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# Theoretical calculational investigation on the regioselectivity of the ring opening of thiiranes with ammonia and amines

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ABSTRACT

The course, especially the regioselectivity, of the nucleophilic ring opening of thiiranes with ammonia and amines was investigated with the density functional theory (DFT) calculation. In the ring-opening reaction, thiiranes could be attacked on either their less or more substituted carbon atoms. The analyses of the potential energy surfaces, the bond lengths, and charges of key species in both pathways indicate that alkyl-substituted thiiranes are attacked dominantly on their less substituted ring carbon atom, whereas arylthiiranes are on their more substituted one due to the existence of the p–π conjugative effect, which stabilizes the transition states generated in the reaction. Furthermore, the Lewis acid can modulate the regioselectivity. However, the steric hindrance of nucleophiles and solvents affect the regioselectivity slightly as they show similar influence on both pathways, despite the fact that they can put an impact on the energy. NBO and MO analyses also support the substituent-depended regioselectivity. This is the first DFT calculational investigation on the regioselective ring opening of thiiranes and provides a rational explanation for the experimental results. The theoretical investigation gives a general understanding and a rule for the rationale and prediction of the regioselectivity in the nucleophilic ring opening of thiiranes, even other three-membered heterocycles.

## 1. Introduction

The first thiirane, also named episulfide or thioepoxide, was synthesized by Staudinger and Pfenninger in 1916,[1] which marks the starting of a fascinating research area in the organo-sulfur chemistry. To date, numerous methods to prepare thiiranes[2] and the treatment of thiiranes as reactants have been reported one after the other.[3] Thiiranes, the sulfur analogs of epoxides or aziridines, are known to be important intermediates in organic synthesis as they can be converted into a large number of bifunctional and even chiral products by various ring-opening reactions or isomerization.[4] They have been widely used in polymer,[5] pesticide, herbicide chemical industry, and pharmaceutical synthesis.[6] Despite a lot of papers deal with thiirane transformations, regioselective ring-opening reactions have, up to now, received only limited interest.

Recently, in our laboratory, the utility of thiiranes was demonstrated in the synthesis of substituted taurines via the ring-opening reactions with nitrogen-containing nucleophiles and subsequent peroxy acid oxidation.[7] The results indicate that (a) in the absence of a Lewis acid, when secondary amines were used as nucleophiles, regiospecific ring-opened products were obtained for aliphatic monosubstituted thiiranes.[7a] However, aromatic monosubstituted thiiranes gave a mixture of 1-substituted and 2-substituted taurines due to poor regioselectivity[7a] and the ring-opening reaction of geminal disubstituted thiiranes with either dibenzylamine or benzylamine cannot occur.[7b] (b) In the presence of the Lewis acid silver nitrate, whatever ammonia, primary or secondary amines as nucleophiles, all alkyl-substituted thiiranes gave rise to α-mono- or α,α-di-alkyl-substituted taurines, whereas all aryl-substituted thiiranes produced aromatic β-mono- or β,β-di-substituted taurines, showing that all alkyl-substituted thiiranes were attacked on their less substituted ring carbon atom, but all aryl-substituted thiiranes were attacked on their more substituted ring carbon atom (Scheme 1).[7c] At that time, experimental results were explained cursorily that alkylthiiranes were attacked on their less substituted ring carbon atom due to lower steric hindrance; the regioselectivity was controlled by the steric hindrance, whereas arylthiiranes were attacked on their more substituted ring carbon atom because their phenyl group could stabilize the benzylic carbocation formed in the transition state (TS) of the ring-opening reaction through the p–π conjugative effect; the regioselectivity was controlled by the electronic effect. Such regioselective ring-opening process has not been rationalized in a theory or a rule.

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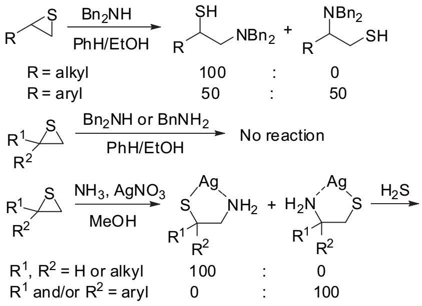
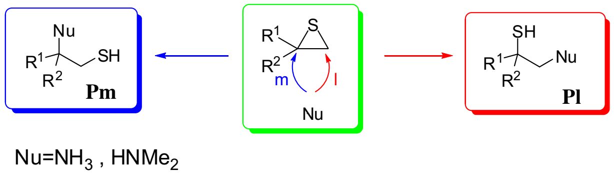


**Scheme 1.** Ring opening of thiiranes with ammonia and amines.

To the best of our knowledge, there are few theoretical computation studies on the ring opening of thiiranes.[8] However, they do not consider the regioselectivity of the ring opening. To explore theoretically what controls the regioselectivity, we conducted a theoretical computation investigation on the question at the DFT B3LYP level with the above-mentioned reactions as a model. It is the first time to explore the influence of substituents, nucleophiles, Lewis acid, the electronic effect of substituents, and solvents on the regioselectivity in theory, and to provide a rational explanation for the experimental regioselectivity. Herein, we present our results and hope to provide a general understanding and a rule for the regioselectivity in the ring opening of thiiranes.

## 2. Results and discussion

The regioselectivity in the ring opening of thiiranes was investigated at the B3LYP/IEFPCM/6-311++G(d,p) & LANL2DZ//B3LYP/6-31+G(d,p) & LANL2DZ level, that nucleophiles, such as ammonia or an amine attacks each side of the unsymmetric three-membered heterocyclic thiiranes, affording the corresponding products 2-substituent aminothiols (**Pm**) and 1-substituent aminothiols (**Pl**) via attacking more (pathway **m**) and less (pathway **l**) substituted carbon atoms, respectively (Scheme 2). The regioselectivity will be discussed on the basis of analyses on the influence of the substituent effect, the steric effect of nucleophiles, Lewis acid, the electronic effect of substituents, and solvent on the regioselectivity, identifying factors, which actually affect the different regioselectivities.



**Scheme 2.** Two pathways in the nucleophilic ring opening of thiiranes.

### 2.1. Substituent effect

Five varieties of thiiranes **1a**–**e** with representative different substitutions were investigated in the widely used Lewis acid promoted ring opening with ammonia at first. The general mechanism shown in Fig. 1 indicates that, in the presence of silver nitrate, thiiranes **1** and the silver cation coordinated with ammonia form the reactive complexes (**RC**), which are defined as the reaction starting points. Ammonia attacks each side of the thiirane ring to obtain the corresponding ring opened intermediates (**INTm** and **INTl**) via the transition states (**TSm** and **TSl**) through pathways **m** and **l**, in which the three-membered ring opens and the N–C bond forms synchronously. At last, S atom gets a proton from the NH$_3^+$ group, or the NH$_3^+$ group transfers a proton to ammonia in solution while the C–C bond circumvolves simultaneously to get the corresponding products (**Pm** and **Pl**, or **Pm**′ and **Pl**′), which all bear stable structure of the five-membered ring (N and S coordinate to Ag), precipitated from the reaction system. From the viewpoint of energy, products **Pm** and **Pl** are more stable than **Pm**′ and **Pl**′. They should generate predominantly.

The structural optimization and single-point energy were obtained at the B3LYP/6-311++G(d,p) & LAN//B3LYP/6-31+G(d,p) & LAN+ΔZPVE level. The free energies in solution were computed by the IEFPCM method in methanol. The energy surfaces were drawn for the ring opening of thiiranes **1a**–**e**, respectively, in Fig. 1. From the energy surfaces, we found by all appearances that the activate energies of all **TS** is from 14.3 to 21.8 kcal/mol, which is in accordance with the room temperature reaction condition. It is not a largely exothermic process from **RC** to form **INT** for most thiiranes as well as the following neutralization (proton-transferring) step, which lead to yield thermodynamic stable products **P** with low energy. At the aspect of thermodynamics, **Pm** is little advantageous than **Pl** in each of cases. There is another proton-transferring step from **INT** to **P**′, which is an endothermic process due to the fact that the basicity of amine is stronger than ammonia. Since the regioselectivity of the reaction depends on the Gibbs free energy barrier of the two **TS**, which implies the competed reactions are controlled by dynamics, the neutralization (proton-transferring) step would not be discussed extensionally.

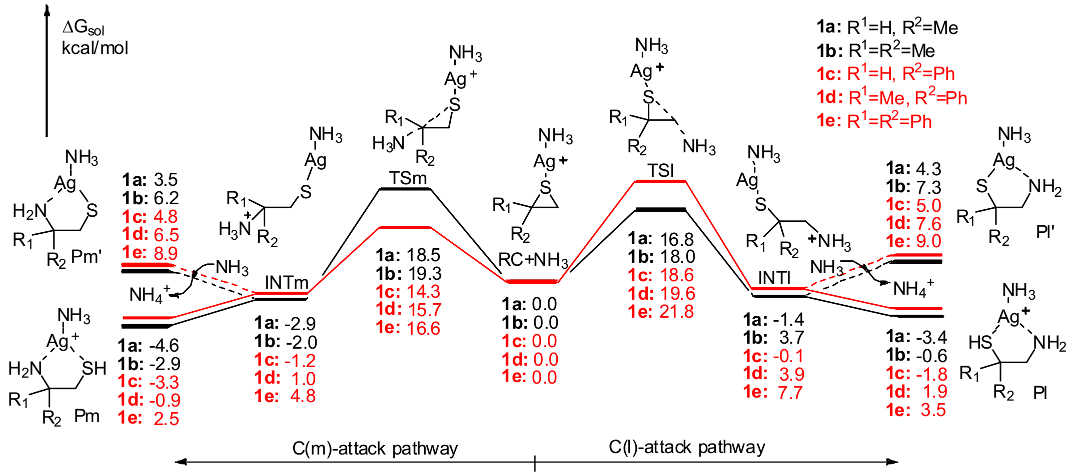


**Fig. 1.** The calculated energy surfaces for the reaction of thiiranes with ammonia in the presence of argentum cation at the B3LYP/6-311++G(d,p) & LAN//B3LYP/6-31+G(d,p) & LAN+ΔZPVE level of theory (methanol was used as solvent within the IEFPCM method).

We also notice that the substituents of the thiiranes dominantly determine the side and pathway of the ring opening. For aliphatic 2-methylthiirane (**1a**) and 2,2-dimethylthiirane (**1b**), ammonia attack at their less hindered side (pathway **l**, the formation of **INTl**-**1a** and **INTl**-**1b**) is favored by 1.7 and 1.3 kcal/mol in terms of the Gibbs free energy compared with the attack at their hindered side (pathway **m**, the formation of **INTm**-**1a** and **INTm**-**1b**). This reveals that it is more favorable to open the ring at the less substituted side via the pathway **l** than at the more substituted side via the pathway **m** for aliphatic thiiranes. However, for 2-phenylthiirane (**1c**), the Gibbs free energy of the less steric transition state (**TSl**-**1c**) is 4.3 kcal/mol higher than that of the more steric one (**TSm**-**1c**).

Similarly, when methyl or phenyl group substitutes the hydrogen atom at the phenyl attached carbon atom, for 2-methyl-2-phenylthiirane (**1d**) and 2,2-diphenylthiirane (**1e**), the Gibbs free energies of **TSl** are 3.9 and 5.2 kcal/mol higher than those of **TSm**, respectively. This implies that ammonia attacks the ring predominantly at the more substituted side via the pathway **m** for aromatic thiiranes, not at less substituted side via the pathway **l** with the favorable steric hindrance. The energy surface analysis indicates that alkyl-substituted thiiranes are favorably attacked at the less substituted ring carbon atom to obtain 1-substituted aminothiols, while all aryl-substituted thiiranes are attacked advantageously at the more substituted ring carbon atom to produce 2-substituent aminothiols in the ammonia nucleophilic ring-opening reaction in the presence of silver nitrate. On the other hand, all the related Gibbs free energies of disubstituted thiiranes are higher than those of monosubstituted ones, leading to relatively lower yields of disubstituted products than monosubstituted ones. That is in reasonable agreement with our experimental results.[7a,b]

To further investigate the influence of the substituents on the regioselectivity, the configurations and the geometric parameters of the optimized structures listed in Fig. 2 were analyzed. It is intuitionistic that the substituted side bears with steric hindrance, especially for methyl, it more or less shields the back of the C(m) atom, while for phenyl, it shows little shield to the C(m) atom as phenyl is planar. So it is a little difficult for nucleophiles to attack the backside of methyl as its steric effect, while it is potential to attack the backside of phenyl due to no great steric difference between the substituted and unsubstituted sides in phenylthiirane (**1c**).

When analyzing in terms of the bond length, the Ag–S coordinated bond in the complexes **RC** is 2.46 Å with partial property of the covalent bond. Additionally, compared with the corresponding bond lengths of thiiranes **1**, both C(m)–S and C(l)–S bonds in the complexes **RC** increase in the length. The C(l)–S bond lengths increase slightly, about 0.023–0.026 Å for all thiiranes, whereas the C(m)–S bond lengths change obviously, increasing 0.047, 0.059, 0.118, 0.129, and 0.133 Å from thiiranes **1a**–**e**, respectively. Importantly, the C(m)–S bond lengths in the aromatic thiiranes **1c**–**e** increase greatly more obvious than those in the aliphatic thiiranes **1a**,**b**. This illustrates that addition of silver nitrate results in a tendency of C(m)–S bond broken. The change of the bond lengths reveals that thiiranes are favorable to break their C(m)–S bond, especially for aromatic thiiranes, in the presence of silver nitrate, with nucleophile attacking. At the same time, we also found that the C(m)–S bond is slightly longer than the C(l)–S bond in thiiranes (0.009, 0.023, 0.030, 0.049, and 0.051 Å for thiiranes **1a**–**e**, respectively). However, the corresponding bond length differences increase to 0.032, 0.059, 0.122, 0.153, and 0.160 Å in complexes **RCa**–**e**, respectively. For alkylthiiranes, the differences are receptible. However, for arylthiiranes, the differences are obvious in particular. The change of the bond length suggests that the C(m)–S bond is obviously favorable to cleave in the ring-opening reaction for the aromatic thiiranes in regard to the influence of the substituent of thiiranes on the regioselectivity in the reaction.

In regard to the bond lengths in **TS**, the N–C(m) bond forms partly and the C(m)–S bond breaks partly simultaneously in **TSm**. In a transverse comparison, from alkyl to aryl cases, the N–C(m) bond length decreases while the C(m)–S bond length increases in **TSm**. This illustrates that the **TSm** of arylthiiranes stands more like late TS and the level of its energy is comparatively closer to the intermediates **INTm** that can perfectly explain the fact that aryl-substituted **TSm** has lower energy. This is also consistent with the energy surface. However, the substituents do not make profound impact on the N–C(l) and C(l)–S bond lengths between **TSl** and **RC**. Comparison with the bond lengths in **TSm** and **TSl**, for aliphatic thiiranes, both the N–C(m) and C(m)–S bond lengths in **TSm** are longer than the N–C(l) and C(l)–S bonds in **TSl**. As a result, their energy of **TSm** is higher than that of **TSl**. For aromatic thiiranes, there is not too much difference between N–C(m) in **TSm** and N–C(l) in **TSl**, while the C(m)–S bond in **TSm** is visible longer than C(l)–S in **TSl**.

In the reaction process, special attention should be paid on the change of the C(m)–C(s) bond length [C(s) is defined as the carbon atom connected to the thiirane ring of substituents]. The C(m)–C(s) bond in **TSm** is slightly shorter than that in **TSl** for aliphatic thiiranes, while it is obviously shorter than that in **TSl** for aromatic thiiranes, which provides great contribution on the bond energy, leading to **TSm** with lower energy in all aromatic cases. In spite of being less obvious for aliphatic thiiranes, the bond length, however, tends to turn short for aromatic thiiranes with the use of the Lewis acid and it becomes even shorter in **TSm**, and then restores to its original length as **INTm** is formed. As to pathway **l**, such change does not exist at all. The reason should be attributed to the p–π conjugation between benzene ring and C(m) in **TSm**, also partially in **RC**. The electronic delocalization reduces **TSm** energy level so that the situation is favorable for the pathway **m** with more steric hindrance. However, for aliphatic thiiranes, the slight change of the C(m)–C(s) bond should be due to weak hyperconjugative effect between the methyl group and the p-orbital. This weak effect cannot lower their **TSm** energies enough to counteract the energies generated from steric hindrance when the ammonia attack occurs at the substituted carbon atom of thiiranes.

For complementarity to the above-mentioned bond analysis, NBO analysis was also carried out. Computed bond indices listed in Table 1 describe the formation and cleavage of bonds in the reaction. The formation of the N–C bond and the cleavage of the S–C bond take place simultaneously at B3LYP/IEFPCM/BS level in the transition state. This explains the concerted synchronous nature of the transition state very well. In **TSm**-**1a**, the N–C(m) bond is formed to 34.7% and S–C(m) bond is cleaved to 57.7% while in **TSl**-**1a** they are 41.2% and 55.7%, respectively. The C–S bond cleaves prior to the formation of the N–C bond. The average values of the bond formation and cleavage ($BFC_{Ave}$) are 46.2% and 48.4%, respectively, also indicating that the **TSl**-**1a** is later TS than **TSm**-**1a**. Thiirane **1b** shows similar behavior with **1a**. This is consistent with the bond length and energy surface analyses, which indicate that **TSl** is closer to the product with low energy difference than **TSm**. In contrary, in **TSm**-**1c**, the N–C(m) bond formation is 41.8% and the S–C(m) bond cleavage is 72.8%, while in **TSl**-**1c** they are 37.9% and 52.0%, respectively. $BFC_{Ave}$ values of 57.3% and 45.0%, respectively, indicate that the **TSm**-**1c** is later TS than **TSb**-**1c**. Thiiranes **1d** and **1e** resemble **1c**. The energy of **TSm** is relatively closer to the products for aromatic thiiranes.

MO analysis was also conducted for **TSm**-**1a** and **TSm**-**1c** (Fig. 3). No visible electronic delocalization between C(m) and the substituent in the HOMO, HOMO-1, and HOMO-2 of **1a** and **1c** was observed. While obvious difference was found in the HOMO-3 between **1a** and **1c**. That is, **1c** shows the electronic delocalization between C(m) and its phenyl substituent while **1a** does not. This agrees very well with the decrease in the C(m)–C(s) bond length of

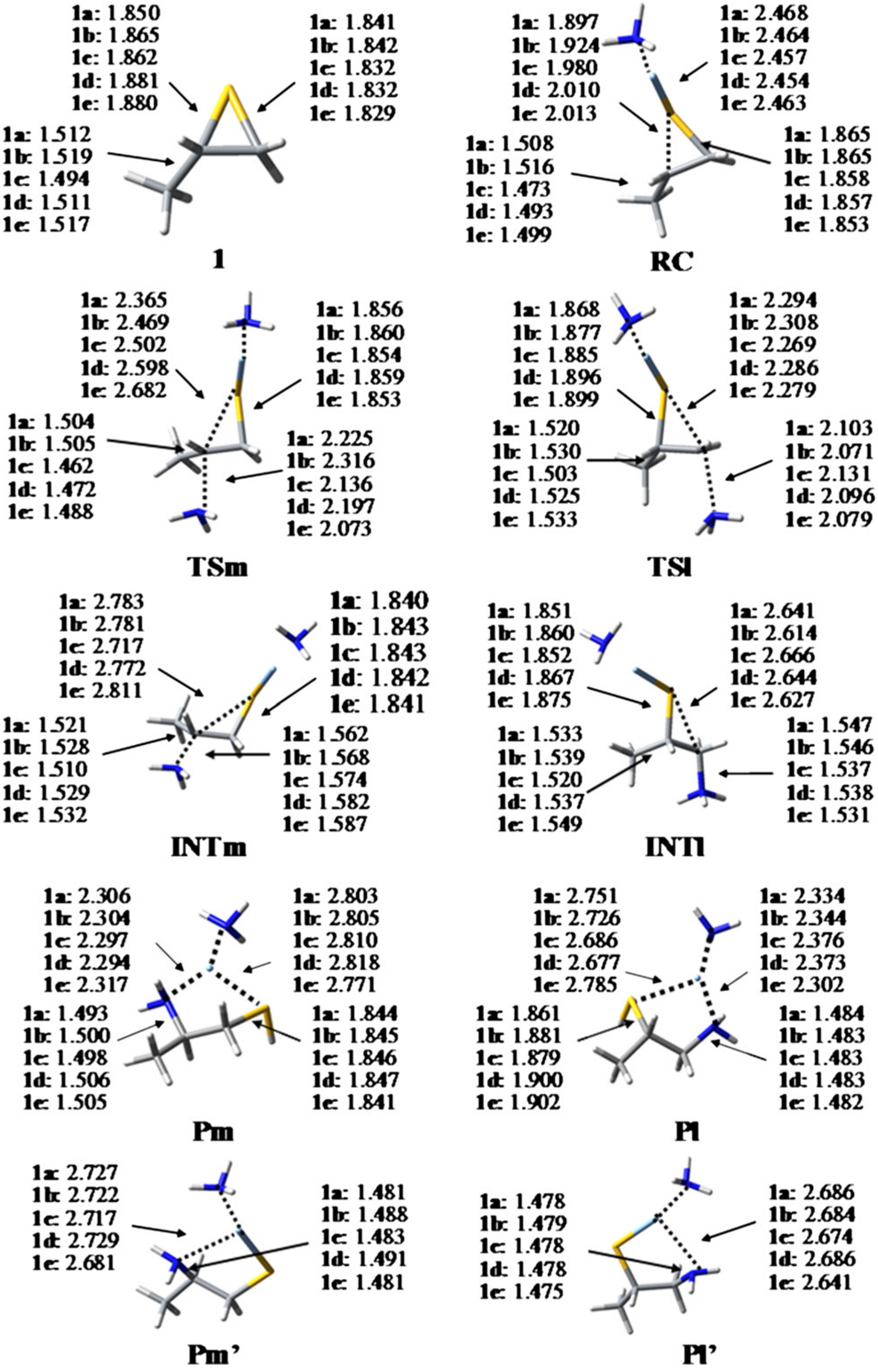


**Fig. 2.** Optimized structures with characteristic distances of the ammonia/substituted thiiranes/$Ag^+$ system.

**TSm**-**1c**, revealing that the lower energy of **TSm** of aromatic thiiranes is indeed caused by the p–π conjugation effect between the C(m) atom and the aromatic ring of aryl substituents.

Finally, the NBO and Mulliken charges on the C(m) and C(l) of **1** and **RC** were also calculated and analyzed (Table 2). The charges on the C(l) atom change slightly from **1** to **RC** for all selected thiiranes. However, the charge changes on the C(m) atom obviously depend on the substituents. Little change for alkyl substituents but significant change for aryl ones were observed for the C(m) atom from **1** to **RC**. The C(m) atom becomes more positive, especially for arylthiiranes, after addition of the Lewis acid, this makes it easy to be attacked by the nucleophile to open the ring at this side.

All of analyses illustrate that aliphatic and aromatic thiiranes show different regioselectivity in the ammonia ring-opening reaction in the presence of silver nitrate. Aliphatic thiiranes are attacked on their less substituted ring carbon atom, whereas aromatic derivatives are on their more substituted one. The reverse regioselectivity of aromatic thiiranes is attributed to the p–π

**Table 1**
Wiberg bond order analysis of the transition states in the ring opening of thiiranes with ammonia and dimethylamine

| Entry | **RC**+**Nu** | **TSm** | | | **TSl** | | |
|---|---|---|---|---|---|---|---|
| | | $B_{N-C(m)}$ formation (%) | $B_{S-C(m)}$ cleavage (%) | $BFC_{AVC}$ (%) | $B_{N-C(l)}$ formation (%) | $B_{S-C(l)}$ cleavage (%) | $BFC_{AVC}$ (%) |
| 1 | **1a**+$Ag^+$+$NH_3$ | 34.7 | 57.7 | 46.2 | 41.2 | 55.7 | 48.4 |
| 2 | **1b**+$Ag^+$+$NH_3$ | 30.7 | 66.0 | 48.4 | 43.8 | 58.2 | 51.0 |
| 3 | **1c**+$Ag^+$+$NH_3$ | 41.8 | 72.8 | 57.3 | 37.9 | 52.0 | 45.0 |
| 4 | **1d**+$Ag^+$+$NH_3$ | 38.6 | 80.8 | 59.7 | 40.9 | 54.8 | 47.9 |
| 5 | **1e**+$Ag^+$+$NH_3$ | 48.4 | 87.7 | 68.0 | 42.1 | 55.4 | 48.8 |
| 6 | **1a**+$Ag^+$+$HNMe_2$ | 25.1 | 46.0 | 35.5 | 26.0 | 38.4 | 32.2 |
| 7 | **1c**+$Ag^+$+$HNMe_2$ | 19.5 | 50.0 | 34.8 | 25.0 | 36.8 | 30.9 |

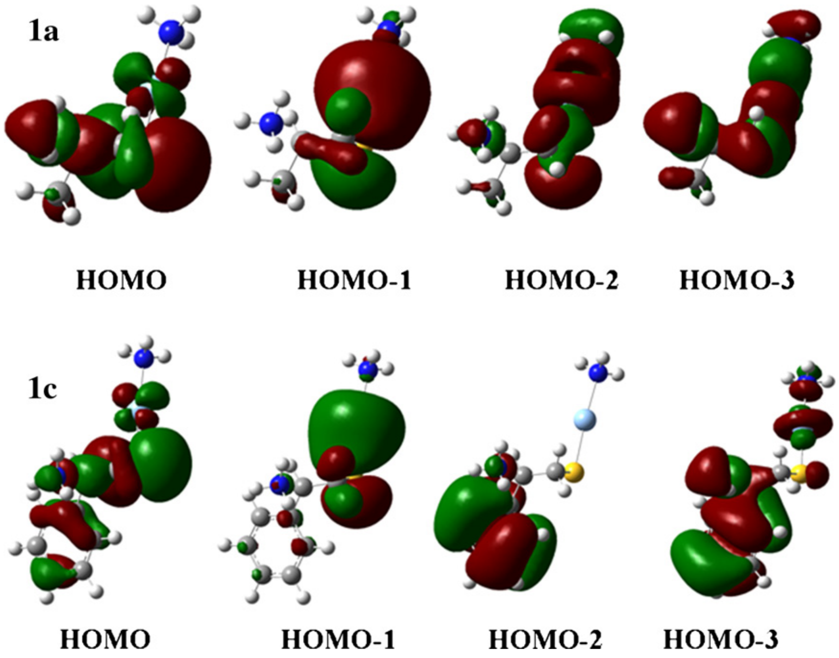


**Fig. 3.** HOMOs [isovalue 0.02 au] of **TSm-1a** and **TSm-1c** for the ammonia ring opening of methyl and phenylthiiranes **1a**,**c**.

**Table 2**
NBO and Mulliken charges on the C(m) and C(l) atoms in thiiranes **1** and their **RC**

| Entry | | Thiirane **1** | | | | **RC** | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Charge on C(m) | | Charge on C(l) | | Charge on C(m) | | Charge on C(l) | |
| | | NBO | Mulliken | NBO | Mulliken | NBO | Mulliken | NBO | Mulliken |
| 1 | **1a** | −0.277 | 0.344 | −0.448 | −0.657 | −0.235 | 0.322 | −0.427 | −0.745 |
| 2 | **1b** | −0.119 | 0.938 | −0.441 | −0.798 | −0.064 | 0.970 | −0.426 | −1.024 |
| 3 | **1c** | −0.277 | 0.623 | −0.444 | −0.961 | −0.188 | 0.956 | −0.441 | −1.284 |
| 4 | **1d** | −0.112 | 0.872 | −0.442 | −1.136 | −0.005 | 1.706 | −0.443 | −1.487 |
| 5 | **1e** | −0.122 | 1.048 | −0.437 | −1.024 | −0.016 | 0.891 | −0.440 | −1.222 |

conjugative effect between the aryl substituent and the formed carbocation in the TS of the ring-opening reaction.

### 2.2. Steric effect of nucleophiles

In the experiments, arylthiiranes show different regioselectivities in the ring-opening reactions with ammonia and dibenzylamine.[7a,b] The influence of the steric effect of nucleophiles on the regioselectivity was explored with discussion on the reaction of methyl and phenylthiiranes with ammonia and dimethylamine in this section. From the analysis of the potential energy surfaces (Fig. 4), it is very intuitive that **TS** and **INT** energies of both sides of methyl and phenylthiiranes attacked by dimethylamine are higher than those attacked by ammonia. As is methylthiirane (**1a**), the **TS** energies of both sides are increased by 0.9 kcal/mol, but the energy difference between both TS does not change. That is, increasing the steric hindrance of nucleophile cannot result in the change of the regioselectivity. For phenylthiirane (**1c**), the energy of **TSm** increases 3.3 kcal/mol, while **TSl** only increases 1.8 kcal/mol, resulting in the energy difference between the two TS decreases from 4.3 to 2.8 kcal/mol from ammonia to dimethylamine. However, the **TSl** is the TS with higher energy in both cases, revealing that the steric nucleophile cannot regulate the ratio of products obviously because the ratios in both cases are more than 99:1 on the basis of the Nernst equation.

It can be seen from the TS structures (Fig. 5), when the steric nucleophile attacks thiiranes, its larger groups (methyl here) always rotate toward the less hindrance direction of C(m) or C(l) in the staggered conformations to greatly reduce the nucleophilic steric effect. Thus, the steric hindrance of nucleophiles can

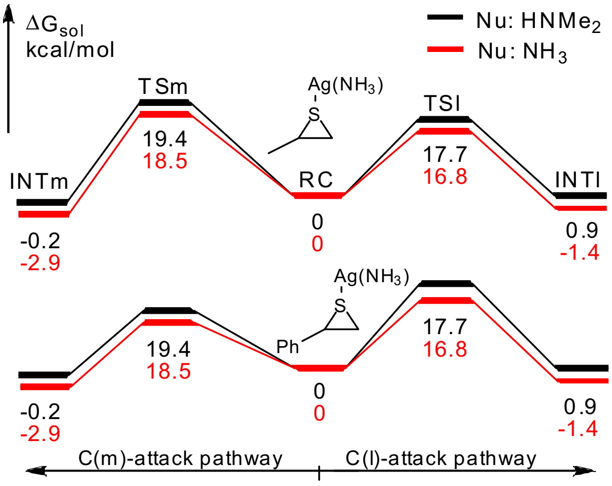
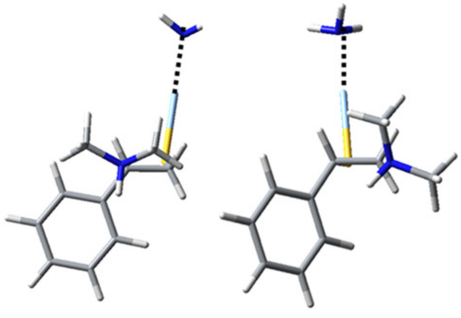


**Fig. 4.** The calculated energy surfaces for the reaction of thiiranes with ammonia or amine in the presence of argentum cation at the B3LYP/6-311++G(d,p) & LAN//B3LYP/6-31+G(d,p) & LAN+ΔZPVE level of theory (methanol was used as solvent within the IEFPCM method).



**TSm-1C** **TSl-1C**

**Fig. 5.** Optimized TS structures of the dimethylamine/phenyl-thiiranes/Ag$^+$complex.

modulate the regioselectivity slightly and cannot reverse the major products in the ring-opening reaction.

As the bond order analysis shown that all of the bond formation, the bond cleavage, and BFC$_{Ave}$ of the thiirane–dimethylamine–silver complexes in both pathways **m** and **l** are smaller than those of the thiirane–ammonia–silver complexes, indicating that the **TS** in the thiirane–dimethylamine–silver complexes are more like early TS (Table 1, entries 6 and 7). Their $\Delta G^{\neq}$ (**TS**) are higher as the structures of their **TS** are more close to the thiirane–dimethylamine–silver complexes. However, the bond formation, the bond cleavage, and BFC$_{Ave}$ values from the ammonia complexes to the dimethylamine complexes change in a similar trend in both pathways **m** and **l**, indicating that the different nucleophiles can only regulate the ratio of products, but not change the major product, which is also in accordance with the results from the analysis of the potential energy surface.

## 2.3. Influence of Lewis acid

The Lewis acid silver nitrate plays an important role in the ring-opening reaction of geminal disubstituted thiiranes in our experiments.[7b] It was considered as a ring-opening promoter due to its coordination with the sulfur atom in thiiranes to activate the ring and as a blocker after the ring-opening reaction because the formed thiolate anions were converted to five-membered cyclic coordinate complexes to avoid further polymerization induced by the attack of thiolate anions to thiiranes.[7b,c] A comparison investigation on the ring-opening reactions of geminal disubstituted thiiranes with secondary amines in the presence and absence of silver nitrate was conducted with the reaction of dimethylthiirane (**1b**) and dimethylamine as a model in this section. From the energy surface drawn in Fig. 6, we found that silver ion can reduce the activate energy of both pathways. It is minished heavily from 25.1 (**TSm-1B$_0$**) to 20.4 (**TSm-1B**) kcal/mol, while slightly from 20.1 (**TSl-1B$_0$**) to 19.4 (**TSl-1B**) kcal/mol. The results indicate that silver nitrate indeed accelerates the ring-opening reaction of geminal disubstituted thiiranes with secondary amines in kinetics. On the other hand, with the above-mentioned different reduced quantity, the regioselectivity can be adjusted by silver ion, as the tendency is met that Lewis acid promotes pathway **m** in favor of pathway **l** in relation to the absence of Lewis acid. In addition, silver nitrate reduces the **INT** energies significantly, from 16.7 (**INTm-1B$_0$**) to 3.1 (**INTm-1B**) kcal/mol and from 17.9 (**INTl-1B$_0$**) to 5.7 (**INTl-1B**) kcal/mol, stabilizing the **INT** greatly, which makes the ring-opening reaction flexible, once again in complete accord with the experimental result that 2,2-dimethylthiirane (**1b**) cannot be converted into the corresponding ring-opening product in the absence of Lewis acid and vice versa.

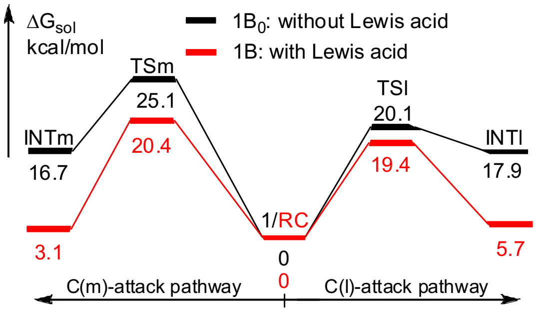


**Fig. 6.** The calculated energy surface for the reaction of **1b** with HNMe$_2$ in the presence of argentum cation at the B3LYP/6-311++G(d,p) & LAN//B3LYP/6-31+G(d,p) & LAN+ΔZPVE level or in the absence of argentum cation at the B3LYP/6-311++G(d,p)//B3LYP/6-31+G(d,p)+ΔZPVE level of theory (methanol was used as solvent within the IEFPCM method).

Although we planned to study the impact of silver nitrate on the regioselectivity in the reactions of phenylthiirane (**1c**) with dimethylamine in the presence and absence of silver nitrate theoretically, which show different values in experiments.[7a,b] However, it is a pity that the **TSm** of phenylthiirane (**1c**) cannot be found in the calculation.

## 2.4. Electronic effect of substituents

Because the conjugative effect of aryl substituents can reverse the regioselectivity in the ring-opening reaction, this inspires us to explore the influence of the inductive effect of alkyl substituents on the regioselectivity. Relatively simple and representative systems, including methyl, fluoromethyl, difluoromethyl, and trifluoromethylthiiranes (**1a**,**f**–**h**), were selected for the investigation. Initially, we supposed that the increase of the fluorine atom number would improve the electron-withdrawing ability of the substituents, which could make the C(m) atom more positive to serve as a stronger electrophile to react with nucleophiles, resulting in the change of the nucleophilic attacking direction. To observe the influence originally, we calculated the reaction systems in the absence of silver nitrate. The NBO and Mulliken charge calculational results show an opposite tendency (Table 3). The addition of the fluorine atom makes the charge of the C(s) atom positive gradually, according to the principle of induced alternate polarities,[9] which results in a gradual reduction of the positive charge on the adjacent C(m) atom. The charge change ends up on the third C(l) atom. Thus, less obvious electronic effect was observed on the C(l) atom. The electrophilicity of the C(m) atom

**Table 3**
NBO and Mulliken charges of methylthiirane **1a** and fluorosubstituted methylthiiranes **1f**–**h**

| Entry | | R | Charge on C(s) | | Charge on C(m) | | Charge on C(l) | |
|---|---|---|---|---|---|---|---|---|
| | | | NBO | Mulliken | NBO | Mulliken | NBO | Mulliken |
| 1 | **1a** | $CH_3$ | −0.592 | −0.655 | −0.277 | 0.344 | −0.448 | −0.657 |
| 2 | **1f** | $CH_2F$ | 0.067 | −0.503 | −0.329 | 0.335 | −0.443 | −0.630 |
| 3 | **1g** | $CHF_2$ | 0.606 | −0.285 | −0.369 | 0.245 | −0.444 | −0.619 |
| 4 | **1h** | $CF_3$ | 1.060 | 0.035 | −0.397 | 0.197 | −0.444 | −0.643 |

decreases steadily with the increase of the electron-withdrawing ability of aliphatic substituents due to loss of their positive charge. This as a whole leads the nucleophile to attack the C(m) difficultly.

Besides, we also found that the energy level of their **TSm** goes up with the rise of the F atom as regards to the potential energy (Table 4). However, such results could be barely noticed as for their **TSl**. The results indicate that when the amount of fluorine increased, the quantity of the positive charge of C(m) drops sharply, but its **TSm** energy rises stably. Both of them illustrate that alkylthiiranes with electron-withdrawing substituents are favorably attacked on their less substituted carbon atom.

**Table 4**
The energy comparison between the two pathways in the ring opening of thiiranes **1a**,**f**–**h** with $HNMe_2$ in the absence of silver cation

| Entry | | $\Delta G^{\neq}$ (**TSm**) kcal/mol | $\Delta G^{\neq}$ (**TSl**) kcal/mol | $\Delta\Delta G^{\neq}$ (**TSm**–**TSl**) kcal/mol |
|---|---|---|---|---|
| 1 | **1a** | 20.60 | 19.31 | 1.29 |
| 2 | **1f** | 25.69 | 21.22 | 4.47 |
| 3 | **1g** | 25.52 | 20.13 | 5.39 |
| 4 | **1h** | 28.17 | 20.04 | 8.13 |

More importantly, we found that the difference of the relative Gibbs free energy barrier between **TSm** and **TSl** with the NBO charge difference on the C(m) and C(l) atoms ($\mathbf{Q}_{C(m)}-\mathbf{Q}_{C(l)}$) have a very good linear correlation ($R^2$=0.96) with a slope of −54.42 (Fig. 7). This suggests that the electronic effect plays a critical role in the ring-opening reaction. It produces an obvious influence on the charge of the substituted carbon atom rather than nonsubstituted one and on the difference of the relative Gibbs free energy barrier between **TSm** and **TSl**. The existence of the electron-withdrawing groups is beneficial to ring opening at the less substituted side. However, methylthiirane (**1a**) with $\Delta\Delta G^{\neq}$ (**TSm**–**TSl**) of 1.29 kcal/mol is attacked regiospecifically on its unsubstituted carbon atom in the experiment. Thus, the fluorosubstituted thiiranes **1f**–**h** with $\Delta\Delta G^{\neq}$ (**TSm**–**TSl**) of 4.47–8.13 kcal/mol will be opened absolutely on their less substituted side. That is, electron-withdrawing substituents cannot regulate the regioselectivity.

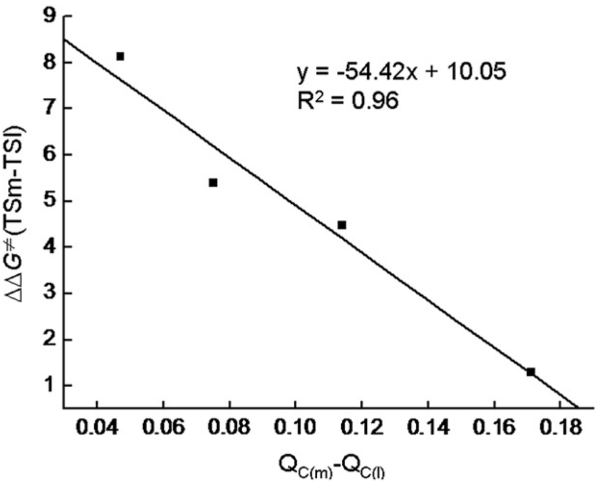


**Fig. 7.** A linear correlation of the difference of the relative Gibbs free energy barriers between **TSm** and **TSl** with the NBO charge difference on the C(m) and C(l) atoms in the ring opening of thiiranes **1a**,**f**–**h** with $HNMe_2$ in the absence of silver nitrate.

## 2.5. Solvents effect

The impact of the solvent effect on ring opening was also investigated. The free energy changes for **1a** in five different solvents were calculated using the IEFPCM/B3LYP/BS method (Table 5). Polar solvents, such as methanol increase the energy barrier of the reaction TS compared with nonpolar solvents, such as benzene. With ZPE explicitly included, we also found that the energy barrier is much lower in liquid phase than in gas phase (see Table 6). Finally, slight influence of solvent on $\Delta\Delta G^{\neq}$ (**TSm**–**TSl**) was observed, which indicates that solvents cannot affect the regioselectivity significantly.

**Table 5**
The free energy of **TSm**, **TSl**, and gaps of thiirane **1a** and ammonia system in five different solvents using IEFPCM/B3LYP/BS

| Entry | Solvent | Dielectric constant $\varepsilon$ | $\Delta G^{\neq}$ (**TSm**) kcal/mol | $\Delta G^{\neq}$ (**TSl**) kcal/mol | $\Delta\Delta G^{\neq}$ (**TSm**–**TSl**) kcal/mol |
|---|---|---|---|---|---|
| 1 | Benzene | 2.25 | 16.10 | 14.88 | 1.22 |
| 2 | THF | 7.58 | 17.35 | 15.81 | 1.54 |
| 3 | Ethanol | 24.55 | 18.33 | 16.83 | 1.50 |
| 4 | Methanol | 32.63 | 18.50 | 16.84 | 1.66 |
| 5 | Water | 78.39 | 17.84 | 16.12 | 1.72 |

**Table 6**
Gibbs free energies in the ring opening reaction of methylthiirane (**1a**) with $HNMe_2$ in different basis sets at B3LYP levels of theory

| Basis set[a] | $\Delta G^{\neq}$ (**TSm**) kcal/mol | $\Delta G^{\neq}$ (**TSl**) kcal/mol | $\Delta\Delta G^{\neq}$ (**TSm**–**TSl**) kcal/mol |
|---|---|---|---|
| 6-31+G(d,p) | 43.24 | 38.66 | 4.58 |
| 6-311++G(d,p)[b] | 42.99 | 38.66 | 4.33 |
| IEFPCM/6-311++G(d,p)[b] | 20.60 | 19.31 | 1.29 |
| IEFPCM/6-311++G(d,p) | 27.01 | 24.45 | 2.56 |

[a] All related free energies are corrected by ΔZPVE.

[b] Values obtained with single-point calculations at the specified level on the B3LYP/6-31+G(d,p) geometries.

## 3. Conclusion

The regioselectivity is one of the crucial issues in the ring-opening reaction of thiiranes. The influence of the substituents (including the electronic and steric effects), nucleophiles, Lewis acid, and solvents on the regioselectivity was investigated with the density functional theory (DFT) calculation. The results of the analyses of the energy surfaces, the bond lengths, and charges of key species in two different reaction pathways indicate that substituents, especially their conjugative electronic effects, dominantly determine the regioselectivity. That is, alkyl-substituted thiiranes are attacked predominantly on their less substituted ring carbon atom, whereas arylthiiranes are on their more substituted one due to the existence of the p–π conjugative effect, which stabilizes the TS generated in the reaction. Furthermore, the Lewis acid can modulate the regioselectivity. However, the steric hindrance of nucleophiles and solvents affect the regioselectivity slightly as both of them produce similar influence on both pathways, despite the fact that they can put an impact on their energy. NBO and MO analyses also support that the substituents control the regioselectivity. Similar regioselectivity exists in the ring opening of aziridines.[15–17] The theoretical investigation provides a rational explanation for the experimental results, and also gives a general understanding and a rule for the rationale and prediction of the regioselectivity in the nucleophilic ring opening of thiiranes, even other three-membered heterocycles.

## 4. Experimental section

### 4.1. General

All optimized geometries and analytical frequencies were calculated at the DFT B3LYP level[10] with the LANL2DZ basis set for Ag and 6-31+G(d,p) for other atoms with the Gaussian 03.[11] The transition states were confirmed by the vibrational analysis and characterized by only one imaginary vibrational mode. Intrinsic reaction coordinate (IRC) calculations for the transition state models were performed in order to further determine, to obtain the reaction pathways, and to identify intermediates.[12] To consider the impact of the solvent effect on the reaction, the integral equation formalism of the polarizable continuum model (IEFPCM) as the default SCRF method was applied. Single-point solvent energy calculations based on the optimized geometries of selected stationary points were carried out at the B3LYP/IEFPCM/6-311++G (d,p) & LAN level. For the veracity and time-saving of the computation, different basis sets were compared (Table 6). Table 6 presents the reaction free energies for the ring opening of methylthiirane at both attacking sides with different basis sets at B3LYP level. **TSl** and **TSm** are for the transition states attacked from less and more substituted ring carbon atoms, respectively. The results reveal that B3LYP/IEFPCM/6-311++G(d,p) & LAN//B3LYP/6-31+G(d,p) & LAN+ΔZPVE level (B3LYP/IEFPCM/BS+ΔZPVE) is appropriate. Bond orders reported here are Wiberg bond indices[13] calculated using the Natural Bond Orbital (NBO) program.[14]

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## Supplementary data

Complete Ref. 11. Molecular modeling coordinates and total energies of all stable and saddle points. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2010.12.063. These data include MOL files and InChiKeys of the most important compounds described in this article.

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