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The Study of Alcoholysis of 1,2-Thiazetidine-1,1-dioxide with Quantum Chemical Method

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Abstract: The alcoholysis mechanism of 1,2-thiazetidine-1,1-dioxide with methanol, in which the relatively stable product is sulfonate ester, has been investigated by quantum chemical method. Our calculations indicate the reaction for alcoholysis of 1,2-thiazetidine-1,1-dioxide proceeds *via* two possible mechanisms: concerted and stepwise. In the stepwise mechanism, two possible reaction pathways can be followed while only one possible reaction pathway can be followed in the concerted mechanism.

Keywords: 1, 2-Thiazetidine-1, 1-dioxide, alcoholysis, quantum chemical method.

1,2-Thiazetidine-1,1-dioxides (β-sultams) are the sulfonyl analogues of β-lactam antibiotics or the cyclized compounds of taurine. They have higher reactivity compared to β-lactam (approx. 10^3 fold more active) [1]. It is appropriate to readily study sulfonyl transfer reactions[2] which are of interest because of the potential use of sulfonyl compounds as sulfonating agents of serine proteases[3] and the use of sulfonamides as peptide mimics[4]. This makes them promising candidates for biological activity from a chemical and pharmacological point on view by many authors[5,6], especially Page M. I. *et al.*[7-10], who have done many experimental studies on the reactivity and reaction mechanism for β-sultams. According to their results, they concluded that the 1,2-thiazetidine-1,1-dioxide can be hydrolyzed. However, the mechanism presented by them was not perfect. Our purpose in this paper is to give a more complete description of the possible alcoholysis mechanisms of 1,2-thiazetidine-1,1-dioxide through theoretical calculations.

Methods

The structures of reactants, intermediates and transition states have been optimized with B3LYP/6-31G* and HF/6-31G* methods and the most stable conformations as well as their energies at every stationary point have been Schemed out. Frequency calculations of all stationary points have been performed and all transition states have been identified by analyzing the vibrational models of their ones and only imaginary frequencies. Herein we only report the results at the B3LYP/6-31G* level, because the calculations show that the reaction processes and mechanisms are similar for these two calculation methods.

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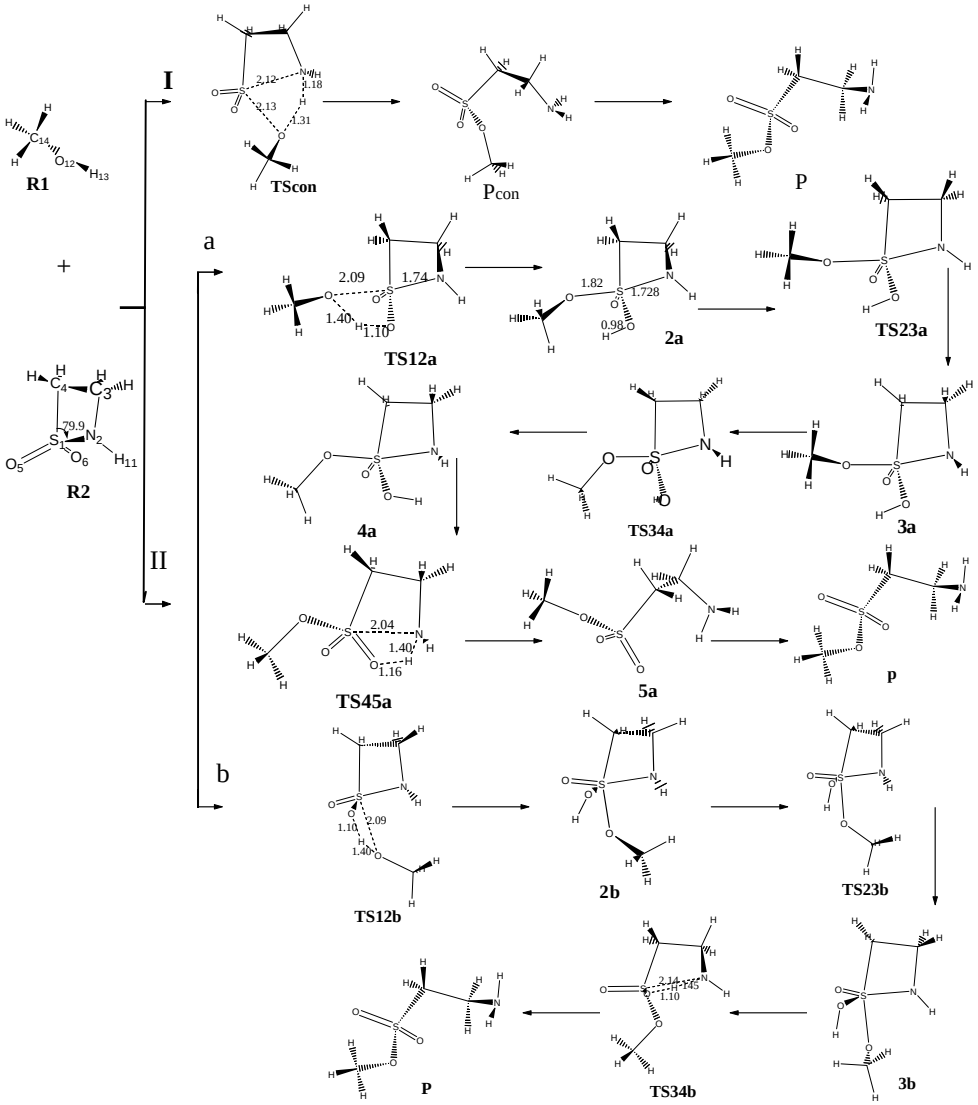
Scheme 1 Reaction mechanism of the alcoholysis of 1,2-thiazetidine-1,1-dioxide



Results and Discussion

The alcoholysis of 1,2-thiazetidine-1,1-dioxide proceeds *via* two possible mechanisms: concerted and stepwise. These two mechanisms are shown in **Scheme 1**.

Process I in **Scheme 1** represents the concerted mechanism. The alcoholysis of 1,2-thiazetidine-1,1-dioxide proceeds *via* only one transition state in the whole reaction processes in this mechanism. The OCH_3 and H_{13} in CH_3OH attack the S_1 atom and the N_2 atom on the ring of 1,2-thiazetidine-1,1-dioxide, at the same time the bond S_1-N_2 breaks. These two processes occur simultaneously and complete through transition state (TScon in **Scheme 1**). The product of this process is P. The energy barriers are 157.7 kJ/mol.

Process II in **Scheme 1** represents the stepwise mechanism. There are two pathways according to the orientation of nucleophilicity of CH_3OH on S_1 in this stepwise mechanism. The nucleophilic attack of OCH_3 on the S_1 atom from C_4 atom side which is marked **a**. The nucleophilic attack of OCH_3 on the S_1 atom from N_2 atom side, which is marked **b**. In each pathway, reaction takes place *via* two steps. The first one is nucleophilic attack to form an intermediate complex compound, and the second one is hydrogen transfer from O_6 atom to N_2 and ring opening. The last two processes occur simultaneously in the second step.

2a, **3a** and **4a** in **Scheme 1** are intermediate complex compounds, which are the results of the nucleophilic attack of CH_3OH to 1,2-thiazetidine-1,1-dioxide ring. This nucleophilic process was completed through transition state (**TS12a** in **Scheme 1**). The relative energy of this transition state is 120.9 kJ/mol.

2a is directed from **TS12a**. In the structure of **4a** the hydrogen H_{13} is oriented toward the nitrogen atom (N_2), which can calibrate the transfer of H_{13} to N_2. The differences of the structures of **2a**, **3a** and **4a** are merely the change in the orientation of H_{13}. We have studied the introversion among these structures. **TS23a** is the transition state from **2a** to **3a**. **TS34a** is the transition state connecting **3a** and **4a.** **4a** is the most stable conformer among these three intermediates. The energy barrier variations of the interconversion among these intermediates are lower.

The structure of **4a** evolves with ring opening and hydrogen transfering from hydroxyl oxygen to nitrogen. These two processes occur simultaneously. The transition state **TS45a** connects **4a** and **5a.** The relative energy of this transition state is 124.6 kJ/mol.

The reaction product is **5a** in which H_{13} has been transferred to N_2 completely. The relative energy of **5a** is -108.5 kJ/mol. In this reaction, the barrier of the second step, of H_{13} transferring, is higher than that of the process of the nucleophilic attack.

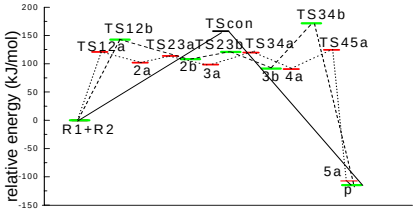
The pathway **b** is similar to the pathway **a** except for the difference of the orientation of the nucleophilic attack for the OCH_3. The relative energy of TS12b is 142.7kJ/mol.

The structures of **2b** and **3b** are only the transformation of the configuration as that of the pathway **a**. They are transformed passing the transition states **TS23b**. The main differences of the two intermediates are the orientation of hydrogen H_{13}. The energy barriers of the transformation of these configurations are also lower.

The transition state connecting **3b** and structure **P** is T**S34b,** which involves the processes of transferring of H_{13} and the opening of S_1-N_2 bond. These two steps occur simultaneously. In the transition state **TS34b**, H_{13} is located between the O_6 and N_2. The relative energy of this transition state is 171.6 kJ/mol. The product of this process is **P**. In this reaction pathway, the energy barrier of the process of H_{13} transferring is also higher than that of the process of nucleophilic attack.

The energy profiles for the alcoholysis of 1,2-thiazetidine-1,1-dioxide are shown in **Figure 1**.

Figure 1 Energy profiles for the alcoholysis of 1,2-thiazetidine-1,1-dioxide



Conclusion

The following conclusions can be drawn:

1. The alcoholysis of 1,2-thiazetidine-1,1-dioxide proceeds *via* two possible mechanisms:

I) Through a single transition structure (**TScon**) in which the nucleophilicity of CH_3OH and the break of bond S_1-N_2 proceed simultaneously.

II) Stepwise mechanism: First step is nucleophilic attack, the second step is hydrogen transfer from O_6 atom to 1, 2-thiazetidine-1, 1-dioxide N_2 and ring opening. These two processes occur simultaneously in the second step.

There are two pathways according to the orientation of nucleophilicity of CH_3OH to S_1. a) nucleophilic attack of OCH_3 on the S_1 atom from C_4 atom side and b) the nucleophilic attack of OCH_3 on the S_1 atom from N_2 atom side. In these two pathways, the alcoholysis of 1,2-thiazetidine-1,1-dioxide begins with the nucleophilic attack of the CH_3OH on the sulfur atom, which is followed by cleavage of the S_1-N_2 bond and hydrogen transfer.

2. The energy barrier of the reaction pathway **a** of stepwise mechanism is the lowest. It is lower than the pathway **b** of stepwise mechanism.

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References

1. N. J. Baxter, L. J. M. Rigoreau, A. P. Laws, M. I. Page, *J. Am. Chem. Soc*., **2000,** *122*, 3375.
2. N. J. Baxter, A. P. Laws, L. J. M. Rigoreau, M. I. Page, *Chem. Commun*., **1999**, 2401.
3. M. Beardsell, P. S. Hinchliffe, M. I. Page, *Chem Commun*., **2001**, 497.
4. J. M. Wood, P. S. Hinchliffe, A. P. Laws, M. I. Page, *J. Chem. Soc. Perkin Trans.2*, **2002**, 938.
5. E. Dieter, W. Stefan, *Tetrahedron lett.*, **2002**, 5109.
6. I.Tetsuo, K. Tadashi, M. Qsumu ,T. Genzoh, *Tetrahedron*, **1998**, 5507.
7. M. I. Page, A. P. Laws, *Tetrahedron***, 2000**, 5631.
8. P . S. Hinchliffe, J. M. Wood, A. M. Davis, *et al*., *J. Chem. Soc. Perkin Trans.2*, **2001**, 2503.
9. P. S. Hinchliffe, J. M. Wood, A. M. Davis, R. P. Austin, R. P. Beckett, M. I. Page, *Org. Biomol. Chem*., **2003,** *1*, 67.
10. J. M. Wood, P. S. Hinchliffe, A. M. Davis, R. P. Austin, M. I. Page, *Chem. Commun.*, **2002**, 772.

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