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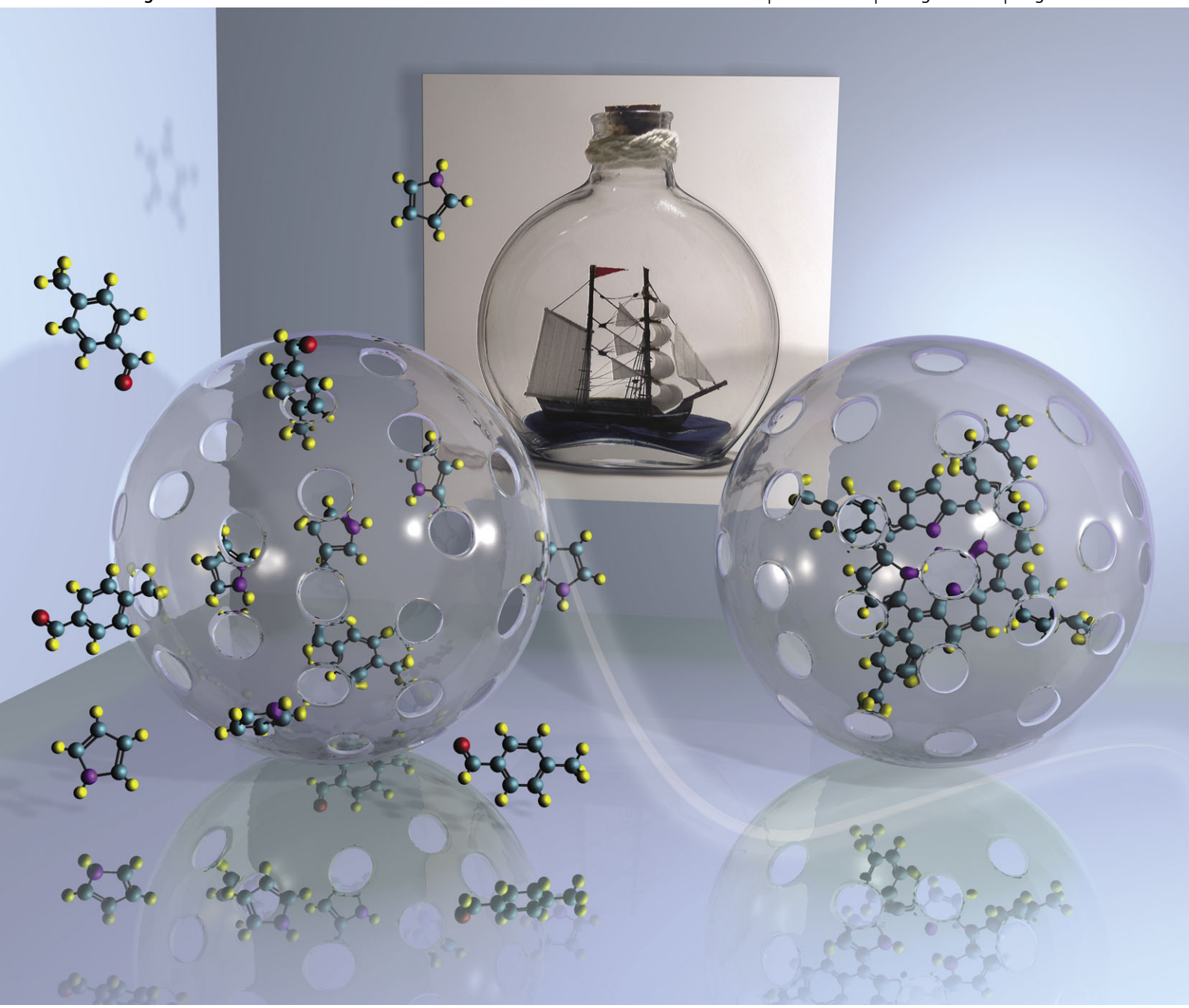

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Ship-in-a-bottle entrapment of molecules in porous nanocapsules†

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Size-selective pores in the shells of hollow polymer nanocapsules enable combined assembly and entrapment of molecules. Small building blocks enter the capsule through the pores. The assembled molecules, which are larger than the pores, remain entrapped in the nanocapsules. Porous nanometre-thin walls permit unhindered functionalization of entrapped molecules.

Entrapment of large and medium sized molecules in porous nanocapsules can lead to new functional nanodevices, such as nanoreactors, sensors, or imaging systems.[1] A common method for entrapment is creating the capsule in the presence of the target molecule.[1,2] Many useful molecules are not compatible with the capsule preparation chemistry. For example, only water-soluble molecules can be entrapped in liposome-templated nanocapsules. New methods for entrapment of molecules will broaden the scope of devices based on nanocapsules.

Here we demonstrate the first example of entrapment of medium-sized molecules created within a porous nanocapsule from small building blocks. In this approach, small building blocks enter hollow nanocapsules through the pores of the shell and are then assembled into a larger molecule (Fig. 1). This larger molecule remains entrapped within the nanocapsule because it is too big to pass through the pores. Hollow polymer nanocapsules that have shells containing nanopores with controlled size and narrow size distribution can be prepared by polymerization in the presence of pore-forming templates in the interior of liposomal bilayers.[2]

Previously, a number of molecules were entrapped in porous materials, such as zeolites or soft porous crystals, where the molecules are immobilized in highly confined spaces.[3] Such entrapped molecules have been used in catalysis.

The entrapment of molecules in hollow nanocapsules, where the interior dimensions greatly exceed the size of the entrapped molecules, is particularly interesting. Entrapped molecules would stay in a homogeneous environment. Their properties are not likely to be negatively affected by the shell of the nanocapsule. Nanometre-thin porous walls will provide ultra-fast communication with the external environment.[2] Sufficient space inside the nanocapsules will permit unhindered interactions with other molecules, such as substrates or analytes.

We chose 5,10,15,20-tetra-*p*-tolyl-21*H*,23*H*-porphine (H_2TTP) for construction within the nanocapsule (Fig. 1A). H_2TTP is an excellent example of a larger molecule (approx. 2 nm in

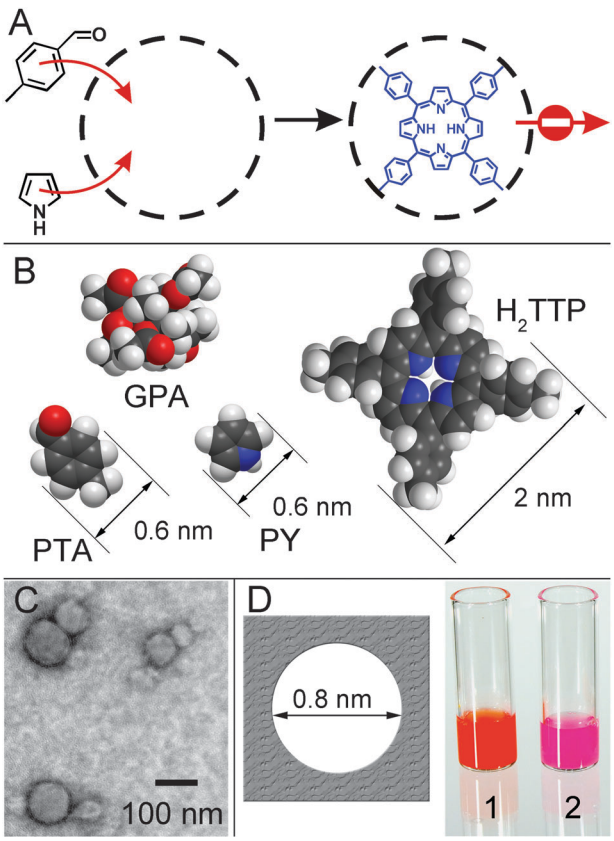

Fig. 1 (A) Combined assembly and entrapment of 5,10,15,20-tetra-*p*-tolyl-21*H*,23*H*-porphine (H_2TTP) in a porous nanocapsule. The synthesis of H_2TTP was carried out by a 30-minute reflux in acetic acid. (B) Space-filling models of building blocks pyrrole (PY) and *p*-tolyl aldehyde (PTA), pore-forming template glucose pentaacetate (GPA), and the assembled molecule (H_2TTP). Approximate smallest cross-sections are shown for PTA, PY, and H_2TTP. (C) TEM image of hollow porous nanocapsules used in this work. (D) Average pore diameter of approx. 0.8 ± 0.2 nm in the shells of nanocapsules confirmed by a colored size probe retention assay, where nanocapsules retain 0.6 nm yellow and 1.1 nm red dyes prior to pore opening (1) and release 0.6 nm probe but retain the 1.1 nm dye after opening the pores (2).[2a–c]

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cross section, Fig. 1B) built from smaller building blocks, pyrrole and *p*-tolyl aldehyde (0.6 nm each, Fig. 1B). It is easily observed with spectroscopic methods, and it can serve as a foundation for creating functional devices. In particular, metallated porphyrin derivatives have been used as catalysts,[4] sensors,[5] and oxygen carriers.[6]

In these experiments, polymer nanocapsules with an average diameter of 100 nm (Fig. 1C) were obtained by polymerization of hydrophobic monomers within the interior of lipid bilayers of liposomes.[2] Glucose pentaacetate (GPA) was used as a pore-forming template leading to the creation of pores with 0.8 ± 0.2 nm diameter (Fig. 1D).[2a–c] The pore size was confirmed with a colored size probe retention assay as described previously.[2a–c] Briefly, 1.1 nm and 0.6 nm size probes were retained within the capsule formed in the absence of pore-forming templates, and 0.6 nm probe but not the 1.1 nm probe was released when GPA was used in the synthesis of nanocapsules. Building blocks, pyrrole and *p*-tolyl aldehyde, were added to the suspension of nanocapsules in acetic acid and allowed to diffuse into the nanocapsule interior. The synthesis of H_2TTP was carried out by the reflux for approximately 30 min.[7] The reaction mixture was then cooled, and nanocapsules were precipitated with methanol.

Unentrapped H_2TTP was removed by washing nanocapsules with a mixture of methanol and chloroform (3 : 5). Nanocapsules form a gel-like precipitate in this mixture, while H_2TTP is sufficiently soluble. The formation of entrapped H_2TTP is apparent due to the strong coloration of nanocapsules. Successful synthesis was further confirmed by the fluorescence spectroscopy (Fig. 2B) that revealed characteristic emission bands $Q_x(0,0)$ at 650 nm and $Q_x(0,1)$ at 720 nm (419 nm excitation wavelength).[8] The position and relative strengths of these bands are identical for free (solid red) and encapsulated (solid black) H_2TTP (Fig. 2B). Light scattering from nanocapsules was present in UV-vis and fluorescence spectra of encapsulated porphyrins.

Entrapped H_2TTP can rapidly communicate with the exterior of the nanocapsules. To illustrate this communication, we carried out the metallation of H_2TTP with different metal salts, zinc acetate, manganese dichloride, and iron acetate (Fig. 2A).[7b] Metallation reactions can be easily observed with fluorescence and UV-vis spectroscopy. By using 419 nm as the excitation wavelength, we observe the decrease of emission at 650 nm and disappearance of the emission peak at 720 nm upon addition of zinc acetate to free and entrapped H_2TTP (Fig. 2B, dashed red and dashed black lines show the fluorescence spectra of free and encapsulated ZnTTP, respectively). Similarly, an absorbance peak at 490 nm nearly disappears immediately upon addition of zinc acetate to entrapped H_2TTP (Fig. 2C; Soret band is shifted to a higher wavelength due to the sonication of the nanocapsule sample in a chlorinated solvent).[9] Identical behavior of free and entrapped H_2TTP and instantaneous (< 1 s) spectral change suggest that the walls of nanocapsules do not hinder the transport of metal ions. These results expand our previous observation of identical protonation and deprotonation rates for entrapped and free pH-sensitive indicator dyes.[2d]

Entrapped porphyrin molecules are retained within the nanocapsules. Nanocapsules with entrapped H_2TTP and

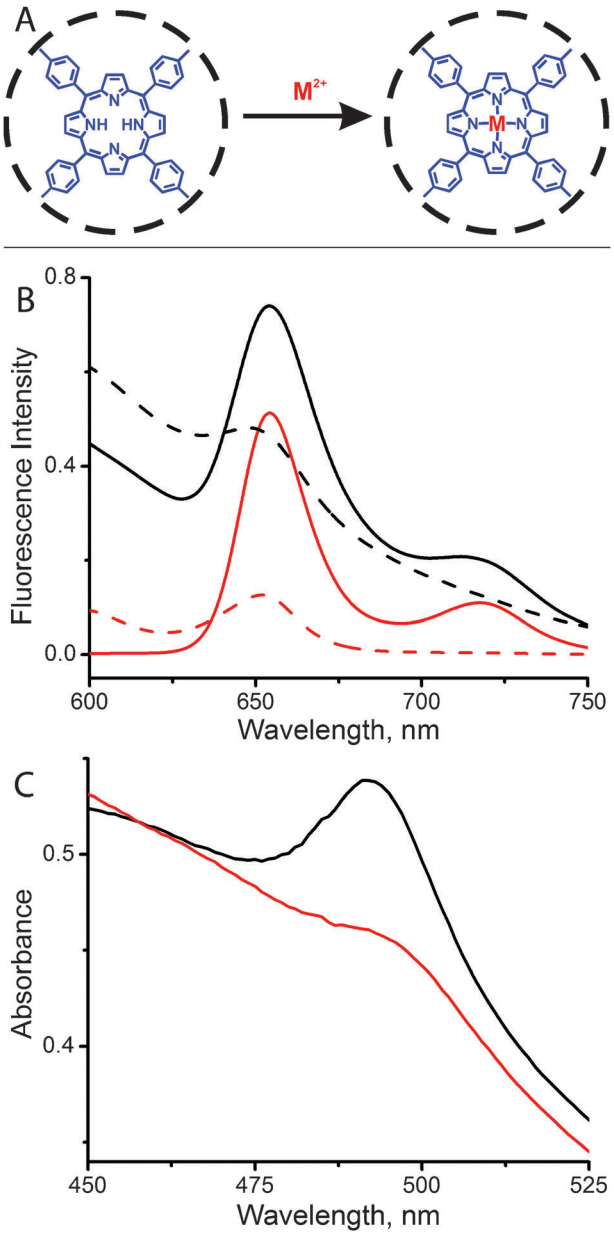

Fig. 2 (A) Schematic representation of metallation of entrapped H_2TTP by $Zn(OAc)_2$, $MnCl_2{\cdot}4H_2O$ and $Fe(OAc)_2$. (B) Fluorescence spectra of free H_2TTP (solid red line), entrapped H_2TTP (solid black line), free ZnTTP (dashed red line), and entrapped ZnTTP (dashed black line). (C) UV spectra of the entrapped porphyrin before (black) and after (red) addition of $Zn(OAc)_2$. All spectra were recorded in methylene chloride.

MnTTPCl have been repeatedly washed with methanol, and no porphyrin was found in the supernatant. The gel-like precipitate of nanocapsules is colored due to entrapped porphyrin molecules (Fig. 3, inset). After two months of standing at ambient conditions, an aliquot of the supernatant taken from the sample containing entrapped MnTTPCl showed no trace of MnTTPCl (Fig. 3, black line). For contrast, a spectrum of free MnTTPCl (Fig. 3, red line) is shown at the concentration corresponding to the release of 10% of MnTTPCl from the nanocapsules into the supernatant (0.7 μM). The amount of entrapped MnTTPCl was measured

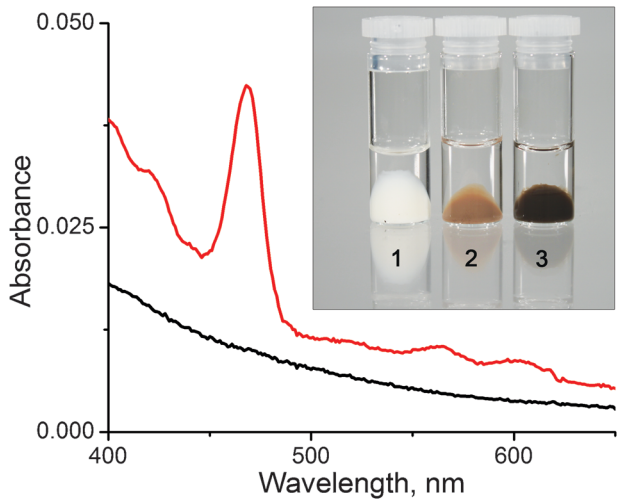

Fig. 3 Black line: UV-vis spectra of supernatant taken from a sample containing nanocapsules with entrapped MnTTPCl (inset, sample 3). Red line: supernatant mixed with free MnTTPCl added in the concentration corresponding to the release of 10% of entrapped MnTTPCl (0.7 μM). Inset: blank nanocapsules (1), nanocapsules with entrapped H_2TTP (2), and nanocapsules with entrapped MnTTPCl (3) in methanol.

by atomic absorption spectroscopy. In similar experiments, no release of H_2TTP, ZnTTP, and FeTTP was observed. Long-term retention of the entrapped porphyrin molecules confirms the successful implementation of the underlying idea of this study, the combined assembly and entrapment of molecules in porous nanocapsules. The ability to vary the pore size by using different pore-forming templates, demonstrated previously,[2b] will permit tuning the pores for entrapment of different molecules. This approach is likely to be broadly applicable to various molecules assembled from small building blocks, including organometallic complexes, macrocycles, *etc*.

In summary, we showed that the size-selective pores in the walls of hollow nanocapsules enable simultaneous assembly and entrapment of molecules. In this approach, building blocks that are smaller than the pore size enter the nanocapsule and assemble into a molecule with the cross section exceeding the pore size. This newly assembled molecule remains entrapped within the nanocapsule. Porous walls permit unhindered communication of entrapped molecules with external components that are smaller than the pores.

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