angiography and furthermore indicates the potential to develop a whole new class of MR contrast agents based on water-soluble calixarene chelates.

Experimental Section

The reaction was carried out under argon. The tetraethyl calix[4]arenetetraacetate **1** was prepared according to the literature procedure.[9] The *N*,*N*-dimethylethylenediamine and $Gd(NO_3)_3 \cdot 5H_2O$ were purchased from Aldrich Chemical Co., Milwaukee, WI. Chemical shifts δ are given relative to the relevant standard tetramethylsilane. The stability constant of the $[Gd^{III}(\mathbf{2})]$ complex was determined by MicroCal Inc., Northampton, MA.[6]

2: Compound **1** (10.0 g) was added in small portions to *N*,*N*-dimethylethylenediamine (30 mL) and the resulting solution was stirred for 18 h under argon. The unconverted amine was removed by evaporation under reduced pressure and the residue treated with diethyl ether. The white precipitate was filtered, rinsed with diethyl ether, and dried in vacuo. Yield: 11.2 g (92%). m.p. 213 °C. Elemental analysis (%) calcd for $C_{52}H_{72}N_8O_8$: C 66.6, H 7.74, N 12.0; found: C 66.7, H 7.86, N 11.8; FAB-MS: m/z: 937.5 $[M^+]$; ^1H NMR ($CDCl_3$): $\delta = 2.19$ (s, 24H; NCH_3), 2.44 (t, 8H; NCH_2), 3.22 (d, 4H; CH_2), 3.41 (q, 8H; CH_2NH), 4.44 (s, 8H; CH_2O), 4.47 (d, 4H; CH_2), 6.58 (m, 12H; ArH), 7.57 (br.s, 4H, D_2O exchangable; NH); ^{13}C NMR ($CDCl_3$): $\delta = 31.03$, 37.04, 45.29, 58.11, 74.13, 123.31, 129.02, 134.48, 155.98, 169.76.

MR dispersion measurements: A HSA stock solution (20% w/v) was prepared in deionized water from 96%–99% albumin (fraction V, Sigma Chemical Co., St. Louis, MO). Relaxation measurements were made on a custom-designed variable field T_1-T_2 analyzer (Southwest Research Institute, San Antonio, TX) at 23 °C. The magnetic field strength was varied from 0.02 to 1.5 T (corresponding to a proton Larmor frequency of 1–64 MHz). T_1 was measured by using a saturation recovery pulse sequence with 32 incremental recovery times. The relaxivities (relaxation rates per mM Gd concentration) were obtained after subtracting the water contribution or the appropriate diamagnetic 2% or 10% HSA solution contribution, respectively. T_2 was measured by using a Carr–Purcell–Meiboom–Gill pulse sequence of 500 echoes and a time interval of 2 msec between echos.

Received: October 5, 1999 [Z14109]

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[1] a) R. B. Lauffer, *Chem. Rev.* **1987**, *87*, 901; b) S. Aime, M. Botta, M. Fasano, E. Terreno, *Chem. Soc. Rev.* **1998**, *27*, 19.

[2] R. B. Lauffer, D. J. Parmelee, S. U. Dunham, H. S. Ouellet, R. P. Dolan, S. Witte, T. J. McMurry, R. C. Walovitch, *Radiology* **1998**, *207*, 529.

[3] P. Caravan, J. J. Ellison, T. J. McMurry, R. B. Lauffer, *Chem. Rev.* **1999**, *99*, 2293.

[4] a) E. M. Georgiev, J. Clymire, G. L. McPherson, D. M. Roundhill, *Inorg. Chim. Acta* **1994**, *227*, 293; b) L. Prodi, S. Pivari, F. Bolletta, M. Hissler, R. Ziessel, *Eur. J. Inorg. Chem.* **1998**, *12*, 1959; c) S. V. Shevchuk, E. A. Alexeeva, N. V. Rusakova, Y. V. Korovin, V. A. Bacherikov, A. I. Gren, *Mendeleev Commun.* **1998**, *3*, 112; d) F. Arnaud-Neu, M. J. Schwing-Weill, *Synth. Met.* **1997**, *90*, 157; e) F. J. Steemers, H. G. Meuris, W. Verboom, D. N. Reinhoudt, E. B. van der-Tol, J. W. Verhoeven, *J. Org. Chem.* **1997**, *62*, 4229; f) F. Arnaud-Neu, S. Cremin, S. Harris, M. A. McKervey, M. J. Schwing-Weill, P. Schwinte, A. Walker, *J. Chem. Soc. Dalton Trans.* **1997**, *3*, 329; g) J. W. Steed, C. P. Johnson, C. L. Barnes, R. K. Juneja, J. L. Atwood, S. Reilly, R. L. Hollis, P. H. Smith, D. L. Clark, *J. Am. Chem. Soc.* **1995**, *117*, 11426; h) F. Arnaud-Neu, *Chem. Soc. Rev.* **1994**, *23*, 235; i) D. M. Roundhill, *Prog. Inorg. Chem.* **1995**, *43*, 533; j) S. Pappalardo, F. Bottino, L. Giunta, M. Pietraszkiewicz, J. Karpiuk, *J. Inclusion Phenom. Mol. Recognit. Chem.* **1991**, *10*, 387; k) J. L. Atwood, S. G. Bott, *J. Less-Common Met.* **1986**, *126*, 396; l) M. H. B. G. Gansey, F. J. Steemers, W. Verboom, D. N. Reinhoudt, *Synthesis* **1997**, 643; m) N. Sabbatini, M. Guardigli, A. Mecati, V. Balzani, R. Ungaro, E. Ghidini, A. Casnati, A. Pochini, *J. Chem. Soc. Chem. Commun.* **1990**, 878; n) M. H. B. G. Gansey, W. Verboom, F. C. J. M. van Veggel, V. Vetrogon, F. Arnaud-Neu, M.-J. Schwing-Weill, D. N. Reinhoudt, *J. Chem. Soc. Perkin Trans. 2* **1998**, 2351.

[5] E. M. Georgiev, D. M. Roundhill, *Inorg. Chim. Acta* **1997**, *258*, 93.

[6] K. A. Connors, *Binding Constants: The Measurement of Molecular Complex Stability*, Wiley, New York, **1987**, pp. 353–355.

[7] G. Hernandez, M. F. Tweedle, R. G. Bryant, *Inorg. Chem.* **1990**, *29*, 5109.

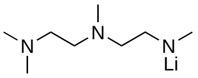
[8] S. H. Koenig, *Invest. Radiol.* **1994**, *29*, S127.

[9] F. Arnaud-Neu, E. M. Collins, M. Deasy, G. Ferguson, S. J. Harris, B. Kaitner, A. J. Lough, M. A. McKervey, E. Marques, B. L. Ruhl, M. J. Schwing-Weill, E. M. Seward, *J. Am. Chem. Soc.* **1989**, *111*, 8681.

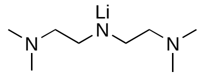
Lithium Amides: Intra-Aggregate Complexation of Lithium and Entropy Control of Basicity

Gerbert L. J. van Vliet, Henri Luitjes, Marius Schakel, and Gerhard W. Klumpp*

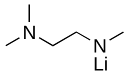
Lithium amides ($LiNR_2$, LiA) are the most widely used reagents for the generation of enolates and their cognate species from carbonyl compounds and related CH acids.[1] This practical importance has led to extensive lists of pK values of secondary amines (HA).[2] However, interpretation of ΔpK values in terms of enthalpy and entropy effects, fundamental to understanding the basicity of lithium amides, is severely limited. Commonly, pK values are determined at a single temperature, usually around 25 °C. This permits only correlation of ΔpK with differences in relative free energy, ΔG_{rel}(LiA(2), LiA(1)), at that temperature.[3] We now report on the prominent influence of entropy on the basicity towards triphenylmethane (TPMH) in THF of lithium *N*-(3,6-diaza-3,6-dimethyl)heptyl-*N*-methylamide (**1**-Li), lithium bis(*N*,*N*-dimethyl-2-aminoethyl)amide (**2**-Li), and lithium *N*-(*N*,*N*-dimethyl-2-aminoethyl)-*N*-methylamide (**3**-Li).[4] Despite the rather special nature of **1**-Li–**3**-Li, our findings have some bearing on the thermodynamics of lithium amides in general.



1-Li



2-Li



3-Li

1-Li and **2**-Li were shown[4] to exist in toluene or THF exclusively as the dimers $(\mathbf{1}\text{-Li})_2$ and $(\mathbf{2}\text{-Li})_2$, with exhaustive intra-aggregate complexation of lithium. Their congener **3**-Li lacks one of the amino groups of **1**-Li and **2**-Li and forms an equilibrium mixture (THF, −108 °C: 2.3:1) of a monomer and a dimer, for which the structures $\mathbf{3}\text{-Li} \cdot 2\,THF$ and $(\mathbf{3}\text{-Li})_2 \cdot THF$ were suggested by THF titration,[4] MNDO calculations,[5] and reaction kinetics.[6]

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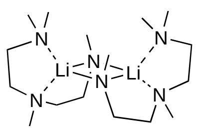
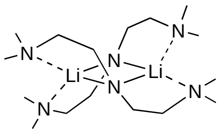
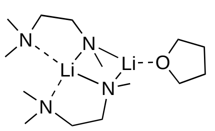


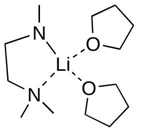
$(\mathbf{1}\text{-Li})_2$



$(\mathbf{2}\text{-Li})_2$



$(\mathbf{3}\text{-Li})_2\cdot$THF



$\mathbf{3}$-Li·2THF

The equilibria of **1**-Li, **2**-Li, and **3**-Li with triphenylmethane [TPMH, Eq. (1a)] in THF were measured in the temperature range −20 to 15 °C.[7] Values of the TPMH-based pK of the conjugate acids **1**-H–**3**-H at 30 °C [the temperature at which numerous pK values were determined;[2] $pK_{\mathrm{Li,THF,30^\circ C}}$, Eq. (1b); $30.4 = pK_{\mathrm{Li,THF,30^\circ C}}(\mathrm{TPMH})^{[2]}$] and of ΔH[Eq. (1a)] and ΔS[Eq. (1a)] are given in Table 1 (entries 1–3).[9]

$$\mathrm{TPMH} + \mathbf{1}\text{-Li}(\mathbf{2}\text{-Li}, \mathbf{3}\text{-Li}) \overset{K}{\rightleftharpoons} \mathrm{Ph_3CLi} + \mathbf{1}\text{-H}(\mathbf{2}\text{-H}, \mathbf{3}\text{-H}) \qquad (1\,a)$$

$$pK_{\mathrm{Li,THF,30^\circ C}}(\mathbf{1}\text{-H }(\mathbf{2}\text{-H}, \mathbf{3}\text{-H})) = 30.4 + \lg K(\mathbf{1}\text{-H }(\mathbf{2}\text{-H}, \mathbf{3}\text{-H}), 30\,^\circ\mathrm{C}) \qquad (1\,b)$$

Table 1. Values of $pK_{\mathrm{Li,THF,30^\circ C}}$ of the conjugate acids of **1**-Li–**3**-Li [Eq. (1b)]; ΔH[Eq. (1a)] [kJ mol^{-1}] and ΔS[Eq. (1a)] [J K^{-1} mol^{-1}].[a]

Entry		$pK_{\mathrm{Li,THF,30^\circ C}}$	ΔH[Eq. (1a)]	ΔS[Eq. (1a)]
1	**1**-Li[b]	25.4 ± 0.3	−36.9 ± 3	−220 ± 20
2	**2**-Li[b]	23.8 ± 0.6	−35.7 ± 10	−240 ± 40
3	**3**-Li[c]	27.9 ± 0.1	−33.8 ± 6	−160 ± 20
4	**1**-Li + 1 equiv **1**-H[d]	27.7 ± 0.4	−20.7 ± 3	−120 ± 20
5	**1**-Li + 2 equiv **1**-H[d]	27.9 ± 0.4	−22.6 ± 3	−120 ± 20

[a] $[\mathbf{1}\text{-Li}]_f$–$[\mathbf{3}\text{-Li}]_f \approx$ [TPMH] ≈ 0.03 M, THF. [b] Average of three determinations. [c] Average of two determinations. [d] Single experiment.

Disregarding intra-aggregate complexation of lithium by the dimethylamino groups, one would expect $pK_{\mathrm{Li,THF,30^\circ C}}$ of **2**-H, **3**-H, and $\mathrm{Me_2NH}$ to follow the same order as those[2] of $\mathrm{Et_2NH}$ (31.7) > EtMeNH (30.9) > $\mathrm{Me_2NH}$ (29.7), for which successive replacements of ethyl by methyl groups change $pK_{\mathrm{Li,THF,30^\circ C}}$ by roughly the same amount ($\Delta pK_{\mathrm{Li,THF,30^\circ C}} = -0.8, -1.2$). In fact, the values of $pK_{\mathrm{Li,THF,30^\circ C}}$ of **2**-H and **3**-H are considerably lower than those of $\mathrm{Et_2NH}$ and EtMeNH, respectively, and their order runs counter to that of the simple dialkylamines: compared to Et → Me, replacement of $\mathrm{CH_2CH_2N(Me)_2}$ by Me affects $pK_{\mathrm{Li,THF}}$ in the opposite sense by amounts that distinctly differ for the two steps ($\Delta pK_{\mathrm{Li,THF,30^\circ C}} = 4.1$, 1.8[10]).

The values of ΔH[Eq. (1a)] and ΔS[Eq. (1a)] provide a clue to the mode by which intra-aggregate complexation of lithium by (alkyl)(methyl)amino groups influences $pK_{\mathrm{Li,THF}}$.[11] The strongly negative reaction entropies are most telling. They indicate that the reactions of **1**-Li–**3**-Li with TPMH in THF involve the binding of a considerable number of THF molecules, that is, the actual reaction product is $\mathrm{Ph_3C^-[Li(thf)_n]^+}$.[12] Detailed analysis is impossible. However, because THF is already bonded to lithium in the reacting **3**-Li species—probably **3**-Li·2THF and $(\mathbf{3}\text{-Li})_2\cdot$THF (see above)[13]—fewer THF molecules are immobilized in the reaction of **3**-Li than in the reactions of **1**-Li and **2**-Li, the $(\mathbf{1}\text{-Li})_2$ and $(\mathbf{2}\text{-Li})_2$ constituents of which do not contain bound THF. Consequently, in the case of **3**-Li, the decrease in entropy is smaller and the basicity $pK_{\mathrm{Li,THF,30^\circ C}}$ is higher, even though the reaction of **3**-Li with TPMH is (slightly) less exothermic than those of **1**-Li and **2**-Li. We recognize a clear case of basicity control by the entropy of THF complexation. The decrease in entropy is smaller, the cost in ΔG[Eq. (1a)] is lower, and the basicity $pK_{\mathrm{Li,THF,30^\circ C}}$ is higher, if **1**-H–**3**-H act as ligands towards lithium. Owing to the polydentate nature of these ligands, the decrease in the number of particles upon complexation/chelation is lower than with THF. Accordingly, when one or two equivalents of **1**-H were added to the equilibrium reaction mixture of **1**-Li (Table 1, entries 4 and 5), $pK_{\mathrm{Li,THF,30^\circ C}}$ rose by approximately 2.4 units, and less negative values of ΔS[Eq. (1a)] and ΔH[Eq. (1a)] were found. This is ascribed to chelation by **1**-H of both $\mathrm{Ph_3CLi}$ and a dimer of **1**-Li.[14] Again, the effect on $pK_{\mathrm{Li,THF,30^\circ C}}$ of the (**1**-H)-induced lowering of $|\Delta S[\mathrm{Eq.}\ (1a)]|$ is stronger than the counteracting influence of the decrease in $|\Delta H[\mathrm{Eq.}\ (1a)]|$.[15, 16]

Clearly, entropies of LiA reactions are strongly influenced by the interdependent modes of aggregation and Lewis base complexation of both the reactant and the product lithium species. This led to the working hypothesis that reactions of lithium amides having the same type of aggregation and complexation (e.g., dimers of lithium amides with tricoordinate lithium such as $(i\mathrm{Pr_2NLi})_2\cdot 2\mathrm{THF}$)[17] with the same substrate (e.g., TPMH) have about the same entropy. Consequently, their $\Delta pK_{\mathrm{Li,THF}}$ should approximately reflect differences in reaction enthalpies and relative enthalpies[3] [$\Delta H^0_{\mathrm{rel}}$; Eq. (2)].[18]

$$2.3\,RT\Delta pK_{\mathrm{Li,THF}}(\mathrm{HA(2), HA(1)}) \approx \Delta H(\mathrm{LiA(2)}) - \Delta H(\mathrm{LiA(1)}) = \Delta H^0_{\mathrm{rel}}(\mathrm{LiA(1)}) - \Delta H^0_{\mathrm{rel}}(\mathrm{LiA(2)}) \qquad (2)$$

The enthalpies of reaction with TPMH of **1**-Li–**3**-Li (ΔH[Eq. (1a)], Table 1) are rather similar, and that of **3**-Li is smallest.[13] This shows that intra-aggregate tetracoordination of lithium by (alkyl)(methyl)amino groups in LiA dimers has no enthalpic advantage over the THF-induced modes of aggregation/coordination (**3**-Li·2THF and $(\mathbf{3}\text{-Li})_2\cdot$THF) that are ascribed to **3**-Li in THF.[19] What, then, is the cause of the special stability of **2**-Li, that is, the strong decrease in basicity on going from $\mathrm{Et_2NLi}$ to **2**-Li, and from EtMeNLi to **3**-Li, as well? An important role is played by the entropically unfavorable structure of **2**-Li. On the simplifying assumption that ΔS[Eq. (1a)] depends solely on the number of THF molecules that are immobilized by formation of $\mathrm{Ph_3C^-[Li(thf)_n]^+}$ and that this number is approximately the same for $(\mathrm{Et_2NLi})_2\cdot 2\mathrm{THF}$[17] and $(\mathrm{EtMeNLi})_2\cdot 2\mathrm{THF}$[17] (immobilization of $n-1$ molecules of THF per lithium atom) and **3**-Li (average of **3**-Li·2THF and $(\mathbf{3}\text{-Li})_2\cdot$THF: ca. $n-1.25$ molecules of THF immobilized per lithium atom), about four units of $\Delta pK_{\mathrm{Li,THF,30^\circ C}}(\mathrm{Et_2NH}, \mathbf{2}\text{-H}) = 7.9$ are caused by the entropy effect (cf. Table 1, entries 2 and 3). We attribute a large part of the remaining four units to inductive stabilization of $\mathrm{N^-}$ in **2**-Li by its two dimethylamino groups. In the case of **3**-Li, about the total of $\Delta pK_{\mathrm{Li,THF,30^\circ C}}(\mathrm{EtMeNH}, \mathbf{3}\text{-H}) = 3$

would be due to this effect. The supposition that two dimethylamino groups per lithium atom in **2**-Li lead to a lowering of $\mathrm{p}K_{\mathrm{Li,THF,30^\circ C}}$ by about four units, while nearly the same effect is produced by a single such group in **3**-Li, implies nonadditivity of these inductive interactions in lithium amides with intra-aggregate complexation.

In conclusion, the values of $\mathrm{p}K_{\mathrm{Li,THF,30^\circ C}}$ (based on that of TPMH) of the conjugate acids of **1**-Li – **3**-Li are 4.3, 5.9, and 1.8 units lower than that of dimethylamine. The differences in basicity of **1**-Li – **3**-Li are due to the entropic consequences of the differences in Lewis base complexation of these lithium amides and $\mathrm{Ph_3CLi}$. The rather similar reaction enthalpies of **1**-Li – **3**-Li indicate that intra-aggregate tetracoordination of lithium in LiA dimers has no enthalpic advantage over THF-induced modes of aggregation/coordination. Besides entropy, inductive stabilization by dimethylamino groups is proposed as a major cause of the basicity differences between **2**-Li, **3**-Li and $\mathrm{Et_2NLi}$, EtMeNLi, respectively. In the wider realm of LiA properties, our findings suggest that within a family of lithium amides of the same aggregation and complexation type, $\Delta\mathrm{p}K_{\mathrm{Li,THF}}$ provides an approximate value of the difference in relative LiA enthalpies.

Received: September 21, 1999 [Z13993]
Revised: December 13, 1999

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[1] J. d'Angelo, *Tetrahedron* **1976**, *32*, 2979 – 2990; C. H. Heathcock in *Comprehensive Carbanion Chemistry, Vol. B* (Eds.: E. Buncel, T. Durst), Elsevier, New York, **1980**, chap. 4; E. J. Corey, A. W. Gross, *Tetrahedron Lett.* **1984**, *25*, 495 – 498.

[2] For example, H. Ahlbrecht, G. Schneider, *Tetrahedron* **1986**, *42*, 4729 – 4741, and references therein.

[3] If the conjugate acids HA do not partake in special interactions they can be assigned equal relative free energies and equal relative enthalpies.

[4] G. L. J. van Vliet, F. J. J. de Kanter, M. Schakel, G. W. Klumpp, A. L. Spek, M. Lutz, *Chem. Eur. J.* **1999**, *5*, 1091 – 1094.

[5] G. L. J. van Vliet, unpublished results. "Asymmetric" complexation as in $(\mathbf{3}\text{-Li})_2\cdot\mathrm{THF}$ was found by G. Hilmersson, P. I. Arvidsson, Ö. Davidsson, *Organometallics* **1997**, *16*, 3352 – 3362.

[6] In *pentane*, the reaction order of THF, added to the system 2-*exo*-bromonorbornane + **3**-Li, is close to one-half. This indicates the presence, in the transition state, of one molecule of THF per two atoms of lithium (G. L. J. van Vliet, unpublished results).

[7] Nearly equivalent amounts of TPMH and LiA ($[\mathrm{TPMH}](=Q)\approx[\mathrm{LiA}]_\mathrm{f}(=R$; formal concentration as obtained by titration) were mixed in an evacuated (4×10^{-6} mbar) and sealed UV cell. $[\mathrm{Ph_3CLi}]$ was measured at $\lambda = 500$ nm, $\varepsilon = 28300\,\mathrm{L\,mol^{-1}\,cm^{-1}}$,[8] and equilibrium constants were calculated as $K[\text{Eq. (1a)}] = [\mathrm{Ph_3CLi}]^2(Q-[\mathrm{Ph_3CLi}])^{-1}(R-[\mathrm{Ph_3CLi}])^{-1}$.

[8] Compare I. S. Antipin, R. F. Gareev, A. N. Vedernikov, A. I. Konovalov, *Zh. Org. Khim.* **1989**, *25*, 1153 – 1160.

[9] While the values of $\Delta H[\text{Eq. (1a)}]$ and $\Delta S[\text{Eq. (1a)}]$ in entries 1 – 3 of Table 1 are specific for reaction with TPMH, the values of $\mathrm{p}K_{\mathrm{Li,THF,30^\circ C}}$ are applicable to all reactions with substrates whose $\mathrm{p}K_{\mathrm{Li,THF,30^\circ C}}$ is based on that of TPMH.

[10] $\Delta\mathrm{p}K_{\mathrm{Li,THF,30^\circ C}}$ between piperidine (30.7)[2] and morpholine (28.8)[2] is nearly the same as that between $\mathrm{Me_2NH}$ and **3**-H and may have similar origins.

[11] For the effects of intramolecular complexation on alkyllithium compounds, see R. F. Schmitz, M. Schakel, M. Vos, G. W. Klumpp, *Chem. Commun.* **1998**, 1099 – 1100, and references therein.

[12] From the similarity of the entropies in entries 1 and 2 with that of another case of lithium salt formation in THF and ascribed—in accord with known structures of THF-complexed lithium salts—to the formation of $[\mathrm{Li(thf)_4}]^+$ (see A. H. J. F. de Keijzer, F. J. J. de Kanter, M. Schakel, R. F. Schmitz, G. W. Klumpp, *Angew. Chem.* **1996**, *108*, 1183 – 1184; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1127 – 1128), we speculate that $\mathrm{Ph_3C^-[Li(thf)_4]^+}$ is formed in solution, although $\mathrm{Ph_3CLi}$ is disolvated in the solid state. (For a discussion of $\mathrm{Ph_3CLi}$ solvation, see C. Lambert, P. von R. Schleyer, *Methoden Org. Chem. (Houben-Weyl), 4th ed. 1952–, Vol. E19d*, **1993**, p. 68.)

[13] A more refined analysis would focus on $\mathrm{p}K_{\mathrm{Li,THF,30^\circ C}}$, $\Delta H[\text{Eq. (1a)}]$, and $\Delta S[\text{Eq. (1a)}]$ of $\mathbf{3}\text{-Li}\cdot 2\,\mathrm{THF}$ and $(\mathbf{3}\text{-Li})_2\cdot\mathrm{THF}$, respectively. This requires knowledge of $\Delta H[\text{Eq. (3)}]$ and $\Delta S[\text{Eq. (3)}]$ which can only be speculated on.

$$0.5\,(\mathbf{3}\text{-Li})_2\cdot\mathrm{THF} + 1.5\,\mathrm{THF} \overset{K}{\rightleftharpoons} \mathbf{3}\text{-Li}\cdot 2\,\mathrm{THF} \qquad (3)$$

[14] a) Recent work (P. I. Arvidsson, G. Hilmersson, P. Ahlberg, *J. Am. Chem. Soc.* **1999**, *121*, 1883 – 1887) showed that secondary amines of the type $\mathrm{HN(R)CHR'CH_2NR_2}$ stabilize by chelation dimers of lithium amides more strongly than does $\mathrm{Me_2NCH_2CH_2NMe_2}$ (TMEDA), and we presume that under the conditions of entries 4 and 5, **1**-H analoguously chelates a dimer of **1**-Li. Exhaustive chelation may already be achieved at a 1:1 (equiv) ratio, and the differences between entries 4 and 5 are probably due to experimental error. b) We have not yet succeeded in detecting such species by ^{13}C NMR spectroscopy. At −106 °C, a 1:2 (equiv) mixture of $(\mathbf{1}\text{-Li})_2$ and **1**-H exhibited separate spectra of the two species. Warming led to extensive coalescence that prevented identification of any new species.

[15] Under the conditions of entries 1 – 3, **1**-H – **3**-H, present in the same (low) concentrations as $\mathrm{Ph_3CLi}$, seem to be unable to compete for the latter with THF, the concentration of which is 10^5 – 10^6 times higher.

[16] The effect of addition of polydentate HA′ might be put to advantage in asymmetric synthesis based on the use of LiA′ with intra-aggregate complexation (e.g., D. Sato, H. Kawasaki, I. Shimada, Y. Arata, K. Okamura, T. Date, K. Koga, *J. Am. Chem. Soc.* **1992**, *114*, 761 – 763).

[17] According to, both experimental results and calculations, the lithium atom in dimers of lithium amides is tricoordinate: F. E. Romesberg, D. B. Collum, *J. Am. Chem. Soc.* **1992**, *114*, 2112 – 2121; B. L. Lucht, D. B. Collum, *J. Am. Chem. Soc.* **1995**, *117*, 9863 – 9874.

[18] a) By using Equation (2), $(\mathrm{Et_2NLi})_2\cdot 2\,\mathrm{THF}$[17] ($\mathrm{p}K_{\mathrm{Li,THF,30^\circ C}} = 31.7$[2]) is calculated to be stabilized enthalpically with respect to $i\mathrm{Pr_2NLi}$ ($\mathrm{p}K_{\mathrm{Li,THF,30^\circ C}} = 34.4$[2]) by $15.6\,\mathrm{kJ\,mol^{-1}}$, which is just $0.8\,\mathrm{kJ\,mol^{-1}}$ outside the lower error limit of the value obtained from the difference of their heats of protonation (*i*PrOH, hexane/diethyl ether 90/10, $\Delta\Delta H = (21.8\pm5.4)\,\mathrm{kJ\,mol^{-1}}$, E. M. Arnett, K. D. Moe, *J. Am. Chem. Soc.* **1991**, *113*, 7068 – 7069). b) The (near) additivity of the α-methyl effect on $\mathrm{p}K_{\mathrm{Li,THF,30^\circ C}}$ observed[2] for a substantial number of lithium dialkylamides of the $(\mathrm{R_2NLi})_2\cdot 2\,\mathrm{THF}$ family[17] supports our guideline. In its light, the $\mathrm{p}K_{\mathrm{Li,THF,30^\circ C}}$ difference of 0.8 units[2] between $(\mathrm{Et_2NLi})_2\cdot 2\,\mathrm{THF}$ and $(\mathrm{EtMeNLi})_2\cdot 2\,\mathrm{THF}$[17] indicates that the ligand change methyl → ethyl increases ΔH^0 of a THF-solvated LA dimer by about $5\,\mathrm{kJ\,mol^{-1}}$ per lithium atom.

[19] The tetracoordination of lithium calculated[5] and found[4] for $(\mathbf{1}\text{-Li})_2$ and $(\mathbf{2}\text{-Li})_2$ and calculated for one lithium atom of $(\mathbf{3}\text{-Li})_2\cdot\mathrm{THF}$[5] is exceptional. Due to the intra-aggregate mode of complexation, adverse effects of entropy loss and steric crowding, both disfavoring intermolecular tetracoordination of THF to LiA dimers, are minimal.