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Formation of Heterodimer Complexes between Analogous Chiral Lithium Amides: NMR Spectroscopic and Computational Studies

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Mixing two analogous lithium amide salts from methyl(1-phenyl-2-(pyrrolidin-1-yl)ethyl)-[^{15}N]amine (**1**) and (2-methoxy-1-phenylethyl)methylamine (**2**) in a 1:1 ratio in diethyl ether resulted in a formation of five different dimer complexes, three homodimers and two heterodimers. Computational studies of the relative stabilities of the different dimers were found to be in concordance with relative concentrations observed by NMR spectroscopy. The desymmetrization of cyclohexene oxide using the mixture of Li-**1** and Li-**2** indicated that the heterodimer exhibited a higher asymmetric induction than either lithium amide by itself according to the "superbases" and the alkyllithium/lithium alkoxide mixtures.

Introduction

Ever since Lochman et al. and later Schlosser mixed equimolar amounts of *n*-butyllithium and potassium *tert*-butoxide, to form the first superbases, the superbases have found many uses and applications in organic synthesis.[1] It is well-known that these heteromixtures of alkali-metal alkoxide or amide complexes show different reactivities compared to the homomixtures.[2] One problem in studying these heterocomplexes in solution is the presence of a non-NMR-susceptible nucleus: i.e., potassium. Therefore, alkyllithium/lithium alkoxide mixtures have been studied as models of the so-called "superbases".[3]

Chiral lithium amides are often used as chiral bases. In the search for the optimum chiral amide base, one must be able to understand all the factors that determine the complexation and reactivity of the chiral amide.[4] Two different chiral lithium amide bases do not show the same reactivities and do not give the same enantiomeric excesses in an enantioselective reaction such as desymmetrization of cyclohexene oxide. If one has a mixture of two different lithium amides, will there be a mixed heterocomplex formed between these two analogous amides? How will the reactivity and asymmetric induction be influenced? Will these mixtures display superbase-like reactivities?

Computational Methods

All ab initio calculations were performed using the Titan program, and all conformer searches were performed using the Spartan program.[5] Equilibrium geometries were optimized using the semiempirical method PM3 and HF/6-31+G(d) basis set levels of theory.[6] The chiral substituents were not included in the structures calculated. No consideration has been taken of solvation in the calculations.

Results and Discussion

To investigate lithium amide heterodimers, we used the closely related chiral amines methyl(1-phenyl-2-

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(1) (a) Lochmann, L.; Pospísil, J.; Lim, D. Czech. Pat. 132.254; appl. December 30, 1964; *Chem. Abstr.* **1970**, 73, 25642f. (b) Schlosser, M. *J. Organomet. Chem.* **1967**, *8*, 9.

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(3) DeLong, G. T.; Panell, D. K.; Clark, M. T.; Thomas, R. D. *J. Am. Chem. Soc.* **1993**, *115*, 7013.

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(5) (a) Titan, version 1.0.5; Wavefunction, Inc., 18401 Von Karman Ave., #370, Irvine, CA and Schrödinger, Inc., 1500 SW First Ave, #1180, Portland, OR 97201, 2000. (b) Spartan, version 5.1.3; Wavefunction, Inc., 18401 Von Karman Ave., #370, Irvine, CA, 1995.

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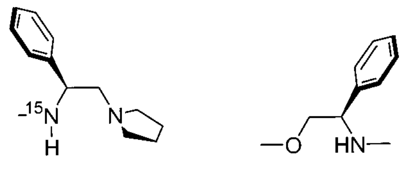
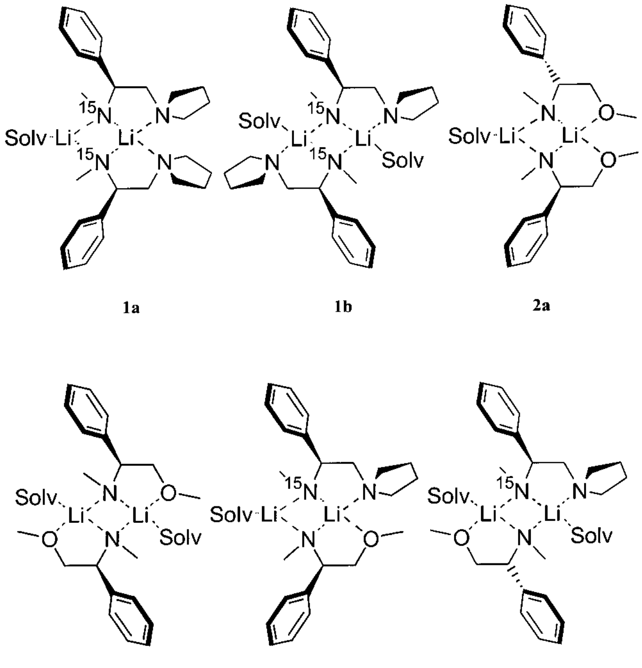
Chart 1



1 2

Chart 2



1a 1b 2a

2b 3a 3b

(pyrrolidin-1-yl)ethyl)[^{15}N]amine (**1**) and (2-methoxy-1-phenyl-ethyl)methylamine (**2**) (Chart 1). The reason for using the [^{15}N]-**1** amine as the sole ^{15}N source is that one can easily observe the formation of homo- or heterocomplexes between the lithium salts of [^{15}N]-**1** and **2**, utilizing ^{6}Li,^{15}N coupling constants.

Using the one-bond ^{15}N$-^{6}$Li coupling constant, $^{1}J_{^{6}\mathrm{Li}^{15}\mathrm{N}}$, we can determine both the aggregation and the solvation state.[7] Monomers have a slightly larger coupling constant than cyclic oligomers, and lithiums that are tricoordinated have larger coupling constants than tetracoordinated ones. Earlier studies of Li-**1** have shown that only asymmetric and symmetric dimers (structures **1a** and **1b** in Chart 2) are observed in DEE.[7]

Since the two lithium atoms in **1a** have different chemical surroundings, they have different chemical shifts and different ^{15}N$-^{6}$Li coupling constants and are observed at δ 2.15 ppm ($^{1}J_{^{6}\mathrm{Li}^{15}\mathrm{N}} = 3.7$ Hz) and δ 2.32 ppm ($^{1}J_{^{6}\mathrm{Li}^{15}\mathrm{N}} = 6.1$ Hz). The most upfield ^{6}Li NMR signal originates from a tetracoordinated lithium cation, whereas the downfield signal originates from a tricoordinated lithium. The lithium cations in **1b** have the same chemical surroundings and would thereby only give rise to one triplet at δ 1.63 ppm ($^{1}J_{^{6}\mathrm{Li}^{15}\mathrm{N}} = 4.5$ Hz).[7]

The lithium cations in nitrogen-unlabeled **2a** have different surroundings and would thereby give rise to two singlets with different ^{6}Li NMR chemical shifts, but in nitrogen-unlabeled **2b** the lithium atoms are equivalent and would therefore only be observed as a singlet.

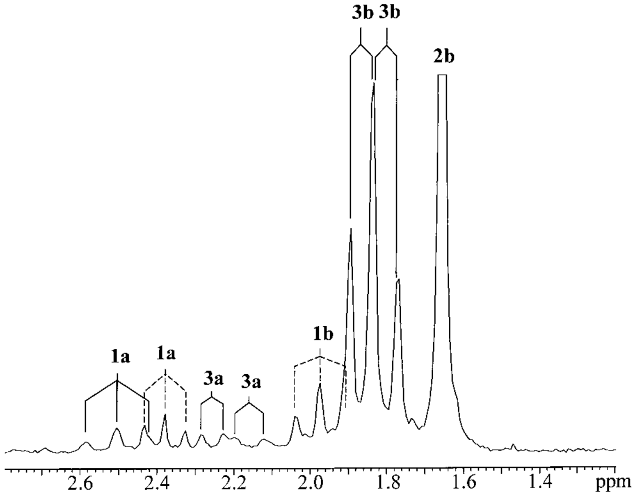


Figure 1. ^{6}Li NMR spectrum of a 1:1:2 mixture of amine **1**, amine **2**, and *n*-BuLi in DEE-d_{10} at -90 °C, showing five different species.

The lithium cations in **3a** are not equivalent, and since both the lithium cations are coupling with one ^{15}N atom, they would be observed as two doublets with different chemical shifts and ^{15}N$-^{6}$Li coupling constants. The lithium cations in **3b** would be observed as two doublets with different chemical shifts, but with the same magnitude of the ^{15}N$-^{6}$Li coupling constants.

NMR Spectroscopic Studies. A mixture of **1** and **2** in a 1:1 ratio in DEE-d_{10} was titrated with 1 equiv of [^{6}Li]*n*-BuLi with respect to the total amount of amine **1** and **2** at -90 °C. In the ^{1}H NMR spectra there were no signals observed from α-protons in *n*-BuLi. In the ^{6}Li NMR spectrum two triplets at δ 2.50 ppm ($^{1}J_{^{6}\mathrm{Li}^{15}\mathrm{N}} = 6.1$ Hz) and δ 2.38 ppm ($^{1}J_{^{6}\mathrm{Li}^{15}\mathrm{N}} = 4.0$ Hz) were observed in a 1:1 ratio. These two triplets originate from the two lithium cations in **1a**. Another triplet at δ 1.97 ppm ($^{1}J_{^{6}\mathrm{Li}^{15}\mathrm{N}} = 4.6$ Hz) was observed, and this was assigned to the two lithium cations in **1b**. Two low intensity doublets, in the ratio 1:1, were observed at δ 2.25 and 2.16 ppm with $^{1}J_{^{6}\mathrm{Li}^{15}\mathrm{N}} = 4.1$ Hz and $^{1}J_{^{6}\mathrm{Li}^{15}\mathrm{N}} = 5.6$ Hz, respectively. At δ 1.86 and 1.80 ppm two large doublets, in the ratio 1:1, were observed with lithium$-$nitrogen couplings of $^{1}J_{^{6}\mathrm{Li}^{15}\mathrm{N}} = 4.7$ Hz and $^{1}J_{^{6}\mathrm{Li}^{15}\mathrm{N}} = 5.2$ Hz, respectively. The signals at δ 2.25 and 2.16 ppm were assigned to the lithium cations in **3a**, since the difference in the magnitudes of the coupling constants would be larger in this complex compared to **3b**. The two doublets at δ 1.86 and 1.80 ppm were assigned to **3b**, on the basis of the coupling pattern and coupling constant magnitudes (see Figure 1). In THF the difference between these two signals became more evident. The singlet observed at δ 1.65 ppm in the ^{6}Li NMR spectrum was assigned to originate from complex **2b**, due to the absence of ^{15}N labeling in this dimer. Furthermore, **2a** would display two singlets in the ^{6}Li NMR spectrum due to different chemical environments at the lithiums.

The ^{13}C NMR spectrum at -80 °C showed five quaternary carbon signals at δ 148.8, 149.0, 150.0, 150.9, and 151.4 ppm (Figure 2). Together with the ^{6}Li

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[7] (a) Arvidsson, P. I.; Davidsson, Ö. *Angew. Chem., Int. Ed.* **2000**, *39*, 8. (b) Koizumi, T.; Morihashi, K.; Kikuchi, O. *Bull. Chem. Soc. Jpn.* **1996**, *69*, 305$-$309. (c) Aubrecht, K. B.; Lucht, B. L.; Collum, D. B. *Organometallics* **1999**, *18*, 2981$-$2987.

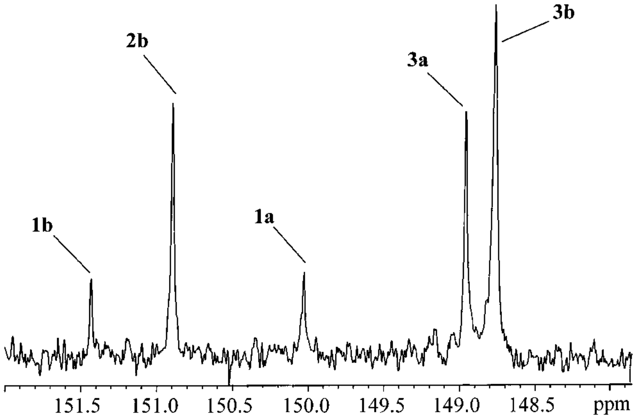


Figure 2. ^{13}C NMR spectrum of a 1:1:2 mixture of amine **1**, amine **2**, and *n*-BuLi in DEE-d_{10} at −90 °C, showing the chemical shift region for quaternary carbon atoms.

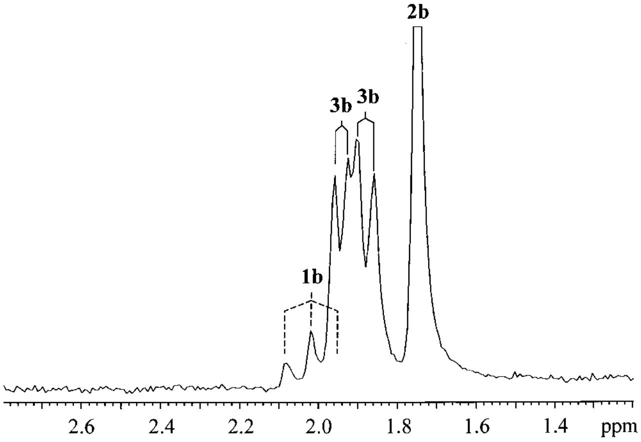


Figure 3. ^{6}Li NMR spectrum of a 1:1:2 mixture of amine **1**, amine **2**, and *n*-BuLi in DEE-d_{10} at −90 °C, with 5 equiv of THF-d_8 added.

NMR spectra, this indicates that there are five species present in solution. The quaternary ^{13}C NMR signals were assigned using the ^{13}C NMR shifts for pure Li-**1** and Li-**2** in DEE and THF solutions, together with a comparison of ^{13}C NMR and ^{6}Li NMR intensities. The chemical shifts for the two quaternary carbon atoms in **3a** are found at the chemical shifts δ 148.8 and 149.0 ppm. The two quaternary carbon atoms of **3b** are also found at the same chemical shifts as for **3a**.

To the NMR tube was added 5 equiv of THF-d_8. The ^{6}Li NMR signals assigned to originate from complexes **1a** and **3a** disappeared. The remaining ^{6}Li NMR signals observed were a singlet at δ 1.76 ppm originating from **2b,** two doublets at δ 1.93 ppm ($^{1}J_{^{6}\mathrm{Li}^{15}\mathrm{N}} = 4.25$ Hz) and δ 1.90 ppm ($^{1}J_{^{6}\mathrm{Li}^{15}\mathrm{N}} = 4.66$ Hz) originating from **3b**, and a triplet at δ 2.02 ppm ($^{1}J_{^{6}\mathrm{Li}^{15}\mathrm{N}} = 4.87$ Hz) originating from **1b** (Figure 3). The ^{15}N NMR spectrum showed two nitrogen signals in a 1:2 ratio, separated by 3.6 ppm. The most downfield ^{15}N NMR signal was assigned to originate from **1b**, and the most upfield signal was assigned to originate from **3b** (Figure 4).

The influence of temperature and concentration upon each species was investigated. A 10-fold increase of the total amine concentration did not affect the relative concentration between the dimeric species. The temperature effect upon dimer equilibria was also not significant.

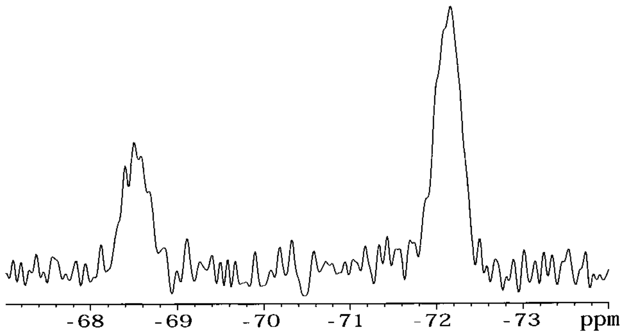


Figure 4. ^{15}N NMR spectrum of a 1:1:2 mixture of amine **1**, amine **2**, and *n*-BuLi in DEE-d_{10} at −90 °C, with 5 equiv of THF-d_8 added.

Table 1. Results from the Conformer Search[a]

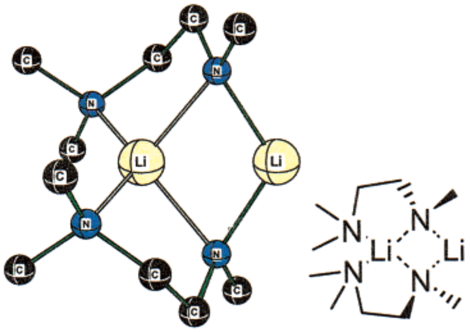
structure	PM3 (kcal mol^{-1})	HF/6-31+G(d) (hartree)	HF/6-31+G(d) (kcal mol^{-1})	rel energy (kcal mol^{-1})
1a* anti	−35.734	−626.544 97	−393 163.2	1.3
	−36.822	−626.542 29	−393 161.2	3.3
	−37.711	−626.538 53	−393 158.9	5.6
1a* syn	−32.260	−626.529 76	−393 153.4	11.1
1b* anti	−39.881	−626.543 02	−393 161.7	2.8
	−37.510	−626.544 77	−393 162.8	1.7
	−34.752	−626.545 90	−393 163.5	1
1b* syn	−36.705	−626.547 43	−393 164.5	0
	−36.704	−626.547 42	−393 164.5	0
2a* anti	−102.945	−588.140 53	−369 064.1	4.2
	−102.730	−588.138 59	−369 062.6	5.7
	−100.539	−588.145 42	−369 066.8	1.5
2a* syn	−99.121	−588.135 07	−369 060.3	8
	−98.947	−588.135 77	−369 060.8	7.5
	−97.629	−588.139 63	−369 063.2	5.1
	−96.418	−588.139 56	−369 063.2	5.1
	−100.061	−588.133 46	−369 059.3	8.7
	−100.108	−588.129 07	−369 056.6	11.7
2b* anti	−104.834	−588.146 90	−369 068.1	0.2
	−101.779	−588.147 83	−369 068.3	0
	−98.693	−588.147 29	−369 068.0	0.3
2b* syn	−103.312	−588.140 95	−369 064.0	4.3
	−104.668	−588.145 87	−369 067.1	1.2
	−103.895	−588.143 32	−369 065.5	2.8
3a* anti	−69.505	−607.341 01	−381 112.3	9.2
3a* syn	−63.979	−607.332 52	−381 104.9	16.6
	−64.240	−607.329 28	−381 103.3	18.2
	−66.353	−607.326 82	−381 103.3	18.2
	−64.245	−607.344 91	−381 114.7	6.8
3b* anti	−71.019	−607.341 97	−381 112.9	8.6
	−68.585	−607.343 85	−381 114.0	7.5
	−70.410	−607.343 24	−381 113.7	7.8
	−72.543	−607.344 49	−381 114.4	7.1
3b* syn	−72.577	−607.340 52	−381 111.9	9.6
	−69.838	−607.355 70	−381 121.5	0

[a] Conformers were optimized semiempirically with PM3, and the most stable conformers were optimized with HF/6-31+G(d).

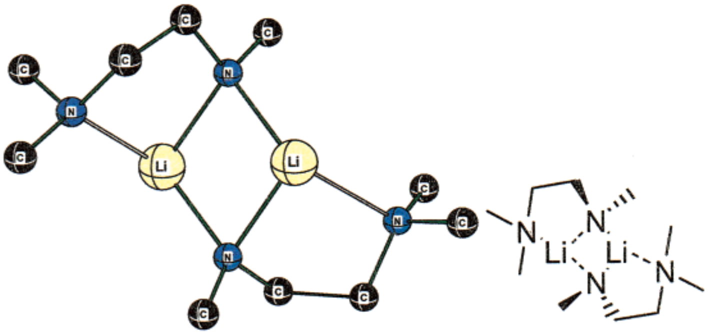
Calculations. The structures used in the calculations are labeled with asterisks.

To determine the energy differences between syn and anti arrangements of the methyl groups on the amido nitrogen, geometry optimizations were performed using HF/6-31+G(d) levels of theory. For the majority of the structures, the anti arrangement was the most stable, but both anti and syn conformers of **1a*** to **3b*** were used in the conformational search using the molecular mechanics program MMFF94. All conformers were geometry-optimized semiempirically with PM3 and by ab initio methods using HF/6-31+G(d). The conformers and their relative energies are presented in Table 1. The most stable conformers are presented in Chart 3.

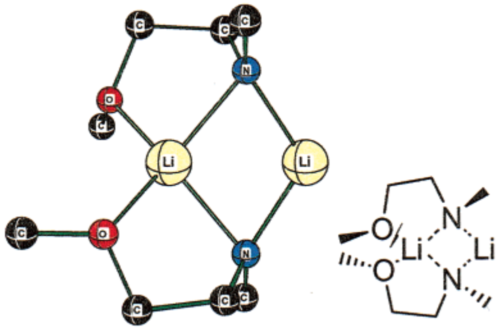
Chart 3



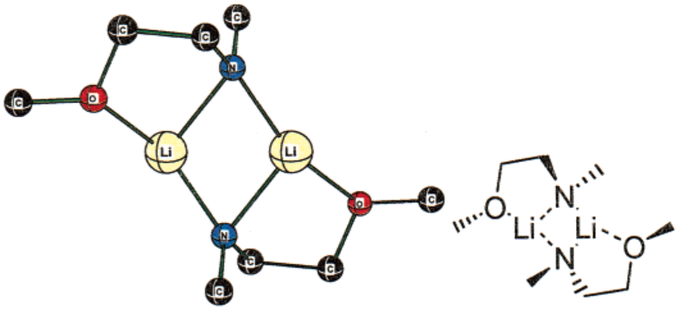
1a*



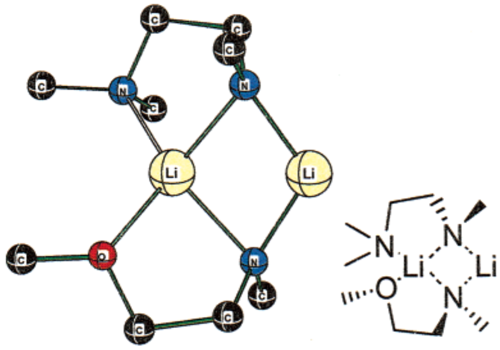
1b*



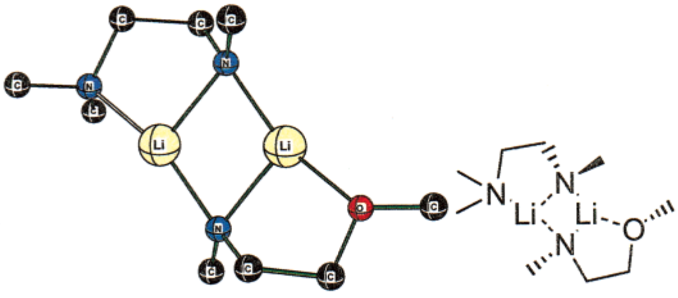
2a*



2b*



3a*



3b*

The calculations showed the symmetric dimers (**1b***, **2b***, and **3b*)** to be more stable than the asymmetric ones (**1a***, **2a***, and **3a*)** according to the energies presented in Table 1. However, the energies of **1a*** and **1b*** were nearly equal, which makes it possible to observe both the asymmetric and the symmetric dimers. This was also verified by the experimental results, where both the symmetric and the asymmetric dimers of **1a** and **1b** were observed in DEE. In THF the asymmetric dimer was less favored due to the higher complexation ability of THF resulting from the larger dipole moment in THF. [5] There is a loss in enthalpy for DEE when it coordinates to lithium, as it adopts a conformation that is higher in energy, although this loss in enthalpy is smaller than the solvation enthalpy. The difference in the ability to coordinate DEE and THF is, in part, caused by a greater loss in vibrational entropy. Clearly, the differences in loss of entropy are due to the fact that when the flexible DEE molecule becomes locked in a single conformation the loss in entropy is greater than when the five-membered cyclic THF compound with mainly ring-puckering vibrations is coordinating.[8]

The relative stabilities of the heterodimers and the homodimers was compared as described in eqs 1 and 2. Both the asymmetric and the symmetric heterodimers are more stable than the asymmetric and symmetric homodimers.

Desymmetrization of Cyclohexene Oxide. The enantioselective deprotonation of cyclohexene oxide using a 1:1 mixture of **1** and **2** and 1 equiv of *n*-BuLi, with respect to **1** and **2**, in THF gave (*S*)-cyclohexanol

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[8] Hilmersson, G. *Chem. Eur. J.* **2000**, *6*, 16, 3069−3075.

in an enantiomeric excess (ee) of 88%. The same reaction with pure Li-**1** gave the *S* enantiomer of cyclohexanol in an enantiomeric excess of 77%, and the reaction with pure Li-**2** gave an ee of 32%.

1a*	+	2a*	$\rightleftharpoons$	2 x 3a*	
-393163.2		-369064.1		-762229.4	kcal/mol
	2.1			0	relative energy in kcal/mol

(1)

1b*	+	2b*	$\rightleftharpoons$	2 x 3b*	
-393164.5		-369068.1		-762243.0	kcal/mol
	10.4			0	relative energy in kcal/mol

(2)

Summary

Both theoretical calculations and experimental data clearly show that the two analogous amides form heterocomplexes in high concentrations. The results also show that symmetrical dimers are more stable than asymmetric dimers both in DEE and in THF. Furthermore, the addition of THF did not dissociate the heterodimers into homodimers.

A simple model cannot explain the stereoselectivity of the 1:1 mixture of Li-**1** and Li-**2** compared to pure Li-**1** and Li-**2**. There are several species present in solution, and all of these might react to give product. There are two species in large concentration, the homodimer **2** and the heterodimer constituted by one molecule of Li-**1** and Li-**2**. Concentration studies showed that the relative concentration between these species was unaffected by increasing the total amide concentration in the solution. The conclusion that could be drawn is that the reactivity of Li-**2** is much lower compared to the mixed heterodimer between Li-**1** and Li-**2**. Furthermore, the selectivity indicates that the mixed heterodimer between Li-**1** and Li-**2** results in higher asymmetric induction in the desymmetrization of cyclohexene oxide. These results indicate that the rate of reaction of a heterocomplex is higher compared to its homoaggregate, which has been observed for the "superbases" and the study of the heterocomplex between alkyllithium and lithium alkoxide by rapid injection NMR.[9]

Experimental Section

General Considerations. All glassware and syringes used for the NMR studies and epoxide-opening reactions were dried at 50 °C in a vacuum oven before transfer to a glovebox. Chromatographic analyses were carried out on a Varian Star 3400 CX gas chromatograph. All GC analyses were run on a chiral stationary phase column (CP-Chirasil-DEX CB, 25 m, 0.32 mm) from Chrompack. All analyses were performed at 135 °C (injector, 225 °C; detector, 250 °C) with He (2 mL min^{-1}) as carrier gas. The NMR analysis were recorded on a Varian Unity 500 spectrometer using a 5 mm ^{1}H, ^{13}C, ^{6}Li, ^{15}N quad resonance probe head custom built by Nalorac.

Synthesis of the Chiral Amines 1 and 2. The amines **1** and **2** were synthesized using published procedures.[10]

Preparation of NMR Samples. The ^{6}Li-labeled lithium amides and the NMR samples were prepared according to published procedures.[11]

Enantioselective Deprotonation of Cyclohexene Oxide. The enantioselective deprotonation of cyclohexene oxide was performed using published procedures.[12]

Acknowledgment. We are most grateful to the Swedish Natural Science Research Council (NFR) and Carl Trygger research foundation for financial support. Sten Nilsson Lill is gratefully acknowledged for valuable suggestions and help with the computational studies.

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