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MeLi + LiCl in THF: One Heterodimer and No Tetramers[†]

Baptiste Lecachey,[‡] Hassan Oulyadi,[‡] Pedro Lameiras,[‡] Anne Harrison-Marchand,[‡]
Hélène Gérard,[§] and Jacques Maddaluno*,[‡]

[‡]CNRS UMR 6014 & FR 3038, Université de Rouen and INSA de Rouen, 76821 Mont St. Aignan Cedex, France, and [§]UPMC Univ Paris 6 and CNRS, UMR 7616, Laboratoire de Chimie Théorique, 4 place Jussieu, 75252 Paris Cedex 05, France

jmaddalu@crihan.fr

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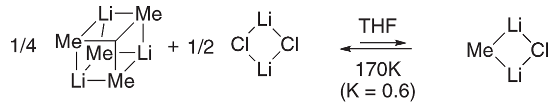

The structure of the aggregates formed when mixing methyllithium and lithium chloride in THF has been studied by multinuclear magnetic resonance at 170 K. The data suggest that only one new entity is observed, that is the dimer [(MeLi)(LiCl)], in equilibrium ($K \approx 0.6$) with $[\mathrm{MeLi}]_4$ and $[\mathrm{LiCl}]_2$. NMR diffusion measurements lead to the conclusion that this dimer is trisolvated in THF at 170 K, a solvation scheme in agreement with DFT computations.

Introduction

Because they easily form mixed aggregates, lithium halides are known to exert a significant influence on the behavior of organometallic reagents, affecting both the reactivity[1] and the selectivity.[2] The enhanced reactivity of Grignard reagents in the presence of LiCl recently reported by Knochel[3] (Turbo-Grignard RMgX-LiCl) provides a spectacular recent example of this effect. Even if the interactions between lithium chloride or bromide and alkyllithiums,[4] lithium amides,[5,6] or lithium enolates[7] have been studied on chemical, spectroscopic, or theoretical grounds, the precise phenomena

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[†] This paper is dedicated to Prof. Saverio Florio on the occasion of his 70th birthday.

(1) See for instance: (a) Huisgen, R.; Mack, W. *Chem. Ber.* **1960**, *93*, 332–340. (b) Glaze, W.; West, R. *J. Am. Chem. Soc.* **1960**, *82*, 4437–4437. (c) Winkler, H. J. S.; Winkler, H. *J. Am. Chem. Soc.* **1966**, *88*, 969–974. (d) Rathman, T. L.; Bailey, W. F. *Org. Process Res. Dev.* **2009**, *13*, 144–151.

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(3) See for instance: (a) Krasovskiy, A.; Straub, B.; Knochel, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 159–162. (b) Clososki, G. C.; Rohbogner, C. J.; Knochel, P. *Angew. Chem., Int. Ed.* **2007**, *46*, 7861–7684. (c) Piller, F. M.; Appukkuttan, P.; Gavryushin, A.; Helm, M.; Knochel, P. *Angew. Chem., Int. Ed.* **2008**, *47*, 6802–6806. (d) Mosrin, M.; Knochel, P. *Org. Lett.* **2008**, *10*, 2497–2500.

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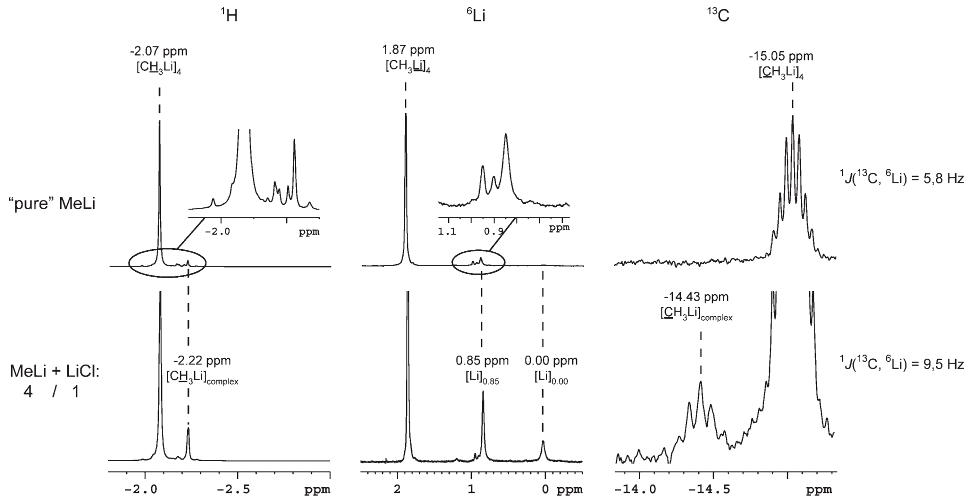

FIGURE 1. ^{1}H (left), ^{6}Li (middle), and ^{13}C (right) NMR spectra of "pure" Me^{6}Li (top) and Me^{6}Li + 0.25 equiv of ^{6}LiCl (bottom) in THF-d_8 (0.3 M, 170 K).

triggered by the salts are often difficult to assign at the molecular level and therefore a "black-box type" description is frequently proposed.[5b,8] Expectedly, the prototypical methyllithium has been the object of particular attention. Early works by Brown,[9] West,[10] and others[4] afforded an important corpus of results on the organization of MeLi−LiBr and MeLi−LiI in ethereal solvents, in particular THF that is commonly employed with these reagents. The mixtures involving the two remaining lithium halides, viz. LiF and LiCl, have never been described to our knowledge.[11] If LiF is strictly insoluble in THF, this void is much more surprising for LiCl, which is a well-known contaminant of all alkyllithiums prepared by reacting metallic lithium with R-Cl. A better knowledge of the species in solution would be especially useful when dealing with the preparation of "salt-free" methyllithium,[12,13] a reagent used commonly for transmetalations and generation of elaborated organometallics.[14] Our previous experience in the characterization of the MeLi−LiBr aggregates, as well as those formed between LiCl and LiNR$_2$,[15] prompted us to undertake an in-depth study on the MeLi−LiCl couple thanks to a set of ^{6}Li and ^{6}Li/^{13}C simple and double-labeling experiments and subsequent NMR and theoretical studies. The results are reported below.

Results and discussion

Spectroscopic Identification of the [(MeLi)$_m$(LiCl)$_n$] Aggregate(s) in THF. A sample of "salt-free"[16] singly labeled Me^{6}Li in THF-d_8 was first prepared[13] and the effect of the addition of known amounts of ^{6}LiCl was followed by ^{1}H, ^{6}Li, and ^{13}C NMR at 170 K (−103 °C).[17] The starting sample of "pure" MeLi is characterized by the expected ^{1}H and ^{6}Li singlets at δ −2.07 ppm ([CH_3Li]$_4$ in Figure 1, top left) and 1.87 ([CH$_3$$Li$]$_4$ in Figure 1, top middle),[18] respectively, plus a ^{13}C heptet at δ −15.05 ppm ([CH$_3$Li]$_4$ in Figure 1, top right; J = 5.8 Hz, in line with a ^{13}C surrounded by three ^{6}Li for which I = 1).[4c,e,f] Minor singlets were also observed at δ −2.16, −2.17, −2.20, and −2.22 ppm on the ^{1}H spectrum and at δ 0.95, 0.90, and 0.85 on the ^{6}Li spectrum (Figure 1, enlargements top line).

When 0.25 equiv of ^{6}LiCl was added to this sample, both the ^{1}H δ −2.22 ppm signal ([CH_3Li]$_{complex}$ in Figure 1, bottom left) and the ^{6}Li δ 0.85 ppm peak ([Li]$_{0.85}$ in Figure 1, bottom middle) were amplified. For this later nucleus, a new singlet also appeared at δ 0.00 ppm ([Li]$_{0.00}$ in Figure 1, bottom middle). In the ^{13}C dimension, a small quintet at δ −14.43 ppm was observed ([CH$_3$Li]$_{complex}$ in Figure 1, bottom right), in contrast to the heptet reported for LiBr or LiI mixed aggregates. This multiplicity is characterized by a coupling constant ($J \approx 9.5$ Hz, Figure 1, bottom right) significantly larger than in the LiBr ($J \approx 5.9$ Hz)[4f−h] and LiI ($J \approx 5.8$ Hz)[4d,f,h] analogues. The multiplicity and the empirical Bauer−Winchester−Schleyer rule for coupling constants (J_{Li-C} = (17 ± 2)/n_C, n_C being the number of lithium cations directly connected to

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[11] The formation of a [Me$_3$ClLi$_4$(THF)$_4$] cubic complex in the solid state that would not evolve toward [Me$_2$Cl$_2$Li$_4$(THF)$_4$] upon addition of LiCl has been proposed. However, they could not be observed: Ogle, C. A.; Huckabee, B. K.; Johnson, H. C., IV; Sims, P. F.; Winslow, S. D.; Pinkerton, A. A. *Organometallics* **1993**, *12*, 1960–1963.

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[16] A total amount of 5−10 mol % chloride was measured by potentiometry after hydrolysis of a sample.

[17] Above 170 K, the high-field ^{6}Li signals collapse in a broad signal centered at 0.4 ppm (see Figure 1S of the Supporting Information).

[18] ^{6}Li chemical shifts are given with respect to an external 0.3 M LiCl solution in THF.

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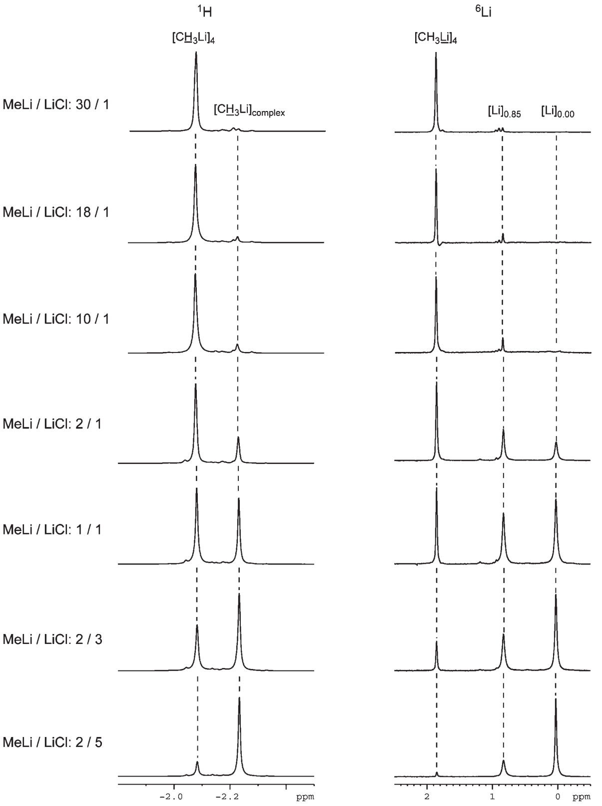

FIGURE 2. ^{1}H (left) and ^{6}Li (right) NMR spectra of "pure" Me^{6}Li (top) and Me^{6}Li + x equiv of ^{6}LiCl ($x = 0.5$ to 2.5) in THF-d_8 (170 K).

the observed carbon)[19,20] suggest that the only complex formed exhibits one methyl surrounded by two lithium cations, and is thus not a mixed cubic tetramer (contaminated by small amounts of putative mixed dimers) as for LiBr or LiI.

The simplicity of these spectra, with respect to those obtained upon addition of LiBr or LiI to MeLi, led us to refine the study by recording a full set of spectra after the addition of known quantities of LiCl (between 3 and 71 mol %). While the ^{1}H and ^{6}Li signals of methyllithium decreased, the ^{1}H signal at δ −2.22 ppm increased continuously, as well as the two ^{6}Li peaks at δ 0.85 and 0.00 ppm, albeit these two latter did not evolve at the same rate and their ratio was not constant. Note that the δ 0.00 ppm signal corresponds to the "free" LiCl oligomer(s), 0.3 M LiCl in THF being taken as the external reference. Since no new signal was observed on the ^{1}H/^{6}Li/^{13}C spectra (Figure 2), whatever the quantity of LiCl added and in contrast to what happens with LiBr or LiI,[4] it seems that one single new species is formed, characterized by one ^{1}H and one ^{6}Li singlet. A bidimensional HOESY[21] run on a 1:2 MeLi/LiCl sample (Figure 2S of the Supporting Information) supports this hypothesis, a correlation being observed between the new signals.[22]

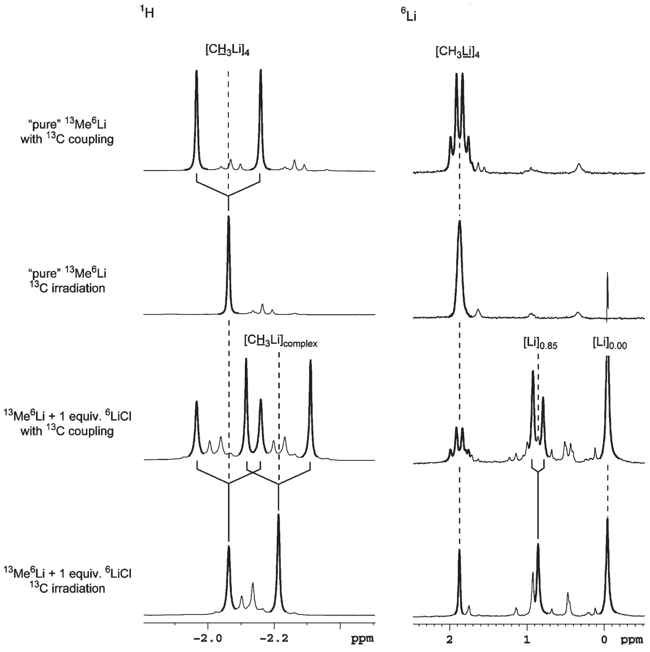

FIGURE 3. ^{1}H (left) and ^{6}Li (right) NMR spectra of "pure" ^{13}CH$_3$^{6}Li (lines 1 and 2) and ^{13}CH$_3$^{6}Li + 1.0 equiv of ^{6}LiCl (lines 3 and 4) in THF-d_8 (0.3 M, 170 K).

The information brought by these experiments implies the existence of a single mixed aggregate [(MeLi)$_m$(LiCl)$_n$] characterized by only one type of Li cation and only one type of methyl appendage directly connected to two Li. The complementary information regarding the surrounding lithiums was furnished by the NMR analysis of doubly labeled ^{13}CH$_3$^{6}Li. This compound, never described before to our knowledge, was synthesized from ^{13}CH$_3$I and n-Bu^{6}Li following Waack and West's procedure.[23] Note that the drawback of this method is that residual amounts of LiI are almost impossible to eliminate, and despite all our efforts to diminish its concentration, we had to work with ^{13}CH$_3$^{6}Li samples contaminated with 7−20% of this salt. This results in spectra displaying major signals (in black, Figure 3) that correspond to the ^{13} Me^{6}Li/^{6}LiCl complex we are interested in, and minor peaks (in gray) that represent the undesired ^{13} Me^{6}Li/^{6}LiI aggregates. Those later could, however, easily be assigned thanks to Günther's previous results[4h] (see Figure 4S in the Supporting Information).

Let us first describe the spectra related to the "pure" doubly labeled methyllithium (Figure 3, lines 1 and 2). The ^{1}H spectrum (top line, left) displays the expected doublet at δ −2.07 ppm (^1J = 97 Hz), which becomes a singlet at the same chemical shift upon ^{13}C irradiation (line 2, left). The ^{6}Li spectrum (top line, right) consists mainly of a quartet (^1J = 5.8 Hz) at δ 1.87 ppm. This multiplicity is characteristic of a lithium cation surrounded by three ^{13}C as expected for the well-known cubic arrangement of methyllithium. The quartet turns into the likely singlet at δ 1.87 ppm upon ^{13}C irradiation (line 2, middle). Complementarily, the ^{13}C−{^{1}H} spectrum (see Figure 5S in the Supporting Information) is not the simple heptet observed for ^{6}Li monolabeled methyllithium. An overmultiplicity is observed that is not related to

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(20) This rule applies not only to homogeneous hydrocarbons lithium aggregates but also to various mixed lithium aggregates (see ref 4).

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(22) It is worth noting that the HOESY spectrum shows a meaningless correlation between the new signal on the ^{1}H dimension and that of LiCl on the ^{6}Li dimension. This extra correlation is due to the strong exchange that takes place between LiCl and the new complex, even at 170 K (see the EXSY spectrum, Figure 3S of the Supporting Information). We warmly thank Prof. David Collum (Cornell University) for pointing out the risk of misinterpreting these results leading to erroneous conclusions.

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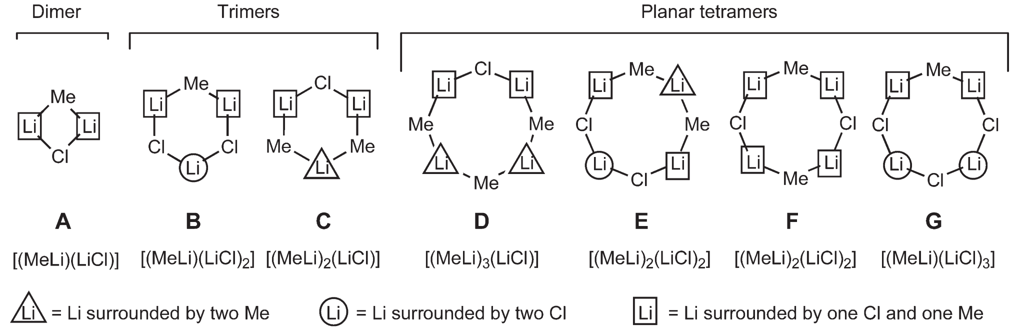

FIGURE 4. $[(\mathrm{MeLi})_m(\mathrm{LiCl})_n]$ aggregates accounting for the preliminary NMR observations.

the fluxional character of the aggregate[24] but to an additional $^2J_{\mathrm{C-C}}$ coupling arising between the magnetically nonequivalent ^{13}C of the cubic arrangement. It transforms the heptet in an AXX′X″ A′XX′X‴ A″XX″X‴ A‴X′X″X‴ system. A spectrum simulation[25] using a $^2J_{\mathrm{C-C}}$ coupling in the 2.5−3.0 Hz range gives a very good account for this observation (Figure 4S, Supporting Information). Note that this value is in line with those computed for the unsolvated optimized methyllithium $^{13}\mathrm{C}_4{}^1\mathrm{H}_{12}{}^6\mathrm{Li}_4$ tetramer ($^2J_{\mathrm{C-C}}$ = 3.3−3.6 Hz, see Computational Details in the Supporting Information, S13). Addition of 1 equiv of ^{6}LiCl to the "pure" $^{13}\mathrm{Me}^6\mathrm{Li}$ sample led to a ^{1}H spectrum showing two main doublets (Figure 3, line 3, left): one corresponds to the signal of the free methyllithium at δ −2.07 ppm while the second matches with the $[(\mathrm{MeLi})_m(\mathrm{LiCl})_n]$ peak at δ −2.22 ppm. The $^{13}\mathrm{C}-^6\mathrm{Li}$ coupled ^{6}Li spectrum (line 3, right) exhibits three signals that correspond to (i) the free methyllithium quartet at δ 1.87 ppm,[26] (ii) a doublet at δ 0.85 ppm (J = 9.6 Hz) consistent with a lithium coupled to one carbon only, and (iii) a singlet at δ 0.00 ppm (LiCl).

Knowing that the $[(\mathrm{MeLi})_m(\mathrm{LiCl})_n]$ complex under investigation contains a single type of Me surrounded by two equivalent lithium cations and a single type of Li bounded to only one methyl group allows us to sort among all possible aggregates exhibiting dicoordinated lithium cations (Figure 4). These characteristics eliminate not only the cubic tetramers (not represented in Figure 4) but also the trimeric complexes $[(\mathrm{MeLi})(\mathrm{LiCl})_2]$ (**B**) and $[(\mathrm{MeLi})_2(\mathrm{LiCl})]$ (**C**) for which two Li signals are expected, and the three pseudo-C_{2v} "planar" tetrameric structures (open cubic tetramers) which are $[(\mathrm{MeLi})_3(\mathrm{LiCl})]$ (**D**), $[(\mathrm{MeLi})_2(\mathrm{LiCl})_2]$ (**E**), and $[(\mathrm{MeLi})(\mathrm{LiCl})_3]$ (**G**), presenting two to three different Li. Finally, only the mixed dimer **A** and pseudo-D_{2h} tetramer $[(\mathrm{MeLi})_2(\mathrm{LiCl})_2]$ (**F**) account for all the spectroscopic data. The unlikely larger oligomers have not been considered.

The consistency of the information we had in hand at this stage was checked by a relative integration of the peaks in ^{1}H and ^{6}Li dimensions. They both fit the ratios imposed by their assignment to the $[(\mathrm{MeLi})(\mathrm{LiCl})]_x$ complexes **A** (x = 1) or **F** (x = 2) and to the free tetrameric methyllithium. The data in Table 1 show that, for x = 1, the relative proportions $[\mathrm{MeLi}]_4/[(\mathrm{MeLi})(\mathrm{LiCl})]_x$ calculated from the ^{1}H integrations are in fine agreement with those obtained from the ^{6}Li spectra and correlate a regular increase of the proportion of the complex with the added LiCl. Obviously, exactly the same correlation would be obtained for x = 2 with different proportions between $[\mathrm{MeLi}]_4$ and $[(\mathrm{MeLi})(\mathrm{LiCl})]_2$.

Discriminating between two highly symmetrical aggregates such as **A** and **F** by NMR is not easy. NMR diffusion experiments (DOSY), a technique that has recently been applied with success to organolithium species,[27] can eventually give access to useful information about the hydrodynamic radius of solvated species and therefore to their molecular weights. We thus ran a ^{1}H DOSY experiment on a mixture of $\mathrm{Me}^7\mathrm{Li}$ and ^{7}LiCl in the presence of three internal references (trimethyl-, tri-*tert*-butyl-, and triphenylbenzene chosen for their solubility, distinct resonance frequencies, and lack of reactivity toward the lithiated species considered here) in THF at 170 K.[28] The fine linear correlation (R^2 = 0.9995, Figure 5 and Supporting Information, S13) observed between the logarithm of the diffusion coefficients and the logarithm of the formula weights of the references provides an equation that can be used to interpolate the formula weight of the solvated mixed aggregate on the basis of the diffusion coefficients. Note that THF was not taken as an internal reference since the signal we observe results from the rapid exchange between molecules coordinated to the lithiated species in the solution and molecules in the bulk.

The result obtained (FW = 277) suggests that we are dealing either with $[\mathbf{A}]\cdot[\mathrm{THF}]_{2.7}$ or $[\mathbf{F}]\cdot[\mathrm{THF}]_{1.9}$. These fractional solvations can be interpreted as the average number of THF molecules that remain coordinated to the cations all along the diffusion delay and are therefore less than or equal to the "maximum" value of 4 and 8 THF molecules, respectively. If the value of 2.7 THF associated to **A** can be understood as a consequence of the lesser coordination energy of the second ether molecule to the same lithium

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[24] For leading references on the fluxionality of organolithium derivatives, see: (a) Fraenkel, G.; Fraenkel, A. M.; Geckle, M. J.; Schloss, F. *J. Am. Chem. Soc.* **1979**, *101*, 4745–4747. (b) Fraenkel, G.; Henrichs, M.; Hewitt, J. M.; Su, B. M.; Geckle, M. J. *J. Am. Chem. Soc.* **1980**, *102*, 3345–3350.

[25] Spectra simulations were performed with the Daisy Bruker software. See the Supporting Information.

[26] In contrast to the ^{13}C spectrum of MeLi, no ^2J coupling constant is observed as $^6\mathrm{Li}-^6\mathrm{Li}$ ^2J coupling is very small, as confirmed computationally (0.07 Hz)

[27] For a recent review about the determination of molecular size in solution by DOSY experiments, see: (a) Macchioni, A.; Ciancaleoni, G.; Zuccaccia, C.; Zuccaccia, D. *Chem. Soc. Rev.* **2008**, *37*, 479–489. For applications to organolithium derivatives, see: (b) Li, D.; Keresztes, I.; Hobson, R.; Williard, P. G. *Acc. Chem. Res.* **2009**, *42*, 270–280. (c) Lecachey, B.; Duguet, N.; Oulyadi, H.; Harrison-Marchand, A.; Fressigné, C.; Yamamoto, Y.; Tomioka, K.; Maddaluno, J. *Org. Lett.* **2009**, *11*, 1907–1910. (d) Kagan, G.; Li, W.; Hopson, R.; Williard, P. G. *Org. Lett.* **2010**, *12*, 520–523.

[28] The large tailing on the DOSY signals presented cannot be suppressed at the low temperature of these experiments. However, this phenomenon has no effect on the accuracy of the diffusion coefficients since the figures are generated by using curve fitting of signal attenuation data values and are not taken directly from the spectra (see the Supporting Information).

TABLE 1. Relative Proportions of the Protons and Lithiums in $[MeLi]_4$ and $[(MeLi)(LiCl)]$ As a Function of LiCl Proportion

	^1H spectra		^6Li spectra			
equiv of LiCl	integrations δ-$[MeLi]_4$[a]/ δ-$[(MeLi)(LiCl)]$[b]	rel proportions (%)	rel integrations δ-$[MeLi]_4$[c]/ δ-$[(MeLi)(LiCl)]$[d]	rel proportions (%)	average (%)	± (%)
0.00	162.3/8.4	82.8/17.2	1272.9/108.9	85.4/14.6	84.1/15.9	1.3
0.25	282.1/54.7	56.3/43.7	879.9/282.9	60.9/39.1	58.6/41.4	2.3
0.50	296.4/105.4	41.3/58.7	1122.9/689.3	44.9/55.1	43.1/56.9	1.8
0.75	136.4/72.6	32.0/68.0	1080.3/1016.8	34.7/65.3	33.3/66.7	1.4
1.00	128.7/97.7	24.8/75.2	872.5/1132.8	27.8/72.2	26.3/73.7	1.5
1.50	76.8/110.2	14.8/85.2	356.9/886.5	16.8/83.2	15.8/84.2	1.0
2.00	38.8/104.1	8.5/91.5	123.9/575.8	9.7/90.3	9.1/90.9	0.6
2.50	19.2/83.5	5.4/94.6	49.5/414. 0	5.6/94.4	5.5/94.5	0.1

[a] ^1H peak at δ −2.07 ppm. [b] ^1H peak at δ −2.22 ppm. [c] ^6Li peak at δ +1.87 ppm. [d] ^6Li peak at δ + 0.85 ppm.

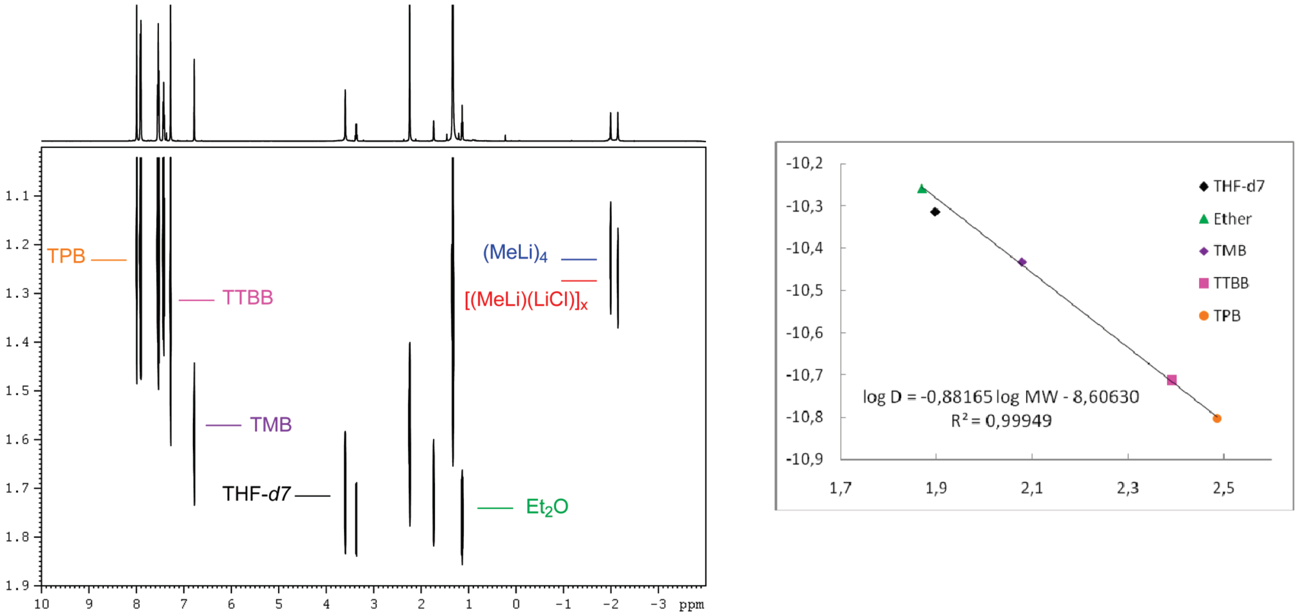

FIGURE 5. ^1H DOSY NMR experiment (THF, 170 K) of $[(MeLi)(LiCl)]_x$ in the presence of three internal references ($C_6H_3Ph_3$, $C_6H_3t\text{-}Bu_3$, and $C_6H_3Me_3$). The bidimensional plot on the left was recorded at 195 K for clarity. TMB: 1,3,5-trimethylbenzene; TTBB: 1,3,5-tri-*tert*-butylbenzene; TPB: 1,3,5-triphenylbenzene.

and thus of the third molecule in the trisolvated dimer,[29] the 1.9 THF coordination proposed for **F** is not very realistic as it requires a full desolvation of two dicoordinated lithium cations. Nevertheless, and to further discriminate between these two structures, we have undertaken a DFT geometry optimization of the $[\mathbf{F}]\cdot[Me_2O]_n$ series of complexes (with $n = 0, 2, 3, 4$) at a theoretical level described in the Supporting Information (S14). If **F** alone ($n = 0$) could be obtained as a planar "octagon" (Figure 6, left) relatively similar to the schematic structure of Figure 4, its partial solvation ($n = 2$) triggers distortions at the lithium cations such that the valence angles get close to the 120° associated to a tricoordination. A ladder structure is then obtained (Figure 6, center left). Increasing n to 3 leads to a more stable structure when the solvent is added on one of the unsolvated lithium cations. This structure exhibits additional out-of-plane distortions (Figure 6, center right). Provided they are favored in THF (which is unlikely in view of the theoretical results given in Table 2S in the Supporting Information, S16), these hyposolvated structures exhibit two types of lithium atoms connected to different ligands ("central" lithium connected to two chloride and a methyl and terminal lithium connected to one chloride and one methyl, see Figure 6) that would not fit the NMR data. Finally, no octagonal structure could be optimized for $n = 4$, and only a cubic structure was localized. All this led us to disregard the tetramer **F**.

We next considered the mixed dimer **A** and examined its solvation state, also from a computational point of view. Explicit THF molecules were used this time to increase the accuracy of the computations and the model considered was $[\mathbf{A}]\cdot[THF]_n$ with $n = 2\text{–}4$. In these conditions, going from $n = 2$ to 3 is associated to -2.6 kcal·mol^{-1} reaction free energy whereas going from $n = 3$ to 4 leads to $\Delta_rG^0 = +0.7$ kcal·mol^{-1}. These data are totally coherent with an average trisolvation for **A** associated to partial decoordination during the NMR measurement.

Finally, the consistency of this information leads us to propose that the mixed aggregate formed when mixing MeLi and LiCl in THF is $[(MeLi)(LiCl)]\cdot[THF]_3$. Note that cases

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[29] See for instance: (a) Yuan, Y.; Desjardins, S.; Harrison-Marchand, A.; Oulyadi, H.; Fressigné, C.; Giessner-Prettre, C.; Maddaluno, J. *Tetrahedron* **2005**, *31*, 3325–3334. (b) Pratt, L. M.; Johns, D.; Sease, A.; Busch, D.; Faluade, E.; Nguyen, S. C.; Thanh, B. T. *Int. J. Quantum Chem.* **2009**, *109*, 34–42.

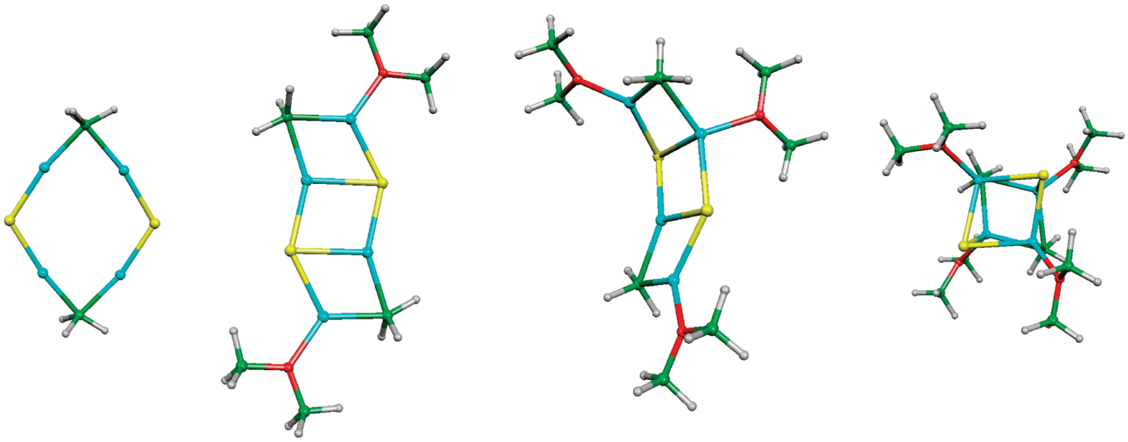

FIGURE 6. Evolution of the optimized geometry of $[(\text{MeLi})_2(\text{LiCl})_2].(\text{OMe}_2)_n$. Left: Planar form in the case $n = 0$. Center left: Ladder form for $n = 2$. Center right: Out-of-plane distortion for $n = 3$. Right: Cubic form and only optimized structure for $n = 4$. Color code: lithium (blue), chlorine (yellow), carbon (green), oxygen (red), hydrogen (gray).

TABLE 2. Value of *K* Calculated at Various Proportions of $(\text{LiCl})_2$ (concentrations in molcdt.L^{-1})

equiv of LiCl added	$[(\text{MeLi})_4]$	[A]	$[(\text{LiCl})_2]$	*K*
0	0.1098	0.0208	0.0072	0.42
0.25	0.0761	0.0539	0.0285	0.61
0.5	0.0552	0.0730	0.0551	0.64
0.75	0.0414	0.0829	0.0804	0.65
1	0.0317	0.0890	0.1050	0.65
1.5	0.0182	0.0974	0.1542	0.67
2	0.0101	0.1005	0.2070	0.70
2.5	0.0057	0.0974	0.2490	0.71

of di-, tri-, and tetrasolvation by THF have been reported before for heterogeneous and homogeneous dimers.[27b]

Calculation of an Equilibrium Constant. Comparing the MeLi/LiCl system to the MeLi/LiBr or MeLi/LiI couples points the finger at an important difference that is the persistent signal of $[\text{MeLi}]_4$ that is observed even in the presence of 2.5 equiv of LiCl. This signal quickly disappears in the presence of LiBr. An equilibrium between the methyllithium, the lithium chloride, and now well-identified dimer **A** is thus taking place and we decided to evaluate its constant *K*. This requires a proper definition of the interacting species. If methyllithium is known to adopt preferentially a tetrameric form in THF, the situation is not as clear-cut for LiCl. From vapor phase osmometric studies, Wong and Popov have proposed that LiCl forms a dimer at 310 K (37 °C) in this solvent.[30] This result was supported by ^{7}Li NMR data published later on by Reich and co-workers.[31] On the other hand, a separated ion pair was proposed by Pregosin and colleagues on the basis of PGSE diffusion NMR spectroscopy.[32] In the presence of HMPA, a tetrasolvated tetramer $(\text{LiCl})_4(\text{HMPA})_4$ was evidenced in the solid state,[33] while a solvated LiCl(HMPA) or LiCl(HMPA)_2 monomer was proposed in THF/HMPA.[31]

The *K* constants derived from the various equations involving LiCl as a monomer, a dimer, or a tetramer have all been evaluated. We found that only for $(\text{LiCl})_2$ is *K* reasonably constant (≈0.65, Table 2) on the range of LiCl concentrations studied here. The equation considered for the equilibrium is:

$$^{1}/_{4}(\text{MeLi})_4 + {}^{1}/_{2}(\text{LiCl})_2 \leftrightarrows [(\text{MeLi})(\text{LiCl})]$$

The corresponding *K* constants have been calculated on the basis of the concentration of $[\text{MeLi}]_4$, **A**, and $[\text{LiCl}]_2$ estimated from the integration of the NMR signals averaged in Table 1. The fact that $K < 1$ shows that the equilibrium does not favor the formation of the mixed dimer.

Theoretical Investigation on the Difference between LiCl and LiBr Behaviors. The difference between the size of the oligomers resulting from a lithium chloride or bromide can be understood within the perspective of a simple “like yields like” principle:[34] tetrameric lithium bromide yields tetrameric mixed aggregates whereas dimeric lithium chloride yields dimeric mixed aggregates. The origin and generality of this simple and useful empirical rule deserved to be explored. The thermodynamic cycles described in Figure 7 were designed in that aim. Because this rule applies to both chloride and bromide in the same solvent, solvation can hardly be a factor of importance here, and thus the solvent effects were not taken into account. We decomposed the transformations tetramers → mixed tetramers (eq 1, Figure 7) and dimers → mixed dimers (eq 2, Figure 7) into two formal sequences tetramer → dimers → monomers for LiX (X = Cl or Br). Along these sequences, the energies of the elementary steps differ marginally between the bromide and chloride, except for two of them. The similarity includes the mixing steps, that is eqs 1 and 2, which are quasi-isoenergetic for chloride and bromide (always less than 2 kcal·mol^{-1} in absolute energy). As a consequence, the energy of formation of mixed aggregates by condensation of two homogeneous aggregates of the same size is not sensitive to the nature of the halide: the energy of formation of the mixed tetramer (eq 1) and of the mixed dimer (eq 2) differ by less than 0.5 kcal·mol^{-1} when changing Cl into Br. The main difference between Cl and Br lies within the formation of the $(\text{Li}_4\text{Me}_n\text{X}_{4-n})$ tetramers from

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(30) Wong, M. K.; Popov, A. I. *J. Inorg. Nucl. Chem.* **1972**, *34*, 3615–3622.

(31) Reich, H. J.; Borst, J. P.; Dykstra, R. R.; Green, D. P. *J. Am. Chem. Soc.* **1993**, *115*, 8128–8741.

(32) Fernández, I.; Martínez-Viviente, E.; Breher, F.; Pregosin, P. S. *Chem.—Eur. J.* **2005**, *11*, 1495–1506.

(33) Barr, D.; Clegg, W.; Mulvey, R. E.; Snaith, R. *J. Chem. Soc., Chem. Commun.* **1984**, 79–80.

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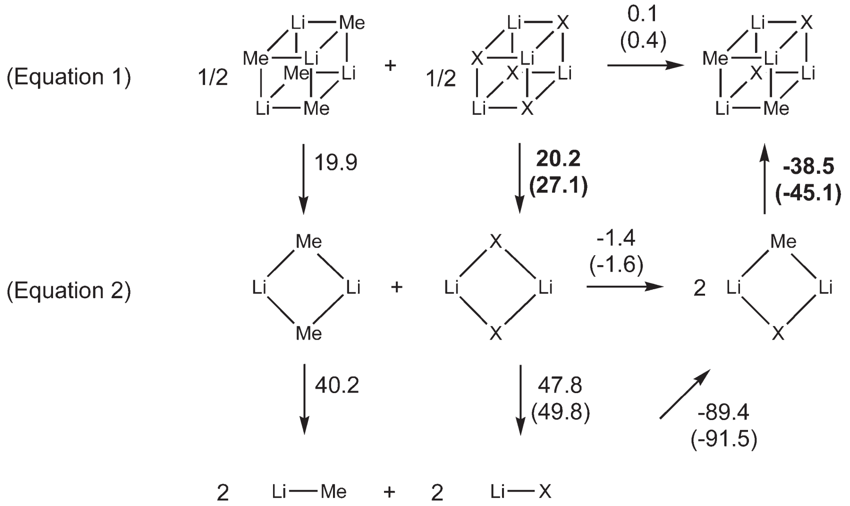

FIGURE 7. Aggregation of MeLi and LiX in homogeneous and heterogeneous dimers and tetramers. Energies are in kcal·mol^{-1}, top values are for X = Cl and values in parentheses for X = Br. Bold figures are used to emphasize steps where chloride and bromide differ by more than 5 kcal·mol^{-1}.

homogeneous or heterogeneous dimers. In both cases, the formation of the bromide-containing tetramer is more exoenergetic by nearly 7 kcal·mol^{-1} than those containing chloride. As a consequence, if the Li_4X_4 fragmentation into two Li_2X_2 is more endothermic (by 6.9 kcal·mol^{-1}) for Li_4Br_4 than for Li_4Cl_4 (+27.1 vs. +20.2 kcal·mol^{-1}), this difference is counterbalanced by the formation of the mixed tetramer as the combination between two Li_2XMe mixed dimers is more exothermic (by 6.6 kcal·mol^{-1}) for Li_2BrMe than for Li_2ClMe (−45.1 vs −38.5 kcal·mol^{-1}). Thus, not only is the dissociation $Li_4Br_4 \rightarrow 2Li_2Br_2$ disfavored with respect to $Li_4Cl_4 \rightarrow 2Li_2Cl_2$ but the recombination $2Li_2MeBr \rightarrow Me_2Br_2Li_4$ is more favorable than the corresponding $2Li_2MeCl \rightarrow Me_2Cl_2Li_4$. Such behavior can be generalized to various compositions of dimer, trimers, and tetramers (see Figure 6S in the Supporting Information for details).

The tendency for bromide to make higher order aggregates can be directly correlated to the molecular characteristics of the lithium halides. The computed dipole moments for LiCl and LiBr are very similar (7.16 D for Cl and 7.12 D for Br): the formation of dimers by interaction of two monomers is thus isoenergtic for Cl and Br. Since the dimers have no dipole moments, their association into tetramer should be related to the interactions between quadrupoles.[35] Actually, these latter are significantly larger for LiBr (−45.8, −30.1, −62.0 D·Å) than for LiCl (−33.3, −12.3, −49.7 D·Å): this leads to larger interaction energies between LiBr dimers. This can explain why cubic tetrameric arrangements are always preferred with LiBr; this constraint is not as compulsory for LiCl.

Conclusions

This paper shows that a mixture of methyllithium and lithium chloride in THF is in equilibrium ($K \approx 0.65$) with a single mixed dimer [(MeLi)(LiCl)], never described before. Our data also suggest that this complex is trisolvated in THF. This finding, unexpected for a MeLi/LiX couple, necessitated the combination of multinuclear low-temperature NMR spectroscopy on monolabeled and doubly labeled $^{13}CH_3{}^6Li$ combined with quantum computations despite the simplicity of the partners involved. Our results also suggest that $(LiCl)_2$ is the stable oligomer in THF at low temperature. The occurrence of a single dimer contrasts sharply with the multiple compact mixed cubic tetramers observed for the MeLi/LiBr or LiI systems[11] and could be at the molecular origin of the different effects induced by these salts in organic, inorganic, and organometallic chemistry. Smaller aggregates and low-coordination complexes in general are expected to be more reactive, even if *the correlation of aggregation state and organolithium reactivity is based more on consensus than on experiment*,[36] and the effect of LiCl on the reactivity has been clearly evidenced in many cases.[37]

Experimental Section

[^{6}Li]-Methyllithium Salt-Free Solution in Ether.[12a,13,15a] Finely cut 6-lithium metal ribbon (0.5 g, 83 mmol), 0.5% (weight) of sodium (ca. 2,5 mg, 0,11 mmol), and three small pieces of broken glass were introduced into a two-necked pear-shaped flask (50 mL) equipped with a glass stopper and a condenser fitted with a balloon of dry argon. The metallic cuttings were covered with octadecane (10 mL) and the solution was heated (reflux of octadecane: 317 °C) with a hot air gun with vigorous stirring. When a maximum amount of the lithium was melted, the flask was placed in a cold bath (−40 °C) allowing the lithium to precipitate as a fine shiny shot. The octadecane was extracted with freshly distilled heptane (10 mL), using a syringe. After intensive stirring, the heptane was removed and the metal was washed twice with this same solvent. Diethyl ether was syringed and the condenser was quickly replaced by a CO_2 condenser fitted

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[35] We also carried out an analysis in terms of distorsions as described by Fressigné et al. (Fressigné, C.; Maddaluno, J.; Giessner-Prettre, C. *J. Chem. Soc., Perkin Trans. 2* **1999**, 2197–2201.) but did not find any difference between bromide and chloride.

[36] Collum, D. B. *Acc. Chem. Res.* **1992**, *25*, 448–454.

[37] See for instance: (a) Reich, H. J.; Sikorski, W. H.; Gudmundsson, B. Ö.; Dykstra, R. R. *J. Am. Chem. Soc.* **1998**, *120*, 4035–4036. (b) Quirk, R. P.; Lee, Y. *J. Polym. Sci., Part A: Polym. Chem.* **2000**, *38*, 145–151. (c) Zune, C.; Archambeau, C.; Dubois, P.; Jérôme, R. *J. Polym. Sci., Part A: Polym. Chem.* **2001**, *39*, 1774–1785. (d) Hodgson, D. M.; Miles, T. J.; Witherington, J. *Tetrahedron* **2003**, *59*, 9729–9742. (e) Gupta, L.; Hoepker, A. C.; Singh, K. J.; Collum, D. B. *J. Org. Chem.* **2009**, *74*, 2231–2233. (f) Ocejo, M.; Carrillo, L.; Badía, D.; Vicario, J. L.; Fernández, N.; Reyes, E. *J. Org. Chem.* **2009**, *74*, 4404–4407.

with a balloon of dry argon. Chloromethane (2,3 mL, 41, 5 mmol) was condensed directly from the sealed cylinder to a graduated trap at −40 °C and then added very slowly (2,3 mL were added over a period of 45 min) connecting the trap to the top of the CO_2 condenser. The formation of a gray salt corresponding to LiCl was observed and the disappearance of the ^{6}Li metal was noticed. After replacing the CO_2 condenser with a septum, the resulting reaction mixture was stirred for 20 h at room temperature under dry argon. The stirring was stopped allowing LiCl to settle. The ethereal solution was then pumped off the flask with a syringe and directly inserted into centrifugation tubes placed under dry argon. The residual traces of salt were centrifuged and the clear final solution was collected in a dry flask flushed under dry argon then titrated[38] (1.4 M, 55% yield) and kept until further use.

[^{6}Li]-Methyllithium "Salt-Free Solution" in Tetrahydrofuran-*d_8*.[23] A solution of [^{6}Li]-methyllithium in ether prepared above (2.5 mL) was syringed into a tube fitted with a septum and flushed under dry argon. The tube was then placed under vacuum (20 mmHg) for 1 h to evaporate the ether. The resulting white solid was then dissolved in freshly distilled tetrahydrofuran-d_8 and concentrated under vacuum for 1 h to evaporate the last traces of ether. THF-d_8 (3 to 3.5 mL) was finally added and the resulting solution was titrated (0.5 to 0.7 M).

[^{6}Li]-Lithium Chloride Solution in Tetrahydrofuran-*d_8*. Residual [^{6}Li]-lithium chloride from the [^{6}Li]-methyllithium synthesis described above was rinsed three times with diethyl ether (3 × 5 mL). Centrifugations were conducted for this operation. The solvent was finally removed and the tube was placed under vacuum (20 mmHg) for 4 h to eliminate a maximum of the diethyl ether. The resulting white solid was dissolved in freshly distilled tetrahydrofuran-d_8 and the solution was concentrated under vacuum for 1 h to evaporate the last traces of diethyl ether. THF-d_8 (2 mL for about 50 mg of "dry" LiCl) was finally added and left for a night at room temperature to completely dissolve the lithium salt. The resulting solution was titrated by a classical potentiometric technique (0.3 to 0.6 M).

Silvermetric Titration of [^{6}Li]-Lithium Chloride Solution in Tetrahydrofuran-*d_8*. A solution of [^{6}Li]-lithium chloride in tetrahydrofuran-d_8 (50 μL) was placed in a beaker and diluted with water (75 mL). The solution was titrated by a silver nitrate solution ($C = 5 \times 10^{-3}$ M) with a Mettler DL 21 Titrator fitted with a silver electrode.

[^{6}Li],[^{13}C]-Methyllithium Salt-Free Solution in Tetrahydrofuran-*d_8*.[23] Labeled [^{13}C]-methyl iodide (0.22 mL) and hexane (2 mL) were introduced into a centrifugation tube placed under dry argon and equipped with a magnetic stirrer. An equimolar amount of [^{6}Li]-*n*-butyllithium in hexane solution was added at −78 °C. The temperature of the reaction mixture was raised from an initial −78 to −30 °C (until cloudiness developed, indicating methyllithium precipitation) and finally to 0 °C over a 20 min period. The precipitated [^{6}Li],[^{13}C]-methyllithium was centrifuged and the hydrocarbon solution, containing residual methyl iodide and *n*-butyl iodide, was pumped off the tube. The solid residue (labeled MeLi) was washed twice with hexane (4 mL), then placed under vacuum (1 mmHg) for 4 h to evaporate a maximum of the hydrocarbon solvent. The resulting white solid was dissolved in freshly distilled tetrahydrofuran-d_8 and concentrated under vacuum for another hour. THF-d_8 (2.5−3.0 mL) was finally added and the resulting solution was titrated[38] (0.7−1.0 M). Note the presence of lithium iodide (5−10%) in the solution.

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Supporting Information Available: Computational, experimental, and instrumental details, supplementary spectra, as well as computed binding energies and relative stabilities of the mixed tetramers. This material is available free of charge via the Internet at http://pubs.acs.org.

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[38] Duhamel, L.; Plaquevent, J. C. *J. Organomet. Chem.* **1993**, *448*, 1–3.