



Short communication

A computational study on the reaction mechanisms of N-formylation of amines under a Lewis acid catalysis

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ARTICLE INFO

Article history:

Received 3 February 2010

Received in revised form 3 April 2010

Accepted 8 April 2010

Available online 13 April 2010

Keywords:

Density functional theory

Lewis acid

N-formylation of amines

Reaction mechanisms

ABSTRACT

The mechanisms of the title reaction have been studied by density functional theory (DFT) and the second order Moller–Pleset (MP2) method. Two possible reaction channels including the non-catalyzed channel (channel 1) and the other catalyzed channel (promoted by Lewis acid ZnCl_2 , channel 2) are shown. The calculated results indicate that the catalyzed channel is more energy favorable than the non-catalyzed channel, and the energy barrier of channel 2 (31.62 kcal/mol at the B3LYP/6-31G(d,p) level and 30.32 kcal/mol at the MP2/6-311++G(2d,2p) level) is not a high energy barrier for the experimental condition (343 K), thus, we think the Lewis acid ZnCl_2 would play an important role in making the title reaction easier to occur, which is in good agreement with the experimental results.

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1. Introduction

Formylation of amines is an important reaction in synthetic organic chemistry. Formamides have wide applications as intermediates in the preparation of pharmaceuticals [1] such as fluoroquinolones and as important reagents for Vilsmeier formylation [2]. They are also in use as Lewis base catalysts in organic transformations such as allylation [3], and hydrosilylation [4] of carbonyl compounds. In addition, the formyl group is one of the important amino-protecting groups in peptides synthesis [5] and the N-formyl derivatives are useful precursors in the preparation of N-methyl compounds [6].

Due to what we have mentioned above, numerous methods have been reported on N-formylation of amines over the past decades. Some of the useful formylation reagents are chloral [7], formic acid-DCC [8], formic acid-EDCI [9], formic acid esters [10], KF-alumina [11], and other solid-supported reagents [12], ammonium formate [13], CDMT [14]. Nevertheless, many of the N-formylation methods have disadvantages such as expensive reagents, formation of side products, thermal instability, and difficult accessibility to reagents. Thus, a mild, convenient, and high yield procedure using inexpensive catalyst would be valuable.

Recently, Rao and co-workers reported a convenient and novel approach for activation of formic acid as an N-formylation agent using Lewis acid as catalyst under solvent-free condition (Scheme

1) [15]. In their study, no reaction was observed when a mixture of aniline and formic acid was heated at 100 °C for 4 h. However, addition of a catalytic amount of Lewis acid to this mixture had rapidly induced N-formylation producing formanilide in high yields. In order to explain why the reaction can occur under the catalysis of Lewis acid, we have investigated the mechanisms of the title reaction. This work would confirm how the Lewis acid affects the reaction, which should be certainly helpful for the new catalyzed reaction designs.

In this project, the reaction of formic acid (**R1**, Scheme 2) with aniline (**R2**, Scheme 2) under Lewis acid (ZnCl_2) catalysis, which mainly generates N-phenylformamide (**P1**, Scheme 2), has been chosen as the object of investigation. The reaction mechanisms have been studied using density functional theory (DFT) (which has been widely used in the study of reaction mechanisms [16–17]) and the second order Moller–Pleset (MP2) method.

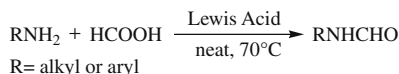
2. Computational details

The geometries of the reactants, transition states, intermediates and products in all reaction channels were optimized at the B3LYP/6-31G(d,p) [18–20] level, which had been shown to give reasonable results in the study of Lewis acid catalysis [21]. The corresponding vibrational frequencies were calculated at the same level to take account of the zero-point vibrational energy (ZPVE) and to identify the transition states. At the same time, the structures of intermediates and the transition states were confirmed by using the intrinsic reaction coordinate (IRC) [22–23]. At last, we optimized all the structures and the geometrical parameters

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Scheme 1. Lewis acid-catalyzed N-formylation of amines with formic acid.

of reactants, transition states and products at the MP2/6-311++G(2d,2p) level, which were compared with the calculated results at the B3LYP/6-31G(d,p) level. All the theoretical calculations were performed using the Gaussian03 [24] suits of programs.

3. Results and discussion

Based on the experimental results, we have suggested two possible reaction channels to lead to three different products in this paper. The products of channel 1 are **P1** and **P2** while the products of channel 2 are **P2** and **P3** (Scheme 2). We set the energies of **R1** + **R2** + **R3** as 0.00 kcal/mol as reference in the energy profiles (Fig. 1). The processes could be illustrated as follows:

As shown in Scheme 2, there is only one step in the reaction channel 1. **R1** reacts with **R2** to generate the products **P1** and **P2** via a four-membered ring (C(1)–O(2)–N(3)–H(4)) transition state **TS1**. The two single-bonds C(1)–O(2) and N(3)–H(4) break and two new single-bonds C(1)–N(3) and O(2)–H(4) generate in this process. With our calculated results, this process is a concerted reaction.

Fig. 2 presents the structures and geometrical parameters of the reactants, transition state and products in channel 1. It can be observed from Fig. 2 that the bond lengths of the C(1)–O(2) and N(3)–H(4) are 1.346 Å in **R1** and 1.011 Å in **R2**, respectively, while the distances of the C(1)–O(2), O(2)–H(4), N(3)–H(4) and C(1)–N(3) are 1.819, 1.313, 1.197 and 1.653 Å in **TS1**. At last, the bond lengths of the C(1)–N(3) and O(2)–H(4) are 1.373 Å in **P1** and 0.965 Å in **P2**, respectively. The energy barrier of this process is 39.95 kcal/mol at the B3LYP/6-31G(d,p) level (Fig. 1), this fact explains why the reaction could not occur even under the experimental condition (343 K), which is consistent with the literature report [15]. Moreover, the energies of products (**P1** and **P2**) is 1.96 kcal/mol higher than that of reactants (**R1** and **R2**), which illuminates that the reaction is an endothermic process.

As we can see from Scheme 2, the O(5) atom of carbonyl group in **R1** can form a coordination bond with Zn(6) atom of Lewis acid ZnCl₂, and **R1** may become **R3**. There is also only one step in the reaction channel 2. **R3** reacts with **R2** to generate the products **P3** and **P2** via a four-membered ring (C(1)–O(2)–N(3)–H(4)) transition state **TS2**. With our calculated results, this process is a concerted reaction too.

Fig. 3 presents the structures and geometrical parameters of the reactants, transition state and products in channel 2. As shown in

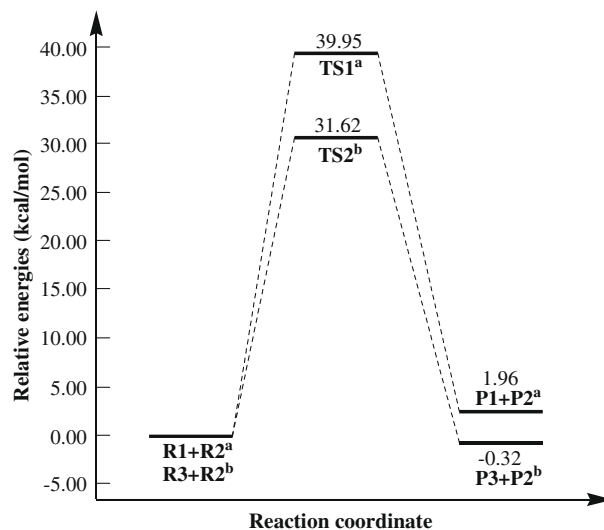
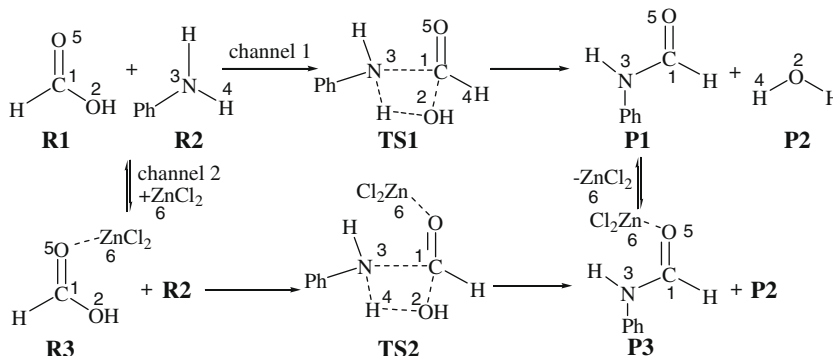


Fig. 1. The energy profiles of channel 1 and channel 2 (unit: kcal/mol, the superscript a represents adding the energy of **R3** and the superscript b represents adding the energy of **R1**).

Fig. 3, the bond length of the O(5)–Zn(6) is 2.006 Å in **R3**, 1.911 Å in **TS2** and 1.999 Å in **P3**, respectively, which reveals that **R1** forms a coordination bond with Zn(6) atom of Lewis acid ZnCl₂. The bond lengths of the C(1)–O(2) and N(3)–H(4) are 1.300 Å in **R3** and 1.011 Å in **R2**, respectively, and the distances of the C(1)–O(2), O(2)–H(4), N(3)–H(4) and C(1)–N(3) are 1.570, 1.216, 1.318 and 1.548 Å in **TS2**, respectively. At last, the bond lengths of the C(1)–N(3) and O(2)–H(4) are 1.334 Å in **P3** and 0.965 Å in **P2**, respectively. The energy barrier of this process is 31.62 kcal/mol (Fig. 1), so the reaction should occur under the experimental condition (343 K). Noteworthy, the energies of products (**P3** + **P2**) is 0.32 kcal/mol lower than that of reactants (**R3** + **R2**), which shows that the reaction is an exothermic process. Furthermore, the energy barrier of channel 2 is 8.33 kcal/mol lower than that of channel 1, videlicet, the reaction can occur more easily under the catalysis of Lewis acid ZnCl₂, which is also in good agreement with the experimental results.

In order to obtain a more precise result, we have optimized all the reactants, transition states and products at the MP2/6-311++G(2d,2p) level. The optimized structures and the geometrical parameters of **TS1** and **TS2** have been shown in Fig. 4. As can be seen from Fig. 4, the distances of the C(1)–O(2), O(2)–H(4), N(3)–H(4) and C(1)–N(3) are 1.895, 1.362, 1.161 and 1.609 Å in **TS1**, respectively, and simultaneously the distances of the C(1)–O(2), O(2)–H(4), N(3)–H(4), C(1)–N(3) and O(5)–Zn(6) are 1.569, 1.220, 1.314, 1.533 and 1.942 Å in **TS2**, respectively. Comparing Figs. 2



Scheme 2. The two possible reaction channels.

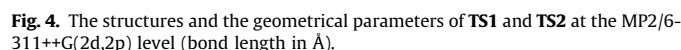
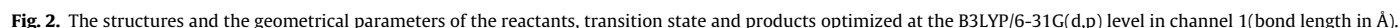


Table 1
Energies (E) and Relative energies (RE) of all the stationary points (SP) optimized at the MP2/6-311++G(2d,2p) level.

and 3 with Fig. 4, we can find that the structures and the geometrical parameters of transition states optimized at the B3LYP/6-31G(d,p) level are similar with those optimized at the MP2/6-311++G(2d,2p) level. In Table 1, the energy barriers of channel 1 and 2 are 37.60 kcal/mol and 30.32 kcal/mol at the MP2/6-311++G(2d,2p) level, respectively, which are very close to the results calculated at the B3LYP/6-31G(d,p) level. As concerned as above, the results calculated at the two levels are consistent and we think that the conclusions should be reliable.

This work studies two possible reaction channels of the title reaction with **P1**, **P2** and **P3** as the products at the B3LYP/6-31G(d,p) level and the MP2/6-311++G(2d,2p) level of theory. In the two reaction channels, the energy barrier of catalyzed channel (channel 2) are much lower than the non-catalyzed channel (channel 1), and the energy barrier of channel 2 is not a high energy barrier the experimental condition (343 K), so we think the Lewis acid should play an important role in making the title reaction easier to occur, which is in good agreement with the experimental results. Moreover, there are very small differences between the structures and the energy barriers at the two different computational levels, hence, the results calculated at the two levels are consistent and the conclusions should be reliable.

The work described in this paper was supported by the National Natural Science Foundation of China (No. 20873126).

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