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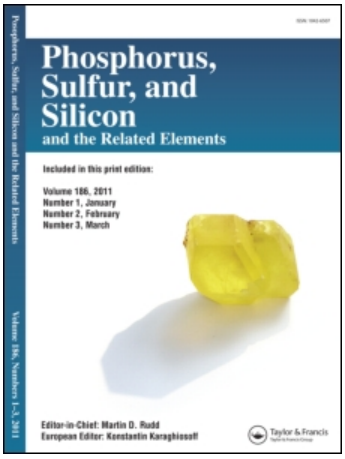

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Sulfur Electrophiles as Mechanistic Probe. New Insight in the Electrophilic Additions

Lucia Pasquato; Riccardo Destro; Vittorio Lucchini; Giorgio Modena

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Sulfur Electrophiles as Mechanistic Probe. New Insight in the Electrophilic Additions

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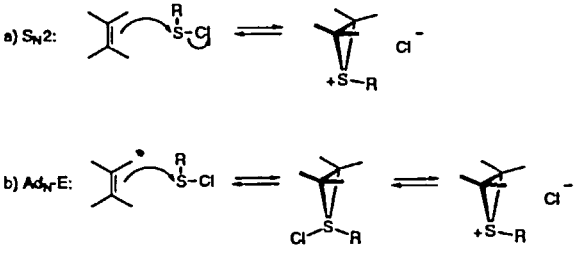
Thiiranium and thiirenium ions are stable intermediates that have been isolated and fully characterized. Structures of *tert*-butyl substituted thiiranium and thiirenium ions have been determined by room temperature single X-ray diffraction. In addition *ab initio* calculations at RHF/3–21G*//RHF/3–21G* level have been performed. Along with the definition of the structural parameters of these ions, the mechanism of their reactions with a series of sulfides has been investigated. We focus in this paper on the nucleophilic attack to sulfonium sulfur. The kinetic data, the molecular geometries, the shapes and energies of the frontier molecular orbitals suggest a mechanism in which the nucleophile approaches the sulfur in the ring plane along a direction parallel to the C-C ring bond. This result implies the intermediacy of a episulfuranic species.

Keywords: thiiranium ions; X-ray structures; ab initio calculations; electrophilic additions; episulfurane, asymmetric synthesis

Thiiranium and thiirenium ions, as intermediates in the addition of sulfenyl halides to alkenes and alkynes, have been considered unstable species.[1-4] However, we have shown that some of these ions, when substituted with one or two *tert*-butyl groups at the ring carbons, are stable enough to be isolated at room temperature as salts of non nucleophilic anions. This discover gave us the opportunity to study these species with particular regard to their reactivity toward nucleophiles.[5,6,7] This investigation is of interest for several reasons.

Mechanistic. The nucleophilic substitution at the charged sulfur is a process which may occur with two different mechanisms, Scheme 1.



SCHEME I

A concerted mechanism, reminiscent of the S_N2 mechanism at the aliphatic carbon, is described by the approach of the nucleophile to sulfonium sulfur from the side opposite the leaving group, which is the C-C double or triple bond. An alternative two-step mechanism, which may be designated as an Ad_N-E process, requires the presence of an episulfuranic intermediate. So far, experimental evidence for the presence of episulfurane species could not be confirmed[8] and their existence is still a matter of speculation.[1-4]

The nucleophilic attack to sulfonium sulfur of thiiranium and thiirenium ions may be considered the reverse reaction of the electrophilic addition of sulfenyl halides to double and triple C-C bonds. Thus, because of the principle of microscopic reversibility, the study of the nucleophilic reactions to these intermediates may give indications as for the sulfenylation of the unsaturated C-C bond.

Synthetic. A few years ago we reported the first asymmetric sulfenylation of unfunctionalized olefins with good enantiomeric excess.[9] Better enantiomeric excesses may be achieved by the utilization of carriers able of a complete facial discrimination and by preventing the nucleophilic attack at the sulfonium sulfur of the thiiranium ion intermediate (a process which generates racemic thiiranium ions). This latter goal requires the knowledge of the relative rates of nucleophilic attack at ring carbon and at sulfur of thiiranium ion as determined by the substituents at these sites. In addition, the understanding of the mechanism of nucleophilic attack at sulfur and in particular of the direction travelled by the nucleophile will allow to design proper exocyclic sulfur substituents to prevent sulfur attack.

Biological. Thiiranium ions are postulated as intermediates in several biological processes. For example, thiiranium ions are believed to be formed in the metabolic process of dihaloethanes via glutathione (GSH) and GSH-S transferase. They may lead to a carcinogenic

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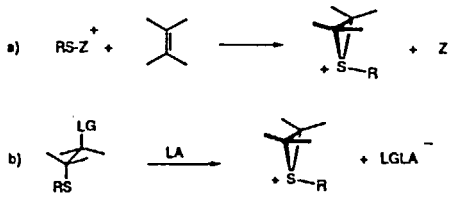
activity, likely because of their interaction with the nucleophilic sites of the DNA.[10] The understanding of the mechanism of the reaction between general nucleophiles and thiiranium ions will increase the comprehension of the biological activity of these cationic species.

Synthesis of thiiranium ions. Thiiranium ions may be prepared with two different procedures, Scheme 2. The transfer to the alkene of a sulfenium cation from an appropriate carrier, which has to be a weak nucleophile, leads to thiiranium ions.[1,2,11] The methyl(bismethylthio)sulfonium hexachloroantimonate and the commercially available dimethyl(methylthio)sulfonium tetrafluoroborate are the most used thiomethylating agents. The alternative procedure is based on the heterolysis of a thioether carrying in β-position a good leaving group by the action of a Lewis acid in non nucleophilic solvents.[1]



Carrier Z = RSSR, RSR, R_3N; LG = leaving group; LA = Lewis Acid

SCHEME 2

Structural studies. To our knowledge only two structures of thiiranium ions have been so far investigated by X-ray diffraction, both at low temperature.[12,13] The structure of the *S*-phenyl thiiranium triflate of adamantilideneadamantane was reported recently.[13] However, this compound does not show the usual reactivity expected for thiiranium ions because of the great steric hindrance exerted by the substituents at the ring carbons. The structure of the *S*-phenyl thiiranium tetrachloroaluminate of 1,2-dimethylacenaphtylene was the first to be reported,[12] but the reactivity of this ion is not documented until now. The X-ray structure of the di-*tert*-butyl-*S*-methylthiirenium tetrafluoroborate **6a** at -100 °C was reported more than twenty years ago by one of us,[14] and the reactivity of this irenium ion is well documented.[6,15,16]

Using the first synthetic procedure described above we prepared numerous stable thiiranium and thiirenium ions carrying one or two *tert*-butyl groups at the ring carbons, as reported in Scheme 3. These ions have been completely characterized and the structure of some of them has been determined by X-ray analysis at room temperature.[17]

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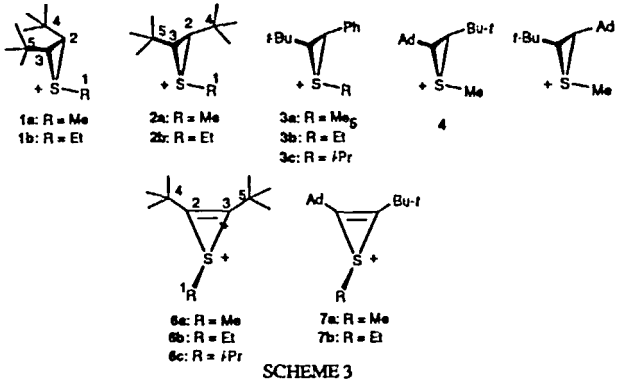

SCHEME 3

The counter ion may be either the tetrafluoroborate or the hexachloroantimonate anion. However, the latter allows a lower precision of the structure with uncertainties of about 0.02 Å in the bond lengths due to the presence of an heavy atom. Selected bond distances and bond angles for the tetrafluoroborates ions **1a**, **2a** and **6a** are reported in Table I. These same structures have been optimized *ab initio* at RHF/3-21G*//RHF/3-21G* level. Experimental and calculated bond distances and bond angles are compared in Table I.

In general, the agreement between experimental structural parameters and those found by *ab initio* calculations is satisfactory. Only in the case of the cis di-*tert*-butylthiiranium ion **1a** we found a relevant difference. The experimental structure is characterized by the presence of a plane of symmetry which bisect the ring plane and contains the sulfur atom and the carbon atom of the methyl group. At variance, in the *ab initio* optimized geometry the reciprocal steric hindrance of the two cis *tert*-butyl groups forces them to different rotational preferences, which are mirrored by different S-C(2) and S-C(3) bond lengths and different angles between *tert*-butyl quaternary carbons and ring carbons. These angles are larger in the cis isomer than in the trans one by about 10°. This causes a shift of the *tert*-butyl groups of the cis isomer towards the ring plane, Figure 1(a).

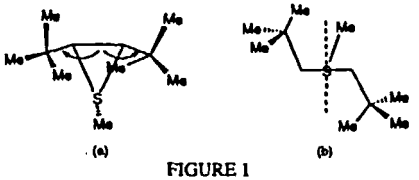

FIGURE 1

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TABLE I

Selected bond lengths and angles for **1a**, **2a** and **6a** obtained from X-ray analysis of the tetrafluoroborate salts (first row) and from *ab initio* geometry optimization at RHF/3-21G*//RHF/3-21G* level (second row, in italic).

	1a	**2a**	**6a**
C(1)-S	1.791	1.807	1.802
	1.820	*1.817*	*1.820*
C(2)-S	1.849	1.850	1.819
	1.880	*1.887*	*1.860*
C(3)-S	1.849	1.868	1.820
	1.891	*1.907*	*1.860*
C(2)-C(3)	1.498	1.455	1.277
	1.492	*1.467*	*1.270*
C(2)-C(3)-C(5)	135.03	126.37	157.3
	136.22	*126.93*	*157.4*
C(3)-C(2)-C(4)	135.03	124.26	156.4
	134.84	*124.66*	*157.4*
S-C(2)-C(4)	119.06	124.95	134.30
	120.07	*125.19*	*132.33*
S-C(3)-C(5)	119.06	116.48	133.20
	119.34	*117.11*	*132.37*

In the trans isomer the *S*-Me bond is shifted away from the plane perpendicular to the ring plane containing the sulfur atom and bisecting the C-C ring bond. As a result, the steric hindrance with the cis *tert*-butyl group is substantially reduced, Figure 1(b). This experimental feature is correctly reproduced by *ab initio* optimization. The structural differences between the cis and the trans di-*tert*-butylthiiranium ions **1a** and **2a** can account for their different reactivity toward external nucleophiles. For example water attacks the cis thiiranium ion **1a** at ring carbons, but the trans thiiranium ion **2a** at sulfonium sulfur, Scheme 4.[7]

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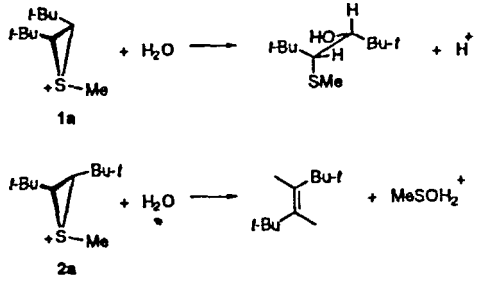
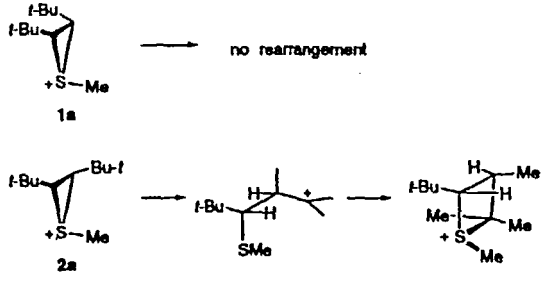


SCHEME 4

On the other hand, a case of internal nucleophilic displacement is more puzzling: the methyl anionotropic migration from one *tert*-butyl group onto the adjacent ring carbon, which generates the thietanium ions **8**, occurs only in the the trans thiiranium ion **2a** (Scheme 5).[5] No difference in the geometric features of thiiranium ions **1a** and **2a** seems to justify this dissimilar behaviour.



SCHEME 5

Reactivity studies. Thiiranium ions have three different sites carrying a partial positive charge that may be subjected to a nucleophilic attack (Scheme 6).

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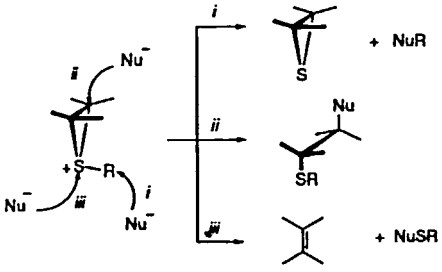

SCHEME 6

(i) The attack at the exocylic *S*-substituent occurs with the formation of a thiirane molecule as leaving group. Only two examples are know of nucleophilic displacement at the exocyclic sulfur substituent: thiiranes are generated from the attack of chloride or bromide ion to the *S*-methyl of the thiiranium ion derived from the methylthiolation of adamantylideneadamantane,[18] or from the desilylation of *S*-trimetylsilyl thiiranium ions.[19]

(ii) The attack at a ring carbon, followed by ring opening, is the second stage of the electrophilic addition of sulphenyl halides to C-C double bonds. The most interesting feature of the thiiranium ions, from a synthetic point of view, is the opening of the ring by reactions at the ring carbons. In fact, the growing interest for the use of thiiranium ions as building blocks in organic synthesis is mainly due to the stereo controlled construction of C-C, C-N, C-O, C-S and C-halogen bonds. The regiochemistry of the process is well known. The Markovnikov isomers are obtained from thiiranium ions when the nucleophilic substitution has a substantial S_N1 character and the cyclic ion can open unassisted to the β-thiovinyl cation. The anti-Markovnikov isomer is the outcome of an S_N2 process and the ring opening requires the assistance of the nucleophile. It follows that the balance between the two regioisomers will mainly depend from the substituents at the ring carbons, but also from the nature of the nucleophile and from the reaction conditions.

Cyclic products are obtained when the nucleophilic center and the thiiranium ring belong to the same molecule.[3,4,9,10,20] The regiochemistry of the internal nucleophilic attack is usually controlled by the relative stability of the two heterocycles which can be formed by *endo* or *exo* ring closure.[21]

(iii) As alredy stated, the attack at the sulfonium sulfur, with the displacement of the C-C double bond, may be considered the reverse reaction of the electrophilic addition to the same bond. The reversibility of the addition of bromine[22] and of sulfenyl halides[1] to unsaturated carbon-carbon bond has been recognised. Because of the principle of the microscopic reversibility, the information acquired by studying the nucleophilic attack to sulfur in thiiranium

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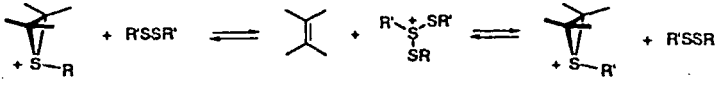
(and thiirenium) ions may give hints as for the process of electrophilic addition to C-C double (and triple) bond.

With this aim we investigated the nucleophilic reaction of some dialkyl disulfides with several *tert*-butyl substituted thiiranium and thiirenium ions.[23] The reaction generates thiiranium or thiirenium ions which can be distinguished from the reactants only by the different substitution at the sulfonium sulfur. For this reason, the *S*-alkyl substituents in the reactants thiiranium or thiirenium ion and in the disulfide must be different. The reaction clearly occurs via the intermediacy of the free alkene and of the mixed alkyl(bisalkylthio)sulfonium ion, that were not detected (Scheme 7). During the reaction course we could only observe the disappearance of the thiiranium (or thiirenium) ion reagent, the formation of the new thiiranium (or thiirenium) ion and the disulfides. We could not gain any evidence for the nucleophilic addition of disulfide to ring carbons.



SCHEME 7

A selection of kinetic data is reported in Table II. The analysis of these data allows the determination of the preferred approaching direction of the nucleophile. It is possible to recognize three different pivotal directions, indicated by the labels x, y and z in Scheme 8.

As the kinetic constants clearly indicate, the reaction is sensitive to the steric hindrance exerted by the substituents at the sulfur and at the ring carbons. It follows that x and z directions are inconsistent with the experimental evidence suggesting that the preferential approach should be along the y axis. The important consequence is that a S_N2 like mechanism has to be ruled out. The shapes of the LUMO orbitals of thiiranium and thiirenium ions (obtained by *ab initio* calculations at RHF/3-21G*//RHF/3-21G* level) are shown in Scheme 9. Their inspection suggests that the greatest interaction between the HOMO of the nucleophile and the LUMO of the cyclic ions occurs when the nucleophile approaches along the y direction. The experimental and the theoretical data strongly suggest that the nucleophile approaches the sulfonium sulfur in the ring plane and from a direction parallel to the carbon-carbon ring bond. This implies the presence of an episulfuranic intermediate in a postulated Ad_N-E process.

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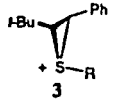
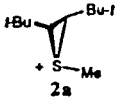
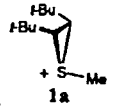
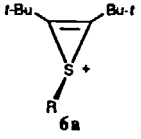
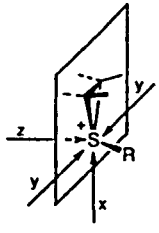
TABLE II

Second order rate constants for the reaction of some *tert*-butyl substituted thiiranium and thiirenium ions with disulfides in CD_2Cl_2 a 25 °C.

Thiiranium or Thiirenium ion	R	Disulfide	k_S, $M^{-1}s^{-1}$
 3	Me	EtSSEt	4.4 (± 0.1) x 10^{-3}
	Et	MeSSMe	1.4 (± 0.1) x 10^{-3}
	i-Pr	MeSSMe	5.9 (± 0.2) x 10^{-5}
 2a		EtSSEt	4.5 (± 0.2) x 10^{-5}
 1a		EtSSEt	no reaction observed
 6a	Et	MeSSMe	3.8 (± 0.4) x 10^{-3}
	i-Pr	MeSSMe	7.8 (± 0.3) x 10^{-5}



SCHEME 8

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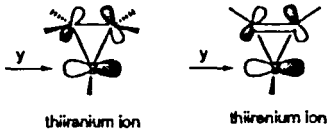
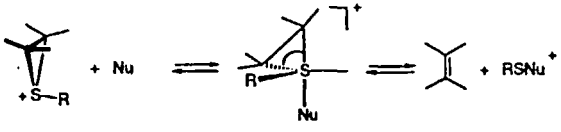


SCHEME 9

The mechanism we propose for the nucleophilic reaction at the sulfur atom of thiiranium and thiirenium ions is the addition of the nucleophile to form a sulfurane-type intermediate which by subsequent pseudo rotation shifts the leaving group in the right position for the elimination of the olefin via "ligand coupling",[24] Scheme 10.



SCHEME 10

The results here reported offer a rational to the observation that the *ortho* substitution with bulky groups in *S*-aryl or *Se*-aryl iranium ions protects them from nucleophilic attack at the heteroatom.[25,26]

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