

Ab-initio modeling of the addition reaction of methylsulfenchloride to functionalized ethenes

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Ab-initio calculations have been applied in order to get more insight into the nature of the experimentally observed regioselectivity of the electrophilic addition reaction of methylsulfide cation to ethene and its methyl, chloro, carboxyl, vinyl substituted derivatives leading to intermediate formation, followed by the further nucleophilic attack of the chloride anion

Key words: ab-initio calculations, addition reaction, regioselectivity

In honor of Prof. L. Rasteikienė on the occasion of her 80th birthday

INTRODUCTION

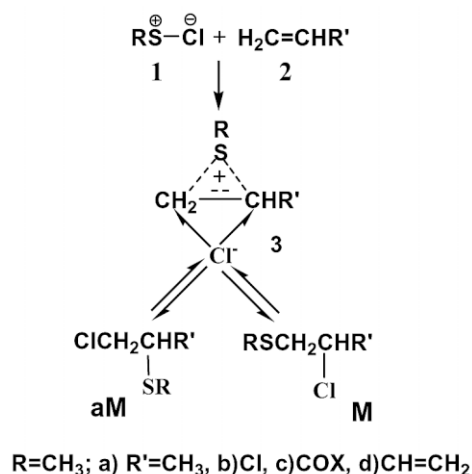
Thioalkylhalogenides are suitable agents for application in biochemistry research and in medicinal chemistry as anticancer agents [1]. To obtain these compounds, synthetic chemists mainly use electrophilic addition reactions of sulfenyl halogenides to the double bonds of functionalized alkenes [2]. As is shown in Scheme, the reaction mechanism involves two main steps: first - formation of a stable intermediate, second – the subsequent nucleophilic displacement of halide to give the chloroalkyl sulfide product. It was determined experimentally that the reaction occurs in a stereospecific *trans* manner, with the nucleophile (halide) attacking one of the unsaturated carbon atoms [2, 3]. The first step is usually reversible, so it is the second step that determines stereochemistry of the products. It is well known that the addition reactions of sulfenyl chlorides to unsymmetrical alkenes give two isomeric adducts: the Markownikoff adduct (M) and the anti-Markownikoff adduct (aM). The ratio of the amounts of these isomeric adducts characteristically differs, in the type of the unsymmetrical alkene used [3]. It was shown (Scheme) that when the α -carbon substituent R of the intermediate structure type **3** is alkyl chloride, the predominant ring-opening reaction occurs by an attack at the terminal \bar{a} carbon atom giving the **aM** products. In the case of methyl substituted intermediate **3a** the ring opening by chloride anion gives kinetically controlled adducts which undergo the further rearrangement into the thermodynamically stable **M**. Meanwhile, the chloro substituted intermediate gives **aM** products which did not show any tendencies to rearrange [3]. By contrast, the addition of sulfenylchloride to the conjugated olefins when the

α -carbon substituents R are vinyl and carboxyl, gives **M** oriented adducts, carboxyl-substituted intermediates give kinetically controlled adducts which undergo the further rearrangement into the thermodynamically stable **aM**. Most discussions about electrophilic addition reaction mechanisms are concerned with stable conformations of sulfonium ion intermediates: carbonium like – open classical, symmetrical bridged and unsymmetrical bridged [4–6]. The ratios of the amounts of the two isomers (formed) are believed to result from the competition between steric and electronic effects of an episulfonium intermediate [4–6].

In the recent experimental studies [4, 7] on the addition reactions of sulfenyl chlorides to the substituted olefins the effects of sulfonium ion intermediates have been investigated and the reaction mechanism has been confirmed. During these investigations it was revealed that the electronic structures and configurational features of episulfonium ion intermediates should be examined using molecular orbital approaches to these problems. Therefore, the nature of the experimentally observed regioselectivity for addition reactions of methylsulfenyl chlorides to methyl, chloro, vinyl, carboxyl substituted ethenes was investigated using quantum chemical Ab-initio methods.

EXPERIMENTAL

Ab-initio Hartree-Fock using 6-31G basis set was carried out for the addition reaction of starting reactants and intermediate structures. Full geometry optimization and other quantum chemical calculations were carried out using GAMESS program package [8]. The calculations of the starting reactants were performed in vacuum as well



Scheme. The addition reaction of methanesulfonyl chloride to the double bonds of functionalized ethenes

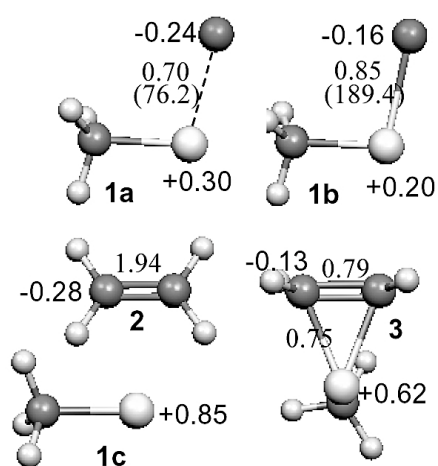


Fig. 1. Charge densities, bond orders and bond dissociation energies (in brackets, Kcal/Mol) of methanesulfonyl chloride calculated with PCM solvent model (for CH₂Cl₂) **1a** and in vacuum **1b** and methanesulfide cation **1c**, ethane **2**

as using the polarizable continuum model (PCM) approach to treat the solution in a polar CH₂Cl₂ model. The visualization of the optimized geometries and orbitals was performed with MOLEKEL [9] program package (version 4.3).

RESULTS AND DISCUSSION

Firstly, electronic states and molecular orbitals of the optimized methanesulfonyl chloride in a solvated media (PCM model for CH₂Cl₂ solvent) **1a**, methanesulfonyl chloride in vacuum **1b** were investigated and compared with the methanesulfonyl cation **1c** (Fig. 1).

The charge distribution of methanesulfonyl chloride **1 a-b** presented in figure 1 shows that the positive charge is mainly located on the sulfur atom, while the negative charge is on the chlorine atom. The charge polarization between those atoms is enhanced by the influence of solvation effects. Moreover, the increase of

positive charge density on the sulfur atom in the methylsulfide cation **1c** compared to that in methylsulfonyl chloride **1 a-b** is so significant that it becomes +0.8. The comparison of **1a** and **1b** shows (Fig. 1) that the solvation effects reflect the tendencies to lower the bond dissociation energy and bond order between S and Cl atoms. These results imply that the polarization of the S–Cl bond (up to the dissociated bond level) in the methylsulfonyl chloride molecule is expected to be sensitive to the polarity of the solvent. This is important for electrophilic addition reactions that may therefore occur fairly easily in polar solvents. The calculated molecular orbital parameters of the starting molecules **1a**, **1b** and **1c** as well as charge distribution and molecular orbital parameters of other starting compounds in vacuum did not show any significant changes comparing to the ones calculated for the solvated media.

Afterwards, the distribution of the frontier molecular orbitals of the methylsulfide cation **1a**, which is one of the possible starting species of the addition reaction was presented. In figure 2 it is shown that for **1a** the electrons of the highest occupied molecular orbital (HOMO) are mainly localized in the *py* atomic orbital (AO) of the S atom, and LUMO is localized in the *pz* of the S atom, which implies that the methylsulfide cation **1c** can easily react with various olefins or nucleophiles forming cationic *pσ*-type intermediates. Therefore, for the further calculations we have considered the methylsulfide cation **1c** as the most plausible electrophilic starting species for the initiation of electrophilic addition reaction to olefins.

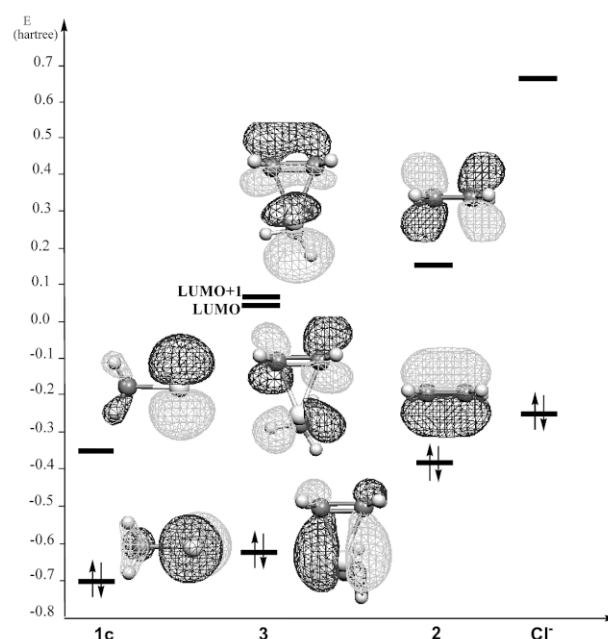


Fig. 2. Frontier molecular orbital diagram for interacting electrophile-methanesulfide cation **1c**, nucleophiles-ethylene **2** and chloride anion, together with the episulfonium cation reaction intermediate **3**

Secondly, in order to get more insight into the nature of the observed regioselectivity of addition reaction and factors controlling the ring opening, stable forms of methanesulfonyl chloride and plausible sulfonium ion intermediates formed by the addition of methanesulfonyl cation to ethylene and its substituted derivatives are discussed in the present paper.

Quantum chemical calculations were carried out in order to study the geometry and electronic structure of

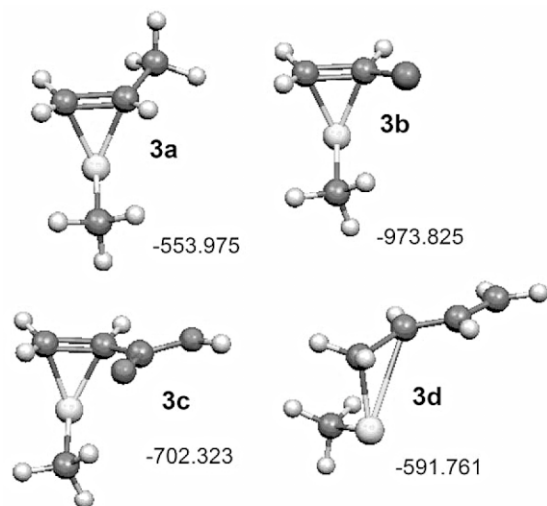


Fig. 3. Equilibrium geometries of intermediate structures **3 a-d** optimized for addition reaction of methylsulfenchloride to substituted ethenes and presented with total energies in Hartree

the lowest energy intermediate structures for the addition reaction of methylsulfide cation **1c** to the double bond ethylene **2** as a model compound and its substituted derivatives prop-1-ene **2a**, chloroethene **2b**, acrylic acid **2c** and vinylene **2d**.

The geometry optimizations revealed a few minimal energy structures from which episulfonium cation type intermediate structures **3 a-d** presented in Fig. 3 are most stable and lowest in energy for the pending addition reaction.

The dihedral angles $C(\alpha)-C(\beta)-S-C$ and $C(\beta)-C(\alpha)-S-C$ of episulfonium intermediate structures **3** type mostly reflect the hybridization of the S atom in the episulfonium fragment and should be 90° for p, 180° for sp^2 and 125.5° for sp^3 hybridizations, respectively. Usually it is considered that in compounds such as ethylene oxide or sulfide, the lone pair of electrons of hetero atoms takes the sp^3 -type configuration. Similarly, the sp^3 configuration may also be seen to be plausible for episulfonium ion intermediates with similar structures. In the fully optimized structures of ethylene-based episulfonium ion intermediate the dihedral angles are about 96° . It follows that the S atom loses the sp^3 character and more closely relates with p hybridization.

The further efforts were concentrated on molecular orbital study, the electronic structure and geometry of starting reactants and the episulfonium intermediate. The molecular orbital diagram of the interacting electrophile-

methylsulfide cation **1c**, nucleophile-ethane **2** and the reaction intermediate episulfonium cation **3** (Figs. 1, 2), suggests that in the electrophilic addition the double bond transfers to the S atom to neutralize the positive charge on the S atom almost completely and then to form a fairly strong bond between the S and C atoms resulting in the weakening of the C=C double bond. The deformation of the double bond also occurs in the process when the methylsulfide group approaches the double bond to form the π -complex episulfonium ion intermediate. A comparison of HOMO and LUMO shapes (Fig. 2) for the reacting ethane **2** and methylsulfide cation **1c** and the episulfonium ion **3** indicates that the charge of π electrons in the double bond is transferred to the vacant orbital on the S atom, and otherwise, the positive charge of the isolated methanesulfonyl cation wholly distributes over the intermediate. Such charge delocalization makes a contribution to the stabilization of the intermediate.

Furthermore, as we discuss about the process during which the nucleophile (chloride anion) attacks α or β carbon atoms of the cationic intermediate causing the regioselective ring opening reaction. In this process, the lowest vacant orbitals of the episulfonium ion intermediates play an important role in predicting the reaction path and the stability of the final adducts. As is illustrated in figure 2, the lowest vacant molecular orbitals, i.e. the LUMO and LUMO+1 of the stabilized episulfonium ion intermediate, are the Walsh-type orbitals [10], which are very similar in energy. LUMO+1 are symmetrically delocalized π -type orbital on the C=C bond, and LUMO orbital are antisymmetrical π -type orbital on the C=C bond, presenting the greatest extension along the p_z direction. According to Klopman's Charge and Frontier Orbital Control Concept [11] and as shown in figure 2 for both reactions (electrophilic addition with methylsulfide cation and nucleophilic displacement of episulfonium ion by chloride anion), the energy gap between the HOMO of the nucleophile and the LUMO of the electrophile is small as compared to that between the orbitals of individual reagents, and therefore the reaction could be frontier-orbital controlled rather than charge-controlled. Besides, as the episulfonium ion LUMO and the next higher vacant orbital LUMO+1 present the greatest extension around the C-C bond along the p_z direction, they offer the greatest interaction with an occupied orbital of the nucleophile (chloride anion) when the nucleophile approaches the intermediate along this direction. The ring opening may therefore occur in the *trans* manner, as described in the experimental investigation in literature [2, 3]. In addition, the regioselective features of episulfonium ring-opening reactions with the chloride anion may be governed by the small energy gap between the LUMO and LUMO+1 of the intermediates [12]. The interaction between the occupied orbital of the nucleophile (chloride anion) approaching the C-C atoms of the intermediate could in some cases be executed predominantly with LUMO+1, and if it is stronger than

the interaction of LUMO with the nucleophile it will control the course of the reaction.

In order to develop further the qualitative understanding of regiochemistry of the episulfonium ring opening by nucleophilic displacement with the chloride anion it was important to examine different reactivities of the C(α)-C(β) carbon atoms of substituted ions **3 a-d** estimating reactivity indexes such as local atomic charges and probability of electron population of LUMOs [12].

The effects of methyl, chloro, carboxyl and vinyl substituents of α -carbon on the C(α)-C(β) bond of the episulfonium ion **3a-d** were considered while performing the examination of Lowdin charges together with the examination of *pz* atomic orbitals electron population probability for C(α) and C(β) atoms involved in two vacant orbitals LUMO and LUMO+1.

The calculated Lowdin charges of α and β carbon atoms for methyl and vinyl substituted **3a** and **3d** show that β carbon is more negatively charged than α carbon, suggesting that the position of α carbon is more favourable for the nucleophilic attack by chloride anions, while α carbon for chloro and carboxyl substituted **3 b-c** is more negative charged, suggesting that the position of β carbon is more favourable for the nucleophilic attack by chloride anions. However, the experimental results [2–4] revealed the opposite (situation): when α carbon is substituted with methyl, the ring-opening reaction occurs at β carbon by chloride attack at the terminal β carbon giving the kinetically controlled **aM** adduct, in case substitution of α carbon with carboxyl **3c** by chlorine attack gives the **M** orientation, leading to ring opening reaction at α carbon. This implies that episulfonium ring-opening regioselectivity can not be fully explained by attractive electrostatic interactions between the reacting centres. This is in agreement with the results outlined in the preceding paragraph that are consistent with the reaction being frontier-orbital controlled. We therefore concentrated our efforts on the examination of probability of electron population and orbital locations for the LUMOs of **3 a-d**, which are important for the interpretation of nucleophilic displacements in episulfonium ions.

The probability of electron populations on *pz* atomic orbitals of C(α) and C(β) atoms for the two lowest

Table. LUMO and LUMO+1 probability of electron population, Lowdin charges for episulfonium ion intermediates **3 a-d**

No.	Atom	Charge	LUMO	LUMO+1
3a	C(α)	+0.004	0.408	0.011
	C(β)	-0.107	0.008	0.249
3b	C(α)	-0.139	0.042	0.024
	C(β)	-0.095	0.184	0.211
3c	C(α)	-0.142	0.002	0.574
	C(β)	-0.066	1.061	0.062
3d	C(α)	-0.136	0.2738	0.199
	C(β)	-0.555	0.003	0.086

vacant orbitals LUMO and LUMO+1 has been presented in table. Those orbitals are formed from out-of-plane *pz* orbitals, which result in π -complex character for all intermediates **3 a-d**. The replacement with methyl, chloro carboxyl and vinyl substituents on the α carbon of the C–C bond resulted in electron population distribution distortions of vacant orbitals for all substituted intermediates **3 a-d**, comparing to the ethylene-based episulfonium **3**.

The episulfonium ion ring-opening regioselectivity is governed by whether the chloride ion attacks C(α) or C(β) of the intermediate, and thus, is considered to be determined by an unsymmetrical extension of the vacant orbital electron population probability on C(α) or C(β); the larger the electron population probability, the easier the chloride anion attack at that site. Also, as the energy differences between LUMO and LUMO+1 are very small as shown in figure 2, it implies that the nucleophilic attack of chloride could be determined by interactions depending on the greater impact of LUMO (energy gap controlled) or greater impact of LUMO+1 (orbital overlap control) [13]. In the case of methyl and chloro-substituted intermediates **3a**, **3b**, it is easy to see (see the table) that the LUMO+1 electron population is more located on the terminal C(β) than on the methyl-substituted C(α) atom. Besides, according to the experiments [2–4], it is apparent that the chloride anion may easier attack the terminal C(β) to give the **aM** structures, while in the case of methyl substituted **3a**, **aM** final orientation is a kinetically controlled reaction adduct. On the other hand, regarding carbonyl and vinyl substituted episulfonium ion intermediates **3c** and **3d**, LUMO+1 is located on the C(α) atom. This leads to the opposite conclusion than that for the methyl substitution case, i.e. carbonyl and vinyl substituted intermediates **3c** and **3d** give adducts with **M** orientation governed by the addition of chloride to the α -carbon atom, while the carboxyl substituted **M** adduct is kinetically controlled and undergoes further rearrangement into a stable **aM** product [2–4]. The electron populations of LUMO+1 for **3 a-d** is consistent with the experimental [2–4] possibility of kinetically controlled adduct formation.

Further investigations show that the electron populations of LUMO for the episulfonium intermediates **3 a-d** are consistent with the possibility of rearrangement to thermodynamically stable products. The localization of the LUMO electron populations on α carbon (see table), compared to the localization on C(β) in the vinyl-substituted episulfonium **3d**, implies that the C(α) position is more susceptible to nucleophilic addition of a chlorine atom. This result is in line with the experimental [2–4] observations showing an exceptional formation of **M**-oriented products that are thermodynamically stable and have not shown any tendencies to rearrange.

The LUMO electron populations of carboxyl-substituted episulfonium **3c** were located on the β -carbon. This result corresponds to the experimental finding [2–4] that the nucleophilic displacement process of car-

boxyl-substituted **M** oriented kinetically controlled adduct **3c** undergoes the rearrangement to **aM** products that are thermodynamically stable. In respect of nucleophilic addition of chloride to the methyl-substituted episulfonium ion **3a**, the subsequent rearrangement of kinetically controlled **aM** adducts to the stable **M** products was observed experimentally [2–4]. Accordingly, the calculated LUMO shapes for **3a** show an enlarged electron population probability along the *pz* direction of the α -carbon atom, which supports the tendency to form **M**-oriented products.

The formation of kinetically controlled adducts is favoured by the possibility of interaction of the episulfonium ion C–C bond with chloride between the HOMO of nucleophile and LUMO+1 – a vacant symmetrical orbital of electrophile. While the formation of thermodynamically stable products is favoured by the interaction of the HOMO of nucleophile (chloride anion) with the LUMO of electrophile (episulfonium ion C–C bond).

CONCLUSIONS

The quantum chemical optimizations of the most likely intermediates indicate that the episulfonium ion is a most stable intermediate structure for reactions of methylsulfenchloride with ethylene, prop-1-ene, chloroethene, vinylene and acrylic acid. For the intermediate ions in this study, the role of sulfur appears to be that of directing the stereochemistry of the addition reaction of chloride, in this case forming *trans* products upon the nucleophilic attack on the C–C bond of the episulfonium ion. This is in agreement with experimental results. A comparison of calculated results in vacuum and in solvated media shows that the ionization of the MeSCL molecule by polar solvents could affect the electrophilic addition reaction. The investigation of the addition of the methylsulfide cation to ethylene with the subsequent attack of chloride anion shows the reaction to be frontier-orbital controlled. The regioselectivity features of episulfonium ion opening by chloride anion depend on the LUMO and LUMO+1 of the episulfonium ion and the HOMO of the approaching chloride. The LUMO+1 of episulfonium ions have the greatest interaction with the nucleophile approaching along *pz* direction, leading to the formation of kinetically controlled adducts, while the episulfonium ion LUMOs show a stronger interaction leading to the subsequent thermodynamically stable product formation.

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Aušra Vektariene

METILSULFENCHLORIDO PRISIJUNGIMO PRIE PAVADUOTŲ ETENŲ REAKCIJOS MODELIAVIMAS TAIKANT AB-INITIO METODĄ

Santrauka

Ab-initio metodas buvo panaudotas: metilsulfido katijono elektrofilinio prisijungimo prie etenų bei tolesnės nukleofilinio halogenido pavadavimo reakcijų interpretavimui, reakcijos metu susidarančių tarpinių episulfonio jono kompleksų elektroninės struktūros ir molekulinę orbitalių analizę paaiškino eksperimentiškai stebimo regioselektyvumo ypatumus.