Thianthrene 5-Oxide (SSO) as a Mechanistic Probe of the Electrophilic Character in the Oxygen Transfer by Dioxiranes

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Thianthrene 5-oxide (SSO) is established as a useful and convenient chemical probe to assess the electronic character (X_{SO}) of oxygen transfer agents. Thus, H_2O_2 under basic conditions (HOOH/nBu$_4$NOH) gives an X_{SO} value of 1.00, while H_2O_2 under acidic conditions (HOOH/$HClO_4$) affords an X_{SO} value near zero. On this X_{SO} scale, dimethyldioxirane (X_{SO} = 0.13 at 0°C) and methyl(trifluoromethyl)dioxirane (X_{SO} = 0.10 at 0°C) are, as expected, definitely strong electrophilic oxidants.

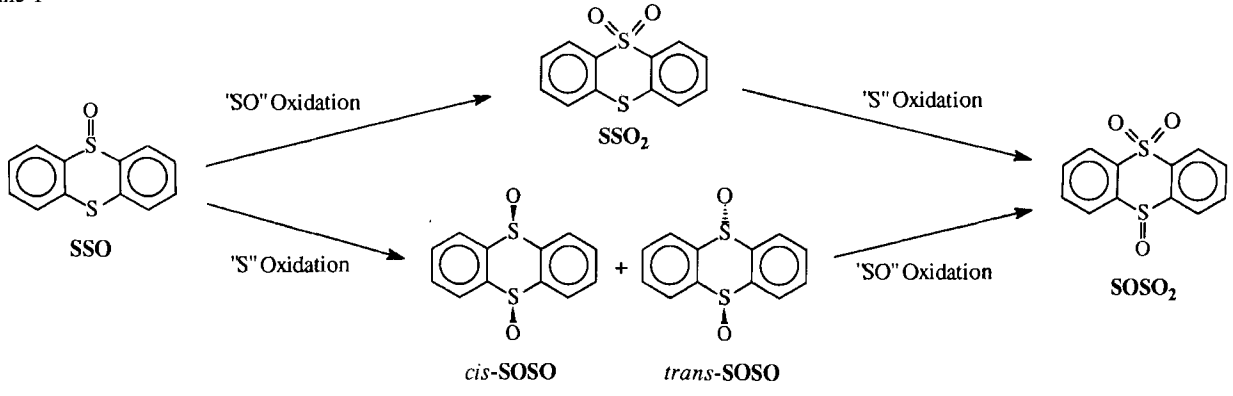
During the last decade, the oxidation of thianthrene 5-oxide (SSO) has been used as a mechanistic probe to determine the electronic character of an oxidant (Scheme 1)[1-4]. Valuable information on the nucleophilic (oxidation at the sulfoxide site, i.e. SO in SSO) versus electrophilic (oxidation at the sulfide site, i.e. S in SSO) nature of oxidants has been acquired by the SSO probe. Diverse oxygen transfer reactions have been examined with this probe, which include peroxometal complexes[5], metalloporphyrin-catalyzed epoxidations[6], hemoprotein oxidizing species[7], dioxygen/aldehyde/heteropolyoxometalate oxidations[8], the singlet oxygenation of sulfides[6], sulfide oxidations with dimethylphenylsilyl hydrotrioxide ($R_3Si-OOOH$)[9], dialkylperoxonium intermediates ($R^1R^2O^+-OH$)[10a,b], and carbonyl oxides versus dioxiranes[2].

For the dioxiranes, however, the results obtained with the SSO probe are in conflict with the established electrophilic character[11,12] of this oxidant. Thus, for dimethyldioxirane (DMD) the X_{SO} parameter (eq. 1) varies from 0.64 to 0.85[4], thus DMD can clearly be characterized as a nucleophilic oxidant. In contrast, all other studies, e.g. epoxidations[11] and also sulfoxidations[12] (Hammett $\varrho = -0.77$), establish the electrophilic nature of DMD.

To reconcile this discrepancy, numerous mechanistic rationales have been suggested during the last few years. Thus, nucleophilic attack of the sulfoxide oxygen on the peroxide bond of the dioxirane[13] was proposed, which would generate an intermediary persulfoxide, and subsequent rearrangement of the latter was supposed to give SSO_2. This hypothesis was recently convincingly disproved[14]. Alternatively, the possibility of an electron transfer process[5,15] to afford the radical cation of SSO and the radical anion of DMD has been invoked, since the latter would undoubtedly act as a nucleophilic oxygen transfer agent. Nonetheless, quantum mechanical calculations[16] confirmed our experiments that the SSO_2 should be the major product.

In a recent application of the SSO probe for a biological oxidation, specifically the hemoprotein oxidizing species[7], in addition to assess its electrophilic nature, the *cis-trans* ratio of SOSO was determined to elucidate the preferred stereochemical approach of the biological oxidant towards thianthrene 5-oxide. In view of its substantially puckered conformation (dihedral angle ca. 133°[17]), the two sulfide lone pairs are stereotopically differentiated, axial attack by the oxidant would generate *trans*-SOSO and the equatorial

Scheme 1



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$$X_{SO} = \frac{n_{SO}}{n_{SO} + n_S} = \frac{(n_{SSO_2} + n_{SOSO_2})}{(n_{SOSO} + n_{SOSO_2}) + (n_{SSO_2} + n_{SOSO_2})} \quad (1)$$

$n_{SO} = (n_{SSO_2} + n_{SOSO_2})$ total "SO" oxidation

$n_S = (n_{SOSO} + n_{SOSO_2})$ total "S" oxidation

one *cis*-SOSO (eq. 2). Steric interactions (repulsion by *peri* hydrogens) would dictate *axial* attack (preference for *trans*-SOSO), but dipole-dipole interactions would favor equatorial attack (preference for *cis*-SOSO). As a result of the puckered conformation of SOSO (these *bis*-sulfoxides are configurationally stable up to 200°C[18]), in the *cis* isomer the bond moments of the sulfoxide functionality effectively cancel to give a low overall dipole moment (μ = 1.70 D)[19], while in the *trans* isomer they reinforce each other to result in a high overall dipole moment (μ = 4.88 D)[19]. During the oxygen transfer process, the already present SO bond moment in SSO senses the developing incipient SO bond moment and to minimize dipole-dipole interactions in the transition state, *equatorial* attack would be favored to give *cis*-SOSO, the thermodynamically more stable isomer[18]. Thus, if steric effects should dominate, kinetic control should direct bulky electrophilic oxidants to attack SSO preferentially *axially*.

It seemed to us mechanistically relevant to assess the stereochemical course of the SSO probe for electrophilic oxidants by determining the ratio of *cis*- and *trans*-SOSO isomers. Thus, besides acquisition of the electrophilic nature (X_{SO}) of such oxidants, the SSO probe would also provide valuable stereochemical insight into the oxygen transfer process by means of this *cis-trans* ratio. For this purpose it was necessary to develop a reliable HPLC method of analysis, which for the sake of convenience would permit in a single chromatographic run to monitor all components of the oxidation mixture, i.e. SSO, *cis*- and *trans*-SOSO, SSO_2, and $SOSO_2$ (the unavoidable overoxidation product).

In our previous HPLC analysis[1] we assumed that the *cis*- and *trans*-SOSO isomers eluted together, but on more careful reexamination we have now observed that *trans*-SOSO (t_R = ca. 2 h) elutes much slower than *cis*-SOSO (t_R = 10.2 min) and even the overoxidized product $SOSO_2$ (t_R = 11.8 min); therefore, *trans*-SOSO was lost in the baseline of the HPLC trace. Of course, these unusually different retention times on the silica gel column[1] are a consequence of the large difference in the dipole moments between *cis*- and *trans*-SOSO[19]. For this reason, we have reinvestigated the X_{SO} values for the oxidations of SSO by acidic and basic H_2O_2 and dimethyldioxirane (DMD). For comparison, we also determined the X_{SO} value for methyl(trifluoromethyl)dioxirane (TFD), whose electrophilic nature was previously not assessed by the SSO probe. Indeed, our present results (Table 1) unequivocally confirm the expected electrophilic character[11,12] of the dioxiranes DMD and TFD and thus establish SSO as a reliable mechanistic probe for the electronic character of oxygen transfer agents.

The new HPLC analysis utilizes a C-18 reversed-phase column and CH_3OH / H_2O / CH_3CN (64:34:2) as eluent (cf. Experimental for details), which enables the convenient analysis of all the five thianthrene oxides (SSO, *cis*-SOSO, *trans*-SOSO, SSO_2, $SOSO_2$) in one single chromatographic run. As the results in Table 1 show, oxidations by H_2O_2 under acidic (entry 1) and basic (entry 2) conditions span the full range of the X_{SO} scale from 0.05 for H_2O^+-OH to 1.00 for HOO^-. Moreover, much to our satisfaction, both DMD (entries 3 and 4) and TFD (entries 5 and 6) are strongly electrophilic oxidants, the latter being expectedly more electrophilic. Their selectivity, as may be anticipated, is slightly enhanced at lower temperatures, cf. entries 3 versus 4 for DMD and entries 5 versus 6 for TFD.

Consequently, these new results obviate all previous considerations of special effects in the oxygen transfer by dioxiranes to thianthrene 5-oxide[5,13]. Moreover, all previous applications of the thianthrene 5-oxide probe which are based on HPLC analysis require revision, unless an explicite effort was made to determine the *cis-trans* ratio of SOSO. Future work should address the stereochemical features of the SSO oxidation process, which is potentially accessible by using the *cis,trans*-SOSO ratio.

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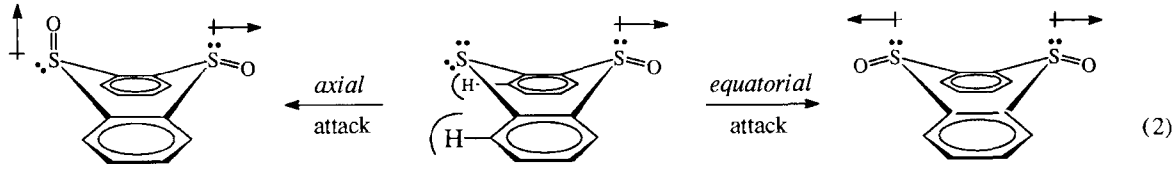
Experimental

HPLC analyses: Kontron analytical system (T-414 pumps, Uvikon 720LC spectrophotometer, Anacomp 220 integrator), C-18 reversed-phase column (250 × 4.6 mm i.d.; particle size 5 μm), $CH_3OH/H_2O/CH_3CN$ (64:34:2) as eluent, detection at λ = 254 nm, flow rate 1.2 ml min^{-1}. Retention times (t_R) 2.30, 3.90, 4.43,

Table 1. Oxidation of thianthrene 5-oxide with different oxidants[a]

Entry	Temp. (°C)	Oxidant	Conv. (%)	Product distribution[b] (%) SSO_2	SOSO *cis-*	SOSO *trans-*	$SOSO_2$	X_{SO}[c]
1	25	H_2O_2 / $HClO_4$	24	0.3	82	13	4.4	**0.05**
2	25	H_2O_2 / NaOH / Bu_4NOH	11	100	0	0	0	**1.00**
3	-50	DMD	52	6.8	3.1	90	0.1	**0.07**
4	0	DMD	56	12	3.9	84	0.3	**0.13**
5	-78	TFD	21	0.8	3.1	96	0.2	**0.01**
6	0	TFD	20	2.8	3.9	85	8.1	**0.10**

[a] In CH_2Cl_2. – [b] Analyzed by HPLC (for conditions cf. Experimental); error ± 3% of the stated values; normalized to 100% (mass balance was in all cases >95%). – [c] Error ± 0.03 units.



(2)

5.48, 7.17, and 10.6 min for *trans*-SOSO (1.00), $SOSO_2$ (1.23), *cis*-SOSO (1.02), SSO_2 (0.596), the internal standard (1.00) and SSO (0.646); the values in parentheses are the calibration factors (error ± 3%) against 1-phenyl-1-penten-3-one. All solvents were purified by following standard methods. – Caroate (potassium monoperoxysulfate), the triple salt $2\ KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$, was used as received. Dimethyldioxirane[20a,b] (as acetone solution) and methyl(trifluoromethyl)dioxirane (as trifluoroacetone solution)[21] were prepared according to published procedures, and their peroxide content was determined by iodometry. The dimethyldioxirane solutions were stored over molecular sieves (4 Å) at −20°C, while trifluorodioxirane solutions were kept at −20°C without drying agent.

General Procedure for the Oxidation of Thianthrene 5-Oxide by the Dioxirianes: To a cooled, stirred solution of 23.2 mg (0.100 mmol) of thianthrene 5-oxide in 7.5 ml of CH_2Cl_2 was added a solution (0.05–0.5 M) of dioxirane (0.2–0.5 equiv.). After 1 h, the peroxide was consumed, and the solvent was evaporated (40°C/12 Torr), the residue was taken up in 5 ml of ethanol/CH_2Cl_2 (1:1, v/v) and the residue analyzed by HPLC as described above; the results are summarized in Table 1.

Oxidation of SSO with H_2O_2/$HClO_4$: To a stirred solution of 26.9 mg (0.116 mmol) of thianthrene 5-oxide in 7.5 ml of CH_2Cl_2 was added 50.0 mg of a H_2O_2 solution (85%, 1.16 mmol, 10.0 equiv.) and 0.25 ml of aqueous $HClO_4$ (60%, $d = 1.53$ kg m^{-3}, 2.3 mmol, 20 equiv.). After 5 min, 20 ml of CH_2Cl_2 was added and the solution washed with 20 ml of 10% aqueous $NaHCO_3$ and subsequently with water (2 × 20 ml). After drying of the organic layer with $MgSO_4$, the solvent was removed by distillation (40°C/12 Torr) and the residue analyzed by HPLC as described above; the results are summarized in Table 1.

Oxidation of SSO with H_2O_2/NaOH: To a stirred solution of 27.2 mg (0.117 mmol) of thianthrene 5-oxide in 7.5 ml of CH_2Cl_2 were added at ambient temperature 62.5 mg (1.56 mmol, 13 equiv.) of NaOH, 0.20 ml of $(n\text{Bu})_4\text{NOH}$ (40%), and 50 mg (85%, 1.2 mmol, 10 equiv.) of a H_2O solution. After stirring for 3.5 h, 20 ml of CH_2Cl_2 was added, the solution was washed first with 20 ml of a 20% aqueous $NaHSO_3$ and then with water (2 × 20 ml). After drying of the organic layer with $MgSO_4$, the solvent was removed by distillation (40°C/12 Torr) and the residue analyzed by HPLC as described above; the results are summarized in Table 1.

[1] W. Adam, W. Haas, G. Sieker, *J. Am. Chem. Soc.* **1984**, *106*, 5020–5022.
[2] W. Adam, H. Dürr, W. Haas, B. B. Lohray, *Angew. Chem.* **1986**, *98*, 85–87; *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 101–103.
[3] W. Adam, B. B. Lohray, *Angew. Chem.* **1986**, *98*, 185–186; *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 188–189.
[4] W. Adam, W. Haas, B. B. Lohray, *J. Am. Chem. Soc.* **1991**, *113*, 6202–6208.
[5] F. P. Ballistreri, G. A. Tomaselli, R. M. Toscano, V. Conte, F. Di Furia, *J. Am. Chem. Soc.* **1991**, *113*, 6209–6212.
[6] T. Akasaka, M. Haranaka, W. Ando, *J. Am. Chem. Soc.* **1991**, *113*, 9898–9900.
[7] J. C. Alvarez, P. R. Ortiz de Montellano, *Biochemistry* **1992**, *31*, 8315–8322.
[8] M. Hamamoto, K. Nakayama, Y. Nishiyama, Y. Ishii, *J. Org. Chem.* **1993**, *58*, 6421–6425.
[9] B. Plesnicar, J. Cerkovnik, J. Koller, F. Kovac, *J. Am. Chem. Soc.* **1991**, *113*, 4946–4953.
[10] a) A. J. Bloodworth, T. Melvin, J. C. Mitchell, *Studies Org. Chem.* **1988**, *33*, 45–52. – b) A. J. Bloodworth, T. Melvin, J. C. Mitchell, *J. Org. Chem.* **1988**, *53*, 1078–1082.
[11] a) A. L. Baumstark, P. C. Vasquez, *J. Org. Chem.* **1988**, *53*, 3437–3439. – b) A. L. Baumstark, D. B. Harden, Jr., *J. Org. Chem.* **1993**, *58*, 7615–7618.
[12] R. W. Murray, R. Jeyaraman, M. K. Pillay, *J. Org. Chem.* **1987**, *52*, 746–748.
[13] R. W. Murray, *Chem. Rev.* **1989**, *89*, 1187–1201.
[14] E. L. Clennan, K. Yang, *J. Org. Chem.* **1993**, *58*, 4504–4505.
[15] M. Matsui, Y. Miyamoto, K. Shibata, Y. Takase, *Bull. Chem. Soc. Jpn.* **1984**, *57*, 2526–2530.
[16] J. J. W. McDouall, *J. Org. Chem.* **1992**, *57*, 2861–2864.
[17] S. Hosoya, *Acta Crystallogr.* **1966**, *21*, 21–26.
[18] K. Mislow, P. Schneider, A. L. Ternay, Jr., *J. Am. Chem. Soc.* **1964**, *86*, 2957–2959.
[19] M. J. Aroney, R. J. W. Le Fèvre, J. D. Saxby, *J. Chem. Soc.* **1965**, 571–575.
[20] a) R. W. Murray, R. Jeyaraman, *J. Org. Chem.* **1985**, *50*, 2847–2853. – b) W. Adam, J. Bialas, L. Hadjiarapoglou, *Chem. Ber.* **1991**, *124*, 2377.
[21] R. Mello, M. Fiorentino, O. Sciacovelli, R. Curci, *J. Org. Chem.* **1988**, *53*, 3890–3891.

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