

# A Multinuclear NMR Study of a Chiral Lithium Amide with an Intramolecular Chelating Methoxy Group in Coordinating Solvents at the Slow Ligand Exchange Limit

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The dynamics and solution structure of the lithium salt of 2-methoxy-[(*R*)-1-phenylethyl][(*S*)-1-phenylethyl]amine (**1**) in diethyl ether (DEE), tetrahydrofuran (THF), dimethoxyethane (DME), *N,N,N',N'*-tetramethylethylene diamine (TMEDA) and toluene were studied by multinuclear NMR spectroscopy at temperatures down to  $-100\text{ }^{\circ}\text{C}$ . The lithium salt of **1** (**3**) is a dimer with  $C_2$  symmetry in DEE with two different lithium resonances in the  $^6\text{Li}$  NMR. The activation parameters for the intra-aggregate lithium exchange in DEE has been determined by line-shape analysis,  $\Delta H^\ddagger = 50 \pm 2\text{ kJ/mol}$ ;  $\Delta S^\ddagger = -10 \pm 10\text{ J/(mol K)}$ . The observed low activation entropy and the concentration-independent coalescence temperature,  $T^c = 250\text{ K}$ , suggest an intra-aggregate lithium exchange without assistance by additional ligands in the rate-limiting transition state. Slow ligand exchange on the NMR time scale for **3** in DEE, THF, DME, and TMEDA were observed by both  $^{13}\text{C}$  and  $^6\text{Li}$  NMR spectroscopy. It was established that **3** coordinates only one solvent ligand indicating that one of the lithiums in **3** is tetracoordinate (two nitrogens and two methoxy groups) and the other is tricoordinate (two nitrogens and one solvent ligand). A slightly broader  $^6\text{Li}$  signal and a much broader  $^7\text{Li}$  signal were observed for the tricoordinate lithium compared to the tetracoordinate one. This effect is probably due to the less symmetric local environment around the tricoordinate lithium. THF titration of **3** in DEE showed that THF has substantially greater affinity for **3** than does DEE. The addition of 0.5 equivalents of THF to a DEE solution of **3** afforded THF solvated **3**. At higher concentrations of THF, monomers of the lithium salt of **1** were observed, and in neat THF only monomers were observed. From a temperature study at low THF concentrations, the enthalpy and entropy for the dimer–monomer equilibrium were determined,  $\Delta_r H^\circ = -33 \pm 1\text{ kJ/mol}$ ;  $\Delta_r S^\circ = -185 \pm 4\text{ J/(mol K)}$ . The  $^6\text{Li}, ^1\text{H}$ -HOESY spectra of **3** ligated by different ethers showed similar dimer structures. Titration of **3** in toluene with DME showed the presence of DME solvated monomers and dimers of **3** with DME probably functioning as a monodentate ligand. Titration of **3** in toluene with TMEDA resulted in the formation of mostly monomers with bidentate TMEDA ligation. Slow ligand exchange was only observed for monosolvated and tricoordinate lithium cations.

## Introduction

The role of solvent in lithiation reactions has been subjected to a number of investigations.<sup>1 a-p</sup> It has been established that solvation of organolithium reagents influence aggregation and reactivity.<sup>1a,b</sup> Changes of solvent have even been reported to invert the stereoselectivity of reactions involving homochiral organolithium reagents.<sup>2</sup> NMR spectroscopic studies of lithium solvation of organolithium compounds are often complicated due to fast ligand exchange rates on the NMR time scale that gives time-averaged signals even at low tempera-

tures. Therefore the number of ligands coordinating to lithium have been inferred from indirect methods such as solid-state structures and studies of aggregation state in solution.

Solid-state structures of organolithium compounds have revealed that the lithium cation often adopts a tetracoordinated ligation.<sup>1b,m</sup> The number of solvent molecules coordinating to lithium in solution may be estimated for the aggregation state in solution, if tetra-coordination of the lithium cation is assumed.<sup>1m,3,4</sup> The lithium cation in a monomer is thereby coordinated with three donor ligands and the anion, in a dimer with two donors ligands and two anions, and in a tetramer with one donor ligand and three anions. The degree of aggregation of organolithium compounds in solution has been obtained from NMR by analyzing the coupling pattern of  $^6\text{Li}$  and  $^{13}\text{C}$ - or  $^{15}\text{N}$ -labeled organolithium compounds.<sup>1b,5-7</sup>

Studies in the slow ligand exchange region of NMR have for the first time recently been reported.<sup>1p,g</sup> Inde-

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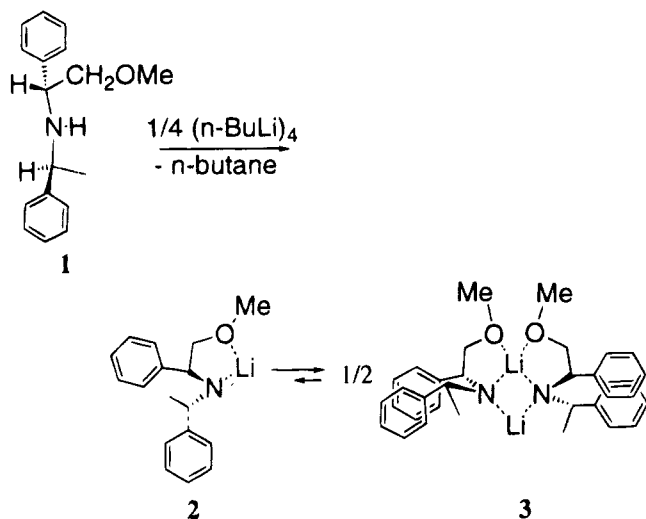
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## Scheme 1



pendent of each other Reich and Snaith observed by NMR that hexamethylphosphoramide (HMPA) exists in both a lithium cation coordinated and a free form.<sup>8</sup> Collum and Lucht later showed the existence of slow ligand exchange in ethereal solvated hexamethyldisilazide (LiHMDS) by NMR. Different <sup>13</sup>C NMR signals were obtained for LiHMDS-coordinated and free ether solvent molecules in toluene solution. They have shown that lithium in LiHMDS dimer is tri- rather than tetracoordinate at low concentrations of ethers.<sup>1p</sup> The observation of slow ligand exchange rates of organolithium compounds gives a unique opportunity to obtain insight into the relationships of solvation, structure, and reactivity of organolithium compounds.

In this paper we report on (1) the lithium exchange between two nonequivalent coordination sites within the dimer of a chiral lithium amide, (2) the slow ethereal ligand exchange observed for the chiral lithium amide, and (3) the effect of solvent upon the aggregation state and solution structure.

## Results and Discussion

The lithiation of the precursor amine **1** with 1 equiv of *n*-butyllithium proceeds very fast at  $-90\text{ }^\circ\text{C}$  and results in the formation of the lithium amide **2**. The equilibrium between the **2** and the dimer (**3**) in diethyl ether has been shown to exclusively favor **3** (0.03–0.8 M) (Scheme 1).

The *C*<sub>2</sub>-symmetric dimer in diethyl-*d*<sub>10</sub> ether (DEE-*d*<sub>10</sub>) has previously been determined by homo- (<sup>1</sup>H, <sup>1</sup>H-NOESY) and hetero- (<sup>6</sup>Li, <sup>1</sup>H-HOESY) nuclear Overhauser effect spectroscopy to be best represented by **3a** (Scheme 3).<sup>9</sup>

**Lithium Exchange within 3 in DEE.** At  $-90\text{ }^\circ\text{C}$  two <sup>6</sup>Li signals (1:1) are observed at  $\delta$  2.72 and 2.92 for **3a**. These signals coalesce at  $-22.5\text{ }^\circ\text{C}$ , ( $\Delta G^\ddagger_{250, \text{Li, Li}} = 53 \pm 1\text{ kJ/mol}$ ). A series of temperature-dependent <sup>6</sup>Li NMR spectra have been obtained and subjected to a complete line shape analysis using the program DNMR5.<sup>10</sup> The calculated and observed NMR spectra are shown in Figure 1.

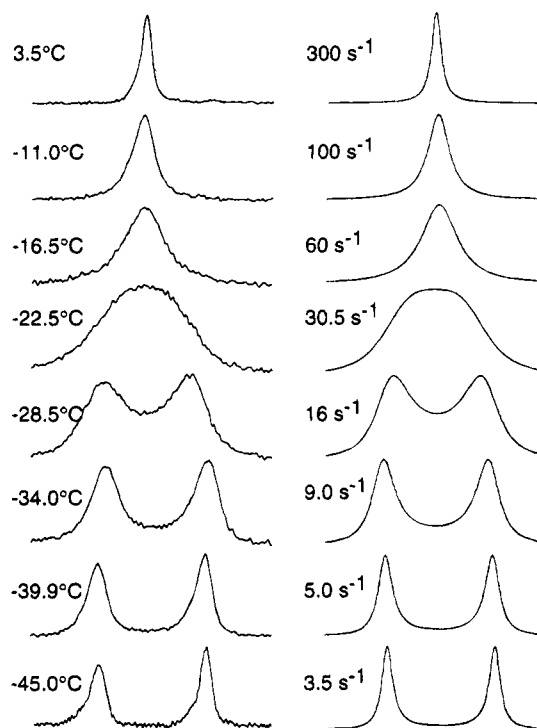


Figure 1. (Left column) <sup>6</sup>Li NMR spectra of **3a** obtained at eight different temperatures and (right column) simulated NMR spectra using the DNMR5 program.

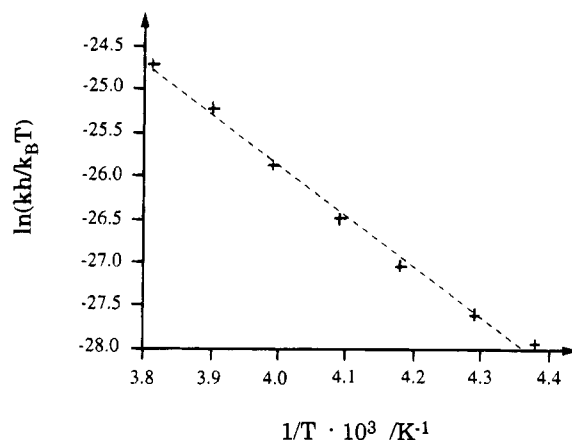


Figure 2. Eyring plot of the lithium exchange in **3a**.

Table 1. Thermodynamic Data for the Lithium Exchange in **3a**

<i>T</i> (K)	<i>k</i> <sub>obs</sub> (s <sup>-1</sup> )	1/ <i>T</i> (10 <sup>-3</sup> K <sup>-1</sup> )	ln( <i>kh</i> / <i>k</i> <sub>B</sub> <i>T</i> )
262.15	100 ± 2	3.81	-24.72
256.65	60 ± 1.5	3.90	-25.21
250.65	30.5 ± 0.5	3.99	-25.87
244.65	16 ± 1	4.09	-26.49
239.15	9 ± 1	4.18	-27.04
233.26	5 ± 0.9	4.29	-27.60
228.15	3.5 ± 0.7	4.38	-27.94

An Eyring plot shows a linear correlation for the lithium exchange in **3a** (Figure 2 and Table 1) with  $\Delta H^\ddagger = 51 \pm 2\text{ kJ/mol}$  and  $\Delta S^\ddagger = -10 \pm 10\text{ J/(K mol)}$ .

The obtained entropy of activation indicates a lithium–lithium exchange within the aggregate without association or dissociation of solvent molecules in the transition state compared to the initial state. Furthermore, the coalescence temperature for **3a** in DEE was invariant of the concentration (0.03–0.8 M) also indicative of a nonassociative lithium–lithium exchange mechanism.

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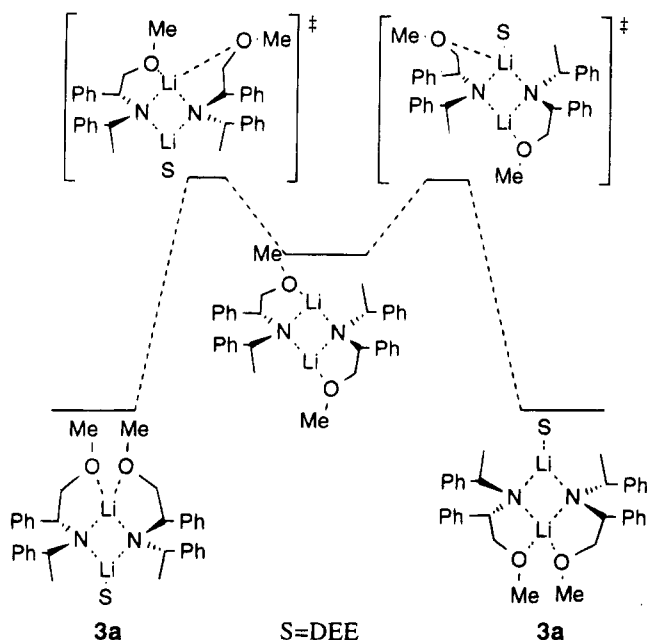
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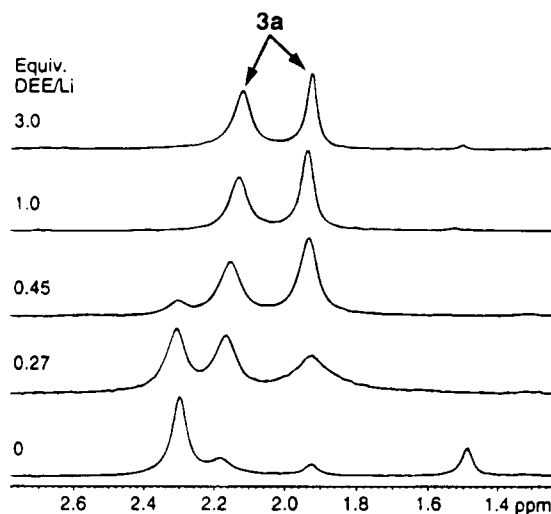
Scheme 2



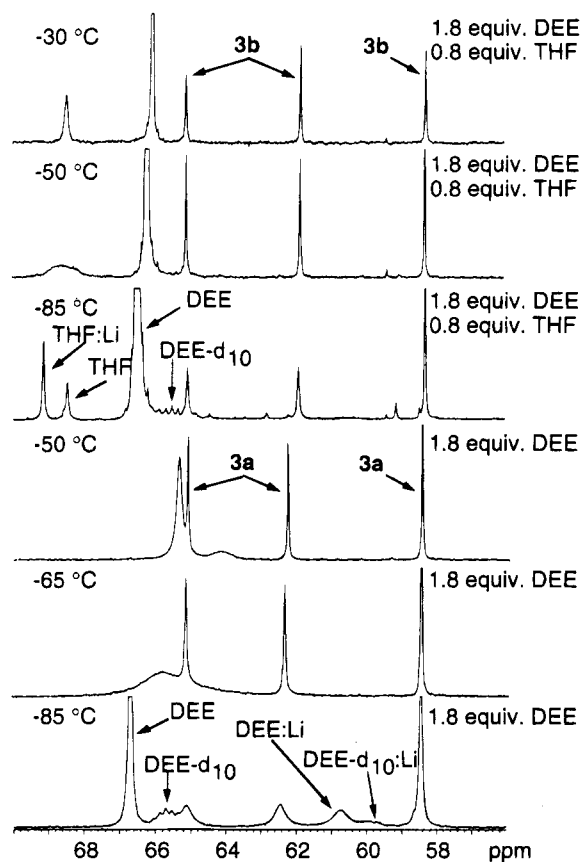
The  $^1\text{H}$  NMR spectrum shows a significant temperature independence in the interval of  $+10$  to  $-90$  °C suggesting that the proposed solution structure of **3a** predominates at all temperatures. We propose the following mechanism for the lithium exchange in **3a**. The rate-limiting transition state occurs either as one of the internal methoxy coordinations are lost or as the association of the methoxy coordinations to the other lithium, yielding a less stable conformation, i.e. a symmetric N–Li core with the methoxy groups coordinating a lithium cation each. The transition state for the ethereal ligand exchange is lower in free energy than the rearrangement of the internal coordination. A schematic representation of the most likely lithium–lithium exchange according to our observations is shown in Scheme 2.

**The Number of DEE Molecules in 3.** A DEE- $d_{10}$  titration of the lithium salt of **1** in toluene- $d_8$  was performed to establish the number of DEE- $d_{10}$  molecules ligating **3a**. The lithium amide in toluene- $d_8$  displayed several  $^6\text{Li}$  NMR signals from different oligomers with one clearly dominating at  $\delta$  2.30. Upon addition of DEE- $d_{10}$  two new  $^6\text{Li}$  signals appeared at  $\delta$  1.94 and 2.13, respectively. These  $^6\text{Li}$  signals were found to increase upon addition of DEE- $d_{10}$  (Figure 3) and were the only observable signals at 0.5 equiv of DEE- $d_{10}$ . The  $^6\text{Li}$  NMR spectrum did not change upon further addition up to 3 equiv DEE- $d_{10}/\text{Li}$ . The differences in chemical shifts of these  $^6\text{Li}$  resonances compared to the chemical shifts in neat DEE- $d_{10}$  of **3a** might be due to a difference in solvation number or a possible solvent bulk effect. Further addition of up to 25 equiv of DEE- $d_{10}$  to the solution of **3a** in toluene resulted in a continuous and simultaneous downfield shift of the  $^6\text{Li}$  signals of approximately  $0.27 \pm 0.02$  ppm.

**Slow Ethereal Ligand Exchange.** The  $^{13}\text{C}$  NMR spectrum of **3a** in a solvent mixture of  $600 \mu\text{L}$  of toluene- $d_8$ ,  $80 \mu\text{L}$  of DEE- $d_{10}$ , and  $100 \mu\text{L}$  of DEE at  $-85$  °C showed the presence of four methylene carbon signals for DEE and DEE- $d_{10}$  (Figure 4 and Table 2): a large sharp singlet at  $\delta$  66.58 for free DEE, a broad singlet at  $\delta$  60.62 for coordinated DEE, a small pentet with observable  $^{13}\text{C}$ – $^2\text{H}$  couplings at  $\delta$  65.58 for free DEE- $d_{10}$ , and a very small and broad signal at  $\delta$  59.84, with unresolved  $^{13}\text{C}$ – $^2\text{H}$  couplings for coordinated DEE- $d_{10}$ . This clearly



**Figure 3.**  $^6\text{Li}$  NMR spectra of **3** and **3a** in toluene- $d_8$  at different equivalents of DEE- $d_{10}$  added at  $-80$  °C.



**Figure 4.**  $^{13}\text{C}$  NMR spectra of **3** in toluene- $d_8$  showing the chemical shift region for the most downfield methylene carbon atoms from free and coordinated solvent molecules of THF, DEE, and DEE- $d_{10}$  at different temperatures.

shows the presence of a slow ligand exchange in **3a** on the NMR time scale.

The coalescence temperature for the  $\alpha$ -carbon resonances for free and coordinated DEE in the  $^{13}\text{C}$  NMR spectrum was found to be  $-72$  °C ( $\Delta G_{201\text{K,DEE}}^\ddagger = 36 \pm 1$  kJ/mol) and it was temperature independent over an 8-fold change in free DEE ligand concentration. This indicates that the ethereal ligand exchange in **3a** proceeds by a dissociative process.<sup>1p</sup> Addition of THF to the above toluene/DEE/DEE- $d_{10}$  solvent mixture resulted in the disappearance of the  $^{13}\text{C}$  NMR signals for coordinated

Table 2. NMR Spectroscopic Data of Different Solvates of **3** and **2** at  $-75\text{ }^{\circ}\text{C}$ 

	$^6\text{Li}$	$^{13}\text{C}$ (THF)	$^{13}\text{C}$ (DEE- $d_{10}$ )	$^{13}\text{C}$ (DEE)	$^{13}\text{C}$ (TMEDA)	$^{13}\text{C}$ (DME)
THF		25.72 68.17				
DEE- $d_{10}$			15.12 (CH <sub>3</sub> ) 65.58 (CH <sub>2</sub> )			
DEE				16.19 (CH <sub>3</sub> ) 66.58 (CH <sub>2</sub> )		
TMEDA					46.06 (CH <sub>3</sub> ) 58.08 (CH <sub>2</sub> )	
DME						58.47 (CH <sub>3</sub> ) 71.75 (CH <sub>2</sub> )
<b>3a</b>	2.72 2.92		11.88 (CH <sub>3</sub> ) 59.84 (CH <sub>2</sub> )	12.91 (CH <sub>3</sub> ) 60.62 (CH <sub>2</sub> )		
<b>3b</b>	2.70 <sup>a</sup> 3.16 <sup>a</sup>	25.11 <sup>d</sup> 69.08 <sup>d</sup>				
<b>3c</b>	2.74 <sup>b</sup> 3.02 <sup>b</sup>					58.47 (CH <sub>3</sub> ) 71.75 (CH <sub>2</sub> ) 70.91 <sup>f</sup> (CH <sub>2</sub> )
<b>3d</b>	1.93 <sup>c</sup> 2.16 <sup>c</sup>					
<b>2b</b>	2.22 <sup>a</sup>	25.77 <sup>d</sup> 67.90 <sup>d</sup>				
<b>2c</b>	2.10 <sup>b</sup>					58.17 <sup>e</sup> (CH <sub>3</sub> ) 71.68 <sup>e</sup> (CH <sub>2</sub> )
<b>2d</b>	2.11 <sup>c</sup>				42.26 (CH <sub>3</sub> ) 43.50 (CH <sub>3</sub> ) 47.20 (CH <sub>3</sub> ) 48.83 (CH <sub>3</sub> ) 55.17 (CH <sub>2</sub> ) 55.44 (CH <sub>2</sub> )	

<sup>a-f</sup> Chemical shifts in (a) 50  $\mu\text{L}$  of THF- $d_8$ /650  $\mu\text{L}$  of DEE- $d_{10}$ ; (b) 75  $\mu\text{L}$  of DME- $d_8$ /650  $\mu\text{L}$  of DEE- $d_{10}$ ; (c) 1 equiv of TMEDA/600  $\mu\text{L}$  of toluene- $d_8$ ; (d) 100  $\mu\text{L}$  of THF- $d_8$ /650  $\mu\text{L}$  of DEE- $d_{10}$ ; (e) 600  $\mu\text{L}$  of DME/600  $\mu\text{L}$  of toluene- $d_8$ ; (f) coordinated DME.

DEE and DEE- $d_{10}$  at  $\delta$  60.62 and 59.84, respectively. Two  $^{13}\text{C}$  NMR signals appeared at  $\delta$  67.90 and 69.08 for free THF and coordinated THF, respectively (Figure 7, Table 2). Very low concentrations of THF quantitatively replaced DEE as lithium ligand. From the above we conclude that THF has a much higher affinity toward lithium in **3** than does DEE. The coalescence temperature between free and coordinated THF was found to be  $\approx -55\text{ }^{\circ}\text{C}$  ( $\Delta G^{\ddagger}_{218\text{K, THF}} = 42 \pm 1\text{ kJ/mol}$ , Figure 4).

Low concentrations of THF- $d_8$  to a DEE- $d_{10}$  solution of **3a** resulted in two new  $^6\text{Li}$  NMR resonances appearing at  $\delta$  2.70 and 3.16 together with those of **3a**, indicating a slow exchange of **3a** and THF- $d_8$  solvated **3**, (**3b**) (see Figure 5).

The  $^6\text{Li}$  NMR resonances for **3a** in DEE- $d_{10}$  had almost completely disappeared in favor of the signals of **3b** when 0.5 equiv of THF- $d_8$ /Li were reached, indicating one THF- $d_8$  per two lithiums of **3b**.

No chemical shift changes of the two new lithium signals at  $\delta$  2.70 and 3.16 were observed upon increasing the THF- $d_8$  concentration to 3 equiv of THF- $d_8$ /Li. Furthermore, **3a/3b** ratio did not change significantly with 25 equiv of DEE- $d_{10}$ /Li.

A temperature study of the ratio **3a** and **3b** showed no concentration dependence in the temperature interval  $-75$  to  $-100\text{ }^{\circ}\text{C}$ . A coalescence for the lithium exchange was instead observed at  $-65\text{ }^{\circ}\text{C}$  between the lithium signals due to a DEE- $d_{10}$  solvated lithium cation ( $\delta$  2.70) and the lithium signal due to a THF- $d_8$  solvated lithium cation ( $\delta$  3.16), with  $\Delta G^{\ddagger}_{208\text{K, Li-Li}} = 46 \pm 1\text{ kJ/mol}$  (Figure 6).

At  $-50\text{ }^{\circ}\text{C}$  two lithium resonances were observed at  $\delta$  3.00 and 2.66. The exchange of DEE- $d_{10}$  with THF- $d_8$  as ligand resulted in a downfield chemical shift of 0.36 ppm for the tricoordinate monosolvated lithium cation. No other observable structural changes of the dimer could be detected in either the  $^1\text{H}$  or the  $^{13}\text{C}$  NMR spectra of **3a** and **3b**. Similar observations were also made by

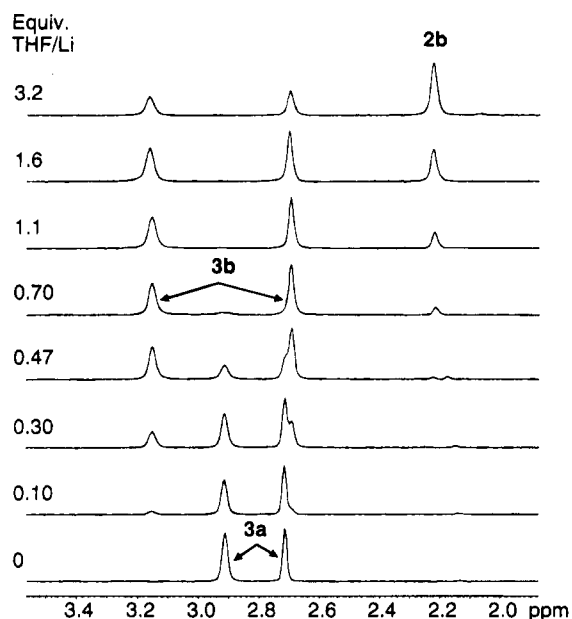
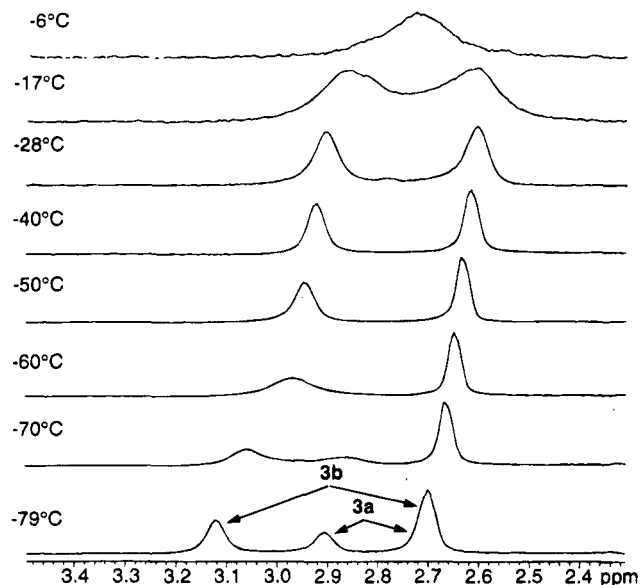


Figure 5.  $^6\text{Li}$  NMR spectra of **3a**, **3b**, and **2b** at different equivalents of THF- $d_8$  added in DEE- $d_{10}$  at  $-80\text{ }^{\circ}\text{C}$ .

Collum and Lucht who reported the  $^6\text{Li}$  resonance of the THF monosolvated dimer of LiHMDS (lithium hexamethyldisilazide) to be 0.39 ppm downfield of the corresponding DEE monosolvated dimer.<sup>1p</sup> The methoxy-coordinated lithium cation appearing at  $\delta$  2.72 in the  $^6\text{Li}$  NMR spectrum was shifted only slightly upfield ( $\delta$  2.70) probably due to a strong internal methoxy coordination. The THF-solvated lithium appears to be  $\approx 0.3$ – $0.4$  ppm downfield of the DEE-solvated lithium. We can thus conclude that the  $^6\text{Li}$  chemical shift of a monosolvated lithium amide is largely dependent upon the ethereal ligand.



**Figure 6.**  $^6\text{Li}$  NMR spectra of **3a** and **3b** in  $\text{DEE-}d_{10}$  at different temperatures.

**Table 3.**  $^{13}\text{C}$  NMR Chemical Shifts for **3a**, **3b**, and **2b** (Phenyl Carbons, Except for the Quaternary Ones, Which Have Been Omitted)

carbon	<b>3a</b> : -91.5 °C <sup>a</sup>	<b>3b</b> : -80 °C <sup>b</sup>	<b>2b</b> : -80 °C <sup>c</sup>
$\text{CH}_3$	27.75	27.92	28.92
$\text{OCH}_3$	58.44	58.36	59.26
CH	62.11	61.78	62.66
CH	≈65	64.95	68.41
$\text{CH}_2$	79.17	79.24	80.44
C	147.92	148.14	148.73
C	154.37	154.16	154.51

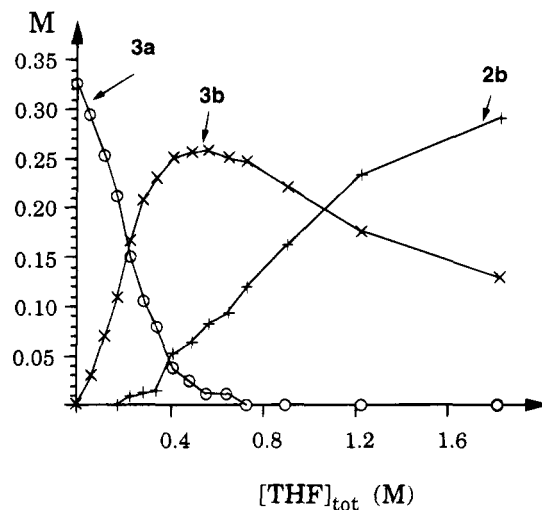
<sup>a</sup> Obtained at -91.5 °C; (b)  $\text{DEE-}d_{10}$ - $\text{THF-}d_8$  solvent mixture 650  $\mu\text{L}/110 \mu\text{L}$  at -80 °C. <sup>c</sup>  $\text{DEE-}d_{10}$ - $\text{THF-}d_8$  solvent mixture 650  $\mu\text{L}/110 \mu\text{L}$  at -80 °C.

Addition of > 1 equiv of  $\text{THF-}d_8$  to the DEE solution of **3b** resulted in the appearance of a new signal at  $\delta$  2.22 in the  $^6\text{Li}$  NMR spectrum together with the former two signals for **3b** at  $\delta$  2.70 and 3.16 (see Figure 5). The chemical shift of the signal at  $\delta$  2.22 was independent of  $\text{THF-}d_8$  concentration. However, it was observed to increase upon further addition of  $\text{THF-}d_8$  at the expense of **3b**. The integral of the signal at  $\delta$  2.22 was equal to the sum of the integrals of the two signals at  $\delta$  2.70 and 3.16 at 3.5 equiv of  $\text{THF-}d_8/\text{Li}$ . The  $^6\text{Li}$  NMR spectrum of **3** in neat  $\text{THF-}d_8$  showed the presence of only one signal at  $\delta$  2.23. The signal at  $\delta$  2.22 is therefore concluded to be due to a  $\text{THF-}d_8$ -solvated monomer (**2b**).

The signal at  $\delta$  3.16 for the tricoordinate lithium in **3b** coordinating  $\text{THF-}d_8$  and the signal at  $\delta$  2.70 for the methoxy coordinated lithium in **3b** are both downfield relative to the lithium signal at  $\delta$  2.22 for **2b**, and the average upfield shift of the two  $^6\text{Li}$  resonances for dimer **3b** upon deaggregation to monomer **2b** is thereby 0.7 ppm. Collum and Lucht observed similar (1.2 ppm) differences in the  $^6\text{Li}$  resonances of the  $\text{THF-}d_8$ -solvated  $\text{LiHMDS}$  dimer and monomer.

There is only a small difference of the  $^{13}\text{C}$  chemical shifts between **3a** and **3b**. However, **2b** has significantly different chemical shifts compared to **3b** as several of the  $^{13}\text{C}$  resonances differing around 1 ppm (see Table 3).

A plot of the concentrations of the different solvation states of **3** against the concentration of  $\text{THF-}d_8$  of a solution of **3** in  $\text{DEE-}d_{10}$  at -91.5 °C assuming that there



**Figure 7.** A plot of molar concentrations of **3a**, **3b**, and **2b** against the total molar concentration of added  $\text{THF}$ .

is only one external solvent molecule coordinating to the lithium cation of **3a** and **3b** is shown in Figure 7. In the light of our observations and those findings by the Collum group it is most likely that there are two solvent molecules/Li needed in **2b**. The possibility of a mixture of solvation numbers would be expected to give a temperature-dependent chemical shift of the  $^6\text{Li}$  resonances.

**Detection of Short Lithium-Proton Distances.** A  $^1\text{H}, ^6\text{Li}$ -HOESY experiment showed that the methoxy groups were close to the lithium observed at  $\delta$  2.70. From  $^1\text{H}$  and  $^1\text{H}, ^6\text{Li}$ -HOESY NMR we could conclude that **3b** has a 3-D structure similar to that of **3a**.<sup>11,12</sup>

A  $^6\text{Li}, ^1\text{H}$ -HOESY spectrum of the lithium salt of **1** in the solvent mixture 110  $\mu\text{L}$  of  $\text{THF-}d_8/650 \mu\text{L}$  of  $\text{DEE-}d_{10}$  at -70 °C showed that the lithium signals at  $\delta$  2.22, 2.70, and 3.16 correlate with the methyl proton signals at  $\delta$  1.55 and  $\delta$  1.41 for **3b** and **2b**. The  $^6\text{Li}, ^1\text{H}$  correlations observed at -70 °C between the two methyl groups and **3b** and **2b** were due to transfer of NOEs between **3b** and **2b**.

A  $^6\text{Li}, ^1\text{H}$ -HOESY spectrum recorded at -91.5 °C reveals correlations between the lithium signal at  $\delta$  2.22 and only the methyl signal at  $\delta$  1.41. Correlations were also seen for the methoxy group at  $\delta$  ≈ 3.32 and protons at  $\delta$  3.00, 3.63, and 3.77. The lithium-6 signal at  $\delta$  2.70 showed correlations with only one of the methyl signals that at  $\delta$  1.55. The methoxy group at  $\delta$  3.43 and the protons at  $\delta$  3.15, 3.70, and 4.10 also correlate. Finally the  $^6\text{Li}$  signal at  $\delta$  3.16 correlates with the methyl signal at  $\delta$  1.55 and signals at  $\delta$  3.70 and 4.10. Very weak cross peaks were seen for the signals at  $\delta$  3.15 and 3.45 (methoxy group). We have shown that the cross peaks obtained at -70 °C were due to transfer of NOEs between **3b** and **2b** that have been frozen out at -91.5 °C (see Figure 8).

The  $^1\text{H}, ^6\text{Li}$ -HOESY experiment showed close contact between the methoxy group at  $\delta$  3.32 and the lithium at  $\delta$  2.22. We also recorded a  $^6\text{Li}, ^1\text{H}$ -HOESY of **3** in  $\text{THF-}d_8$  at -91.5 °C; the same correlations with proton resonances were observed for the  $^6\text{Li}, ^1\text{H}$ -HOESY of **2b** in the  $\text{DEE-}d_{10}/\text{THF-}d_8$  mixture. It is interesting that the correlations found in the  $^6\text{Li}, ^1\text{H}$ -HOESY for **3b** are

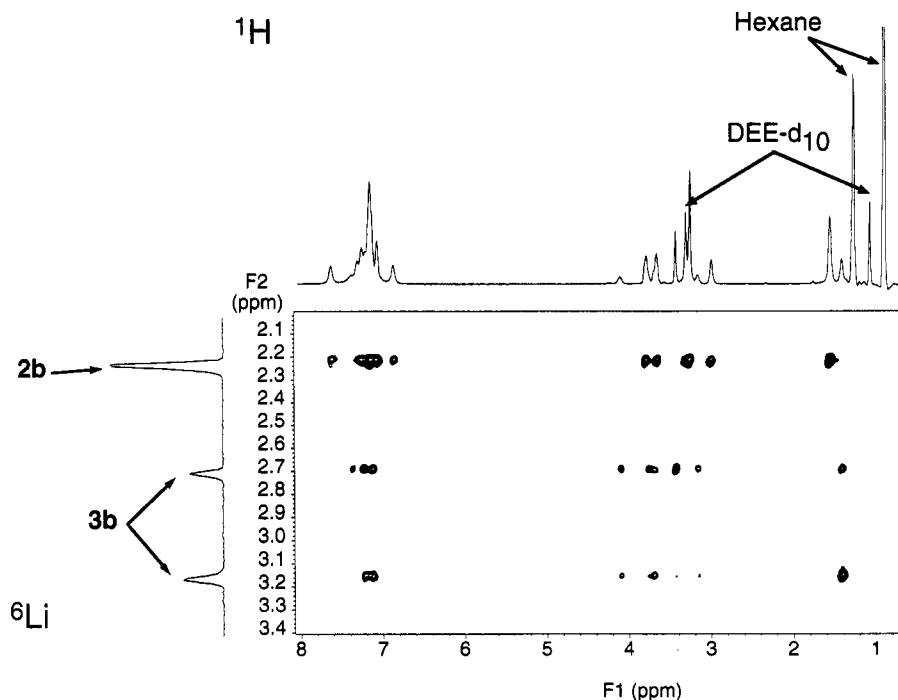


Figure 8.  ${}^6\text{Li}$ ,  ${}^1\text{H}$ -HOESY NMR spectrum of **3b** and **2b** in  $\text{DEE-}d_{10}$  at  $-91.5\text{ }^\circ\text{C}$ .

similar to those previously obtained for **3a**.<sup>11</sup> This shows that the solution structure of **3a** is similar to **3b**. Furthermore, the strong correlations between the lithium at  $\delta$  2.22 for **2b** and the phenyl ring protons suggest a 3-D structure of **2b** where in the lithium is close to at least one of the phenyl rings.

**The Dimer–Monomer Equilibrium.** Exchange between **3b** and **2b** is slow even at temperatures up to  $-50\text{ }^\circ\text{C}$ . At higher temperatures the ratio **3b/2b** favors **3b** to such an extent that no **2b** is observed. A series of  ${}^6\text{Li}$  NMR spectra were obtained at  $-60$  to  $-100\text{ }^\circ\text{C}$  revealed chemical shifts of **3b** and **2b** that were invariant with temperature, which may indicate temperature-independent solvation number of **3b** and **2b**. The total concentration of **3b** and **2b** as a function of the total concentration of added THF was measured and the normalized integrals of **3b** and **2b** were used to calculate the amount of free THF:

$$[\text{THF}]_{\text{free}} = [\text{THF}]_{\text{tot}} - [\mathbf{3a}] - 2[\mathbf{2a}]$$

The equilibrium between **3b** and **2b** is then (see Scheme 3)

$$K_{\text{eq}} = [\mathbf{2b}]^2/[\mathbf{3b}][\text{THF}]^3$$

From a van't Hoff plot of  $\ln(K_{\text{eq}})$  vs  $1/T$  we obtained ( $\Delta_r S^\circ = -185 \pm 4\text{ J}/(\text{mol K})$ ,  $\Delta_r H^\circ = -33.4 \pm 1\text{ kJ}/\text{mol}$  and  $\Delta_r G^\circ_{298, \text{dimer}-\text{monomer}} = 22 \pm 2\text{ kJ}/\text{mol}$  (see Table 4 and Figure 9).

The thermodynamic data especially the large negative entropy suggests that there is an immobilization of solvent molecules upon going from dimers to monomers.

**Chelating Ligands.** One of the most important additives in organolithium chemistry is TMEDA, al-

though the effect that TMEDA has on structures and reactivities of organolithium compounds is not clear.<sup>1d</sup> TMEDA coordinates in both a monodentate ( $\eta^1$ ) and a bidentate ( $\eta^2$ ) fashion.<sup>12 a-d</sup> Dimeric organolithium reagents are often coordinated by two donor ligands and, therefore, ligands such as TMEDA or DME would be useful in the formation of dimers.

**TMEDA.** A toluene- $d_8$  solution of the lithium salt of **1** was titrated with TMEDA and studied at various temperatures. The  ${}^6\text{Li}$  NMR spectrum at  $-90\text{ }^\circ\text{C}$  with 1 equiv of TMEDA/Li revealed three  ${}^6\text{Li}$  resonances at  $\delta$  1.00, 1.93, and 2.16, with the approximate intensities 4:1:1, ascribed to the TMEDA complexed monomer (**2d**) and the the TMEDA complexed dimer (**3d**). The ratio **3d/2d** was found to be largely temperature dependent; the  ${}^6\text{Li}$  NMR spectrum at  $-90\text{ }^\circ\text{C}$  afforded the ratio **3d/2d** to be approximately 0.07 at 1.6 equiv of TMEDA/Li. And temperatures above  $0\text{ }^\circ\text{C}$  afforded large concentrations of **2d** (at  $10\text{ }^\circ\text{C}$  the ratio **3d/2d** was approximately 0.6). The intermolecular lithium exchange is sufficiently low to allow direct detection of the  ${}^6\text{Li}$  signals for both **3d** and **2d** even at this high temperature.

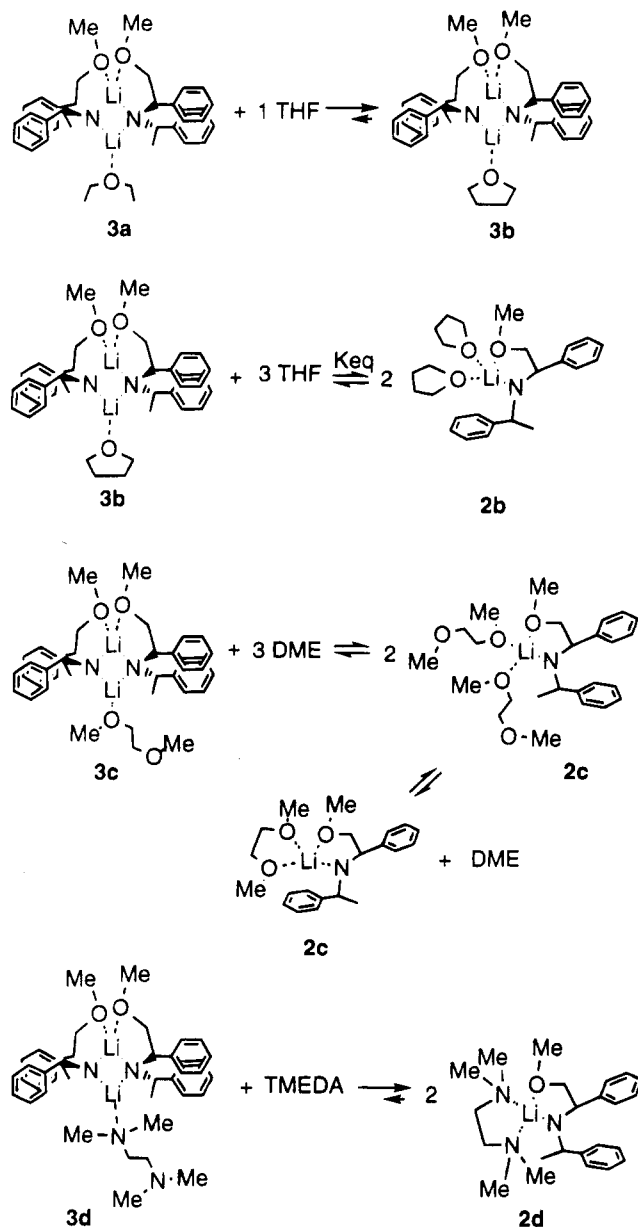
The  ${}^{13}\text{C}$  NMR spectrum of crystals of **2d** dissolved in toluene- $d_8$  displays a single set of resonances at  $-50\text{ }^\circ\text{C}$  and a minor, less than 10%, single set of signals from **3d** (Figure 10).

At  $-100\text{ }^\circ\text{C}$  free and coordinated TMEDA in **2d** gives rise to two different  ${}^{13}\text{C}$  NMR spectra establishing: (a) one TMEDA/Li in **2d** and (b) a slow exchange between free and coordinated TMEDA on the NMR time scale. The coordinated TMEDA at  $-100\text{ }^\circ\text{C}$  also gives rise to two  ${}^{13}\text{C}$  NMR signals for the nonequivalent methylene groups, at  $\delta$  55.17 and 55.44 respectively, and four signals for the nonequivalent methyl groups at  $\delta$  42.36, 43.55, 47.23,

(11) The  ${}^1\text{H}$  NMR chemical shift for **3b** in  $\text{THF-}d_6/\text{DEE-}d_{10}$  1:6 at  $-40\text{ }^\circ\text{C}$ :  $\delta$  1.41 (d, 3H,  $\text{CH}_3$ ) 3.15 (dd, 1H,  $\text{HC}(9)$ ) 3.43 (s, 3H,  $\text{OCH}_3$ ) 3.70 (q, 1H,  $\text{HC}(10)$ ) 3.76 (dd, 1H,  $\text{HC}(9)$ ) 4.10 (dd, 1H,  $\text{HC}(2)$ ) 7.05–7.39 (m, 10H,  $\text{HC}(\text{Ph})$ ). The  ${}^1\text{H}$  NMR chemical shift for **2b**  $\text{THF-}d_6/\text{DEE-}d_{10}$  1:6 at  $-40\text{ }^\circ\text{C}$ :  $\delta$  1.55 (d, 3H,  $\text{CH}_3$ ) 3.00 (dd, 1H,  $\text{HC}(9)$ ) 3.32 (s, 3H,  $\text{OCH}_3$ ) 3.32 (dd, 1H,  $\text{HC}(9)$ ) 3.63 (q, 1H,  $\text{HC}(10)$ ) 3.77 (dd, 1H,  $\text{HC}(9)$ ) 7.00–7.33 (m, 10H,  $\text{HC}(\text{Ph})$ ).

(12) (a) Wehman, E.; Jastrzebski, T. B. H.; Ernsting, J.-M.; Grove, D. M.; van Koten, G. *J. Organomet. Chem.* **1988**, *353*, 145. (b) Bauer, W.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1989**, *111*, 7191. (c) Fraenkel, G.; Chow, A.; Winchester, W. R. *J. Am. Chem. Soc.* **1990**, *112*, 1282. (d) Bernstein, M. P.; Romesberg, F. E.; Fuller, D. J.; Harrison, A. T.; Collum, D. B.; Liu, Q.-Y.; Williard, P. G. *J. Am. Chem. Soc.* **1992**, *114*, 5100.

Scheme 3



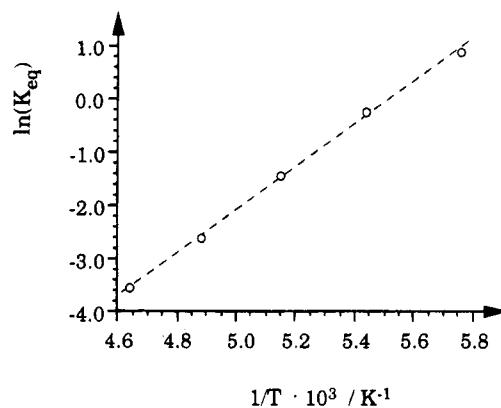
**Table 4. Experimental Data, Equilibrium Constants and Thermodynamic Data for the Equilibrium between 3b and 2b Obtained in a THF/DEE (110  $\mu$ L/650  $\mu$ L) Solvent Mixture**

<i>K</i>	[3b] <sup>a</sup>	[2b] <sup>a</sup>	[THF]	<i>K</i> <sub>(eq)</sub>	1/ <i>T</i>	ln( <i>K</i> <sub>(eq)</sub> )
173.6	0.077	0.396	0.948	2.378	0.005762	0.87
183.9	0.114	0.322	1.059	0.762	0.005439	-0.27
194.2	0.154	0.242	1.178	0.234	0.005151	-1.45
204.7	0.190	0.170	1.287	0.071	0.004886	-2.64
215.4	0.214	0.123	1.357	0.028	0.004644	-3.65

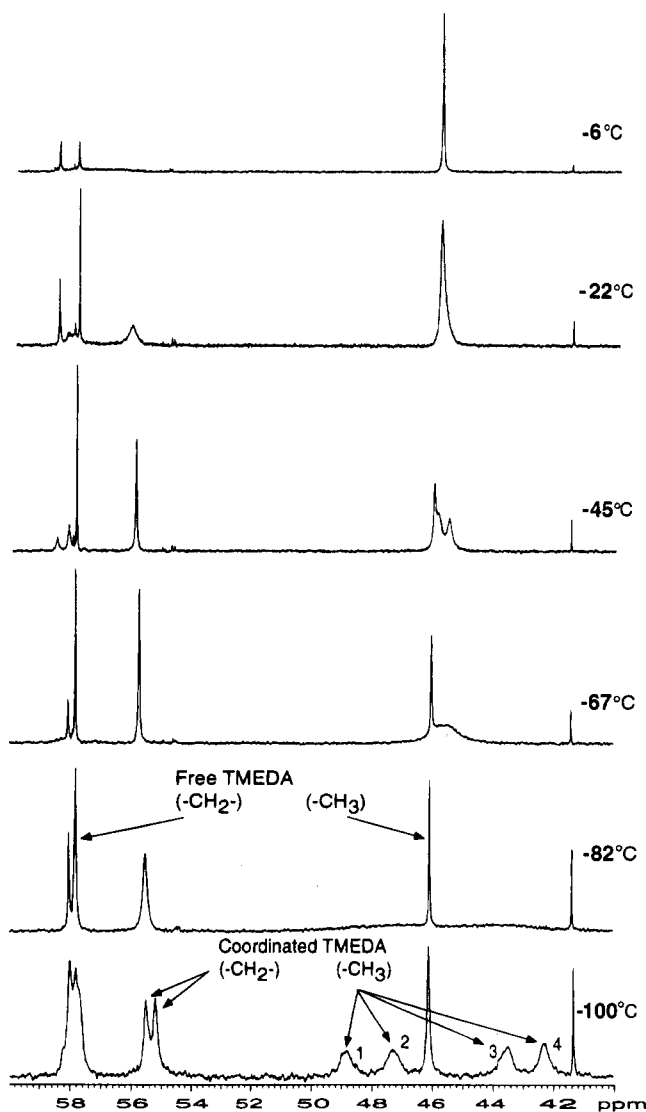
<sup>a</sup> Calculated using normalized integrals. [Li]<sub>tot</sub> = 0.55 M. [THF]<sub>tot</sub> = 1.82 M.

and 48.76. Dynamic effects are displayed among the TMEDA resonances, and upon increasing the temperature, signal averaging is observed among the two methylene carbons and the four methyl carbons of TMEDA; see Figure 10.

At -45 °C two different <sup>13</sup>C resonances are observed for the four methyl groups of the lithium-coordinated TMEDA; see Figure 11. Such an intermediate averaged spectra would be expected if the four nonequivalent methyl groups of TMEDA were exchanging two by two,

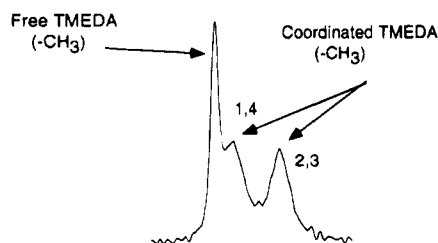


**Figure 9.** A Van't Hoff plot for the equilibrium between **3b** and **2b**.

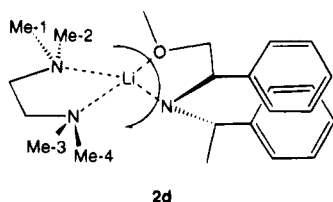


**Figure 10.** <sup>13</sup>C NMR spectra of **3d** in toluene-*d*<sub>8</sub>/TMEDA showing the chemical shift region for free and coordinated TMEDA at different temperatures.

i.e. the signal at  $\delta$  42.36 exchanges with the signal at 48.76 and the signal at  $\delta$  43.55 with that at 47.23. Such a temperature-dependent line-shape dependence would be expected for the TMEDA resonances upon rotation of the TMEDA:Li moiety with respect to diastereomeric structure of the anion; see Figure 12. This implies that



**Figure 11.**  $^{13}\text{C}$  NMR resolution-enhanced spectra of **2d** in toluene- $d_8$ /TMEDA showing the methyl region for free and coordinated TMEDA at  $-45^\circ\text{C}$ . The two different pairs of methyl groups are clearly resolved in the spectrum.



**Figure 12.** The four nonequivalent methyl groups of the lithium coordinate TMEDA.

methyl group 1 would exchange with methyl group 4 and similarly 2 with 3; see Figures 11 and 12.

The dynamics of TMEDA solvated allyllithiums have previously been investigated by dynamic  $^{13}\text{C}$  NMR and three mechanisms have been discussed to account for the appearance of two nonequivalent methyl signals and two nonequivalent methylene signals for allyllithium complexed TMEDA: (1) rotation of the anion moiety with respect to the lithium;<sup>11c</sup> (2) inversion of the Li:NCCN five-membered ring;<sup>12,13</sup> and (3) breaking of one of the TMEDA N–Li interactions, formation of a monodentate TMEDA·Li complex, followed by recombination.<sup>14</sup> MNDO calculations have been performed establishing that these suggested transition states are all possible due to their small difference in free energy compared to the accuracy of the calculation method. As **2d** is a diastereomeric complex, the four nonisochronous methyl groups were expected at low temperature where both rotation and ligand exchange rate are slow. However, the two by two exchange is best explained by a mechanism with rotation of the anion with respect to the lithium cation, first suggested by Fraenkel and co-workers [Fraenkel, G.; Chow, A.; Winchester, W. R. *J. Am. Chem. Soc.* **1990**, *112*, 1382]. Since slow inversion would give rise to eight different  $^{13}\text{C}$  resonances at low exchange rates we claim this process to be fast on the NMR time scale. We conclude that the rotation mechanism is responsible for the averaging of the four nonequivalent methyl groups in this system. At higher temperature exchange of the free and coordinated TMEDA gives the time-averaged  $^{13}\text{C}$  spectrum.

Addition of large amounts of TMEDA to a DEE- $d_{10}$  solution of **3a** (0.3 M) resulted in the appearance of a new signal at  $\delta$  2.11 in addition to those previously observed for **3a** at  $\delta$  2.72 and 2.92, respectively. The signal at  $\delta$  2.11 was assigned for the monomer **2d**. The intensity of the signal for **2d** increased upon further addition of TMEDA. The differences in chemical shifts

of **2d** in toluene and DEE- $d_{10}$  solution are likely due to solvent bulk effects already mentioned for **3a**, **3b**, and **2c**. No resonances for **3d** were observed in the DEE solution; they are possibly buried under the larger signal for **3a**.

A  $^6\text{Li}$ ,  $^1\text{H}$ -HOESY spectrum of a mixture of **3a** and **2d** in 500  $\mu\text{L}$  of DEE/150  $\mu\text{L}$  of TMEDA (recorded at  $-60^\circ\text{C}$ ) revealed cross peaks between the lithium signal at  $\delta$  2.11 for **2d** and the protons for TMEDA at  $\delta$  2.24 and 2.40 (see Figure 13). The only other correlations observed were to the phenyl ring, the methoxy, and the methyl group. The dimer **3a** displayed several correlations between proton signals of **3a** and the lithium signals not observed for **3d**. There is a slow interaggregate lithium exchange rate since there are no observable cross peaks arising for transfer of NOEs between **3a** and **2d**. The lithium signals for **3a** did not show any cross peaks with the TMEDA protons. This tells us that the lithium in **2d** is probably coordinated in a bidentate fashion by TMEDA. Addition of small amounts (1 equiv/Li) of THF to the above solution resulted in the appearance of new  $^6\text{Li}$  NMR signals for both **3b** and **2b** together with the former signal for **2d**, but no signals for **3a**. This result shows that THF has a much stronger affinity toward lithium than does both DEE and TMEDA.

**DME.** We also performed a titration study of **3a** in DEE- $d_{10}$  with DME. Upon addition of 0.5 equiv of DME, two new  $^6\text{Li}$  signals at  $\delta$  2.74 and 3.02 appeared, assigned to the DME solvated dimer (**3c**), along with equal amounts of **3a**. Further addition of DME above 1 equiv resulted in the appearance of a third signal at  $\delta$  2.10 probably for a monomer (**2c**). The amount of **2c** increased at the expense of **3c** at lower temperatures as would be expected for a dimer–monomer equilibrium. This titration study showed that DEE is expelled by DME. DME, which is potentially a bidentate ligand, seems to function as a monodentate ligand as more than 1 equiv is needed for obtaining **2c**. Almost 14 equiv of DME/Li was needed to obtain equal amounts of **3c** and **2c**, whereas only 3 equiv of THF/Li resulted in the same relationship between **3a** and **2b**. This tells us that THF is a much better ligand than DME in DEE- $d_{10}$  solution and that DME probably functions as a monodentate ligand in both **2c** and **3c**. Since we have shown that **3a** and **3b** are both complexed by only one ether ligand it is most likely that there is a monodentate coordination to the lithium cation in **3c**.

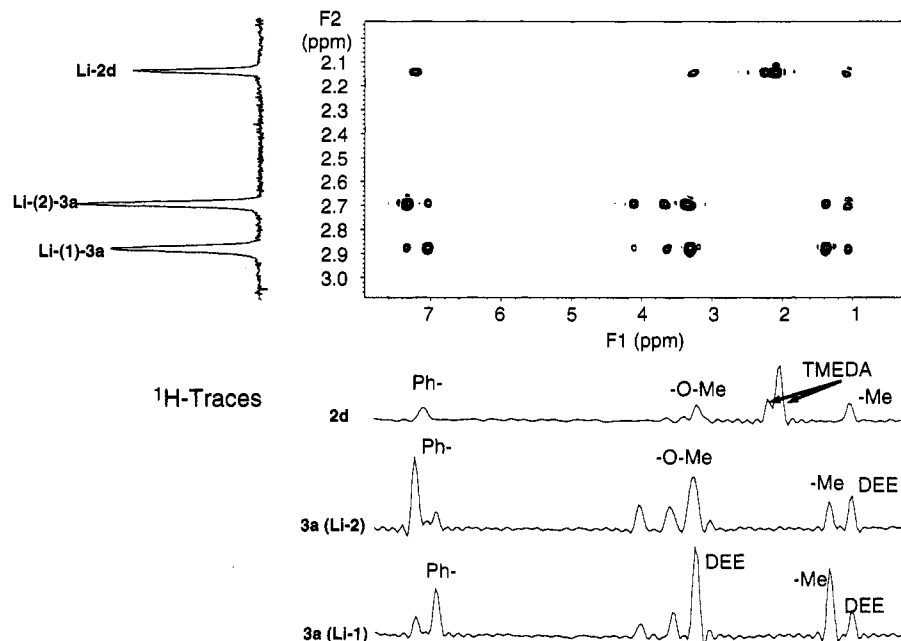
The  $^{13}\text{C}$  NMR of **3c** with 0.8 equiv of DME/Li in toluene- $d_8$  at  $-90^\circ\text{C}$  showed the presence of three signals for DME, two signals at  $\delta$  58.47 and 71.75, and one broad signal at  $\delta$  70.91. The broad signal at  $\delta$  70.91 coalesces with the signal at  $\delta$  71.75 upon raising the temperature, while the signal at  $\delta$  58.47 seems unaffected. At least four different  $^{13}\text{C}$  NMR signals are expected for free and coordinated DME. We believe that the observation of only three  $^{13}\text{C}$  NMR signals for DME could be due to accidental chemical shift degeneracy. A possible explanation could also be that the ligand exchange rate in **3c** is in the medium-fast exchange region.<sup>15</sup> If the  $^{13}\text{C}$  NMR chemical shift difference between the  $-\text{OCH}_3$  groups in the coordinated and free DME is very small, then the  $^{13}\text{C}$  NMR line shapes would be invariant at the available temperatures. On the other hand if the chemical shift difference between the  $-\text{OCH}_2-$  groups in the coordinated and free DME is large one would be able to freeze

(13) Boche, G.; Fraenkel, G.; Cabral, J.; Harms, K.; van Eikema Hommes, N. J. R.; Lohrenz, J.; Marsch, M.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1992**, *114*, 1562.

(14) Gregory, K.; Bremer, M.; Bauer, W.; Schleyer, P. v. R.; Lorenzen, N. P.; Kopf, J.; Weiss, E. *Organometallics* **1990**, *9*, 1485.

(15) Unfortunately the solvent mixture was frozen at temperatures below  $-90^\circ\text{C}$ .





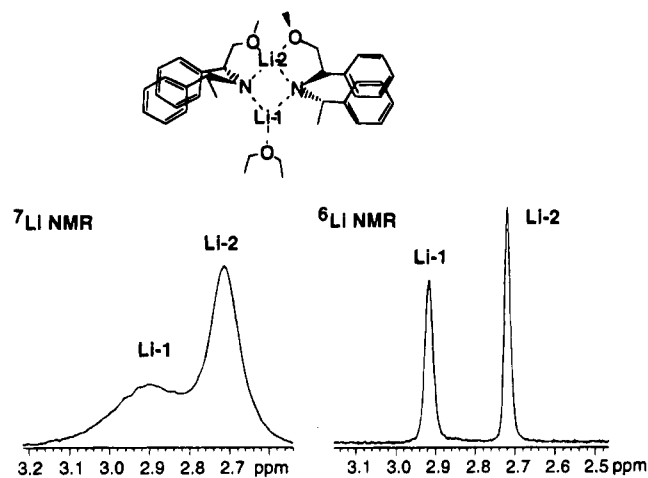
**Figure 13.**  $^6\text{Li}$ ,  $^1\text{H}$ -HOESY NMR spectrum of **3a** and **2d** in  $\text{DEE-}d_{10}/\text{TMEDA}$  (500/200 v/v) at  $-60^\circ\text{C}$ .

out the ligand exchange in **3c**, affording a new broad  $^{13}\text{C}$  NMR signal at  $\delta$  70.91. Further addition of DME above 0.8 equiv to 14 equiv affects all the chemical shifts assigned to DME; the signal at  $\delta$  58.47 is shifted upfield to 58.17, and the signal at  $\delta$  71.75 is shifted upfield to  $\delta$  71.68, and the broad signal at  $\delta$  70.91 is shifted upfield to  $\delta$  70.63. However, the  $^{13}\text{C}$  NMR chemical shifts for **3c** are unaffected by the high concentration of DME. One explanation for these  $^{13}\text{C}$  NMR upfield chemical shifts could be that there is a fast equilibrium between free DME and DME coordinated to **2c** that is seen as a continuous upfield chemical shift instead of the appearance of new signals.

In DEE we observed the coalescence temperature of the lithium exchange of **3a** to be independent of the free ethereal ligand concentration. In contrast the lithium exchange of **3c** was found to be dependent upon the ethereal ligand (DME) concentration. A 0.5 M toluene- $d_8$  solution of **3c** with 1.5 equiv of DME/Li gave  $T^c = -50^\circ\text{C}$  ( $\Delta G^\ddagger_{223\text{K}, \text{Li-Li}} = 41.5 \pm 1 \text{ kJ/mol}$ ). At 15 equiv of DME/Li coalescence temperatures were also observed  $T^c = -75^\circ\text{C}$  giving a  $\Delta G^\ddagger_{198\text{K}, \text{Li-Li}} = 47.0 \pm 1 \text{ kJ/mol}$ . These  $\Delta G^\ddagger$ s are in the same size as for **3a** but the DME concentration dependence suggests an associative mechanism to be responsible for the lithium exchange in **3c**.

**12-Crown-4.** The addition of the lithium-selective crown ether 12-crown-4 is expected to give crown ether-solvated monomers of **3a**. Addition of 1 equiv of 12-crown-4/Li to a **3a** solution in  $\text{DEE-}d_{10}$  at  $-70^\circ\text{C}$  resulted in the disappearance of the two  $^6\text{Li}$  signals for **3a** and the appearance of only one new signal at  $\delta$  2.77 for a 12-crown-4 complexed **3**. This new signal is logically attributed to 1:1 crown ether complexed monomers.

**Electric Field Gradient Effect.** The  $^6\text{Li}$  resonances of **3a** differed significantly in line width,  $W_{1/2} = 1.30 \text{ Hz}$  for the lithium signal at  $\delta$  2.92 and  $W_{1/2} = 1.10 \text{ Hz}$  for the lithium signal at  $\delta$  2.72, during proton decoupling. We found that the differences in line widths between the two signals were larger in the  $^7\text{Li}$  NMR spectrum of **3a**. The most upfield lithium signal showed to have a line width of  $W_{1/2} = 16 \text{ Hz}$  and the most downfield signal had a line width of  $W_{1/2} = 35 \text{ Hz}$ . The transverse relaxation times ( $T_2$ ) of the  $^6\text{Li}$  resonances were also measured using



**Figure 14.**  $^7\text{Li}$  and  $^6\text{Li}$  NMR spectra of **3a** at  $-80^\circ\text{C}$ .

the CPMG sequence to account for the differences in line widths.<sup>16</sup> The  $T_2$  at  $-100^\circ\text{C}$  in  $\text{DEE-}d_{10}$  were found to be 0.6 and 1.5 s for the  $^6\text{Li}$  NMR signal at  $\delta$  2.72 and 2.92, respectively (Figure 14).

The very small quadrupolar moment of spin  $I = 1$   $^6\text{Li}$  results in fairly narrow line widths more like spin  $I = 1/2$  nuclei (often less than 1 Hz), due to substantial dipole-dipole relaxation compared to the quadrupolar relaxation mechanism. The spin  $I = 3/2$   $^7\text{Li}$  on the other hand has a much larger quadrupole moment causing it to relax mainly through the more efficient quadrupolar relaxation mechanism that gives larger line widths. For a quadrupolar nucleus the line width is given by the following expression:

$$\nu_{1/2} = \frac{3}{10} \pi \frac{2I + 3}{I^2(2I - 1)} \left( \frac{e^2 Q q_{zz}}{h} \right)^2 \tau_C$$

The differences in line width of the two lithium signals for **3** are thus explained by a difference in the local electric field gradient ( $q_{zz}$ ) surrounding the lithium

(16) (a) Carr, H. Y.; Purcell, E. M. *Phys. Rev.* **1954**, *94*, 630. (b) Meiboom, S.; Gill, D. *Rev. Sci. Instr.* **1958**, *29*, 688.

cations. Nuclei surrounded by a highly symmetrical environment cause a smaller electric field gradient and thereby smaller line widths.<sup>17</sup>

The conclusion that could be drawn is that the lithium at  $\delta$  2.92 is tricoordinated due to a larger line width compared to the tetracoordinated lithium at  $\delta$  2.72. The difference is clearly observed in the <sup>7</sup>Li NMR spectrum of **3a** due to a larger contribution of quadrupolar relaxation to the overall relaxation rate in which the local environment at the lithium cation affects the relative importance of the electric field gradient  $q_{zz}$ . To our knowledge this effect has not been observed for Li resonances before.

### Summary

There is a slow ligand exchange (DEE, THF, DME, TMEDA) between the free and the coordinated states in lithium salt of **1** on the NMR time scale. The rate-limiting transition state of the intraaggregate lithium exchange observed in **3a** does not involve additional solvation or deaggregation into monomers, neither does it proceed by a rate-limiting association or dissociation of DEE molecules. Furthermore, there is only one solvent molecule coordinated to the dimer, giving a tricoordinate lithium cation while the other lithium in the dimer is tetracoordinated (two nitrogen anions and two methoxy groups).

DME was found to function as a monodentate ligand in the dimer, and there is also evidence that it functions as a monodentate ligand in the monomer. The lithium–lithium exchange within the DME solvated dimer **3c** were not independent of the DME concentration, indicating that the lithium exchange proceeds via an associative mechanism. Therefore, the rate-limiting transition state for lithium–lithium exchange is different in DME and DEE. In contrast to DME, the equilibrium of TMEDA-coordinated monomers and dimers was observed to favor monomers. Monodentate coordination of TMEDA (in the dimer) has thus a much weaker affinity for **3** than does DME. In the TMEDA-solvated monomer a tetracoordinated lithium has been shown to be the major species. The TMEDA complexed monomer displays a dynamic process among the <sup>13</sup>C NMR resonances of TMEDA, best described as due to rotation of the TMEDA·Li moiety with respect to the diastereomeric anion. Addition of THF to the TMEDA solvated monomer results in the formation of THF-solvated dimers and monomers among TMEDA-solvated monomers. Thus THF has a higher affinity for the lithium than TMEDA. The THF-solvated monomer most likely contains a tetracoordinated lithium cation. Analysis of line widths for **3a** showed that the tricoordinated lithium has a larger line width than the tetracoordinated lithium cation. We believe this to be due to differences in electric field gradients surrounding the lithium cation that affects the relaxation rate of the lithium. This could therefore be used to differentiate between tri- and tetracoordinate lithium cations within the same molecule.

(17) For instance NMe<sub>3</sub> has a lower symmetry than the tetracoordinated nitrogen in [NMe<sub>4</sub>]<sup>+</sup>, the line widths of the <sup>14</sup>N NMR are 77 and <0.5 Hz, respectively. See also: (a) Harris, R. K. *Nuclear magnetic resonance spectroscopy*; Pitman books limited: London, 1983; pp 133. (b) Benn, R.; Rufin'ska A. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 861 and references therein.

### Experimental Section

**General.** All glassware was dried overnight in a 120 °C oven (syringes were dried at 50 °C in a vacuum oven) before transfer into a glovebox (Mecaplex GB 80 equipped with a gas purification system that removes oxygen and moisture) with nitrogen atmosphere. Typical moisture content was less than 0.5 ppm. All manipulations of the lithium compounds were carried out in the glovebox using gas-tight syringes. Ethereal solvents were stored and freshly distilled from dry Deporex (FLUKA AG), and TMEDA was distilled from *n*-butyllithium prior to use.

**Preparation of [2-Methoxy-(*R*)-1-phenylethyl][(S)-1-phenylethyl]amine (1).** The amine [2-methoxy-(*R*)-1-phenylethyl][(S)-1-phenylethyl]amine was synthesized according to the literature.<sup>18</sup>

**[2-Methoxy-(*R*)-1-phenylethyl][2-<sup>6</sup>Li]lithio-(S)-1-phenylethyl]amide in Situ Preparation.** [2-Methoxy-(*R*)-1-phenylethyl][(S)-1-phenylethyl]amine (**1**) (100 mg  $\approx$  0.35 mmol) was transferred into a dry 5 mm NMR tube. The NMR tube was fitted with a Wilmad/Omnifit Teflon valve assembly OFV with Teflon/silicon septum. The solvent was added via syringe. To the solution of **1** at –78 °C was added 10 M [<sup>6</sup>Li]-*n*-butyllithium ( $\approx$  30  $\mu$ L, 0.37 mmol) with a syringe.<sup>19</sup> The mixture containing the lithium salt of **1** (96% in <sup>6</sup>Li atom) was then put into the precooled NMR probe.

**Instrumental.** All NMR spectra were recorded using a Varian Unity 500 spectrometer equipped with three channels using a 5 mm <sup>1</sup>H, <sup>13</sup>C, <sup>6</sup>Li triple resonance probe head, and an X,<sup>1</sup>H indirect detection probe, custom built by the Nalorac company. Measuring frequencies were 500 MHz (<sup>1</sup>H), 125 MHz (<sup>13</sup>C), 194 MHz (<sup>7</sup>Li), and 74 MHz (<sup>6</sup>Li). The <sup>1</sup>H and <sup>13</sup>C spectra were referenced to the solvent signals: DEE-*d*<sub>10</sub>  $\delta$  1.06 (<sup>1</sup>H–CH<sub>3</sub>) and  $\delta$  67.57 (<sup>13</sup>C –OCH<sub>3</sub>); THF-*d*<sub>8</sub>  $\delta$  68.00 (<sup>13</sup>C –OCH<sub>2</sub>)  $\delta$  1.73 (<sup>1</sup>H–CH<sub>2</sub>); toluene-*d*<sub>8</sub>  $\delta$  2.09 (<sup>1</sup>H–CH<sub>3</sub>) and  $\delta$  20.40 (<sup>13</sup>C –CH<sub>3</sub>). Lithium spectra were referenced to external 0.3 M [<sup>7</sup>Li]Cl in MeOH-*d*<sub>4</sub> ( $\delta$  = 0.0) and 0.3 M [<sup>6</sup>Li]Cl in MeOH-*d*<sub>4</sub> ( $\delta$  = 0.0).

The 1-D proton and carbon spectra were recorded with standard parameters. Lithium spectra were recorded with and without proton waltz-16 decoupling. A typical 90° <sup>6</sup>Li pulse was 20  $\mu$ s.

Probe temperatures were measured, after more than 1 h of temperature equilibration, both with a calibrated methanol–Freon NMR thermometer and with the standard methanol thermometer supplied by Varian.<sup>20</sup>

**2-D NMR Measurements.** All 2-D spectra were acquired using nonspinning 5 mm samples with deuterium field-frequency locking. Spectra were processed in the phase-sensitive mode with square sine bell weighting both in  $f_1$  and  $f_2$ .

For the <sup>6</sup>Li, <sup>1</sup>H-HOESY spectrum the following parameters were used: spectral window of 1000 Hz ( $f_2$  = <sup>6</sup>Li) and 8000 Hz ( $f_1$  = <sup>1</sup>H); 128 increments and 32 scans per increment in  $t_1$ ; mixing time = 1.0 s; 28  $\mu$ s proton 90° decoupler pulse. The <sup>6</sup>Li, <sup>1</sup>H-HOESY sequence is described in detail.<sup>21</sup>

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