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Evidence for the Involvement of a Sulfurane Intermediate in the Oxidation of Simple Sulfides by Methyl(trifluoromethyl)dioxirane.

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Abstract: Methyl(trifluoromethyl)dioxirane reacts with sulfides to give preferentially sulfones, even in the presence of competing sulfoxides. The sulfoxide yield increases at the expense of the sulfone when 2,2,2-trifluoroethanol is used as co-solvent. The reaction of dioxirane **1b** with phenylmethyl sulfide in the presence of 1,1,1-trifluoropropanone-^{18}O-hydrate (48% atom labelled), leads to the obtention of 23% atom ^{18}O-labelled sulfoxide and 6.1% atom ^{18}O-labelled sulfone. The involvement of a cyclic hypervalent sulfurane intermediate is proposed as reactive intermediate.

The oxidation of sulfides is one among the earliest studied O-transfer reactions of dioxiranes.[1] Dimethyldioxirane (**1a**) (hereafter DMDO) reacts with sulfides[2,3] to give sulfoxides, which can further react with DMDO (**1a**) to give sulfones in a sequential process (Equation 1). Since sulfides are better nucleophiles than sulfoxides, the oxidation can be controlled at the sulfoxide stage when the stoichiometric amount of DMDO (**1a**) is used. Now we report the first detailed study on the oxidation of simple sulfides and sulfoxides by methyl(trifluoromethyl)dioxirane (**1b**) (hereafter TFDO), a dioxirane that exhibits a stronger electrophilic character.[1,3] The results of the oxidation of phenylmethyl sulfide (**2**) with TFDO (**1b**) to afford phenylmethyl sulfoxide (**3**) and phenylmethyl sulfone (**4**) at 0 °C in different solvents are shown in Table 1.[4,5] Surprisingly, the oxidation of **2** by TFDO (**1b**) produced **4** as the main product, even in the presence of a large excess of **2** relative to TFDO (**1b**). It should be noted that the ratio sulfone/sulfoxide (**4**/**3**) decreases in the presence of trifluoroethanol. The oxidation of dibenzyl sulfide and dibutyl sulfide by TFDO (**1b**) proceeded with similar results. Methyl or trifluoromethyl esters resulting from the radical chain decomposition of **1a**[6] or **1b**[5] were not detected in any case allowing us to disregard a radical mechanism for these oxidations. By analogy with the case of the oxidations carried with DMDO, the oxidation of sulfides to sulfones by TFDO were expected to proceed in a sequential fashion as depicted in Eq. 1.[3] In that case, from our results, phenylmethyl sulfoxide (**3**) appears to react with TFDO (**1b**) faster than sulfide **2**.[7] In order to clarify this surprising conclusion, we performed a series of competitive oxidations of a pair sulfide/sulfoxide bearing minor structural differences, namely phenyl(trideuteromethyl) sulfide (**2**-d^3) and phenylmethyl sulfoxide (**3**), with TFDO (**1b**). Reactions were carried out as described and the products analyzed by GC-MS. The results are shown in Table 2.

$$\mathrm{RSR'} \xrightarrow{\mathrm{DMDO}} \mathrm{RSOR'} \xrightarrow{\mathrm{DMDO}} \mathrm{RSO_2R'}$$

Equation 1

The reaction of an equimolar mixture of **2**-d^3 and **3** with DMDO (**1a**) yielded the sulfoxide **3**-d^3 and small amounts of the sulfones **4**-d^3 and **4** while most of the sulfoxide **3** remained unchanged (entry 1, Table 2). By contrast, when a mixture of sulfide **2**-d^3 and sulfoxide **3** reacted with TFDO (**1b**), *sulfone **4**-d^3 was the main oxidation product from sulfide **2**-d^3* even in the presence of excess of sulfoxide **3** (entries 2 and 3, Table 2).[8] We should remark that, although sulfoxide **3** is also oxidized by TFDO (**1b**) to sulfone **4**, oxygen transfer occurs *preferentially* to sulfide **2**-d^3. The same trend is observed in trifluoroethanol solution, but in this case the **4**-d^3/**3**-d^3 ratio decreases (entry 4, Table 2). These data allow us to conclude that the conversion of sulfide **2** into sulfone **4** by TFDO (**1**) cannot occur *only* through the oxidation of the intermediate sulfoxide **3** as depicted in Eq. 1, and suggest the involvement of a sulfide-derived reactive intermediate that, *i*) is oxidized by TFDO (**1b**) faster than either sulfides or sulfoxides and, *ii*) is readily converted into a sulfoxide by the action of protic acidic solvents such as trifluoroethanol. Then, we designed ^{18}O-tracer experiments addressed to trap the suspected intermediate (**5**). We carried out the oxidation of 0.031 M phenylmethyl sulfide (**2**) at 0 °C under inert atmosphere with the equimolar amount of TFDO (**1b**) in 4:1 CH_3CN/CH_2Cl_2 in the presence of a 100-fold excess of 1,1,1-trifluoroacetone-^{18}O-hydrate (**6**-^{18}O, 49 atom % labelled[9]), a suitable acidic reagent for trapping of a polar intermediate. Effectively, under these conditions GC-MS analysis of the reaction mixture revealed[10] that a 23.0 atom % of

Table 1. Oxidation of Phenyl Methyl Sulphide (**2**) by TFDO (**1b**)[a]

run	**2**:**1b**[b]	solvent[c]	reaction mixture (%)[d]			**4**/**3**
			2	**3**	**4**	ratio
1	1:1	DC	42	12	46	3.8
2	10:1	DC	93	3	4	1.3
3	2:1	DC	68	9	23	2.6
4	2:1	DC/AC 1:19	71	8	21	2.6
5	2:1	DC/AN 1:19	68	9	23	2.6
6	2:1	DC/TFE 1:7	66	18	16	0.9

[a] The reactions were carried out at 0 °C with an initial concentration of **1b** ranging between 0.030 to 0.063 M; identical results were obtained when TFDO solution was added dropwise. [b] Molar ratio. [c] DC: dichloromethane; AC: acetone; AN: acetonitrile; TFE: trifluoroethanol; [d] Values are the average of at least two identical runs within a standard error of ±2%.

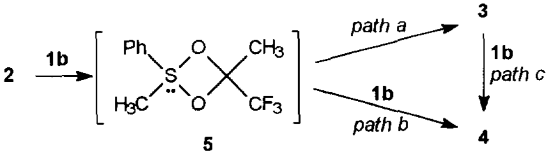
Table 2. Competitive Oxidations of $PhSCD_3$ (**2**-d^3) and $PhSOCH_3$ (**3**) by Dioxiranes **1**.[a]

entry	reagents	**1**	molar ratio	solvent[b]	reaction mixture (%)[c]			O-transfer[d]	ratio
			1: **2**-d^3:**3**		**2**-d^3	**3**-d^3 (**3**)	**4**-d^3 (**4**)	**2**-d^3 / **3**	**4**-d^3/**3**-d^3
1	**2**-d^3 + **3**	**1a**	1:1:1	DC/AC 1:1	13	80 (93)	7 (7)	13.4	0.1
2	**2**-d^3 + **3**	**1b**	1:1:1	DC	58	11 (66)	31 (34)	2.1	2.8
3	**2**-d^3 + **3**	**1b**	1:1:3	DC	73	9 (80)	18 (20)	2.3	2.0
4	**2**-d^3 + **3**	**1b**	1:1:1	DC/TFE 1:9	53	21 (70)	26 (30)	2.4	1.2

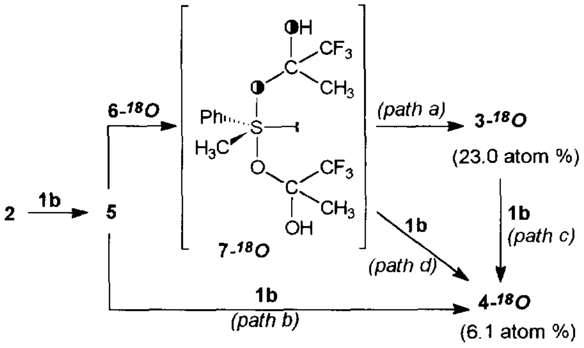
[a] Reactions carried out at 0 °C with a concentration of the substrates ranging between 0.03-0.06 M. [b]DC: Dichloromethane; AC: acetone; TFE: trifluoroethanol. [c] Mixture composition have been calculated separately for CD_3- and CH_3- substituted compounds and the values are the average of at least two identical runs within a standard error of ±2%. [d] Calculated as ([**3**-d^3]+ 2x[**4**-d^3]/[**4**]).

the sulfoxide (34 % yield) and a 6.1 atom % of the sulfone (66% yield) were ^{18}O-labelled with a 56% sulfide conversion. In control experiments it was ascertained that sulfoxide **3** and sulfone **4** do not undergo oxygen exchange with 1,1,1-trifluoropropanone -^{18}O- hydrate (**6**-^{18}O) under identical conditions.

To explain all the above observations we propose the involvement of the cyclic sulfurane[11] **5** in the oxidation of sulfides to sulfones (Scheme 1). Sulfurane **5** would lead to sulfoxide **3** or sulfone **4** either by ß-elimination of 1,1,1-trifluoropropanone (*path a*, Scheme 1) or by further oxidation by TFDO (*path b*, Scheme 1). The influence of the solvent in the product distribution and the ^{18}O-incorporation in the tracer experiments are explained by the known ligand exchange reactivity shown by sulfuranes[13] when reacting with active hydrogen substrates, which derives from their basic character due to the negative charge density localised on the oxygen atoms. So, the reaction of **5** with the acidic solvent trifluoroethanol (run 6, Table 1) would promote ring opening to afford sulfoxide **3** and trifluoroacetone (*path a*, Scheme 1). On the other hand, the formation of 7-^{18}O by ligand exchange of **5** with **6**-^{18}O (Scheme 2) accounts for the sulfoxides 3-^{18}O and **3** upon ß-elimination of 1,1,1-trifluoropropanone or 1,1,1-trifluoropropanone-^{18}O, respectively. Since 23% ^{18}O-labelled sulfoxide is formed, the sulfoxide should derive almost exclusively from the sulfurane 7-^{18}O, from which the expected maximum statistical ^{18}O-label incorporation in the sulfoxide is 24.5%. Additional alternative routes are suggested in Scheme 2 to account for the formation of sulfone.



Scheme 1



Scheme 2

In conclusion, the oxidation of simple sulfides by TFDO (**1b**) to give sulfones does not proceed, at least as the main route, through oxidation of an initially formed sulfoxide. Furthermore, solvent effects and ^{18}O-labelling techniques suggest for this process the involvement of a highly reactive intermediate, most likely the hypervalent sulfurane 5. The mechanistic details of the oxygen transfer step from dioxirane **1b** to sulfuranes **5** and/or 7 to give sulfone are presently under investigation.

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4. Reactions were carried out at 0 °C under inert atmosphere by adding in one batch in the dark a thermostated dioxirane **1b** solution (0.3-0.6 M) in ketone-free methylene chloride[5] to a stirred solution of the sulfide in the selected solvent. The analysis of the reaction mixtures was performed by GC and ^{1}H NMR.
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8. A relative reaction rate value k_H/k_D of 0.94 $\pm$3% was obtained in the competitive oxidation of sulfoxides **3**:**3**-d^3 by TFDO.
9. 1,1,1-Trifluoroacetone-^{18}O -hydrate (**6**-^{18}O) was generated *in situ* by adding to a solution of 1,1,1-trifluoroacetone in CH_3CN/CH_2Cl_2, under inert atmosphere at 0 °C, an equimolar amount of $H_2{}^{18}O$ (98 atom %, supplied by Aldrich). MS analysis showed that the incorporation of $H_2{}^{18}O$ into the hydrate **6**-^{18}O was complete.
10. ^{18}O-Labelled % was calculated by applying the equation $100 \times [(I+2)-(I+2)_{natural}] / [I+(I+2)]$ to the normalized relative intensities corresponding to the peaks 125 (M^+-CH_3) and 140 (M^+) for the sulfoxide **3/3**-^{18}O, and to the peaks 141 (M^+-CH_3) and 156 (M^+) for the sulfone **4/4**-^{18}O, respectively, and obtaining the average value. Mass spectra were recorded at least three times. The estimated error was less than 1%.
11. The involvement of an hypervalent sulfur adducts has been proposed in the oxidation of sulfides with a variety of peroxidic oxidants.[12] By analogy with dioxetanes,[12c] the intermediacy of a sulfurane intermediate has been suggested in the oxidation of sulfides by dioxiranes,[1] although it has not been demonstrated up to now. An alternative zwiterionic structure such as $PhMeS^+$-$OCCH_3CF_3O^-$ could be depicted.
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