JOC*Note*

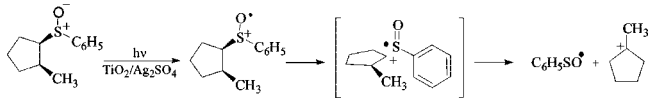
Stereochemistry of the C−S Bond Cleavage in *cis*-2-Methylcyclopentyl Phenyl Sulfoxide Radical Cation

Enrico Baciocchi, Osvaldo Lanzalunga,* Andrea Lapi, and Laura Maggini

Dipartimento di Chimica and Istituto CNR di Metodologie Chimiche-IMC, Sezione Meccanismi di Reazione c/o Dipartimento di Chimica, Sapienza Università di Roma, P.le A. Moro 5, 00185 Rome, Italy

osvaldo.lanzalunga@uniroma1.it

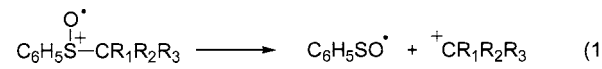
Received November 26, 2008



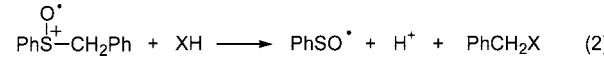
The TiO_2 photocatalyzed oxidation of *cis*-2-methylcyclopentyl phenyl sulfoxide in the presence of Ag_2SO_4 in MeCN/H_2O leads to the formation of 1-methylcyclopentanol, 1-methylcyclopentyl acetamide, and phenyl benzenethiosulfonate as the main reaction products. It is suggested that the C−S heterolysis in the radical cation is an unimolecular process leading to an ion radical pair. Fast 1,2-hydride shift in the secondary carbocation leads to 1-methylcyclopentyl carbocation that forms the observed products by reaction with H_2O and MeCN. Attack of H_2O on the ion radical pair may also occur, but as a minor route (<3%), with formation of *trans*-2-methylcyclopentanol.

Sulfoxides are substrates of great interest for their importance in organic synthesis as well as for their biological activity and involvement in the general metabolism of many biologically important sulfides.[1] Despite this, few studies are presently available for sulfoxide radical cations, although these species should be of interest given their possible role in oxidative chemical[2] and biochemical transformations.[3]

To cover this gap, the long-standing interest in the chemistry of radical cations[4] has led our group to investigate aspects concerning generation, spectral properties, and structure of aromatic sulfoxide radical cations.[5] More recently, we have studied the C−S bond fragmentation reactions of species generated by photooxidation sensitized by 3-cyano-*N*-methylquinolinium perchlorate (3-CN-NMQ^+).[6] A conclusion of the latter study was that with tertiary and secondary benzylic systems, a fast unimolecular C−S bond cleavage takes place leading to the formation of the phenylsulfinyl radical $C_6H_5SO^\bullet$ and the carbocation $R_1R_2R_3C^+$ (eq 1).



However, direct evidence for the formation of a carbocation was obtained only when $R_1 = H$ and $R_2 = R_3 = Ph$. In the other cases the formation of the cation was only inferred by product and kinetic studies. Moreover, an intriguing result was obtained with benzyl phenyl sulfoxide radical cation. The fragmentation rate of this radical cation (1.1×10^6 s^{-1}) was very close to that of *tert*-butyl phenyl sulfoxide radical cation (1.8×10^6 s^{-1}) despite the fact that the C−S bond dissociation free energy is about 8.5 kcal mol^{-1} less negative in the former than in the second radical cation. Among the possible explanations, it was considered that the cleavage of the primary benzylic system might be nucleophilically assisted (a bimolecular process with the solvent XH as the nucleophile, eq 2) without involving the intermediacy of a benzyl carbocation.



Indeed, it is well recognized that in the fragmentation reactions of radical cations a mechanistic dichotomy is possible between an unimolecular and a bimolecular pathway which, when cleavage at carbon is concerned, very closely resembles that between the S_N1 and S_N2 mechanisms in the nucleophilic substitutions at carbon.[7] Clearly, the fragmentation of an alkyl sulfoxide radical cation can be usefully seen as a type of nucleophilic substitution where the leaving group is the sulfinyl radical.

Since the nucleophilically assisted fragmentation of a radical cation is expected to occur with inversion of configuration,[8] we considered that further interesting information on the possible role of a bimolecular pathway in the fragmentation of alkyl phenyl sulfoxide radical cations might be obtained by a study of the stereochemistry of the fragmentation process of *cis*-2-methylcyclopentyl phenyl sulfoxide radical cation ($\mathbf{1}^{+\bullet}$). Accordingly, in this case the operation of this pathway should lead to a *trans*-2-methylcyclopentyl derivative (path **a** in Scheme 1), whereas, in the case of an unimolecular process (path **b** in

(1) Carreno, M. C. *Chem. Rev.* **1995**, *95*, 1717–1760. Fernandez, I.; Khiar, N. *Chem. Rev.* **2003**, *103*, 3651–3705. Clarke, M. J.; Zhu, F.; Frasca, D. R. *Chem. Rev.* **1999**, *99*, 2511. Lipponer, K. G.; Vogel, E.; Keppler, B. K. *Metal Based Drugs* **1996**, *3*, 243. Caligaris, M.; Carugo, O. *Coord. Chem. Rev.* **1996**, *153*, 83. Shin, J. M.; Cho, Y. M.; Sachs, G. *J. Am. Chem. Soc.* **2004**, *126*, 7800–7811. Legros, J.; Dehli, J. R.; Bolm, C. *Adv. Synth. Catal.* **2005**, *347*, 19–31. Bentley, R. *Chem. Soc. Rev.* **2005**, *34*, 609–624.

(2) Adaikalasamy, K.; Venkataramanan, N. S.; Rajagopal, S. *Tetrahedron* **2003**, *59*, 3613–3619. Ganesan, M.; Sivasubramanian, V. K.; Rajagopal, S.; Ramaraj, R. *Tetrahedron* **2004**, *60*, 1921–1929.

(3) Watanabe, Y.; Iyanagi, T.; Oae, S. *Tetrahedron Lett.* **1982**, *23*, 533–536.

(4) Baciocchi, E.; Bietti, M.; Lanzalunga, O. *Acc. Chem. Res.* **2000**, *33*, 243–251. Baciocchi, E.; Bietti, M.; Lanzalunga, O. *J. Phys. Org. Chem.* **2006**, *19*, 467–478.

(5) Baciocchi, E.; Del Giacco, T.; Gerini, M. F.; Lanzalunga, O. *J. Phys. Chem. A* **2006**, *110*, 9940–9948.

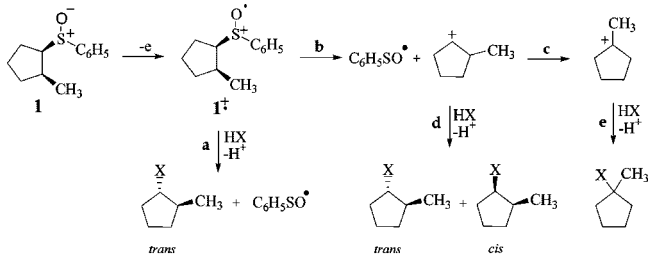
(6) Baciocchi, E.; Del Giacco, T.; Lanzalunga, O.; Mencarelli, P.; Procacci, B. *J. Org. Chem.* **2008**, *73*, 5675–5682.

(7) (a) Baciocchi, E.; Fasella, E.; Lanzalunga, O.; Mattioli, M. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1071–1073. (b) Shaik, S.; Reddy, A. C.; Ioffe, A.; Dinnocenzo, J. P.; Danovich, D.; Cho, J. K. *J. Am. Chem. Soc.* **1995**, *117*, 3205.

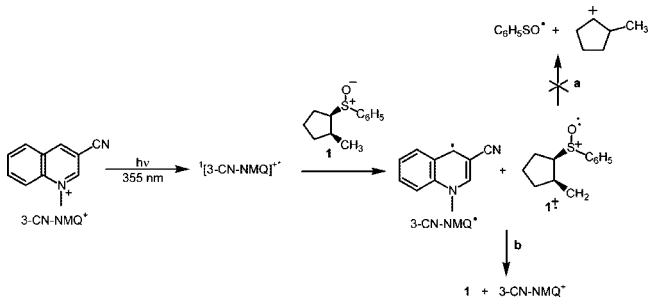
(8) Dinnocenzo, J. P.; Todd, W. P.; Simpson, T. R.; Gould, I. R. *J. Am. Chem. Soc.* **1990**, *112*, 2462. (a) Shaik, S.; Dinnocenzo, J. P. *J. Org. Chem.* **1990**, *55*, 3434.

10.1021/jo802619y CCC: $40.75 © 2009 American Chemical Society
Published on Web 01/15/2009

SCHEME 1



SCHEME 2



Scheme 1), products deriving from the 2-methylcyclopentyl carbocation (which can rearrange to the tertiary 1-methylcyclopentyl carbocation) should be observed (paths **c** and **e**).

It should be noted that in $\mathbf{1}^{+\bullet}$ a secondary, not activated, alkyl moiety is present with a much smaller tendency to form a carbocation than that of the systems examined before[6] and therefore with a greater susceptibility to exhibit nucleophilic assistance in the fragmentation process. The results of this study are presented in this Note.

In our previous investigation, the alkyl phenyl sulfoxide radical cations were generated by photooxidation sensitized by 3-CN-NMQ$^+$.[6,9] This method, however, could not be applied to the oxidation of **1** since no products were observed in the steady-state photolysis experiment carried out by irradiating for 3 h a solution of **1** (0.01 M) in N_2-saturated MeCN at around 355 nm in the presence of 3-CN-NMQ$^+$ (0.004 M). This is probably due to the fact that the fragmentation rate of $\mathbf{1}^{+\bullet}$ (Scheme 2, path **a**) is too slow to compete with back electron transfer from the reduced sensitizer 3-CN-NMQ$^\bullet$ to $\mathbf{1}^{+\bullet}$ (Scheme 2, path **b**).

Thus, we used another method for the generation of $\mathbf{1}^{+\bullet}$, namely, photooxidation sensitized by TiO_2, a well-known system for obtaining the one-electron transfer oxidation of organic substrates,[10] where it is also possible to minimize back electron transfer by capturing the photogenerated electron by Ag^+.[11] As shown in Scheme 3, irradiation of TiO_2 leads to charge separation, $TiO_2(h^+)$ and $TiO_2(e^-)$ (eq 3). $TiO_2(h^+)$ can oxidize a substrate to the corresponding radical cation (eq 4), which may then undergo a fragmentation reaction (eq 5), whereas Ag^+ (Ag_2SO_4) captures $TiO_2(e^-)$ (eq 6).

As $TiO_2(h^+)$ is a strong oxidant (E_{red} = 2.4 V vs SCE in MeCN),[12] sulfoxides (E_{ox} = 2.0 V vs SCE) are suitable substrates. Accordingly, photoelectrochemical studies have

SCHEME 3

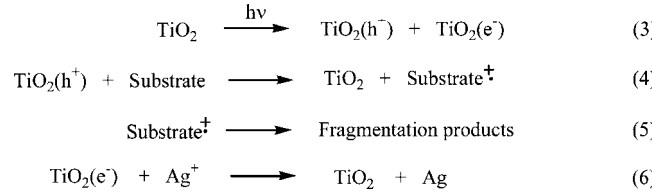


TABLE 1. Products and Yields in TiO_2 Photosensitized Oxidation of *cis*-2-Methylcyclopentyl Phenyl Sulfoxide (1) in N_2-Saturated MeCN in the Presence of Ag_2SO_4

% H_2O	Unreacted substrate	Product yields (%)[a]		
				
2.5	54	10.7	0.4	10.5
5	50	27.3	0.8	5.5

[a] Yields (%) referred to the starting material. The average error is ±10%

shown the occurrence of an electron transfer process from aryl methyl sulfoxides to $TiO_2(h^+)$.[13] A further support to an ET process is provided by the previous finding that 4-methoxybenzyl phenyl sulfoxide undergoes a clean C−S bond cleavage with formation of benzylic products when the TiO_2 sensitized photolysis of this substrate is carried out in MeCN in the presence of Ag_2SO_4.[14]

The photolysis of **1** (0.01 M) was carried out in deareated MeCN containing 2.5% or 5% H_2O (the addition of H_2O assured the presence of a species with nucleophilic character much higher than that of MeCN)[15] by external irradiation for 30 min in a photoreactor equipped with 10 lamps with emission centered at 355 nm in the presence of TiO_2 (0.06 M) and Ag_2SO_4 (0.01 M) at room temperature. After usual workup of the reaction mixture, significant amounts of fragmentation products of $\mathbf{1}^{+\bullet}$ (1-methylcyclopentanol, 1-methylcyclopentyl acetamide and *trans*-2-methylcyclopentanol) from the alkyl moiety and phenyl benzenethiosulfonate ($PhSO_2SPh$) accompanied by small amounts of phenyl benzenethiosulfinate (PhSOSPh), and diphenyl disulfide (PhSSPh), deriving from the phenyl sulfinyl radical,[16] were observed. Products were identified and quantitated, after extraction of the reaction mixtures with dichloromethane, by GC−MS, GC, HPLC, and ^{1}H NMR analysis, by comparison with authentic specimens. No products were detected without irradiation or in the absence of TiO_2. The alkyl fragmentation products and the yields referred to the starting material are reported in Table 1.

It can be immediately noted that 1-methylcyclopentanol and 1-methylcyclopentyl acetamide are by far the largely predominant reaction products in both 2.5% and 5% aqueous MeCN.

(9) The reduction potential of the 3-CN-NMQ$^+$*/3-CN-NMQ$^\bullet$ couple is 2.72 V vs SCE, large enough to convert the aromatic sulfoxides into the corresponding radical cations.

(10) Fox, M. A.; Dulay, M. T. *Chem. Rev.* **1993**, *93*, 341–357.

(11) Baciocchi, E.; Rol, C.; Rosato, G. C.; Sebastiani, G. V. *J. Chem. Soc., Chem. Commun.* **1992**, 59–60.

(12) Fox, M. A.; Chen, C.-C. *J. Am. Chem. Soc.* **1981**, *203*, 6757–6759.

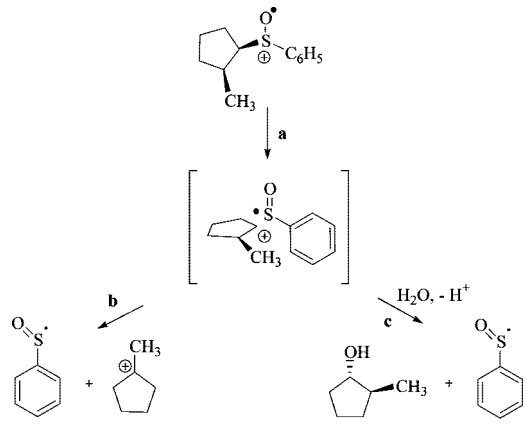
(13) An increase in the photocurrent has been observed on decreasing the aryl methyl sulfoxide oxidation potential. Somasundaram, N.; Srinivasan, C. *J. Photochem. Photobiol. A: Chem.* **1998**, *115*, 169–173.

(14) Baciocchi, E.; Del Giacco, T.; Ferrero, M. I.; Rol, C.; Sebastiani, G. V. *J. Org. Chem.* **1997**, *62*, 4015–4017.

(15) The use of stronger nucleophiles can present problems related to their possible oxidations by $TiO_2(h^+)$.

(16) The main reaction of the sulfinyl radical is the dimerization to give phenyl benzenethiosulfonate. Chatgilialoglu, C. In *The Chemistry of Sulfones and Sulfoxides*; Patai, S., Rappoport, Z., Stirling, C. J. M., Eds.; John Wiley & Sons: Chicester, England, 1988; Chapter 24.

SCHEME 4



trans-2-Methylcyclopentanol is also formed but in very small amounts (<3% of the total yields of alkyl fragmentation products).[17]

Clearly, this result indicates that the main pathway of the fragmentation process involves the formation of a secondary cyclopentyl carbocation that very rapidly rearranges to the more stable tertiary carbocation by 1,2-hydride shift (Scheme 1, path **c**). Reaction with the solvent (path **e** in Scheme 1) follows to produce the tertiary alcohol (from H_2O) and the tertiary acetamide (from MeCN). As expected, the ratio between alcohol and acetamide increases as the proportion of H_2O in the mixed solvent increases. When the reaction is carried out in the presence of 2.5% H_2O, acetamide and alcohol are formed in comparable amounts, whereas a larger amount of alcohol is observed in the presence of 5% H_2O. It also appears that no significant proton loss from the tertiary cyclopentyl carbocation takes place since the presence of 1-methylciclopentene among the products was excluded on the basis of direct ^{1}H NMR analysis of the reaction mixture in CD_3CN/D_2O.[18]

Thus, the fragmentation reaction of $\mathbf{1}^{+\bullet}$ in slightly aqueous MeCN is substantially an unimolecular process, and the fact that this outcome is observed when a secondary nonactivated alkyl group is involved, as in $\mathbf{1}^{+\bullet}$, makes it difficult that the unexpectedly large fragmentation rate of benzyl phenyl sulfoxide radical cation could be due to the operation of nucleophilic assistance. Other hypotheses and further investigations appear necessary to clarify this interesting point.

The secondary cyclopentyl carbocation that rearranges to the tertiary one, however, cannot be a free species, as in that case we should have observed both *cis*- and *trans*-2-methylcyclopentanol as well as *cis*- and *trans*-2-methylcyclopentyl acetamide (Scheme 1, path **d**). The fact that only the *trans* alcohol is observed leads us to suggest that very likely in the heterolysis of the radical cation a tight secondary carbocation-radical pair is first formed (Scheme 4, path **a**), as previously observed for the fragmentation of 1-phenylethyl phenyl sulfide radical cation.[7a,19]

For this pair, the largely dominant pathway (path **b**) involves a very fast rearrangement of the secondary 2-methylcyclopentyl carbocation to the tertiary one. Cage escape and reaction with the solvent of the tertiary carbocation ensues. However, we can also envisage that, as a very minor route, the stronger nucleophilic species in the medium (H_2O) attacks the ion radical pair in competition with the hydride shift (Scheme 4, path **c**). In this case it is reasonable that, as observed, the inverted *trans* alcohol is formed as in the pair the *cis* face of the cyclopentyl ring is protected by the sulfinyl radical leaving group.

The step leading to the ion-radical pair should be irreversible, as it was found that the unreacted substrate maintained the *cis* configuration. On the other hand, a substantially irreversible heterolysis may be predicted for $\mathbf{1}^{+\bullet}$ by the exergonicity of the process, which can be estimated around 6.9 kcal mol^{-1} on the basis of a thermochemical cycle[20] and by the additional driving force provided by the 1,2-hydride shift leading to the more stable tertiary carbocation.

Interestingly, the mechanism displayed in Scheme 4 is very close to that suggested by Kim and Brown[21] and Imhoff, Shiner, and co-workers[22] for the solvolysis of *cis*-2-substituted cyclopentyl arenesulfonates, a reaction which, as in our case, led to products deriving from the tertiary 1-substituted cyclopentyl carbocation, accompanied by minor amounts of the inverted product.[23]

In summary, it seems possible to conclude that the C−S bond cleavage in *cis*-2-methylcyclopentyl phenyl sulfoxide radical cation in aqueous MeCN occurs by an unimolecular process. The initially formed carbocation radical pair leads to the tertiary 1-methylcyclopentyl carbocation by hydride shift (the largely dominant path) and to the inverted product (*trans*-2-methylcyclopentanol) by H_2O attack.

Experimental Section

Oxidation Photosensitized by 3-CN-NMQ$^+$ClO$_4^-$. A 5-mL solution of 3-CN-NMQ$^+$ClO$_4^-$ (4.0×10^{-3} M) and **1** (1.0×10^{-2} M) in N_2-saturated CH_3CN plus 5% H_2O (v/v) as cosolvent was placed in a water-cooled jacketed pyrex tube and irradiated at room temperature for 3 h in a photoreactor equipped with 10 phosphor-coated fluorescent lamps (15 W each) with emission centered at ca. 355 nm. No formation of photoproducts was revealed by ^{1}H NMR analysis; the substrate and the sensitizer were quantitatively recovered.

TiO_2 Photocatalyzed Oxidation. Reactions have been carried out at room temperature by external irradiation (30 min), in a photoreactor equipped with 10 lamps (355 nm) under magnetic stirring, of a water-cooled jacketed pyrex tube containing a N_2-degassed solution of *cis*-2-methylcyclopentyl phenyl sulfoxide (0.05 mmol), TiO_2 (25 mg), and Ag_2SO_4 (0.05 mmol) in 5 mL of acetonitrile plus 2.5% or 5% H_2O (v/v) as cosolvent. After double paper filtration of TiO_2, the reaction mixture was poured into water and extracted with dichloromethane. GC−MS analysis of the reaction mixtures indicated the presence of methylcyclopentyl

(17) GC analysis of the reaction mixtures carried out before and after derivatization with the silylating agent *N*,*O*-bis(trimethylsilyl)-trifluoroacetamide (see Experimental Section) showed the absence, even in traces amounts, of *cis*-2-methylcyclopentanol and 2-methylcyclopentyl acetamides (comparison with authentic specimens).

(18) GC analysis of 1-methylcyclopentene is hindered by the coelution of this compound with the solvent.

(19) That in the heterolysis of a radical cation the two fragments can form a pair in a solvent cage has also been shown by Moiroux, Saveant, and coworkers. Anne, A.; Frauoa, S.; Moiroux, J.; Saveant, J.-M. *J. Am. Chem. Soc.* **1996**, *118*, 3938–3945.

(20) The C-S bond dissociation free energy (BDFE) value for $\mathbf{1}^{+\bullet}$ (−6.9 kcal mol^{-1}) was estimated by the usual thermochemical cycle (details in Supporting Information).

(21) Kim, C. J.; Brown, H. C. *J. Am. Chem. Soc.* **1972**, *94*, 5043–5050.

(22) Imhoff, M. A.; Ragain, M.; Moore, K., Jr. *J. Org. Chem.* **1991**, *56*, 3542–3549.

(23) In both ref 21 and ref 22 the possibility that hydride migration is concerted with the departure of the leaving group was dismissed. Thus, we consider that this possibility is unlikely also in our case. On the other hand, it should be considered that in the cyclopentane ring substantial energy is required to obtain the anti periplanar relationship between the C-H bond and the leaving group, which is thought to be the most convenient one for hydride migration concerted with leaving group departure.

acetamides and methylcyclopentanols as alkyl fragmentation products. By comparison with authentic specimens, the only acetamide identified was 1-methylcylopentyl acetamide. No traces of *cis*- or *trans*-2-methylcyclopentyl acetamides were detected. In order to identify the structure of methylcyclopentanols it was necessary to derivatize the reaction mixture with the silylating agent *N*,*O*-bis(trimethylsilyl)trifluoroacetamide. 1-Methylcyclopentyl-trimethylsilyl ether accompanied by minor amounts of *trans*-2-methylcyclopentyl-trimethylsilyl ether were observed after GC−MS analysis. Phenyl benzenethiosulfinate (PhSOSPh), diphenyl disulfide (PhSSPh), and phenyl benzenethiosulfonate ($PhSO_2SPh$) were identified by HPLC analysis by comparison with authentic specimens. By ^{1}H NMR analysis it was found that the unreacted substrate maintained the *cis* configuration, no traces of *trans*-2-methylcyclopentyl phenyl sulfoxide[24] having been detected. Quantitative analysis of the alkyl fragmentation products has been carried out by GC using bibenzyl as internal standard. The amount of unreacted substrate was determined by ^{1}H NMR analysis. Material balance was always >80% versus the amount of starting material.

Acknowledgment. Financial support from the Ministero dell'Istruzione, dell'Università e della Ricerca (MIUR) is acknowledged.

Supporting Information Available: Instrumentation, materials, C−S BDFE for *cis*-2-methylcyclopentyl phenyl sulfoxide radical cation. This material is available free of charge via the Internet at http://pubs.acs.org.

JO802619Y

(24) Ke, B.-W.; Lin, C.-H.; Tsai, Y.-M. *Tetrahedron* **1997**, *53*, 7805–7826.