J. Am. Chem. Soc. **1995,** *117,* 6621−6622

Chelation Effects in Chiral Organolithium Reagents[1]

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Received March 24, 1995

Chelation effects are frequently used as an organizing feature in controlling the formation, structure, and reactivity of organolithium reagents.[2] We report spectroscopic studies of a series of silicon- and sulfur-substituted organolithium reagents (**1**−**6**)[3] designed to determine how chelation competes with solvation by THF and HMPA and to elucidate the effects of chelation on ion pair structure, solvation, and configurational stability.

The HMPA titration[1a,4] is a sensitive tool for studying the strength of coordination between lithium and its counterion. The ^{7}Li NMR spectra in Figure 1 define the coordination state of compounds **1**−**6** at an informative point in the HMPA titration (2 equiv of HMPA).[5] There are pronounced differences between the model systems **1** and **2** and their analogs with groups capable of forming a 5-membered chelate. The pyrrolidine derivatives **5** and **6** showed mostly the contact ion pair coordinated with two molecules of HMPA (triplet due to ^{7}Li−^{31}P coupling, $J_{\text{Li-P}} = 8.3$ Hz) and only a trace of separated ion pairs, whereas **1**[6] and **2** formed mostly separated ion pairs, with some mono-HMPA complex (doublet, $J_{\text{Li-P}} = 9.4$ and 10.0 Hz) and only a trace of the bis-HMPA complex for **2**.[7] In the ^{31}P spectra, **5** and **6** had a detectable amount of free HMPA present at this point, whereas the model compounds **1** and **2** showed none at <3 equiv. Complete ion pair separation required 6−8 equiv of HMPA for **5** and >10 equiv for **6**, whereas **1** and **2** were completely separated with 3 equiv. The methoxymethyl (**3**) and (2-methoxyethoxy)methyl (**4**) substituted lithium reagents showed behavior intermediate between that of **2** and **5**.[8] We conclude that **3** and **4** are weakly chelated in THF, that **5** and **6** are strongly chelated, and that their mono- and bis-HMPA complexes are also chelated. This latter observation is especially striking since the stereochemical and regiochemical effects attributed to chelation are often sharply diminished or disappear altogether in coordinating solvents.[2c,f,9] Furthermore, chelation results in more difficult ion pair separation,[10] and this effect is stronger for chelation by amino than by ether groups.[11]

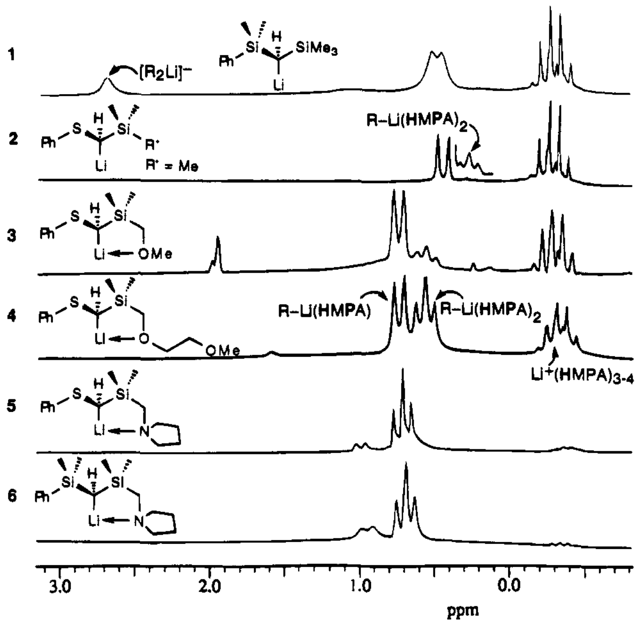

Figure 1. ^{7}Li NMR spectra (139.9 MHz) with 2 ± 0.2 equiv of HMPA, −113 to −135 °C in 6:4 THF/Et$_2$O (**1**−**5**) or THF/Me$_2$O (**6**), 0.3 M LiCl in MeOH reference.

Stereochemical inversions of organolithium reagents can occur through either associative[1b,12] or dissociative mechanisms.[1b,13] The latter is at least a three-step process with decoordination of lithium, inversion (or ion pair reorganization), and recoordination; each step could be rate determining. In the case of some sulfur- and selenium-substituted carbanions, rotation around the S−C or Se−C bond is an important part of the process.[1b,13a,14]

Compounds **1**−**6** were designed to study chelation effects on lithium reagent inversion barriers. The diastereotopic methyls at silicon exchange at the same rate as the carbanion center inverts. For **6** (Figure 2), DNMR rates between 4 s^{-1} (−75.7 °C) and 3000 s^{-1} (−16.3 °C) were obtained. Figure 3 shows a $\Delta G^{\ddagger}$ vs T plot of the data obtained for **1** and **6**; Table 1 includes additional activation parameters (some solvates and compounds were not fully analyzed, but a single rate was measured at the coalescence point).

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[5] The lithium reagents **1**−**6** appear to be monomeric in THF and mixed solvents containing ethyl and methyl ether. In all cases, the carbanion carbon shows *J*-coupling to only one lithium.

[6] Compound **1** also forms a small amount of triple ion (broad singlet at δ 2.7). Lithium triple ions have been detected previously:[4a,7] Cambillau, C.; Ourevitch, M. *J. Chem. Soc., Chem. Commun.* **1981**, 996. Eaborn, C.; Hitchcock, P. B.; Smith, J. D.; Sullivan, A. C. *J. Chem. Soc., Chem. Commun.* **1983**, 827. Fraenkel, G.; Hallden-Abberton, M. P. *J. Am. Chem. Soc.* **1981**, *103*, 5657. Jackman, L. M.; Scarmoutzos, L. M.; Porter, W. *J. Am. Chem. Soc.* **1987**, *109*, 6524.

[7] Chelated β-dicarbonyl compounds have higher ion pair association constants than do nonchelated ones: Olmstead, W. N.; Bordwell, F. G. *J. Org. Chem.* **1980**, *45*, 3299.

[8] The ^{7}Li and ^{13}C chemical shift evidence suggests that both oxygens of the (methoxyethoxy)methyl group are coordinated to Li in THF.

[9] There are exceptions, most notably a nitrogen-chelated lithium amide complexed to HMPA: Sato, D.; Kawasaki, H.; Shimada, I.; Arata, Y.; Okamura, K.; Date, T.; Koga, K. *J. Am. Chem. Soc.* **1992**, *114*, 761.

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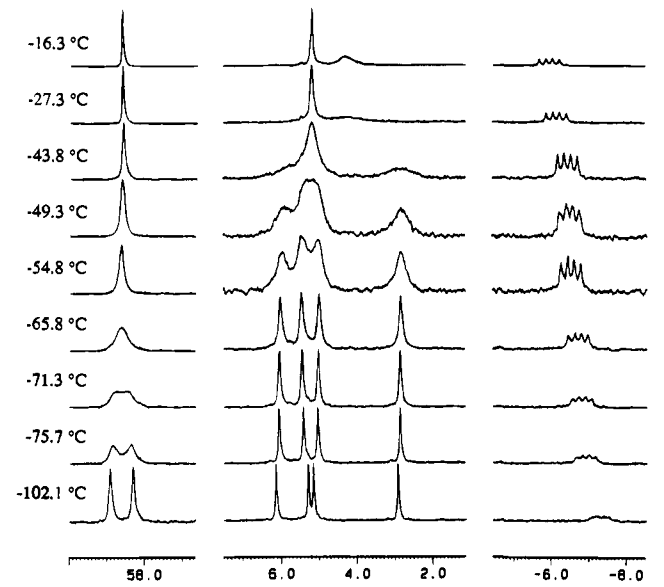

Figure 2. Temperature-dependent ^{13}C NMR spectra (90.6 MHz) of **6**, 0.30 M in THF/ether/pentane 6:4:1. Ring NCH_2 groups (left), $SiMe_2$ groups (middle), and carbanion carbon (right).

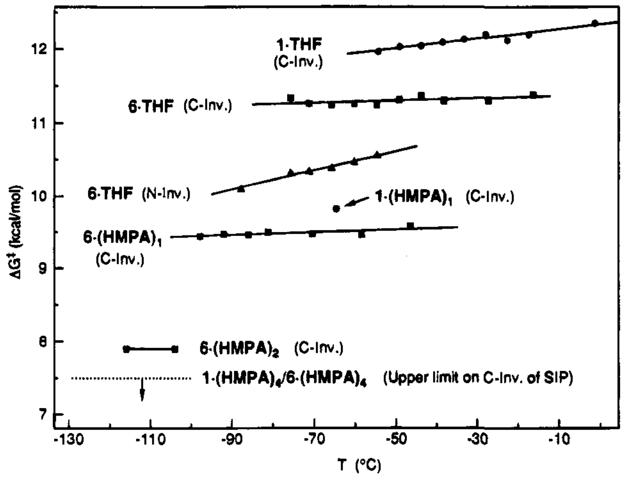

Figure 3. Temperature dependence of $\Delta G^{\ddagger}$ for lithium reagents **1** and **6** in THF/ether/pentane 6:4:1.

The mechanism for inversion of the chelated compounds **4**−**6** in THF was unambiguously unimolecular since the $^{7}Li-^{13}C$ *J*-coupling was observable well above the coalescence temperature of the $SiMe_2$ group. Thus, the rate of *intermolecular* exchange of lithium cations is at least 1000 times slower for **6** than the inversion process (see carbanion quartet at δ −7, Figure 2).[15] In addition, the activation entropies for the chelated compounds are zero within experimental error, which is expected for a unimolecular reaction. The coordination of additional solvent molecules (formation of solvent separated ion pairs) at the transition state is unlikely, since this should result in negative $\Delta S^{\ddagger}$ values.[10a,16] Possibly a "conducted tour" mechanism[17] is operative, with lithium remaining coordinated to nitrogen.

Table 1. DNMR Activation Parameters ($\Delta G^{\ddagger}$)[a] for Organolithium Inversion (−50 to −135 °C)

compd	exchanging group	RLi (THF)	RLi $(HMPA)_1$	RLi $(HMPA)_2$	$R^-//Li^+$ $(HMPA)_4$
6	$SiMe_2$	10.7[b]	8.9[c]	7.4	<7.0[d]
6	$N(CH_2)_2$	9.5	8.8		
1	$SiMe_2$	11.2[e]	9.3[f]		<7.0[d]
5	$SiMe_2$	10.5[g]	9.7[h]	9.5	≥9.4[i]
5	$N(CH_2)_2$		8.6	8.8	
3	$SiMe_2$	10.0	10.0		9.4
4	$SiMe_2$	9.3	9.3		9.6
2a, R = *i*-Bu	$SiMe_2$	8.2	7.7−8.8		9.7
2b, R = Ph[j]	$SiMe_2$	8.0[k]	8.0		9.5[l]
2c, R = *t*-Bu	$SiMe_2$	6.7	6.6		9.5

[a] ±0.2−0.3 kcal/mol. [b] $\Delta H^{\ddagger} = 10.5 \pm 0.2$ kcal/mol, $\Delta S^{\ddagger} = -1.3 \pm 0.4$ eu. [c] $\Delta H^{\ddagger} = 8.7 \pm 0.2$ kcal/mol, $\Delta S^{\ddagger} = -1.6 \pm 0.4$ eu. [d] No separate signals observable at any temperature. [e] $\Delta H^{\ddagger} = 10.1 \pm 0.2$ kcal/mol, $\Delta S^{\ddagger} = -6.3 \pm 0.4$ eu. [f] Exchange also observed with triple ion. [g] $\Delta H^{\ddagger} = 9.75 \pm 0.2$ kcal/mol, $\Delta S^{\ddagger} = -3.6 \pm 0.4$ eu. [h] $\Delta H^{\ddagger} = 9.2 \pm 0.3$ kcal/mol, $\Delta S^{\ddagger} = -2.7 \pm 0.7$ eu. [i] Signals move together. [j] Reference 1b. [k] $\Delta H^{\ddagger} = 7.9 \pm 0.2$ kcal/mol, $\Delta S^{\ddagger} = -0.5 \pm 0.6$ eu. [l] $\Delta H^{\ddagger} = 9.5 \pm 0.4$ kcal/mol, $\Delta S^{\ddagger} = 0.3 \pm 1.1$ eu.

The diastereotopic ring NCH_2 carbons of **6** (δ 58.6, Figure 2) exchange about 1 order of magnitude faster than do the $SiMe_2$ groups ($\Delta G^{\ddagger} = 9.4$ kcal/mol, −117 °C). Thus, decoordination of nitrogen from lithium, followed by nitrogen inversion and recoordination, occurs faster than inversion at carbon. The N-inversion barrier is higher than the inversion barriers of uncoordinated N-methylpyrrolidines (7.4−7.9 kcal/mol).[18] Addition of HMPA to **6** decreases the barrier for N-inversion to 8.8 kcal/mol.

The carbon inversion barrier $\Delta G^{\ddagger}$ for the nonchelated compound **1** is higher than that for **6**. Replacement of THF with HMPA on lithium in the bis-silicon-substituted lithium reagents **1** and **6** results in a stepwise decrease of $\Delta G^{\ddagger}$ by 1.5−2 kcal/mol for each HMPA for the inversion process (Figure 3). This is consistent with decoordination of the carbanion from lithium as the rate-determining step, which gets easier with decreasing electrophilicity of the lithium cation.

The sulfur-substituted lithium reagents show some interesting differences from those with two silicon groups. The nonchelated compounds **2a**−**c** have lower inversion barriers than the chelated ones, **3**−**5**. The fully separated $R^-//Li(HMPA)_4^+$ ion pairs all have the same barrier of $\Delta G^{\ddagger} = 9.5 \pm 0.2$ kcal/mol, which is due to rotation rather than inversion.[1b,13a] In contrast, no diastereotopic nonequivalence of either $SiMe_2$ group could be detected for the separated ions from **1** and **6**.[19] The inherently small 6-fold rotation barriers in silanes lead to undetectably small inversion barriers, whereas the PhS-substituted carbanions **2**−**5** have high 2-fold barriers which render the SIPs chiral.[1b,14]

Conclusion. Proposals have been made that chelation might increase[20a] or decrease[20b] the configurational stability of organolithium reagents. In this study, we have found examples of both effects: for the bis-silicon reagent **6**, nitrogen chelation increases the racemization rate, whereas for the phenylthio-substituted compounds **2**−**5**, chelation retards the rate. We have also found that nitrogen chelation in both types of lithium reagents makes ion pair separation by HMPA more difficult.

Acknowledgment. We thank the National Science Foundation for support of this work. K.J.K. thanks the Swiss National Science Foundation for a Postdoctoral Fellowship.

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(15) The nonchelated compounds **1** and **2** lose Li−C coupling close to the temperature at which $SiMe_2$ coalescence occurs. However, even here the Li−C exchange does not appear to be mechanistically related to the inversion process.[1b]

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