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A Theoretical and Experimental Investigation of the Electrophilic Oxidation of Thioethers and Sulfoxides by Peroxides

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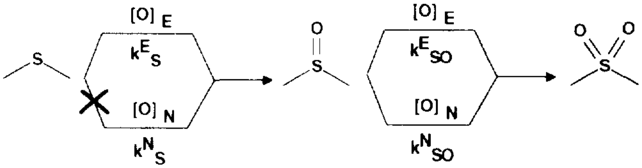
Abstract: In the electrophilic oxidation by peroxides the reactivity of sulfoxides is considerably less affected by structural effects than that of thioethers. This feature has not been, so far, rationalized. We have calculated by semiempirical methods the charge on the sulfur atom, **Q(S)**, and the energy of the HOMO for a series of thioethers and sulfoxides. Then we have correlated the rate constants for the oxidation of thioethers by $H_3O_2^+$ and of sulfoxides by perbenzoic acid with **Q(S)** and with **F** (**F** = $(E_{LUMO}^{Ox} - E_{HOMO}^{Sub})^{-1}$ respectively. We find that the reactivity of thioethers is mainly dependent on **Q(S)**, while that of sulfoxides is dominated by **F**.

INTRODUCTION

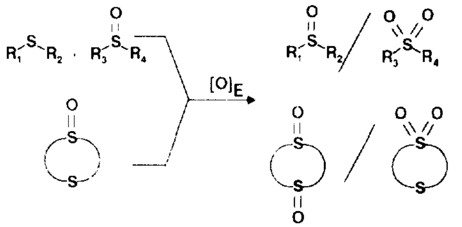
Thioethers are oxidized to sulfoxides only by electrophilic oxidants, $[O]_E$, while sulfoxides are oxidized to sulfones by both electrophilic and nucleophilic, $[O]_N$, oxidants. (Scheme 1)[1]

Scheme 1



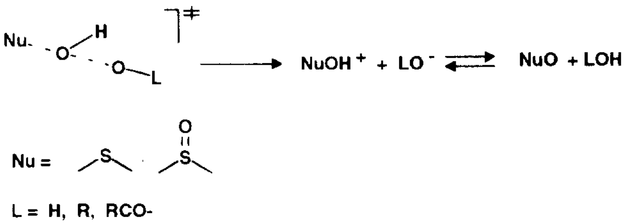
The biphilic nature of sulfoxides usually does not affect the selectivity of simple thioethers oxidation since the ratio k_S^E/k_{SO}^E is sufficiently large to avoid overoxidation to sulfone.[2] By contrast, when a thioether and a sulfoxide group, either of two different compounds or inserted in the same molecule, are competing against each other for an electrophilic oxidant, Scheme 2, and the k_S^E/k_{SO}^E ratio is small, a mixture of products is obtained.[3,4]

Scheme 2



Small k_S^E/k_{SO}^E ratios may result from the fact that the nucleophilic reactivity of thioethers is more affected by structural effects than that of sulfoxides.[1] Therefore, the rates of thioethers oxidation may be depressed by the substituents at the sulfur atom to a level comparable with that of sulfoxides. It is not obvious why, in the frame of the commonly accepted mechanism of electrophilic oxidation, shown in Figure 1,[5] which amounts to a S_N2-type displacement operated by the nucleophile on the O-O bond of the peroxide,[5] a different extent of the effect of the substituents for thioethers and sulfoxides should be observed.

Figure 1



We have addressed this aspect by examining from both an experimental and a theoretical point of view the oxidation of thioethers and sulfoxides by peroxidic reagents. In particular we have confirmed that the nucleophilic reactivity of thioethers is considerably more affected than that of sulfoxides by the nature of the groups attached to the sulfur atom, independently of the oxidant employed. We have also investigated the relevance of the parameters which likely affect the reactivity of the two classes of substrates. Thus, we have calculated by semiempirical methods the charge at the sulfur atom and the energy of the HOMO for both thioethers and sulfoxides.

RESULTS

Structural effects in thioethers and sulfoxides oxidation.

Table 1 collects a series of data, taken also from the literature,[6,7] illustrating the effect of the substituents at the sulfur atom in the oxidation of thioethers and sulfoxides by peroxidic compounds. Even though the rho values have been obtained under different experimental conditions,[6,7] a trend clearly emerges. In particular those of thioethers are consistently larger, *ca.* two-fold, than those of sulfoxides. Their negative sign confirm that in all cases we are dealing with electrophilic oxidations.

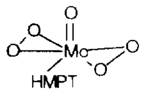
Owing to our long standing interest in the oxidative chemistry of peroxo complexes of metal such as Ti, V, Mo and W[8] we decided to investigate the behavior of these reagents in thioethers and sulfoxides oxidation. In fact, while for simple peroxidic compounds it is difficult to envisage plausible alternatives to the bimolecular electrophilic mechanism shown in Figure 1, for peroxometal complexes, *e.g.* **MoO_5HMPT**,[9] the situation may be more complicated.[1] Theoretical calculations confirm the electrophilic nature of the oxygen transferred from the peroxocomplex to nucleophiles such as olefins and thioethers indicating, at the same time, that an interaction of the substrate with the metal, placing the nucleophile in the most appropriate position to receive the peroxo oxygen, may occur.[10]

Table 1. Oxidation of Thioethers and Sulfoxides by Electrophilic Oxidants.

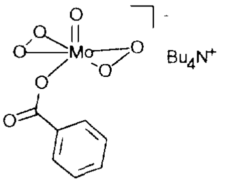
#	Oxidant	Substrate	rho	Ref.
1	HOOH, H^+	X-Ar-S-CH_3	-1.13	(6)
		X-Ar-S-Ph	-0.98	(6)
2	*t*BuOOH,H^+	X-Ar-S-CH_3	-1.20	this work
3	C_6H_4-COOH	X-Ar-S-CH_3	-0.90[a]	this work
		X-Ar-SO-CH_3	-0.64	(7)
		X-Ar-SO-Ph	-0.54	(7)

a)meta-chloroperbenzoic acid was used.

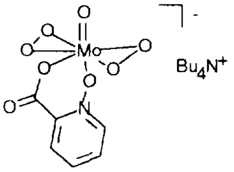
In order to establish whether such an effect has relevance on the relative sensitivity of thioethers and sulfoxides oxidation to structural effects, the behavior of **MoO$_5$HMPT** was compared with that of **MoO$_5$Benz**[11] and **MoO$_5$PICO**.[12] **MoO$_5$HMPT** is a neutral and a coordinatively unsaturated species, **MoO$_5$Benz** is anionic but still coordinatively unsaturated and **MoO$_5$PICO** is anionic and coordinatively saturated. Therefore for both **MoO$_5$Benz** and **MoO$_5$PICO** the interaction of the nucleophile with the metal center should be weaker than for **MoO$_5$HMPT**. The pertinent data are collected in Table 2.



MoO$_5$HMPT

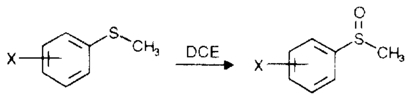
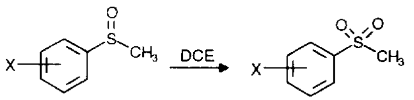


MoO$_5$Benz



MoO$_5$PICO

Table 2. Oxidation of Thioethers and Sulfoxides with Peroxomolybdenum complexes in DCE at 40°C.

		
Complex	**rho**	**rho**
MoO$_5$HMPT[a]	-0.70	-0.20
MoO$_5$Benz[b]	-0.65	-0.35
MoO$_5$PICO[c]	-0.50	-0.10

a) ref.3 and 13; b) this work; c) ref 12b.

The rho values obtained are all negative as expected for electrophilic oxidants and comparable with those obtained with other peroxidic oxidants. No significant differences in the behavior of these three complexes are observed in spite of their rather different ability to coordinate nucleophiles.[11,12] Also for peroxo molybdenum complexes the rho values for thioethers are larger than those for sulfoxides. The consequence is that the selectivity k^E_S/k^E_{SO} decreases with decreasing their reactivity, as shown in Table 3 for MoO_5HMPT and, for comparison purposes, also for perbenzoic acid.

Table 3. Selectivities (k^E_S/k^E_{SO}) for the Oxidation of Thioethers and Sulfoxides with **MoO_5HMPT** and Perbenzoic acid.

MoO_5HMPT		**Ph-COOOH**	
Substrates	k^E_S/k^E_{SO}	Substrates	k^E_S/k^E_{SO}
$(Bu^n)_2S$ / $(Bu^n)_2SO$	400^b	$(Ph)_2S$ / $(Ph)_2SO$	100^d
$(Ph)\text{-}S\text{-}CH_3$ / $(Ph)\text{-}SO\text{-}CH_3$	100^b	$(pNO_2Ph)_2\text{-}S$ / $(pNO_2Ph)_2\text{-}SO$	42^e
$(Ph)_2S$ / $(Ph)_2SO$	30^b	DBT / DBTO[a]	11^e
DBT / DBTO[a]	5^c	-	-

a) DTB = dibenzothiophene, DTBO = dibenzothiophene-oxide; b) ref. 13; c) ref 14; d) ref. 15; e) ref. 7,16

The data of Table 3 confirm that indeed the reactivity of thioethers and sulfoxides may be in some cases rather similar. Moreover, the larger sensitivity of thioethers compared with sulfoxides to structural effects appears to be independent of the nature of the peroxidic oxidants. Consequently, this feature should be related to some properties of the substrates. We have considered two of these properties which affect their nucleophilic character, *e.g.* the charge on the sulfur atom and the energy of the HOMO of a series of thioethers and sulfoxides, which may be calculated as described in the next paragraph.

Calculations

Austin Model (AM1) semiempirical molecular orbital calculations were performed on the thioethers **1-17** (Tables 4 and 5) and on the sulfoxides **18-29** (Table 6) using Spartan 3.0 software.[17] The AM1 semiempirical method[18] is a modification of MNDO[19] offering more accurate parametrizations for polar systems. For our calculations, the geometry of a given molecule was first optimized at the empirical level using an MM2 molecular mechanics routine[20] followed by unrestricted geometry optimization at the semiempirical level using an SCF calculation. For several of the thioethers and sulfoxides more than one stable conformation was found. For these species the optimization was carried on until the lowest energy conformation was found. For all electronic energy and atomic charges calculations, the ground-state (S_0) optimized geometry was used and the RHF closed-shell calculations were performed using configuration interaction (CI). The results are collected in Tables 4,5 and 6. In the same Tables are reported the rate constants of the oxidation of **1-13** by $H_3O_2^+$ and **14-29** by perbenzoic acid (PBA). By using the same theoretical calculations, energy values of -7.82 eV and -0.679 eV have been obtained for the LUMO's of $H_3O_2^+$ and of PBA respectively. Therefore, in Tables 4,5 and 6 the F parameter values, which are defined as $(E_{LUMO}^{Ox} - E_{HOMO}^{Sub})^{-1}$, are also reported.

Even though the number of thioethers of Table 5 is small, the data of Tables 4 and 5 may be useful in making a comparison between the two oxidants, $H_3O_2^+$ and PBA.

Table 4. Calculated **Q(S)** and **F** Parameters and Experimental log k Values for the Oxidation of a Series of Thioethers with $H_3O_2^+$ in ethanol at 25°C.[6,7]

#	Substrate	log k	E_{HOMO}[a]	Q(S)[b]	F[c]
1	(Bu^n)-S-(Bu^n)	-1.692	-8.43	0.067	1.63
2	Ph-CH_2-S-CH_3	-1.796	-8.53	0.083	1.41
3	Ph-S-CH_2-CH_3	-2.396	-8.11	0.221	3.44
4	Ph-S-$CH(CH_3)_2$	-2.448	-8.10	0.209	3.59
5	Ph-S-$C(CH_3)_3$	-2.652	-8.06	0.195	4.07
6	Ph-CH_2-S-Ph	-2.690	-8.15	0.244	2.99
7	Ph-S-CH_3	-2.428	-8.13	0.240	3.27
8	pCH_3O-Ph-S-CH_3	-2.105	-7.92	0.233	10.11
9	pCH_3-Ph-S-CH_3	-2.198	-8.03	0.240	4.79
10	pCl-Ph-S-CH_3	-2.644	-8.25	0.256	2.33
11	mCl-Ph-S-CH_3	-2.851	-8.31	0.256	2.03
12	pNO_2-Ph-S-CH_3	-3.502	-8.86	0.295	0.96
13	Ph-S-Ph	-3.420	-7.90	0.368	12.93

a) eV. b) Atomic charge density. c) $E_{LUMO}^{H_3O_2^+} = -7.82$ eV; $E_{HOMO}^{H_3O_2^+} = -19.23$ eV.

Table 5. Calculated **Q(S)** and **F** Parameters and Experimental log k Values for the Oxidation of a Series of Thioethers with Perbenzoic-acid (PBA) in dioxane/water 50/50 v/v at 25°C.[7,16]

#	Substrate	log k	E_{HOMO}[c]	Q(S)[d]	F[e]
14	Ph-S-Ph	+0.699	-7.900	0.367	0.235
15	pNO_2-Ph-S-Ph	-0.278	-8.662	0.404	0.234
16	DBT[a]	-1.402	-8.201	0.458	0.234
17	BT[b]	-2.397	-8.430	0.495	0.228

a)DTB = dibenzothiophene. b) BT = benzothiophene. c) eV. d) Atomic charge density. e) $E_{LUMO}^{PBA} = -0.679$ eV; $E_{HOMO}^{PBA} = -10.235$ eV.

Unfortunately, such a comparison cannot be made for sulfoxides since their oxidation with $H_3O_2^+$ does not proceed.[1,5] Therefore, the oxidation of sulfoxides with PBA has been taken as the model reaction. Note that negative charge **Q(S)** of sulfoxides is consistently and remarkably smaller than that of thioethers.

Table 6. Calculated **Q(S)** and **F** Parameters and Experimental log k Values for the Oxidation of a Series of Sulfoxides with PBA dioxane/water 50/50 v/v at 25°C.[21]

#	Substrate	log k	E_{HOMO}[a]	Q(S)[b]	F[c]
18	pCH_3O-Ph-SO-CH_3	-1.137	-8.999	1.464	0.219
19	pCH_3-Ph-SO-CH_3	-1.215	-9.174	1.452	0.215
20	Ph-SO-CH_3	-1.387	-9.27	1.452	0.212
21	pCl-Ph-SO-CH_3	-1.456	-9.376	1.460	0.218
22	mCl-Ph-SO-CH_3	-1.569	-9.409	1.461	0.217
23	pNO_2-Ph-SO-CH_3	-1.796	-9.908	1.465	0.223
24	pCH_3O-Ph-SO-Ph	-1.403	-8.874	1.519	0.221
25	pCH_3-Ph-SO-Ph	-1.420	-9.195	1.506	0.217
26	Ph-SO-Ph	-1.494	-9.259	1.503	0.217
27	pCl-Ph-SO-Ph	-1.602	-9.372	1.510	0.217
28	mCl-Ph-SO-Ph	-1.678	-9.430	1.508	0.216
29	pNO_2-Ph-SO-Ph	-1.903	-9.820	1.517	0.223

a) eV. b) Atomic charge density. c) E_{LUMO}^{PBA} = -0.679 eV; E_{HOMO}^{PBA} = -10.235 eV.

DISCUSSION

Figure 2a shows that the reactivity of the series of thioethers considered and the **F** parameters are almost uncorrelated with each other. By contrast, Figure 2b indicates that the rates are correlated with **Q(S)**.

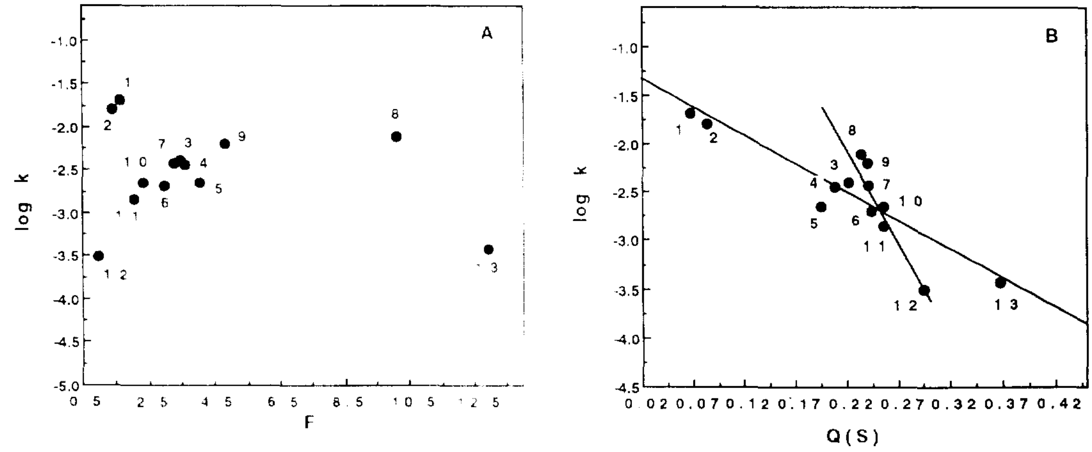


Figure 2. (a) Dependence of log k values on F in the oxidation of **1-13**, Table 4; (b) Dependence of log k values on **Q(S)** in the oxidation of **1-13**, Table 4

In particular, Figure 2b shows that two families of thioethers may be identified. The first one includes aryl-methyl thioethers, *e.g.* **7-12**, whose reactivity exhibits a dependence on **Q(S)** stronger than that of the second family which includes all the other thioethers, both dialkyl- or diaryl compounds.

If the hypothesis is considered that both **F** and **Q(S)**, though to a different extent, contribute to the reactivity of thioethers and that the rate constants of the oxidation may be calculated according to the simple expression of Eq.1,

$$\log k = aQ(S) + bF + c \tag{1}$$

it is possible to obtain by means of multilinear regression,[22] the values of a, b and c. Once that these values are available, the reliability of the hypothesis is tested by plotting the experimental log k values against the calculated ones provided by Eq. 1 in which a = -6.9, b = 0.89 and c = 6.4. The straight line of Figure 3 is obtained, which now includes all the thioethers considered.

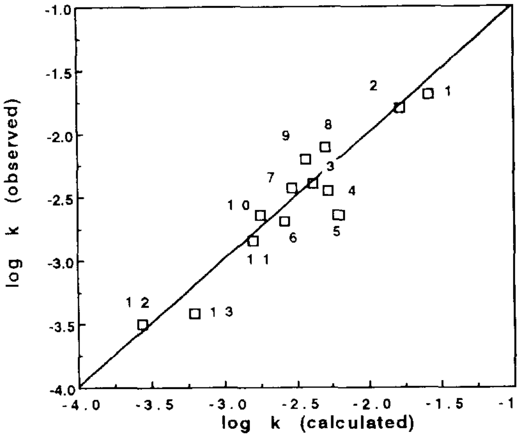


Figure 3. Plot of calculated, Equation 1, log k values against experimental, Table 4, log k values.

This result does not disagree with that provided by Figure 2a. In fact, the weight of **Q(S)**, measured by the a value, in determining the reactivity of thioether is, by far, the dominant one. However, also **F** plays a role. In particular it appears that the role of **F** in determining the oxidative behavior is larger for aryl methyl thioethers than for the other substrates.

The correlation shown in Figure 4 for the oxidation of thioethers **14-17** with PBA, though limited to only four substrates, may be taken as evidence that also with an oxidant other than $H_3O_2^+$ the reactivity of thioethers is dominated by **Q(S)**. No correlation is observed with **F**.

A completely opposite situation is found in the case of the oxidation of sulfoxides by PBA as shown in Figure 5. While no correlation exists between log k and **Q(S)**, Figure 5a, a satisfactory correlation with **F** is observed, Figure 5b.

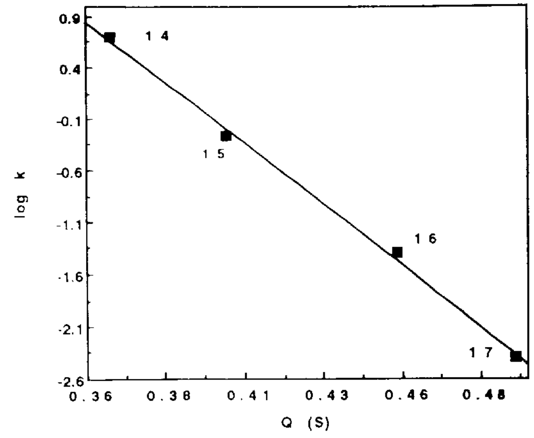


Figure 4. Dependence of log k values on Q(S) in the oxidation of **14-17**, Table 5.

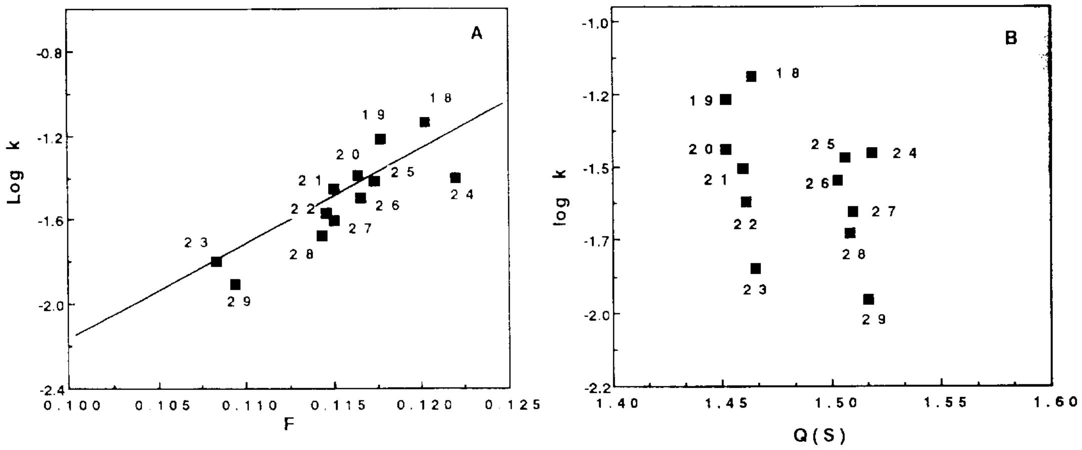


Figure 5. (a) Dependence of log k values on F in the oxidation of **18-29**, Table 6; (b) Dependence of log k values on Q(S) in the oxidation of **18-29**, Table 6.

In addition, the relevance of Q(S) in determining the reactivity of sulfoxides is almost negligible. Indeed, if Q(S) were the only parameter which determines their reactivity, one should conclude that sulfoxides are too weak nucleophiles to react with PBA.

Therefore our investigation reveals an important difference in the behavior of the two classes of substrates in the oxidation by peroxides. The reactivity of thioethers is dominated by the charge of the sulfur atom whereas that of sulfoxides is due to an efficient overlap between the HOMO of the substrate and the LUMO of the oxidant. Although it is likely that the substituents at the sulfur atom affect both the charge and the HOMO of the substrates, it is conceivable that the effect on Q(S) could be larger than that on the HOMO as it is experimentally observed.

CONCLUSIONS

The aim of this work was to provide a rationale to the experimental finding that the reactivity of sulfoxides in oxidation reactions is less affected by structural effects than that of thioethers. We have shown that the reactivity of thioethers depends almost exclusively on the charge on the sulfur atom. Such charge is rather small in sulfoxides so that, for these substrates, the interaction HOMO (sulfoxide)-LUMO(oxidant) becomes the relevant factor. This has been directly established for $H_3O_2^+$ and PBA but likely applies to other peroxidic oxidants. The reason why the charge of the sulfur atom in sulfoxides is so small is not yet clear. The presence of the oxygen atom must play a role. Our results call for some important differences in the transition state of the electrophilic oxidation of the two kinds of substrates. Thus, more sophisticated calculations are necessary.

EXPERIMENTAL SECTION

Materials: Complexes **MoO_5HMPT, MoO_5Benz** and **MoO_5PICO** were obtained and purified ($[O_{act}] \geq$ 95%, (iodimetric titre) according to published procedures.[9,11,12] All thioethers employed were commercially available products (Aldrich) purified by column chromatography (Silica-Gel, eluent CH_2Cl_2). Sulfoxides and sulfones were prepared by oxidation of the corresponding thioethers with hydrogen peroxide in the presence of catalytic amounts of $MoO_2(acac)_2$ in ethanol by using 1 or 2 equivalent of H_2O_2 respectively.[12a] All sulfoxides and sulfones were purified by column chromatography (Silica-Gel eluent light petroleum ether/ ethyl ether 50/50 v/v) and identified by their spectroscopic and MS properties.

1,2 dichloroethane (DCE) (99% Aldrich) was washed with concentrated sulfuric acid, dried over $CaCl_2$ and distilled over P_2O_5. All the other products were commercially available used without further purification.

Procedures. The oxidation of thioethers and sulfoxides with peroxo molybdenum complexes is typically carried out as follows: 5mL of DCE containing 6.0 mmol of substrate are added to a DCE solution, 10 mL, containing the oxidant (0.3 mmol) and the internal standard (eicosane) in a jacketed glass reactor maintained at the appropriate temperature. Aliquots of the reaction mixture are withdrawn at various times, quenched with $P(Ph)_3$ in excess, and the amount of the product, either sulfoxide or sulfone, determined by quantitative GC analysis on a FFAP 3% on Chromosorb WAW DMCS, 50 cm lenght, glass column. Kinetic measurements are carried out under pseudo-first-order conditions by using an excess of the substrate over the oxidant, and by monitoring the appearance of the products as a function of the time. Pseudo-first-order rate constants obtained from plots of $\ln([Product]_\infty - [Product]_t)$ vs. time, are linear up to 80% reaction.

The rho values of Table 1, referring to the oxidation of aryl-methyl thioethers with MCPBA at 0°C and with t-BuOOH/H^+ at 25°C were obtained by competitive experiments. Equal amounts (0.5 mmol) of the two substrates together with 0.08 mmol of the internal standard (eicosane) were dissolved in methanol (5 mL). To this solution the oxidant (0.01-0.013 mmol in 5mL of methanol) was added. After its disappearance (iodometric titre) the oxidation products were quantitatively analyzed by GC analysis on a FFAP 3% on Chromosorb WAW DMCS, 50 cm lenght, glass column. Duplicate runs agreed within 3-5%. The k(X)/k(H) values were obtained from the ratios of the yields of the products according to the following relationships: $[pX\text{-}C_6H_4\text{-}SO\text{-}CH_3]_\infty / [pX'\text{-}C_6H_4\text{-}SO\text{-}CH_3]_\infty = k(X) / k(X')$ and $k(X) / k(H) = k(X) / k(X') \times k(X')/k(H)$. The data used in the Hammett plots[23] for the oxidation of thioethers with MCPBA are: X = p-OCH_3, log k(X)/k(H) = 0.14, X = p-CH_3, log k(X)/k(H) = 0.05, X = m-Cl, log k(X)/k(H) = -0.35, X = p-NO_2, log k(X)/k(H) = -0.97. The data used in the Hammett plots[23] for the oxidation of thioethers with t-BuOOH/H^+ are: X = p-OCH_3, log k(X)/k(H) = 0.112, X = p-CH_3, log k(X)/k(H) = 0.05, X = m-Cl, log k(X)/k(H) = -0.34, X = p-NO_2, log k(X)/k(H) = -1.43. In both cases a σ value of 1.00 for X=NO_2 has been employed.[6,7]

Instrumentation: The GC analyses were performed on a Varian 3700 gas-chromatograph, equipped with a Varian CDS 401 integrator. ^{1}H-NMR spectra were recorded on a Bruker WP-200 spectrometer. GC-MS analyses were carried out with a Hewlett-Packard 5890 gas chromatograph, connected with a Hewlett-Packard 5970 mass selective detector, using a 15 m OV-17 capillary column, 0.25 mm i.d.

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