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Ab initio study of Lewis acid catalyzed nitrone cycloaddition to electron deficient alkenes. Does a Lewis acid catalyst change the reaction mechanism?

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Abstract—Theoretical study of Lewis acid catalyzed nitrone cycloadditions to α,β-unsaturated carbonyl compounds is reported. Ab initio calculation using the 6-31++G** basis set has been applied to the model reaction between the parent nitrone (CH_2=N(O)H) and acrolein (CH_2=CHCHO) in the presence of BH_3 or BF_3 catalyst. Although the nitrone/BH_3 complex is predominantly formed at the early stage of the reaction, the acrolein/BH_3 complex as minor contributor shows high rate acceleration, giving the electronically controlled endo-isoxazolidine-4-carbaldehyde complex as the major regio- and stereoisomeric cycloadduct. On the other hand, the nitrone cycloaddition reaction of acrolein in the presence of BF_3 leads to the formation of the corresponding Michael adduct complex intermediate which then cyclizes to the isoxazolidine-4-carbaldehyde complex. These calculation studies indicate that the nitrone cycloadditions with electron-deficient alkenes may proceed through a stepwise mechanism when catalyzed by a strong Lewis acid.

1. Introduction

1,3-Dipolar cycloaddition reactions offer one of the most powerful routes to heterocyclic compounds.[1] High stereospecificity and stereoselectivity are the reason why these reactions are synthetically so useful in organic synthetic field.[2] Based on a number of reports on stereochemical, kinetic, and theoretical studies, 1,3-dipolar cycloaddition reactions are concluded to proceed through a concerted mechanism.[3] Recently, the study of stereochemical and regiochemical control of these reactions by the aid of external reagents has appeared.[4] Metal reagent-assisted chirality control and improvement of reactivity are the major purposes. And now, the catalyzed variants of enantioselective nitrone cycloaddition reactions are known.[5]

When electron-deficient alkenes such as α,β-unsaturated carbonyl compounds are activated by coordination to a Lewis acid catalyst, the carbon–carbon bond of the alkene should be highly polarized to increase the electrophilicity of the β-carbon. In 1,3-dipolar cycloaddition reactions of α,β-unsaturated carbonyl acceptors activated by a Lewis acid, attack of the nucleophilic atom of 1,3-dipoles to the β-carbon should become more favored rather than the bond formation at the α-carbon. As a result, it is easily to expect that the bond formation at the β-carbon of dipolarophile would precede that at the α-carbon. Accordingly, one simple question arises; 'Do the Lewis acid catalyzed 1,3-dipolar cycloadditions proceed through a concerted mechanism or a stepwise mechanism?' This question has been rarely answered.[6] Jørgensen and coworkers have reported semiempirical calculations of the magnesium catalyzed nitrone cycloaddition reactions to α,β-unsaturated carbonyl acceptors.[5c] They have pointed out that the forming bond between the β-carbon of the acceptor and the nitrone oxygen was relatively shortened in the transition state. However, their major interest was focused to explain the origin of stereoselectivity. The calculation method was limited to a semiempirical level.

In this paper, we would like to report the theoretical study by application of ab initio calculations to the nitrone cycloaddition reactions with an α,β-unsaturated carbonyl compound in the presence of Lewis acid catalysts.

2. Computational methods

Theoretical study was performed for the model nitrone cycloaddition reaction between *N*-methyleneamine *N*-oxide (**1**) as the parent nitrone and acrolein (**2**) as the simplest α,β-unsaturated carbonyl dipolarophile in the presence of borane (BH_3) or boron trifluoride (BF_3) as Lewis acid catalyst. Structures were optimized by the step by step calculations starting with the semiempirical calculation using the MOPAC program,[7] then moving to the ab initio calculation with a lower level of basis set of 3-21G*,

Keywords: nitrone; Lewis acid catalyst; ab initio calculation; transition state; Michael reaction; reaction mechanism.

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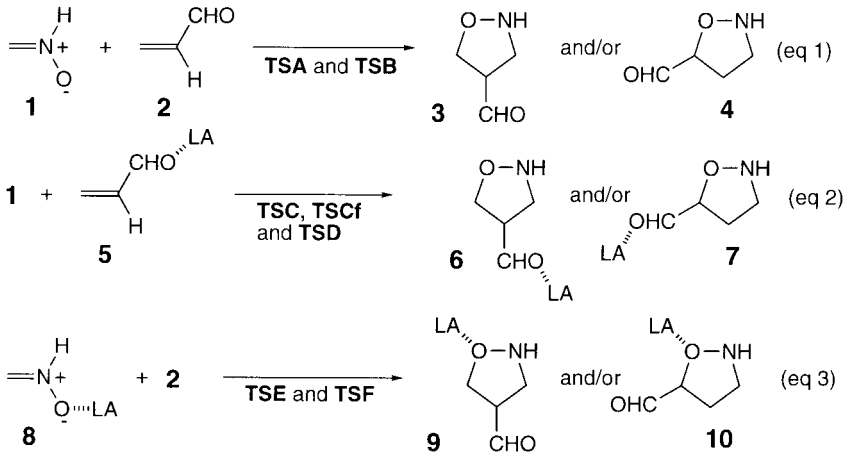

Scheme 1.

Table 1. Total energies for the reactants, TS and products and their relative energies

	Energy total (Hartree)	ΔE (kcal/mol)	ΔE_a (kcal/mol)[h]
BH_3	−26.3935422		
BF_3	−323.2089340		
Nitrone (**1**)	−168.8271336		
Acrolein (**2**)	−190.7770969		
Acrolein/BH_3 (**5**)	−217.1836487	−8.2[a]	
Nitrone/BH_3 (**8**)	−195.2514153	−19.4[b]	
Acrolein/BF3 (**11**)	−514.0014280	−9.7[c]	
Nitrone/BF3 (**12**)	−492.0577594	−24.9[d]	
***exo*-Cycloaddition**			
Uncatalyzed reaction			
exo-**TSA**	−359.5632405		25.7
exo-**3**	−359.6557592	−32.3[e]	
exo-**TSB**	−359.5546112		31.1
exo-**4**	−359.6592805	−34.5[e]	
Via acrolein/BH_3			
exo-**TSC**	−385.9841542	8.5[f]	16.7
exo-**6** (LA=BH_3)	−386.0620937	−40.3[f]	
exo-**TSD**	−385.9628367	21.9[f]	30.1
exo-**7** (LA=BH_3)	−386.0636976	−41.3[f]	
Via nitrone/BH_3			
exo-**TSE**	−385.9800824	11.1[f]	30.5
exo-**9** (LA=BH_3)	−386.0613049	−39.8[f]	
exo-**TSF**	−385.9716161	16.4[f]	35.8
exo-**10** (LA=BH_3)	−386.0635718	−41.3[f]	
Via nitrone/BF_3			
MA (LA=BF_3)	−682.8226366	−5.9[g]	
TSG	−682.8154961	−1.5[g]	4.4
6 (LA=BF_3)	−682.8782271	−40.8[g]	
***endo*-Cycloaddition**			
Uncatalyzed reaction			
endo-**TSA**	−359.5640426		25.2
endo-**3** (LA=BH_3)	−359.6556159	−32.2[e]	
endo-**TSB**	−359.5551464		30.8
Acrolein/BH_3			
endo-**TSC**	−385.9906080	4.5[f]	12.7
endo-**6** (LA=BH_3)	−386.0609002	−39.6[f]	
endo-**TSD**	−385.9645959	20.8[f]	29.0
Nitrone/BH_3			
endo-**TSE**	−385.9816099	10.1[f]	29.5
endo-**9** (LA=BH_3)	−386.0616745	−40.1[f]	

[a] Energy relative to **2** and BH_3.
[b] Energy relative to **1** and BH_3.
[c] Energy relative to **2** and BF_3.
[d] Energy relative to **1** and BF_3.
[e] Energy relative to **1** and **2**.
[f] Energy relative to **1**, **2** and BH_3.
[g] Energy relative to **1**, **2** and BF_3.
[h] Activation energy from acrolein and nitrone or thier correspounding Lewis acid complex.

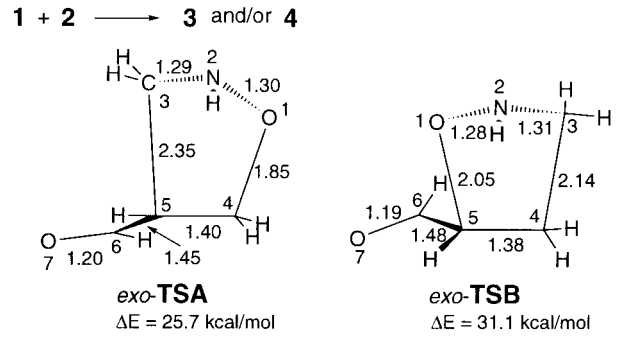

Figure 1. The *exo*-transition structures calculated by the RHF/6-31++G** levels of theory for the reaction of **1** with **2** under the uncatalyzed conditions leading to *exo*-**3** (**TSA**) and/or *exo*-**4** (**TSB**). Energy difference ΔE is based on the energy of the ground state components. Bond length is in angstroms.

and finally the calculation was completed by the ab initio calculation with the 6-31++G** basis set.[8] Stationary points were converged in all cases within default threshold of force constant and displacement. The vibration associated with the imaginary frequency was checked to the consistency with the formation of C–C and C–O bonds. In the case of the transition structure **TSC** of the reaction BH_3/acrolein complex, IRC calculation was carried out to confirm the concerted bond formations.

Calculations were performed for the following reactions (Scheme 1):

1. The reactions between **1** and **2** under uncatalyzed conditions to give regioisomeric cycloadducts, isoxazolidine-4-carbaldehyde (**3**) and isoxazolidine-5-carbaldehyde (**4**), through the transition structures **TSA** and **TSB**, respectively (Eq. (1)).
2. The reactions between **1** and **2** under catalyzed conditions via the CH_2=CHCHO/BH_3 complex (**5**) leading to the isoxazolidine-4-carbaldehyde complex (**6**) and the isoxazolidine-5-carbaldehyde complex (**7**), through the transition structures **TSC** and **TSD**, respectively (Eq. (2), LA=BH_3).
3. The reactions between **1** and **2** under catalyzed conditions via the CH_2=N(O)H/BH_3 complex (**8**) giving the isoxazolidine-4-carbaldehyde complex (**9**) and the isoxazolidine-5-carbaldehyde complex (**10**), through the transition structures **TSE** and **TSF**, respectively (Eq. (3)).
4. The reaction between **1** and **2** under catalyzed conditions via the CH_2=CHCHO/BF_3 complex (**5f**) forming the Michael adduct complex **MA**, followed by its cyclization to give the isoxazolidine-4-carbaldehyde complex (**6f**) through the transition structure **TSG** (Eq. (2), LA=BF_3).

3. Results and discussion

3.1. Uncatalyzed reaction

The uncatalyzed cycloaddition reactions between nitrone (**1**) and acrolein (**2**), leading to two regioisomeric cycloadducts **3** and **4**, were both calculated to proceed through the concerted mechanisms. Two diastereomeric transition structures are possible,[9] and the *endo*-transition structure was slightly more stable than the *exo*-transition structure. The activation energies for the transition structure **TSA** leading to the *endo*- and *exo*-isoxazolidine-4-carbaldehydes (*endo*-**3** and *exo*-**3**) were 25.2 and 25.7 kcal/mol, respectively (Table 1). Similarly the activation energies for the transition structure **TSB** leading to the *endo*- and *exo*-isoxazolidine-5-carbaldehydes (*endo*-**4** and *exo*-**4**) were 30.8 and 31.1 kcal/mol, respectively. The transition structures **TSA** were more stable than **TSB** by 5.6 and 5.4 kcal/mol for the *endo*- and *exo*-isomers, respectively. This regioselectivity preference for the electronically controlled cycloadduct **3** rather than the sterically controlled cycloadduct **4** is consistent with the experimental results often observed in nitrone cycloadditions of electron-deficient dipolarophiles under the uncatalyzed conditions.[10] Since the energy difference for the *endo*- and *exo*-transition structures was not big enough for the calculation errors, only the *exo*-reactions were chosen for the following calculations unless otherwise discussed. In Fig. 1, the *exo*-transition structures **TSA** and **TSB** are illustrated.

3.2. Catalyzed reaction via acrolein/BH_3 complex

Reaction between **1** and **2** under the catalysis of a weak Lewis acid BH_3 was calculated (6-31++G**, Fig. 2). Since the frontier orbital theory[11] teaches us that electron-deficient alkenes can be activated when coordinated to a Lewis acid catalyst in the reaction with nucleophiles, reaction of nitrone (**1**) with the acrolein/BH_3 complex (**5**) was first chosen for calculation. The acrolein complex **5** was estimated to be 8.2 kcal/mol more stable than the total

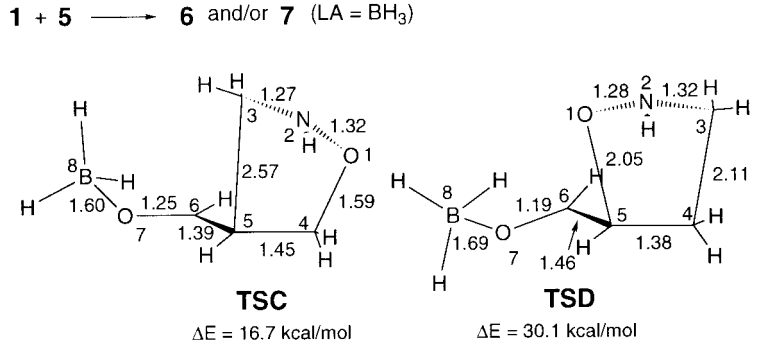

Figure 2. Transition structures calculated by the RHF/6-31++G** levels of theory for the reaction of **1** with the acrolein/BH_3 complex **5** leading to **6** (**TSC**) and/or **7** (**TSD**). Energy difference ΔE is based on the total energy of the starting components (**1**+**5**). Bond length is in angstroms.

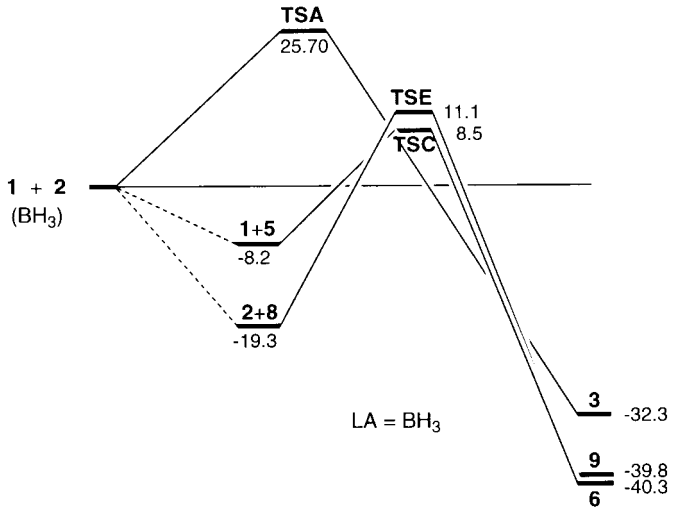

Figure 3. Energy profiles of the nitrone cycloaddition with acrolein in the presence of BH_3 leading to *exo*-isoxazoline-4-carbaldehyde and complexes. Energy difference ΔE is based on the total energy of the starting components.

energy calculated for the starting components, **2** and BH_3 (Fig. 3). This complex **5** next reacts with nitrone (**1**) to give regioisomeric cycloadduct complexes, the isoxazolidine-4-carbaldehyde complex **6** as the electronically controlled regioisomer via **TSC** and/or the isoxazolidine-5-carbaldehyde complex **7** as the sterically controlled regioisomer via **TSD**.

The complex **5** was found to react with nitrone (**1**) through a concerted reaction mechanism (Scheme 1, Eq. (2), LA=BH_3). Activation energies leading to **TSC** and **TSD** based on components **1**, **2**, and BH_3 were calculated to be 8.5 and 21.9 kcal/mol (both producing *exo*-cycloadducts), respectively. Especially, the reaction leading to the isoxazolidine-4-carbaldehyde complex **6** as the electronically controlled regioisomer was more favored than that leading to its regioisomeric cycloadduct complex **7**, and the energy difference observed (13.4 kcal/mol) under the catalyzed conditions was much bigger than that observed in the uncatalyzed reaction (5.4 kcal/mol). Thus, an excellent regioselectivity in favor for the isoxazolidine-4-carbaldehyde regioisomer can be expected under the Lewis acid catalyzed conditions. This preference for the formation of electronically controlled cycloadduct **6** had been readily anticipated at the early stage of this work by a simple electronic analysis of the reaction. Coordination of the carbonyl oxygen of **2** to BH_3 should make this carbonyl group more electron-withdrawing so that the β-carbon of **2** becomes more electrophilic. Accordingly, *under the Lewis acid catalyzed conditions, the attack of nucleophilic nitrone oxygen should become more favored to occur at the β-position.*

When the optimized transition structures of *exo*-**TSA** (Fig. 1) for the uncatalyzed reaction and *exo*-**TSC** (Fig. 2) for the BH_3-catalyzed reaction, both leading to the electronically controlled regioisomers **3** and complex **6**, were compared, origin of the expected regioselectivity can be understood as follows. Under the catalyzed conditions the O(1)–C(4) bond was shortened (**TSA**: 1.85 Å, **TSC**: 1.59 Å), while the C(3)–C(5) bond was lengthened instead (**TSA**: 2.35 Å, **TSC**: 2.57 Å). This indicates that the β-carbon of acceptor **2** becomes more electrophilic by coordination to the catalyst BH_3. The bond formation between the O(1) and C(4) atoms in the transition structure **TSC** can be highly stabilized by the polarized carbonyl double bond of the acceptor **2**. As a result, *the synchronousness of bond formation between O(1)–C(4) and C(3)–C(5) in a Lewis acid catalyzed nitrone cycloaddition reaction starts to collapse.*

On the other hand, two transition structures **TSB** and **TSD** for the reactions leading to the sterically controlled isoxazolidine-5-carbaldehydes **4** and complex **7**, respectively, were close to each other regardless of the presence of BH_3. The reason would be that the activation effect by coordination to the catalyst BH_3 is indirect in this case. Although the *endo*- and *exo*-transition states **TSA** leading to the diastereomeric isoxazolidine-4-carbaldehydes **3** were comparable in stabilization energies (0.5 kcal/mol difference) under the uncatalyzed conditions, *endo*-**TSC** was much more stabilized than *exo*-**TSC** under the BH_3-catalyzed conditions (4.0 kcal/mol difference). This indicates that *under the Lewis acid catalyzed conditions, the diastereoselectivity preference for the formation of endo-cycloadducts results.*

3.3. Catalyzed reaction via nitrone/BH_3 complex

Nitrones as a typical 1,3-dipole are nucleophiles as strongly coordinating ligands to a Lewis acid catalyst so that the nitrone/Lewis acid complex should be mostly formed in the first stage of the Lewis acid-catalyzed nitrone cycloadditions to electron-deficient alkenes. Accordingly, we calculated the cycloaddition reactions of acrolein (**2**) with the nitrone/BH_3 complex **8** (Fig. 3). As anticipated, the nitrone/BH_3 complex **8** was calculated to be highly stabilized with a stabilization energy of 19.3 kcal/mol lower from the ground state including **1**, **2**, and BH_3. When an activation energy as high as 30.4 kcal/mol is given to this complex **8**, the reaction reaches to a transition state **TSE**, and then goes down to the *exo*-isoxazolidine-4-carbaldehyde complex (*exo*-**9**). Thus, this reaction was also estimated to be concerted. The reaction path from the complex **8** leading to the regioisomeric cycloadduct

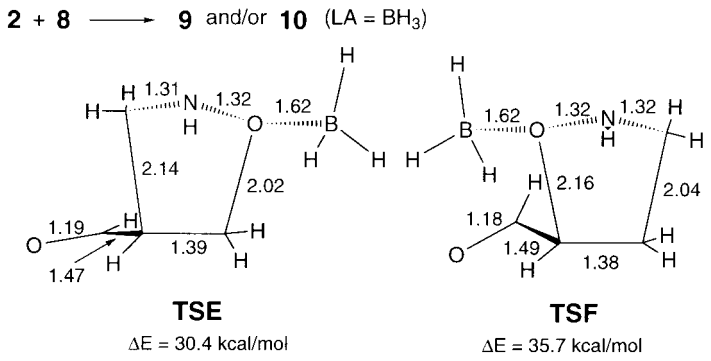

Figure 4. Transition structures calculated by the RHF/6-31++G** levels of theory for the reaction of **2** with the nitrone/BH_3 complex **8** leading to **9** (**TSE**) and/or **10** (**TSF**). Energy difference ΔE is based on the total energy of the starting components (**2**+**8**). Bond length is in angstroms.

complex *exo*-**10** needed even a little bigger activation energy (35.7 kcal/mol, Fig. 4).

Based on the relative stability between the acrolein/BH_3 complex (**5**) and the nitrone/BH_3 complex (**8**), it is apparent that the reaction of nitrone (**1**) with an electron-deficient alkene **2** in the presence of a Lewis acid catalyst BH_3 predominantly forms the nitrone complex **8** rather than the acrolein complex **5**. The latter acceptor complex **5** should be much more desired for the high rate acceleration by a Lewis acid catalyst, according to the frontier orbital theory.[11] However, the stabilization energy preference was estimated to be 11.1 kcal/mol in favor for **8**. Therefore, there is little opportunity that the desired acceptor complex **5** can participate in the catalyzed cycloaddition reactions. However fortunately, *the reaction of nitrone/BH_3 complex **8** with acrolein **2** is rather deactivated than the uncatalyzed reaction* between **1** and **2** (Fig. 3). As a result, *the catalyzed reactions from the acceptor complex **5** become the major reaction path if the uncatalyzed reaction is inhibited.*

3.4. Catalyzed reaction via nitrone/BF_3 complex

Among the calculation data collection shown above for the BH_3-catalyzed cycloaddition reactions between nitrone (**1**) and acrolein (**2**) leading to the regioisomeric cycloadduct complexes, via the acrolein/BH_3 complex **5** (Scheme 1, Eq. (2), LA=BH_3) and the nitrone/BH_3 complex **8** (Scheme 1, Eq. (3), LA=BH_3), the reaction of free nitrone (**1**) with the acrolein/BH_3 complex (**5**) leading to the isoxazolidine-4-carbaldehyde complex **6** was energetically most favored. Accordingly, BH_3 was replaced with a relatively strong Lewis acid BF_3 in the same reaction, and ab initio calculation was further applied (Scheme 1, Eq. (2), LA=BF_3). Although the corresponding transition structure could not be figured out, *the product structure optimized was not the cycloadduct complex **6** but the corresponding Michael adduct complex intermediate **MA*** (Figs. 5 and 6).

The bond distance between O(1)–C(4) of **MA** was estimated to be 1.53 Å indicating that the carbon–oxygen bond formation was almost complete in this stage, while the bond distance between C(3)–C(5) was estimated to be 3.04 Å showing no bond formation. Thus, the structure of **MA** was confirmed to be the Michael adduct complex, which is then transformed to the cyclized product complex **9** through a transition state **TSG**. In the transition structure **TSG** optimized, the C(3)–C(5) bond distance was shortened (2.39 Å). Except for the shortened bond length of C(3)–C(5), structures of **MA** and **TSG** are quite close each other. The energy difference of 4.5 kcal/mol between **MA** and **TSG** is consistent with the close structural resemblance (Fig. 6).

The existence of Michael adduct complex intermediate **MA**

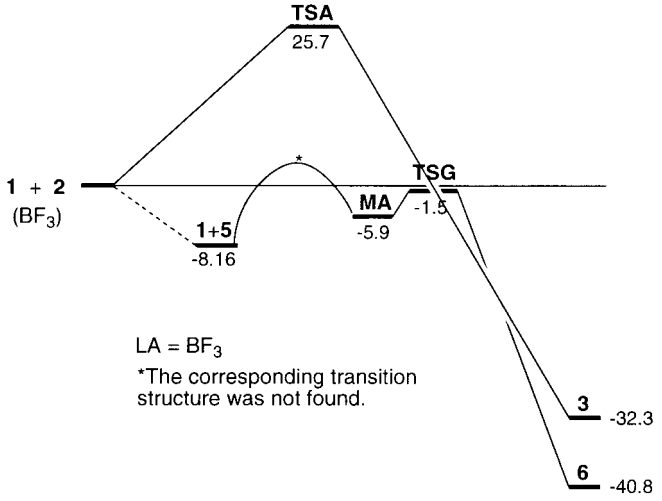

Figure 5. Energy profiles of the nitrone cycloaddition with acrolein in the presence of BF_3 leading to isoxazoline-4-carbaldehyde and complexes.

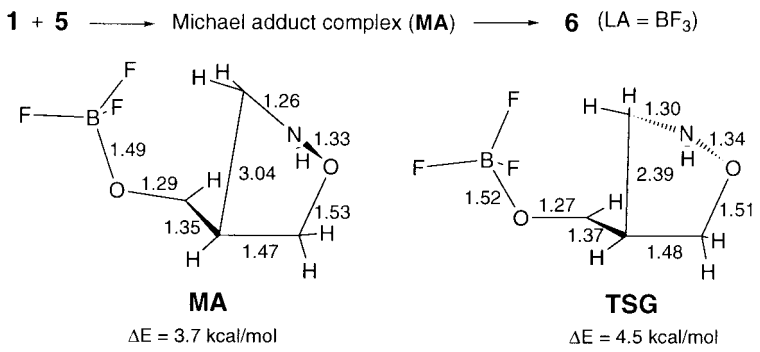

Figure 6. Structures of the Michael adduct complex **MA** and the transition structure for the cyclization of **MA** leading to **6** in the reaction of **1** with the acrolein/BF_3 complex, both optimized by the RHF/6-31++G^{**} levels of theory. Energy difference ΔE is based on the total energy of the starting components (**1**+**5** or **MA**). Bond length is in angstroms.

shows that the BF_3-catalyzed reaction proceeds in a stepwise mechanism in place of concerted mechanism. In the reaction using a weak Lewis acid such as BH_3, the stability of Michael adduct complex is not so high enough to stay at the stage of Michael adduct formation. Then, the BH_3-catalyzed reaction was observed to proceed through a concerted mechanism. Accordingly, the reaction mechanism may change depending upon the acidity of Lewis acid used. It was previously calculated that the cycloaddition reaction of methylene imine as the parent azomethine ylide to acrolein proceeded in a concerted manner in the absence of Lewis acid catalyst, while the same reaction was calculated to be a stepwise reaction via the Michael adduct intermediate in the presence of lithium ion.[12] Such change of reaction mechanism depending upon the absence or presence of Lewis acid catalyst was experimentally confirmed. Although we have no direct experimental evidences for the stepwise mechanism in the present nitrone cycloaddition reactions, we believe the present study shows clearly that *the nature of concertedness of 1,3-dipolar cycloadditions should depend upon the presence of a Lewis acid catalyst.*

4. Conclusion

In conclusion, ab initio calculation study of the Lewis acid-catalyzed nitrone cycloadditions to acrolein has been performed. Nitrone and Lewis acids form very stable complexes, because the difference of energies of corresponding acrolein complex were 10.2 kcal/mol in the case of BH_3 and 15.2 kcal/mol in the case of BF_3. Then, the predominant species in the reaction mixture was nitrone-Lewis acid complexes but these undesired complexes do not contribute to the actual cycloaddition reactions. In actual, the activatoin energy of the reaction of acrolein/BH3 complex is 16.7 kcal/mol which is comparable low level with that of uncatalyzed reaction (25.7 kcal/mol) and nitrone/BH3 complex (30.5 kcal/mol). Then, rate acceleration arises from the less stable acrolein-Lewis acid complexes giving the isoxazolidine-4-carbaldehyde complexes. Moreover, the acrolein/BF_3 complex and nitrone form a Michael adduct complex intermediate which then produces cycloadduct. These results suggest that acidity of Lewis acid catalyst induces the reaction mechanism to change to stepwise one.

References

1. Padwa, A., Ed.; In *1,3-Dipolar Cycloaddition Chemistry*, Wiley-Interscience: New York, 1984; Vols. 1–2.
2. Recent application for natural product synthesis. (a) Pandey, G.; Sahoo, A. K.; Gadre, S. R.; Bagul, T. D.; Phalgune, U. D. *J. Org. Chem.* **1999**, *64*, 4990. (b) Werner, K. M.; de los Santos, J. M.; Weinreb, S. M.; Shang, M. *J. Org. Chem.* **1999**, *64*, 4865. (c) Young, D. G. J.; Gomez-Bengoa, E.; Hoveyda, A. H. *J. Org. Chem.* **1999**, *64*, 692. (d) Pearson, W. H.; Ren, Y. *J. Org. Chem.* **1999**, *64*, 688. (e) Werner, K. M.; de los Santos, J. M.; Weinreb, S. M.; Shang, M. A. *J. Org. Chem.* **1999**, *64*, 686. (f) Chiacchio, U.; Rescifina, A.; Iannazzo, D.; Romeo, G. *J. Org. Chem.* **1999**, *64*, 28. (g) Dirat, O.; Kouklovsky, C.; Langlois, Y. *J. Org. Chem.* **1998**, *63*, 6634. (h) Pearson, W. H.; Lovering, F. E. *J. Org. Chem.* **1998**, *63*, 3607. (i) Gong, Y.-D.; Najdi, S.; Olmstead, M. M.; Kurth, *J. Org. Chem.* **1998**, *63*, 3081. (j) Lee, J. C.; Jin, S.-J.; Cha, J. K. *J. Org. Chem.* **1998**, *63*, 2804. (k) Denmark, S. E.; Middleton, D. S. *J. Org. Chem.* **1998**, *63*, 1604. (l) Snider, B. B.; Lin, H. *J. Am. Chem. Soc.* **1999**, *121*, 7778. (m) Tamura, O.; Mita, N.; Kusaka, N.; Suzuki, H.; Sakamoto, M. *Tetrahedron Lett.* **1997**, *38*, 429.
3. Huisgen, R. 1,3-Dipolar Cycloaddition. Introduction, Survey, Mechanics. In *1,3-Dipolar Cycloaddition Chemistry*, Padwa, A., Ed., Wiley-Interscience: New York, 1984; Vol. 1, pp 1–176.
4. (a) Kanemasa, S.; Uemura, T.; Wada, E. *Tetrahedron Lett.* **1992**, *33*, 7889. (b) Kanemasa, S.; Tsuruoka, T.; Wada, E. *Tetrahedron Lett.* **1993**, *34*, 87. (c) Kanemasa, S.; Turuoka, T.; Yammoto, H. *Tetrahedron Lett.* **1995**, *36*, 5019. (d) Kanemasa, S.; Tsuruoka, T. *Chem. Lett.* **1995**, 49.
5. (a) Gothelf, K. V.; Jørgensen, K. A. *J. Org. Chem.* **1994**, *59*, 5687. (b) Gothelf, K. V.; Hazell, R. G.; Jørgensen, K. A. *J. Am. Chem. Soc.* **1995**, *117*, 4435. (c) Gothelf, K. V.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **1996**, *61*, 346. (d) Gothelf, K. V.; Thomsen, I.; Jørgensen, K. A. *J. Am. Chem. Soc.* **1996**, *118*, 59. (e) Jensen, K. B.; Gothelf, K. V.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **1997**, *62*, 2471. (f) Seerden, J. P. G.; Scholte op Reimer, A. W. A.; Scheeren, H. W. *Tetrahedron Lett.* **1994**, *35*, 4419. (g) Seerden, J. P. G.; Kuypers, M. M. M.; Scheeren, H. W. *Tetrahedron* **1997**, *53*, 11843. (h) Seerden, J. P. G.; Kuypers, M. M. M.; Scheeren, H. W. *Tetrahedron: Asymmetry* **1995**, *6*, 1441. (i) Simonsen, K. B.; Bayon, P.; Hazell, R. G.; Gothelf, K. V.; Jørgensen, K. A. *J. Am. Chem. Soc.* **1999**, *121*, 3845.

6. (a) Leroy, G.; Nguyen, M. T.; Sana, M. *Tetrahedron* **1978**, *34*, 2459. (b) Pascal, Y. L.; Chanet-Ray, J.; Vessiere, R.; Zeroual, A. *Tetrahedron* **1992**, *48*, 7197. (c) Rispens, M. T.; Keller, E.; de Lange, B.; Zijlstra, R. W. J.; Feringa, B. L. *Tetrahedron: Asymmetry* **1994**, *5*, 607. (d) Liu, J.; Niwayama, S.; You, Y.; Houk, K. N. *J. Org. Chem.* **1998**, *63*, 1064. (e) Rastelli, A.; Gandolfi, R.; Amade, M. S. *J. Org. Chem.* **1998**, *63*, 7425.
7. Stewart, J. J. P. *J. Comput. Chem.* **1989**, *10*, 209.
8. Gaussian 94, Revision D. 3, Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Gill, P. M. W.; Johnson, B. G.; Robb, M. A.; Cheeseman, J. R.; Keith, T.; Petersson, G. A.; Montgomery, J. A.; Raghavachari, K.; Al-Laham, M. A.; Zakrzewski, V. G.; Ortiz, J. V.; Foresman, J. B.; Cioslowski, J.; Stefanov, B. B.; Nanayakkara, A.; Challacombe, M.; Peng, C. Y.; Ayala, P. Y.; Chen, W.; Wong, M. W.; Andres, J. L.; Replogle, E. S.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Binkley, J. S.; Defrees, D. J.; Baker, J.; Stewart, J. P.; Head-Gordon, M.; Gonzalez, C.; Pople, J. A. Gaussian, Inc., Pittsburgh PA, 1995.
9. *endo*- and *exo*-Stereoisomers are structurally equivalent through the inversion of nitrogen for both isoxazolidine-4-carbaldehyde (**3**) and isoxazolidine-5-carbaldehyde (**4**). However, the endo- and exo-transition structures have different energies.
10. Tufariello, J. J. Nitrones. In *1,3-Dipolar Cycloaddition Chemistry*, Padwa, A., Ed., Wiley-Interscience: New York, 1984; Vol. 2, pp 83–168.
11. Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*, Wiley: Chichester, 1976.
12. Tatsukawa, A.; Kawatake, K.; Kanemasa, S.; Rudzinski, J. M. *J. Chem. Soc., Perkin Trans. 2* **1994**, 2525.