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Correlation between the ^{6}Li,^{15}N Coupling Constant and the Coordination Number at Lithium

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Abstract: The ^{6}Li,^{15}N coupling constants of lithium amide dimers and their mixed complexes with *n*-butyllithium, formed from five different chiral amines derived from (*S*)-[^{15}N]phenylalanine, were determined in diethyl ether (Et_2O), tetrahydrofuran (THF) and toluene. Results of NMR spectroscopy studies of these complexes show a clear difference in ^{6}Li,^{15}N coupling constants between di-, tri- and tetracoordinated lithium atoms. The lithium amide dimers with a chelating ether group exhibit ^{6}Li,^{15}N coupling constants of ~3.8 and ~5.5 Hz for the tetracoordinated and tricoordinated lithium atoms, respectively. The lithium amide dimers with a chelating thioether group show distinctly larger ^{6}Li,^{15}N coupling constants of ~4.4 Hz for the tetracoordinated lithium atoms, and the tricoordinated lithium atoms have smaller ^{6}Li,^{15}N coupling constants, ~4.9 Hz, than their ether analogues. In diethyl ether and tetrahydrofuran, mixed dimeric complexes between the lithium amides and *n*-butyllithium are formed. The tetracoordinated lithium atoms of these complexes have ^{6}Li,^{15}N coupling constants of ~4.0 Hz, and the ^{6}Li,^{15}N coupling constants of the tricoordinated lithium atoms differ somewhat, depending on whether the chelating group is an ether or a thioether; ~5.1 and ~4.6 Hz, respectively. In toluene, mixed trimeric complexes are formed from two lithium amide moieties and one *n*-butyllithium. In these trimers, two lithium atoms are tricoordinated with ^{6}Li,^{15}N coupling constants of ~4.6 Hz and one lithium is dicoordinated with ^{6}Li,^{15}N coupling constants of ~6.5 Hz.

Keywords: chiral lithium amides · coordination number · coupling constants · lithium · NMR spectroscopy

Introduction

Alkyllithium compounds and lithium amides constitute some of the most frequently used organometallic reagents in organic synthesis. In recent years, there have been extensive efforts to develop new chiral lithium amides for use in asymmetric synthesis. In addition, Asami, Simpkins, Koga, O'Brien, Singh and Andersson have reported various chiral lithium amides that mediate enantioselective deprotonation reactions and asymmetric epoxide rearrangements.[1] In 1994, Asami and co-workers reported that cyclohexene oxide could be rearranged to cyclohexen-3-ol under substoichiometric conditions.[2] This lead to an intensified interest in developing catalytic systems. Ahlberg and co-workers explained and developed the concept of achiral bulk bases in these catalytic systems.[3,4] Chiral lithium amides were also successfully employed as chiral inducers in stereoselective 1,2-addition reactions.[5–8] Maddaluno, Williard and our group have reported NMR studies revealing the reactive species in stereoselective additions of *n*-butyllithium (*n*BuLi), methyllithium and lithioacetonitrile to aldehydes.[7–11]

Because of the importance of chiral lithium amides with chelating groups, it is essential that their structures and the effect of chelating groups are better understood. Recently, there has been an increased focus on studies of structure–reactivity relationships for the development of efficient and selective transformations, often needed within, for example, the pharmaceutical industry.[12] Solution-state studies are advantageous as they give information about all species present in the solution, including mixed aggregates and the complex equilibrium. NMR spectroscopy techniques are particularly suitable for analysis of organolithium compounds because there are two stable isotopes of lithium, each having an observable nuclear spin, allowing direct observation by NMR spectroscopy. Although both lithium isotopes have quadrupole nuclei, the quadrupole moment of the ^{6}Li isotope is very small and the dipole relaxation mechanism is

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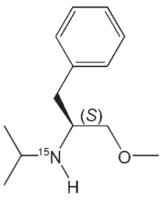
dominating, yielding sharp signals in the ^{6}Li NMR spectra even at low temperatures. The linewidths of the ^{6}Li NMR signals are typically less than 1.0 Hz at half height. The aggregation state of a ^{6}Li,^{15}N doubly labelled lithium amide is obtained directly from the multiplicity of the ^{6}Li NMR signal, due to scalar coupling between the nitrogen-15 and lithium-6 nuclei. A lithium nucleus bonded directly to one nitrogen-15 appears as a doublet, whereas lithium bonded to two nitrogen-15 nuclei is split into a triplet. Extensive NMR studies of ^{6}Li,^{15}N doubly labelled lithium amides by Collum and his group have increased considerably the knowledge of solution structures and the aggregation state of several frequently used lithium amides.[13] This technique has also been used by us and other groups to establish the aggregation state of several chiral lithium amides, as well as the aggregation state of the mixed complexes they form with other organolithium compounds.[4,8,10,11,14,15]

It is known that the specific solvation at lithium may affect not only the reactivity, but also the stereoselectivity obtained in reactions with chiral lithium amides. Unfortunately, the design of new and powerful chiral lithium amides and catalytic systems is limited by lack of a thorough understanding of the factors determining the solvation at lithium. Jackman and co-workers have shown that the magnitude of the ^{7}Li,^{15}N quadrupole splitting constant of lithium arylamides and enolates corresponds very well to the aggregation and solvation at lithium.[16] Kikuchi and co-workers have reported, based on theoretical studies, that the magnitude of the ^{6}Li,^{15}N coupling constant reflects the coordination at the lithium atom bonded to nitrogen.[17] There have been some reports, by Davidsson and Maddaluno respectively,[15,18] in which the ^{6}Li,^{15}N coupling constant ($^1J(^6\text{Li},^{15}\text{N})$) was used to estimate the coordination number at lithium based on the results reported by Kikuchi. However, these studies presented only scattered results and there has been no systematic report that proves the existence of a $^1J(^6\text{Li},^{15}\text{N})$-dependence on the coordination number at lithium. Thus, we decided to establish if there is a correlation between the $^1J(^6\text{Li},^{15}\text{N})$ and the coordination number at lithium. Such a finding would be important for improving the study of and understanding the interactions between lithium and the coordinating solvent molecules or internal coordinating groups. We have synthesised and studied five ^{6}Li,^{15}N doubly labelled lithium amides from the corresponding ^{15}N-labelled amines (**1**–**5**), as well as the mixed complexes they form with *n*BuLi, and have determined the coupling constants in diethyl ether (Et_2O), tetrahydrofuran (THF) and toluene. Here, we report the measured $^1J(^6\text{Li},^{15}\text{N})$ for several different lithium amide dimers and mixed *n*BuLi/lithium amide complexes in Et_2O, THF and toluene, respectively.



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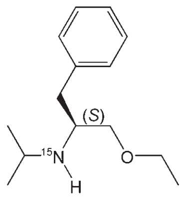

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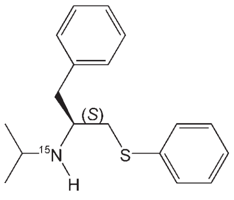

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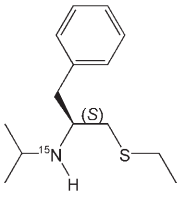

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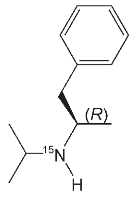

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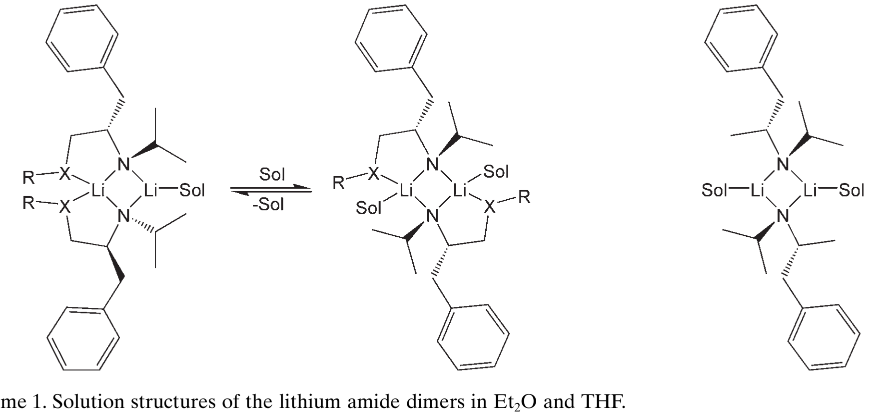
Results

The ^{15}N-labelled chiral amines (**1**–**5**) were all synthesised from (*S*)-[^{15}N]phenylalanine. Amines **1**–**4** were made according to previously published methods.[5] The key step in preparing amine **5** from (*S*)-[^{15}N]phenylalanine was the SmI_2-mediated reduction of the *tert*-butyloxycarbonyl (*t*BOC)-protected aminoiodide to the corresponding *t*BOC-protected amine by using a procedure developed in our laboratory.[19]

Lithium amide dimers: Initially, we studied the aggregates of the lithium amides Li-**1**–Li-**5** in Et_2O and THF, respectively. The degree of aggregation of the complexes was deduced directly from the splitting of the ^{6}Li NMR signals, due to coupling to ^{15}N nuclei. All lithium amides were observed to exist exclusively as dimers in both Et_2O and THF (Scheme 1). Chelating lithium amide dimers can exist as either equivalently or nonequivalently solvated dimers. The equivalently solvated dimers give rise to one ^{6}Li NMR signal, whereas nonequivalently solvated dimers give rise to two ^{6}Li NMR signals in a 1:1 ratio. The ^{1}H and ^{13}C NMR spectra display only one set of signals for the lithium amides, irrespective of whether the lithium atoms are equiv-



Scheme 1. Solution structures of the lithium amide dimers in Et_2O and THF.

alently or nonequivalently solvated, indicating that the complexes are C_2-symmetric.

The ^{6}Li NMR chemical shifts of lithium amides are known to be sensitive to solvents, in particular coordinating solvents or ligands. The number of ethers specifically coordinated to the respective lithium amide was determined by conducting volumetric titration of Et_2O or THF in small quantities (0.3 to 10 equiv) to the respective lithium amide in [D$_8$]toluene. The titration experiments revealed that the chelating amides, Li-**1**–Li-**4**, are only monosolvated, that is, only one ether is coordinated at low concentrations of ether, yielding nonequivalently solvated lithium atoms in the dimers (Figure 1). However, such monosolvated amides were not observed for Li-**5** in either Et_2O or THF.

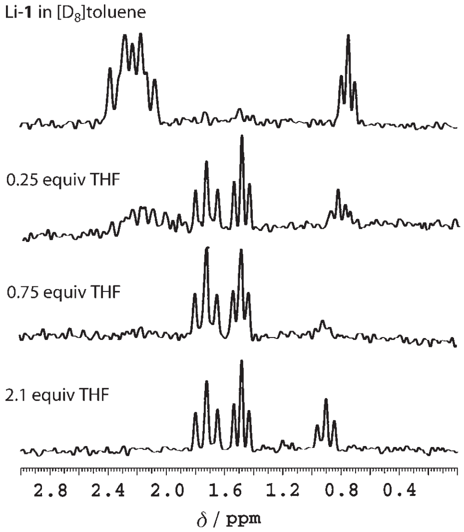


Figure 1. ^{6}Li NMR spectra of a THF titration of a solution of Li-**1** in [D$_8$]toluene at −90 °C. In pure toluene, Li-**1** exists as an oligomer, however, upon addition of a small amount of THF, two triplets from the nonequivalently solvated (Li-**1**)$_2$ appear at $\delta = 1.5$ ($J = 3.8$ Hz) and 1.7 ppm ($J = 5.7$ Hz). Upon further addition of THF, these signals are eventually replaced by a single triplet of the equivalently solvated (Li-**1**)$_2$ at $\delta = 0.9$ ppm ($J = 4.2$ Hz).

Addition of equivalent amounts of THF to the Et_2O solvates results in almost complete replacement of the Et_2O ligand by THF in the nonequivalently solvated dimers. Thus, THF binds much tighter than Et_2O to lithium. Upon further addition of THF, the lithium amides Li-**1**, Li-**3** and Li-**4** become disolvated dimers, with equivalently solvated lithium atoms. Surprisingly, THF does not favour an equivalently solvated lithium amide dimer of Li-**2**, which was observed to exist as a nonequivalently solvated dimer also at high THF concentrations (10 M). The lithium amide Li-**3** is also unique because it forms disolvated lithium amide dimers with equivalently solvated lithium atoms at higher concentrations of Et_2O, which is not observed for any of the other lithium amide dimers with an internal chelating group.[11] The lithium amide Li-**5** was observed to be an equivalently disolvated dimer in both Et_2O and THF.

In the presence of added nondeuterated ethers, the specific solvent coordination of Et_2O or THF to the lithium nuclei of the respective lithium amides was supported by strong heteronuclear NOE, between the α protons of the ether and the lithium nucleus coordinated by the solvent, observed in the respective ^{6}Li,^{1}H-HOESY[20] spectra.

In the nonequivalently solvated dimers, one lithium is tetracoordinated by two nitrogen anions and two chelating groups, and the other is tricoordinated by two nitrogen anions and one coordinated solvent molecule. In contrast, in equivalently solvated dimers both lithium atoms are tetracoordinated by two nitrogen anions, the chelating group and a solvent molecule. The observed $^{1}J(^{6}\mathrm{Li},^{15}\mathrm{N})$ for the nonequivalently solvated lithium amide dimers are given in Table 1, and the $^{1}J(^{6}\mathrm{Li},^{15}\mathrm{N})$ for the equivalently solvated lithium amide dimers are given in Table 2. The difference in coordination around the lithium atoms is clearly reflected in the observed $^{1}J(^{6}\mathrm{Li},^{15}\mathrm{N})$.

Table 1. Coupling constants, $^{1}J(^{6}\mathrm{Li},^{15}\mathrm{N})$, and chemical shifts [in parenthesis, in ppm] of the nonequivalently solvated dimeric lithium amide complexes observed in the ^{6}Li NMR spectra recorded in Et_2O and toluene at −90 °C.

Entry	Complex	$^{1}J(^{6}\mathrm{Li},^{15}\mathrm{N})$ [Hz] Tetracoordinated Li	$^{1}J(^{6}\mathrm{Li},^{15}\mathrm{N})$ [Hz] Tricoordinated Li
1[a]	(Li-**1**)$_2$·Et_2O	3.7 (1.7)	5.4 (1.8)
2[b]	(Li-**1**)$_2$·THF	3.8 (1.5)	5.7 (1.7)
3[a]	(Li-**2**)$_2$·Et_2O	3.8 (1.7)	5.5 (1.9)
4[b]	(Li-**2**)$_2$·THF	3.8 (1.3)	5.5 (1.8)
5[b]	(Li-**3**)$_2$·Et_2O	4.6 (3.0)	4.9 (1.2)
6[b]	(Li-**3**)$_2$·THF	4.6 (2.9)	4.8 (1.3)
7[a]	(Li-**4**)$_2$·Et_2O	4.4 (3.2)	5.2 (1.8)
8[b]	(Li-**4**)$_2$·THF	4.4 (2.7)	4.9 (1.3)

[a] Complex studied in [D$_{10}$]Et_2O. [b] Complex studied in [D$_8$]toluene.

Table 2. Coupling constants, $^{1}J(^{6}\mathrm{Li},^{15}\mathrm{N})$, and chemical shifts (in parenthesis, in ppm) of the equivalently solvated dimeric lithium amide complexes observed in the ^{6}Li NMR spectra recorded in Et_2O, THF or toluene at −90 °C.

Entry	Complex	$^{1}J(^{6}\mathrm{Li},^{15}\mathrm{N})$ [Hz] Tetracoordinated Li	$^{1}J(^{6}\mathrm{Li},^{15}\mathrm{N})$ [Hz] Tricoordinated Li
1[a]	(Li-**1**)$_2$·2THF	4.2 (0.9)	–
2[a]	(Li-**3**)$_2$·2Et_2O	4.4 (0.9)	–
3[a]	(Li-**3**)$_2$·2THF	4.5 (1.3)	–
4[a]	(Li-**4**)$_2$·2THF	4.4 (1.2)	–
5[b]	(Li-**5**)$_2$·2Et_2O	–	5.2 (2.3)
6[c]	(Li-**5**)$_2$·2THF	–	5.0 (2.0)

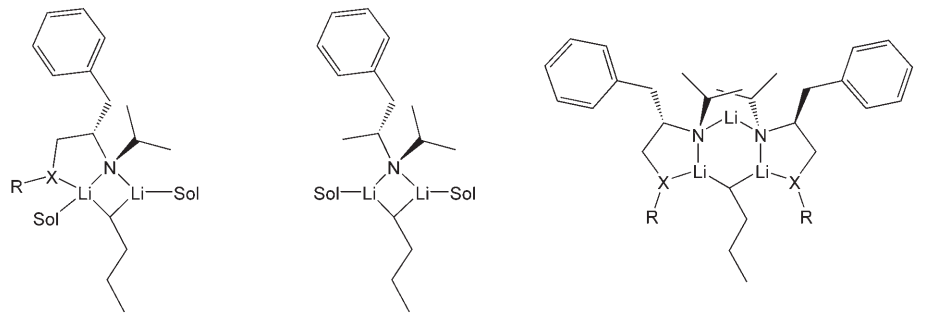
[a] Complex studied in [D$_8$]toluene. [b] Complex studied in [D$_{10}$]Et_2O. [c] Complex studied in [D$_8$]THF.

The $^{1}J(^{6}\mathrm{Li},^{15}\mathrm{N})$ of the tetracoordinated lithium nuclei of the equivalently and nonequivalently solvated lithium amide dimers were observed to be between 3.7 and 4.6 Hz. All of the tetracoordinated lithium atoms of the nonequivalently solvated lithium amide dimers with a chelating ether group have $^{1}J(^{6}\mathrm{Li},^{15}\mathrm{N})$ close to 3.8 Hz, whereas the thioether analogues have substantially larger $^{1}J(^{6}\mathrm{Li},^{15}\mathrm{N})$ of around 4.5 Hz.

The difference in $^1J(^6Li,^{15}N)$ between the ether and thioether lithium amide analogues is not as large for the equivalently solvated dimers; 4.2 and 4.4 Hz, respectively.

The $^1J(^6Li,^{15}N)$ of the tricoordinated lithium nuclei of the nonequivalently solvated lithium amide dimers are observed to be between 4.8 and 5.7 Hz, which is clearly larger than those of the tetracoordinated lithium atoms. Again, there is a rather substantial difference between the $^1J(^6Li,^{15}N)$ of the lithium amides with a chelating ether group and their analogues with a chelating thioether group. The ether chelates exhibit $^1J(^6Li,^{15}N)$ close to 5.5 Hz, whereas the thioether chelates have smaller $^1J(^6Li,^{15}N)$ of around 4.9 Hz. The $^1J(^6Li,^{15}N)$ for the lithium amide dimer without a chelating group, (Li-**5**)$_2$, in Et_2O and THF are 5.0 and 5.2 Hz, respectively. The average values of the $^1J(^6Li,^{15}N)$ are 5.2 Hz for the tricoordinated lithium atoms and 4.2 Hz for the tetracoordinated lithium atoms.

Mixed complexes: Mixed complexes are formed upon addition of *n*BuLi to the respective chiral lithium amides. The characteristic carbanionic carbon signal, a quintet with $^1J(^6Li,^{13}C) \approx 8$ Hz, observed at chemical shifts of around 10 ppm in the ^{13}C NMR spectra, is clear evidence for the formation of a mixed complex between *n*BuLi and the lithium amide. In the noncoordinating solvent [D$_8$]toluene, only mixed cyclic trimers were observed, as indicated by two ^6Li NMR signals in an intensity ratio of 1:2. In contrast, only 1:1 mixed dimers were observed in Et_2O and THF. The ^6Li NMR signals of the mixed dimers become well-resolved doublets, due to coupling to one nitrogen-15. In contrast, the mixed trimers give rise to a doublet and a triplet, due to coupling to one and two nitrogen atoms, respectively (Scheme 2).



Scheme 2. Different mixed complexes formed from the lithium amides and *n*BuLi.

Table 3. Coupling constants, $^1J(^6Li,^{15}N)$, and chemical shifts (in parenthesis, in ppm) of the mixed dimeric *n*BuLi/lithium amide complexes observed in the ^6Li NMR spectra recorded in Et_2O and THF at −90 °C.

Entry	Complex	$^1J(^6Li,^{15}N)$ [Hz] Tetracoordinated Li	$^1J(^6Li,^{15}N)$ [Hz] Tricoordinated Li
1[a]	(*n*BuLi/Li-**1**)·2 Et_2O	4.0 (2.1)	5.1 (2.7)
2[a]	(*n*BuLi/Li-**1**)·2 THF	3.9 (2.0)	5.1 (2.6)
3[a]	(*n*BuLi/Li-**2**)·2 Et_2O	4.1 (2.1)	5.2 (2.7)
4[a]	(*n*BuLi/Li-**2**)·2 THF	4.1 (2.1)	5.2 (2.8)
5[a]	(*n*BuLi/Li-**3**)·2 Et_2O	4.3 (2.7)	4.7 (2.8)
6[b]	(*n*BuLi/Li-**3**)·THF	–	4.4 (2.6), 4.9 (2.8)
7[a]	(*n*BuLi/Li-**3**)·2 THF	4.0 (1.9)	4.5 (2.5)
8[a]	(*n*BuLi/Li-**4**)·2 Et_2O	4.1 (2.7)	4.9 (2.8)
9[b]	(*n*BuLi/Li-**4**)·THF	–	4.4 (2.5), 4.9 (2.8)
10[c]	(*n*BuLi/Li-**4**)·2 THF	3.9 (1.5)	4.4 (2.1)
11[a]	(*n*BuLi/Li-**5**)·2 Et_2O	–	4.8 (3.2)
12[c]	(*n*BuLi/Li-**5**)·2 THF	–	4.5 (1.8), 4.7 (2.2)

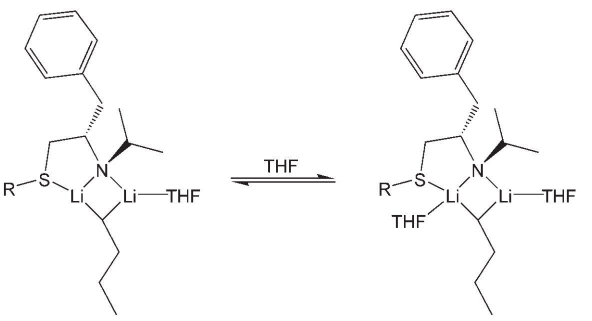
[a] Complex studied in [D$_{10}$]Et_2O. [b] Complex studied in [D$_8$]toluene. [c] Complex studied in [D$_8$]THF.

Table 4. Coupling constants, $^1J(^6Li,^{15}N)$, and chemical shifts (in parenthesis, in ppm) of the mixed trimeric *n*BuLi/lithium amide complexes observed in the ^6Li NMR spectra recorded in [D$_8$]toluene at −90 °C.

Entry	Complex	$^1J(^6Li,^{15}N)$ [Hz] Tricoordinated Li	$^1J(^6Li,^{15}N)$ [Hz] Dicoordinated Li
1	*n*BuLi/(Li-**1**)$_2$	4.5 (2.2)	6.5 (1.5)
2	*n*BuLi/(Li-**2**)$_2$	4.5 (2.2)	6.6 (1.5)
3	*n*BuLi/(Li-**3**)$_2$	4.8 (3.2)	6.4 (1.1)
4	*n*BuLi/(Li-**4**)$_2$	4.8 (3.0)	6.4 (1.1)

The measured coupling constants for the dimeric mixed complexes containing the chiral lithium amides Li-**1**–Li-**5** and *n*BuLi in Et_2O and THF are given in Table 3, and the $^1J(^6Li,^{15}N)$ for the trimeric complexes observed in toluene are given in Table 4. The coupling constants clearly fall into one of three different categories corresponding to di-, tri- or tetracoordinated lithium atoms. The dicoordinated lithium atoms have $^1J(^6Li,^{15}N)$ between 6.4 and 6.6 Hz, the tricoordinated lithium atoms have $^1J(^6Li,^{15}N)$ between 4.4 and 5.2 Hz and the tetracoordinated lithium atoms have $^1J(^6Li,^{15}N)$ between 3.9 and 4.3 Hz. The difference in $^1J(^6Li,^{15}N)$ between the lithium amides with chelating ether and those with chelating thioether groups is smaller for the mixed complexes than for the lithium amide dimers. The $^1J(^6Li,^{15}N)$ of the tricoordinated lithium atoms are slightly smaller for the thioethers, whereas those of the tetracoordinated lithium atoms are virtually identical. The $^1J(^6Li,^{15}N)$ of the tricoordinated lithium atoms in the mixed trimers are smaller, ~4.6 Hz, than those of the tricoordinated lithium atoms of the mixed dimers, ~4.9 Hz, indicating some degree of tetracoordination, which is possible in a ladder-type arrangement.

Titration of solutions of the mixed trimeric complexes between two lithium amides and one *n*BuLi in toluene with THF resulted in the formation of the respective nonequivalently solvated lithium amide dimers together with free *n*BuLi. If the lithium amido ethers, Li-**1** and Li-**2**, were used, further addition of THF caused the lithium amide dimers to dissociate and form mixed dimeric complexes with *n*BuLi. Neither the $^1J(^6\mathrm{Li},^{15}\mathrm{N})$ of the lithium resonances nor the chemical shifts varied greatly upon increased addition of THF, indicating that the disolvated mixed complexes were formed. However, the lithium amido thioethers behaved differently. Addition of THF to the nonequivalently solvated lithium amide dimer of Li-**3** did not result in formation of the mixed complex. Instead, the lithium amide dimer solvated by two THF molecules was formed before any mixed dimeric complex. Upon addition of more THF, the two doublets of the mixed dimeric complex appeared. Interestingly, the $^1J(^6\mathrm{Li},^{15}\mathrm{N})$ of the doublets, 4.9 and 4.4 Hz, respectively, differed markedly from the coupling constants measured in Et_2O and THF. Continued addition of THF caused the lithium resonance with the larger coupling constant to drift upfield. Simultaneously, the signal broadened into a poorly resolved doublet and the $^1J(^6\mathrm{Li},^{15}\mathrm{N})$ decreased. Eventually, the lithium resonance had shifted more than 1.2 ppm upfield and the $^1J(^6\mathrm{Li},^{15}\mathrm{N})$ coupling constant decreased to 4.2 Hz. This indicates that the mixed complex was initially solvated by one THF molecule with both lithium atoms tricoordinated, but as more and more THF was added, another molecule of THF coordinates to the complex resulting in the same complex that is present in ethers (Scheme 3). Titration of the complexes containing Li-**4** resulted in spectra similar to those of Li-**3**, with the exception that the equivalently solvated lithium amide dimer was formed simultaneously to the mixed complex, rather than before. The mixed complex with *n*BuLi that initially formed exhibited $^1J(^6\mathrm{Li},^{15}\mathrm{N})$ coupling constants of 4.9 and 4.4 Hz, and continued addition of THF caused the downfield resonance to move upfield and the $^1J(^6\mathrm{Li},^{15}\mathrm{N})$ to decrease. Eventually, the $^1J(^6\mathrm{Li},^{15}\mathrm{N})$ coupling constants for the mixed complex between Li-**4** and *n*BuLi were measured to be 4.4 and 4.3 Hz, respectively.



Scheme 3. Equilibrium between the monosolvated and disolvated mixed complexes of lithium amido thioethers and *n*BuLi.

From our observations, it is evident that the coupling constants are affected only slightly by the replacement of the nitrogen anion by the carbanion of *n*BuLi. The observed $^1J(^6\mathrm{Li},^{15}\mathrm{N})$ of the tetracoordinated lithium atoms of the mixed complexes with a lithium amide containing a chelating thioether group is about 0.4 Hz smaller than those of the lithium amide dimer, whereas the tetracoordinated lithium atoms of the mixed complexes between *n*BuLi and a lithium amide containing an ether group experience a slight increase in $^1J(^6\mathrm{Li},^{15}\mathrm{N})$ of about 0.2 Hz. The $^1J(^6\mathrm{Li},^{15}\mathrm{N})$ for the tricoordinated lithium atoms of the mixed complexes of all lithium amides are reduced by about 0.4 Hz upon progression from the lithium amide dimers to the corresponding mixed complex with *n*BuLi.

Discussion

The $^1J(^6\mathrm{Li},^{15}\mathrm{N})$ of 20 different tetracoordinated lithium atoms in chiral lithium amides and their mixed complexes with *n*BuLi were measured and range from 3.7 to 4.6 Hz, with an average value of 4.1 Hz. The $^1J(^6\mathrm{Li},^{15}\mathrm{N})$ of 25 different tricoordinated lithium atoms were also measured and range from 4.5 to 5.7 Hz, with an average value of 4.9 Hz. This value is clearly larger than that of the tetracoordinated lithium atoms. Four dicoordinated lithium atoms were studied and exhibit an average $^1J(^6\mathrm{Li},^{15}\mathrm{N})$ of 6.5 Hz.

Interestingly, these values differ slightly with solvent and amide structure. The $^1J(^6\mathrm{Li},^{15}\mathrm{N})$ of the tetracoordinated lithium atoms of the lithium amides containing a chelating ether group are all smaller than those measured for the lithium amides with a chelating thioether group. The situation is reversed for the tricoordinated lithium atoms of the lithium amide dimers, for which the $^1J(^6\mathrm{Li},^{15}\mathrm{N})$ is larger for the lithium amides with a chelating ether group. The $^1J(^6\mathrm{Li},^{15}\mathrm{N})$ for the tricoordinated lithium atoms of the monodentate lithium amides exhibit values between those measured for the lithium amides with chelating groups.

The mixed complexes are even more insensitive to differences in the amide structure, but notably, the measured $^1J(^6\mathrm{Li},^{15}\mathrm{N})$ for the tricoordinated lithium in all mixed complexes formed between the lithium amides and *n*BuLi are approximately 0.4 Hz smaller than those of the corresponding lithium amide dimers. The lithium atoms of the lithium amides with a chelating thioether group experience a lowering of the $^1J(^6\mathrm{Li},^{15}\mathrm{N})$ of the same magnitude as for the tetracoordinated lithium atoms, whereas the tetracoordinated lithium atoms of the mixed complexes with a chelating ether groups experience a slight increase in $^1J(^6\mathrm{Li},^{15}\mathrm{N})$. The solvent–lithium interaction in these mixed dimers is clearly different, due to the presence of an anionic carbon bonded to the lithium.

In summary, these results show that a good estimation of the coordination number for a given lithium nucleus in a lithium amide or its mixed complex can be obtained directly from the magnitude of the $^1J(^6\mathrm{Li},^{15}\mathrm{N})$ coupling constant. Kikuchi and co-workers did report, based on quantum chemical calculations, that the coupling constant should show a dependence on the coordination number at lithium, and our findings support their results by showing that the $^1J(^6\mathrm{Li},^{15}\mathrm{N})$, in fact, decreases as solvation at the lithium increases. It is tempting to assume that the magnitude of the $^1J(^6\mathrm{Li},^{15}\mathrm{N})$ coupling constant reflects the covalent character of the N–Li bond, because scalar couplings are known to arise through a Fermi contact mechanism between the nuclei.

The lithium atom in a nonsolvated dimer only interacts with two anions with some degree of covalent character in the N−Li bond. The fraction of covalency in the N−Li bond should be expected to decrease upon coordination of a Lewis base to the atom. Although this dependency does not rely on a theoretical basis, it serves as a rough guide in the analysis of the observed $^1J(^6\mathrm{Li},^{15}\mathrm{N})$ coupling constants. Based on our findings, it is possible to estimate the number of ether molecules actually coordinating to a lithium nucleus. Such information is crucial for the understanding of the reactivity of, for example, chiral lithium amides in ethereal solvents.

Experimental Section

Synthesis of the amines

The chiral ^{15}N-labelled amines **1**–**4** were prepared from (*S*)-[^{15}N]phenylalanine according to previously published methods.[5]

*(*R*)-2-Isopropylamino-1-phenylpropane ((*R*)-**5**)*: (*S*)-2-[(*tert*-Butoxycarbonyl)amino]-1-iodo-3-phenylpropane[21] (4.30 g, 11.9 mmol, 1.0 equiv) was dissolved in a solution of SmI_2 (270 mL, 0.11 M, 29.8 mmol, 2.5 equiv) in THF under nitrogen atmosphere. Triethylamine (6.02 g, 8.25 mL, 59.5 mmol, 5.0 equiv) followed by water (1.61 mL, 89.3 mmol, 7.5 equiv) were added by using gas-tight syringes and the mixture was stirred at RT for 20 min. The septum was removed and air was allowed to react with the excess SmI_2 until the solution was decolourised. The mixture was filtered and the precipitate was extracted with THF (3×25 mL). The combined filtrates were concentrated under reduced pressure and the resulting solid was dissolved in Et_2O, washed with brine (50 mL), dried over Na_2SO_4 and again concentrated under reduced pressure, resulting in a white solid (2.69 g, 96%), (*R*)-2-[(*tert*-butoxycarbonyl)amino]-phenylpropane (spectral data consistent with literature[21]).

The amide (2.69 g, 11.4 mmol, 1.0 equiv) was dissolved in dichloromethane (100 mL) and trifluoroacetic acid (7.80 g, 5.08 mL, 68.4 mmol, 6.0 equiv) was added to the solution. The resulting mixture was stirred overnight at RT before a NaOH solution (100 mL, 2.0 M) was added. The phases were separated and the aqueous phase was extracted with dichloromethane (3×25 mL). The combined organic extracts were washed with brine (100 mL), dried over Na_2SO_4 and concentrated under reduced pressure yielding a clear yellow oil (1.54 g, quantitative yield), (*R*)-2-amino-1-phenylpropane (spectral data consistent with literature[22]).

The amine (1.54 g, 11.4 mmol. 1.0 equiv) and acetone (2.65 g, 3.35 mL, 45.6 mmol, 4.0 equiv) were dissolved in benzene (50 mL) and refluxed by using a Dean–Stark trap for 6 h. The mixture was allowed to cool to RT and the solvent and excess acetone were removed under reduced pressure. The residue was dissolved in dry ethanol (50 mL), $NaBH_4$ (0.86 g, 22.8 mmol, 2.0 equiv) was added and the mixture was stirred overnight at RT. Water (50 mL) was added and the ethanol was removed under reduced pressure. The residue was extracted with dichloromethane (3×50 mL) and the combined organic extracts were washed with brine (50 mL), dried over Na_2SO_4 and concentrated under reduced pressure yielding a clear yellow oil. The crude product was purified by column chromatography (aluminium oxide, ethyl acetate/hexane 1:4) yielding the desired product as a clear colourless oil (1.01 g, 50%, spectral data consistent with literature[23]).

The chiral ^{15}N-labelled amine (*R*)-[^{15}N]**5** was prepared from (*S*)-[^{15}N]phenylalanine by following the same procedure as the preparation of (*R*)-**5** above.

NMR spectroscopy studies: The chiral lithium amides and their mixed complexes with *n*BuLi were generated in situ in septum-sealed NMR tubes by the careful addition of the respective amine and *n*BuLi through gas-tight syringes to the deuterated solvent. During this procedure, the solutions were kept cooled to −78 °C over an acetone/dry-ice cooling bath. For experimental details regarding the ^{6}Li,^{1}H-HOESY experiments, see previous studies.[24]

NMR spectroscopy instrumentation: The NMR studies were conducted by using a Varian Unity 500 spectrometer equipped with a 5 mm ^{13}C,^{6}Li,^{1}H triple-resonance probe head manufactured by the Nalorac Company. Measuring frequencies were 500 (^{1}H), 125 (^{13}C) and 73 MHz (^{6}Li). The ^{1}H and ^{13}C NMR spectra were referenced to the solvent [D$_{10}$]Et$_2$O signals at $\delta = 1.06$ (^{1}H, $-CH_3$) and $\delta = 65.5$ ppm (^{13}C, $-CH_2$), the [D$_8$]THF signals at $\delta = 1.72$ (^{1}H, $-CH_3$) and $\delta = 67.6$ ppm (^{13}C, $-CH_2$) and the [D$_8$]toluene signals at $\delta = 2.09$ (^{1}H, $-CH_3$) and $\delta = 20.4$ ppm (^{13}C, $-CH_3$). The ^{6}Li NMR spectra were referenced to external 0.3 M ^{6}LiCl in [D$_1$]methanol ($\delta = 0.0$ ppm). Probe temperatures were measured after more than 1 h of temperature equilibrium by using both a calibrated methanol–freon NMR spectroscopy thermometer and the standard methanol thermometer supplied by Varian Instruments.

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