Dynamics of Solvent Exchange in Organolithium Reagents. Lithium as a Center of Chirality[1]

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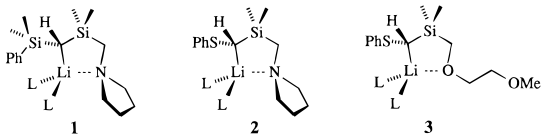
Coordinating solvents have a profound influence on the reactivity, stereochemistry, and regiochemistry of organolithium reagents. Solvation by HMPA has been extensively documented because it is unique among monodentate coordinating solvents in that slow dynamic exchange on the NMR time scale can be achieved at moderately low temperatures (below −100 °C) in solvents such as THF and ether.[1a,2] For polydentate amines the kinetics of exchange between free and coordinated ligands is also slow enough for direct NMR observation.[3,4] However, the detailed nature of interactions with ethers in solution has had to be surmised indirectly because only averaged NMR spectra could be observed.[5] A major advance was the recent report by Lucht and Collum that individual ether solvates of a lithium amide can be detected by NMR spectroscopy in *hydrocarbon* solvent.[6] We report the results of an NMR study of a series of chelated organolithium reagents during which we detected for the first time individual *diastereomeric* ether solvates (Me_2O, THF, oxetane, pyridine) under slow exchange in *dimethyl ether* solution, which allowed direct evaluation of the relative coordinating ability of these solvents.

The organolithium reagents **1**, **2**, and **3** (previously used to study the effects of chelation on stereochemical inversion at the carbanion center)[1b] are unusual in that they form bis-HMPA contact ion pairs (CIP, **2**·$(HMPA)_2$) identified by the triplet at 0.7 ppm in the ^{7}Li NMR spectrum (Figure 1 shows an HMPA titration of **2**). Nonchelated analogs form only trace amounts of this species and instead form separated ion pairs (SIP).[1b] *The two HMPA groups are diastereotopic by virtue of the asymmetric center at the lithium-bearing carbon* (two 1:1:1:1 quartets at 26.8 and 27.0 ppm in the ^{31}P NMR spectra). The reagents **1** and **3** show very similar behavior, as do analogs with amine, ether, pyridyl, and imidazole chelated groups.[1c]



At higher temperatures (−106 °C for **1**, −100 °C for **2**, and −108 °C for **3**) the diastereotopic HMPA signals coalesce. Above coalescence the Li−P coupling can again be resolved, proving that the exchange process is intramolecular. From coalescence temperatures, we estimate activation energies for the "configurational inversion" at the lithium center to be approximately 7.6 kcal/mol for **1**, 8.6 kcal/mol for **2**, and 7.5 kcal/mol for **3**.

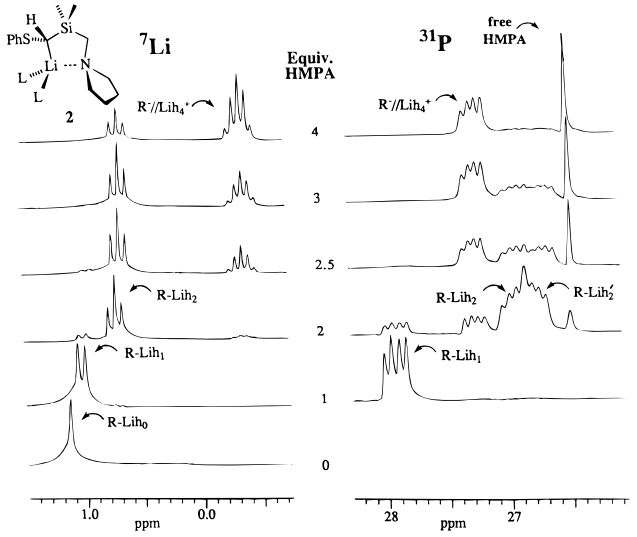


Figure 1. ^{7}Li (139.905 MHz) and ^{31}P (145.784 MHz) NMR spectra during the HMPA titration (−108 °C) of **2**, 0.28 M, THF:ether:pentane 10:8:3 (h = HMPA). ^{7}Li shifts referenced to external 0.3 M LiCl in methanol.

We can consider three distinct rate-determining steps for the coalescence of the diastereotopic HMPA groups: (1) decoordination of lithium from carbon and inversion at carbon or (2) inversion at lithium, and (3) decoordination of lithium from the chelating group and inversion at lithium. Intermolecular mechanisms such as dissociative or associative substitutions at lithium by free HMPA (through tri- and pentacoordinated lithiums) are ruled out by the maintenance of P−Li coupling during the process. For **2**, the carbon inversion barrier (coalescence of the $SiMe_2$ groups) is about 1 kcal/mol higher, whereas the amine inversion barrier is within experimental error of the HMPA exchange process, so inversion must be occurring at the lithium center, probably after decoordination of nitrogen. Mechanism 1 is a real possibility for **1**, since the barrier to inversion at carbon is identical within experimental error to the Li-inversion barrier.[1b] The barrier to inversion at carbon for **3** has not been measured.

The mono-HMPA complexes of **1** and **2** showed multiple ^{31}P signals at temperatures below −135 °C in the mixed THF/Me_2O and THF/ether solvents we usually use for very low temperature work. The use of pure Me_2O as solvent at temperatures below −145 °C gave insight into this phenomenon. The two Li-coupled ^{31}P signals observed for **1**·HMPA (Figure 2A) were identified as diastereomeric **1**·HMPA complexes; they coalesced to a single 1:1:1:1 quartet at −120 °C. Furthermore, *the signals of two sets of diastereomeric solvates were observed in the ^{31}P NMR spectra of the mono-HMPA complexes of **1** and **2** when mixed solvents were used*. Figure 2 shows a sample set of spectra for the titration of **1**·HMPA in Me_2O with oxetane below −147 °C. Similar spectra were obtained for titration of **1** with THF, 3,3-dimethyloxetane, and pyridine, and for **2** with THF and 3,3-dimethyloxetane. In pure Me_2O, one pair of ^{31}P signals was observed; a second pair of peaks grew in as the cosolvent was added. Thus, under these conditions, not only

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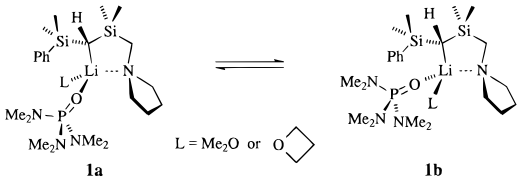

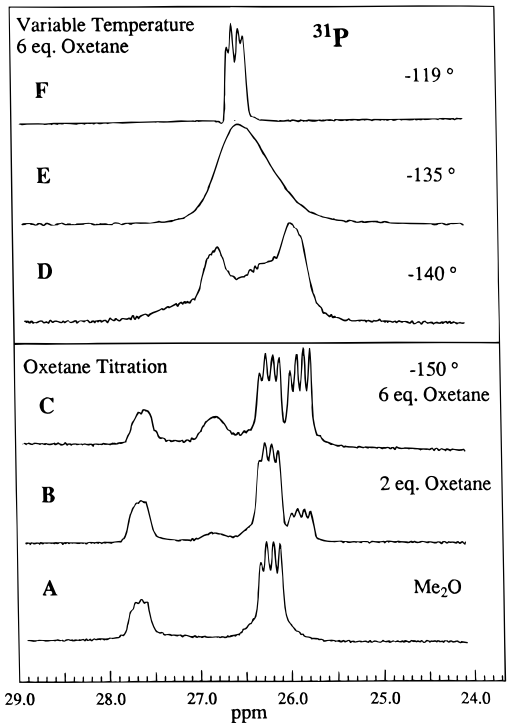

Figure 2. (A−C) ^{31}P NMR spectra of the titration of **1**·HMPA in Me_2O with oxetane. (C−F) Variable temperature spectra at 6 equiv of oxetane.

the intermolecular exchange of HMPA but also exchange of the ether solvent and cosolvent, as well as configurational inversions at lithium and carbon, are all slow on the NMR time scale ($\Delta G^{\ddagger} > 6.0$ kcal/mol).

The dynamic behavior of a 1:1 ratio of the dimethyl ether and oxetane solvates of **1**·HMPA is shown in Figure 2C−F. The dimethyl ether diastereomers exchange faster (Figure 2C,D) than the oxetane solvates. All four signals coalesce to a single common quartet in the phosphorus NMR spectrum (Figure 2F, δ 26.53, $J = 9-10$ Hz) and a doublet in the lithium NMR spectrum (δ 1.28, $J = 9.9$ Hz). Like the HMPA exchange of **2**·$(HMPA)_2$ discussed above, the dynamic processes for **1**·HMPA are intramolecular for HMPA (no loss of Li−P coupling), but the exchange of the ether solvents must be intermolecular, since all four signals collapse to one. If the only stereochemical process were inversion at lithium, the higher temperature spectrum (−119 °C) would show two ^{31}P signals for the Me_2O and oxetane solvates.

The ^{31}P signals in all of the titrations could be integrated, and this has allowed a direct measurement of relative lithium−solvent association constants (eq 1). For **1** the relative K_{Solv} values at −150 °C were Me_2O:THF:3,3-dimethyloxetane:oxetane:pyridine:HMPA = 1:7:13:16:100:2000. Compound **2** behaves similarly, except that the diastereomer ratio was ≈7:1 (vs 2.6:1 for **1**), the ^{31}P shift of the major diastereomer was downfield rather than upfield, and the rate of diastereomer equilibration was somewhat slower. The relative K_{Solv} values measured for **2** (Me_2O:THF:3,3-dimethyloxetane = 1:7:11.5) were identical within experimental error to the K's for **1**. This suggests that we are dealing with inherent solvent donor strengths toward lithium without significant steric effects, since **1** and **2** differ substantially in steric hindrance at the carbanion center.

$$\mathrm{R{-}Li{\cdot}HMPA{\cdot}OMe_2} + \mathrm{Solv} \overset{K_{Solv}}{\rightleftharpoons} \mathrm{R{-}Li{\cdot}HMPA{\cdot}Solv} + \mathrm{OMe_2} \quad (1)$$

The behavior of the solvates of **1** and **2** differs in significant ways from that of the lithium bis(trimethylsilyl)amide dimer solvates reported by Lucht and Collum.[6] The organolithium reagents **1** and **2** are tetracoordinated, whereas the amide dimer has tricoordinated lithiums. Secondly, the activation free energies for intermolecular solvent exchange are substantially higher in the amide solvates. NMR coalescence between the bis-THF solvated dimer and free solvent occurred at −47 °C ($\Delta G^{\ddagger}_{226K} = 10.8$ kcal/mol), whereas coalescence between the diasteromeric solvates **1a** and **1b** (L = THF) occurred at −139 °C ($\Delta G^{\ddagger}_{135K} = 6.0-6.5$ kcal/mol[7]).

In light of the strong intramolecular coordination of the pyrrolidine group in **1** and **2** and the weaker chelation of similar reagents with pendant ether groups,[1b] it is interesting that addition of *N*-methylpyrrolidine caused no significant changes in the NMR spectra of **1** in dimethyl ether.[8] Propylene oxide (up to 28 equiv) also showed no sign of coordination to **1** or **2**.[9] The solvation free energy of HMPA vs THF ($\Delta\Delta G°_{123K} = -1.4$ kcal/mol) in **1** is surprisingly small compared to the value of −7.4 kcal/mol estimated for lithium picrate by an electrochemical method.[10] Apparently the strongly coordinated (and perhaps sterically hindered) lithium of **1**·HMPA has greatly reduced electrophilicity compared to the THF solvate of lithium picrate.

The results reported here have provided detailed insights into the coordination behavior of a chelated lithium reagent in ethereal solvent. Even with one or two strongly electron donating HMPA ligands attached to lithium, the solvation structure is tetracoordinate, capable of sustaining diastereotopic or diastereomeric solvation on the NMR time scale. The diastereomeric solvates of **1** (2.6:1) and **2** (7:1) provide models for asymmetric induction at carbon from asymmetric solvation at lithium.[11]

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(7) The activation parameters were estimated from line shape simulations which did not specifically include the effects of Li−P coupling.

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