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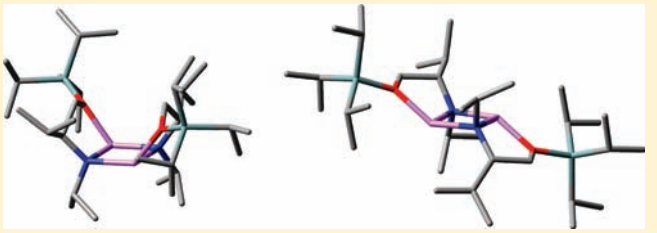
Characterization of Dimeric Chiral Lithium Amide Structures Derived from *N*-isopropyl-*O*- triisopropylsilyl Valinol

Gerald Kagan,[†] Weibin Li,[†] Deyu Li, Russell Hopson, and Paul G. Williard*

Department of Chemistry, Brown University, 324 Brook Street, Providence, Rhode Island, 02912 United States

Supporting Information

ABSTRACT: The dimeric structure is characterized for a chiral amide base complex consisting of an (*S*)-*N*-isopropyl-*O*-triisopropylsilyl valinol ligand and lithium. The complex is characterized by a variety of NMR techniques, including multinuclear one- and two-dimensional NMR experiments and diffusion-ordered NMR spectroscopy (DOSY) as well as diffusion coefficient-formula weight (D-fw) correlation analyses. Spartan calculations are presented which support the structural assignment. This structural characterization leads to an explanation of the behavior and the reactivity of these complexes in solution.



INTRODUCTION

Chiral amide bases have long been of interest in coordinating various organometallic species.[1] These complexes are used in asymmetric addition and deprotonation reactions. For this reason, chiral amides have been a focus of research of several groups for more than 15 years. Many groups have carried out ^{6}Li NMR or ^{6}Li{^{15}N} heteronuclear single-quantum coherence (HSQC) studies of chiral amide bases, however, the results do not point to any general conclusions. Dimeric structures are proposed but cannot be established unambiguously because several possible complexes exist that are consistent with the experimental results.[1]

In solution, these chiral reagents are proposed to adopt several different aggregation patterns. These are depicted in Figure 1 as dimers consisting of two lithium amides (**1**), trimers with *n*-butyllithium (*n*-BuLi) comprised of two lithium amides and one molecule of *n*-BuLi (**3**), or mixed dimers containing one lithium amide molecule complexed with one molecule of *n*-BuLi (**4**).[1f,q,s] Dimers with a general structure **2**, containing two lithium amides, are relatively uncommon and are referred to as "ladder" dimers. The more common dimers of type **1** and the trimers of type **3** incorporate a C_2 axis of symmetry, as depicted. The type **4** dimer lacks a symmetry axis. Dimers of type **2** incorporate a C_2 axis of symmetry perpendicular to the N−Li−N−Li ring, as shown (Figure 1).

We report that the amide base derived from *N*-isopropyl-*O*-triisopropylsilyl protected valinol forms exclusively the uncommon ladder-type dimer **2** in hydrocarbon solvent.[2] This is significant because only a small number of examples of lithium amide bases forming type **2** ladder dimers are known.[1f,s] These prior examples all form in the presence of lithium coordinating solvents, such as tetrahydrofuran or diethyl ether.

Identification of a type **2** dimer generated from a previously synthesized[3] ligand in toluene-d_8 was made possible by a variety of methods. The experiments performed include diffusion-ordered NMR spectroscopy (DOSY), diffusion coefficient-formula weight (D-fw) correlation analyses, and other multinuclear NMR experiments and computational methods. We use DOSY and D-fw methods to determine the aggregation number, ^{6}Li NMR to determine the symmetry, and energetic calculations to provide evidence of conformation and support the NMR data. By using this systematic method, we can determine the structure of the ladder-type dimer **2** unambiguously.

DOSY techniques were used first to establish the formula weight of the complex in solution and by inference to define the aggregate type (dimer, trimer, etc.). DOSY NMR arrays resonances on a second axis according to their diffusion coefficients. Resonances from same compound are expected to generate the same diffusion coefficient.[4] Our group has pioneered the application of DOSY with internal references to determine the formula weights of complexes via D-fw correlation analysis for many different nulcei.[5] In this method, the logarithms of experimentally determined diffusion coefficients of references are plotted against the logarithms of their known formula weights. From the linear plot of the NMR diffusion data of internal reference compounds, we can interpolate or extrapolate formula weight data for unknown complexes in solution from their diffusion data.[1r,3,5,6] This is advantageous because highly reactive complexes can be identified and individually characterized.[1r,3,4,5c,6,7] These complexes are not otherwise amenable to characterization by traditional mass spectrometric methods. Also, complexes can be studied directly in solution.

Having unambiguously established the aggregation state by D-fw analysis, one- and two-dimensional (1- and 2-D) multinuclear NMR were used to refine the dimeric form, vis-à-vis

Received: October 7, 2010
Published: April 12, 2011

dx.doi.org/10.1021/ja109041z | *J. Am. Chem. Soc.* 2011, 133, 6596–6602

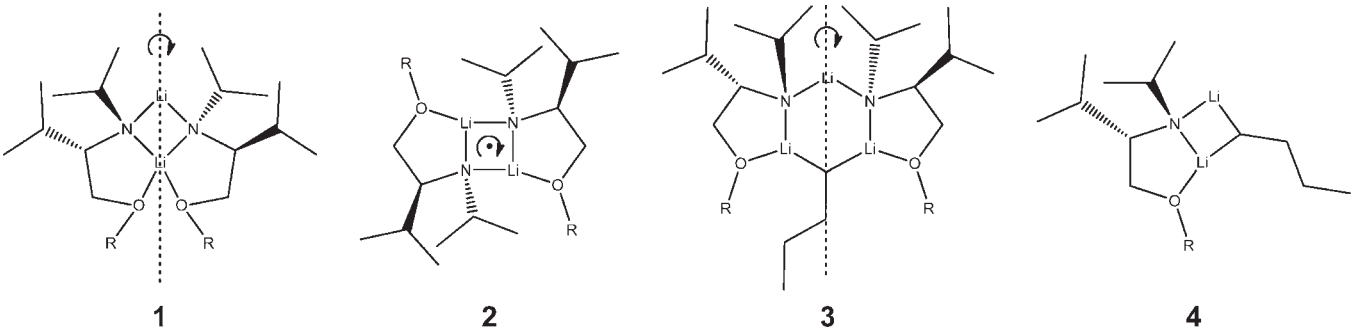


Figure 1. Structures of representative dimer **1**, ladder dimer **2**, mixed trimer **3**, and mixed dimer **4**. Structures **1**−**3** are shown with their C_2 axis of symmetry.

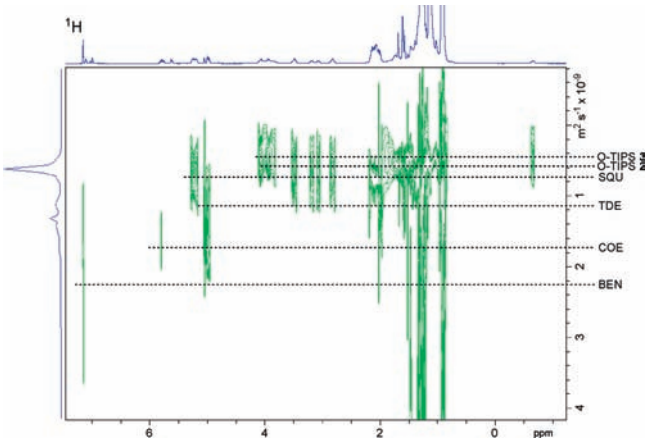


Figure 2. ^{1}H DOSY of *O*-TIPS **2** and *O*-TIPS **3**.

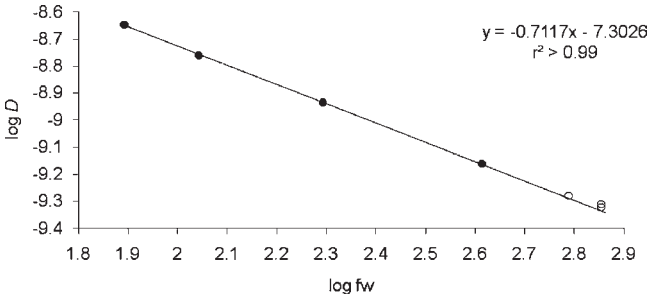


Figure 3. D-fw analysis of ^{1}H DOSY data of *O*-TIPS **2** and *O*-TIPS **3**. Reference compounds are shown as solid circles, and *O*-TIPS **2**, *O*-TIPS **3**, and *n*-BuLi are shown as open circles.

Figure 1. ^{6}Li NMR methods were used. ^{6}Li data was correlated to ^{1}H data by ^{1}H{^{6}Li} heteronuclear multiple-bond coherence NMR spectroscopy (HMBC) or ^{1}H{^{6}Li} heteronuclear Overhauser effect NMR spectroscopy (HOESY). These correlations are known to yield conclusive information about the solution structure of organolithium compounds.[1q,5b,6b,8]

Once the aggregation state had been determined by DOSY and D-fw methods and the connectivity established by 1- and 2-D NMR methods, computations were performed on a variety of possible isomers. The computation results combined with the NMR results provide insight to the specific conformer formed in solution. All of these methods support the proposed solution structure of the ladder dimer above.

RESULTS AND DISCUSSION

DOSY data are required to initially determine the aggregation state of the complex. ^{1}H and ^{13}C NMR experiments were performed on complexes of the triisopropylsilyl (TIPS) protected ligand by formation of the complexes in toluene-d_8 from *n*-BuLi directly in the NMR tube. Samples for ^{6}Li NMR experiments were prepared in a similar fashion with 1 equivalent of *n*-Bu^{6}Li. Toluene-d_8 was chosen as the solvent because hydrocarbons do not exhibit tight binding to lithium as ethereal solvents do, such as diethyl ether and tetrahydrofuran.[1q,r] Similarly, internal references for ^{1}H and ^{13}C DOSY experiments were hydrocarbonaceous in nature. These were benzene (BEN, 78.11 g mol^{-1}), cyclooctene (COE, 110.2 g mol^{-1}), 1-tetradecene (TDE, 196.4 g mol^{-1}), and squalene (SQU, 410.7 g mol^{-1}). About 100 μL of a 1:3:3:1 solution of BEN:COE:TDE:SQU was added to each sample such that the distinctive olefinic proton resonances used for D-fw analysis would be of approximately equal intensity.

^{1}H DOSY was carried out on a solution of complexes formed by addition of *n*-BuLi to the *O*-TIPS ligand. Adding 1.25 equivalents of *n*-BuLi yields both the *O*-TIPS **2** dimer and the *O*-TIPS **3** trimer in solution. Using this method, we can readily distinguish *O*-TIPS **2** and *O*-TIPS **3** in solution. Distinct resonances from the bound ligand between 2.0 and 4.5 ppm were used for D-fw analysis (Figure 2).

The ^{1}H DOSY D-fw plot has a high correlation (r^2 > 0.99). This D-fw correlation analysis yields a predicted formula weight (fw*) for resonances of *O*-TIPS **2** of 597 g mol^{-1} compared to 615.0 g mol^{-1} for the expected weight of the dimer, a 2.9% difference. The fw* is significantly heavier than that of the free ligand, indicating aggregation. The *O*-TIPS **3** trimer has a fw* of 683 g mol^{-1} (ligand resonance, 4.4% difference) or 663 g mol^{-1} (*n*-BuLi resonance, 7.2% difference), indicating binding of *n*-BuLi in a complex with 2 equivalents of ligand (Figure 3, Table 1). This is confirmed in the ^{6}Li NMR with ^{6}Li-enriched samples made from *n*-Bu^{6}Li as three resonances, two having integrations of 2:1 due *O*-TIPS **3** and a single peak due to *O*-TIPS **2**. These spectra are included in the Supporting Information. Thus, a single equivalent of *n*-BuLi generates the dimer, while 1.5 equivalents generate the trimer, and both complexes are formed from an intermediate amount.

A fresh sample of *O*-TIPS **2** was prepared from the addition of 1 equivalent of *n*-BuLi to the ligand. ^{13}C DOSY shows a variety of resonances from the bound ligand between δ = 20 and 70 ppm. The DOSY spectrum shows that these ligand resonances diffuse more slowly than any of the references. This indicates complexation,

dx.doi.org/10.1021/ja109041z |*J. Am. Chem. Soc.* 2011, 133, 6596–6602

Table 1. Tabulated DOSY Data of ^{1}H and ^{13}C Experiments and D-fw Results

resonance	experiment	fw (g mol^{-1})	$D \times 10^{-10}$ (m^2 s^{-1})	log fw	log D	fw* (g mol^{-1})	% error
O-TIPS **2**	^{1}H DOSY	615.03	5.268	2.789	−9.278	597	2.9
O-TIPS **3**	^{1}H DOSY	714.70	4.786	2.854	−9.320	683	4.4
n-BuLi	^{1}H DOSY	714.70	4.889	2.854	−9.311	663	7.2
O-TIPS **2**	^{13}C DOSY	615.03	6.368	2.789	−9.196	613	0.3
O-TIPS ligand	^{13}C DOSY	301.58	9.453	2.479	−9.024	287	4.9

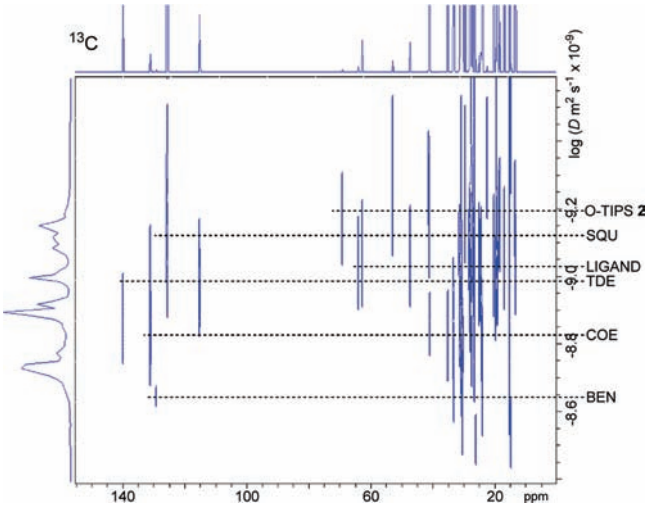


Figure 4. ^{13}C DOSY of *O*-TIPS **2**.

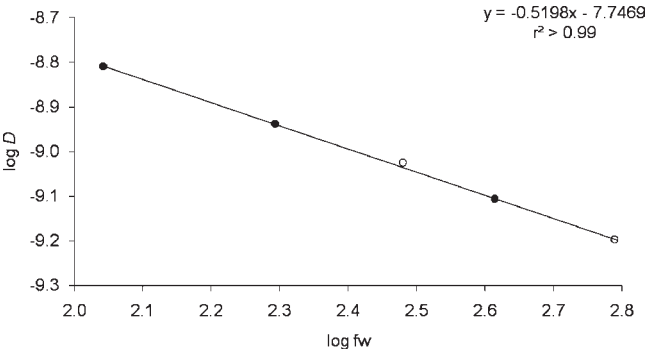


Figure 5. D-fw analysis of ^{13}C DOSY data of *O*-TIPS **2**. Reference compounds are shown as solid circles, and *O*-TIPS **2** and excess *O*-TIPS ligand are shown as open circles.

as the weight of the bare ligand is 301.6 g mol^{-1}, which is less than that of the heaviest reference, squalene. Some excess ligand is also present in the spectrum, diffusing more quickly than squalene (Figure 4).

Correlation of the references in the D-fw analysis of the ^{13}C DOSY data is also very high ($r^2 > 0.99$). Formation of the dimer is confirmed by ^{13}C DOSY, from which D-fw correlation analysis gave a fw* of 613 g mol^{-1}, a 0.3% difference. Excess free ligand is also included on the plot. The fw* of the free ligand was 287 g mol^{-1} (4.9% difference) (Figure 5, Table 1).

Both the ^{1}H and ^{13}C DOSY data support the formation of a dimer, but further data are required to determine the dimer type. ^{6}Li NMR of the [^{6}Li]*O*-TIPS **2** complex generated from 1 equivalent of *n*-Bu^{6}Li shows only a single major peak. According

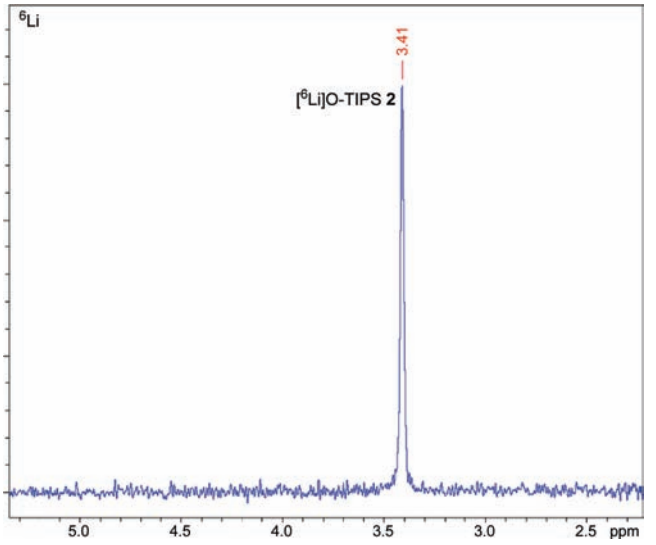


Figure 6. ^{6}Li NMR of [^{6}Li]*O*-TIPS **2**.

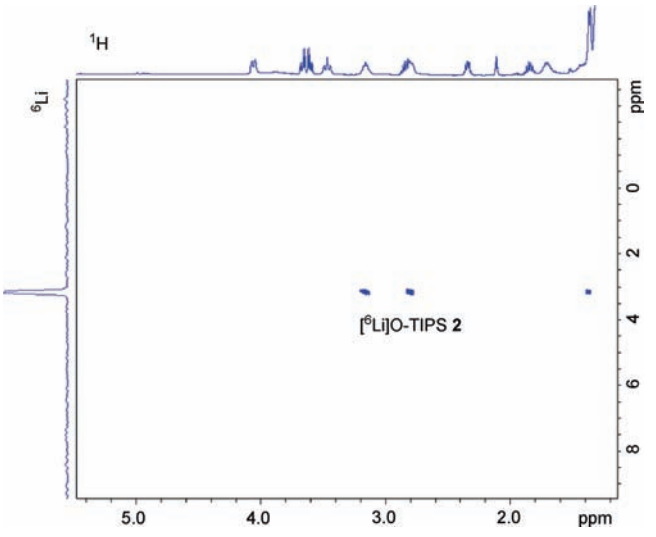


Figure 7. ^{1}H{^{6}Li} HMBC of [^{6}Li]*O*-TIPS **2**.

to ^{1}H{^{6}Li} HMBC NMR spectroscopy, this single resonance correlates to proton resonances of the ligand in the complex (Figures 6 and 7). Cooling the sample as low as −60 °C had no effect on the ^{6}Li NMR spectrum. ^{6}Li DOSY is expectedly sparse, having a single peak with a single diffusion coefficient.

Labeling the *O*-TIPS ligand with ^{15}N and generating the dimer complex with *n*-Bu^{6}Li shows a triplet in the ^{6}Li spectrum, indicating that the single lithium atom type is bound to exactly two nitrogen atoms in [^{6}Li,^{15}N]*O*-TIPS **2** (Figure 8). The

dx.doi.org/10.1021/ja109041z |*J. Am. Chem. Soc.* 2011, 133, 6596–6602

$^1J(^6Li,^{15}N)$ coupling constant (~5.0 Hz) is consistent with a tricoordinated lithium atom.[1f]

The type **2** ladder dimer as proposed is consistent with the above data. Both ^1H and ^{13}C DOSY data and subsequent D-fw correlation analyses demonstrate that formula weight of the complex formed is that of an unsolvated dimer. 1-D ^6Li NMR confirms a single lithium resonance from the complex due to the unique C_2 axis this type of complex possesses, as opposed to the 1:1 peaks expected for a dimer of type **1** or mixed dimer of type **4** or the 1:2 peaks observed for trimer type **3**.[1q] 2-D $^1H\{^6Li\}$ HMBC experiments show long-range coupling between the protons within the ligand and the coordinated lithium atoms. 1-D ^6Li NMR of the $[^6Li,^{15}N]$ enriched complex verifies that the lithium atoms in the complex are bound to two nitrogen atoms, as proposed in the ladder dimer.

Several energetic calculations were performed using Spartan 06.[9] Semi-empirical pm3[10] calculations were performed to find the lowest energy conformer, and single point energy calculations were performed at the B3LYP 6-31+G* level.[11] Single point energies were calculated for the selected conformers (Table 2). Seven possible dimer structures were studied to find their lowest energy conformations. These include conformers of both the type **1** dimer and the type **2** ladder dimer with differing geometry. These complexes differ in three key stereochemical aspects arising from the manner in which the lithium atoms are coordinated. These stereochemical variants arise because: (a) *N*-isopropyl (*N*-*i*Pr) groups can be cis or trans (C/T) across the N−Li−N−Li ring, (b) the nitrogen atoms can be *RR*, *SS*, *RS*, or *SR*, and (c) lithium atoms can be *R*, *S*, or achiral (*A*). Stereochemistry on the lithium atoms is due to the destruction of C_2 symmetry in *RS* and *SR* nitrogen complexes (Figure 9).[12]

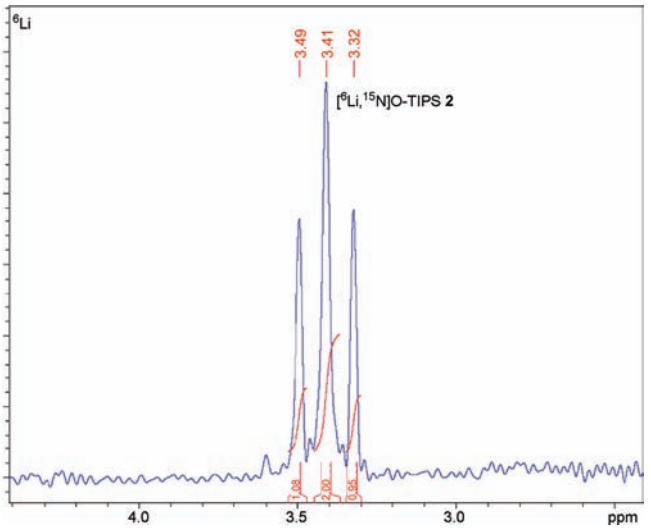


Figure 8. ^6Li NMR of $[^6Li,^{15}N]$*O*-TIPS **2**.

The two trans type **1** conformers (TRRA and TSSA) may have interaction between the large *O*-TIPS groups, as they are trans across the N−Li−N−Li ring, but the oxygen atoms are each coordinated to the same lithium atom, and therefore the *O*-TIPS groups are separated by only four bonds. In addition to this interaction, the two cis type **1** conformers with opposite geometry nitrogen atoms (CSRS and CSRR) are relatively high in energy. This is most likely due to ring strain imposed by having the opposite stereochemistry on the nitrogen atoms, which destroys symmetry and forces one of the Li−O bonds to stretch. The lowest energy configurations, i.e., TSRA, CSSA, and CRRA, agree well with the NMR data. The trans type **2** ladder dimer (TSRA) lacks a C_2 symmetry axis, unlike the cis dimers with *SS* or *RR* nitrogen atoms and achiral tricoordinate lithium atoms (CSSA and CRRA) (Figure 10). These have the C-*i*Pr group endo (CSSA) or exo (CRRA) to the tricyclic system. Results from density functional theory (DFT) and semi-empirical single point energy calculations differ on the lowest energy conformer given the same pm3 minimized inputs. Semi-empirical calculations on *O*-Me protected dimers give a type **1** dimer in the style of TRRA as the lowest energy conformation (Supporting Information).

We conclude from these calculations that, in addition to solvation, the steric effect of the protecting group plays a very important role in aggregate formation, and so it is unsurprising that differently protected ligands have different reactivities.[1c−e,g,h,o,3] The steric bulk of the relatively large TIPS group is too large for the type **1** dimer to form, while compounds containing smaller protecting groups on oxygen lack the steric interaction needed to form the ladder dimer. Hence, we conclude that this steric effect is the primary reason why complexes generated from the *O*-TIPS protected ligand have shown higher enantioselectivity in their reactions.[3]

CONCLUSION

We have confirmed the formation of an unsolvated ladder-type dimer from a valine-derived chiral ligand in hydrocarbon solution. Dimer formation is confirmed through ^1H and ^{13}C DOSY NMR and D-fw techniques. Internal dimer structure is confirmed by a variety of 1-D NMR data, including ^1H, ^{13}C, and especially ^6Li spectra as well as $^1J(^6Li,^{15}N)$ coupling data. Energetic calculations at the pm3 and B3LYP 6-31+G* levels

Table 2. Summary of Energetic Calculations

					relative energy (kcal mol^{-1})	
entry	code[a]	dimer type	*i*Pr/*N*/*N*/*i*Pr θ	Li/O distance (Å)	pm3	B3LYP 6-31+G*
1	TRRA	**1**	150.4	2.08/2.04	1.4	15.9
2	TSSA	**1**	154.5	2.12/2.05	5.8	31.1
3	CSRS	**1**	6.3	4.27/2.04	4.8	31.9
4	CSRR	**1**	14.6	3.63/2.07	6.0	21.9
5	TSRA	**2**	174.5	1.97/2.01	1.5	**0.0**
6	CSSA	**2**	9.5	2.03/2.02	**0.0**	7.1
7	CRRA	**2**	3.3	2.01/2.01	1.6	5.6

[a] Code derived from: (1) *N*-*i*Pr groups C (cis) or T (trans); (2) nitrogen atoms *RR*, *SS*, *RS*, or *SR*; and (3) lithium atoms *R*, *S*, or *A* (achiral).

dx.doi.org/10.1021/ja109041z |*J. Am. Chem. Soc.* 2011, 133, 6596–6602

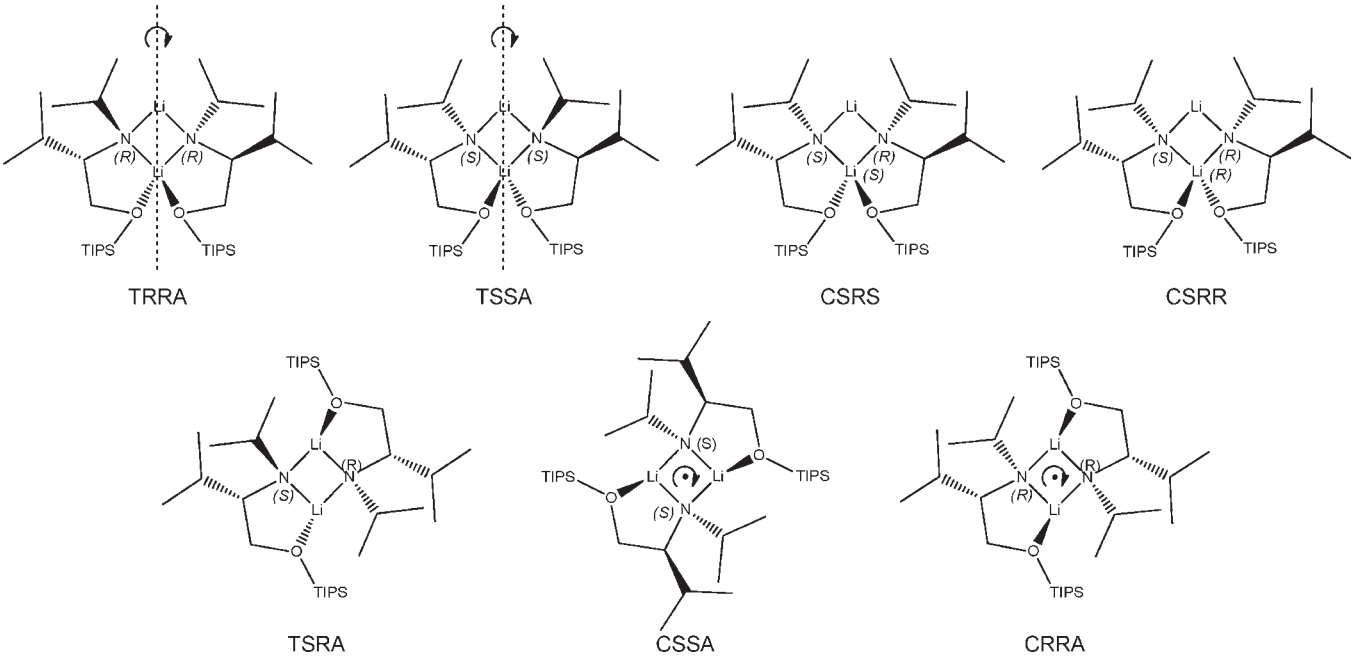


Figure 9. Possible dimer structures. Code derived from: (1) *N*-*i*Pr groups C (cis) or T (trans); (2) nitrogen atoms *RR*, *SS*, *RS*, or *SR*; and (3) lithium atoms *R*, *S*, or *A* (achiral). Complexes with C_2 axes of symmetry as shown.

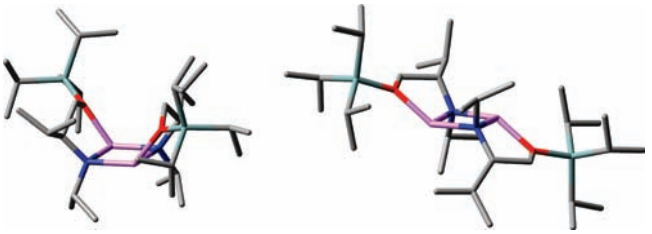


Figure 10. Spartan pm3 minimized structures of the *O*-TIPS ladder dimer of **2**: pm3 minimum (CSSA, left) and DFT minimum (TSRA, right) energy conformers.

agree well with the experimental results and support particular aggregate conformations.

The complete characterization of this dimer furthers the understanding of steric effects on complex formation. This understanding gives insight into of the reactivity and the enantioselectivity of this class of compounds. Specifically, this information clarifies the particular selectivity of *O*-TIPS valine-derived ligands in reactions.[3] Furthermore, we conclude that the steric bulk exerted by the specific protecting group on the oxygen atom for the entire class of chiral lithium amide aggregates derived from protected amino alcohols is of utmost importance in dictating the specific aggregation state adopted by these complexes in solution. By inference, this effect controls their enantioselectivity. We are currently performing additional extensive work on the mechanism and the reactivity of organolithium intermediates derived from this class of ligands to demonstrate the applicability of this conclusion.

EXPERIMENTAL SECTION

Procedures for NMR Experiments. NMR samples were prepared in tubes sealed with serum septa and Parafilm. Tubes were evacuated in vacuo, flame-dried, and filled with argon. NMR experiments were performed at 25 °C unless otherwise noted. ^{1}H chemical shifts were referenced to toluene-d_8 at 7.09 ppm. ^{13}C chemical shifts were referenced to toluene-d_8 at 137.86 ppm. ^{6}Li chemical shifts were calibrated to saturated LiBr in D_2O as an external reference at 0 ppm. DOSY experiments were performed on a Bruker DRX400 spectrometer equipped with an Accustar *z*-axis gradient amplifier and an ATMA BBO probe with a *z*-axis gradient coil. Maximum gradient strength was 0.214 T/m. ^{6}Li DOSY was performed using the standard Bruker dstebpgp3s program, using double stimulated echo, LED, with bipolar gradient pulses and 3 spoil gradients. Diffusion time was 50 ms, and rectangular gradient pulse duration was 2000 μs. Gradient recovery delays were 200 μs. Individual rows of the quasi-2-D diffusion databases were phased and baseline corrected. Actual diffusion coefficients used for D-fw analysis were obtained in the Bruker Topspin software using the T1/T2 analysis module.

The dimeric complex *O*-TIPS **2** was formed in situ. About 50 mg of ligand was added via syringe to a NMR tube. Toluene-d_8 was added via syringe to bring the total volume up to 600 μL. One equivalent of *n*-BuLi in hexanes or *n*-Bu^{6}Li in heptane was added dropwise to the tube to form *O*-TIPS **2**.

The concentration of *O*-TIPS **2** was 0.2 M. The internal references (in a ratio of 1:3:3:1 for BEN, COE, TDE, and SQU, respectively) were titrated into the NMR tube monitored by ^{1}H NMR. The titration was stopped when the peak intensity of benzene was similar to that of the dimeric complex. Upon cooling to −60 °C, the ^{6}Li NMR and the ^{1}H NMR spectra of *O*-TIPS **2** remained unchanged. See Table 3 for detailed sample information.

Synthesis of *n*-Bu^{6}Li. About 1.0 g (166 mmol) of finely cut ^{6}Li metal was placed into a flame-dried flask flushed with argon. The flask was fitted with a serum septum and sealed with Parafilm. The metal was washed with dry pentane by adding 10 mL of pentane to the flask via syringe. The flask was then placed in ultrasound for 5 min. Pentane was then removed via syringe. This was repeated until the washings were clear, with no white solid suspended in the wash (3 times). Dry heptane (15 mL) was added to the flask, followed by 9.6 g (10.9 mL, 104 mmol) of 1-chlorobutane, dropwise. This mixture was kept under ultrasound overnight at room temperature, after which a purple slurry was obtained.

dx.doi.org/10.1021/ja109041z |*J. Am. Chem. Soc.* 2011, 133, 6596–6602

Table 3. Compositions of Various NMR Samples

O-TIPS ligand[a]	nitrogen	n-BuLi[a]	lithium	complexes	internal references[b]	temperature
0.28	^{14}N	0.35	^{7}Li	*O*-TIPS **2**, *O*-TIPS **3**	0.10:0.29:0.29:0.10	25 °C
0.28	^{14}N	<0.28	^{7}Li	*O*-TIPS ligand, *O*-TIPS **2**	0.10:0.29:0.29:0.10	25 °C
0.28	^{14}N	0.28	^{6}Li	[^{6}Li]*O*-TIPS **2**	–	25 °C
0.28	^{14}N	0.28	^{6}Li	[^{6}Li]*O*-TIPS **2**	–	−60 °C
0.28	^{15}N	0.28	^{6}Li	[^{6}Li,^{15}N]*O*-TIPS **2**	–	25 °C

[a] Values refer to concentration (M). [b] Values refer to concentration (M) of BEN:COE:TDE:SQU, respectively.

The suspension was transferred via syringe to a clean, flame-dried vial flushed with argon and fitted with a serum septum. The vial was centrifuged until the solid was separated. The supernatant was transferred to a second identical vial and centrifuged again. The supernatant was transferred to a third identical vial. This *n*-Bu^{6}Li solution in heptane was titrated using 2,2-diphenylacetic acid in tetrahydrofuran and found to be 1.04 M.

■ ASSOCIATED CONTENT

Supporting Information. Supplemental NMR data for all compounds as well as Spartan calculation results for all conformers. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

pgw@brown.edu

Author Contributions

[†]These researchers contributed equally.

■ ACKNOWLEDGMENT

This research was funded by NSF grant no. 0718275.

■ REFERENCES

(1) (a) Toriyama, M.; Sugasawa, K.; Motohashi, S.; Tokutake, N.; Koga, K. *Chem. Pharm. Bull.* **2001**, *49* (4), 468–472. (b) Yamashita, T.; Sato, D.; Kiyoto, T.; Kumar, A.; Koga, K. *Tetrahedron Lett.* **1996**, *37* (45), 8195–8198. (c) Corruble, A.; Valnot, J.-Y.; Maddaluno, J.; Duhamel, P. *Tetrahedron: Asymmetry* **1997**, *8* (10), 1519–1523. (d) Granander, J.; Sott, R.; Hilmersson, G. *Tetrahedron* **2002**, *58* (23), 4717–4725. (e) Granander, J.; Sott, R.; Hilmersson, G. *Tetrahedron: Asymmetry* **2003**, *14* (4), 439–447. (f) Granander, J.; Sott, R.; Hilmersson, G. *Chem.—Eur. J.* **2006**, *12* (15), 4191–4197. (g) Arvidsson, P. I.; Davidsson, O.; Hilmersson, G. *Tetrahedron: Asymmetry* **1999**, *10* (3), 527–534. (h) Granander, J.; Eriksson, J.; Hilmersson, G. *Tetrahedron: Asymmetry* **2006**, *17* (13), 2021–2027. (i) Sott, R.; Granander, J.; Williamson, C.; Hilmersson, G. *Chem.—Eur. J.* **2005**, *11* (16), 4785–4792. (j) Sott, R.; Granander, J.; Hilmersson, G. *J. Am. Chem. Soc.* **2004**, *126* (21), 6798–6805. (k) Corruble, A.; Valnot, J.-Y.; Maddaluno, J.; Prigent, Y.; Davoust, D.; Duhamel, P. *J. Am. Chem. Soc.* **1997**, *119* (42), 10042–10048. (l) Arvidsson, P. I.; Hilmersson, G.; Davidsson, O. *Chem.—Eur. J.* **1999**, *5* (8), 2348–2355. (m) Sott, R.; Granander, J.; Diner, P.; Hilmersson, G. *Tetrahedron: Asymmetry* **2004**, *15* (2), 267–274. (n) Sott, R.; Granander, J.; Hilmersson, G. *Chem.—Eur. J.* **2002**, *8* (9), 2081–2087. (o) Corruble, A.; Valnot, J.-Y.; Maddaluno, J.; Duhamel, P. *J. Org. Chem.* **1998**, *63* (23), 8266–8275. (p) Williard, P. G.; Sun, C. *J. Am. Chem. Soc.* **1997**, *119* (48), 11693–11694. (q) Hilmersson, G.; Malmros, B. *Chem.—Eur. J.* **2001**, *7* (2), 337–341. (r) Li, D.; Sun, C.; Liu, J.; Hopson, R.; Li, W.; Williard, P. G. *J. Org. Chem.* **2008**, *73* (6), 2373–2381. (s) Hilmersson, G.; Davidsson, O. *J. Org. Chem.* **1995**, *60* (23), 7660–7669.

(2) isopropyl = *i*Pr, triisopropylsilyl = TIPS.

(3) Liu, J.; Li, D.; Sun, C.; Williard, P. G. *J. Org. Chem.* **2008**, *73* (11), 4045–4052.

(4) (a) Chen, A.; Wu, D.; Johnson, C. S., Jr. *J. Am. Chem. Soc.* **1995**, *117* (30), 7965–70. (b) Cohen, Y.; Avram, L.; Frish, L. *Angew. Chem., Int. Ed.* **2005**, *44* (4), 520–554. (c) Johnson, C. S., Jr. *Prog. Nucl. Magn. Reson. Spectrosc.* **1999**, *34* (3,4), 203–256. (d) Morris, K. F.; Johnson, C. S., Jr. *J. Am. Chem. Soc.* **1992**, *114* (8), 3139–41. (e) Wu, D.; Chen, A.; Johnson, C. S., Jr. *J. Magn. Reson., Ser. A* **1996**, *123* (2), 215–218.

(5) (a) Kagan, G.; Li, W.; Hopson, R.; Williard, P. G. *Org. Lett.* **2009**, *11* (21), 4818–4821. (b) Kagan, G.; Li, W.; Hopson, R.; Williard, P. G. *Org. Lett.* **2010**, *12* (3), 520–523. (c) Li, D.; Kagan, G.; Hopson, R.; Williard, P. G. *J. Am. Chem. Soc.* **2009**, *131* (15), 5627–5634. (d) Li, D.; Hopson, R.; Li, W.; Liu, J.; Williard, P. G. *Org. Lett.* **2008**, *10* (5), 909–911. (e) Socha, A. M.; Kagan, G.; Li, W.; Hopson, R.; Sello, J. K.; Williard, P. G. *Energy Fuels* **2010**, *24* (8), 4518–4521. (f) Li, W.; Kagan, G.; Yang, H.; Cai, C.; Hopson, R.; Sweigart, D. A.; Williard, P. G. *Org. Lett.* **2010**, *12* (12), 2698–2701. (g) Li, W.; Kagan, G.; Yang, H.; Cai, C.; Hopson, R.; Dai, W.; Sweigart, D. A.; Williard, P. G. *Organometallics* **2010**, *29* (6), 1309–1311.

(6) (a) Li, D.; Keresztes, I.; Hopson, R.; Williard, P. G. *Acc. Chem. Res.* **2009**, *42* (2), 270–280. (b) Li, D.; Sun, C.; Williard, P. G. *J. Am. Chem. Soc.* **2008**, *130* (35), 11726–11736.

(7) (a) Groves, P.; Palczewska, M.; Molero, M. D.; Batta, G.; Canada, F. J.; Jimenez-Barbero, J. *Anal. Biochem.* **2004**, *331* (2), 395–397. (b) Floquet, S.; Brun, S.; Lemonnier, J.-F.; Henry, M.; Delsuc, M.-A.; Prigent, Y.; Cadot, E.; Taulelle, F. *J. Am. Chem. Soc.* **2009**, *131* (47), 17254–17259. (c) Durand, E.; Clemancey, M.; Lancelin, J.-M.; Verstraete, J.; Espinat, D.; Quoineaud, A.-A. *J. Phys. Chem. C* **2009**, *113* (36), 16266–16276. (d) Oliva, A. I.; Gomez, K.; Gonzalez, G.; Ballester, P. *New J. Chem.* **2008**, *32* (12), 2159–2163. (e) Viel, S.; Capitani, D.; Mannina, L.; Segre, A. *Biomacromolecules* **2003**, *4* (6), 1843–1847. (f) Simpson, A. J. *Magn. Reson. Chem.* **2002**, *40* (Spec. Issue), S72–S82. (g) Greco, J. F.; McNevin, M. J.; Shoemaker, R. K.; Hagadorn, J. R. *Organometallics* **2008**, *27* (8), 1948–1953. (h) Rymden, R.; Carlfors, J.; Stilbs, P. *J. Inclusion Phenom* **1983**, *1* (2), 159–67. (i) Bockmann, A.; Guittet, E. *FEBS Lett.* **1997**, *418* (1,2), 127–130. (j) Wimmer, R.; Aachmann, F. L.; Larsen, K. L.; Petersen, S. B. *Carbohydr. Res.* **2002**, *337* (9), 841–849. (k) Brand, T.; Cabrita, E. J.; Morris, G. A.; Guenther, R.; Hofmann, H.-J.; Berger, S. *J. Magn. Reson.* **2007**, *187* (1), 97–104. (l) Martinek, T. A.; Hetenyi, A.; Fulop, L.; Mandity, I. M.; Toth, G. K.; Dekany, I.; Fulop, F. *Angew. Chem., Int. Ed.* **2006**, *45* (15), 2396–2400. (m) Pages, G.; Delaurent, C.; Caldarelli, S. *Angew. Chem., Int. Ed.* **2006**, *45* (36), 5950–5953. (n) Keresztes, I.; Williard, P. G. *J. Am. Chem. Soc.* **2000**, *122* (41), 10228–10229. (o) Morris, K. F.; Johnson, C. S., Jr. *J. Am. Chem. Soc.* **1993**, *115* (10), 4291–9. (p) Carrara, C.; Viel, S.; Delaurent, C.; Ziarelli, F.; Excoffier, G.; Caldarelli, S. *J. Magn. Reson.* **2008**, *194* (2), 303–306. (q) Hinton, D. P.; Johnson, C. S., Jr. *J. Phys. Chem.* **1993**, *97* (35), 9064–72. (r) Kapur, G. S.; Cabrita, E. J.; Berger, S. *Tetrahedron Lett.* **2000**, *41* (37), 7181–7185. (s) Kapur, G. S.; Berger, S. *Tribotest* **2000**, *6* (4), 323–336.

(8) (a) Wehrli, F. W. *J. Magn. Reson.* **1976**, *23* (3), 527–32. (b) Sun, C.; Williard, P. G. *J. Am. Chem. Soc.* **2000**, *122* (32), 7829–7830. (c) Liou, L. R.; McNeil, A. J.; Toombes, G. E. S.; Collum, D. B. *J. Am.*

Chem. Soc. **2008**, *130* (51), 17334–17341. (d) Liou, L. R.; McNeil, A. J.; Ramirez, A.; Toombes, G. E. S.; Gruver, J. M.; Collum, D. B. *J. Am. Chem. Soc.* **2008**, *130* (14), 4859–4868. (e) Eppers, O.; Guenther, H. *Helv. Chim. Acta* **1992**, *75* (8), 2553–62. (f) Eppers, O.; Fox, T.; Guenther, H. *Helv. Chim. Acta* **1992**, *75* (3), 883–91.

(9) *Spartan 06 program*; Wavefunction Inc.: Irvine, CA.

(10) (a) Stewart, J. J. P. *J. Comput. Chem.* **1989**, *10* (2), 209–220. (b) Stewart, J. J. P. *J. Comput. Chem.* **1989**, *10* (2), 221–264. (c) Stewart, J. J. P. *J. Comput. Chem.* **1991**, *12* (3), 320–341. (d) Stewart, J. P. *J. Mol. Model* **2004**, *10* (2), 155–164.

(11) (a) Rassolov, V. A.; Ratner, M. A.; Pople, J. A.; Redfern, P. C.; Curtiss, L. A. *J. Comput. Chem.* **2001**, *22* (9), 976–984.(b) *Spartan '06 for Windows and Linux Tutorial and User's Guide*; Wavefunction, Inc.: Irvine, CA, 2006; (c) Vosko, S. H.; Wilk, L.; Nusair, M. *Can. J. Phys.* **1980**, *58* (8), 1200–11. (d) Becke, A. D. *J. Chem. Phys.* **1993**, *98* (7), 5648–5652. (e) Stephens, P. J.; Devlin, F. J.; Chabalowski, C. F.; Frisch, M. J. *J. Phys. Chem.* **1994**, *98* (45), 11623–11627. (f) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37* (2), 785.

(12) This set of complexes represents all reasonable diastereomers and excludes enantiomers.