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

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S *Supporting Information*

ABSTRACT: An easily accessible polyoxomolybdate−calix[4]arene hybrid **1** has been synthesized and applied as a heterogeneous catalyst in the sulfoxidation of thioethers to sulfoxides and to sulfones under strictly stoichiometric amounts of 30% H_2O_2 in CH_3CN as the solvent. This study represents the first promising example of successful employment of calixarenes−polyoxometalate (POM) hybrid materials in the area of catalytic oxidations.
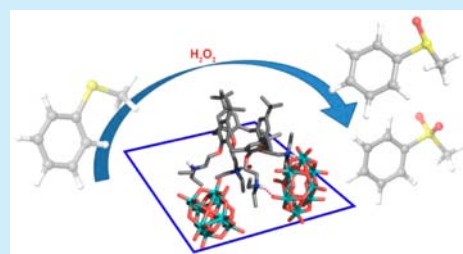
In recent decades, research interest in calixarene[1] chemistry has increased dramatically thanks to their applications in several fields related to supramolecular chemistry, which include molecular recognition,[2] self-assembling systems,[3] mechanically interlocked molecules,[4] and nanoporous materials.[5] 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 co-workers[8] 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 nonracemic sulfoxides are relevant pharmacophores of widely used drugs such as omeoprazole 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 H_2O_2 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 a strictly stoichiometric amount of aqueous H_2O_2 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 functionalized hybrids.[17]

Mizuno and co-workers investigated a variety of POM-catalyzed oxidations using stoichiometric amounts of H_2O_2 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 a stoichiometric loading of 30% H_2O_2 as the oxidant (Scheme 1).

Scheme 1. Synthesis of Catalysts 1 and 5
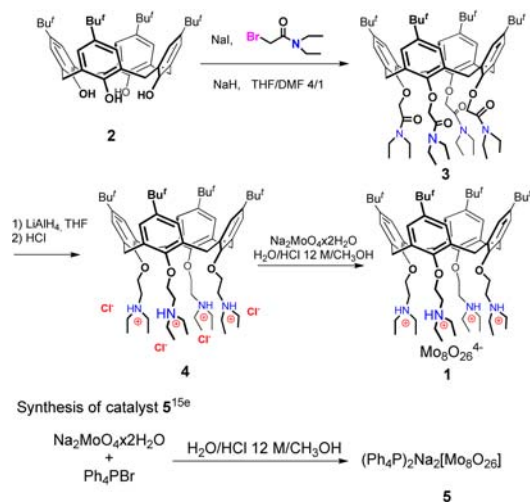
According to the relevant literature,[19d,e] we envisaged an octamolybdate as the most promising anionic cluster. The designed POM-calixarene **1**, bearing a well-organized architecture of four trialkylammonium units anchored within the macrocyclic scaffold, might have potentially good catalytic properties.

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 $LiAlH_4$ 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 $Na_2MoO_4 \cdot 2H_2O$ acidified with 12 M aqueous HCl (Scheme 1). The solid obtained was then crystallized to give POM−calixarene **1** in crystalline form. For the purpose of comparison, POM derivative **5** was also synthesized by following a literature procedure.[15e] Surprisingly, the X-ray structure of POM-calixarene **1** showed the presence of both α and β isomers[23] of the octamolybdate $Mo_8O_{26}{}^{4-}$ 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 CD_3CN and CD_3OD using 30% H_2O_2 (1.0 equiv) at room temperature, showed POM−calixarene **1** to be a highly active catalyst in CD_3CN with respect to CD_3OD achieving a very good conversion to the sulfoxide and low amount of sulfone (<10%) detected after 30 min (Figure 2).[24]

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 interactions[9] displayed by the large calix[4]arene tetra-ammonium portion of the hybrid with the organic sulfide and thus improving the mass
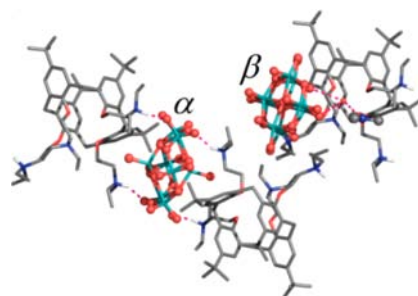

Figure 1. Solid state assembly of POM/calix[4]arene **1** with the fundamental interactions of the α- and β-$[Mo_8O_{26}]^{4-}$ isomeric clusters.
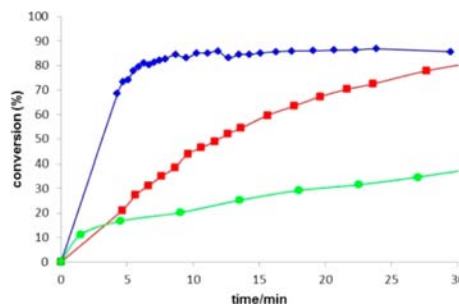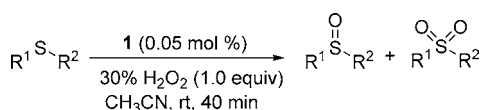

Figure 2. Reaction progress profile for the oxidation of phenyl methyl sulfide at room temperature: H_2O_2 (1.0 equiv), **1** (0.1 mol %) at [sulfide] = 0.5 M. (◆) in CD_3CN; (■) in CD_3OD; (●) using **5** (0.1 mol %) in CD_3CN.

transfer between the inorganic POM and the organic substrate[17,18] and helping its oxidation at the interface where peroxo-Mo(VI) species are formed.[22] Further reduction of the loading to 0.05 mol % did not modify the reaction outcome.[22]

With the optimized conditions in hand, the scope of the oxidation was studied, using 0.05 mol % of catalyst **1** with a stoichiometric amount of H_2O_2 (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 a C═C bond (entries 7, 10, 11, and 14). The oxidation of heterocyclic sulfide 2-(methylthio)-benzimidazole proceeded smoothly (entry 13), showing suitability in accessing pharmaceutically important sulfoxides such as precursors of the proton pump inhibitors[12] under particularly mild oxidative conditions. Acyclic and cyclic dialkyl sulfoxides were easily obtained in high yield (entries 14−16). Finally, we thought it would be useful to explore the diastereocontrol of this system in the oxidation of 2-phenyl-1,3-dithiane and dithiolane. Interestingly, the corresponding trans monosulfoxides were isolated in high yield and chemoselectivity with an excellent level of diastereoselectivity (entries 17 and 18).

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**/H_2O_2 among the best performing POMs/H_2O_2 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
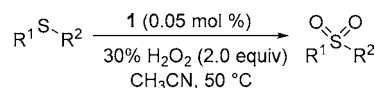
Table 1. Sulfoxidation of Thioethers to Sulfoxide with 30% H₂O₂ Catalyzed by POM−Calixarene Hybrid 1a[a]

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

entry	sulfide	yield (%)[b]	selectivity[c]
1	methyl phenyl sulfide	81	91
2	methyl (4-methylphenyl) sulfide	84	89
3	methyl (4-methoxyphenyl) sulfide	88	90
4	methyl (2-methoxyphenyl) sulfide	92	98
5	methyl (4-chlorophenyl) sulfide	78	82
6	methyl (2-bromophenyl) sulfide	91	99
7	methyl (4-formylphenyl) sulfide	78	85
8	ethyl phenyl sulfide	83	86
9[d]	cyclopropyl phenyl sulfide	80	86
10[d]	allyl phenyl sulfide	78	80
11	2-(phenylthio)ethanol	86	90
12	methyl (phenylthio)acetate	83	95
13[e]	2-(methylthio)benzimidazole	78	92
14	benzyl methyl sulfide	83	88
15[f]	n-C₈H₁₇−S−CH₃	87	93
16[g]	tetrahydrothiopyran-4-one	93	93
17	2-phenyl-1,3-dithiane	90 (t/c > 99/1)[h]	92
18	2-phenyl-1,3-dithiolane	86 (t/c 95/5)[h]	94

[a]Reaction conditions: sulfide (0.2 mmol), H₂O₂ (0.2 mmol), **1** (0.0001 mmol), in CH₃CN (400 μL) stirred at room temperature for 40 min. [b]Isolated yields. [c]Calculated as SO/(SO + SO₂). [d]Carried out for 60 min. [e]Carried out for 105 min. [f]Carried out for 90 min. [g]Carried out for 75 min. [h]The *trans/cis* ratio determined by ¹H NMR analysis.

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.

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 a 0.2 mol % loading of

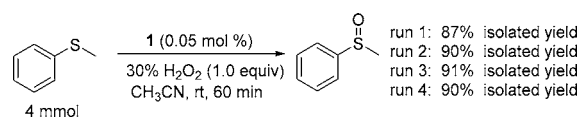**Table 2. Sulfoxidation of Thioethers to Sulfones with 30% H₂O₂ Catalysed by POM-Calixarene 1[a]**

$$R^1{\sim}S{\sim}R^2 \xrightarrow[\substack{\text{30\% H}_2\text{O}_2\ (2.0\ \text{equiv})\\ \text{CH}_3\text{CN, 50 °C}}]{\textbf{1}\ (0.05\ \text{mol \%})} R^1{\sim}\overset{\text{O}\ \ \text{O}}{\underset{}{S}}{\sim}R^2$$

entry	sulfide	time (min)	yield (%)[b]
1	methyl phenyl sulfide	60	98
2	methyl (4-nitrophenyl) sulfide	110	97
3	methyl (4-methoxyphenyl) sulfide	60	98
4	cyclopropyl phenyl sulfide	180	98
5[c]	diphenyl sulfide	105	95
6	allyl phenyl sulfide	130	97
7	2-(phenylthio)ethanol	170	96
8	benzyl methyl sulfide	100	98
9	n-C₈H₁₇−S−CH₃	180	90
10[d]	benzothiophene	180	77

[a]Reaction conditions: sulfide (0.2 mmol), H₂O₂ (0.4 mmol), **1** (0.0001 mmol), in CH₃CN (400 μL) stirred at 50 °C. [b]Isolated yields. [c]Carried out with 0.1 mol % of catalyst **1**. [d]Carried out with 0.2 mol % of catalyst **1** at 60 °C.

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 of the potential reusability of hybrid catalyst **1** (Scheme 2). Interestingly, the activity was maintained after four cycles.

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

$$\text{PhSCH}_3 \xrightarrow[\substack{\text{30\% H}_2\text{O}_2\ (1.0\ \text{equiv})\\ \text{CH}_3\text{CN, rt, 60 min}}]{\textbf{1}\ (0.05\ \text{mol \%})} \text{PhS(O)CH}_3$$

4 mmol

run 1: 87% isolated yield
run 2: 90% isolated yield
run 3: 91% isolated yield
run 4: 90% isolated yield

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.

The attractive features of this system are as follows: (i) high catalytic activity at a low catalyst loading, mild reaction conditions, and wide substrate scope, with a strictly stoichiometric amount of H₂O₂; (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 POMs 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

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02607.

> Details of experimental procedures, characterization of the catalyst, tables of crystal data (PDF)
> Crystallographic data for **1** (CIF)

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Notes
The authors declare no competing financial interest.

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(24) The lower catalytic activity in CD$_3$OD can be ascribed to its higher hydrophilicity, which should disfavor the mass transfer between the polar POMs and the lipophilic organic substrates. This difference can be also appreciated by considering the TON and TOF values that are always higher for CD$_3$CN (Table S1).

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