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Biologically Relevant Arene Ruthenium Metalla-Assemblies

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Arene ruthenium complexes are known for 50 years and the number of publications involving arene ruthenium complexes is in constant progression ever since their discovery. Following the synthesis and characterisation of the first arene ruthenium complexes, they have been initially tested as catalysts. Then later on, with the emergence of bio-inorganic chemistry, the biological activity of arene ruthenium complexes was explored. And lately, arene ruthenium complexes have become popular building blocks for the preparation of metalla-assemblies. In this highlight article, we present our contributions in the field of water soluble metalla-assemblies with an emphasis on their biological potentials, revealing that arene ruthenium complexes have found a new playground.

Introduction

The controversy surroundings the biological safety of nanoparticles remains a topical issue, and this is especially true for the smallest nanoparticles (< 10 nm), those who can easily spread throughout the body.[1] Other than the size, several factors can influence the biological safety of nanoparticles, such as the geometry, the surface area, the chemical composition, the stability and the solubility. Another challenge that nanoparticles is facing concern their fabrication; the smallest modification during their synthesis can modify completely their biological behaviour,[2] thus complicating even more their safety approval. Therefore, we believe that a bottom up approach, in which discrete and perfectly defined nano-objects are used to perform tasks devoted to nanoparticles, offers a better alternative.

The field of coordination-driven self-assembly is by now well established.[3] The choice of the metal ions dictates the geometry, while selecting the appropriate connectors allows the formation of predictable metalla-assemblies. This strategy has already produced nano-scale metalla-assemblies with large hollow space capable of encapsulating guest molecules.[4] Recently, the protein ubiquitin was encapsulated in the cavity of a large $[Pd_{12}L_{24}]^{24+}$ cage,[5] confirming the potential of using coordination-driven self-assembly to synthesise discrete nano-objects of biological relevance.

Among metal ions, we have focused our attention to ruthenium, more specifically to arene ruthenium complexes. The reasons behind this choice are multiple: Despite being of octahedral geometry, the ruthenium centre has only three coordination sites available, the arene ligand occupying in a facial arrangement three of the six coordination sites. Consequently, this limited number of remaining sites at 90° from each other facilitates the design and the controlled synthesis of metalla-assemblies. Moreover, dealing with ruthenium complexes in the oxidation state +2 is an advantage. Several studies have shown that +2 is often the preferred oxidation state of biologically active ruthenium species *in vivo*.[6] In addition, the chemistry of arene ruthenium complexes is compatible with water,[7] and the arene ligand can be appended to insert additional functional groups.[8] Therefore, arene ruthenium complexes possess all the prerequisites to generate metalla-assemblies of biological significance.

Organometallic half-sandwich complexes

Arene ruthenium complexes are part of the organometallic half-sandwich family, also called piano stool complexes. The most common derivatives are presented in Figure 1, showing the *p*-cymene (arene) ruthenium and osmium complexes as well as the pentamethylcyclopentadienyl (Cp*) rhodium and iridium analogues. In these complexes, the metal possesses and octahedral geometry, but they are often regarded as pseudo-tetrahedral complexes due to the presence of the η^6-arene or η^5-Cp* ligand, which is depicted as a monodentate ligand.

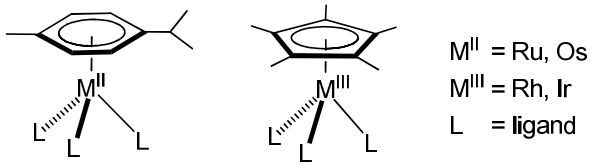

Fig. 1 Most common organometallic Ru^{II}, Os^{II}, Rh^{III} and Ir^{III} half-sandwich complexes.

The organometallic Ru^{II}, Os^{II}, Rh^{III} and Ir^{III} half-sandwich complexes are isoelectronic, and therefore, they normally react in a similar fashion and give rise to isostructural complexes. This implies that the metal centre can be interchanged without modifying the resulting structure. For instance, the first metalla-cycle, which was obtained by mixing 9-alkyladenine and $[Cp^*Rh(OH_2)_3]^{2+}$,[9] was a few years later replicated with Cp*Ir and (benzene)Ru units.[10,11] All half-sandwich complexes give with 9-alkyladenine a cationic trinuclear structure. These metalla-cycles are isoelectronic and isostructural, in which the 9-alkyladenine acts as tridentate bridging ligands. In Figure 2, the molecular structure of the 9-ethyladenine Cp*Ir derivative, $[\{Cp^*Ir(9\text{-ethyladenine})\}_3]^{3+}$,[10] is presented.

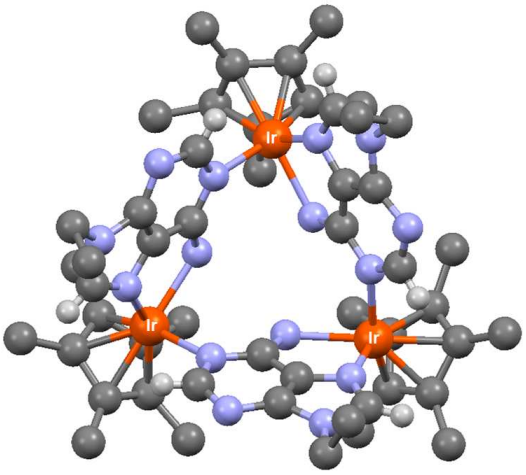

Fig. 2 Molecular structure of the trinuclear complex $[\{Cp^*Ir(9\text{-ethyladenine})\}_3]^{3+}$, adapted from reference 10 (CCDC 140158).

Consequently, the combination of tridentate ligands with organometallic half-sandwich complexes has produced several metalla-assemblies of various sizes and geometries.[12] However, another strategy introduced by Süss-Fink in the late 1990s has proven to be also quite effective in preparing arene ruthenium metalla-assemblies.[13] It involves stable dinuclear clips, such as $(p\text{-cymene})_2Ru_2(oxalato)Cl_2$, and linear bidentate ligands, for example 4,4'-bipyridine (bpy). As emphasised in Figure 3, the reaction requires two steps with no necessity of isolating the intermediate complex:[14] The first step being the removal of the chloride atoms, which paves the way to the formation of the metalla-cycle.

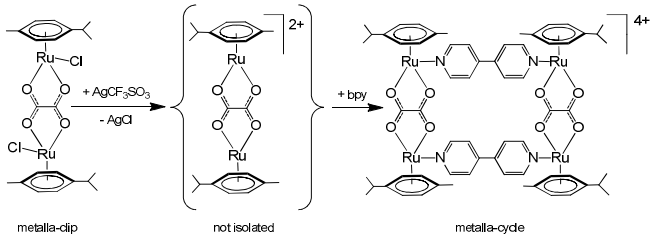

Fig. 3 Synthetic route to the tetracationic tetranuclear complex $[(p\text{-cymene})_4Ru_4(oxalato)_2(bpy)_2]^{4+}$.[13]

The presence of this highly reactive dinuclear intermediate, after removal of the chloride atoms by precipitation of AgCl upon addition of $AgCF_3SO_3$, is a key step in the reaction (Fig. 3). This intermediate, which is generally not isolated prior to the formation of the final metalla-assembly, shows a rapid *cis–trans* conversion and a dynamic exchange of the pyridyl-based ligands.[15] However, upon closure of the metalla-assembly, the overall stability of the metalla-cycle is significantly improved, and the dynamic processes are stopped, giving rise to stable and isolable metalla-assemblies.[16] In recent years, this strategy has been extensively used to generate 2D and 3D metalla-assemblies for biological applications.[17]

Arene ruthenium metalla-cycles

The first application of arene ruthenium metalla-cycles has involved the trinuclear complexes derived from arene ruthenium units and 2,3-dihydroxypyridine ligands. These analogues of crown ethers display an affinity for lithium and sodium salts, which can be limited to lithium by changing the steric hindrance of the arene ligands (Fig. 4).[18] The metalla-cycles incorporating the smallest arenes (benzene, *p*-cymene, ethylbenzoate) bind both cations, Li^+ and Na^+, but not K^+, while the complexes with the most sterically demanding arene ligands (triethylbenzene, hexamethylbenzene) only interact with Li^+ (Fig. 4).

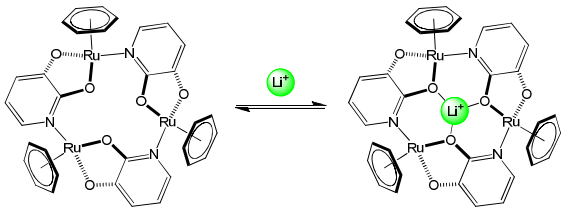

Fig. 4 Binding of Li^+ in the core of an arene ruthenium metalla-cycle.[16]

A series of analogous trinuclear complexes incorporating aminomethyl-substituted 3-hydroxy-2-pyridone and Cp*Rh and (*p*-cymene)Ru ions has been synthesised and evaluated as anticancer agents against various cancer cells.[19] The complexes appear to interconvert between trimeric and monomeric species as a function of the pH, which suggests the presence of the monomeric form in the reduced pH environment of cancer cells; the trimeric structure being considered a prodrug compound. All complexes were found to be moderately cytotoxic on ovarian carcinoma and fibroblast cells, with IC_{50} values > 340 µM (IC_{50} = concentration corresponding to 50% inhibition of cell growth).

The water solubility and the stability under physiological conditions are both crucial for the biological application of arene ruthenium metalla-assemblies.[17] Two qualities generally encountered with cationic tetranuclear arene ruthenium metalla-cycles obtained from the assembly of two dinuclear clips and two N∩N bidentate ligands. In 2009, our group[20] as well as the

group of Barea and Navarro[21] published independently two reports on the biological activity of *p*-cymene ruthenium based metalla-cycles (Fig. 5). In both studies the metalla-cycles show IC_{50} values in the micromolar range on the human ovarian A2780 cancer cells, and for the oxonato derivatives developed by Navarro and Barea, non-covalent interactions with DNA were observed for the cationic metalla-cycles.[21] Following these initial studies, other groups have investigated the biological activity of tetranuclear arene ruthenium metalla-cycles.[22]

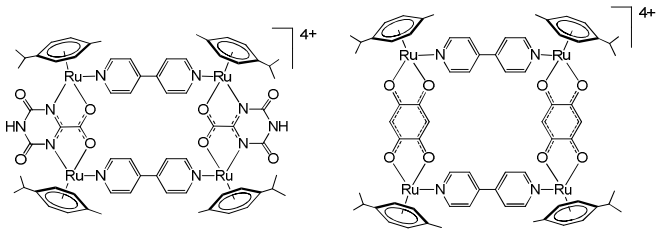

Fig. 5 Molecular structures of the first biologically active cationic tetranuclear complexes $[(p\text{-cymene})_4Ru_4(oxonato)_2(bpy)_2]^{4+}$ (left),[21] and $[(p\text{-cymene})_4Ru_4(dihydroxybenzoquinonato)_2(bpy)_2]^{4+}$ (right).[20]

For instance, Stang, Chi and coworkers have reported several tetranuclear arene ruthenium metalla-cycles and studied their antiproliferative activity and ability to interact with anions, DNA strands and proteins.[23] The metalla-cycle built from the arene ruthenium 5,11-dioxydo-6,12-tetracenequinonato (dotq) metalla-clip and dipyridyloxalamide N∩N connector (dpo) (Fig. 6) has showed a high affinity for oxalate over the acetate or halide anions, thus providing an interesting sensor for this biologically relevant marker.[24]

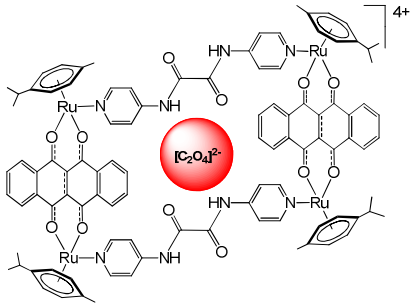

Fig. 6 Molecular structure of the cationic tetranuclear complex $[(p\text{-cymene})_4Ru_4(dotq)_2(dpo)_2]^{4+}$, showing interactions with an oxalate anion.[24]

Likewise, the more spacious and flexible metalla-cycle, $[(p\text{-cymene})_4Ru_4(dotq)_2(dppd)_2]^{4+}$ (dppd = dipyridyl-pyridine-2,6-dicarboxamide) (Fig. 7), which possesses similar donor and acceptor groups in its core, interacts strongly with polyanionic species such as oxalate, tartrate and citrate but not with the monoanions.[25] A 1:1 binding ratio between the polyanion and the cationic metalla-cycle was determined by UV-vis titrations, again confirming that arene ruthenium metalla-cycles can be designed to act as sensors.

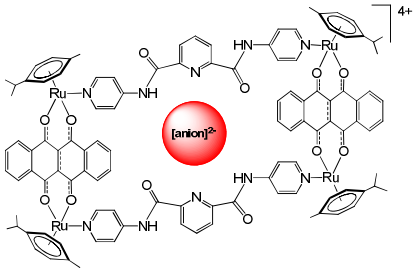

Fig. 7 Molecular structure of the cationic tetranuclear metalla-cycle $[(p\text{-cymene})_4Ru_4(dotq)_2(dppd)_2]^{4+}$, interacting with polyanionic species.[25]

An extended version of $[(p\text{-cymene})_4Ru_4(dotq)_2(dppd)_2]^{4+}$ (Fig. 7), including additional ethynylbenzene spacers, has been recently synthesised by Kim, Chi and coworkers.[26] The cationic tetranuclear metalla-cycle combines oxalato bridged *p*-cymene ruthenium metalla-clips and bis{4-pyridin-4-ylethynyl)phenyl}pyridine-2,6-dicarboxamide (bpep) connectors (Fig. 8). The conformation of the enhanced green fluorescent protein (EGFP) was disrupted in solution by the presence of the metalla-cycle. The presence of donor and acceptor groups appears to be crucial for the metalla-cycle protein interactions to take place, an analogous metalla-cycle with no pyridine-2,6-dicarboxamide units within the N∩N connectors has showed no affinity for EGFP.

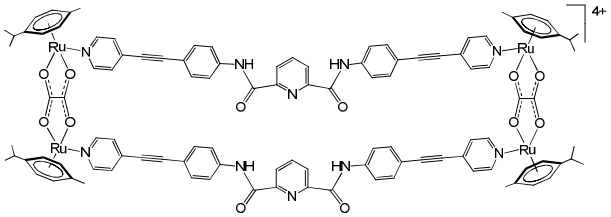

Fig. 8 Molecular structure of the cationic tetranuclear complex $[(p\text{-cymene})_4Ru_4(oxalato)_2(bpep)_2]^{4+}$, able to interact with EGFP.[26]

A series of hexanuclear arene ruthenium helicates has been obtained by mixing in water, dihydroxypyridine ligands, NEt_3 and the $(toluene)_2Ru_2(\mu\text{-}Cl)_2Cl_2$ dimeric complex.[27] The helicate obtained from the spacer 4,4'-[{4,4'-(propane-1,3-diyl)bis(piperidine-4,1-diyl)}bis(methylene)]bis(pyridine-2,3-diol) ($ppmpH_2$) is presented in Figure 9. Interestingly, these hexanuclear complexes are chiral, and they can be considered as expanded triple-stranded helicates.

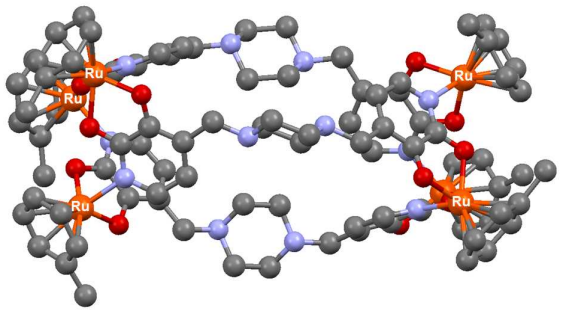

Fig. 9 Molecular structure of the hexanuclear arene ruthenium helicate $(toluene)_6Ru_6(ppmp)_3$.[27]

Hexanuclear and octanuclear arene ruthenium metalla-assemblies have been recently designed by Mukherjee.[28] The large cationic assemblies were used to detect nitroaromatic molecules, also confirming the sensing ability of arene ruthenium metalla-cycles for non-biological applications.

Arene ruthenium metalla-cages

Cavities of arene ruthenium metalla-cycles are ideal for rapid and reversible host-guest interactions. In addition, metalla-cycles provide flexibility, adaptability and easy access of their cavities, thus giving them all the necessary features for sensing. However, to carry, transport and protect guest molecules, the host-guest interactions need to be stronger, and the host-guest exchange kinetics slower. To achieve that, additional host-guest interactions can be introduced (H-bonding, π-stacking, electrostatic, etc.), or the apertures from which the guest is released lessen. Following the same approach as for preparing arene ruthenium metalla-cycles, the synthetic strategy developed by Süss-Fink[13] was extended to arene ruthenium metalla-cages.

The first biological application of an arene ruthenium metalla-cage was published in 2008. The cationic hexanuclear metalla-prism $[(p\text{-cymene})_6Ru_6(tpt)_2(dhbq)_3]^{6+}$ (tpt = 2,4,6-trispyridyl-1,3,5-triazine; dhbq = 2,5-dihydroxy-1,4-benzoquinonato) was used to encapsulate square-planar complexes (Fig. 10).[29] The metalla-prism is water soluble and it shows an IC_{50} of 23 μM on human ovarian A2780 cancer cells. However, with $Pd(acac)_2$ sitting inside the cavity, the complex-in-a-complex system is 20 times more cytotoxic with an IC_{50} of only 1 μM. Like the legendary Trojan horse, the metalla-cage hides in its cavity a destructive guest, and after internalisation within the diseased cells, the killing agent escapes to perform its deadly act.

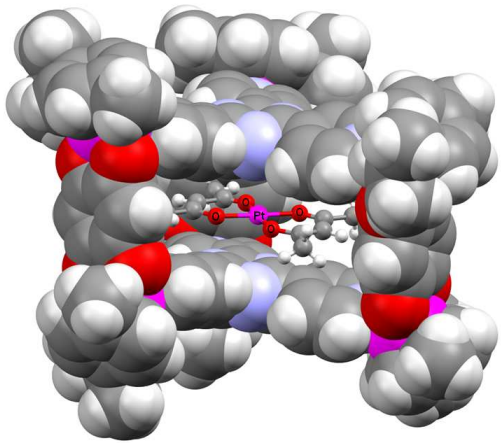

Figure 10. Complex-in-a-complex system $[Pt(acac)_2 \subset (p\text{-cymene})_6Ru_6(tpt)_2(dhbq)_3]^{6+}$.[29]

Encapsulation of other Pt-based complexes was also performed with the slightly more spacious metalla-prism $[\{(p\text{-cymene})Ru\}_6(donq)_3(tpt)_2]^{6+}$ (donq = 5,8-dioxydo-1,4-naphthoquinonato). Among platinum complexes, {2-(pyridin-1-yl)pyridine}Pt(acac) (**A**), {2-(4-(pyridin-1-yl)phenyl)pyridine}Pt(acac) (**B**) and {2-phenyl-6-(2-(piperidin-1-yl)ethoxy)-1,10-phenanthroline}PtCl (**C**) (Fig. 11), were encapsulated. As previously observed, the complex-in-a-complex systems appear to be more cytotoxic than the empty metalla-cages. Complexes **A** and **B** are both hydrophobic complexes,[30] and could enter cells only upon encapsulation.

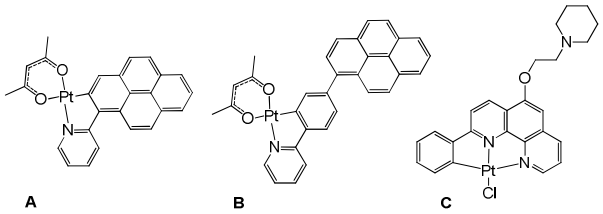

Figure 11. Platinum complexes encapsulated in metalla-cages.[30,31]

Recently, it was showed that complex **C** (Fig. 11), an excellent quadruplex DNA stabilizer,[31] was unable to enter osteosarcoma U2OS cells. However, after encapsulation in the water-soluble metalla-cage $[\{(p\text{-cymene})Ru\}_6(donq)_3(tpt)_2]^{6+}$, not only the platinum complex was found inside the cells, but confocal fluorescence microscopy has demonstrated that complex C has reached the nucleus and interacted with DNA. This study further supports the effectiveness of using water-soluble metalla-cages to act as delivery vectors.

To further explore the capacity of the arene ruthenium metalla-cages to internalize guest molecules to cells, a fluorescent pyrenyl derivative, 1-(4,6-dichloro-1,3,5-triazin-2-yl)pyrene, has been encapsulated. Interestingly, the fluorescence of this fluorescent-pyrene was quenched when trapped in the cavity of the arene ruthenium metalla-cages, thus providing an elegant probe for studying uptake and release of guest molecules *in vitro*.[32] Confocal fluorescence microscopy was used to follow the release of the guest, showing an excellent correlation between the portal size of the metalla-cage and the release of the guest molecule in cancer cells.

In view of increasing the value of the load delivered by arene ruthenium metalla-cages, a series of pyrenyl-functionalized compounds were prepared and encapsulated in the cavity of the host. Among these pyrenyl derivatives, pyrenyl-functionalized floxuridine conjugates (**D**, Fig. 12),[33] pyrenyl-arene ruthenium complexes (**E**, Fig. 12),[34] and pyrenyl-modified dendrimers (**F**, Fig. 12),[35] have been internalize to cancer cells using arene ruthenium metalla-cages.

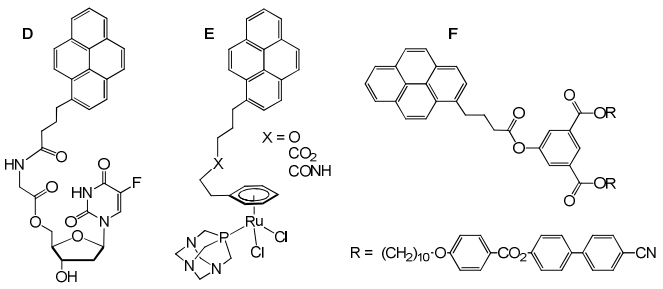

Figure 12. Pyrenyl-functionalized guest molecules, floxuridine conjugate (**D**), pyrenyl-arene ruthenium complexes (**E**), pyrenyl-dendrimer (**F**).[33-35]

In these systems, the pyrenyl unit is hiding inside the hydrophobic cavity of the metalla-prisms, while the functional group is dangling out, as illustrated in Figure 13. The metalla-cage helps to solubilize the pyrenyl-functionalized compound, and subsequently contributes to the internalisation of the guest within cells.

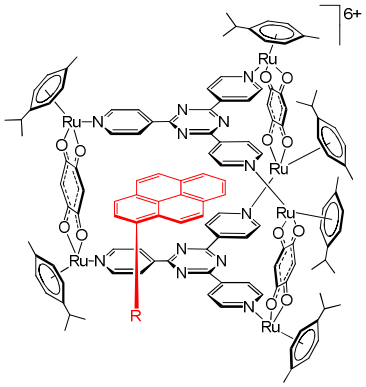

Figure 13. Schematic representation of a pyrenyl-functionalized derivative encapsulated in an arene ruthenium metalla-prism.

Firstly, a series of pyrenyl-functionalised floxuridine conjugates (Fig. 12**D**) were synthesised and evaluated *in vitro* as anticancer agents.[33] Fluxoridine is a FDA approved drug with limited water solubility. After encapsulation of the pyrenyl group in the metalla-prisms $[\{(p\text{-cymene})Ru\}_6(dhbq)_3(tpt)_2]^{6+}$ and $[\{(p\text{-cymene})Ru\}_6(donq)_3(tpt)_2]^{6+}$, all adducts were tested on human ovarian cancer cells (A2780 and A2780cisR). All systems showed excellent uptake of the conjugated-floxuridine derivatives with IC_{50} in the lower μM range.

Among arene ruthenium complexes with chemotherapeutic potentials, RAPTA-C is one of the most promising compound.[36] This complex is weakly cytotoxic *in vitro*, but quite selective and efficient on metastasis *in vivo*.[36] Unfortunately, to be effective *in vivo*, it requires high doses. Therefore, in order to increase the uptake and potentially reduce the dose needed to obtain a therapeutic effect, RAPTA-C analogues with a pyrenyl dangling arm connected to the arene ligand were synthesised (Fig. 12**E**).[35] The pyrenyl group of the pyrenyl-arene ruthenium complexes was encapsulated in the metalla-cage $[\{(p\text{-cymene})Ru\}_6(donq)_3(tpt)_2]^{6+}$. The cytotoxicity of the pyrenyl-functionalised RAPTA-C analogues was found to be at least 10 times higher than the reference compound RAPTA-C, while the cytotoxicity of the encapsulated pyrenyl-arene ruthenium systems was 50 times more potent than RAPTA-C on several cancer cell lines (A549, A2780, A2780cisR, Me300, HeLa). Using the fluorescence property of the pyrenyl-group, uptake of the pyrenyl-arene ruthenium derivatives with and without association to the metalla-cage was compared. Encapsulation of the pyrenyl-group in the water-soluble metalla-cage $[\{(p\text{-cymene})Ru\}_6(donq)_3(tpt)_2]^{6+}$ doubled the uptake.

During the development of a tumour, several differences in the vascular structure and physiology of tumour tissues compared to healthy tissues can be observed. Angiogenesis and vasculogenesis in healthy tissues form well defined vessels, while the vascular network in tumours shows high blood vessel permeability and poor lymphatic drainage. Because of these tumour particularities, Maeda observed that macromolecules accumulate predominantly in solid tumour due to the high blood vessel permeability and after internalisation were retained for prolonged periods due to the poor lymphatic drainage (Fig. 14).[37] This phenomenon was coined the "Enhanced Permeability and Retention" (EPR) effect, and nowadays, the EPR effect has become a popular strategy for large molecules to target cancers.

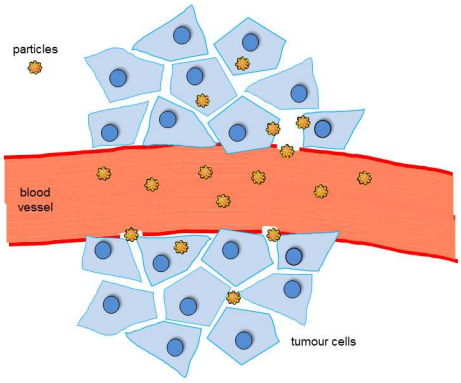

Figure 14. Schematic representation of the EPR effect.

Consequently, in view to better target cancer cells by exploiting the EPR effect, pyrenyl-modified dendrimers (Fig. 12**F**) were coupled with the water-soluble metalla-cage $[\{(p\text{-cymene})Ru\}_6(donq)_3(tpt)_2]^{6+}$, thus significantly increasing the overall size of the host-guest systems.[35] Three generations of pyrenyl-cyanobiphenyl dendrimers were synthesised and after encapsulation, the host-guest properties were studied by UV-visible and NMR spectroscopy. This study has showed that organometallic metalla-cages are able to deliver hydrophobic guest molecules with extremely large appendages into cancer cells. The molecular weight of the system incorporating the highest generation of pyrenyl-cyanobiphenyl dendrimer (P_2), $[P_2\subset\{(p\text{-cymene})Ru\}_6(donq)_3(tpt)_2](CF_3SO_3)_6$, was 6366.7 $g{\cdot}mol^{-1}$ and the size of the host-guest system was estimated to be approximately 20 x 25 x 85 Å.

To further increase the size of a host-guest system, not only the size of the guest, as illustrated with pyrenyl-dendrimers, can be enhanced. Indeed, to better exploit the EPR effect, even larger water-soluble metalla-assemblies can be synthesised. In this respect, several strategies can be employed to prepare larger arene ruthenium metalla-assemblies; the tridentate tpt ligands can be replaced with larger tridentate or even by tetradentate ligands to form octanuclear species,[38] the dinuclear dihydroxy-1,4-benzoquinonato or naphthoquinonato arene ruthenium connectors can be replaced by macrocyclic dinuclear systems[39] or by hydroxy-benzoquinone derivatives with appendages,[40] and the arene ligands can also be embedded with functional groups.[8] All strategies can significantly increase the overall size of the metalla-assemblies as well as altering their biological properties. Nevertheless, exploiting the EPR effect by preparing large metalla-assemblies is certainly an important aspect to consider when studying arene ruthenium metalla-cages, which can ultimately increase the selectivity for these hybrid drug delivery systems.

Other interesting guest molecules can be inserted in the cavity of arene ruthenium metalla-assemblies. For instance, porphin has been encapsulated in the metalla-prism $[\{(p\text{-cymene})Ru\}_6(dhbq)_3(tpt)_2]^{6+}$ and in the metalla-cube $[\{(p\text{-cymene})Ru\}_8(donq)_4(tpvb)_2]^{8+}$ (tpvb = 1,2,4,5-tetrakis-{2-(pyridin-4-yl)vinyl}benzene).[41] In the metalla-prism, porphin is unable to escape unless the cage is broken, however, in the octanuclear assembly, porphin acts as a guest; the fenestration of the metalla-cube being wide enough to allow porphin to escape freely in solution (Fig. 15).

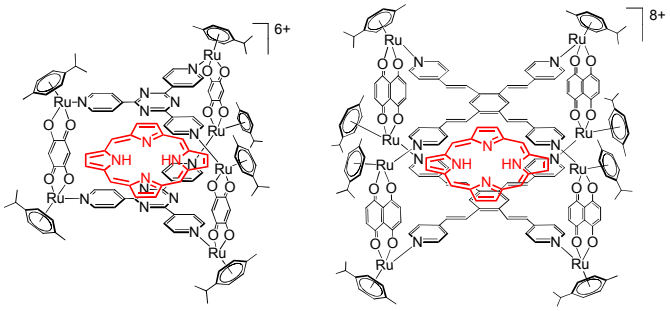

Figure 15. Porphin encapsulated in an arene ruthenium metalla-prism (left) and an arene ruthenium metalla-cube (right).[41]

The benefits of encapsulating porphin in the hydrophobic cavity of a water soluble metalla-assembly are multiple. It enables the internalization of hydrophobic photosensitizers to cells without having to synthetically modify the porphyrinic core, and it shields the photo-chemical properties of porphin. Therefore, using the porphin in the cage compounds for photodynamic therapy (PDT) offers interesting advantages,[42] PDT being already used in the clinic for the treatment of cancers.[43]

PDT treatments involve the injection of a photosensitizer, which is later on activated by light at a specific wavelength. Upon irradiation, the photosensitizer reaches a high-energy triplet state, which can react with cellular oxygen to produce reactive oxygen species (ROS). The spatially-controlled activation of the photosensitizer allows negligible toxicity and consequently minimal side effects. However, patients receiving PDT treatments can suffer from an undesired photo-activation from the Sun of the photosensitizers accumulated in skin tissues.

Attaining a selective and spatially-controlled release of guest molecules with arene ruthenium metalla-assemblies remains a difficult task. To achieve that, introduction of stimuli-responsive building blocks within the metalla-assembly is required. Different stimuli can potentially be employed to provoke guest release; pH, temperature, polarity, light, electric field, or metal ion. Recently, Clever and coworkers have synthesised a Pd-based metalla-cage which includes light-responsive dithienylethene (DTE) spacers.[44] The external stimulus induces a geometrical change of the DTE ligands, which modified the size of the cavity, thus forcing the initially encapsulated $[B_{12}F_{12}]^{2-}$ guest molecule to remain outside (Fig. 16). So far, no biologically relevant stimuli-responsive arene ruthenium metalla-assembly has been synthesised, however, attempts in that direction have been made.

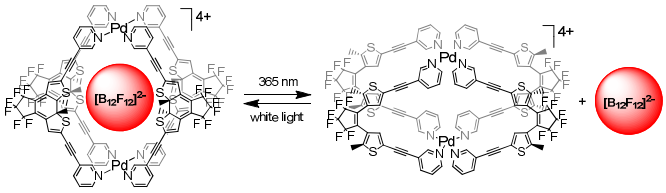

Figure 16. Stimuli-responsive $[Pd_2L_4]^{4+}$ metalla-cage.[44]

Indeed, our first strategy was to block the apertures of the metalla-cage with long alkyl chains (Fig. 17).[45] Unfortunately, in water, the alkyl chains hide inside the hydrophobic cavity of the metalla-prism, thus occupying the hydrophobic pocket normally used to transport guest molecules. Then, we tried to design pH sensitive metalla-clips, to obtain breakage of the metalla-cage under acidic conditions, cancer cells being known to have an acidic environment.[46] Accordingly, a zwitterion-bridged metalla-cage was synthesised (Fig. 17),[47] which appears to be sensitive to pH, however, below the value of the physiological pH of cancer cells, which is between 5 and 7.

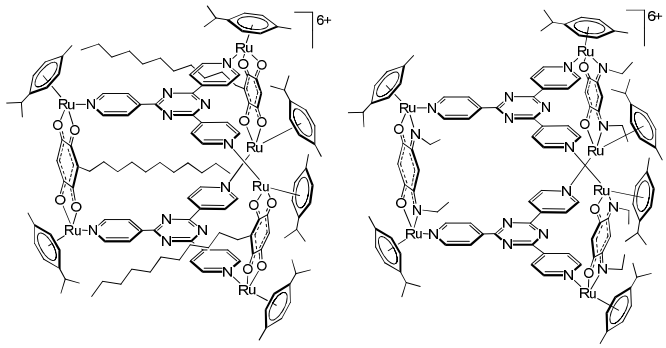

Figure 17. Metalla-cages with alkyl chains (left) and with zwitterion-bridged dinuclear arene ruthenium clips (right).[45,47]

Nevertheless, to develop an ideal drug delivery vector, controlling the release of the guest molecule is essential and we are still working on this issue. Among our current projects, we have envisaged to insert stimuli-responsive gates in front of the apertures of the metalla-cage, to incorporate photo-active connectors within the metalla-assembly, or to add redox-sensitive spacers. These strategies are all aiming at the development of the next generation of metalla-cages, in view of getting the best possible drug delivery vector for a future *in vivo* study.

Conclusions

Arene ruthenium metalla-assemblies are known for many years, and like coordination-driven self-assembly, applications are now driving the field. Among these applications, we have focussed our attention to the biomedical and biochemical applications, taking advantages in the presence of ruthenium: Ruthenium being one of the most popular bio-inorganic metals.[48] As illustrated in this highlight article, the size, geometry, solubility, functionality, or host-guest properties are all easily tuneable within these arene ruthenium metalla-assemblies, thus offering endless possibilities. Moreover, even if not discussed here, the analogous metalla-assemblies with pentamethylcyclopentadienyl rhodium and iridium[49] as well as with arene osmium[50] complexes can be obtained if desired, without synthetic challenges. Obviously, despite being an emerging field, the biological side of water soluble arene ruthenium metalla-assemblies is already showing great promises, and the next generation of metalla-assemblies with biological applications is already starting to appear in the literature.

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Notes and references

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Biography

Bruno Therrien completed his undergraduate degree at the University of Montreal, Canada, and obtained his PhD at the University of Berne, Switzerland, under the supervision of Professor Thomas R. Ward. Then, he undertook several postdoctoral positions (Weizmann Institute, Massey University, Tokyo University) and he currently hold an Associate Professor position at the University of Neuchatel, Switzerland. His main research interests are bio-organometallic chemistry and coordination-driven self-assembly.

Table of contents entry:

Arene ruthenium complexes have become popular building blocks for the preparation of metalla-assemblies with biological applications, opening a new era for arene ruthenium complexes.