

Titanium(IV)–(*R,R,R*)-Tris(2-phenylethoxy)amine–Alkylperoxy Complex Mediated Oxidations: The Biphilic Nature of the Oxygen Transfer to Organic Sulfur Compounds

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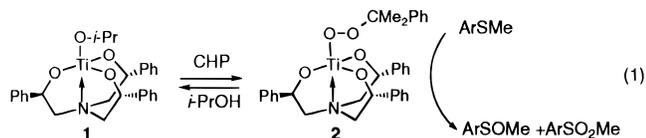
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The oxidation chemistry of transition metal peroxides is a matter of general interest ranging from biological processes^{1,2} to industrial applications.² A key point for the understanding of the oxidative mechanism is to establish the electronic nature of the oxidant.² In this respect, the selectivity of the two-step thioether oxidation, *i.e.*, the k_S/k_{SO} ratio, provides a useful probe.³ This is based on the assumption that electrophilic oxidants oxidize thioethers to sulfoxides and these to sulfones with $k_S/k_{SO} > 1$ ⁴ while nucleophilic ones oxidize exclusively sulfoxides ($k_S = 0$).⁵

Peroxo complexes of d⁰ transition metals such as Ti(IV), V(V), Mo(VI), and W(VI) are strong electrophiles^{2–4} exhibiting a remarkably high selectivity in the oxidation of dialkyl and aryl alkyl sulfides; ratios of $k_S/k_{SO} > 100$ are usually found, the sulfoxide being the only observed product.^{3a}

We have recently reported the synthesis and characterization of a new class of Ti(IV)/homochiral C₃ symmetric trialkanolamines–alkylperoxy complexes which display an atypical reactivity behavior in the enantioselective sulfoxidation of alkyl aryl sulfides (enantiomeric excess (ee) up to 84%, eq 1).⁶



The oxidation of methyl *p*-tolyl sulfide by Ti(IV)/N(CH₂-CHPhO)₃(OiPr), **1**, and cumyl hydroperoxide yields both the sulfoxide and the sulfone with comparable reaction rates ($k_S/k_{SO} = 3.2$).^{6,7} Such a low difference in reactivity, and also the

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(5) Nucleophilic oxidations of sulfoxides are usually performed by peroxyanion species, see: ref 4b. For nucleophilic metal peroxy complexes, see: Strukul, G. In *Catalysis by Metal Complexes, Catalytic Oxidations with Hydrogen Peroxide as Oxidant*; Strukul, G., Ed.; Kluwer Academic Publisher: Dordrecht, The Netherlands, 1992; Vol. 9, pp 177–222.

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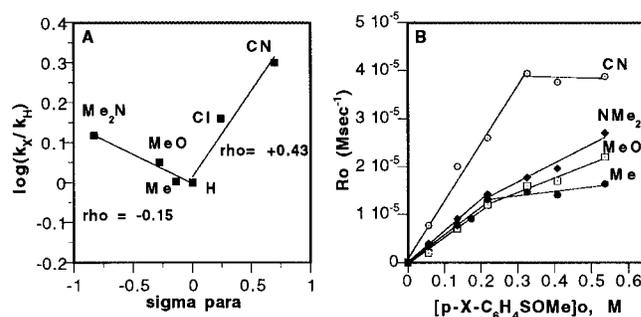


Figure 1. (a) Hammett plots for the oxidation of *p*-substituted aryl methyl sulfoxides by **2** in DCE at $-20\text{ }^\circ\text{C}$; for $\sigma \leq 0$, $\rho = -0.15$ ($r = 0.980$), for $\sigma \geq 0$, $\rho = +0.43$ ($r = 0.980$). (b) Plot of initial velocity (R_o) versus initial substrate concentration showing saturation behavior for *p*-substituted aryl methyl sulfoxides (see ref 15).

inversion of the selectivity ratio ($k_S/k_{SO} < 1$) obtained for electron-poor substrates,⁸ hardly fits within the generally accepted mechanistic scheme involving two consecutive electrophilic oxygen transfer steps to the sulfur atom.^{3,4}

In this paper we present mechanistic evidence that **2**, derived from the addition of cumylhydroperoxide to **1**, has a biphilic nature, behaving as an electrophilic oxidant toward sulfides while a nucleophilic pathway dominates the oxidation of sulfoxides. Our results, which include kinetic studies and theoretical calculations, suggest that the mechanistic modification of the reactivity is triggered by coordination of the sulfoxide to the metal center which promotes an unprecedented switch of the electronic character (“*umpolung*”) of the oxygen transfer step from electrophilic to nucleophilic.^{9,10}

A linear Hammett correlation^{11,12} with negative slope ($\rho = -0.60$) is obtained for the monooxidation of *p*-substituted thioanisoles by **2**, as expected for an electrophilic oxidation where electron-rich substrates display a high reactivity.^{4,13} On the contrary, under identical experimental conditions, the oxidation of the corresponding *p*-substituted sulfoxides to sulfones gives rise to a curved Hammett plot¹⁴ (Figure 1a) having a concave shape with a minimum for *p*-X = H ($\sigma = 0$). More specifically, two intersecting linear correlations with opposite slopes can be drawn leading to a positive $\rho = +0.43$ for electron-withdrawing substituents ($\sigma > 0$) and to a negative $\rho = -0.15$ for electron-donating ones ($\sigma < 0$).¹² Nonlinear Hammett behavior is diagnostic of reactions which occur by two concurrent pathways having opposite electronic demand, since the relative relevance of the two processes depends on the electronic nature of the substrate as determined by the substituents.¹⁴

In Figure 1b, initial rates, R_o , of the oxidation of four representative aryl methyl sulfoxides by **2** are plotted versus initial substrate concentration. In all cases, a marked deviation

(7) Independent kinetic experiments provided $R_o(S) = 4.70 \times 10^{-5} \text{ M s}^{-1}$ and $R_o(SO) = 1.47 \times 10^{-5} \text{ M s}^{-1}$; [Substrate]₀ = 0.32 M, [CumOOH] = $5.4 \times 10^{-2} \text{ M}$ in DCE at $-20\text{ }^\circ\text{C}$.

(8) In the oxidation of *p*-nitrophenyl methyl sulfide the sulfone is the major product, see: ref 6.

(9) Such a possibility has been suggested for ketone Baeyer–Villiger and aromatic sulfoxide oxidations by methylrhodium peroxide: Herrmann, W. A.; Fischer, R. V.; Correia, J. D. G. *J. Mol. Catal.* **1994**, *94*, 213. Abu-Omar, M. M.; Espenson, J. H. *Organometallics* **1996**, *15*, 3553. Brown, K. N.; Espenson, J. H. *Inorg. Chem.* **1996**, *35*, 7211. For Ti(IV)-catalyzed Baeyer–Villiger oxidations of cyclobutanones, see: Lopp, M.; Paju, A.; Kanger, T.; Pehk, T. *Tetrahedron Lett.* **1996**, *37*, 7583.

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(12) See Table S1 in the Supporting Information.

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from linearity is observed for $[\text{substrate}]_0 > 0.2 \text{ M}$, thus indicating that the Ti(IV) oxidant displays a saturation behavior with respect to substrate concentration.^{15,16}

Three main pieces of information provided by Figure 1b are worthy of discussion: (i) the saturation behavior fits with the occurrence of an intramolecular oxidation taking place by coordination of the sulfoxide to the Ti(IV) center;^{9,17} (ii) the subsequent internal oxygen transfer is likely to proceed *via* a nucleophilic pathway as indicated by the highest reactivity of the *p*-cyano-substituted sulfoxide;¹⁵ (iii) for $[\text{substrate}]_0 > 0.2 \text{ M}$ the reaction rates further increase originating a second linear regime with slopes increasing in the order $p\text{-NMe}_2 > p\text{-OMe} > p\text{-Me} > p\text{-CN}$, reaching a definite plateau value only for the latter electron-poor substrate.¹⁸

These findings suggest the concomitant presence of an electrophilic bimolecular oxidative process, contemporary and parallel to the nucleophilic intramolecular one. In the former case, the oxidation rate is characterized by a linear dependence on the substrate concentration, while in the second one, it approaches a limiting maximal value. Therefore, the electrophilic pathway becomes the dominant one in the oxidations of electron-donating substituted sulfoxides when performed in the presence of large excesses of the substrate, *i.e.*, under catalytic conditions (substrate:Ti(IV) = 100:1, Figure 1a). The latter observation predicts that a linearization of the Hammett plot could be observed by reducing the excess of the sulfoxide over the catalyst. In fact, by employing a substrate:Ti(IV) = 10:1 ratio, an appreciable improvement of the correlation ($\rho = +0.45$, $r = 0.997$) is observed.¹² Only the more activated *p*-NMe₂ and *p*-OMe derivatives now lie out of the nucleophilic correlation.¹² Alternatively, the addition of an antagonist nonoxidizable ligand, which competes with the sulfoxide for the coordination to the Ti(IV) center, is expected to draw the oxidation toward the external electrophilic pathway by depressing the intramolecular one. Indeed, the presence of an excess of hexamethylphosphoric triamide (HMPA) affects the reactivity as expected and levels off all of the k_X/k_H ratios.^{12,19}

We have used theoretical *ab initio* calculations at the RHF/3-21G(*) level²⁰ to confirm whether an intramolecular nucleophilic oxygen transfer due to the coordination of the sulfoxide to the transition metal peroxide would be a feasible process.^{9,17} In Figure 2 we report the results obtained for the model system (η^2 -methylperoxy)titanatranne (**3**)²¹ interacting with dimethylsulfoxide (DMSO). Complexation of the sulfoxide to the Ti(IV) nucleus results in the formation of peroxo species **4** with a calculated stabilization energy of 19.3 kcal mol⁻¹ relative to the separated species.²² Complex **4** displays an octahedral geometry in which DMSO occupies the apical position *trans* to the nitrogen atom and the peroxidic moiety moves in the equatorial plane, thus loosening the η^2 mode of binding. The

(15) The sulfoxide concentration was varied in the range of 0.054–0.54 M. $[\text{CumOOH}] = [\mathbf{1}] = 0.054 \text{ M}$ in DCE at -20°C . When $[p\text{-X-C}_6\text{H}_4\text{-SOMe}] \leq 0.22 \text{ M}$, $k(\text{NMe}_2) = 6.54 \times 10^{-5} \text{ M}^{-1} \text{ s}^{-1}$ ($r = 0.999$), $k(\text{MeO}) = 5.52 \times 10^{-5} \text{ M}^{-1} \text{ s}^{-1}$ ($r = 0.996$), $k(\text{Me}) = 5.72 \times 10^{-5} \text{ M}^{-1} \text{ s}^{-1}$ ($r = 0.995$), $k(\text{CN}) = 1.20 \times 10^{-4} \text{ M}^{-1} \text{ s}^{-1}$ ($r = 0.995$); when $[p\text{-XC}_6\text{H}_4\text{SOMe}] \geq 0.22 \text{ M}$, $k(\text{NMe}_2) = 3.95 \times 10^{-5} \text{ M}^{-1} \text{ s}^{-1}$ ($r = 0.981$), $k(\text{MeO}) = 3.03 \times 10^{-5} \text{ M}^{-1} \text{ s}^{-1}$ ($r = 0.988$), $k(\text{Me}) = 9.32 \times 10^{-6} \text{ M}^{-1} \text{ s}^{-1}$ ($r = 0.904$), $k(\text{CN}) \approx 0 \text{ M}^{-1} \text{ s}^{-1}$ for $[\text{Sub}]_0 > 0.33 \text{ M}$.

(16) A simple, first-order dependence was found in the methyl *p*-tolyl sulfide monooxidation by **2**, see Table S2 in the Supporting Information.

(17) To the best of our knowledge, this is the first evidence based on kinetic data of the coordination of a sulfoxide to a peroxotitanium complex. See also: Calligaris, M.; Carugo, O. *Coord. Chem. Rev.* **1996**, *153*, 83. The cationic adduct $\text{Ti}[\text{N}(\text{CH}_2\text{CHMeO})_3]\text{DMSO}^+$ ($m/z = 314$) has been identified *via* electrospray ionization mass spectrometry (ESI-MS) (Bonchio, M.; Bortolini, O.; Licini, G.; Modena, G.; Moro, S.; Nugent, W. A. Manuscript in preparation).

(18) The electron-poor sulfoxide ($\text{X} = \text{CN}$) shows saturation at higher $[\text{sub}]_0 \approx 0.30 \text{ M}$. This is consistent with its lower basicity.

(19) The rate of oxidation of methyl *p*-tolyl sulfoxide [0.54 M] by **1** [0.054 M]/CumOOH [0.054 M] in the presence of HMPA [0.54 M], in DCE at -20°C is reduced to the extent of 50% (see ref 3a). In the oxidation of aryl methyl sulfoxides, coordinatively saturated peroxometal complexes show Hammett ρ values close to zero (see ref 4d).

(20) Calculations were performed using the Spartan 4.0 program.

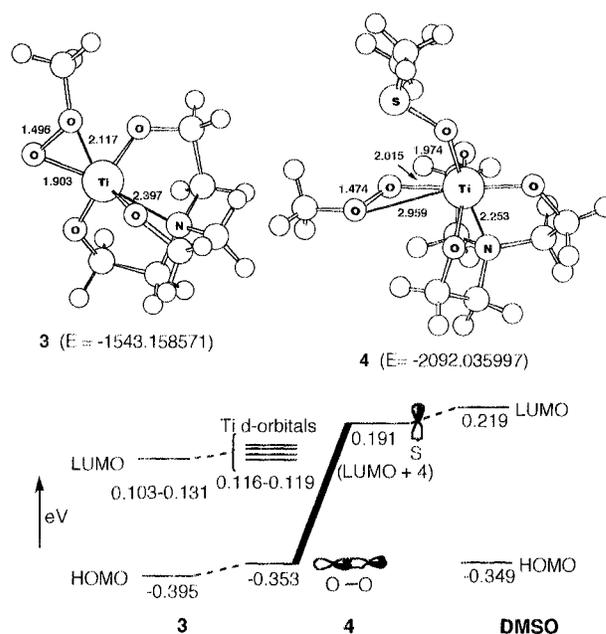


Figure 2. Optimized geometry for the model peroxo species **3** and the corresponding adduct **4** with DMSO at the RHF/3-21G(*) level, distances and energies are given respectively in angstroms and Hartrees. The frontier orbital energy diagram shows a lower HOMO–LUMO gap in species **4** favoring an intramolecular oxygen transfer pathway.

location and the energies of the frontier orbitals of **4** are consistent with the “*umpolung*” of reactivity of the peroxo functionality. The HOMO of the molecule is found at -0.353 eV and may be considered mainly the σ^* O–O orbital, while an energetically accessible LUMO²³ (0.191 eV) may be represented by the unoccupied 3p_y orbital of the sulfur atom. This implies that the electronic interaction occurring in the transition state could be described as the donation of electron density from the peroxide moiety to the sulfoxide fragment, in line with the experimental observations concerning the nucleophilic intramolecular oxygen transfer pathway.

According to this mechanistic picture, the Lewis acid metal center in the Ti(IV) peroxo complex **2** plays a multiple role in activating the hydroperoxide and the sulfoxide, both by coordination, in a template oxidative process. This behavior, in connection with the mechanism of the enantioselection of the process and, more generally, with the scope of such versatile oxidants, is currently under investigation.

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Supporting Information Available: Tables of kinetic data (1 page). See any current masthead page for ordering and Internet access instructions.

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(21) The achiral *tert*-butylperoxy analogue, whose structure has been determined by X-ray analysis, is a highly symmetric dimer at the solid state, including two heptacoordinated titanium centers. On the contrary, ¹H NMR spectrum of peroxo complexes **2** at -40°C and ESI-MS evidence are consistent with a monomeric structure of the acting species under turnover conditions. See: Bonchio, M.; Bortolini, O.; Licini, G.; Modena, G.; Moro, S.; Nugent, W. A.; Traldi, P. *Chem. Commun.* **1997**, 689. While differences between calculated and experimental geometrical parameters concerning the η^2 -peroxide moiety are expected, our findings nicely compare with previous calculations performed on other monomeric transition metals peroxides. See: Boche, G.; Möbus, K.; Harms, K.; Marsch, M. *J. Am. Chem. Soc.* **1996**, *118*, 2770 and ref 14 therein.

(22) Previous calculations have shown that the coordination of H₂S to Ti(H₂)OOH corresponds to a decrease in energy of 6 kcal mol⁻¹ relative to the separated species. Jorgensen, K. A. *J. Chem. Soc., Perkin Trans. 2* **1994**, 117.

(23) Lower energy unoccupied orbitals are located on the metal, thus exhibiting some d orbital character.