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Gas-Phase Reactions of Lithium Dimethylaminoborohydride and Related Species

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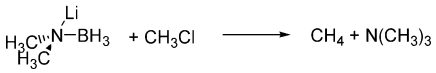
ACTIVATION BARRIERS



Ab initio and density functional theory (DFT) calculations were used to examine the mechanisms of reduction and amination of chloromethane by lithium dimethylaminoborohydride (LAB) in the gas phase. For comparison, the amination of chloromethane by lithium dimethylamide and the reduction by borane, diborane, and borohydride ions were also examined. The reduction of chloromethane by LAB occurred most readily from a conformation that allowed coordination of the lithium atom to the chloride leaving group, and the most favorable amination pathway occurred by a backside attack of the nitrogen nucleophile on chloromethane.

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 halogenated benzonitriles.[1−12] Lithium dimethylaminoborohydride reacts with benzyl halides as an amine nucleophile at 0 °C and as a hydride reducing agent at 65 °C. In this paper, we investigate the nucleophilic substitution and reduction reactions of LAB with chloroalkanes. The mechanism of these reactions is not yet well understood but could possibly occur via either the monomeric or dimeric form of lithium dialkylaminoborohydrides. Previous computational studies indicate that LAB reagents are predominantly monomeric in THF solution but largely dimeric in the gas phase.[13,14]

Although amination and reduction reactions are performed in solution, the gas-phase mechanisms are of interest for several reasons. First, the gas-phase mechanisms are expected to be similar to the solution-phase mechanisms in noncoordinating solvents. These include hydrocarbon solvents, provided that the reagents are sufficiently soluble, and unreactive halogenated solvents, such as vinyl chlorides and chlorobenzenes. These solvents may change the activation energies primarily by dielectric effects but will probably not change the basic reaction mechanisms. Second, a set of several possible reaction mechanisms is likely in the gas phase, and some of these are likely to be eliminated by steric effects from coordinating solvents such as diethyl ether and THF. By examining the gas-phase reactions, we will determine which of these mechanisms are most energetically favorable and interesting, and these will be chosen for further

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investigation in solution. Finally, the gas-phase study will provide additional data on the performance of the popular B3LYP density functional method. This method has been used in several computational studies of reaction mechanisms,[15−19] although we have recently shown that it can be unreliable for the study of lithium enolate reactions.[20]

Computational Methods

All geometry optimizations, transition structure searches, and frequency calculations were performed with the Gaussian 98 or Gaussian 03 program.[21] Transition structures were located with either the QST3 method or the further optimization of a previously located transition structure at a different level of theory using the Opt = TS keyword. Geometry optimizations were performed at the following levels of theory for both the reactants and transition structures: HF/6-31+G(d), B3LYP/6-31+G(d), and MP2/6-31+G(d). Single-point energies were obtained at the MP4/6-31+G(d)//MP2/6-31+G(d) level of theory for all species except the lithium dimethylaminoborohydride dimer and its transition structures. Harmonic frequencies of the reactants and transition structures were calculated at the HF/6-31+G(d) level on HF/6-31+G(d) optimized geometries. The thermal corrections to the free energies at 298.15 K were taken from the Hartree−Fock frequency calculations and added to the internal energies at each level of theory, to obtain the approximate free energies of each reactant and transition structure.

Results and Discussion

The activation free energies of chloromethane reduction were calculated for the lithium dimethylaminoborohydride (referred to as LAB in this paper) monomer via a conventional S_N2-like backside attack, with both anti and gauche arrangements of the H−B−N−Li dihedral angle, as shown in Figure 1. The activation free energy was also calculated for a frontside attack of the hydride nucleophile, in a transition structure analogous to that reported by Streitwieser for some ion-pair S_N2 reactions.[22] The lowest energy reaction pathway was the one with the gauche H−B−N−Li dihedral angle, as that arrangement allowed for coordination between the LAB lithium atom and the chloride leaving group. The conventional backside S_N2 attack of the hydride nucleophile in the anti conformation and the frontside attack had nearly the same activation free energies at each level of theory. The calculated activation free energies for chloromethane reduction by the LAB monomer and dimer, borane, diborane, and the borohydride ion are listed in Table 1. The highest practical level of theory was MP4 for most molecules and MP2 for the largest systems, and these were used for comparison with the other levels of theory.

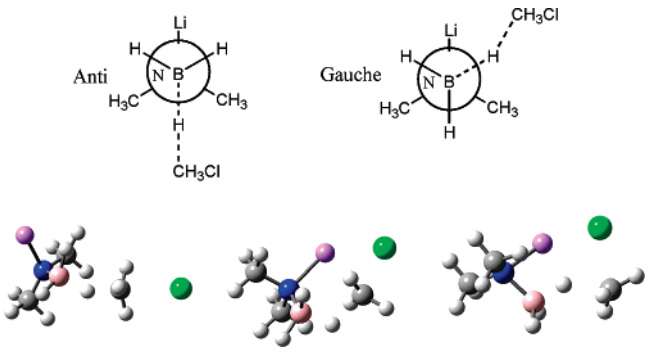

FIGURE 1. MP2 optimized transition structure geometries for chloromethane reduction by the LAB monomer. Left: anti. Center: gauche. Right: frontside attack. Gray: carbon. White: hydrogen. Pink: boron. Green: chlorine. Blue: nitrogen. Violet: lithium.

TABLE 1. Calculated Activation Free Energies (kcal/mol) for the Reduction of Chloromethane by Boron Reducing Agents

reduction	HF	B3LYP	MP2	MP4
LAB monomer anti	50.9	40.6	49.8	48.8
LAB monomer gauche	43.2	33.5	36.8	34.9
LAB monomer frontside	50.2	40.0	50.1	47.2
LAB dimer anti	51.6	40.7	49.9	
LAB dimer gauche	33.1	24.9	27.8	
LAB dimer frontside	61.5	49.0	57.7	
BH_3	75.4	50.4	57.9	56.9
B_2H_6	84.5	72.4	80.6	80.2
BH_4^-	14.6	5.79	14.8	13.7

In the gauche reaction pathway, the Hartree−Fock calculation overestimated the activation barrier compared to MP2 and MP4, as is expected for uncorrelated methods. Although B3LYP predicted a lower barrier, as is common for density functional theory (DFT) methods, the predicted barrier was only about 1.5 kcal/mol lower than that calculated by MP4. With the two higher energy pathways, the Hartree−Fock and MP2 methods generated nearly the same activation free energies, which were about 10 kcal/mol higher than the B3LYP energy.

Similar transition structures were calculated for the LAB dimers, as shown in Figure 2. Once again, the lowest

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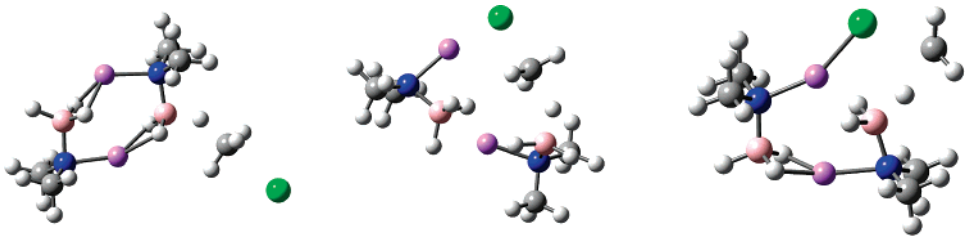

FIGURE 2. MP2 optimized transition structure geometries for chloromethane reduction by the LAB dimer. Left: anti. Center: gauche. Right: frontside attack.

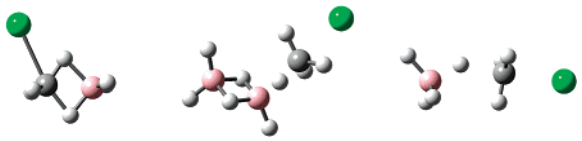

FIGURE 3. MP2 optimized transition structure geometries for chloromethane reduction by boron hydride reagents. Left: borane. Center: diborane. Right: borohydride ion.

activation free energy was found with the H−B−N−Li gauche conformation in an S_N2-like backside attack by the hydride. The chloromethane reduction via the LAB dimer was about 9 kcal/mol lower than the reaction via the monomer. This can be rationalized by the angle strain of chloromethane in the transition structure. In the dimeric gauche transition structure, the H−C−Cl bond angle is near 180° and the corresponding angle is bent in the corresponding transition structure of the monomer. In both cases, lithium coordination to the chloride leaving group appears to significantly lower the activation barrier. This lithium-leaving group coordination also explains why the frontside attack of the hydride nucleophile had nearly the same activation free energy as the anti S_N2-like backside attack in the monomer, even though a frontside attack would usually be expected to occur with a higher energy barrier.

In the gauche dimer reaction pathway, the activation barrier was overestimated by the Hartree−Fock calculation and underestimated by B3LYP, compared to MP2. In the two higher energy pathways, the Hartree−Fock overestimated the activation barriers by about 2−4 kcal/mol compared to MP2 and B3LYP underestimated the barriers by about 8−9 kcal/mol. Thus, for LAB reduction reactions, it appears that the B3LYP method can provide qualitatively correct relative activation barriers, but it is unreliable for the calculation of accurate activation free energies.

Because of the superficial similarity of LAB to other boron hydride reducing agents, activation free energies were calculated for the chloromethane reduction by borane, diborane, and a borohydride ion. The MP2 optimized transition structures are shown in Figure 3. The reaction with borane took place via an unusual transition structure that appears to be analogous to diborane. This reaction has been described in detail[23] and is shown here for completeness. The reductions of chloromethane by both borane and diborane were calculated to have high-activation free energies of 56.9 and 80.2 kcal/mol, respectively, at the MP2/6-31+G(d) level. In contrast, the reduction by the borohydride ion was

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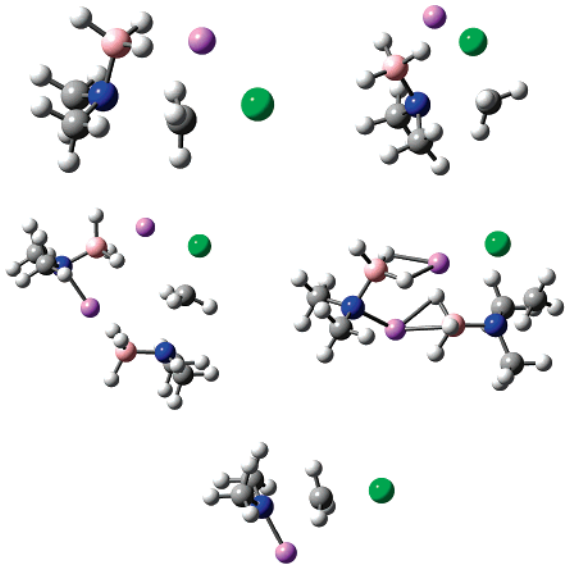

FIGURE 4. MP2 optimized transition structure geometries for chloromethane amination by LAB and LiDMA. Top left: LAB monomer, backside attack. Top right: LAB monomer, frontside attack. Middle left: LAB dimer, backside attack. Middle right: LAB dimer, frontside attack. Bottom: LiDMA amination.

calculated to have a barrier of only 13.7 kcal/mol at the same level of theory. The commonality between LAB and the borohydride ion is the extra coordinated atom with its pair of electrons, compared to borane and diborane. However, we have previously shown that reduction of chloromethane by BH_3−Me_2O or BH_3−Me_2S has an activation free energy only slightly different from that of free borane.[23] The reduction by the LAB monomer in the anti conformation can be considered analogous to reduction by borane−ether or borane−dimethyl sulfide complexes, in that no lithium coordination to the leaving group occurs. This reaction has a calculated activation barrier of 48.8 kcal/mol at the MP4 level, and this may be explained by the partial ionic character of the N−Li bond, which releases more electron density into the borane hydride donor compared to dimethyl ether or dimethyl sulfide. Lithium coordination to the chloride leaving group is possible in the gauche conformer, resulting in additional lowering of the activation barrier by about 13 kcal/mol.

Amination of alkyl halides with LAB is an important method for the preparation of tertiary amines without overalkylation to the quaternary ammonium salt. Two reaction pathways for the gas-phase amination of chloromethane were found, a backside attack in a conventional S_N2-like mechanism and a frontside attack. The

TABLE 2. Calculated Activation Free Energies (kcal/mol) for the Amination of Chloromethane by LAB and Lithium Dimethylamide

amination	HF	B3LYP	MP2	MP4
LAB monomer backside	39.7	28.5	29.6	27.8
LAB monomer frontside	58.0	42.4	47.0	43.6
LAB dimer backside	31.9	25.0	23.2	
LAB dimer frontside	64.8	49.4	51.7	
LiDMA	33.4	22.8	26.0	24.8

transition structures are shown in Figure 4, and the activation free energies are given in Table 2. For both the LAB monomer and dimer, the backside attack is the most favorable reaction pathway. However, for the monomer, the difference in the free energies of activation between the frontside and backside attacks is about 17 kcal/mol at the MP2/6-31+G(d) level and about 28 kcal/mol for the dimer. Examination of the transition structures in Figure 4 shows that, for the monomer, the N−C−Cl angle is bent away from the ideal 180° value for an S_N2 transition structure to enable lithium coordination to the chloride leaving group. In the dimer, much less bending of this angle is required for the lithium to assist the departure of the leaving group. Amination of chloromethane by lithium dimethylamide (LiDMA) occurred with an activation barrier slightly higher than that for the LAB dimer. No transition structure was found corresponding to a frontside attack by LiDMA. Compared to LAB, LiDMA is expected to be a stronger nucleophile, but the transition structure geometry does not allow for the lithium atom to assist the departure of the leaving group.

As in the reduction reactions, the Hartree−Fock calculations overestimated the activation free energies compared to MP2, and B3LYP generally gave qualitatively correct results. In one case, the B3LYP barrier was slightly higher than the MP2 barrier.

Conclusions

LAB can reduce alkyl halides by three possible pathways in the gas phase. The most favorable mechanism is a backside attack by the hydride nucleophile with a gauche conformation of the H−B−N−Li dihedral angle. This conformation allows the lithium atom to assist the departure of the chloride leaving group. The lithium atom also assisted the departure of the chloride ion in the amination reaction, and the more favorable geometry of the LAB dimer transition structure makes the dimer mechanism the most energetically favorable pathway in the gas phase. The calculated activation free energies show that LAB reagents reduce alkyl halides much more readily than borane, diborane, borane−ether, or borane−dimethyl sulfide complexes. This appears to result both from the ability of the lithium amide fragment to release electrons onto boron and from the ability of the lithium atom to assist the departure of the leaving group. Although the B3LYP DFT method often underestimates activation barriers, sometimes severely, it produced reasonable qualitative results for the compounds of this investigation.

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Supporting Information Available: Tables of MP2 optimized geometries and energies of all reactants and transition structures. This material is available free of charge via the Internet at http://pubs.acs.org.

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