Lithium Amides in Solution

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The Donor-Base-Free Aggregation of Lithium Diisopropyl Amide in Hydrocarbons Revealed by a DOSY Method**

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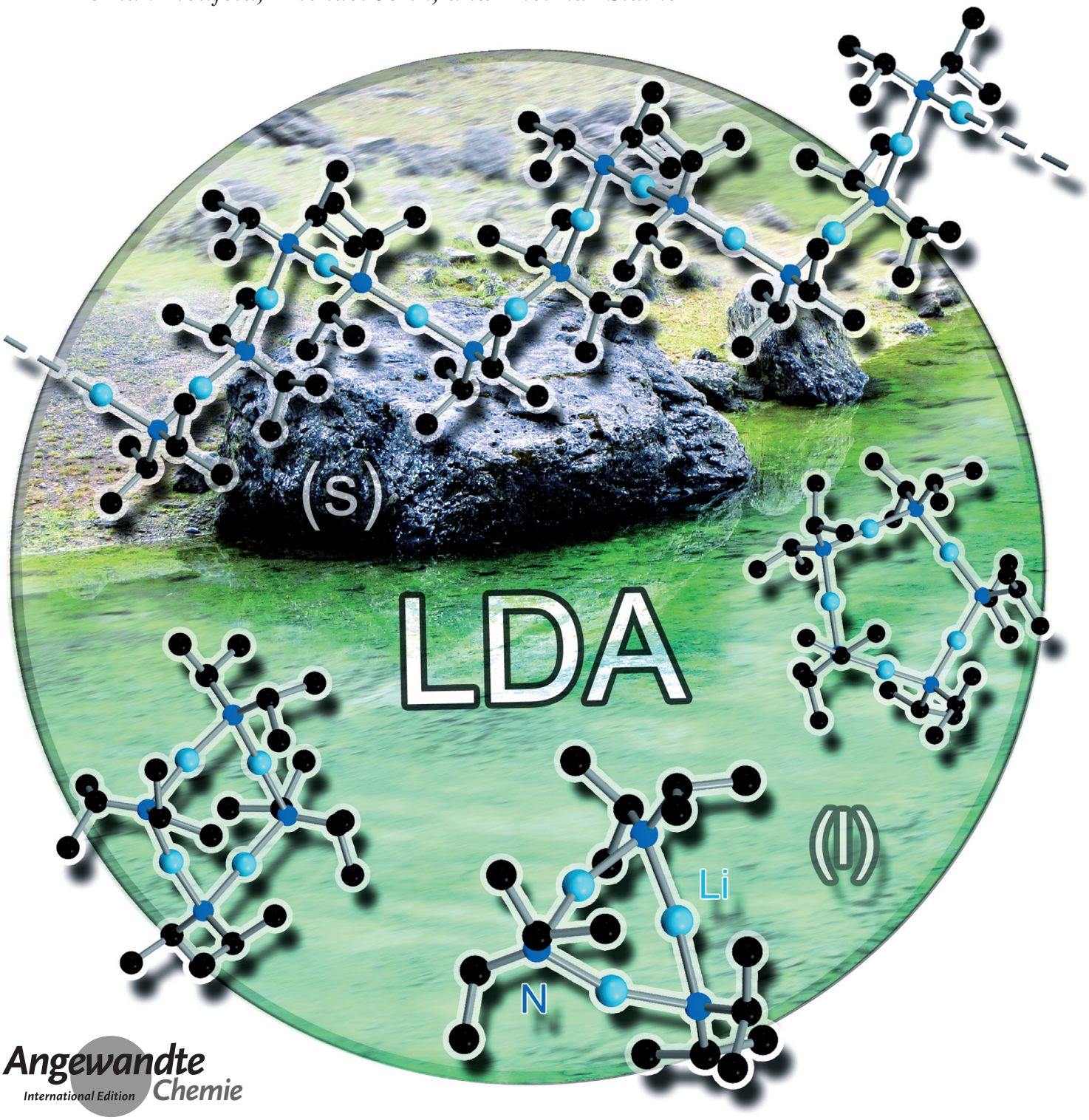
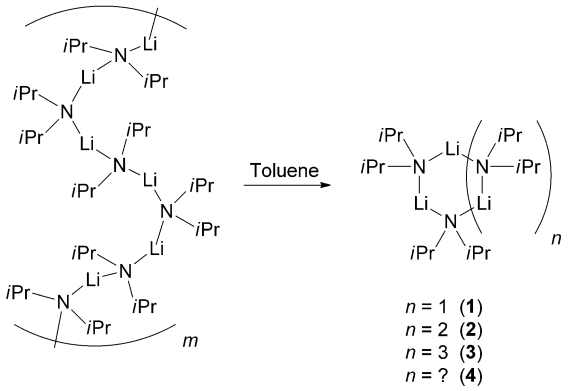


Abstract: *Lithium diisopropyl amide (LDA) is a very prominent reagent that plays a key role in organic synthesis, serving as a base par excellence for a broad range of deprotonation reactions. However, the state of aggregation in solution in the absence of donor bases was unclear. In this paper we solved this problem by employing DOSY NMR experiments based on a newly elaborated external calibration curve (ECC) approach with normalized diffusion coefficients.*

Although lithium diisopropyl amide (LDA, Scheme 1) is one of the most common and widely used non-nucleophilic Brønsted bases[1] its donor-base-free solid-state crystal structure was only determined in 1991.[2] It consists of an infinite



Scheme 1. LDA in the solid state and in toluene solution.

helical chain with four units per turn in the helix. In solution in all monodentate donating solvents LDA exists as a single observable aggregate—the solvated dimer.[3] That makes LDA an ideal template for studying organolithium reactivity[4] and is why LDA is one of the best examined lithium amides.[5] Collum et al. provided deeper insights into LDA-mediated reaction mechanisms, solution kinetics, structure–reactivity relationships, reaction rates, and selectivity.[6] However, the aggregation of LDA in donor-base-free solvents was still unclear. In 1991 Kim and Collum et al. investigated [^{6}Li]LDA and [^{6}Li,^{15}N]LDA in hexane by ^{6}Li and ^{15}N NMR spectroscopy.[6b] They observed a mixture of three major cyclic oligomers and suggested that they correspond to cyclic dimers, trimers, and higher oligomers. Unfortunately they were not able to quantify these observations because "*a severe overlap renders the effort required for a detailed study unjustifiable*".[6b]

In addition to NMR and mass spectrometry experiments conducted with isotopically labeled compounds, diffusion-ordered NMR spectroscopy (DOSY)[7] has become increasingly important for identifying species in solution.[8] The DOSY experiment separates NMR signals of species according to their diffusion coefficients.[9] This is why a polymer chemist has called this technique "*chromatography by NMR*".[10] However, there is no simple relationship between the diffusion coefficient and the molecular weight (MW). A number of empirical methods for relating diffusion coefficients to the MW have been proposed.[11] The empirically derived power law[12] [Eq. (1)] that correlates the MW and the

$$D = K \cdot \mathrm{MW}^{\alpha} \quad (1)$$

diffusion coefficient is particularly effective, but is restricted to a specific class of compounds.[13] The polymer community in particular has applied it to estimate the MW distribution of polymer solutions such as globular proteins,[13] oligosaccharides,[14] polyethyleneoxides,[15] and denatured peptides[16] in various solvents. Recently we developed a power law based external calibration curves (ECC) for small molecules. These ECCs facilitate the determination of accurate MWs for small molecules with different geometries, independent of NMR-specific properties and differences in temperature or viscosity.[17] Here we describe ^{1}H DOSY NMR ECC-MW determinations of LDA solvated in [D_8]toluene over a temperature range of −75 °C to 100 °C. We will show that the aggregation state of LDA is highly temperature dependent and that the trimeric and tetrameric LDAs are the most populated species in toluene solution.

LDA is polymeric in the solid state and shows little solubility in toluene. The highest concentrations that we could observe at room temperature (RT) were in the range of 7–15 mM. The ^{7}Li NMR spectra of these highly dilute LDA solutions at RT show one broad signal at 2.81 ppm.[18] In the ^{1}H NMR spectrum two sets of two main signals corresponding to the α-CH (3.12 ppm and 3.01 ppm) and CH_3 groups (1.14 ppm and 1.11 ppm) are present. A third compound was also evidenced by an additional α-CH signal at 3.19 ppm, but with very low intensity (Figure 1 A). Due to its poor intensity we were not able to determine the diffusion coefficient of this third compound at RT, but although the other two main signals at 3.12 ppm and 3.01 ppm show some overlap, we could measure their self-diffusion.

The ECC-MW results (Table 1 B) agree best with a trimer **1** in Scheme 1 ($MW_{det} = 318\ g\,mol^{-1}$, $MW_{err} = 1\,\%$) and a tetramer **2** ($MW_{det} = 390\ g\,mol^{-1}$, $MW_{err} = 9\,\%$).[19] The method employs normalized diffusion coefficients. Taking the shape of the molecules into account enables accurate MW predictions with a maximum error of ±9%. The addition of multiple internal references is not necessary. One internal reference (which can also be the solvent) is sufficient. If the solvent signal is not accessible, 16 other internal standards (aliphatics and aromatics) are available that avoid problems with signal overlap. This method is independent of NMR spectrometer parameters and variations in temperature or viscosity and hence provides an easy and robust method to determine accurate MWs.[17] Careful integration of the two signals reveals that **1** and **2** exist together in a ratio of 2:1 at +25 °C. It is also evident that dimers, like those anticipated by Kim, for example, are not present in this mixture (MW_{err} =

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[**] DOSY = diffusion-ordered NMR spectroscopy.

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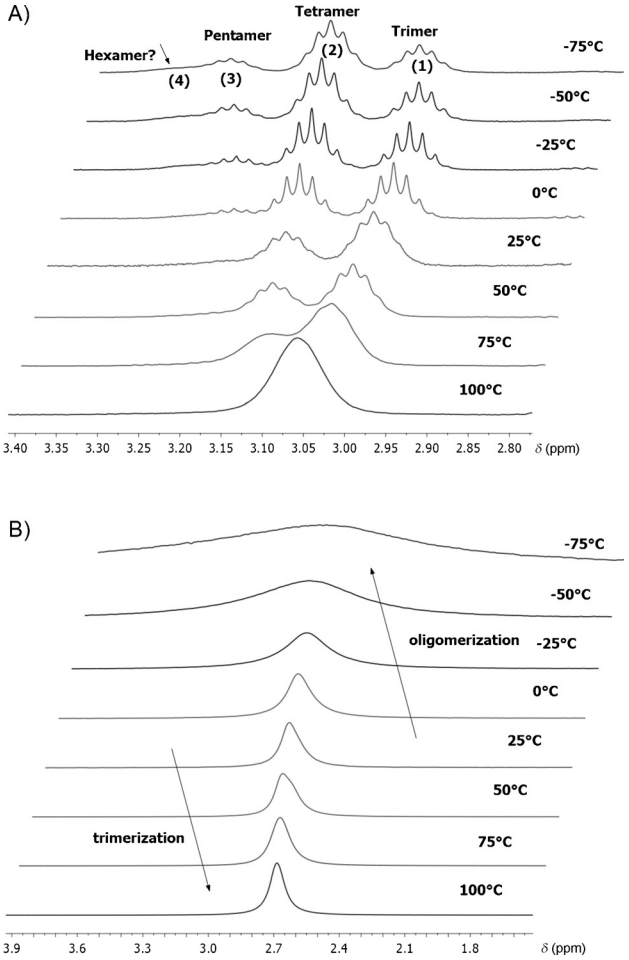

Figure 1. ^{1}H NMR spectra (A; α-CH signals) and ^{7}Li NMR spectra (B) of LDA in [D_8]toluene at various temperatures.

−48% and −82%) at any temperature. The other low-field-shifted species **3** with weak intensity has to be an aggregate larger than the tetramer. At −50 °C the integral of **3** increases significantly at the expense of **1**. The signal separation was suitable for the ECC-MW determination. Table 1 A illustrates that **3** shows the best agreement with a pentameric LDA aggregate that has a MW_{det} of 520 g mol^{-1} (MW_{err} = 3%). We were also able to estimate the MW of the residual diisopropyl amine present in solution (DA, MW = 101 g mol^{-1}, MW_{det} = 100 g mol^{-1}, MW_{err} = 1%) showing that DA does not coordinate to the oligomeric species. This result is consistent with previous investigations, which showed that DA is a very poor ligand for LDA.[3c]

At −50 °C an additional multiplet appears, which belongs to oligomer **4**, at the left-hand side of the signal attributed to the pentamer **3**. Unfortunately that signal was too weak for a MW determination. Further cooling did not improve the signal-to-noise ratio. At temperatures below −50 °C all signals decrease due to the reduced solubility of LDA in toluene.

In 1999, Rutherford and Collum showed by low-temperature ^{6}Li and ^{15}N NMR spectroscopy that the lighter congener of LDA, lithium diethyl amide (LiDEA), can exist as several oligomers in THF and oxetane solutions.[20] In neat THF or oxetane, LiDEA is a cyclic dimer. At lower concentrations of donor base, cyclic oligomers appear. At low THF concentrations (2–10 equiv) a cyclic trimer and a four-rung ladder form. Higher-order ladders were not observed within the solubility limits of LiDEA, but at substoichiometric oxetane concentrations they noticed a relatively complex LiDEA equilibrium of cyclic dimers, trimers, and ladders of tetramers, pentamers, and hexamers. According to this work and to the lithium amide ring-stacking and laddering principle,[21] the assumption that this signal from oligomer **4** stems from the LDA hexamer appears to be valid. Cooling the sample shifts the position of the oligomer equilibrium. While the tetramer concentration increases, that of the trimer decreases. Obviously low temperatures stabilize the higher aggregates due to entropy. The conversion of the trimer to the corresponding oligomers is also reflected in the ^{7}Li NMR spectrum (see Figure 1 B). The ^{7}Li signal becomes broader at lower temperature. This could be due to a relatively faster quadrupolar relaxation or due to the increase of oligomeric structures. Warming up the solution causes the opposite trend. The oligomer concentration decreases, while the trimer concentration increases.

At +50 °C a shoulder at the main ^{7}Li signal is apparent, revealing two main species: the trimer **1** and the tetramer **2**. In the ^{1}H NMR spectrum at +100 °C all signals coalesce to one set of signals at 3.06 ppm and 1.10 ppm, respectively. The ECC-MW determination estimates a MW_{det} of 333 g mol^{-1}, which best fits the trimeric LDA species **1** with an MW deviation of only −4% (Table 1 C).[22]

It is known that less bulky lithium dialkyl amides tend to form ladder structures as in the case of LiDEA.[23] Increasing the bulk of the R groups favors cyclic arrangements. Donor-

Table 1: ECC-MW determination of the LDA species **1**, **2**, and **3** in [D_8]toluene at various temperatures.[a]

		Dimer (214 g mol^{-1})	Trimer (321 g mol^{-1})	Tetramer (428 g mol^{-1})	Pentamer (536 g mol^{-1})	Hexamer (643 g mol^{-1})
	MW_{det} [g mol^{-1}]	MW_{err} [%]				
A) −50 °C						
Species **1**	332	−55	*−3*	22	38	48
Species **2**	423	−98	−32	*1*	21	34
Species **3**	520	−143	−62	−21	*3*	19
B) +25 °C						
Species **1**	318	−48	*1*	26	41	51
Species **2**	390	−82	−21	*9*	27	39
C) +100 °C						
Species **1**	333	−56	*−4*	22	38	48

[a] ECC^{TOL}_{DSE} was used to determine the MWs. The accuracy of this method is in the range of $MW_{err} \leq \pm 9\%$.[17] None of the species are in agreement with the dimer ($MW_{err} > -48\%$). The deviation was calculated by $MW_{err} = [1 - MW_{det}/MW] \times 100\%$, where MW_{det} is the experimentally determined and MW is the calculated molecular weight.

base-free lithium hexamethyldisilazide, for example, adopts a cyclic trimeric structure in the solid state[24] and exists as a cyclic tetramer–dimer mixture in hydrocarbon solvents.[25] Similarly lithium tetramethylpiperidide adopts a cyclic tetramer[26] and trimer[27] in the solid state and appears to form both cyclic oligomers in pentane.[28] In view of this trend and the infinite helical arrangement in the crystal structure,[2] we think that LDA is bulky enough to avoid ladder formation. A cyclic arrangement is more likely for the main LDA oligomers.

The ECC-MW determination provides a reliable and straightforward indication of the degree of aggregation of organometallic compounds in solution. In this article we showed that at room temperature LDA in toluene forms trimeric and tetrameric aggregates in a 2:1 ratio. This equilibrium mixture ranges from trimers and tetramers through pentamers to higher oligomers as the temperature decreases. The lower the temperature, the closer the solution structure approaches the solid-state structure.

Experimental Section

Donor-base-free LDA: Diisopropyl amine (15.58 g, 0.15 mol, 1.07 equiv) was dissolved in in 150 mL pentane. At 0 °C *n*-buthyllithium (5.64 mol L^{-1}, 25 mL, 0.14 mol, 1.00 equiv) was added dropwise to the solution. After 20 min the reaction mixture was warmed up to RT and then stirred for 1 h. The reaction mixture was then slowly cooled down to −78 °C. After 3 h the mother liquor was removed via a syringe. Finally the solvent was evaporated at RT under vacuum (ca. 6 h) to afford LDA as a white solid (10.41 g, 0.10 mol, 71 %).

[D_8]Toluene (Aldrich) was stored over 4 Å molecular sieves under argon. The NMR samples were prepared by dissolving base-free LDA and the DOSY reference adamantane (ADAM) in an equimolar ratio (each 15 mM) in [D_8]toluene. The diffusion coefficients of the LDA species were normalized to the fixed diffusion value of the reference ADAM ($\log D_{ref,fix}(ADAM) = -8.8454$; for more information see the Supporting Information). NMR spectra were recorded on a Bruker Advance 400 spectrometer equipped with an obverse broadband probe with *z*-axis gradient coil having a maximum gradient strength of 57 G cm^{-1}. All spectra were acquired using 5 mm NMR tubes, which were not spinning during the measurements. All DOSY experiments were performed using a double-stimulated echo sequence with bipolar gradient pulses and three spoil gradients with convection compensation (dstebpgp3s).[29] The duration of the magnetic field pulse gradients was adjusted for every temperature in a range of $\delta/2 = 400$–3500 µs. The diffusion time was $\Delta = 0.1$ s. The delay for gradient recovery was 0.2 ms and the eddy current delay 5 ms. In each PFG NMR experiment, a series of 16 spectra on 32 K data points were collected. The pulse gradients were incremented from 2 to 98 % of the maximum gradient strength in a linear ramp. The air flow was set at 400 L h^{-1} in order to avoid any temperature fluctuations. After Fourier transformation and baseline correction, the diffusion dimension was processed with the Topspin 3.1 software. Diffusion coefficients, processed with a line broadening of 2 Hz, were calculated by Gaussian fits with the T1/T2 software of Topspin.

Keywords: aggregation · lithium amides · NMR spectroscopy · reactive intermediates

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