

Drug Delivery by Water-Soluble Organometallic Cages

Bruno Therrien

Abstract Until recently, organometallic derivatives were generally viewed as moisture- and air-sensitive compounds, and consequently very challenging to synthesise and very demanding in terms of laboratory requirements (Schlenk techniques, dried solvent, glove box). However, an increasing number of stable, water-soluble organometallic compounds are now available, and organometallic chemistry in aqueous phase is a flourishing area of research. As such, coordination-driven self-assemblies using organometallic building blocks are compatible with water, thus opening new perspectives in bio-organometallic chemistry.

This chapter gives a short history of coordination-driven self-assembly, with a special attention to organometallic metalla-cycles, especially those composed of half-sandwich complexes. These metalla-assemblies have been used as sensors, as anticancer agents, as well as drug carriers.

Keywords Bio-organometallic chemistry · Drug delivery · Half-sandwich complexes · Host–guest systems · Supramolecular chemistry

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Abbreviations

bipy	4,4'-Bipyridine
bpe	1,2-Bis(4-pyridyl)ethylene
bpp	5,15-Bis(4-pyridyl)-10,20-diphenylporphyrin
bpy	2,2'-Bipyrimidine
Cp	Cyclopentadienyl
Cp*	Pentamethylcyclopentadienyl
DAniF	<i>N,N'</i> -Di(<i>p</i> -anisyl)formamidinate
dc bq	2,5-Dichloro-1,4-benzoquinone-3,6-diolato
dhbq	1,4-Benzoquinone-2,5-diolato
doa q	1,4-Anthraquinone-9,10-diolato
donq	1,4-Naphthoquinone-5,8-diolato
dotq	Tetracene-5,12-dione-6,11-diolato
en	Ethylenediamine
phen	4,7-Phenanthroline
tpp	5,10,15,20-Tetra(4-pyridyl)porphyrin
tppp	5,10,15-Tris(4-pyridyl)-20-phenylporphyrin
tp t	1,3,5-Tris(4-pyridyl)triazine

1 Introduction

The design of molecular hosts to encapsulate guest molecules in a confined environment is receiving considerable attention due to the analogy of these systems with the mode of action of enzymes. The “lock and key” model developed by Fischer [1] to explain the specificity between a substrate and the active site of an enzyme (Fig. 1) has been the bases for the development of host–guest chemistry [2]. Pioneered by Cram, Lehn and Pedersen [3], winners of the Nobel Prize in chemistry in 1987 for their contributions to the development and use of molecules with structure-specific interactions of high selectivity, synthetic molecular hosts were initially dominated by purely organic molecules: cyclodextrins, carcerands, cryptands, cucurbiturils and cavitands. However, the last 20 years have seen the emergence of discrete inorganic and organometallic metalla-hosts able to encapsulate, temporarily or permanently, various guest molecules in their cavity, thus opening new perspectives in coordination chemistry.

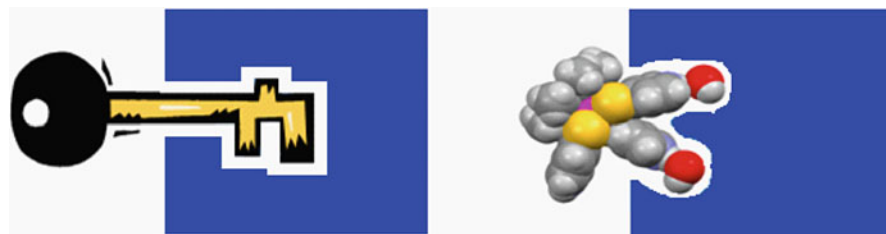


Fig. 1 Fischer’s “lock and key” model

2 Inorganic Metalla-Assemblies

In the early 1990s, Fujita [4], Stang [5], and others [6] combined 90° coordination building blocks of square-planar metal ions with linear bidentate ligands to form triangular, square and rectangular architectures. For example, the combination of $\text{Pt}(\text{PMe}_3)_2$ corner units with 1,2-bis(4-pyridyl)ethylene (bpe) has generated a triangular structure, $[\{\text{Pt}(\text{PMe}_3)_2\}_3(\text{bpe})_3]^{6+}$ (Fig. 2a) [7], while $\text{Pd}(\text{en})$ units (en = ethylenediamine) and 4,4'-bipyridine (bipy) gave a cationic square $[\{\text{Pd}(\text{en})\}_4(\text{bipy})_4]^{8+}$ (Fig. 2b) [8]. The same approach was used a few years later to generate three-dimensional assemblies by replacing linear bidentate ligands with multi-dentate connectors.

Some of the three-dimensional assemblies possess cavities large enough to accommodate guest molecules. Indeed, the $\text{M}_6(\text{tpt})_4$ cage compounds [where $\text{M} = \text{Pd}, \text{Pt}$; $\text{tpt} = 1,3,5\text{-tris(4-pyridyl)triazine}$] developed by Fujita and coworkers in 1995 [9] remain some of the most studied host–guest systems (Fig. 3a). The cavity of the cationic $\text{M}_6(\text{tpt})_4$ cages has been exploited in different ways, ranging from stabilisation of reactive species to microreactors. A tremendous number of other cage compounds using square-planar metal centres has been prepared in the last 15 years, such as the very large $\text{Pt}_{12}\text{L}'_4$ (where $\text{L}' = \text{hexapyridyl ligand}$) cage compound (Fig. 3b) from Stang [10]. These examples illustrate the potential and versatility of using coordination chemistry to generate a multitude of two- and three-dimensional structures. Nowadays, transition metals with octahedral geometry are also commonly used to prepare two- and three-dimensional architectures [11].

A series of tetrahedral assemblies built from four metal ions (e.g., Ga^{3+} , Al^{3+} , In^{3+} , Fe^{3+} , Ti^{4+} , Ge^{4+}) and six bis-catechol ligands has been prepared by Raymond's group (Fig. 4a). These chiral hosts possess a small hydrophobic cavity

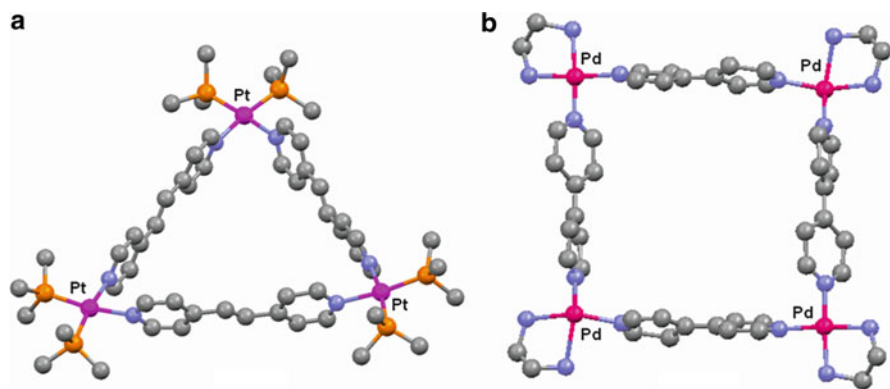


Fig. 2 Two-dimensional structures using square-planar metal ions, $[\{\text{Pt}(\text{PMe}_3)_2\}_3(\text{bpe})_3]^{6+}$ (a) [7] and $[\{\text{Pd}(\text{en})\}_4(\text{bipy})_4]^{8+}$ (b) [8]

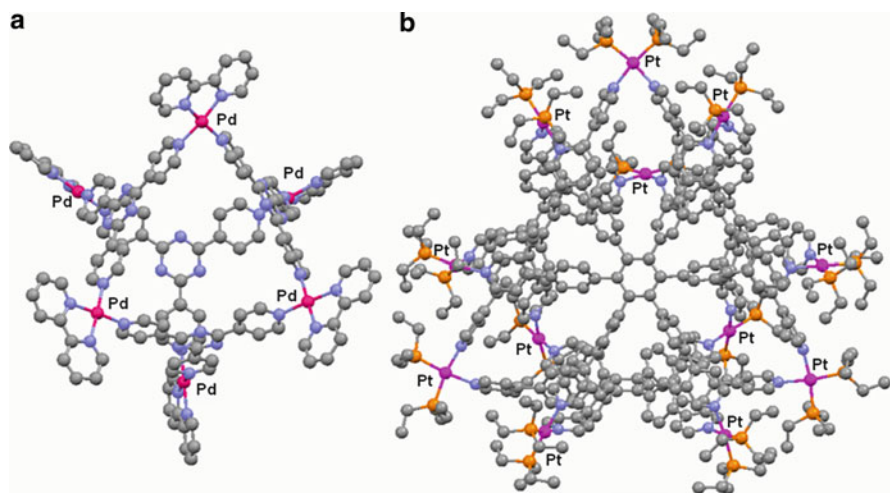


Fig. 3 Three-dimensional structures using square-planar metal ions, $[\{\text{Pd}(2,2'\text{-bipyridine})\}_6(\text{tpt})_4]^{12+}$ (a) [9] and $[\{\text{Pt}(\text{PET}_3)_2\}_{12}(\text{L}')_4]^{24+}$ (b) [10]

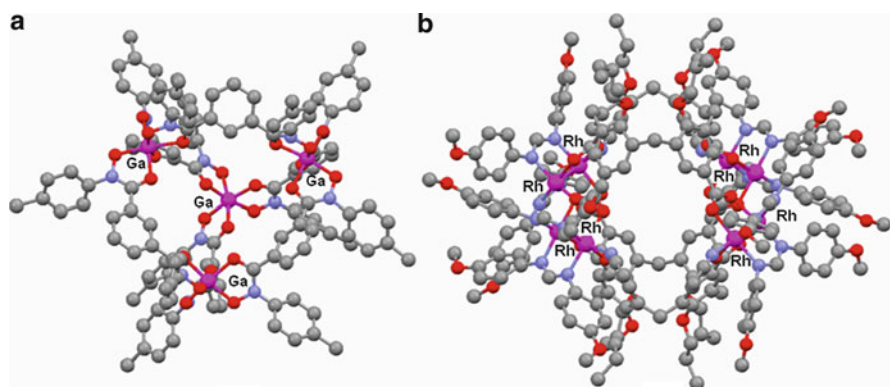


Fig. 4 Inorganic three-dimensional assemblies using octahedral metal ions, $[\text{Ga}_4\{\text{isophthal-di-}N\text{-(4-methylphenyl)hydroxamate}\}_6]$ (a) [12] and $[\{\text{Rh}_2(\text{DAniF})_2(\text{CH}_3\text{CN})\}_4(\text{calix[4]arene-tetracarboxylate})_2]$ (b) [13]

capable of accommodating cationic or neutral guest molecules [12]. Using metal–metal paddlewheel units, Cotton and Murillo have prepared several two- and three-dimensional inorganic assemblies [14]. For the largest assemblies, such as $[\{\text{Rh}_2(\text{DAniF})_2(\text{CH}_3\text{CN})\}_4(\text{calix[4]arene-tetracarboxylate})_2]$ [where $\text{DAniF} = N, N'\text{-di}(p\text{-anisyl})\text{formamidinate}$] (Fig. 4b), guest molecules have been observed in the cavity [13].

Large polyhedral coordination cages using flexible bridging pyrazolyl–pyridine chelating ligands have been prepared by Ward and coworkers [15]. These large

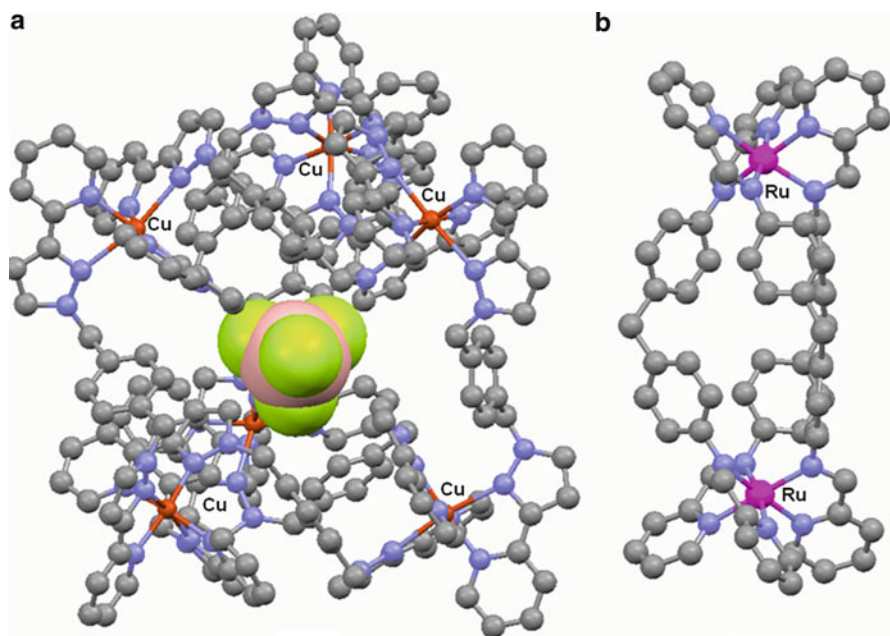


Fig. 5 Inorganic three-dimensional assemblies using octahedral metal ions, $[\text{BF}_4\text{Cu}_6\{1,4\text{-bis}((3\text{-(2-pyridyl)-1-pyrazolyl)methyl)benzene}\}_9]^{12+}$ (a) (the BF_4 anion being represented by space-filling model) [15], and $[\text{Ru}_2\{\text{bis(2-pyridylmethylene)benzene-1,4-diamine}\}_3]^{4+}$ (b) [16]

structures show dynamic behaviour in solution, thus generating M_6L_9 , M_8L_{12} or $\text{M}_{16}\text{L}_{24}$ assemblies (where $\text{M} = \text{Ni}^{2+}$, Cu^{2+} , Zn^{2+} , Cd^{2+}) depending on the nature of the metal ions used (Fig. 5a). Triple-stranded helicates composed of three bis-pyridyl-imine ligands coordinated to two ruthenium centres have been synthesised by Hannon. These supramolecular cylinders (Fig. 5b) interact with DNA [17] and some of them exhibit anticancer activity [16].

So far, these inorganic metalla-cages have been used to generate a confined environment to not only encapsulate solvent molecules, but also to protect or stabilise sensitive compounds, to recognise and trap specific guest molecules, or to act as a microreactor for specific reactions [18]. Consequently, it is not surprising that the strategies developed to build up inorganic metalla-assemblies have been applied to organometallic chemistry.

3 Organometallic Metalla-Assemblies

Built on the experience gained from the synthesis of inorganic metalla-assemblies, both, two- and three-dimensional architectures have been obtained with organometallic building blocks. The *fac*- $\text{Re}(\text{CO})_3$ corner unit was possibly the first

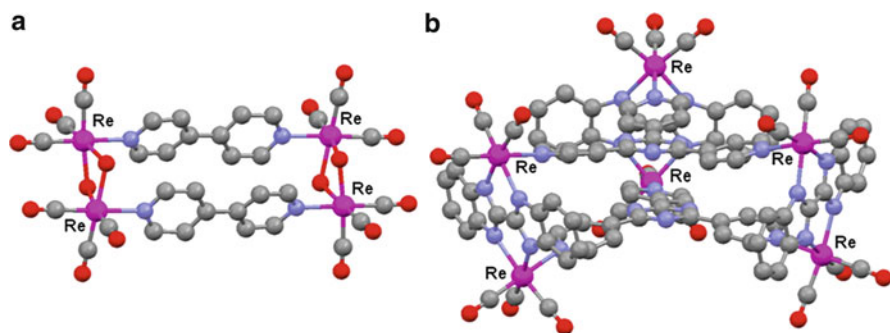


Fig. 6 Organometallic assemblies built with *fac*- $\text{Re}(\text{CO})_3$ units, $\{\text{Re}(\text{CO})_3\}_4(\text{bipy})_2(\mu\text{-O})_4$ (a) [20] and $\{\text{Re}(\text{CO})_3\}_6(\text{bpy})_3(\text{tpt})_2$ (b) [21]

organometallic building block used for the rational design of metalla-cycles and three-dimensional metalla-assemblies [19]. The facial arrangement of the carbonyl groups controls the accessibility of the three remaining coordination sites of the octahedral rhenium centre, thus preventing the formation of polymeric species. Consequently, two- and three-dimensional architectures can be obtained from *fac*- $\text{Re}(\text{CO})_3$ corners, if assembled with linear connectors and bidentate or tridentate ligands, thus forming metalla-assemblies such as the two-dimensional rectangle $[\text{Re}(\text{CO})_3]_4(\text{bipy})_2(\mu\text{-O})_4$ (Fig. 6a) [20] or the triangular metalla-prism $\{\text{Re}(\text{CO})_3\}_6(\text{bpy})_3(\text{tpt})_2$ (where $\text{bpy} = 2,2'$ -bipyrimidine) [21] (Fig. 6b).

Among other metal carbonyl derivatives, the reaction of $\text{Ru}_3(\text{CO})_{12}$ with dicarboxylic acid leads, after addition of axial ligands, to cage-like macrocycles, tetranuclear loops, hexanuclear triangles or octanuclear squares, depending on the nature of the dicarboxylato spacers [22]. Molecular triangles are obtained using terephthalic acid [23] or 4,4'-diphenyldicarboxylic acid [24], while squares are isolated with oxalic acid [25] (Fig. 7a). The hexanuclear macrocycle synthesised from 4,4'-diphenyldicarboxylic acid, $\text{Ru}_3(\text{CO})_{12}$ and trimethylphosphine, $\{\text{Ru}_2(\text{CO})_4\}_3(\text{OOC}\text{C}_6\text{H}_4\text{COO})_3(\text{PMe}_3)_6$ [23], possesses a cavity of $11.1 \times 11.1 \times 11.1 \text{ \AA}^3$, which can accommodate solvent molecules in the hydrophobic hollow space of its triangular structure (Fig. 7b).

Using a directional bonding approach, Stang and coworkers have prepared a series of dinuclear organometallic clips from platinum metal atoms coordinated to σ -bonded acetylene derivatives to generate, after addition of two tridentate ligands, organometallic metalla-prisms of different cavity sizes [26]. Similarly, dinuclear organometallic clips obtained from platinum σ -bonded acetylene were used to prepare two-dimensional assemblies of the type cyclotris[$\{2,9\text{-bis}(\text{trans-Pt}(\text{PET}_3)_2)\text{phenanthrene}\}(\text{L}'')$] (where $\text{L}'' = \text{dicarboxylic acids}$) (Fig. 8a) [27]. On the other hand, three-dimensional assemblies using gold σ -bonded alkynyl ligands have been isolated after transformation of the alkynyl units into μ_4 -methylidyne ligands under basic conditions (Fig. 8b) [28].

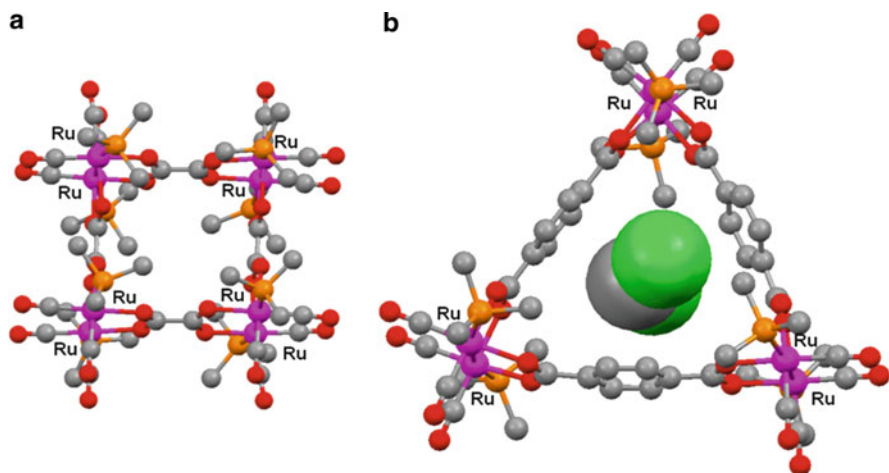


Fig. 7 Organometallic assemblies built with dinuclear ruthenium carbonyl building blocks, $\{\text{Ru}_2(\text{CO})_4\}_4(\text{OOCCH}_2)_4(\text{PMe}_3)_8$ (a) [25] and $[\text{CH}_2\text{Cl}_2 \subset \{\text{Ru}_2(\text{CO})_4\}_3(\text{OOCCH}_2)_3(\text{PMe}_3)_6]$ (b) (CH_2Cl_2 being represented by space-filling model) [23]

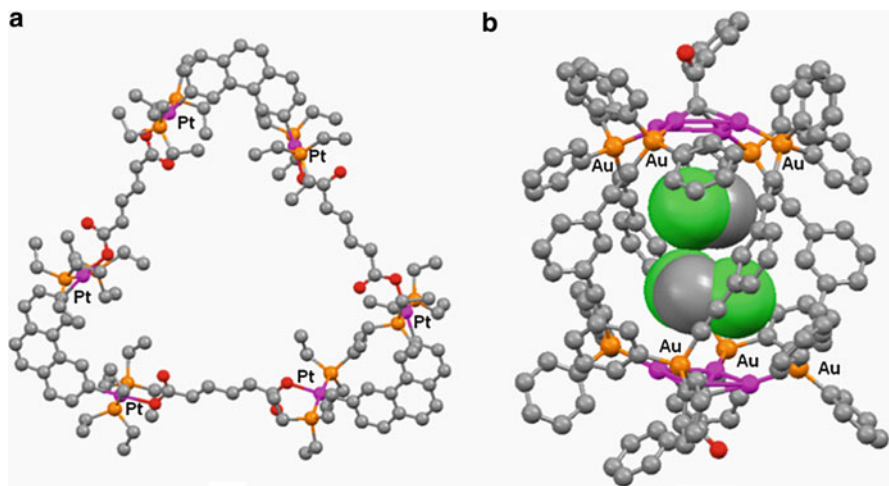


Fig. 8 Organometallic assemblies built from σ -bonded ligands, $[\{2,9\text{-bis}(\text{Pt}(\text{PEt}_3)_2)\text{phenanthrene}\}(\text{OOCCH}_2)_3]_3$ (a) [27] and $[(\text{CH}_2\text{Cl}_2)_2 \subset \text{Au}_8(\text{COPh})_2(\text{Ph}_2\text{PC}_6\text{H}_4\text{PPh}_2)_4]^{2+}$ (b) (CH_2Cl_2 being represented by space-filling models) [28]

Nevertheless, among the large family of organometallic building blocks that can be used to prepare metalla-assemblies, half-sandwich complexes are certainly the most studied. Mainly employed in catalysis [29], half-sandwich complexes are now being extensively evaluated as anticancer agents [30], and they have also been used to generate metalla-assemblies [31].

4 Organometallic Metalla-Assemblies Composed of Half-Sandwich Complexes

In analogy to the three carbonyl groups in the *fac*-Re(CO)₃ unit, η^5 -cyclopentadienyl and η^6 -arene ligands can be used to control accessibility of the remaining coordination sites of an octahedral metal centre. The aromatic ligand occupies three of the six coordination sites at the metal centre, and the resulting coordination geometry is pseudo-tetrahedral, thus allowing better control of the synthesis of two- or three-dimensional assemblies. Indeed, CpM and Cp^{*}M (where M = Rh, Ir, Ru; Cp = C₅H₅; Cp^{*} = C₅Me₅) units have been extensively used to generate metalla-cycles, rectangles, trigonal prisms, hexagonal prisms and other supramolecular assemblies [31, 32]. Arene ruthenium and to a lesser extent arene osmium complexes (where arene = C₆H₆, C₆H₅Me, *p*PrⁱC₆H₄Me, C₆Me₆) have been used to prepare similar two and three-dimensional assemblies [33].

Using tridentate ligands with various functionalities and coordinating abilities, a series of neutral and cationic tri-, tetra- and hexanuclear metalla-cycles have been synthesised [34]. Cyclic tetramers composed of Cp^{*}Ir, Cp^{*}Rh or (arene)Ru half-sandwich complexes and 6-purinethione derivatives have been isolated as triflate salts [35]. The cationic complex [(Cp^{*}Ir)₄(L¹)₄] (where L¹ = 2-amino-6-purinethione), presented in Fig. 9a, forms in the solid state an infinite channel-like structure with S₄ symmetry. Replacing the 6-purinethione with pyridine-4-thiolato bridging ligands (L²), the trinuclear metalla-cycle [(Cp^{*}Ir)₃(L²)₃] was obtained (Fig. 9b) [36].

In order to generate elongated structures, longer and more flexible spacers connecting two tri-functional ligands coordinated to six arene ruthenium units have been combined [37]. The {(*p*PrⁱC₆H₄Me)Ru}₆(μ-L³)₂ (where L³ = 2,3-

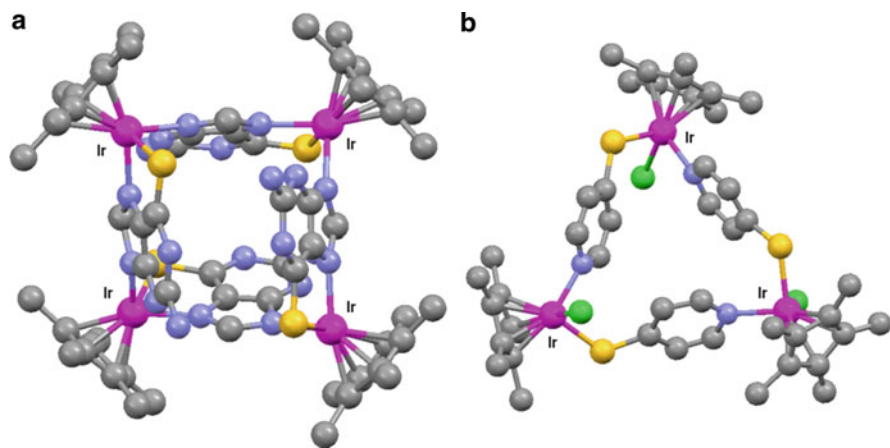


Fig. 9 Two-dimensional assemblies using half-sandwich complexes, [(Cp^{*}Ir)₄(2-amino-6-purinethione)₄] (a) [35] and [(Cp^{*}Ir)₃(pyridine-4-thiolato)₃] (b) [36]

dihydroxypyridine-based ligands) cylindrical structure is over 3 nm long. Coordinating tpt and the flexible dinuclear arene ruthenium clip, $[(p\text{Pr}^i\text{C}_6\text{H}_4\text{Me})\text{Ru}]_2(\mu\text{-L}^4)_2$ (where $\text{L}^4 = 3,6\text{-dimethoxynaphthalene-2,7-dicarboxylato}$), a guest-adaptable trigonal prism was obtained [38]. In its empty form, the distance between the two tpt panels is 3.4 Å, whereas in the presence of two coronenes as guest molecules, the tpt–tpt distance reaches 10.9 Å (Fig. 10), and the host–guest system $[(\text{coronene})_2 \subset \{(p\text{Pr}^i\text{C}_6\text{H}_4\text{Me})\text{Ru}\}_6(\mu\text{-L}^4)_6(\text{tpt})_2]^{6+}$ is observed.

Inspired by Prussian Blue, Rauchfuss group prepared anionic, cationic and neutral metalla-cages incorporating half-sandwich complexes [39]. Cationic derivatives such as $[\{\text{CpCo}(\text{CN})_3\}_4\{\text{Cp}^*\text{Rh}\}_4]^{4+}$ [40] show no affinity for anions, whereas neutral and anionic cages interact strongly with small molecules. Indeed, the metalla-cage $[\{\text{CpCo}(\text{CN})_3\}_4\{\text{Cp}^*\text{Ru}\}_4]$ reacts with monocations (where $\text{mc} = \text{K}^+, \text{Cs}^+, \text{Rb}^+, \text{Tl}^+$) to generate the corresponding host–guest systems $\{\text{mc} \subset [\text{CpCo}(\text{CN})_3\}_4\{\text{Cp}^*\text{Ru}\}_4\}^+$ (Fig. 11a). Organometallic cryptands built from two Cp^*M

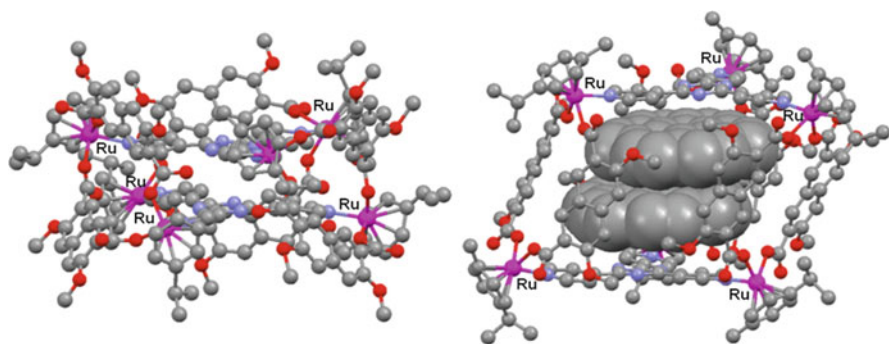


Fig. 10 Guest-adaptable metalla-cage $[(p\text{Pr}^i\text{C}_6\text{H}_4\text{Me})\text{Ru}]_6(\mu\text{-L}^4)_6(\text{tpt})_2$, empty (left) and encapsulating two coronene molecules (right) (coronene being represented by space-filling model) [38]

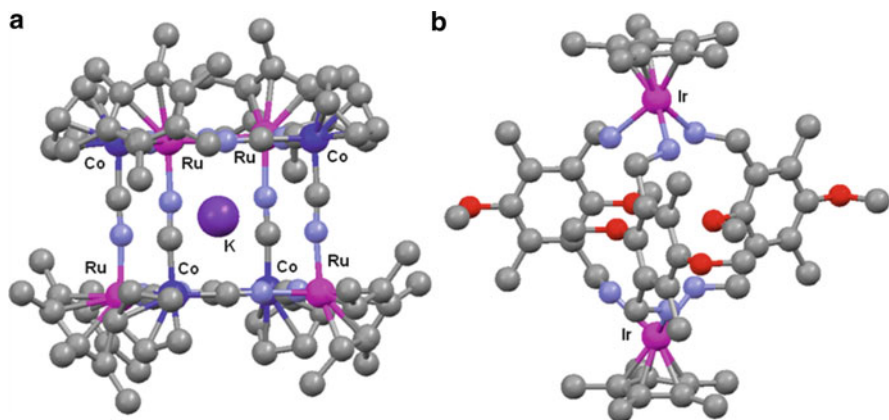


Fig. 11 Organometallic metalla-cages $\{\text{K} \subset [\text{CpCo}(\text{CN})_3\}_4\{\text{Cp}^*\text{Ru}\}_4\}^+$ (a) [40] and $[(\text{Cp}^*\text{Ir})_2(\text{L}^5)_3]^{4+}$ (b) [41]

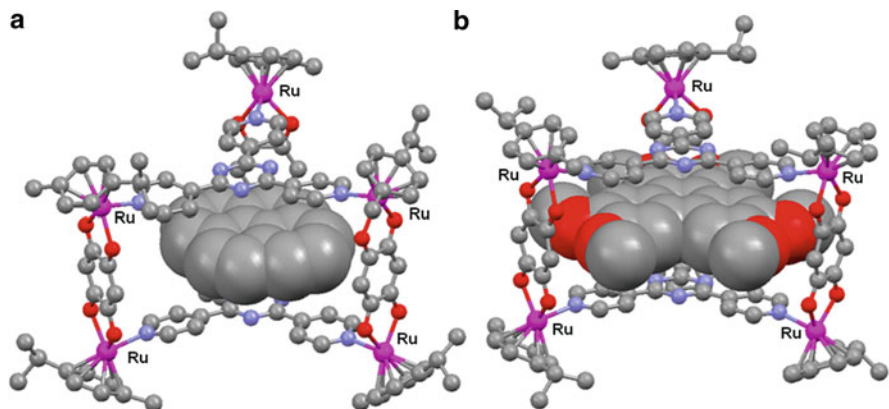


Fig. 12 Organometallic metalla-cages [pyrene $\subset$ {(*p*PrⁱC₆H₄Me)Ru}₆(μ-tpt)₂(μ-dhbq)₃}⁶⁺ (a) [45] and [hexamethoxytriphenylene $\subset$ {(*p*PrⁱC₆H₄Me)Ru}₆(μ-tpt)₂(μ-dhbq)₃}⁶⁺ (b) (guest molecules being represented by space-filling models) [46]

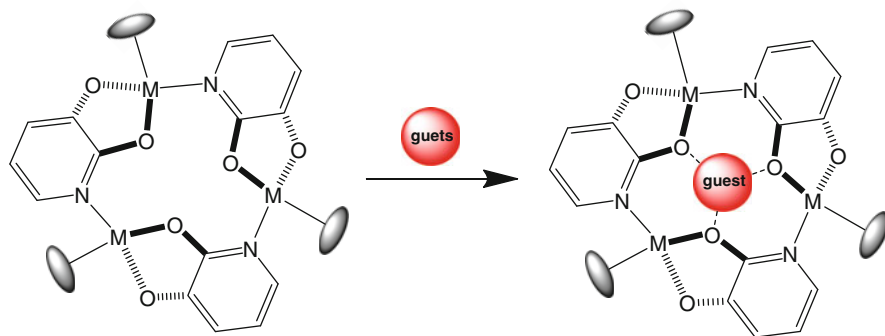
(where M = Rh, Ir) units and three diamino ligands have been found to encapsulate tetrafluoroborate anions in their cavities (Fig. 11b) [41]. The host–guest system [BF₄⊂(Cp*Ir)₂(L⁵)₃]³⁺ [where L⁵ = 1,3-bis(aminomethyl)benzene] was confirmed by various NMR experiments.

Recently, we have shown the cationic metalla-prisms [{(*p*PrⁱC₆H₄Me)Ru}₆(μ-tpt)₂(μ-C₂O₄)₃}⁶⁺ [42] and [(Cp*Rh)₆(μ-tpt)₂(μ-C₂O₄)₃}⁶⁺ [43] to possess “double-rosette”-type chirality with *P* or *M* configuration. Moreover, a concerted rotation of the aromatic rings of the tridentate tpt ligand was observed, creating additional three-bladed propeller chirality. In the more spacious 1,4-benzoquinone-2,5-diolato (dhbq) metalla-cage [{(*p*PrⁱC₆H₄Me)Ru}₆(μ-tpt)₂(μ-dhbq)₃}⁶⁺, planar aromatic molecules such as pyrene, triphenylene [44] or hexamethoxytriphenylene [45] were found to fit inside the cavity (Fig. 12). In these systems, which are called carceplexes, the guest molecules are permanently encapsulated in the cavity of the host.

These examples illustrate the versatility of half-sandwich complexes in the construction of two- and three-dimensional assemblies, thus providing a multitude of possibilities for producing new metalla-hosts for various applications.

5 Organometallic Assemblies Composed of Half-Sandwich Complexes for Biological Applications

Most macrocycles composed of half-sandwich complexes are positively charged and water soluble. The water solubility and stability of organometallic compounds are advantageous, and organometallic chemistry in aqueous-phase is growing rapidly [18]. The overall hydrophilicity of the metalla-cycles combined with potential inner hydrophobic interactions with guest molecules have been exploited previously.



Scheme 1 Trinuclear metalla-cycles comprise of half-sandwich complexes, analogues of 12-crown-3, able to bind guest molecules in their inner cavity

The potential of using half-sandwich assemblies for sensing was first introduced by Fish in the early 1990s [46]. A series of metalla-cycles with specific interactions with small anions was described (Scheme 1). Molecular modelling suggested classic π - π interactions between the aromatic groups of various substituted aromatic carboxylic acids and the cavity of the trinuclear hosts. These trinuclear hosts are analogues to crown-ethers, thus offering alternatives to traditional cryptands [47]. Similar trinuclear metalla-cycles were recently evaluated on human cancer and fibroblast cells [48]. However, these compounds were found to be poorly cytotoxic towards ovarian (A2780 and A2780cisR) and fibroblast (VS79 and GS78) cancer cell lines.

Cationic tetranuclear metalla-cycles composed of arene ruthenium units bridged by tetradentate $OO\cap OO$ or $ON\cap ON$ chelating ligands and connected by bipyridyl linkers have been synthesised. The 4,7-phenanthroline (phen) and 4,4'-bipyridine linkers react with the dinuclear arene ruthenium complex $[(p\text{Pr}^i\text{C}_6\text{H}_4\text{Me})\text{Ru}]_2(\mu\text{-LHoxo})(\text{CF}_3\text{SO}_3)_2$ (where LH_3oxo = 4,6-dihydroxy-2-carboxy-1,3,5-triazine acid) to form the tetranuclear complexes $[(p\text{Pr}^i\text{C}_6\text{H}_4\text{Me})\text{Ru}]_4(\mu\text{-LHoxo})_2(\mu\text{-phen})_2]^{4+}$ (Fig. 13a) and $[(p\text{Pr}^i\text{C}_6\text{H}_4\text{Me})\text{Ru}]_4(\mu\text{-LHoxo})_2(\mu\text{-bipy})_2]^{4+}$, respectively [49]. These cationic metalla-cycles have been found to interact with DNA and to show good cytotoxicity on human ovarian cancer cell lines. Similarly, the dinuclear arene ruthenium complexes of the general formula $[(p\text{Pr}^i\text{C}_6\text{H}_4\text{Me})\text{Ru}]_2(\mu\text{-}OO\cap OO)\text{Cl}_2$ [where $OO\cap OO$ = dhbq; 2,5-dichloro-1,4-benzoquinone-3,6-diolato (dcbq); 1,4-naphthoquinone-5,8-diolato (donq)] react with bipyridyl linkers (bpe, bipy, phen) in the presence of AgCF_3SO_3 to generate the corresponding tetranuclear metalla-cycles $[(p\text{Pr}^i\text{C}_6\text{H}_4\text{Me})\text{Ru}]_4(\mu\text{-}OO\cap OO)_2(\mu\text{-bipyridyl})_2]^{4+}$ [50, 51]. The molecular structure of $[(p\text{Pr}^i\text{C}_6\text{H}_4\text{Me})\text{Ru}]_4(\mu\text{-dcbq})_2(\mu\text{-bipy})_2]^{4+}$ is presented in Fig. 13b. Accordingly, a series of tetranuclear osmium analogues have been synthesised recently [52]. Interestingly, they possess a lower general toxicity on A2780 and A2780cisR ovarian cancer cells than their ruthenium analogues

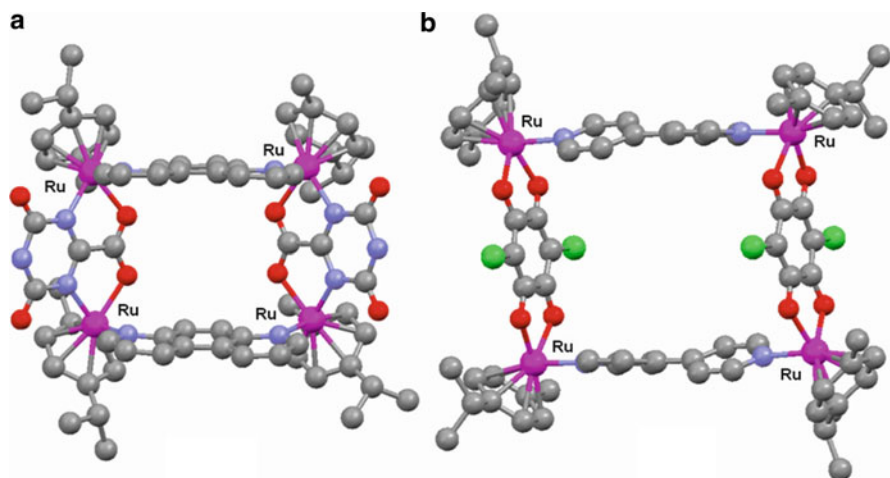


Fig. 13 Tetranuclear metalla-cycles, $[(p\text{Pr}^i\text{C}_6\text{H}_4\text{Me})\text{Ru}]_4(\mu\text{-phen})_2(\mu\text{-LHoxo})_2]^{4+}$ (a) [49] and $[(p\text{Pr}^i\text{C}_6\text{H}_4\text{Me})\text{Ru}]_4(\mu\text{-bipy})_2(\mu\text{-dcbq})_2]^{4+}$ (b) [50]

except for the tetranuclear complex, $[(p\text{Pr}^i\text{C}_6\text{H}_4\text{Me})\text{Os}]_4(\mu\text{-dhbq})_2(\mu\text{-bipy})_2]^{4+}$, which is ten times more active than $[(p\text{Pr}^i\text{C}_6\text{H}_4\text{Me})\text{Ru}]_4(\mu\text{-dhbq})_2(\mu\text{-bipy})_2]^{4+}$.

The supramolecular metalla-cubes $[(p\text{Pr}^i\text{C}_6\text{H}_4\text{Me})\text{Ru}]_8(\mu\text{-tpp})_2(\mu\text{-}OO\cap OO)_4]^{8+}$, containing $OO\cap OO$ bridging ligands and 5,10,15,20-tetra(4-pyridyl)porphyrin (tpp) panels, interact strongly with duplex and human telomeric quadruplex DNA (Fig. 14). The interactions with duplex and human telomeric quadruplex DNA was studied by fluorescent intercalation displacement (FID) assay and surface plasmon resonance (SPR) experiments. These studies have shown the octacationic arene ruthenium metalla-boxes to be promising quadruplex DNA stabilisers and to possess a degree of selectivity for quadruplex over duplex DNA [53]. Moreover, all metalla-cubes have shown to be equally cytotoxic ($\text{IC}_{50} = 7\text{--}15\text{ }\mu\text{M}$) (IC_{50} being the drug concentration necessary for 50% inhibition of cell viability) against both A2870 and cisplatin-resistant A2780cisR cancer cells [54], thus clearly suggesting a mechanism of action different to that of cisplatin.

Cationic metalla-assemblies have been prepared using the same dinuclear arene ruthenium clips and 5,15-bis(4-pyridyl)-10,20-diphenylporphyrin (bpp) or 5,10,15-tris(4-pyridyl)-20-phenylporphyrin (tppp) instead of 5,10,15,20-tetra(4-pyridyl)porphyrin (tpp) (Fig. 15). The *in vitro* study showed that, despite having less ruthenium atoms per metalla-assemblies and a reduced overall charge as compared to the octanuclear arene ruthenium metalla-cubes, the cytotoxicity of these tetra- and hexanuclear metalla-assemblies was similar to those observed for the octanuclear metalla-cubes [55].

These large metalla-assemblies show several interesting features. They possess multiple metal centres, they are water soluble, and in some cases they can reach sizes approaching small enzymes. These features are quite valuable with a view to

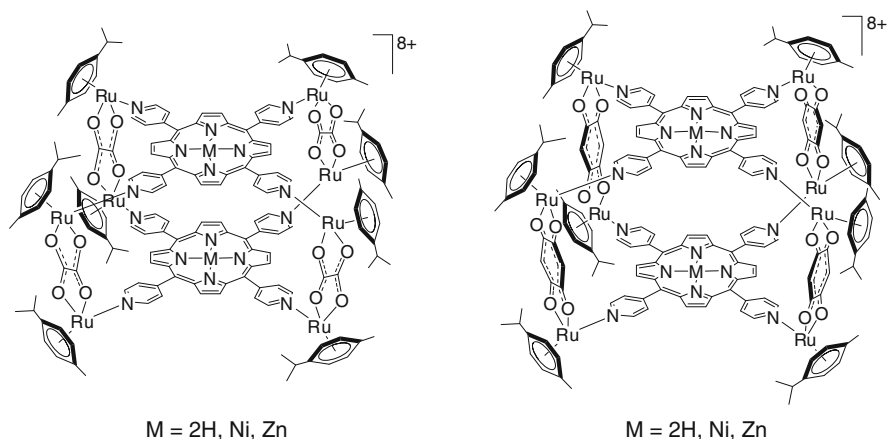


Fig. 14 Organometallic metalla-cubes, $[\{(pPr^iC_6H_4Me)Ru\}_8(\mu-tpm-M)_2(\mu-OOO)_4]^{8+}$, able to interact with DNA and to inhibit cancer cell growth [53, 54]

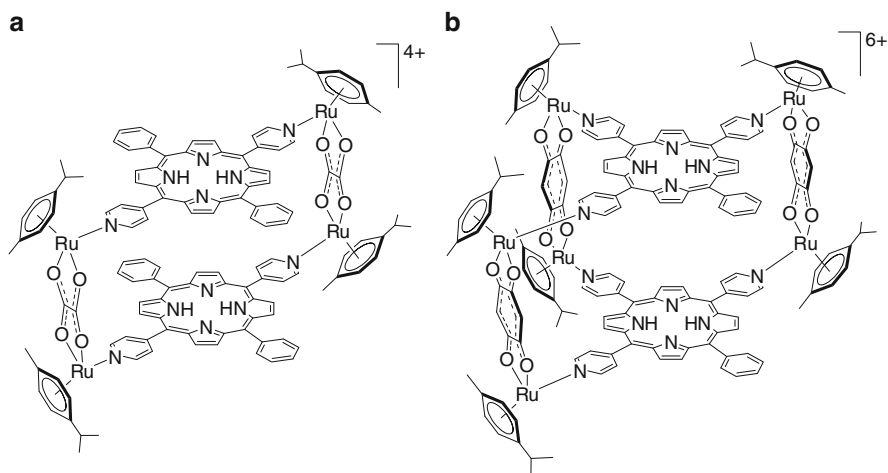


Fig. 15 Organometallic metalla-assemblies $[\{(pPr^iC_6H_4Me)Ru\}_4(\mu-bpp-2H)_2(\mu-C_2O_4)_2]^{4+}$ (a) and $[\{(pPr^iC_6H_4Me)Ru\}_6(\mu-tppp-2H)_2(\mu-dhbq)_3]^{6+}$ (b) [55]

producing new anticancer agents. For instance, the multinuclear approach to improve the activity of anticancer metal-based drugs has been demonstrated [56], and large molecules are known to specifically target cancer cells by exploiting the enhanced permeability and retention (EPR) effect [57]. Consequently, the construction of large metalla-assemblies offers great potential for generating highly selective metal-based drugs for the treatment of cancer.

6 Organometallic Assemblies Composed of Half-Sandwich Complexes for Drug Delivery

Strategies to deliver drugs or prodrugs remain an active field of research. New drug delivery systems are essential to overcome drug resistance mechanisms, to better target cancers, and to regulate drug release. Therefore, it is quite common to find in the literature that the ultimate drug delivery system should possess high selectivity, be biodegradable, and be able to release the drug in a time-controlled manner [58]. However, we consider that if the carrier selectively targets cancer cells, having a cytotoxic drug delivery agent can be advantageous. Synergetic or at least additive effects can be envisaged if both the host and the guest are cytotoxic, and could consequently provide a multidrug therapy in a single host–guest compound.

This idea was first applied using an hexacationic arene ruthenium cage synthesised from the dinuclear complex $[(p\text{-Pr}^i\text{C}_6\text{H}_4\text{Me})\text{Ru}]_2(\mu\text{-dhbq})\text{Cl}_2$ and tpt panels in the presence of silver triflate [59]. If the synthesis was performed in the presence of platinum or palladium bisacetylacetonate, the square-planar complex was encapsulated within the cage, thus giving rise to the carceplex systems $[\text{M}(\text{acac})_2] \subset \{(p\text{-Pr}^i\text{C}_6\text{H}_4\text{Me})\text{Ru}\}_6(\mu\text{-dhbq})_3(\text{tpt})_2\}^{6+}$ (where $\text{M} = \text{Pd}, \text{Pt}$). These systems are active against human ovarian cancer cells: The empty cage possesses an IC_{50} value of 23 μM ; by using the platinum-containing cage the cytotoxicity doubles, and by using the palladium-containing cage the activity reaches 1 μM . The free $\text{M}(\text{acac})_2$ complexes are inactive due to their insolubility in water. Based on these results, the “Trojan horse” concept for delivery of metal-containing guest molecules to cancer cells using a water-soluble organometallic host was proposed (Fig. 16).

This concept was further developed using pyrenyl derivatives with a dangling arm standing out of the cage [60]. The *in vitro* study revealed that the nature of the

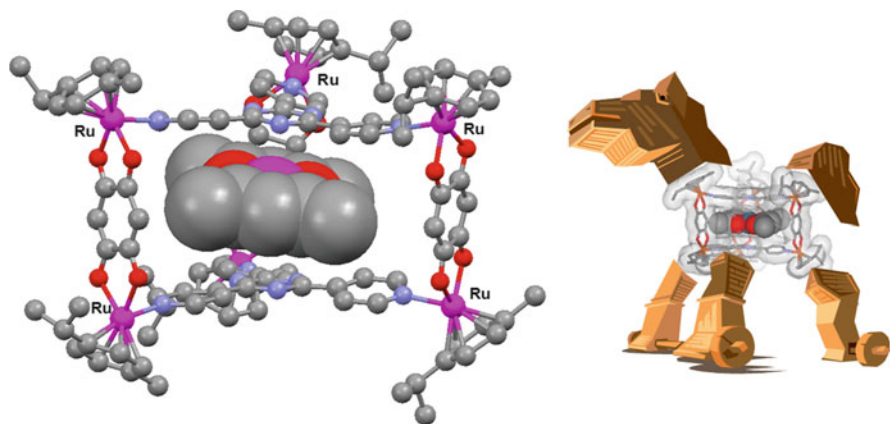


Fig. 16 “Trojan horse” concept illustrated by the platinum bisacetylacetonate complex being encapsulated in the metalla-cage, $[\text{Pt}(\text{acac})_2] \subset \{(p\text{-Pr}^i\text{C}_6\text{H}_4\text{Me})\text{Ru}\}_6(\mu\text{-dhbq})_3(\text{tpt})_2\}^{6+}$ ($\text{Pt}(\text{acac})_2$ being represented by space-filling model) [59]

functional group attached on the pyrenyl unit strongly influences the overall cytotoxicity of the host–guest systems. Therefore, this simple strategy of pyrenyl functionalisation offers the possibility to generate highly cytotoxic agents by fine tuning the nature of the functional group connected to the pyrenyl unit. Optimisation of this strategy is currently being investigated in our laboratory.

The encapsulation of a fluorescent pyrenyl derivative, 1-(4,6-dichloro-1,3,5-triazin-2-yl)pyrene (pyrene-R), has provided direct evidence for the release of a hydrophobic molecule from the metalla-cage $[\{(p\text{Pr}^i\text{C}_6\text{H}_4\text{Me})\text{Ru}\}_6(\mu\text{-dhbq})_3(\text{tpt})_2]^{6+}$, following uptake into cancer cells [61]. The fluorescence of pyrene-R has allowed monitoring of cellular uptake and accumulation, as well as an estimation of the efficiency of the $[\text{pyrene-R} \subset \{(p\text{Pr}^i\text{C}_6\text{H}_4\text{Me})\text{Ru}\}_6(\mu\text{-dhbq})_3(\text{tpt})_2]^{6+}$ system to transport and release its cargo (Fig. 17).

This fluorescent pyrenyl derivative (pyrene-R) was also encapsulated in the cavity of the more spacious metalla-cages $[\{(p\text{Pr}^i\text{C}_6\text{H}_4\text{Me})\text{Ru}\}_6(\mu\text{-donq})_3(\mu\text{-tpt})_2]^{6+}$, $[\{(p\text{Pr}^i\text{C}_6\text{H}_4\text{Me})\text{Ru}\}_6(\mu\text{-doaq})_3(\mu\text{-tpt})_2]^{6+}$ (where doaq = 1,4-anthraquinone-9,10-diolato) and $[\{(p\text{Pr}^i\text{C}_6\text{H}_4\text{Me})\text{Ru}\}_6(\mu\text{-dotq})_3(\mu\text{-tpt})_2]^{6+}$ (where dotq = tetracene-5,12-dione-6,11-diolato) [62]. In contrast to the carceplex $[\text{pyrene-R} \subset \{(p\text{Pr}^i\text{C}_6\text{H}_4\text{Me})\text{Ru}\}_6(\mu\text{-dhbq})_3(\text{tpt})_2]^{6+}$ system, the association constants (K_a) were determined for these three host–guest systems. Interestingly, a perfect correlation between the association constants and the fluorescence recorded by flow cytometry after incubation for 24 h on cancer cells was observed, thus paving the way for the rational design of organometallic metalla-cages that can function in a time-

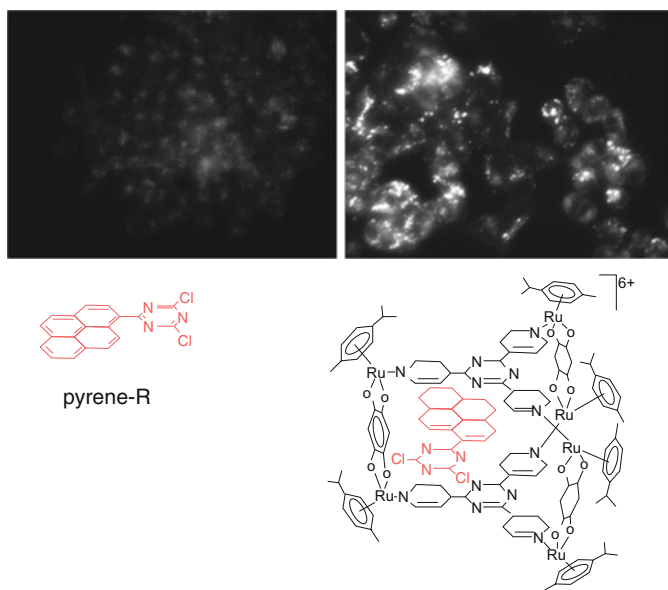


Fig. 17 Microscopy images (fluorescent light) of cancer cells incubated (2 μM , 24 h) with pyrene-R alone (*left*) and $[\text{pyrene-R} \subset \{(p\text{Pr}^i\text{C}_6\text{H}_4\text{Me})\text{Ru}\}_6(\mu\text{-dhbq})_3(\text{tpt})_2]^{6+}$ (*right*) [61]

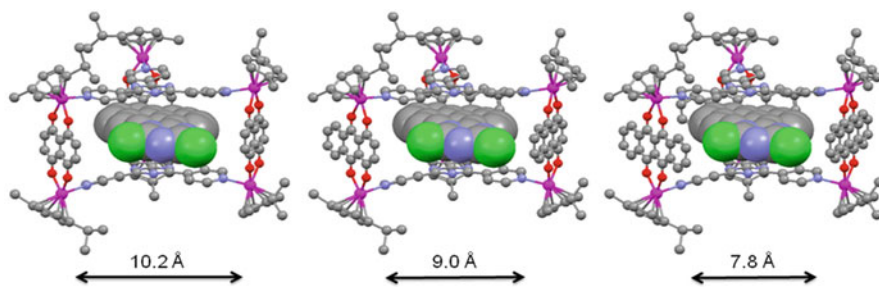


Fig. 18 Organometallic metalla-cages [pyrene- $\text{R}\{(\text{pPr}^i\text{C}_6\text{H}_4\text{Me})\text{Ru}\}_6(\mu\text{-donq})_3(\text{tpt})_2\}^{6+}$ (a), [pyrene- $\text{R}\{(\text{pPr}^i\text{C}_6\text{H}_4\text{Me})\text{Ru}\}_6(\mu\text{-doaq})_3(\text{tpt})_2\}^{6+}$ (b) and [pyrene- $\text{R}\{(\text{pPr}^i\text{C}_6\text{H}_4\text{Me})\text{Ru}\}_6(\mu\text{-dotq})_3(\text{tpt})_2\}^{6+}$ (c), showing the width of the portals (pyrene-R being represented by space-filling models) [62]

controlled manner. These metalla-cages possess similar cavity sizes but different portals (Fig. 18), thus controlling the release of the guest molecule after internalisation.

To better target cancer cells, pyrenyl-modified dendrimers have been encapsulated in the water-soluble metalla-cage $[\{(\text{pPr}^i\text{C}_6\text{H}_4\text{Me})\text{Ru}\}_6(\mu\text{-donq})_3(\mu\text{-tpt})_2]^{6+}$ [63]. Three generations of pyrenyl-cyanobiphenyl dendrimers (P_0 , P_1 and P_2) were synthesised, and the host–guest properties were studied after encapsulation using UV and NMR spectroscopy. A molecular simulation of the highest generation of pyrenyl-modified dendrimer (P_2) in the cavity of the metalla-cage is presented in Fig. 19. This study has shown that organometallic metalla-cages are able to deliver hydrophobic guest molecules with extremely large appendages into cancer cells.

The same strategy was recently applied to solubilise and evaluate the cytotoxicity of a well-known family of dendrimers composed of benzyloxy core with dodecanyloxy endgroups [64]. These kinds of dendrimers are lipophilic, and so far have never been evaluated in biological media. The pyrenyl-modified poly-benzyloxy dendrimers (generations G_0 to G_2) encapsulated in the cavity of the metalla-cage $[\{(\text{pPr}^i\text{C}_6\text{H}_4\text{Me})\text{Ru}\}_6(\mu\text{-donq})_3(\mu\text{-tpt})_2]^{6+}$ (Fig. 20) showed cytotoxicities comparable to those of cisplatin on human ovarian cancer cell lines, confirming the delivery ability of these organometallic metalla-cages.

We are now investigating the possibility of using pyrenyl derivatives with biological functions to tune up the properties of these systems to target specific diseases as well as to increase selectivity, activity and solubility. Recently, we have shown that organometallic-modified porphyrin compounds possess excellent chemotherapeutic and photodynamic properties at low concentration [65]. Therefore, the encapsulation of photosensitisers within $[\{(\text{pPr}^i\text{C}_6\text{H}_4\text{Me})\text{Ru}\}_6(\mu\text{-donq})_3(\mu\text{-tpt})_2]^{6+}$ and other cages has been performed in order to combine the cytotoxicity of half-sandwich complexes and photodynamic treatment. Porphyrins and phthalocyanines are the most common photosensitisers; being planar aromatic molecules and poorly soluble in water, they are the perfect candidates for encapsulation in organometallic metalla-cages. The *in vitro* activity and photo-activity of these [photosensitiser@cage] systems are under investigation and the results will be published soon.

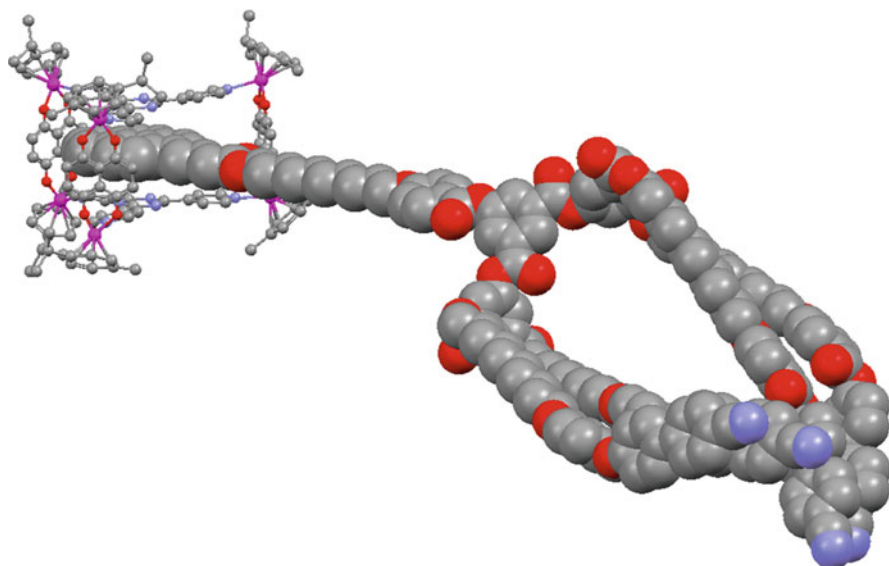


Fig. 19 Molecular structure of $[P_2C\{(pPr^iC_6H_4Me)Ru\}_6(\mu-donq)_3(tpt)_2]^{6+}$ showing the pyrenyl-modified dendrimer (P_2) (space-filling model) being encapsulated in the cavity of the metalla-cage [63]

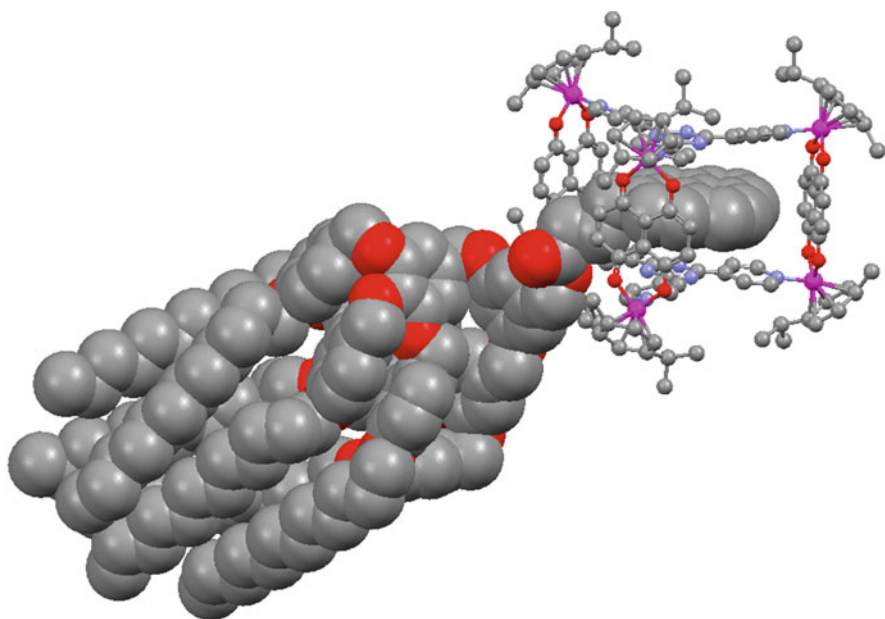


Fig. 20 Molecular structure of $[G_2C\{(pPr^iC_6H_4Me)Ru\}_6(\mu-donq)_3(tpt)_2]^{6+}$ (G_2 represented by space-filling model) [64]

7 Outlook

The use of water-soluble organometallic cages as drug carriers to deliver hydrophobic molecules offers great potential. The cage itself is cytotoxic, and selectivity can be achieved by exploiting the EPR effect. The cavity of the cage allows the transport to cancer cells of lipophilic molecules. Therefore, by judiciously selecting the guest molecule, targeting of a specific disease, adding selectivity, or increasing solubility can be achieved by these host–guest biological agents. Consequently, this multifunctional host and guest approach, in which both players possess distinct qualities and specificities, is certainly a winning strategy for the development of organometallic metalla-cages with synergistic effects, and will ultimately provide a new weapon in chemotherapy.

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