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Novel Diborane-Analogue Transition Structures for Borane Reactions with Alkyl Halides[†]

Lawrence M. Pratt*

Department of Chemistry, Fisk University, 1000 17th Ave. N., Nashville, Tennessee 37209

Ngân Văn Nguyễn

University of Pedagogy, 280 An Duong Vuong, District 5, Hồ Chí Minh City, Vietnam

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Ab initio and DFT calculations were performed to examine the mechanisms of reduction of alkyl halides and formaldehyde by borane. With alkyl halides, the optimized transition structure geometry resembled diborane, with a pair of hydrogen atoms bridging the boron and carbon atoms by three-center−two-electron bonds. A similar transition structure was found for the reduction of formaldehyde, although it was not the lowest-energy transition structure. Solvation by dimethyl ether or dimethyl sulfide disrupted this bridging with chloromethane, while both ligands dissociated from borane during the reduction of formaldehyde. The high calculated activation free energies of alkyl halide reduction are consistent with their observed lack of reactivity with borane.

Introduction

Boranes are important reagents in organic synthesis, being used as reducing agents for many functional groups. Lithium dialkylaminoborohydrides (LABs) are a related class of reducing agents, and both classes of compounds have been the subject of previous theoretical investigations.[1−5] Unlike borane, lithium aminoborohydrides reduce alkyl halides to the corresponding alkanes. During a theoretical study of this reaction, we sought to compare the reactivity of borane with that of LAB reagents, and we found an unusual transition structure (1) for the reaction of borane with chloromethane. This transition structure is an analogue of diborane and is isoelectronic with diborane if the chloride ion leaving group is neglected. To our knowledge, such a transition structure has not previously been reported, so we investigated whether a similar transition structure was possible for the borane reduction of formaldehyde. Such a transition structure was found, although it was not the lowest-energy reaction pathway.[6,7] Stable molecules that are transition structure analogues are of current interest because of their use as substrates for the development of catalytic enzymes and catalytic antibodies.[8,9] In this paper, the details of these novel transition structures and their potential implications in reaction mechanisms are discussed.

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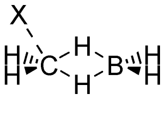

Computational Methods

All geometry optimizations, transition structure searches, and frequency calculations were performed with the Gaussian 98 or Gaussian 03 program.[10] Transition structures were located either with the QST3 method or by 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 HF/6-31+G(d), B3LYP/6-31+G(d), and MP2/6-31+G(d) levels of theory for both the reactants and the transition structures. Single-point energies were obtained at the MP4/6-31+G(d)//MP2/6-31+G(d) level of theory. Harmonic frequencies of the reactants and transition structures were calculated at the HF/6-31+G(d), B3LYP/6-31+G(d), and MP2/6-31+G(d) levels. The thermal corrections to the free energies at 298.15 K were taken from the frequency calculations and added to the electronic energies at the corresponding level of theory, to obtain the free energies of each reactant and transition structure. MP2 thermal corrections were added to the single-point MP4 energies to obtain an approximate MP4 free energy.

Results and Discussion

Transition structures were located and activation free energies were calculated for the reduction of the following molecules with borane: chloromethane, bromomethane, chloroethane, bromoethane, allyl chloride, and allyl bromide. To determine whether this kind of transition structure is unique to the reduction of alkyl halides, the calculations were also performed on the reduction of formaldehyde by borane by this mechanism and by a B−H−C−O cyclic transition structure. With allyl chloride and allyl bromide, the reduction could proceed by two different transition mechanisms; hydride attack on carbon 3 or an S_N2'-like attack on carbon 1 of the allyl halide. The optimized transition structures are shown in Figure 1, and the optimized bond lengths are listed in Table 1. These include the lengths of the breaking B−H bond (reactive B−H), of the unreactive B−H bonds, of the C−H bond of the alkyl halide or aldehyde coordinated to borane (reactive C−H), and of the unreactive C−H bond. The calculated activation free energies are reported in Table 2.

The reactive and unreactive B−H bonds ranged from 1.22 to 1.28 and from 1.18 to 1.19 Å, respectively, for the series of compounds studied. The boron-coordinated (reactive) hydrogen C−H bonds were 0.07−0.10 Å longer than the uncoordinated

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[*] To whom correspondence should be addressed. E-mail: lpratt@fisk.edu.

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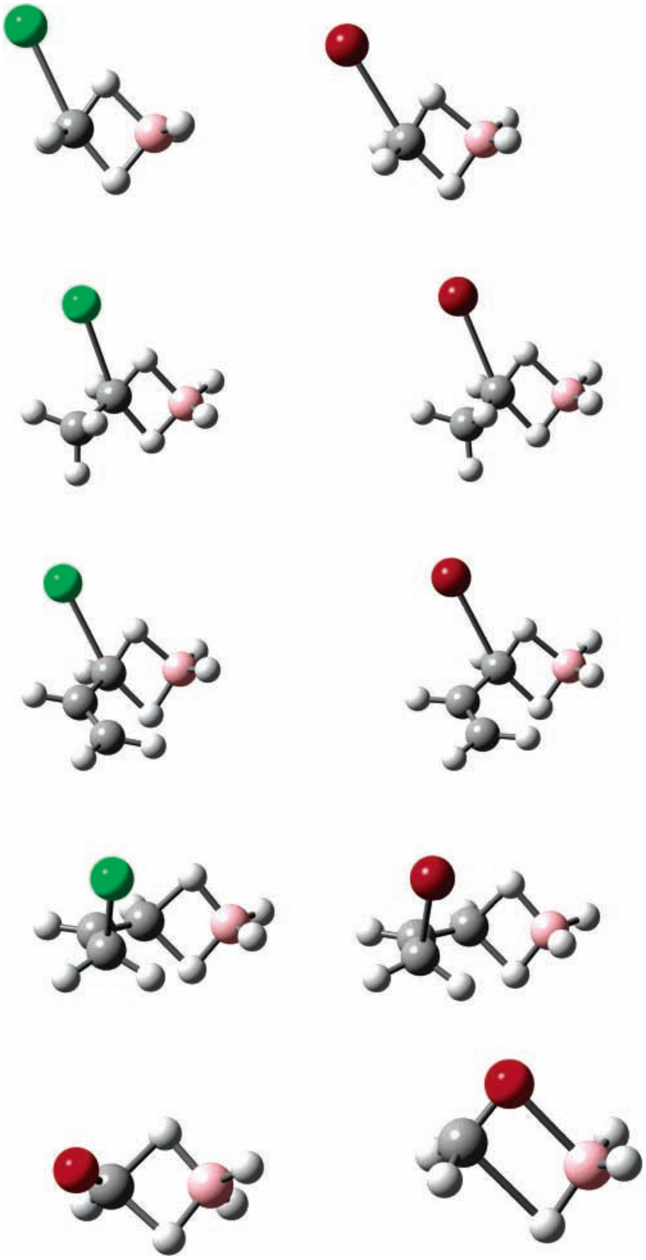

Figure 1. Optimized transition structure geometries for borane reductions. Top row: chloromethane and bromomethane. Second row: chloroethane and bromoethane. Third row: allyl chloride and allyl bromide, C3 attack. Fourth row: allyl chloride and allyl bromide, C1 attack. Bottom: formaldehyde (1, left) and formaldehyde (2, right). Gray, carbon; white, hydrogen; pink, boron; green, chlorine; dark red, bromine; light red, oxygen.

hydrogen C−H bonds for each of the S_N2-like alkyl halide reductions, indicating a substantial weakening of these bonds in the transition structure.

TABLE 1: Bond Lengths (Å) for MP2/6-31+G(d)-Optimized Transition Structures

TS	reactive B−H	unreactive B−H	reactive C−H	unreactive C−H
BH_3−MeCl	1.278	1.186	1.163	1.080
BH_3−MeBr	1.276	1.186	1.161	1.081
BH_3−EtCl	1.263	1.179	1.188	1.083
BH_3−EtBr	1.264	1.188	1.176	1.084
BH_3−allylCl	1.271	1.187	1.188	1.084
BH_3−allylBr	1.272	1.186	1.186	1.084
BH_3−allylCl S_N2'	1.264	1.190	1.391	1.087
BH_3−allylBr S_N2'	1.269	1.189	1.385	1.087
BH_3−HCHO (1)	1.263	1.192	1.408	1.100
BH_3−HCHO (2)	1.220	1.189	N/A	1.098

TABLE 2: Calculated Activation Free Energies (kcal/mol) for the Reaction of Alkyl Halides and Aldehydes with BH_3

substrate	HF	B3LYP	MP2	MP4
MeCl	75.4	50.0	57.9	56.9
MeBr	70.7	45.6	50.8	50.2
EtCl	75.1	49.3	56.4	55.2
EtBr	70.0	45.2	49.4	48.6
allylCl	77.1	50.0	56.9	55.7
allylBr	72.3	46.4	50.6	49.8
allylCl SN2′	72.6	42.8	44.5	46.3
allylBr SN2′	71.0	41.2	42.5	43.3
allyl cation	16.3	2.87	5.12	6.57
formaldehyde (1)	49.8	21.8	25.1	24.5
formaldehyde (2)	24.3	11.4	13.2	13.2

The calculated activation free energies showed that Hartree−Fock calculations overestimated the barrier heights and B3LYP underestimated them, compared to MP4 calculations. This is consistent with our recent work on barrier heights of lithium enolates.[11] Although the diborane-like transition structure was located for the reduction of formaldehyde, the B−H−C−O cyclic transition structure (formaldehyde 2, Figure 1) was lower in energy by about 12 kcal/mol. For the S_N2-like reductions of alkyl halides, the activation free energies for the alkyl bromides were about 5 kcal/mol lower than the alkyl chlorides. The S_N2' reaction at carbon 1 was favored over the S_N2 reaction on carbon 3 for allyl chloride and allyl bromide by several kilocalories per mole. Although the large activation free energies indicate that reductions of alkyl halides by borane are not likely to occur except at high temperatures, we hypothesized that similar transition structures might be possible for the reduction of carbocations resulting from the solvolysis of alkyl halides in the presence of borane or dialkylboranes. To test this hypothesis, calculations were performed on the reduction of the methyl and allyl cations with BH_3. The reduction resulted in an analogous complex between borane and the methyl cation, but the frequency analysis showed that it was a mininum rather than a transition structure. The reaction with the allyl cation did yield a transition structure, but not the same one as the reduction of the allyl halides. These two structures are shown in Figure 2. It is interesting to note that the formation of the unique diborane-like transition structure with alkyl halide reduction apparently depends on the presence of the leaving group.

Activation free energies and reaction mechanisms are potentially affected by substituents on the reducing reagent as well as on the substrate. To determine the nature and magnitude of these effects, the calculations for the activation free energies for the reduction of chloromethane, bromomethane, and formaldehyde were repeated using dimethylborane (electron-releasing groups) and dichloroborane (electron-withdrawing groups). The data in Table 3show that the activation free energies for alkyl halide reduction by dimethylborane were not significantly different than those for reduction by borane. In contrast, reduction of formaldehyde by dimethylborane had a higher

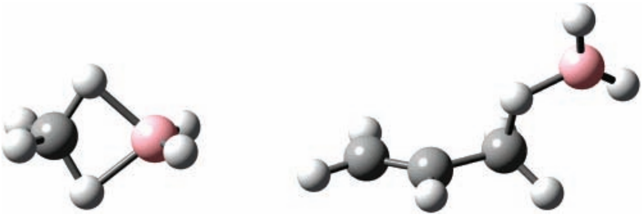

Figure 2. Optimized geometries of (left) the methyl cation with borane and (right) the transition structure for the reduction of the allyl cation. Gray, carbon; white, hydrogen; pink, boron.

TABLE 3: Calculated Activation Free Energies (kcal/mol) for the Reaction of Alkyl Halides and Aldehydes with Dimethylborane and Dichloroborane

reaction	HF	B3LYP	MP2	MP4
BH_3 + MeCl	75.4	50.0	57.9	56.9
Me_2BH + MeCl	71.2	56.0	61.2	60.5
Me_2BH + MeBr	66.1	51.3	53.1	52.7
Me_2BH + formaldehyde	59.2	34.0	34.1	34.0
Cl_2BH + MeCl	92.1	67.0	72.1	71.0
Cl_2BH + MeBr	86.9	60.5	62.9	62.5
Cl_2BH + formaldehyde	69.5	44.3	46.1	45.7
BH_3 + 2-chloroethanol	73.8	47.6	54.7	53.3
BH_3 + chlorotrifluoroethane	90.7	60.2	67.4	65.7

TABLE 4: Effects (kcal/mol) of Coordinated Dimethyl Ether or Dimethyl Sulfide Ligands on BH_3 Reactivity toward Alkyl Halides and Formaldehyde

reaction	HF	B3LYP	MP2	MP4
BH_3 + MeCl	75.4	50.0	57.9	56.9
BH_3-Me_2O + MeCl	56.0	45.0	56.9	55.5
BH_3-Me_2S + MeCl	60.2	50.4	58.1	56.8
BH_3-Me_2O + formaldehyde	Me_2O ligand dissociated			
BH_3-Me_2S + formaldehyde	Me_2S ligand dissociated			

activation free energy by about 9 kcal/mol. Dichloroborane reduction of all three compounds had a substantially higher activation free energy than borane reduction. The latter compound is analogous to diiodoborane, which has been used as its pyridine complex for the hydroboration of alkenes.[12]

The effects of electron-releasing and electron-withdrawing substituents on the substrate were modeled by reduction of 2-chloroethanol and 1-chloro-2,2,2-trifluoroethane, respectively. The results are presented in Table 3. Compared to chloromethane, the electron-releasing effect of the neighboring oxygen atom had only a small impact on the activation barrier, whereas the electron-withdrawing effects of the adjacent trifluoromethyl group raised the activation free energy by about 11 kcal/mol.

Borane is often used as a complex with a Lewis base, such as THF, dimethyl sulfide, or an amine, and these complexes can have different reactivity toward alkyl halides and aldehydes than free borane. Transition structure optimizations were performed for the reduction of chloromethane and formaldehyde by borane complexes with dimethyl ether and dimethyl sulfide, and the calculated activation free energies are reported in Table 4. With formaldehyde, both the dimethyl ether and dimethyl sulfide complexes dissociated into the gas-phase transition structure and free ligand. The reduction of chloromethane occurred via the borane complexes with dimethyl ether and dimethyl sulfide, but through a transition structure that did not involve coordination of one of the alkyl halide hydrogens to borane. The MP2/6-31+G(d)-optimized transition structures are shown in Figure 3. The latter mechanism resulted in a slightly lower activation free energy. This suggests that the diborane-like transition structure results from the Lewis acid character of borane, and the need to coordinate to another hydrogen atom is eliminated when borane complexes with Lewis bases are used.

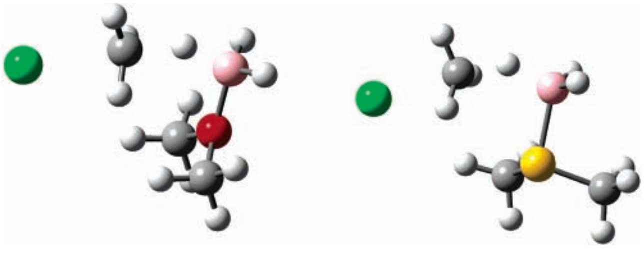

Figure 3. Optimized transition structures of borane−dimethyl ether and borane−dimethyl sulfide reductions of chlormethane. Gray, carbon; white, hydrogen; pink, boron; green, chlorine, yellow, sulfur; red, oxygen.

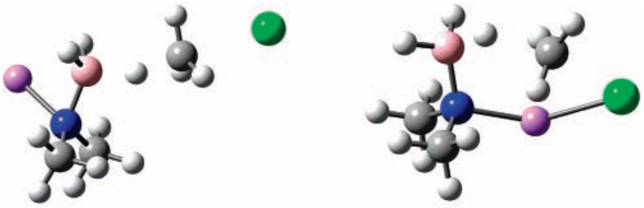

Figure 4. Transition structures for the reduction of chloromethane by LAB: (left) anti, (right) gauche. Gray, carbon; white, hydrogen; pink, boron; green, chlorine; blue, nitrogen; violet, lithium.

The nature of the diborane-like transition structure can perhaps be better understood by comparison to the reduction of alkyl halides by lithium dimethylaminoborohydride (LAB). Two transition structures, shown in Figure 4, are identified as anti or gauche, as defined by the Li−N−B−reactive H dihedral angle. The anti and gauche activation free energies were calculated to be 48.8 and 34.9 kcal/mol, respectively, at the MP4/6-31+G(d) level. In both cases, the coordination sphere of boron was satisfied by coordination to nitrogen. The activation free energies were considerably lower than for the same reduction by borane, and the transition structure was more similar to that of borane−ether or borane−dimethyl sulfide, rather than free BH_3. In the gauche transition structure, the leaving group is assisted by coordination to lithium, but there is still sufficient C−Cl coordination to prevent borane from coordinating to a free carbocation, as in Figure 2. From comparison of transition structures of free borane, borane−Lewis base complexes, and LAB, it appears that the unusual diborane-like transition structures arise from the Lewis acid character of borane. This Lewis acid behavior raises the activation free energies, compared to reaction pathways where the three-center−two-electron bonds are not involved. Similar coordination between the borane hydrogens and another Lewis acid (lithium) are observed in the anti transition structure of LAB, and this interaction might contribute to the higher activation free energy in that conformer.

Figure 5 shows the HF/6-31+G(d) highest occupied molecular orbitals (HOMOs) of diborane at the MP2/6-31+G(d) geometry, the transition structure for the reduction of chloromethane by BH_3, and the transition structure for the analogous reduction of formaldehyde by BH_3. Although all three structures appear to have three-center−two-electron bonds, their orbitals are quite different, apparently influenced by the chloride leaving group or the carbonyl group of formaldehyde. The HOMO of diborane contains a node at the center of the molecule; and it has bonding character between the boron atoms and the four terminal hydrogen atoms and antibonding character between the two boron atoms. The HOMO of the chloromethane reduction transition structure is bonding between the carbon and boron atoms and antibonding between the CH_3 unit and the chloride leaving group. It is bonding between the boron, carbon, and one bridging hydrogen atom and antibonding with the other bridging hydrogen. The HOMO of the formaldehyde reduction transition structure is bonding between the carbon, boron, and bridging hydrogen atoms, and also contains C=O π^* character.

Conclusions

Examination of the reduction of alkyl halides by borane resulted in the discovery of a novel type of transition structure that is analogous to, and isoelectronic with, diborane if the

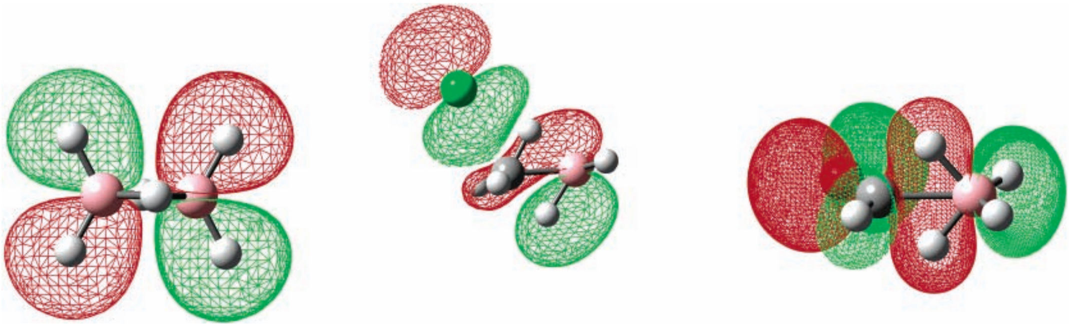

Figure 5. MP2/6-31+G(d)-calculated HOMO: (left) diborane, (center) BH_3−MeCl transition structure, (right) BH_3−formaldehyde transition structure.

leaving group is neglected. This transition structure is also possible for the reduction of aldehydes, although it is not the lowest-energy pathway. The formation of this novel structure is apparently the result of the need to fill the coordination sphere of boron and is sensitive to coordination of the boron atom to Lewis bases. The orbital shapes of this transition structure are sensitive to substituents on the carbon atom, and the HOMOs of these transition structures are different from that of diborane. The use of borane−dimethyl ether or borane−dimethyl sulfide complexes for the reduction of chloromethane results in a different transition structure and a slightly lower activation barrier. Lithium aminoborohydrides reduce alkyl halides by a mechanism similar to borane−ether or borane−dimethyl sulfide, but with a much lower activation free energy.

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Supporting Information Available: Tables of optimized geometries and energies of all reactants and transition structures and complete citation for ref 10. This material is available free of charge via the Internet at http://pubs.acs.org.

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