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## A Theoretical Studies on the Methylsulfenylchloride Addition to the Propene

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### Abstract

Thiiranium heterocycles play an important role in a biocatalytic processes of cells. Usually formation of thiiranium ions are known to proceed by the electrophilic additions of sulfenylhalides to a substituted olefins. We focused attention on the electrophilic addition reaction of methylsulfenyl chloride to the propene. In our work this reaction have been modeled using Ab-initio methods at the MP2/6-31+G(d,f) level of theory to look into the mechanism of the reaction and to explain how the regioselectivity of the reaction is controlled. Calculations of the intrinsic reaction coordinate on the minimum energy pathway revealed the stepwise mechanism for the addition reaction.

**Keywords:** Ab initio calculations, thiiranium ion, addition reaction, regioselectivity.

### Introduction

Ring-opening reactions of the three membered thiiranium heterocycles play an important role in a variety of biologically relevant processes and especially in the

biocatalytic reactions [1-4]. Thiiranium-based biomolecules are inhibitors of the cysteine proteases. Moreover they are versatile electrophilic building blocks that are widely used in a bioorganic chemistry [5-13]. In many cases the formation of thiiranium intermediate ions are known to proceed via electrophilic addition of sulfenylhalides to the substituted olefins, followed by the nucleophilic attack of halide on either C-1 or C-2 carbon atoms of the thiiranium intermediate ions to give respectively two isomeric adducts Markovnikoff (M) or anti-Markovnikoff (aM) (Scheme 1). The rate determining step for this reaction - the formation of the thiiranium intermediate is known from the kinetic and spectroscopic experimental data [13-24].

At low temperatures, this reaction goes under a kinetic control. Obtained adducts of the kinetically controlled reaction undergoes further rearrangement to the thermodynamically stable products [13-24]. Usually the nucleophilic halide attacks the substituted C-1 carbon atom of the thiiranium intermediate to give M-adducts, while propene, iso-butylene and other nonconjugated olefins first give kinetically controlled aM-adducts of the halide attack on the C-2 carbon atom [13-18]. This experimental observation was explained as resultant competition between a steric and electronic effects [13-24]. The electronic effect contends that the  $\pi$  electron density on the C-2 carbon atom of the thiiranium intermediate increases with the conjugation effect between the double bond and the substituent, subsequently chloride attacks the less negative carbon atom C-1 forming M product. While, if the substituent is aliphatic, the addition occurs conversely as mentioned above forming aM product, and the steric factor between the chloride and the substituent was introduced to explain the resulting orientation of the adducts [13-24].

Additionally to the above mentioned experimental investigations [13-24] recent theoretical computational researches [25-26] extended known reactivity pattern. The investigation of chloride anion attack on either the C-1 or C-2 carbon atoms of the thiiranium ion shows the reaction to be frontier-orbital controlled. These studies gave same information about the stereoselectivity and regioselectivity features

of such reactions, however, quantum mechanical studies of the electrophilic addition reaction mechanism was not performed yet.

In this work we investigated the reaction mechanism by analyzing computed potential energy profiles of the methylsulfenyl chloride addition reaction to propene presented in Scheme 1. The reaction is comprising of: the electrophilic addition of methylsulfenyl chloride to propene, leading to the thiiranium ion intermediate formation; the subsequent nucleophilic attack of chloride anion on either 1-C or 2-C carbon atom of the intermediate to give two distinct types of isomeric adducts M 1-chloro and aM 2-chloro; the isomerisation of kinetically controlled reaction adduct to thermodynamically stable product.

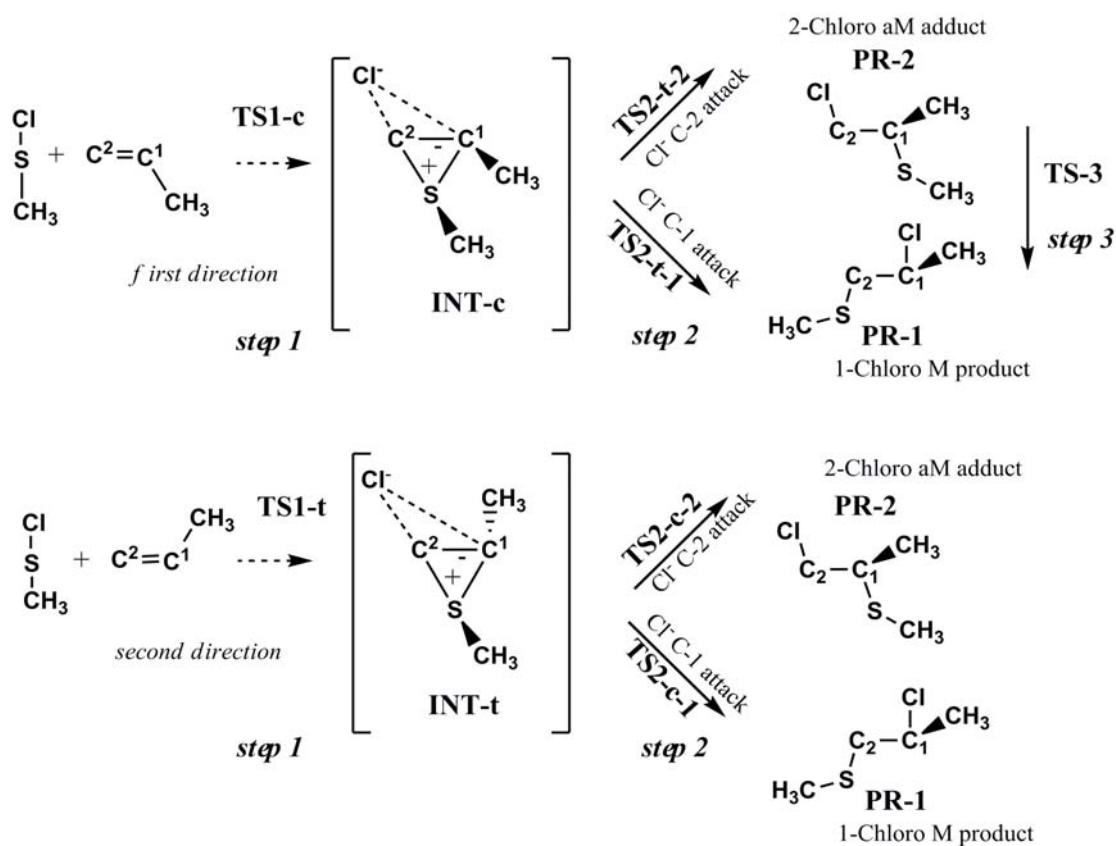
## Results and Discussions

The two alternative directions ( Scheme 1) have been studied theoretically for the addition reaction of methylsulfenyl chloride to the double bond of methyl substituted ethene (propene). The first direction occurs when the sulfur atom of the methylsulfenyl chloride approaches to the double bond of propene forming cis methyl oriented thiiranium intermediate. The second direction goes when the sulfur atom of methylsulfenyl chloride and the double bond of propene forms the trans methyl oriented thiiranium intermediate. The processes of first and second directions can be described by the three main steps involving intermediate and transition states (TS) formation. These steps are as follows:

step 1 - the addition of methylsulfenyl chloride to the double bond of propene up to the intermediate formation,

step 2 - the regioselective thiiranium intermediate ring opening course by the chloride anion,

step 3 - the isomerization of the adduct of kinetically controlled reaction to the thermodynamically favorable product.



**Scheme 1.** The addition reaction of methylsulfenyl chloride to propene

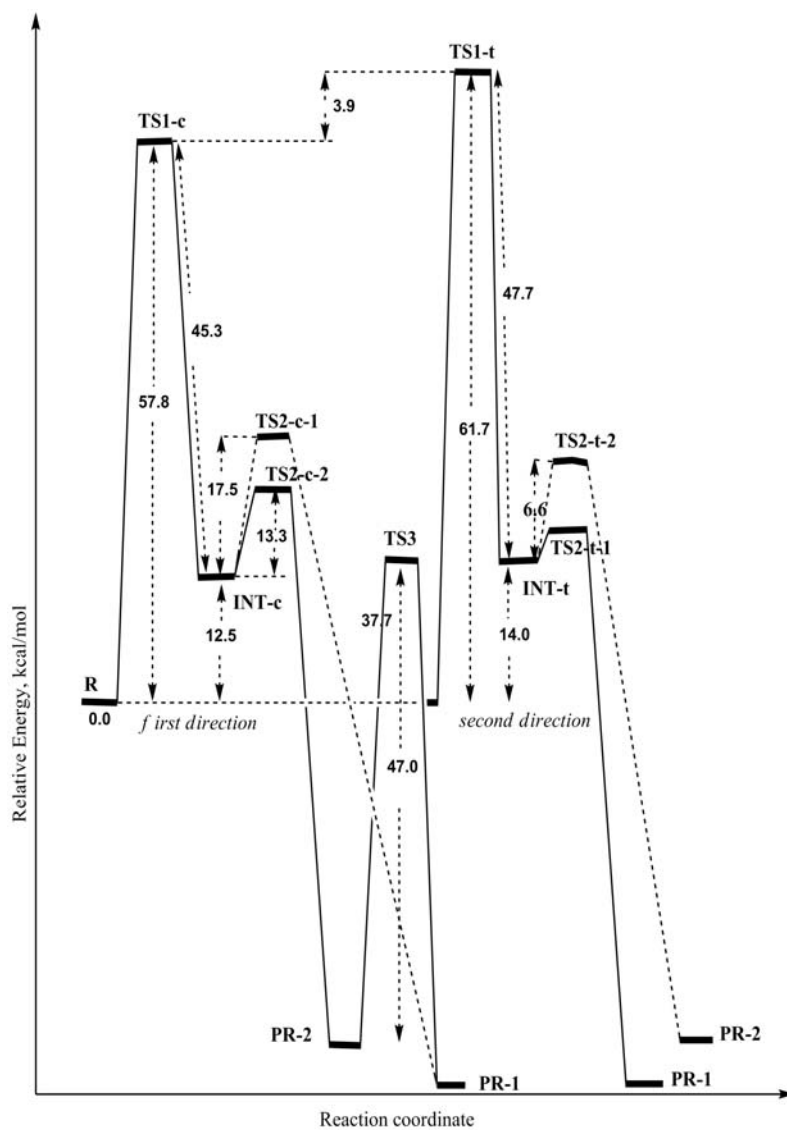
Section 'Results and Discussion' discuss the reaction potential energy surface profiles (PES) calculation results for the first and second directions. Since each direction consists of the three main steps, Section 'Results and Discussion' is divided into three subsections.

The schematic representation of the methylsulfenyl chloride addition reaction to propene for the first and the second directions consisting of the three main steps are given in the Scheme 1.

The relative energies of the optimized stationary points and the imaginary frequencies of the optimized transition states are presented in Table 1. The intrinsic reaction coordinates (IRCs) were calculated to find the reaction minimal potential energy profile and to detail the reaction mechanism. In Fig. 1 the schematic potential energy surface profiles are presented for the first and the second directions of the pending reaction. The optimized geometries and the main parameters of the reactants, TSs, intermediates and the final products are displayed in Fig. 2 and 3.

### **1. The addition of methylsulfenyl chloride to the double bond of propene (step 1)**

The *step 1* – the addition reaction of methylsulfenyl chloride to the double bond of propene, goes by the attack of the sulfur atom to the double bond of propene and forms two bonds with the C-1 and C-2 carbons (Scheme 1, Fig.1-3). Approach of the sulfur atom to the double bond of propene can undergo two possible directions: the first direction occurs when the methyl groups of reacting molecules (propene and methylsulfenyl chloride) take cis orientation with respect to the C(1)=C(2) double bond forming the cis oriented intermediate **INT-c**. The second direction occurs when the methyl groups of the reacting molecules take trans orientation to the C(1)=C(2) double bond fostering the trans oriented thiiranium intermediate **INT-t** formation. As pictured in Fig. 1 *step 1* occurs through the formation of the transition state **TS1-c** (for the first direction, Fig. 2) and **TS1-t** (for the second direction, Fig. 3). It finishes with the formation of the thiiranium intermediate either **INT-c** or **INT-t** respectively for first or second direction. The *step 1* presents very high activation barriers for the formation of both intermediates. The relative activation energies of the transition states **TS1-c** and **TS1-t** to form the **INT-c** and **INT-t** intermediates are 57.8 and 61.7 kcal/mol respectively. The thiiranium ring formation up to the **INT-c** and **INT-t** is energetically favourable process.



**Fig. 1.** The potential energy profile for methylsulfenyl chloride addition reaction to propene, relative reaction energies presented in kcal/mol.

**Table 1.** The relative energies (RE) with zero point energy correction at the MP2/6-31+G(d,f) level (in kcal/mol) for the stationary points represented in fig 2 and 3, the lowest harmonic vibrational frequencies (LHVF) (in  $\text{cm}^{-1}$ ) for the TSs corresponding to the presented in scheme 1 and fig 1 electrophilic addition reaction.

	<i>RE</i>	LHVF for TS ( $\text{cm}^{-1}$ )
<b>R</b>	0.0	-
<b>TS1-c</b>	57.8	306.36i
<b>INT-c</b>	12.5	-
<b>TS2-c-1</b>	30.0	63.16i
<b>TS2-c-2</b>	25.8	62.74i
<b>TS3</b>	14.7	424.64
<b>PR-1</b>	-34.3	-
<b>PR-2</b>	-32.3	-
<b>TS1-t</b>	61.7	302.14i
<b>INT-t</b>	14.0	-
<b>TS2-t-1</b>	15.2	73.62i
<b>TS2-t-2</b>	20.6	59.75i

It is worth to mention that the calculated activation energy for **TS1-c** is less by 3.9 kcal/mol than that for **TS1-t**. Moreover the formation of the intermediate **INT-c** is 1.5 kcal/mol more energetically favourable than **INT-t**. It indicates that a steric interaction between methyl and chloride in **INT-t** is more destabilizing than interaction of two methyl groups in the intermediate **INT-c**. The experimentally obtained Taft steric constants [29] supports our calculations showing that chloride is more bulky than methyl group.

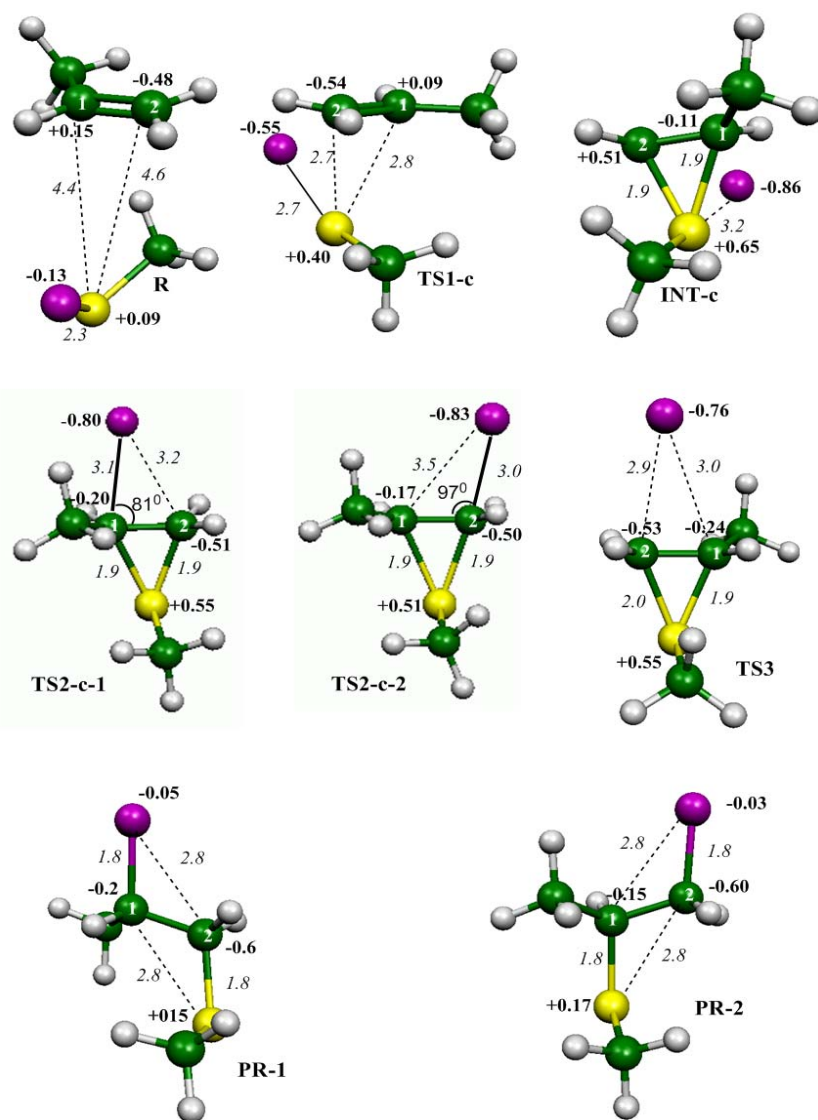
Moreover the activation energy difference value 3.9 kcal/mol between **TS1-c** and **TS1-t** is not large but satisfactory to suppose that the formation of the cis oriented intermediate **INT-c** in the first direction is more probable than formation of the intermediate **INT-t** in the second one.

At this step (Fig. 2, 3) the sulfur atom of methylsulfenyl chloride approaches perpendicularly to the double bond of propene through the concerted synchronous transition states **TS1-c**, **TS1-t** to form the thiiranium intermediates **INT-c**, **INT-t**. Herewith S-C(1) and S-C(2) bonds are developing synchronously with the process of weakening of the S-Cl bond as the reaction progresses from the reactants **R** to the transition states **TS1-c**, **TS1-t**. For example in the reaction progress to **TS1-c** the S-C(1) and S-C(2) bonds lengths have been shortened from 4.4 Å and 4.6 Å up to 2.7 Å and 2.8 Å respectively. It courses the simultaneous S-Cl bond lengthening from 2.3 Å for the **R** to 2.7 Å for the **TS1-c**. Further as the reaction goes from the transition states **TS1-c**, **TS1-t** to the intermediates **INT-c**, **INT-t** S-C(1) and S-C(2) are shortened from 2.8 up to 1.9 Å. Moreover the distances between the chloride atom and the sulfur, carbon atoms of the thiiranium intermediate becomes close to van der Waals interaction distance based on the sum of the van der Waals radii. It stabilizes system, forms the thiiranium cation and the chloride anion.

For the first direction of step 1 the negative charge transfers to the chloride atom from -0.13 to -0.55 simultaneously rising grow up of positive charge on the sulfur atom from +0.09 up to +0.40 as the reaction progresses from the reactant **R** to the transition state **TS1-c**. Further reaction progress from the **TS1-c** to the intermediate **INT-c** shows a high negative charge increase on the chloride up to -0.86 and reduce of relative electron density on the sulfur atom generating positive charge grows up to +0.65 for the intermediate **INT-c**. This charge transfer results in polarization, lengthening and weakening of the S-Cl bond up to the ionic bond level.

The same tendencies of the charge transfer and bonds progress also was observed for the step 1 of the second direction.





**Fig. 2.** The geometries, charges and bond lengths (in Å) of the stationary points were located for the first reaction direction: transition structures corresponding to the intermediate formation **TS1-c**, for the intermediate ring opening reaction **TS2-c-1**, **TS2-c-2**, **TS3**, the reaction intermediate **INT-c**, reactants **R**, and final products **PR-1** and **PR-2**.

## 2. The thiiranium intermediate ring opening processes by chloride anion (step 2)

At the *step 2*, the intermediate **INT-c** or **INT-t** reacts with the nucleophilic chloride anion by two-regioisomeric pathways to give two distinct types of the products. For the one type of product the chloride forms bond with the C-2 carbon of the intermediate resulting in the formation of aM type 2-chloro C(2)-Cl derivative **PR-2**. For the other type of product, the chloride makes bond with the C-1 carbon of intermediate resulting M type 1-chloro C(1)-Cl substituted derivative **PR-1**. The C(1)-Cl bond formation process stimulates the C(1)-S bond cleavage and conversely the C(2)-Cl bond formation causes the C(2)-S bond cleavage accordingly. So the *step 2* corresponds with the ring-opening reaction of the intermediates **INT-c** and **INT-t**.

Considering the ring-opening process of **INT-c** two regioisomeric pathways proceeding via the transition states **TS2-c-1** and **TS2-c-2** depending on the nucleophilic attack of the chloride anion either on the C-1 or C-2 carbon atoms of the thiiranium intermediate **INT-c** cation to give either 1-chloro **PR-1** or 2-chloro **PR-2** addition products accordingly. This step presents very low activation barrier. For the thiiranium ring opening reaction the relative activation energies of transition states **TS2-c-1** and **TS2-c-2** starting from the intermediate **INT-c** are 17.5 and 13.3 kcal/mol respectively. In consequence the **TS2-c-2** is less in energy than **TS2-c-1** by 4.2 kcal/mol. Possibly transition states energy difference is determined by steric interaction of the bulky methyl group with chlorine [29]. As presented in Fig. 2 the Cl-C(1)-C(2) angle  $81^\circ$  in **TS2-c-1** is closer in regard to open Cl-C(1)-C(2) angle  $97^\circ$  for **TS2-c-2**. It shows that attack of chlorine on C(1) atom is hindered. Hence the formation of 2-chloro adduct **PR-2** predicted to go firstly with the lower activation energy. In accordance with experiment this reaction at low temperatures goes under kinetic control forming unstable 2-chloro adduct **PR-2** [13-24].

Our computational result supports experimentally observed preceding formation of aM adduct **PR-2** in the reaction mixture [13-24].

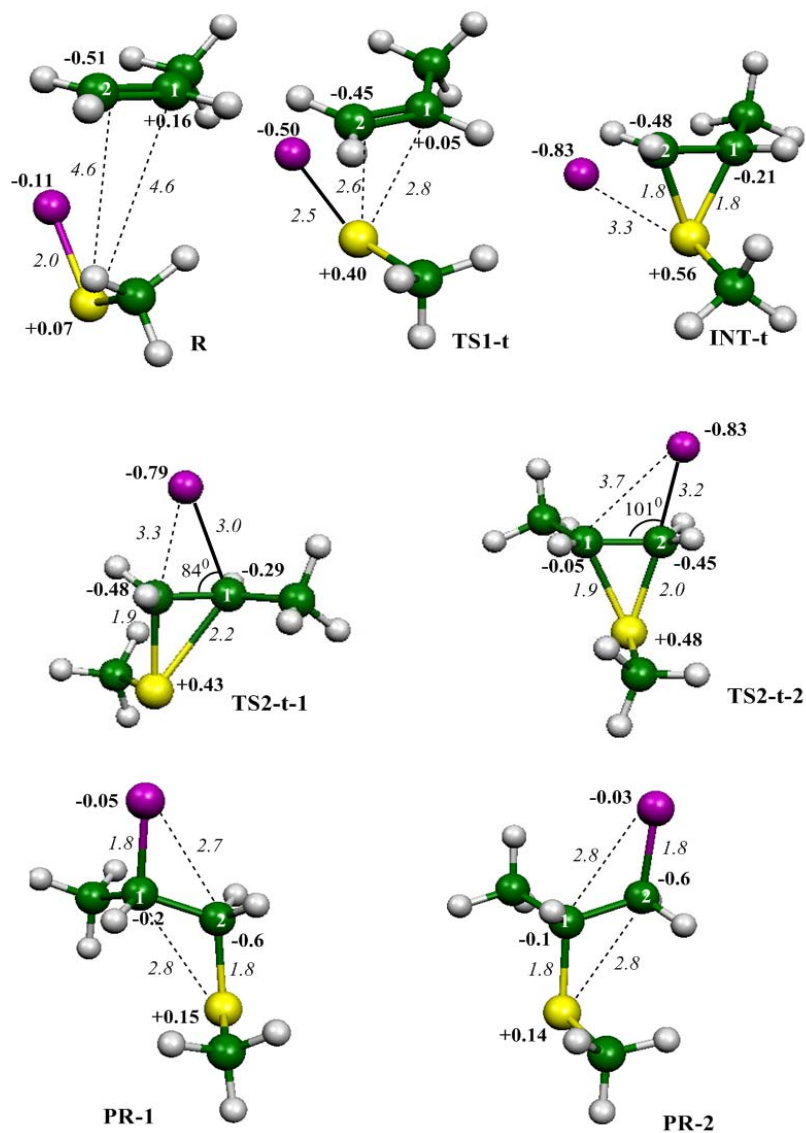
The ring opening process of the intermediate **INT-t** (the second direction) occurs via transition states **TS2-t-1** and **TS2-t-2**. The activation barrier for **TS2-t-2** is 6.6 kcal/mol relatively higher to the intermediate **INT-t**, while the reaction pathway via **TS2-t-1** requires 1.2 kcal/mol. The activation barrier of the transition state **TS2-t-1** is less in energy than for **TS2-t-2** by 5.4 kcal/mol. Comparison of transition states **TS2-t-1** and **TS2-t-2** geometries shows that the geometry of **TS2-t-1** is more close to geometry of final product **PR-1** than **TS2-t-2**. The Leffler Hammond postulate [30-32] allows us to suppose that this transition state might have lower energy. So in the second direction the formation of 1-chloro product **PR-1** might go first. The presented energy profile for second direction (step 2) presume greater propensity of **PR-1** formation.

The calculated energy profile for the second direction is incompatible with experimental findings. Experimentally this reaction goes under kinetic control forming unstable 2-chloro adduct **PR-2** at low temperatures [13-24].

Our calculations show that in the first direction the intermediate ring-opening process goes firstly by the chloride anion attack to the C-2 carbon of the thiiranium intermediate via **TS2-c-2** forming unstable 2-chloro addition adduct **PR-2** of kinetically controlled reaction. So the calculated energy profile for the first direction is in agreement with experimental observations.

### **3.The isomerization of kinetically controlled reaction adduct to thermodynamically favorable product (step 3)**

At the *step 3* we theoretically investigated possibility of the isomerization pathway of aM type 2-chloro addition adduct **PR-2** to more energetically favourable M type 1-chloro product **PR-1**.



**Fig. 3.** Geometries, charges and bond lengths (in Å) of the stationary points were located for the second reaction direction: transition structures corresponding to the intermediate formation **TS1-t**, and for intermediate ring opening reaction **TS2-t-1**, **TS2-t-2**, also the intermediate **INT-t**, reactants **R**, and final products **PR-1** and **PR-2**.

Experimentally it was shown that the aM type 2-chloro adduct **PR-2** was obtained in the reaction mixture at low temperatures as the unstable adduct of kinetically controlled reaction. This adduct by heating undergoes further rearrangement to the thermodynamically stable aM type 2-chloro product [5-26].

As pictured in Fig. 1 and shown in Table 1 the final reaction product **PR-1** is in 2 kcal/mol less in energy than initial adduct **PR-2**. The small energy difference between **PR-1** and **PR-2** means the difference in thermodynamic stability of those isomers. It confirms theoretical possibility to undergo isomerization reaction for the **PR-2** to the most stable and less in energy product **PR-1**. Calculation of the PES for the *step 3* shows that the isomerization reaction goes via the transition state **TS-3** with the high activation barrier 47.7 kcal/mol to more stable **PR-1** product.

The experimental findings of the reaction kinetics suggests that under isomerization process the adducts are not reverting to thiiranium intermediate, they rather undergoes reaction with different reaction rate constant than the formation of thiiranium ion [13-24]. Our calculation revealed the possibility of isomerization via transition state **TS-3**.

Summarizing, our computational result supports the experimental kinetic and spectroscopic studies [13-24] showing that the ring closure step is the rate-limiting step for the addition reaction leading to the formation of the thiiranium cation as the reaction intermediate. The thiiranium intermediate ring formation step has the highest energy barriers for both directions.

Assuming results obtained for the calculated addition reaction energy profile for the first and the second directions we consider that the first direction is more profitable.

Consequently, the electrophilic addition reaction of methylsulfenyl chloride to propene undergoes the first direction via the cis methyl oriented intermediate **INT-c**

formation and the further regioselective thiiranium intermediate ring opening reaction by one-in-two possible regioisomeric pathways. Our calculations show that the intermediate ring-opening process goes firstly by the chloride anion attack to the C-2 carbon of the thiiranium intermediate via **TS2-c-2** forming unstable 2-chloro addition adduct **PR-2** of kinetically controlled reaction. The isomerization reaction of the adduct **PR-2** proceeded via transition state **TS-3** to form the product **PR-1**.

## Computational details

To study the mechanism of the reaction, quantum chemical calculations were carried out by means of ab initio Hartree-Fock calculations using GAMESS program [33]. Full geometry optimization of the reactants, intermediates, transition states, and products was fulfilled. The MP2/6-31+G(d,f) level of theory has been used throughout calculations. More often for optimization geometries involving thiirans the MP2/6-31+G(d) level is used [28]. We use 6-31+G(d,f) instead of the standard one 6-31++G(d,p) with the intention better estimate behavior of heavy atoms C, S and Cl which are essential for pending reaction. Standard basis set 6-31++G(d,p) has diffuse and polarization *p* functions to H and the diffuse and polarization *d* functions for heavy atoms C, S and Cl. Our goal was to choose a basis set which well describes reactions with heavy atoms from the third row such as S and Cl [28a]. Therefore we added additional *f* functions to heavy atoms. Hydrogen atoms in the reactions are passive. So to keep a relatively simplified basis set and to shorten calculations, we unexploited diffuse and polarization *p* functions for H. Thus, our basis set 6-31+G(d, f) has the additional diffuse and polarization functions *d* and *f* for heavy atoms C, S and Cl, and does not contain diffuse and polarization functions *p* for hydrogen. Analogous reasoning for basis set choice is presented in [28a]. Vibrational frequencies were calculated doing numerical differentiation of analytically computed

MP2 gradients. Scale factor for vibrational frequencies, displacement size, as well as other quantities are left in their default values.

The total energy of molecule  $E$  according to the adiabatic Born-Oppenheimer approximation consists of total electronic energy  $E_{elec}$  and vibrational energy  $E_{vib}$ .

$$E = E_{elec} + E_{vib} \quad (1)$$

So, the electronic energies were adjusted by a vibrational zero point energies (ZPE) for the initial molecules, reaction products, intermediates and transition states, in order to have a proper ground and transition state energies

$$E = E_{elec} + ZPE, \quad (2)$$

where

$$ZPE = \frac{1}{2} \sum_i \hbar \omega_i \quad (3)$$

is simply a half of summation over whole real vibration frequencies  $\omega_i$ , where  $\hbar$  is Planck constant.

All stationary points located have been characterized as either minima or transition states (first order saddle points) by computing vibrational frequencies. Transition states have a single imaginary frequency while minima have all real frequencies. Transition states have been confirmed by the animating their imaginary frequency using MOLEKEL [34] and by the IRC calculations and analysis. Each transition state was verified to connect the defined reactants and products by performing the IRC calculations and analysis. At the RHF/6-31+G(d,f) level of theory the minimum energy paths have been obtained with a gradient step size of 0.05 amu<sup>1/2</sup> bohr<sup>-1</sup> in mass-weighted Cartesian coordinates. MP2 correction for IRC path was applied to obtain corrected electronic structure dependence on reacting system

coordinates. Visualization of the obtained structures was performed with MOLEKEL program [29].

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