

On the Mechanism of the Oxygen Transfer to Sulfoxides by (Peroxo)[tris(hydroxyalkyl)amine]Ti^{IV} Complexes – Evidence for a Metal-Template-Assisted Process

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Oxidation of *p*-XC₆H₄SOMe (X = NC, F₃C) by (alkylperoxo)-[tris[(2*R*)-2-hydroxy-2-phenylethyl]amine]titanium (**2b**) has been shown to follow Michaelis–Menten kinetics demonstrating the occurrence of an intramolecular nucleophilic oxygen transfer to the Ti^{IV}-coordinated sulfoxide. The reac-

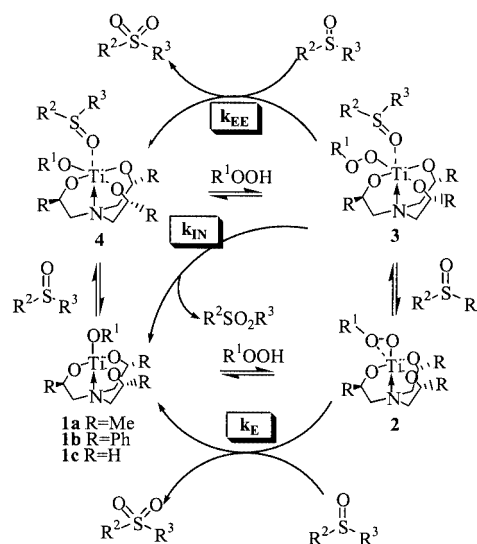
tion of the titanium(IV) precursors **1** with sulfoxides has been studied by ESI-MS techniques together with ab initio calculations.

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Introduction

We have recently reported a highly efficient enantioselective oxidation of organic sulfur compounds with (alkylperoxo)Ti^{IV} complexes containing C₃-symmetric tris(hydroxyalkyl)amines as ligands, reaching an enantiomeric excess of up to 84% and a turnover of up to 1000.^[1,2] The stereoselection of the process is based on two independent oxidations cooperating in building up the same enantiomer: namely the direct asymmetric oxidation of the sulfide to the sulfoxide and its subsequent kinetic resolution by further oxidation to the sulfone.^[3] In this reaction the title peroxides follow a biphasic mechanism.^[4] While they behave as electrophiles towards thioethers, as expected within the class of d⁰ transition metal peroxides, an atypical nucleophilic pathway with regard to sulfoxides emerges from Hammett LFER studies.^[2] For explaining the umpolung of the perox-

ide functionality^[5,6] towards sulfoxides, the occurrence of an intramolecular nucleophilic oxygen transfer step (*k*_{IN}) triggered by coordination of the substrate to the titanium center is considered (Scheme 1).^[4,7–12]



Scheme 1. Mechanism of the [C₃-tris(hydroxyalkyl)amine]Ti^{IV}-mediated oxidation of sulfoxides by alkyl hydroperoxides (R¹ = CPhMe₂, *i*Pr; R² = Me, CD₃, *n*Bu; R³ = Ar, Me, CD₃, *n*Bu)

In particular, assuming the existence of sulfoxide equilibria, the solution speciation of the titanium complexes should include precursors **1** and **4** and two diverse peroxides, namely complexes **2** and **3**. Therefore, at least three

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different modes of oxidation may be envisaged to account for the type of reactivity observed: (i) a bimolecular electrophilic oxygen transfer (k_E) by the parent peroxide;^[13] (ii) an inner-sphere nucleophilic oxygen transfer (k_{IN}) proceeding in complex **3** at the level of the Lewis acid activated sulfoxide; and (iii) a bimolecular (outer-sphere) electrophilic oxidation (k_{EE}) performed by **3** at non-ligated sulfoxides.

According to this mechanism, the electronic nature of the sulfoxide and its interaction with the titanium atom play a key role in tuning the catalytic activity of the peroxide^[2,4] and the global stereoselectivity of the process, as the over-oxidation of the sulfoxide to the sulfone is pivotal in enhancing the enantiomeric excess of the sulfoxide by kinetic resolution. We addressed this issue through a series of kinetic and mass spectrometric studies in order to verify: (i) the observation of Michaelis–Menten behavior in the oxidation of appropriate substrates demonstrating fast reversible formation of complex **3** prior to the rate-limiting oxygen transfer;^[14] and (ii) the structural modification of **1** induced by the sulfoxide binding. For this latter purpose, the use of electrospray ionization mass spectrometry (ESI-MS)^[15,16] has allowed the monitoring of the formation of DMSO adducts with the chiral titanatrane unit in solution, whose structure and properties have also been studied employing *ab initio* calculations.

Results and Discussion

The first positive evidence that Michaelis–Menten kinetic behavior might be exhibited in the reaction under study was obtained from the oxidation of different *para*-substituted aryl methyl sulfoxides catalyzed by **1b** ($R^1 = iPr$) in the presence of cumyl hydroperoxide.^[4] A set of experiments designed to evaluate the dependence of the initial rate of oxidation (R_0) on the initial substrate concentration showed a marked deviation from linearity, thus indicating a plausible saturation behavior of the Ti^{IV} peroxide with respect to the sulfoxide. In our previous work, we also realized that the oxidation of electron-rich aryl methyl sulfoxides, carrying the electron-donating substituents *p*-Me₂N, *p*-MeO, or *p*-Me, was complicated by the presence of different concurrent oxidation pathways, as the oxygen transfer in the inner-sphere (k_{IN}) was accompanied by a residual reactivity involving the non-coordinated sulfoxide (k_{EE}).^[2,4]

Therefore, in order to further examine the relationship between the electronic demand of the oxygen transfer step and substrate binding to the Ti^{IV} center, more detailed studies using Michaelis–Menten analysis have been undertaken for the oxidation of the electron-poor sulfoxides *p*-XC₆H₄SOMe (X = NC, F₃C).^[17] Figure 1 displays the initial velocities for the reaction of these substrates with **1b** ($R^1 = iPr$)/cumyl hydroperoxide plotted as a function of the initial sulfoxide concentration.^[18]

The mathematical interpolation of the experimental curves, based on the Michaelis–Menten model, provides good fitting of V_{max} and K_M values associated to the rate of the inner-sphere oxidation of the sulfoxide and to the

dissociation constant of the reactive complex **3b** ($R^1 = Me_2PhC$; $R^2 = p-XC_6H_4$; $R^3 = Me$), respectively. The comparison of V_{max} and K_M values with the Hammett substituent constant (σ),^[19,20] which establishes a relative estimate of the nucleophilic nature of the substrate, is shown in Figure 1.

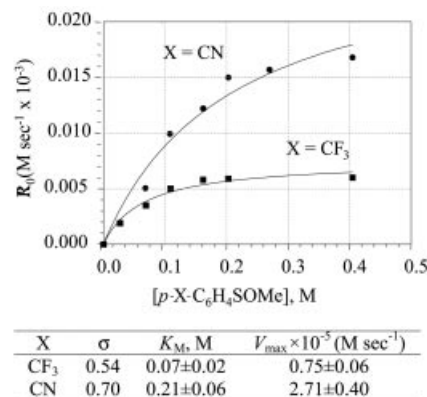


Figure 1. Experimental and calculated plot of initial velocities versus initial sulfoxide concentration for the catalytic oxidation of *p*-NC-C₆H₄-SO-Me (●) and *p*-F₃C-C₆H₄-SO-Me (■) performed by **1b** ($R^1 = iPr$) cumyl hydroperoxide (ref.^[17])

Accordingly, it is possible to confirm the nucleophilic character of the oxygen transfer step as the *p*-NC-substituted sulfoxide turns out to be the more reactive substrate. Also, the highest value of binding constant (ca. $1/K_M$) is expected for the more basic sulfoxide, as is indeed observed.

Beside the kinetic studies, further evidence concerning the coordination of sulfoxides to catalyst **1** has been obtained by ESI-MS after speciation of the titanatrane complexes in the presence of DMSO. To the best of our knowledge, there are only two reports dealing with DMSO coordination to Ti^{IV} complexes. Two X-ray structures of cationic Ti^{IV} complexes *O*-coordinated to five {as in $[TiOCl_2(DMSO)_5]^+$ } or three {as in $[Ti_4O_6(DMSO)_{12}Cl_4]^+$ } *O*-bonded DMSO molecules have been solved,^[21] and the formation of four mononuclear, octahedral $[Ti(OiPr)Cl_3(PhCHO)(DMSO)]$ complexes, which rapidly interconvert, has been detected by VT ¹H NMR experiments after addition of 2 equiv. of DMSO to $[Ti(OiPr)Cl_2(PhCHO)(\mu-Cl)_2]$.^[22,23]

The ESI-MS measurements were initially performed with complex **1a** ($R^1 = iPr$) in acidic chloroform as mobile phase and recording the positive ion mass spectra upon addition of increasing amounts of DMSO.^[24] Under the ESI-MS conditions, addition of a large excess of DMSO (> 1000 equiv.) leads to the appearance of a new peak at $m/z = 314$ (ion **I**) with a relative intensity of 6–8% of the base peak at $m/z = 724$ of the trinuclear ion $\{[TiN(CH_2CHMeO)_3]_3O^+\}$, associated to the parent catalyst **1a** ($R^1 = iPr$).^[25] The experimental cluster of **I** corresponds to the mononuclear cationic species $[TiN(CH_2CHMeO)_3(DMSO)]^+$ (Figure 2), likely derived from the neutral precursor **4a** ($R^1 = iPr$) by loss of the alkoxide ligand and revealed as such under positive ESI-MS mode.^[26]

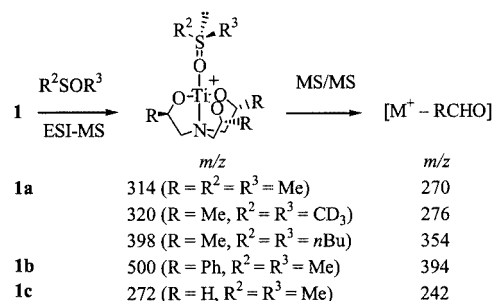


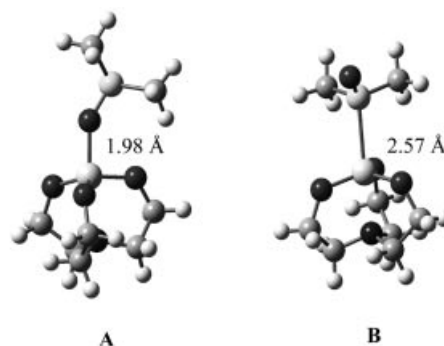
Figure 2. Data for ESI-MS experiments on complexes **1a–c** (R¹ = *i*Pr) after addition of dialkyl sulfoxides (> 1000 equiv.)^[24]

The structure of ion **I** was further confirmed by labelling experiments. In fact, addition of [D₆]DMSO produced a peak at *m/z* = 320 (ion **II**) with six extra mass units. A sulfoxide adduct was also obtained in the presence of di-*n*-butyl sulfoxide (ion **III**, *m/z* = 398). Analogous results were obtained by using complexes **1b** (R¹ = *i*Pr) and **1c** (R¹ = *i*Pr) and DMSO, leading to the observation of ions at *m/z* = 500 (**I'**) and *m/z* = 272 (**I''**), respectively (Figure 2).

Tandem MS² analysis on ions **I**, **I'**, **I''**, **II**, and **III** revealed that, upon collision-induced dissociation (CID), a common fragmentation pattern could be observed, where the major peak originates from the loss of one aldehyde molecule (M⁺ – R'CHO)^[27] while the sulfoxide remains coordinated to the titanium atom (Figure 2).^[28]

The binding mode of the sulfoxide^[29,30] to the titanatrane unit has also been addressed using the computational approach by carrying out ab initio calculations. As already reported, ab initio studies of sulfur-containing molecules are difficult and often show large basis-set effects.^[31,32] Large split-valence basis sets, such as 6-311+G(d,p) or 6-311+G(2df,2p), were often required for obtaining reliable equilibrium structures.^[33,34] Moreover, density functional theory methods have been shown recently to provide accurate equilibrium geometries and good harmonic vibrational frequencies for a number of sulfur-containing molecules and ions.^[34–36] In our computational studies, we combined Becke's hybrid functional (B3LYP) with the 6-311+G(d,p) basis set to obtain reliable equilibrium structures of sulfoxide/titanatrane complexes. The B3LYP/6-311+G(d,p) relative energies have also been compared with Hay and Wadt's effective core potentials (ECP) applied in DFT calculations. Both methods gave comparable results (Figure 3). The optimized geometry obtained for ion **I''** with the DMSO residue through *O* or *S* coordination (structures **A** and **B**, respectively) is given in Figure 3, together with the calculated energies.

Interestingly, the calculated energy difference between the *O*- and *S*-coordinated isomers shows that DMSO-*S* isomer is less stable by ca. 230 kJ·mol^{–1} with respect to the DMSO-*O* one, using both B3LYP/6-311+G(d,p) and B3LYP/LANL2DZ calculations. This supports the proposal that the Ti–S bond *trans* to the nitrogen atom of the tris-(hydroxyalkyl)amine moiety is destabilized in favor of *O*-bonding of the DMSO-*O* isomer.



	<i>E</i> _A ^a [a.u.]	<i>E</i> _B ^a [a.u.]	Δ <i>E</i> _(A–B) ^b [kJ/mol]
RHF/3-21G*	-1903.668854	-1903.572729	-252.3
RHF/6-311+G(d,p)	-1913.816557	-1913.695571	-317.6
B3LYP/6-311+G(d,p)	-1919.197259	-1919.109089	-231.4
B3LYP/LANL2DZ	-739.377341	-739.271633	-227.4

Figure 3. B3LYP/6-311+G(d,p)-optimized geometries of ion **A** and **B**; energies are reported in atomic units (1 au = 2612.9 kJ·mol^{–1}); total binding energy has been calculated as Δ*E*_(A–B) = *E*_A – *E*_B in kJ·mol^{–1}

The calculated Ti–O (DMSO) bond length is shorter (1.98 Å) in structure **A** than that experimentally found for the other Ti(DMSO) complexes by X-ray analysis (> 2.00 Å).^[21,22] Moreover, we observed a strong S–O elongation with respect to free DMSO caused by the coordination to the titanatrane cation. In fact, the S–O distance changes from an average value of 1.492 Å in free sulfoxides to that of 1.571 Å in the *O*-coordinated isomer.^[21] This result is consistent with the peculiar robustness of the sulfoxide ligand as observed in the MS² fragmentation mode of the titanatrane adducts. On the contrary, the *S*-coordinated isomer displays a very long Ti–S distance (2.573 Å), and consequently the calculated S–O distance (1.475 Å) is found to be much shorter than in free DMSO.

Conclusion

In summary, we have delineated a unique titanium template oxidation mode, which is dominant in the case of electron-poor aryl sulfoxides. The study of the stereoelectronic nature of the intermediates involved is warranted for expanding the reaction scope and understanding the mechanistic basis for enantioselectivity in the kinetic resolution. Towards this latter aim, a detailed examination of the binding and oxidation kinetic of enantiopure sulfoxides will be pursued in the future.

Experimental Section

General Remarks: ¹H NMR spectra were recorded with a 200- or 250-MHz instrument. Kinetic runs were monitored by quantitative GC analysis with an SE-30 15 m × 0.25 mm (i.d.) capillary column, using 4-methylbenzophenone as internal standard. ESI-MS and ¹H NMR experiments were performed as already reported.^[15] HPLC

grade solvents were generally used. [D₆]DMSO (Fluka) was used in the labelling experiments. 1,2-Dichloroethane (DCE) was washed three times with 10% concentrated H₂SO₄ and several times with water until pH = 7, dried overnight with CaCl₂, distilled from P₂O₅, and stored over molecular sieves. Cumyl hydroperoxide (80%, Fluka) was stored over molecular sieves at 0 °C. Titanium(IV) isopropoxide (Aldrich) was distilled under vacuum (b.p. 60–63 °C/0.1 Torr). Racemic methyl *p*-(trifluoromethyl)phenyl sulfoxide^[37] and *p*-cyanophenyl methyl sulfoxide^[38] were prepared by oxidation of the corresponding sulfides.^[39] Enantiopure tris(hydroxyalkyl)amines **1a,b** were prepared according to the literature procedure.^[40] Tris(2-hydroxyethyl)amine (Aldrich) was distilled under reduced pressure (b.p. 190–193 °C/5 Torr).

Computational Study: All calculations were carried out using Gaussian 98 (rev. A7),^[41] with an SGI O2 R10000 workstation. Hartree–Fock (HF) and density functional theory (DFT) calculations were run with 3-21G(*) or 6-311++ basis sets.^[42–45] Moreover, density functional theory calculations were carried out with Becke's hybrid 3-parameter functional with Lee–Yang–Parr non-local correlation (B3LYP).^[41,46] These calculations had to be run with the (99,302) numerical integration grid^[41] and with full accuracy at all stages in order to achieve SCF convergence. Hay and Wadt's effective core potentials (ECP)^[47,48] for titanium were used in DFT calculations. However, Ti^{IV} compounds have a 3d⁰ configuration, and therefore ECPs incorporating up to the outermost core orbitals (3s²3p⁶) will not give satisfactory results. Accordingly, the ECPs developed specifically for these cases^[47,48] (i.e., explicitly treating 3s²3p⁶ electrons) were used; this basis set is denoted as LANL2DZ in Gaussian98. The calculated total energies, and the complete geometries (Cartesian atomic coordinates) are given as Supporting Information.

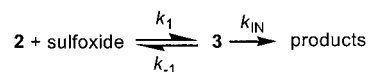
General Conditions for the Kinetic Experiments: In a 3-mL volumetric flask, complex **1b** (0.08 mmol), the internal standard (0.070 mmol), and an appropriate amount of substrate (0.027–0.405 M, see Figure 1) were dissolved in DCE. After cooling to –20 °C, cumyl hydroperoxide (0.015 mL, 0.081 mmol) was added under magnetic stirring. At increasing reaction times, samples of the mixture (0.025 mL) were taken out, immediately quenched with an excess of di-*n*-butyl sulfide, and analyzed by quantitative GC analysis. Values of initial rates of the oxidation (*R*₀) (Figure 1) were determined on the basis of the following equation: *R*₀ = *k*[Sub]₀[CumOOH]₀, where *k* is derived from the kinetic data according to the second-order integrated law.

Acknowledgments

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- [18] In the case under study, parallel to enzyme kinetics,^[14] the simple Michaelis–Menten equation can be applied (see general scheme at the end of the reference) where *R*₀ = *V*_{max} × [*p*-XC₆H₄SOME]₀/(*K*_M + [*p*-XC₆H₄SOME]₀), *V*_{max} = *k*_{IN} × [**2**]₀, *K*_M = (*k*_{–1} + *k*_{IN})/*k*₁. *V*_{max} and *K*_M values have been determined by least-square fitting of the experimental data (Scientist™-MicroMath® Scientific Software, P. O. Box 21550, Salt Lake City, Utah 84121, USA, **1995**), according to the above described model.



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- [24] ESI-MS experiments were performed under the same reported experimental conditions.^[16]
- [25] Under ESI-MS conditions, catalyst **1** is expected to yield the trinuclear oxonium ion {[TiN(CH₂CHMeO)₃]³⁺}.^[16]
- [26] The hexacoordinated complex [TiN(CH₂CHPhO)₃(MeO)-(DMSO)Na]⁺, carrying both alkoxide and sulfoxide residues, could be detected by ESI-MS at *m/z* = 555.
- [27] The loss of aldehyde, derived from decomposition at the tetradentate trialkoxy ligand, was already observed in MS² experiments performed on [tris(hydroxyalkyl)amine]Ti^{IV} protonated complexes, and it is indicative of the coordination of the tris-(hydroxyalkyl)amine to the metal center.^[16] In fact, upon CID, the free protonated tris(hydroxyalkyl)amines lose one, two or three water molecules.
- [28] Only in the case of ion **III** another fragment ion [*m/z* = 342

- (M⁺ – 56)], corresponding to the loss of a molecule of butene from the alkyl chain of the di-*n*-butyl sulfoxide, was detected. Moreover, in all the spectra another peak at *m/z* = 254 (MS² of ions I, I', and I''), *m/z* = 440 (MS² of ion II), and *m/z* = 121 (MS² of ion III) at much lower intensity (12–27%), was detected. These ions correspond to the formal adducts of water to the titanatrane cations [TiN(CH₂CHRO)₃OH₂]⁺ and very likely they originate from ion-molecule exchange processes occurring with adventitious water molecules present inside the ion trap. Such a hypothesis was proved by running MS² experiments on ion I with methanol as mobile phase. As expected, an additional peak at *m/z* = 268, corresponding to the [TiN(CH₂CHMeO)₃MeOH]⁺ cation, was observed.
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