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Water-Soluble Pd_8L_4 Self-assembled Molecular Barrel as an Aqueous Carrier for Hydrophobic Curcumin

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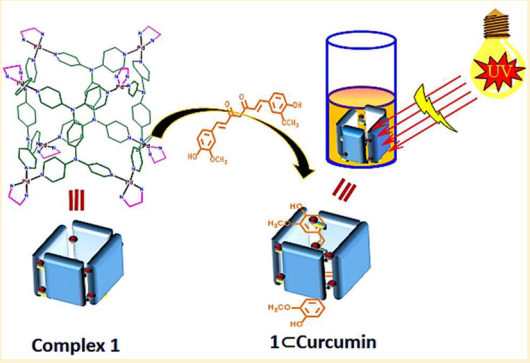
Supporting Information

ABSTRACT: A tetrafacial water-soluble molecular barrel (**1**) was synthesized by coordination driven self-assembly of a symmetrical tetrapyridyl donor (**L**) with a *cis*-blocked 90° acceptor [*cis*-(en)$Pd(NO_3)_2$] (en = ethane-1,2-diamine). The open barrel structure of (**1**) was confirmed by single crystal X-ray diffraction. The presence of a hydrophobic cavity with large windows makes it an ideal candidate for encapsulation and carrying hydrophobic drug like curcumin in an aqueous medium. The barrel (**1**) encapsulates curcumin inside its molecular cavity and protects highly photosensitive curcumin from photodegradation. The photostability of encapsulated curcumin is due to the absorption of a high proportion of the incident photons by the aromatic walls of **1** with a high absorption cross-sectional area, which helps the walls to shield the guest even against sunlight/UV radiations. As compared to free curcumin in water, we noticed a significant increase in solubility as well as cellular uptake of curcumin upon encapsulation inside the water-soluble molecular barrel (**1**) in aqueous medium. Fluorescence imaging confirmed that curcumin was delivered into HeLa cancer cells by the aqueous barrel (**1**) with the retention of its potential anticancer activity. While free curcumin is inactive toward cancer cells in aqueous medium at room temperature due to negligible solubility, the determined IC_{50} value of ~14 μM for curcumin in aqueous medium in the presence of the barrel (**1**) reflects the efficiency of the barrel as a potential curcumin carrier in aqueous medium without any other additives. Thus, two major challenges of increasing the bioavailability and stability of curcumin in aqueous medium even in the presence of UV light have been addressed by using a new supramolecular water-soluble barrel (**1**) as a drug carrier.



INTRODUCTION

Coordination driven self-assembly has emerged as a convincing tool to design and construct a wide variety of discrete assemblies ranging from two-dimensional (2D) to three-dimensional (3D) architectures.[1,2] The unique interior environment of these 3D architectures has been exploited for myriad applications, such as host−guest chemistry,[3] stabilization of reactive species,[4] drug delivery,[5] supramolecular catalysis,[6] and as sensors.[7] Various design strategies, such as edge- and face-directed self-assembly, symmetry interaction model, and molecular library approach have been utilized to synthesize coordination cages with varying cavity size.[8] The final fate of a self-assembly is not only controlled by the direction and predictable nature of the metal−ligand coordination sphere but also by the reaction conditions. Symmetrical ligands owing to their predictable coordination ability and the ease of convergence have always been the choice to construct discrete closed-shell architectures. Most of the reported 3D discrete architectures of Pd(II)/Pt(II) acceptors have closed-shell topology with smaller windows in comparison to their large internal cavity space, which in turn restricts both the ingress and egress of the bigger guest molecules.[9] In this respect, cylindrical and barrel-shaped architectures are very promising, as they have windows similar to their cavity size. Barrel-shaped molecules have immense importance in biological systems, as β-barrel proteins allow the diffusion of small molecules and ions through cell membranes.[10] Despite the fact that there has been mounting interest in barrel-shaped molecules with large cavities due to various applications, the synthesis of discrete water-soluble barrel-shaped architectures by metal−ligand self-assembly remains very challenging.[11]

On the other hand, turmeric has been a favorite choice as a spice, topical household remedy for treatment of sprains and swellings, as well as in Ayurveda for various ailments.[12] The main active component of turmeric is curcumin, which is widely known for its pharmacological activities, including anti-inflammatory, antitumor, antioxidant, and antiamyloid properties.[13] Phase I clinical trials in humans have shown that curcumin is safe even at high doses (12g/day).[14] Despite its

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