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Solution structure of a key intermediate used in asymmetric alkylation reactions. ^{1}H,^{1}H-NOESY and ^{6}Li,^{1}H-HOESY studies of mixtures of a chiral lithium amide and n-butyllithium

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Abstract

NMR spectroscopy involving ^{6}Li,^{1}H-HOESY and ^{6}Li,^{6}Li-COSY studies in combination with ^{1}H,^{1}H-NOESY has been used to determine the detailed structures of two complexes, are the novel mixed 1 : 1 complex between lithium-(2-methoxy-(R)-1-phenyl-ethyl)-((S)-1-phenyl-ethyl)-amide (**1**) and *n*-butyllithium, and the other the dimeric complex of **1**. Both the mixed dimer between **1** and *n*-butyllithium and the dimeric complex of **1** were formed when **1** was mixed with *n*-butyllithium in molar ratio of 1.5 : 1 in diethyl ether (DEE-d$_{10}$) at −80°C. The ^{6}Li NMR spectrum of the solution, containing the complex between **1** and *n*-butyllithium and the dimer of **1** showed the presence of four ^{6}Li resonances at −80°C, indicative of two non-equivalent lithiums within each complex. The complex between **1** and *n*-butyllithium is responsible for the asymmetric induction in the alkylation reaction.

Keywords: Lithium; Asymmetric induction; Nuclear magnetic resonance

1. Introduction

In the past decade, the development of new NMR techniques has improved the prediction of the structures of organolithium compounds in solution. In particular, the introduction of ^{6}Li,^{1}H-heteronuclear Overhauser effect spectroscopy, ^{6}Li,^{1}H-HOESY, by Schleyer and Bauer [1] has made it possible to determine the structure of reactive lithium reagents in solution. Use of chiral complexing ligands for alkyllithium reagents in asymmetric synthesis has been only partly explored. Knowledge of the solution structure of asymmetric lithium complexes used in enantioselective reactions is essential to finding ways of improving and simplifying such reactions [2]. An efficient ligand for inducing asymmetry in the addition of *n*-butyllithium to benzaldehyde is lithium-(2-methoxy-(R)-1-phenyl-ethyl)-((S)-1-phenyl-ethyl)-amide (**1**), which has been reported to give 90% *ee* of (S)-1-phenylbutanol [3]. In view of the absence of solution studies of this important class of organolithium reagents we decided to study lithium-6 isotopically enriched **1** by use of the newly available NMR techniques ^{6}Li,^{1}H-HOESY [1], ^{6}Li,^{6}Li-COSY [4] and ^{6}Li,^{6}Li-EXSY [5].

2. Experimental results and discussion

The ^{6}Li NMR spectrum of a mixture of [^{6}Li]*n*-butyllithium and (2-methoxy-(R)-1-phenyl-ethyl)-((S)-1-phenyl-ethyl)-amine in a 1 : 1 molar ratio in DEE-d$_{10}$ at −80°C showed two resonances, at 2.72 ppm and 2.90 ppm, respectively. Further addition of [^{6}Li]*n*-butyllithium resulted in the appearance of three new lithium signals at 2.27 ppm, 3.61 ppm and 1.90 ppm, together with the two at 2.72 ppm and 2.90 ppm (Fig. 1).

The signal at 1.90 ppm was assigned to tetrameric *n*-butyllithium [7]. Short Li–H distances may be detected by the two-dimensional heteronuclear Overhauser effect spectroscopy (^{6}Li,^{1}H-HOESY) [1], and so this technique was used for the structure assignment of the two lithiums in the 1 : 1 mixture between (2-methoxy-(R)-1-phenyl-ethyl)-((S)-1-phenyl-ethyl)-amine and [^{6}Li]*n*-butyllithium. In the ^{6}Li,^{1}H-HOESY study, the lithium signal at 2.72 ppm showed correlations to

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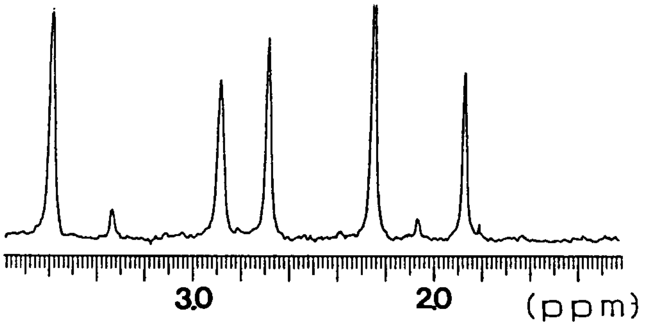


Fig. 1. ^{6}Li NMR spectrum of **1** and [^{6}Li]*n*-butyllithium in DEE-d_{10} at −80°C recorded with a Varian Unity 500 spectrometer. The ^{6}Li resonances are referenced to 0.3 mol dm^{-3} [^{6}Li]Cl/MeOH (0.0 ppm) [6].

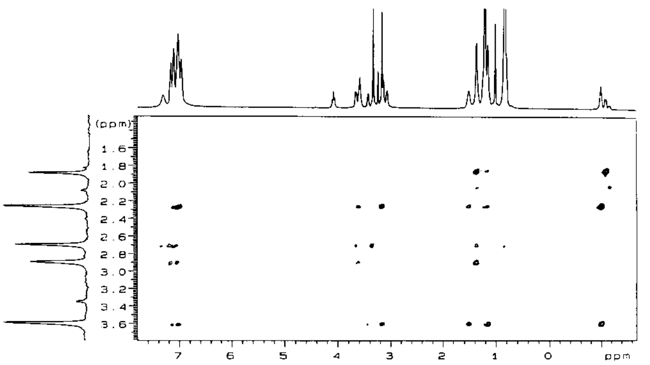


Fig. 2. Two-dimensional phase-sensitive ^{6}Li,^{1}H-HOESY contour plot of the mixture of **2**, [^{6}Li]*n*-butyllithium and **3**, (−80°C, $c = 0.4$ mol dm^{-3} (^{6}Li), 73.556 MHz, $t_m = 1.0$ s, enriched 96% with ^{6}Li) in DEE-d_{10} (spectrometer and reference as for Fig. 1). The ^{1}H resonances were referenced to the further upfield signal from DEE, which was set to 1.06 ppm.

the methoxy proton signal at 3.40 ppm, one of the methylene proton signals at 3.72 ppm, and a weak correlation with the methyl proton signal at 1.39 ppm, all indicative of short lithium–proton distances. The lithium signal at 2.90 ppm showed correlations to the methyl-proton signal at 1.39 ppm and the two methine proton signals, at 3.65 ppm and 4.14 ppm respectively, indicative of short proton–lithium distances. Both lithium signals also showed strong correlations to the unresolved phenyl ring proton signals at 7.05–7.33 ppm (Fig. 2, Table 1).

Table 1
Proton chemical shifts for **1**

^{1}H NMR (500 MHz, DEE-d_{10}, −20°C):
1.40 (d, J(H,H) = 6.6 Hz CH_3),
3.13 (dd, J(H,H) = 10.6 Hz, J(H,H) = 4.3 Hz, 1H, CH_2),
3.40 (s, 3H, OCH_3), 3.65 (q, J(H,H) = 6.6 Hz, 1H, CH),
3.72 (dd, J(H,H) = 12.1 Hz, J(H,H) = 4.1 Hz, 1H, CH_2), 4.14
(t, J(H,H) = 11.3 Hz, 1H, CH), 7.05–7.33 (m, 10H, Ph) ppm.

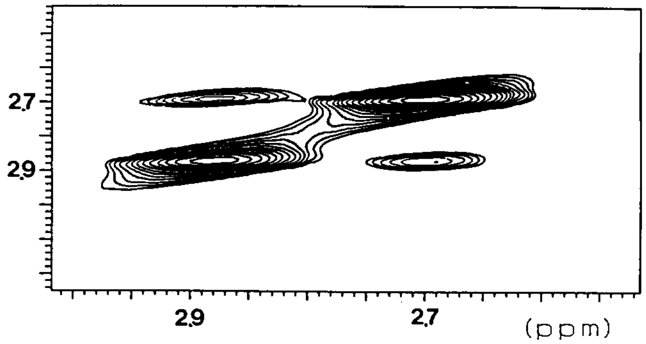
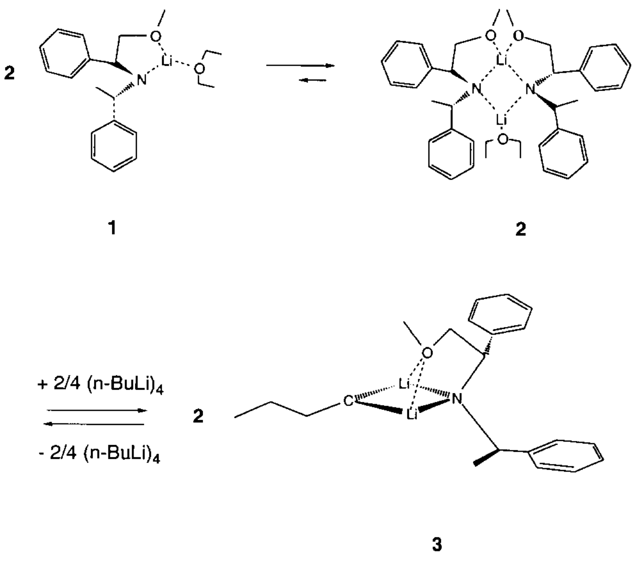


Fig. 3. Two-dimensional phase-sensitive ^{6}Li-^{6}Li-EXSY contour plot of **2** (−20°C, $c = 0.3$ mol dm^{-3}, 73.556 MHz, $t_m = 3.5$ s, enriched 96% with ^{6}Li) in DEE-d_{10}. (spectrometer and reference as for Fig. 1.)

The integrals of the ^{6}Li signals at 2.72 ppm and that of the ^{6}Li signal at 2.90 ppm were found to be in a ratio of 1 : 1 independent of the concentration (0.4–0.05 M). When a ^{6}Li,^{6}Li-EXSY study was carried out, crosspeaks were observed between the lithium signal at 2.72 ppm and 2.90 ppm, indicative of an intramolecular exchange between these lithiums, (Fig. 3).

In contrast to the lithium NMR spectrum, which contained two lithium NMR signals, only single sets of ^{1}H NMR and proton-decoupled ^{13}C NMR resonances were observed.

We conclude that the two ^{6}Li NMR signals at 2.72 ppm and 2.90 ppm are from lithium atoms within the same complex, and that this complex is a dimer of **1** with C_2 symmetry, shown as compound **2** in Scheme 1 [8]. Our reasons are as follows (a) the two methoxy groups are coordinated to one and the same lithium, and from several other features in the ^{6}Li-^{1}H HOESY and the ^{1}H-^{1}H NOESY spectra we derive the three-di-



Scheme 1.

mensional structure for **2**; (b) the two lithium signals (2.72 ppm, 2.90 ppm) could be caused by an equilibrium between monomer-dimer or dimer-tetramer. However, variation of the concentration caused no change in the integral ratio for the two signals, indicating that the two lithiums are situated in the same complex; and (c) the appearance of only single sets of ^{1}H and ^{13}C NMR resonances show that there is only one lithium amide complex present in solution.

The ^{13}C NMR proton decoupled spectrum of a mixture of **1** and [^{6}Li]*n*-butyllithium in a molar ratio of 1.5 : 1 recorded at −80°C showed the presence of two signals in the α-carbon region of [^{6}Li]*n*-butyllithium (^{6}Li–^{13}CH$_2$–), a quintet (11.63 ppm, $J_{\text{C-Li}} \approx 8$ Hz) and a septet (10.92 ppm, $J_{\text{C-Li}} \approx 5.4$ Hz). The septet had the same chemical shift as that for tetrameric [^{6}Li]*n*-butyllithium, and it was observed to increase upon addition of [^{6}Li]*n*-butyllithium in DEE-d$_{10}$ to a solution of **1**. Correlations in the ^{6}Li,^{1}H HOESY study also confirm that this signal comes from tetrameric [^{6}Li]*n*-butyllithium [7].

The observation of a quintet at δ 11.63 shows that this α-carbon is coupled with two [^{6}Li]-lithiums [9]. This quintet is from *n*-butyllithium, probably complexed with **1**, i.e. compound **3** in Scheme 1.

The ^{6}Li,^{1}H HOESY experiment, Fig. 1, revealed correlations of the two lithium signals at 2.27 ppm and 3.61 ppm to the same [^{6}Li]*n*-butyllithium α-proton signal at −0.96 ppm (there was no correlation to the tetrameric [^{6}Li]*n*-butyllithium α-proton signal at −1.03 ppm) and correlations to the methoxy proton signal at 3.23 ppm indicating short ^{1}H–^{6}Li distances consistent with [^{6}Li]*n*-butyllithium complexed with **1**. The observation of NOEs between the methoxy protons and the lithiums in **3** could be a result of a fast exchange between the two lithiums or coordination of the methoxy oxygen to both lithiums. Correlations between the methyl proton signal at 1.20 ppm and the lithium signal at 3.61 ppm were also observed, again indicating short proton–lithium distances, (Table 2, Fig. 2).

The integrals of the ^{6}Li signals at 2.27 ppm and at 3.61 ppm were in a ratio of 1 : 1 independent of the concentration (0.05–0.8 M). To ascertain whether these two lithiums were present in the same complex we performed a ^{6}Li,^{6}Li-COSY experiment. The spin–spin connectivity observed in the ^{6}Li,^{6}Li-COSY spectrum, (Fig. 4), between the two signals at 2.27 ppm and 3.61 ppm showed that the two lithiums at these chemical shifts couple with each other, and so are present in the same complex.

Table 2
Proton chemical shifts for **3**

^{1}H NMR (500 MHz, DEE-d$_{10}$, −80°C):
−0.96 (t, J(H,H) = 8 Hz, 2H, CH$_2$Li), 1.20(d, J(H,H) ≈ 6 Hz, CH$_3$), 3.20 (overlapped m, 1H, CH$_2$), 3.21 (overlapped m, 1H, CH$_2$), 3.23 (s, 1H, OCH$_3$), 3.49 (q, J(H,H) ≈ 6 Hz, 1H, CH), 3.65 (overlapped m, 1H, CH), 7.02–7.24 (m, 10H, Ph) ppm.

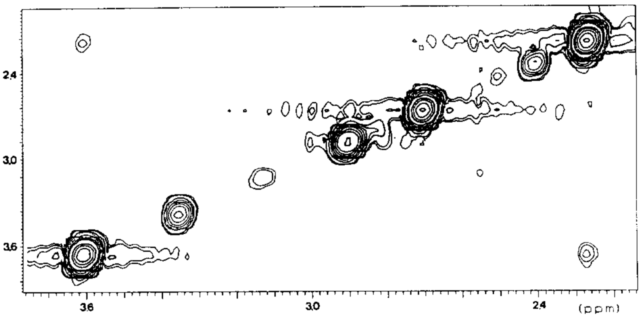


Fig. 4. Two-dimensional absolute value ^{6}Li,^{6}Li-COSY contour plot of **3** (−80°C, c = 0.3 mol dm^{-3}, 73.556 MHz, t = 0.25 s, enriched 96% with ^{6}Li) in DEE-d$_{10}$ (spectrometer and reference as for Fig. 1).

The ^{6}Li,^{6}Li-EXSY showed crosspeaks between the two lithium signals at 2.27 ppm and 3.61 ppm, indicating intramolecular exchange between these lithiums.

Comparison of the integrals of the ^{1}H NMR signals from the α-protons in the complexed [^{6}Li]*n*-butyllithium at −0.96 ppm with the integral for the signal from the methoxy group in **1** at 3.23 ppm revealed a 1 : 1 ratio. The methoxy group in **1** not complexed with [^{6}Li]*n*-butyllithium was observed at 3.40 ppm, and was not used in the comparision (Table 1). We also performed a ^{1}H,^{1}H-NOESY study: the correlations in the spectrum revealed short distances between the α-protons at −0.96 ppm of the complexed [^{6}Li]*n*-butyllithium and the methoxy protons at 3.23 ppm in **3**. The most likely explanation of these data is that there is a 1 : 1 complex between **1** and [^{6}Li]*n*-butyllithium (see Scheme 1, compound **3**). This type of mixed complex between lithium amides and alkyllithium compounds has been suggested previously. [2]

The ratio of **2** to **3** showed a [^{6}Li]*n*-butyllithium concentration dependence, which can be attributed to the presence of an equilibrium between **2**, **3** and [^{6}Li]*n*-butyllithium, (Scheme 1). Addition of hydrocarbon solvents caused a shift of this equilibrium towards tetrameric [^{6}Li]*n*-butyllithium and **2** [10], and so, one reason for the different extents of asymmetric induction obtained in different solvents could be that solvent effects on the equilibrium shown in Scheme 1, result in the formation of non-complexed [^{6}Li]*n*-butyllithium. To our surprise we could not totally remove tetrameric [^{6}Li]*n*-butyllithium from the solutions despite the use of a large excess of **1**. Futhermore, upon addition of benzaldehyde to a solution containing the complexes **2**, **3** and tetrameric [^{6}Li]*n*-butyllithium, the first signal to disappear from the ^{6}Li NMR spectrum was that from tetrameric [^{6}Li]*n*-butyllithium. This shows that [^{6}Li]*n*-butyllithium is more reactive towards benzaldehyde which means that the enantiomeric excess will be lowered.

3. Conclusions

We have shown that there is only one mixed complex between [^{6}Li]*n*-butyllithium and **1** that could induce asymmetry in the alkylation of benzaldehyde and therefore that it is (monomeric) [^{6}Li]*n*-butyllithium in a mixed dimer with **1** that is involved in the reaction with benzaldehyde. We have also shown that the reported variation in *ee* with change in solvent is probably a result of a shift of the equilibrium between **2**, **3** and tetrameric [^{6}Li]*n*-butyllithium. We have also shown that at low temperatures, [^{6}Li]*n*-butyllithium is strongly complexed with **1** in the species **3**, for which no intermolecular exchange with non-complexed tetrameric [^{6}Li]*n*-butyllithium could be detected. We have also shown that even if **2** is present in large excess there is still some tetrameric [^{6}Li]*n*-butyllithium present together with **3** and this will affect the enantiomeric excess in the alkylation reaction, because tetrameric [^{6}Li]*n*-butyllithum is more reactive than **3** towards benzaldehyde.

4. Experimental details

4.1. General

All experiments were performed under nitrogen and all glassware, including the gas-tight syringes and NMR tubes, were dried in a vacuum oven and stored in a glovebox under nitrogen with a water content of less than 0.5 ppm. All solvents were dried and distilled prior to use.

4.2. [^{6}Li]-Lithium-(2-methoxy-(R)-1-phenyl-ethyl)-((S)-1-phenyl-ethyl)-amide

Compound **1** in the NMR tube was generated in situ by addition of [^{6}Li]*n*-butyllithium (c = 10 mol dm^{-3}) to a solution of the amine in DEE at −78°C.

4.3. (2-Methoxy-(R)-1-phenyl-ethyl)-((S)-1-phenyl-ethyl)-amine

This was made as previously described [3,11].

4.4. Preparation of [^{6}Li]n-butyllithium

A block of ^{6}Li (0.25 g, 41.6 mmol, 96% in atom ^{6}Li) was cut into small pieces with a sharp knife and placed in a 50 ml flask equipped with a silicone–teflon septum. The ^{6}Li was rinsed with 10 ml of 2-propanol, 10 ml dry hexane was added, and the flask was placed in an ultrasonic bath for ca. 3 min. The hexane suspension of LiOH was removed with a syringe, 10 ml of dry hexane were added, and the mixture was replaced in the ultrasonic bath for some minutes, and the suspension of lithium hydroxide in hexane was then removed. This procedure was repeated several times until the hexane remained clear and the previously black lithum pieces showed a metallic sheer. Addition of 15 ml of dry hexane was followed by dropwise addition of 1-chlorobutane (2.09 ml, 20.0 mmol) during 5 min. The flask was kept in the ultrasonic bath for 3 h at 20–30°C. The reaction started immediately, as indicated by the development of a deep purple colour in the previously colourless mixture. After a further 12 hours at 10–15°C the resulting purple suspension was centrifuged, and the supernantant liquid was transferred to a glass vessel, equipped with high-vacuum teflon valves. The solvent was removed under vacuum (10^{-4} torr). The concentration of *n*-butyllithium was 10 M, as determined by the Gilman double titration [12]. The [^{6}Li]*n*-butyllithium was stored under argon in a glass vessel at −30°C.

Acknowledgement

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References and notes

[1] For an account of the ^{6}Li,^{1}H-HOESY method, see: W. Bauer and P.v.R. Schleyer, *Magn. Reson. Chem.*, *26* (1988) 827–833.

[2] E. Juaristi, A.K. Beck, J. Hansen, T. Mutt, T. Mukhopadhay, M. Simson and D. Seebach, *Synthesis* (1993) 1271; D.B. Collum, *Acc. Chem. Res.*, *26* (1993) 227–234, and references cited therein.

[3] M.B. Eleveld and H. Hogeveen, *Tetrahedron Lett.*, *25* (1984) 5187–5190. Eleveld and Hogeveen reported formation of *ee* of 90% of (R)-1-phenylbutanol after addition of *n*-butyllithium to benzaldehyde in the presence of **1**. (In diethyl ether (DEE) the *ee* was 74%.)

[4] For an account of the ^{6}Li,^{6}Li-COSY method, see: H. Günther, D. Moskau, R. Duajardin and A. Maercker, *Tetrahedron Lett.*, *27* (1986) 2251.

[5] For an account of the ^{6}Li,^{6}Li-EXSY method, see: B.H. Meier and R.R. Ernst, *J. Am. Chem. Soc.*, *101* (1979) 6441; J. Jeener, B.H. Meier, P. Bachman and R.R. Ernst, *J. Chem. Phys.*, *71* (1979) 4546. For excellent reviews of NMR on organolithium compounds see, R.D. Thomas, in E. Buncel and J.R. Jones (eds.), *Isotopes in the Physical and Biomedical Sciences: Isotope Applications in NMR Studies*, Elsevier, Amsterdam, 1991, pp. 367–409; W. Bauer and P.v.R. Schleyer, in *Advances in Carbanion Chemistry*, Vol. 1, 1992 pp. 89–175.

[6] The ^{6}Li NMR spectra were referenced to external 0.3 M [^{6}Li]Cl/MeOH, set to 0.0 ppm, as specified by Reich and co-workers. H.J. Reich and D.P. Green, *J. Am. Chem. Soc.*, *111* (1989) 8729.

[7] The self association of *n*-butyllithium in DEE results exclusively in tetrameric complexes, see P. West and R. Waack, *J. Am. Chem. Soc.*, *89* (1967) 4395. The ^{6}Li and ^{13}C shifts of the signals resemble that of [^{6}Li]*n*-butyllithum in diethyl ether-d$_{10}$. Furthermore, the height of the ^{6}Li signal at δ 1.90 was increased by addition of [^{6}Li]*n*-butyllithium.

[8] The structure of 1 resembles that revealed by X-ray diffraction for the dimer derivative containing two methoxy groups investigated by D. Barr, D.J. Berrisford, R.V.H. Jones, A.M.Z. Slawin, R. Snaith, J.F. Stoddart and D.J. Williams, *Angew. Chem., Int. Edn. Engl.*, *28* (1989) 1044–1047.

[9] The ^{13}C NMR spectrum of dimeric *n*-butyllithium in THF shows a quintet at 14 ppm with $J_{C-Li} \approx 7.6$ Hz, see also J. Heinze; J.F.M. Oth and D. Seebach, *Helv. Chem. Acta*, *68* (1985) 1848.

[10] In toluene-d_8, also a non-coordinating solvent with a similar solvating ability to *n*-heptane, Hogeveen and Eleveld [3] observed a high yield of 95% at the expense of lower *ee*, viz 18% at −100°C, compared to the observed yield of 83% and a *ee* of 74% at −100°C in DEE in the alkylation of benzaldehyde.

[11] C.G. Overberger, N.P. Marullo and R.G. Hiskey, *J. Am. Chem. Soc.*, *83* (1961) 1374–1378.

[12] B.J. Wakefield, *Organolithium Methods*, Academic Press, London, 1988, p. 18.