

Helicene grafting on halloysite nanotubes for drug delivery: layer structure, surface selectivity and pH triggered drug release

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Halloysite nanotubes (HNTs) have recently emerged as promising candidates for targeted drug delivery [1]. HNTs are low-toxic and low-cost aluminosilicate clays with nanotubular structure, presenting a positively charged $\text{Al}(\text{OH})_3$ inner lumen and a negatively charged SiO_2 outer surface, which can support a selective functionalization of the two surfaces. In this work, we investigated the loading and release mechanisms of the tetrathia[7]helicene (7-TH) derivative linked via an imine bond to HNTs. The 7-TH scaffold displays promising intercalation properties for DNA, with a high degree of enantioselective recognition [2]. Moreover, a 7-TH derivative showed potent inhibitory activity against telomerase, demonstrating the great potential of 7-TH as therapeutic cytotoxic molecules [2,3]. We analyzed functionalized HNTs as well as Al_2O_3 and SiO_2 layers, as models of the inner and outer surfaces, by means of surface-sensitive synchrotron-based techniques (XPS, UPS and NEXAFS spectroscopies). The oxide surfaces were analyzed both before and after functionalization with helicene derivatives through a (3-aminopropyl)triethoxysilane (APTES) linker [4]. Furthermore, the effect of a treatment in acidic conditions was investigated to prove the release of the helicene moiety from the oxide carrier at the extracellular pH of tumor cells. The surface state and atomic ratios of key elements within the organic layer determined by XPS proved the successful coupling of the helicene aldehyde to the APTES-functionalized films, clarifying differences in the reactivity of the two oxides. The sulfur peak confirmed the results obtained on the model films, supporting the reliability of the two adopted model surfaces. Moreover, NEXAFS results provided indication of a preferential orientation of helicene moieties at the oxide surface, which is lacking in APTES-functionalized layers. A further confirmation of the complete release of helicene moieties upon treatment in mild acidic conditions was given by NEXAFS spectra, showing a random orientation of the C and N functional groups after the release treatment. Preliminary *in vitro* toxicity tests on cancer cell lines characterized by different extracellular pH values show data consistent with a pH-triggered release of the 7-TH moiety, as also supported by kinetics data about the release in various physiological conditions. Work is currently under way to achieve a selective functionalization of the inner and outer surfaces by orthogonal functionalization strategies.

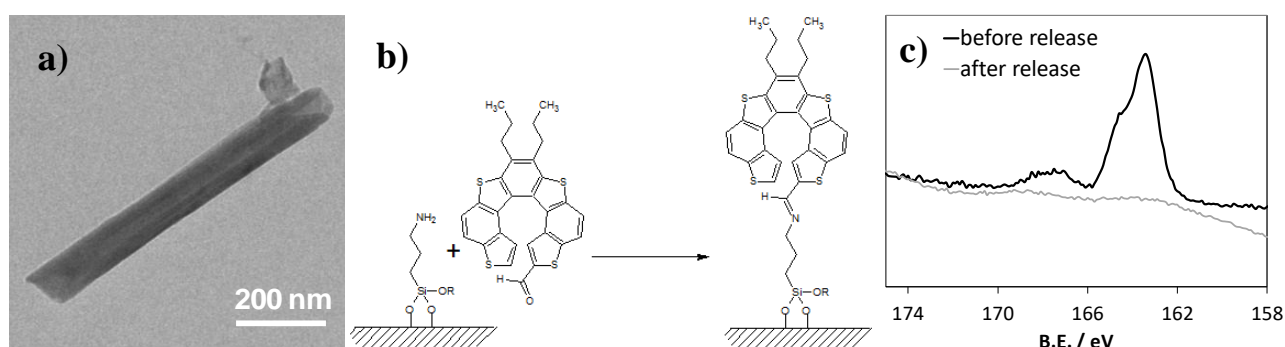


Figure 1. a) TEM image of a halloysite nanotube; b) Proposed reaction mechanism between the helicene derivative and the APTES-grafted surface; c) S 2p region of alumina films functionalized with helicene before and after release.

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