

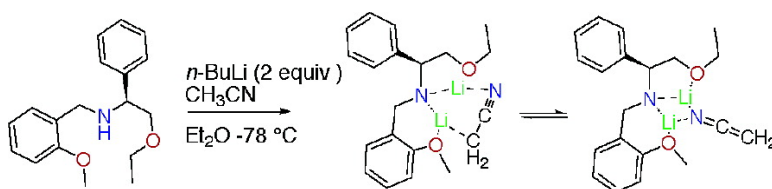
Article

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## Mixed Complexes Formed by Lithioacetonitrile and Chiral Lithium Amides: Observation of ${}^6\text{Li}$ , ${}^{15}\text{N}$ and ${}^6\text{Li}$ , ${}^{13}\text{C}$ Couplings Due to Both C–Li and N–Li Contacts

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**Abstract:** NMR spectroscopic studies have been performed on the mixed complexes formed by the lithium salt of acetonitrile ( $\text{LiCH}_2\text{CN}$ ) and the chiral lithium amides  $\text{Li}-(\text{S})\text{-}N\text{-}(2\text{-methoxybenzyl})\text{-}1\text{-amino}\text{-}1\text{-phenyl}\text{-}2\text{-ethoxyethane}$  (**Li-1**) and  $\text{Li}-(\text{S})\text{-}N\text{-isopropyl}\text{-}2\text{-amino}\text{-}1\text{-phenyl}\text{-}3\text{-methoxypropane}$  (**Li-2**) in diethyl ether and tetrahydrofuran solvent. In diethyl ether **Li-1** and  $\text{LiCH}_2\text{CN}$  form a mixed dimeric (1:1) complex, while **Li-2** and  $\text{LiCH}_2\text{CN}$  form a mixed trimeric (2:1) complex. The dimer undergoes fast exchange between ketenimine and bridged structures. Both  ${}^1J({}^{15}\text{N}, {}^6\text{Li})$  and  ${}^1J({}^{13}\text{C}, {}^6\text{Li})$  couplings were observed for the respectively isotopically labeled compounds. In the trimeric complex the  $\text{CH}_2\text{CN}$  anion also undergoes fast degenerate exchange between ketenimine and bridged structures, and the complex appears  $C_2$ -symmetric on the NMR spectroscopy time scale. Both the dimer and trimer complexes have the bridged acetonitrile anion in common, as indicated by the highly shielded  $\alpha$ -carbon  ${}^{13}\text{C}$  NMR shifts ( $\delta$   $-6.1$  and  $-7.4$ , respectively). In tetrahydrofuran only  $N$ -metalated mixed  $\text{LiCH}_2\text{CN}$  dimers were observed for both **Li-1** and **Li-2** with the less shielded  ${}^{13}\text{C}$  NMR shifts of  $\delta$   $-2.5$  and  $-2.2$  for the  $\alpha$ -carbon of  $\text{LiCH}_2\text{CN}$  of the complexes.

### Introduction

The development of chiral ligands for asymmetric synthesis has been of major interest for the organic chemists for many years.<sup>1</sup> There are numerous reports of chiral ligands for use in the asymmetric addition of organolithium reagents to carbonyl compounds resulting in optically active alcohols.<sup>2,3</sup> So far these investigations have focused on simple alkyllithium compounds such as *n*-butyllithium (*n*-BuLi) and methyllithium (MeLi), especially in the form of mixed complexes with chiral lithium amides.<sup>4–6</sup> Only minor attention has been devoted to mixed aggregates formed by nitrile-stabilized carbanions and chiral

ligands. Such mixed chiral aggregates are potentially useful for the asymmetric addition of nitrile anions to aldehydes, yielding  $\beta$ -hydroxy nitriles, which constitute an important group of synthetic intermediates.

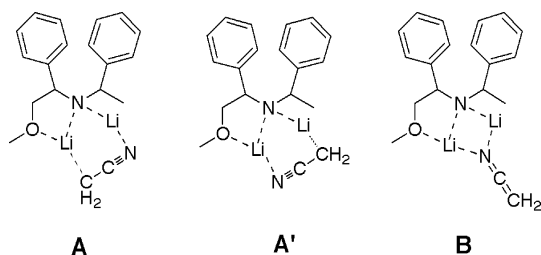
The position of the metal cation has been the subject of discussion in a number of studies of nitrile-stabilized carbanions.<sup>7–9</sup> In these reports, *N*-lithiated nitriles have been found to dominate,<sup>7</sup> although there is one known X-ray structure with a bridged lithiated nitrile.<sup>8</sup> There is a substantial number of reports on lithiophenylacetonitrile, but surprisingly little is known about the more simple analogue lithioacetonitrile ( $\text{LiCH}_2\text{CN}$ ).

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**Table 1.** Selected <sup>1</sup>H and <sup>13</sup>C NMR Chemical Shifts for the “Et<sub>2</sub>O Solvated” Mixed Complex **C** at –87 °C

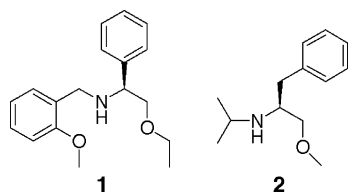
solvent	nucleus	CH <sub>2</sub> CN	OCH <sub>3</sub>	OCH <sub>2</sub> CH	CH <sub>2</sub> CH <sub>3</sub>	NCH	NCH <sub>2</sub>	CH <sub>2</sub> CH <sub>3</sub>
Et <sub>2</sub> O	<sup>1</sup> H	0.4	4.06	4.12, 3.05	3.44	4.11	3.26, 3.49	1.2
	<sup>13</sup> C	–6.1	56.7	59.1	67.2	72.6	81.0	15.1

We recently reported on the structure and selectivity of mixed aggregates formed by LiCH<sub>2</sub>CN and lithium amides with a chelating ether group.<sup>9</sup> One of these chiral ligands, developed by Eleveld and Hogeveen,<sup>3</sup> induced an enantiomeric excess (ee) of 55% in the asymmetric addition of LiCH<sub>2</sub>CN to benzaldehyde in tetrahydrofuran (THF), while the same reaction carried out in diethyl ether (Et<sub>2</sub>O) resulted in 45% ee of the opposite enantiomer. NMR spectroscopic studies indicated the formation of the “Et<sub>2</sub>O solvated” mixed complexes **A**, **A'** and the “THF solvated” mixed complex **B**. Although extensive structure



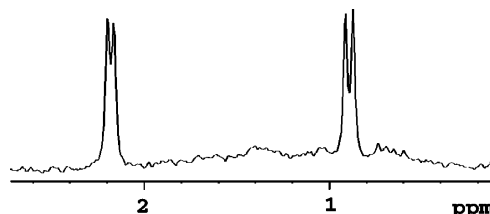
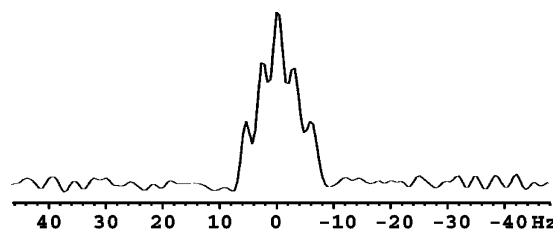
investigation of these complexes by multinuclear NMR spectroscopy was performed at low temperatures, no direct evidence, such as <sup>1</sup>J(<sup>13</sup>C,<sup>6</sup>Li) or <sup>1</sup>J(<sup>6</sup>Li,<sup>15</sup>N) couplings, was observed, probably due to fast intermolecular exchange.

Herein we wish to report the NMR spectroscopic studies on the mixed complexes formed by LiCH<sub>2</sub>CN and two different chiral lithium amides with chelating ether groups, Li–(*S*)-*N*-(2-methoxybenzyl)-1-amino-1-phenyl-2-ethoxyethane (**Li-1**) and Li–(*S*)-*N*-isopropyl-2-amino-1-phenyl-3-methoxypropane (**Li-2**). The mixed complexes, formed between these lithium amides and LiCH<sub>2</sub>CN, have been studied in Et<sub>2</sub>O and THF solvents using <sup>6</sup>Li, <sup>13</sup>C, and <sup>15</sup>N labeled compounds.



## Results

**Mixed Complex Formed by Li-1 and LiCH<sub>2</sub>CN in Et<sub>2</sub>O Solution (C and D).** A mixture of 600 μL of Et<sub>2</sub>O-*d*<sub>10</sub>, 0.4 mmol of *n*-Bu[<sup>6</sup>Li], 0.2 mmol of **1**, and 0.2 mmol of acetonitrile was carefully prepared in an NMR tube at –78 °C. The <sup>6</sup>Li NMR spectrum obtained at –100 °C of the mixture shows two singlets at δ 2.2 and 0.9, respectively. These <sup>6</sup>Li signals are proposed to be from a mixed complex and not from the homoaggregated chiral lithium amide (δ 1.8 and 2.3) or from LiCH<sub>2</sub>CN (δ 0.4). When <sup>15</sup>N-labeled acetonitrile was used the two signals in the <sup>6</sup>Li NMR spectrum appear as doublets.<sup>10</sup> The less shielded <sup>6</sup>Li NMR signal has a coupling constant of 2.6 Hz and the more shielded signal has a coupling constant of 3.1 Hz, due to scalar <sup>6</sup>Li,<sup>15</sup>N couplings (Figure 1).

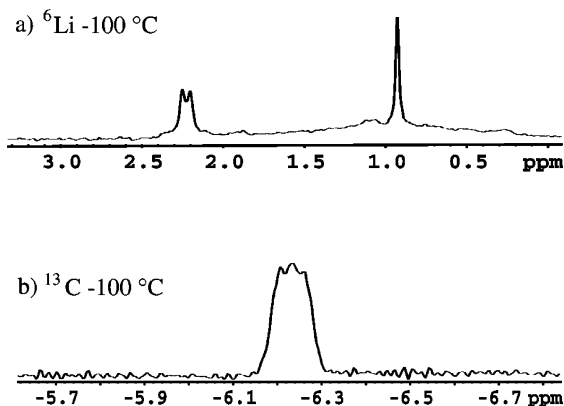
**Figure 1.** <sup>6</sup>Li NMR spectrum of the mixture of 0.2 M CH<sub>3</sub>C[<sup>15</sup>N], 0.4 M *n*-Bu[<sup>6</sup>Li], and 0.2 M **1** in Et<sub>2</sub>O-*d*<sub>10</sub> (**C**) at –87 °C.**Figure 2.** <sup>15</sup>N NMR spectrum of the mixture of 0.2 M CH<sub>3</sub>C[<sup>15</sup>N], 0.4 M *n*-Bu[<sup>6</sup>Li], and 0.2 M **1** in Et<sub>2</sub>O-*d*<sub>10</sub> (**C**) at –87 °C.

The <sup>15</sup>N NMR spectrum (Figure 2) of the same solution shows a resolved quintet (<sup>1</sup>J(<sup>15</sup>N,<sup>6</sup>Li) = 2.8 Hz), indicating that the complex is an *N*-lithiated, mixed aggregate structure in which the nitrogen of acetonitrile coordinates to the two different lithiums.

The <sup>13</sup>C and <sup>1</sup>H NMR shifts of the mixed complex are presented in Table 1. The <sup>13</sup>C NMR spectrum shows only one set of carbon signals at temperatures between –67 and –116 °C. The <sup>13</sup>C NMR signals have different chemical shifts from those of the lithium amide and LiCH<sub>2</sub>CN, respectively. The α-carbon signal of the complexed LiCH<sub>2</sub>CN appears at δ –6.1 in the <sup>13</sup>C NMR spectrum but no <sup>1</sup>J(<sup>13</sup>C,<sup>6</sup>Li) couplings are observed at any temperature between –67 and –125 °C (in Et<sub>2</sub>O:hexane mixtures). Since the <sup>1</sup>J(<sup>13</sup>C,<sup>1</sup>H) coupling is known to relate to the amount of s-character of the carbon we also obtained a coupled <sup>13</sup>C NMR spectrum. The α-carbon is a triplet (<sup>1</sup>J(<sup>13</sup>C,<sup>1</sup>H) = 148 Hz), indicating that the α-carbon of LiCH<sub>2</sub>CN is sp<sup>3</sup>- rather than sp<sup>2</sup>-hybridized. The amount of s-character in the mixed complex was also estimated from a natural bond orbital calculation on the PM3 geometry-optimized bridged structure and the formula <sup>1</sup>J(<sup>13</sup>C,<sup>1</sup>H) = 500/(% s-character). This leads to an estimated <sup>1</sup>J(<sup>13</sup>C,<sup>1</sup>H) coupling of 152 Hz, which is very close to the experimentally observed value. It should however be noted that the correlation of <sup>13</sup>C–<sup>1</sup>H coupling constants with s-hybridization should be done with caution, especially when dealing with anions.

To gain further information about this mixed complex, we employed <sup>13</sup>C-labeled acetonitrile, which allowed us to acquire a <sup>13</sup>C NMR spectrum at a significantly lower concentration (0.05 M instead of 0.2 M). A doublet at δ 2.2 (<sup>1</sup>J(<sup>6</sup>Li,<sup>13</sup>C) = 3.5 Hz)

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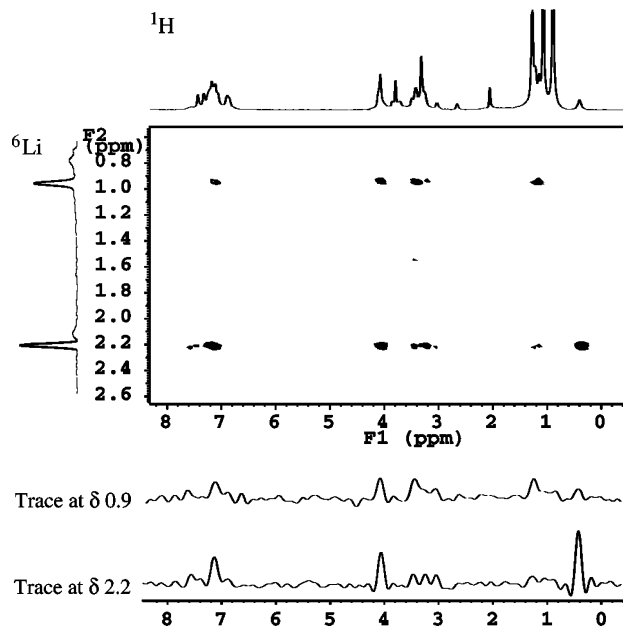
**Figure 3.** (a)  ${}^6\text{Li}$  NMR spectrum of the mixture of 0.05 M  $[{}^{13}\text{C}]\text{H}_3\text{CN}$ , 0.10 M  $n\text{-Bu}[{}^6\text{Li}]$  and 0.05 M **1** in  $\text{Et}_2\text{O}-d_{10}$  (**C**) at  $-100\text{ }^\circ\text{C}$  and (b) a selected region of the  ${}^{13}\text{C}$  NMR showing the carbanion signal of the same mixture.

and a singlet at  $\delta$  0.9 are observed in the  ${}^6\text{Li}$  NMR spectrum obtained at  $-100\text{ }^\circ\text{C}$  of a solution of  $\text{Li}-[{}^{13}\text{C}]\text{H}_2\text{CN}$  and **Li-1**. The  ${}^{13}\text{C}$  NMR spectrum of the same solution obtained at  $-100\text{ }^\circ\text{C}$  reveals a 1:1:1 triplet ( ${}^1J({}^{13}\text{C},{}^6\text{Li}) = 3.5\text{ Hz}$ ) of the  $\text{CH}_2$  carbon signal, see Figure 3. The observed coupling between the carbon of  $\text{CH}_2\text{CN}$  and the lithium unambiguously establishes a C–Li contact.

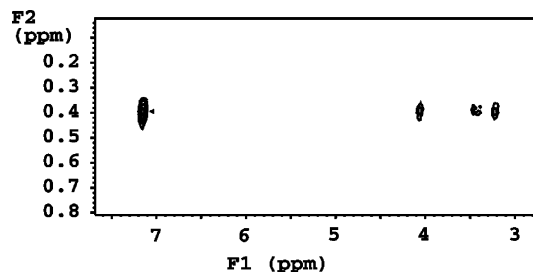
The heteronuclear Overhauser effect experiment ( ${}^6\text{Li},{}^1\text{H}$ -HOESY), introduced by Bauer et al., is one of the most powerful NMR spectroscopic techniques available for structure elucidation of organolithium compounds and has extensively been used by our group in the studies of various chiral mixed organolithium complexes.<sup>5,11</sup> Lithium nuclei proximate to protons give rise to cross-peaks, which provide information about the three-dimensional structure of the complex, including coordinated ligands. The  ${}^6\text{Li},{}^1\text{H}$ -HOESY spectrum of the mixed complex in  $\text{Et}_2\text{O}$  solution at  $-87\text{ }^\circ\text{C}$  (Figure 4) shows strong NOE cross-peaks between the lithium signal at  $\delta$  2.2 and the  $\alpha$ -protons of the  $\text{LiCH}_2\text{CN}$  at  $\delta$  0.4, the protons of **Li-1** at  $\delta$  3.05 ( $\text{OCH}_2$ ),  $\delta$  3.26 ( $\text{NCH}_2$ ),  $\delta$  3.44 ( $\text{CH}_2\text{CH}_3$ ), and  $\delta$  4.06–4.11 ( $\text{OCH}_3$  and  $\text{NCH}$ ), and the aromatic protons in the region of  $\delta$  7–8. The lithium signal at  $\delta$  0.9 shows strong NOE to the protons of the lithium amide at  $\delta$  1.20 ( $\text{OCH}_2\text{CH}_3$ ),  $\delta$  3.44 ( $\text{CH}_2\text{CH}_3$ ), and  $\delta$  4.10 ( $\text{NCH}$  or  $\text{OCH}_2\text{CH}$ ) and weak NOE's to the aromatic protons but very small, if any, NOE to the  $\alpha$ -protons of acetonitrile at  $\delta$  0.4. The NOE between the  $\text{LiCH}_2\text{CN}$  protons and the more deshielded lithium signal, in addition to the  ${}^1J({}^6\text{Li},{}^{15}\text{N})$  and  ${}^1J({}^6\text{Li},{}^{13}\text{C})$  couplings, are consistent with a mixed dimer **C** in fast exchange with the mixed dimer **D** (Scheme 1).

A  ${}^1\text{H},{}^1\text{H}$  NOESY experiment of the mixed dimer complex also supports the conclusion of a C-lithiated acetonitrile. NOE cross-peaks are observed between the lithioacetonitrile protons and the proton signals at  $\delta$  3.26, ( $\text{NCH}_2$ ),  $\delta$  3.44 ( $\text{CH}_2\text{CH}_3$ ), and  $\delta$  4.06 ( $\text{OCH}_3$ ) and the aromatic protons at  $\delta$  7.2, see Figure 5.

Quantitative 2D NMR exchange spectroscopy (EXSY) is a powerful method for the determination of site-to-site exchange

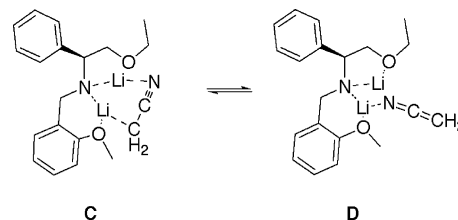


**Figure 4.**  ${}^6\text{Li},{}^1\text{H}$ -HOESY experiment of the mixture of 0.3 M  $\text{CH}_3\text{CN}$ , 0.6 M  $n\text{-Bu}[{}^6\text{Li}]$ , and 0.3 M **1** in  $\text{Et}_2\text{O}-d_{10}$  (**C**) at  $-87\text{ }^\circ\text{C}$ .



**Figure 5.** Selected region of the  ${}^1\text{H},{}^1\text{H}$  NOESY experiment of the mixture of 0.05 M  $\text{CH}_3\text{CN}$ , 0.1 M  $n\text{-Bu}[{}^6\text{Li}]$ , and 0.05 M **1** in  $\text{Et}_2\text{O}-d_{10}$  (**C**) at  $-87\text{ }^\circ\text{C}$ .

**Scheme 1** Fast Exchange of the 1:1 Mixed Dimer (**C** and **D**) Formed from **Li-1** and  $\text{LiCH}_2\text{CN}$



rate constants.<sup>12</sup> This method is especially advantageous, over, for example, line-shape analysis, when there are simultaneous exchange processes that may complicate the analysis. There is a slow Li–Li exchange within the complex on the NMR spectroscopy time scale. The cross-peaks in the 2D EXSY spectra are a graphical display of the exchange processes. From the signal intensities in the  ${}^6\text{Li},{}^6\text{Li}$ -EXSY spectrum, the rate constants for direct two-site exchanges were determined using the D2DNMR program.<sup>12c</sup> The rate constant for the intra-aggregate exchange was determined to be  $0.35\text{ s}^{-1}$  from the intensities of the cross-peaks between the two Li signals in the  ${}^6\text{Li},{}^6\text{Li}$ -EXSY spectrum of **C**, corresponding to a  $\Delta G^\ddagger$  of  $12.6\text{ kcal mol}^{-1}$  at  $-62\text{ }^\circ\text{C}$ .

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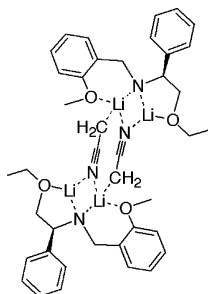
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**Table 2.** Selected <sup>1</sup>H and <sup>13</sup>C NMR Chemical Shifts for the “THF Solvated” Mixed Complex **D** at –87 °C

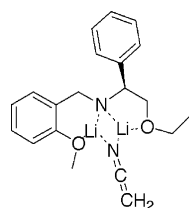
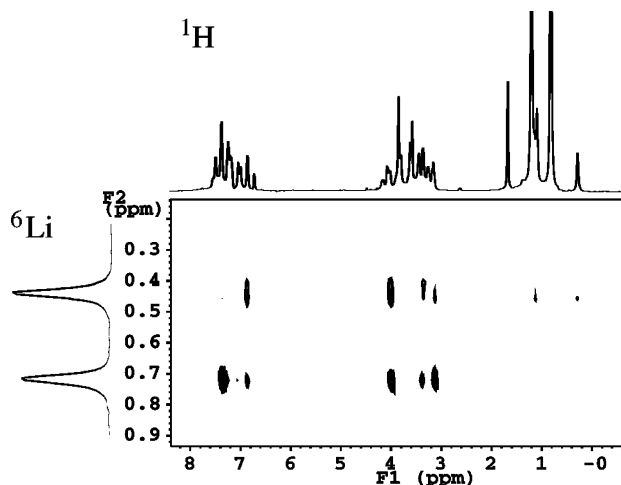
solvent	nucleus	CH <sub>2</sub> CN	OCH <sub>3</sub>	OCH <sub>2</sub> CH	CH <sub>2</sub> CH <sub>3</sub>	NCH	NCH <sub>2</sub>	CH <sub>2</sub> CH <sub>3</sub>
THF	<sup>1</sup> H	0.3	3.9	3.3, 4.0	3.6, 3.9	4.1	3.4, 3.1	1.1
	<sup>13</sup> C	–2.5	55.8	67.4	55.4	69.5	80.8	15.4

These results may also suggest that the mixed aggregate may be a tetrameric complex in which two bridging LiCH<sub>2</sub>CN coordinated by two Li-**1** form an eight-membered ring (**H**). An

**H**

experiment using 1 equiv of Li-**1**, 1 equiv of *n*-BuLi, 0.5 equiv of <sup>15</sup>N-labeled acetonitrile, and 0.5 equiv of <sup>13</sup>C-labeled acetonitrile was performed in order to determine whether the complex is tetrameric or dimeric. In the case of the tetramer, a multiplet at  $\delta$  2.2 resulting from three signals with 1:1:1 intensities is expected, two doublets with  $^1J(^{13}\text{C}, ^6\text{Li}) = 3.5$  Hz and  $^1J(^6\text{Li}, ^{15}\text{N}) = 2.6$  Hz and a singlet. The proposed dimer **C** in fast exchange with **D** would result in a multiplet at  $\delta$  2.2 formed by two doublets ( $^1J(^{13}\text{C}, ^6\text{Li}) = 3.5$  Hz and  $^1J(^6\text{Li}, ^{15}\text{N}) = 2.6$  Hz) and a singlet in 1:1:2 intensity. Unfortunately, the experiment yielded a multiplet at  $\delta$  2.2 in the <sup>6</sup>Li NMR spectrum, too poorly resolved to exclude any of these aggregates.

**Mixed Complex Formed by Li-1 and LiCH<sub>2</sub>CN in THF Solution (D).** A mixture of 600  $\mu\text{L}$  of THF-*d*<sub>8</sub>, 0.4 mmol of *n*-Bu[<sup>6</sup>Li], 0.2 mmol of **1**, and 0.2 mmol of CH<sub>3</sub>C[<sup>15</sup>N] was carefully prepared in a sealed NMR tube at –78 °C. At –87 °C the <sup>6</sup>Li NMR spectrum of the mixture shows two signals at  $\delta$  0.45 and 0.8 in a 1:1 intensity ratio, which we propose to be from a mixed dimeric complex consisting of Li-**1** and LiCH<sub>2</sub>CN. In the <sup>13</sup>C NMR spectrum only one set of carbon signals is observed, with different chemical shifts than those of the homoaggregates of Li-**1** and LiCH<sub>2</sub>CN. In the <sup>1</sup>H NMR spectrum, the proton signal of the complexed LiCH<sub>2</sub>CN is observed at  $\delta$  0.3, i.e., at a lower shift than in Et<sub>2</sub>O. In the <sup>13</sup>C NMR spectrum, the  $\alpha$ -carbon signal appears at  $\delta$  –2.5 with a  $^1J(^{13}\text{C}, ^1\text{H})$  coupling constant of 160 Hz.<sup>9</sup> According to semiempirical PM3 calculations of the amount of *s*-character of the ketenimine structure, we estimate the  $^1J(^{13}\text{C}, ^1\text{H})$  coupling constant of the  $\alpha$ -carbon to around 160 Hz. On the basis of these observations, we propose that the mixed complex **D** dominates in THF solution. Selected <sup>1</sup>H and <sup>13</sup>C NMR shifts of “THF solvated” **D** are presented in Table 2.

**D****Figure 6.** <sup>6</sup>Li,<sup>1</sup>H-HOESY experiment of the mixture of 0.3 M CH<sub>3</sub>CN, 0.6 M *n*-Bu[<sup>6</sup>Li], and 0.3 M **1** in THF-*d*<sub>8</sub> at –87 °C.

Neither  $^1J(^{13}\text{C}, ^6\text{Li})$  nor  $^1J(^6\text{Li}, ^{15}\text{N})$  couplings were observed in the mixture of Li-**1** and <sup>15</sup>N-labeled LiCH<sub>2</sub>CN at any temperature down to –117 °C (in THF:Et<sub>2</sub>O mixtures). The <sup>15</sup>N NMR spectra only displayed a broad unresolved signal at all temperatures. A similar loss of scalar coupling in THF solution has been observed earlier.<sup>7k</sup>

From the observed cross-peaks in the <sup>6</sup>Li,<sup>6</sup>Li-EXSY spectrum of the above solution obtained at –78 °C, the rate constant of the intra-aggregate exchange was determined to be 0.28 s<sup>–1</sup>, which corresponds to a  $\Delta G^\ddagger$  of 11.7 kcal mol<sup>–1</sup>.<sup>12</sup> Compared to the “Et<sub>2</sub>O solvated” complex, the lithium cations of this complex are in fast exchange.

Further structural information was obtained from a <sup>6</sup>Li,<sup>1</sup>H-HOESY experiment at –87 °C. The spectrum shows strong NOE's between the lithiums and the lithium amide protons at  $\delta$  3.3 and 4.0 (OCH<sub>2</sub>), see Figure 6. There also appears to be a weak NOE cross-peak between the CH<sub>2</sub>CN protons at  $\delta$  0.3 and the lithium signal at  $\delta$  0.5. Interestingly, there is no observable NOE cross-peak at  $\delta$  3.9 (<sup>1</sup>H), which may indicate that the methoxy group is not coordinated to any of the lithiums.

**Trimeric Mixed Complex Formation by LiCH<sub>2</sub>CN and Li-2 in Et<sub>2</sub>O Solution (E, F, and E').** The <sup>6</sup>Li NMR spectrum of a mixture of 0.27 mmol of *n*-BuLi, 0.09 mmol of CH<sub>3</sub>CN, and 0.18 mmol of the chiral amino ether **2** in 650  $\mu\text{L}$  of Et<sub>2</sub>O-*d*<sub>10</sub> at –87 °C displays two signals at  $\delta$  1.1 and 2.8 in a 2:1 intensity ratio. The signal intensity ratio is temperature independent between –67 and –117 °C, indicating the formation of a trimeric complex (**E**) with three lithiums of which two are magnetically equivalent. Only one set of <sup>13</sup>C NMR resonances is observed from the lithium amide and LiCH<sub>2</sub>CN, significantly different from their respective homoaggregates. The  $\alpha$ -carbon resonance of LiCH<sub>2</sub>CN in **E** is observed at  $\delta$  –7.4, with a  $^1J(^{13}\text{C}, ^1\text{H})$  coupling of 152 Hz. No  $^1J(^{13}\text{C}, ^6\text{Li})$  couplings are observed for the  $\alpha$ -carbon of LiCH<sub>2</sub>CN at any temperature between –60 and –125 °C. This indicates that the 2:1 mixed complex consists of two molecules of the lithium amide and one molecule of LiCH<sub>2</sub>CN. Unfortunately, experiments with

**Table 3.** Selected  $^1\text{H}$  and  $^{13}\text{C}$  NMR Shifts of “Et<sub>2</sub>O Solvated” Rapidly Exchanging **E**, **F**, and **E'** at  $-87\text{ }^\circ\text{C}$ 

solvent	nucleus	CH <sub>2</sub> CN	OCH <sub>3</sub>	OCH <sub>2</sub>	CH <sub>2</sub> Ph	NCH	CH(CH <sub>3</sub> ) <sub>2</sub>	CH(CH <sub>3</sub> ) <sub>2</sub>
Et <sub>2</sub> O	$^1\text{H}$	0.3	3.23	3.17, 3.30	3.44, 1.74	3.43	3.70	1.1, 1.2
	$^{13}\text{C}$	-7.4	59.0	80.6	39.9	63.0	48.3	24.0, 29.0

**Figure 7.**  $^6\text{Li}$  NMR spectrum of the mixture of 0.13 M CH<sub>3</sub>C[ $^{15}\text{N}$ ], 0.26 M *n*-Bu[ $^6\text{Li}$ ], and 0.13 M [ $^{15}\text{N}$ ]**2** in Et<sub>2</sub>O-*d*<sub>10</sub> at  $-87\text{ }^\circ\text{C}$ .

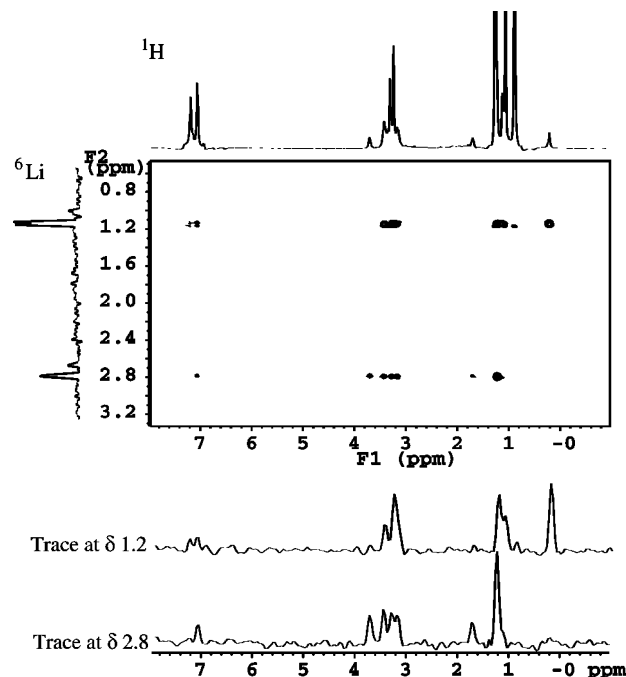
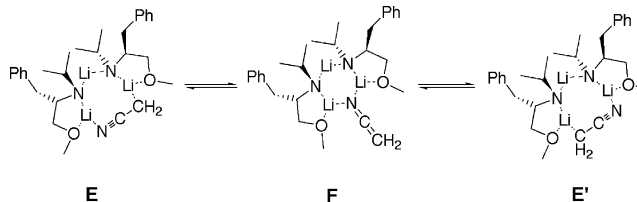
$^{13}\text{C}$ -, and  $^6\text{Li}$ -, or  $^7\text{Li}$ -labeled LiCH<sub>2</sub>CN also result in a broad resonance without resolved couplings for the  $\alpha$ -carbon in the  $^{13}\text{C}$  NMR spectrum. Selected  $^1\text{H}$  and  $^{13}\text{C}$  NMR shifts of the “Et<sub>2</sub>O solvated” **E** are presented in Table 3.

To gain more information about the mixed complex, we employed  $^{15}\text{N}$ -labeled acetonitrile. The larger peak at  $\delta$  1.1 became a doublet with a surprisingly small coupling constant of 2.1 Hz due to coupling to one  $^{15}\text{N}$ . In addition, an experiment using both  $^{15}\text{N}$ -labeled acetonitrile and  $^{15}\text{N}$ -labeled **2** was performed. With this doubly  $^{15}\text{N}$ -labeled complex, the lithium signal at  $\delta$  2.8 is a triplet ( $^1J(^6\text{Li},^{15}\text{N}) = 5.4\text{ Hz}$ ), while the signal at  $\delta$  1.1 is a doublet of a doublets ( $^1J(^6\text{Li},^{15}\text{N}) = 2.1, 4.5\text{ Hz}$ ), see Figure 7.

Two signals in a 2:1 intensity ratio were observed in the  $^{15}\text{N}$  NMR spectrum of the  $^6\text{Li}$ - and  $^{15}\text{N}$ -labeled complex. The amide nitrogen signal is a quintet ( $^1J(^{15}\text{N},^6\text{Li}) = 4.5\text{ Hz}$ ), while the more shielded signal from the nitrile anion is broad and unresolved at temperatures down to  $-87\text{ }^\circ\text{C}$ . The corresponding  $^7\text{Li}$ -labeled compounds were also prepared, as the  $^{15}\text{N}$ - $^7\text{Li}$  couplings should be larger by a factor of 2.6, due to its greater magnetogyric ratio. Unfortunately, only a broad unresolved  $^{15}\text{N}$  NMR signal was detected for the corresponding mixed complex. However, the observed  $^6\text{Li}$ ,  $^{15}\text{N}$ -scalar coupling supports the proposed symmetry of the trimer **E** made from one *N*-lithiated acetonitrile and two lithium amides. The two lithium signals also show cross-peaks in the EXSY spectrum, corresponding to an intramolecular rate constant for the Li–Li exchange of  $0.38\text{ s}^{-1}$ , or a  $\Delta G^\ddagger$  of  $13.8\text{ kcal mol}^{-1}$  at  $-42\text{ }^\circ\text{C}$ .<sup>12</sup>

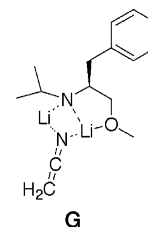
The  $^6\text{Li}$ ,  $^1\text{H}$ -HOESY spectrum of the mixed trimer at  $-97\text{ }^\circ\text{C}$  shows strong NOE cross-peaks between the  $\alpha$ -proton signal of LiCH<sub>2</sub>CN at  $\delta$  0.3 and the lithium signal at  $\delta$  1.1 (Figure 8). The observed strong NOE shows that they must be proximate while these lithiums also show coupling to the nitrogen of LiCH<sub>2</sub>CN. This surprising observation is only consistent with a mixed *C*<sub>2</sub>-symmetric trimer structure with the CH<sub>2</sub>CN anion undergoing a fast degenerate intramolecular exchange, i.e., a fast 180° flip between **E** and **E'** as shown in Scheme 2.

The methoxy–lithium interaction is indicated by the cross-peaks between the proton signal at  $\delta$  3.2 and the lithium signal at  $\delta$  1.1. Heteronuclear Overhauser effects are also observed between the lithium signal at  $\delta$  2.8 and the protons at  $\delta$  3.1,  $\delta$  3.3 (OCH<sub>2</sub>), and  $\delta$  3.7 (CHCH<sub>3</sub>) of **2**. Both lithiums showed NOE's to the proton signals at  $\delta$  1.2 (CHCH<sub>3</sub>) and 3.4 (CH<sub>2</sub>-Ph). These results are also consistent with the trimeric structure in which the lithiums at  $\delta$  1.1 are not only proximate to the acetonitrile protons but also coordinated by the methoxy groups of the amide.

**Figure 8.**  $^6\text{Li}$ ,  $^1\text{H}$ -HOESY spectrum of the mixture of 0.3 M CH<sub>3</sub>C[ $^{15}\text{N}$ ], 0.6 M *n*-Bu[ $^6\text{Li}$ ], and 0.3 M **2** in Et<sub>2</sub>O-*d*<sub>10</sub> at  $-97\text{ }^\circ\text{C}$ .**Scheme 2** Fast Exchange of the 2:1 Mixed Dimers (**E**, **F**, and **E'**) Formed from Two Li-**2** and One LiCH<sub>2</sub>CN

The  $^1\text{H}$ ,  $^1\text{H}$  NOESY spectrum recorded at  $-87\text{ }^\circ\text{C}$  of the mixed complex **E** shows a cross-peak between the LiCH<sub>2</sub>CN protons and the methoxy protons at  $\delta$  3.2; no other intermolecular homonuclear NOE's are observed. The NMR spectroscopic results of the amide Li-**2** complexed with LiCH<sub>2</sub>CN are only consistent with a 2:1 mixed complex that undergoes a rapid exchange, i.e., rapidly exchanging **E**, **F**, and **E'**.

**Mixed Complex Formation by LiCH<sub>2</sub>CN and Li-**2** in THF Solution (**G**).** In a 1:1 mixture of the lithium amide and LiCH<sub>2</sub>CN in THF-*d*<sub>8</sub>, only signals from **G** are observed in the  $^{13}\text{C}$ ,



$^6\text{Li}$ , and  $^1\text{H}$  NMR spectra. The  $\alpha$ -carbon signal of **G** appears at

**Table 4.** Selected <sup>1</sup>H and <sup>13</sup>C NMR Chemical Shifts for the “THF Solvated” Mixed Complexes **G** at –87 °C

solvent	nucleus	CH <sub>2</sub> CN	OCH <sub>3</sub>	OCH <sub>2</sub>	CH <sub>2</sub> Ph	NCH	CH(CH <sub>3</sub> ) <sub>2</sub>	CH(CH <sub>3</sub> ) <sub>2</sub>
THF	<sup>1</sup> H	0.3	3.2	3.1, 3.2	3.3	3.3	3.4	1.0
	<sup>13</sup> C	–2.2	58.8	78.7	40.2	64.5	49.6	25.1, 28.3

$\delta$  –2.2 with no coupling to <sup>6</sup>Li but with a <sup>1</sup>J(<sup>13</sup>C,<sup>1</sup>H) coupling of 162 Hz. No <sup>1</sup>J(<sup>15</sup>N,<sup>6</sup>Li) coupling is observed using <sup>15</sup>N-labeled acetonitrile. In pure THF solution, the lithium signals appear at  $\delta$  0.7 and 0.5 at –87 °C. The <sup>6</sup>Li,<sup>1</sup>H-HOESY spectrum of the mixed aggregate at –97 °C shows two major NOE cross-peaks between the lithium signals, the methoxy group protons, and the protons at  $\delta$  1.0 (CHCH<sub>3</sub>). The lack of NOE between the LiCH<sub>2</sub>CN protons and any of the lithium signals further supports the formation of an *N*-lithiated mixed ketenimine dimer in THF. Table 4 shows the <sup>1</sup>H and <sup>13</sup>C NMR chemical shifts of selected signals for the “THF solvated” mixed complex **G** at –87 °C.

Unfortunately, the diagonal peaks and the cross-peaks of the <sup>6</sup>Li,<sup>6</sup>Li-EXSY spectrum overlapped. The rate constant (*k<sub>c</sub>*) for the intramolecular exchange of the two <sup>6</sup>Li NMR signals was therefore determined at the coalescence temperature using the following equation:

$$k_c = \pi^* \delta \nu_A / \sqrt{2}$$

The coalescence temperature is –57 °C, corresponding to a rate constant of 37.6 s<sup>–1</sup> and an activation energy  $\Delta G^\ddagger$  of 10.9 kcal mol<sup>–1</sup>. The intramolecular exchange rate is similar to that of **D**, which is fast compared to that of the “Et<sub>2</sub>O solvated” **C** and **E**. Similar relationships were observed in our previous studies of mixed LiCH<sub>2</sub>CN complexes, which indicate a significant structural difference between the Et<sub>2</sub>O and “THF solvated” mixed complexes.<sup>9</sup>

## Discussion

**Et<sub>2</sub>O Solutions of Mixed Complexes Formed by the Chiral Lithium Amides (Li-1 and Li-2) and LiCH<sub>2</sub>CN.** The NMR spectroscopy results indicate that the chiral lithium amide Li-1 and LiCH<sub>2</sub>CN form mixed aggregates, which exist as two rapidly exchanging dimers, one with the LiCH<sub>2</sub>CN as a ketenimine (**D**) and one with a bridged LiCH<sub>2</sub>CN (**C**). These mixed complexes are rapidly exchanging on the NMR time scale. The observed <sup>1</sup>J(<sup>15</sup>N,<sup>6</sup>Li) couplings to both lithiums in addition to the strong hetero NOE cross-peak between the more deshielded lithium and the lithioacetonitrile protons strongly indicate the formation of a mixed complex with bridged LiCH<sub>2</sub>CN and lithium amides. Interestingly the  $\alpha$ -carbon of CH<sub>2</sub>CN only inserts close to the methoxy group and not on the other side of the asymmetric dimer.

We have previously reported, based on GIAO-DFT calculations, that a <sup>13</sup>C NMR chemical shift of approximately  $\delta$  –5 or more shielded for the  $\alpha$ -carbon indicates bridging of the nitrile anion.<sup>9</sup> Thus, the strongly shielded  $\alpha$ -carbon of LiCH<sub>2</sub>CN ( $\delta$  –6.1) indicates the presence of the bridged mixed complex **C**. Furthermore, the observed splitting of the  $\alpha$ -carbon resonance into a 1:1:1 triplet shows that there is substantial C–Li contact in the mixed complex. However, the observed <sup>1</sup>J(<sup>13</sup>C,<sup>6</sup>Li) coupling constant is only 3.5 Hz, i.e., considerably smaller than the “normal” values of 7–8 Hz, generally observed for alkyllithium dimers. This may indicate a possible delocalization of the negative charge of the acetonitrile anion but is more likely

the result of a fast exchange between *C*- and *N*-lithiated complexes, i.e., **C** and **D**. Such averaging of scalar coupling constants has been observed earlier.<sup>13</sup> Also the well-known <sup>1</sup>J(<sup>13</sup>C,<sup>6</sup>Li) coupling constants for fluxional and static aggregates of, for example, alkyllithium tetramers are considered to be the result of analogous dynamics.<sup>14</sup> The magnitudes of the <sup>1</sup>J(<sup>13</sup>C,<sup>6</sup>Li) coupling constants are given by the approximation <sup>1</sup>J(<sup>13</sup>C,<sup>6</sup>Li) = (17 ± 2)/*n*, where *n* refers to the number of <sup>6</sup>Li attached to <sup>13</sup>C, a relation that holds for both static and fluxional aggregates. It should be emphasized that the transfer of coupling information requires fast intramolecular exchange. There are however reports of <sup>1</sup>J(<sup>13</sup>C,<sup>6</sup>Li) coupling constants that fall outside this empirical rule.<sup>15</sup> Such small coupling constants have been suggested to arise if there is a small but detectable C–Li covalency.

Thus the observed coupling constant of 3.5 Hz indicates that the mixed complex is present as structure **C** for about 50% of the time. Interestingly, the <sup>13</sup>C NMR spectra of the more concentrated solution used for the natural abundance studies showed no resolved <sup>13</sup>C–<sup>6</sup>Li coupling. The observation of the <sup>13</sup>C–<sup>6</sup>Li coupling only at the lower concentration indicates that there is fast intermolecular exchange at higher concentration. Such intermolecular exchange is much slower in the 0.05 M solution compared to the 0.2 M solution.

Some of the experimental data of the mixed complex formed by Li-1 and LiCH<sub>2</sub>CN in Et<sub>2</sub>O may also suggest the formation of the tetramer **H**. Despite the failure to distinguish the tetramer **H** from the dimer **C** by a single experiment, it appears as if most of the NMR spectroscopic data of this complex are characteristic for a dimeric aggregate. The relatively small coupling constants (<sup>1</sup>J(<sup>13</sup>C,<sup>6</sup>Li) and <sup>1</sup>J(<sup>15</sup>N,<sup>6</sup>Li)) indicate a fast exchange between *C*- and *N*-lithiated nitrile anions, which is inconsistent with the formation of **H**. In addition, the <sup>13</sup>C and <sup>1</sup>H chemical shifts of the CH<sub>2</sub>CN anion are similar to those of our previously studied mixed dimer aggregates.<sup>9</sup>

The novel 2:1 mixed complex **E** is formed from one molecule of LiCH<sub>2</sub>CN and two molecules of the chiral lithium amide Li-2 in Et<sub>2</sub>O. As indicated by the <sup>1</sup>J(<sup>15</sup>N,<sup>6</sup>Li) couplings, the less shielded lithium is attached to the amide nitrogens while the two chemically equivalent lithiums are coupled to the nitrogens of both CH<sub>2</sub>CN and the amide. The observed heteronuclear <sup>6</sup>Li,<sup>1</sup>H NOE between the upfield lithium signal and the CH<sub>2</sub>CN protons, in addition to the observed <sup>1</sup>J(<sup>15</sup>N,<sup>6</sup>Li) coupling, are only consistent with a mixed trimer with a bridging lithioac-

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etonitrile in rapid exchange. This process appears to be fast at all temperatures as no characteristic line-broadening is observed at lower temperatures.

No resolved  $^1J(^{13}\text{C}, ^6\text{Li})$  coupling was observed, even at low concentration employing  $^{13}\text{C}$  isotopically enriched lithioacetonitrile. This may indicate that complex **E** is slightly more fluxional than complex **C**, whereas the simultaneously observed  $^{15}\text{N}, ^6\text{Li}$  scalar coupling indicates slow intermolecular exchange. Hence, the mixed complex must be mainly a ketenimine type complex (**F**). However, the mixed trimer must exist as a bridged complex at least to a significant fraction in order to explain the observed hetero NOE cross-peaks between lithium and the  $\text{LiCH}_2\text{CN}$  protons in the  $^6\text{Li}, ^1\text{H}$ -HOESY spectrum. In addition, the observed  $^1J(^{13}\text{C}, ^1\text{H})$  coupling constant of 152 Hz suggests that the  $\alpha$ -carbon anion in the mixed trimer is more  $\text{sp}^3$ - than  $\text{sp}^2$ -hybridized. Although metalation at nitrogen is generally preferred, the charge delocalization makes it favorable to coordinate the lithium to the  $\alpha$ -carbon as well.

Interestingly, the intramolecular lithium–lithium exchange is faster in **C** than in **E** as determined by  $^6\text{Li}, ^6\text{Li}$  EXSY experiments. The activation barriers ( $\Delta G^\ddagger$ ) of **C** and **E** are 12.6 and 13.8 kcal mol $^{-1}$  at  $-62$  and  $-42$  °C, respectively. The difference in  $\Delta G^\ddagger$  between **C** and **E** illustrates the structural difference between these complexes. The mechanism for the lithium exchange of **E** involves three lithiums while in **C** only two lithiums exchange and these aggregates have different N–Li bond angles and Li–Li distances, which influence the Li–Li exchange rate. The difference in mixed complex between the amides Li-1 and Li-2 and  $\text{LiCH}_2\text{CN}$  in  $\text{Et}_2\text{O}$  manifests the large structural diversity that is often encountered among lithium amides and their mixed complexes.

**THF Solutions of Mixed Complexes Formed by the Chiral Lithium Amides and  $\text{LiCH}_2\text{CN}$  (**D** and **G**).** In THF solution both amides Li-1 and Li-2 form 1:1 mixed dimers with  $\text{LiCH}_2\text{CN}$ . In these complexes the ketenimine structures of the acetonitrile anion dominate, which our previous studies of mixed dimers with other amides also have shown. Unfortunately, there are no resolved  $^1J(^6\text{Li}, ^{15}\text{N})$  or  $^1J(^{13}\text{C}, ^1\text{H})$  couplings from the mixed complexes formed by  $^{15}\text{N}$ - and  $^{13}\text{C}$ -labeled Li– $\text{CH}_2\text{CN}$  and Li-1 and Li-2, respectively. The absence of such  $^1J(^6\text{Li}, ^{15}\text{N})$  couplings in THF solutions has previously been reported for the lithiophenylacetonitrile and LiHMDS mixed aggregate by Carlier et al.<sup>7k</sup> They suggested that THF facilitates rapid chemical interaggregate exchange. We also recently reported on the absence of  $^1J(^{13}\text{C}, ^1\text{H})$  coupling between the nitrile anion and lithium in THF solution.<sup>9</sup> To the best of our knowledge, there has not been any report of observed  $^1J(^6\text{Li}, ^{15}\text{N})$  or  $^1J(^{13}\text{C}, ^1\text{H})$  couplings using  $^{15}\text{N}$ - or  $^{13}\text{C}$ - and  $^6\text{Li}$ -labeled  $\alpha$ -lithiated nitriles in THF.<sup>7k–m</sup> The less shielded  $\alpha$ -carbon of  $\text{LiCH}_2\text{CN}$  from the mixed complexes **D** and **G** in THF appear, at  $\delta$   $-2.5$  and  $-2.2$  respectively, in the  $^{13}\text{C}$  NMR spectra. This indicates *N*-lithiated  $\text{CH}_2\text{CN}$  anions in agreement with our previous study.<sup>9</sup> The  $^1J(^{13}\text{C}, ^1\text{H})$  coupling constants of 160 and 162 Hz are also significantly larger than those of the “ $\text{Et}_2\text{O}$  solvated” mixed complexes, i.e., 148 and 152 Hz, respectively. This also indicates more  $\text{sp}^2$  character for the complexes in THF than in  $\text{Et}_2\text{O}$ , consistent with *N*-lithiated, ketenimine dimer structures.

The  $^6\text{Li}, ^1\text{H}$ -HOESY spectrum of **D** shows weak NOE interactions between lithium and the  $\alpha$ -protons of  $\text{LiCH}_2\text{CN}$ .

The distance between Li and the protons of  $\text{CH}_2\text{CN}$  is too large to explain the observed NOE, which may indicate the presence of a minor fraction of **C** also in THF solution. The rate constants for the intramolecular exchange of the “THF solvated” (**D** and **G**) are higher than those of the “ $\text{Et}_2\text{O}$  solvated” (**C** and **E**), a relationship generally observed for lithium amides.<sup>6</sup>

## Conclusion

We have shown, using multinuclear NMR spectroscopy, that both Li-1 and Li-2 form mixed complexes with  $\text{LiCH}_2\text{CN}$  in  $\text{Et}_2\text{O}$  and THF solvent. In  $\text{Et}_2\text{O}$  the mixed dimer complex formed by Li-1 and  $\text{LiCH}_2\text{CN}$  rapidly exchanges between bridged (**C**) and ketenimine (**D**) structures, while  $\text{LiCH}_2\text{CN}$  and Li-2 form a trimeric aggregate in which the acetonitrile anion undergoes fast exchange between complexes **E**, **F**, and **E'**, making the complex  $C_2$ -symmetric on the NMR spectroscopy time scale.

Ketenimines have been shown to dominate both in solution and in the solid state in all previous studies of lithiated nitriles. The amides Li-1 and Li-2 are no exceptions as they both form *N*-metalated mixed  $\text{LiCH}_2\text{CN}$  dimers in THF.

So far, our studies on mixed complexes of  $\text{LiCH}_2\text{CN}$  and lithium amides have shown a large diversity of structures. This may reflect the complex nature of the nitrile anion, but these structures also represent a new family of potential reagents for asymmetric synthesis, which motivate structural and dynamic investigations. Our intention is to utilize these complexes in nucleophilic addition reactions, resulting in optically active  $\beta$ -hydroxynitriles.

## Experimental Section

Glassware and syringes were dried at 50 °C in a vacuum oven before transfer into a glovebox (Braun equipped with a gas purification system that removes oxygen and moisture) containing a nitrogen atmosphere. Typical moisture content was less than 1.5 ppm. All manipulations concerning the addition reactions were carried out using gastight syringes. Ethereal solvents, distilled under nitrogen from sodium and benzophenone, were kept over 4 Å molecular sieves in septum-sealed flasks inside the glovebox. Acetonitrile was distilled from  $\text{CaH}_2$  and further dried over molecular sieves.

**Preparation of Amines 1, 2, and  $^{15}\text{N}$ 2.** The chiral amines **1** and **2** were prepared according to published methods.<sup>16</sup> The  $^{15}\text{N}$ -labeled amine **2** was prepared from  $^{15}\text{N}$ phenylalanine following the procedure for the preparation of **2**.

**NMR Spectroscopy Instrumental.** All NMR spectra were recorded using a Varian Unity 500 spectrometer equipped with three channels using either a 5 mm  $^{13}\text{C}, ^6\text{Li}, ^1\text{H}$  triple-resonance probe head or a  $^1\text{H}, ^{13}\text{C}, ^6\text{Li}$  and  $^{15}\text{N}$  quadruple resonance probe head, both built by the Nalorac Company. Measuring frequencies were 500 MHz ( $^1\text{H}$ ), 125 MHz ( $^{13}\text{C}$ ), and 73 MHz ( $^6\text{Li}$ ). The  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were referenced to the solvent  $\text{Et}_2\text{O}-d_{10}$  signals at  $\delta$  1.06 ( $^1\text{H}$  - $\text{CH}_3$ ) and  $\delta$  65.5 ( $^{13}\text{C}$  - $\text{CH}_2$ ), and the THF- $d_8$  signals at  $\delta$  1.72 ( $^1\text{H}$  - $\text{CH}_2$ ) and  $\delta$  67.6 ( $^{13}\text{C}$  - $\text{CH}_2$ ), respectively. Probe temperatures were measured after more than 1 h of temperature equilibrium with both a calibrated methanol–freon NMR spectroscopy thermometer and the standard methanol thermometer supplied by Varian instruments.<sup>17</sup>  $^6\text{Li}, ^1\text{H}$ -HOESY experiments were performed with  $\tau_M = 1.0$  s in both THF and  $\text{Et}_2\text{O}$ . For further data of the  $^6\text{Li}, ^1\text{H}$ -HOESY experiments, see previous studies.<sup>4</sup> The  $^6\text{Li}, ^6\text{Li}$ -EXSY spectra were recorded with  $\tau_M = 2$  s in THF and  $\tau_M = 2$  s in  $\text{Et}_2\text{O}$ .

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