N,*O*-Dilithio-2-(*N*-methylamino)ethanol: An Intramolecular Mixed Aggregate

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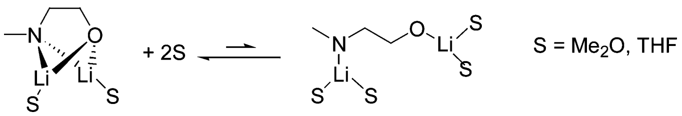

Density functional theory and infrared spectroscopy were used to determine the structure of *N*,*O*-dilithio-2-(*N*-methylamino)ethanol, a mixed intramolecular aggregate. The calculations indicated that the cyclic form of this compound is more stable than the open form, and that conclusion is consistent with the infrared spectra. The solid-state spectra showed lower Li−N and Li−O vibrational frequencies than were calculated for the gas phase, which is consistent with coordination of lithium to electronegative atoms on adjacent molecules in the solid state.

Introduction

Mixed aggregates are complexes between different lithium compounds with chemical properties that are different from those of either component. The changes in chemical properties may be minor, with reactivity of the mixed aggregate differing only slightly from that of the parent organolithium compound, or the mixed aggregate may cause major changes in chemical reactivity. The formation of mixed aggregates is often discovered by empirical observation of how changes in reaction conditions change the course of reactions. For example, the use of highly purified lithium reagents may yield a different product distribution than that obtained from reagents that have been exposed to small amounts of air, or from alkyllithium compounds that contain residual lithium halides. Many organic reactions are performed in the presence of lithium salts because the salts generate higher yields or purer products, although the mode of action remains unknown.[1−5]

Mixed aggregates may be formed in a number of ways. Lithium salts or other organic lithium compounds may be intentionally added to the reaction mixture based on empirical observations of their effects on reactivity. This had been common practice even before the structure of mixed aggregates were known, and even today, lithium salts are commonly used in synthesis without a detailed understanding of mixed aggregate formation in the specific systems of interest. Mixed aggregates may be formed inadvertently from impurities in the reaction mixture. These include residual lithium halides formed in the preparation of alkyllithiums, lithium oxides and lithium hydroxide from exposure of alkyllithiums to small amounts of air, and the use of an excess of alkyllithium or lithium dialkylamide base in synthetic reactions. Finally, mixed aggregates may be formed during the course of a reaction from the newly formed lithium-containing products, such as a newly formed lithium enolate generated by lithium diisopropylamide (LDA). Several such lithium dialkylamide−lithium enolate mixed aggregates have been characterized and often result in autocatalysis, autoinhibition, or changes in the course of enolization reactions as the reaction progresses. Common applications include polymer preparation, stereoselective synthesis, and changes in reaction rates caused by mixed aggregates.

Because mixed aggregate formation can change the reaction mechanism and product distribution during the course of a reaction, it would be beneficial to synthesize a stable, intramolecular mixed aggregate whose structure will not change due to formation of other mixed aggregates. Such a novel mixed aggregate is reported here, which was characterized by computational methods and infrared spectroscopy. Although this particular mixed intramolecular aggregate is likely to be of limited utility

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in synthesis because it is insoluble in THF, it serves as a model for similar systems that may be soluble.

Computational Methods

All geometry optimizations and frequency calculations were performed using Gaussian 98 or Gaussian 03[6] Solvation was modeled by microsolvation with explicit dimethyl ether or THF ligands on the lithium atoms. Dimethyl ether is often used to approximate the effects of coordinated THF ligands because of the lower computational cost. Although the use of continuum solvent models in combination with microsolvation sometimes generates slightly better energies than microsolvation alone, the continuum solvent models have proven inconsistent with lithium compounds and were not used in this study. The free energies of each species were obtained by adding the thermal correction to the free energy, obtained from the frequency calculations, to the calculated internal energies.

All frequency calculations in this paper were carried out for a temperature of 200 and 298 K. The standard-state molar free energy of a solute in the liquid phase at these temperatures are given by $G^{o}_{T}(\text{liq}) = G^{o}_{T}(\text{gas}) + \Delta G^{o}_{S}$ ($T = 200$ or 298 K)where liq denotes a solute in the liquid phase and ΔG^{o}_{S} is the standard-state free energy of solvation. The microsolvation model assumes that ΔG^{o}_{S} is adequately represented by the coordinated ethereal ligands, so that $G^{o}_{T}(\text{liq}) \approx G^{o}_{T}(\text{gas})$ of the "supermolecule" composed of the organolithium compound plus its coordinated ethereal ligands. Furthermore, $G^{o}_{T}(\text{gas}) = E_{en} + E^{vib}_{0} + G^{trans,o}_{T} + G^{rot}_{T} + G^{vib}_{T} + RT$ where R is the gas constant. The individual terms were calculated as follows:

E_{en}, the electronic energy plus nuclear repulsion, by the B3LYP hybrid density functional method[7,8] with the 6-31+G(d) basis set.[9,10]

E^{vib}_{0}, the y = unscaled zero point energy, by B3LYP calculations with the MIDIX[11] basis set.

$G^{trans,o}_{T}$, the standard-state thermal translational energy for a standard state of 1 mol /L (not 1 atm) from the masses.

G^{rot}_{T}, the thermal rotational free energy, from B3LYP/MIDIX geometries.

G^{vib}_{T}, the thermal vibrational free energy, from unscaled B3LYP/MIDIX vibrational frequencies.

ΔG^{o}_{S}, from B3LYP/6-31+G(d) microsolvated calculations, with a gas-phase standard state as specified above and a liquid-phase standard state of 1 mol/L.

The formulas given above are correct for solutes and will be applied to $(\text{RLi})_n$(liq) and $(\text{RLi})_n{\cdot}m\text{E}$(liq), where R is an alkyl group and E is an ether molecule. However, for E(liq), since E is the solvent we must use a standard state of the pure liquid. This requires an extra term:[12] $G^{o}_{S}(\text{solvent}) = G^{o}_{S}(\text{liq}) + RT \ln M^{o}_{liq}/M^{o}_{solvent}$ where M^{o}_{liq} is the standard state molarity of liquid solutes (taken as 1 M in this work) and $M^{o}_{solvent}$ is the molarity of the pure THF solvent, which was calculated in each case from its tabulated density at 200 or 298 K. This term is numerically equal to −1.0273 kcal/mol per THF at 200 K and −1.4884 kcal/mol at 298 K.

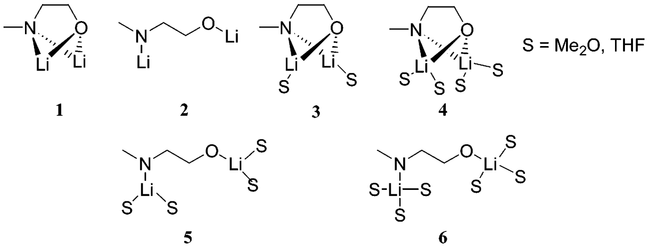

FIGURE 1. Possible structures for gas-phase and solvated *N*,*O*-dilithio-2-(*N*-methylamino)ethanol.

TABLE 1. Third and Fourth Solvation Free Energies of 3

solvent	T (K)	ΔG of solvation, kcal/mol
Me_2O	200	9.33
Me_2O	298	18.53
THF	200	1.63
THF	298	11.28

TABLE 2. Fifth and Sixth Solvation Free Energies of 5

solvent	T (K)	ΔG of solvation, kcal/mol
Me_2O	200	9.35
Me_2O	298	18.72
THF	200	5.17
THF	298	14.19

Results and Discussion

The mixed intramolecular aggregate, *N*,*O*-dilithio-2-(*N*-methylamino)ethanol, could potentially exist as either a cyclic (**1**) or open form (**2**). Furthermore, the cyclic form may be unsolvated or solvated with one ethereal ligand (dimethyl ether or THF) per lithium (**3**) or two ligands per lithium (**4**). Likewise, the open form may be solvated with two (**5**) or three (**6**) ligands per lithium. These possible structures are illustrated in Figure 1. The third and fourth solvation free energies of **3** are listen in Table 1 according to the reaction $\mathbf{3} + 2\text{S} \rightarrow \mathbf{4}$; S = Me_2O, THF.

The data in Table 1 show that THF binds more strongly to lithium than dimethyl ether despite its larger size. Even so, the cyclic intramolecular mixed aggregate is predicted to exist mostly as a disolvate at 200 K and entirely as a disolvate at 298 K. The temperature dependence of the solvation number can be understood from the loss in translational entropy of two solvent molecules in going from the disolvate to the tetrasolvate.

The solvation state of the open form (**5**) was similarly predicted from the calculations, as shown in Table 2 according to the equation $\mathbf{5} + 2\text{S} \rightarrow \mathbf{6}$. With both dimethyl ether and THF as the solvent, the open form was shown to exist exclusively as the tetrasolvated form, and increased temperatures make the hexasolvate even more energetically unfavorable.

The calculated free energies for the ring opening reactions of the cyclic intramolecular mixed aggregate

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TABLE 3. Ring-Opening Free Energies of the Unsolvated and Disolvated Mixed Intramolecular Aggregate in the Gas Phase and in Solution

solvent	*T* (K)	Δ*G* of ring opening, kcal/mol
gas	200	28.53
gas	298	27.94
Me_2O	200	23.63
Me_2O	298	30.99
THF	200	15.24
THF	298	23.45

TABLE 4. Ring-Opening Free Energies of the Tetrasolvated Mixed Intramolecular Aggregate

solvent	*T* (K)	Δ*G* of ring opening, kcal/mol
Me_2O	200	14.29
Me_2O	298	12.45
THF	200	13.60
THF	298	12.27

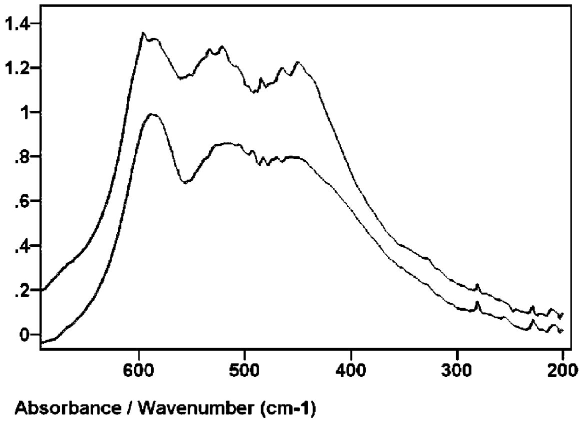

FIGURE 2. Infrared spectra of solid *N*,*O*-dilithio-2-(*N*-methylamino)ethanol. Top: sample prepared with excess THF. Bottom: sample prepared without THF

are shown in Table 3, for the equations **1** → **2** and **3** + 2S → **5**, for the gas-phase and solution reactions, respectively. The calculated energies indicate that the cyclic form exists almost exclusively in both the gas phase and in solution. Furthermore, the lack of significant temperature dependence of the ring opening free energy in the gas phase suggests that the solution temperature dependence is almost entirely due to the change in the number of coordinating solvent molecules in the cyclic and open forms. This point is further illustrated when comparing the ring-opening free energies of the tetrasolvated cyclic and tetrasolvated open forms, as shown in Table 4, in which the temperature dependence is less than 2 kcal/mol over a 98° temperature range.

TABLE 5. Observed and Calculated Frequencies (cm^{-1}) Involving Li−N and Li−O Vibrations

vibration	obsd	calcd monomer gas	calcd monomer THF	calcd dimer
1	454	650	372	262
2	517	665	525	331
3	587	727	547	389
4			644	446
5			654	574
6				641
				681
				811

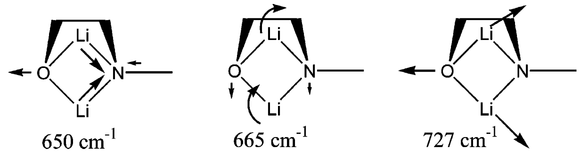

FIGURE 3. Calculated Li−N and Li−O vibrations of *N*,*O*-dilithio-2-(*N*-methylamino)ethanol.

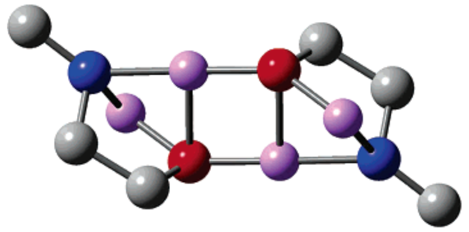

FIGURE 4. Optimized geometry of the *N*,*O*-dilithio-2-(*N*-methylamino)ethanol dimer. Hydrogens omitted for clarity. Key: gray, carbon; red, oxygen; blue, nitrogen; violet, lithium.

The infrared spectra of solid *N*,*O*-dilithio-2-(*N*-methylamino)ethanol are shown in Figure 2. The top spectrum was prepared in a solution containing THF and the bottom spectrum is of a THF free sample. Infrared spectra of dilithio-*N*,*N*′-dimethyl-1,3-propanediamine have previously been reported in solution[13] and some importance differences are noted here. First, in the solid phase the THF containing sample and the THF free sample gave nearly identical spectra, while in solution, the dilithiodiamine spectra showed significant differences in the Li−N stretching vibrations in the presence and absence of THF. Second, in the dilithiodiamine case, the calculated and observed frequencies matched up well, while in the solid sample of *N*,*O*-dilithio-2-(*N*-methylamino)ethanol, the observed frequencies were lower than the calculated gas-phase frequencies for vibrations involving Li−N and Li−O movement, as shown in Table 5. The calculated vibrations involving large lithium movements in the gas phase are shown in Figure 3. Both of these differences can be understood as a result of the latter compound being a solid. Unless THF is part of the crystal lattice, it will not have a major effect on the vibrational frequencies, and even if it is incorporated into the crystal structure, its effect on the frequencies may be significantly smaller than coordinating oxygen or nitrogen atoms from neighboring molecules. Thus, the samples prepared with and without THF have very similar spectra. The crystal structure with the coordination from electronegative atoms on neighboring molecules will also tend to restrict the movement of the lithium atoms, resulting in lower vibrational frequencies. This hypothesis was tested by geometry optimization and frequency calculation of the *N*,*O*-dilithio-2-(*N*-methylamino)ethanol dimer, which serves as an approximation for a partial unit cell in the solid state. Although the dimer is a very crude model for the solid state, it did result in a lowering of most vibrational frequencies involving major Li−N and Li−O movement, compared to the gas-phase calculation. The optimized geometry of the dimer is shown in Figure 4. The calculated frequencies of the hypothetical THF solution of *N*,*O*-dilithio-2-(*N*-methylamino)ethanol are also lower than those in the gas phase, again consistent

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with lithium coordination to the THF oxygen atoms. Calculations on the open form revealed no significant infrared active vibrations in the same region.

Conclusions

N,*O*-Dilithio-2-(*N*-methylamino)ethanol exists exclusively as a THF-insoluble cyclic mixed intramolecular aggregate. Samples prepared with and without THF show nearly identical solid-state infrared spectra, which suggests that coordination of the lithium atoms by electronegative atoms on neighboring molecules has a larger effect on the vibrational frequencies than any coordination by THF. The observed frequencies involving Li−N and Li−O movement are lower than the calculated frequencies in the gas phase.

Experimental Section

N,*O*-Dilithio-2-(*N*-methylamino)ethanol is a THF-insoluble white solid. It was prepared as a Nujol mull for infrared analysis as follows:

Without THF. 2-(*N*-Methylamino)ethanol (5.0 mmol) was added to 2.0 mL of Nujol under dry nitrogen. Butyllithium (1.6M in hexanes, 10.5 mmol) was added while swirling the flask, and upon completion of the reaction the hexane was removed under a stream of nitrogen, leaving a suspension of *N*,*O*-dilithio-2-(*N*-methylamino)ethanol in Nujol.

With THF. The *N*,*O*-dilithio-2-(*N*-methylamino)ethanol was prepared as above, but with 2.0 mL of THF added to the mixture prior to butyllithium addition. The hexane and excess THF were removed under a stream of nitrogen.

The suspensions of *N*,*O*-dilithio-2-(*N*-methylamino)ethanol were transferred in a glovebag under argon and ground to a mull for infrared analysis. The infrared spectra were acquired on a spectrometer with a polyethylene liquid cell which is transparent in the spectral region of interest, 200−700 cm^{-1}. One hundred scans were co-added to obtain each spectrum with a 4 cm^{-1} resolution.

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Supporting Information Available: Tables of optimized geomerties and energies of compounds **1**−**6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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