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Calixresorcinarene-capped silver nanoparticles as new supramolecular hybrid nanocontainers

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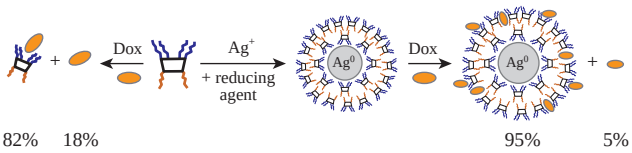
The synthesis of small (2–3 nm) silver nanoparticles in the presence of new amidoaminocarboxylic tetrapentylcalix[4]-resorcinarene and the binding of the antitumor drug Doxorubicin by a macrocycle in solution and on the surface of nanoparticles are described.



Silver nanoparticles (Ag NPs) are widely used in biology and medicine due to their antimicrobial, antifungal and antibacterial activity; recently, they were also used for targeted drug delivery.[1,2] Despite of the discussed toxicity of Ag NPs, they exhibit advantages, such as simple synthesis routes, tunable morphology,[3] high surface-to-volume ratios, intracellular delivery, and large plasmon field areas,[4,5] and can be recommended as ideal biosensors or photo-controlled delivery systems. A combination of NPs with drugs improved the efficiency, specificity, tolerability and therapeutic index of a drug.[6] The surface modification of NPs by supramolecular macrocycles significantly enhanced the characteristics of both components.[7,8] On the one hand, it increased the stability and biocompatibility of NPs and the permeability of lipid membranes to them, and, on the other hand, it improved the receptor properties of macrocycles. As a rule, amphiphilic calixresorcinarenes are low toxic; they easily stabilize the metal NPs surface through noncovalent interactions[9,10] and enhance the receptor properties owing to the cooperative effect of molecules in self-associates in solution and on the surface.[11,12] The aim of this work was to synthesize silver NPs stabilized by amphiphilic calix[4]resorcinarene, and to study the concentration of the biologically active substrate Doxorubicin (Dox) on the shells of NPs due to its binding by macrocycle molecules. Doxorubicin is a well-known anticancer drug;[13] however, its low therapeutic index requires the use of large doses that cause side effects.[1] The latter can be decreased by the concentration and targeted delivery of Dox as a part of nanocarriers (such as liposomes[13,14] and dendrimer–Dox conjugates[15,16]) or supramolecular NPs.[1]

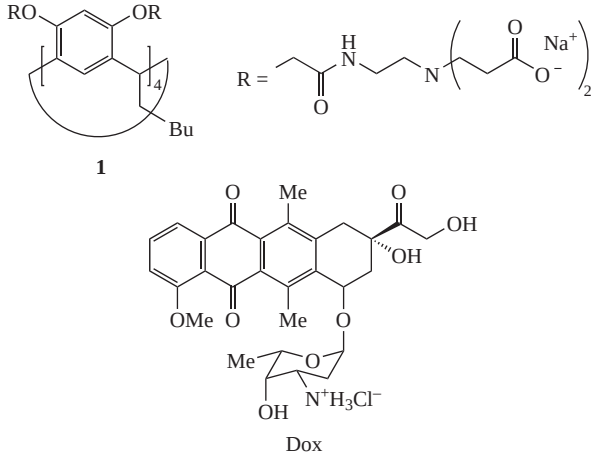


Figure 1 Structures of macrocycle **1** and Doxorubicin hydrochloride (Dox).

For the effective stabilization of silver NPs and drug binding, we synthesized tetrapentylcalixresorcinarene **1** modified with amidoaminocarboxylic groups at the upper rim (Figure 1). The carboxy groups of the macrocycle stabilize the silver NPs due to electrostatic interactions with residual silver ions on their surface, and they can participate in electrostatic interactions with the ammonium groups of Dox. The aromatic macrocycle cavity promotes π–π interaction with the anthracene moiety of Dox. Alkyl substituents in the lower rim provide hydrophobic interactions, which are necessary for the self-association of macrocycle molecules on the NPs surface *via* tail-to-tail interactions. The amino and amido groups of the upper rim substituents can form intra- and intermolecular hydrogen and donor–acceptor bonds, bringing the macrocycle closer to biological objects and providing the additional binding of Dox. The synthesis of macrocycle **1** was carried out in several steps (Figure S1, Online Supplementary Materials). Its structure was confirmed by ^{1}H and ^{13}C NMR and FTIR spectroscopy and elemental analysis (Figures S2, S3). The ^{1}H NMR spectrum of the macrocycle contains two sets of proton signals of aromatic rings (6.38, 6.81 and 5.84, 7.23 ppm, Figure S2), indicating the slow conformational boat-cone–boat exchange[17,18] in **1** due to bulky hydrophilic substituents. The boat conformation of the molecules of **1** suggests the existence of distinct hydrophilic and hydrophobic areas in the molecules that define their tendency to form self-associates in aqueous solutions. We used Fourier transform pulsed-gradient spin-echo NMR (FT-PGSE NMR) spectroscopy for determining the self-diffusion coefficients of the particles in solution. A decrease in the self-diffusion coefficient of macrocycle **1** with increasing its concentration indicates the enhancement of self-association in solution (Table 1, see Online Supplementary Materials for experimental details).

The Ag NPs stabilized by **1** were prepared by chemical reduction. An aqueous solution of sodium borohydride (0.5 mM) was added to an aqueous solution of silver nitrate (0.5 mM) and the macrocycle (0.5 mM) with stirring at room temperature.