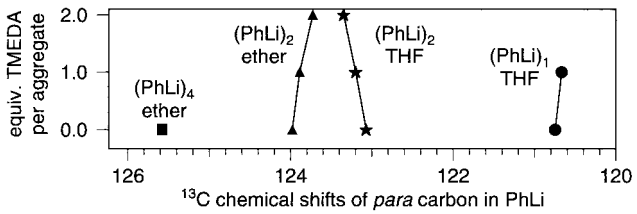


Figure 14. The effect of aggregation and solvation on *para* carbon chemical shifts in PhLi.

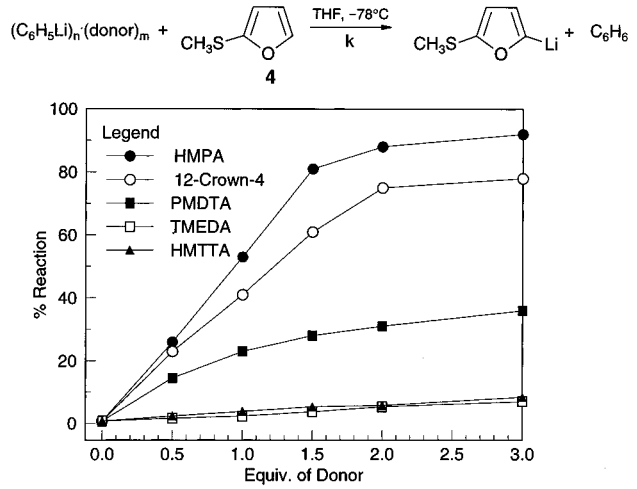


Figure 15. Percent reaction of 0.12 M PhLi with **4** (0.12 M) after 60 min at −78 °C in THF containing various donor additives.

of electron density from the carbanion carbon through the aromatic ring. The change in aggregation from tetramer to dimer to monomer covers a range of 4.8 ppm (Figure 14). Replacement of ether by THF in the dimer gives a much smaller effect (0.8 ppm) in the expected upfield direction (stronger donor solvent results in weaker C−Li coordination). The stepwise coordination of one and two TMEDA molecules to the ether- and THF-solvated dimer has opposite shift effects; the *para* carbon moves upfield when TMEDA replaces ether and downfield when TMEDA replaces THF. This suggests that TMEDA is a stronger donor than ether and a weaker one than THF. Interestingly, the THF monomer shows the opposite shift effect compared to the dimer, showing a small but unmistakable upfield shift as TMEDA replaces THF. It may be this is also a reflection of electron density at the carbanion carbon, since TMEDA has a small but well-defined accelerating effect on the metalation of 2-methylthiofuran with PhLi in THF (vide infra).

Reactivity Effects

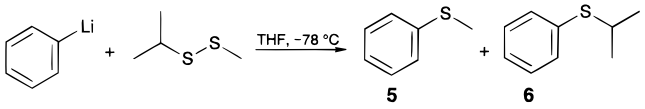
With considerable qualitative and some quantitative information in hand about the behavior of PhLi in ethereal solvents and solvent−donor combinations, we examined the effects of these changes in coordination at lithium on reactivity. Figure 15 presents rate plots for the metalation of 2-methylthiofuran (**4**) with PhLi in pure THF with increasing amounts of added donor solvents. We were not able to determine the effect of DMPU because PhLi reacts with it on the time scale of the experiment.

From a comparison of initial rates, we can estimate that the relative activating effect of HMPA, 12-crown-4, PMDTA, HMTTA, TMEDA, and THF is approximately 37:33:21:3:2.3:1. HMPA is the most effective donor for increasing reaction rate. Since the first equivalent of HMPA complexes quantitatively to PhLi (Figure 10) and the rate continues to increase

after that, it is clear the reactive species cannot be PhLi·$(HMPA)_1$ but must be some higher solvate. Kinetic simulation of the data in Figure 15 and similar experiments gave a best fit for a tris-HMPA solvate, but the data are neither extensive nor accurate enough to securely identify the order in HMPA.

The effect of 12-crown-4 on the metalation reactivity of PhLi is remarkable, considering that spectroscopic studies (Figure 12) showed 12-crown-4 complexed PhLi in at most substoichiometric amounts.[5c] Clearly small concentrations of highly reactive crown-complexed species are being formed which are responsible for the enhanced rates. Additional insight into the nature of the reactive species in these reactions is provided by selectivity tests performed with isopropyl methyl disulfide (eq 3) and 3-methylthiophene (eq 4).

The ratio of attack at the less and more hindered sulfur atoms of isopropyl methyl disulfide is approximately 100/1 for solutions of PhLi in THF and with added TMEDA, PMDTA, or HMTTA. However, the ratio of **5** to **6** with HMPA and 12-crown-4 were much lower and decreased further as concentration of the cosolvent was increased.

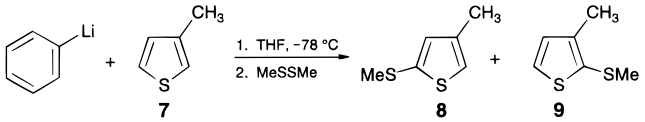


5 **6**

THF	90/1
THF/TMEDA (1 equiv)	107/1
THF/PMDTA (1 equiv)	133/1
THF/HMTTA (1 equiv)	112/1
THF/HMPA (1 equiv)	11/1
THF/HMPA (5 equiv)	3/1
THF/12-Crown-4 (1 equiv)	29/1
THF/12-Crown-4 (5 equiv)	5/1

(Eq. 3)

Similarly, the ratio of the two regioisomers **8** and **9** formed by metalation of 3-methylthiophene with PhLi was found to be 6.4 in THF. The amine complexing agents PMDTA, TMEDA and HMTTA gave slightly higher ratios, from approx 7 for TMEDA to 8 for HMTTA. However, the more strongly activating cosolvents 12-crown-4 and HMPA gave quite different results. HMPA gave ratios from 2.4 to 5.4. Apart from some tendency for the higher values to be obtained at high conversions, the variability seemed to be random, and it was eventually found that some equilibration between isomers was occurring during the metalation.



7 **8** **9**

THF	6.4/1
THF/TMEDA (1 equiv)	7.1/1
THF/PMDTA (1 equiv)	7.3/1
THF/HMTTA (1 equiv)	7.7/1
THF/HMPA (1 equiv)	2.4-3.7/1
THF/12-Crown-4 (1 equiv)	2.3/1

(Eq. 4)

12-Crown-4 also gave much lower ratios, but here no equilibration was detected, and the ratios changed systematically with the concentration of 12-crown-4. Figure 16B gives the results from one set of experiments at constant reaction time with varying [12-crown-4]. Our working hypothesis for both the HMPA and 12-crown-4 data is that in these solvents there is a substantial contribution from a mechanism involving a separated ion pair (SIP, $Ph^-//Li(solv)_n^+$), although such a species has not been detected in our extensive NMR studies of PhLi. An SIP would be much more reactive than a contact ion pair

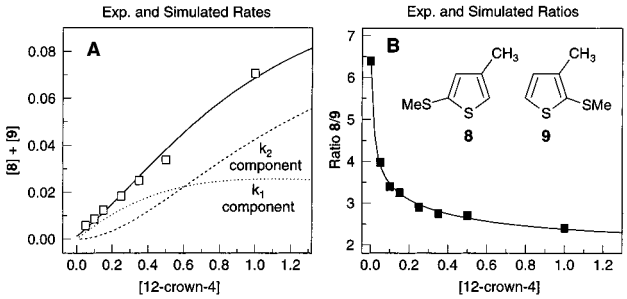


Figure 16. Metalation of 3-methylthiophene by PhLi in THF for 90 min at −78 °C as a function of the concentration of 12-crown-4. A: product formation. The lines are simulations using eq 5, with k_0 = 0.000016 M^{-1}, k_1 = 0.00067 M^{-2}, k_2 = 0.016 M^{-3}. B: product ratio (**8**/**9**). The line is a simulation using the above rate constants and $Ratio_0$ = 6.4, $Ratio_1$ = 3.5 and $Ratio_2$ = 1.9.

(CIP), its fractional contribution varying with the amount of donor present, and it should give lower selectivity in the reactions with isopropyl methyl disulfide and 3-methylthiophene.[1m]

Our analysis of the rates of reaction as a function of crown concentration gives a reasonable fit for eq 5. The value for k_0

$$-\mathrm{d[PhLi]} = [\mathrm{PhLi}][\mathbf{7}](k_0 + k_1[\mathrm{crown}] + k_2[\mathrm{crown}]^2)\mathrm{d}t \quad (5)$$

(the uncatalyzed rate constant) was measured independently from experiments in THF, and k_1 and k_2 were optimized to fit the experimental rate data. The kinetic simulation was performed assuming that the complexation of 12-crown-4 with PhLi had a small equilibrium constant (as shown by the NMR studies). Figure 16A shows the experimental and simulated data for one set of experiments and also shows the contribution from the k_1 and k_2 processes to the overall rate (k_0 makes an insignificant contribution when even a small amount of crown is present). At low crown concentrations the k_1 process dominates, at higher concentrations the k_2 process contributes more. Each of the three components (k_0, k_1, and k_2) will give a different ratio of the products **8** and **9**. The value for the ratio of the k_0 process ($Ratio_0$ = 6.4) was measured from the THF experiment. Figure 16B shows a simulation in which optimal ratios of the products **8** and **9** for the k_1 ($Ratio_1$ = 3.5) and k_2 ($Ratio_2$ = 1.9) processes were obtained by fitting the product data using the rate constants determined from the rate data.

Although our kinetic data is rather limited and other interpretations are possible, we believe the internal consistency between partition of the rates into first- and second-order components and partition of the product between **8** and **9** is supportive of the mechanistic postulate. The complexation of one 12-crown-4 to PhLi (the k_1 process) gives a substantially increased rate and a slightly lower selectivity (3.5 vs 6.4) in reaction with **7**. Complexation of two crown ethers to PhLi (the k_2 process) cannot easily occur without breaking the C−Li bond and forming the SIP $Ph^-//Li^+(crown)_2$. This (presumably highly reactive) species gives a still lower selectivity ($Ratio_2$ = 1.9) in reaction with **7**.

For the nucleophilic attack at the isopropyl methyl disulfide a similar qualitative explanation seems likely, although a change in mechanism, from S_N2 substitution at sulfur to a SET process, is also plausible.[26] A SET process would be expected to show little or no steric effect, since the product determining step would

(26) Yamataka, H.; Sasaki, D.; Kuwatani, Y.; Mishima, M.; Tsuno, Y. *J. Am. Chem. Soc.* **1997**, *119*, 9975.

be fragmentation of the disulfide radical anion to $R-S^-$ and R'-S$^\cdot$. The intervention of SIPs in reactions of PhLi with substrates is also indicated by other effects. For example, PhLi/HMPA reacts with all enolizable ketones to give only enolization and no carbonyl addition.

Summary. The aggregation state of PhLi in ethereal solvents has been determined previously by indirect methods. We have reported the first observation of fully resolved *ipso* carbon signals for all of the PhLi aggregates to firmly establish the tetramer and dimer structures in ether and the dimer and monomer structures in THF. Furthermore, the effects of adding polar additives, such as 2,5-dimethyltetrahydrofuran, THF, dioxolane, DME, TMEDA, PMDTA, HMTTA, HMPA, DMPU, and 12-crown-4, to PhLi solutions in THF and/or ether have been studied by low-temperature NMR techniques (^{13}C, ^{6}Li, ^{7}Li, and ^{31}P). We have described in detail the rich number of structures that PhLi forms when complexed to these polar additives. In addition, the reactivities of these PhLi solutions were measured by determining the rate and regioselectivity of metalation of substituted furans and thiophenes, resulting in the following trend for enhancing PhLi reactivity: HMPA > 12-crown-4 > PMDTA > HMTTA > TMEDA.

Experimental Section[17]

General. All glassware was dried in a 110 °C oven overnight or flame dried and flushed with N_2 to remove air and moisture. All reactions were performed under an atmosphere of dry N_2.

Solvents and Materials. Tetrahydrofuran (THF) and diethyl ether (ether) were freshly distilled from sodium benzophenone ketyl prior to use. Dimethyl ether (bp −24.9 °C) was first condensed into THF/sodium benzophenone ketyl solution at −78 °C and subsequently distilled through a cannula into a collection vessel cooled to −78 °C. HMPA was distilled at reduced pressure (0.7 mm, 84−88 °C) from CaH_2 and stored over molecular sieves. TMEDA, PMDTA, HMTTA, and 12-crown-4 were distilled at reduced pressure from Na metal and stored over molecular sieves (TMEDA: 40 mm, 24−29 °C; PMDTA: 6.0 mm, 58−62 °C; HMTTA: 0.01 mm, 82−85 °C; 12-Crown-4: 6.5 mm, 65−68 °C). All compounds were commercially available, except for methyl isopropyl disulfide[27] and HMTTA[28] which were prepared according to literature procedures.

Salt-free PhLi (reaction of PhI with *n*-BuLi)[1g,29] and *n*-butyllithium-^{6}Li (reaction of n-BuCl with ^{6}Li metal)[1g,6a] were also prepared according to literature procedures. ^{6}Li metal (95.5%) was purchased from Oak Ridge National Lab. Solutions of lithium reagents in ether and THF were titrated against *n*-propanol with 1,10-phenanthroline as indicator[30] or quenched with dimethyl disulfide and analyzed by GC.

NMR Spectroscopy. All low-temperature multinuclear NMR experiments were conducted on a Bruker AM-360 spectrometer equipped with a 10 mm wide-bore broadband probe tuned at 90.556 MHz (^{13}C), 52.984 MHz (^{6}Li), 139.905 MHz (^{7}Li), or 145.785 MHz (^{31}P). All spectra were acquired in a combination of the protio solvents THF, ether, and/or dimethyl ether with the spectrometer unlocked. The digital resolution was 0.6−1.2 Hz for ^{13}C, 0.2−0.8 Hz for ^{6}Li, 0.5−1.0 Hz for ^{7}Li, and 0.6−1.2 Hz for ^{31}P. (Note: Although the spectrometer was unlocked during acquisition, the field was generally very stable, and only occasionally did a spectrum have to be retaken due to a field shift.)

Lorenzian multiplication (LB) was applied to ^{13}C spectra. Gaussian multiplication was applied to ^{7}Li and ^{31}P spectra, where the Gaussian broadening (GB) was equal to the duration of the free induction decay and the Lorenzian broadening (LB) was set to -(digital resolution/GB). ^{6}Li spectra were not enhanced.

Probe temperatures were measured using a platinum resistance thermometer or a thermocouple before and after the acquisition of each spectrum and varied by less than 1 °C between each of the two measurements. Twenty minutes were allowed between acquisitions for the temperature to equilibrate.

Referencing NMR Spectra. ^{13}C chemical shifts are reported in ppm relative to internal C_6H_6 (δ 129.0). Both ^{6}Li and ^{7}Li chemical shifts are referenced to external 0.30 M LiCl/methanol standard (δ 0.0) at −100 °C. ^{31}P chemical shifts are reported relative to external 0.1 M PPh_3 in THF (δ −6.0) at −100 °C.

Product Analysis. GC analyses were performed on a Varian 3700 analytical GC with a flame ionization detector and a 12 m × 0.32 mm 3*12QC3/SE−30 capillary column (He pressure of 6.0 psi, column flow rate (split ratio 300:1) of 3 mL/min and column temperature: 85 °C for 4 min, increased at 20 °C/min to 145 °C, after 2 min at 145 °C, returned to 85 °C). Retention times and response factors (R_f) with respect to *n*-undecane are as follows: thioanisole: 3.1 min, 1.65; *n*-undecane: 4.0 min, 1.00; 2,5-(dimethylthio)furan: 7.20 min, 2.40; 2-methylthio-3-(methyl)thiophene: 7.7 min, 2.20; 2-methylthio-4-(methyl)thiophene: 8.3 min, 2.20. R_f's are defined for a 1:1 molar solution of *n*-undecane to compound, where R_f = (peak area *n*-undecane)/(peak area compound).

Typical Procedure for an NMR Study of PhLi in THF, Ether, and/or Dimethyl Ether with the Addition of Cosolvents. An oven dried 10 mm NMR tube was fitted with a 9 mm i.d. rubber septum and flushed with N_2 until the tube was cool. The rubber septum was wrapped with Parafilm, the tube was cooled to −78 °C with positive N_2 pressure, and ∼3.6 mL total volume of THF, ether, and/or dimethyl ether was added. The desired amount (∼0.4 mL) of PhLi stock solution in THF or ether was slowly added, the tube was shaken briefly, and the septum was sealed with grease. Before the experiment was begun, the shim values were checked and adjusted for $CDCl_3$. The instrument was unlocked, and the sweep was turned off. The NMR probe was cooled to below −100 °C, and the sample was inserted into the probe. After 10 min, optimization of the FID of C-3 of THF or C-1 of ether was done. Both ^{13}C and $^{6/7}$Li NMR spectra were acquired. The sample was removed and stored at −78 °C. The grease from the septum top was removed, a desired amount of cosolvent was added, and the top of the septum was greased. The NMR tube was placed in the probe and after 10 min, both ^{13}C and $^{6/7}$Li NMR spectra were acquired. This process was repeated for additional equiv of cosolvent.

Standardization of PhLi Solution for Kinetic Studies. A 50 mL 24/40 Erlenmeyer flask was dried, equipped with a septum, and purged with N_2. To the flask was added 1.5 M PhLi in THF (20 mL, 30 mmol), and then the solution diluted with 10 mL of THF. To the solution was added *n*-undecane (0.634 mL, 3.0 mmol) to be used as a GC standard. A 1.0 mL aliquot of the resulting solution was syringed into each of three dry, purged 5 mL round-bottomed flasks equipped with septa and stir bars. Each was quenched with 100 μL of MeSSMe (1.1 mmol). Saturated NH_4Cl solution (∼0.10 mL) was added to each flask, causing a white precipitate, and the solutions were dried over Na_2SO_4. Analysis by capillary GC gave the concentrations of PhLi and *n*-undecane to be 0.90 and 0.11 M, respectively.

Typical Procedure To Study the Effect of Donor Additives on the Reactivity of PhLi. Six long-necked 5 mL round-bottom flasks were dried, equipped with septa and stir bars, and purged with N_2. THF and the desired amount of cosolvent were added to give a total solvent volume of 2.1 mL. The solutions were cooled to −78 °C while keeping positive N_2 pressure in each flask. Stock PhLi in THF solution (0.90 M, 0.33 mL, 0.30 mmol; 0.11 M *n*-undecane, 0.0363 mmol) was added down the side of each flask, and the solutions were mixed thoroughly. After 10 min at −78 °C, 1 equiv of substrate (0.30 mmol) was added using a microsyringe. After stirring at −78 °C for a given time, each solution was quenched with 100 μL of MeSSMe (1.1 mmol). The cold bath was removed, and the flasks were allowed to warm to room temperature while stirring. Saturated NH_4Cl solution (0.2 mL) and pentane (0.5 mL) were added to each, and the solutions were dried over Na_2SO_4. Subsequent analysis by capillary GC was done to determine the concentrations of unreacted PhLi and reacted substrate.

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Supporting Information Available: Additional experimental details, figures, and data analysis (12 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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