

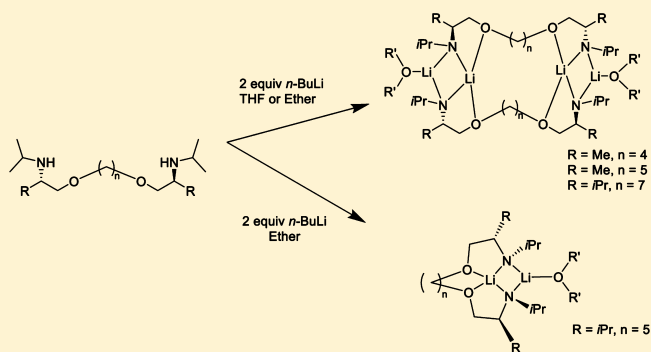
Chiral Lithium Diamides Derived from Linked *N*-Isopropyl Valinol or Alaninol

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S Supporting Information

ABSTRACT: Four different chiral diamino diethers synthesized from *N*-isopropyl valinol or *N*-isopropyl alaninol were lithiated with *n*-butyllithium in tetrahydrofuran or diethyl ether. Crystal structures of the dilithiated diamino diethers were determined by X-ray diffraction. Three dilithiated diamino diethers including (2*S*,2'*S*)-1,1'-(butane-1,4-diylbis(oxy))bis(*N*-isopropylpropan-2-amine) **7**, (2*S*,2'*S*)-1,1'-(pentane-1,5-diylbis(oxy))bis(*N*-isopropylpropan-2-amine) **8**, and (2*S*,2'*S*)-1,1'-(heptane-1,7-diylbis(oxy))bis(*N*-isopropyl-3-methylbutan-2-amine) **9** are dimers, whereas dilithiated (2*S*,2'*S*)-1,1'-(pentane-1,5-diylbis(oxy))bis(*N*-isopropyl-3-methylbutan-2-amine) **10** is a monomer. The lithium atoms in all crystal structures adopt a nonequivalent coordination protocol and exist in two different environments in which one of the lithium atoms is tetra-coordinated while the other one is tri-coordinated. The solution structures of the dilithiated diamino diethers are also characterized by a variety of NMR experiments including diffusion-ordered NMR spectroscopy (DOSY) with diffusion coefficient-formula (D-FW) weight correlation analyses and other one- and two-dimensional NMR techniques.

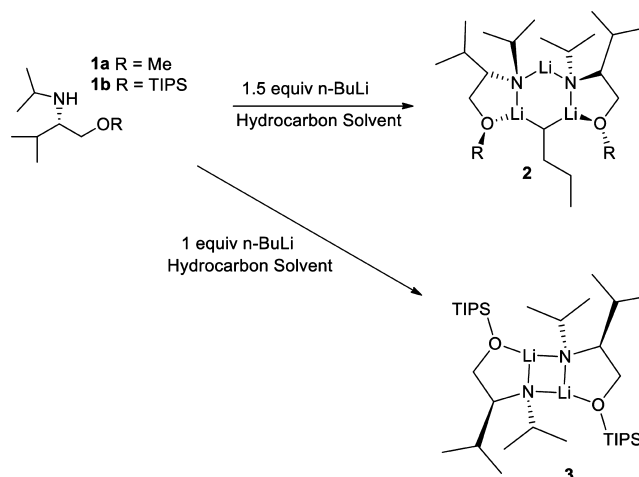


INTRODUCTION

Non-nucleophilic organolithium amide bases such as lithium diisopropylamide and lithium hexamethyldisilazide have long been widely employed in the deprotonation of various organic compounds.¹ Chiral lithium amide bases were also developed for asymmetric addition and deprotonation.² Recently, chiral lithium amide bases have also proven useful in catalytic dynamic resolution in enantioselective synthesis,³ enantioselective alkylation of aryl acetic acids,⁴ and catalytic enantioselective addition of an alkyllithium to an aldehyde.⁵ Current research suggests that the aggregation state of chiral amide bases influences their reactivity and stereoselectivity.⁶ Several research groups are now actively involved in elucidating the aggregation and reactivity of mixed species that incorporate chiral lithium amides.⁷ Thus, it is recognized that it is crucial to determine the aggregation state of chiral lithium amides as well as the solvation to fully elucidate a reaction mechanism and to design more efficient chiral amines.

In 1997, we reported the crystal structures of a mixed trimer containing 1 equiv of commercially available alkyl lithium reagents with 2 equiv of a lithiated chiral amino ether derived from *N*-isopropyl valinol **1a** (Scheme 1).⁸ Later, we carried out solution-state characterization of a lithiated chiral amino ether derived from **1b**, which is structural similar to **1a**.⁹ We also reported the asymmetric addition of the alkyl lithium portion of **1a** and **1b** to aldehydes with these reagents.⁴ The result showed that lithiated chiral amino ether

Scheme 1. Trimeric Complexes **2** and the Homodimer **3**

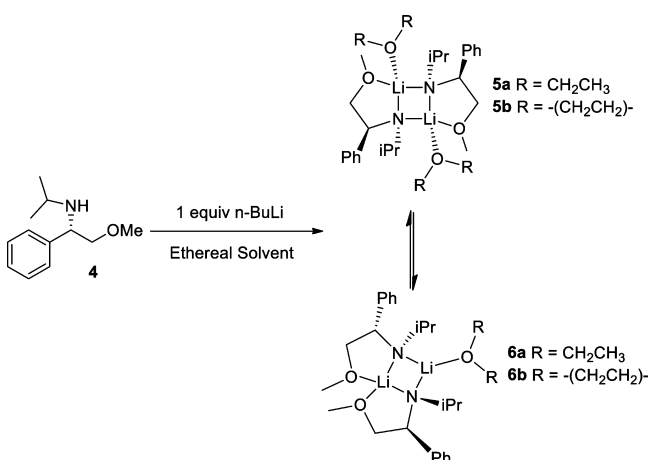


1b formed a 2:1 mixed trimer with *n*-butyllithium (*n*-BuLi) in toluene when there was excess *n*-BuLi in the solution. However, a ladder-type dimer is formed if there is only lithiated chiral amino ether **1b** in the solution without excess *n*-BuLi.¹⁰ In ethereal solution, lithiated chiral amino ether **4** exists as both a symmetrically solvated dimer **5** and

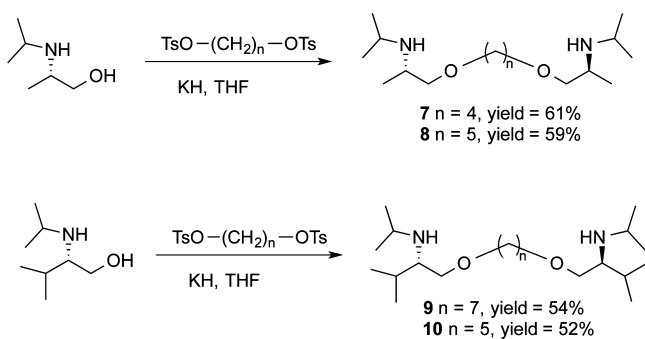
Received: May 23, 2014

Published: July 23, 2014

Scheme 2. Equivalently Solvated Dimer 5 and Non-equivalently Solvated Dimer 6



Scheme 3. Synthesis of Chiral Diamino Ethers 7–10



nonequivalently solvated dimer **6** as reported by Hilmersson and his co-workers (Scheme 2).¹¹ Herein we reported the syntheses as well as the solid- and solution-state characterization of four structurally related chiral diamino ethers

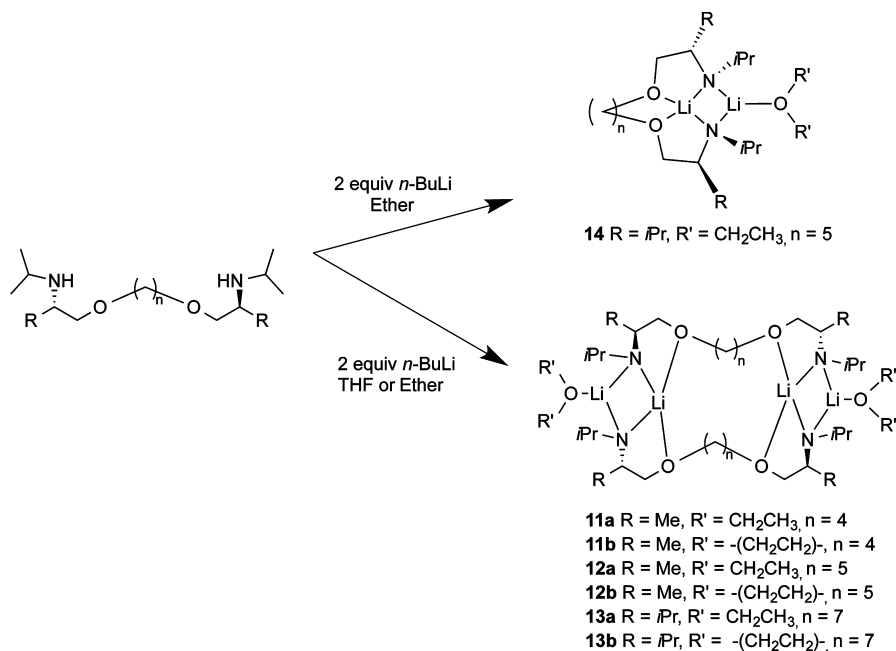
derived from *N*-isopropyl valinol or alaninol. The most commonly observed aggregation of lithium amide bases is a simple dimer. The structural motif of the chiral lithium amide bases reported herein is new, and a more complex aggregation pattern is observed with these reagents. With the exception of one intramolecular dimer (vide infra), the new structural motif reported is described as a dimer of dimers formed by intermolecular association of dimeric lithium amide bases linked together by homologous methylene chains.

RESULTS AND DISCUSSION

Solid-State Characterization of Dilithiated Diamino Ethers 7–10. (2*S*,2'*S*)-1,1'-(Butane-1,4-diylbis(oxy))bis(*N*-isopropylpropan-2-amine) **7** and (2*S*,2'*S*)-1,1'-(pentane-1,5-diylbis(oxy))bis(*N*-isopropylpropan-2-amine) **8** were synthesized from *N*-isopropyl alaninol, whereas (2*S*,2'*S*)-1,1'-(heptane-1,7-diylbis(oxy))bis(*N*-isopropyl-3-methylbutan-2-amine) **9** and (2*S*,2'*S*)-1,1'-(pentane-1,5-diylbis(oxy))bis(*N*-isopropyl-3-methylbutan-2-amine) **10** were synthesized from *N*-isopropyl valinol as depicted in Scheme 3. In this synthesis, two amino alcohol molecules were linked together with an alkyl chain to form a symmetrical diamino diether. Homologous analogues containing alkyl chains of four, five, and seven methylene groups were used to prepare the diamino diethers. Reaction of the chiral diamino diethers **7**, **8**, **9**, or **10** with 2 equiv of *n*-butyllithium (*n*-BuLi) yielded products whose crystal structures were determined. These structures incorporated tetrahydrofuran (THF) and diethyl ether (DEE). Dilithiated chiral diamino ethers **7**, **8**, and **9** form dimers in the solid state, whereas dilithiated chiral diamino ethers **10** crystallizes as a monomer, Scheme 4.

Crystal Structure of Dilithiated (2*S*,2'*S*)-1,1'-(Butane-1,4-diylbis(oxy))bis(*N*-isopropylpropan-2-amine) **11a and **11b**.** The crystal structure of THF- or DEE-coordinated dilithiated chiral diamino diether **7** was generated by reacting the diamino diether with 2 equiv of *n*-BuLi in DEE solution. THF was added to the DEE solution to prepare the THF-solvated

Scheme 4. Crystallization of Dilithiated Chiral Diamino Ethers 7–10 in Ethereal Solvents



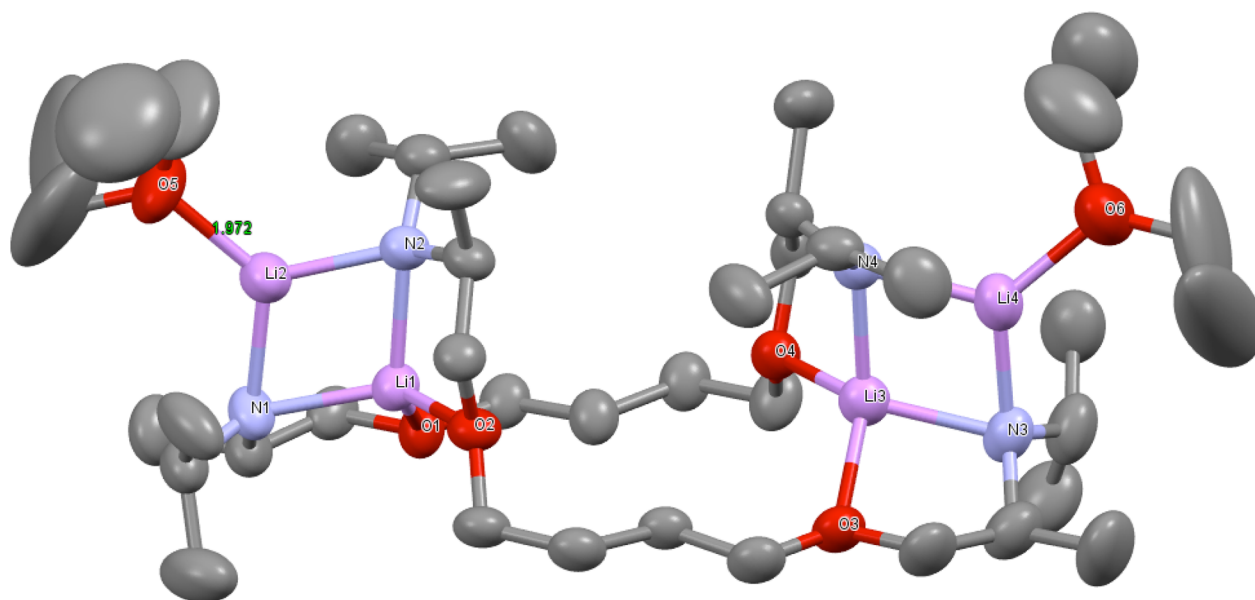


Figure 1. Crystal structure of DEE-coordinated dilithiated chiral diamino diethers **11a**. Thermal ellipsoid plots are at the 50% probability level. Hydrogen atoms have been omitted for clarity.

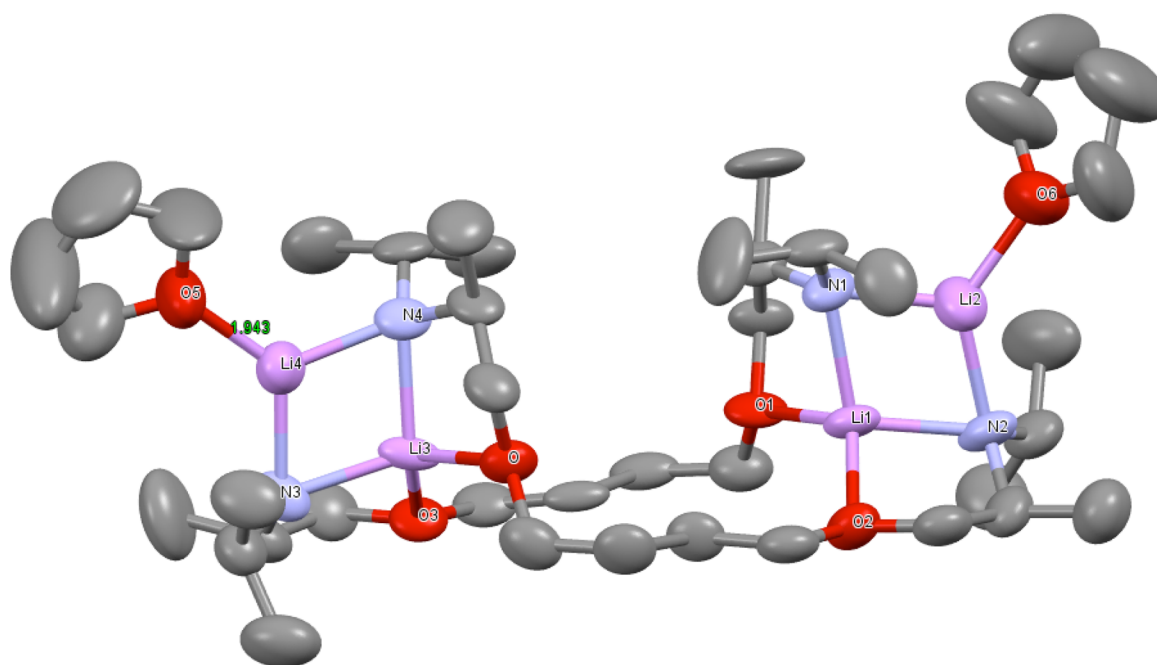


Figure 2. Crystal structure of THF-coordinated dilithiated chiral diamino diethers **11b**. Thermal ellipsoid plots are at the 50% probability level. Hydrogen atoms have been omitted for clarity.

crystal. Crystals grew overnight after storing the lithium amide solutions at $-50\text{ }^{\circ}\text{C}$. X-ray diffraction analysis reveals dimeric aggregates for both the DEE-coordinated and the THF-coordinated dilithiated chiral diamino diether **11**. As depicted in Figures 1 and 2, the crystal structures of the dimeric aggregates adopt the nonequivalent coordination protocol analogous to dimer **6**. One of the lithium atoms is tri-coordinated, while the other one is tetra-coordinated. Two subunits that structurally resemble dimer **6** are linked together by two alkyl chains. Within one subunit, there is a Li_2N_2 core and both oxygen atoms from the ether groups are coordinated to the same lithium atom rendering it tetra-solvated. The other lithium from the Li_2N_2 core is coordinated to the

oxygen atom of a solvent molecule, i.e., diethyl ether (DEE) or tetrahydrofuran (THF), and is trisolvated. The solid-state structures of these alaninol-derived lithium diamides solvated by different ethereal solvents (THF or DEE) are very similar to each other. It is noteworthy that THF more strongly coordinates to the lithium atoms than DEE because the THF-solvated crystals are grown from diethyl ether solution. It is also noteworthy that the THF-solvated dimer has a slightly shorter Li–O distance (1.94 Å) than that of DEE-solvated dimer (1.97 Å). Both structures appear to have a C_2 axis of symmetry roughly perpendicular to a plane that includes all of the methylene carbons in the linkers.

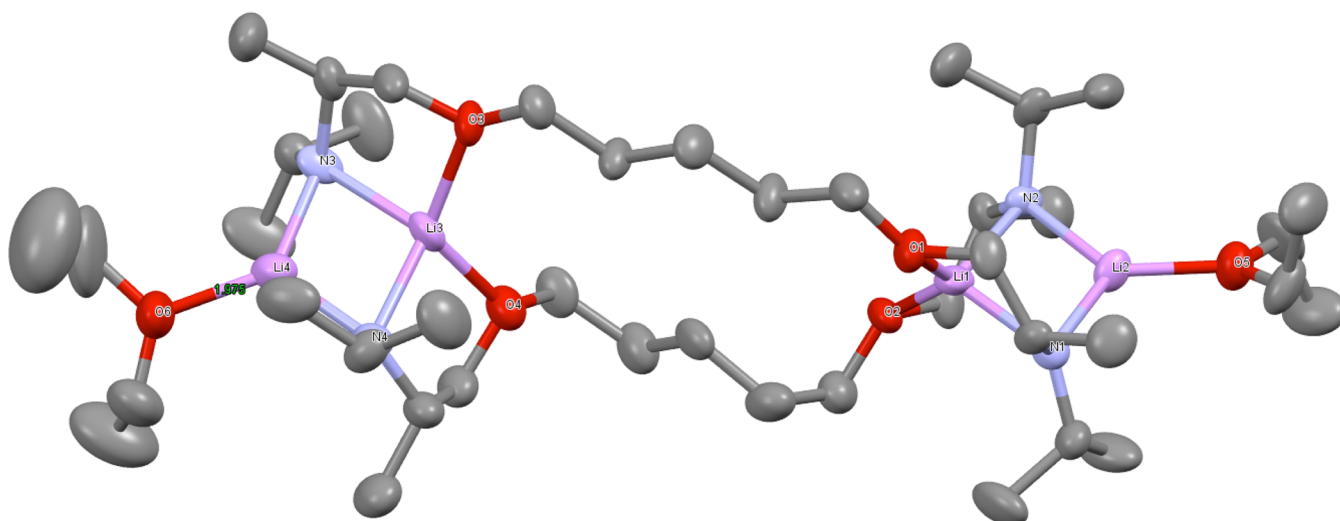


Figure 3. Crystal structure of DEE-coordinated dilithiated chiral diamino diethers **12a**. Thermal ellipsoid plots are at the 50% probability level. Hydrogen atoms have been omitted for clarity.

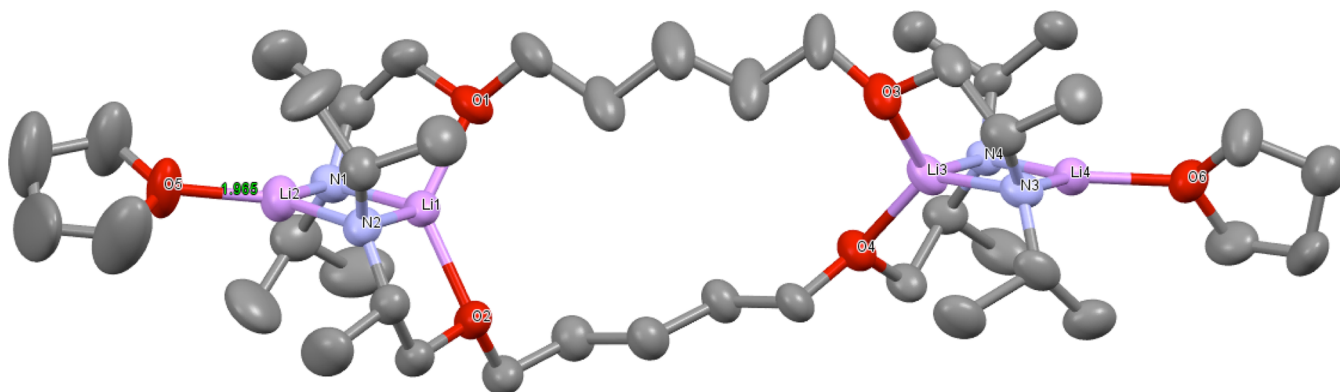


Figure 4. Crystal structure of THF-coordinated dilithiated chiral diamino diethers **12b**. Thermal ellipsoid plots are at the 50% probability level. Hydrogen atoms have been omitted for clarity.

Crystal Structure of Dilithiated (2*S*,2'*S*)-1,1'-(Pentane-1,5-diy)bis(oxy))bis(*N*-isopropylpropan-2-amine) **12a and **12b**.**

The crystal structures of THF- and DEE-coordinated dilithiated chiral diamino diether **8** were generated using the same method as those of dilithiated chiral diamino diether **7**. The crystal structures of DEE-solvated and THF-solvated dilithiated chiral diamino diether **8** are also dimeric; see Figures 3 and 4. However, the crystal structures of the dilithiated chiral diamino diether **8** are different from the structures of dilithiated chiral diamino diether **7**. The carbon chains of aggregates **11**, which have four carbon linkers, array parallel to each other in a relatively ordered manner as depicted in Figures 1 and 2. The distances between corresponding carbon atoms in the alkyl linker chains are relatively constant at around 4.6–4.9 Å, as illustrated in Figure 5a. In contrast, the arrangement of the alkyl chains of aggregates **12** is relatively disordered. The distances between corresponding carbon atoms in the alkyl chains range from 3.9 to 5.3 Å. We speculate that the constant distances between carbon atoms in linkers with even numbers of methylene groups is due to favorable van der Waals interactions between the adjacent hydrocarbon chains.

Crystal Structure of Dilithiated (2*S*,2'*S*)-1,1'-(Heptane-1,7-diy)bis(oxy))bis(*N*-isopropyl-3-methylbutan-2-amine) **13a and **13b**.**

The crystal structures of dilithiated (2*S*,2'*S*)-

1,1'-(heptane-1,7-diy)bis(oxy))bis(*N*-isopropyl-3-methylbutan-2-amine) **9** were formed by adding 2 equiv of *n*-BuLi to the diamino diether DEE solution. The solution was then stored at –50 °C for a few days until some white solid formed. After the removal of the solvent at –78 °C, the white solid were recrystallized by the addition of a small amount of DEE or THF (for the THF-coordinated complex) at room temperature. Crystals grew after storing at –20 °C overnight.

The crystal structures for both the DEE-coordinated and THF-coordinated dilithiated chiral diamino diether **9** are dimers that are structurally similar to those of dilithiated chiral diamino diether **8**. As depicted in Figures 6 and 7, the chains array in a relatively ordered manner similar to the alkyl chains of crystal structures **11a** and **11b**. The distances between each carbon atom in the alkyl chains are relatively constant at around 4.4–4.7 Å as depicted in Figure 8. Although the reason for the disordered behavior of **12**, which has a five carbon atoms unit in the alkyl chains, is not known, we did observe a difference in the arrangement of the structures of **12** compared to that of **11**. This difference is even more pronounced for the lithiated (*S*)-valinol-derived diamino diether containing five carbon atom linkers, because its crystal structure is monomeric instead of dimeric.

Crystal Structure of Dilithiated (2*S*,2'*S*)-1,1'-(Pentane-1,5-diy)bis(oxy))bis(*N*-isopropyl-3-methylbutan-2-amine) **14.** A

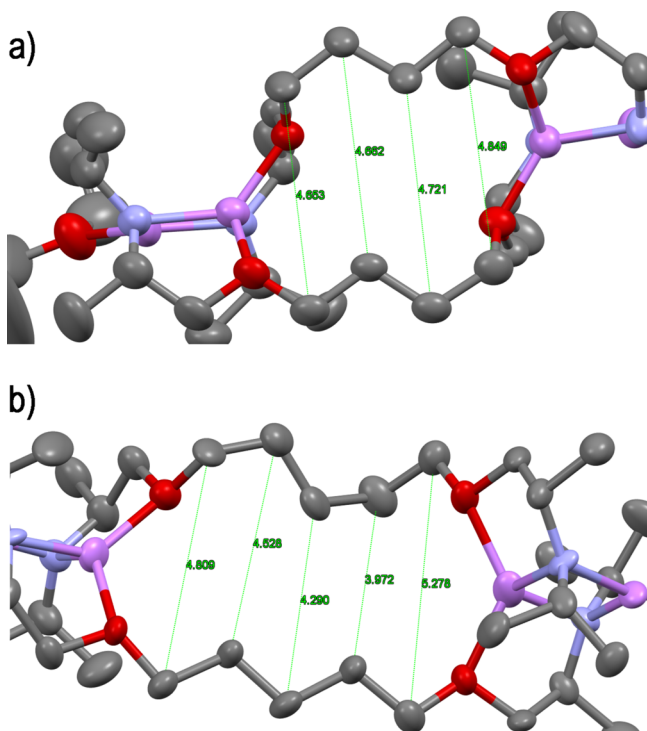


Figure 5. (a) Distances between alkyl chains of **11a**. (b) Distances between alkyl chains of **12a**.

crystal structure of dilithiated (2*S*,2'*S*)-1,1'-(pentane-1,5-diylbis(oxy))bis(*N*-isopropyl-3-methylbutan-2-amine) **10** was obtained using the same procedure that was used with aggregates **13a,b**.

Unlike the previous six structures, the crystal structure of DEE-coordinated dilithiated (2*S*,2'*S*)-1,1'-(pentane-1,5-diylbis(oxy))bis(*N*-isopropyl-3-methylbutan-2-amine) **10** is a monomer that also incorporates two lithium atoms with different coordination numbers. One of the lithium atoms is tri-coordinate, while the other one is tetra-coordinate. Both oxygen atoms of the linking ether are coordinated to the same lithium atom making it tetra-coordinate, while the other lithium atom from the Li_2N_2 core is coordinated to the oxygen atom of DEE and is tri-coordinate. The alkyl chain of

the monomer bends to form an eight-membered ring incorporating Li1, O1, and O2 as clearly seen in Figure 9. The crystallization conditions used to obtain all of these structures was virtually identical, and thus we cannot easily explain why this particular complex prefers the monomeric motif. Most likely this represents another example suggesting that subtle steric interactions dictate the aggregation state of dimeric lithium amide bases.¹² We were unable to obtain crystalline material suitable for X-ray diffraction analysis of the analogue of complex **10** solvated with THF.

Solution-state Characterization of Lithiated Diamino Ethers 9 and 10. The solution structure of dilithiated-**9** was investigated by multinuclear magnetic resonance spectroscopy. A 0.2 M solution of dilithiated-**9** in toluene- d_8 (0.4 mL)/THF- d_8 (0.1 mL) was prepared by adding ligand **9** (0.1 mmol) to *n*-Bu⁶Li (0.2 mmol). At low temperature (below -20 °C), three peaks appear in the ⁶Li NMR spectrum excluding *n*-Bu⁶Li (Figure 10). However, if dilithiated-**9** has a similar solvated dimer structure in solution as its solid-state structure **13b**, we expected to observe a pair of ⁶Li peaks with integration ratio 1:1. After repeating several times to exclude the possibility that the three observed peaks arose from variable impurities, e.g., *n*-BuO⁶Li, CD₂CD₂O⁶Li, etc., the integration ratio of three peaks was consistently around 3.5:2.3:1, which indicated the integration of the biggest peak was nearly equal to the sum of the other two.

Reducing the temperature from -20 to -70 °C had no effect on the frequency of the three resonances or their integrals. Surprisingly changing the solvent to 100% THF- d_8 shifted all of the peaks slightly upfield, while the biggest peak separated into two peaks (Figure 11a). We have no explanation for this unexpected observation. Now two sets of peaks with a 1:1 ratio appeared in the ⁶Li NMR spectrum, Li(*x,x'*) and Li(*y,y'*). Similarly, two sets of signals were also found in ¹³C NMR (Figure 12). The multiplicity edited ¹H-¹³C HSQC (Figure 13) and COSY spectra (Figure 14) allowed us to assign the four methylene carbons (72.08, 72.45, 74.15, 74.22 ppm) adjacent to oxygen and the four methine carbons (50.8, 52.3, 66.47, 67.4 ppm) adjacent to nitrogen for dilithiated-**9**. Prior to lithiation, only two methylene carbon chemical shifts adjacent to oxygen and two methine carbon peaks adjacent to nitrogen were observed. This suggests an

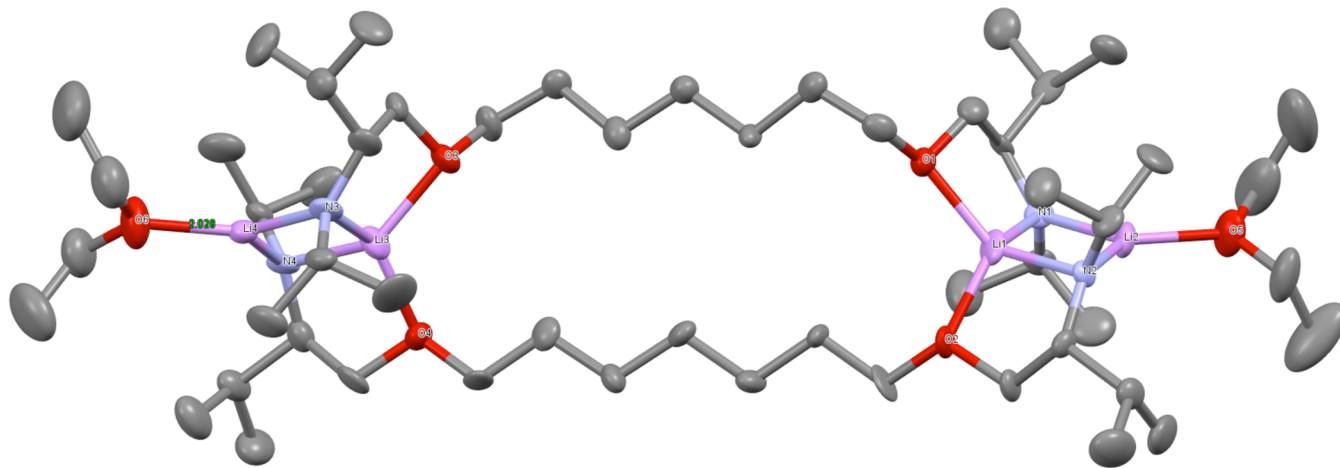


Figure 6. Crystal structure of DEE-coordinated dilithiated chiral diamino diether **13a**. Thermal ellipsoid plots are at the 50% probability level. Hydrogen atoms have been omitted for clarity.

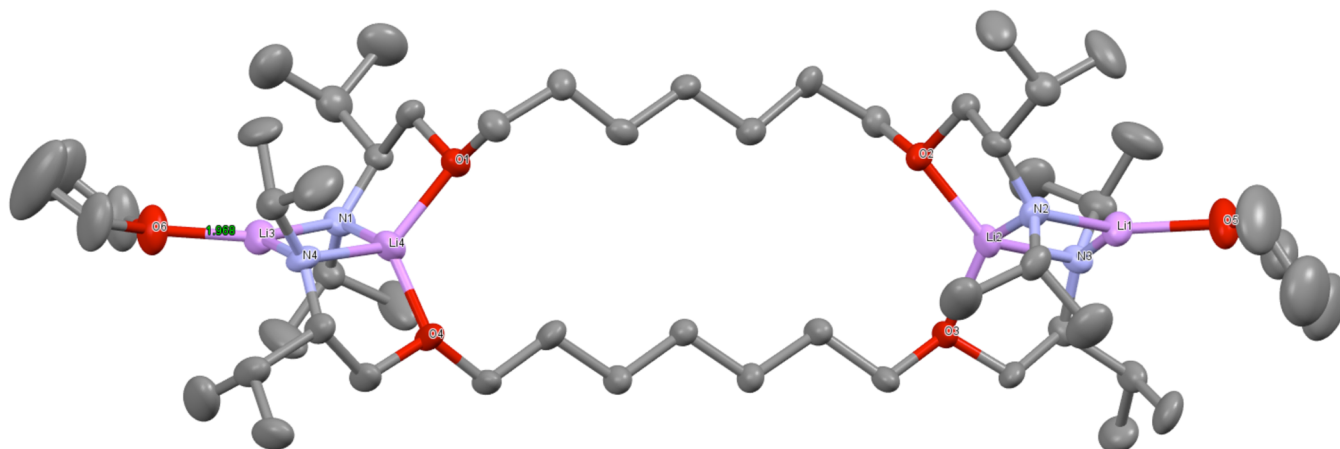


Figure 7. Crystal structure of THF-coordinated dilithiated chiral diamino diether **13b**. Thermal ellipsoid plots are at the 50% probability level. Hydrogen atoms have been omitted for clarity.

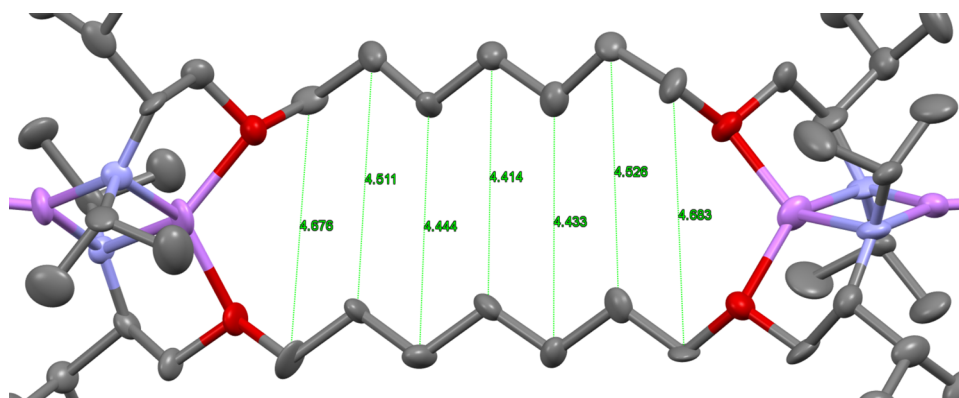


Figure 8. Distances between alkyl chains of **13a**.

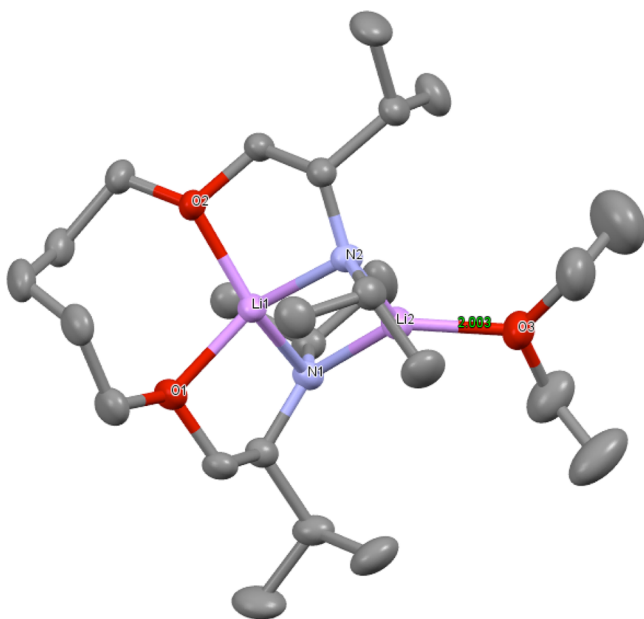


Figure 9. Crystal structure of DEE-coordinated dilithiated chiral diamino ethers **14**. Thermal ellipsoid plots are at the 50% probability level. Hydrogen atoms have been omitted for clarity.

additional dilithiated molecule in solution. Further support for a second structure is evidenced in the ^6Li DOSY (Figure 11b)

where the two sets of resonances, $\text{Li}(y,y')$ and $\text{Li}(x,x')$, share similar diffusion coefficient values. Moreover, the diffusion coefficient of $\text{Li}(y,y')$ is smaller than the diffusion coefficient of $\text{Li}(x,x')$, implying that $\text{Li}(y,y')$ belongs to a heavier complex than $\text{Li}(x,x')$. In the ^6Li EXSY spectrum (Figure 15), there are cross peaks between $\text{Li}(x)$ and $\text{Li}(x')$ and also between $\text{Li}(y)$ and $\text{Li}(y')$, but not between the x and y species. All of these observations support the existence of two different complex dilithiated molecules in solution.

A better understanding of the molecular weights of the two dilithiated complexes in solution comes from the diffusion-formula weight (D-FW) experiment with internal references (Figures 16 and 17).¹³ Consequently, we added benzene (BEN, 78.1 g/mol), cyclooctene (COE, 110 g/mol), 1-tetradecene (TDE, 196 g/mol), and squalene (SQU, 410 g/mol) as internal references (with a molar ratio around 1:3:3:1 for BEN, COE, TDE, SQU) to the sample solution of dilithiated-9 in order to carry out D-FW correlation analysis. At -70°C , the experimentally determined FW of the smaller complex is 462 g/mol, while the larger one is 941 g/mol. In the solid state, dilithiated-9 forms a disolvated dimer (**13b**) with a FW of 952 g/mol. Therefore, we assumed that complex **13b** is larger. According to the D-FW analysis, the smaller complex is nearly half the FW of the larger one and has two ^6Li peaks with similar intensity and integration. In analogy to Hilmersson's nonequivalently solvated dimer **6**, we surmised the smaller complex has a similar structure. This conclusion was then supported by the crystal structure of

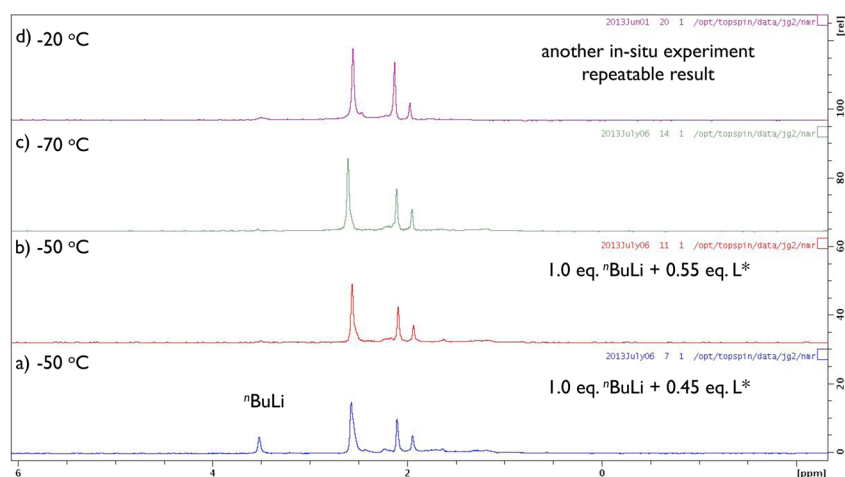


Figure 10. ^6Li NMR of dilithiated-9 in $\text{Tol-}d_8/\text{THF-}d_8$ (4:1). L^* is chiral ligand 9. In all four spectra (a–d), the integration of the highest peak is close to the sum integrations of the other smaller peaks (relaxation delay is 10 s, equal to 5 times T_1 relaxation time). Moreover, spectra b, c, and d were taken at different low temperatures without significant difference, which indicates this system is not temperature-sensitive.

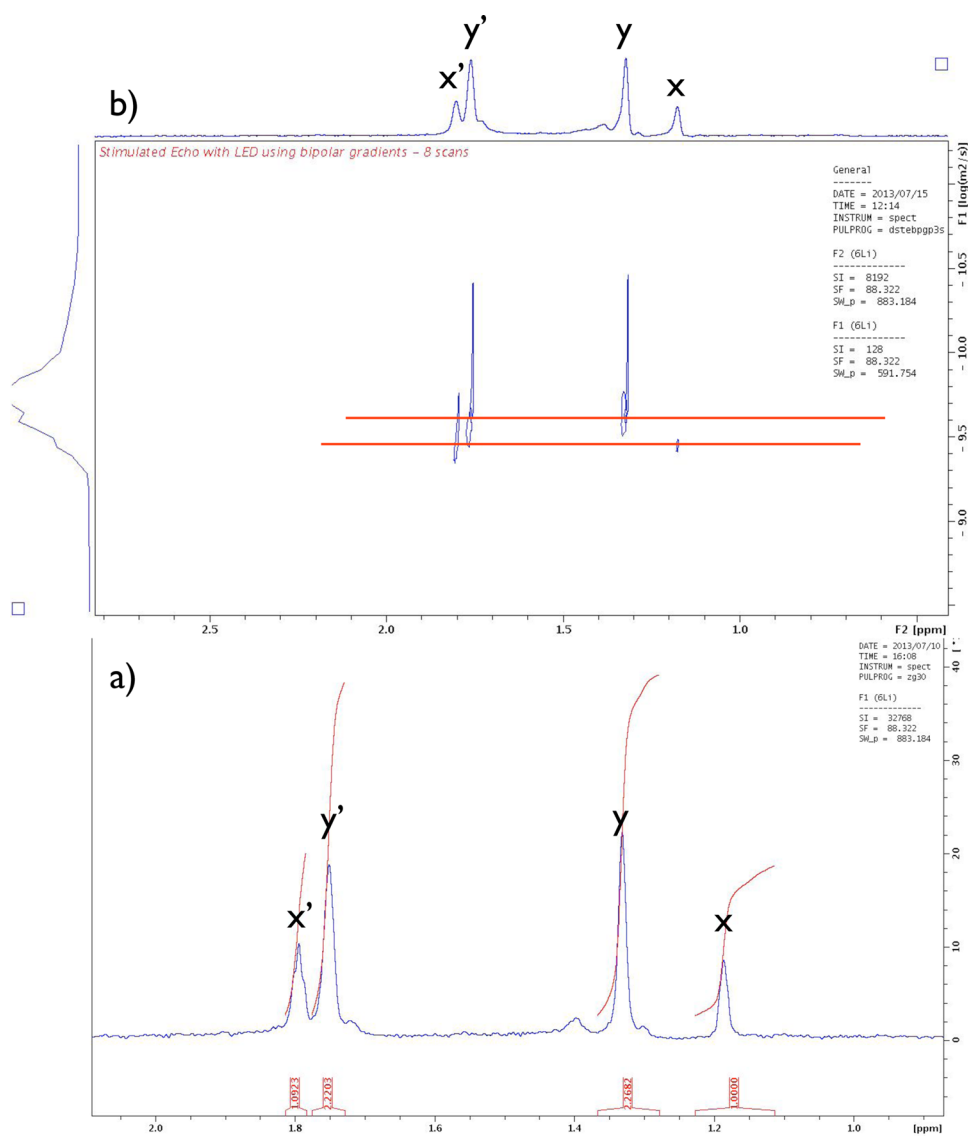


Figure 11. ^6Li NMR (a) and ^6Li DOSY (b) of dilithiated-9 in $\text{THF-}d_8$ at $-30\text{ }^\circ\text{C}$.

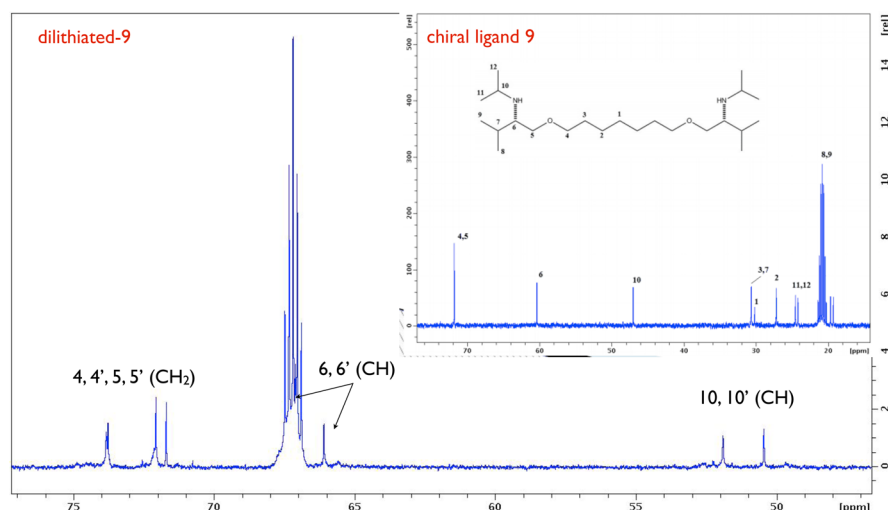


Figure 12. ^{13}C NMR of chiral ligand **9** and dilithiated-**9**. After lithiation, the number of carbons beside oxygen atom or nitrogen atom (40–80 ppm region) was doubled.

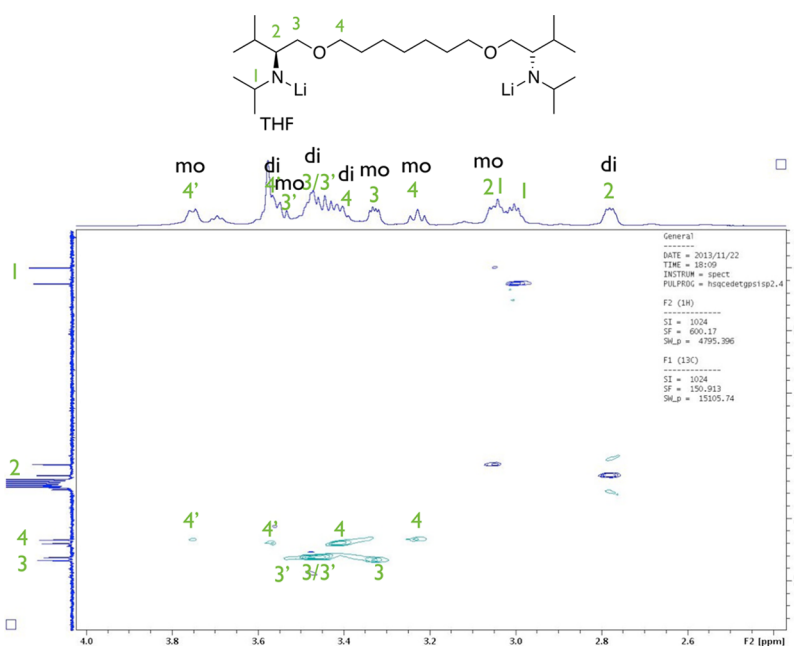
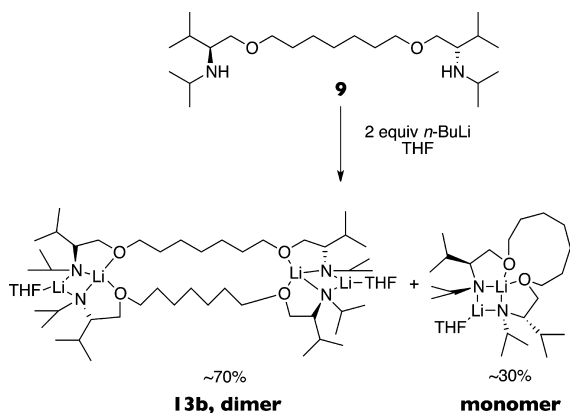


Figure 13. Multiplicity edited ^1H – ^{13}C HSQC spectrum of dilithiated-**9** in THF-d_8 at $-30\text{ }^\circ\text{C}$. Blue spots indicate CH_3 or CH ; green cross-peaks indicate CH_2 (mo = monomer; di = dimer).

Scheme 5. Solution State of Dilithiated-**9** in THF



monosolvated **14** (vide supra). If the monosolvated **13b** has a similar structure as **14**, then its FW should be 476 g/mol (monosolvated by THF), which is quite close to our experimentally determined DOSY result of 462 g/mol (error –3%). Hence we conclude that dilithiated-**9** exists as both dimer **13b** and monomer in ethereal solution as depicted in Scheme 5 and that disolvated dimer **13b** is the major species.

Solution-State Characterization of Lithiated Diamino Ethers 10. On the basis of multiplicity edited HSQC (Figure 17), we observe only one dominant complex in the solution. ^6Li NMR (Figure 18) and the corresponding ^6Li DOSY summarized in Figure 18 indicate that approximately 90% of dilithiated-**10** exists as monomer **14** in ethereal solution with an experimentally determined FW of 403 g/mol (error –9%) by ^1H DOSY D-FW analysis (Figure 19).

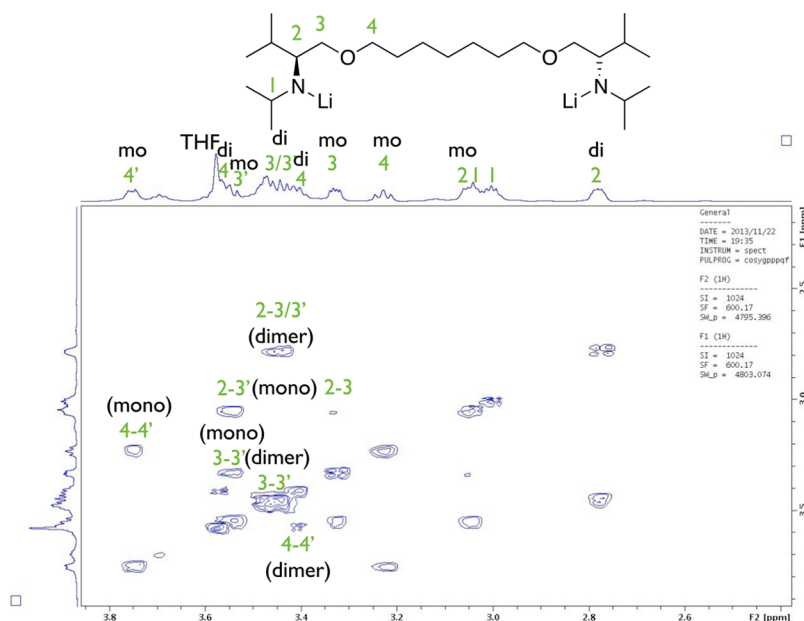


Figure 14. ^1H – ^1H COSY spectrum of dilithiated-9 in $\text{THF-}d_8$ at $-30\text{ }^\circ\text{C}$ (mo = monomer; di = dimer).

CONCLUSION

Four chiral diamino diether ligands have been synthesized from *N*-isopropyl valinol or alaninol. Upon lithiation, the crystal structures of the lithium chiral diamido diethers reveal one monomer and six dimeric structures that are solvated by ethereal solvents. X-ray diffraction experiments reveal that the dimers contain two subunits linked together by two alkyl chains. Each subunit adopts a nonequivalent coordination protocol in which one of the lithium atoms is tetra-coordinated while the other one is tri-coordinated. Moreover, the alkyl chain with five carbon atom linker unit is found to array differently from those of four and seven carbon atoms units. Steric interactions most likely influence both the solid and solution phase structures of these complexes.

EXPERIMENTAL SECTION

Procedures for NMR Experiments. NMR samples were prepared in tubes sealed with rubber septum caps and parafilm. NMR tubes were evacuated in vacuo, flame-dried, and filled with argon before use. ^1H chemical shifts were referenced to toluene- d_8 at 7.09 ppm, and ^{13}C chemical shifts were referenced to toluene- d_8 at 137.86 ppm. All NMR experiments were acquired on a 600 MHz spectrometer. For DOSY experiments a z-axis gradient amplifier was equipped with a z-axis gradient coil with maximum gradient strength 0.5 T/m. Both ^1H and ^6Li DOSY were performed using the standard programs, employing a double stimulated echo sequence, bipolar gradient pulses for diffusion, and 3 spoil gradients. For ^1H DOSY, diffusion time was 100 ms, and the rectangular gradient pulse duration was 1300 μs . Gradient recovery delays were 200 μs . For ^6Li DOSY, diffusion time was 1500 ms, and the rectangular gradient pulse duration was 1300 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 using the T1/T2 analysis module in commercially available software.

The $n\text{-Bu}^6\text{Li}$ sample was prepared by laboratory synthesized $n\text{-Bu}^6\text{Li}$ heptane solution. About 100–200 μL of the $n\text{-Bu}^6\text{Li}$ heptane solution was added via syringe to a NMR tube. After the addition, the NMR tube was evacuated in vacuo for 5–10 min at $0\text{ }^\circ\text{C}$ in order to remove the hydrocarbon solvent. After the tube was filled with argon, deuterium-labeled solvent was added via syringe to bring the total volume up to 500–600 μL .

Materials and Methods. Tetrahydrofuran (THF), diethyl ether (DEE), dichloromethane (DCM), and pyridine were used from a dry solvent dispensing system. Solvents for extraction and chromatography were technical grade. Unless otherwise stated, purchased chemicals were used as received. All reactions under anhydrous conditions were conducted using flame- or oven-dried glassware and standard syringe techniques under an atmosphere of argon.

NMR spectra were recorded at either 400 or 600 MHz using CDCl_3 or C_6D_6 as the solvent. Chemical shifts are reported in ppm and were referenced to residual protonated solvent for ^1H NMR (δ 7.27 ppm for CHCl_3 , 7.16 ppm for C_6H_6) and ^{13}C NMR (δ 77.00 ppm for CDCl_3 , 128.39 ppm for C_6D_6). Data are represented as follows: chemical shift (multiplicity [br = broad, s = singlet, d = doublet, q = quartet, sp = septet, m = multiplet], integration, coupling constants in Hz). Mass spectra were obtained using electrospray ionization method.

Synthesis of $n\text{-Bu}^6\text{Li}$. The $n\text{-Bu}^6\text{Li}$ solution was prepared in heptane according to the method that our group has published previously.⁷

General Procedures for the Synthesis of Chiral Diamines 7–10. (*S*)-2-(Isopropylamino)propan-1-ol and (*S*)-2-(isopropylamino)-3-methylbutan-1-ol were prepared according to the methods described by Shioiri.¹⁴ Butane-1,4-diyl bis(4-methylbenzenesulfonate), pentane-1,5-diyl bis(4-methylbenzenesulfonate), and heptane-1,7-diyl bis(4-methylbenzenesulfonate) were prepared according to the methods described by Bulkowski,¹⁵ Jackson,¹⁶ and Herdering,¹⁷ respectively.

Typical Procedure. About 7.36 g (55.1 mmol, 2 equiv) of potassium hydride (30 wt % dispersion in mineral oil) was placed into a flame-dried flask flushed with argon. About 5 mL of dry pentane was added to the flask via syringe, and the suspension was stirred for 5 min. The mineral oil/pentane solution was then removed via syringe. This washing was repeated three times before 80 mL of anhydrous THF was added to the flask. A solution of 4.00 g (27.5 mmol, 1 equiv) of (*S*)-2-(isopropylamino)-3-methylbutan-1-ol [(*S*)-2-(isopropylamino)propan-1-ol for **9** and **10**] dissolved in 20 mL of anhydrous THF was added slowly to the potassium hydride THF suspension stirring at room temperature for 30 min using a syringe pump. The yellow suspension was stirred for 4 h at room temperature. After that, 6.07 g (13.8 mmol, 0.5 equiv) of heptane-1,7-diyl bis(4-methylbenzenesulfonate) [butane-1,4-diyl bis(4-methylbenzenesulfonate) was used for **7**, and pentane-1,5-diyl bis(4-methylbenzenesulfonate) was used for **8** and **10**] dissolved in 40 mL of anhydrous THF was added to the suspension dropwise using

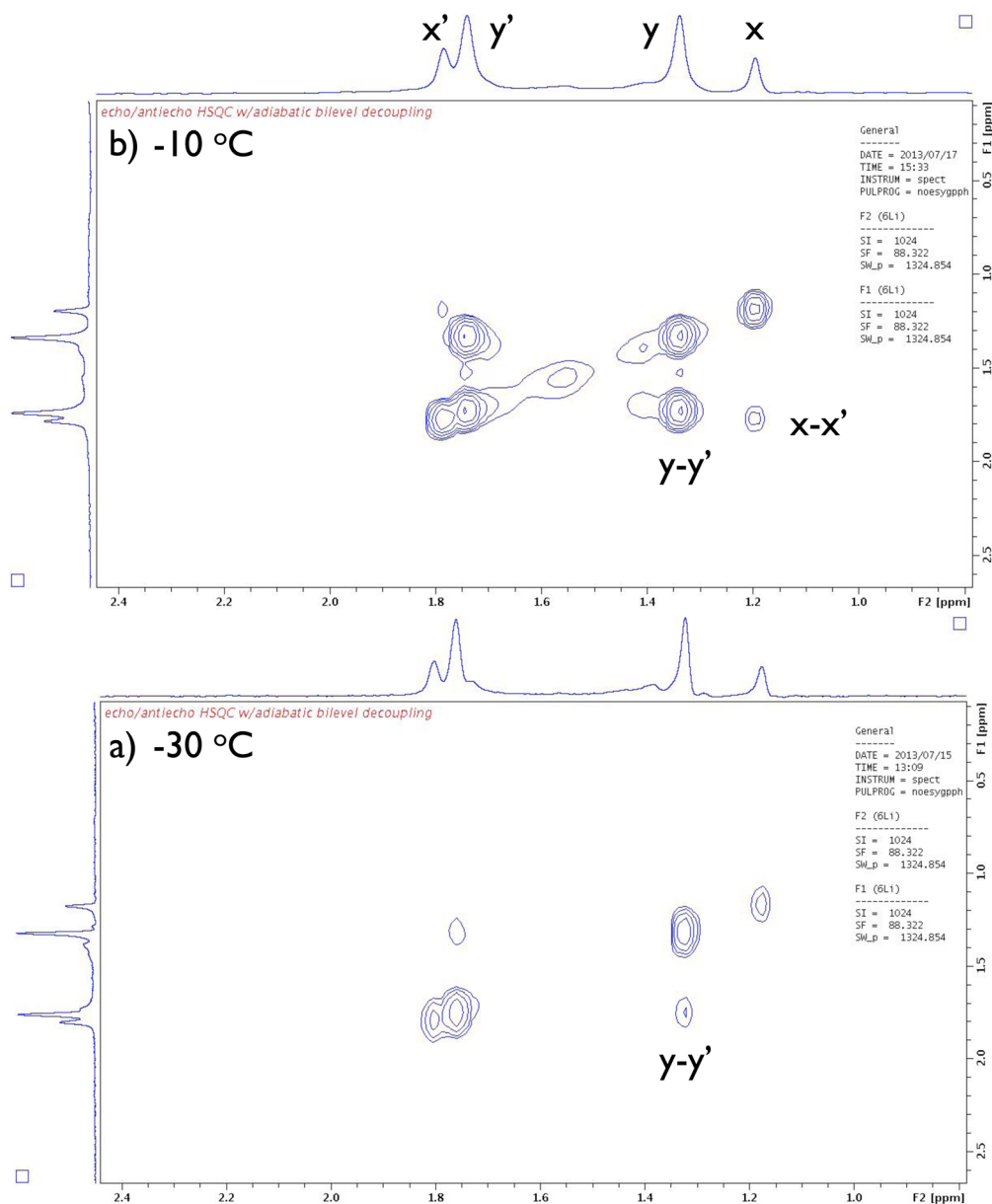


Figure 15. ⁶Li EXSY NMR of dilithiated-9 in THF-*d*₈ at -30 °C (a) and -10 °C (b). Mixing time of spectrum a is 1 s and only cross peak between y and y' is observed. Mixing time of spectrum b is 2.4 s and cross peak between x and x' is also observed, due to higher temperature and longer mixing time.

a syringe pump. The suspension was allowed to stir overnight at room temperature. The suspension was placed into an ice bath for 10 min before quenching slowly with 30 mL of water. The mixture was then extracted with 60 mL of ethyl acetate three times, and the organic phase was washed with brine and dried over NaSO₄. Evaporation of the solvent and purification of crude product by flash column chromatography on silica gel (elution with hexanes/EtOAc 5:1 with 1% triethyl amine) gave pure (2*S*,2'*S*)-1,1'-(heptane-1,7-diylbis(oxy))bis(*N*-isopropyl-3-methylbutan-2-amine) **9** as a light yellow oil (2.87 g, 7.4 mmol, 54%). The purification of (2*S*,2'*S*)-1,1'-(butane-1,4-diylbis(oxy))bis(*N*-isopropylpropan-2-amine) **7**, (2*S*,2'*S*)-1,1'-(pentane-1,5-diylbis(oxy))bis(*N*-isopropylpropan-2-amine) **8**, and (2*S*,2'*S*)-1,1'-(pentane-1,5-diylbis(oxy))bis(*N*-isopropyl-3-methylbutan-2-amine) **10** was achieved by vacuum distillation after the evaporation of the solvent by rotary evaporation.

(2*S*,2'*S*)-1,1'-(Butane-1,4-diylbis(oxy))bis(*N*-isopropylpropan-2-amine) **7.** (2*S*,2'*S*)-1,1'-(Butane-1,4-diylbis(oxy))bis(*N*-isopropylpropan-2-amine) was obtained from (*S*)-2-(isopropylamino)propan-1-ol (3.00 g, 25.6 mmol) as described above. Purification (bp

= 137–139 °C, 4 mmHg) gave a light yellow oil (2.25 g, 7.8 mmol, 61%). ¹H NMR (CDCl₃, 400 MHz) δ 3.51–3.37 (m, 4H), 3.34–3.21 (m, 4H), 3.00–2.83 (m, 4H), 1.70–1.58 (m, 4H), 1.58–1.38 (br, 2H), 1.13–0.95 (m, 18H); ¹³C NMR (CDCl₃, 100 MHz) δ 75.4, 70.9, 49.4, 45.4, 26.4, 24.0, 22.8, 17.9. HRMS-ESI *m/z*: [M + H]⁺ calcd for C₁₆H₃₇N₂O₂ 289.2850, found 289.2848.

(2*S*,2'*S*)-1,1'-(Pentane-1,5-diylbis(oxy))bis(*N*-isopropylpropan-2-amine) **8.** (2*S*,2'*S*)-1,1'-(Pentane-1,5-diylbis(oxy))bis(*N*-isopropylpropan-2-amine) was obtained from (*S*)-2-(isopropylamino)propan-1-ol (3.00 g, 25.6 mmol) as described above. Purification (bp = 149–151 °C, 4 mmHg) gave a light yellow oil (2.28 g, 7.5 mmol, 59%). ¹H NMR (C₆D₆, 600 MHz) δ 3.32–3.18 (m, 8H), 3.00–2.94 (m, 2H), 2.86 (sp, 2H, *J* = 6.2 Hz), 1.57–1.50 (m, 4H), 1.46–1.38 (m, 2H), 1.20–1.11 (br, 2H), 1.06–1.01 (m, 12H), 0.99 (d, 6H, *J* = 6.2 Hz); ¹³C NMR (C₆D₆, 150 MHz) δ 86.5, 81.6, 60.3, 56.0, 40.4, 34.8, 33.8, 33.5, 28.8. HRMS-ESI *m/z*: [M + H]⁺ calcd for C₁₇H₃₉N₂O₂ 303.3006, found 303.3004.

(2*S*,2'*S*)-1,1'-(Heptane-1,7-diylbis(oxy))bis(*N*-isopropyl-3-methylbutan-2-amine) **9.** (2*S*,2'*S*)-1,1'-(Heptane-1,7-diylbis-

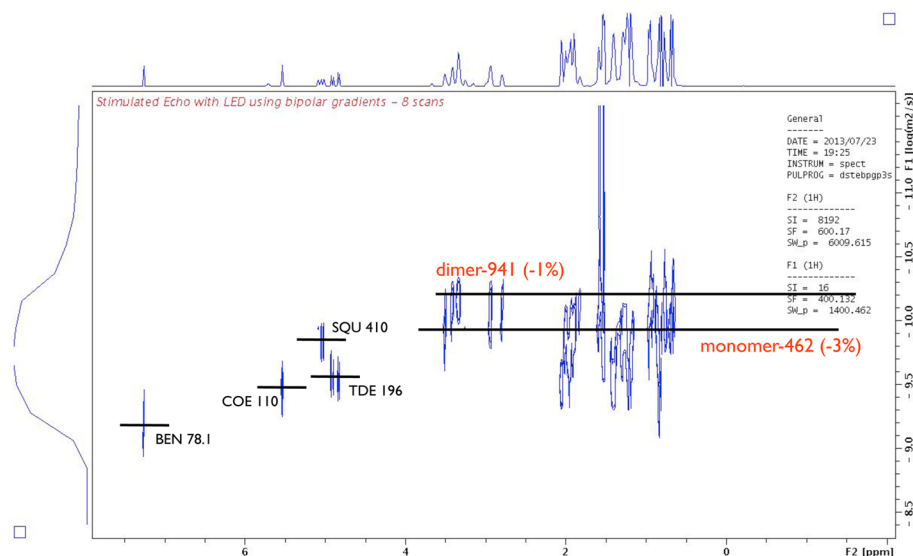


Figure 16. ^1H DOSY (with internal references) of dilithiated-9 in $\text{THF-}d_8$ at $-70\text{ }^\circ\text{C}$.

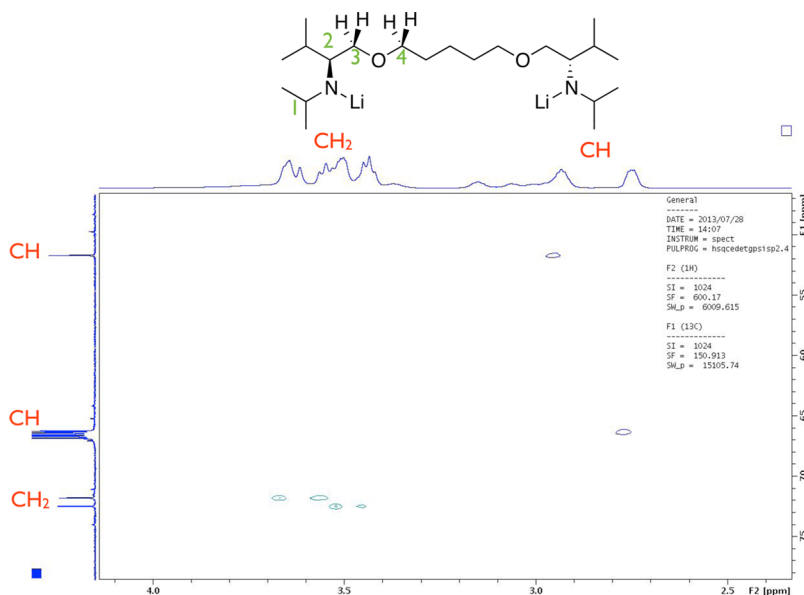


Figure 17. Multiplicity edited ^1H - ^{13}C HSQC spectrum of dilithiated-10 in $\text{THF-}d_8$ at $-50\text{ }^\circ\text{C}$. Blue spots indicate CH_3 or CH ; green cross-peaks indicate CH_2 .

(oxy))bis(*N*-isopropyl-3-methylbutan-2-amine) (2.87 g, 7.4 mmol, 54%) was obtained from (*S*)-2-(isopropylamino)-3-methylbutan-1-ol (4.00 g, 27.5 mmol) as described above. ^1H NMR (CDCl_3 , 400 MHz) δ 3.42–3.34 (m, 6H), 3.32–3.26 (m, 2H), 2.84 (sp, 2H, J = 6.1 Hz), 2.52 (q, 2H, J = 5.4 Hz), 1.87–1.75 (m, 2H), 1.63–1.46 (m, 4H), 1.40–1.24 (m, 6H), 1.04 (d, 6H, J = 2.2 Hz), 1.02 (d, 6H, J = 2.2 Hz), 0.91 (d, 6H, J = 1.6 Hz), 0.90 (d, 6H, J = 1.5 Hz); ^{13}C NMR (CDCl_3 , 100 MHz) δ 71.3, 71.2, 59.5, 46.6, 29.6, 29.3, 29.3, 26.2, 23.6, 23.5, 18.6, 18.5; HRMS-FAB m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{23}\text{H}_{51}\text{N}_2\text{O}_2$ 387.3951, found 387.3966.

(2*S*,2'*S*)-1,1'-(Pentane-1,5-diylbis(oxy))bis(*N*-isopropyl-3-methylbutan-2-amine) 10. (2*S*,2'*S*)-1,1'-(Pentane-1,5-diylbis(oxy))-bis(*N*-isopropyl-3-methylbutan-2-amine) (1.93 g, 5.4 mmol, 52%) was obtained from (*S*)-2-(isopropylamino)-3-methylbutan-1-ol (3.00 g, 20.7 mmol) as described above. ^1H NMR (CDCl_3 , 600 MHz) δ 3.46–3.36 (m, 3H), 3.33–3.24 (m, 1H), 2.85 (septet, 1H, J = 6.2 Hz), 2.53 (m, 1H), 1.82 (m, 1H), 1.65–1.54 (m, 2H), 1.46–1.34 (m, 1H), 1.10–1.00 (m, 6H), 0.95–0.87 (m, 6H); ^{13}C NMR (CDCl_3 , 150 MHz) δ 71.4, 71.1, 59.5, 46.6, 29.5, 29.3, 23.6, 23.5,

22.9, 18.6, 18.6; HRMS-ESI m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{21}\text{H}_{47}\text{N}_2\text{O}_2$ 359.3638, found 359.3628.

General Procedures for the Crystallization of Lithium Chiral Diamides 11a and 12a. To a solution of the chiral diamine 7 or 8 (0.10 g) in 1 mL of diethyl ether at $0\text{ }^\circ\text{C}$ under Ar atmosphere was slowly added 2 equiv of *n*-BuLi. The reaction mixture was allowed to stir at $0\text{ }^\circ\text{C}$ for 5 min. The clear yellowish solution was then stored in a $-50\text{ }^\circ\text{C}$ freezer, and XRD quality crystals were grown at $-50\text{ }^\circ\text{C}$ overnight.

General Procedures for the Crystallization of Lithium Chiral Diamides 11b and 12b. To a solution of the chiral diamine 7 or 8 (0.10 g) in 0.9 mL of diethyl ether at $0\text{ }^\circ\text{C}$ under Ar atmosphere was slowly added 2 equiv of *n*-BuLi. Anhydrous THF (0.05 mL) was then added to the solution, and the reaction mixture was allowed to stir at $0\text{ }^\circ\text{C}$ for 5 min. The clear yellowish solution was then stored in a $-50\text{ }^\circ\text{C}$ freezer, and XRD quality crystals were grown at $-50\text{ }^\circ\text{C}$ overnight.

General Procedures for the Crystallization of Lithium Chiral Diamides 13a and 14. To a solution of the chiral diamine 9 or 10 (0.05 g) in 1 mL of diethyl ether at $0\text{ }^\circ\text{C}$ under Ar

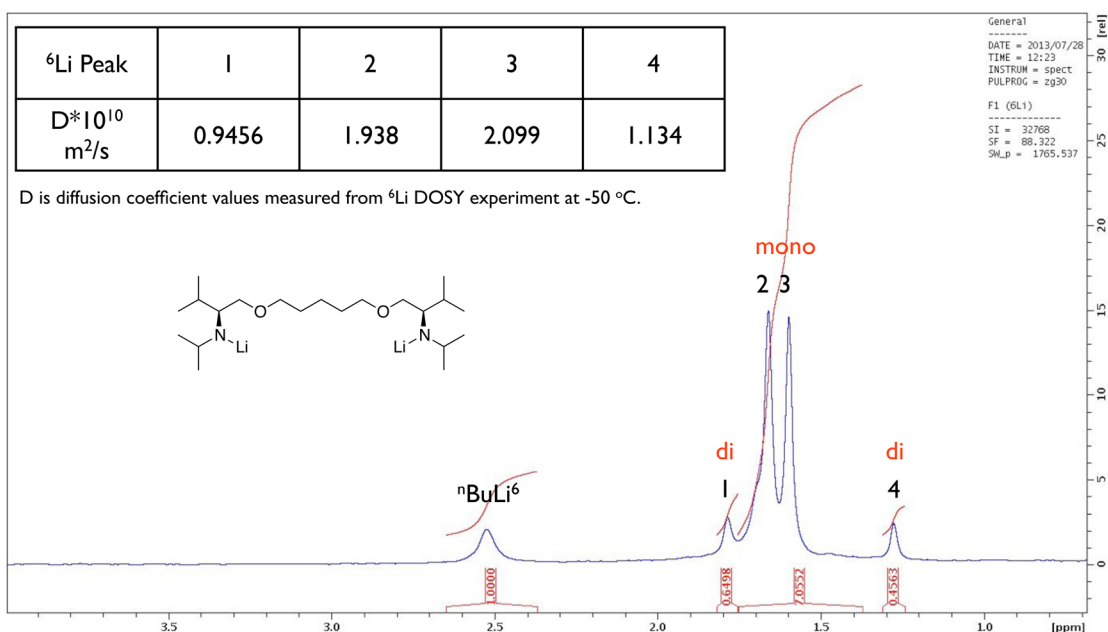


Figure 18. ${}^6\text{Li}$ NMR of dilithiated-10 in $\text{THF-}d_8$ at $-50\text{ }^\circ\text{C}$ and diffusion coefficient values of each ${}^6\text{Li}$ peak (mono = monomer; di = dimer).

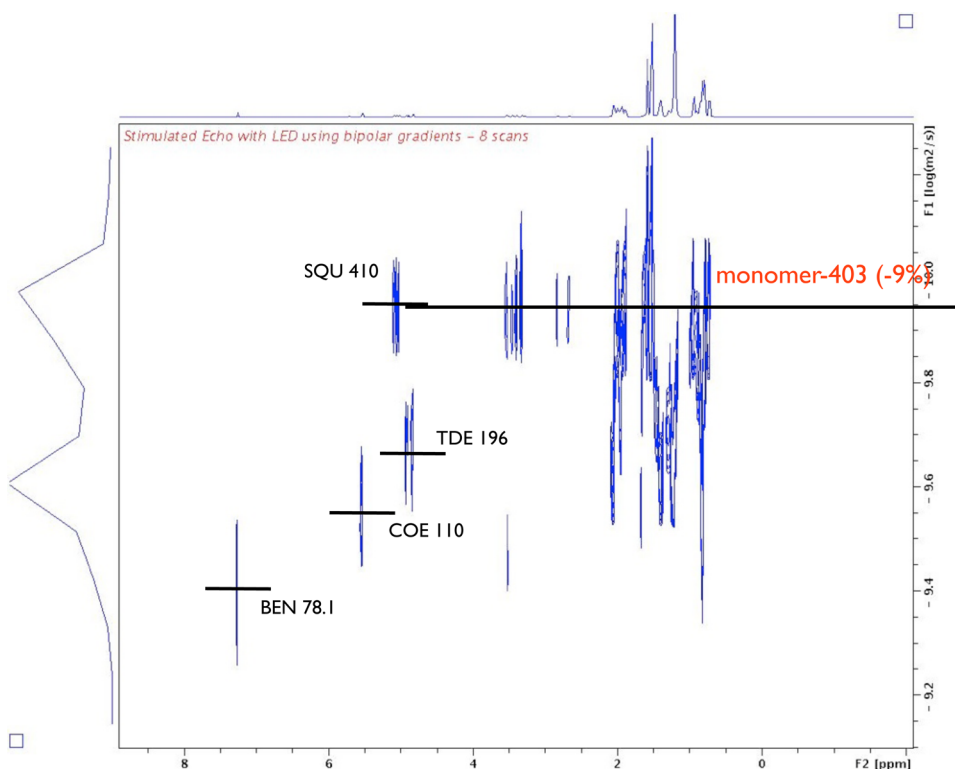


Figure 19. ${}^1\text{H}$ DOSY (with internal references) of dilithiated-10 in $\text{THF-}d_8$ at $-70\text{ }^\circ\text{C}$.

atmosphere was slowly added 2 equiv of *n*-BuLi. The reaction mixture was allowed to stir at $0\text{ }^\circ\text{C}$ until a white precipitate formed. Anhydrous diethyl ether was then added slowly to the mixture until all of the precipitate dissolved into the solution and the solution became clear. XRD quality crystals were grown when the solution was stored at $-20\text{ }^\circ\text{C}$ overnight.

General Procedures for the Crystallization of Lithium Chiral Diamides 13b. To a solution of the chiral diamine 9 (0.05 g) in 1 mL of diethyl ether at $0\text{ }^\circ\text{C}$ under Ar atmosphere was slowly added 2 equiv of *n*-BuLi. The reaction mixture was allowed to stir at $0\text{ }^\circ\text{C}$ until a white precipitate formed. Anhydrous THF was

then added slowly to the mixture until all of the precipitate dissolved into the solution and the solution became clear. XRD quality crystals were grown when the solution was stored at $-20\text{ }^\circ\text{C}$ overnight.

■ ASSOCIATED CONTENT

📄 Supporting Information

NMR and crystallographic data. This material is available free of charge via the Internet at <http://pubs.acs.org>. CCDC 961338, 961339, 961340, 961341, 961342, 961343, and 961344 contain complete crystallographic data for this

paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

This work was supported through NSF grant 1058051 to P.G.W.

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