Toward Solution-State Structure. A ^{6}Li,^{1}H HOESY NMR, X-ray Diffraction, Semiempirical (PM3, MNDO), and ab Initio Computational Study of a Chiral Lithium Amide

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Abstract: Computational studies of a chiral lithium amide (lithium (2-methoxy-(*R*)-1-phenylethyl)((*S*)-1-phenylethyl)amide, **3**) using the solid-state structure as a reference geometry showed that there were only small differences between the X-ray and ab initio and PM3 calculated structures. Furthermore, we have shown that reference distances from either X-ray or ab initio/PM3 can be used for the calculation of Li−H distances using Li−H NOE data. The calculations of Li−H distances using HOESY buildup rates showed that the solution structure of **3**·THF is similar to the structure obtained in the gas phase (calculated) and in the solid phase (X-ray). Small variations of ±0.2 Å were observed between X-ray/ab initio and NOE data for distances less than 4 Å.

Introduction

Organolithium compounds as reagents in preparative organic and organometallic chemistry are indispensable. However, it seems that the large potential of chiral organolithium reagents in asymmetric synthesis has only partially been realized, possibly due to an incomplete understanding of this class of compounds. Therefore, detailed structural studies of organolithium complexes, particularly chiral ones, are of great importance.

To date, X-ray analysis has been the only tool used for the determination of 3D structures of organolithium compounds.[1] However, many of these compounds and complexes are difficult to obtain as single crystals and hence much of the present knowledge of organolithium compounds comes from studies using NMR spectroscopy. The aggregation state, dynamics, and, in some cases, kinetics of organolithium compounds have been thoroughly investigated using either of the two NMR-active and stable lithium isotopes, ^{6}Li (7.4% of natural abundance) and ^{7}Li (92.6%).[2] Both are quadrupole nuclei with spins 1 and $^3/_2$, respectively, although ^{6}Li has the smallest quadrupole moment known and hence relaxation mechanisms other than quadrupole relaxation often dominate, i.e. dipole−dipole. This makes it a particularly good nucleus for quantitative structure determination.

In the organic chemistry literature there is, however, a paucity of quantitative structure determinations of small molecules using NMR and, in particular, nuclear Overhauser effects (NOE). More often qualitative measurements or signal assignments are made using techniques such as ^{1}H,^{1}H NOESY spectroscopy. The two-dimensional (2D) ^{6}Li,^{1}H HOESY NMR experiment introduced by Bauer and co-workers in 1986[3] has also been used to provide mainly qualitative structural information and resonance assignments.

The initial buildup rates, *f*, of transient heteronuclear NOEs are proportional to the corresponding distances raised to the power of 6 (eq 1), where H^X is a proton of unknown lithium

$$f(^6\text{Li}-\text{H}^\text{A})/f(^6\text{Li}-\text{H}^\text{X}) = \{r(^6\text{Li}-\text{H}^\text{X})/r(^6\text{Li}-\text{H}^\text{A})\}^6 \quad (1)$$

separation and H^A is a proton of known lithium separation obtained from solid-state measurements. Thus, from the ^{6}Li,^{1}H NOE buildup rate and a known reference distance, all Li−H distances of an organolithium compound in solution can be quantified. Using this approach there have been a few reports in which Li−H distances have been determined using Li−H NOEs.[4−7] However, using data from the solid state to obtain solution structural information should be considered carefully

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since the crystal structure and solution structure are not necessarily identical, especially for small molecules where crystal lattice packing forces and solvation may play important roles.

Calculated Li—H distances are relatively insensitive to the accuracy of the measured NOEs since the magnitudes of the NOEs are proportional to the sixth power of the distance.[8] For the distance calculations it may be argued that the extremely low intensity of the NOE sets an upper bound restraint of any proton—lithium distance measurable by this method to about 4—5 Å.

Computational studies using Hartree—Fock (HF) and density functional theory (DFT) with standard basis sets (3-21G, 6-31G*, 6-31+G*, and 6-31++G**) have also contributed significantly toward a better understanding of organolithium compounds and in particular the C—Li and N—Li bonds.[9,10] However, for larger systems, the use of high-level ab initio calculations becomes limited. Recently developed semiempirical computational methods such as PM3 (parameters optimized for lithium) have reproduced high-level ab initio geometries of smaller structures rather well.[11] It should therefore be possible to calculate energies and geometries of solvated larger compounds and aggregates with reasonable accuracy. This ability is important as the lithium coordinating ligands are often found to control the types of structures that are found and the reaction mechanisms associated with them.
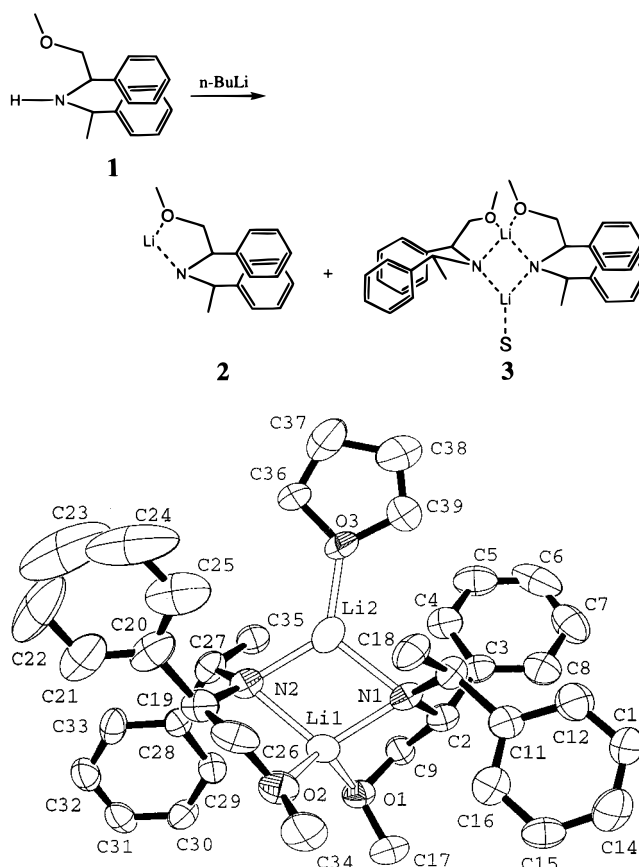
There is clearly a big difference in the interactions of an organolithium reagent (a) in ethereal solvents (NMR spectroscopy), (b) in the absence of interactions, as in a vacuum (computational methods), and (c) in the solid state (X-ray crystallography).

In this paper we report on a comparison among the solid-state structure of a chiral lithium amide with solid-state structures containing isostructural elements found in the CSD (Cambridge Structural Database), semiempirical (PM3, MNDO) and ab initio computational studies, and a series of ^{6}Li,^{1}H HOESY experiments from which relative Li—H distances have been determined using ^{6}Li,^{1}H NOE buildup rates. The scope of this work is to obtain a link between solid-state geometries and solution-state geometries and to describe how well solid-state geometries model solution-state geometries. The potential of using computational methods to describe solid- and solution-state geometries is also discussed.

Results and Discussion

The chiral amine 2-methoxy-((*R*)-1-phenylethyl)((*S*)-1-phenylethyl)amine (**1**) was prepared according to published procedures.[12] The lithium salt of **1**, compound **2**, is quantitatively formed upon addition of 1 equiv of *n*-BuLi to the amine. The above-formed lithium amide is found in solution as monomers

(8) For a typical case where the intensity error is ±20% for the large peaks and ±100% for the small peaks, the error in distance will only be ±3% and ±20%, respectively. Thus the method of determining Li—H distances by measuring NOE buildup rates does not rely on accurate intensities but rather is quite forgiving of moderate inaccuracies.

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Scheme 1

Figure 1. Crystallographic numbering of (*R*,*S*)-**3**·THF.

2, dimers **3**, and/or larger oligomers depending on solvent, temperature, and concentration (Scheme 1).[13] Slow ligand exchange rates on the ^{13}C NMR time scale was used to determine that only one solvent molecule is coordinated to **3**.[13,14]

Solid-State Structure. A single-crystal X-ray diffraction experiment revealed that molecule **2**, crystallized from a hexane—THF (40:1) solution, is dimeric in the solid state in the form of **3** shown in Scheme 1. The molecular structure and the crystallographic numbering that are used in this paper are given in Figure 1. The properties of the X-ray crystal structure of **3**·THF have recently been described.[15]

Is this solid-state structure of **3**·THF representative for lithium amide solid-state structures in general? Is it possible to use the solid-state geometry of **3**·THF as a reference structure for semiempirical and ab initio calculations? To investigate this we compared the solid-state structure of **3**·THF with solid-state structures of lithium amides containing isostructural elements to **3**·THF that we found in the CSD. The result of this investigation is described below. Numbers in parantheses are distances obtained from the X-ray geometries.

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Out of 15 dimeric structures found in the CSD[16] with Li coordinated with two nitrogens and one oxygen, the mean Li−N distance is 2.06 Å (2.05 Å) and the mean Li−O distance is 1.99 Å (1.94 Å). In the CSD, we found 277 structural fragments of the type Li−THF and these had a mean Li−O distance of 1.94 Å (1.94 Å), although there are examples with Li−O distances from 1.72 to 2.27 Å. It was also found that this distance is relatively independent of the aggregation state or the steric requirements of the ligands. Among the solid-state structures in CSD with a THF ligand solvating a three-coordinated lithium (a total of 100), the angle between the plane described by Li(2) and its two ligands N(1), N(2), and the THF oxygen O(3) is 169°. The average angle between the plane defined by oxygen O(3) and the two α-carbons C(36) and C(39) in THF and Li(2) is 168°. The average dihedral angle between the THF molecule and the other two lithium ligands in CSD are 1.7°, which is close to zero. Thus, the C−O−C plane of the coordinated THF in **3·THF** is also almost coplanar with the N₂Li plane, 2.2°. These results shows that the geometry of the solid-state structure of **3·THF** can be used as a reference geometry in the calculations. Interestingly, we found that one proton in each of the two methyl groups shows close proximity to the tricoordinated lithium. The short Li−C distances Li-(2)C(18) = 2.80 Å and Li(2)C(35) = 2.90 Å indicate a possibility of a weak Li···H interaction, and the nearly linear arrangement of H···Li···H is also indicative of the presence of an interaction. The H···Li distances are Li(2)C(18)H = 2.31 Å and Li(2)C(35)H = 2.35 Å, respectively. This is slightly smaller than the sum of the van der Waals radii of Li (1.34 Å) and H (1.1 Å).[17] These short Li−H distances could either be attributed to a weak agostic interaction or to packing effects in the crystal state forcing the methyl group protons toward the empty space close to the lithium. If these weak agostic interactions are included in the coordination sphere, the lithium would be in the center of a trigonal bipyramid (see Figure 2).
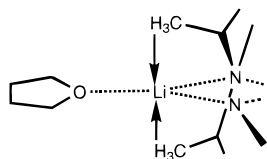
Figure 2. Coordination sphere surrounding Li(2) showing the possible Li−H agostic interactions.

Semiempirical and ab Initio Computational Methods. Standard enthalpies calculated using a semiempirical computational method (PM3) showed that there are several conformers of **3** with only small differences in structure and energy. The conformer with the most structural similarity to the solid-state structure **3·THF** was also shown to represent the global minimum on the potential energy surface. By optimizing the structure using semiempirical PM3 and MNDO methods as well as at the HF/STO-3G and HF/6-31G(d) levels of theory, each resulted in a fairly C_2 symmetrical geometry for the lithium core in **3·THF**. The Li(1)Li(2) distance in the HF/6-31G(d)-calculated geometry is 2.42 Å, which is close to the distance found in the solid state (2.43 Å) (Figure 3).

Even the structure optimized using the minimal basis set showed close agreement to the solid state for the Li(1)Li(2) distance (2.37 Å). In the PM3-optimized geometry a Li(1)Li-(2) distance of 2.80 Å was calculated, which is far from the

(16) The QUEST 3D and VISTA 2.0 program packages were used for data searching and evaluation of the CSD.

(17) Israelachvili, J. *Intermolecular surface forces*, 2nd ed.; Academic Press: London, 1991; p 124.

Li(1)Li(2) distances found in the ab-initio-calculated geometries and the solid-state structure; the MNDO-calculated geometry was slightly more accurate, giving a Li(1)Li(2) distance of 2.71 Å (Table 1).

To find the computational method best suited for structural analysis of complexes such as **3·THF**, a computational study on the model system **4** was undertaken. This system represents

4
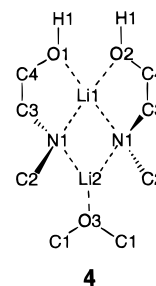
a dimeric structure with C_2 symmetry in which the dimeric core of **3·THF** is preserved, still keeping the structure simple enough for higher level ab initio and density functional calculations to be performed using limited computer resources. The results from these calculations, summarized in Table 2, show that the most expensive method, i.e. B3LYP/6-31+G(d), does indeed describe the lithium core best (also regarding angles and dihedral angles), as compared to the X-ray structure. It should be noted that calculations without diffuse functions, i.e. HF/6-31G(d), give very similar results (Table 2).

However, the simpler ab initio (HF/STO-3G and HF/3-21G) methods generally give structures less accurate than those obtained using semiempirical methods. PM3 is clearly superior over MNDO for most structural parameters. PM3 often produces results in accordance with those obtained using much more expensive methods such as B3LYP/6-31+G(d). One may therefore conclude that PM3 ought to be the method of choice for structural analysis of lithium compounds when large systems need to be analyzed using limited computer resources. (Note added in proof: Abbotto, A.; Streitwieser, A.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1997**, *119*, 11255.)

Selected Li−H distances in the full system **3·THF** are given in Table 3. Inspection of the optimized geometries (ab initio and PM3) shows that the Li−H, Li−N, and Li−O distances are surprisingly close to those found in the solid state, although the PM3-calculated Li−O and Li−N distances were slightly longer. The MNDO-calculated geometry, on the other hand, showed deviations in the Li−H and lithium core distances compared to those found by X-ray and calculated by PM3 and ab initio methods. Hence PM3 is again shown to be superior to MNDO in describing the bonding and interactions of this type of complex.

As predicted from the model system calculations, PM3 and ab initio geometry optimizations reproduced the solid-state structure with satisfying results. However, the PM3 calculation gave a significantly larger Li−Li distance and most Li−H distances were found to be larger (0−0.4 Å) in the PM3-calculated structure compared to the solid state. The ab initio-calculated geometry of **3·THF** gave a Li−Li distance very close to that found in the X-ray structure. However, most of the Li−H distances were found to be somewhat larger in the calculated structure as compared to the X-ray structure, as might be expected from gas-phase geometries. The MNDO-calculated geometry, however, deviated from both the PM3- and ab initio-calculated geometries as well as the X-ray geometry.

It has been established that MNDO parametrization signifi-
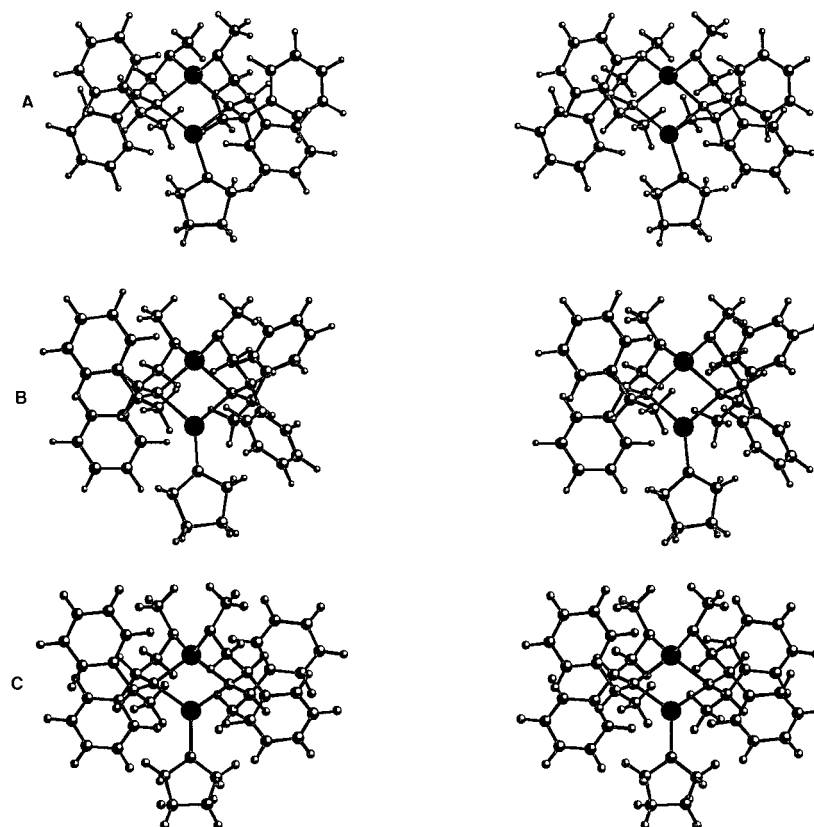
Figure 3. Ball and stick stereoviews of **3**·THF: (a) crystal structure, (b) PM3-geometry-optimized structure, and (c) HF/6-31G(d)-geometry-optimized structure.

Table 1.   Internuclear Distances Found in the Lithium Core of **3**·THF for X-ray and Calculated Geometries

	Li(1)Li(2)	Li(1)N(1)	Li(1)N(2)	Li(2)N(1)	Li(2)N(2)
X-ray	2.43	2.04	2.10	2.06	1.98
PM3	2.80	2.12	2.12	2.12	2.14
MNDO	2.71	2.24	2.24	2.27	2.27
HF/STO-3G	2.37	1.97	1.97	1.93	1.93
HF/6-31G(d)	2.42	2.08	2.09	2.04	2.04

	Li(1)O(1)	Li(1)O(2)	Li(2)O(3)	N(1)N(2)
X-ray	1.95	1.92	1.94	3.29
PM3	2.06	2.07	1.99	3.19
MNDO	2.24	2.24	2.46	3.60
HF/STO-3G	1.85	1.85	1.80	3.09
HF/6-31G(d)	2.01	2.01	2.03	3.34

Table 2.   Internuclear Distances in the Lithium Core of the Model System **4** at Different Levels of Theory and/or Basis Sets[a]

| distance	STO-3G	HF/3-21G	HF/6-31G(d)	HF/6-31+G(d)	B3LYP/6-31+G(d)	MNDO	PM3	X-ray
Li(1)Li(2)	2.37	2.36	2.43	2.41	2.42	2.65	2.71	2.43
Li(1)N(1,2)[b]	1.93	2.04	2.07	2.06	2.06	2.16	2.06	2.04
								2.10
Li(2)N(1,2)[b]	1.87	1.93	1.96	1.95	1.94	2.10	2.04	2.06
								1.98
Li(1)O(1,2)[b]	1.82	1.91	2.02	2.02	2.02	2.19	2.04	1.95
								1.92
Li(2)O(3)	1.78	1.85	1.97	1.97	1.95	2.17	1.93	1.93
N(1)N(2)	2.98	3.19	3.22	3.20	3.19	3.34	3.08	3.29

[a] Distances from the X-ray diffraction of **3**·THF are shown for comparison. [b] Two distances are given by X-ray due to the C_1 symmetry of **3**·THF.

cantly overestimates the lithium−carbon strength and thereby gives incorrect geometries.[11b,10c,18]

Quantitative Determination of Li−H Distances in Solu-

tion. To the best of our knowledge only three reports have been published where Li−H and Li−C distances have been obtained on the basis of Li−H and Li−C NOE data. Smith and co-workers used steady-state NOE buildup and correlation times (from molecular volume) to calculate the Li−H distances in a lithium−boron compound (error limits were not given).[7] Berger and co-workers have used both ^{6}Li,^{13}C and ^{6}Li,^{1}H NOEs for the calculation of Li−C and Li−H distances.[5] They found deviations of ±0.2−0.5 Å in the Li−H distances of a lithium silyl compound compared to X-ray data. The Li−C distances were found to be much easier to calculate accurately; a deviation of only ±0.01 Å from the X-ray data was reported. Bauer determined the ^{6}Li−^{1}H transient NOE buildup rates for the Li−H for ethenyllithium using a series of ^{6}Li,^{1}H HOESY experiments with varying mixing times. From the ^{6}Li,^{1}H NOE buildup curves he could correlate the solid-state and solution-state structures.[6] He claimed that the compound had the same structure in the solid as in the solution, and on the basis of that, he reported an accuracy of ±0.2 Å in the distances derived from the HOESY experiments. These investigations encouraged us to correlate Li−H NOE data obtained from several ^{6}Li,^{1}H HOESY experiments on **3**·THF with X-ray and calculated Li−H distances.

In DEE solution compound **2** exists exclusively as dimers of the form **3**·DEE. This was determined previously using almost exclusively the ^{6}Li,^{1}H HOESY experiment.[14j] A ^{6}Li,^{1}H HOESY experiment obtained from a solution of **3**·THF in toluene-d_8 (for NMR see the Supporting Information) indicated a close similarity between the structures **3**·THF and **3**·DEE. The correlations found in the NMR spectra indicated that the solution structure of **3**·THF is quite similar to the solid-state structure. However, the NOE effects obtained in this experiment with only

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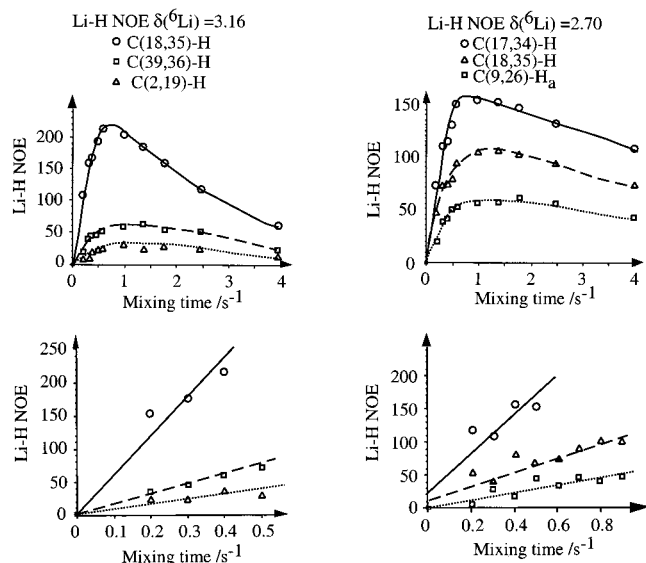
Figure 4. (a) ^{6}Li,^{1}H HOESY NOE cross-peak intensities vs mixing time (0−4 s) for Li(2) at δ 3.16 in **3**·THF (toluene-d_8, −80 °C, c = 0.5 M). (b) ^{6}Li,^{1}H HOESY NOE cross-peak intensities vs mixing time (0−4 s) for the Li(1) at δ 2.70 in **3**·THF (toluene-d_8, −80 °C, c = 0.5 M). (c) Linear regression to initial NOEs (0−0.5 s) for Li(2) at δ 3.16. (d) Linear regression to the initial NOEs (0−0.5 s) for Li(1) at δ 2.70.

a single mixing time cannot be used for quantitative distance determinations.

For accurate determination of the Li−H distances in **3**·THF NOE buildup curves were used. The NOE buildup curves of **3**·THF in toluene-d_8 were determined through a series of 2D ^{6}Li,^{1}H HOESY experiments with varying mixing times (0−4 s) obtained at −85 °C. After zero-filling the f_1 dimension five times, the resulting peaks were well defined and the intensities could be measured directly from the corresponding f_1 projections, one for each of the two lithium resonances. The intensities were used since we have found them to provide greater accuracy than peak volumes due to partially overlapping signals. Furthermore, all cross-peaks have roughly the same shape. Each lithium resonance was treated independently since each exhibits a different relaxation behavior. The cross-peak intensities of a few resonances from **3**·THF vs mixing times are given in Figure 4. The buildup rates for the transient heteronuclear NOE were determined from linear fits of the NOE cross-peak intensities to the mixing times (initial buildup range 0−0.5 s).

The average of the NOE buildup rates from two different experiments with different samples was used. From the HOESY experiments ^{6}Li,^{1}H NOE buildup rates for all Li−H distances in **3**·THF were measured. All Li−H distances smaller than 5 Å measured in the X-ray-, PM3-, and HF/6-31G(d)-determined structures were used separately as standard references in eq 1. Thus in Table 4 the values in the three left columns correspond to X-ray-, PM3-, and HF/6-31G(d)-measured Li−H distances. Each of these was used as the standard reference distance to calculate the Li−H distance using eq 1 and the measured NOE buildup rates (f). The three right columns X-ray, PM3, and HF/6-31G(d) in Table 4 were obtained from the above calculation.

Most of the data in Table 4 are indicative of a similar structure in the solid state, in solution state, and in the gas phase (calculated). However, the Li(1,2)C(9,26)−H distance seems to be shorter in the NMR-derived structure than in the solid state. This is also evident for the gas phase. A significant deviation between the X-ray- and NMR-derived structures is found for the Li(2)C(34,17)−H distances, which appears shorter

Table 3. Selected Li−H Distances Obtained from the X-ray Structure, Semiempirical Calculations (PM3, MNDO), and ab Initio Calculations of **3**·THF[a]

(i) Li(1) at δ 2.70 (Methoxy Coordinated)

proton	average Li−H distances (Å)				
	X-ray	PM3	MNDO	STO3G	6-31G(d)
C(18,35)−H	3.82	3.91	3.95	4.04	3.97
C(17,34)−H	3.35	3.32	3.89	3.40	3.45
C(36,39)−H	5.45	5.48	6.03	5.23	5.50
C(37,38)−H	7.16	7.20	8.10	6.96	7.17
C(2,19)−H	3.17	3.47	3.54	3.27	3.30
C(9,26)−H$_a$	3.57	3.78	3.91	3.56	3.67
C(9,26)−H$_b$	2.91	2.89	2.92	2.71	2.78
C(10,27)−H	3.99	4.15	4.25	4.04	4.12

(ii) Li(2) at δ 3.16 (THF Coordinated)

proton	average Li−H distances (Å)				
	X-ray	PM3	MNDO	STO3G	6-31G(d)
C(18,35)−H	3.03	3.11	2.85	3.40	3.15
C(17,34)−H	5.25	5.63	6.18	5.40	5.48
C(36,39)−H	3.22	3.14	3.60	3.60	3.34
C(37,38)−H	4.74	4.99	5.46	4.70	4.79
C(2,19)−H	3.91	4.16	4.37	3.91	4.05
C(9,26)−H$_a$	3.27	3.44	3.70	3.05	3.17
C(9,26)−H$_b$	4.49	4.80	5.06	4.45	4.57
C(10,27)−H	3.19	3.40	3.42	3.39	3.37

[a] The average distances from (i) the Li at δ 3.16 (THF coordinated) and (ii) the Li at δ 2.70 (methoxy coordinated) to the two sets of protons in the dimeric structure are given. For the OCH$_3$, CH$_3$, and CH$_2$ groups the average distance of all protons was used.

Table 4. Heteronuclear Buildup Rate Correlation of Distances for Li(2) and Li(1)[a,b]

proton	measd distances[c]			calcd distances from NOE buildup rates[d]		
	X-ray	PM3	HF/6-31G(d)	X-ray	PM3	HF/6-31G(d)
methyl-CH$_3$	3.03[a]	3.11[a]	3.15[a]	3.05[a]	3.01[a]	2.97[a]
C(18,35)	3.82[b]	3.91[b]	3.97[b]	3.65[b]	3.79[b]	3.58[b]
methoxy-OCH$_3$	5.25[a]	5.63[a]	5.48[a]	4.58[a]	4.47[a]	4.57[a]
C(34,17)	3.35[b]	3.32[b]	3.45[b]	3.34[b]	3.70[b]	3.30[b]
C(9,26)	4.49[a]	4.80[a]	3.88[a]	4.14[a]	4.14[a]	4.03[a]
	3.57[b]	3.78[b]	3.23[b]	3.34[b]	3.67[b]	3.38[b]
THF(α)	3.22[a]	3.14[a]	3.34[a]	3.46[a]	3.45[a]	3.37[a]
C(36,39)	5.45[b]	5.48[b]	5.50[b]	5.08[b]	4.67[b]	4.96[b]
THF(β)	4.74[a]	4.99[a]	4.79[a]	4.16[a]	3.95[a]	3.82[a]
C(38,37)	7.19[b]	7.20[b]	7.17[b]	5.26[b]	4.97[b]	5.37[b]

[a] For Li(2) at δ 3.16 (THF-coordinated lithium). [b] For Li(1) at δ 2.70 (methoxy-coordinated lithium). [c] Distances measured in respective geometries. [d] The distances in each row calculated using eq 1 (the slopes of the NOE rise curves obtained from the HOESY experiments were used together with several X-ray or calculated distances) are average distances; for more details, see the Supporting Information. The experimental S/N ratios in the experiments were approximately 30−80. The NOE buildup rates for methyl groups are divided by 3 since there are three protons at the same resonance. This requires that the methyl group rotates rapidly compared with the overall tumbling rate of the molecule. All distances of the methyl groups and methylene groups are the average distances measured in the crystal state. These approximations are standard in protein structure determinations.[25]

in solution ($\approx$4.6 vs 5.2 Å in the solid state). These deviations are significantly larger than the error in the method, and they indicate that the solution structure of **3**·THF is in fact slightly different from the calculated and solid-state structures.

Further examination of the data in Table 4 reveals a small difference of less than 0.2 Å between the X-ray, computational, and NOE data for other Li−H distances less than 4 Å. These

small differences are within the error of the method and are not discussed further. Distances longer than 4 Å, however, are measured less accurately due to problems with small NOEs and spin diffusion. Spin diffusion is therefore likely to be a significant source of error in the determination of solution structures of other lithium organic compounds using transient nuclear Overhauser spectroscopy. This is for instance clearly seen for the C(17,34)−H proton Li(2) distance and the C(37,-38)−H proton Li(1) distance, where the calculated distances from NOEs buildup rates become much shorter. It also seems that Li−THF distances are somewhat underestimated using the NOE buildup rates. This is likely due to the presence of the slow ligand exchange on the NMR time scale which interferes with the detection of the heteronuclear cross relaxation. For more detailed information on calculated Li−H distances from NOE buildup data using X-ray and calculated Li−H reference distances, see the Supporting Information.

Conclusion

In summary, we have shown that the PM3- and ab initio-calculated geometries of **3·THF** model the crystal structure very well. MNDO, on the other hand, does not give satisfactory geometries. From computational studies of the model system **4**, designed to mimic the lithium core in **3·THF**, we could see that the geometry of the lithium core in **4** showed only small variations if HF/6-31G(d) was used compared to the more time-consuming B3LYP/6-31+G(d) method. We therefore conclude that sufficiently accurate geometries of lithium compounds of this type are obtained using the HF/6-31G(d) level of theory. However, if only limited computer resources are available, the semiempirical PM3 method is a very good alternative for geometry optimizations in this area of research.

The small differences among the X-ray and ab initio and PM3 calculated structures have shown that reference distances from either source can be used for the calculation of Li−H distances using Li−H NOE data. The calculations of Li−H distances using HOESY buildup rates showed that the solution structure of **3·THF** is similar to the structure obtained in the gas phase (calculated) and in the solid phase (X-ray). Only small variations ±0.2 Å were observed between X-ray/ab initio and NOE data if the distances calculated were less than 4 Å. Distances longer than 4 Å showed deviations, which could be attributed to spin diffusion problems.

We have thus demonstrated that HOESY experiments can be used, in conjunction with crystallographic and/or computational methods, for the description of initial state geometries of organolithium complexes in solution.

Experimental Section

General Procedure. All glassware was dried overnight in a 120 °C oven (syringes were dried at 50 °C in a vacuum oven) before transfer into a glovebox (Mecaplex GB 80 equipped with a gas purification system that removes oxygen and moisture) containing a nitrogen atmosphere. Typical moisture content was less than 0.5 ppm. All manipulations of the lithium compounds were carried out in the glovebox using gastight syringes. Deuterated ethereal solvents were stored and freshly distilled from Deporex (Fluka AG) prior to use.

Preparation of (2-Methoxy-(*R*)-1-phenylethyl)((*S*)-1-phenylethyl)-amine (1). A previously reported procedure was used to synthesize (2-methoxy-(*R*)-1-phenylethyl)((*S*)-1-phenylethyl)amine (**1**).[12]

In Situ Preparation of (2-Methoxy-(*R*)-1-phenylethyl)(2-[⁶Li]-lithium-(*S*)-1-phenylethyl)amide. Into a dry 5-mm NMR tube was transferred (2-methoxy-(*R*)-1-phenylethyl)((*S*)-1-phenylethyl)amine (**1**) (100 mg, 0.35 mmol). The NMR tube was fitted with a Wilmad/Omnifit Teflon valve assembly OFV with a Teflon/silicone septum.

Either toluene-d_8 or DEE-d_{10} was added via syringe. To the solution of **1** at −78 °C were then added approximately 10 M [⁶Li]-*n*-butyllithium (approximately 30 μL, 0.37 mmol) and 30 μL of THF with a syringe. The solution mixture containing the lithium salt of **1**, i.e. **3** (96% in ⁶Li atom), was then put into the precooled NMR probe.

X-ray Crystallography. [⁶Li]Lithium (2-methoxy-(*R*)-1-phenyl-ethyl)((*S*)-1-phenylethyl)amide·THF Dimer (5·THF). Crystals of **3·**THF were obtained at −30 °C from a solution of hexane−THF (40:1 v/v). It was necessary to use hexane instead of diethyl ether to get high-quality crystals of **3·**THF.

For more general X-ray crystallographic details see experimental section of ref 15.

NMR Instrumental Procedure. All NMR spectra were recorded using a Varian Unity 500 spectrometer equipped with three channels using a 5-mm ¹H,¹³C,⁶Li triple-resonance probe head custom built by Nalorac. Measuring frequencies were 500 MHz (¹H) and 74 MHz (⁶Li). The ¹H and spectra were referenced to the solvent signals: DEE-d_{10} δ 1.06 (¹H−CD₂H). Lithium spectra were referenced to external 0.3 M [⁶Li]Cl in MeOH-d_4 (δ = 0.0). A typical 90° ⁶Li pulse was 20 μs. Probe temperatures were measured after more than 1 h of temperature equilibrium with both a calibrated methanol−Freon NMR thermometer and the standard methanol thermometer supplied by Varian instruments.[19]

NMR Data Collection. Two sets of HOESY data were obtained, each one under identical conditions: a probe temperature of −85 °C, nonspinning 5-mm samples, and deuterium field-frequency locking. Spectral windows of 1000 Hz (f_2 = ⁶Li) and 8000 Hz (f_1 = ¹H) were used. 48 scans were collected in 96 blocks (t_2 acquisition time of 1 s) using the hypercomplex method with a repetition rate of 1 scan/8 s. The value 8 s is consistent with the convention of using a recycle time on the order of $1.5T_1$ (for the lithium resonance at δ 2.70, T_1 = 2.5 s, and for the lithium resonance at δ 3.16, T_1 = 5.5 s). For most protons, T_1 = 0.3−1.5 s, while the aromatic protons have T_1 = 1.5−2 s. The following mixing times were used: 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.4, 1.8, 2.5, and 4.0 s. A homospoil pulse was used in the beginning of each relaxation delay to defocus remaining transversal magnetization. The inversion recovery experiment was used to determine the spin−lattice relaxation times of the two lithiums and all protons in **3·THF**.

NMR Data Processing. The phase-corrected spectra were processed in phase-sensitive mode with square sine bells weighting both in f_1 and f_2, with one time zero filling in f_2 and five times zero filling in f_1. Cross-peak intensities for rise curves were obtained by plotting f_1 slices through the intensity maximum of the lithium-6 signals, respectively. The S/N ratios in the HOESY experiments were between 30 and 80. Cross-peak intensities between lithium and methyl protons were scaled by dividing by 3. Similarly cross-peaks between lithium and methylene protons and the ortho protons were scaled by dividing by 2.[20]

Computational Methods. Geometry optimizations using the semiem-pirical methods PM3[21] and MNDO[22] (with lithium parameters) as well as the HF/STO-3G[23] calculation on the full system were performed on a Silicon Graphics INDY workstation using the Spartan program package.[24] The HF and B3LYP[25] DFT calculations on the model system

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4 were done on the same machine, using the Gaussian 94 program.[26] Standard valence double-ζ basis sets 3-21G,[27] 6-31G(d),[28] and 6-31+G-(d)[29] were used as implemented in the program. The HF/6-31G(d) optimization of the full system was done on a Cray C90 computer, also using Gaussian 94. The PM3 geometry was used as starting point for the ab initio calculations on the full system. All geometries were characterized as minima on the potential energy surface by calculating the corresponding vibrational frequencies.[30] Cartesian coordinates and energies of all optimized structures can be found in the Supporting Information.

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Supporting Information Available: ^{6}Li,^{1}H HOESY of **3**·THF with traces, tables of selected geometrical parameters and energies obtained from the computational studies on model system **4**, tables of Cartesian coordinates and energies for the MNDO, PM3, and ab initio calculations on **3**·THF, and tables with computational and X-ray heteronuclear NOE buildup rate correlations of Li–H distances from HOESY spectra (18 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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