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Arene Ruthenium Cages: Boxes Full of Surprises

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Self-assembly of polypyridyl ligands with dinuclear arene ruthenium building blocks bridged by chlorido, oxalato or benzoquinonato ligands has allowed the construction of a wide range of cationic metalla complexes possessing different architectures and functionalities: (i) metalla-rectangles showing host–guest possibilities and allowing intramolecular template-controlled photochemical [2 + 2] dimerisation reactions; (ii) metalla-prisms allowing encapsulation of molecules and giving rise to potential drug delivery systems; (iii) metalla-boxes that can be used to stabilise the formation of G-quadruplex DNA. This microreview covers the synthetic and structural aspects of these metalla complexes, as well as their most promising applications, with a particular focus on their potential biological applications.

Introduction

Boxes have undoubtedly been made as receptacles for every conceivable object. They come in all shapes and sizes and can be found everywhere in our everyday lives. They can be purely aesthetic or have a specific purpose such as to protect, hide, support or transport objects, and the robustness of the box will depend on its purpose. With a view to performing similar functions, the synthesis of molecular boxes has attracted a great deal of interest from synthetic chemists, and the self-assembly of transition-metal complexes with polydentate ligands to give discrete supramolecular boxes has been studied by several groups. Pioneered by Fujita in the 1990s,[1] and subsequently developed by others,[2] the combination of 90° coordination building blocks and linear ligands to form square and rectangular architectures has been extensively exploited. A few years later, the same approach was used to generate three-dimensional networks.[3] So far, a multitude of two- and three-dimensional structures incorporating transition metals with square-planar geometry have been synthesised.[4] These molecular boxes have been used to generate confined environments to encapsulate compounds,[5] to protect or stabilise an otherwise too sensitive molecule,[6] to recognise and trap specific guest molecules[7] or to act as microreactors for specific reactions.[8]

In the search for new building blocks for the synthesis of supramolecular boxes with comparable properties, there is an increasing interest in using transition-metal complexes with octahedral geometry.[9] Cotton and co-workers have built up two- and three-dimensional architectures from metal–metal paddlewheel units.[10] Similarly, the *fac*-Re$(CO)_3$ corner system was judiciously chosen to prepare molecular rectangles[11] or triangular prisms.[12] The tridentate ligand 1,4,7-trithiacyclononane, which coordinates facially to ruthenium, was used to form a supramolecular cube,[13] while polypyrazolyl chelating ligands coordinated to cobalt, manganese and zinc were used to generate various polyhedral cages.[14] The underlying strategy in those examples implies the blocking of concomitant coordination sites at the octahedral metal centres, thus generating a preorganised arrangement before the formation of the supramolecular assembly.

In a similar manner, cyclopentadienyl or arene ligands can be used to control the accessibility of coordination sites at an octahedral metal centre. The use of these η^5 or η^6

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Born and raised in Canada, Bruno Therrien studied chemistry at the University of Montreal, where he learnt crystallography in the group of André Beauchamp. He left Canada to obtain his Ph.D. in 1998 at the University of Bern, Switzerland, under the supervision of Thomas R. Ward. He undertook several postdoctoral positions (Weizmann Institute, Massey University, Tokyo University) and currently holds an independent Senior Researcher position at the University of Neuchatel. His main research interests are supramolecular assemblies and biological applications of arene ruthenium complexes.

ligands has its advantages: (i) The aromatic ligand occupies three of the six coordination sites at the metal centre, thus limiting the number of available coordination sites and therefore allowing better control for the synthesis of two- or three-dimensional assemblies. (ii) The strongly bonded aromatic ligand allows different substituents that can enhance the solubility or add new properties to the molecular assembly. In this respect, CpM and Cp*M (M = Rh, Ir; Cp = C_5H_5; Cp* = C_5Me_5) units have been extensively used to generate metalla-cycles, -rectangles, -prisms and other supramolecular assemblies.[15] To a lesser extent, arene ruthenium complexes (arene = C_6H_6, C_6H_5Me, *p-i*PrC_6H_4Me, C_6Me_6) were utilised to build up similar supramolecular assemblies with diverse functionalities and properties. By using tridentate ligands with various functionalities and coordinating abilities, a series of neutral and cationic tri-, tetra- and hexanuclear metalla-cycles have been synthesised[16] (see Figure 1). With flexible spacers which connect two trifunctional units, expanded helicates with six arene ruthenium moieties have been obtained.[17] In some cases, these systems are capable of binding small molecules with great specificity; therefore, applications as sensors have been sought for these metalla complexes. Reviews dealing with these supramolecular architectures incorporating half-sandwich complexes with polyfunctional ligands have been published in recent years.[18]

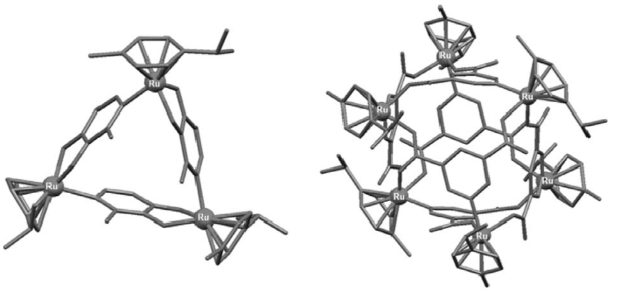


Figure 1. Examples of tri-[16c] and hexanuclear[16f] metalla-cycles.

Recently we have used arene ruthenium complexes as building blocks for the assembly of a series of cationic metalla-rectangles, cationic triangular metalla-prisms and cationic metalla-boxes containing bridging chlorido (Cl^-), oxalato ($C_2O_4^{2-}$), 2,5-dihydroxy-1,4-benzoquinonato ($C_6H_2O_4^{2-}$) and 2,5-dichloro-1,4-benzoquinonato ($C_6Cl_2O_4^{2-}$) ligands and connected by rigid polypyridyl ligands. The starting arene ruthenium materials are easily prepared in gram scale, they are stable and some are even commercially available. The most common method of preparation of arene ruthenium complexes is the reaction of $RuCl_3\cdot nH_2O$ with a cyclohexadiene derivative in an EtOH/H_2O solvent mixture.[19] This simple strategy allows the introduction of a wide range of η^6-arene ligands (**a**: arene = C_6H_5Me; **b**: arene = *p-i*PrC_6H_4Me; **c**: arene = C_6Me_6, see Figure 2). The resulting chlorido-bridged dimers $[Ru_2(arene)_2(\mu\text{-}Cl)_2Cl_2]$ (**1**) are generally air-stable and can react with a wide variety of ligands, by cleavage of the chlorido-bridges, to afford mono- or polynuclear arene ruthenium complexes in excellent yield.[20] Indeed, the synthesis of dinuclear building blocks is straightforward: Reaction of $[Ru_2(arene)_2(\mu\text{-}Cl)_2Cl_2]$ (**1**) with ammonium oxalate ($[NH_4]_2[C_2O_4]$) or 1,4-benzoquinone derivatives (2,5-dihydroxy-1,4-benzoquinone = $C_6H_4O_4$; 2,5-dichloro-1,4-benzoquinone = $C_6H_2Cl_2O_4$) affords the corresponding dinuclear arene ruthenium building blocks with various metal–metal distances: $[Ru_2(arene)_2(\mu\text{-}C_2O_4)Cl_2]$ (**2**), $[Ru_2(arene)_2(\mu\text{-}C_6H_2O_4)Cl_2]$ (**3**) and $[Ru_2(arene)_2(\mu\text{-}C_6Cl_2O_4)Cl_2]$ (**4**), which are shown in Figure 2.

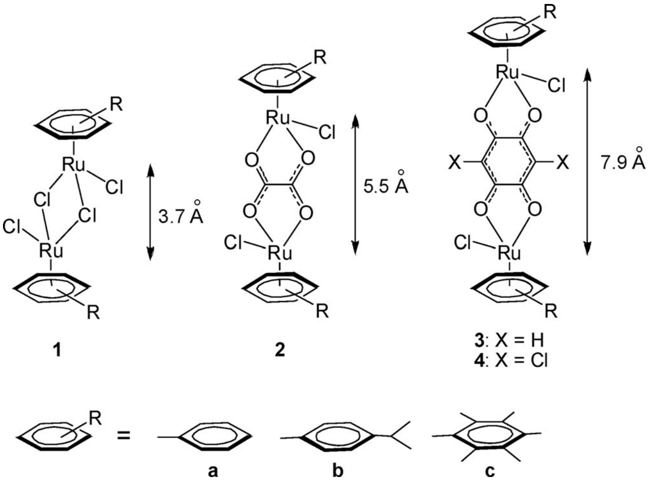
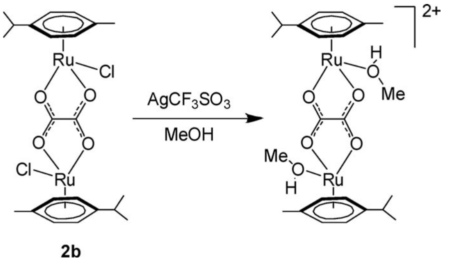


Figure 2. Dinuclear arene ruthenium building blocks.

The dinuclear clips **2**, **3** and **4** can further react with two equivalents of $AgCF_3SO_3$ to generate, after removal of AgCl, the coordinatively unsaturated moieties $[Ru_2(arene)_2(\mu\text{-}C_2O_4)]^{2+}$ (**2′**), $[Ru_2(arene)_2(\mu\text{-}C_6H_2O_4)]^{2+}$ (**3′**) and $[Ru_2(arene)_2(\mu\text{-}C_6Cl_2O_4)]^{2+}$ (**4′**), respectively. These intermediate moieties are occasionally isolated as solvated species, for example the reaction of **2b** in methanol with $AgCF_3SO_3$ for which the dicationic methanol derivative [Ru$_2$(*p-i*PrC_6H_4Me)$_2$(CH_3OH)$_2$(μ-C_2O_4)]$^{2+}$ was isolated and fully characterised (see Scheme 1).[21] The X-ray structural analysis of [Ru$_2$(*p-i*PrC_6H_4Me)$_2$(CH_3OH)$_2$(μ-C_2O_4)](CF_3SO_3)$_2$ reveals an *anti* geometry of the two coordinated methanol molecules. However, it is worth mentioning that, to form discrete supramolecular assemblies, a *syn* geometry of the incoming polypyridyl ligands is needed. The removal of the two chlorido ligands, which generates a highly reactive unsaturated clip, is an important feature in the synthesis of these supramolecular assemblies. It gives opportunities to the preorganised dinuclear clips to react with linear bipyridyl ligands to form metalla-rectangles, with planar tripyridyl ligands to form triangular metalla-prisms and with tetrapyridyl porphyrin ligands to form metalla-boxes.

This review intends to give a concise overview of these arene ruthenium assemblies connected with polypyridyl ligands with a particular focus on the synthetic methods and the potential applications for these systems. A special emphasis has been placed on our personal contributions in this field over the last three years, although contributions from other groups are also discussed.



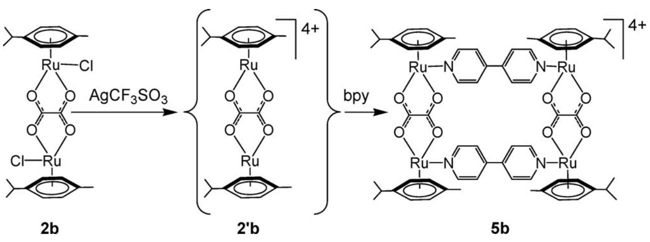
Scheme 1. Synthesis of the solvated dinuclear oxalato clip [Ru_2(*p*-*i*$PrC_6H_4Me)_2(CH_3OH)_2(\mu$-$C_2O_4)]^{2+}$.[21]

Supramolecular Arene Ruthenium Assemblies

Arene Ruthenium Metalla-Rectangles

The synthesis of various size polygons such as triangles, squares, pentagons or hexagons has been successfully developed and used as potential sensors, probes, photonic devices, catalysts and in basic host–guest chemistry.[22] Despite their relative simplicity, molecular rectangles are more difficult to obtain than symmetrical polygons. Simultaneous mixing of two different connector ligands with metal corners does not favour the formation of the desired rectangle. Indeed, due to the strong enthalpic driving force, the formation of two molecular squares is favoured in general. However, to overcome this problem, the use of dinuclear arene ruthenium building blocks shows great potential.

The first entry in the field of supramolecular assemblies of metalla-rectangles incorporating arene ruthenium complexes dates back to 1997:[21] The tetranuclear complex, [Ru_4(*p*-*i*$PrC_6H_4Me)_4(\mu$-bpy$)_2(\mu$-$C_2O_4)_2]^{4+}$ (**5b**), a molecular rectangle in which four arene ruthenium units (arene = *p*-*i*PrC_6H_4Me) are bridged by two oxalato ligands and two 4,4′-bipyridine (bpy) units, was synthesised in methanol from the dinuclear complex **2b** in the presence of $AgCF_3SO_3$ (see Scheme 2). The key aspect in the exclusive formation of rectangle **5b** was a two-step strategy, in which two preorganised bimetallic units (**2′b**) were connected together by two rigid bidentate ligands. However, this macrocyclic arrangement was too small to accommodate guest molecules between the two bpy units, the metal–metal distances being 5.532(9) and 11.315(10).



Scheme 2. Two-step synthesis of metalla-rectangle [Ru_4(*p*-*i*$PrC_6H_4Me)_4(\mu$-bpy$)_2(\mu$-$C_2O_4)_2]^{4+}$ (**5b**).[21]

Using a similar approach as for the synthesis of rectangle **5b**, Jin's group has synthesised a series of metalla-rectangles by the combination of the unsaturated dinuclear arene ruthenium clip **4′** and various linear bidentate pyridyl connectors, pyrazine (prz), 4,4′-bipyridine (bpy), 4,4′-bipyridylethylene (bpe) and 4-[5-(4-pyridyl)-1,3,4-oxadiazol-2-yl]pyridine (bpo) to generate the corresponding metalla-rectangles [Ru_4(*p*-*i*$PrC_6H_4Me)_4(\mu$-prz$)_2(\mu$-$C_6Cl_2O_4)_2]^{4+}$ (**6b**), [Ru_4(*p*-*i*$PrC_6H_4Me)_4(\mu$-bpy$)_2(\mu$-$C_6Cl_2O_4)_2]^{4+}$ (**7b**), [Ru_4(*p*-*i*$PrC_6H_4Me)_4(\mu$-bpe$)_2(\mu$-$C_6Cl_2O_4)_2]^{4+}$ (**8b**) and [Ru_4(*p*-*i*$PrC_6H_4Me)_4(\mu$-bpo$)_2(\mu$-$C_6Cl_2O_4)_2]^{4+}$ (**9b**), which are shown in Figure 3.[23]

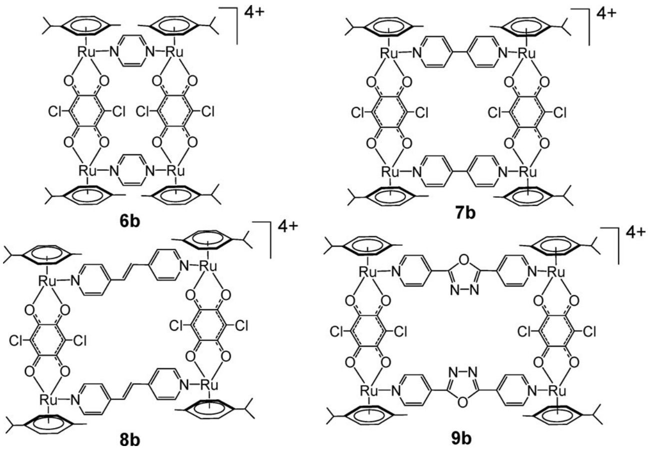


Figure 3. Molecular structures of metalla-rectangles **6b**, **7b**, **8b** and **9b**.[23]

Following the same strategy, we recently synthesised two analogous metalla-rectangles: [$Ru_4(C_6Me_6)_4(\mu$-bpe$)_2(\mu$-$C_6Cl_2O_4)_2]^{4+}$ (**8c**) and [$Ru_4(C_6Me_6)_4(\mu$-bpy$)_2(\mu$-$C_6H_2O_4)_2]^{4+}$ (**10c**), shown in Figure 4. X-ray structural analyses of **8c** and **10c** have been performed.

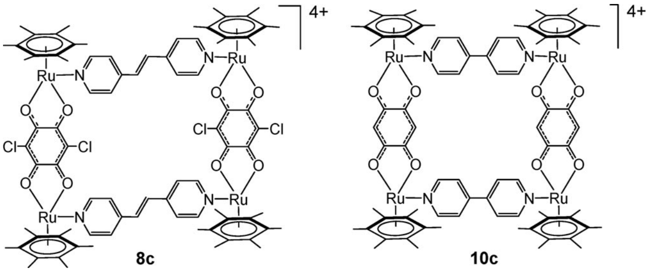


Figure 4. Metalla-rectangles [$Ru_4(C_6Me_6)_4(\mu$-bpe$)_2(\mu$-$C_6Cl_2O_4)_2]^{4+}$ (**8c**) and [Ru_4(*p*-*i*$PrC_6H_4Me)_4(\mu$-bpy$)_2(\mu$-$C_6H_2O_4)_2]^{4+}$ (**10c**).[24,25]

Interestingly, in the solid state, [**10c**]$(CF_3SO_3)_4$ forms one-dimensional channels with Ru–Ru separations of 7.9 and 11.3 Å[24] (see Figure 5). A similar arrangement has been found in the crystal structure of [**7b**]$(CF_3SO_3)_4$, the Ru–Ru separations being almost identical at 7.9 and 11.2 Å, respectively.[23] In both structures, the triflate anions are found between the rectangular channels. In [**7b**]$(CF_3SO_3)_4$, disordered water molecules are observed in the cationic molecular rectangles as compared to [**10c**]$(CF_3SO_3)_4$, for which no solvent molecules are observed in the cavity. However, these systems could be seen as cationic nanotubes and potentially used for storage of small anions or small neutral molecules.

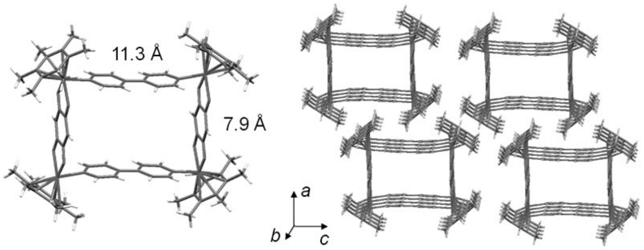


Figure 5. Molecular structure of cation **10c** with a view of the molecular channels along the *b* axis.[24]

As expected, the molecular structure of [**8c**]$(CF_3SO_3)_4$ shows a larger cavity (7.9×13.6 Å^2), which can accommodate guest molecules[25] (see Figure 6). Upon crystallisation of [**8c**]$(CF_3SO_3)_4$ in a chloroform/diethyl ether mixture, two diethyl ether molecules are encompassed in the hydrophobic cavity of cation **8c**. A similar crystal packing has also been observed in [**8b**]$(CF_3SO_3)_4$, in which highly disordered solvent molecules were found in the rectangular (13.5×7.9 Å^2) cavity,[23] thus confirming the potential of such systems for host–guest chemistry and storage possibilities.

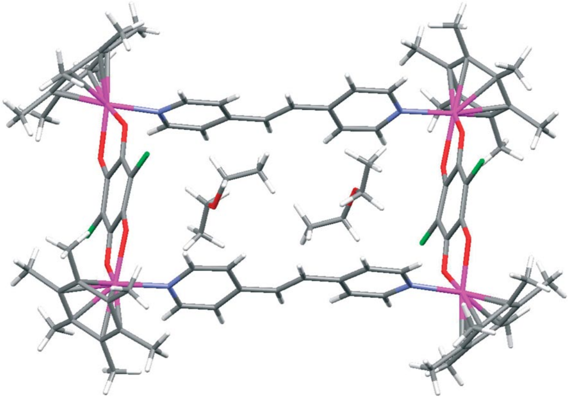
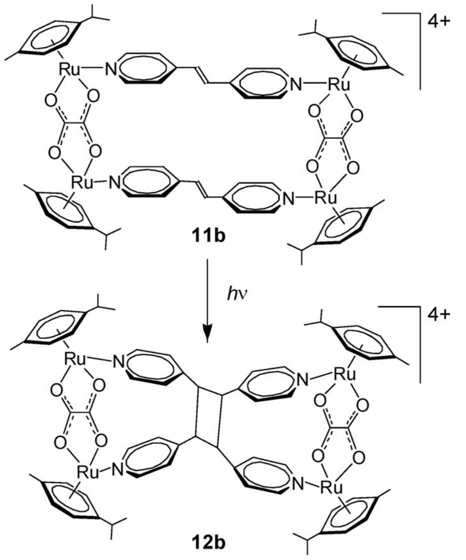


Figure 6. Molecular structure of cation **8c** showing two encapsulated diethyl ether molecules.[25]

Linear 4,4′-bipyridylethylene (bpe) connectors and oxalato bridging ligands allow the formation of the compact metalla-rectangle $[Ru_4(p\text{-}i\text{Pr}C_6H_4Me)_4(\mu\text{-bpe})_2(\mu\text{-}C_2O_4)_2]^{4+}$ (**11b**), in which two olefin double bonds are perfectly positioned parallel to each other.[26] These two olefin double bonds can react in solution under UV irradiation to form the intramolecular [2 + 2] cycloaddition adduct $[Ru_4(p\text{-}i\text{Pr}C_6H_4Me)_4(\mu\text{-tpcb})(\mu\text{-}C_2O_4)_2]^{4+}$ [tpcb = tetrakis(4-pyridyl)cyclobutane] (**12b**), shown in Scheme 3.

The photodimerisation reaction in CD_3OD of **11b** to give **12b** upon UV irradiation can be easily monitored by ^1H NMR spectroscopy. The [2 + 2] cycloaddition reaction of the olefin double bonds is followed by the disappearance of the signal of the olefin protons at $\delta = 7.49$ ppm and with the emergence of a new signal at $\delta = 4.99$ ppm, which is assigned to the cyclobutane protons. Upon formation of **12b**, diastereotopic protons are observed for the pyridyl groups, which suggests a non-equivalent environment. This is in accordance with the X-ray structural analysis of the iridium pentamethylcyclopentadienyl analogue $[Ir_4(C_5Me_5)_4(\mu\text{-tpcb})(\mu\text{-}C_2O_4)_2]^{4+}$, in which only the *rctt*-cyclobutane isomer was observed.[27]



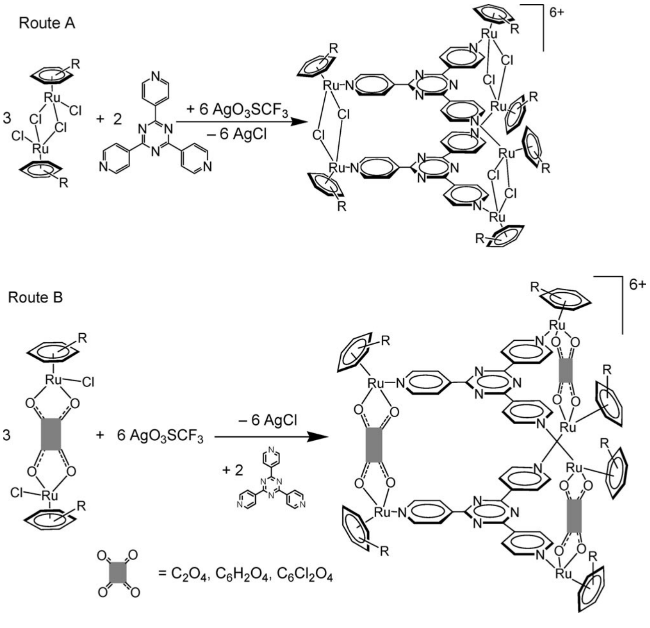
Scheme 3. [2 + 2] photodimerisation of **11b** to give **12b**.[26]

Arene Ruthenium Metalla-Prisms

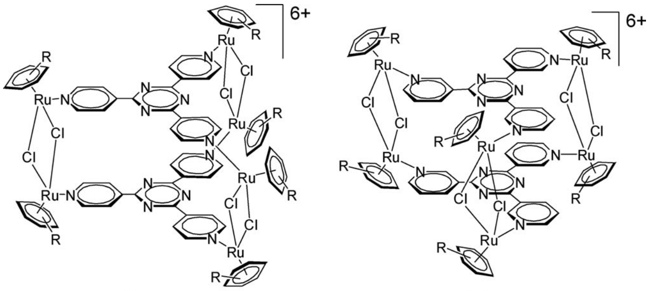
The simplest three-dimensional construction that involves the fewest components is the triangular prism. If the components of the prism do not contain stereogenic elements and if the two planar triangular subunits are perfectly eclipsed, the triangular prism obtained is achiral.[28] The same dinuclear arene ruthenium units **1**, **2**, **3** and **4** have been used to generate metalla-prisms. The synthesis of these hexanuclear arene ruthenium trigonal-prismatic cages can be divided into two routes (see Scheme 4): (A) the dinuclear arene ruthenium units react with two tridentate ligands prior to the addition of silver triflate or (B) the dinuclear arene ruthenium clips react with silver triflate before addition of the tridentate panels. In most cases both synthetic routes work equally well, affording the desired assemblies in similar yield; however, only route A can be used to afford chlorido-bridged triangular prisms.[29]

The molecular structures of **14** and **15** are presented in Figure 7. The chlorido-bridged metalla-prisms $[Ru_6(p\text{-}i\text{Pr}C_6H_4Me)_6(\mu\text{-4-tpt})_2(\mu\text{-Cl})_6]^{6+}$ (**14b**), $[Ru_6(C_6Me_6)_6(\mu\text{-4-tpt})_2(\mu\text{-Cl})_6]^{6+}$ (**14c**), $[Ru_6(p\text{-}i\text{Pr}C_6H_4Me)_6(\mu\text{-3-tpt})_2(\mu\text{-Cl})_6]^{6+}$ (**15b**) and $[Ru_6(C_6Me_6)_6(\mu\text{-3-tpt})_2(\mu\text{-Cl})_6]^{6+}$ (**15c**) are obtained in good yield from the dinuclear arene ruthenium complexes **1b** or **1c** and the corresponding 2,4,6-tri(pyridin-4-yl)-1,3,5-triazine (4-tpt) or 2,4,6-tri(pyridin-3-yl)-1,3,5-triazine (3-tpt) ligands followed by the addition of $AgCF_3SO_3$ (Route A).[29]

The molecular structures of the two chlorido-bridged metalla-prisms **14b** and **14c** are presented in Figure 8. Due to the proximity of the two 4-tpt units, strong parallel π-stacking interactions between the aromatic rings are observed. The centroid···centroid distances (3.4 Å) between



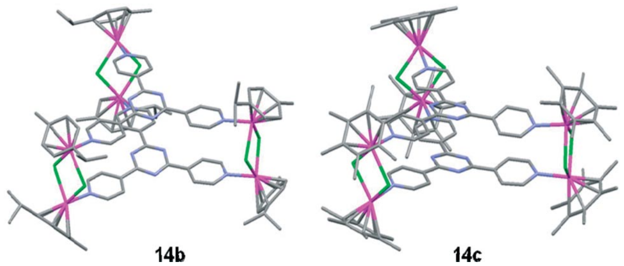
Scheme 4. Two major synthetic routes to arene ruthenium metalla-prisms.



14 **15**

Figure 7. Molecular structures of **14** and **15**.[29]

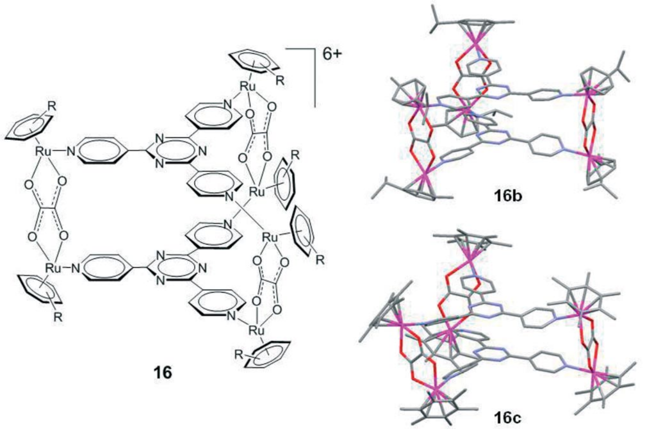
the corresponding triazine rings are slightly shorter than the average metal–metal distances of the chlorido bimetallic connectors (3.7 Å). In these systems, a slight deviation from a perfectly eclipsed conformation of the two 4-tpt subunits is observed, giving rise to chiral systems.



14b **14c**

Figure 8. Molecular structures of **14b** and **14c**.[29]

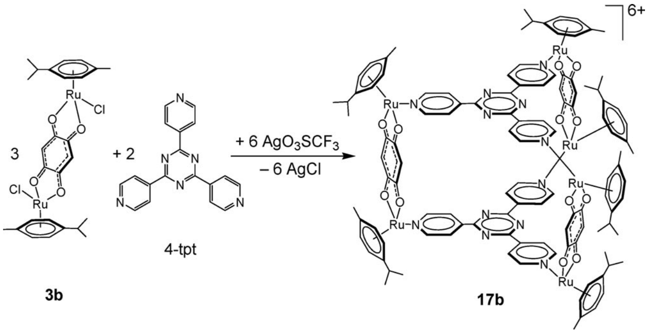
A more important deviation of the eclipsed conformation is observed in the cationic triangular metalla-prisms $[Ru_6(p\text{-}i PrC_6H_4Me)_6(\mu\text{-}4\text{-tpt})_2(\mu\text{-}C_2O_4)_3]^{6+}$ (**16b**) and $[Ru_6(C_6Me_6)_6(\mu\text{-}4\text{-tpt})_2(\mu\text{-}C_2O_4)_3]^{6+}$ (**16c**), which contain bridging oxalato ligands.[30] In these systems, a concerted rotation of the aromatic rings of the tritopic 4-tpt subunits is observed, which created an additional three-bladed propeller chirality element, a common feature in this kind of triangular metalla-prism.[31] These two stereogenic elements are observed in the solid state and seen to persist in solution, as evidenced by ^1H NMR spectroscopic experiments in the presence of the anionic chiral NMR solvating agent Δ-binphat.[30] The molecular structures of **16b** and **16c** have been established by single-crystal X-ray structural analysis of the triflate salts (see Figure 9). Surprisingly, despite a metal–metal distance of about 5.5 Å, the two central triazine units are very close. The centroid···centroid distance between the two triazine moieties is only 3.4 Å in **16b** and 3.8 Å in **16c**, where the 4-tpt ligands adopt a slightly staggered conformation. In **16b**, the twist angle of the oxalato clips is only 4.0°, whereas the pyridyl rings of the two 4-tpt units are tilted by 16.6° out of the plane of the triazine ring, while in **16c**, the ruthenium oxalato clips are twisted by 20.5° out of the plane of the 4-tpt subunits and the pyridyl rings are tilted by 36.1°. This deviation from a perfectly eclipsed conformation of the trigonal metalla-prisms occurs in order to improve the π-stacking interaction between the two 4-tpt ligands.



16 **16b** **16c**

Figure 9. Molecular structures of **16b** and **16c**.[30]

The more spacious cationic hexanuclear metalla-prisms, $[Ru_6(p\text{-}i PrC_6H_4Me)_6(\mu\text{-}4\text{-tpt})_2(\mu\text{-}C_6H_2O_4)_3]^{6+}$ (**17b**), $[Ru_6(C_6Me_6)_6(\mu\text{-}4\text{-tpt})_2(\mu\text{-}C_6H_2O_4)_3]^{6+}$ (**17c**), $[Ru_6(p\text{-}i PrC_6H_4Me)_6(\mu\text{-}4\text{-tpt})_2(\mu\text{-}C_6Cl_2O_4)_3]^{6+}$ (**18b**) and $[Ru_6(C_6Me_6)_6(\mu\text{-}4\text{-tpt})_2(\mu\text{-}C_6Cl_2O_4)_3]^{6+}$ (**18c**), incorporating *p*-cymene or hexamethylbenzene ruthenium building blocks bridged by 2,5-dihydroxy-1,4-benzoquinonato or 2,5-dichloro-3,6-dihydroxy-1,4-benzoquinonato ligands and connected by two 4-tpt subunits, have been synthesised by following the same strategy (Route B).[32] The synthesis of derivative **17b** is presented in Scheme 5. The encapsulation of a flat molecule within the cavity of these hexanuclear metalla-prisms can either enhance or weaken the chirality.[31] Moreover, if the encapsulated molecule possesses the proper symmetry and fits perfectly into the cavity, the triangular prismatic conformation can be locked, thus suppressing chirality.

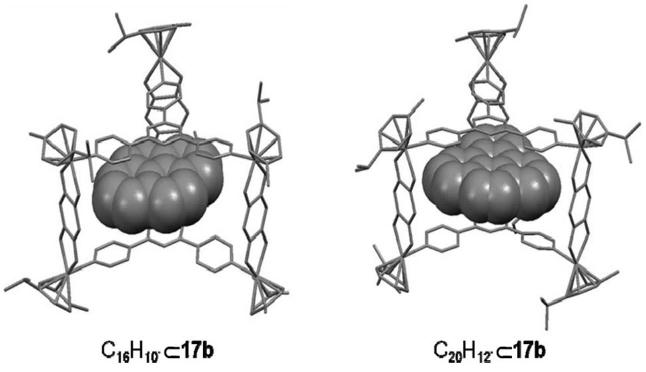


3b

17b

Scheme 5. Synthesis of metalla-prism **17b**.[32]

Indeed, these systems have allowed the permanent encapsulation of large aromatic molecules such as pyrene ($C_{16}H_{10}$), fluoranthene ($C_{16}H_{10}$), triphenylene ($C_{18}H_{12}$), benzo[*e*]pyrene ($C_{20}H_{12}$) and coronene ($C_{24}H_{12}$),[33] or the encapsulation of functionalised triphenylene molecules hexahydroxytriphenylene [$C_{18}H_6(OH)_6$] and hexamethoxytriphenylene [$C_{18}H_6(OMe)_6$].[34] The structures of [$C_{16}H_{10}\subset$**17b**](CF_3SO_3)$_6$ and [$C_{20}H_{12}\subset$**17b**](CF_3SO_3)$_6$, obtained by single-crystal X-ray structural analysis, are presented in Figure 10. However, despite the presence of these large aromatic molecules (pyrene and benzo[*e*]pyrene) in the cavity of **17b**, the staggered conformation of the two 4-tpt units remains, thus conserving the chirality of the metalla-prism **17b**.



$C_{16}H_{10}\subset$**17b** $C_{20}H_{12}\subset$**17b**

Figure 10. Molecular structures of [$C_{16}H_{10}\subset$**17b**](CF_3SO_3)$_6$ and [$C_{20}H_{12}\subset$**17b**](CF_3SO_3)$_6$.[33]

Single-crystal X-ray structural analysis of the carceplex system [$C_{18}H_6(OMe)_6\subset$**17b**](CF_3SO_3)$_6$ has been performed as well.[34] Because of its size and the presence of six methoxy groups, the hexamethoxytriphenylene is strongly encapsulated in **17b**, and the twists of the two 4-tpt units, as well as the rotation of the pyridyl groups, are locked in this system (see Figure 11). Therefore, this system shows no chirality in the solid state and crystallises in the trigonal space group $R\bar{3}c$.

The assembly of **17b** can also be achieved in the presence of the square-planar complexes $Pd(acac)_2$ and $Pt(acac)_2$ (acac = acetylacetonato) to give the "complex-in-a-complex" cations [$(acac)_2Pd\subset$**17b**]$^{6+}$ and [$(acac)_2Pt\subset$**17b**]$^{6+}$.[32] Both cations are isolated as their triflate salts. The molecular structure of [$(acac)_2Pt\subset$**17b**](CF_3SO_3)$_6$ is confirmed by single-crystal X-ray structural analysis (see Figure 12). The $Pt(acac)_2$ complex is strongly held between the triazine units of the 4-tpt ligands, the platinum triazine···centroid separation being 3.4 Å. To accommodate the $Pt(acac)_2$ complex within the cavity of **17b**, the $Ru_2(\mu\text{-}C_6H_2O_4)^{2+}$ dinuclear units are tilted out of the plane of the 4-tpt subunits by as much as 14°.

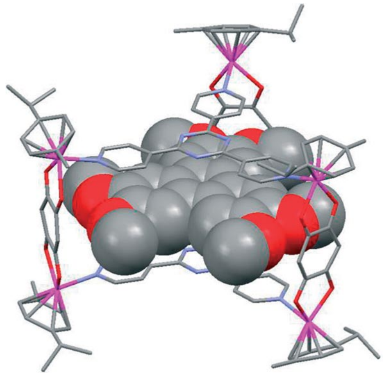


Figure 11. Molecular structure of [$C_{18}H_6(OMe)_6\subset$**17b**](CF_3SO_3)$_6$.[34]

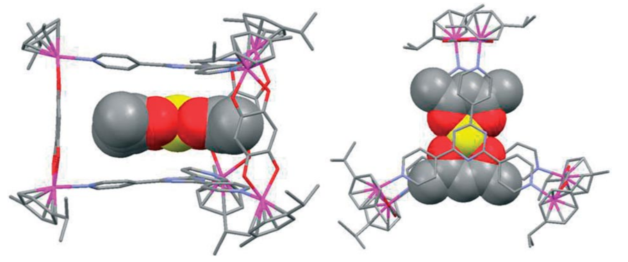


Figure 12. Molecular structure of [$(acac)_2Pt\subset$**17b**]$^{6+}$.[32]

The cytotoxic activities on human ovarian cancer cells of the "complex-in-a-complex" derivatives [$(acac)_2M\subset$**17b**]$^{6+}$ were evaluated in comparison with free $M(acac)_2$. Like a "Trojan Horse", they allow non-water-soluble molecules such as $M(acac)_2$ to be taken up by cancer cells.[32] This water-soluble metalla-prism is also used also to encapsulate functionalised aromatic molecules (pyrene-R) in a manner

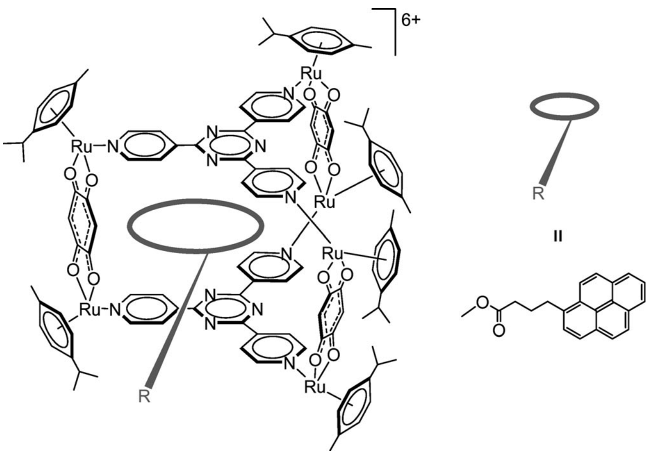


Figure 13. Molecular structure of [pyrene-R$\subset$**17b**]$^{6+}$.[33]

such that the aromatic part is encapsulated (pyrenyl moiety) while a functional group (R group) hangs out of the cage (see Figure 13).[33] The encapsulation of methyl 4-(pyren-1-yl)butanoate in **17b** was confirmed by ^{1}H NMR spectroscopy and ESI mass spectrometry.

Work is currently in progress to encapsulate monofunctionalised pyrene derivatives incorporating various biological groups to confirm the potential of these water-soluble metalla-prisms to act as drug carriers.

Arene Ruthenium Metalla-Boxes

Self-assembly of transition-metal complexes with porphyrin and metalla-porphyrin ligands is receiving a great deal of attention in chemical research. The self-assembly of porphyrin-containing squares by metal-ion coordination was first reported by Drain and Lehn in 1994.[35] The combination of square-planar transition-metal coordination to bind multifunctional porphyrin ligands in a linear fashion (180°) or at right angles (90°) was cleverly exploited in that initial paper. Many groups have followed this square-planar transition-metal coordination strategy to build up porphyrin-containing molecular assemblies.[36] Studies involving the introduction of octahedral transition metals to assemble such systems appeared a few years later.[37] The *fac*-Re(CO)$_3$ corner system was exploited by Hupp,[38] while Alessio used the *fac*-RuCl$_2$(Me$_2$SO)$_3$(CO) complex[39] to generate multiple porphyrin-containing molecular assemblies. Similarly, arene ruthenium building blocks can be exploited to generate metalla-boxes.

Last year, Jin and his co-workers synthesised the metalla-box [Ru$_8$(*p*-*i*PrC$_6$H$_4$Me)$_8$(μ-tpp-H$_2$)$_2$(μ-C$_2$O$_4$)$_4$]$^{8+}$ (**19b**) [tpp-H$_2$ = 5,10,15,20-tetra(4-pyridyl)porphyrin] incorporating tetradentate porphyrin ligands and oxalato bridging connectors.[40] The molecular structure of **19b** was determined by X-ray structural analysis of its triflate salt (see Figure 14).

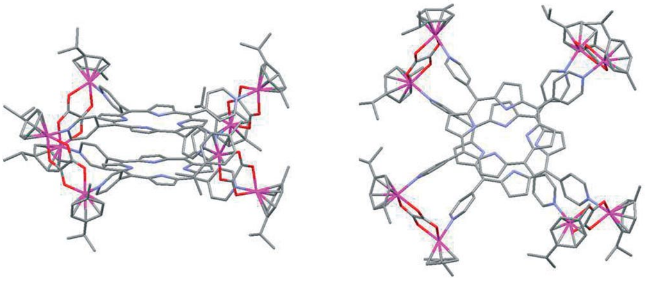
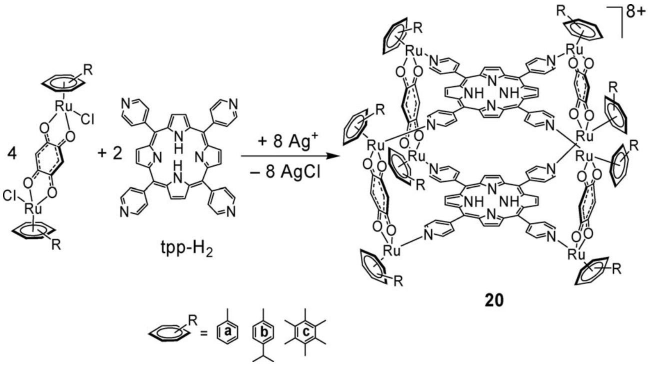


Figure 14. Molecular structure of the metalla-box **19b**.[40]

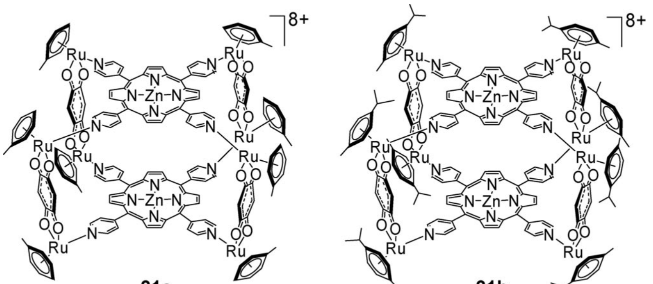
The X-ray structural analysis of **19b** showed the metalla-box to possess helical chirality, the porphyrin···porphyrin separation to be 4.1 Å and the volume of the box to be approximately 800 Å^3. Despite this large volume, the cavity of the octanuclear metalla-box was too narrow to accommodate a guest molecule, and strong π-stacking interactions between the two porphyrin panels were observed.

Using the same strategy but employing 2,5-dihydroxy-1,4-benzoquinonato instead of oxalato bridges, we synthesised a series of cationic octanuclear metalla-boxes of the general formula [Ru$_8$(arene)$_8$(μ-tpp-H$_2$)$_2$(μ-C$_6$H$_2$O$_4$)$_4$]$^{8+}$ (**20a**: arene = C$_6$H$_5$Me; **20b**: arene = *p*-*i*PrC$_6$H$_4$Me; **20c**: arene = C$_6$Me$_6$, see Scheme 6).[41]



Scheme 6. Synthesis of metalla-boxes **20**.[41]

Similarly, cationic metalla-boxes incorporating toluene or *p*-cymene ruthenium building blocks bridged by 2,5-dihydroxy-1,4-benzoquinonato ligands and connected by the zinc metallo-porphyrin 5,10,15,20-tetra(4-pyridyl)porphyrin-Zn^{II} (tpp-Zn) tetradentate ligand were synthesised: [Ru$_8$(C$_6$H$_5$Me)$_8$(μ-tpp-Zn)$_2$(μ-C$_6$H$_2$O$_4$)$_4$]$^{8+}$ (**21a**) and [Ru$_8$(*p*-*i*PrC$_6$H$_4$Me)$_8$(μ-tpp-Zn)$_2$(μ-C$_6$H$_2$O$_4$)$_4$]$^{8+}$ (**21b**) (see Figure 15).[42]



21a **21b**

Figure 15. Molecular structures of **21a** and **21b**.[42]

The G-quadruplex motif has became a promising target for cancer therapy, as G-quadruplexes inhibit the enzyme telomerase, an enzyme involved in the immortality of cancer cells.[43] Until recently, G-quadruplex stabilisers were purely organic molecules with large aromatic surfaces and positive charges to interact with the grooves of the quadruplex.[44] These two features can be easily achieved by coordination chemistry. Indeed, square-planar metal complexes with salphen- and salen-type ligands have been used successfully to stabilise telomeric quadruplex DNA.[45] Similarly, the self-assembled square [Pt$_4$(en)$_4$(μ-bpy)$_4$]$^{4+}$, which has been developed by Fujita,[1] showed a good binding affinity for G-quadruplexes.[46] Therefore, we were interested in studying the ability of cationic octanuclear metalla-boxes, which possess large aromatic surfaces and are highly positively charged, to stabilise G-quadruplexes and to act as telomerase inhibitors.[42]

The supramolecular metalla-boxes **20a**, **20b**, **21a** and **21b** interact strongly with duplex and human telomeric quadruplex DNA. The interactions with duplex and human telomeric quadruplex DNA was studied by fluorescent intercalation displacement assay (FID)[47] and surface plasmon resonance (SPR)[48] experiments. These studies have shown the octacationic arene ruthenium metalla-boxes to be promising quadruplex DNA stabilisers and to possess a high degree of selectivity for quadruplex over duplex.[42] These results, which will be published soon, open new perspectives for arene ruthenium metalla-boxes and other supramolecular assemblies.

Conclusions

In this review article, the synthetic strategies to obtain metalla-rectangles, triangular metalla-prisms and metalla-boxes have been extensively described. This straightforward strategy can be easily exploited and modified to build up other supramolecular architectures. Some of these systems show great potential for host–guest chemistry and for biological applications. However, this is just the beginning, and more surprises will come out over the forthcoming years from arene ruthenium cages.

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