Solvent Effects on the Aggregation State of Lithium Dialkylaminoborohydrides

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DFT calculations were performed to determine the effects of ethereal solvents on the aggregation state of lithium dialkylaminoborohydrides (LABs). The calculations included dimerization energies in the gas phase, with continuum solvation only, microsolvation with coordinating ethereal ligands, and a combination of the microsolvation and continuum models. The continuum model alone overestimates the stability of the dimers, apparently due to the lack of steric effects from the coordinating ethereal ligands. The use of the combined microsolvation and continuum solvation models predicts lithium dimethylaminoborohydride to be a mixture of monomer and dimer in THF, and more sterically hindered lithium aminoborohydrides to exist primarily as monomers. The kinetics of amination of 1-chlorodecane by lithium dimethylaminoborohydride showed no detectable change in reaction rate with time, suggesting that the LAB reagent may exist primarily as a monomer in THF.

Introduction

Lithium dialkylaminoborohydrides (LAB) are versatile synthetic reagents with the dual properties of nitrogen nucleophiles and hydride reducing agents. Among the reactions of LAB reagents are reduction of a variety of carbonyl compounds, amination of primary alkyl halides and sulfonates, and tandem amination and reduction of halogentated benzonitriles.[1–12] The mechanism of these reactions is not yet well understood, but could possibly occur via either the monomeric or dimeric form of lithium dialkylaminoborohydrides.

Our previous work found that lithium dimethylaminoborohydride exists largely as a hydrogen-bridged dimer

(**1**) in the gas phase.[13] The calculations also suggested that the dimer may coexist in equilibrium with the monomer (**2**) in ethereal solvents, particularly with more
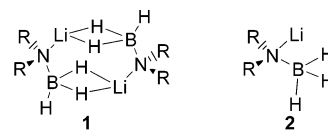
sterically hindered lithium dialkylaminoborohydrides. That study used a common but crude microsolvation solvation model, which consisted of dimethyl ligands coordinated to the lithium atoms in gas-phase supermolecules,[14–18] which are presumed to serve as good models for the solution behavior of organolithium compounds. The choice of ligands is often determined by the computational cost and chemical intuition. For example, dimethyl ether is frequently used in place of THF because of the lower computational cost. Both ligands have similar dielectric constants and have similar steric bulk in the vicinity of the coordinated lithium atom. Although water has been occasionally used as a model ligand, it is a poor

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choice because of the higher dielectric constant, and because of computational artifacts resulting from hydrogen bonding. The use of these simple models was justified as being the best available, and to date little has been done to test the validity of the approximations of this model. Microsolvation with dimethyl ether instead of THF makes many problems in organolithium chemistry tractable with ab initio methods, and microsolvation is likely to capture at least some of the solvent dielectric effects.

The importance of solvation in organolithium chemistry cannot be overestimated. Solvent effects dramatically influence the aggregation state and reactivity of alkyllithiums, lithium dialkylamides, and other organolithium compounds.[19-23] Solvation of organolithium compounds is a complex issue, and no single existing solvation model is appropriate for all such compounds. Hydrocarbon solvents involve little or no coordination to the lithium atoms, and solvent effects consist primarily of dielectric polarization, dispersion, and cavitation. Hexamethylphosphoramide (HMPA) is at the other extreme, coordinating so strongly to lithium that two-bond NMR spin coupling can be observed between lithium and phosphorus.[24,25] Ethereal solvents such as THF are intermediate in their binding ability with lithium. Rapid exchange of THF ligands prevents the observation of lithium−carbon spin coupling, although coordination of several ethers to lithium dialkylamides has been observed indirectly.[26,27] The steric effects of coordinating ether ligands are important in reproducing the aggregation state of organolithium compounds, and may not be adequately represented by continuum solvent models. On the other hand, bulk solvent effects may not be adequately represented by microsolvation, particularly the effects of the second solvation sphere. In this paper we compare the effects of continuum solvation alone, microsolvation alone, and the combined use of both models. In particular, the following questions will be addressed.

(1) Is microsolvation by ethereal ligands alone sufficient to model the solvent effects on the aggregation state?

(2) Can solvent effects on alkyllithium aggregation be adequately represented by the CPCM continuum solvent model without including microsolvation?

(3) Does microsolvation by the computationally cheaper dimethyl ether ligand generate results comparable to microsolvation by THF?

Computational Methods

All calculations were performed with Gaussian 98 revisions A.9 and A.10, and the continuum solvation calculations were performed with the Conductor-like Polarizable Continuum Model (CPCM)[28] with parameters for THF at 298 K. In this model, the dielectric polarization effects are approximated by a cavity model in a continuous dielectric. The mirror charges, induced in the dielectric by partial atomic charges, reside on the surface of the dielectric. Thus, the conductor-like terminology is used for the CPCM model. In all continuum solvent calculations the default UAHF force field atomic radii were used, which are identical with those of the UFF force field for the atoms used in this study. The radii are 1.950 Å for methyl and methylene groups, 1.500 Å for oxygen, and 1.370 Å for lithium.[29] The dielectric constant parameters for THF were 7.58 (default) at 298 K. The solution energies reported were the "total free energy in solution", which is actually a hybrid of electronic internal energy and free energy of solvation. The solvation free energy terms were obtained directly from the CPCM calculations, and include terms for solute−solvent interaction, solute polarization, cavitation energy, dispersion energy, and repulsion energy. Microsolvation of the lithium dialkylaminoborohydrides used either dimethyl ether or THF ligands. Each molecule was optimized in the gas phase, with or without ethereal ligands, followed by single-point calculations with the CPCM continuum solvation model. All geometry optimizations were performed with use of the Berny algorithm, using redundant internal coordinates. All geometry optimizations and solvated single-point energy calculations were performed with the B3LYP hybrid density functional method[30] and the 6-31+G(d) basis set.[31] All reported energies include zero-point energy corrections.

Experimental Methods

The kinetic reaction order in lithium dimethylaminoborohydride was determined for the amination of 1-chlorodecane The reaction was monitored under pseudo-first-order conditions in alkyl halide by titration of the remaining LAB reagent with *tert*-butyl alcohol and a 1,10-phenanthroline indicator, and the reaction order was determined from a plot of −ln([LAB]/[LAB]$_0$) vs time. Lithium dimethylaminoborohydride (approximately 1 M, 4.0 mL) was added to 8.0 mL of THF and titrated against a solution of *tert*-butyl alcohol (0.0125 N) and 1,10-phenanthroline indicator (0.01 M) in THF. Note: *tert*-Butyl alcohol reacts rapidly with 2 mol of LAB hydride ion. 1-Chlorodecane (8.2 mL) was added at 25.0 °C and aliquots were titrated against 1.0 mL of the *tert*-butyl alcohol-indicator solution.

Results and Discussion

Geometry optimizations were performed for lithium dimethylaminoborohydride, lithium diisopropylaminoborohydride, lithium pyrrolidinoborohyride, and lithium morpholinoborohyride. Each of the lithium dialkylaminoborohydride dimers optimized to structures in which the lithium and boron atoms are bridged by a pair of hydrogen atoms, similar to the three-center-two-electron bonds in diborane. The optimized geometries of the THF disolvated monomers are shown in Figure 1, and the dimers in Figure 2.

Three different stationary points were located for the lithium morpholinoborohydride monomer. The most stable form was the chair conformation of the morpholine ring. The least stable form had the borane coordinated to the

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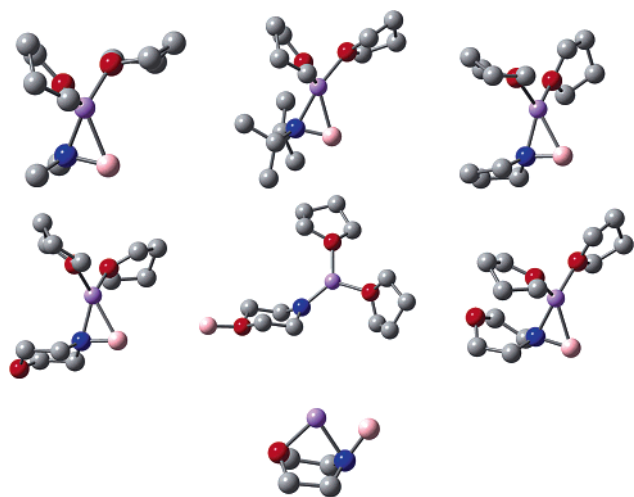(27) Lucht, B. L.; Collum, D. B. *J. Am. Chem. Soc.* **1995**, *117*, 9863.

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FIGURE 1. Optimized geometries of lithium dialkylamide monomers: top left, lithium dimethylaminoborohydride; top center, lithium diisopropylaminoborohydride; top right, lithium pyrrolidinoaminoborohydride; middle row left, lithium morpholinoborohydride (chair); middle row center, lithium morpholinoborohydride with BH3 coordinated to oxygen; middle row right, lithium morpholinoborohydride twist-boat; third row, lithium morpholinoborohydride twist-boat gas phase with Li−O coordination. Gray, carbon; white, boron; red, oxygen; blue, nitrogen; violet, lithium.

morpholine oxygen instead of the nitrogen, represented by BH_3−O in Table 1. In the gas phase the morpholine could exist in a boat conformation with the oxygen chelating the lithium atom. The dimethyl ether and THF solvated analogues of that structure optimized to a twist-boat conformation with little or no chelation of the lithium by oxygen. An analogous gas-phase chelated boat conformation was found for the gas-phase dimer, and microsolvation of that structure by dimethyl ether or THF resulted in an unchelated twist-boat conformation. The relative energies of the lithium morpholinoborohydride monomers and dimers are shown in Table 1. In the monomer the boat conformer was less stable than the chair by about 6−8 kcal/mol with and without solvation by ethereal ligands, suggesting that the additional stability from chelation is offset by the additional ring strain of the boat or twist-boat conformation. In the gas-phase dimer, the chelated boat conformation is less stable than the chair conformation by only 1−2 kcal/mol, but it becomes less stable when ethereal ligands are added. The energy difference between the gas-phase boat structures with and without use of the continuum solvation model is only 0.6 kcal/mol, compared to 10−12 kcal/mol when explicit solvating ligands are used. Thus, the continuum solvation model alone does not account for the steric effects of coordinated solvent molecules on the stability of the chair conformer.

The gas-phase dimerization energies of lithium dialkylaminoborohydrides were calculated. To determine how well the CPCM continuum model works on this system, the dimerization energies were also calculated with the continuum solvation parameters for THF on the gas-phase geometries. The results are shown in Table 2. Although the calculated dimerization energies were less exothermic by about 10 kcal/mol when the continuum solvation model is used, the lithium aminoborohydrides
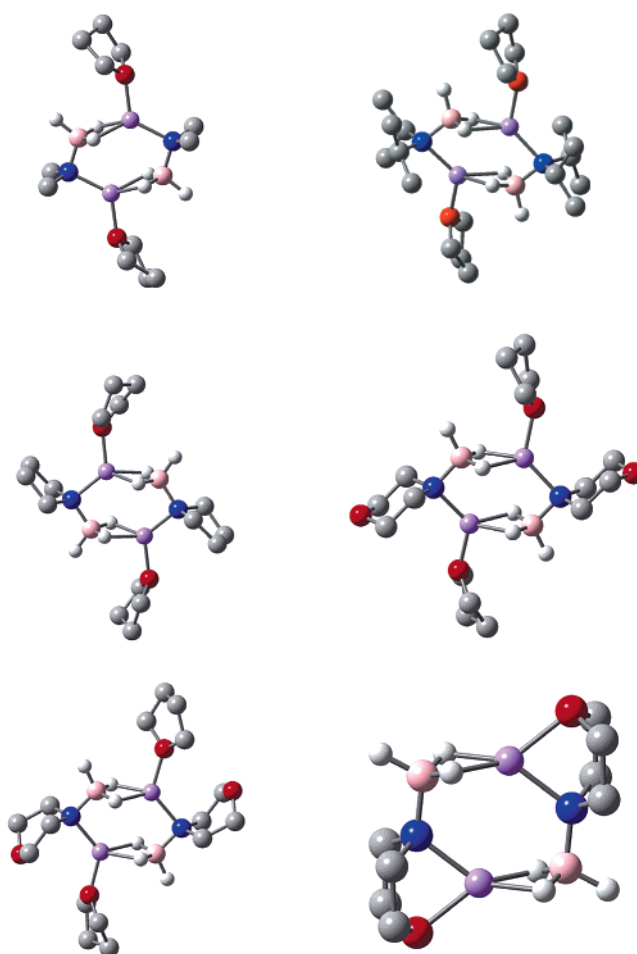
FIGURE 2. Optimized geometries of lithium dialkylamide dimers: top left, lithium dimethylaminoborohydride; top right, lithium diisopropylaminoborohydride; middle left, lithium pyrrolidinoaminoborohydride; middle right, lithium morpholinoborohydride (chair); bottom left, lithium morpholinoborohydride twist-boat; bottom right, lithium morpholinoborohydride boat in the gas phase with Li−O coordination.

TABLE 1. Relative Energies of Lithium Morpholinoborohydride Structures (kcal/mol)

structure	monomer chair	monomer boat	monomer BH_3−O	dimer chair	dimer boat
gas	0	6.6	40	0	1.0
gas + CPCM	0	7.9	33	0	1.7
Me_2O	0	6.3	35	0	9.7
Me_2O+CPCM	0	7.1	34	0	12
THF	0	5.6	35	0	12
THF +CPCM	0	6.9	34	0	14

are predicted to exist entirely as dimers in solution by this model.

The calculated dimerization energies of microsolvated lithium aminoborohydrides are shown in Table 3. When microsolvation alone was used, the dimerization energies were exothermic with dimethyl ether ligands and endothermic with THF. Examination of the lithium−oxygen bond distances in the microsolvated monomers and dimers showed that in each case, the THF oxygen was 0.02−0.03 Å closer to the lithium atom than with dimethyl ether. The more strongly binding THF ligand

TABLE 2.   Dimerization Energies of Lithium Dialkylaminoborohydrides without Microsolvation (kcal/mol)

$LiNR_2Li-BH_3$	solvation model	dimerization energy
R = methyl	gas	−35
R = methyl	gas + CPCM	−25
R = isopropyl	gas	−31
R = isopropyl	gas + CPCM	−21
R = −CH_2CH_2CH_2CH_2−	gas	−35
R = −CH_2CH_2CH_2CH_2−	gas + CPCM	−25
R = −CH_2CH_2OCH_2CH_2−	gas	−34
R = −CH_2CH_2OCH_2CH_2−	gas + CPCM	−24

TABLE 3.   Dimerization Energies of Lithium Dialkylaminoborohydrides with Microsolvation by Dimethyl Ether and THF (kcal/mol): 2 Monomer·2S → Dimer·2S + 2S (S = Me_2O, THF)

Li NR_2Li−BH_3	solvation model	dimerization energy
R = methyl	Me_2O only	−3.8
R = methyl	Me_2O + CPCM	−1.3
R = methyl	THF only	4.5
R = methyl	THF + CPCM	−0.11
R = isopropyl	Me_2O only	−2.2
R = isopropyl	Me_2O + CPCM	2.4
R = isopropyl	THF only	5.3
R = isopropyl	THF + CPCM	3.6
R = −CH_2CH_2CH_2CH_2−	Me_2O only	−3.1
R = −CH_2CH_2CH_2CH_2−	Me_2O + CPCM	0.017
R = −CH_2CH_2CH_2CH_2−	THF only	5.4
R = −CH_2CH_2CH_2CH_2−	THF + CPCM	2.2
R = −CH_2CH_2OCH_2CH_2−	Me_2O only	−1.4
R = −CH_2CH_2OCH_2CH_2−	Me_2O + CPCM	1.8
R = −CH_2CH_2OCH_2CH_2−	THF only	6.7
R = −CH_2CH_2OCH_2CH_2−	THF + CPCM	2.7

is therefore expected to favor the monomer, which is more highly solvated than the dimer.

Use of the CPCM continuum model with the dimethyl ether microsolvated structures appears to favor the monomer, while it tends to stabilize the dimer with the THF microsolvated molecules. Because the THF microsolvated monomer is already stabilized by solvation relative to the dimethyl ether solvate, it is reasonable to expect the continuum solvation model to stabilize the dimethyl ether microsolvated monomer more than the THF microsolvated one. Conversely, continuum solvation will stabilize both the dimethyl ether and THF microsolvated dimers, and the net result will be to favor the monomer with dimethyl ether microsolvation and the dimer with THF microsolvation.

Several factors affect the accuracy of the calculations. First, the microsolvated structures are not static, but represent a typical conformation of the molecules with coordinated solvent ligands. The energy required for rotation about an oxygen−lithium bond is typically a fraction of a kelocalorie per mole, and conformational effects are not expected to have a large influence on the relative energies of the aggregates and solvates. Neither the microsolvation nor the continuum solvation models are perfect and here arises one of the most significant uncertainties in the computational accuracy. However, the combined use of both models does address the steric effects of coordinated solvent ligands, bulk dielectric effects, and solvation of other parts of the molecule that are not microsolvated by coordinating ethers. Although

the experimental data for this particular system are limited, the combined models have done a good job in reproducing the experimental aggregation states of alkyllithiums.[32] The same investigation showed that although the dielectric constant of THF increases with decreasing temperature, this has a minimal effect on the alkyllithium aggregation state even over a 75-deg temperature range. Reactions with LAB reagents are normally performed at temperatures between 0 and 35 °C, and the temperature dependence of the dielectric constant will have a minimal effect on the aggregation state over this temperature range.

Entropy effects on the dimerization energies are not explicitly taken into account in these calculations. As the dimers are disolvated, dimerization results in a gain of translational entropy of THF, estimated to be 12.4 eu,[33] or about 3.4 kcal/mol at a typical reaction temperature of 273 K. This entropy gain will be largely offset by the loss of translational entropy of the monomers upon dimerization. Upon dimerization two particles (disolvated dimers) rearrange into three (disolvated dimer + ether), resulting in a net entropy gain of one particle, or about 3 kcal/mol. However, the ether molecules are not tightly bound to lithium and are rapidly exchanged, as evidenced by several NMR experiments with lithium amides.[34−36] The gain in translational entropy is therefore likely to be less than 3 kcal/mol. Thus, the actual free energies of dimerization are not expected to be greatly different from the calculated dimerization energies.

The question remains as to whether the lithium dialkylaminoborohydrides are monomeric or dimeric in solution. CPCM calculations imply a standard state of a 1 molar solution, and dilution will favor the monomeric forms. The calculations using the combined continuum and THF microsolvation models predict that lithium dimethylaminoborohydride will exist as a monomer− dimer equilibrium in THF, and that the more sterically hindered analogues will exist primarily as monomers. If lithium dimethylaminoborohydride is largely dimeric in a 1 M solution in THF, more monomer should form as the solution becomes increasingly dilute in LAB, e.g., as LAB reacts. Thus, the reaction rate should change if the reaction took place largely through the dimer initially. This hypothesis was tested by reaction of lithium dimethylaminoborohydride with 1-chlorodecane. A first-order plot of $-\ln[LAB]/[LAB]_0$ vs time is shown in Figure 3. The graph is linear with no detectable change in rate as the reaction progressed, although slight curvature cannot be ruled out. A linear plot is consistent with the following possibilities. First, the monomer−dimer mixture reacted via the monomer and continued to react via the monomer at low concentrations of LAB; second, the LAB reagent was primarily monomer at the outset; or finally, by an unlikely coincidence the monomer and dimer were nearly

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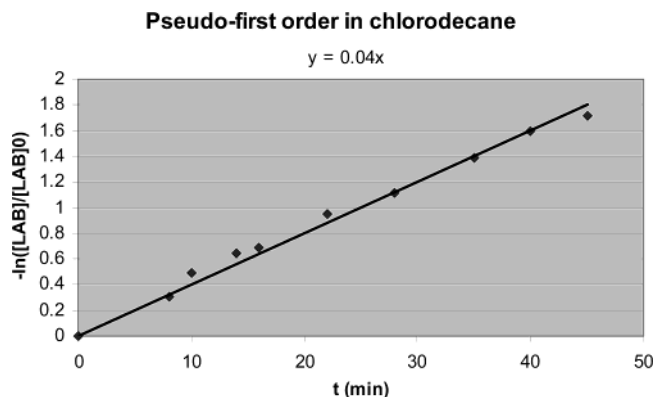
FIGURE 3. Kinetics plot of the amination of 1-chlorodecane by lithium dimethylaminoborohydride.

equally reactive. Our preliminary calculations of transition structures indicated that the reaction via the dimer has a lower activation energy by about 6 kcal/mol than the monomer, making the first and third scenarios unlikely.[33] Although slight curvature of the kinetic plot from a monomer–dimer equilibrium cannot be ruled out, we tentatively conclude that the lithium aminoborohydrides exist primarily as monomers in THF solution.

Conclusions

Solvation of lithium dialkylaminoborohydrides is best represented by a combination of microsolvation with coordinating ligands and a continuum solvation model. The continuum model alone fails to adequately represent the steric effects of coordinated ether ligands, while the microsolvation model alone does not sufficiently represent the second solvation sphere, effects of the bulk dielectric, or solvation of other parts of the molecule. The combined model predicts a monomer–dimer equilibrium for lithium dimethylaminoborohydride, and predicts more hindered lithium dialkylaminoborohydrides to exist primarily as monomers. The kinetics of amination of 1-chlorodecane by lithium dimethylaminoborohydride is consistent with the monomer being the dominant species in solution, although the possibility of a monomer–dimer equilibrium cannot be ruled out.

Supporting Information Available: Tables S1–S35 of optimized geometries of lithium dialkylaminoborohydrides. This material is available free of charge via the Internet at http://pubs.acs.org.

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