A Theoretical Study on *n*BuLi/Lithium Aminoalkoxide Aggregation in Hexane and THF

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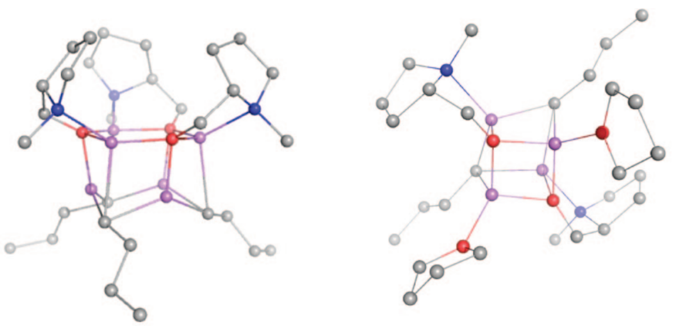

In Hexane: $(nBuLi)_3(LiPM)_3$ In THF: $(nBuLi)_2(LiPM)_2(THF)_2$

Theoretical calculations on aggregation of *n*BuLi/lithium aminoalkoxide superbases, such as *n*BuLi/LiDMAE (LiDMAE = $Me_2N(CH_2)_2OLi$) and *n*BuLi/LiPM (LiPM = Li-*N*-methyl-2-pyrrolidine methoxide) in gas phase and solution are reported. The combination of equimolar amounts of each component in hexane induced unusual reactivity of the resulting superbase, which remains misunderstood. In order to elucidate the corresponding reaction mechanisms, it is imperative to get a deeper insight into the energetics of aggregation and the effect of the medium on equilibrium constants. In the present study, we compute and compare the stability of $(n\text{BuLi})_n$, $(\text{LiPM})_n$, and equimolecular mixed aggregates $(n\text{BuLi:LiPM})_n$ in gas phase, hexane, and THF. Calculations have been carried out at the density functional theory level (B3LYP/6-31G(d)) using continuum and discrete continuum models of solvation. Higher-level calculations (MP2/aug-ccpVQZ) have been done in some cases for test purposes. Enthalpic and entropic contributions have been discussed and were shown to play an opposite role in hexane (or gas phase) and THF. The characteristics of LiPM and mixed *n*BuLi/LiPM solutions are found to be significantly different from those of *n*BuLi solutions. These calculations are in accordance with experimental data in both hexane and THF. Further comparison of theoretical and experimental results for gas-phase Li^+−THF and Li^+−DME complexes has enabled a discussion on computational errors for entropic contributions in THF. The value for the release of a THF solvent molecule is proposed to be $\Delta S \approx 23$ eu. These results provide new insights to the aggregation of organolithium compounds in solution and will be useful for the investigation of other systems.

Introduction

We report a theoretical investigation on *n*BuLi/lithium aminoalkoxide aggregates as part of a research project intended to rationalize, optimize, and extend the synthetic applications of alkyllithium−lithium aminoalkoxide superbases that are described hereafter. The reactions are most probably kinetically controlled, and therefore both the relative stability of aggregates and the activation energies of the processes need to be determined in order to clarify the reaction mechanisms involved. Relative stabilities of aggregates, including a detailed analysis of solvent effects is discussed herein, whereas reaction mechanisms will be further explained in a forthcoming study.

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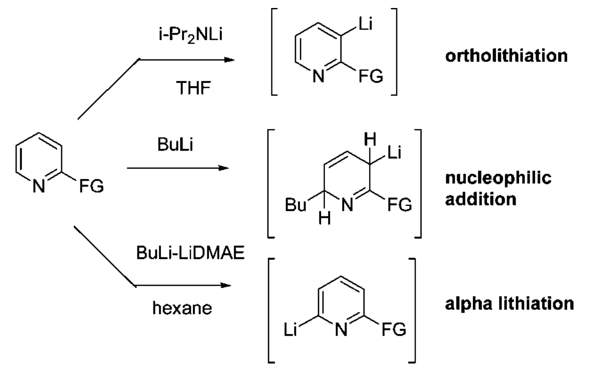
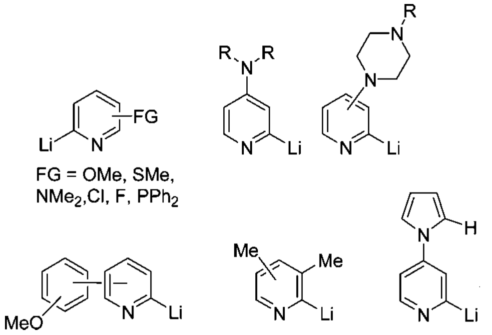
The regioselective lithiation of heterocyclic aromatic compounds, especially pyridine derivatives, has drawn much attention in the past decades due to its fast access to a wide range of functional compounds. In this context, deprotonative lithiation represents a straightforward route. Unfortunately, the π-deficiency of pyridines has long limited the scope of this latter reaction due to nucleophilic attack on the azomethine bond by alkyllithiums.[1−5] To overcome this side reaction and favor lithiation, one alternative has been to turn alkyllithium species into sterically hindered non-nucleophilic lithium dialkylamides such as LDA[6−11]or LTMP.[12−16] These reagents have successfully effected the metalation of several pyridine derivatives, but equilibrated reactions were observed in some cases and implied in situ trapping of lithio intermediates.[17] As a consequence, efforts have been devoted to turn nucleophilic alkyllithiums into metalating agents by increasing their metalation/nuclephilic addition ratio, with a particular focus on the most common and easily handled *n*-BuLi. One way to increase this ratio was to enhance the basicity through association with lithium-chelating diamines such as TMEDA[18,19] or to employ the superbase known as LICKOR (*n*BuLi/*t*BuOK) developed by Schlosser et al.[20,21] and Lochman et al.,[22−24] which contains potassium alkoxide as a highly electron-rich complexing agent. This family of bimetallic reagents has proven powerful in the aliphatic, aromatic, and heteroaromatic series.[25,26]

More recently, a new class of superbases associating *n*-BuLi and aminoalkoxides has emerged.[27] The most popular reagent named BuLi-LiDMAE (LiDMAE = $Me_2N(CH_2)_2OLi$) effected an unprecedented clean α metalation of numerous pyridine derivatives instead of the usual nucleophilic addition encountered with *n*-BuLi or ortho-directed lithiation promoted by dialkylamides (Scheme 1). A wide range of lithiopyridine intermediates was generated with tolerance of sensitive functionalities (Scheme 2).[28−33]

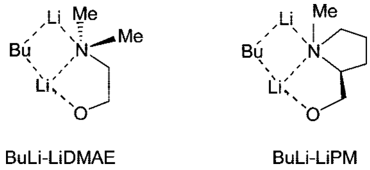
SCHEME 1. Lithiating Agents and Selectivity Obtained in Lithiation of Pyridines



SCHEME 2. Various Lithiopyridines Generated by BuLi-LiDMAE



SCHEME 3. Schematic Representation of the Two Relevant Superbases for C-6 Lithiation of Pyridines



The selectivity was dependent on the aminoalkoxide's structure, and to date, BuLi-LiDMAE and BuLi-LiPM (LiPM = Li(*N*-methylpyrrolidine) methoxide) have been found to be suitable superbases (Scheme 3). The latter reagent favored asymmetric addition of pyridyllithium to prochiral carbonyl compounds.[34]

BuLi-LiDMAE and related bases are now recognized reagents included in the portfolio of metallating agents. However, questions concerning their structures as well as their behavior in solution leading to the observed selectivities remain.

A feature common to all metalations with these reagents was the substantial effect of solvent on chemoselectivity. While the

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regioselective C-6 lithiation was maintained in noncoordinating solvents such as hexane, toluene, or cumene, switching to THF, Et_2O, or dioxane promoted nucleophilic addition instead of lithiation.[28]

In order to rationalize these experimental results, it was fundamental to first identify the actual reactive species in each reaction medium. Unfortunately, such an objective was not trivial owing to both, the marked trend of organolithium compounds to aggregate, and the large influence of solvent effects on aggregation.[26,35−37]

For symmetry reasons, solvation effects in noncoordinating solvents are not expected to be large for homoaggregates since they should exhibit a small or even negligible dipole moment (note that monomers, in contrast, are highly polar and should be quite sensitive to electrostatic solute−solvent interactions). Predicting qualitative solvation effects on heteroaggregates in noncoordinating solvents is less straightforward, and theoretical calculations have been useful in this case. Moreover, in the case of coordinating solvents such as THF, one can anticipate intricate medium effects due to competition between solvent coordination and aggregation. An extremely important aspect in this regard is the entropy change. As a matter of fact, in gas phase and in noncoordinating solvents, aggregation is entropically unfavorable ($\Delta S < 0$) since the number of translational and rotational degrees of freedom decreases. In contrast, when aggregation takes place in a coordinating solvent, the overall entropy balance may be positive since one expects the number of coordinating solvent molecules to decrease with increasing order of the aggregate. McGarrity and Ogle[38] investigated the aggregation of *n*BuLi in THF using NMR experiments. The authors showed that tetramers coexist with dimers in this solvent. Each lithium atom in the dimer binds two THF molecules instead of a single one in the tetramer. Thus, in all cases, a total coordination number of four is obtained. Accordingly, aggregation of two dimers to form a tetramer involves the release of four THF molecules (eq 1).

$$2(n\mathrm{BuLi})_2(\mathrm{THF})_4 \rightarrow (n\mathrm{BuLi})_4(\mathrm{THF})_4 + 4\mathrm{THF} \qquad (1)$$

The authors reported a value $\Delta S = 13.8$ eu, confirming that entropy effects in this case favor aggregation of *n*BuLi dimers into tetramers, in contrast to expectations in noncoordinating apolar solvents.

The relative concentrations of aggregates in a given medium are certainly connected to the chemical behavior of organolithium reagents. Unfortunately, though some experimental[38−46] and theoretical results[47−57] have been reported, equilibrium constants are generally difficult to determine. Experimentally, ^1H, ^6Li, and ^{13}C NMR have been used by several groups to determine the number of aggregation of organolithium in solution (see ref 58 for instance). Also the size of the aggregates has been evaluated using DOSY (Diffusion-Ordered Spectroscopy).[59] The main problem with *n*BuLi aggregates is the complexity of lithium and proton NMR spectra often implying the use of labeled compounds or branched derivatives for simplification purpose (e.g., *s*-BuLi, neopentyl-Li). The spectra are even more complex when additional coordinating anionic species like alkoxides are added. Nevertheless, the structure of some mixed aggregates have been reported by Collum and co-workers.[45,46] Equilibria between the various aggregates are also often very fast, and specific tools have been developed such as RINMR (rapid injection NMR)[60,61] to observe them at the NMR time scale. This technique allowed for the determination of some thermodynamic data about the equilibria between the potentially formed aggregates, as in the work of McGarrity and Ogle[38] mentioned above. From the theoretical point of view, the main difficulty in computing equilibrium constants is the size of the systems, which on one hand preclude carrying out high-level ab initio calculations and on the other hand require statistical simulations to obtain accurate entropy variations. Previous theoretical works discussing solvent effects on organolithium aggregation have mainly been devoted to lithium enolates,[53,62−64] lithium amides,[11,65−72] lithium amines,[57,71] lithium imines,[73] lithium aminoborohydrides,[69,74] lithium carbonides,[50,55,75,76] lithium cyanides,[77] and alkyllithium compounds.[47,54,67] Very recently, calculations have also been reported for some mixed alkyllithium−lithium alkoxide aggregates.[78]

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In the present work, mixed *n*BuLi/LiPM aggregates have been studied. LiPM was chosen rather than LiDMAE because (1) their structures are close and results for LiPM can easily be extrapolated to LiDMAE, (2) though LiPM is slightly larger than LiDMAE, computations are not necessarily more expensive due to its larger rigidity, and (3) *n*BuLi/LiPM superbases possess interesting asymmetric induction properties that will be analyzed in future investigations on the basis of results reported here.

An exhaustive investigation of the aggregates in different media is however a huge and difficult task, and some restrictive choices are necessary. Here, our main aim is to determine the structure of the major aggregate in hexane and THF, as well as the main factors explaining solvent effects. As noted above, only stoichiometric mixtures of *n*BuLi/LiPM superbases lead to suitable metalation properties. In such conditions, one may expect the major aggregate to involve an equivalent number of *n*BuLi and LiPM monomers, i.e., to be of the form $(n\text{BuLi})_n$-$(\text{LiPM})_n$. Indeed, equimolecular mixed aggregates have been experimentally observed for related systems in THF/pentane[45,46] where the 2:2 tetramer was shown to be the main component in stoichiometric mixtures. It is important to note, however, that in the same investigations, asymmetric tetramers were detected as well and that the latter may become the major component if one organolithium compound is in excess.

On the basis of these remarks, this study has focused on the relative stability of equimolecular $(n\text{BuLi:LiPM})_n$ mixed aggregates ($n = 1,2,3$), i.e., 1:1 dimers, 2:2 tetramers and 3:3 hexamers, as a function of the solvent. The systematic study of nonequimolecular aggregates, particularly in the case of hexamers, would be unfeasible. However, we have studied $(n\text{BuLi})_1(\text{LiPM})_3$, and $(n\text{BuLi})_3(\text{LiPM})_1$ tetramers in THF to check whether such aggregates can indeed play a role in that solvent. It is important to note that computations on 2:2, 1:3, and 3:1 tetramers in model RLi/R′OLi mixed aggregates have recently been reported by Pratt et al.[78] The formation of $(n\text{BuLi})_n$ and $(\text{LiPM})_n$ homoaggregates have also been described for comparison. In fact, *n*BuLi aggregation, a fundamental process in organolithium chemistry, is described in greater detail than previous studies. In particular, the results for the $2(n\text{BuLi})_2 \rightarrow (n\text{BuLi})_4$ equilibrium are compared with experimental data reported in the literature.

Methods

The structure of the *n*BuLi, LiPM, and mixed *n*BuLi:LiPM aggregates has been investigated at the Density Functional Theory B3LYP/6-31G(d) level. This level has been chosen as a compromise between accuracy and computational cost due to the size of the systems considered (126 atoms). Calculations at higher level (MP2/aug-cc-pVQZ in particular) were also performed for model aggregates $(\text{CH}_3\text{Li})_n$ to validate the approach. For simplicity, the latter results are only reported as Supporting Information (Table S1). They confirm the suitability of the B3LYP/6-31G(d) level to estimate aggregation energies: largest errors for aggregation enthalpies are below 1 kcal/mol for dimer formation and 3−4 kcal/mol for tetramer formation (roughly 2% and 8%, respectively). The use of diffuse functions on heavy atoms only slightly improves the results (see Table S1, Supporting Information); however, the computational cost is substantially higher, and in that respect diffuse functions have not been included. It is worth mentioning that previous studies on related systems considered a similar method.[51,63,64,79−82] Calculations have been done in gas phase and in two different solvents, hexane and THF. In the first case, the computations have been carried out using a dielectric continuum model[83−87] to represent the solvent (we simply use here $\varepsilon = 2.0$). In the case of THF, a discrete-continuum solvent model has been used. Accordingly, several THF molecules interacting with the Li atoms are explicitly included in the quantum mechanical computation and the corresponding aggregate−solvent complex (the so-called supermolecule) is embedded in a dielectric continuum medium ($\varepsilon = 7.58$). The number of THF molecules to be considered depends on the aggregate type and also on temperature. In the present work, we assume a temperature of 195 K that corresponds to that used in the above-mentioned superbase experiments[28,34] and is not far from the temperature used in the study of McGarrity and Ogle[38] on *n*BuLi aggregation in THF (188 K). Preliminary calculations (see below) have suggested that at this temperature and for all the aggregates considered in this work the lithium atom binds as many THF molecules as required to achieve a coordination number of 4.

Full geometry optimization has been carried out for all the species both in gas phase and solution. Atomic coordinates of all systems are provided as Supporting Information (Table S2). We have considered several molecular conformations in each case, though only results for the most stable one will be reported here. Note that due to the large number of geometrical degrees of freedom and limited computational capabilities, it is not possible to carry out a systematic conformational investigation for these systems, and therefore, strictly speaking, we cannot guarantee that the geometries reported here correspond to the global energy minima. Indeed, other structural arrangements close in energy to those reported below have been located, but the existence of other significantly more stable structures seems unlikely. In order to compute zero-point energy, thermal corrections to enthalpy, and entropy terms, we have used standard procedures that assume ideal gas behavior. Such a calculation requires the evaluation of vibrational frequencies, which has been done at the B3LYP/6-31G(d) level in gas phase for all systems except for the $(\text{LiPM})_6$ and $(n\text{BuLi:LiPM})_3$ hexamers due to computational time limitations. Thermodynamic properties in the latter case have been obtained by combining B3LYP/6-31G(d) electronic energies and thermo-

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dynamic contributions estimated from PM3 calculations. The $(\text{LiPM})_6$ and $(n\text{BuLi:LiPM})_3$ hexamers were therefore reoptimized at this semiempirical level (lithium atom PM3 parameters were taken from ref 88), and the corresponding thermodynamic contributions were obtained. We then employed the expression $G^{\text{corr}}_{\text{B3LYP}} = 1.05G^{\text{corr}}_{\text{PM3}}$, where the free energy correction contains the zero-point energy, the thermal correction to enthalpy, and the entropy term. The factor 1.05 comes from the comparison between B3LYP and PM3 results for $(\text{LiPM})_n$ and $(n\text{BuLi:LiPM})_n$ aggregates, which is provided as Supporting Information (Figure S1). As shown, there is a very good linear correlation for those systems so that the estimation made for the hexamer may be used with confidence. The suitability of this approach is supported by previous semiempirical calculations on related organolithium compounds.[48,63] Note that frequency calculations have not been carried out with the dielectric continuum model of the solvent, again due to computational time limitations. However, it is reasonable to assume that zero-point energy, thermal corrections to enthalpy and entropy terms do not change much when long-range electrostatic solvation effects are incorporated, and therefore we have used the same values in gas phase and in the continuum.

Though a substantial number of low frequencies of vibration are obtained in some cases, it has been verified that their contribution to the computed equilibria free energy is not too large, confirming the conclusions reached by other authors.[54,76] Errors in free energy will be discussed in further detail below. Reference states assume 1 atm in gas phase and 1 M concentration in solution. The conversion is done as follows:[76]

$$G^{*} = G^{\circ} + \Delta G^{\circ \rightarrow *} \qquad (2)$$

$$\Delta G^{\circ \rightarrow *} = RT \ln(22.46) \qquad (3)$$

where the asterisk refers to 1 M reference state and the correction factors amounts 1.1 kcal/mol in the range 188−200 K.

As discussed in the introduction, we consider dimers, tetramers, and hexamers (as well as monomers for comparison). However, hexamers are only studied in hexane, as they are known to be important species in apolar media[35,89] but not in THF. The continuum calculations have been carried out using the Multipole Expansion model (MPE) developed in our group.[85−87] All computations have been done using the Gaussian 03 code[90] using extra links to account for solvation effects.

Results and Discussion

Aggregation in Gas Phase and Hexane. Figure 1 displays the structure of the optimized aggregates, and Table 1 contains the value of some geometrical and electronic parameters. For simplicity, only gas phase results are shown, the values in hexane being not too different (note that all geometries are included in Supporting Information, Table S2). As shown, Li−C distances vary in the range 2.00−2.27 Å, whereas Li−O distances are much shorter and vary in the range 1.71−1.96 Å. Net atomic charges (computed using Natural Population Analysis[91,92]) are quite large, as expected: they are close to −1.1 e for both C and O atoms and slightly smaller than +0.9 e on Li atoms. Concerning the dipole moment, the following remarks can be made: (1) the monomers exhibit large values (>5 D), (2) the *n*BuLi:LiPM mixed dimer has a dipole moment smaller than that of either of the monomers due to opposite directions of their respective dipoles, and (3) for all the other aggregates, the dipole moment is negligible due to symmetry.

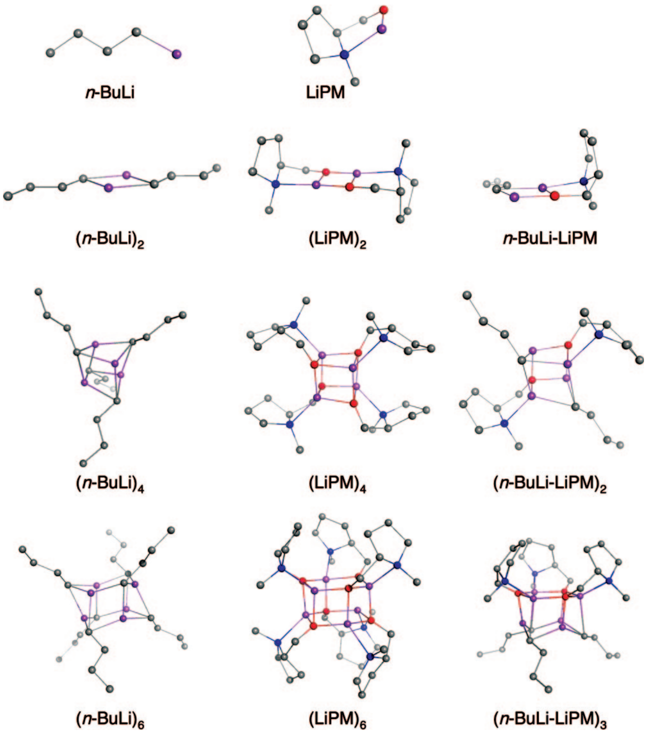

FIGURE 1. Optimized structures (gas phase, B3LYP/6-31G(d) level) of *n*BuLi, LiPM, and mixed *n*BuLi/LiPM aggregates.

TABLE 1. Structural Parameters of Aggregates Obtained at the B3LYP/6-31G(d) Level in Gas Phase[a]

	$d_{\text{Li-C}}$	$d_{\text{Li-O}}$	q_{Li}	q_{C}	q_{O}	μ
*n*BuLi	2.004		0.744	−1.070		5.48
LiPM		1.708	0.878		−1.034	5.28
$(n\text{BuLi})_2$	2.132		0.836	−1.151		0.00
$(\text{LiPM})_2$		1.822	0.846		−1.072	0.13
*n*BuLi:LiPM	2.162	1.793	0.853	−1.177	−1.091	2.57
$(n\text{BuLi})_4$	2.208		0.852	−1.186		0.00
$(\text{LiPM})_4$		1.950	0.890		−1.111	0.00
$(n\text{BuLi:LiPM})_2$	2.266	1.896	0.866	−1.176	−1.103	0.09
$(n\text{BuLi})_6$	2.204		0.829	−1.167		0.00
$(\text{LiPM})_6$		1.960	0.902		−1.128	0.47
$(n\text{BuLi:LiPM})_3$	2.270	1.913	0.868	−1.197	−1.223	0.00

[a] Bond distances in Å, NPA charges in electron units, and dipole moments in debye.

Table 2 summarizes the results for the energetics of monomer aggregation. The tendency of organolithium compounds to aggregate is confirmed. All considered processes are highly

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TABLE 2. Computed Aggregation Energies in Gas Phase and Hexane ($\varepsilon = 2.0$)[a]

		ΔE	ΔH	$-T\Delta S$	ΔG	$\Delta G/n$
		Dimers				
$2n$BuLi → (nBuLi)$_2$	gas	−44.8	−43.5	7.2	−36.3	−18.2
	$\varepsilon = 2.0$	−38.6	−37.3	6.1	−31.2	−15.6
2LiPM → (LiPM)$_2$	gas	−63.6	−62.0	7.4	−54.6	−27.3
	$\varepsilon = 2.0$	−57.4	−55.7	6.3	−49.4	−24.7
nBuLi + LiPM → nBuLi:LiPM	gas	−54.5	−53.1	7.1	−46.0	−23.0
	$\varepsilon = 2.0$	−48.6	−47.1	6.0	−41.1	−20.6
		Tetramers				
$4n$BuLi → (nBuLi)$_4$	gas	−132.4	−128.5	24.4	−104.1	−26.0
	$\varepsilon = 2.0$	−118.9	−115.0	21.1	−93.9	−23.5
4LiPM → (LiPM)$_4$	gas	−155.5	−151.3	27.2	−124.1	−31.0
	$\varepsilon = 2.0$	−142.3	−138.2	23.9	−114.3	−28.6
$2n$BuLi + 2LiPM → (nBuLi:LiPM)$_2$	gas	−152.8	−148.7	25.5	−123.2	−30.8
	$\varepsilon = 2.0$	−139.5	−135.4	22.2	−113.2	−28.3
		Hexamers				
$6n$BuLi → (nBuLi)$_6$	gas	−211.2	−204.1	40.3	−163.8	−27.3
	$\varepsilon = 2.0$	−190.6	−183.5	34.8	−148.7	−24.8
6LiPM → (LiPM)$_6$	gas	−254.8	−240.8	44.2	−196.6	−32.8
	$\varepsilon = 2.0$	−234.6	−220.6	38.7	−181.9	−30.3
$3n$BuLi + 3LiPM → (nBuLi:LiPM)$_3$	gas	−242.9	−227.3	39.5	−187.8	−31.3
	$\varepsilon = 2.0$	−223.1	−207.5	34.0	−173.5	−28.9

[a] Value n represents the number of monomers in the aggregate. Energies in kcal/mol at $T = 195$ K. Entropies in solution take account of the 1 atm to 1 M reference state conversion. Thermodynamic corrections for (LiPM)$_6$ and (nBuLi:LiPM)$_3$ have been calculated using corrected PM3 results (see details in Methods).

exothermic and exergonic, despite a significant positive contribution of the entropy term to the free energy. An interesting result is that all free energies of aggregation undergo a systematic decrease in going from gas phase to hexane, about 2−3 kcal/mol per monomer. This can be mainly explained by the dipole moment values that, as shown above, are large for the monomers and small or negligible for the aggregates. It must be noted, however, that owing to the large net atomic charges carried by the Li, C, and O atoms, the aggregates exhibit strong multipole moments that also contribute to the solvation energy. As a result, the decrease of the aggregation energy (in absolute value) in going from gas phase to solution is much smaller than what would be predicted on the basis of dipole moment values.

Results for nBuLi aggregation energies are quite comparable to previous theoretical studies on alkyllithium compounds.[47,49,52,54,67,80,81,88,93−95] Note that formation of LiPM dimer is much more exothermic than that of nBuLi dimer, whereas the heterodimer nBuLi:LiPM displays an intermediate dimerization energy. In the case of tetramers, the energetics for the formation of (LiPM)$_4$ and (nBuLi:LiPM)$_2$ are quite similar, both formation processes being more exergonic than that leading to (nBuLi)$_4$. Formation of the (LiPM)$_6$ and (nBuLi:LiPM)$_3$ hexamers is more exothermic and exergonic than formation of (nBuLi)$_6$.

The general trend shown by the $\Delta G/n$ values is that tetramers are much more stable than dimers and hexamers more stable than tetramers (though to a smaller extent). This point is also illustrated in Table 3, which summarizes the energetics for a series of selected processes involving dimers, tetramers, and hexamers chosen to illustrate some particular (though fundamental) aspects of the aggregation phenomenon. According to the computed free energies, it may easily be concluded that hexamers should be predominant species in hydrocarbon solvents, as experimentally reported for nBuLi.[35,89] Thus, for equal initial concentrations of nBuLi and LiPM, the mixed (nBuLi:LiPM)$_3$ hexamer should be the major aggregate, though other hexamers not described here could be present too. Tetramers might be perhaps observable for low-concentration solutions with only one component, as reported for nBuLi,[35] or eventually for mixed solutions with slightly different initial concentrations.

From the values in Table 3, comparative remarks concerning nBuLi and LiPM aggregates or between homo- and heteroaggregates can be made. Thus, for instance, dimer → tetramer conversion is much more exothermic and exergonic for nBuLi than for LiPM (process A versus process B, respectively). Moreover, formation of heterodimers from homodimers (process C) is shown to be only slightly favorable while formation of heterotetramers from homotetramers (process F) is quite exothermic and exergonic.

Aggregation in THF. In coordinating solvents such as THF, the large positive charge on Li atoms may be stabilized by coordination with solvent molecules, and this interaction must be considered in order to analyze the relative stability of aggregates. As mentioned earlier, Li atoms are assumed to have a coordination number of 4 in all systems considered in this study. This is in agreement with experimental observations for nBuLi.[38,39,59] In the case of LiPM, experimental data are not available. Free energy calculations for the following processes have been carried out:

$$\text{LiPM(THF)}_n + \text{THF} \rightarrow \text{LiPM(THF)}_{n+1} \quad (n = 0-2) \quad (4)$$

The analysis of the results suggests that LiPM monomers bind two THF molecules and that the Li atom interacts with the amino N atom, as shown in Scheme 4. The N$\cdots$Li interaction is preferred to the interaction with a third THF molecule. On the basis of these results, a Li coordination number of 4 has

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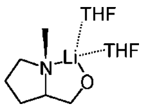
TABLE 3. Equilibrium Energies between Dimers and Tetramers in Gas Phase and Hexane ($\varepsilon = 2.0$)[a]

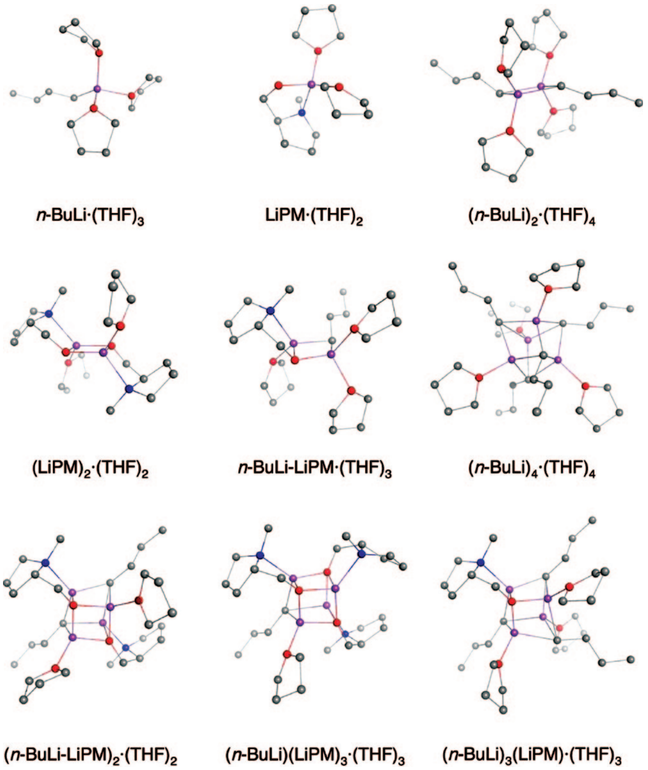
			ΔE	ΔH	$-T\Delta S$	ΔG
A	$2(n\mathrm{BuLi})_2 \rightarrow (n\mathrm{BuLi})_4$	gas	−42.8	−41.6	9.9	−31.7
		$\varepsilon = 2.0$	−41.6	−40.4	8.8	−31.6
B	$2(\mathrm{LiPM})_2 \rightarrow (\mathrm{LiPM})_4$	gas	−28.2	−27.4	12.5	−14.9
		$\varepsilon = 2.0$	−27.6	−26.8	11.4	−15.4
C	$(n\mathrm{BuLi})_2 + (\mathrm{LiPM})_2 \rightarrow 2(n\mathrm{BuLi{:}LiPM})$	gas	−0.7	−0.8	−0.5	−1.3
		$\varepsilon = 2.0$	−1.1	−1.3	−0.5	−1.8
D	$2(n\mathrm{BuLi{:}LiPM}) \rightarrow (n\mathrm{BuLi{:}LiPM})_2$	gas	−43.7	−42.4	11.4	−31.0
		$\varepsilon = 2.0$	−42.4	−41.1	10.3	−30.8
E	$(n\mathrm{BuLi})_2 + (\mathrm{LiPM})_2 \rightarrow (n\mathrm{BuLi{:}LiPM})_2$	gas	−44.3	−43.2	10.9	−32.3
		$\varepsilon = 2.0$	−43.5	−42.4	9.8	−32.6
F	$(n\mathrm{BuLi})_4 + (\mathrm{LiPM})_4 \rightarrow 2(n\mathrm{BuLi{:}LiPM})_2$	gas	−17.7	−17.5	−0.6	−18.1
		$\varepsilon = 2.0$	−17.8	−17.6	−0.6	−18.2
G	$3/2(n\mathrm{BuLi})_4 \rightarrow (n\mathrm{BuLi})_6$	gas	−12.7	−11.3	3.8	−7.5
		$\varepsilon = 2.0$	−12.3	−11.0	3.3	−7.7
H	$3/2(\mathrm{LiPM})_4 \rightarrow (\mathrm{LiPM})_6$	gas	−21.6	−13.7	3.4	−10.3
		$\varepsilon = 2.0$	−21.1	−13.3	2.9	−10.4
I	$3/2(n\mathrm{BuLi{:}LiPM})_2 \rightarrow (n\mathrm{BuLi{:}LiPM})_3$	gas	−13.8	−4.3	1.2	−3.1
		$\varepsilon = 2.0$	−13.9	−4.4	0.7	−3.7

[a] Energies in kcal/mol at $T = 195$ K. Entropies in solution take account of the 1 atm to 1 M reference state conversion. Thermodynamic corrections for $(\mathrm{LiPM})_6$ and $(n\mathrm{BuLi{:}LiPM})_3$ have been calculated using corrected PM3 results (see details in Methods).

SCHEME 4. Schematic Representation of LiPM Coordinated to Two THF Molecules



been assumed not only in LiPM aggregates but also in mixed *n*BuLi:LiPM aggregates. In addition, for all aggregates Li atoms in LiPM subunits are assumed to interact with N-atoms. The optimized structure of the aggregates in gas phase is presented in Figure 2, and structural parameters are summarized in Table 4 (geometries optimized in the continuum are included in Supporting Information, Table S2). As stated in the introduction, 1:3 and 3:1 tetramers in THF have been considered. Hexamers will not be considered in THF but it is important to note that geometry optimization of several $(n\mathrm{BuLi})_6(\mathrm{THF})_n$ systems was attempted and systematically led to dissociation.


n-BuLi·(THF)$_3$ LiPM·(THF)$_2$ (n-BuLi)$_2$·(THF)$_4$

(LiPM)$_2$·(THF)$_2$ n-BuLi-LiPM·(THF)$_3$ (n-BuLi)$_4$·(THF)$_4$

(n-BuLi-LiPM)$_2$·(THF)$_2$ (n-BuLi)(LiPM)$_3$·(THF)$_3$ (n-BuLi)$_3$(LiPM)·(THF)$_3$

FIGURE 2. Optimized structures (gas phase, B3LYP/6-31G(d) level) of *n*BuLi, LiPM, and mixed *n*BuLi:LiPM aggregates interacting with THF molecules. The coordination of the lithium atoms is always 4.

The structure of the aggregates are not excessively modified by complexation with THF molecules (compare values in Tables 1 and 4), but it can be noticed that Li−C and Li−O (LiPM) distances are a slightly larger for the THF-coordinated aggregates. Li−O (THF) distances are around 2.01−2.06 Å and are therefore intermediate between the Li−C and Li−O (LiPM) distances in the aggregate.

Table 5 summarizes the aggregate−THF interaction energies in gas phase (isolated complexes) and in solution (complexes in a dielectric continuum). As shown, the interaction energy per THF molecule in the aggregates varies roughly in the range 7.5−13.1 kcal/mol ($\Delta H/m$ in solution), with the largest values being obtained for the monomers. These results may be compared to those proposed in the literature and derived from experimental measurements for *n*BuLi (−9.6 kcal/mol[38]) and *t*BuLi (−7.6 kcal/mol[96]). However, since the number of interacting THF molecules depends on the aggregate, the largest total interaction energy (ΔE or ΔH) does not correspond to the monomers but to $(n\mathrm{BuLi})_2$. Note that interaction energies may appreciably change in going from gas phase to the dielectric continuum (especially for the monomers). Entropy contributions are all positive and roughly proportional to the number of THF molecules participating to the process (7−8 kcal/mol per THF molecule). As a result, the free energies for these processes are much smaller (in absolute value) than the corresponding enthalpies though negative values are obtained in all cases.

One may note in Table 5 that free energies for microsolvation (i.e., for complex formation with THF molecules) are highly dependent on aggregates. The smallest absolute value corresponds to the LiPM dimer ($\Delta G = -1.3$ kcal/mol), whereas the largest one corresponds to the *n*BuLi monomer ($\Delta G = -19.6$ kcal/mol in the continuum). Considering this remarkable disparity, one can anticipate a substantial solvent effect on the relative stability of the aggregates in THF. To discuss this point, let us

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TABLE 4. Structural Parameters of Complexes with THF Molecules Obtained at the B3LYP/6-31G(d) Level in Gas Phase[a]

	$d_{\mathrm{Li-C}}$	$d_{\mathrm{Li-O}}$		q_{Li}	q_{C}	q_{O}		μ
		LiPM	THF			LiPM	THF	
$n\mathrm{BuLi}\cdot3\mathrm{THF}$	2.109		2.060	0.800	−1.048		−0.641	6.39
$\mathrm{LiPM}\cdot2\mathrm{THF}$		1.808	2.018	0.877		−1.032	−0.661	4.85
$(n\mathrm{BuLi})_2\cdot4\mathrm{THF}$	2.226		2.019	0.835	−1.122		−0.638	1.07
$(\mathrm{LiPM})_2\cdot2\mathrm{THF}$		1.884	2.055	0.886		1.086	−0.645	0.88
$n\mathrm{BuLi{:}LiPM}\cdot3\mathrm{THF}$	2.228	1.884	2.050	0.866	−1.148	−1.076	−0.643	3.12
$(n\mathrm{BuLi})_4\cdot4\mathrm{THF}$	2.288		2.059	0.847	−1.168		−0.641	1.01
$(n\mathrm{BuLi{:}LiPM})_2\cdot2\mathrm{THF}$	2.308	1.916	2.007	0.872	−1.162	−1.113	−0.652	6.65
$(n\mathrm{BuLi})(\mathrm{LiPM})_3\cdot\mathrm{THF}$	2.320	1.936	2.008	0.882	−1.170	−1.112	−0.652	3.46
$(n\mathrm{BuLi})_3(\mathrm{LiPM})\cdot3\mathrm{THF}$	2.291	1.905	2.014	0.862	−1.166	−1.109	−0.645	4.00

[a] Bond distances in Å, NPA charges in electron units, and dipole moments in debye.

TABLE 5. Computed Complexation Energies of Monomers and Aggregates with THF Molecules in Gas Phase and in THF ($\varepsilon = 7.58$)[a]

		ΔE	ΔH	$\Delta H/m$	$-T\Delta S$	ΔG
$n\mathrm{BuLi} + 3\mathrm{THF} \rightarrow (n\mathrm{BuLi})\ (\mathrm{THF})_3$	gas	−49.5	−46.2	−15.4	22.3	−23.9
	$\varepsilon = 7.58$	−41.9	−38.6	−12.9	19.0	−19.6
$\mathrm{LiPM} + 2\mathrm{THF} \rightarrow (\mathrm{LiPM})\ (\mathrm{THF})_2$	gas	−34.8	−32.6	−16.3	15.5	−17.1
	$\varepsilon = 7.58$	−28.3	−26.1	−13.1	13.3	−12.8
$(n\mathrm{BuLi})_2 + 4\mathrm{THF} \rightarrow (n\mathrm{BuLi})_2\ (\mathrm{THF})_4$	gas	−52.6	−48.8	−12.2	29.6	−19.2
	$\varepsilon = 7.58$	−47.2	−43.3	−10.8	25.2	−18.1
$(\mathrm{LiPM})_2 + 2\mathrm{THF} \rightarrow (\mathrm{LiPM})_2\ (\mathrm{THF})_2$	gas	−18.6	−17.1	−8.6	15.8	−1.3
	$\varepsilon = 7.58$	−16.4	−14.9	−7.5	13.6	−1.3
$n\mathrm{BuLi{:}LiPM} + 3\mathrm{THF} \rightarrow (n\mathrm{BuLi{:}LiPM})\ (\mathrm{THF})_3$	gas	−37.2	−34.0	−11.3	24.1	−9.9
	$\varepsilon = 7.58$	−32.4	−29.2	−9.7	20.8	−8.4
$(n\mathrm{BuLi})_4 + 4\mathrm{THF} \rightarrow (n\mathrm{BuLi})_4\ (\mathrm{THF})_4$	gas	−43.9	−39.7	−9.9	28.4	−11.3
	$\varepsilon = 7.58$	−39.6	−35.3	−8.8	24.0	−11.3
$(n\mathrm{BuLi{:}LiPM})_2 + 2\mathrm{THF} \rightarrow (n\mathrm{BuLi{:}LiPM})_2\ (\mathrm{THF})_2$	gas	−24.0	−22.4	−11.2	13.9	−8.5
	$\varepsilon = 7.58$	−22.5	−20.8	−10.4	11.7	−9.1
$(n\mathrm{BuLi})(\mathrm{LiPM})_3 + \mathrm{THF} \rightarrow (n\mathrm{BuLi})(\mathrm{LiPM})_3(\mathrm{THF})$	gas	−12.3	−11.6	−11.6	7.1	−4.4
	$\varepsilon = 7.58$	−11.2	−10.5	−10.5	6.0	−4.5
$(n\mathrm{BuLi})_3(\mathrm{LiPM}) + 3\mathrm{THF} \rightarrow (n\mathrm{BuLi})_3(\mathrm{LiPM})(\mathrm{THF})_3$	gas	−34.7	−32.2	−10.7	20.4	−11.7
	$\varepsilon = 7.58$	−31.7	−29.1	−9.7	17.1	−12.0

[a] Value m represents the number of THF molecules in the aggregate. Energies in kcal/mol at $T = 195$ K. Entropies in solution take account of the 1 atm to 1 M reference state conversion.

TABLE 6. Equilibrium Energies between Dimers and Tetramers Coordinated to THF Molecules in Gas Phase and in THF ($\varepsilon = 7.58$)[a]

			ΔE	ΔH	$-T\Delta S$	ΔG
A′	$2(n\mathrm{BuLi})_2(\mathrm{THF})_4 \rightarrow (n\mathrm{BuLi})_4(\mathrm{THF})_4 + 4\mathrm{THF}$	gas	18.5	16.3	−20.9	−4.6
		$\varepsilon = 7.58$	14.7	12.5	−17.6	−5.1
B′	$2(\mathrm{LiPM})_2(\mathrm{THF})_2 \rightarrow (\mathrm{LiPM})_4 + 4\mathrm{THF}$	gas	9.1	6.7	−19.1	−12.4
		$\varepsilon = 7.58$	6.6	4.2	−15.8	−11.6
C′	$(n\mathrm{BuLi})_2(\mathrm{THF})_4 + (\mathrm{LiPM})_2(\mathrm{THF})_2 \rightarrow 2(n\mathrm{BuLi{:}LiPM})(\mathrm{THF})_3$	gas	−3.7	−3.0	2.4	−0.6
		$\varepsilon = 7.58$	−2.7	−2.0	1.3	−0.7
D′	$2n\mathrm{BuLi{:}LiPM}\ (\mathrm{THF})_3 \rightarrow (n\mathrm{BuLi{:}LiPM})_2\ (\mathrm{THF})_2 + 4\mathrm{THF}$	gas	6.6	3.3	−22.9	−19.6
		$\varepsilon = 7.58$	1.8	−1.6	−19.6	−21.2
E′	$(n\mathrm{BuLi})_2(\mathrm{THF})_4 + (\mathrm{LiPM})_2(\mathrm{THF})_2 \rightarrow (n\mathrm{BuLi{:}LiPM})_2\ (\mathrm{THF})_2 + 4\mathrm{THF}$	gas	2.9	0.2	−20.5	−20.3
		$\varepsilon = 7.58$	−0.9	−3.6	−17.2	−20.8
F′	$(n\mathrm{BuLi})_4(\mathrm{THF})_4 + (\mathrm{LiPM})_4 \rightarrow 2(n\mathrm{BuLi{:}LiPM})_2(\mathrm{THF})_2$	gas	−21.8	−22.5	−1.2	−23.7
		$\varepsilon = 7.58$	−23.1	−23.8	−1.2	−25.0
G′	$1/4(n\mathrm{BuLi})_4\cdot4\mathrm{THF} + 3/4(\mathrm{LiPM})_4 \rightarrow (n\mathrm{BuLi})(\mathrm{LiPM})_3\cdot\mathrm{THF}$	gas	−8.7	−8.9	−0.3	−9.2
		$\varepsilon = 7.58$	−8.6	−8.8	−0.3	−9.1
H′	$3/4(n\mathrm{BuLi})_4.4\mathrm{THF} + 1/4(\mathrm{LiPM})_4 \rightarrow (n\mathrm{BuLi})_3(\mathrm{LiPM})\cdot3\mathrm{THF}$	gas	−7.3	−7.8	−1.4	−9.2
		$\varepsilon = 7.58$	−7.6	−8.1	−1.4	−9.5

[a] Energies in kcal/mol at $T = 195$ K. Entropies in solution take account of the 1 atm to 1 M reference state conversion.

focus on the processes A′−F′ shown in Table 6 involving dimers and tetramers. A first remark on this table is that solvent effects arising from the dielectric continuum are relatively small.

Free energies for dimer → tetramer processes (A′, B′, D′, E′) are all exergonic, likewise for hexane. However, important changes are predicted in switching the solvent. As a rule, reaction free energies are always smaller in THF (absolute value), though the differences are more or less pronounced, depending on the process. The most dramatic change corresponds to the *n*BuLi dimer → tetramer process: ΔG changes from −31.6 kcal/mol in hexane (process A, Table 3) to −5.1 kcal/mol in THF (process A′, Table 6). In the case of LiPM aggregates the change is much smaller: ΔG changes from −15.4 kcal/mol in hexane (process B, Table 3) to −11.6 kcal/mol in THF (process B′, Table 6). An intermediate free energy decrease is predicted for the two processes involving the formation of mixed tetramers (D−D′ and E−E′).

An interesting point is that the factors explaining the larger stability of tetramers with respect to dimers in hexane and THF are contrasting. Enthalpy and entropy play complementary roles.

Thus, for the dimer → tetramer processes A′, B′, D′ and E′, enthalpy values in THF are positive or slightly negative (Table 6), whereas they are strongly negative in gas phase or hexane (Table 3). On the other hand, entropy contributions ($-T\Delta S$) for the same processes in THF are negative, favoring tetramer formation, whereas in gas phase or hexane the contributions are obviously positive and oppose tetramer formation. Increasing the temperature in THF solution will therefore favor tetramers over dimers, while the opposite occurs in hexane.

Regarding the data in Table 6, in the case of homodimer/heterodimer conversion (C′), the computed free energy in THF is small and does not change much with respect to hexane. In addition, the homotetramer/heterotetramer equilibrium conversion (F′) is quite exergonic, the free energy being slightly larger in absolute value than that obtained in hexane. Finally, energetics for processes G′ and H′ (not considered in hexane solvent) show that the two asymmetric tetramers are more stable than the homotetramers and both present similar stabilities. By combining equations G′ + H′ − F′ one obtains $2(n\mathrm{BuLi{:}LiPM})_2(\mathrm{THF})_2 \rightarrow (n\mathrm{BuLi})(\mathrm{LiPM})_3(\mathrm{THF}) + (n\mathrm{BuLi})_3(\mathrm{LiPM})(\mathrm{THF})_3$ with $\Delta G = +6.4$ kcal/mol; in other words, the asymmetric tetramers are less stable that the 2:2 tetramer. These results are partially in accordance with experimental data reported for related mixed systems in THF/pentane.[45,46] In that particular study, the symmetric tetramer was shown to be the major component in stoichiometric mixtures, as predicted here. However, only one of the two asymmetric tetramers was observed, which is in contrast to the similar stabilities of the 1:3 and 3:1 tetramers predicted for *n*BuLi/LiPM. Differences in the chemical systems and also in the solvent nature (we consider here pure THF solvent) may be at the origin of that discrepancy.

Comparison of experimental data for *n*BuLi in THF with computational results of this study could be worthwhile. Within this aim, however, it is necessary to make certain conversions to the calculated free energies. The equilibrium constant is defined from the measured concentrations as

$$K = \frac{[\mathrm{tetramer}]}{[\mathrm{dimer}]^2} \tag{5}$$

Free energies in Table 6 refer to 1 M, and therefore it is necessary to account for solvent concentration. Following other authors,[54] one defines K' as

$$K' = \frac{[(n\mathrm{BuLi})_4 \cdot 4\mathrm{THF}][\mathrm{THF}]^4}{[(n\mathrm{BuLi})_2 \cdot 4\mathrm{THF}]^2} \tag{6}$$

$$\Delta G = \Delta G' + 4RT\ln[\mathrm{THF}] \tag{7}$$

Values of $RT\ln[\mathrm{THF}]$ at 188−200 K amounts to roughly 1 kcal/mol.[54]

Using the appropriate corrected ΔG values it is easy to show that equilibrium A′ (see Table 6) prevails for *n*BuLi in THF, in good agreement with experiment. For instance, for a 1 M solution of *n*BuLi, values of log *C* (obtained using the ChemEQL program[97]) amount to −0.602, −4.611, and −5.446 for the tetramer, dimer, and monomer, respectively. The experimental free energy for equilibrium A′ reported by McGarrity et al.[38] at 188 K was $\Delta G = -1.1$ kcal/mol (Heinzer et al.[39] reported a slightly different value $\Delta G = -1.4$ kcal/mol; note that in these papers, the equilibrium was written in the opposite direction). Using the value $\Delta G' = -5.1$ kcal/mol at $T = 195$ K in Table 6, we obtain a corrected free energy $\Delta G = -0.8$ kcal/mol at $T = 188$ K, again in excellent agreement with experimental data.

Log *C* calculations for LiPM leads to the conclusion that only the tetramer would be significantly present in THF solution, the predicted dimer concentration being extremely low (log *C* equals −0.602 and −8.256 for the tetramer and dimer respectively). In the case of *n*BuLi/LiPM mixtures, dimer concentrations (for both homo- and heterodimers) would be also negligible. The 2:2 tetramers would be the major component (log $C = -0.602$) but the 1:3 and 3:1 tetramers would be present in small amounts (log $C = -4.077$ for each asymmetric tetramer assuming an equivalent concentration of both).

One should be aware that the excellent agreement between theoretical and experimental ΔG values for process A′ involves some error compensation between enthalpy and entropy contributions. This point must be further elaborated. Main errors in the enthalpies are most likely due to basis set superposition errors (BSSE) in the calculation of aggregates−THF complexation energies. Owing to that, the reported values are probably overestimated, and counterpoise calculations for equilibrium A′ gave a BSSE of 2.5 kcal/mol per THF molecule. Entropy errors, on the other hand, arise from the presence of a large number of low-frequency modes, which formally should not be treated as harmonic vibrations, and the neglect of conformational disorder. Large error cancelation for low-frequency modes has been demonstrated in computing the entropy change for related processes.[54] We assume that errors coming from the ligands do indeed cancel when we compare dimers and tetramers. As a further effort to evaluate the error related to THF coordination, we have made a comparison of our results with experimental and theoretical data reported by Taft et al.[98] and Jarek et al.[99] for Li^+ complexation to DME and THF. We conclude that $T\Delta S$ values are probably overestimated by 2−3 kcal/mol per THF molecule at 195 K. Therefore, enthalpy and entropy values appear to be both overestimated and affected by a similar absolute error. However, since they display opposite signs, errors tend to cancel and computed free energies should be reliable, as verified for *n*BuLi. At different temperatures, the entropy error will change and the extent of error cancelation should be reconsidered.

We have seen that a fundamental quantity needed to better understanding organolithium aggregation in THF is the entropy increase related to the release of one THF solvent molecule. Different authors have already examined this point but there is still a large uncertainty, probably due to the difficulty of making a sound theoretical estimation. In addition, some confusion has been introduced in the literature by the fact that comparison between theoretical and experimental quantities has not always been made using consistent reference states. We have estimated here $T\Delta S = 4-5$ kcal/mol at 195K (i.e., $\Delta S \approx 23$ eu), but further work is clearly necessary to get a more accurate estimation. Further work in this direction using statistical simulations and combined quantum−classical force-fields is currently underway.

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Conclusions

Calculations in this study highlight the role of solvation on free energy of formation, both entropic and enthalpic contributions, in *n*BuLi, LiPM, and mixed *n*BuLi:LiPM aggregates. The energetic balance in hexane and THF is quite different due to the possibility for coordination of the aggregates with solvent molecules in THF. Calculations show that long-range solvent effects on aggregation are moderate. In hexane, aggregation up to hexamers is always favorable from the enthalpic point of view and unfavorable from the entropic point of view. In THF, enthalpy disfavors aggregation due to the decrease of the number of coordinating solvent molecules. However, as already described by other authors for related systems, entropy plays a fundamental role in THF. In particular, it explains the larger stability of tetramers with respect to dimers experimentally observed for *n*BuLi. Our calculated free energies for the dimer/tetramer equilibrium of *n*BuLi in THF are in excellent agreement with experimental data.[38] In the case of LiPM, the corresponding equilibrium in THF is shifted toward the tetramer but the free energy difference is much larger than that for *n*BuLi, so the concentration of the dimer should be negligible in this case. For *n*BuLi/LiPM mixtures, it has been also found that heterotetramers should predominate over homotetramers and dimers.

The analysis reported in this work focus on the major species in hexane (3:3 hexamers) and THF (2:2 tetramers) for initial stoichiometric concentrations of *n*BuLi and LiPM. From these results, it would be tempting to draw conclusions about the peculiar reactivity exhibited by *n*BuLi/LiPM superbases in hexane, not in THF, toward pyridine-based substrates. However, this point requires further research. On the one hand, the major species in a given medium is not necessarily the most reactive one, and it would be important to consider other hexamers in hexane (not studied here) or tetramers in THF that might be present in significant amounts. On the other hand, kinetic constants have to be computed and combined to aggregation equilibrium constants before a general mechanistic scheme can be proposed. This is a work currently in progress.

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Supporting Information Available: Comparison of aggregation energies computed at B3LYP/6-31G(d) and high ab initio levels for some model systems, atomic coordinates and total energies for all the structures at the B3LYP/6-31G(d) level in gas phase and solution, correlation between computed PM3 and B3LYP/6-31G(d) corrections to free energy (ZPE+H(T)-TS) for LiPM and mixed *n*BuLi:LiPM aggregates. This material is available free of charge via the Internet at http://pubs.acs.org.

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