Use of electrospray ionization mass spectrometry to characterize chiral reactive intermediates in a titanium alkoxide mediated sulfoxidation reaction

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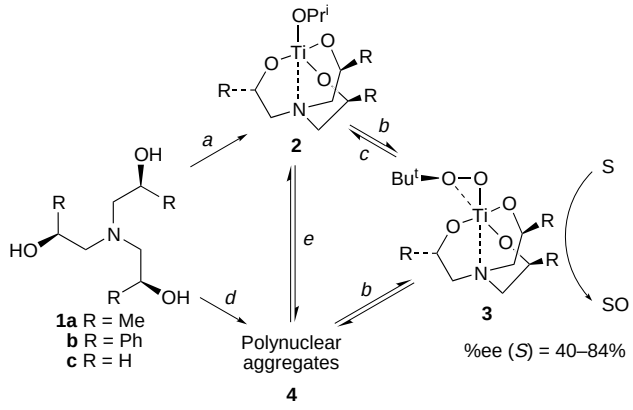
The ESIMS technique, combined with ^{1}H NMR evidence, provides a precise inventory of the catalytic Ti^{IV} precursors and the characterization of the reactive peroxometal complex involved in enantioselective sulfoxidation employing the Ti^{IV}–homochiral trialkanolamine–alkylhydroperoxide system.

In the field of titanium(iv) alkoxide mediated homogeneous enantioselective oxidation using alkyl hydroperoxides as oxygen donors,[1] excellent results have been obtained in the asymmetric epoxidation of allylic alcohols[2] and in the sulfoxidation of sulfur containing compounds.[3] Characterization of the active catalysts in many of these reactions is complicated by the tendency of the alkoxides to form mixtures of polynuclear species equilibrating in solution.[4] In all cases a chiral titanium η^2-alkylperoxo species has been postulated as the reactive intermediate.[5] In this respect, the solid-state structure of the achiral η^2-*tert*-butylperoxo titanatrane dimer, in which the peroxide moiety has an η^2 arrangement, is so far the only characterized titanium(iv) peroxo complex.[6]

We recently developed a highly robust titanium alkoxide catalyst[7] for the enantioselective oxidation of organic sulfides to sulfoxides.[8] Catalyst **2** is generated *in situ* by addition of a stoichiometric amount of the homochiral trialkanolamine **1**, to a $CHCl_3$ solution of $Ti(OPr^i)_4$ (Scheme 1, pathway *a*).[7,8]

Described here is the novel observation that the catalytically active polynuclear titanium(iv)-based species **4** forms from the interaction of **2** and excess of ligand **1** (Scheme 1, pathway *e*). Our results include electrospray ionization mass spectrometric (ESIMS) studies[9]† which, together with ^{1}H NMR evidence, allow (*i*) identification of the components in **4**, (*ii*) delineation of their reactivity with oxygen nucleophiles and (*iii*) characterization of the monomeric chiral titanium(iv) peroxo species **3** arising from the interaction of **2** and **4** with Bu^{t}OOH (Scheme 1, pathway *b*).



Scheme 1 *Reagents and conditions*: *a*, stoichiometric $Ti(OPr^i)_4$, $CHCl_3$, 20 °C; *b*, Bu^{t}OOH; *c*, Pr^{i}OH; *d*, $Ti(OPr^i)_4$ (0.75 equiv.), CH_2Cl_2, 20 °C, followed by solvent removal; *e*, excess of **1**

^{1}H NMR studies in $CDCl_3$ indicate that when a precise 1 : 1 ligand : titanium ratio is employed the discrete monomeric complex **2** is formed.‡ Further addition of **1** causes the progressive disappearance of the resonances of the apical isopropoxy ligand in **2** and the synchronous appearance of two broader signals indicating the formation of a mixture of aggregates.§ The room-temperature ^{1}H NMR spectrum of **4b** shows broad resonances and the absence of isopropoxy signals.¶ At lower temperature (−20 °C) the system freezes out and a complicated spectrum of sharper signals is obtained, consistent with the presence of a steady composition of aggregates. In contrast, at 60 °C only three broad singlets are observed, each corresponding to a different set of protons. However, regardless of the amount of **1** in excess, addition of Bu^{t}OOH to the system always restores a simple ^{1}H NMR spectrum consistent with the mononuclear *tert*-butylperoxotitanium species **3**.[8]

ESIMS analysis, which has already been applied successfully to the characterization of various polynuclear complexes,[9,10] allowed us to identify the diverse species present in solution.

The positive ion ESI mass spectrum of preformed catalyst **4a** using methanol as the mobile phase is shown in Fig. 1.

The most significant ions, whose structures have been assigned on the basis of MS/MS analysis and comparison between the theoretical and experimental cluster ion peaks, are indicated. The overall ESIMS spectrum of Fig. 1 shows the molecular peaks of the species originated in the equilibrium reactions involving the titanium centre and the oxygen nucleophiles available in solution, *i.e.* trialkanolamine **1a**, methanol and water, present in traces in the mobile phase. Interaction of **4a** with water, gives rise to ions **I** (*m/z* 254), **IV** (*m/z* 489) and **VII** (*m/z* 724) which are mono-, di- and tri-nuclear titanium containing species, respectively. Those ions show incorporation of ^{18}O ($\geqslant$65%) when $H_2{}^{18}O$ is added to the mobile phase. The reaction of **4a** with methanol is responsible for the appearance of ions **II** (*m/z* 268) and **V** (*m/z* 503), whose mass peaks show an increment of four and three mass units, respectively, when CD_3OD is used as the mobile phase. Multiple interaction of **1a** with Ti^{IV} [11] affords species **VIII** (*m/z* 897) and the lower homologue ions **VI** (*m/z* 662) and **III** (*m/z* 427).‖ These latter ions were also observed in the positive-ion ESI mass spectrum collected for an acidic chloroform solution of **4a** *i.e.* under conditions similar to those employed in catalytic sulfoxidation.[8] Complexes **4b** and **4c** give analogous ESI mass spectra where the same reactivity pattern can be recognized.**

Additional support for the NMR results comes from the characterization of the protonated titanium(iv) peroxo complex **3a** (*m/z* 326), achieved by ESIMS[13] when an excess of *tert*-butylhydroperoxide was added to the mobile phase containing **4a**. The structure of the cluster ion peaks and the MS/MS analysis of the 326 mass peak (Fig. 2) are consistent with the

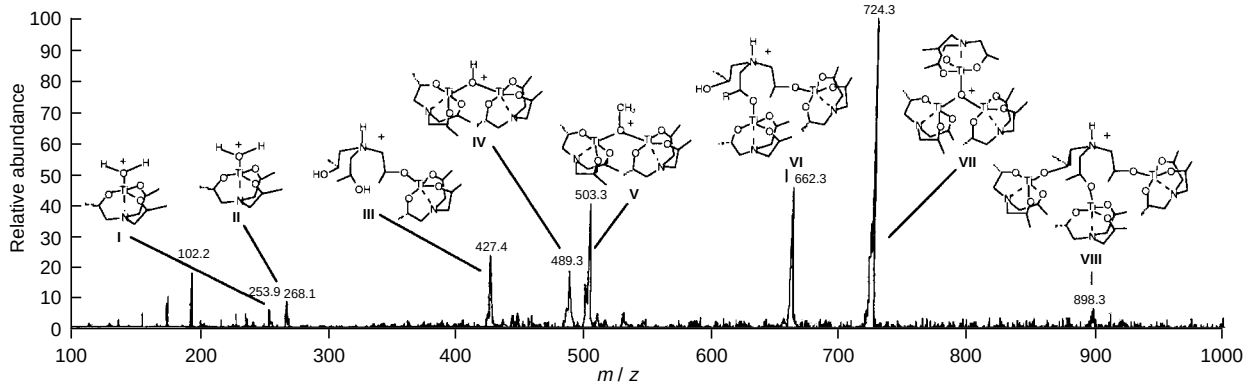


Fig. 1 ESI mass spectrum of complex **2a** with peak assignments indicated

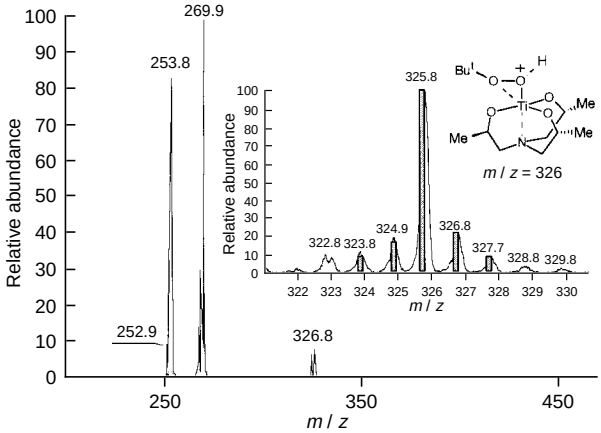


Fig. 2 MS/MS fragment ions of the *m/z* 326 peak after collision induced dissociation. Calculated and observed isotope distribution patterns are shown in the inset.

monomeric character of the peroxometal complex **3a**.[8]†† Its fragmentation pattern (CID) occurs through the breaking of the O–Bu^t bond (*m/z* 270, $M^+ - C_4H_8$) and of the peroxidic O–O bond yielding the water adduct, ion **I** (*m/z* 254, $M^+ - C_4H_8O$). The latter mode of decomposition is consistent with the proposed O–O bond scission during catalytic sulfoxidation.

ESIMS allowed also the characterization of the achiral peroxometal complex **3c** (*m/z* 284),‡‡ which, under the conditions employed, appears as a monomeric species.[6]

In conclusion, ESIMS allowed us to confirm the identity of the chiral peroxidic intermediate **3a** and that of the achiral analogue **3c**, both of which are monomeric complexes. Moreover, titanium(iv) aggregates with ligand-controlled architecture were identified, which react with *tert*-butylhydroperoxide yielding **3**. The fact that several highly labile and reactive metal complexes survive the conditions of the electrospray experiments bodes well for the extension of this approach to other early transition-metal alkoxide catalysts.

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Footnotes

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† *Standard conditions*: Finnigan MAT LCQ ESI mass spectrometer with upper mass limit of *m/z ca*. 1850; direct infusion *via* a syringe pump; sample concentration = 0.5 μmol ml^{-1}; flow rate = 8 μl min^{-1}; nebulizing gas, N_2; spray voltage = 4 kV; capillary voltage = 25 V; capillary temperature = 80 °C.

‡ For complex (*S*,*S*,*S*)-**2a** see ref. 7; (*R*,*R*,*R*)-**2b**: ^{1}H NMR ($CDCl_3$) δ 1.43 (6 H, dd, *J* 6.1, 1.7 Hz), 3.25 (3 H, dd, 12.4, 4.4 Hz), 3.32 (3 H, dd, 12.4, 10.5 Hz), 4.74 (1 H, spt, *J* 6.1 Hz), 5.87 (3 H, dd, *J* 10.5, 4.4 Hz), 7.24–7.39 (15 H, m).

§ For complex **2b** resonances appear at δ 3.54 (t, CH_2, *J* 11.3 Hz) and 6.02 (d, CH, *J* 11.3 Hz). A slight excess of ligand **1** strongly promotes the displacement of the isopropoxide group. When 2 equiv. of ligand **1a** are added to the *in situ* formed complex **2a**, 80% of the isopropoxide ligand is displaced.

¶ In the enantioselective sulfoxidation protocol, the active titanium(iv) peroxo complex **3** is normally generated from **4**, due to the higher reactivity (absence of Pr^{i}OH) and to the practical advantage in handling. **4b**: ^{1}H NMR ($CDCl_3$) δ, 3.29 (6 H, br), 5.95 (3 H, br), 7.16–7.51 (15 H, m).

‖ Selected MS/MS spectra and isotopic distributions: **III**: *m/z* (%) 427 (M^+, 100), 409 ($M^+ - H_2O$, 10), 383 (M^+ − MeCHO, 22), 236 (M^+ − **1a**, 16), 174 (**1a** − H_2O, 80). Isotopic distribution (%) (exptl., theory), 425 (11, 11), 426 (12, 12), 427 (100, 100), 428 (23, 25), 429 (9, 14). **VI**: *m/z* (%) 662 (M^+, 29), 644 ($M^+ - H_2O$, 3), 489 (**IV**, 13), 409 [$M^+ - Ti(CH_2CHMeO)_3 - OH$, 100]. Isotopic distribution (%) (exptl., theory): 660 (21, 17), 661 (24, 24), 662 (100, 100), 663 (45, 38), 664 (25, 21), 665 (6, 5). **VIII**: *m/z* (%): 897 (M^+, 8), 644 [$M^+ - Ti(CH_2CHMeO)_3 - OH$, 18], 489 ($M^+$, **IV**, 4), 409 [$M^+ - 2Ti(CH_2CHMeO)_3 - O$, 100]. Isotopic distribution (%) (exptl., theory): 895 (18, 16), 896 (29, 30), 897 (100, 100), 898 (64, 60), 899 (35, 33), 900 (13, 13).

** **4b**: 440 (**I′**), 454 (**II′**), 799 (**III′**), 861 (**IV′**), 875 (**V′**), 1220 (**VI′**), 1282 (**VII′**), 1641 (**VIII′**), **4c**: 212 (**I″**), 226 (**II″**), 343 (**III″**), 473 (**V″**), 536 (**VI″**), 729 (**VIII″**).

†† Isotopic distribution (%): 323 (11), 324 (12), 325 (19), 326 (100), 327 (22), 328 (9).

‡‡ CID for peak at *m/z* 284, 228 ($M^+ - C_4H_8$), 212 (**I″**).

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