

## Photobleaching resistant polymer supported hexanuclear molybdenum iodide cluster for photocatalytic oxygenations and photodynamic inactivation of *Staphylococcus aureus*

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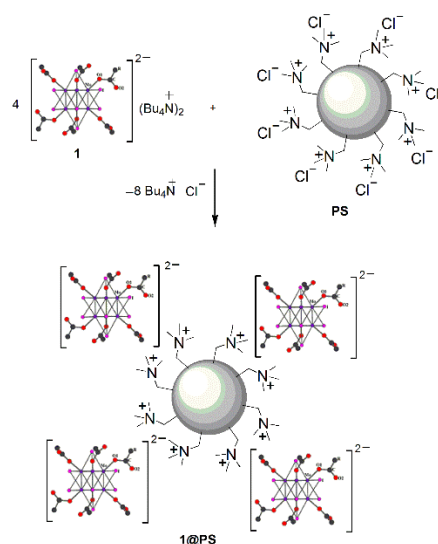
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The ability of hexanuclear molybdenum cluster  $[\text{Mo}_6\text{I}_6(\text{CH}_3\text{COO})_6]^{2-}$  to carry out, upon irradiation, singlet oxygen mediated photocatalytic oxygenation reactions has been tested. This complex has been also supported onto a solid polymeric matrix, yielding an immobilized photosensitizer with remarkable photostability and recyclability. Preliminary studies of antibacterial photoinactivation of *Staphylococcus aureus* have been conducted, with positive results.

Photosensitization to produce reactive oxygen species (ROS) is widely used in a variety of fields, from photocatalysis to photodynamic therapy of cancer and photodynamic inactivation of microorganisms. In the first area, production of fine chemicals can be achieved by means of photocatalysed oxygenation reactions.<sup>1</sup> In the second realm, treatment of tumours or inactivation of bacteria can be done by the appropriate choice of photosensitizer and irradiation conditions.<sup>2</sup> For any application the requisite of photostability is of key importance and great effort is devoted to the development of photosensitizers resistant to the self-generated ROS species.<sup>3</sup> An outstanding library of photocatalytic and photodynamic agents has been developed so far.<sup>4</sup> Hexanuclear clusters of molybdenum  $[\text{Mo}_6\text{X}_6\text{L}_6]$  (X = Cl, Br, I; L is a ligand) are well known photochemical generators of singlet oxygen ( $^1\text{O}_2$ ).<sup>5</sup> However, in comparison to other families of photosensitizers, they remain a less known group of ROS generating compounds, with virtually unexplored potential in photochemical synthesis and photobiology. Most of the studies dealing with the generation of  $^1\text{O}_2$  are focused on photophysical measurements. Reactivity with  $^1\text{O}_2$  traps like cycloalkenes is shortly described in some reports.<sup>5</sup> The photobiological activity of silica

nanoparticles doped with hexanuclear Mo clusters has been only recently reported for the treatment of Hep-2 carcinoma cells.<sup>6</sup> However, the use of this class of compounds for photodynamic bactericidal applications is not reported so far.

Here we report on the activity of  $(\text{Bu}_4\text{N})_2[\text{Mo}_6\text{I}_6(\text{CH}_3\text{COO})_6]$  (**1**, see Figure 1) as photosensitizer for oxygenations involving  $^1\text{O}_2$ . Also a new polymeric photosensitizer derived from **1** is described, which shows not only outstanding stability for repeated use in photocatalytic cycles, but also photodynamic antimicrobial activity against *S. aureus*, which is, to the best of our knowledge, the first demonstrated bactericidal photodynamic application of this class of complexes, thus adding a new agent to the current toolbox for the treatment of bacterial infections.<sup>7,8</sup>



**Figure 1.** Anion exchange process to obtain supported photosensitizer **1@PS** from  $(\text{Bu}_4\text{N})_2[\text{Mo}_6\text{I}_6(\text{CH}_3\text{COO})_6]^{2-}$  (**1**) and cationic resin **PS**. Note that in this representation R is methyl.<sup>9</sup>

The synthesis and characterization of **1** has been reported.<sup>10</sup> In order to explore the potential application of this complex in photocatalysis and photoinactivation of microorganisms, cluster **1** was immobilized onto a solid polystyrene matrix to yield **1@PS**. Immobilization of the  $\text{Mo}_6$  clusters on

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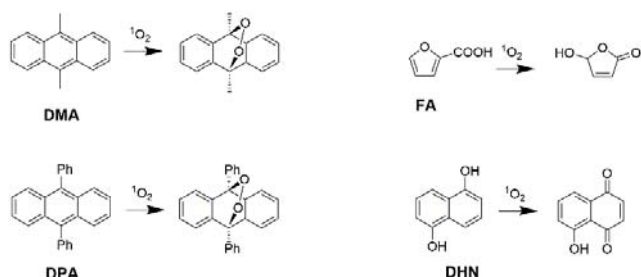
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† Electronic Supplementary Information (ESI) available: Synthetic, photochemical and photobiological procedures.

nanocomposites, silica nanoparticles, thin films, cyclodextrin hydrogel and polymers is often a pre-requisite for optical and nanobiotechnology applications.<sup>11</sup> The preparation of **1@PS** was accomplished by ion exchange on Amberlite IRA 900 resin (**PS**) as indicated in the experimental section (see supporting information). This resin contains a backbone of crosslinked polystyrene functionalized with permanent positive charges due to trimethyl ammonium groups (balanced with chloride counterions). Hence, in the exchange process chloride is replaced by the intact anionic cluster, releasing tetrabutyl ammonium chloride in solution, and  $[\text{Mo}_6\text{I}_8(\text{CH}_3\text{COO})_6]^{2-}$  remains grafted onto the solid (Figure 1). The presence of the intact cluster in the polymer was confirmed by means of emission spectroscopy (Figure S3 in the supporting information). As it can be seen, the red phosphorescence of grafted **1** was recorded under nitrogen atmosphere, with a maximum at 680 nm. As expected, the triplet state, origin of this phosphorescence, can be efficiently deactivated by oxygen since exposure of the sample to air leads to quenching of the emission in few seconds.<sup>5</sup>

In order to select the most appropriate reaction conditions to test **1@PS** as heterogeneous photocatalyst, preliminary screening of photooxygenation reactions was conducted, with **1** taken as homogeneous photosensitizer. Four well-known substrates for singlet oxygen were assayed: 9,10-dimethylantracene (**DMA**), 9,10-diphenylantracene (**DPA**), furoic acid (**FA**) and 1,5-dihydroxynaphthalene (**DHN**) (Scheme 1). We and others have used those oxygenations to test the ability of photoactive materials to produce  $^1\text{O}_2$  and we consider them as reliable benchmark reactions.<sup>12</sup> **FA** is relevant from the synthetic point of view taking into account that is a starting product for the synthesis of, for instance, alkaloids and prostanoids,<sup>13</sup> and the oxidation product of **DHN** is juglone (5-hydroxy-1,4-naphthalenedione), a natural insecticide and food dye (C.I. Natural Brown 7).<sup>14</sup>

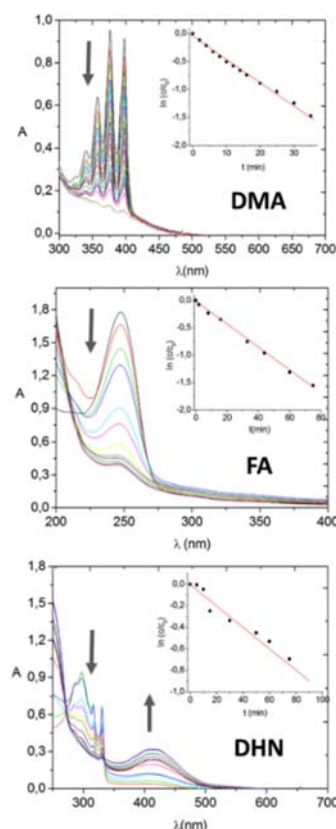


**Scheme 1.** Structures and reactions with singlet oxygen of substrates 9,10-dimethylantracene (**DMA**), 9,10-diphenylantracene (**DPA**), furoic acid (**FA**) and 1,5-dihydroxynaphthalene (**DHN**).

The pseudo-first order rate constants ( $k_{\text{obs}}$ ) for the photooxidations of **DMA**, **DPA**, **FA** and **DHN** under different conditions were determined following the disappearance of the respective absorption bands by means of UV-vis spectroscopy. Illustrative examples of some photoreactions can be seen in Figure 2. A summary of the kinetic values can be found in Table 1 together with the time needed for 100% conversion in each reaction. The table also includes complementary data such as a blank experiment in the absence of oxygen, one reaction upon irradiation with solar light and two reactions in the presence of

the well-known photosensitizer Rose Bengal (**RB**). The kinetic description presented in Table 1 is novel within the realm of hexanuclear Mo clusters and it is relevant since it allows to compare the new system to other supported photosensitizers (not only Mo-based) described in the literature.<sup>12</sup>

As it can be seen, there are notable differences, depending on the substrate and the solvent. The reaction with **DMA** in acetonitrile, photosensitized by **1**, is particularly fast, with quantitative conversion in ca. 4 min ( $k_{\text{obs}} = 1.1956 \text{ min}^{-1}$ ), very similar to the reaction catalysed by **RB** (completion in ca. 3 min and  $k_{\text{obs}} = 1.3070 \text{ min}^{-1}$ ).



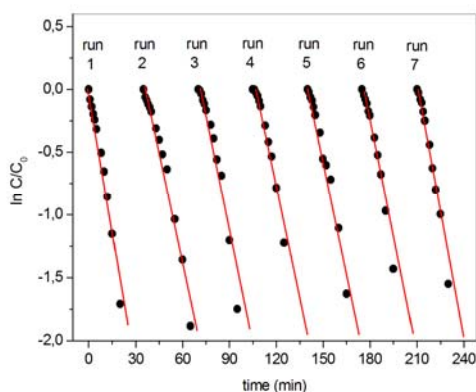
**Figure 2.** Illustrative examples of the photoreactions with: (top) **DMA**  $10^{-4}$  M, EtOH; (middle) **FA**  $4 \times 10^{-5}$  M,  $\text{CH}_3\text{CN}$  and (bottom) **DHN**  $10^{-4}$  M,  $\text{CH}_3\text{CN}$ .

Accordingly, this substrate and solvent were selected to test the heterogeneous photosensitizer **1@PS**. In the experiment, 500 mg of the supported photosensitizer were suspended in acetonitrile containing **DMA** in the concentration of  $10^{-4}$  M. Irradiation in air and under continuous stirring was continued until complete photooxidation of **DMA**. In this case the reaction was slower than in solution (full conversion in 30 min), but with the notable advantage of recyclability, since the polymer can be easily separated from the solution and used again. The photocatalyst was filtered off, suspended in a fresh  $10^{-4}$  M solution of **DMA** and irradiated again. No sign of leaching out of the anionic cluster was detected by UV-vis spectroscopy during the experiments. Irradiations were carried out in a repetitive manner and up to seven cycles were performed without loss of activity (see almost identical kinetic traces in Figure 3, with an average  $k_{\text{obs}} = (0,056 \pm 0,012) \text{ min}^{-1}$ ).

**Table 1.** Pseudo-first order rate constants and time needed for 100% conversion in the photooxidation reactions of **DMA**, **DPA**, **FA** and **DHN**.

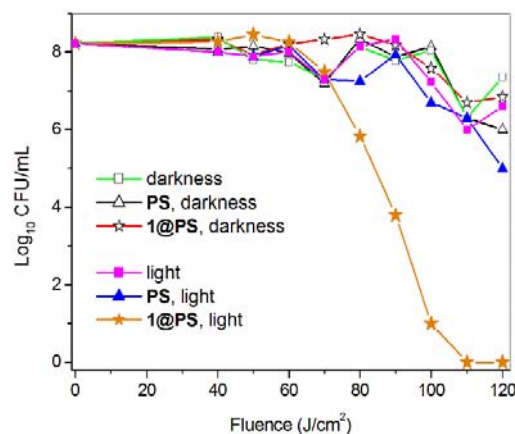
Substrate (concentration)	Photosensitizer (concentration)	Solvent	Atmosphere	Light source	$k_{\text{obs}}$ ( $\text{min}^{-1}$ )	Time for 100% conversion (min.)
<b>DMA</b> ( $10^{-4}\text{M}$ )	<b>1</b> ( $2 \times 10^{-5}\text{M}$ )	EtOH	Air	LED	0.0409	100
<b>DMA</b> ( $10^{-4}\text{M}$ )	<b>1</b> ( $2 \times 10^{-5}\text{M}$ )	EtOH	Air	Solar	0.1772	20
<b>DPA</b> ( $10^{-4}\text{M}$ )	<b>1</b> ( $2 \times 10^{-5}\text{M}$ )	EtOH	Air	LED	0.0027	> 600
<b>DMA</b> ( $10^{-4}\text{M}$ )	<b>1</b> ( $2 \times 10^{-5}\text{M}$ )	$\text{CH}_3\text{CN}$	Air	LED	1.1956	4
<b>DMA</b> ( $10^{-4}\text{M}$ )	<b>1</b> ( $2 \times 10^{-5}\text{M}$ )	$\text{CH}_3\text{CN}$	Nitrogen	LED	<0.0001	$\infty$
<b>DMA</b> ( $10^{-4}\text{M}$ )	none	$\text{CH}_3\text{CN}$	Air	LED	<0.0001	$\infty$
<b>FA</b> ( $4 \times 10^{-5}\text{M}$ )	<b>1</b> ( $2 \times 10^{-5}\text{M}$ )	$\text{CH}_3\text{CN}$	Air	LED	0.0214	150
<b>DHN</b> ( $10^{-4}\text{M}$ )	<b>1</b> ( $2 \times 10^{-5}\text{M}$ )	$\text{CH}_3\text{CN}$	Air	LED	0.0081	> 300
<b>DMA</b> ( $10^{-4}\text{M}$ )	<b>RB</b> ( $1.5 \times 10^{-6}\text{M}$ )	$\text{CH}_3\text{CN}$	Air	LED	1.3070	3
<b>DPA</b> ( $10^{-4}\text{M}$ )	<b>RB</b> ( $1.5 \times 10^{-6}\text{M}$ )	EtOH	Air	LED	0.0148	240

The photostability showed by **1@PS** is very advantageous for applications where recyclability of the catalyst is needed. The drawback of photobleaching of the sensitizer by autooxidation is a well-known handicap in photocatalysis and also in photobiological applications.<sup>3</sup> As it can be seen in the supporting information, fast and complete photobleaching of **RB** was observed in the photooxygenation of **DHN** in a single irradiation, under our experimental setup (Figure S4). A number of cases of instability of the photosensitizer have been reported in the literature. For instance, Pessoni and coworkers reported the immobilisation of **RB** grafted on polystyrene and the use of this photocatalyst for the oxidation of **DHN**, but the reaction resulted quite inefficient (only 15% conversion after 16h) due to the photobleaching of **RB** (85% degradation after 8h of irradiation).<sup>15</sup> In another example Gerdes and coworkers reported a significant loss of activity of **RB** immobilized on a polymeric support, already in the third cycle of oxidation of citronellol.<sup>16</sup> Our photosensitizer, on the contrary, is very resistant to this oxidative fatigue. This is true for both **1@PS** and for **1** in solution. As it can be deduced from the absorption spectra, the sensitizer is apparently unchanged after the repeated irradiations: the absorption tail at  $\lambda > 400$  nm which corresponds to **1** remains unaltered throughout the irradiation time (see Figure S5).

**Figure 3.** Photooxygenation cycles performed with the same sample of **1@PS**. Substrate: **DMA**  $10^{-4}$  M in  $\text{CH}_3\text{CN}$ .

Finally, providing the cytotoxic nature of singlet oxygen, a sample of **1@PS** was evaluated as a potential photodynamic agent against *S. aureus*, the main cause of nosocomial

infections.<sup>17</sup> A sample of the polymeric photosensitizer was placed in a RODAC plate with a suspension of *S. aureus* as indicated in the experimental section. The plate was irradiated with blue light from a LED lamp at different light fluences, and the surviving colonies counted by means of a colony counter. At  $80 \text{ J/cm}^2$  the population of microorganisms decreased by approximately two orders of magnitude, at  $100 \text{ J/cm}^2$  the reduction accounted up to 7 log<sub>10</sub> colony-forming units (CFU) units, and at  $110 \text{ J/cm}^2$  the killing was complete (Figure 4).

**Figure 4.** Photodynamic inactivation of *S. aureus* with **1@PS**.

A control sample with the parent cationic polystyrene matrix **PS** was also irradiated, showing no phototoxicity. Also samples in the darkness were prepared (with **PS** or **1@PS**) and the survival of *S. aureus* evaluated. As it can be seen in Figure 4 only the combination of supported photosensitizer and light resulted positive for the inactivation of the pathogens. In Figure S6 a series of illustrative pictures illustrating of the assays are shown. These are only preliminary results but they are worth mentioning since they offer the first evidence of photodynamic antibacterial activity of a molybdenum cluster. Although the absorption properties of the described supported photosensitizer could seem as not optimal for all PDT applications, since the absorption in the visible range is low, it must be recalled that a number of materials for use in photodisinfection have been described (for instance sterilisable catheters) not requiring long wavelength absorptions<sup>8</sup> (our photosensitizer can be activated simply with blue light<sup>18</sup> from a LED lamp).

It is worth to note that the dianionic cluster remains tightly bound to the cationic polymeric matrix during all the photochemical experiments, which could be the key for the excellent performance of the new material. As Kubeil et al. have demonstrated for related clusters (hexarhenium) encapsulated in poly(propyleneamine) dendrimer-based supports, the retardation of the ion exchange can be understood and controlled by thermodynamic and kinetic factors.<sup>19</sup> Hence, it seems clear that the role of the cationic matrix is not merely to serve as a simple support for the photosensitizer, and consequently this consideration will be taken into account in future studies with a comprehensive series of polymer matrices.

In summary, a hexanuclear molybdenum cluster has been immobilized onto a cationic polystyrene matrix, and its photocatalytic and photobiological properties tested. The new polymeric hybrid material is able to perform catalytic photooxidations with excellent recyclability (up to seven cycles without loss of activity) due to a high degree of photostability and low degree of leaching. Moreover the immobilized cluster causes photoinactivation of *S. aureus*, which is the first time that a hexanuclear molybdenum cluster is used with positive results for a photodynamic antibacterial application.

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