1H Pure Shift DOSY: a Handy Tool to Evaluate the Aggregation and Solvation of Organolithium Derivatives

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Experimental Section

Preparation of the sample

All syntheses and sample preparations of air-sensitive compounds were performed in an argon atmosphere. All solvents were dried over sodium, and degassed in a vacuum system before being used.

Preparation of \textit{n}-Butyllithium Solution in Tetrahydrofuran-$d_8$

A solution of commercial \textit{n}-butyllithium in pentane (1 mL) was syringed in a tube fitted with a septum and flushed under dry argon. The tube was then placed under vacuum (20 mmHg) for 2 h to remove the main part of the pentane. Freshly distilled tetrahydrofuran-$d_8$ was then added (1 mL) at $-78 \, ^\circ\text{C}$ to the resulting concentrated solution, and the resulting solution was titrated$^1$.

Preparation of LDA/\textit{n}-BuLi/\textit{n}-BuOLi with internal references:

Freshly distilled diisopropylamine (0.14 mL) dissolved in THF (0.3 mL) was introduced into an NMR tube placed under argon. The solution (0.34M) was treated first with an equimolar amount of \textit{n}-BuLi ($c = 1 \text{M}$) in THF at 185K. The quantitative formation of the amide was controlled by 1D $^1\text{H}$ and $^6\text{Li}$ NMR experiments. Then, two equivalents of \textit{n}-BuLi were added into the solution. A second step consisted of the progressive addition of \textit{n}-BuOH into the LDA/\textit{n}-BuLi mixture until a (1: 2: 0.9) ratio was reached. Then 0.15 mL from a mixture containing SQA (0.1 mL), CDDE (0.1 mL) and TPB (30 mg) preliminarily diluted in THF-$d_8$ (5 mL) was added to the above sample as internal references for the DOSY experiments.

Preparation of \textit{n}-BuLi/\textit{n}-BuOLi with internal references:

Controlled aliquots of \textit{n}-BuOH were added to the solution of pure \textit{n}-BuLi ($c = 1 \text{M}$) until a (1:0.66) ratio was reached. Then 0.15 mL from a mixture containing SQA (0.1 mL), CDDE (0.1 mL) and TPB (30 mg) preliminarily diluted in THF-$d_8$ (5 mL) was added to the above sample as internal references for the DOSY experiments.

NMR parameters and conditions

NMR spectra were recorded at 185K on a Bruker AVIII 500 spectrometer operating at 500.13 MHz for $^1\text{H}$, 194.40 MHz for $^7\text{Li}$, 125.13 MHz for $^{13}\text{C}$ and 73.60 MHz for $^6\text{Li}$. Experiments were run under TopSpin (version 2.1, Bruker Biospin, Karlsruhe) with a BBFO \{4H,X\} probe and a z gradient coil giving a maximum gradient of 50 G.cm$^{-1}$.
$^1$H DOSY experiments was acquired with the standard Bruker ledbpgp2s program\(^2\) using 16 \(t_1\) increments of 32 transients. The acquisition time was 1 s and the relaxation delay was 2.5 s (D1). Diffusion time was between 0.5 and 0.6 s (D20) and rectangular gradient pulse duration was between 1.5 and 2 ms (P30). Gradient recovery delays of 150 \(\mu s\) followed the application of each gradient pulse. Data was accumulated by linearly varying the diffusion encoding gradients over a range from 2 to 95\% for 16 gradient increment values.

$^7$Li DOSY experiment was acquired with the standard Bruker dstebpgp3s program\(^3\) using double stimulated echo, LED, with bipolar gradient pulses and 3 spoil gradients for 16 \(t_1\) increments of 32 transients. The acquisition time was 2.5 s, and the relaxation delay (D1) was 5 s. Diffusion time was 0.9 s (D20) and rectangular gradient pulse duration was 4 ms (P30). Gradient recovery delays of 150 \(\mu s\) followed the application of each gradient pulse. Data was accumulated by linearly varying the diffusion encoding gradients over a range from 2 to 95\% for 16 gradient increment values.

$^1$H PS-DOSY\(^4\) experiments were acquired with the sequence of Figure 1 with one stimulated echo using a 20 ms Rsnob selective pulse with 100 Hz bandwidth, with Gz2=1.8 G.cm\(^{-1}\); 16 \(t_1\) increments of 32 transients were acquired with 1/SW = 20 ms in a total time of 5 h. Coherence transfer selection gradient pulses were rectangular with a width of 1 ms and the amplitudes Gz1a, G z1b, and G z1c of 25, -25, and -50 G.cm\(^{-1}\). The delays \(\tau_a\) and \(\tau_b\) were 0.0038 s and 0.0029 ms, respectively. Individual rows of the pseudo-2-D diffusion databases for PS-DOSY were phased and baseline corrected. Diffusion time was between 0.25 - 0.4 s and rectangular gradient pulse duration was between 2 - 2.5 ms. Gradient recovery delays were 150 \(\mu s\) followed the application of each gradient pulse. Data was accumulated by linearly varying the diffusion encoding gradients over a range from 2 to 95\% for 16 gradient increment values.

**DOSY processing**

$^1$H DOSY experiments were processed using DOSYm\(^®\) software which is based on Gif MaxEnt algorithm proposed by Marc-Andre Delsuc\(^5\).

$^1$H PS-DOSY experiments were processed using dynamic center software (Bruker software). This program allows the use of the pure exponential equation for relevant processing methods:

\[
S(g) = I_0 \exp \left( -\gamma^2 \cdot g^2 \cdot \delta^2 \cdot (\Delta - \delta/3) \cdot D \right)
\]

The diffusion coefficient was determined by fitting the peak areas to the Stejskal-Tanner equation from \(T_1/T_2\) analysis.
Figure S1. $^1$H Pure Shift DOSY sequence
Figure S2. $^6$Li (left) and $^1$H (right) spectra of LDA/$n$-BuLi mixtures in THF-$d_8$ at 185K: (a) pure LDA (0.34M), b) LDA/$n$-BuLi (1 : 0.66) ; (c) LDA/$n$-BuLi/ (1 : 1.33) d) LDA/$n$-BuLi/ (1 : 2)
Figure S3. 2D $^6$Li-$^1$H HOESY spectrum (mixing times $\tau_m=860$ ms) for LDA/$n$-BuLi (1 : 2) in THF-$d_8$ at 185K
Figure S4. $^6$Li (left) and $^1$H (right) spectra of LDA/$n$-BuLi/$n$-BuOH mixtures in THF-$d_8$ at 185K: (a) pure LDA (0.34M), b) LDA/$n$-BuLi (1 : 2) ; (c) LDA/$n$-BuLi/$n$-BuOH (1 : 2 : 0.9)
Figure S5. (a) $^1$H DOSY spectrum for LDA/$n$-BuLi/$n$-BuOH (1 : 2 : 0.9) in THF-$d_8$ at 185K with internal references (Butane, Cyclododecene (CDDE), Squalene (SQA), 1,3,5-Triphenylbenzene (TPB). (b) Zoom of alpha methylene region

Figure S6. Log(D)-Log(FW) analysis of $^1$H DOSY spectrum for LDA/$n$-BuLi/$n$-BuOH (1 : 2 : 0.9)
Figure S7. Log(D)-Log(FW) analysis of $^1$H PS-DOSY spectrum for LDA/$n$-BuLi/$n$-BuOH (1 : 2 : 0.9)
Figure S8. $^6$Li (left) and $^1$H (right) spectra of $n$-BuLi/$n$-BuOLi mixtures in THF-$d_8$ at 185K: (a) pure $n$-BuLi; (b) $n$-BuLi/$n$-BuOLi (1 : 0.25); (c) $n$-BuLi/$n$-BuOLi (1 : 0.66)
Figure S9. $^6$Li (a) and $^7$Li (b) spectra of $n$-BuLi/$n$-BuOLi mixture (1 : 0.66) in THF-$d_8$ at 185K

Figure S10. $^7$Li DOSY spectrum for $n$-BuLi/$n$-BuOLi (1 : 0.66) in THF-$d_8$ at 185K
Figure S11. $^1$H DOSY spectrum for $n$-BuLi/$n$-BuOLi (1 : 0.66) in THF-$d_8$ at 185K with internal references (Butane, Cyclododecene (CDDE), Squalene (SQA), 1,3,5-Triphenylbenzene (TPB)). (b) Zoom for alpha methylene region

Figure S12. Log(D)-Log(FW) analysis of $^1$H DOSY spectrum for $n$-BuLi/$n$-BuOLi (1 : 0.66)
Figure S13. $^1$H (a) and $^1$H PS (b) spectra of $n$-BuLi/$n$-BuOLi mixture (1 : 0.66) in THF-$d_8$ at 185K
Figure S14. (a) $^1$H PS-DOSY spectrum for $n$-BuLi/$n$-BuOLi (1 : 0.66) in THF-$d_8$ with internal references (CDDE, SQA, TPB). (b) Zoom for alpha methylene region.

Figure 15. Log(D)-Log(FW) analysis of $^1$H PS-DOSY spectrum for $n$-BuLi/$n$-BuOLi (1 : 0.66)

\[ y = -0.5236x - 9.7988 \]
\[ R^2 = 0.9814 \]
Figure S16. Signal attenuation curves from $^1$H PS-DOSY of (a) THF, (b) CDDE, (c) TPB (d) SQA

Figure S17. Signal attenuation curves from $^1$H PS-DOSY of (a) $(n$-BuLi)$_4$, (b) $(n$-BuLi)$_3(n$-BuOLi)$_1$, (c) $(n$-BuLi)$_2$, (d) $(n$-BuLi)$_2(n$-BuOLi)$_2$
Table S1. Analysis of \(^1\text{H}\) DOSY results for \(n\)-BuLi \(/n\)-BuOLi (1 : 0.66) in THF-\(d_8\) (FW*: Theoretical mass of solvated specie)

<table>
<thead>
<tr>
<th>Compounds</th>
<th>FW (gmol(^{-1}))</th>
<th>Log(D) m(^2).s(^{-1})</th>
<th>N*THF</th>
<th>FW* (gmol(^{-1}))</th>
<th>Error %</th>
</tr>
</thead>
<tbody>
<tr>
<td>THF</td>
<td>64</td>
<td>3.5330</td>
<td>72</td>
<td>72</td>
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<tr>
<td>Squalene (SQA)</td>
<td>411</td>
<td>3.4959</td>
<td>411</td>
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<td></td>
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<tr>
<td>Triphenylbenzene (TPB)</td>
<td>306</td>
<td>3.5011</td>
<td>306</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclododecene (CDDE)</td>
<td>166</td>
<td>3.5140</td>
<td>166</td>
<td></td>
<td></td>
</tr>
<tr>
<td>((n\text{-BuLi})_4) (\bullet) (THF)(_4)</td>
<td>477.4</td>
<td>3.4925</td>
<td>(\sim) 4</td>
<td>544</td>
<td>6.5%</td>
</tr>
<tr>
<td>((n\text{-BuLi})_3(n\text{-BuOLi})_1) (\bullet) (THF)(_4)</td>
<td>440.1</td>
<td>3.4941</td>
<td>(\sim) 3</td>
<td>560</td>
<td>12%</td>
</tr>
<tr>
<td>((n\text{-BuLi})_2(n\text{-BuOLi})_2) (\bullet) (THF)(_4)</td>
<td>425.9</td>
<td>3.4948</td>
<td>(\sim) 2</td>
<td>576</td>
<td>15%</td>
</tr>
</tbody>
</table>

Table S2. Analysis of \(^1\text{H}\) DOSY results for LDA/\(n\)-BuLi/\(n\)-BuOH (1 : 2 : 0.9) (FW*: Theoretical mass of solvated specie)

<table>
<thead>
<tr>
<th>Compounds</th>
<th>FW (g.mol(^{-1}))</th>
<th>Log(D) m(^2).s(^{-1})</th>
<th>N*THF</th>
<th>FW* (g.mol(^{-1}))</th>
<th>Error %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Butane</td>
<td></td>
<td>3.3910</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>THF</td>
<td>72</td>
<td>3.3706</td>
<td>72</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclododecene (CDDE)</td>
<td>166</td>
<td>3.3331</td>
<td>411</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triphenylbenzene (TPB)</td>
<td>306</td>
<td>3.3003</td>
<td>306</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Squalene (SQA)</td>
<td>411</td>
<td>3.2930</td>
<td>166</td>
<td></td>
<td></td>
</tr>
<tr>
<td>((\text{LDA})_2) (\bullet) (THF)(_2)</td>
<td>304</td>
<td>3.3040</td>
<td>2</td>
<td>358</td>
<td>4.5%</td>
</tr>
<tr>
<td>((\text{LDA})(n\text{-BuLi})_2) (\bullet) (THF)(_2)</td>
<td>309</td>
<td>3.3031</td>
<td>2</td>
<td>315</td>
<td>1%</td>
</tr>
<tr>
<td>((n\text{-BuLi})_4) (\bullet) (THF)(_4)</td>
<td>507</td>
<td>3.2780</td>
<td>4</td>
<td>544</td>
<td>3.5%</td>
</tr>
</tbody>
</table>

Table S3. Analysis of \(^1\text{H}\) PS-DOSY results for \(n\)-BuLi \(/n\)-BuOLi (1 : 0.66) in THF-\(d_8\) (FW*: Theoretical mass of solvated specie)

<table>
<thead>
<tr>
<th>Compounds</th>
<th>FW (gmol(^{-1}))</th>
<th>Log(D) m(^2).s(^{-1})</th>
<th>N*THF</th>
<th>FW* (gmol(^{-1}))</th>
<th>Error %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Squalene (SQA)</td>
<td>411</td>
<td>-11.16</td>
<td>411</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triphenylbenzene (TPB)</td>
<td>306</td>
<td>-11.09</td>
<td>306</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclododecene (CDDE)</td>
<td>166</td>
<td>-11.00</td>
<td>166</td>
<td></td>
<td></td>
</tr>
<tr>
<td>THF</td>
<td>72</td>
<td>-10.76</td>
<td>166</td>
<td></td>
<td></td>
</tr>
<tr>
<td>((n\text{-BuLi})_4) (\bullet) (THF)(_4)</td>
<td>566</td>
<td>-11.24</td>
<td>(\sim) 4</td>
<td>544</td>
<td>2%</td>
</tr>
<tr>
<td>((n\text{-BuLi})_3(n\text{-BuOLi})_1) (\bullet) (THF)(_4)</td>
<td>579</td>
<td>-11.25</td>
<td>(\sim) 4</td>
<td>560</td>
<td>1.7%</td>
</tr>
<tr>
<td>((n\text{-BuLi})_2) (\bullet) (THF)(_4)</td>
<td>490</td>
<td>-11.21</td>
<td>(\sim) 4</td>
<td>416</td>
<td>8.2%</td>
</tr>
<tr>
<td>((n\text{-BuLi})_2(n\text{-BuOLi})_2) (\bullet) (THF)(_4)</td>
<td>612</td>
<td>-11.26</td>
<td>(\sim) 4</td>
<td>576</td>
<td>3%</td>
</tr>
</tbody>
</table>
References


