

Diffusion-Ordered NMR Spectroscopy (DOSY) of THF Solvated *n*-Butyllithium Aggregates

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Organolithium reagents have been used extensively in synthetic organic chemistry. Considerable amount of work has been done on the structural characterization of organolithium aggregates such as *n*-butyllithium (*n*-BuLi).¹ In particular, NMR spectroscopy has been an invaluable tool in determining the solution structures of aggregates of this common reagent. Experiments based on scalar coupling,² the Overhauser effect,³ and chemical exchange⁴ were adapted to organolithium aggregates. An NMR technique not previously utilized in the field of organolithium chemistry is diffusion ordered NMR,⁵ although it has been applied to transition metal coordination complexes⁶ and Seebach has recently used this technique to demonstrate the existence of a copper catalyst in solution.⁷ Direct information on aggregate size in solution was hitherto derived from colligative property measurements, such as cryoscopy.^{1e,8} We are intrigued by the possibility of expanding the wealth of information available by NMR spectroscopy with the application of diffusion ordered NMR techniques to a variety of organolithium reagents in solution.

To establish the usefulness of these NMR experiments, our initial studies focused on *n*-BuLi in THF solution, as it is easily accessible and its solution structure is well characterized. *n*-BuLi

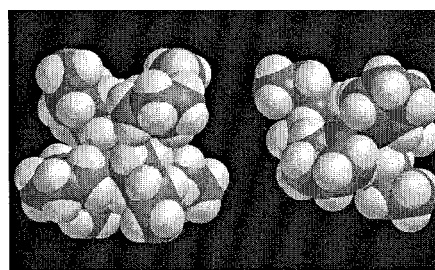


Figure 1. PM3 optimized structures of $[n\text{-BuLi}]_4\cdot\text{THF}_4$ and $[n\text{-BuLi}]_2\cdot\text{THF}_4$.

Table 1. Calculated and Measured Diffusion Coefficients for THF Solvated *n*-BuLi Aggregates at $-84\text{ }^\circ\text{C}$ ($\times 10^{11}\text{ m}^2\text{ s}^{-1}$)

	calculated		experimental ^a	
	X-ray	PM3	¹ H	⁷ Li
tetramer	8.89	8.54	8.83 ± 0.45	8.63 ± 0.06
dimer	9.94 ^b	9.53	10.11 ± 0.28	n.d. ^c
diff (%)	10.6	10.4	13.2 ± 2.2^d	

^a Average of four experiments. Errors reported are three standard deviations. ^b TMEDA solvated aggregate. ^c Not determined. ^d Determined directly from experimental data.

was shown to exist in equilibrium between tetrasolvated dimeric and tetrasolvated tetrameric aggregates in THF solutions by NMR spectroscopy^{1a–d} and cryoscopy.^{1e} The solid-state structures of the tetrameric aggregate and a TMEDA solvated dimer have also been determined by X-ray crystallography.⁹

We wish to report that it is possible to distinguish these aggregates in THF solution by diffusion ordered NMR spectroscopy. The theoretical diffusion coefficients of the *n*-BuLi aggregates were calculated¹⁰ based on the available crystal structures, as well as gas-phase structures optimized at the PM3 semiempirical level (Figure 1),¹¹ to evaluate the feasibility of diffusion ordered NMR studies (Table 1). The calculated diffusion coefficients predicted a small but measurable difference in diffusion rates.

The ¹H NMR spectrum of a 0.2 M *n*-BuLi solution in THF-*d*₈ at $-84\text{ }^\circ\text{C}$ shows two resolved multiplets in the upfield region at -1.00 and -1.12 ppm. These resonances are assigned to the $\alpha\text{-CH}_2$ groups in the tetrameric and dimeric aggregates, respectively.^{1b} 2D-TOCSY experiments allowed the assignment of all other, partially resolved, butyl resonances. The ⁷Li spectrum shows two major resonances, a sharp singlet at 1.42 ppm ($w_{1/2} = 3.5$ Hz) and a broad singlet at 1.83 ppm ($w_{1/2} = 12.7$ Hz). These resonances are assigned to the tetrameric and dimeric aggregates, respectively.^{1b} ⁷Li EXSY spectra indicated that interaggregate lithium exchange is slow under the experimental conditions.

Diffusion ordered NMR experiments were performed with ¹H and ⁷Li detection. A double stimulated echo (DSTE) sequence¹² with longitudinal eddy current delay¹³ (LED) was used, to

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(10) The theoretical diffusion coefficients were calculated from the Stokes–Einstein equation: $D = (k_B T) / (6\pi\eta r)$, where D is the diffusion coefficient, k_B is the Boltzmann constant, T is the temperature in Kelvin, η is the viscosity of the solution, and r is the radius of the molecular sphere. Molecular volumes, including coordinating solvent molecules, were used to calculate molecular radii. The viscosity of neat THF was used. Hogen-Esch, T. E.; Smid, J. *J. Am. Chem. Soc.* **1966**, *88*, 318.

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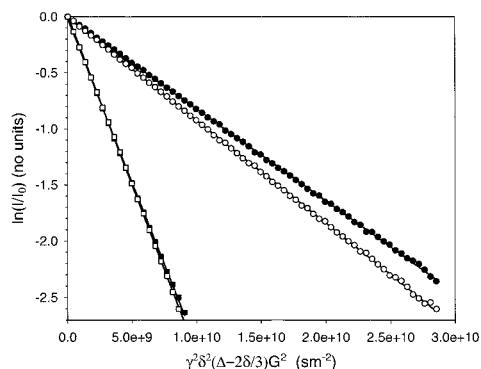


Figure 2. ^1H PFG-DSTE NMR of *n*-BuLi in THF- d_8 at -84 °C. A typical Stejskal-Tanner plot of experimental peak areas: THF- d_7 (α -CDH), \blacksquare ; THF- d_7 (β -CDH), \bullet ; tetramer (butyl αCH_2 -1.00 ppm), \bullet ; and dimer (butyl αCH_2 -1.12 ppm), \circ . The solid lines represent linear least-squares fits to the data.

suppress convection artifacts.¹⁴ For ^1H -detected experiments, the residual THF signals (3.58, 1.76 ppm) and the resonances assigned to the butyl $\alpha\text{-CH}_2$ groups in the tetrameric (-1.00 ppm) and dimeric (-1.12 ppm) aggregates were integrated. In ^7Li -detected experiments the signal of the tetrameric aggregate was integrated. The ^7Li signal of the dimeric aggregate could not be observed in the DSTE experiments due to its short T_1 relaxation time. The diffusion coefficients were determined by fitting¹⁵ the peak areas to the Stejskal-Tanner equation^{4a,12,16} (Figure 2, Table 1). The relative diffusion rate of dimeric and tetrameric *n*-BuLi was also determined from experimental data¹⁷ (Figure 3).

The experimental diffusion coefficients are close to the theoretical values. Diffusion coefficients determined from ^1H - and ^7Li -detected experiments were insensitive to experimental parameters and in good agreement with each other. The measured diffusion coefficients varied with exact sample composition by up to 12%, but the relative rates of diffusion were within 5% over all samples. As expected, tetrameric *n*-BuLi diffuses slower than the dimeric aggregate and both aggregates diffuse much slower than THF. We note that the large difference between the diffusion coefficients of the aggregates and solvent can be exploited to suppress solvent signals in ^1H spectra of lithium aggregates by size-resolved NMR spectroscopy.¹⁸

Experimental datasets were also processed¹⁹ and presented in a 2D Diffusion Ordered Spectroscopy (DOSY) form²⁰ (Figure

(14) NMR spectra were collected on a Bruker DRX-400 instrument equipped with an Accustar z -axis gradient amplifier, operating at 400.13 MHz for ^1H observation, and a QNP probe with a z -axis gradient coil. ^1H spectra were referenced to the residual signals of THF- d_7 at 1.76, as an internal standard. ^7Li spectra were referenced to 0.3 M LiBr in D_2O at 25 °C as an external standard. Sample temperature was calibrated with a standard methanol sample. The DSTE-LED experiments were performed with a spectral width of 2400 Hz and 4k complex data points. 16 to 64 transients were collected for each gradient value. Sinusoidal gradients were used with total durations of 2.5 to 5 ms. The gradient strength was varied between 0.007 and 0.327 T/m in 16 to 128 square spaced increments. Diffusion times were between 0.6 and 1 s. Eddy current delay was 3 to 10 ms. Data processing was accomplished with XWINNMR 2.6 (Bruker GmbH).

(15) Linear least-squares fit. SigmaPlot for Windows 4.01, SPSS Inc.

(16) $\ln(I/I_0) = -[\gamma^2 \delta^2 G^2 (\Delta - \delta/3)]D$, where I is the peak area, I_0 is the peak area in the absence of gradients, γ is the magnetogyric ratio of the observed nucleus, δ is the gradient duration, G is the strength of the gradient pulse in T/m, Δ is the diffusion time and D is the diffusion coefficient.

(17) $\ln(I^T/I_0^T)/\ln(I^D/I_0^D) = (D^T/D^D)$, where the T superscript denotes the tetramer and D denotes the dimer.

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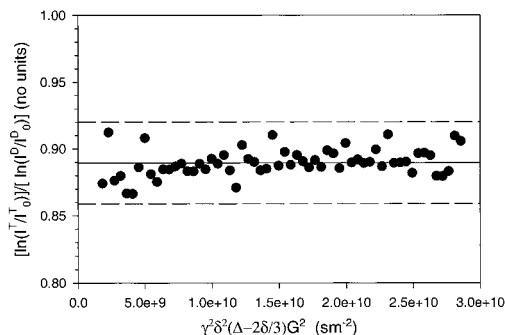


Figure 3. ^1H PFG-DSTE NMR of *n*-BuLi in THF- d_8 at -84 °C. A typical plot for measuring relative diffusion rates. The solid line is the mean and dashed lines are three standard deviations.

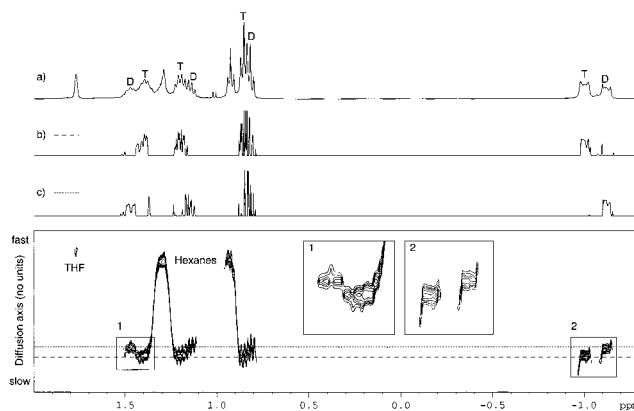


Figure 4. 2D diffusion ordered ^1H spectrum (DOSY) of *n*-BuLi in THF- d_8 at -84 °C. (a) ^1H spectrum at 187 K, the labeled butyl resonances of dimeric (D) and tetrameric (T) *n*-BuLi were assigned by 2D-TOCSY. (b) Slice of the 2D DOSY spectrum at the diffusion coefficient of the tetramer (---). (c) Slice of the 2D DOSY spectrum at the diffusion coefficient of the dimer (-)

4). The resolved α and partially resolved β and γ CH_2 groups in the dimer are centered at a higher diffusion coefficient value than the corresponding peaks in the tetrameric aggregate. Slices taken at the diffusion coefficients of the aggregates agree well with their respective ^1H spectra. The CH_3 peaks that are not resolved in the NMR spectrum are not resolved in the diffusion dimension either. The aggregates are very well separated from hexanes and THF.

To the best of our knowledge, this is the first successful application of diffusion-ordered NMR (DOSY) to distinguish different organolithium aggregates in solution. We are currently pursuing the application of this methodology to the study of other organolithium reagents in solution.

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Supporting Information Available: ^1H , TOCSY, and ^7Li spectra of *n*-BuLi at -84 °C and representative stack plots of ^1H and ^7Li detected DSTE experiments (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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