

## Gold nanoshells with silica-coated magnetic cores for multimodal imaging and sensing

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Complex nanoparticles combining multimodal imaging with local sensing of physical properties or specific chemical species may lead to novel applications in biomedical research and diagnostics. However, reports that demonstrate the contrast effect of a single nanosized probe in several imaging modalities and its sensing performance at the same time are very scarce. Gold nanoshells with magnetic cores and specific organic functionalization may enable the development of such smart contrast agents with extended applicability. Their magnetic cores provide contrast effect in magnetic resonance imaging (MRI) or act as tracers in magnetic particle imaging (MPI). The gold nanoshells can be used as an exogenous contrast agent in photoacoustic imaging (PAI), and importantly, they enable surface-enhanced Raman spectroscopy (SERS). The SERS measurements can be employed either to analyze the local physical conditions based on suitable reporter molecules or to detect certain analytes based on molecular sensors. Such SERS-active molecules thus form an indispensable part of the organic functionalization, which can, however, comprise also other molecules convenient for imaging, e.g. a fluorescent tag.

The present contribution describes complex gold nanoshells with silica-coated Mn-Zn ferrite cores and an organic functionalization of two types. The functionalization of the first type is designed for pH sensing and involves a fluorescent tag as well. The performance of respective gold nanoshells is analyzed by <sup>1</sup>H NMR relaxometry, fluorescence spectroscopy, proof-of-concept PAI study, and SERS study on aqueous suspensions of varying pH. The functionalization of the second type combines a urea-based receptor and an internal standard for sensing of fluoride anions.

The complex gold nanoshells were achieved by a multistep procedure (transmission electron

micrographs of selected intermediates in Fig. 1): (i) hydrothermal synthesis of Mn<sub>0.6</sub>Zn<sub>0.4</sub>Fe<sub>2</sub>O<sub>4</sub> nanoparticles with the mean crystallite size of 12 nm [1], (ii) encapsulation into silica by the Stöber process, (iii) electrostatic self-assembly of a polyelectrolyte multilayer (formed by alternating layers of poly(sodium 4-styrenesulfonate) and poly(diallyldimethylammonium chloride)) that alters the negative zeta potential of silica to positive values, (iv) adsorption of negatively charged ≈3 nm gold seeds, (v) growth of the gold seeds to coalescence by reduction of a soluble Au(III) precursor [2], and (vi) specific organic functionalization.

For the construction of the multimodal contrast agent capable of pH sensing, the gold surface was co-functionalized with 4-mercaptobenzoic acid (MBA) as a SERS-active pH sensor and 7-mercapto-4-methylcoumarin (MMC) as the fluorescent tag [3]. The <sup>1</sup>H NMR relaxometry evidenced a very high transverse relaxivity of  $r_2 \approx 900 \text{ s}^{-1} \text{ mmol(f.u.)}^{-1} \text{ L}$  (f.u. denotes the formula unit of the Mn<sub>0.6</sub>Zn<sub>0.4</sub>Fe<sub>2</sub>O<sub>4</sub> ferrite), demonstrating its excellent properties as a negative contrast agent for T<sub>2</sub>-weighted MRI. The PAI study (Fig. 2) revealed a strong contrast effect with the maximum photoacoustic signal at ≈700 nm, which corresponded to the maximum of the surface plasmon resonance in the UV-Vis spectrum. Finally, the SERS measurements showed a pH-dependent spectral response, which can be attributed to the different extent of protonation of the MBA reporter molecules (Fig. 3).

For the case study on the use of gold nanoshells for sensing of fluoride anions, the nanoshells were co-functionalized with the molecular sensor *N*-(4-thiophenyl)-*N'*-(4-nitrophenyl)urea, synthesized directly on the gold surface, and the internal standard 4-nitrothiophenol (NTP). The SERS study in acetonitrile solutions of tetrabutylammonium fluoride (Bu<sub>4</sub>NF) (Fig. 4) showed that the spectral response of the urea sensor was dependent on the concentration of the fluoride in the range of 10<sup>-5</sup>–10<sup>-1</sup> mol L<sup>-1</sup> (Fig. 5). To facilitate the analysis, a model urea-based sensor was synthesized and Raman spectroscopy measurements free of gold nanostructures were carried out. The interpretation of the spectra and fluoride-induced effects was performed based on an extensive DFT study.

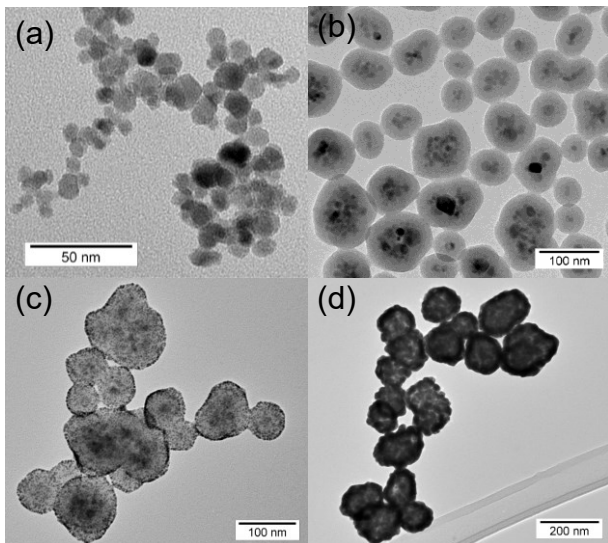
### Acknowledgement

The participation of the first author in the conference is supported by the ESIF and MEYS (project FZU researchers, technical and administrative staff mobility - CZ.02.2.69/0.0/0.0/18\_053/0016627). The experimental work was primarily supported by the Czech Science Foundation (project no. 19-02584S).

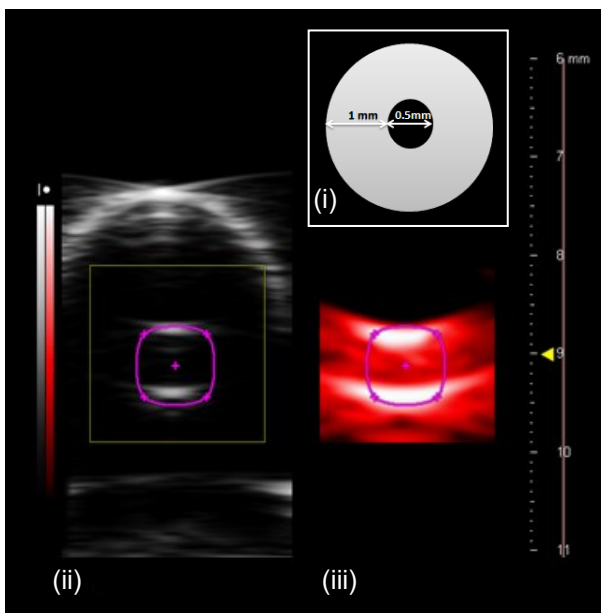
## References

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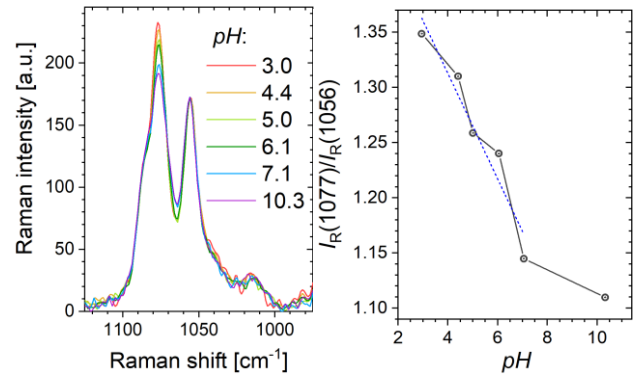
## Figures



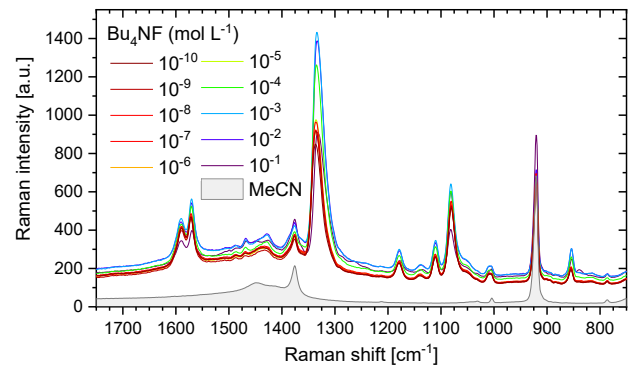
**Figure 1.** Transmission electron micrographs illustrating the main intermediates in the multistep synthesis of gold nanoshells with magnetic cores: (a)  $\text{Mn}_{0.6}\text{Zn}_{0.4}\text{Fe}_2\text{O}_4$  ferrite nanocrystallites, (b) silica-coated nanoparticles, (c) the intermediate decorated with ultrafine gold seeds, and (d) the final gold nanoshells.



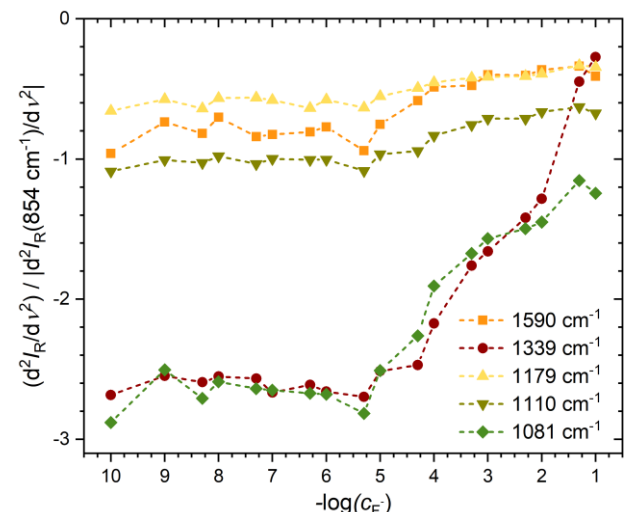
**Figure 2.** PAI study on an aqueous suspension of gold nanoshells, functionalized with MMC and MBA, in a silicone tube: (i) schematic cross-section of the tube filled with the suspension with a concentration of  $0.64 \text{ mmol(f.u.) L}^{-1}$ , where f.u. denotes  $\text{Mn}_{0.6}\text{Zn}_{0.4}\text{Fe}_2\text{O}_4$ , (ii) ultrasound image, (iii) photoacoustic image at 680-nm excitation.



**Figure 3.** SERS study on pH sensing by the gold nanoshells functionalized with MMC and MBA. (a) Detail of the spectral region with the pH-dependent MBA band at  $1077 \text{ cm}^{-1}$  and the MMC band at  $1056 \text{ cm}^{-1}$ , to which the spectra were normalized. (b) The dependence of the ratio of band intensities at  $1077 \text{ cm}^{-1}$  and  $1056 \text{ cm}^{-1}$  on pH, complemented by linear fit in the range of  $\text{pH} = 3\text{--}7$ .



**Figure 4.** SERS spectra of gold nanoshells functionalized with the urea-based sensor and NTP and measured in acetonitrile with varying concentration of  $\text{Bu}_4\text{NF}$ .



**Figure 5.** The evolution of intensities of selected bands in the second derivative with the addition of  $\text{Bu}_4\text{NF}$ , rescaled to achieve the unit intensity of the NTP band at  $854 \text{ cm}^{-1}$ .