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DFT Studies of Amide Reduction by Borane and Alane: Structural Stability and Reaction Mechanisms

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ABSTRACT

An amide reduction to an amine is an important transformation reaction for the development of pharmaceutical drugs. In the present work, the reduction of modeled amide, *N*,*N*-dimethylacetamide using BH_3 (borane) or AlH_3 (alane) to give *N*,*N*-dimethylethanamine has been studied using the DFT calculations. The reaction pathways were searched by intrinsic reaction coordinate analysis. Two possible transition states of amide reduction were found. The first transition state is BH_3 or AlH_3 insertion and the second transition state is the hydrogenation couple with the cleavage of BH_2-O-BH_2 (or AlH_2-O-AlH_2) group. Structural, electronic and thermodynamic properties of all species have been reported. The rate determining step is the second step which has the highest activation free energies. All of results point that borane and alane can reduce a modeled amide to form an amine.

1 Introduction

Amide reduction to amine is an important transformation for the development of pharmaceutical drugs such as antibacterials, HIV inhibitors, and ocular hypertension drugs.

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Recently, research on amide reduction has focused on new catalyst design or new reactive reagent. Borane (BH_3) and alane (AlH_3) complex reagents are well known as catalysts or reactive reagents in polymerization process and organic synthesis. In the last decades, borane and alane have been reported as powerful reducing agent in the reduction of amide or nitrile groups to amines (Wehmschulte, 2000 and Burkhardt, 2006). The reduction of tertiary amides is generally faster than that of secondary or primary amides. The understanding of the mechanism involved in amide reductions using borane or alane such as complex stability and the rate determining step might play a crucial role in increasing the performances of reduction process. It is difficult to detect all intermediates and determine all thermodynamic properties for each step involved in the amide reductions by experiments. In the present work, the research is aimed to investigate the possible mechanism pathways of the reaction of modeled amide, *N*,*N*-dimethylacetamide with AlH_3 and BH_3 by using the density functional theory method.

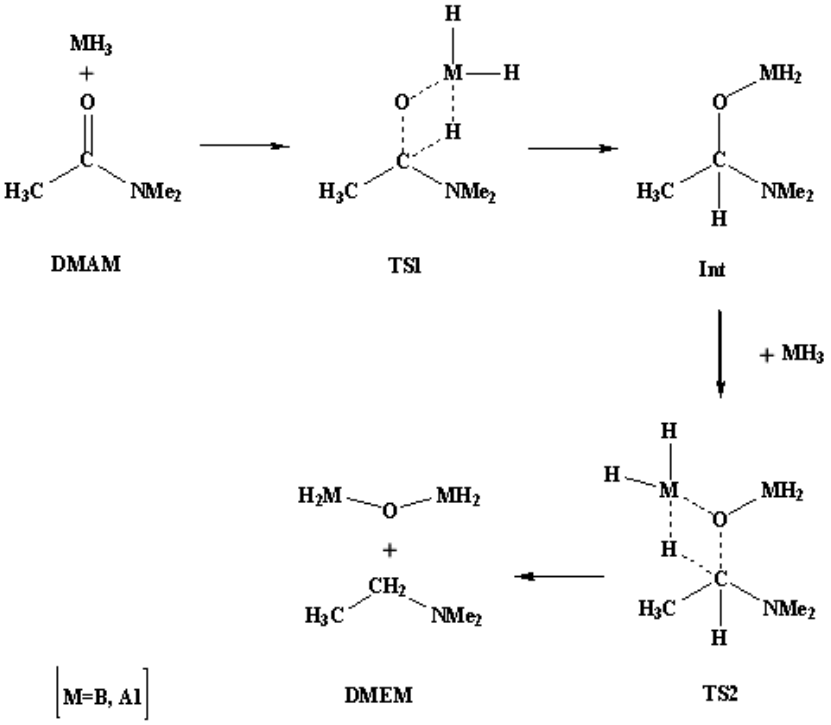

Figure 1: The proposed pathway of amide reduction.

2 Computational Methods

The density functional theory (DFT) has been applied to optimize the structures of all species i.e., the reactants, intermediates, transition states and products found in this amide reduction. The DFT calculation has been performed using the Becke's three-parameter

exchange functional with the Lee–Yang–Parr correlation functional (B3LYP) (Becke, 1988) at B3LYP/6-31G(d,p) level of theory (Lee *et al.*, 1988). Single point calculations were performed at B3LYP/6-311G(d,p)//B3LYP/6-31G(d,p) and B3LYP/6-311++G(d,p)//B3LYP/6-31G(d,p) levels of theory. The vibrational frequency computations have been carried out at 298.15 K and standard pressure. Stationary points have been fully optimized and characterized by vibrational frequency calculations, which also provided zero point vibrational energies (Ochterski, 2000). All transition states were characterized by a single imaginary frequency. The highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) energies have also been computed. The standard enthalpy ($\Delta H°$) and Gibbs free energy changes ($\Delta G°$) of amide reduction were compared with reactants and reported. The rate constant, k(T) derived from transition-state theory was computed from Gibbs free energy of activation ($\Delta^{\neq}G$), using $k(T) = \frac{k_B T}{hc°} e^{-\Delta^{\neq}G/RT}$, where $c°$ factor is assigned to unity as applied in our previous work (Wanno and Ruangpornvisuti, 2006). The equilibrium constant K at 298.15 K and 1 atm was computed using a thermodynamic relation, $\Delta G° = -RT \ln K$. All calculations were performed with the GAUSSIAN 03 program (Frisch *et al.*, 2008). The molecular graphics of all related species were generated with the MOLEKEL 4.3 program (Flükiger *et al.*, 2000).

3 Results and Discussion

To investigate the amide reduction of modeled compound, *N*,*N*-dimethylacetamide (DMAM) to *N*,*N*-dimethylethanamine (DMEM) using BH_3 or AlH_3, the possible mechanism was studied using the DFT method. The proposed mechanism of amide reduction of DMAM to form DMEM using BH_3 or AlH_3 is shown in Figure 1. The proposed mechanism processes via two transition states, one is an insertion of the first MH_3 (M= B or Al) into C=O bond (TS1) to form an intermediate (Int) and the other is an insertion of the second MH_3 into C-O bond (TS2) of Int. For the TS2, the insertion of the second MH_3 induces the hydrogenation and the cleavage of MH_2-O-MH_2 to form DMEM product (see Figure 1).

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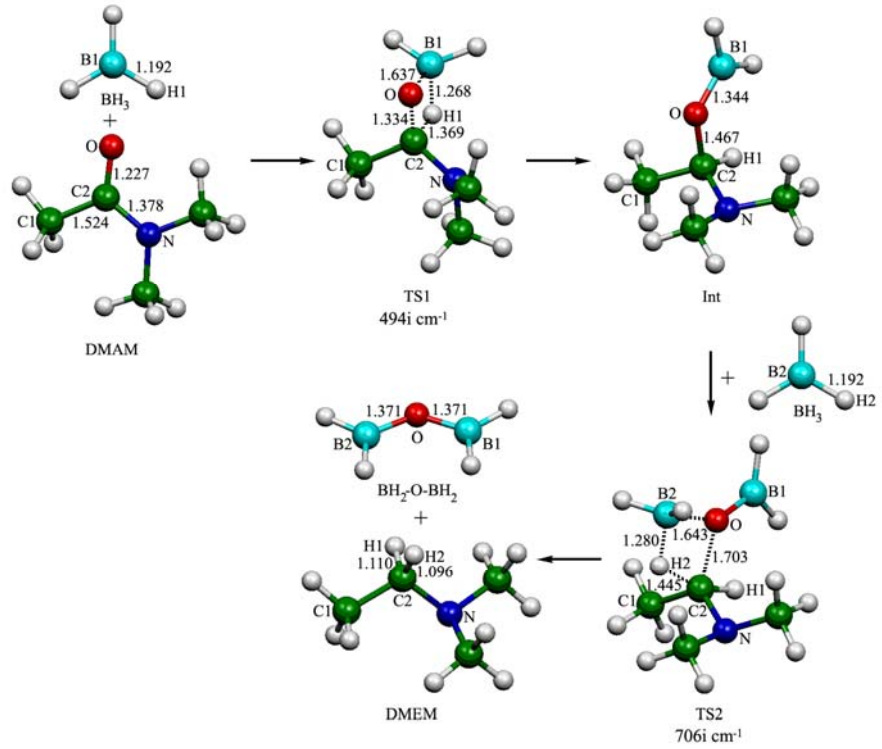
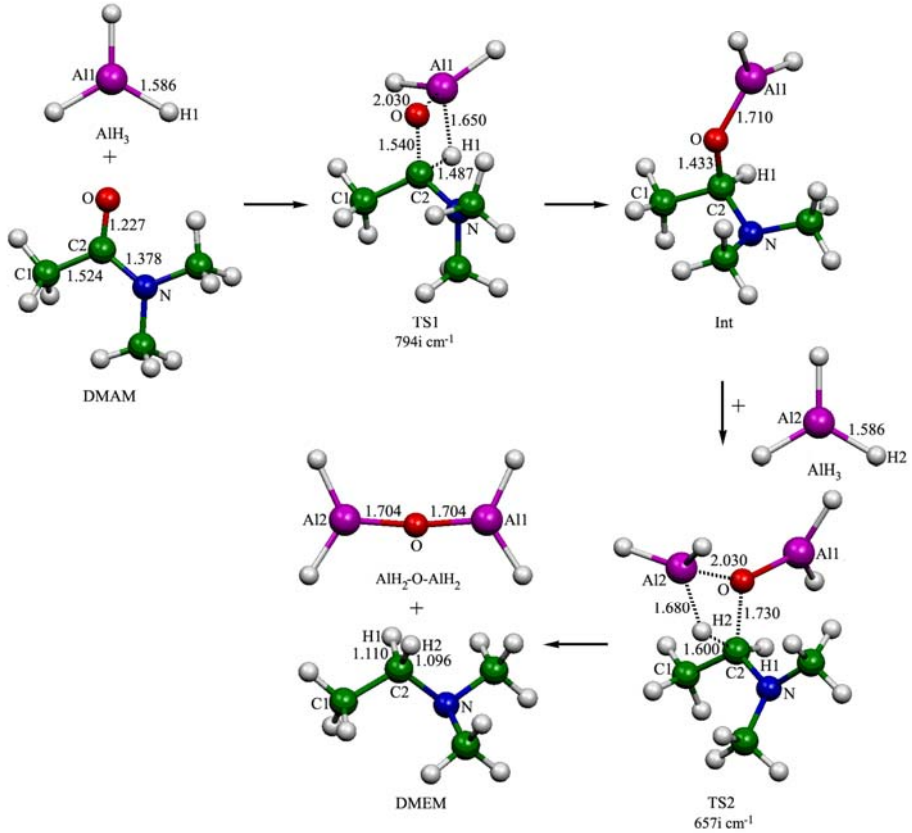


a) Amide reaction with BH_3



b) Amide reaction with AlH_3

Figure 2: The B3LYP/6-31G(d,p) optimized structures for amide reduction by (a) BH_3 and (b) AlH_3, bond distances are in Å.

3.1 Structural properties

The B3LYP/6-31G(d,p) optimized structures for amide reduction with BH_3 and AlH_3 including atomic labeling and their imaginary frequencies found in the transition states are displayed in Figure 2.

The molecular structure of DMAM was optimized at B3LYP/6-31G(d,p) and compared with experimental data reported by Lv and Ng (2007). The results indicated that the computed structure is in good agreement with experimental data. For example, the computed and experimental (in parenthesis) C2-O, C1-C2 and C2-N bond distances are 1.227 (1.246), 1.524 (1.543) and 1.378 (1.292) Å, respectively. The B3LYP/6-31G(d,p) optimized structures of BH_3 and AlH_3 molecules show that both molecular symmetries are found to be D_{3h} whereas the average B-H and Al-H bond distances are 1.192 and 1.586 Å, respectively (see Figure 2). Because the experimental structures of both BH_3 and AlH_3 molecules have not been reported before, the geometrical structures of BH_3 and AlH_3 molecules were optimized at various higher levels of theory for comparison. The results indicate that all molecules have the same symmetry as those obtained at B3LYP/6-31G(d,p) level. The computed bond distances obtained at B3LYP/6-311++G(d,p), MP2(fc)/6-311++G(d,p) and CCSD/6-311++G(d,p) levels are 1.189, 1.191 and 1.194 Å, respectively for the B-H bonds and are 1.584, 1.575 and 1.577 Å, respectively for the Al-H bonds. Geometrical data optimized at the B3LYP/6-31G(d,p) level and at various higher levels are not much different. Then the B3LYP/6-31G(d,p) approach was regularly applied in all of the optimizations.

As shown in Figure 2, each reaction occurs via two steps with major transition states. The first step is DMAM molecule reacts with the first BH_3 (or AlH_3) molecule to form an intermediate via the TS1. In the course of the reaction, two different bonds are being formed: a O – B1 (or Al1) and H1 – C2 bond. This step gives an intermediate. In the next step, the second BH_3 (or AlH_3) molecule reacts with the intermediate at the opposite position of the first BH_3 (or AlH_3). Then O – B2 (or Al2) and C2 – H2 bonds are being formed while the O – C2 and H2 – B2 (or Al2) were broken to give the DMEM amine product. It should be noted that the imaginary frequencies found in TS1 and TS2 are within the range of 494i to 794i cm^{-1}.

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3.2 Electronic properties

Frontier molecular orbital energy gaps (E_{gap}) between the lowest unoccupied molecular orbital (LUMO) and the highest occupied molecular orbital (HOMO) computed at the B3LYP/6-311++G(d,p)//B3LYP/6-31G(d,p) level of theory, chemical hardness (η), chemical potential (μ) and Mulliken electronegativity (χ) of all species found in the amide reductions are presented in Table 1. The chemical hardness, electronic chemical potential and electronegativity are important tools to study the stabilities of species. According to the Pearson's maximum hardness principle (Pearson, 2001) which states that the minimum energy structure has the maximum chemical hardness and the energy gap, the DMEM structure which has the maximum chemical hardness (3.98 eV) and the energy gap (7.96 eV) is the most stable structure. All transition state structures which have the lowest value of chemical hardness and energy gap are the highest reactivity species.

Table 1: Frontier molecular orbital energy gap (E_{gap}) and chemical indices of all species for amide reduction with BH_3 or AlH_3 obtained at B3LYP/6-311++G(d,p)//B3LYP/6-31G(d,p) level of theory.

Species	E_{gap} [a, b]	η [a, c]	μ [a, d]	χ [a, e]
DMAM	5.43	2.72	-3.64	3.64
DMEM	7.96	3.98	-1.65	1.65
Amide reduction with BH_3				
BH_3	7.75	3.88	-5.68	5.68
TS1	6.95	3.48	-3.35	3.35
Int	6.26	3.13	-3.01	3.01
TS2	5.31	2.66	-3.30	3.30
BH_2-O-BH_2	6.74	3.37	-4.88	4.88
Amide reduction with AlH_3				
AlH_3	6.40	3.20	-5.14	5.14
TS1	5.46	2.73	-3.80	3.80
Int	4.91	2.46	-3.48	3.48
TS2	4.25	2.13	-3.78	3.78
AlH_2-O-AlH_2	6.15	3.07	-4.47	4.47

[a] In eV. [b] $E_{gap} = E_{LUMO} - E_{HOMO}$. [c] Chemical hardness, $\eta = (E_{gap})/2$. [d] Chemical potential, $\mu = (E_{HOMO} + E_{LUMO})/2$. [e] The Mulliken electronegativity, $\chi = -(E_{HOMO} + E_{LUMO})/2$.

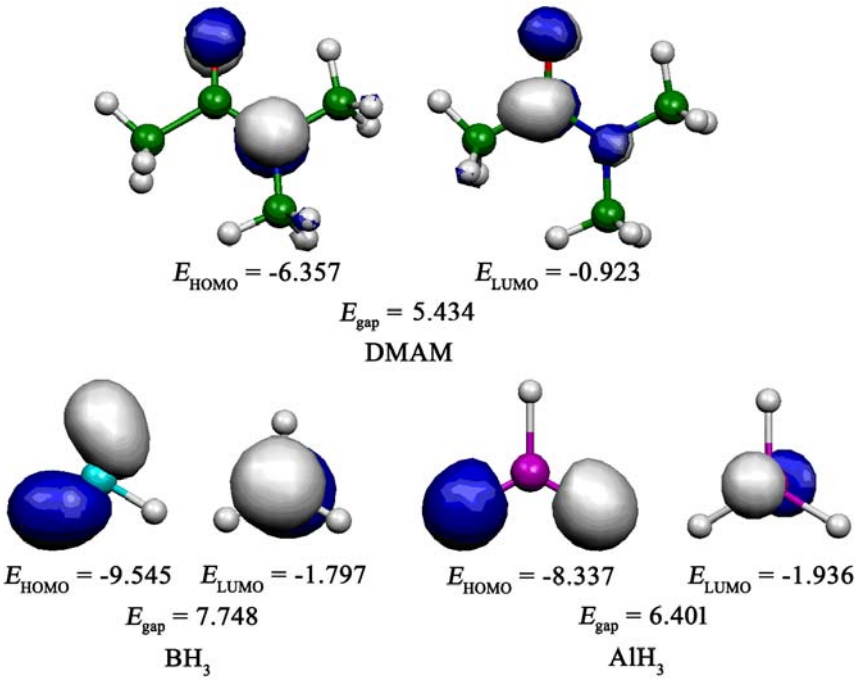

Figure 3: Calculated isosurfaces (isovalue = 0.08 au) of HOMOs and LUMOs for BH_3, AlH_3, and DMAM obtained at B3LYP/6-311++G(d,p)//B3LYP/6-31G(d,p) level of theory.

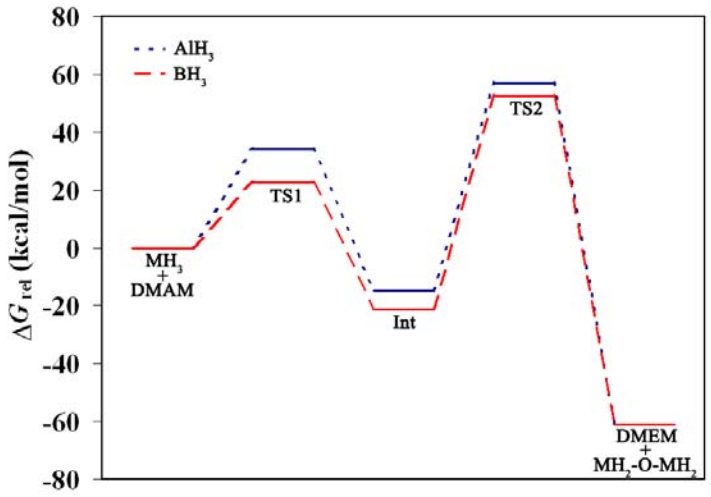

Figure 4: Potential free energy profile for DMAM reduction by AlH_3 and BH_3 obtained at B3LYP/6-311++G(d,p)//B3LYP/6-31G(d,p) level of theory.

The HOMO and LUMO orbitals of reactants, BH_3, AlH_3, and DMAM obtained at B3LYP/6-311++G(d,p)//B3LYP/6-31G(d,p) level of theory presented over isosurface value of 0.08 au are displayed in Figure 3. It is found that the HOMO and LUMO orbitals of BH_3 and AlH_3 locate on the same area; the HOMOs locate on the hydrogen atoms whereas the LUMOs locate on boron or aluminium atom. For the DMAM molecule, the HOMO orbital locates on

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oxygen and nitrogen atoms while the LUMO orbital locates on oxygen and carbon (C2) atoms.

Table 2: The thermodynamic property changes, rate constants (k) and equilibrium constants (K) for amide reduction with BH_3 and AlH_3 computed at the B3LYP/6-31G(d,p), B3LYP/6-311G(d,p)//B3LYP/6-31G(d,p) (in parenthesis) and B3LYP/6-311++G(d,p)//B3LYP/6-31G(d,p) [in bracket] levels of theory.

Reactions/systems	$\Delta^{\ddagger}E^{a,b}$	$\Delta^{\ddagger}G^{a,b}$	k^{c}	ΔE^{a}	ΔG^{a}	K
Amide reduction with BH_3						
BH_3 + DMAM → TS1 → Int	15.17	25.88	6.60×10^{-7}	-27.89	-17.47	6.41×10^{12}
	(14.58)	(25.19)	(2.11×10^{-6})	(-29.31)	(-18.92)	(7.41×10^{13})
	[12.12]	[22.63]	$[1.59\times10^{-4}]$	[-31.59]	[-21.35]	$[4.49\times10^{15}]$
BH_3 + Int → TS2 →	66.51	76.44	5.75×10^{-44}	-32.80	-38.55	1.83×10^{28}
DMEM + BH_2-O-BH_2	(66.06)	(75.93)	(1.35×10^{-43})	(-36.10)	(-38.28)	(1.15×10^{28})
	[65.29]	[73.78]	$[5.12\times10^{-42}]$	[-35.74]	[-38.77]	$[2.63\times10^{28}]$
$2BH_3$ + DMAM →				-64.31	-56.02	1.17×10^{41}
DMEM + BH_2-O-BH_2	-	-	-	(-65.41)	(-57.20)	(8.52×10^{41})
				[-67.79]	[-60.12]	$[1.18\times10^{44}]$
Amide reduction with AlH_3						
AlH_3 + DMAM → TS1 → Int	26.36	36.31	1.50×10^{-14}	-22.35	-12.44	1.31×10^{9}
	(26.16)	(36.04)	(2.35×10^{-14})	(-23.10)	(-13.16)	(4.44×10^{9})
	[24.23]	[34.17]	$[5.54\times10^{-13}]$	[-24.79]	[-14.59]	$[4.93\times10^{10}]$
AlH_3 + Int → TS2 →	61.48	73.59	7.06×10^{-42}	-48.69	-50.56	1.16×10^{37}
DMEM + AlH_2-O-AlH_2	(60.49)	(71.74)	(1.58×10^{-40})	(-47.56)	(-49.64)	(2.46×10^{36})
	[60.40]	[71.66]	$[1.81\times10^{-40}]$	[-44.96]	[-48.35]	$[2.76\times10^{35}]$
$2AlH_3$ + DMAM →				-70.04	-63.00	1.52×10^{46}
DMEM + AlH_2-O-AlH_2	-	-	-	(-70.66)	(-62.80)	(1.09×10^{46})
				[-69.75]	[-60.97]	$[1.36\times10^{46}]$

[a] In kcal/mol. [b] Activation energy. [c] In s^{-1}.

3.3 Energetically and thermodynamic properties

The potential free energy profile for DMAM reduction by BH_3 and AlH_3 obtained at B3LYP/6-311++G(d,p)//B3LYP/6-31G(d,p) level of theory are presented at Figure 4. It appear that the complexes and the transition states for the system of the amide reduction by BH_3 are the most stable species which imply that reduction with BH_3 is more favorite than that of AlH_3. The activation energies, free energies of activation, rate constants and equilibrium constants of the DMAM reductions computed at the B3LYP/6-31G(d,p), B3LYP/6-311G(d,p)//B3LYP/6-31G(d,p) and B3LYP/6-311++G(d,p)//B3LYP/6-31G(d,p) levels of theory are reported in Table 2. Rate constants of DMAM reductions were computed from their activation free energies using transition-state theory. In both DMAM reductions with BH_3 and AlH_3, the activation energy of the first step (BH_3 or AlH_3 + DMAM → TS1→ Int) is lower than the second step (BH_3 or AlH_3 + Int → TS2→ DMEM + BH_2-O-BH_2 +

AlH_2-O-AlH_2) indicating that the second step is the rate determining step. For the reduction (DMAM↔DMEM) with BH_3, its forward rate constants for the first and the second steps computed at 298.15 K and at B3LYP/6-311++G(d,p)//B3LYP/6-31G(d,p) level of theory are 1.59×10^{-4} and 5.12×10^{-42} s^{-1}, respectively and its forward equilibrium constants computed at the same level are 4.49×10^{15} and 2.63×10^{28}, respectively. It can be concluded here that borane and alane can reduce a modeled amide to form an amine.

4 Conclusion

The reduction of modeled amide, *N*,*N*-dimethylacetamide, using BH_3 (borane) or AlH_3 (alane) to give amine, *N*,*N*-dimethylethanamine, has been studied using the DFT methods. The reaction pathways were searched by intrinsic reaction coordinate analysis. Two possible transition states of amide reduction were found. The first transition state is BH_3 or AlH_3 insertion and the second transition state is the hydrogenation couple with the cleavage of BH_2-O-BH_2 (or AlH_2-O-AlH_2) group. Structural, electronic and thermodynamic properties of all species have been reported. The rate determining step is the second step which has the highest activation free energies. All of results point that borane and alane can reduce a modeled amide to form an amine.

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