Lozano-Torres, B.; Pascual, L.; Bernardos Bau, A.; Marcos Martínez, MD.; Jeppesen, JO.; Salinas Soler, Y.; Martínez-Máñez, R.... (2017). Pseudorotaxane capped mesoporous silica nanoparticles for 3,4-methylenedioxymethamphetamine (MDMA) detection in water. Chemical Communications. 53(25):3559-3562. https://doi.org/10.1039/c7cc00186j

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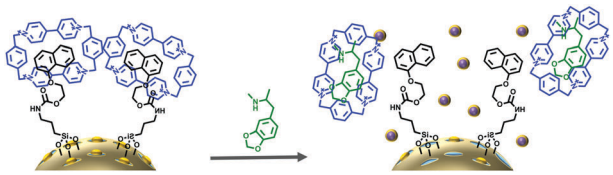

Pseudorotaxane capped mesoporous silica nanoparticles for 3,4-methylenedioxy-methamphetamine (MDMA) detection in water Q1

Beatriz Lozano-Torres, Lluis Pascual, Andrea Bernardos, María D. Marcos, Jan O. Jeppesen, Yolanda Salinas, Ramón Martínez-Máñez* and Félix Sancenón* Q2

MDMA, a principal ecstasy component, is detected by using pseudorotaxane-capped mesoporous silica nanoparticles.

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Pseudorotaxane capped mesoporous silica nanoparticles for 3,4-methylenedioxymethamphetamine (MDMA) detection in water†

Cite this: DOI: 10.1039/c7cc00186j

Received 9th January 2017,
Accepted 28th February 2017

DOI: 10.1039/c7cc00186j

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Mesoporous silica nanoparticles loaded with fluorescein and capped by a pseudorotaxane, formed between a naphthalene derivative and cyclobis(paraquat-*p*-phenylene) ($CBPQT^{4+}$), were used for the selective and sensitive fluorogenic detection of 3,4-methylenedioxymethamphetamine (MDMA).

Consumption and abuse of drugs is a problem of general concern in our society and a number of agencies and authorities are on alert to detect and stop illegal drug trade.[1] Inside the vast realm of drugs, 3,4-methylenedioxymethamphetamine (MDMA), commonly known as ecstasy, is one of the most widely consumed.[2] MDMA is a psychostimulant used primarily as a recreational drug.[3] The effects of MDMA include increased empathy, euphoria and heightened sensations.[4] When taken by mouth, the effects begin after 30–45 minutes and last for 3–6 hours.[5] It is also sometimes snorted, orally ingested or smoked.[6] The adverse effects of MDMA include addiction, memory problems, paranoia, difficulty in sleeping, teeth grinding, blurred vision, sweating and a rapid heartbeat. Consumption may also lead to depression and fatigue.[7] Moreover, deaths have been reported due to increased body temperature and dehydration.[8] Normally, MDMA is usually detected and quantified by using capillary electrophoresis, near infrared spectroscopy, gas chromatography and liquid chromatography.[9] However, these methods require the use of expensive technical equipment under the supervision of trained personnel. Moreover, there has also been an interest in the design and development of methods for rapid "*in situ*" detection of MDMA and in this context detection techniques based on the use of portable ion mobility spectrometers, Fourier transform infrared and Raman spectrometers and colorimetric tests (Mandelin, Mecke and Simon) have been developed.[10] In this scenario, the design of simple to use chromo-fluorogenic probes for selective and sensitive MDMA detection is highly appealing.

From another point of view, gated materials have found remarkable applications as controlled release devices, especially in the design of advanced drug delivery systems.[11] Moreover, gated materials have also been applied in sensing and recognition protocols as an alternative to classical chromo-fluorogenic molecular probes.[12] These sensing "gated materials" are prepared using an inorganic porous support, which is loaded with a reporter and then capped with a gating scaffold that allows a selective cargo release upon interaction with a target analyte.[13] These new sensing systems are clearly different from classic "binding site-signalling subunit" molecular-based systems because they make signalling independent of the binding site–analyte interaction. Besides, the use of "gated materials" allows sensing systems with amplification features to be obtained because the presence of few analyte molecules can induce the release of large quantities of reporter molecules.[14]

Pseudorotaxanes are complex supramolecular systems containing one or more macrocyclic rings encircling a rodlike component. Rotaxane- and pseudorotaxane-based systems have been widely used in the design of artificial machines that have found use in applications such as molecular switches and molecular shuttles.[15] One of the most used macrocycles in the preparation of rotaxanes and pseudorotaxanes is cyclobis (paraquat-*p*-phenylene) ($CBPQT^{4+}$), also known as "blue box".[16] This macrocycle, composed of two electron deficient paraquat subunits, forms strong inclusion complexes with electron donating guests such as benzene and naphthalene derivatives functionalised with donor atoms and neurotransmitters.[17]

In addition, rotaxanes and pseudorotaxanes have also been applied in the design of gated materials. Since the first example reported by Stoddart, Zink and co-workers,[18] several examples have been published in which changes in the location of the

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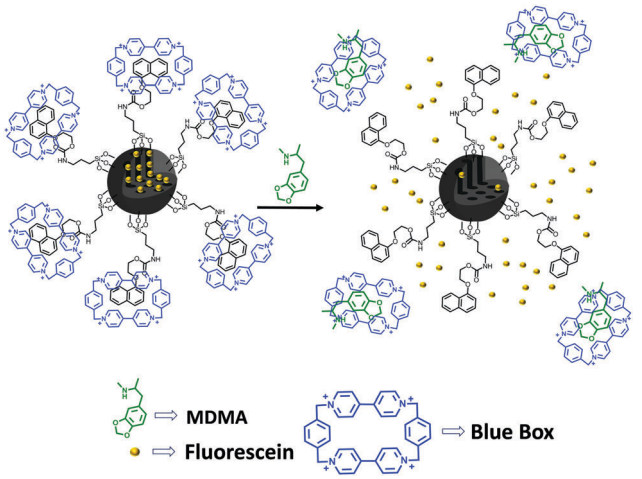
† Electronic supplementary information (ESI) available: Synthesis and characterization of compound **3** and solids **S1** and **S2**. See DOI: 10.1039/c7cc00186j



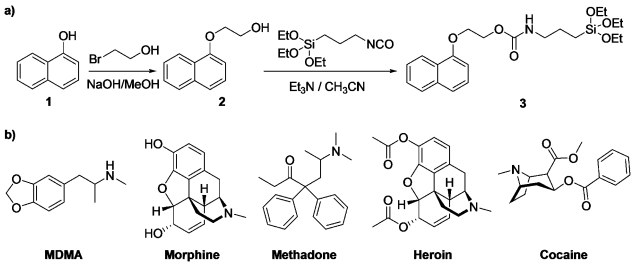
Scheme 1 Mesoporous silica nanoparticles loaded with fluorescein and capped with a pseudorotaxane formed between a grafted naphthol derivative and $CBPQT^{4+}$ (**S2**). Dethreading of the pseudorotaxane in the presence of MDMA induced fluorescein release.

macrocycle, by both chemical and photochemical inputs, allows payload delivery.[19] However, to the best of our knowledge, materials gated with pseudorotaxanes have never been used for the design of gated probes for sensing applications.

Bearing these facts in mind and our interest in the development of gated hybrid materials for their application in new sensing protocols,[20] herein, we report the synthesis and characterisation of mesoporous silica nanoparticles (**S2** in Scheme 1) loaded with fluorescein and functionalised on the external surface with a pseudorotaxane (formed between a grafted naphthalene derivative and the $CBPQT^{4+}$ macrocycle) followed by their use for the selective fluorogenic detection of MDMA. The underlying idea is that the capped material would remain closed, yet in the presence of MDMA, $CBPQT^{4+}$ would detach from the surface of the nanoparticles with subsequent fluorescein release (see Scheme 1). Dethreading of the capping pseudorotaxane is expected to occur due to the formation of strong MDMA ⊂ $CBPQT^{4+}$ donor acceptor supramolecular complexes.

MCM-41 nanoparticles were prepared following well-known procedures using tetraethylorthosilicate (TEOS) as a hydrolytic inorganic precursor and hexadecyltrimethylammonium bromide (CTABr) as a micellar template.[21] The as-made solid was then calcined at 550 °C to obtain the starting nanoparticles with empty pores. Pores were loaded with fluorescein (solid **S0**) and the external surface was functionalised with the naphthalene derivative **3** (see Scheme 2) yielding **S1** nanoparticles. The final sensory material **S2** was obtained after stirring an aqueous suspension of **S1** and the $[CBPQT][PF_6]_4$ macrocycle (see the ESI† for experimental details). The naphthalene derivative **3** was synthesised from 1-naphthol (**1**) (see also Scheme 2). **1** was alkylated with 2-bromoethanol, using a Williamson ether synthesis, yielding **2**. Finally, **3** was obtained from the reaction between **2** and (3-isocyanatopropyl)triethoxysilane.

The prepared solids were characterised using standard techniques, *e.g.* powder X-ray diffraction (PXRD), transmission electron microscopy (TEM), N_2 adsorption–desorption isotherms



Scheme 2 (a) Synthetic procedure used for the preparation of naphthalene derivative **3**. (b) Chemical structure of MDMA and the drugs used as potential interferents.

and elemental and thermogravimetric analyses. The structure of the as-made and calcined MCM-41 nanoparticles was confirmed by PXRD (see curves a and b in Fig. 1). The structure of the nanoparticles was also confirmed by TEM studies (see Fig. 2e), in which the spherical morphology and the mesoporous structure of the material were clearly observed. N_2 adsorption–desorption isotherms of the calcined nanoparticles showed a typical type IV curve for mesoporous materials (see ESI†). With the application of BET and BJH models, a specific surface area of 1260.3 $m^2\ g^{-1}$, a pore size of 2.31 nm and a pore volume of 0.54 $cm^3\ g^{-1}$ were calculated. The PXRD pattern of **S1** and **S2** shows the characteristic (100) diffraction peak (curves c and d in Fig. 1). The N_2 adsorption–desorption isotherm of **S1** showed a marked reduced pore volume (0.36 $cm^3\ g^{-1}$) and surface area (849.0 $m^2\ g^{-1}$), when compared with the starting nanoparticles. Thermogravimetric and elemental analysis studies indicated an organic matter content of 15.2% in **S1** (0.87 and 0.80 mmol g^{-1} of solid for fluorescein and **3** respectively) and 24.4% in **S2** (0.83, 0.73 and 0.23 mmol g^{-1} of solid for fluorescein, **3** and $CBPQT^{4+}$ respectively). Besides, the addition of $CBPQT^{4+}$ clearly inhibited the delivery of the cargo (*vide infra*), strongly suggesting the

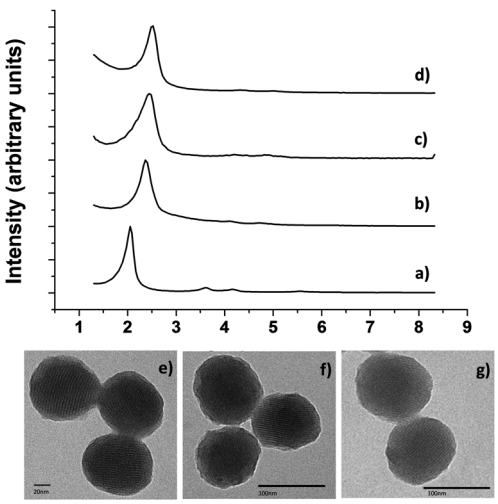


Fig. 1 Top: powder X-ray diffraction (PXRD) patterns of solids (a) MCM-41 as synthesized, (b) calcined mesoporous silica nanoparticles, (c) solid **S1** and (d) **S2** nanoparticles. Bottom: TEM images of (e) calcined MCM-41, (f) solid **S1** and (g) **S2** nanoparticles, showing the typical porosity of the mesoporous silica matrix.

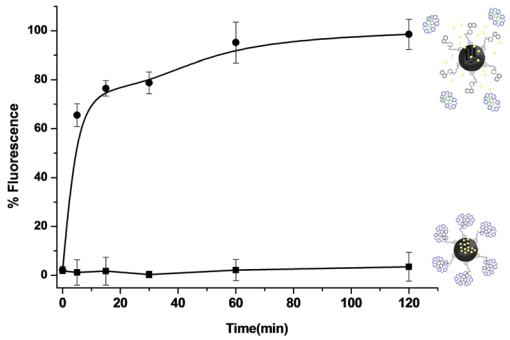


Fig. 2 Release profiles of fluorescein from aqueous suspensions of solid **S2** at pH 7.0 in the absence and presence of MDMA (10 μmol). Error bars are expressed as 3σ.

formation of naphthalene ⊂ $CBPQT^{4+}$ inclusion complexes. Moreover, TEM images of **S2** showed the typical porosity of a mesoporous silica matrix (see Fig. 2g).

After characterisation of the prepared materials, the controlled release of fluorescein from **S2** in the presence and absence of MDMA was studied. For this purpose, **S2** was added to water at pH 7.00 and the suspension was separated in two aliquots. MDMA was added to one aliquot whereas water was added to the other. Both suspensions were stirred at 25 °C and aliquots of 150 μL were taken at programmed times, centrifuged to remove the solid and the emission of the released fluorescein was measured at 520 nm (λ_{exc} = 495 nm). The release profiles obtained are shown in Fig. 2.

As can be seen, in the absence of MDMA, a very low cargo release was observed indicating that **S2** nanoparticles were tightly closed by the pseudorotaxanes formed between **3** and $CBPQT^{4+}$. However, when MDMA was present in the solution, a remarkable enhancement in the fluorescence at 520 nm was found. This emission enhancement was ascribed to pore opening and fluorescein release due to a preferential coordination of MDMA with $CBPQT^{4+}$ (calculated constant from ^{1}H-NMR titrations $\log K = 2.65 \pm 0.25$) that induced the dethreading of the pseudorotaxane grafted onto the external surface of solid**S2**. The crucial role played by $CBPQT^{4+}$ in the gating mechanism was assessed by measuring the delivery profiles of the uncapped solid **S1** in the absence and presence of MDMA. A marked fluorescein release was observed in both cases (see ESI†) pointing out the importance of grafted pseudorotaxane in the controlled release features of **S2**.

In a further step, to assess the selective response of **S2** nanoparticles toward MDMA, the fluorogenic response of the $CBPQT^{4+}$-capped solid was tested in the presence of cocaine, heroin, methadone and morphine (see Scheme 2). Fig. 3a shows the emission (at 520 nm) due to fluorescein release after 10 min upon addition of selected drugs (10 μmol) to aqueous suspensions of **S2**. Inspection of Fig. 3a reveals that the **S2** nanoparticles are highly selective toward MDMA and other drugs were unable to induce a marked fluorescein release. This suggested that **S2** or similar systems could be used for the detection of MDMA.

The observed selectivity of **S2** nanoparticles toward MDMA could be explained bearing in mind that this drug forms strong inclusion complexes with $CBPQT^{4+}$. The remarkable stability of these complexes resulted from the well-defined cavity of $CBPQT^{4+}$, which is formed by two electron-acceptor paraquat groups separated by about 3.7 Å, which is ideally sized for the inclusion of an electron-rich aromatic subunit such as that in MDMA by donor–acceptor interactions. In order to demonstrate the formation of MDMA ⊂ $CBPQT^{4+}$ complexes ^{1}H NMR studies in D_2O were carried out. As can be seen in Fig. 4, the aromatic part of the $CBPQT^{4+}$ spectrum showed three signals centered at 7.64, 8.33 and 9.13 ppm. The singlet centered at 7.64 ppm can be ascribed to the resonances associated with the protons of the *p*-phenylene bridges (Ha in the structure of $CBPQT^{4+}$ in Fig. 4), whereas the doublets resonating at 8.33 and 9.13 ppm, respectively, can be assigned to the protons on paraquat units (Hb and Hc protons, respectively). As can be seen in the set of spectra shown in Fig. 4, addition of increasing quantities of MDMA induced moderate chemical shifts of the three $CBPQT^{4+}$ aromatic protons and the most remarkable are the downfield shifts observed for Ha (0.06 ppm) and Hc (0.03 ppm) protons. These downfield shifts are consistent with the formation of donor–acceptor complexes by the inclusion of the electron donor MDMA into the electron accepting cavity of $CBPQT^{4+}$.

Then, in order to test the sensitivity of **S2**, the fluorogenic response of water suspensions of the nanoparticles upon addition of increasing amounts of MDMA was studied. The fluorescein emission at 520 nm was gradually enhanced with increasing MDMA concentrations (see ESI†). From the titration profile, a limit of detection of 4.9 μM (0.95 μg mL^{-1}) for MDMA was determined.

Finally, the ability of **S2** to detect MDMA in a more realistic sample was tested. For this purpose we prepared an ecstasy tablet by mixing MDMA and commonly used additives (*i.e.* sucrose, chalk and paracetamol, see ESI†). Then we measured the emission intensity of fluorescein released from **S2** in the presence of the individual components mixed together or alone. The results obtained are depicted in Fig. 3b which shows that only MDMA (alone or mixed with the other ecstasy

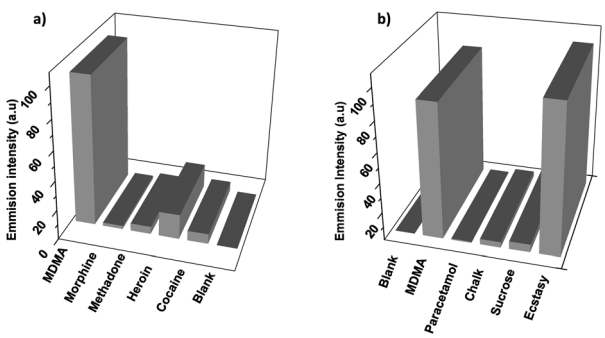


Fig. 3 (a) Emission intensity of fluorescein at 520 nm (excitation at 495 nm) released from **S2** nanoparticles (water pH 7.0) in the presence of selected drugs (10 μmol) after 10 min of addition. (b) Emission intensity of fluorescein at 520 nm (excitation at 495 nm) released from **S2** nanoparticles (water pH 7.0) in the presence of components of an ecstasy tablet.

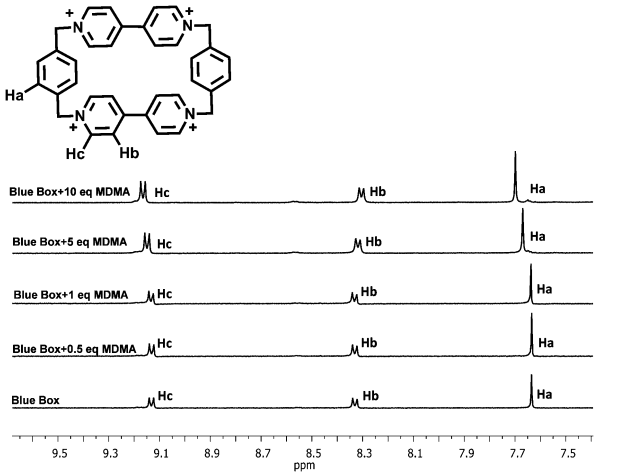


Fig. 4 ^{1}H NMR spectra (400 MHz, 298 K) recorded in D_2O of $CBPQT^{4+}$ in the presence of increasing quantities of MDMA.

components) is able to induce pseudorotaxane dethreading, pore opening and fluorescein release.

In summary, we have shown here a new protocol for the selective and sensitive fluorogenic detection of MDMA by using capped nanoparticles. Our sensing material consisted of mesoporous silica nanoparticles loaded with fluorescein and capped by a pseudorotaxane formed by a grafted naphthalene derivative and the $CBPQT^{4+}$ macrocycle. The sensing mechanism arises from a displacement reaction by the formation of an inclusion complex between MDMA and $CBPQT^{4+}$ that detaches the macrocycle from the surface of the nanoparticles. The fluorogenic response obtained is highly selective, and other drugs (*i.e.* morphine, methadone, heroin and cocaine) were unable to induce any significant fluorescence response. Besides, the sensitivity of capped nanoparticles is remarkable with an MDMA limit of detection of 4.9 μM in water. Taking into account the sensitivity and selectivity of solid **S2** and its easy synthesis and handling, this material could be used as a probe for an accurate "*in situ*" and "*at site*" MDMA identification from other illicit drugs.

The authors acknowledge the financial support from the Spanish Government (projects MAT2015-64139-C4-1-R and AGL2015-70235-C2-2-R) and the Generalitat Valenciana (project GVA/2014/13). B. L-T. is grateful to the Ministerio de Economía y Competitividad for her PhD grant. A. B. thanks the Spanish Government for the financial support "Juan de la Cierva-Incorporación" (IJCI-2014-21534). J. O. J. thanks The Danish Natural Science Research Council (FNU, project no. 11-106744) and the Villum Foundation for financial support.

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