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NMR Spectroscopy of Organolithium Compounds, Part XVI [1]

The Aggregation Behavior of Butyllithium, Phenyllithium, and Lithium Diisopropylamide in Dimethoxy- and Diethoxymethane

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Abstract: The aggregation behaviour of butyllithium (BuLi), phenyllithium (PhLi), and lithium diisopropylamide (LDA) in dimethoxy- and diethoxymethane (methylal and ethylal, respectively) has been studied by NMR spectroscopy using the isotopic fingerprint method and ^{13}C,^{6}Li as well as ^{15}N,^{6}Li spin-spin coupling constants. In both solvents, LDA exists as a dimer, while BuLi forms a tetramer. PhLi forms a dimer in methylal, whereas two major aggregates exist in ethylal. Due to solvent viscosity at lower temperatures, their structure could not be determined.

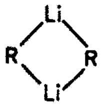
Introduction

For the reactivity of organolithium compounds, their strong tendency to form oligomeric aggregates in solution is an important factor. Both, the cluster size and the number of aggregates depend on the solvent and on the presence of complexing agents, as for example tetramethylethylenediamine (TMEDA), and varies from monomers through dimers and tetramers to hexamers. [2] Even higher aggregates have been observed in hydrocarbon solvents in a few cases. [3]

A notable observation in this respect was reported in 1964 by Schöllkopf and Küppers, [4] who found that the reaction of chloromethylmethyl ether with lithium in diethyl ether or tetrahydrofuran failed, while in dimethoxymethane (methylal) stable solutions of methoxy-methyl lithium could be prepared. Since then, methylal has been used frequently as solvent in metalation reactions [5] and it seemed of interest to study the aggregation behaviour of some of the most important organolithium compounds, butyllithium (BuLi), phenyllithium (PhLi), and lithium diisopropylamide (LDA), in this solvent and in the related solvent diethoxymethane (ethylal).

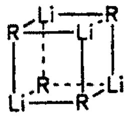
Methods of investigation. Structure determinations of organolithium clusters in solution depend primarily on NMR spectroscopy. [6,7] Various one- and two-dimensional methods are available today and the variety of techniques which are at hand to tackle structural problems is still increasing. So far, the determination of cluster size has relied heavily on ^{13}C,^{6}Li and ^{13}C,^{7}Li spin-spin coupling constants and the multiplicity of ^{13}C-multiplets observed for metalated carbons in the organolithium compounds of interest. [6,8,9] Because of its favourable properties for NMR measurements, the nuclide ^{6}Li is preferred and as a spin-1 nucleus it leads to characteristic multiplets in the ^{13}C NMR spectrum: 1:1:1 triplets for monomers, 1:2:3:2:1 quintuplets for dimers, and 1:3:6:7:6:3:1 septuplets for tetramers.

More recently, the *isotopic fingerprint method* [10] has been introduced as a new tool which is based on deuterium-induced isotope shifts of the ^{6}Li resonance. For different oligomers, typical ^{6}Li multiplets which are characteristic of the aggregation state can be expected for 1:1 mixtures of deuterated and non-deuterated RLi compounds. The principle of this new technique, which is closely related to the SIMPLE NMR method for the assignment of ^{13}C NMR spectra of polyalcohols, [11] is best explained with an example. Given a dimeric structure of type **1**, like that of PhLi (R = C_6H_5) in the presence of TMEDA, and a 1:1 mixture of deuterated and non-deuterated ligands (**d** and **h**, respectively) the environments **2** - **4** for ^{6}Li exist:



1

[h,h]	**[h,d] ≡ [d,h]**	**[d,d]**
2	**3**	**4**



5

[h,h,h]	**[h,h,d]**	**[h,d,d]**	**[d,d,d]**
6	**7**	**8**	**9**

According to a straightforward statistical consideration, a ^{6}Li triplet with an intensity distribution of 1:2:1 should then result in the case of slow *inter*aggregate exchange, if a ^{2}H/^{1}H isotope effect for $\delta(^6\mathrm{Li})$ exists. Each line of this multiplet [12] is characteristic for a different ^{6}Li environment. In turn, for a monomer we should find a doublet and for a tetramer of structure **5**, where the environments **6** - **9** are present, a quadruplet with an intensity distribution of 1:3:3:1 is expected. Thus, clusters of different size are characterized by isotopic fingerprints. An attractive feature of this method as compared to the determination of the aggregation number from scalar ^{13}C,^{6}Li or ^{13}C,^{7}Li spin-spin coupling constants is its sensitivity which is achieved by twofold isotopic enrichment (^{2}H and ^{6}Li).

If only the *inter*aggregate exchange is slow and the *intra*aggregate exchange still fast on the NMR time scale, the situation changes for clusters with aggregation numbers > 2. The ^{6}Li nucleus then interacts with all ligands of the particular clusters, including the remote ones. Consequently, for a dynamic tetramer of structure **5** the environments **10** - **14** must be considered, and a 1:4:6:4:1 ^{6}Li quintuplet is expected. Now, each line of the multiplet corresponds to a different aggregate. Such a situation was found for PhLi in diethyl ether at 170 K. [13]

|h,h,h,h|	**|h,h,h,d|**	**|h,h,d,d|**	**|h,d,d,d|**	**|d,d,d,d|**
10	**11**	**12**	**13**	**14**

In the present study, we employed the isotopic fingerprint method as well as spin-spin coupling patterns.

Results and Discussion

Isotopically Labelled Materials. [^{2}H$_5$]PhLi, [α-^{2}H$_2$]BuLi, [^{2}H$_{14}$]LDA, as well as [^{15}N]LDA were synthesized following standard procedures (see Exp. Part). For all compounds 100% ^{6}Li enchrichment was used.

NMR Spectra in Methylal. The ^{6}Li-NMR spectra of BuLi, PhLi, and LDA in methylal at 200 K, where *inter*-aggregate exchange is slow on the NMR time scale, are shown in Figure 1. Except for small signals due to minor components or impurities, they display one dominant ^{6}Li resonance with chemical shifts of 1.28, 1.55, and 1.82 ppm, respectively, relative to the external ^{6}Li signal of 0.1M LiBr in THF. This documents that essentially only one aggregate is present. In order to determine the aggregation state, the isotopic fingerprint method was applied and 1:1 mixtures of deuterated and non-deuterated BuLi, PhLi, and LDA were investigated at low temperature. The results obtained at 200 K are shown in Figure 1b. According to the multiplet structures observed, *dimers* are present for PhLi and LDA (triplet), while BuLi exists as dynamic tetramer (quintuplet). The isotope shifts are 5.6 ppb for BuLi, 12.6 ppb for PhLi, and 11.2 ppb for LDA. In all cases, the multiplet lines are equidistant within experimental error (digital resolution 0.07 Hz).

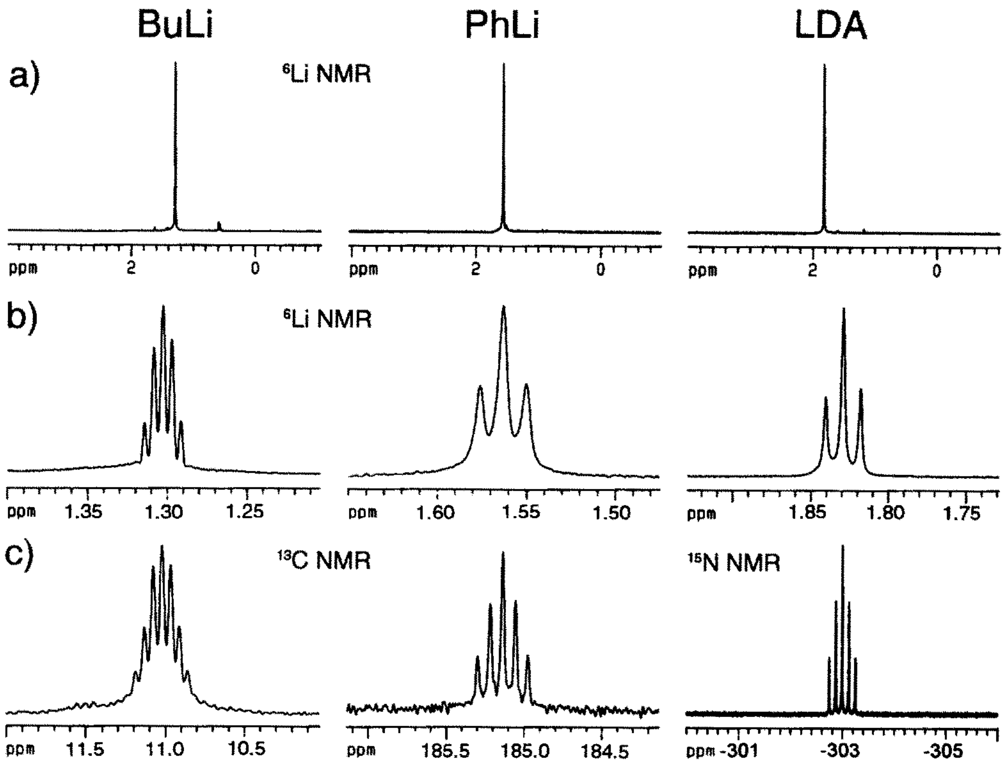


Figure 1. (a) 58.9 MHz ^{6}Li NMR spectra of PhLi, BuLi, and LDA in methylal with 10% [^{2}H$_{10}$]diethyl ether as lock substance at 200 K; external reference 0.1 M ^{6}LiBr in THF; (b) ^{6}Li NMR multiplet structures observed with the isotopic fingerprint method at the same temperature (cf. text); (c) ^{13}C NMR and ^{15}N NMR spin-spin multiplet observed for the metalated carbons and nitrogen, respectively, at 200 K.

These findings are corroborated for PhLi by the ^{13}C NMR spectra of the non-deuterated compound, which shows the expected quintuplet for C-1 and a coupling of 8.1 Hz, typical for a dimeric structure (Fig. 1c). [9b] The ^{13}C chemical shift is 185.1 ppm (rel. to TMS), and similar to the value found for the PhLi dimer in diethyl ether in the presence of TMEDA (187.3 ppm). [13] Similarly, the ^{15}N resonance of ^{15}N enriched (33%) LDA shows a quintuplet at $\delta(^{15}N)$ = -303 ppm (rel. to ext. CH_3NO_2) with $J(^{15}N,^6Li)$ = 5.1 Hz (Fig. 1c). This is identical to the data found in THF solution (5.0 Hz) were LDA exists as a dimer. [14-16]

In the case of BuLi, on the other hand, a ^{13}C septuplet with a coupling of 5.5 Hz is observed (Fig. 1c), which indicates a static tetramer of structure **5**. The apparent contradiction to the results obtained with the isotopic fingerprint method are resolved if one considers the different line splittings involved with both techniques. The larger splitting due to $^{13}C,^6Li$ scalar coupling renders BuLi static on the corresponding NMR time scale, while due to the smaller isotope shift (0.33 Hz) the compound is still in the fast *intra*aggregate exchange regime on the NMR time scale of the isotopic fingerprint method. [17] Accordingly, the transition to the multiplet structure of a tetramer static on the slower NMR time scale of the isotopic fingerprint method is achieved only at lower temperature, where the expected quadruplet [18] appears below 195 K (Fig. 2). Assuming 195 K as the coalescence temperature, the rate and the energy barrier for the pseudo-monomolecular *intra*aggregate exchange reaction can be estimated from the simple equation [19] $k_{coal} = \pi\Delta\nu/\sqrt{2}$ to approx. $k_{195} \approx 1\ s^{-1}$ and $\Delta G^{\neq}(195) \approx 37$ kJ/mol, where $\Delta\nu$ is the isotope shift between two lines of the quintuplet (0.33 Hz). This is not very different from the energy barrier for the *inter*aggregate exchange between tetramers and dimers found in THF ($\Delta G^{\neq}(195)$ = 41 kJ/mol as calculated from the given $\Delta H^{\neq}$ and $\Delta S^{\neq}$ values). [20]

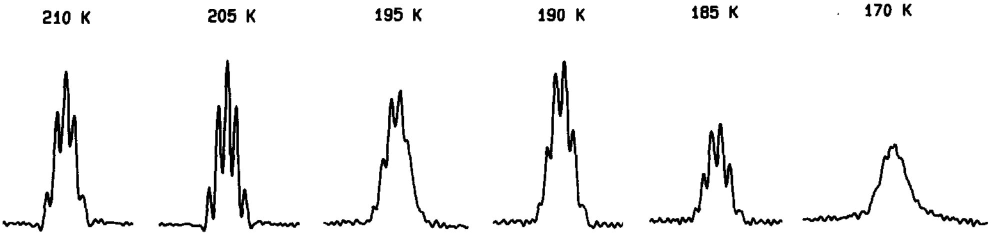


Figure 2. Temperature dependence of the ^6Li NMR isotopic fingerprint observed for BuLi in methylal.

Since our measurements were initially performed with samples that contained 10% $[^2H_{10}]$diethyl ether as lock substance, it was desirable to secure that this additive did not affect the results. We, therefore, repeated the measurements in $[^2H_8]$methylal, where the solvent served as lock substance, and found the spectra unchanged. A possible influence of sample concentration on the BuLi results, on the other hand, which were obtained for a 2 M solution, was excluded by experiments repeated with a more dilute sample (0.5 M), which yielded identical results.

In view of these observations, it seemed of interest to monitor the aggregation behaviour of BuLi in diethyl ether by ^{13}C and ^6Li NMR as well as by the isotopic fingerprint method. Earlier work based on $^{13}C,^7Li$ interactions [21] has established under these conditions the presence of a tetramer. Figure 3a shows the ^{13}C resonance of C-1 for a 0.15 M BuLi solution at 183 K, where a multiplet is observed at 10.9 ppm with a coupling of 5.4 ± 0.1 Hz. The simulation of the signal pattern reveals slightly better agreement with a nonuplet than with a septuplet, which means that on the NMR time scale governed by the coupling constant the tetramer still shows *intra*aggregate exchange. On the other hand, the magnitude of the coupling supports a static situation. [6] A clearer picture comes from the ^6Li NMR isotopic fingerprint measured for an equimolecular mixture of $[^6Li]BuLi/[\alpha\text{-}^2H_2,^6Li]BuLi$ at 167

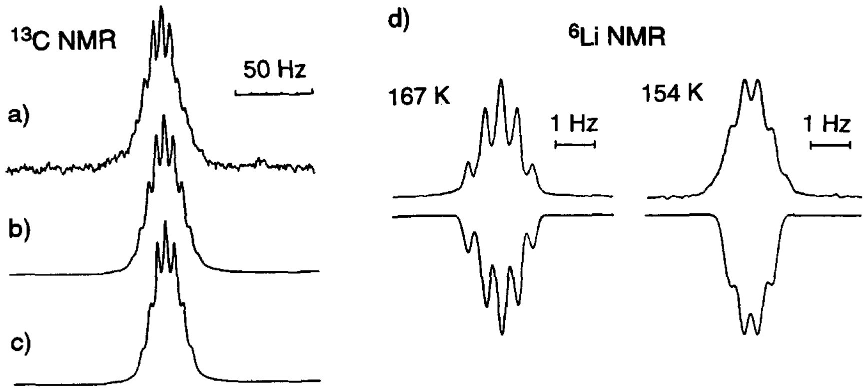


Figure 3. ^{13}C- and ^{6}Li-NMR spectra of BuLi in diethyl ether; (a) multiplet observed for C-1 in the 100 MHz ^{13}C NMR spectrum at 180 K with simulated spectra for a septuplet (c) and a nonuplet (b); J(^{13}C,^{6}Li) = 5.4 Hz; (d) ^{6}Li NMR isotopic fingerprint for an equimolar mixture of [^{6}Li]BuLi and [α-$^{2}H_2$,^{6}Li]BuLi at 167 and 154 K.

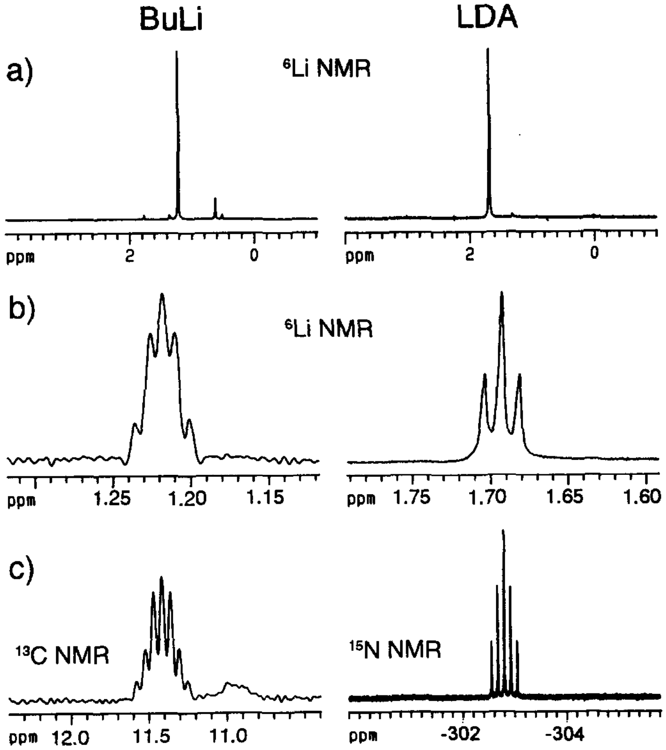


Figure 4. (a) Low-temperature 58.9 MHz ^{6}Li NMR spectra for BuLi and LDA in ethylal; (b) ^{6}Li NMR isotopic .fingerprints for 1:1 mixtures of.[^{6}Li]BuLi and [α-$^{2}H_2$.^{6}Li]BuLi and LDA/[$^{2}H_{14}$]LDA, respectively, in the same solvent; (c) 100 MHz ^{13}C NMR multiplet of C-1 of [^{6}Li] BuLi and 40.54 MHz ^{15}N NMR spectrum of [^{6}Li,^{15}N]LDA, respectively, in ethylal at 230 K; J(^{13}C,^{6}Li) = 5.5 Hz, J(^{15}N,^{6}Li) = 5.1 Hz.

K (Fig. 3d). The transition from the dynamic to the static tetramer is documented by the transformation of the observed quintuplet (isotope effect 8.0 ppb or 0.47 Hz) into a quadruplet at 154 K.

NMR Spectra in Ethylal. In this solvent the measurements partly suffered from the higher viscosity as compared to methylal. The results are summarized in Figure 4. In the case of BuLi, again the signals typical for a tetramer are observed with a ^{6}Li chemical shift of 1.20 ppm, a quintuplet for the ^{6}Li NMR isotopic fingerprint (isotope effect 8.8 ppb), and a ^{13}C septuplet at 11.41 ppm with a ^{13}C,^{6}Li coupling of 5.5 Hz (Fig. 4a-c). The structure of an apparently minor component with a ^{6}Li signal at 0.62 ppm and a broad ^{13}C absorption at 10.94 ppm could not be determined. For LDA, the results are virtually identical to those obtained in methylal, with only one cluster present ($\delta(^6Li)$ = 1.68 ppm) which has a dimeric structure as derived from the triplet observed for the 1:1 mixture of LDA/[$^2H_{14}$] LDA (isotope shift 11.2 ppb) and the quintuplet resolved in the ^{15}N NMR spectrum [$\delta(^{15}N)$ = -301.3 ppm, $J(^{15}N,^6Li)$ = 5.1 Hz) (Fig. 4a-c)].

With PhLi, the slow exchange limit was not accessible and severe line broadening prevented the observation of the multiplet structures due to isotope shifts and spin-spin coupling (Fig. 5). The important aspect, however, is the existence of *two* distinct ^{6}Li NMR signals at 205 K with chemical shifts of 1.94 and 1.34 ppm. These temperature dependent line shape changes are completely reversible. Assuming that the chemical shift of the dimer is similar to the value found in methylal, the signal at 1.34 ppm can be assigned tentatively to this kind of aggregate. The low-field signal should than result from a tetramer, in agreement with the usual ^{6}Li chemical shift hierarchy which shows the higher aggregates at lower field. [6]

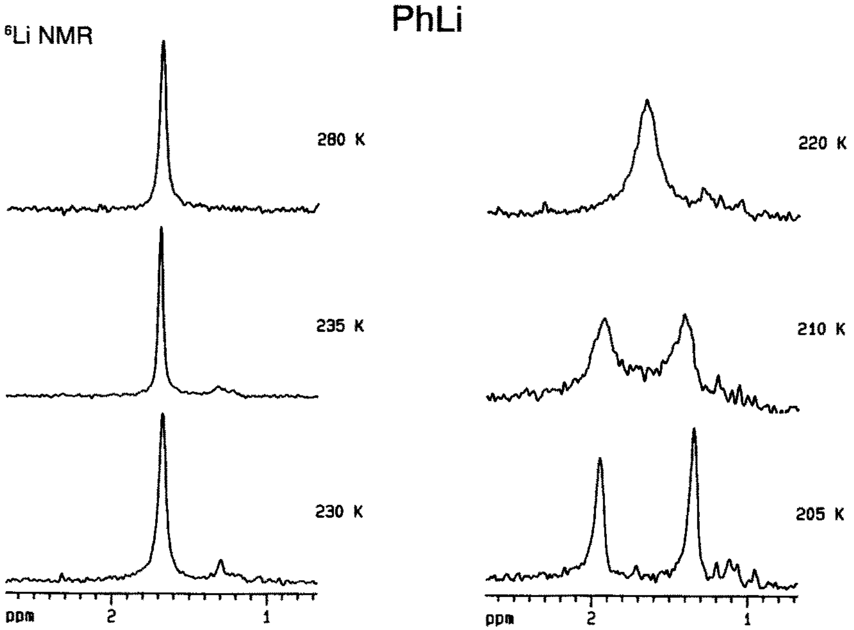


Figure 5. Temperature dependence of the 58.9 MHz ^{6}Li NMR spectrum of [$^2H_5$,^{6}Li]PhLi/[^{6}Li]PhLi (1:1) in ethylal.

Conclusion

To summarize our results we can state that LDA forms dimers in both methylal and ethylal and thus behaves like in other ethereal solvents (THF, [14] diethyl ether [22]). For BuLi we find in both solvents tetramer formation, which is the same situation as found for diethyl ether. In the case of PhLi, methylal stabilizes the dimer like the solvent system THF/ TMEDA, [9b] while its behaviour in ethylal is unexpected and needs further study.

Experimental Part

Compounds. - For the synthesis of [α-$^2H_2$,^6Li]BuLi from ^6Li metal and the corresponding chloride. [23] [α-$^2H_2$]butanol was prepared by Li[Al$^2H_4$] reduction of butyric acid chloride and transformed into [α-$^2H_2$]butyl chloride. [24,25] The synthesis of [$^2H_5$,^6Li]PhLi followed the route previously described. [13] Perdeuterated and ^{15}N-labelled diisopropyl amine were prepared according to the reaction sequence published by Collum et al. [26] using N^2H_4Cl and $^{15}NH_4Cl$, respectively, and subsequently metalated with [^6Li]BuLi. Perdeuterated methylal was synthesized from [$^2H_2$]para-formaldehyde and [$^2H_4$]methanol according to the literature. [27] Sample concentration in methylal (ethylal) where 2 M (2 M) for BuLi, 0.5 M (0.3 M) for PhLi, and 0.5 M (0.5 M) for LDA.

NMR Spectra. Samples for NMR measurements were prepared under argon and transferred to 5 mm o. d. sample tubes, which were sealed. Spectra were obtained with a 400 MHz (^1H) Bruker AMX FT NMR spectrometer operating at 58.88 MHz for ^6Li, 100.13 MHz for ^{13}C, and 40.54 MHz for ^{15}N, equipped with deuterium lock and the Bruker low-temperature unit. ^6Li NMR spectra were referenced to external 0.1 M LiBr in THF, ^{13}C NMR spectra to TMS, and ^{15}N NMR spectra to exterrnal CH_3NO_2.

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17 It should be kept in mind that "static" on the NMR time scale does not imply the presence of rigid structures, it only means that the *intra-* as well as the *inter*aggregate exchange is slow enough to allow the detection of separate NMR signals.

18 Due to the viscosity of the solvent, measurements at temperatures lower then 185 K failed. It is therefore not clear if the small lines of the observed multiplet at highest and lowest frequency are still due to slow exchange or if they truly belong to the multiplet of the static tetramer.

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