Locating the Position of Lithium in Solution by Combined $^{13}C,^{6}Li$ and $^{1}H,^{6}Li$ HOESY Measurements

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$^{13}C,^{6}Li$ HOESY measurements were developed and performed for the first time on the ^{13}C-labeled benzyllithium compound **1**. 1D NOE difference, $^{1}H,^{6}Li$ HOESY, and spin lattice relaxation measurements were used to obtain information on the position of the lithium ion in solution.

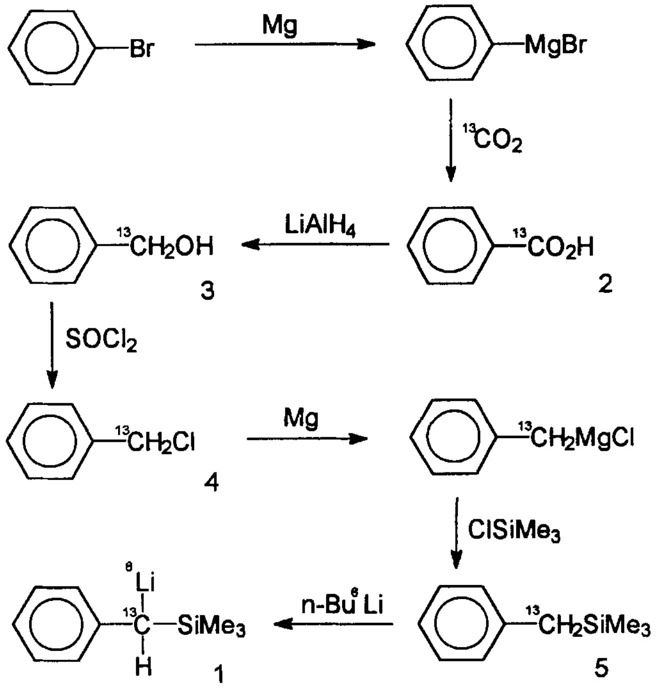
Although the HOESY method was introduced for the spin pairs $^{1}H,^{13}C$[1,2] and $^{1}H,^{31}P$[3], this method is predominantly applied in organolithium chemistry[4]. The NOE experiment provides a unique tool for obtaining structural information on organolithium compounds, due to the lack of spin-spin coupling between lithium and hydrogen or carbon atoms in many cases. However, so far only $^{1}H,^{6}Li$ or $^{1}H,^{7}Li$ measurements have been performed[4]. These experiments may yield information concerning the distance between lithium and protons[5], although the often more interesting chemical question is the lithium distance from a specific carbon atom which can be only indirectly obtained by these measurements or, in some cases, not at all, if the carbon atom in question bears no hydrogen atoms. Furthermore, quantitative evaluation of the lithium ion position may be difficult due to proton-proton cross relaxation (three-spin effects)[6] and other complications.

We have therefore considered alternative methods that may possibly give structural information and report on preliminary results concerning NOE measurements between a carbon and lithium atom. There are two important prerequisites for such an experiment. The organolithium compound studied must be labeled with both ^{13}C and ^{6}Li, since the achievable sensitivity in natural abundance prohibits such a measurement. In addition, for this kind of investigation a three-channel spectrometer must be available with a probehead that can be simultaneously tuned to ^{6}Li, ^{13}C, and ^{1}H for decoupling purposes.

Results and Discussion

We chose [α-^{6}Li,α-^{13}C]lithiophenyl(trimethylsilyl)methane (**1**) as a test compound for this investigation. This compound offers several advantages. It forms a relatively stable benzyl anion due to the electronic and steric stabilization of the trimethylsilyl group which can be studied in overnight measurements without excessive decomposition. The labeled carbon atom bears a hydrogen atom, so that $^{1}H,^{6}Li$ HOESY measurements are possible. Finally, an X-ray structure is available which allows a comparison between solution- and solid-state structures[7]. The labeling synthesis also proved to be manageable (Scheme 1). Thus **1** was prepared via ^{13}C-labeled benzoic acid (**2**) obtained by reaction of $^{13}CO_2$ (liberated from $Ba^{13}CO_3$) and phenylmagnesium bromide[8]. Compound **2** was reduced to benzyl alcohol (**3**) which was converted into benzyl chloride (**4**) by reaction with thionyl chloride. Replacement of the chlorine atom by a trimethylsilyl group using a Grignard reaction provided **5**[9]. Reaction of **5** with $nBu^{6}Li$ in [D_8]THF in the presence of one equivalent of *N,N,N′,N′*-tetramethylethylenediamine (TMEDA) gave the required product **1** which was used for the NMR measurements.

Scheme 1



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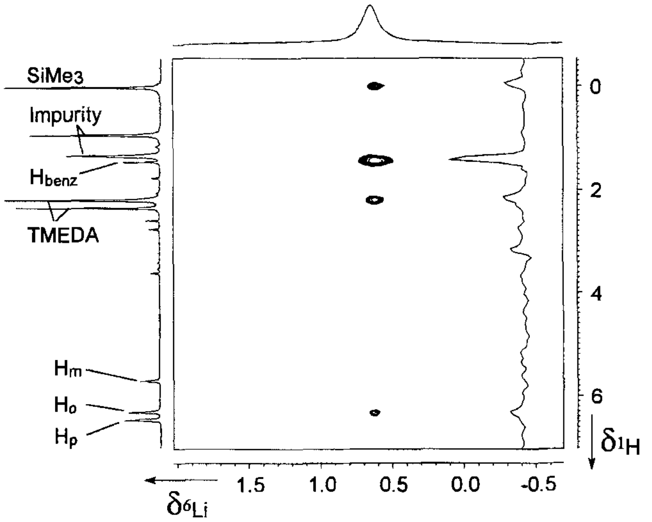
$^1H,^6Li$ HOESY measurements performed as previously described[10] revealed through-space connectivity between the lithium ion and the benzylic proton, the trimethylsilyl group, the *ortho* aromatic protons and the methyl groups of TMEDA. A typical spectrum is shown in Figure 1. The expected $^{13}C,^6Li$ NOE effect as estimated from typical C–Li distances and ^6Li relaxation times is less than 1%. For the $^{13}C,^6Li$ HOESY measurement the standard HOESY pulse program was modified to use three RF channels with ^1H decoupling throughout and the phase-sensitive TPPI mode in F_1. The pulse sequence used together with the phase cycle is shown in Figure 2.

Figure 1. $^1H,^6Li$ HOESY spectrum of **1** with the high-resolution 1D ^1H and ^6Li spectra on the F_1 and F_2 axes. The 1D trace inserted in the 2D spectrum shows the column taken from the 2D matrix at the ^6Li chemical shift position



A HOESY signal such as that shown in Figure 3 was reproducible. The best results were obtained by using a repetition time of 9 s and a mixing time of 1.7 s.

Quantitative Evaluation

In principle, geometry information can be obtained from 2D NOE data. However, since 2D measurements are transient methods[11], the initial rate approximation must be assumed which requires many spectra to be recorded with varying mixing times. We therefore explored whether it is possible to obtain meaningful results by using 1D heteronuclear Overhauser effect difference measurements, which offer the advantage of being a steady-state method. Assuming the same correlation time for the lithium ion and the organic anion and assuming overall isotropic motion (both of which seem like reasonable approximations for the TMEDA complex of **1**), we can describe the NOE of carbon on lithium $\eta^{13}C\rightarrow{}^6Li$ by equation (1), where the spin lattice relaxation time of lithium $T_1(^6Li)$ can be measured and the dipolar relaxation time of lithium $T_{1\text{-DD}}(^6Li)$ is given by equation (2).

$$\eta^{13}C\rightarrow{}^6Li = \frac{\gamma_C}{\gamma_{Li}} \cdot \frac{T_1(^6Li)}{2\,T_{1\text{-DD}}(^6Li)} \qquad (1)$$

$$\frac{1}{T_{1\text{-DD}}(^6Li)} = \frac{\gamma_{Li}^2 \gamma_C^2 \hbar^2}{r_{C-Li}^6} \cdot \tau_c \qquad (2)$$

Figure 2. Pulse scheme for 2D $^{13}C,^6Li$ HOESY measurement with ^1H decoupling. Pulse phased used: P1: $x, x, y, y, -x, -x, -y$, incremented by TPPI; P2: $x, -y, -y, -x, x, -y, y$; P3: $(x)_8, (y)_8, (-x)_8, (-y)_8$; P4: $x, -x, y, -y, -x, x, -y, y$; P3: $(x)_8, (y)_8, (-x)_8, (-y)_8$; P4: $x, -x, y, -y, -x, x, -y, y$; receiver: $x, x, y, y, -x, -x, -y, -y$

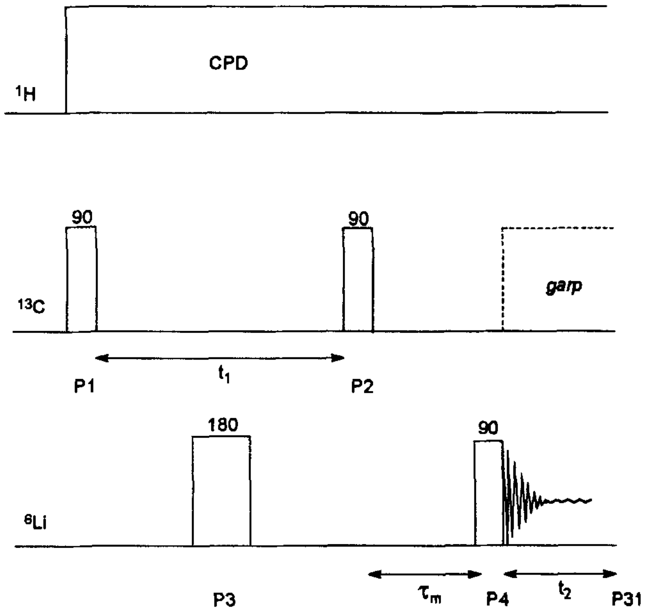
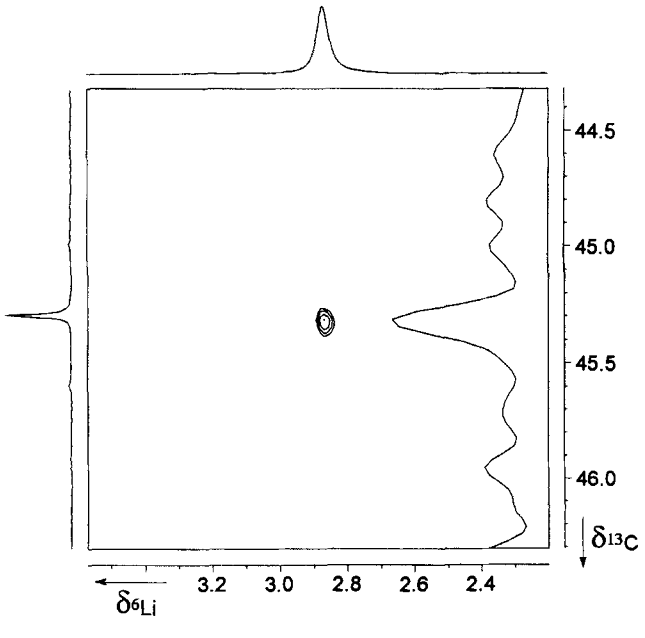


Figure 3. $^{13}C,^6Li$ HOESY spectrum of **1** with the high-resolution 1D ^{13}C and ^6Li spectra on the F_1 and F_2 axes. The 1D trace inserted in the 2D spectrum shows the column taken from the 2D matrix at the ^6Li chemical shift position



From equation (2) the carbon-lithium distance r^6C-Li cannot be calculated because the molecular correlation time τ_c is still unknown. τ_c is obtained by measuring both the spin lattice relaxation time of the carbon atom $T_1(^{13}C)$ and the NOE of protons on the carbon atom. This allows the calculation of the dipolar relaxation time of carbon

$T_{1-DD}(^{13}C)$. Equations (3) and (4) summarize the necessary relationships.

$$\frac{1}{T_{1-DD}(^{13}C)} = \frac{\gamma_H^2 \gamma_C^2 \hbar^2}{r_{C-H}^6} \tau_c \qquad (3)$$

$$\eta_{^{1}H \rightarrow ^{13}C} = \frac{\gamma_H}{\gamma_C} \cdot \frac{T_1(^{13}C)}{2\,T_{1-DD}(^{13}C)} \qquad (4)$$

Combination of equations (1–4) yields expression (5) which contains four experimentally determinable values and the C–H distance, which can be taken from a standard value or from an X-ray measurement if available.

$$r_{C-Li}^6 = \frac{T_1(^{6}Li)}{T_1(^{13}C)} \cdot \frac{\eta_{H \rightarrow C}}{\eta_{C \rightarrow Li}} \cdot \frac{\gamma_{Li} \cdot \gamma_C^2}{\gamma_H^3} \cdot r_{C-H}^6 \qquad (5)$$

Thus, the distance between the lithium and carbon atoms can be calculated by measuring the spin lattice times of the lithium and the carbon atom and the two heteronuclear 1D NOEs of the proton on the carbon atom and of the carbon atom on lithium. Although both spin lattice relaxation times and 1D-heteronuclear Overhauser effects of protons on the carbon atom can be obtained by standard methods, the determination of $\eta_{C \rightarrow Li}$ poses a problem, since the expected value is less than 1% and must be reliably determined. We have therefore developed a heteronuclear NOE difference pulse program which measures lithium under proton broad-band decoupling and which alternates the carbon atom irradiation frequency between two offset values. This ensures that all relevant instrumental parameters of the spectrometer remain unchanged during the measurements. Furthermore, the pulse sequence was programmed in such a manner that the reference offset was chosen before and after the offset on resonance for the signal of the labeled carbon atom (see Figure 4). Thus the desired Overhauser effect should be observable in the difference spectra between 1 and 2 or between 2 and 3, while the difference spectrum between 1 and 3 indicates any instrument instabilities. In this manner we obtained the values given in Table 1, from which the C–Li distance was evaluated using equation (5).

Figure 4. Pulse scheme for 1D $^{13}C,^{6}Li$ NOE difference measurement with ^{1}H decoupling. Three different ^{6}Li spectra were recorded with three different frequency settings on the ^{13}C channel, where only O2 was adjusted correctly to the resonance of the labeled carbon atom. The three spectra were recorded in an interleaved mode

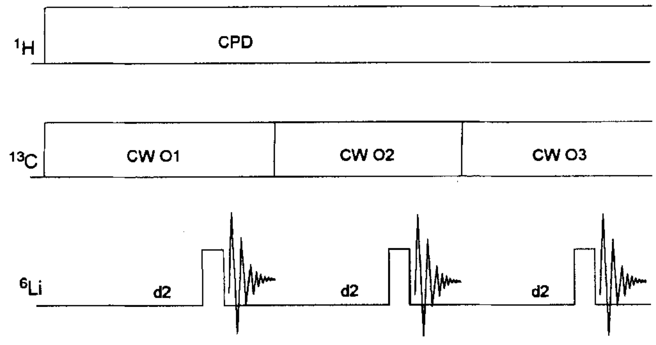


Table 1. NMR data and bond lengths of [α-^{6}Li,α-^{13}C]lithiophenyl(trimethylsilyl)methane (**1**)

$T_1(^{13}C)$	$T_1(^{6}Li)$	$\eta_{H \rightarrow C}$	$\eta_{C \rightarrow Li}$	τ_c	r_{C-Li}
2.1 s	26.0 s	1.42	0.0028	$1.49 \cdot 10^{-11}$ s	214 pm

	Li–H bond distances from X-ray[a]	bond distances from $^{1}H,^{6}Li$ HOESY
benzylic H	235	235[b]
ortho H	311	341
$SiMe_3$	461	420
$TMEDA-CH_3$	327	425

[a] Values for equivalent hydrogen atoms averaged. – [b] Used for adjustment.

The obtained r_{C-Li} value of 214 pm is in fair agreement with the value of 212.7 pm determined by an X-ray measurement. One might be tempted to interpret this difference by assuming that in solution the Li ion is slightly more separated from the anion. However, considering the various sources of experimental error this cannot be proofed and might only be fortuitous, although due to the sixth power of the distance errors of NOE measurements are minimized.

The volume integrals of the $^{1}H,^{6}Li$ HOESY spectrum can be related to the Li–H distances determined from the X-ray structure. At room temperature the *ortho* and *meta* hydrogen atoms of the phenyl group are averaged. Within the limits of accuracy is a reasonable agreement between both methods. However, the complexing agent TMEDA is somewhat more separated from the anion in solution. The relevant values are also given in Table 1. Thus, **1** is an example of X-ray and NOE results obtained by different NMR methods that are in agreement with each other.

Conclusion

We have shown in this work that 1D and 2D $^{13}C,^{6}Li$ heteronuclear Overhauser effects can be measured and used for C–Li distance calculation. These data allow us to gain structural insights by which the position of a lithium ion with respect to the organic anion can be located in solution. However, both ^{13}C labeling and a three-channel NMR spectrometer are required for these experiments.

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Experimental

NMR: Bruker AMX-500, residual solvent signal of $CDCl_3$ as an internal standard: δ = 7.26 (^{1}H), 77.0 (^{13}C). ^{1}H- and ^{13}C-NMR spectra of organolithium compounds in [D$_8$]THF are referenced to the THF signal at high field: δ = 1.73 (^{1}H), 25.2 (^{13}C). ^{6}Li-NMR spectra were referenced to $^{6}LiCl$ in water as an external standard. Spectra were recorded at 300 K if not stated otherwise.

$^{1}H,^{6}Li$ HOESY NMR spectra were recorded by using a 5-mm broad-band probe. The deuterium stop filter was removed from the BB channel because of the similarity of the deuterium and lithium frequency. When this probe was used the 90° ^{6}Li pulse was usually 10 μs, the 90° ^{1}H pulse 12 μs. A relaxation delay of 6 s and a mixing time of 1.7 s were applied. 128 free induction decays of 16 transients were measured on 256 data points. After weighting with an exponential window in F_1 and a quadratic sinusoidal window in F_2, the matrix was processed by using 256 × 512 data points.

Quadrature detection in F_1 was achieved by means of the RSH method.

^{13}C,^{6}Li HOESY NMR spectra were recorded by using a 5-mm triple resonance broad-band probe (^{1}H/^{13}C/X). With this probe the 90° ^{6}Li pulse and 90° ^{13}C pulse were 23 μs and 19 μs, respectively. 64 free induction decays of 192 transients were measured on 512 data points. The matrix was processed by using 64 × 256 data points. Other conditions were identical with those employed for the ^{1}H,^{6}Li HOESY measurements.

[α-^{13}C]Benzoic Acid, [α-^{13}C]Benzyl Alcohol, and [α-^{13}C]Benzyl Chloride: Preparation according to literature procedures[7].

([α-^{13}C]Benzyl)trimethylsilane was prepared by a modified method of Jansen and Godefroi[8]. 1.70 g (70 mmol) of magnesium turnings was suspended in 50 ml of diethyl ether in a 100-ml-three-necked flask. 2.21 g (17.5 mmol) of [α-^{13}C]benzyl chloride was added to the solution, and the mixture was refluxed for 1 h. Subsequently 1.90 g (17.5 mmol) of trimethylsilyl chloride was added, and the mixture was heated at reflux for 10 h. The product was poured onto 80 ml of water, and insoluble impurities were removed by filtration. The aqueous layer was separated and the organic phase washed with water, 0.1 M HCl, a saturated aqueous sodium hydrogen carbonate solution, and water again. The ether was removed by distillation after drying with magnesium sulfate, and the crude product was purified by preparative gas chromatography. Yield 1.98 g (11.9 mmol, 68%), bp 153°C/35 Torr. – ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.03$ [s, $Si(CH_3)_3$], 2.09 (d, CH_2, $^1J_{C,H} = 120.0$ Hz), 6.89–7.04 (m, H_o), 7.08 (t, $J = 7.3$ Hz, H_p), 7.22 (t, $J = 7.6$ Hz, H_m). – ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = -1.8$ [$Si(CH_3)_3$], 27.1 (benzylic CH_2), 124.0 (*p*), 128.1 (*o*), 128.2 (*m*), 140.5 (*i*).

[α-^{6}Li,α-^{13}C]Lithiophenyl(trimethylsilyl)methane (**1**): 0.56 ml of a 1.20 M solution of *n*Bu^{6}Li in *n*-hexane was placed into a 25-ml flask flushed with nitrogen and equipped with a septum cap, and the solvent was removed in vacuo. The residue was dissolved in 1 ml of [D_8]THF at 0°C. Then 0.01 ml (0.67 mmol) of TMEDA and 0.1 ml (100 mg, 0.61 mmol) of [α-^{13}C]benzyltrimethylsilane were added to the solution. The mixture was stirred for 3 h at 0°C and transferred to an NMR tube with a joint, which was sealed in vacuo. The concentration was about 0.6 M. – ^{1}H NMR (300 MHz, [D_8]THF): $\delta = 0.10$ [s, $Si(CH_3)_3$], 1.45 (d, benzylic H, $^1J_{C,H} = 120.0$ Hz), 2.18 (s, TMEDA-CH_3), 2.33 (s, TMEDA-CH_2), 5.72 (t, $^3J_{H,H} = 7.0$ Hz, H_p), 6.32 (d, $^3J_{H,H} = 8.0$ Hz, H_o), 6.49 (dd, $^3J_{H,H} = 7.0, 8.0$ Hz, H_m). – ^{13}C NMR (75 MHz, [D_8]THF): $\delta = 2.23$ [$Si(CH_3)_3$], 40, 77 (benzylic CH), 107.96 (*p*), 120.54 (*o*), 128.22 (*m*), 159.90 (*i*). – ^{6}Li NMR (73 MHz, [D_8]THF): $\delta = 0.62$ (s).

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