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## COMMUNICATION

# Accurate Measurement of Effective Li-Li Scalar Coupling Constants: the NMR Missing Link for Alkylolithium Aggregates

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**Scalar coupling in organolithium systems can provide access to useful structural and dynamic informations. In this work, we propose a robust method for the accurate measurement of the effective  ${}^2J_{\text{Li-Li}}$  coupling constant in tetrameric organolithium aggregates. This crucial information, unavailable to date, gives a simple access to various structural factors, including the dynamics, solvation and the operative steric hindrance of alkyl chains.**

Organolithium compounds are among the most commonly used reagents in organic chemistry for the formation of carbon-carbon bonds.<sup>[1]</sup> Their high reactivity due to their nucleophilic, but also basic,<sup>[1,3]</sup> properties make them reagents of choice for the generation of a wide variety of carbanions and amides (derived from primary, secondary amines) or alkoxides. In solution, these compounds tend to form diverse aggregates, of which distribution influences the reactivity. The structure and abundance of these aggregates depends on several factors, such as temperature and concentration, but also the nature of the solvent.<sup>[2]</sup> Electron-donor solvents, such as THF or diethylether, promote the formation of dimer or tetramer aggregates, alike chelating agents such as HMPA or TMEDA. NMR spectroscopy is currently the most frequently used technique for characterising the structures of organolithium derivatives in solution.<sup>[3]</sup> Their aggregation is generally deduced from the multiplicity of the signal of the X nucleus directly connected to the lithium atom and by the value of the Li-X (X =  ${}^{13}\text{C}$  or  ${}^{15}\text{N}$ ) scalar coupling constant.<sup>[4]</sup> However, in the case of amides that are not labelled with nitrogen 15, alkoxides, enolates or even lithium halides, the multiplicity of the signal of the X nucleus and the Li-X scalar coupling constant are not observable. In these cases, other detailed studies are needed, but they often remain inconclusive. Hence, the accurate measurement of the lithium-lithium homonuclear scalar coupling constant and the understanding of its relationship with

the structure of the complexes would dramatically enrich the NMR toolbox and give an exquisitely direct access to the organolithium aggregation state.

Recently, we demonstrated that it is possible, for the first time, to measure the  ${}^2J_{\text{Li-Li}}$  scalar coupling constants observing  ${}^7\text{Li}$  in complex systems such as *n*-BuLi/MeLi and *n*-BuLi/*n*-BuOLi mixtures.<sup>[5]</sup> Correlation between the values of the  ${}^2J_{\text{Li-Li}}$  constants measured in the tetrameric aggregates (*n*-BuLi)<sub>4-n</sub>(RLi)<sub>n</sub> (R= MeLi or *n*-BuOLi) and the exchange rates determined from 2D  ${}^7\text{Li}$  EXSY experiments showed that the scalar coupling between two lithium nuclei in a mixed aggregate strongly depends on the rate of exchange of lithium cations within the tetramer. Likewise, functional density theory (DFT) calculations were performed on simple (MeLi)<sub>4-n</sub>(MeOLi)<sub>n</sub> aggregates, which made it possible to better understand the association between the Li-O and Li-C molecular fragments and explain the differences observed in the Li-Li couplings between the alkyl and alkoxy aggregates.

As part of this work, we completed our results obtained on tetrameric alkylolithium mixed aggregates by measuring the  ${}^2J_{\text{Li-Li}}$  homonuclear scalar coupling in (R<sup>1</sup>Li)<sub>n</sub>(R<sup>2</sup>Li)<sub>4-n</sub> (R<sup>1</sup> = Et, *n*-Bu; R<sup>2</sup> = Me, *n*-BuLi) static aggregates and we very precisely quantified the influence on the  ${}^2J_{\text{Li-Li}}$  coupling of several factors, including dynamics, solvation, and the steric hindrance of the alkyl chains. This information is central to apprehend the relationship between the  ${}^7\text{Li}$ - ${}^7\text{Li}$  scalar coupling and the structure and dynamics of tetrameric organolithium aggregates in solution.

**Solution of *n*-BuLi/MeLi (1:1)** - For *n*-BuLi/MeLi (1:1) solution, the lithium 7 spectrum in THF-*d*<sub>8</sub> at 260K consist of one large singlet at 1.91 ppm (Fig. 1S). This is consistent with the known intermediate dynamic exchange. Upon cooling, the singlet peaks reform, below 240K, into eight signals and the resolution becomes satisfactory below 220K. We thus worked at 185 K, that is to say in conditions similar to those used in our previous studies.<sup>[5, 6]</sup>

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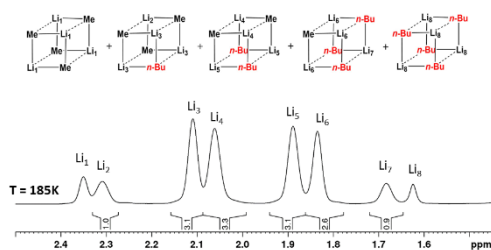


Fig. 1 1D  $^7\text{Li}$  spectrum of MeLi/*n*-BuLi solution (1:1) in THF- $d_8$  at 185K and tetrameric aggregates formed between MeLi and *n*-BuLi.

The 1D  $^7\text{Li}$  NMR spectrum of a 1:1 solution of MeLi/*n*-BuLi in THF- $d_8$  at 185K displays eight broad singlet signals (Fig. 1). They are assigned to  $(\text{MeLi})_{4-n}(\text{n-BuLi})_n$  mixed tetramers on the basis of the integration of signals on the 1D  $^7\text{Li}$  NMR spectrum and the correlations observed on the 2D  $^7\text{Li}$ - $^7\text{Li}$  COSY spectrum between the signals at  $\delta = 2.31$  ppm (1Li) and  $\delta = 2.12$  ppm (3Li) associated to the  $(\text{MeLi})_3(\text{n-BuLi})_1$  aggregate,  $\delta = 2.06$  ppm (2Li) and  $\delta = 1.92$  ppm (2Li) associated to the  $(\text{MeLi})_2(\text{n-BuLi})_2$  aggregate and  $\delta = 1.84$  ppm (3Li) and  $\delta = 1.68$  ppm (1Li) for the  $(\text{MeLi})_1(\text{n-BuLi})_3$  (Fig. 2).

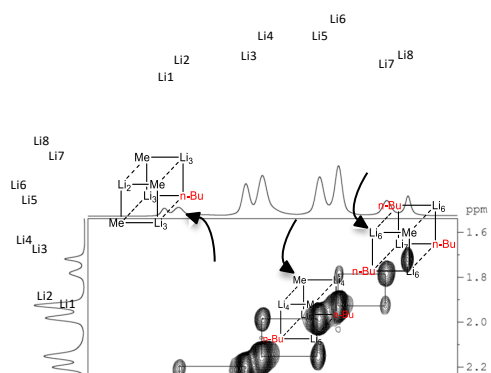


Fig. 2 2D  $^7\text{Li}$ - $^7\text{Li}$  COSY spectrum of an MeLi/*n*-BuLi solution (1:0.8) in THF- $d_8$  at 185 K.

However, the  $^2J_{\text{Li-Li}}$  scalar couplings at the origin of the 2D  $^7\text{Li}$ - $^7\text{Li}$  COSY correlations was too weak to be resolved and measured on the 1D  $^7\text{Li}$  spectrum. To carry out the precise measurement of the homonuclear scalar coupling of lithium, we resorted to the 2D  $^7\text{Li}$ - $^7\text{Li}$  COSY experiment at a constant time (CT-COSY).<sup>[5]</sup> By carrying out a series of experiments with different  $\Delta$  delays and then plotting the intensity curve of the normalized correlation to the intensity of the diagonal as a function of  $\Delta$ , the coupling constant  $^2J_{\text{Li-Li}}$  was determined in each system.

**$^2J_{\text{Li-Li}}$  scalar coupling measurement** - A series of 2D  $^7\text{Li}$ - $^7\text{Li}$  COSY spectra with  $\Delta = 0.1$ - $0.7$  s was then carried out on a *n*-BuLi/MeLi (1:1) mixture to determine the  $(\text{MeLi})_{4-n}(\text{n-BuLi})_n$  aggregates coupling constants. For each  $(\text{MeLi})_{4-n}(\text{n-BuLi})_n$  ( $0 < n < 4$ ) mixed aggregate, an integration value of the correlation peak ( $I_C$ ) normalized to the peak on the diagonal ( $I_D$ ) was obtained for each  $\Delta$  delay. When plotting the  $I_C/I_D$  ratios as a function of the  $\Delta$  delay, according to a  $I_C/I_D = A \tan(3\pi\Delta)$  tangent function, a discontinuity is observed for  $\Delta = 1/6J$  (Fig. 2S), giving access to the apparent scalar coupling constant associated to the experimental points. We thus obtained  $^2J_{\text{Li-Li}} = 0.561 \pm 0.001$  Hz

for the  $(\text{MeLi})_3(\text{BuLi})_1$  aggregate,  $^2J_{\text{Li-Li}} = 0.525 \pm 0.001$  Hz for  $(\text{MeLi})_2(\text{BuLi})_2$  and  $^2J_{\text{Li-Li}} = 0.472 \pm 0.001$  Hz for  $(\text{MeLi})_1(\text{BuLi})_3$ .

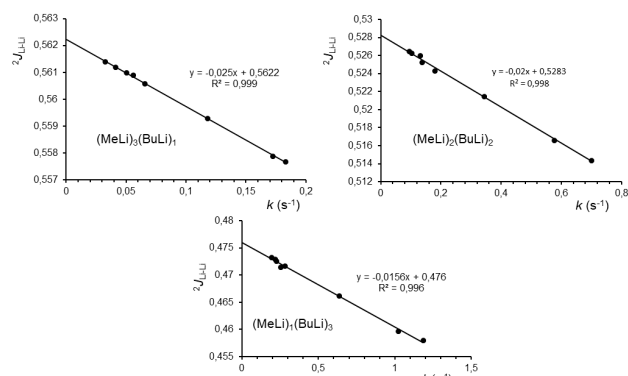
The 1D  $^7\text{Li}$  spectrum of the MeLi/*n*-BuLi solution in THF- $d_8$  at 185K exhibits two signals for each mixed aggregate indicating that, at this temperature, the intra-aggregate exchange is slow on the NMR time scale. In order to be able to study and quantify the exchange existing between two lithium nuclei, a series of 2D  $^7\text{Li}$ - $^7\text{Li}$  EXSY experiments was carried out on this mixture.<sup>[6]</sup> The 2D  $^7\text{Li}$ - $^7\text{Li}$  EXSY map showed only intra-aggregate exchange, i.e. between two lithium atoms belonging to the same aggregate. Using a series of 2D  $^7\text{Li}$ - $^7\text{Li}$  EXSY experiments with variable mixing times allowed the precise quantification of the exchange constant (Fig. 3S). We thus determined an exchange rate constant  $k_1 = 0.066 \pm 0.005$  s $^{-1}$  for the  $(\text{MeLi})_3(\text{n-BuLi})_1$  aggregate,  $k_2 = 0.136 \pm 0.008$  s $^{-1}$  for the  $(\text{MeLi})_2(\text{n-BuLi})_2$  aggregate and  $k_3 = 0.249 \pm 0.004$  s $^{-1}$  for the  $(\text{MeLi})_1(\text{n-BuLi})_3$  aggregate.

To determine the influence of the intramolecular dynamics on the value of the  $^2J_{\text{Li-Li}}$  coupling constant, 2D  $^7\text{Li}$ - $^7\text{Li}$  CT-COSY and EXSY series were run between 165 and 205K with the aim of acquiring 8 scalar coupling constants ( $^2J_{\text{Li-Li}}$ )/exchange constant ( $k_{\text{Li-Li}}$ ) couples (Table 1S). Fig. 3 shows the variation of the coupling constant as a function of the exchange constant for each  $(\text{MeLi})_{4-n}(\text{n-BuLi})_n$  mixed aggregate and in particular, a proportionality relationship between these two parameters. This proportionality relationship was used to extrapolate the value of the coupling constant at zero exchange ( $k_{\text{Li-Li}} = 0$ ) to zero the influence of the dynamics. The effective value of the  $^2J_{\text{Li-Li}}$  scalar coupling at zero exchange was found to be  $0.562 \pm 0.001$  Hz, for the  $(\text{MeLi})_3(\text{n-BuLi})_1$  aggregate,  $0.528 \pm 0.001$  Hz for the  $(\text{MeLi})_2(\text{n-BuLi})_2$  aggregate and  $0.476 \pm 0.002$  Hz for the  $(\text{MeLi})_1(\text{n-BuLi})_3$  aggregate. These values indicate that the  $^2J_{\text{Li-Li}}$  constant decreases with an increasing number of butyl chains in the tetramer, highlighting the effect of steric hindrance on  $^2J_{\text{Li-Li}}$ . This decrease can be linked to a deformation of the tetramer, as suggested previously for  $(\text{Me}^6\text{Li})_{4-n}(\text{LiBr})_n$  mixed aggregates.<sup>[7]</sup>

To check this hypothesis, we measured lithium scalar coupling constants for mixtures, in THF- $d_8$ , of tetrameric alkyllithiums with different chain lengths.

**Solutions of EtLi/RLi (R=*n*-BuLi, MeLi)** - The 1D  $^7\text{Li}$  spectra obtained for these mixtures at 185K were similar to the 1D  $^7\text{Li}$  spectrum of the MeLi/*n*-BuLi solution; they exhibit eight signals corresponding to the five mixed tetramers with the formula  $(\text{R}_1\text{Li})_{4-n}(\text{R}_2\text{Li})_n$  (Fig. 4S). The scalar coupling constants associated with the different mixed tetramer aggregates obtained were determined by the same 2D  $^7\text{Li}$ - $^7\text{Li}$  CT-COSY and EXSY experiment series at different temperatures, as to extrapolate the scalar coupling constant at zero exchange (Table 1).

The scalar coupling constants obtained show a decrease of  $^2J_{\text{Li-Li}}$  when the steric hindrance increases within the tetramer. We next plotted the value of  $^2J_{\text{Li-Li}}$  at zero exchange as a function of the number of the longer chain incorporated within each mixed aggregate, and this for MeLi/*n*-BuLi, MeLi/EtLi and EtLi/*n*-BuLi mixtures (Fig. 4). The strong dependence of  $^2J_{\text{Li-Li}}$  on the steric hindrance generated by the floppy alkyl chain is obvious and follows a linear correlation ( $R^2 > 0.99$ ).



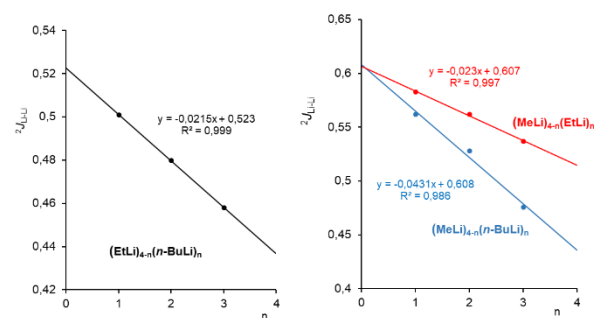
**Fig. 3**  ${}^2J_{\text{Li-Li}}$  apparent scalar coupling constant for  $(\text{MeLi})_{4-n}(\text{n-BuLi})_n$  aggregates as a function of exchange rate  $k$ .

**Table 1**  ${}^2J_{7\text{Li}-7\text{Li}}$  effective scalar coupling constant and lithium chemical shift in hetero-tetramers  $(\text{EtLi})_{4-n}(\text{RLi})_n$  ( $R = \text{Me}, n\text{-Bu}$ ) in THF- $d_8$ .

Solutions	Tetramers	$\delta$ ${}^7\text{Li}$ (ppm)	${}^2J_{\text{Li-Li}}$ (Hz)
MeLi/EtLi (1:0.8)	$(\text{MeLi})_3(\text{EtLi})_1$	2.57 2.42	$0.583 \pm 0.001$
	$(\text{MeLi})_2(\text{EtLi})_2$	2.36 2.23	$0.562 \pm 0.001$
	$(\text{MeLi})_1(\text{EtLi})_3$	2.18 2.05	$0.537 \pm 0.001$
MeLi/n-BuLi (1:1)	$(\text{MeLi})_3(\text{n-BuLi})_1$	2.31 2.12	$0.562 \pm 0.001$
	$(\text{MeLi})_2(\text{n-BuLi})_2$	2.07 1.89	$0.528 \pm 0.001$
	$(\text{MeLi})_1(\text{n-BuLi})_3$	1.84 1.69	$0.476 \pm 0.002$
EtLi/n-BuLi (1:0.8)	$(\text{EtLi})_3(\text{n-BuLi})_1$	1.97 1.85	$0.501 \pm 0.002$
	$(\text{EtLi})_2(\text{n-BuLi})_2$	1.81 1.71	$0.480 \pm 0.002$
	$(\text{EtLi})_1(\text{n-BuLi})_3$	1.66 1.57	$0.458 \pm 0.003$

Finally, a linear model allows the extrapolation of the  ${}^2J_{\text{Li-Li}}$  scalar coupling constants to pure aggregates ( $n = 0$  and  $n = 4$ ). These values are inaccessible to NMR, due to the equivalence of the lithium nuclei. Table 2 shows that our method is both robust and precise: extremely similar  ${}^2J_{\text{Li-Li}}$  coupling constants are extrapolated for the homo-tetramers  $(\text{RLi})_4$  ( $R = \text{Me}, \text{Et}, n\text{-Bu}$ ), independently of the mixture studied.

**Solvation effect on  ${}^2J_{\text{Li-Li}}$  scalar coupling** – It is known that solvation alters the aggregation and dynamics of organolithiated species, influencing the measured scalar coupling constants.<sup>[8]</sup> In the case of organolithiums, Hilmersson *et al.* highlighted the influence of solvation on the  ${}^1J_{\text{Li-N}}$  scalar coupling constant. Values between 4.1 Hz for tetacoordinated lithium and 4.9 Hz for tricordinated lithium were recorded.<sup>[9]</sup>



**Fig. 4**  ${}^2J_{\text{Li-Li}}$  effective scalar coupling constant as a function of the number of the longer alkyl chains within the mixed aggregates ( $n$ ).  $(\text{EtLi})_{4-n}(\text{n-BuLi})_n$  (right),  $(\text{MeLi})_{4-n}(\text{EtLi})_n$  (left, red) and  $(\text{MeLi})_{4-n}(\text{n-BuLi})_n$  (left, blue).

**Table 2.**  ${}^2J_{7\text{Li}-7\text{Li}}$  effective scalar coupling constant ( $k=0$ ) extrapolated for  $(\text{RLi})_4$  ( $R = \text{Me}, \text{Et}, n\text{-Bu}$ ) in THF- $d_8$ .

Solutions	Tetramers	${}^2J_{\text{Li-Li}}$ (Hz)
MeLi/EtLi (1:0.8)	$(\text{MeLi})_4$	0.607
	$(\text{EtLi})_4$	0.520
MeLi/n-BuLi (1:1)	$(\text{MeLi})_4$	0.608
	$(\text{n-BuLi})_4$	0.435
EtLi/n-BuLi (1:0.8)	$(\text{EtLi})_4$	0.523
	$(\text{n-BuLi})_4$	0.435

To explore the influence of solvation on  ${}^2J_{\text{Li-Li}}$ , we prepared in diethylether ( $\text{Et}_2\text{O}$ ) the mixtures of alkyllithiums studied above in THF ( $\text{MeLi}/\text{EtLi}$  and  $\text{MeLi}/n\text{-BuLi}$ ).  $\text{Et}_2\text{O}$  is less coordinating and less polar than THF.<sup>[10]</sup> We thus characterised, by  $\{^1\text{H}, ^7\text{Li}, ^{13}\text{C}\}$  NMR, these mixtures in  $\text{Et}_2\text{O}-d_{10}$  at low temperature and observed statistical distributions of  $(\text{R}_1\text{Li})_{4-n}(\text{R}_2\text{Li})_n$  mixed aggregates comparable to those in THF- $d_8$ .<sup>3a</sup> The scalar coupling constants for the different tetramers were determined by the same series of 2D  ${}^7\text{Li}-{}^7\text{Li}$  CT-COSY and  ${}^7\text{Li}-{}^7\text{Li}$  EXSY, run at different temperatures to extrapolate the coupling constant to zero exchange (Table 3). Comparing the data in THF- $d_8$  to those in  $\text{Et}_2\text{O}-d_{10}$  shows that the  ${}^2J_{\text{Li-Li}}$  coupling constant decreases slightly with the increase of the polarity of the solvent, and therefore of the solvation of lithium, the tiny variation being in the  $1\text{-}3 \times 10^{-3}$  Hz range.

We next decided to extend this study to a less polar medium in which, however, cubic structures were likely to be replaced by larger aggregates of different composition. We retained  $n\text{-Bu}_2\text{O}$ , a coordinating while significantly less polar solvent ( $E_T^N = 0.071$  for  $n\text{-Bu}_2\text{O}$ , 0.117 for  $\text{Et}_2\text{O}$  and 0.207 for THF)<sup>[10]</sup> in which  $\text{MeLi}$ ,  $\text{EtLi}$  and  $n\text{-BuLi}$  are all soluble. To our knowledge, no NMR structural investigation has been devoted yet to alkyllithiums in  $\text{Bu}_2\text{O}$  mixtures. Fortunately, we were able to show that mixtures of  $\text{MeLi}/\text{EtLi}$  and  $\text{MeLi}/n\text{-BuLi}$  in THF- $d_8$ ,  $\text{Et}_2\text{O}-d_{10}$  and  $\text{Bu}_2\text{O}/\text{Tol}-d_8$ <sup>[11]</sup> are composed, at low temperature, of comparable cubic mixed aggregates  $(\text{MeLi})_{4-n}(\text{RLi})_n$  ( $R = \text{Et}, n\text{-Bu}$ ). In fact, the NMR analysis of various mixtures of  $\text{MeLi}/\text{EtLi}$  and  $\text{MeLi}/n\text{-BuLi}$  in  $\text{Bu}_2\text{O}/\text{Tol}-d_8$  (80:20) gives access to all the Li signals of the  $(\text{MeLi})_n(\text{RLi})_{4-n}$  ( $R = \text{Et}, n\text{-Bu}$ ) aggregates (Fig. 5S).

The relative variation of the concentration of the five possible aggregates as a function of the  $\text{MeLi}/\text{RLi}$  ( $R = \text{Et}, n\text{-Bu}$ ) ratio in  $\text{Bu}_2\text{O}/\text{Tol}-d_8$  solutions has been determined. These data, displayed in Fig. 6S correspond to a thermodynamic equilibrium between tetramers having the same free energy of formation (Fig. 7S). (ref) The good match between theoretical and spectroscopical data indicates that the populations of complexes in THF- $d_8$ ,  $\text{Et}_2\text{O}-d_{10}$  and  $\text{Bu}_2\text{O}/\text{Tol}-d_8$  solutions are similar and follow a pure statistical distribution.

The scalar coupling constants associated with  $(\text{MeLi})_n(\text{RLi})_{4-n}$  ( $R = \text{Et}, n\text{-Bu}$ ) aggregates in  $\text{Bu}_2\text{O}/\text{Tol}-d_8$  were determined by the same procedure based on 2D  ${}^7\text{Li}-{}^7\text{Li}$  CT-COSY and  ${}^7\text{Li}-{}^7\text{Li}$  EXSY at different temperatures to extrapolate the coupling constant at zero exchange (Table 3).

The differences between the scalar coupling constants measured in  $\text{Et}_2\text{O}-d_{10}$  or  $\text{Bu}_2\text{O}/\text{Tol}-d_8$  follow the trend observed between THF- $d_8$  and  $\text{Et}_2\text{O}-d_{10}$ : going from a polar ( $\text{Et}_2\text{O}$ ) to a more less polar solvent ( $\text{Bu}_2\text{O}/\text{Tol}$ ) decreases the solvation of

lithium atoms and increases the scalar coupling constant at zero exchange, with a difference of  $\approx 3 \times 10^{-3}$  Hz.

**Table 3.**  ${}^2J_{7\text{Li}-7\text{Li}}$  effective scalar coupling constant in mixed tetramers  $(\text{MeLi})_4(\text{RLi})_n$  (R=Et, *n*-Bu) in THF-*d*<sub>8</sub>, Et<sub>2</sub>O-*d*<sub>10</sub> and Bu<sub>2</sub>O/Tol-*d*<sub>8</sub>.

Tetramers	${}^2J_{\text{Li-Li}}$ (Hz) $\pm 0.001$		
	THF- <i>d</i> <sub>8</sub>	Et <sub>2</sub> O- <i>d</i> <sub>10</sub>	Bu <sub>2</sub> O/Tol- <i>d</i> <sub>8</sub>
(MeLi) <sub>3</sub> (EtLi) <sub>1</sub>	0.582	0.585	0.588
(MeLi) <sub>2</sub> (EtLi) <sub>2</sub>	0.562	0.564	0.566
(MeLi) <sub>1</sub> (EtLi) <sub>3</sub>	0.537	0.538	0.540
(MeLi) <sub>3</sub> ( <i>n</i> -BuLi) <sub>1</sub>	0.562	0.564	0.567
(MeLi) <sub>2</sub> ( <i>n</i> -BuLi) <sub>2</sub>	0.528	0.531	0.534
(MeLi) <sub>1</sub> ( <i>n</i> -BuLi) <sub>3</sub>	0.476	0.478	0.480

In summary, our data point out the strong influence of the dynamics on the  ${}^2J_{\text{Li-Li}}$  scalar coupling constant and demonstrate there is a linear correlation between these two parameters. The protocol implemented, based on a series of 2D NMR  ${}^7\text{Li}$ - ${}^7\text{Li}$  CT-COSY and EXSY experiments at different temperatures, gives access to a dynamics-free value of the  ${}^2J_{\text{Li-Li}}$  coupling constant at zero exchange.

Applying this protocol to different alkyl lithium mixtures allowed us to clarify the influence of the size of the alkyl chain on the effective scalar coupling constant:  ${}^2J_{\text{Li-Li}}$  decreases when the alkyl chain lengthens, i.e. when its steric hindrance increases. The apparent linear correlation between the number of alkyl chains in mixed aggregates and the effective  ${}^2J_{\text{Li-Li}}$  coupling constant measured allowed extrapolation to the  ${}^2J_{\text{Li-Li}}$  of the pure (homogeneous) tetramers, a value not directly accessible to NMR.

Finally, the effect of the solvent polarity, and therefore of the lithium solvation, was studied. In accordance with the data in the literature, the data obtained show that the  ${}^2J_{\text{Li-Li}}$  coupling constant depends on solvent effects. These effects are tiny, from 0.001 Hz when going from THF to Et<sub>2</sub>O, up to 0.004 Hz when switching to a less polar solvent such as Bu<sub>2</sub>O.

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## Conflicts of interest

There are no conflicts to declare.

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