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The smaller, the better? How aggregate size affects the reactivity of (trimethylsilyl)methyllithium

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Weighting both the basicity and the nucleophilicity of an organolithium compound is crucial for an effective use of these reagents in syntheses. To achieve this, an aggregate of optimal size and reactivity has to be formed by adding suitable donating agents. Against usual expectations, this is not inevitably the smallest possible aggregate. In this work, we show that the monomeric complex of (trimethylsilyl)methyllithium stabilized by the bidentate ligand (*R*,*R*)-TMCDA shows no significant reactivity. On contrary, two dimeric aggregates stabilized by monodentate quinuclidine were obtained, exhibiting enhanced reactivity compared to the parent compound and to the monomeric complex.

Introduction

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The reactivity of alkyllithium compounds is strongly related to their structure.¹ Depending on steric demands and electronic effects, a variety of structural motifs can be observed.² In most synthetic applications of these reagents, the admixture of Lewis-basic additives aims to stabilize smaller and therefore as assumed in literature – more reactive aggregates,³ aspiring the formation of the supposedly ideal case of a monomeric species of a primary organolithium compound. However, our work presented here will give a more differentiated view on this relationship. In general, the steric demand of the additive as well as the size of the alkyl moiety determine the degree of deaggregation (see Figure 1 top). According to this, the addition of sterically demanding (-)-sparteine enables the formation of monomeric tert-butyllithium,4 whereas the smaller primary alkyllithium compound n-butyllithium forms tetramers in presence of the sterically less demanding additive tetrahydrofurane (thf).5 The heteroatom-stabilized primary (trimethylsilyl)methyllithium, Me₃SiCH₂Li, combines both tendencies. Whereas it is - identical to likewise primary n-butyllithium hexameric in the absence of donating agents,⁶ the addition of the bidentate ligands (-)-sparteine or N,N,N',N'-tetramethylethylenediamine (tmeda) leads to the formation of dimeric aggregates.7 An interesting octameric coordination mode was obtained by the group of Stalke upon the addition of 1,4-Diazabicyclo[2.2.2]octane (dabco). Instead of the formation of a coordination polymer, a molecular assembly of four dimeric units linked by dabco is observed, leading to an increased reactivity compared to the parent hexameric aggregate.⁸ A monomeric compound can be obtained by addition of the tridentate ligand



 Me2
 SiMe3

 2
 3, 4

 monomeric
 dimeric

 Figure 1: Top: Deaggregation of alkyllithium compounds by donor bases.

 Bottom: Formation of small aggregates of Me3SiCH2Li by the addition of bidentate (*R*,*R*)-TMCDA (5) and monodentate quinuclidine (6).

N,N,N',N'',N''-pentamethyldiethylenetriamine (pmdta).⁷ In contrast, no monomeric aggregate is known to date for *n*-butyllithium. The knowledge of these principles is crucial for an effective use of the different commercially available organolithium reagents. When planning a synthesis, a compromise of cost and use can be accomplished when considering the known structures of the most widely used alkyllithium reagents. Nevertheless, unexpected reactivities are encountered in some syntheses, where the use of the most reactive base system does not lead to the best results. This is, among others, observed for Me₃SiCH₂Li. For instance, Stalke *et al.* observed the formation of pure crystalline benzyllithium by using Me₃SiCH₂Li for the deprotonation of toluene.⁹ Here, the use of other – presumably

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Electronic Supplementary Information (ESI) available: Experimental details, NMR spectra, crystallographic data and details of DFT calculations. CCDC 1908867, 1908868, 1908869. For ESI and crystallographic data see DOI: 10.1039/x0xx00000x

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Figure 2: Monomeric Me₃SiCH₂Li stabilized by (*R*,*R*)-TMCDA (compound **2**). Left: Molecular structure of **2** in the crystal (top view). Selected bond lengths [Å] and angles [°]:C1-Li1 2.069(3), N1-Li1 2.050(2), N2-Li1 2.049(4), Si1-C1 1.8075(17), Si1-C2 1.887(2), Si1-C3 1.8958(18), Si1-C4 1.887(2); Si1-C1-Li1 114.64(12), C1-Si1-C2 110.44(10), C1-Si1-C3 117.89(9), C1-Si1-C4 110.37(10), C2-Si1-C3 105.09(12), C2-Si1-C4 107.60(10), C3-Si1-C4 104.84(11). Right: Connolly surface of compound **2**, calculated with a probe radius of 1.4 Å (side view).

more reactive - alkyllithium reagents leads to undesired side reactions like ortho or meta dilithations. Avoiding side reactions and reagent degradation when using Me₃SiCH₂Li instead of other alkyllithiums was also achieved by the group of Gros, who established a base system formed by Me₃SiCH₂Li and DMAE to give a reagent capable of functionalizing bromo- and chloropyridines selectively under mild conditions.¹⁰ They encountered another advantage of Me₃SiCH₂Li since it exhibits a strongly decreased nucleophilicity compared to other primary organolithium compounds. Especially in the conversion of multi-functionalized substrates a consideration of the basicity and nucleophilicity of alkyllithium compounds is crucial since it determines the regioselectivity of the organolithium reagent's attack. Nevertheless, a decreased nucleophilicity mostly results in increased deprotonation barriers. It might therefore be desirable to increase this reactivity of Me₃SiCH₂Li by the addition of a suitable donating agent to give a potent base system. While fundamental works on the structural chemistry of Me₃SiCH₂Li combined with common chelating agents was previously performed by the group of Stalke,⁷ we focused on the interrelation of structure and reactivity. A detailed knowledge of the reagent's structure is pivotal for understanding reaction pathways which proceed via transition states closely related to the starting material. Regarding alkyllithium reagents, significant reactivity can be observed for compounds in which the lithium centers are accessible for a donating site of the substrate. In our work presented here we were able to show that this can be achieved not in a monomeric complex of (trimethylsilyl)methyllithium, but in dimeric aggregates. This allows deprotonation reactions on the substrate to take place more easily, which is referred to in this work as "reactivity".

Results and Discussion

We tested two different nitrogen-based donor ligands on their ability to form reactive aggregates of Me_3SiCH_2Li . The first one was the bidentate (*R*,*R*)-TMCDA (5), whose chelating

coordination mode might lead to the formation of small aggregates. The second one was the strained monodentate ligand quinuclidine (6), which offers increased donating properties due to its strongly directed lone pair. Herein we present solid state structures of small aggregates of Me_3SiCH_2Li stabilized by these donating agents. The stabilizing effects as well as the synthetic impact of these systems are discussed, based on experimental as well as theoretical findings.

Deaggregation of (trimethylsilyl)methyllithium by bidentate (*R*,*R*)-TMCDA (5)

In the presence of the chiral bidentate ligand (R,R)-TMCDA (**5**), we observed a monomeric complex of Me₃SiCH₂Li, the structure of which is shown in Figure 2. It adds to the small number of monomeric complexes of primary alkyllithium compounds.⁷ Compound **2** crystallizes in the monoclinic crystal system in the space group $P2_1$. The lithium cation is coordinated by both nitrogen atoms of the (R,R)-TMCDA ligand, resulting in an incomplete coordination sphere with a coordination number of three. To the best of our knowledge, based on a structure search in the CCDC database, this is the first example of a primary organolithium compound exhibiting such a low coordination number in a monomeric complex.

The formation of a monomeric species of a primary alkyllithium compound is an unusual observation. For the most common of these, *n*-butyllithium, the smallest aggregate known to date is a dimer, since the lack of stabilizing substituents at the carbanionic center results in a higher degree of aggregation. In contrast, Me₃SiCH₂Li benefits from the additional stabilizing effect of the neighboring silicon atom, which can stabilize an adjacent negative charge via the α -effect. This is often explained by negative hyperconjugation of the negative charge into the anti-binding molecular orbital of the Si–C bonds to an antiperiplanar oriented substituent, resulting in a weakening and elongation of this contact. ¹¹This is not observed for complex **2**, in which the Si–C contacts of the trimethylsilyl group show no significant differences [Si1–C2 1.887(2) Å, Si1–C3 1.8958(18) Å, Si1–C4 1.887(2) Å]. Additional quantum chemical calculations

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Figure 3: Dimeric aggregates of Me₃SiCH₂Li stabilized by two (left, aggregate **3**, ^a = 1–x, y, 1.5–z) and three (right, aggregate **4**, half a molecule of co-crystallized quinuclidine omitted for clarity) molecules of quinuclidine (**6**). Selected bond lengths [Å]: Aggregate **3**: Si1-C1 1.8306(10), Si1-C2 1.8878(11), Si1-C3 1.8855(11), Si1-C4 1.8971(11), N1-Li1 2.0822(19), C1-Li1 2.185(2), Si1-C1-Li1 94.79(6), N1-Li1-C1 123.67(9), C2-Si1-C4 107.80(5), C2-Si1-C3 104.87(5), C1-Si1-C3 117.29(5); aggregate **4** Si1-C8 1.887(2), Si1-C9 1.885(2), Si1-C1 1.885(2), Si2-C11 1.837(2), Si2-C12 1.8331(19), Si2-C13 1.885(2), Si2-C14 1.883(2), Si2-C15 1.896(2), N1-Li1 2.123(4), N2-Li2 2.141(4), N3-Li2 2.164(4), C11-Li1 2.169(4), C11-Li2 2.280(4), C12-Li1 2.181(4), C12-Li2 2.284(4), Li1-C11-Li2 65.84(14), Li1-C12-Li2 65.60(14), C11-Li1-C12 117.95(17), C11-Li2-C12 109.55(15), N2-Li2-N3 109.14(16), N1-Li1-C11 121.00(18), N1-Li1-C12 115.71(17), N2-Li2-C11 108.15(16), N2-Li2-C12 106.86(16).

[B3LYP, 6-31+G(d), gd3 dispersion correction] also revealed no elongation of the Si–C bonds. This hints on a stabilization of the negative charge by polarization of the silicon center, which is further stressed by a short Si1–C1 distance of 1.8075(17) Å.

In contrast to our expectations and to the usual principles of organolithium compounds, this monomeric species with a threefold coordinated Li⁺ exhibits no significant reactivity. Although the carbanionic center has only one contact to the adjacent lithium cation and might therefore be accessible to substrates, as it can be observed for monomeric sec-butyllithium stabilized by (R,R)-TMCDA,¹² complex **2** was not capable of deprotonating any of the model compounds we employed in test reactions, as benzene, toluene, and N,N-dimethylbenzylamine (7). Motivated by these experimental findings we conducted guantum chemical calculations to obtain information on the aggregate's sterical accessibility, which can be described by the so-called Connolly surface. It can be understood as the distance to which a probe body of a defined radius can approach the molecule (see Figure 2, right). In accordance with the experimental results, the simulation of the surface clarifies the steric shielding of the lithium cation of complex 2. The methyl groups

of the ligand $\mathbf{5}$ as well as the CH₂ protons of the carbanionic center prohibit the approach of a substrate to the lithium cation, which is assumed to be the first step in a deprotonation reaction of an organolithium reagent. Due to its chelating character, the bidentate ligand is not expected to release a single coordination site. To give space for a reaction at the carbanionic center, a full detachment of the ligand would be necessary, leading to the formation of a "naked" monomeric alkyllithium compound and therefore an unreachable high energy demand. As a consequence, no reasonable reaction path for a deprotonation reaction can be modeled, wherefore we performed no calculations of any activation energies for these reactions. As this example shows, the detailed knowledge of the structure and the related reactivity of an organolithium base system is essential to ensure an effective use in synthetic applications. Within this, the use of the smallest aggregate does not inevitably lead to the most satisfying results.



Scheme 1: Deprotonation reactions of N,N-dimethylbenzylamine by Me₃SiCH₂Li in the absence (left) and presence (right) of quinuclidine (6).

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Scheme 2: Calculated isodesmic reaction of the replacement of one donating quinuclidine (6) by substrate 7 as a first step to a deprotonation of 7 [B3LYP/6-31+G(d)/gd3].

Deaggregation of (trimethylsilyl)methyllithium by monodentate quinuclidine (6)

This finding is also stressed by our examinations of two dimeric aggregates of Me₃SiCH₂Li stabilized by the strained monodentate ligand quinuclidine (6). Within these aggregates, the number of stabilizing donor base molecules varies from two to three (see Figure 3). According to the increased number of ligands, the N-Li bond lengths differ in both structures. Whereas aggregate 3 is a symmetric dimer with N-Li distances of 2.0822(19) Å, aggregate 4 exhibits an unsymmetrical coordination of the Li cations. Li1 is coordinated by one molecule of 6 at a distance of 2.123(4) Å. At Li2, two Li-N contacts are observed, with lengths of 2.141(4) Å for Li2-N2 and of 2.164(4) Å for Li2-N3, respectively. This hints on a relatively weak coordination of the third ligand molecule, enabling the coordination of a substrate to be deprotonated and therefore giving rise to a synthetic application of the dimeric aggregates. We probed this in the synthetically relevant deprotonation reaction of (N,N)-dimethylbenzylamine (7) with subsequent trapping with trimethylchlorosilane (see Scheme 1). 13 Whereas no reaction was observed in the absence of donating agents, the

addition of quinuclidine (6) leads to an isolated yield of 82% of the trapping product after reacting for three hours in refluxing heptane. The use of non-polar solvents contributes to a distinct control of the base system's reactivity by avoiding the occupation of reactive sites by donating solvent molecules.

Again, quantum chemical calculations were used to substantiate these experimental findings. Our first goal was to determine the quantum chemical method which describes the experimental findings best. Previous benchmarking work in our own group revealed that the functional M062X gives the smallest deviations of experimental bond lengths in gas phase calculations of organolithium compounds.14 In the case of aggregates **3** and **4**, the Li–N distances obtained by calculations on the M062X level of theory and the basis set 6-31+G(d) were slightly too small (see supplementary information for a detailed comparison of the theoretical and experimental results). Whereas bond lengths determined on the B3LYP level of theory showed to be slightly elongated, the experimental results were reflected best by an additional gd3 dispersion correction on the B3LYP functional. In the following calculations, this method was used in combination with the basis set 6-31+G(d).



Reaction coordinate

Figure 4: Relative energies (kI·mol⁻¹) and optimized geometries of the assumed mixed aggregate **9** and the transition state **9-TS** of its deprotonation by quinuclidine-stabilized Me₃SiCH₂Li [B3LYP/6-31+G(d)/gd3].

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On the basis of the varying number of quinuclidine molecules in the solid state, we assumed that the replacement of one donor base by the substrate is the first step in the deprotonation of (N,N)-dimethylbenzylamine (7) by Me₃SiCH₂Li (see Scheme 2). Calculations of the underlying isodesmic reaction revealed an energy need of only 6 kJ/mol for the replacement, hinting on an equilibrium of both aggregates. Starting from the assumed mixed aggregate 9, the transition state 9-TS of the deprotonation reaction was calculated to give an energy barrier of 96 kJ/mol (see Figure 4). The addition of both processes – building aggregate 9 and its deprotonation – gives a total activation energy of 102 kJ/mol (see Supporting Information for further details on the performed calculations). This explains the need of high temperatures for the deprotonation reaction since it was conducted in refluxing heptane. In the transition state 9-TS, two lithium centers are involved in stabilizing the carbanionic species, stemming from the two Me₃SiCH₂Li moieties of the pervious dimeric aggregate 4. Upon deprotonation of substrate 7, one of these lithium centers establishes a stabilizing contact to the deprotonated ortho carbanionic center. Its proton is abstracted by one of the Me₂SiCH₂ carbanions, leading to the formation of tetramethylsilane and releasing the formerly coordinated lithium cation. This cooperative effect of both Me₃SiCH₂Li moieties, which might be crucial for the observed reactivity, cannot take place in a monomeric complex. This again stresses the impact of the organolithium's structure on its ability to be involved in any chemical conversions. Although dimers 3 and 4 are not the smallest possible aggregates of Me₃SiCH₂Li, our experimental and supplementary theoretical observations show that they exhibit reactivity towards N,Ndimethybenzylamine (7), in contrast to the monomeric complex 2 formed in presence of (R,R)-TMCDA, underlining the importance of a detailed knowledge of the structure of the organolithium base to achieve sufficient reactivity and best efficiency of a deprotonation reaction.

Experimental Section

General Remarks

All experiments were performed under an atmosphere of argon by using standard Schlenk techniques. n-heptane was dried by refluxing over sodium and distilled under an atmosphere of argon prior to use. All reagents were used as commercial products without further purification. NMR spectra were recorded on a Bruker AV Avance III HD spectrometer. All NMR spectra were recorded at room temperature (ca. 22 °C). ¹H NMR and ${^{1}H}^{13}C$ NMR chemical shifts (δ) are reported in parts per million (ppm) and referred to tetramethylsilane (TMS, δ = 0.0 ppm) with the deuterium signal of the solvent serving as internal lock and residual solvent signals as an additional reference. {1H}29Si NMR chemical shifts are reported in ppm, referenced to an external standard of TMS (δ = 0.0 ppm), and measured via the INEPT puls sequence. For the assignment of the multiplicities the following abbreviations were used: s = singlet, m = multiplet.

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Quantumchemical Calculations

All quantumchemical calculation were performed using Gaussian09, Revision E.0115 on the B3LYP/6-31+G(d) level of theory with additional gd3 empirical dispersion correction according to Grimme.¹⁶ The starting structures were modeled using the GaussView interface and their energies were optimized. A subsequent frequency calculation confirmed ground structures by showing no imaginary frequencies. In the case of transition states, one imaginary frequency was observed. For the comparison of energies, zero-point corrected energies were used, enabling the discussion of ΔH values. The visualization of the optimized structures was aimed by the software Molekel V4.3.17 Connolly surfaces were calculated by Molekel V4.3, representing the surface to which a probe body with a radius of 1.4 Å can approach the molecule. For further details and complete results including absolute energies in Hartree, see Supporting Information.

Experimental Details

Crystallization of Me₃SiCH₂Li·(R,R)-TMCDA (2). A solution of 0.170 g (1 mmol, 1 eq.) (R,R)-TMCDA in 3 mL dry *n*-pentane was cooled to -30 °C. After the addition of 1 mL (1 mmol, 1 eq.) of a 1 M Solution of Me₃SiCH₂Li in pentane, the mixture was stored at -80 °C for crystallization. After one week colorless needles of compound **2** were obtained. ¹H NMR (400.25 MHz, C_6D_6): δ = -1.54 (s, 2H, SiCH₂), 0.44 [s, 12 H; CH₂Si(CH₃)₃], 0.58 - 0.70 [m, 4 H; (CH₃)₂NCHCH₂CH₂], 1.33 – 1.43 [m, 4 H; (CH₃)₂NCHCH₂CH₂], 1.79 – 1.81 [m, 2 H; (CH₃)₂NCHCH₂CH₂], 1.93 [s, 12 H; (CH₃)₂N] ppm. {¹H}¹³C NMR (100.64 MHz, C₆D₆): $\delta = -5.7$ [1C; (CH₃)SiCH₂], 6.6 [3C; (CH₃)SiCH₂], 22.0 [2C; (CH₃)₂NCHCH₂CH₂], 25.3 [2C; $(CH_3)_2NCHCH_2CH_2],$ 40.5 [4C; (*C*H₃)₂N], 64.2 [2C: $(CH_3)_2NCHCH_2CH_2$] ppm. ⁷Li NMR (155.55 MHz, C₆D₆): δ = 2.8 [1Li; (CH₃)SiCH₂Li] ppm. {¹H}²⁹Si NMR (79.52 MHz, C₆D₆): δ = -3.6 [1 Si; (CH₃)SiCH₂Li] ppm.

Deprotonation reactions utilizing Me₃SiCH₂Li·(*R***,***R***)-TMCDA (2). Solutions of 0.170 g (1 mmol, 1 eq.) (***R***,***R***)-TMCDA (5) and 1 mmol of the substrate [0.170 g (***N***,***N***)-dimethylbenzylamine (7), 0.08 mL benzene, 0.10 mL toluene] in dry** *n***-pentane were cooled to -30 °C and each added 1.0 mL (1 mmol, 1 eq.) of a 1M solution of Me₃SiCH₂Li in pentane. The reaction mixtures were warmed to rt and stirred for 3 h. After cooling to -30 °C, 0.13 mL (1 mmol, 1 eq.) Me₃SiCl was added each. The mixtures were warmed to rt again and stirred for 1 h. After quenching with 5 mL aqueous NH₄Cl, the layers were separated and the organic layers were analyzed by GC/EI-MS. No reaction products could be observed in all reactions.**

Crystallization of (Me₃SiCH₂)₂ · n quinuclidine (3: n=2; 4: n=3). A solution of 0.111 g (1 mmol, 1 eq.) quinuclidine in 3 mL dry *n*-pentane was cooled to -50 °C. At this temperature, 1 mL (1 mmol, 1 eq.) of a 1 M solution of Me₃SiCH₂Li in pentane was added. Upon warming to -20 °C, crystallization began. The solution was stored at -80 °C. After two weeks, colorless diamond-shaped plates of **3** and hexagonal plates of **4** were obtained. ¹H NMR (400.25 MHz, C₆D₆): $\delta = -1.87$ (s, 2H; SiCH₂), 0.35 [s, 9H; CH₂Si(CH₃)₃], 1.12 – 1.17 (m, 6H; NCH₂CH₂CH), 1.35 – 1.38 (m, 1H; NCH₂CH₂CH), 2.69 – 2.73 (m, 6H; NCH₂CH₂CH)

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ppm. {¹H}¹³C NMR (100.64 MHz, C₆D₆): $\delta = -5.8$ (1C; SiCH₂), 5.5 [3C; CH₂Si(CH₃)₃], 20.9 (1C; NCH₂CH₂CH), 26.3 (3C; NCH₂CH₂CH), 48.0 (3C; NCH₂CH₂CH) ppm. ⁷Li NMR (155.55 MHz, C₆D₆): $\delta = 2.7$ [1Li; (CH₃)₃SiCH₂Li] ppm. {¹H}²⁹Si NMR (79.52 MHz, C₆D₆): $\delta = -1.22$ [1Si; (CH₃)₃SiCH₂Li] ppm.

Deprotonation of N,N-Dimethylbenzylamine (7). A solution of 0.83 g (7.5 mmol, 1.5 eq.) quinuclidine and 0.75 mL (5 mmol, 1 eq.) N,N-dimethylbenzylamine (7) in 40 mL dry n-heptane was cooled to 0 °C and added 7.5 mL (7.5 mmol, 1.5 eq.) of a 1 M solution of Me₃SiCH₂Li in pentane. After warming to rt the solution was stirred for 1 h and then refluxed for 4 h. After cooling to -50 °C, 0.65 mL (5 mmol, 1 eq.) Me₃SiCl was added. The solution was left to warm to rt and stirred overnight. The reaction was guenched by the addition of 40 mL of 2 M agueous HCl and the phases were separated. The aqueous layer was cooled by the addition of ice and brought to pH 14 by the addition of KOH. It was then extracted with 3x 40 mL Et₂O. The combined organic layers were dried over Na_2SO_4 and the volatiles were removed under reduced pressure. The residue was distilled by Kugelrohr distillation at 40 °C and 9.8 · 10⁻¹ mbar to give 3-trimethylsilyl-N,N-dimethylbenzylamine (8) as a yellowish oil (0.85 g, 4.1 mmol, 82%). Spectral data was consistent with previously reported data.13

Conclusions

To conclude, we herein presented three different solid state structures of small aggregates of Me₃SiCH₂Li, an organolithium compound offering advantages due to decreased nucleophilicity and simplified handling,¹⁸ stabilized by nitrogen donors. Although the monomeric species 2 is formed in the presence of the bidentate ligand (R,R)-TMCDA, no significant reactivity is observed for this complex. This is in contrast to expectations based on the usual principles of organolithium compounds, since the remarkably low coordination number of three at the Li center would suggest notable reactivity. Quantum chemical calculations confirmed the hindered reactivity due to steric overload. In contrast to this, the quinuclidine-stabilized dimeric aggregates 3 and 4 exhibit reaction capabilities, which can be traced back to a weak coordination of one donor molecule, foreshadowing the coordination of a substrate to be deprotonated. By employing this base system in non-polar solvents, the occupation of reactive sites by donating solvent molecules can be avoided. By combining experimental and theoretical results we were able to stress the importance of a detailed knowledge of a reagent's structure to achieve optimal reactivity,¹⁹ which is not inevitably reached by the smallest possible aggregate.

Conflicts of interest

There are no conflicts to declare.

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An unexpected influence of the nature of stabilizing additives to alkyllithium compounds on an aggregate's reactivity was examined experimentally and theoretically.