NMR Methods

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^{7}Li Residual Quadrupolar Couplings as a Powerful Tool To Identify the Degree of Organolithium Aggregation**

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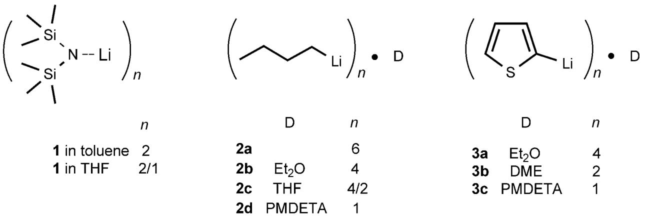
Organolithium and lithium amide compounds rank among the most widely used reagents in synthesis,[1] and knowledge of their structure and/or aggregation state is of great importance.[2] Structural studies in solution (where the reactions are mostly carried out) have been dominated by NMR spectroscopy, traditionally using ^{13}C and $^{6/7}$Li chemical shifts[3] or lithium–carbon couplings.[4] More recently, Williard et al. could show that diffusion-ordered spectroscopy (DOSY)[5] is an efficient tool to discriminate different aggregates of *n*-butyllithium (*n*BuLi; **2**) by comparison with reference substances of defined molar masses.[6] Nevertheless, in many cases the differentiation is hampered by similar masses of various donor-ligated aggregates or rapid dissociation of the ligands. We could recently characterize 2-thienyllithium (2-ThiLi; **3**) with various donor bases in toluene by applying relatively time-consuming ^{1}H,^{7}Li-HOESY experiments[7] and comparing the distance information from these data with the crystal structures.[8] The rather long measurement time and the additional interpretation and comparison of the data clearly underline the need for a more straightforward method to judge on aggregation. Herein, we present such a method based on ^{7}Li residual quadrupolar couplings (RQCs) that were obtained with text book lithium compounds (Scheme 1) in swollen polystyrene gels.

The importance of anisotropic NMR spectroscopic parameters for structure elucidation of organic compounds has been underlined by various publications in recent years. Meanwhile, residual dipolar couplings (RDCs),[9] residual chemical shift anisotropies (RCSAs),[10] and ^{2}H residual quadrupolar couplings (RQCs)[11] are conveniently measured using liquid-crystalline phases, such as poly(γ-benzyl-L-glutamate) (PBLG)[12] or stretched polymer gels (strain-induced alignment in a gel; SAG).[13] Nevertheless, applications of such alignment media to inorganic or organometallic compounds[14] or quadrupolar nuclei other than ^{2}H[15] are still rare.

Quadrupolar couplings originate from the interaction between the nuclear electric quadrupole moment Q (nuclear spin $I > \frac{1}{2}$) and the electric field gradient (efg, tensor $\mathbf{V}$) produced by a non-symmetric electronic environment of the nucleus. The interaction averages to zero in isotropic solution, but gives rise to a splitting into $2I$ lines if the molecule is weakly aligned along the magnetic field axis (as described by the alignment tensor $\mathbf{A}$). Thus, in the case of ^{7}Li ($I = 3/2$), a triplet is expected with line separations given by Equation (1).[16]



Scheme 1. The common organolithium and lithium amide reagents used. The degree of aggregation *n* depends on the solvent or stoichiometric donor base D (DME = dimethoxyethane, PMDETA = *N,N,N′,N″,N″*-pentamethyldiethylentriamine). Aggregation: *n* = 6 hexamer, *n* = 4 tetramer, *n* = 2 dimer, *n* = 1 monomer. If two numbers are given for *n*, an equilibrium is present.

$$\Delta\nu_Q = \frac{eQ}{2h}\sum_{i,j=x,y,z} A_{ij}V_{ij} \qquad (1)$$

Where e is the elementary charge, h Planck's constant, A_{ij} and V_{ij} are the components of the alignment and efg tensors in the molecular axis system x,y,z (second-order quadrupolar effects are neglected). The formula implies that in molecules which are spherically shaped ($A_{ij} = 0$) or contain ^{7}Li in a highly symmetric environment ($V_{ij} = 0$) no splitting is expected.[17] We chose to study ^{7}Li rather than ^{6}Li ($I = 1$) because of its higher sensitivity and larger quadrupole moment (−4.01 vs. −0.081 fm^2) which should give rise to RQCs comparable to ^{2}H RQCs in typical C–^{2}H groups.

The first challenge was the design of an alignment medium that would withstand highly reactive organolithium compounds. We chose polystyrene (PS) cross-linked with divinylbenzene (DVB) which has no functional groups that could possibly be attacked. The polymer sticks were swollen directly with solutions of the respective lithium compound in [D$_8$]toluene. Toluene was chosen as solvent because it is chemically rather inert, closely resembles the polymer environment, and easily allows the deaggregation of the lithium compound by stoichiometric addition of more polar solvents or donor bases.[8] Additionally, we slightly modified the preparation reported by Luy et al.[18] in that we abstained from using 2,2′-azobis(2-methylpropionitrile) (AIBN) as the initiator of the polymerization. Instead, the reactants were thoroughly degassed and thermally polymerized at 115 °C for

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at least two days. The linker concentration could easily be varied between 0.1 and 0.4 vol %; higher amounts led to the observation of inhomogeneous "popcorn" polymer.[19] All polymer sticks (diameter 3.8 mm, length 1 cm) were stored in an argon dry box and always handled under an inert gas atmosphere. Diffusion of the colored lithium compounds into the gel could, in many cases, be directly monitored optically (Figure 1). Swelling was typically complete after one week, and the quality of the swollen polymer was verified by the quadrupolar splitting in the ^{2}H NMR spectrum (Figure 2 a).[13a]

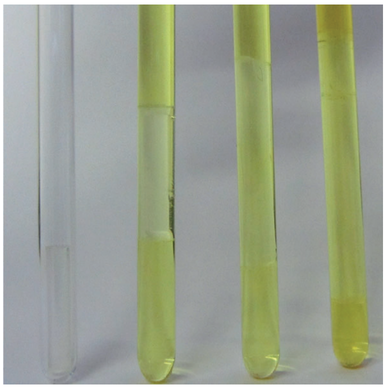

Figure 1. Polystyrene sticks inside a 5 mm NMR tube. From left to right: Dry stick, adjusted stick directly after addition of the organolithium solution, stick after 3 days of swelling, stick after 7 days of swelling.

The method was tested on lithium hexamethyldisilazane (LiHMDS; **1**), which is only moderately reactive and forms a $(NLi)_2$ cyclic dimer in toluene solution.[20] In the ^{7}Li NMR spectrum recorded at room temperature, a triplet with an integral ratio of 3:4:3 and a quadrupolar splitting of 75 Hz could be observed for the linker (DVB) concentration of 0.2 vol % (Figure 2 b). The outer lines of the triplet are broader than the central line (17 vs. 11 Hz), which is due to differential transverse relaxation of the individual transitions in a spin 3/2 nucleus[21] and in agreement with earlier findings.[15d] The ^{7}Li quadrupolar splitting increases with increasing linker concentration (Figure 2 c) and thereby follows the trend reported by Luy et al.[13b] This scalability of the splitting thus presents an alternative to the use of a stretching apparatus.[15d,22] Furthermore, all samples were stable for at least four weeks, and the splittings were highly reproducible and independent of the LiHMDS concentration in the range of 25–150 mg per 0.5 mL of deuterated solvent.

We were interested whether our PS gels would also be compatible with and show observable ^{7}Li quadrupolar splittings at the low temperatures at which reactive organolithium reagents are typically employed. For this purpose a swollen polymer containing **1** in [D$_8$]toluene was stepwise cooled to 228 K. Interestingly, the measured ^{7}Li splitting increases slightly from 107 Hz (298 K) to about 190 Hz (248 K); at temperatures below 238 K the outer lines become too broad to be observable (Figure 3 a). Line broadening was likewise observed in the ^{2}H NMR spectra (see Supporting Information) and, as for the ^{7}Li NMR spectra, found to be fully reversible. We also tested a sample of **1** dissolved in [D$_8$]THF, where **1** forms an equilibrium between THF-solvated monomeric and dimeric species[23] resulting in separate signals in the isotropic ^{7}Li NMR spectrum below 273 K (Figure 3 b). Inside the PS gel, each of the two lines splits into a quadrupolar triplet with RQCs of 71 and 45 Hz for the dimer and monomer, respectively (Figure 3 c). The higher quadrupolar coupling in the dimer can be rationalized in terms of two instead of one negatively polarized nitrogen atom in the lithium environment.

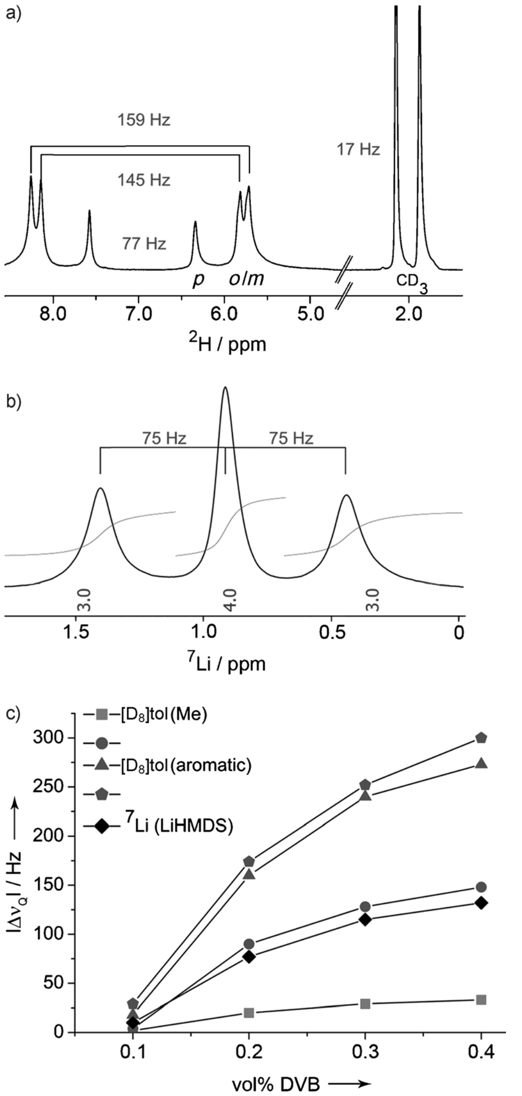

Figure 2. ^{2}H and ^{7}Li quadrupolar splittings of LiHMDS (**1**) in PS/[D$_8$]toluene at room temperature. a) ^{2}H NMR spectrum of [D$_8$]toluene using PS with 0.2 vol % DVB, b) ^{7}Li NMR spectrum of the same sample and c) dependence of the ^{2}H and ^{7}Li quadrupolar splittings on the linker concentration in vol %. Note that the ^{2}H and ^{7}Li NMR spectra yield only the absolute value of $\Delta\nu_Q$.

After providing proof of principle we applied our polymer sticks to *n*-butyllithium (**2**) and 2-thienyllithium (**3**) in toluene solution containing stoichiometric amounts of donor bases. In contrast to diethyl ether or THF as neat solvents,[24] these solutions are remarkably stable at room temperature, and the desired organolithium compound could be detected inside the PS gel without major side-products (see Supporting Informa-

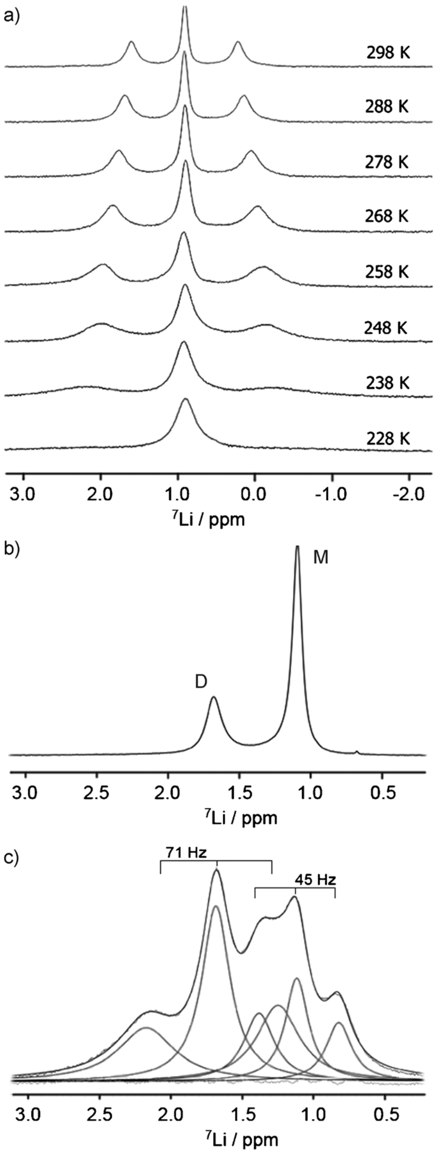

Figure 3. Low-temperature ^{7}Li NMR spectra of LiHMDS (**1**). a) Variable-temperature spectra of **1** in PS (0.3 vol% DVB)/[D$_8$]toluene. b) Isotropic spectrum of **1** in [D$_8$]THF at 273 K. The integral ratio monomer–dimer is about 2:1. c) Anisotropic spectrum of **1** in PS/[D$_8$]THF at 273 K. The spectrum (black line) was fitted to two quadrupolar triplets with overall six Lorentzians (gray lines). The fit residual is also shown (light gray line). The monomer/dimer ratio (about 1:2) is reversed because of the less-polar polymer environment.

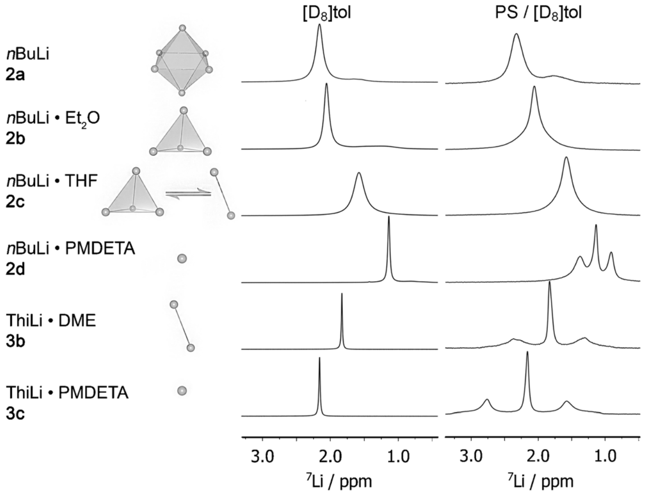

Figure 4. Structures (left side) and room-temperature ^{7}Li NMR (right side) spectra of *n*BuLi (**2**) and 2-ThiLi (**3**) in the presence of stoichiometric amounts of donor bases. The isotropic spectra (left) were recorded in [D$_8$]toluene. The anisotropic spectra (right) were recorded in PS/[D$_8$]toluene.

tion). The ^{7}Li NMR spectra in isotropic and anisotropic environment are shown in Figure 4. ^{7}Li quadrupolar splittings similar to that of LiHMDS are observed for *n*BuLi in the presence of PMDETA (**2d**), and for 2-ThiLi in the presence of DME (**3b**) and PMDETA (**3c**). **3b** forms a $(CLi)_2$ dimeric structure similar to that of **1**,[8] while **3c** (and presumably **2d**)[25] are monomeric.

In contrast, no ^{7}Li quadrupolar splitting was observed for *n*BuLi without additional donor bases (**2a**) or in the presence of Et_2O (**2b**) or THF (**2c**), or for 2-ThiLi with Et_2O (**3b**, not shown). **3b** suffered from low solubility and precipitation. Both, the isotropic and anisotropic spectrum, do look alike except for some line broadening of the anisotropic spectrum because of a slight inhomogeneity of gel and magnetic field. In three of these four cases the organolithium compound forms higher aggregates containing Li_4 tetrahedra (**2b**,[26] **3a**)[8] or Li_6 octahedra (**2a**)[27] such that electric-field gradients within the molecule are effectively averaged to zero. In **2c**, the efg is averaged to zero owing to fast equilibration between tetrameric and dimeric species.[6b] Although RQCs have been observed in tetrahedral molecules as a result of rotational–vibrational coupling[28] they are generally at least one order of magnitude smaller in size, so do not interfere. Thus, discrimination between aggregates of higher symmetry and those of lower symmetry can be achieved by measuring a single ^{7}Li NMR spectrum in an anisotropic environment. In the future, even quantification of RQCs may become feasible as a result of constantly increasing knowledge about efg tensor parameters from solid-state NMR spectroscopy data,[29] ^{7}Li relaxation times[30] and DFT calculations.[31] We are also confident that the currently rather long sample preparation may be simplified if 1) polymer sticks become commercially available, 2) swelling is speeded up at higher temperature and/or pressure, and 3) polymer gels are recycled by rinsing with neat solvent.

In summary, we have shown that ^{7}Li residual quadrupolar couplings are highly valuable to qualitatively distinguish different aggregation states of lithium amide, aliphatic and aromatic organolithium compounds. Polystyrene is stable towards these highly reactive species and can also be used at low temperatures. The method can easily be extended to other solvent systems (benzene, diethyl ether, THF, acetone) that likewise form gels with polystyrene. We therefore anticipate that RQCs of ^{7}Li and other quadrupolar nuclei may one day have the same significance for the structure determination of molecules as RDCs. Currently we are extending our investigations to other lithium compounds with unknown aggregation states.

Experimental Section

All solvents were dried over appropriate alkali metals, distilled, and degassed prior to use. LiHMDS and 2-thienyllithium (ThiLi·D, D = donor) were synthesized according to literature methods.[8,20a] and employed in pure, crystalline form. *n*BuLi was supplied by Chemetall GmbH, dried in vacuo, and dissolved in [D$_8$]toluene. To this solution the necessary amount of donor base (Et$_2$O, THF, PMDETA) was added prior to swelling. Polystyrene (PS) sticks were prepared with variable linker concentrations (0.1–0.4 vol% DVB). Higher linker concentrations led to the formation of "popcorn" polymers, which were inhomogeneous and therefore not suitable as alignment medium. All reactants were thoroughly degassed using several freeze–pump–thaw cycles. Glass tubes of 3.8 mm ID were treated with a 1:1 mixture of chlorotrimethylsilane and dichlorodimethylsilane for several hours, washed with dichloromethane, and dried afterwards. The degassed monomer solution was filled into the glass tubes and polymerized at 115 °C for at least two days (temperatures above 100 °C were necessary to initiate the polymerization thermally as no radical starter is used). In a next step, the glass tubes were broken and the homogeneous parts of the polystyrene material cut into sticks of 1 cm length, which were stored and handled in an argon dry box. The sticks were put to swell in a solution of the particular compound in [D$_8$]toluene or [D$_8$]THF. 0.2 mL of the solution were filled into the NMR tube, the stick was put on top holding the NMR tube horizontally until the swelling has started and the position of the stick is fixed. Then another 0.3 mL of the solution were added. Swelling was complete after roughly one week for toluene and 5 days for THF. The diffusion into the gel can be easily monitored optically for colored compounds and the transparency of the polymeric gel in general is a good indicator for its homogeneity.

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