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A Photoactivated Molecular Gate

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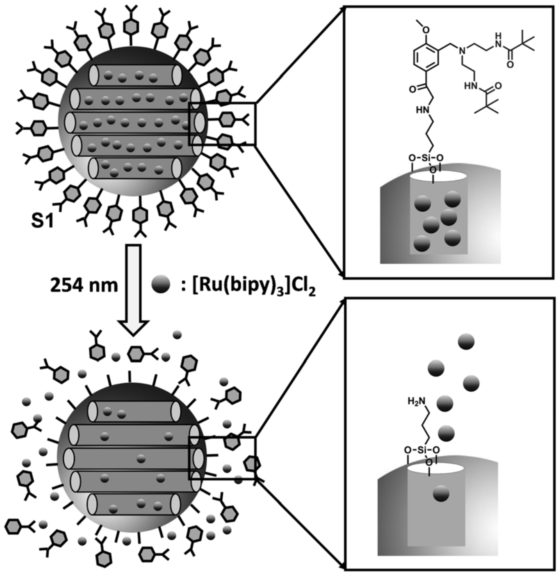
The design and synthesis of mesoporous hybrid capped materials, which can be selectively opened upon the application of external stimuli and release an entrapped cargo, have recently caught the interest of the scientific community.[1] In general, these hybrid materials are composed of two main subunits: an inorganic scaffold (with a porous network in which certain chemicals can be stored) and molecular entities grafted onto the outer surface, which act as molecular gates (to control the delivery of the entrapped cargo).

As inorganic scaffolds, mesoporous silica nanoparticles (MSNs) have been widely used because of their unique properties, such as large load capacity, biocompatibility, large surface area and well-known functionalisation procedures.[2] In fact, gated MSNs have recently been used as supports for the development of on-command delivery nano-devices using several physical and chemical triggers.[3] In this area, MSNs showing controlled release features driven by redox reactions,[4] pH changes[5] and biomolecular interactions[6] have been described.

In this field, light is also a powerful tool for the control of open/closed protocols in mesoporous systems. In particular, by using light-driven gated systems, the release of the cargo can be controlled spatially and temporally by finely tuning the area and the time of the light stimulus. However, there are relatively few examples of photochemically driven molecular gates,[7] some of which are based on reversible photo-isomerisation reactions.[8] Recently, we described MSNs functionalised with spiropyran photochrome units and capped with PAMAM dendrimers (G1.5), and MSNs capped with gold nanoparticles, which were opened using light as a stimulus.[9] In contrast, only one photo-driven controlled example using a photo-cleavable gate anchored on the surface of MSNs has been reported.[10] In this work, Kim and co-workers prepared an *o*-nitrobenzyl ester derivative bearing a cyclodextrin moiety that was selectively opened by the addition of specific enzymes and by UV irradiation. In particular, the solid was able to release the entrapped cargo (calcein) after UV irradiation at 350 nm due to the photolysis of an *o*-nitrobenzyl ester fragment.

By considering our interest in developing gated materials and the aforementioned ideas, we report herein the synthesis and controlled release studies of a new nanoscopic mesoporous system capped with a photo-cleavable *o*-methoxybenzylamine fragment. A schematic representation of the controlled delivery paradigm is shown in Scheme 1. The *o*-methoxybenzylamine group was selected for its well-known photo-cleavage properties, which have been used in a wide range of applications.[11] Based on this methoxybenzylamine fragment, we designed compound **7** which, other than the photo-cleavable group, also contains two bulky *tert*-butyl



Scheme 1. Schematic representation of solid **S1** and the photo-driven uncapping mechanism.

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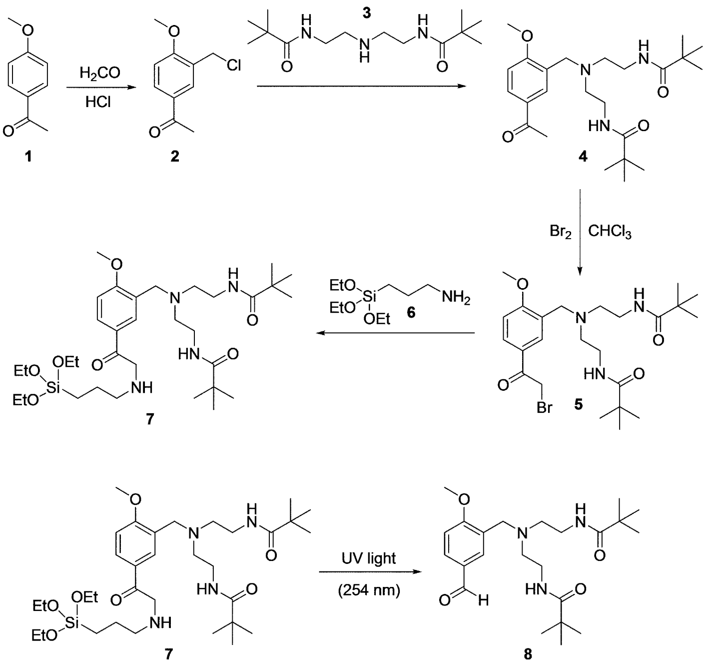
moieties to obtain effective pore blockage in the final hybrid material, as well as one trialkoxysilane moiety for anchoring **7** on the external MSN surface. Compound **7** was expected to be bulky enough to preclude the delivery of the entrapped cargo but, at the same time, it was expected to undergo photolysis upon UV irradiation. As a result of photolysis, the steric hindrance of the capping molecule would decrease considerably, thus allowing the release of the entrapped dye.

The synthesis of **7** (see Scheme 2) began with a reaction between 4-methoxyacetophenone (**1**) and aqueous formaldehyde in hydrochloric acid, which yielded compound **2**. Then a nucleophilic substitution reaction of **2** with amine **3** (prepared following a well-known procedure)[12] gave the bulky tertiary amine **4** equipped with two *tert*-butylamide moieties. Treatment of tertiary amine **4** with bromine in chloroform gave **5** through an α-bromination reaction. Finally, trialkoxysilane derivative **7** was prepared by a nucleophilic aliphatic reaction between **5** and (3-aminopropyl)triethoxysilane (**6**) in acetonitrile/K_2CO_3.



Scheme 2. Synthesis of trialkoxysilane derivative **7** that acts as a molecular gate and its photolysis reaction.

All the synthesised products were characterised by ^{1}H and ^{13}C NMR spectroscopy and HRMS (see the Supporting Information). The ^{1}H NMR spectrum of trialkoxysilane derivative **7** shows the presence of singlets centred at $\delta = 1.10$ ppm assigned to the methyl groups of both *tert*-butyl subunits. The ethoxy moieties appeared as a triplet centred at $\delta = 1.22$ ppm and as a quadruplet centred at $\delta = 3.85$ ppm, whereas the aromatic signals were a pair of doublets centred at $\delta = 6.89$ and 7.88 ppm and a singlet at $\delta = 7.90$ ppm. Methylene directly linked with the aromatic ring and the tertiary amine nitrogen appeared at $\delta = 2.51$ ppm, whereas the methylene positioned between the aromatic ketone and the secondary amine gave a signal at $\delta = 3.60$ ppm. Finally, the methylene protons linked with amide nitrogen appeared as triplets centred at $\delta = 3.30$ ppm.

Prior to anchoring **7** on MSNs and to test the feasibility of **7** as a photo-cleavable molecule, photolysis studies were carried out. Acetonitrile solutions of **7** were irradiated with a mercury lamp (254 nm) and the photodegradation compounds were studied by gas chromatography coupled with a mass spectrometer. A complete photodegradation of **7** was achieved in three hours, from which aldehyde **8** was the major product of this reaction. Product **8** was isolated and characterised by NMR spectroscopy (see Scheme 2 and the Supporting Information).

After assessing **7** as a suitable photo-cleavable molecule, preparation of the capped materials shown in Scheme 1 was carried out. We selected mesoporous MCM-41 silica nanoparticles of approximately 100 nm in diameter as the inorganic carrier vehicle. This support was prepared by following well-known procedures using tetraethyl orthosilicate (TEOS) as a hydrolytic inorganic precursor and the surfactant hexadecyltrimethylammonium bromide. After surfactant removal by calcination, MCM-41 nanoparticles were obtained. The structure of the nanoparticulated calcined MCM-41 starting material was confirmed by powder X-ray diffraction analysis and TEM microscopy (Figure 1). The N_2 adsorption–desorption isotherms of the prepared nanoparticles showed a typical type-IV curve, with a specific surface of 965.6 $m^2 g^{-1}$ and a pore volume of 0.77 $cm^3 g^{-1}$. From the

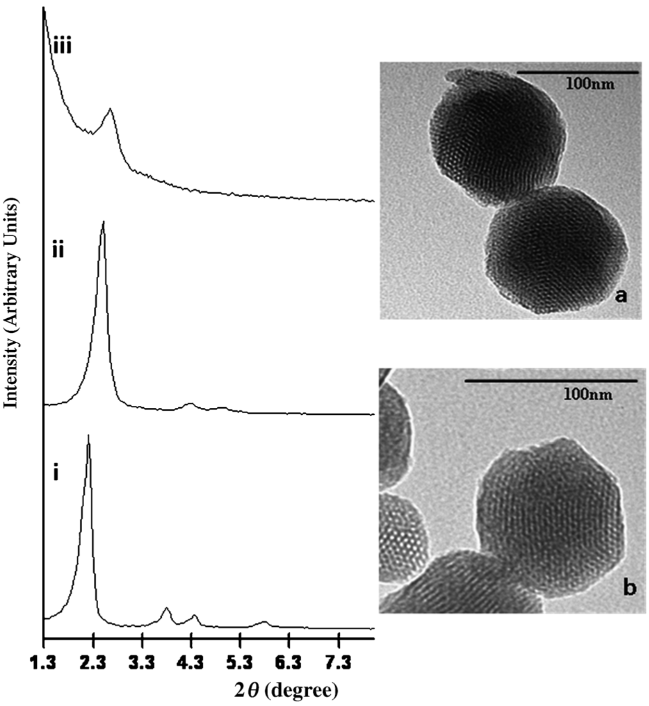


Figure 1. Left: Powder-X ray diffractograms showing the MSN patterns as synthesised (i), calcined MSNs (ii) and solid **S1** (iii). Right: TEM images of calcined MSN (a) and of final solid **S1** (b).

XRD, porosimetry and TEM studies, the a_0 cell parameter (4.34 nm), the pore diameter (2.67 nm) and a wall thickness value (1.67 nm) can be determined.

To prepare the final capped material, the inorganic support was first loaded with the $[Ru(bipy)_3]Cl_2$ fluorophore, which was used as a suitable dye for monitoring the light-triggered protocol. Then, the surface of the solid was functionalised with compound **7** to obtain the final hybrid material **S1**. Finally, the charged orange solid was filtered, intensively washed with acetonitrile and dried overnight at 36 °C.

Figure 1 shows the powder X-ray diffraction patterns of the MSN material as synthesised, the calcined MSNs and the final **S1** nanoparticles. The hybrid material **S1** displays the expected features of the MCM-41 phase, indicating that the mesopore in the inorganic scaffolding is preserved throughout the filling process with the ruthenium complex and the anchoring of bulky derivative **7** at the pore outlets. Figure 1 a and b provides TEM images of the MSN support and of the final hybrid nanoparticles **S1**. Both TEM images show the typical porosity associated with the inorganic support and their spherical form of about 100 nm in diameter. Additionally, the N_2 adsorption–desorption isotherm of **S1** (see the Supporting Information) was typical of mesoporous systems with filled mesopores, and the N_2 volume adsorbed and the surface area ($53.6\,m^2g^{-1}$) significantly decreased when compared with calcined MSN samples. The contents of ruthenium complex and capping molecule **7** in **S1** were determined by thermogravimetric analyses and amounted to $119\,mmol\,g^{-1}\,SiO_2$ and $109\,mmol\,g^{-1}\,SiO_2$, respectively.

After synthesising and characterising the capped MSNs, the gating properties of **S1** were studied. In a typical experiment, solid **S1** (3 mg) was suspended in anhydrous acetonitrile. Then the sample was stirred and exposed to 254 nm irradiation in a closed photoreactor for a given time. As a control experiment, dye release was also determined by using suspensions of **S1** under similar conditions but in the absence of light (see the Supporting Information for details). Photo-triggered molecular gate performance was monitored through the emission band ($\lambda_{em}=619$ nm, $\lambda_{ex}=451$ nm) of the ruthenium fluorophore delivered to the solution. The dye delivery versus time for both the irradiated and non-irradiated samples is shown in Figure 2.

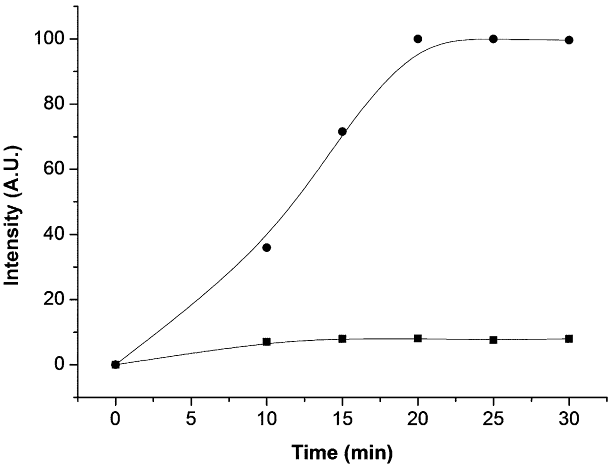


Figure 2. Kinetics of the $[Ru(bipy)_3]^{2+}$ dye release from solid **S1** in the absence of light (■) and upon irradiation with UV light (●).

As explained above, compound **7** was expected to be bulky enough to preclude the release of the entrapped dye in **S1**. In fact, as Figure 2 illustrates, the release of the ruthenium dye in the absence of light was completely inhibited (the gate was closed). The profile obtained upon UV irradiation clearly differed and a remarkable cargo release was observed due to the photo-cleavage of the methoxybenzylamine fragment. A maximum dye release was noted after about 20 min of UV irradiation. Moreover, the presence in the solution, upon irradiation, of the aldehyde **8** was also confirmed.

To summarise, we report herein the synthesis of a new photo-cleavable organic molecule which, when grafted on the surface of MSNs, acts as a molecular gate by allowing the controlled release of an entrapped cargo by simple UV irradiation. The photolysis of the methoxybenzylamine group diminished the steric crowding around the pore outlets, which accounts for the dye delivery and the emission enhancement observed. The design of light-responsive materials is a promising research field that may be of relevance in the development of custom-made materials for advanced delivery applications.

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Keywords: controlled release · mesoporous materials · molecular devices · nanoparticles · photochemistry

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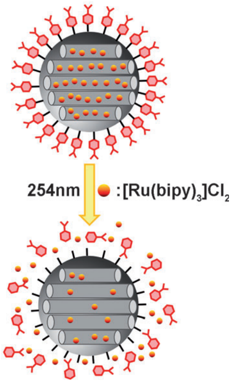
Light-controlled gate: A novel capped silica nanoscopic mesoporous hybrid material for photo-driven cargo release applications has been designed and prepared. The capped system, which shows a zero release, contains a photo-cleavable bulky *o*-methoxybenzylamine derivative. Upon irradiation at 254 nm, photo-degradation of the *o*-methoxybenzylamine framework and the subsequent delivery of a fluorescent cargo were observed (see figure).



Molecular Devices

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A Photoactivated Molecular Gate