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# Theoretical evidence on O–N type smiles rearrangement mechanism: a computational study on the intramolecular cyclization of *N*-methyl-2-(2-chloropyridin-3-yloxy)-acetamide anion

**Hui Sun[a], Jinghua Li[b], Dongju Zhang[a]*, Chen Ma[a]* and Chengbu Liu[a]**

**Smiles rearrangement (SR) falls under a broad category of organic synthesis for many important compounds. A complete understanding toward SR process appeals to the assistance of theoretical research. Herein, by performing quantum chemistry calculations, we give a theoretical evidence for the mechanism of a representative O–N type SR, the intramolecular cyclization of *N*-methyl-2-(2-chloropyridin-3-yloxy)acetamide anion. It is found that the SR to the *ipso*-position involves a two-step mechanism and is energetically more favorable than the direct nucleophilic attack by N atom on the *ortho*-position. The present result rationalizes well the experimentally observed *ipso*-SR product and provides a consistent picture of the O–N SR process. Copyright © 2008 John Wiley & Sons, Ltd.**

**Keywords:** smiles rearrangement; mechanism; DFT

## INTRODUCTION

Smiles rearrangement (SR) is an intramolecular aromatic nucleophilic substitution reaction at the *ipso*-position under basic condition,[1] which is usually applicable to aromatic compounds bearing electron-withdrawing group and results in the migration of an aromatic system from one heteroatom to another (Scheme 1). This procedure falls under a broad category of organic synthesis for many important compounds, such as olefin,[2,3] pyridine derivatives,[4–6] aminobenzofuran,[7] and *N*-heterocycle-fused [1,4]oxazines.[8–13]

Compounds containing benzo-fused and heterocycle-fused [1,4]oxazine ring have received intensive attention in recent years owing to their wide applications as substructures embedded in biologically active agents and pharmaceuticals.[14–18] So far, many synthetic methods have been well established.[16–19] However, most of them usually suffer from low yield, complicated processes or harsh terms. Thus, simple but effective methods for generating these compounds are still in great demand at present. Recently, Shin *et al*. have developed an operationally simple and economic method for synthesizing *N*-heterocylce-fused [1,4]oxazines, such as pyrido[1,4]oxazines[8,9] and pyridazino[1,4]oxazines.[10–13] As shown in Scheme 2 for the synthesis of pyrido[1,4]oxazines in acetonitrile solvent, the key step of the reaction involves the ring closure of *N*-methyl-2-(2-chloropyridin-3-yloxy)acetamide anion (denoted as **1**) via a O–N type SR involving nucleophilic attack on the *ipso*-position (path I) to afford the observed product pyrido[2,3-b][1,4]oxazine (denoted as **2**).

To the best of our knowledge, O–N type SR mechanism is still not well understood, although a few relevant theoretical studies have been reported.[20–24] A detailed, higher level theoretical study of the SR is still highly desired. In this paper, we focus our attention on the representative SR process shown in Scheme 2. By performing quantum chemistry calculations, we show the details of mechanism for the O–N type SR process. To rationalize the experimental fact that the product, pyrido[3,2-b][1,4]oxazine (denoted as **3**), were not observed, we also considered the possibility of the direct nucleophilic attack by N atom on the *ortho*-position (path II in Scheme 2) and compared the results with those of the *ipso*-SR.

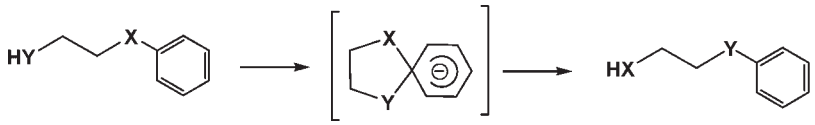
## COMPUTATIONAL DETAILS

Our calculations were carried out at both the B3LYP/6-31G(d,p) and MP2/6-31G(d,p) levels by including the dielectric solvent effect of acetonitrile, which was taken into account using a simple self-consistent reaction field (SCRF) method,[25,26] based on the polarizable continuum model (PCM).[27,28] The dielectric constant of acetonitrile was taken as 36.64. Structures **1**, **2**, and **3** shown in Scheme 2, as well as the transition states involved during the formation of **2** and **3** have been located by performing full geometry optimization without any symmetric restriction, and

* *School of Chemistry and Chemical Engineering, Shandong University, Jinan 250100, P.R. China.*

a *H. Sun, D. Zhang, C. Ma, C. Liu*
*School of Chemistry and Chemical Engineering, Shandong University, Jinan 250100, P.R. China*
*E-mail: zhangdj@sdu.edu.cn*

b *J. Li*
*College of Life Science, Shandong University, Jinan 250100, P.R. China*




**Scheme 1.** General smiles rearrangement

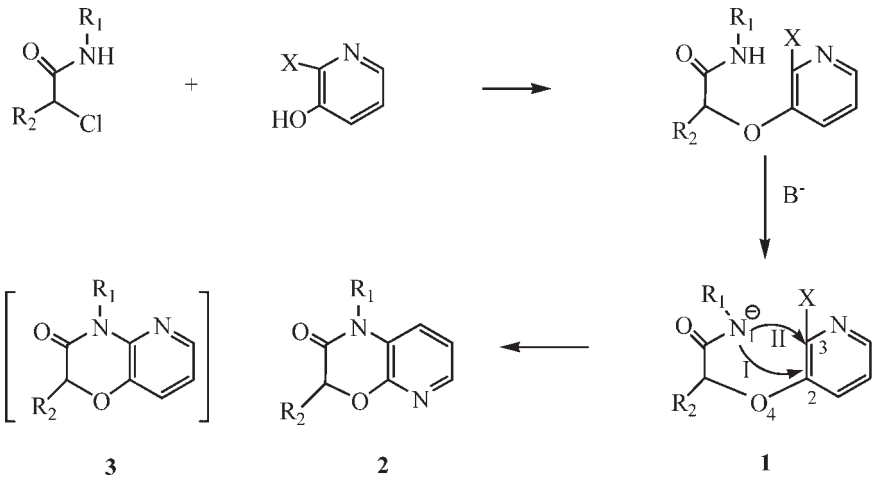
their nature (local minima or first-order saddle points) has been identified by performing frequency calculations, from which the zero-point energies (ZPEs) were also derived. The reaction pathways have been examined by tracing intrinsic reaction coordinate (IRC) calculations. The atomic charge assignments are based on the natural population analysis (NPA). For all cited energies, the ZPE corrections have been included. All calculations were performed by using Gaussian 03 program package.[29] In the following sections, the results quoted are generally from the MP2/6-31G(d,p) calculations unless otherwise specified.

## RESULTS AND DISCUSSION

The intramolecular cyclization of compound **1** may proceed in two possible pathways to afford different fused pyrido[1,4]oxazine ring system. As shown in Scheme 2, path I involves the SR to the *ipso*-position via the nucleophilic attack of N1 atom on C2 atom, resulting in the formation of product **2**, while in path II the nucleophilic attack of N1 atom occurs on the *ortho*-position, giving rise to compound **3**. To show the mechanism details along these two paths, we optimized geometries of all stationary points involved and drawn out the potential energy profiles along the reaction coordinate, as shown in Figs. 1 and 2, respectively.

Path I involves a two-step mechanism, in which two transition state structures (**TS1** and **TS3**) and one intermediate **IM1** have been located at the MP2/6-31G(d,p) level. Complex **1** is first converted to a spirocyclic intermediate **IM1** via the five-membered ring transition structure **TS1**. This transition structure is characterized by an imaginary frequency of 233i $cm^{-1}$, and the transition vector corresponds to the expected components of the reaction coordinate in which N1 atom carrying partial negative charge is attacking at C2 atom on the pyridine ring to induce ring closure. The forming N1—C2 distance is 1.988 Å, and the C2—O4 bond is slightly elongated to 1.411 Å. The barrier height from **1** to **TS1** is calculated to be 11.93 kcal $mol^{-1}$. **IM1** is calculated to be 3.52 kcal $mol^{-1}$ less stable than **1**. In **IM1**, N1—C2 bond has formed, and the C2—O4 distance is 1.522 Å, which is longer by 0.202 Å than that in compound **1**. This can be attributed to the electrostatic repulsion between two negatively charged atoms (N1 and O4), which makes the spirocyclic intermediate unstable. Along the reaction coordinate, **IM1** disassociates into product **2** accompanied by the release of $Cl^-$ anion via saddle point **TS3**, where C2—O4 and C3—Cl bonds are breaking and C3—O4 bond is forming. The imaginary frequency of this transition state is 301i $cm^{-1}$ and the normal mode mainly corresponds to large-amplitude motions of O4, C3, and Cl atoms in the desired directions. The forming C3—O4 bond is shortened to 2.088 Å, and the breaking C2—O4 and C3—Cl bonds are elongated to 2.508 and 1.792 Å, respectively. **TS3** lies 12.81 kcal $mol^{-1}$ above **1**. The barrier from **IM1** to **TS3** is calculated to be 9.29 kcal $mol^{-1}$, lower by 2.64 kcal $mol^{-1}$ than that of the initial N1—C2 bond formation. The total reaction is exothermic by 54.27 kcal $mol^{-1}$, and the rate-determining step is the first step with a barrier of 11.93 kcal $mol^{-1}$.

For comparison, the calculated DFT geometries and energies have also been shown in Figs. 1 and 2. Generally, the geometries and relative energies from the DFT calculations are in fair agreement with those from the MP2 calculations. However, it should be noted that our DFT calculations have located another minimum **IM2** between **IM1** and **TS3**. As shown in Fig. 1, the geometry of **IM2** is similar to that of **IM1** except for C2—O4 distance, which is 2.275 Å and in contrast to 1.536 Å in **IM1**. At the B3LYP/6-31G(d,p) level, **IM2** is only 1.97 kcal $mol^{-1}$ above **IM1**. Furthermore, we have also identified the first-order saddle connecting **IM1** and **IM2**, **TS2**. It is a five-membered-ring-containing transition state structure, where O4 atom is getting away from C2 atom, as indicated by the geometrical parameters and the vibrational mode corresponding to the imaginary frequency of 144i $cm^{-1}$. The length of the breaking C2—O4 bond is 1.987 Å. The barrier from **IM1** to **TS2** is calculated to be 2.09 kcal $mol^{-1}$, indicating a less energy requirement than the




**Scheme 2.** Reaction of 2-choroacetamide with 2-halo-3-hydroxypyridine to form either the smiles rearrangement product or the *ortho*-nucleophilic substitution product



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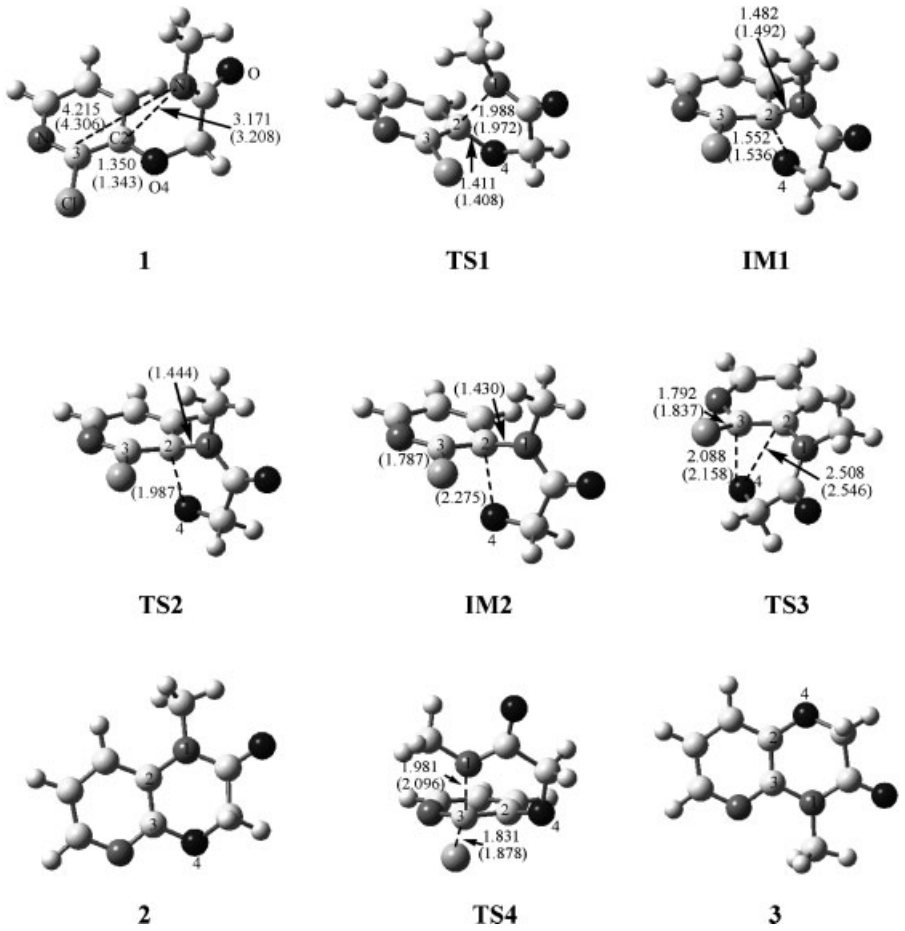


**Figure 1.** Optimized geometries with selected bond distances (Å) for reactant, transition states, intermediates, and products involved in the intramolecular cyclization reaction of compound **1**. The values with and without parentheses are from the B3LYP/6-31G(d,p) and MP2/6-31G(d,p) calculations, respectively

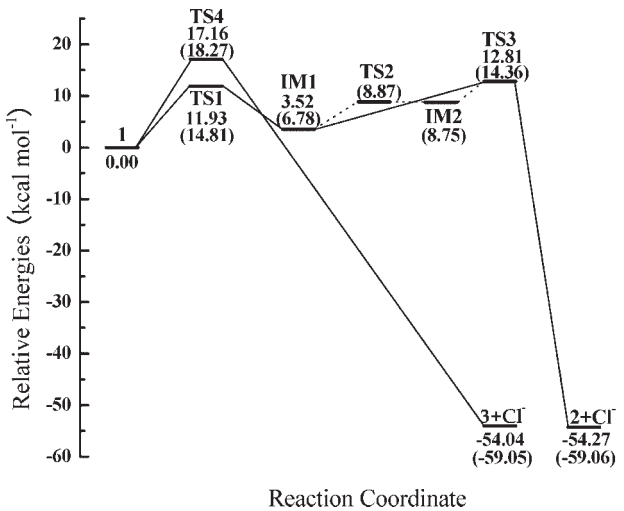


**Figure 2.** Calculated potential energy surface profiles along paths I and II for the intramolecular cyclization reaction of compound **1**. The values of the relative energies with and without parentheses are from the B3LYP/6-31G(d,p) and MP2/6-31G(d,p) calculations, respectively

other processes in path I. From Fig. 2, we see that the potential energy surface in the vicinity of **TS2** and **IM2** is so shallow that these two structures at more accurate MP2 level disappear. This fact indicates that **TS2** and **IM2** may not represent the stationary points anymore but only distortions on the reaction coordinate connecting **IM1** and **TS3**.

The intramolecular cyclization reaction proceeding along path II is initiated by the nucleophilic attack of N1 anion at C3 atom on the pyridine ring. As shown in Fig. 2, this process involves only one elementary step. Transition structure **TS4** (Fig. 1) has been identified as the first-order saddle point along this path, in which N1—C3 bond (1.981 Å) is forming and C3—Cl (1.831 Å) bond is breaking. The imaginary frequency of **TS4** is 272i $cm^{-1}$, and the transition vector mostly corresponds to the nucleophilic addition of N1 to C3. The barrier height from compound **1** to **TS4** is calculated to be 17.16 kcal $mol^{-1}$, which is energetically less favorable by 5.23 kcal $mol^{-1}$ than that of the rate-determining step in path I. Our IRC calculation demonstrates that along the reaction coordinate **TS4** converges to the product **3** with the release of $Cl^-$. This path is exothermic by 54.04 kcal $mol^{-1}$ relative to the reactant, which is similar to that along path I. From the results shown in Figs. 1 and 2, we find that the B3LYP calculations give almost the same conclusion with the MP2 calculations.

On the basis of the above results, it is clear that path I is found to be considerably less energy demanding than path II. This is in



  

**Table 1.** Calculated NPA charges on N1, C2, and C3 atoms of reactant **1**

| | *Q* (au) | | |
|---|---|---|---|
| | N1 | C2 | C3 |
| MP2/6-31G(d,p) | −0.810 | 0.338 | 0.191 |
| B3LYP/6-31G(d,p) | −0.703 | 0.293 | 0.155 |

good agreement with the observed *ipso*-SR product rather than *ortho*-nucleophilic substitution product.[11] To better understand this result, we calculated the NPA charges on the relevant atoms in compound **1**. From the data shown in Table 1, it is clear that the DFT and MP2 calculations identically indicate the high charge density is centered on N1 atom, endowing it with a strong nucleophilic character. While the charge on C2 and C3 atoms is 0.338 and 0.191 *e*, respectively, clearly indicating C2 position is the more electrophilic site. This can be attributed to the larger electronegativity of O atom than Cl atom, which confers on the C2 atom (*ipso*-position) a greater positive charge, permitting a more facile nucleophilic attack by N1. Furthermore, the preferred *ipso*-SR product can also be understood by considering the steric effect. Comparing the geometry of **TS4** involved in path II, with that of **TS1**, the transition state structure involved in the rate-determining step in path I, it is found that the *N*-methyl-acetamide unit in the former is much more severely distorted than that in the latter, leading to the higher energy required to form the *ortho*-nucleophilic addition product along path II than that to form the *ipso*-SR product along path I.

## CONCLUSIONS

In summary, we have performed a mechanism study for the representative O–N type SR process, the intramolecular cyclization of *N*-methyl-2-(2-chloropyridin-3-yloxy)acetamide anion by performing quantum chemistry calculations. The results at the MP2/6-31G(d,p) level show that the SR to *ipso*-position involves a two-step mechanism, the nucleophilic attack of N atom on the *ipso*-carbon followed by the nucleophlic attack of O atom on the *ortho*-carbon, while the direct nucleophilic attack by N atom on the *ortho*-position occurs via a single-step mechanism. The calculated lower barrier by 5.23 kcal $mol^{-1}$ at the MP2/6-31G(d,p) level for the former than for the latter provides theoretical support for the observed *ipso*-SR product, which has been rationalized in terms of electronic and steric effects. It is expected that a similar mechanistic picture also applies to other SR processes.

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