Modular Metal–Organic Polyhedra Superassembly: From Molecular-Level Design to Targeted Drug Delivery

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Targeted drug delivery remains at the forefront of biomedical research but remains a challenge to date. Herein, the first superassembly of nanosized metal–organic polyhedra (MOP) and their biomimetic coatings of lipid bilayers are described to synergistically combine the advantages of micelles and supramolecular coordination cages for targeted drug delivery. The superassembly technique affords unique hydrophilic features that endow individual MOP to act as nanobuilding blocks and enable their superassembly into larger and well-defined nanocarriers with homogeneous sizes over a broad range of diameters. Various cargos are controllably loaded into the MOP with high payloads, and the nanocages are then superassembled to form multidrug delivery systems. Additionally, functional nanoparticles are introduced into the superassemblies via a one-pot process for versatile bioapplications. The MOP superassemblies are surface-engineered with epidermal growth factor receptors and can be targeted to cancer cells. In vivo studies indicated the assemblies to have a substantial circulation half-life of 5.6 h and to undergo renal clearance—characteristics needed for nanomedicines.

The desire to improve drug efficacy, enhance targeted delivery to specific sites, and reduce side effects by controlling drug pharmacokinetic and biodistribution profiles has remained the main driving force for the development of drug delivery systems over the past two decades.[1] Among all of the developed nanocarriers (e.g., micelles, liposomes, and mesoporous silica nanoparticles (NPs)),[2] nanosized metal–organic polyhedra (MOP) obtained upon metal–ligand coordination have attracted increasing attention for drug delivery owing to the highly designable nanoarchitectures, well-defined pore cavities, as well as diverse chemical properties and functions.[3] In this field, Therrien et al. presented a series of organometallic cages as anticancer drug delivery vehicles for photodynamic therapy.[4a,b] Lippard and co-workers reported a well-defined metal–organic octahedron that can enhance the delivery of cis-platin prodrugs to cancer cells.[4c] In addition, Isaacs and co-workers highlighted the potential of host–guest interactions, by combining MOP with cucurbituril, for enhanced delivery of chemotherapeutic drugs.[4d,e] Although many MOP-based supramolecular systems have been developed for drug delivery applications,[5] compared to the well-developed NP-based systems such as mesoporous silica NPs,[6] the use of MOP for drug delivery is still in its infancy. This is especially the case of research concerning targeted drug delivery for cancer therapy. A major limitation of MOP as nanocarriers is their rapid renal clearance and short circulation time owing to their small size, which is typically below the filtration barrier of the glomerulus (i.e., ≈5.5 nm).[4d,e] Furthermore, using coordination complexes for targeted therapy requires their functionalization with various targeting ligands consisting of small molecular moieties or large antibodies. However, the design and synthesis of the required organic linkers are highly challenging.

To overcome these limitations, we describe for the first time the superassembly of MOP. The proposed fabrication technique affords a simple synthesis process and the organization...
of individual MOP to form advanced hierarchical structures. Specifically, the superassembly of MOP supported micelles (MOP$_{sa}$@micelle) for targeted drug delivery is described (see Scheme 1a). The key fabrication point is the decoration of the outer surface of the MOP with hydrophobic chains to transform MOP units into nanobuilding blocks that can self-assemble into larger and well-defined superassemblies within micelles. This approach is different from the reported molecular building block (MBB) approach that is used to construct metal–organic framework (MOF)-based lipid bilayers,[2d] where the open metal sites of MOF units allow further coordination of additional organic ligands to form MOF NPs (Scheme 1b). Nonetheless, the MBB approach typically affords limited size control, whereas the superassembly approach described herein provides homogeneous size distributions in broad ranges of diameters through the simple control of the MOP concentration to obtain ultrasmall single MOP@micelle and MOP$_{sa}$@micelle. In addition, owing to the highly porous nature of the MOP, various cancer drugs were controllably loaded into individual MOP units with high payloads and subsequently integrated into MOP superassemblies to form multiple drug delivery systems. Furthermore, the MOP superassembly approach enabled the modular assembly of MOPs with additional functional NPs such as fluorescent quantum dots (QDs) for multifluorescence imaging or gold NPs for enhanced bioimaging. To demonstrate the potential of the MOP superassembly concept for drug delivery, a Fujita-type MOP composed of dozens of dodecyl chains was chosen as a prototype. A dose-dependent assay for MOP$_{sa}$@micelles of different sizes demonstrated negligible hemolytic activities and long-term colloidal stability in various media, thereby mitigating possible concerns of structure disassembly during circulation. Cell viability tests further demonstrated the good biocompatibility of the MOP$_{sa}$@micelles that is related to the NP size and the molecular weight of the polyethylene glycol (PEG) that was used for surface modification. Importantly, designing MOP$_{sa}$@micelle nanocarriers with targeting moieties enabled targeted cancer cell delivery and in vivo experiments using a mouse model also confirmed the good circulation. Taken together, this novel and modular superassembly approach combines the synergistic advantages of micelles (e.g.,

**Scheme 1.** Schematic illustration of a) the design and construction of drug delivery nanocarriers (single MOP or MOP superassembly-supported micelle) based on a modular superassembly approach and b) the solution synthesis of MOF NP-supported lipid bilayers based on MBB approach.
low inherent toxicity and long circulation time) and the MOP superassembly (e.g., highly controlled architecture, stability, and high payloads of multiple cargos), and promotes the design of MOP-inspired nanocarriers for targeted cancer therapies.

A giant Pd\textsubscript{24}L\textsubscript{48} Fujita-type spherical framework (≈7.2 nm) composed of up to 48 decorations of dodecyl chains (denoted as Pd\textsubscript{24}L\textsubscript{48}-C\textsubscript{12}) was first prepared for proof of concept (Figure 1a).\textsuperscript{[6]} Dipyridyl-3-dodecyl-thiophene was first synthesized as an organic linker (ligand 1) using the Suzuki–Miyaura reaction. To prepare the coordination sphere, ligand 1 (0.1 mmol) and Pd(BF\textsubscript{4})\textsubscript{2} (50 µmol) were heated in a mixture of acetonitrile and chloroform at 70 °C for 24 h. Then, an excess amount of a mixed solution of ethyl acetate and diethyl ether (1:1 v/v) was added to promote the precipitation. The structure of Pd\textsubscript{24}L\textsubscript{48}-C\textsubscript{12} MOP was first determined by Fourier-transform infrared spectroscopy. As shown in Figure S1 (Supporting Information), the characteristic peak at 1589 cm\textsuperscript{-1} assigned to the vibration of C=N in the pyridine ring was shifted to 1610 cm\textsuperscript{-1}, indicating the coordination of Pd\textsuperscript{2+} metal ions. Based on chemical analysis, the ratio of organic ligand to Pd\textsuperscript{2+} was calculated to be ≈1.8, which is close to the exact ratio of 2. Moreover, in nuclear magnetic resonance (NMR) spectra (Figure 1b), the b and c protons of the pyridyl or thiophene groups (H\textsubscript{b} and H\textsubscript{c}) were shifted downfield by 0.20 and 0.22 ppm, respectively, upon coordination to Pd\textsuperscript{2+}. Compared with the \textsuperscript{1}H signal of free ligand 1, the \textsuperscript{1}H signal of Pd\textsubscript{24}L\textsubscript{48}-C\textsubscript{12} MOP was much broader. Diffusion-ordered NMR measurements also demonstrated a single product given the diffusion coefficient of 5.7 \times 10^{-10} m\textsuperscript{2} s\textsuperscript{-1}, which was indicative of the

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**Figure 1.** a) Self-assembly of Pd\textsubscript{24}L\textsubscript{48}-C\textsubscript{12} MOP with hydrophobic chain decoration and lateral fusion of micelles. b) \textsuperscript{1}H NMR spectra of free ligand and Pd\textsubscript{24}L\textsubscript{48}-C\textsubscript{12} MOP in DMSO-d\textsubscript{6} solvent. c) HR-TEM image of the Pd\textsubscript{24}L\textsubscript{48}-C\textsubscript{12} MOP assembly; the distance between two closed packed cages is also highlighted. d) Optimized structures of Pd\textsubscript{24}L\textsubscript{48}-C\textsubscript{12} MOP based on MM calculations. e) Dark-field STEM image of single Pd\textsubscript{24}L\textsubscript{48}-C\textsubscript{12} MOP-supported micelle and the related size distribution. f) DLS data of P\textsubscript{6}LEL-based micelle before and after loading with single Pd\textsubscript{24}L\textsubscript{48}-C\textsubscript{12} MOP NPs.
formation of larger chemical species. Furthermore, electrospray ionization and matrix-assisted laser desorption ionization time of flight mass spectrometry techniques were used to confirm the coordination structure. Although the molecular weight of the Pd24L48 cage was determined by a series of prominent peaks in \([\text{Pd}_{24}\text{L}_{48}-(\text{BF}_4^-)^m]^{m+}\) \((m/z = 17, 24, 27, \text{and } 33; \text{Figure S2, Supporting Information})\), the molecular weight of the Pd24L48-C12 cage could not be quantified by the same technique, presumably due to presence of the multiple dodecyl chains. Nevertheless, high-resolution transmission electron microscopy (HR-TEM) displayed a dense packing of Pd24L48-C12 MOPs with a distance of 4.8 nm between closest neighbors (Figure 1c). Atomic force microscopy (AFM) imaging also showed single cages with sizes of \(\approx 5.0\) nm (Figure S3, Supporting Information). All this structural information confirmed the successful formation of giant coordination spheres. Based on molecular mechanics (MM) calculations, the optimized structure of Pd24L48-C12 was obtained. As shown in Figure 1d, the rhombicuboctahedral structure of Pd24L48-C12 is highly spherical with an inscribed sphere with a diameter of 3.6 nm and a circumscribed sphere, with alkane chains, of 7.2 nm in diameter. The distance between antipodal palladium atoms was measured to be 4.0 nm.

Subsequently, the preparation of single MOP@micelle NPs followed by MOP superassembly was performed using the Pd24L48-C12 MOP nanobuilding blocks. First, to promote the superassembly of the hydrophobic Pd24L48-C12 MOP cages in an aqueous solution, a micellar solution assembled by polyoxyethylene (6) lauryl ether (\(\text{P}_6\text{LEL}\)) was added (Figure 1a,e,f). A small drop \((1 \mu\text{L})\) of an MOP solution \((0.17 \times 10^{-3} \text{ M in dimethyl sulfoxide (DMSO)})\) was added to the micellar solution, and the resulting mixture was sonicated to promote the formation of single MOP-supported micelle NPs (Figure 2a).

![Figure 2](image-url)

**Figure 2.** a) Schematic illustration of the construction of single MOP@micelle and MOP\(_{sa}\)@micelles with different size scales. b) DLS data of Pd24L48-C12 MOP-supported micelles with ultrasmall, nanometer, and micrometer sizes. c) DLS data showing size control of MOP\(_{sa}\)@micelles. d) AFM images of MOP\(_{sa}\)@micelles with nanometer size. e,f) HR-TEM images and g) simulated structure of the dense packing of Pd24L48-C12 MOP in the superassembly.
High-magnification dark-field scanning transmission electron microscopy (STEM) of the superassembly showed uniform sizes of $4.2 \pm 0.7$ nm (Figure 1e), well correlated with the molecular shell of $\text{Pd}_{24}\text{L}_{48}\text{C}_{12}$ MOP defined by the coordinated palladium ions. The hydrodynamic diameters of the micelle and MOP–micelle conjugate were determined by dynamic light scattering (DLS) to be $13.6$ and $18.8$ nm (Figure 1f), respectively. These data confirm the successful formation of single MOP-supported micelles. Moreover, with the increase of MOP concentration, larger MOP superassemblies with nanometer or micrometer sizes were generated (Figure 2a,b). Notably, the size could easily be tuned in a broad range by gradually increasing the MOP concentration (Figure 2c). The monodisperse particle size distributions of the single MOP-supported micelle ($6.8 \pm 0.6$ nm) and MOP superassemblies ($65.8 \pm 4.8$ and $100.4 \pm 14.6$ nm) were further confirmed by AFM images (Figure 2d; Figure S4, Supporting Information). TEM imaging of the air-dried samples revealed a hexagonal packing of MOPs inside the superassemblies with a long-range order on a scale of $100$ nm $\times 100$ nm (Figure 2e). The enlarged image shown in Figure 2f reveals the overlaying hexagons with a $5.4$ nm dimension. The hydrophobic interactions from the long alkane chains of closest MOPs are presumably the main driving force for the superassembly of MOP and may as a result lead to high stability during in vivo circulation. The surface area and pore volume of the MOPsa@micelle NPs were found to be inaccessible using standard argon adsorption–desorption measurements due to the kinetically closed pore of the cages and shell blocking effect as a result of dense packing of the long PEG chains (Figure S5, Supporting Information).

The cargo loading capabilities of the MOPsa@micelle nanomaterials were then investigated. The high inherent porosity of $\text{Pd}_{24}\text{L}_{48}\text{C}_{12}$ as well as the relatively large pore windows ($1.4$ nm $\times 1.4$ nm) of the cages (Figure S6, Supporting Information) suggested that various guest molecules could be loaded into the MOP nanocavity in a controlled manner. To evaluate the cargo loading capacities of our nanocarriers, three types of molecules were separately loaded, including doxorubicin hydrochloride (DOX·HCl) as a hydrophilic drug for chemotherapy, sulforhodamine B as a fluorescent dye for labeling, and Mn(III)tetra (4-sulfonatophenyl) porphyrin (MnTPPS4) as a contrast agent for magnetic resonance imaging. The successful loading of the guest molecules was confirmed in the particles after cargo loading by the characteristic absorption bands of the guest molecules displayed in the UV–vis spectra (see 503, 561, and 467 nm in Figure 3a and Figure S7 in the Supporting Information). Based on calculations from the UV–vis spectra, one $\text{Pd}_{24}\text{L}_{48}\text{C}_{12}$ MOP entity was estimated to be loaded with $22$ DOX·HCl, $38$ sulforhodamine B, and $13$ MnTPPS4, confirming the high loading efficacy. Note that the structure of the cargo-loaded MOPsa@micelle nanocarriers remained unaffected by the cargo loading (see TEM image in Figure S8 in the Supporting Information). In addition, multiple guest molecules were loaded within individual MOP, which were then superassembled simultaneously with a highly controlled molar ratio. For instance, three fluorescent molecules (6-aminocoumarin, fluorescein isothiocyanate, and sulforhodamine B) were individually loaded into different $\text{Pd}_{24}\text{L}_{48}\text{C}_{12}$ MOP samples and then integrated into MOP superassemblies with tunable sample ratios for potential multifluorescence imaging, as confirmed by UV–vis spectroscopy (Figure 3b). This controllable superassembly scheme provides a powerful approach to prepare multi-drug delivery nanosystems with precise control of the ratio for each drug by simply tuning the MOP sample ratios.

The superassembled MOP–micelle particles were then incorporated with functional materials and nanomaterials for a range of proof-of-concept studies. First, several functional nanomaterials, such as fluorescent QDs and gold nanomaterials (Figure S9, Supporting Information), were incorporated into the MOPsa@micelle carriers via one-pot during the superassembly of MOP–micelle nanocarriers. As depicted in Figure 3c, the fluorescent peak at $627$ nm for CdSe/ZnS quantum dot@MOPsa@micelle and the typical plasmon resonance peak at $529$ nm for Au NPs@MOPsa@micelle confirmed the successful doping of the MOPsa@micelle particles (Figures S10 and S11, Supporting Information). Such incorporation of functional nanomaterials into the MOPsa@micelle nanocarriers can diversify the utility and potential of our platform. Additionally, we found that the MOP superassemblies could be deposited onto polypropylene membranes as prototypes for separation applications (Figure 3d). The fabrication of the mixed membrane was realized with a controlled thickness of $\approx 2$ μm, as shown by SEM (Figure 3e). After five deposition cycles (Figure 3d), a film consisting of a dense packing of MOP superassemblies was obtained and was then applied to separate mixtures. Owing to the porosity and the reversible host–guest interactions of MOPs, the resultant membrane showed promising separation properties for sulforhodamine B-containing solutions, even after a few cycles of separation (Figure 3f).

All of these results point to multifunctional MOPsa@micelle nanocarriers and novel mixed membranes based on MOP nanocages for biomedical and separation applications.

The biocompatibility and colloidal stability of the MOPsa@micelles were then studied in view of future biomedical applications. To evaluate the concentration-dependent lysis of red blood cells (RBCs), the nanomaterials were incubated with RBCs at concentrations varying from 1 to $200$ μg mL$^{-1}$ in $1\times$ phosphate-buffered saline (PBS) solution for $3$ h. As shown in Figure 4a,b, the hemolysis percentage of RBCs for all samples increased in a dose-dependent manner. The smaller single MOP@micelle carriers caused a higher release of hemoglobin than the larger carriers. The same trend was observed with mesoporous silica nanoparticles.[8] Nevertheless, all of the nanocarriers showed negligible hemolytic activities, thus meeting the essential prerequisites of biomedical applications. The colloidal stabilities of the MOPsa@micelles were then tested in various media (PBS solution, Dulbecco’s modified Eagle medium (DMEM), and F-12K). DLS data of the MOPsa@micelle samples with different sizes showed narrow hydrodynamic size distributions with low PDI values of less than $0.2$ (Figure 4c). Notably, long-term exposure in various media ($7$ days) caused insignificant size changes, indicating long-term colloidal stability. It can be surmised that the polymeric PEG chains act as protective layers to prevent particle aggregation. The cytotoxicity profiles of the single MOP@micelle or MOPsa@micelle-based nanocarriers with different PEG chain lengths and sizes were also evaluated against two human cancer cell lines: A549 cell (lung cancer cell) and HeLa cell (cervical cancer cell). The
corresponding IC₈₀ values (concentration required to reduce cell viability to 80%) are summarized in Figure 4e. As shown in Figure 4e and Figure S12 (Supporting Information), free nanometric MOP exhibited higher cytotoxicity (IC₈₀ = 25 µg mL⁻¹) on A549 cells than MOP superassemblies with different PEG chain lengths (6, 10, and 23) (IC₈₀ = 62, 103, and 200 µg mL⁻¹, respectively), thus confirming the low inherent toxicity of PEGylation. In addition, higher PEG repetitive unit numbers ranging from 6 to 23 led to considerably reduced cytotoxicity for the MOP superassemblies, which correlates with the reported molecular weight-dependent cytotoxicity of PEG samples.[9] Additionally, size-dependent cytotoxicity effects were observed (Figure S12, Supporting Information). For ultrasmall single MOP@micelle particles, the IC₈₀ value (82 µg mL⁻¹) was much higher than that for MOPₙ micelles with larger sizes. In summary, increasing the particle size leads to reduced toxicity, and the high cell viabilities of all MOP@micelle-based nanocarriers (even at high concentrations) suggest the good biocompatibility of the hybrid nanocarriers developed herein for biomedical applications.

The potential of the biocompatible MOP–micelle carriers for cargo release was then tested in aqueous solution. The DOX drug was selected as it is a widely used anticancer drug. Drug release experiments were carried at room temperature in fresh PBS buffer solution at pH 7.4 and 5.5. The absorbances of the supernatant collected at fixed time intervals were measured to
determine the amount of DOX released under these conditions. As displayed in the release profiles of Figure 4d, nearly 36% of the total drug release at pH 7.4 and 5.5 occurred within the first 4 h, and 5% more of the total drug was released after 7 h. In this configuration of MOP and cargo, the pH had negligible influence on the release kinetics. Note that DOX may have quite strong host–guest interactions with Pd24L48-C12 MOP due to collective, weak, noncovalent interactions. When the concentration of DOX inside the MOP cavity was high, the interactions between DOX and MOP may be weakened to a certain extent due to both DOX/DOX and DOX/MOP interactions. Following the release of DOX from the MOP cavity, there may be a balance between releasing and rebinding, which leads to only a partial release of loaded drugs. Nevertheless, given the versatility of MOP and drug structure, controllable release via stimuli-responsive MOPs (e.g., light) could be envisioned to promote the construction of smart drug delivery systems with higher extents of release.

The potential of the MOPsa@micelle carriers for targeted drug delivery was eventually assessed on cancer cells. The A549 cancer cell line was selected owing to the high expression of the epidermal growth factor receptor (EGFR). Targeting was accomplished through the conjugation of biotin–NeutrAvidin–biotin moieties onto MOPsa@micelle with anti-EGFR monoclonal antibodies as depicted in Figure 5a. The preparation involved polyoxethylene (23) lauryl ether (P23LEL):1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[biotinyl(polyethylene glycol)-2000] (ammonium salt) (DSPE-PEG-2000-biotin):1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[methoxy...
Figure 5. a) Schematic illustration of the construction of EGFR-modified MOPsa@micelle for targeted drug delivery. Fluorescence microscopy images of A549 cells treated with MOPsa@micelles b) without and c) with EGFR modification after incubation for 45 min at 37 °C. Flow cytometry analysis of A549 cancer cells incubated with red fluorescent dye-loaded MOPsa@micelles d) without or e) with EGFR modification at multiple time points. f) Sustained viability of A549 cells after incubation of MOPsa@micelle with or without EGFR modification or DOX loading for 1 h.
(polyethylene glycol)-2000) (ammonium salt) (DSPE-PEG2000) with molar ratios of 92:4:4. To examine the targeting specificity, MOPsa@micelles with or without EGFR modification were incubated with A549 cells. The confocal laser scanning microscopy images of A549 cells cultured with both red fluorescent dye sulfonohodamine B-labeled MOPsa@micelles (50 µg mL⁻¹) at 37 °C for 45 min are shown in Figure Sb,c. The cellular filamentous actin network and nuclei were stained with fluorescent probes Alexa Fluor 488 phalloidin and Hoechst 33342, respectively. Significant selective binding and internalization of the EGFR-modified MOPsa@micelles to A549 cells were observed. Binding or internalization of particles without EGFR functionalization was not observed. It was thus concluded that the MOPsa@micelles were mostly internalized into the cells via receptor-mediated endocytosis. To elucidate the receptor–ligand binding kinetics, both dye-labeled MOPsa@micelles were incubated with A549 cells for different times. After incubation for 15 min, a small binding shift occurred for the control samples, even after extending the incubation time to 45 min (Figure Sd,e). Regarding the EGFR-modified samples, however, an obvious binding shift was observed within 15 min, and a maximal binding shift was observed after 45 min. The targeted cell killing efficacy of MOPsa@micelles nanocarriers against A549 cells was also measured. The viabilities of the A549 cells after being incubated for 2 h with a series of concentrations of free DOX and MOPsa@micelles with or without DOX loading were quantified. As shown in Figure S13 (Supporting Information), free DOX exhibited dose-dependent toxicity to A549 cells. In contrast, MOPsa@micelles with the same DOX loading displayed a lower toxicity, indicating that DOX had been trapped in the MOPsa@micelle nanocarrier and thus reduced the killing efficacy of DOX to the cells. To evaluate the target-specific drug delivery, A549 cells were incubated with increasing concentrations of MOPsa@micelles with or without EGFR modification or DOX loading in complete media under standard culturing conditions. In Figure 5f, compared to the MOPsa@micelles with (18.0%) or without EGFR modification (0.1%), the DOX-loaded targeted MOPsa@micelle causes much higher cell death of ~42.0%, indicating an enhanced killing efficacy that was attributed to the successful release of DOX inside A549 cells.

Furthermore, to evaluate the potential in vivo application of our newly created MOPsa@micelles, the related circulation and biodistribution were assessed using a mouse model. Mice were injected with CdSe/ZnS QD (627 nm) labeled MOPsa@micelles by retro-orbital injection at a dose of 150 µg NPs/mouse. To study the circulation half-life, at various time points following the injection, blood was collected from the eye socket of the mice to evaluate the NPs remaining in circulation. At 24 and 48 h postinjection, the MOPsa@micelles exhibited 12% and 3% overall retention in mice blood (Figure S14, Supporting Information), respectively, similar to the 11% and 2% exhibited by PEG-coated NPs.[11] The semilog plot of retention-circulation time (Figure S15, Supporting Information) illustrates an exponential decrease in particle concentration over time, indicating that the MOPsa@micelle NP circulation followed a one-way nonlinear clearance model. Based on this pharmacokinetic model, the half-life (i.e., time at which 50% of the particles are cleared) of MOPsa@micelle NP was calculated to be 5.6 h. Moreover, to analyze the related biodistribution, at 6, 12, 24, and 48 h postinjection, mice were euthanized and their liver, spleen, kidneys, heart, lungs, and blood were harvested for fluorescence analysis (Figure S16, Supporting Information). The majority of fluorescence signal was found in the two primary filtering organs (Figure S17, Supporting Information), respectively, similar to the 11% and 2% exhibited by PEG-coated NPs.[13,14] This behavior is consistent with the behavior of nanocarriers employed currently for in vivo delivery.[14] After 24 h a visible signal was found in the feces (Figure S16, Supporting Information), indicating the MOPsa@micelle NPs can be cleared from the body. These results demonstrate that our developed MOPsa@micelle NP has good in vivo residence time and clearance behavior needed for targeted cancer therapies.

In summary, we have described the first superassembly of nanosized metal–organic polyhedra and their biomimetic coatings of lipid bilayers to synergistically combine the advantages of micelles and supramolecular coordination cages for biomedical applications. The hydrophobic self-assembly of the MOP nanocages was facilitated via their surface modification using dodecyl groups, and remarkable long-range hexagonal order was visualized via high-resolution electron micrographs. Homogeneous and tunable size distributions of MOPsa@micelle particles were obtained by simply adjusting the MOP concentration. PEGylated nanomaterials showed good bio-compatibility and were stable in biorelevant media, as demonstrated by systematic in vitro studies. The MOP superassembly could be loaded with various dyes and drugs, QDs and gold nanoparticles, and could function as multidrug delivery systems with specific cargo loading amounts through the precise mixing of multiple cargo-loaded MOP samples. Through the surface modification with targeting moieties, the MOPsa@micelles were successfully synthesized and applied to cancer cells where we observed selective cytotoxicity. Finally, in vivo experiments in a mouse model demonstrated good in vivo circulation of MOPsa@micelles. The metal–organic polyhedra supra-assembly within micelles concept has thus been validated and expected to be applicable to a range of biomedical applications as well as for separation, sensing, and catalytic processes.

Supporting Information
Supporting Information is available from the Wiley Online Library or from the author.

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