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Investigations of Different Chemoselectivities in Primary, Secondary and Tertiary Amide Reactions with Sodium Borohydride

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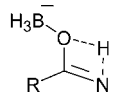
The mechanisms for the different chemoselectivities in sodium borohydride reactions with primary, secondary and tertiary amides have been investigated both at the B3LYP/6-31++G(d,p)//B3LYP/6-31G(d,p) and B3LYP/6-31++G(d,p)//HF/6-31G(d,p) levels of theory. The predicted structures of the key intermediates were then confirmed by experiments. Primary amides generate the corresponding nitriles when treated with sodium borohydride. Nitrile formation occurs by initial proton abstraction from the primary amide's nitrogen atom by a hydride ion, followed by loss of hydrogen and the coordination of the amide nitrogen atom to BH_3. Three subsequent steps produce acetonitrile. The computational predictions agree well with the experimental results.

Introduction

Sodium borohydride reductions are important widely employed reactions. For example, sodium borohydride reductions of esters have been reported,[1–3] and the reductions of amides with different borohydrides have been widely studied.[4–6] The different chemoselectivities observed in the reactions of primary, secondary and tertiary amides with sodium borohydride have puzzled the experimental chemists for over 40 years.[7–9] Instead of forming the expected corresponding primary amines, the production of nitriles was observed during reactions of primary amides with $NaBH_4$ at elevated temperatures.[7–9] Secondary amides do not react with $NaBH_4$ even at high temperatures without an auxiliary or a catalyst, such as I_2, present.[10–11] Only tertiary amides are reduced to their corresponding amines. In 1960, Newman proposed that 2 mol of hydrogen was produced per 1 mol of primary amide in an early attempt to explain nitrile formation.[9] After Newman's work, no mechanism study explained the different chemoselectivities reported. We later demonstrated that only 1 equiv. of hydrogen gas per 1 mol of primary amide was initially and rapidly formed during the $NaBH_4$ reaction with acetamide in diglyme.[12]

We initially proposed a reaction mechanism which proceeded through a four-membered-ring transition-state (TS) geometry, the structure of which is illustrated below.[12]



However, the predicted barrier ($\Delta E^{\neq}$) was very high [59.8 kcal/mol in THF at the B3LYP/6-31++G(d,p)//HF/6-31G(d,p) (DFT//HF) level, or 60.0 kcal/mol in THF at the B3LYP/6-31++G(d,p)//B3LYP/6-31G(d,p) (DFT//DFT) level] showing that this mechanism was not reasonable. Theoretical studies of itself have appeared,[13–16] but no computational studies of chemoselective reaction mechanisms have appeared to elucidate how these reactions proceed. Theoretical investigations of the effect of solvent on the reaction of amides with has not yet been reported. Although this is an old question in chemistry, it is important and basic to most experimental chemists. $NaBH_4$ reductions are so widely used, that an understanding of the specific mechanisms which operate during each type of functional group reaction clearly represents an important goal. Discovering and understanding the detailed mechanisms involved in these reactions would help chemists predict and design new reactions. Herein, we have probed the mechanism of primary amide reactions with sodium borohydride to generate the corresponding nitriles. Frequencies, IRCs and eigenvalues were calculated for the TS structures. Following the calculations, experiments were carried out to confirm the presence of predicted intermediate structures. These experiments agree well with predictions from the computations.

Results and Discussions

Acetamide, *N*-methyl- and *N*,*N*-dimethylacetamides were selected as model molecules for mechanistic computations

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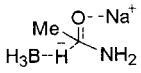
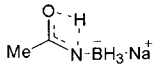
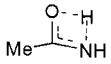
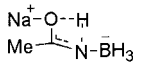
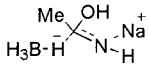
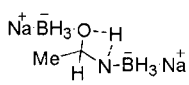
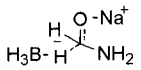
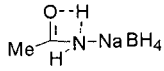
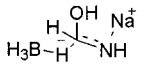
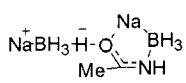
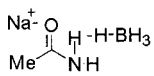
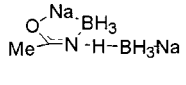
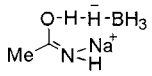
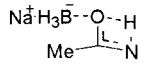
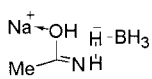
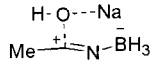
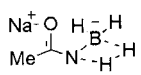
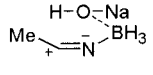
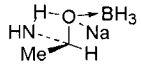
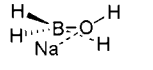
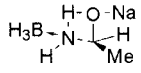
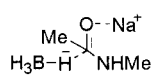
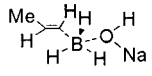
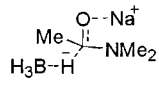
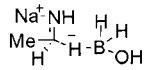
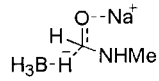
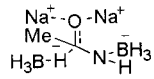
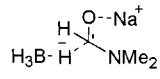
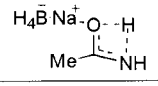
that characterize the TS barriers and intermediates formed in reactions with $NaBH_4$. Formamide, *N*-methyl- and *N*,*N*-dimethylformamide were also selected as the models in these computations to investigate the effect of the *N*-methyl group on the mechanism. All the $NaBH_4$ and amide atoms were included in optimizations of both the TS structures and the conformations of intermediates formed during these reactions. Our earlier calculated barriers to the four-membered-ring TS structure mentioned above in the acetamide → nitrile reaction in THF gave very similar values using DFT//HF and DFT//DFT theory levels. Also, our previous calculations using the DFT//HF theory satisfactorily explained why natural Lancifodilactone G from *Schisandra Lancifolia* exists in the enol form rather than in the keto form.[17a] Thus, mechanistic calculations were performed herein, both at the DFT//HF and DFT//DFT levels

Table 1. Computed barriers, $\Delta E_a^{\neq}{}_{298}$ in THF [at the B3LYP/6-31++G(d,p)//HF/6-31G(d,p) level] and $\Delta E_b^{\neq}{}_{298}$ in THF [at the B3LYP/6-31++G(d,p)//B3LYP/6-31G(d,p) level] in reactions of acetamide with sodium borohydride.

TS No.	TS structure	$\Delta E_a^{\neq}{}_{298}$	$\Delta E_b^{\neq}{}_{298}$	TS No.	TS structure	$\Delta E_a^{\neq}{}_{298}$	$\Delta E_b^{\neq}{}_{298}$
1		38.8	43.0	**16**		51.6	51.0
2		47.0	47.2	**17**		46.0 46.4 [a]	46.1
3		46.0	49.6	**18**		42.4	64.7
4		30.5	42.3	**19**		58.7	57.6
5		40.7	42.0	**20**		91.8	-
6		31.3 34.3 [a]	27.2	**21**		4.9	7.6
7		26.5 18.4 [a]	12.9	**22**		59.8	60.0
8		37.4 44.6 [a]	-	**23**		14.8 15.5 [a]	17.4
9		63.8	64.1	**24**		33.8 21.2 [a]	35.3
10		49.6	47.9	**25**		8.1	8.1
11		29.4	21.5	**26**		42.2	43.7
12		26.3	15.7	**27**		42.4	49.2
13		19.7	16.2	**28**		34.2	45.8
14		48.5	49.8	**29**		36.3	46.2
15		50.5	55.5				

[a] The geometries were obtained by full optimizations in THF at the HF/6-31G(d,p) level using the PCM model.

for reactions with different amides. All single-point energy calculations at the B3LYP/6-31++G(d,p) level were performed in the solvent THF by the use of the PCM model. These single-point energy calculations were based on the HF/6-31G(d,p)- or B3LYP/6-31G(d,p)-optimized structures obtained in the gas phase.[18] It is notable that the energies were obtained by comparing the optimized TS energies with the optimized energy of *the most stable conformation of their precursor intermediates*.[19]

Experimental reactions of amides with sodium borohydride were performed in diglyme. However, an experimental value of diglyme's dielectric constant was not found. THF has a dielectric constant of 7.58, while that of glyme is 7.20. Diglyme's dielectric constant is between 7.58 and 7.20. Thus, THF was used as a solvent in the barrier computations with the PCM model. The TSs (**TS-1** through **TS-29**) and their barriers ($\Delta E^{\neq}_{298}$), which were found by investigating all the possible reasonable pathways that could be imagined, are listed in Table 1. The complete geometry of the calculated 3-D structures for all 29 of these TSs are shown in the Supporting Information. Six of the TSs are selected below. Figure 1 summarizes the several (but not all) of the reaction pathways found in reactions of acetamide with $NaBH_4$. It also lists the calculated $\Delta E^{\neq}_{298}$ values obtained in THF at both the DFT//HF (in parentheses) and DFT//DFT levels of theories, respectively (the complete Figure 1 is also summarized in the Supporting Information). In addition, six key TSs were selected and full optimizations were performed on both them and their precursor complexes in THF at the HF/6-31G(d,p) level. These calculation were made to see if the sequence of the barriers (and their relative magnitudes) encountered in

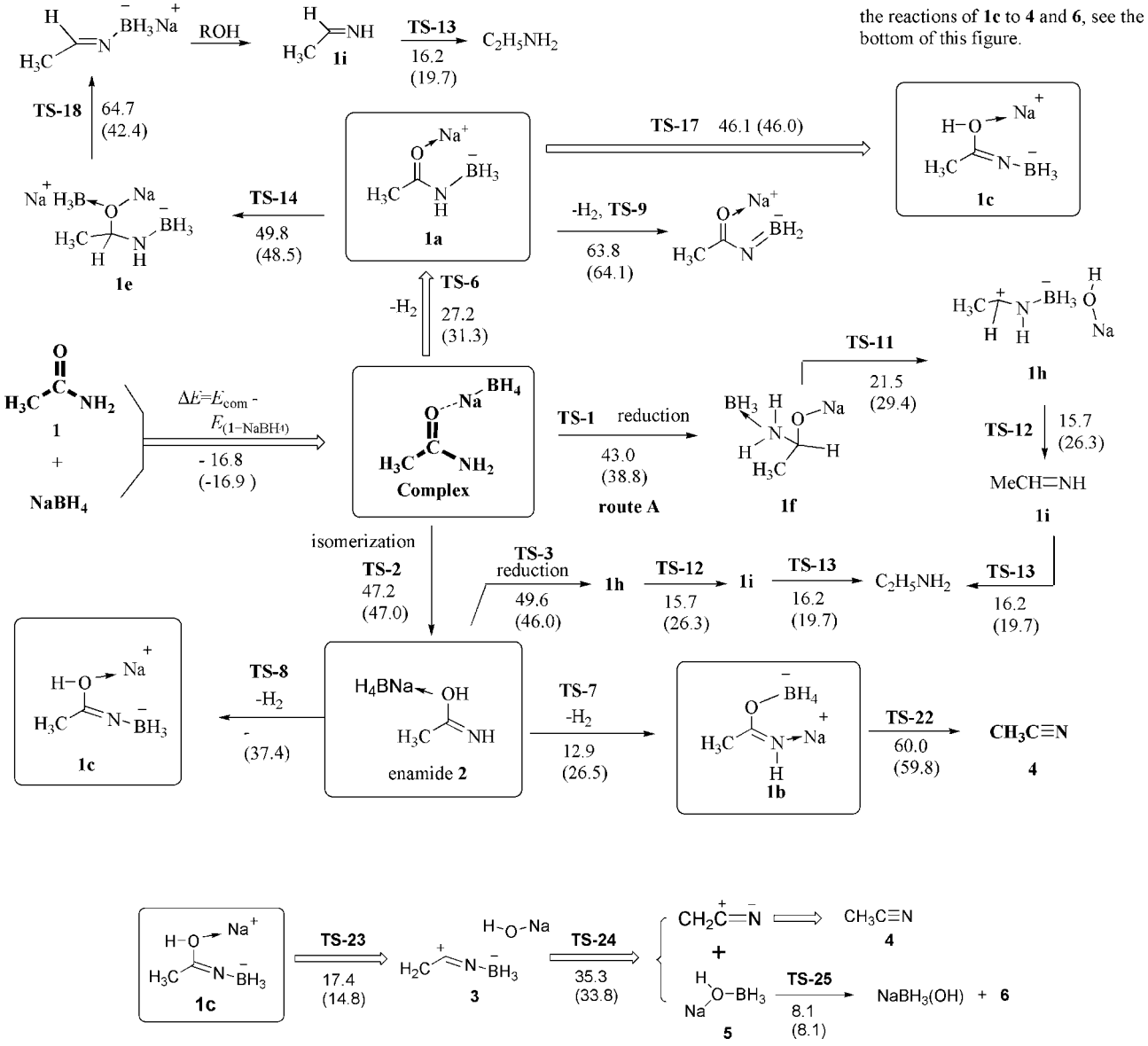


Figure 1. Full scheme for the mechanistic pathways found in acetamide reactions with sodium borohydride ["⇒" means the most favorable reaction direction, and the energies are in kcal/mol in THF at the B3LYP/6-31++G(d,p)//B3LYP/6-31G(d,p) level; the data in parentheses are those obtained at the B3LYP/6-31++G(d,p)//HF/6-31G(d,p) level].

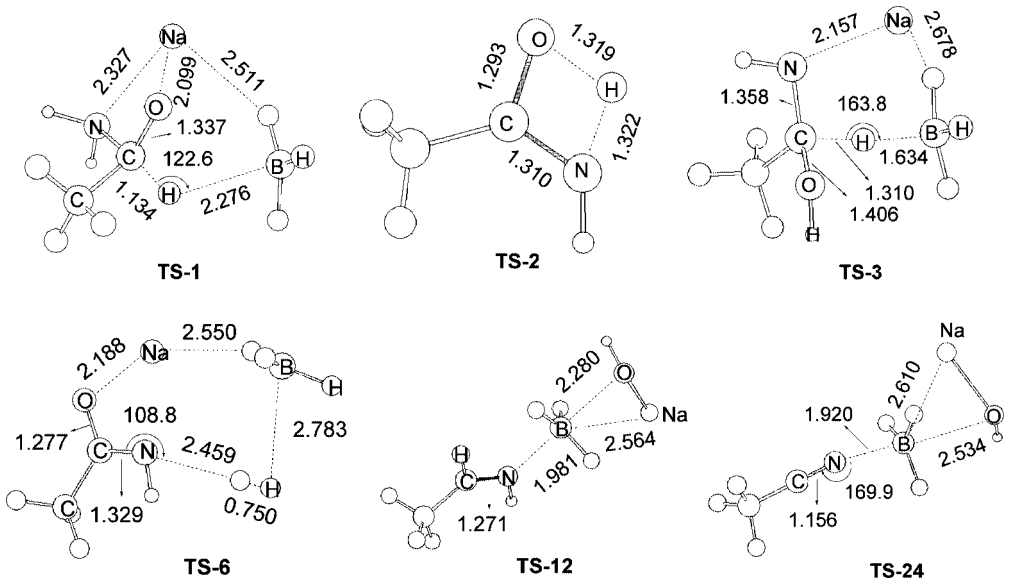


Figure 2. Six key TS structures.

the predicted mechanism was the same as (or different than) those obtained at the DFT//HF and DFT//DFT levels. The order of the barrier magnitudes in the reaction sequences is the same. For example, the order of the barrier values in the sequence of hydrogen gas formations via **TS-6**, **-7** and **-8** is the same using all three methods. The barrier data obtained by the DFT//DFT method were selected for discussions of the reaction paths for the model substrates in order to avoid duplication. Other mechanistic pathways, which were investigated beyond those shown in Figure 1, are also presented in the Supporting Information. These high-energy pathways could not compete with those shown in Figure 1. The six key TS structures are illustrated in Figure 2.

An $NaBH_4$/acetamide complex is formed initially in THF solution, and this is the species which must be considered in all amide reactions. This complex could further react through several different pathways which are summarized in Figure 1. (1) Direct reduction could occur via **TS-1** to ethylamine through route **A**. (2) The formation of H_2 via **TS-6** could generate the intermediate **1a** irreversibly. Intermediate **1a** could then proceed through **TS-14**, **-18** and **-13** to afford ethylamine. Alternatively, **1a** can follow another route through **TS-17** to **1c** (other routes to **1c** were found, e.g. **TS-16**, **-20** and **-21**, see Supporting Information for details). Then intermediate **1c** could go through **TS-23** and then **TS-24** to form acetonitrile (**4**) (see bottom of Figure 1). (3) Tautomerization of the complex of **1**/$NaBH_4$ to the enamide **2** could proceed through the favorable **TS-2**. **TS-15** and **-19** are higher energy routes listed in Table 1 and they are also summarized in the Supporting Information. Enamide **2** could then be reduced via **TS-3** to **1h** and then through **TS-12** and **-13** to ethylamine. Alternatively, **2** can generate a molecule of H_2 gas through **TS-7** or **-8** to generate intermediates **1b** or **1c**, respectively. Intermediate **1b** can yield acetonitrile **4** via **TS-22**. All of these paths were computationally investigated and compared. The final products which could form in these reactions depend on the TS barriers encountered.

Direct Reductions

The TS geometry for the hydride attack on the carbonyl carbon atom (**TS-1**) of acetamide **1** is shown below. This illustrates the transfer of a hydride ion to the carbonyl carbon atom.

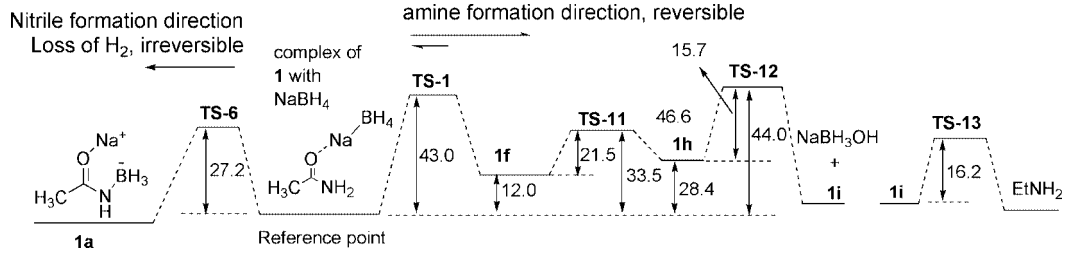
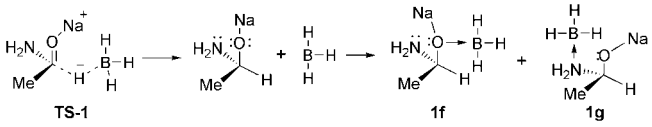
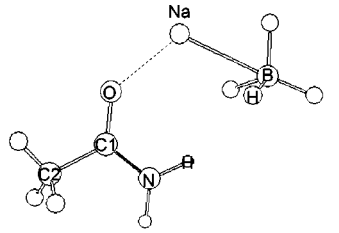


Figure 3. Energy diagram for two reaction pathways between acetamide and $NaBH_4$ in THF (with energies in kcal/mol). The energy of the $NaBH_4$ complex of **1** was selected as the reference point (zero point).



The hydride attack on the acetamide's carbonyl carbon atom occurs through **TS-1**, where Na^+ coordinates with the carbonyl oxygen atom, and the hydride transfer has a high barrier (43.0 kcal/mol in THF). Once this hydride transfer is completed, **TS-1** can decay directly to **1f**. Route **A** was the lowest energy pathway found to convert intermediate **1f** to ethylamine. Route **A** to ethylamine proceeds from **1f** to **1h** via **TS-11**. Then **1h** is converted to **1i** via **TS-12**. Finally, **1i** forms ethylamine via **TS-13**. The barriers to **TS-11**, **-12** and **-13** are 21.5, 15.7 and 16.2 kcal/mol in THF, respectively. A higher energy route via **TS-10** (shown in Table 1) exists but was not included in Figure 1. The conversion of the acetamide/$NaBH_4$ complex to ethylamine via **1f**, **1h** and **1i** must pass through **TS-1** with its 43.0 kcal/mol barrier. This route to ethylamine is never followed because the complex can irreversibly loose hydrogen to form **1a** through a much lower energy barrier. These two routes are illustrated in Figure 3. Once **1a** is generated, the reaction can never return to the acetamide/$NaBH_4$ complex. Thus, the conversion of **1a** to acetonitrile or ethylamine must be evaluated. First, the formation of **1a** is examined more closely.



Hydrogen Formation via TS-6

Direct hydride attack on an amino proton of **1** to form H_2 was explored.[20] The barrier in THF for this process is 27.2 kcal/mol via **TS-6** (Figure 1). This produces H_2 and **1a**. This barrier is much lower than the barrier for the reduction of amide by hydride attack at the carbonyl carbon atom via **TS-1**. Therefore, the hydride attack is predicted to occur on an amino group proton to give 1 equiv. of hydrogen through **TS-6**. The reaction of the second proton on the nitrogen atom with a hydride ion, after 1 mol of hydrogen gas had formed, requires the surmounting of a huge energy barrier (63.8 kcal/mol in THF via **TS-9**). Therefore, this process does not occur. This prediction agrees with the rapid generation of a single equivalent of hydrogen that we observed experimentally during $NaBH_4$ reactions with acetamide at 162 °C.[12] Thus, after 1 mol of hydrogen evolves, only **1a** is produced.

Reduction of 1a to Ethylamine

This reaction was explored because **1a** is the only product predicted to readily form upon the reaction of acetamide with $NaBH_4$. An extensive computational search revealed only one reasonable route from **1a** to ethylamine. Proceeding from **1a** via **TS-14** (Figure 1) requires two molecules of $NaBH_4$ and passes over a very high barrier in THF (49.8 kcal/mol). This reaction generates **1e**, followed by the formation of $NaBH_3(OH)$ and $[CH_3CH{=}NBH_3]^-Na^+$ via the high-energy **TS-18** ($\Delta E^{\neq}_{298}$ = 64.7 kcal/mol in THF). Finally, **1i** forms by hydrolysis and is then reduced by $NaBH_4$ to $EtNH_2$ ($\Delta E^{\neq}_{298}$ = 16.2 kcal/mol in THF). However, this route will not contribute to the actual reaction pathway because of the very high (64.7 kcal/mol) energy barrier present. In contrast, a lower energy process is available for **1a** to reach **1c**. This is achieved through **TS-17** by passing over a barrier of 46.1 kcal/mol in THF. Therefore, **1a** proceeds to **1c** via **TS-17** and eventually to acetonitrile (**4**) rather than traversing the higher barrier through **TS-14**.

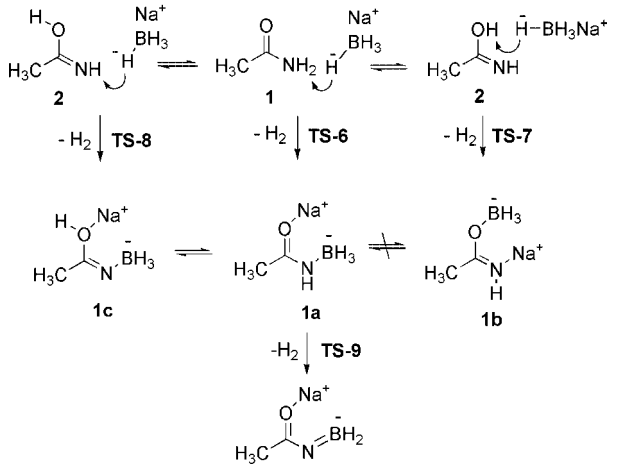
Other high-energy processes were uncovered to convert **1a** to **1c** in THF through **TS-16** (50.5 kcal/mol) or **TS-20** (91.8 kcal/mol at DFT//HF), but these cannot compete with the process through **TS-17** (46.1 kcal/mol). It is the lowest predicted energy path from **1a** to **1c**.

Tautomerization

It seemed possible that the enamide **2** [Equation (1)] could be formed at higher temperatures in the basic reaction environment. There might be a competing mechanism from **2** to acetonitrile. Therefore, we also investigated if initial hydrogen generation could result from the hydride attack on either the hydroxy or imino proton of the enamide **2** to generate either **1b** or **1c**, respectively (Scheme 1). The availability of reasonable routes from **2** to acetonitrile was also explored.

(1)

The lowest barrier in THF for the isomerization of **1** to the enamide tautomer **2** [Equation (1)] through **TS-2** was found to be 47.2 kcal/mol in THF (Table 1, Figure 1). Thus, the enamide **2** will not form if lower energy pathways are available. A careful search for other mechanisms from acetamide (**1**) to **2** was conducted. Two other pathways were found. These proceed through **TS-15** and **-19**, respectively (Table 1, see Supporting Information). However, the predicted activation barriers to each exceed 47.2 kcal/mol. These two pathways to **TS-15** and **-19** require 55.5 and 57.6 kcal/mol, respectively, in THF. Furthermore, the barrier for the hydride attack on the enamide **2** through **TS-3** in THF is high (49.6 kcal/mol) to give the precursor **1h**. Complex **1h** leads to **1i** and finally ethylamine. While the enamide **2** could afford ethylamine more readily than aceto-



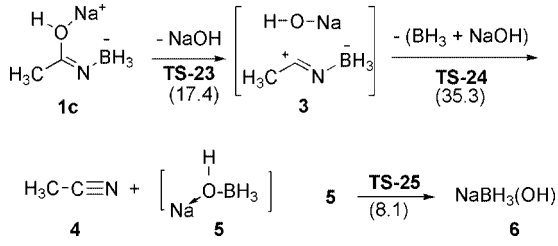
Scheme 1.

nitrile, it would generate **1c**. The enamide **2** requires 37.4 kcal/mol (DFT//HF) in THF to reach **TS-8** on the way to **1c**. Clearly, **2**, if formed, would generate **1c**. This route to **1c** is a more unfavorable one than the pathway from the $NaBH_4$ complex of acetamide. Conversion of **2** to **1b** by the hydride attack on the hydroxy proton via **TS-7** (Figure 1) needs only 12.9 kcal/mol in THF, but the subsequent transformation of **1b** to acetonitrile (**4**) through **TS-22** is a very high-energy path (60.0 kcal/mol in THF). All the barriers are much larger than the barrier from the acetonitrile/$NaBH_4$ complex to **TS-6** (27.2 kcal/mol) to form **1a** (Figure 1). Thus, the formation of acetonitrile or ethylamine through the enamide **2** is clearly not feasible.

Nitrile Formation Procedure

Pathways were found to convert the complexes **1a**, **1b** and **1c** to acetonitrile. A high-energy pathway from **1a** to the nitrile through **TS-20** must pass over a 91.8 kcal/mol (DFT//HF) barrier and followed by a small barrier (7.6 kcal/mol) through **TS-21** which leads to **1c**. In contrast, the lowest energy path from **1a** to **1c** is through **TS-17** ($\Delta E^{\neq}$ = 46.1 kcal/mol). Another conversion of **1a** to **1c** by direct proton transfer from N to O has a large (51.0 kcal/mol) calculated barrier in THF proceeding through **TS-16** (Figure 1). Therefore, it is unlikely to compete with proton transfer from N to O, via **TS-17** with its 46.1 kcal/mol barrier, which is 3.7 kcal/mol (or 2.5 kcal/mol by DFT//HF) smaller than the 49.8 kcal/mol barrier for reduction of complex **1a** to ethylamine via **TS-14**. Complex **1b** (derived from enamide **2** as shown in Figure 1) must pass through the high-energy **TS-22** (60.0 kcal/mol barrier) to form acetonitrile (Figure 1). Acetamide (**1**), is 13.5 kcal/mol more stable than **2** and must surmount a 47.2 kcal/mol barrier to generate **2**. Combining these results with the irreversible formation of **1a** (from the $NaBH_4$ complex of **1**) through **TS-6** means that **1c** only arises from **1a**. Finally, acetonitrile must form from **1c**.

After an examination of all the transition states and pathways found in this comprehensive search, the reaction of acetamide with $NaBH_4$ is predicted to proceed from **1** to **1a** and then from **1a** through **TS-17** to form the complex **1c**. This conclusion is reached whether the calculations were performed using DFT//HF or DFT//DFT computations in THF. The lowest energy pathway from **1c** to acetonitrile (**4**) then follows the two-step sequence shown in Scheme 2 and Figure 1. First, **1c** undergoes carbon–oxygen bond elongation and Na^+ coordinates more strongly to the developing hydroxy oxygen atom through **TS-23**. This gives intermediate **3** by crossing a small 17.4 kcal/mol barrier in THF. Coordination of BH_3 to the nitrogen atom stabilizes the positive charge at the nitrile carbon atom in intermediate **3**. Then BH_3 separates from N and coordinates with the oxygen atom of the hydroxy group, while the boron–nitrogen distance elongates while passing through **TS-24** with an activation energy in THF of 35.3 kcal/mol. **TS-24** proceeds to acetonitrile (**4**) and intermediate complex **5** is formed during the loss of NaOH and BH_3. Complex **5** then rearranges through an 8.1 kcal/mol barrier to form $NaBH_3OH$ (**6**) via **TS-25**. An energy diagram for the most favorable mecha-



Scheme 2.

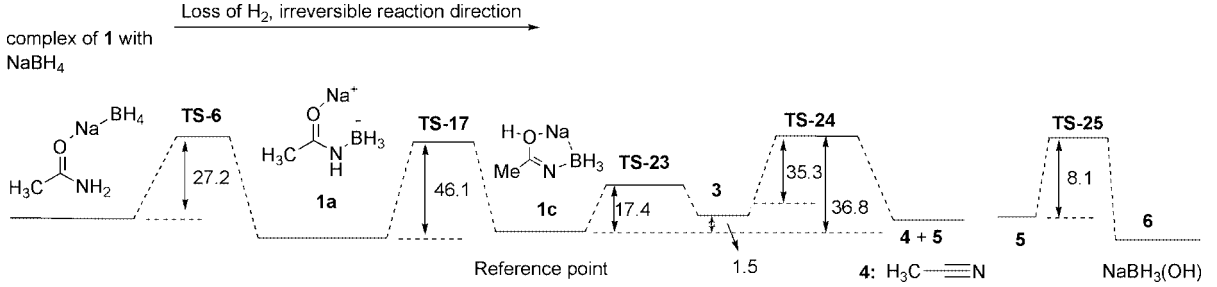
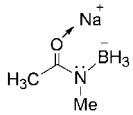


Figure 4. The lowest energy mechanism predicted for the conversion of acetamide (**1**) to acetonitrile (**4**) with $NaBH_4$ in THF (energies in kcal/mol). The energy of complex **1c** was selected as the reference point (zero point).

nism for the conversion of acetamide to acetonitrile is illustrated in Figure 4.

Secondary and Tertiary Amide Reductions

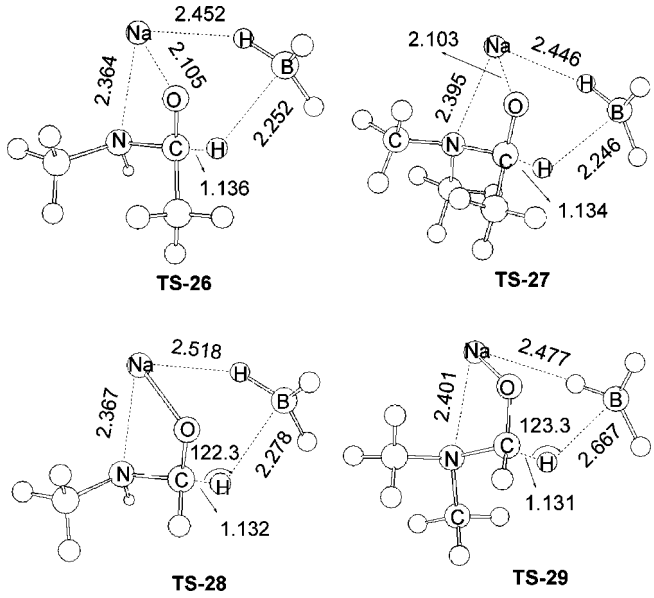
Calculations were extended to secondary and tertiary amide model compounds. *N*-Methylacetamide cannot react with $NaBH_4$ to form an intermediate analogous to **1c** as it has only a single proton on the nitrogen atom. Furthermore, it is impossible to form the corresponding nitrile. However, hydride attack on the –NHMe proton can give the *N*-methyl complex **7** with the loss of 1 equiv. of hydrogen. The zwitterion **7** is the *N*-methyl analog of **1a**. Reduction of complex **7** to the amine must proceed through a TS barrier that will be greater than the 49.8 kcal/mol barrier encountered during the conversion of acetamide via **1a** to **TS-14** on the route to ethylamine. Complex **7** will encounter more steric repulsions due to its *N*-methyl group than would **1a** which has no *N*-methyl substituent. This predicted high barrier agrees with our inability to experimentally reduce *N*-methylacetamide with $NaBH_4$, even at 162 °C in glyme solvents. Direct hydride transfer to the carbonyl carbon atom occurs through **TS-26** with a barrier of 43.7 kcal/mol but no subsequent low-energy paths are available, so this step will reverse.



7

Tertiary amides have no NH hydrogen atom. Thus, no complexes analogous to **1a**, **1b** or **1c** can be formed. The barrier for the $NaBH_4$ hydride transfer to the carbonyl carbon atom of *N*,*N*-dimethylacetamide is 49.2 kcal/mol and occurs via **TS-27**. This predicts that tertiary amides will be very difficult to reduce. In fact, our experiments demonstrate that they can only be reduced by $NaBH_4$ at high temperatures in the presence of Li^+.[12] The TS structures in reactions of *N*-methylacetamide, *N*,*N*-dimethylacetamide, *N*-methylformamide and *N*,*N*-dimethylformamide with sodium borohydride, **TS-26** to **TS-29**, are listed below, respectively.

The effect of a single *N*-methyl group on the TS barriers for the transfer of a hydride ion by $NaBH_4$ to the amide carbonyl carbon atom was minor but two *N*-methyl groups raise the barrier. Hydride transfer to acetamide via **TS-1** has a barrier in THF of 43.0 kcal/mol. The corresponding hydride transfers to *N*-methylacetamide and *N*,*N*-dimethylacetamide have computed barriers in THF of 43.7 (via **TS-26**) and 49.2 kcal/mol (via **TS-27**), respectively. The corresponding barriers in THF for direct hydride transfer to the carbonyl carbon atoms of formamide, *N*-methylformamide and *N*,*N*-dimethylformamide are 42.3 (via **TS-4**), 45.8 (via **TS-28**) and 49.2 kcal/mol (via **TS-29**), respectively. Again, the effect of replacing a hydrogen atom with the first methyl group on the N atom is small. However, the effect of replacing a hydrogen atom with a second methyl group



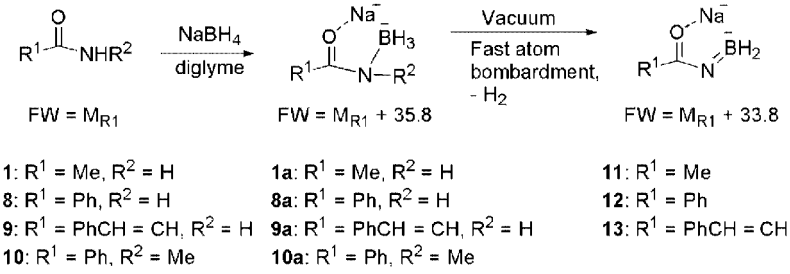
on the N atom becomes substantial. The difference in difficulty of directly transferring a hydride ion to formamide vs. acetamide in THF is predicted to be quite small (42.3 kcal/mol for formation vs. 43.0 kcal/mol for acetamide).

Conclusion

Theoretical investigations of the $NaBH_4$ reaction of amides at B3LYP/6-31++G(d,p)//HF/6-31G(d,p) and B3LYP/6-31++G(d,p)//B3LYP/6-31G(d,p) levels revealed many previously unknown features of the mechanism. The mechanism of nitrile formation from primary amides and sodium borohydride was predicted. The involvement of sodium is important in the TS geometry optimizations. The key intermediate predicted in computations was confirmed by experiments. The mechanism predicted in computations involved attack by a hydride ion on a proton of the amide group to produce 1 equiv. of hydrogen gas and a complex with Na^+ coordinated to the carbonyl function and BH_3 bound to the nitrogen atom. Subsequently, three additional steps convert this complex to the nitrile with the largest predicted activation barrier of 46.1 kcal/mol in THF.

Experimental Section

A general procedure is described below for the isolation of the intermediates from the primary amide or secondary amide reactions.[12] A primary or secondary amide (1.0 mmol) was dissolved in dried diglyme (20 mL); 1 equiv. of $NaBH_4$ was added to this diglyme solution. This mixture was then heated to 100 °C rapidly and kept at this temperature for 20 min. The diglyme solution was then cooled quickly to room temperature. Dried diethyl ether (10 mL) was then added dropwise to the diglyme solution, and a white solid appeared. This solid (the intermediate complex) was then filtered and washed with dried diethyl ether until no diglyme could be detected in the washings (with diethyl ether). Each intermediate was then dried under reduced pressure (< 1 Torr) to a constant weight. The intermediates obtained were used for high-



(2)

resolution MS determinations and elemental analyses. Evidence was found to confirm the structures of **1a** or **7** analogs. The reaction of primary amides and secondary amides with sodium borohydride rapidly generated 1 mol of hydrogen gas and formed the intermediate complexes. These complexes only dissolved in diglyme but were insoluble in [D_8]toluene or [D_5]pyridine, precluding NMR analyses. Primary and secondary amides were consumed to form the intermediate complexes in solution after $NaBH_4$ addition at 100 °C [Equation (2)]. However, the intermediates **1a** and **7** existed in solution for a long time as their conversions to nitrile have very high barriers (e.g., 49.8 kcal/mol for **1a**). Therefore, after hydrogen evolution, the intermediate complexes, such as **1a** or **7** [e.g., **1a**, **8a** to **10a**; Equation (2)] could be obtained in diglyme. Thus, these intermediate complexes were isolated, and their existence confirmed the structures predicted by computations.

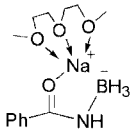
None of the starting materials in the experiments to generate **1a**, **8a** to **10a** [Equation (2)] were detected by mass spectrometry (MS) when a mixture of amyl acetate (HO-free, high-boiling solvent) and diglyme was used as a matrix. During high-resolution mass determinations, complexes **11** to **13** were formed by loss of hydrogen [Equation (2)]. Accurate molecular masses were measured using ESI and/or FAB^+ methods. The molecular masses are summarized in Table 2. The molecular masses of the intermediate complexes (e.g., structures **1a** and **7**) formed in primary and secondary amide reactions with sodium borohydride are 33.8 or 35.8 mass units larger than those of the corresponding amides. Similar experiments with tertiary amides gave mass spectra only of these tertiary amides. No complexes were detected. Primary and secondary amides reacted with sodium borohydride to form the intermediate complexes after loss of one molecule of hydrogen gas, but tertiary amides cannot react in this manner.

The masses of the primary amide intermediate complexes were determined using a mixture of glycerine and diglyme as a matrix. Mass determinations after glycerine addition exhibited peaks of starting materials because glycerine caused a loss of diglyme from the complexes. The molecular masses of the intermediates **1a**, **8a**–**10a**, formed by loss of a single equivalent of H_2 and complexed by one molecule of diglyme and not decomposed by glycerine, were observed (Figure 5). The molecular masses of these complexes contain a coordinated diglyme. The loss of a sodium atom was observed by high-resolution MS ([– Na] was used to present the molecular mass after sodium loss in HRMS determinations). These high-resolution molecular masses are in excellent agreement with the calculated values.

Finally, the elemental analyses (EA) were performed on the isolated intermediates. The found percentages of C, H and N agree well

Table 2. Molecular masses from high-resolution mass spectrometry for the intermediate complexes formed in reactions of four representative amides with in diglyme at 100 °C.

Entry	Substrate (mol. mass)	Mol. mass for **1a**, **8a**–**10a** (calcd./found)	Mol. mass for **11**–**14** (calcd./found)
1	acetamide (59)	**1a**: 95.0518/–	**11** [+ H]: 94.0555/94.0513
2	benzamide (121)	**8a**: 157.0674/–	**12**: 155.0633/155.0628
3	cinnamamide (147)	**9a**: 183.0831/–	**13**: 181.0789/181.0776
4	*N*-methylbenzamide (135)	**10a**: 171.0946/171.0940	–

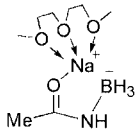


MS: Calcd.: FW=291
Found: FW=291

HRMS: Calcd. [-Na]: FW=291.1617
Found [-Na]: FW=291.1625

EA: Calcd.: C: 53.61, H: 7.11, N: 4.81
Found: C: 53.38, H: 7.28, N: 4.62

15

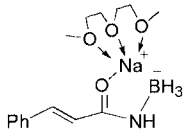


Calcd.: FW=229
Found: FW=229
[-Na]: 206

Calcd. [-Na]: FW=229.1460
Found [-Na]: FW=229.1469

Calcd.: C: 41.92, H: 9.17, N: 6.11
Found: C: 41.67, H: 9.33, N: 5.82

16

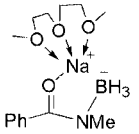


Calcd.: FW=317
Found: FW=317
[-Na]: 295

Calcd. [-Na]: FW=295.1955
Found [-Na]: FW=295.1950

Calcd.: C:34.07, H: 7.89, N: 4.42
Found: C: 33.88, H: 8.14, N: 4.20

17



Calcd.: FW=305
Found [-Na]: 282

Calcd.[-Na]: FW=282.1991
Found [-Na]: FW=282.1996

Calcd.: C: 55.08, H: 8.20, N: 4.59
Found: C: 54.73, H: 8.52, N: 4.40

18

Figure 5. HR-MS-determined molecular masses and elemental analyses for the intermediates formed by treating primary and secondary amides with $NaBH_4$ in diglyme after the evolution of 1 equiv. of H_2.

with the calcd. values, when 1 equiv. of diglyme was present. The percenages of B in each intermediate were also analyzed and these values agree with the calcd. ones. These results are listed in Figure 5. All such experiments confirm the formation of **1a** analogs complexed to diglyme in each reaction studied. The long reaction time (3 h) at 162 °C required to form the nitriles in primary amide reactions with sodium borohydride confirm the presence of large barriers. This agrees well with the high activation barriers predicted in the computational mechanistic investigations.

Supporting Information (see footnote on the first page of this article): Details of computations and experiments.

Acknowledgments

H.-J. Z. thanks the for the support from CAS ("Hundred Talents Program" Fund) and The Sciences and Technology Committee of Yunnan Province. C. U. P. thanks the Ferro Corporation (Grant Chemical Division) for partial support. H. L. Liang is thanked for the HR-MS measurements of all the intermediates reported in this paper.

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[19] The $NaBH_4$/amide complex formed in solution is the reagent which leads to the TS. This complex has several conformations. Only the most stable conformational energy (lowest energy) was used in the barrier computations.

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