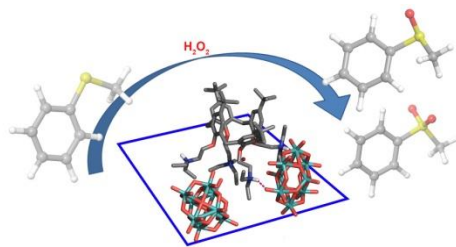


Polyoxomolybdate-Calix[4]arene Hybrid: a Catalyst for Sulfoxidation Reactions with Hydrogen Peroxide

Sara Meninno,[‡] Alessandro Parrella,[‡] Giovanna Brancatelli,[§] Silvano Geremia,[§] Carmine Gaeta,[‡] Carmen Talotta,[‡] Placido Neri,^{*,‡} and Alessandra Lattanzi^{*,‡}

[‡]Dipartimento di Chimica e Biologia “A. Zambelli”, Università di Salerno, Via Giovanni Paolo II 132, I-84084 Fisciano (Salerno), Italy, and [§]Centro di Eccellenza in Biocristallografia, Dipartimento di Scienze Chimiche e Farmaceutiche, Università di Trieste, via L. Giorgieri 1, I-34127 Trieste, Italy

Supporting Information Placeholder



ABSTRACT: An easily accessible polyoxomolybdate-calix[4]arene hybrid **1** has been synthesized and applied as heterogeneous catalyst in the sulfoxidation of thioethers to sulfoxides and to sulfones under strictly stoichiometric amounts of 30% H₂O₂ in CH₃CN as the solvent. This study represents the first promising example of successful employment of calixarenes-POM hybrid materials in the area of catalytic oxidations.

In the last decades research interest in calixarene¹ chemistry has increased dramatically thanks to their applications in several fields related to supramolecular chemistry, which include molecular recognition,² self-assembling systems,³ mechanically interlocked molecules,⁴ and nanoporous materials.⁵ Their use in catalysis has been also explored,⁶ where the most promising approach arises from the association of calixarene derivatives with single or multiple metal centers. Thus, our group has showed that Ti(IV)/calixarene complexes,⁷ are efficient catalysts in aldol reactions, while Mandolini and coworkers⁸ reported metallo-calixarene derivatives which showed phosphodiesterase activity. Recently, a hybrid inorganic-organic polyoxometalate/calixarene material has been proposed, which showed catalytic activity in the desulfurization process.⁹

The development of selective and environmentally friendly oxidative systems is a vast and relevant area of investigation in organic synthesis.¹⁰ The sulfoxidation of thioethers either to sulfoxides and to sulfones is the most straightforward approach to these compounds, which are of particular interest due to their notable applications in the pharmaceutical industry, as chiral auxiliaries in asymmetric synthesis, in the desulfurization of fuel oil, and in the polymer industry.¹¹ Indeed, chiral non-racemic sulfoxides are relevant pharmacophores of widely used drugs such as omeprazole and sulmazole.¹² Several stoichiometric common oxidants can be applied for sulfide oxidations,^{11a} although they are not atom-efficient and generate undesirable waste.

In consideration of the demanding environmental concerns, ever-increasing efforts have been paid to develop catalytic metal-based or metal-free cost effective systems^{11b,13} with favorable environmental impact: i) by using benign and highly atom-efficient oxidants such as hydrogen peroxide and molecular oxygen in harmless solvents at room temperature; ii) by supporting the metal catalyst for recycling. A plethora of metal complex-catalyzed sulfide oxidations employing low cost and environmentally friendly aqueous H₂O₂ are known.^{11,14} Nevertheless, only a handful of procedures can be considered really mild, green and effective, reaching either satisfactory TON/TOF levels and high chemoselectivity when working under strictly stoichiometric amount of aqueous H₂O₂ at room temperature.

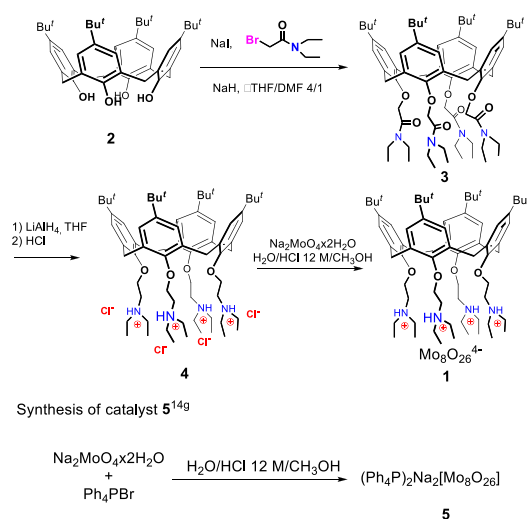
Polyoxometalates (POMs) are transition metal-oxygen nanosize anionic clusters of W, V, Mo, Ti, Fe, Co, and Nb showing interesting Brønsted acid and redox properties amenable of several applications in catalysis, material and medicine science, magnetism, and photochemistry.¹⁵ Their thermal and oxidative redox stability attracted a lot of interest as competitive candidates with respect to classical metal-complexes in oxidation processes.¹⁶ Being inorganic materials, they are mostly soluble in polar solvents. One approach to improve the scarce mass transfer between POMs and organic substrates is based on a counterion exchange with cation surfactants, giving inorganic-organic functionalised hybrids.¹⁷

Mizuno and co-workers investigated a variety of POM-catalyzed oxidations using stoichiometric amounts of H₂O₂ as the oxidant achieving a remarkable efficiency.¹⁸ In contrast to

tungsten-based POMs, only a few examples of cheap and readily available molybdenum-containing counterparts have been reported as catalysts in oxidations.¹⁹ These and other studies,¹⁸ highlighted the importance of the cation carbon chain lengths, hydrogen bonding, nature of the heteroatom charged species and anionic cluster in modulating POMs activity.

Being interested in the development of stereo- and chemoselective methodologies for the sulfoxidation of thioethers,²⁰ in this contribution we decided to address the issue of developing an effective and convenient system by using a calix[4]arene tetra-ammonium octamolybdate hybrid material **1** and by evaluating its activity in the sulfoxidation of thioethers using stoichiometric loading of 30% H₂O₂ as the oxidant (Scheme 1).

Scheme 1. Synthesis of Catalysts **1** and **5**



According to the relevant literature,^{19c,f} we envisaged an octamolybdate as the most promising anionic cluster. The designed POM-calixarene **1**, bearing a well-organized architecture of four trialkylammonium units anchored within the macrocyclic scaffold, might have potentially good catalytic properties.

The synthesis of hybrid **1** is presented in Scheme 1. *p*-*tert*-Butylcalix[4]arene **2** was exhaustively alkylated with α -bromo-*N,N*-diethylacetamide,²¹ to give derivative **3**.²² Reduction with LiAlH₄ gave the corresponding tetra-amine derivative which was directly treated with HCl leading to tetra-ammonium calix[4]arene derivative **4**. Finally, a solution of **4** in methanol was added to an aqueous solution of Na₂MoO₄·2H₂O acidified with 12 M aqueous HCl (Scheme 1). The solid obtained was then crystallized to give POM-calixarene **1** in crystalline form. For comparative purpose, POM derivative **5** was also synthesized by following a literature procedure.^{15g} Surprisingly, the X-ray structure of POM-calixarene **1** showed the presence of both α and β isomers²³ of the octamolybdate Mo₈O₂₆⁴⁻ cluster (Figure 1).²²

A preliminary investigation on the oxidation of model phenyl methyl sulfide with catalysts **1** and **5** at 0.1 mol% loading, carried out in CD₃CN and CD₃OD using 30% H₂O₂ (1.0 equiv) at room temperature, showed POM-calixarene **1** to be a highly active catalyst in CD₃CN with respect to CD₃OD achieving a very good conversion to the sulfoxide and low amount of sulfone (< 10%) detected after 30 minutes (Figure 2).²⁴

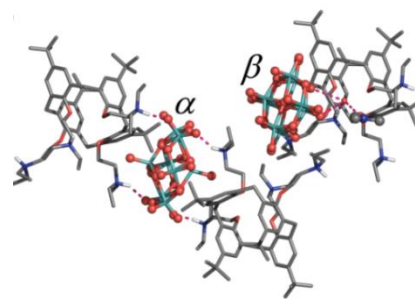


Figure 1. Solid state assembly of POM/calix[4]arene **1** with the fundamental interactions of the α - and β -[Mo₈O₂₆]⁴⁻ isomeric clusters.

Moreover, we were pleased to observe that the activity of hybrid **1** is dramatically enhanced by the presence of the calix[4]arene tetra-ammonium unit, when compared to the conversion observed when using catalyst **5**. This result might be rationalized by invoking favorable homophilic interactions⁹ displayed by the large calix[4]arene tetra-ammonium portion of the hybrid with the organic sulfide and thus improving the mass transfer between the inorganic POM and the organic substrate^{17,18} and helping its oxidation at the interface where peroxy-Mo(VI) species are formed.²² Further reduction of the loading to 0.05 mol % did not modify the reaction outcome.²²

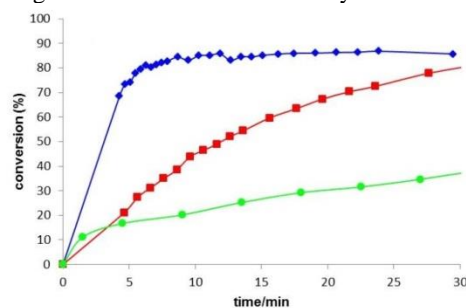


Figure 2. Reaction progress profile for the oxidation of phenyl methyl sulfide at room temperature: H₂O₂ (1.0 equiv), **1** (0.1 mol %) at [sulfide] = 0.5 M. \blacklozenge : in CD₃CN; \blacksquare : in CD₃OD; \bullet : using **5** (0.1 mol %) in CD₃CN.

With the optimized conditions in hand, the scope of the oxidation was studied, using 0.05 mol % of catalyst **1** under stoichiometric amount of H₂O₂ (Table 1). Differently substituted phenyl methyl sulfides were rapidly oxidized in fairly good to high yield and chemoselectivity to the corresponding sulfoxides (entries 1-7). Interestingly, more hindered *ortho*-substituted derivatives were isolated with the highest yield and the best chemoselectivity (entries 4 and 6). The presence of sterically demanding and functionalized substituents in the sulfide was well-tolerated (entries 8-12) including groups that could suffer easy oxidation such as formyl, hydroxyl, benzyl, and C=C bond (entries 7, 10, 11, and 14). The oxidation of heterocyclic sulfide 2-(methylthio)benzimidazole proceeded smoothly (entry 13), showing the suitability to access pharmaceutically important sulfoxides such as precursors of the proton pump inhibitors¹² under particularly mild oxidative conditions. Acyclic and cyclic dialkyl sulfoxides were easily obtained in high yield (entries 14-16). Finally, we thought useful to explore the diastereocontrol of this system in the oxidation of 2-phenyl-1,3-dithiane and dithiolane. Interestingly, the corresponding *trans* mono-sulfoxides were isolated in high yield,

chemoselectivity and excellent level of diastereoselectivity (entries 17 and 18).

Table 1. Sulfoxidation of Thioethers to Sulfoxide with 30% H₂O₂ Catalysed by POM-Calixarene Hybrid **1a**^a

$$\text{R}^1\text{S-R}^2 \xrightarrow[\text{CH}_3\text{CN, rt, 40 min}]{\text{1 (0.05 mol \%), 30\% H}_2\text{O}_2 \text{ (1.0 equiv)}} \text{R}^1\text{S(=O)-R}^2 + \text{R}^1\text{S(=O)}_2\text{-R}^2$$

entry	sulfide	yield (%) ^b	selectivity ^c
1		81	91
2		84	89
3		88	90
4		92	98
5		78	82
6		91	99
7		78	85
8		83	86
9 ^d		80	86
10 ^d		78	80
11		86	90
12		83	95
13 ^e		78	92
14		83	88
15 ^f		87	93
16 ^g		93	93
17		90 (t/c > 99/1) ^h	92
18		86 (t/c 95/5) ^h	94

^aReaction conditions: sulfide (0.2 mmol), H₂O₂ (0.2 mmol), **1** (0.0001 mmol), in CH₃CN (400 μL) stirred at room temperature for 40 minutes. ^bIsolated yields. ^cCalculated as SO/(SO+SO₂). ^dCarried out for 60 min. ^eCarried out for 105 min. ^fCarried out for 90 min. ^gCarried out for 75 min. ^hThe *trans/cis* ratio determined by ¹H NMR analysis.

It is worth pointing out that the TON (up to 1880) and TOF (2806 h⁻¹) calculated for entry 4 are very encouraging, placing catalyst hybrid **1**/H₂O₂ among the best performing POMs/H₂O₂ systems.^{18,19,25}

On the basis of the gratifying results reported in Table 1, we studied this system in the oxidation of sulfides to sulfones.

The reactions were carried out at 50 °C in CH₃CN using the same catalyst loading and a stoichiometric amount of 30% H₂O₂ (2.0 equiv) (Table 2). Typical time-dependent relative ratios of thioether, sulfoxide, and sulfone are reported in Figure S4.

Table 2. Sulfoxidation of Thioethers to Sulfones with 30% H₂O₂ Catalysed by POM-Calixarene **1a**^a

$$\text{R}^1\text{S-R}^2 \xrightarrow[\text{CH}_3\text{CN, 50 }^\circ\text{C}]{\text{1 (0.05 mol \%), 30\% H}_2\text{O}_2 \text{ (2.0 equiv)}} \text{R}^1\text{S(=O)}_2\text{-R}^2$$

entry	sulfide	time (min)	yield (%) ^b
1		60	98
2		110	97
3		60	98
4		180	98
5 ^c		105	95
6		130	97
7		170	96
8		100	98
9		180	90
10 ^d		180	77

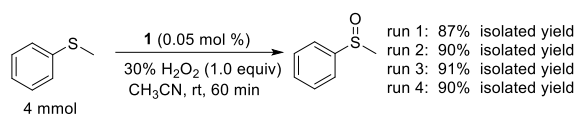
^aReaction conditions: sulfide (0.2 mmol), H₂O₂ (0.4 mmol), **1** (0.0001 mmol), in CH₃CN (400 μL) stirred at 50 °C. ^bIsolated yields. ^cCarried out with 0.1 mol % of catalyst **1**. ^dCarried out with 0.2 mol % of catalyst **1** at 60 °C.

As a general remark, the oxidation of aryl alkyl, diphenyl, and dialkyl sulfides proceeded in short reaction times to give sulfones in excellent yields. Moreover, the oxidation of sensitive sulfides occurred with complete chemoselectivity (entries 6-8). The oxidation of model benzothiophene, a refractory sulfide, afforded the corresponding sulfone in 77% yield after a relatively short reaction time using only 0.2 mol % loading of the catalyst (entry 10). This is a promising example of an oxidative desulfurization, a process applied to remove undesired aromatic sulfur containing compounds present in fuels.^{26,9}

Exploratory experiments on the reusability of catalyst **1** in a model oxidation working on a large scale of phenyl methyl sulfide under previously optimized conditions gave a positive indication on the potential reusability of hybrid catalyst **1** (Scheme 2). Interestingly, the activity was maintained after four cycles.

In summary, we reported the first effective catalytic application of a calix[4]arene based POM in sulfoxidation. The designed calix[4]arene tetra-ammonium octamolybdate **1** has been successfully used to develop environmentally friendly sulfoxidation of thioethers either to sulfoxides or to sulfones with hydrogen peroxide.

Scheme 2. Reusability of Catalyst 1 in the Oxidation of Phenyl Methyl Sulfide



The attractive features of this system are: i) high catalytic activity at low catalyst loading, mild reaction conditions and wide substrate scope, under strictly stoichiometric amount of H_2O_2 ; ii) high chemoselectivity, tolerance of sensitive groups present in the sulfide and suitability for recycling. We expect this study will pave the way for further investigations on calixarene-based POM in catalytic oxidations, taking into account the structural variety of the readily available racemic or chiral calixarene macrocycles and the potential involvement of their supramolecular properties in substrate recognition.

ASSOCIATED CONTENT

Supporting Information. Details of experimental procedures, characterization of the catalyst, tables of crystal data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

AUTHOR INFORMATION

Corresponding Author

*E-mail: lattanzi@unisa.it.

*E-mail: neri@unisa.it.

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