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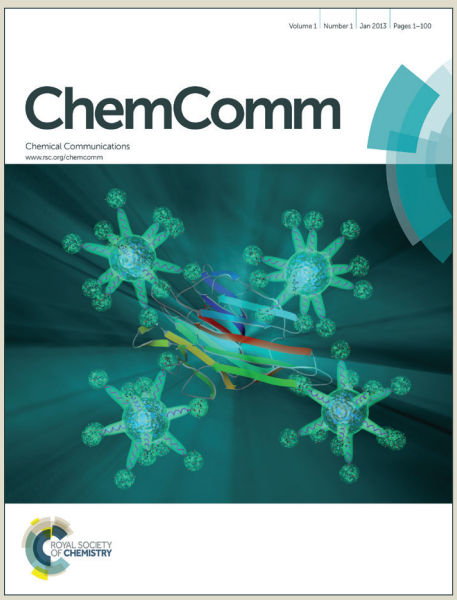

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ARTICLE

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

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Determining the structure and solvation states of organolithium aggregates in complex solution remains a challenging task. Here, we show that ^{1}H Pure Shift DOSY NMR provides better resolution spectra without overlapping, even for complex solutions of mixed aggregates of *n*-BuLi/*n*-BuOLi. This ensures the direct observation of the apparent diffusion constant for each component in the solution and therefore allows a fast assignment of aggregation states, and solvation degree.

Alkyllithium compounds in solution most often afford dynamic mixtures of rapidly reorganizing species differing by their aggregation state and their solvation degree. Access to this information is crucial since it helps to understand and master their reactivity as bases or nucleophiles[1]. The modern structural determination of organolithium clusters in solution is often based on NMR spectroscopy[2–5].

Diffusion ordered spectroscopy (DOSY), recently introduced to organometallic chemistry, has been established as an efficient method for the identification of formula weights and particle size estimation in complex mixtures[6,7]. Williard et al.[8] have shown the value of ^{1}H-DOSY to discriminate different aggregates of organolithium compounds in solution.

It is recognized that alkyllithium compounds can react with oxygen to give peroxides, and subsequently alkoxides[9,10]. Noteworthy is the fact that commercially available solutions of organolithium can contain significant amounts of lithium alkoxides from oxygen contamination during handling. Together with the alkyllithium, these undesired species form alkyllithium/lithium alkoxide mixed aggregates which often have different and usually greater reactivity than the original alkyllithium compound[11]. This type of mixed aggregate is of interest for several reasons: they have been exploited in numerous applications such as polymerization[12] and asymmetric synthesis[13]. So, investigating the structure, and degree of solvation, of alkyllithium/lithium alkoxide mixed aggregates is important for a better understanding of their reactivity[14] and to reformulate our thinking about the relationship of this parameter to solvation and aggregation.

Our continuous experience in the field[15] leads us to report here on the usefulness of ^{1}H Pure Shift DOSY (^{1}H PS-DOSY) NMR for the characterization and quantitative estimation of aggregation state and solvation degree of various complexes of *n*-BuLi in THF, pure or mixed with alkoxides. This study, in line with the pioneering work of McGarrity[11] on *n*-BuLi/*n*-BuOLi combinations, ultimately aims at a better understanding of the solvation effects on aggregation states for this system.

The ^{1}H NMR spectrum of a THF solution of "regular" (not sublimed) *n*-butyllithium displays two major multiplets at -0.97 ppm and -1.10 ppm, corresponding to protons on a lithiated carbon (Fig. 1a), as accepted in literature[11]. The corresponding ^{6}Li spectrum at natural abundance also exhibits two major singlets at 1.93 and 1.52 ppm. One weak unidentified signal appeared at ≈ 0.81 ppm, the intensity of which depended on the presence of traces of oxygen in the solution. This latter signal was thus assigned to a lithium butoxide or butylperoxide. Accordingly, when a solution of butyl alcohol (0.2 eq) was added (Fig. 1b), the peak at 0.81 ppm increases and three other resonances appeared at 1.59 ppm, 0.94 ppm and 0.31 ppm. The corresponding ^{1}H spectrum in the region of the α-CH_2 methylene was difficult to analyse at this stage since it featured a broad signal corresponding to several species.

As further aliquots of butyl alcohol were added (Fig. 1c,d), the intensity of the new peaks in the ^{6}Li spectra increased at the expense of the others. This corresponds to the successive replacement of alkyl groups by alkoxy groups in the tetrameric *n*-butyllithium structure, according to equations (1-3):

$$3Bu_4Li_4. + Li_4(OBu)_4 \quad \rightleftharpoons \quad 4Bu_3Li_4OBu \quad (1)$$
$$2Bu_3Li_4OBu + Li_4(OBu)_4 \rightleftharpoons 3Bu_2Li_4(OBu)_2 \quad (2)$$
$$Bu_2Li(OBu)_2 + Li_4(OBu)_4 \rightleftharpoons 2BuLi_4(OBu)_3 \quad (3)$$

The details of the mixed aggregation of these species have been clearly described by McGarrity[11] using proton NMR spectroscopy, but little is known about their solvation degree.

The purpose of this work was to use high resolution DOSY to measure apparent diffusion coefficients of *n*-BuLi/*n*-BuOLi aggregates in solution. Consequently, the formula weight (FW) and therefore the solvation degree and the aggregation states of all reactive intermediates may be determined.[16,17]

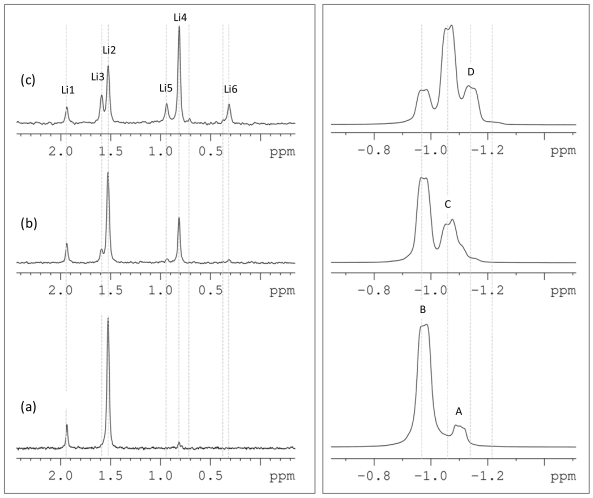


Fig. 1 ^{6}Li (left) and 'H (right) spectra of *n*-butyllithium-lithium butoxide mixtures in THF-d_8 at 185K: (a) pure *n*-BuLi ; (b) *n*-BuLi/*n*-BuOLi (1:0.25) ; (c) *n*-BuLi/*n*-BuOLi (1:0.66)

^{1}H DOSY NMR experiments were run in an *n*-BuLi/*n*-BuOLi (1:0.66) solution. However, due to the similar structures of mixed aggregates of $(n\text{-BuLi})_x/(n\text{-BuOLi})_{4-x}$ in solution and the harsh analysis conditions that require low temperatures limiting the exchange processes, poorly resolved ^{1}H spectra were obtained with overlapping and broad peaks, hence leading to major difficulties in determining the diffusion coefficient in ^{1}H DOSY experiment (Fig. S11).

On the other hand, the ^{6,7}Li spectrum provides better resolution, a relatively wide chemical shift range and an absence of homo-nuclear couplings (Fig. S10). Even if these conditions seem optimal to determine the aggregation state and the solvation degree in ^{6,7}Li DOSY NMR experiments, the lower gyromagnetic value of ^{6,7}Li and the exchange processes (making the use of lithiated internal reference difficult) led us to look for an alternate method, ideally more efficient, accurate and easier to assign.

To come back to ^{1}H DOSY, the extensive overlapping of ^{1}H spectra, even at the highest fields, remains a serious problem despite the methodological developments in processing methods. The key issue is the multiplet structure due to homo-nuclear scalar $J_{H\text{-}H}$ couplings; if the multiplet structure could be suppressed, the density of signals in a spectrum would typically decrease by almost one order of magnitude, with each multiplet collapsing down to one single line at the appropriate chemical shift. Then, it may be possible to avoid the use of an inverse Laplace transform by using a simple mono-exponential fit.

Recently, an elegant method "Pure Shift" was introduced to obtain homo-nuclear decoupled proton spectra.[18,19] This technique can be readily extended to a DOSY experiment[19], providing fully resolved signals in the spectral dimension, thus warranting high resolution in the "Pure Shift DOSY" diffusion dimension.

Encouraged by our recent successful applications of diffusion coefficient-formula weight (logD-logFW) correlation analysis to the determination of the solvation and aggregation states of organolithium compounds,[15] we decided to apply this ^{1}H Pure Shift-DOSY (^{1}H PS-DOSY) technique to the model case of *n*-BuLi/*n*-BuOLi aggregates in THF.

The ^{1}H PS-DOSY spectrum of *n*-BuLi/*n*-BuOLi in THF-d_8 using four classical internal references (Squalene (SQA), Triphenylbenzene (TPB), Cyclododecene (CDDE) and Lithium diisopropylamide LDA showed an efficient separation of eight components that were clearly identified in the diffusion dimension (Fig. 2). Additional NMR measurements carried out on solution of LDA/*n*-BuLi, performed in the same conditions as regards the solvent, concentration and temperature than the solution under study, were used to show that LDA is present in the solution as a homogeneous dimer $(LDA)_2{\bullet}THF_c$ and unknown mixed aggregates $(LDA)_a/(n\text{-BuLi})_b{\bullet}THF_c$ (Fig. S2). First, we established a good calibration line (r^2 = 0.99) by plotting the logarithm of the diffusion coefficient values of the references, measured from the ^{1}H PS-DOSY experiment versus the logarithm of their formula weight (Fig. S7). This graph led to an accurate formula weight prediction for the disolvated homodimers of LDA (FW = 312), in accord with the literature[20]. Thus, the unknown molecular weight of $(LDA)_a/(n\text{-BuLi})_b{\bullet}THF_c$ and $(n\text{-BuLi})_a/(n\text{-BuOLi})_b{\bullet}[THF]_c$ could be evaluated by a simple extrapolation.

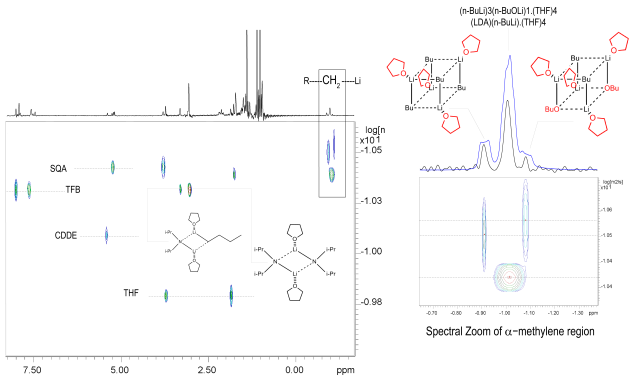


Fig. 2 ^{1}H PS-DOSY NMR spectrum of LDA/*n*-BuLi/*n*-BuOH (1:2:0.9) in THF-d_8 with internal references (TPB, SQA, LDA, CDDE) at 185K.

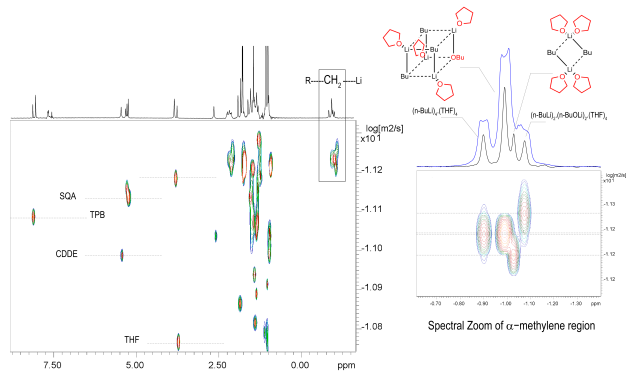


Fig. 3 ^{1}H PS-DOSY NMR spectrum of *n*-BuLi/*n*-BuOLi (1:0.66) in THF-d_8 with internal references (TPB, SQA, CDDE) at 185K.

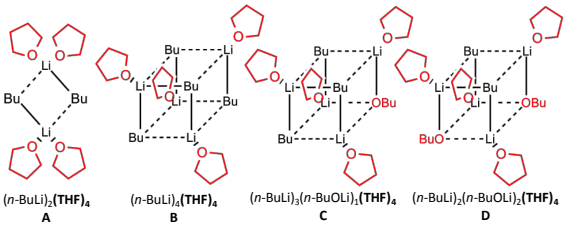
In increasing order of diffusion coefficient, the ^{1}H PS-DOSY experiment suggested the presence of a tetrasolvated mixed tetramer (*n*-BuLi)$_2$/(*n*-BuOLi)$_2$·THF$_4$ (FW=589), tetrasolvated homogeneous tetramer (*n*-BuLi)$_4$·THF$_4$ (FW=534), disolvated homogeneous dimer (LDA)$_2$·THF$_2$ (FW=312) and disolvated mixed dimer (LDA/*n*-BuLi) ·THF$_2$ (FW=300).

Unfortunately, the (*n*-BuLi)$_3$/(*n*-BuOLi)$_1$ and the (*n*-BuLi)$_2$ solvation degree was still unresolved due to strong overlapping with the (LDA/*n*-BuLi) signal around –1 ppm. Running a ^{1}H PS-DOSY experiment on the same *n*-BuLi/*n*-BuOLi solution but without LDA eliminates this overlapping (Fig. 3) and the correlation between log FW and log D of the linear least-squares fit to reference points of all components in this mixture is extremely high, r = 0.98 (Fig. S15). This new data suggest the presence of a tetrasolvated mixed tetramer (*n*-BuLi)$_3$/(*n*-BuOLi)$_1$·THF$_4$ (FW=579) and tetrasolvated homogeneous dimer (*n*-BuLi)$_2$·THF$_4$ (FW=490) (Table 1).

This confirms that cubic structures are stable arrangements for both 3:1 and 2:2 (*n*-BuLi/*n*-BuOLi) mixed aggregates. Besides, each Li nucleus is bonded to one molecule of THF, so that they all exhibit a classical[21] total coordination number of 4 (Schema 1).

Compounds	D†. 10^{-11} m^2.s^{-1}	FW g.mol^{-1}	THF	FW* g.mol^{-1}	Error %
THF	0.155			72	
SQA	3.87			411	
TPB	4.9			306	
CDDE	8.05			166	
(LDA)$_2$	**4.83**	**312**	**~2**	**358**	**6.6%**
(LDA)/(*n*-BuLi)	**5.01**	**300**	**~2**	**315**	**2.4%**
(*n*-BuLi)$_4$	**3.15**	**534**	**~4**	**544**	**0.9%**
(*n*-BuLi)$_2$/(*n*-BuOLi)$_2$	**2.91**	**589**	**~4**	**576**	**-1%**

Table 1 Analysis of ^{1}H PS-DOSY results for LDA/*n*-BuLi/*n*-BuOH (1 : 2: 0.9). (D†: Apparent diffusion coefficient; FW*: Theoretical mass of solvated species)



Scheme 1 Representation of solvated (*n*-BuLi)$_x$ and (*n*-BuLi)$_x$/(*n*-BuOLi)$_{4-x}$ in THF.

This new method improves the resolution of the standard DOSY. Consequently, we determined the aggregation state and solvation degree more accurately. The average deviation in formula weight prediction, possibly due to convection, was only 1% overall, while a 4.4% difference was obtained with the standard ^{1}H DOSY experiment. This establishes confidence in using ^{1}H PS-DOSY experiments, especially for organometallic aggregates with comparable formula weights.

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Notes and references

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1. F. Paté, N. Duguet, H. Oulyadi, A. Harrison-Marchand, C. Fressigné, J.-Y. Valnot, M.-C. Lasne, and J. Maddaluno, *J. Org. Chem.* 2007, **72**, 6982.
2. (a) G. Fraenkel, M. Henrichs, J. M. Hewitt, B. M. Su, and M. J. Geckle, *J. Am. Chem. Soc.*1980, **102**, 3345; (b) R. D. Thomas, R. M. Jensen, and T. C. Young, *Organometallics* 1987, **6**, 565.
3. W. Bauer, W. R. Winchester, and P. von R. Schleyer, *Organometallics* 1987, **6**, 2371.
4. P. I. Arvidsson, P. Ahlberg, and G. Hilmersson, *Chem. – Eur. J.* 1999, **5**, 1348.
5. (a) A. C. Jones, A. W. Sanders, M. J. Bevan, and H. J. Reich, *J. Am. Chem. Soc.* 2007, **129**, 3492; (b) K. J. Kolonko, D. J. Wherritt, and H. J. Reich, *J. Am. Chem. Soc.* 2011, **133**, 16774; (c) H. J. Reich, *Chem. Rev.*, 2013, **113**, 7130.
6. (a) Y. Cohen, L. Avram, and L. Frish, *Angew. Chem. Int. Ed.*, 2005, **44**, 520; (b) P. S. Pregosin, *Acta Cryst.* 2013, **69**, 1433; (c) P. S. Pregosin, P. G. A. Kumar, and I. Fernández, *Chem. Rev.*, 2005, **105**, 2977.
7. A. Macchioni, G. Ciancaleoni, C. Zuccaccia, and D. Zuccaccia, *Chem. Soc. Rev.* 2008, **37**, 479.
8. (a) D. Li, R. Hopson, W. Li, J. Liu, and P. G. Williard, *Org. Lett.*, 2008, **10**, 909; (b) D. Li, C. Sun, J. Liu, R. Hopson, W. Li, and P. G. Williard, *J. Org. Chem.* 2008, **73**, 2373; (c) W. Li, G. Kagan, R. Hopson, and P. G. Williard, *ARKIVOC* 2011, **5**, 180; (d) D. Li, I. Keresztes, R. Hopson, and P. G. Williard, *Accounts Chem. Res.* 2009, **42**, 270.
9. R. D. Thomas and H. Huang, *J. Am. Chem. Soc.* 1999, **121**, 11239.
10. G. T. DeLong, D. K. Pannell, M. T. Clarke, and R. D. Thomas, *J. Am. Chem. Soc.* 1993, **115**, 7013.
11. J. F. McGarrity and C. A. Ogle, *J. Am. Chem. Soc.* 1985, **107**, 1805.
12. L. Cazzaniga and R. E. Cohen, *Macromolecules* 1989, **22**, 4125.
13. M. E. Pierce, R. L. Parsons, L. A. Radesca, Y. S. Lo, S. Silverman, J. R. Moore, Q. Islam, A. Choudhury, J. M. D. Fortunak, D. Nguyen, C. Luo, S. J. Morgan, W. P. Davis, P. N. Confalone, C. Chen, R. D. Tillyer, L. Frey, L. Tan, F. Xu, D. Zhao, A. S. Thompson, E. G. Corley, E. J. J. Grabowski, R. Reamer, and P. J. Reider, *J. Org. Chem.* 1998, **63**, 8536.
14. J. F. Remenar, B. L. Lucht, and D. B. Collum, *J. Am. Chem. Soc.* 1997, **119**, 5567.
15. (a) G. Barozzino Consiglio, P. Queval, A. Harrison-Marchand, A. Mordini, J.-F. Lohier, O. Delacroix, A.-C. Gaumont, H. Gérard, J. Maddaluno, and H. Oulyadi, *J. Am. Chem. Soc.* 2011, **133**, 6472; (b) B. Lecachey, H. Oulyadi, P. Lameiras, A. Harrison-Marchand, H. Gérard, and J. Maddaluno, *J. Org. Chem.* 2010, **75**, 5976; (c) B. Lecachey, N. Duguet, H. Oulyadi, C. Fressigné, A. Harrison-Marchand, Y. Yamamoto, K. Tomioka, and J. Maddaluno, *Org. Lett.* 2009, **11**, 1907.
16. (a) A. Chen, D. Wu, and C. S. Johnson, *J. Am. Chem. Soc.* 1995, **117**, 7965; (b) P. S. Pregosin, *Prog. Nucl. Magn. Reson. Spectrosc.* 2006, **49**, 261.
17. D. Li, G. Kagan, R. Hopson, and P. G. Williard, *J. Am. Chem. Soc.* 2009, **131**, 5627.
18. K. Zangger and H. Sterk, *J. Magn. Reson.* 1997, **124**, 486.
19. (a) J. A. Aguilar, S. Faulkner, M. Nilsson, and G. A. Morris, *Angew. Chem. Int. Ed.*, 2010, **49**, 3901; (b) R. W. Adams, L. Byrne, P. Kiraly, M. Foroozandeh, L. Paudel, M. Nilssonac, J. Clayden and G. A. Morris, *Chem. Commun.* 2014, DOI: 10.1039/C3CC49659G.
20. (a) D. B. Collum, A. J. McNeil, A. Ramirez, *Angew. Chem., Int. Ed.* 2007, **46**, 3002; (b) P. G. Williard, J. M. Salvino, *J. Org. Chem.* 1993, **58**, 1.
21. (a) L. M. Pratt, O. Kwon, T. C. Ho, and N. Van Nguyen, *Tetrahedron* 2008, **64**, 5314; (b) H. K. Khartabil, M. T. C. Martins-Costa, P. C. Gros, Y. Fort, and M. F. Ruiz-López, *J. Phys. Chem. B* 2009, **113**, 6459.