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Preparation of polycyclodextrin hollow spheres by templating gold nanoparticles

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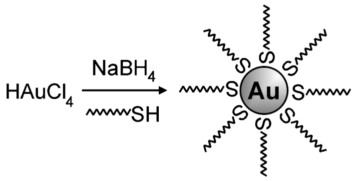
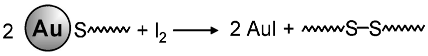
Oxidation of gold nanoparticles protected by thiolated β-cyclodextrin molecules, leads to formation of water-soluble polycyclodextrin nanocapsules held together by S–S bonds.

Recent advances in supramolecular chemistry have given chemists unprecedented control over the composition and shape of nanoscopic objects. An example of such development is the synthesis of nanometer-sized organic hollow spheres, which can find numerous applications in drug delivery/targeting, extraction and as nanoreactors.[1] Here, we describe a new method for preparation of nanometer-sized hollow, monolayer-thick spheres using thiolated β-cyclodextrins templated around gold nanoparticles.

Reduction of Au(III) compounds in the presence of thiols results in the formation of Au nanoparticles coated with organic shells [[eqn. (1)].[2] Re-oxidation of such nanoparticles with iodine is known to dissolve gold as a mixture of Au(I) and Au(III) complexes[3] and liberate organic substrates as disulfides [eqns. (2) and (3)].[4,5]



(1)



(2)

$$\mathrm{AuI} + \mathrm{I_3}^- \rightleftarrows \mathrm{AuI_4}^- \quad (3)$$

Our strategy relies on these disulfide bridges to form hollow spheres. Indeed, if organic substrate molecules (R–SH) possess several thiol groups, then formation of multiple S–S bonds in reaction (2) would cross-link the whole structure. Such disulfide bridges are often used to stabilize supramolecular assemblies.[6] A minimum of three thiol groups per substrate molecule is required for efficient cross-linking.

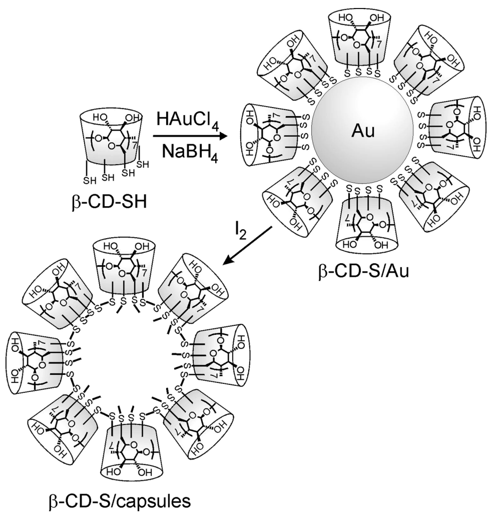
To test this hypothesis, we synthesized 2.3 nm Au nanoparticles coated with a monolayer of thiolated β-cyclodextrin molecules (Scheme 1, β-CD-S/Au), according to a recently published procedure.[7] Every molecule of thiolated β-cyclodextrin (β-CD-SH) contains seven thiol groups, and formation of disulfide bonds will therefore lead to multiple cross-linking of the organic shell (Scheme 1).

Aqueous β-CD-S/Au nanoparticles were added to a dilute solution of excess I_2 in aqueous KI to effect oxidation (Scheme 1). Reaction could be monitored by the disappearance of the brown colour of the Au nanoparticles. Excess iodine is required to prevent decomposition of unstable gold iodide [eqn. (4)].[3]

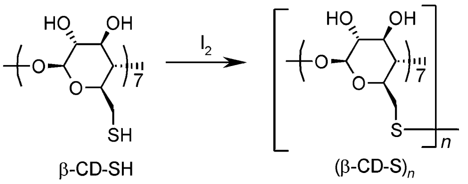
$$\mathrm{AuI_2}^- \rightleftarrows \mathrm{Au}^0 + \mathrm{I_2} \quad (4)$$

After reaction was complete, gold complexes and excess iodine were extracted into ethyl acetate, and the aqueous phase was exhaustively dialysed to remove KI and filtered to eliminate a small amount of water-insoluble material.

The resulting nanocapsules were characterized by ^{1}H NMR and FTIR spectroscopy. Importantly, NMR spectra of the nanoparticles before (β-CD-S/Au) and after removal of gold (β-CD-S/capsules) were almost identical, an observation consistent with formation of well defined structures containing β-CD-S units (Fig. 1). FTIR spectra of the nanocapsules were found to be identical with the spectrum of a polymer $(\beta\text{-CD-S})_n$ obtained by oxidation of β-CD-SH with I_2 in DMSO [eqn. (5)]. This further confirmed the proposed macrocomposition of the nanocapsules.



Scheme 1 Preparation of polycyclodextrin hollow spheres.



(5)

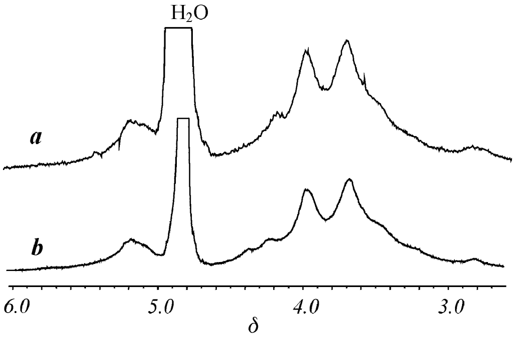


Fig. 1 ^{1}H NMR spectra (D_2O) of thiolated β-cyclodextrin/Au nanocomposites before (β-CD-S/Au, a) and after removal of Au template (β-CD-S/capsules, b).

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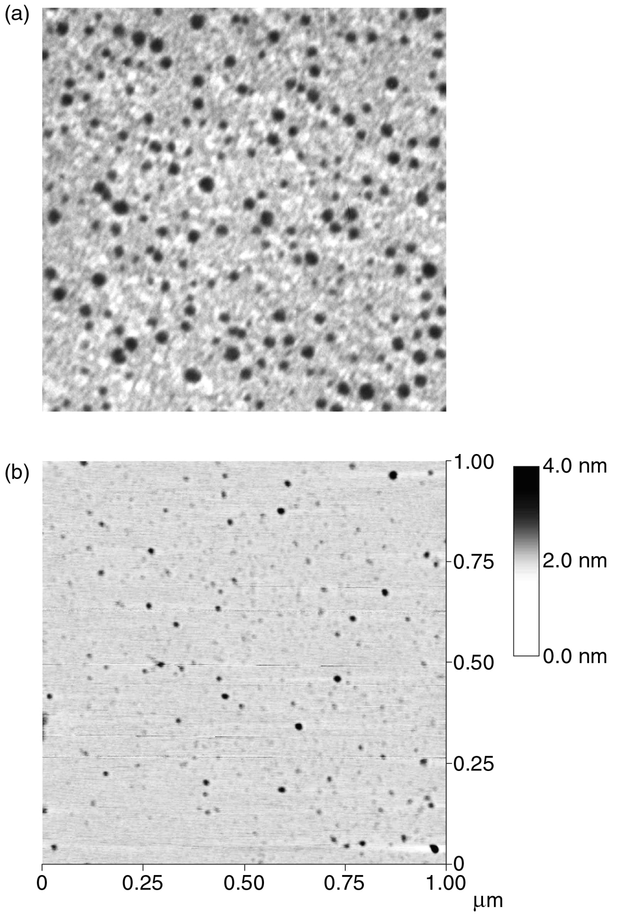

Fig. 2 (a) TEM image (100 nm × 100 nm) of Au nanoparticles protected with thiolated β-cyclodextrin (β-CD-S/Au). (b) AFM image of poly-cyclodextrin hollow spheres (β-CD-S/capsules) deposited on mica.

It proved more difficult to confirm the nanostructure of the materials obtained, *i.e.*, that they are indeed hollow spheres. Strong evidence came from solubility experiments. β-CD-SH is completely insoluble in water due to the hydrophobic nature of the SH group. At the same time, β-CD-S/Au nanoparticles are very soluble in water, as all hydrophobic groups are now hidden inside the nanoparticles, their surface being dominated by the hydrophilic OH groups (Scheme 1). Importantly, β-CD-S/capsules are also very soluble in water, which is consistent with the retention of the shell structure. In contrast, most (> 90%) of the polymer $(\beta\text{-CD-S})_n$ [eqn. (5)] is insoluble in water.

This very different water solubility of polymers $(\beta\text{-CD-S})_n$ and β-CD-S/capsules (materials which have the same molecular composition) confirms the hydrophilic nature of the proposed hollow shell structure.

Prolonged storage (over several weeks) of hollow shells in aqueous solution at room temperature leads to precipitation of insoluble disulfide polymer $(\beta\text{-CD-S})_n$ as a result of a disproportionation reaction (6) which is known to be fast for hydrophilic disulfides in water.[8]

$$2R^1\text{–SS–}R^2 \rightarrow R^1\text{–SS–}R^1 + R^2\text{–SS–}R^2 \qquad (6)$$

This further supports a non-equilibrium structure for the nanocapsules obtained and is consistent with the hollow sphere model. A better understanding of the kinetics of reaction (6) might lead to a means for controlled release of small molecules within the capsules.

The ultimate proof of the hollow shell structure should come from microscopy. Unfortunately, we have been unable to obtain electron microscopy (TEM) images of hollow spheres due to their small size and low contrast. However, AFM analysis of hollow spheres deposited on mica from a dilute aqueous solution, showed nearly monodisperse round features.[9] The diameter of these features (*ca.* 30 nm) substantially exceeds the diameter of the Au particles [*ca.* 2.3 nm, Fig. 2(a)] due to the tip convolution,[10] which is a familiar scanning probe microscopy phenomenon. The height of the features [*ca.* 1.6 nm, Fig. 2(b)] corresponds approximately to the double height of the β-CD-SH molecule (*ca.* 0.78 nm). This might suggest that the nanocapsules collapse on the mica surface upon drying in air, but one must be cautious in interpreting height data as not much is known about the tip–surface interactions.[11] We believe that our observation of monodisperse round features strongly supports formation of hollow spheres.

The inner surface of the hollow spheres is dominated by the disulfide bonds and is therefore hydrophobic. To probe if the voids inside nanocapsules can accommodate external guests, we studied solubilisation of ferrocene, a hydrophobic molecule, in aqueous β-cyclodextrin (β-CD) and β-CD-S/capsules. Ferrocene is known to form inclusion complexes with β-CD, leading to its partial solubilisation in β-CD solutions.[12] We have found that β-CD-S/capsules can solubilise *ca.* 50 times more ferrocene than β-CD in aqueous solution.[13] This result can be explained either by accumulation of ferrocene in the inner voids of the hollow spheres, or by an increase in the value of the ferrocene-β-CD binding constant. More experiments are needed to distinguish unambiguously between these possibilities.

In conclusion, we have demonstrated a new strategy for synthesizing nanometer-scale organic hollow spheres using Au colloids as templates. The whole structure is held together by S–S bonds. We are currently working on broadening the described strategy to other substrates/templates and probing the encapsulation properties of the hollow spheres.

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13 Powdered ferrocene was vigorously stirred overnight with aqueous solutions of β-CD or β-CD-S/capsules. The resultant mixture was then filtered through a 0.45 µm filter and analysed by UV spectroscopy.