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Rational Design of an Amphiphilic Coordination Cage-Based Emulsifier

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Supporting Information

ABSTRACT: Self-assembled, porous coordination cages with a functional interior find application in controlled guest inclusion/release, drug delivery, separation processes, and catalysis. However, only few studies exist that describe their utilization for the development of self-assembled materials based on their 3-dimensional shape and external functionalization. Here, dodecyl chain-containing, acridone-based ligands ($\mathbf{L^A}$) and shape-complementary phenanthrene-derived ligands ($\mathbf{L^B}$) are shown to self-assemble to heteroleptic coordination cages *cis*-$[Pd_2(\mathbf{L^A})_2(\mathbf{L^B})_2]^{4+}$ acting as a gemini amphiphile (**CGA-1**; Cage-based Gemini Amphiphile-1). Owing to their anisotropic decoration with short polar and long nonpolar side chains, the cationic cages were found to assemble into vesicles with diameters larger than 100 nm in suitable polar solvents, visualized by cryo-TEM and Liquid-Cell Transmission Electron Microscopy (LC-TEM). LC-TEM reveals that these vesicles aggregate into chains and necklaces via long-range interactions. In addition, the cages show a rarely described ability to stabilize oil-in-oil emulsions.

Molecular self-assembly is a bottom-up approach for the fabrication of nanoscale 3D architectures (macrocycles, cages, links, knots etc.) and aggregates (vesicles, gels etc.) that requires rational design of building blocks and predictable assembly pathways to yield desired structures.[1] In most of the cases, a self-assembled structure (as a discrete entity or higher-order aggregate) is a function of the "shape complementarity" of the building blocks.[2] Often, building blocks with asymmetric structure undergo directional self-assembly leading toward larger aggregates of well-defined shape; e.g., fibers, vesicles, discs, lamellae, cylinders, monolayers, and many others.[3] The recent past has seen an upsurge in the study of supramolecular aggregation of self-assembled molecules, viz. self-assembled macrocycles and cages, in solution.[4] Interestingly, the aggregation behavior of these supramolecules also tends to depend on their respective shape. Self-assembled cages have garnered a lot of attention as they possess accessible pores that make them interesting for applications in structure elucidation, stabilization of reactive molecules, reaction control and catalysis.[5] These three-dimensional nanoscale objects offer a larger variety of shapes than their two-dimensional siblings, macrocycles, which are mainly circles or polygons with a central cavity.[4] There are reports in the literature that describe the supramolecular assembly of highly symmetric coordination cages.[6,7] Recently, Stang,[8a] Johnson,[8b,c] Nitschke,[8d] and Kato[8e] reported new types of metal−organic gels by tethering coordination cages with suitable linkers (polymer chains or small-molecule-based linkers). However, rational approaches to make well-defined higher-order aggregates from this kind of supramolecules without the aid of any cross-linker are rare.[9]

Herein, we show that rationally designed, structurally anisotropic building blocks form well-defined, higher order supramolecular structures via self-aggregation. In this context, members of a new family of heteroleptic coordination cages, made up of more than one type of ligand, nonstatistically combined within the same self-assembly, offer structural anisotropy along with the ease of asymmetric functionalization in a modular fashion.[10]

Recently, we reported a Pd(II)-based heteroleptic coordination cage (C3; Figure S6) consisting of two shape-matching pairs of different bis-monodentate ligands (with backbones comprising acridone, $\mathbf{L^A}$, and phenanthrene, $\mathbf{L^B}$) that forms as exclusive thermodynamic product driven by an enthalpic effect.[10b] This result provided us with the opportunity to convert this anisotropic cage into an amphiphile by functionalizing the ligands $\mathbf{L^A}$ and $\mathbf{L^B}$ with nonpolar and polar side groups, respectively.

Based on this work, a new cage-based gemini amphiphile **CGA-1** (Cage-based Gemini Amphiphile-1; $[Pd_2(\mathbf{L^A})_2(\mathbf{L^B})_2]$·$(BF_4)_4$, $\mathbf{L^A}$ = dodecyl-functionalized acridone-based bis-monodentate ligand and $\mathbf{L^B}$ = methoxy-functionalized phenanthrene-based bis-monodentate ligand; Figure 1), which assembles into vesicles in polar solvents, was rationally designed. Interestingly, **CGA-1** was found to act as a surfactant that can stabilize oil-in-oil emulsions (herein, an emulsion of a polar solvent and a nonpolar oil; e.g., hexadecane-in-acetonitrile) that are usually stabilized by amphiphilic block copolymers[11a,b] and solid particles (Pickering emulsions).[11c] The unique set of ligands, $\mathbf{L^A}$ and $\mathbf{L^B}$, was chosen upon

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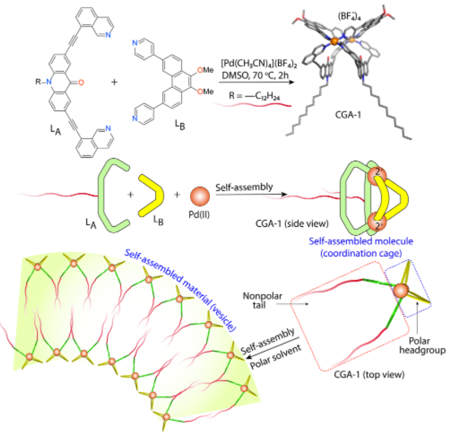

Figure 1. Shape-complementary assembly of amphiphilic cage **CGA-1** (showing its PM6-optimized structure) and cartoon representation of its aggregation to vesicles in the presence of polar solvents or solvent mixtures (acetonitrile, acetonitrile–water, and DMSO–water).

screening four differently functionalized ligand combinations (two L_A and two L_B). Each of these combinations comprised of a nonpolar (acridone-based $\mathbf{L^A}$, functionalized with alkyl chains of different length, dodecyl and hexadecyl) and a polar bis-monodentate organic ligand ($\mathbf{L^B}$, functionalized with methoxy or $(OCH_2CH_2)_2OCH_3$ ethylene glycol chains) in order to create an amphiphilic cage (Supporting Information Figures S8–S12). Intriguingly, the combinations containing longer oligoethylene glycol-functionalized $\mathbf{L^B}$ were always found to render mixtures of homoleptic cages (cages containing only one type of ligand), under otherwise identical reaction conditions, rather than the desired heteroleptic ones. This result impressively exhibits that a mere alteration in the exohedral functionalization of one of the building blocks can be sufficient to change the assembly mode from the herein desired integrative to narcissistic self-sorting (Section 1.2.3, Supporting Information).[12] Ligands $\mathbf{L^A}$ and $\mathbf{L^B}$ were prepared by following literature reported procedures (Section 1.2.1, Supporting Information).[10b] Heteroleptic coordination cage **CGA-1** = $[Pd_2(\mathbf{L^A})_2(\mathbf{L^B})_2]^{4+}$ was obtained by heating a mixture of $\mathbf{L^A}$, $\mathbf{L^B}$ and $[Pd(CH_3CN)_4](BF_4)_2$ in a 1:1:1 ratio in DMSO for 2 h at 70 °C.

It is worth mentioning that ligands $\mathbf{L^A}$ and $\mathbf{L^B}$ are able to separately react with $[Pd(CH_3CN)_4](BF_4)_2$ [Pd(II):ligand = 1:2] to form homoleptic cages $[Pd_2(\mathbf{L^A})_4]^{4+}$ (**C1**) and $[Pd_4(\mathbf{L^B})_8]^{8+}$ (**C2**), respectively (Figure S7, Supporting Information).[10b] In context of the integrative assembly experiment, however, ^1H NMR spectroscopy, $^1H-^1H$ COSY analyses and high-resolution ESI mass spectrometry (HRMS) affirmed the quantitative formation of cage **CGA-1** (Figures S4, S5, S6, and S7; Supporting Information). DFT calculations indicated that the formation of *cis*-$[Pd_2(\mathbf{L^A})_2(\mathbf{L^B})_2]$ is energetically more favorable than a tentative *trans*-configuration.[10b] Interestingly, the shape of cage **CGA-1** (top view; Figure 1) resembles a typical cationic gemini amphiphile,[13] comprising of two polar headgroups (two Pd(II) centers separated by the coordinating ligands $\mathbf{L^A}$ and $\mathbf{L^B}$) and two nonpolar alkyl chains, extending from one face of the globular body. Additionally, the presence of methoxy groups (four per cage) on $\mathbf{L_B}$ reinforce the polarity of the headgroup (Figure 1). Gemini amphiphiles are known to aggregate to micellar structures in suitably polar media.[13] This perception motivated us to probe the aggregation behavior of cage **CGA-1** in different solvents and solvent mixtures. It was seen that **CGA-1** shows limited solubility in nonpolar solvents and water but shows much superior solubility in polar aprotic solvents such as DMSO, acetonitrile and DMF. Figure 2 shows that the solid amphiphilic cage **CGA-1** (lyophilized powder obtained from as-synthesized cage solution in DMSO) forms translucent, golden-yellow solutions in acetonitrile (sample A), acetonitrile–water (1:9; sample AW) and DMSO–water (1:9; sample DW). Dynamic light scattering (DLS) studies on solutions of **CGA-1** in different solvents exhibited well-dispersed colloidal particles with various hydrodynamic diameters (100–1500 nm; Figure 2; Figure S13).

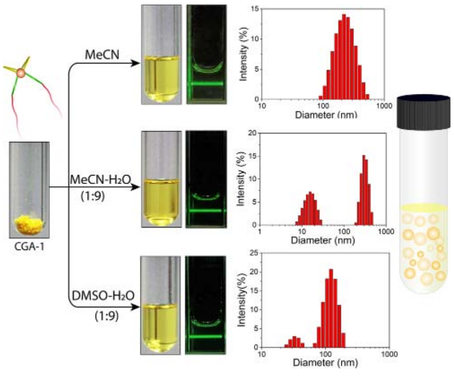

Figure 2. Preparation of colloidal solutions from freeze-dried cage **CGA-1** in acetonitrile, acetonitrile–water, DMSO–water. Each colloidal solution was found to exhibit a Tyndall effect (images of green laser-illuminated cuvettes are shown; λ = 532 nm). The graphs next to each solution show its DLS data.

To ascertain the elemental composition, the samples were analyzed using High-Angle Annular Dark-Field Scanning Transmission Electron Microscopy (HAADF-STEM, dry state) and Energy Dispersive Spectroscopy (EDS) revealing clear evidence for the uniform distribution of the elements Pd, N, S (from DMSO), and F (from BF_4^- counteranions; Figure 3 and S12) within the deformed particles. As dry-state TEM analysis was unable to identify the true nature of the aggregates,[14] we performed electron microscopy under cryogenic conditions (cryo-TEM)[15] and Liquid-Cell-TEM (LC-TEM),[16] which are well-known methods for analyzing particles in vitrified liquids and in the liquid state at ambient conditions, respectively. Cryo-TEM analysis of sample A revealed the abundance of hollow spherical particles with diameters of 200–1000 nm (Figure 3a,b, Figure S15) and a membrane thickness of 3–5 nm, which can be considered as large unilamellar vesicles (LUVs; typical diameters 100–1000 nm).[17] The small white circles around the vesicles indicate melting of the solvent during the experiment. In situ LC-TEM

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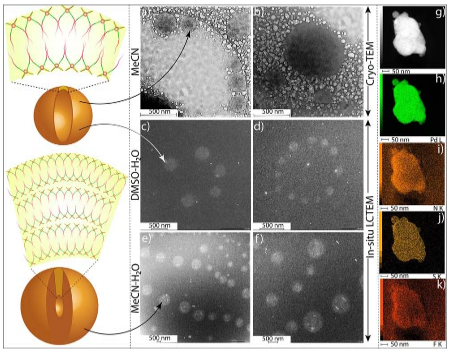

Figure 3. (left panel) Cartoon representation of the polar solvent-mediated assembly of cage-based amphiphile **CGA-1** to a large unilamellar vesicle (top) and multilamellar vesicles (bottom); (middle panel) cryo-TEM images of the hollow spherical vesicles (panels a and b) in acetonitrile (Figure S15); HAADF-STEM images of monodispersed vesicles (∼200 nm; panels c and d) in DMSO−water (1:9) and polydispersed vesicles (100−1500 nm; panels e and f) in acetonitrile−water (1:9); (right panel) HAADF-STEM image (g) and EDS maps (h−k) of a deformed vesicle (in the dry state) showing a uniform distribution of elements Pd, N, S, and F.

has been widely utilized in the recent past, primarily for the visualization of the nucleation and growth of inorganic nanomaterials from solution,[18] further in electrochemistry[19] and biology.[20] However, there are very few reports on the visualization of soft materials utilizing this technique as these are usually composed of elements with low atomic numbers ($Z < 18$, typically C, H, N, and O) and hence show weak scattering intensities (proportional to Z^2).[21] LC-TEM analysis of sample AW shows the presence of polydispersed vesicles[17] of diameters 100 to 1500 nm (Figure 3), whereas sample DW consists of monodisperse vesicles[17] of diameter ∼200 nm (Figure 3; for details, see the Supporting Information). This apparent disparity in particle size can be attributed to the inferior solubility of **CGA-1** in the acetonitrile−water (1:9) mixture than in DMSO, DMSO−water (1:9), and acetonitrile. To the best of our knowledge, these **CGA-1**-based vesicles are rare examples[22] of supramolecular materials that could be visualized by liquid-phase TEM techniques, rendering the observed vesicles formed from heavy metal-containing **CGA-1** as a prototypical case for the visualization of supramolecular materials using LC-TEM. Amphiphiles are mostly used as stabilizers for a wide variety of oil- and water-based emulsions.[23] Oil-in-oil emulsions, which can be produced in quasi-infinite number of combinations from a variety of solvents, have a plethora of practical applications in several fields; e.g., pharmaceutical science (encapsulation of hydrolytically unstable drugs, transdermal formulations, biocides etc.),[24] and industrial chemistry (reaction medium for water sensitive reactions, polymerizations using water-sensitive monomers, initiators or catalysts, etc.).[11b] In general, these biphasic systems are formed by combination of a polar liquid (formamides, acetonitrile, DMSO, polyols etc.), a nonpolar liquid (hexane, cyclohexane, higher alkanes, dichloromethane, vegetable oil etc.), and a surfactant.[11] However, in most of the cases, polymeric surfactants or solid particles (Pickering emulsion)[11c] are employed to stabilize this kind of emulsions, except for a few cases in which simple molecular surfactants were used.[25] The superior solubility of **CGA-1** in polar solvents (DMSO, acetonitrile, DMF etc.) and moderate solubility in some oils (hexadecane, isopropyl palmitate etc.) encouraged us to check its ability to stabilize an oil-in-oil emulsion system (combination of acetonitrile and hexadecane). According to the Bancroft rule, the acetonitrile should form the continuous phase in this case, as **CGA-1** has a higher solubility in it than in hexadecane.[26] Indeed, a mixture of acetonitrile and hexadecane (4:1) in the presence of 0.1 wt % (of total volume) of **CGA-1** solid produced an opaque emulsion within 10 min of homogenization (Figure 4). This emulsion remained stable for 24 h without any significant phase separation (Figure S19). On the other hand, an emulsion of acetonitrile and hexadecane containing a higher amount of the latter (e.g., acetonitrile: hexadecane = 1:4) could not be stabilized by **CGA-1** under similar experimental conditions (Figure S16), probably due to the inferior solubility

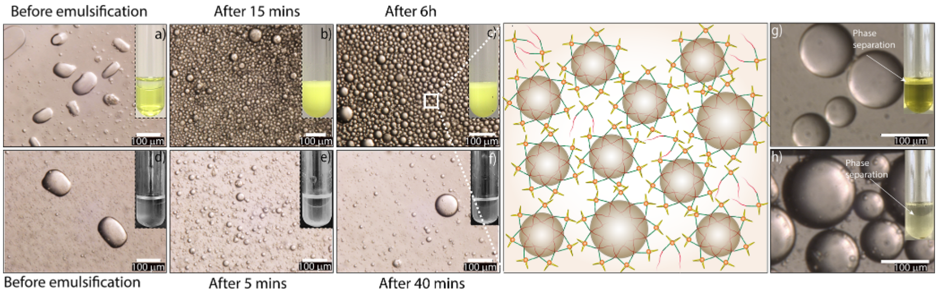

Figure 4. (a and d) Mixtures of acetonitrile and hexadecane (4:1) in presence (0.1 wt %) and absence of **CGA-1** surfactant, respectively; panels b and c show the stable emulsions of mixtures containing **CGA-1** upon homogenization; panels e and f represent no formation of emulsions in mixtures without any surfactant, which is clearly evident from the phase separation. The cartoon image represents the formation of emulsion droplets (hexadecane) in a continuous phase (acetonitrile) by **CGA-1**; panels g and h show the inability of homoleptic cages to stabilize emulsions (**C1** in DMSO−hexadecane (4:1) and **C2** in MeCN−hexadecane (4:1), respectively), proven by rapid phase separation (5 min after homogenization). All shown pictures are light-microscopy images; insets are digital photographs.

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of **CGA-1** in hexadecane than in acetonitrile. In order to figure out whether the anisotropic structure of cage **CGA-1** is responsible for its amphiphilic nature, we tried to form stable emulsions from DMSO−hexadecane (1:4) and acetonitrile−hexadecane (1:4) mixtures using the homoleptic cages (**C1** and **C2**) instead of **CGA-1** in otherwise similar conditions. Interestingly, both of these cages fail to form a stable emulsion, which verifies that the structural anisotropy and asymmetric functionalization of **CGA-1** drives it to act as a surfactant in suitable polar media (Figure S21).

In conclusion, we have reported the formation of supramolecular aggregates via a successive, two-step self-assembly process, commencing with the formation of a heteroleptic coordination cage. Cage **CGA-1**, rationally designed to act as a gemini amphiphile, forms vesicular structures in different polar solvents. These vesicles are rare examples of supramolecular materials that can be visualized by an in situ liquid cell transmission electron microscopy technique (LC-TEM). In addition, oil-in-oil emulsions (hexadecane-in-acetonitrile) could be stabilized by this cage-based amphiphile. This result opens up promising opportunities to develop tailor-made emulsifier systems based on heteroleptic coordination cages. Owing to the countless possibilities of asymmetric functionalization, a diverse library of modular cage-based surfactants, featuring different polarities, spatial dimensions, cavity sizes, and further functionalization, may emerge.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.8b10991.

Synthesis and characterization details; DLS, TEM, and emulsification experiment results (PDF)

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Notes

The authors declare no competing financial interest.

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