Personal Account

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THE CHEMICAL RECORD

Unmasking Arene Ruthenium Building Blocks

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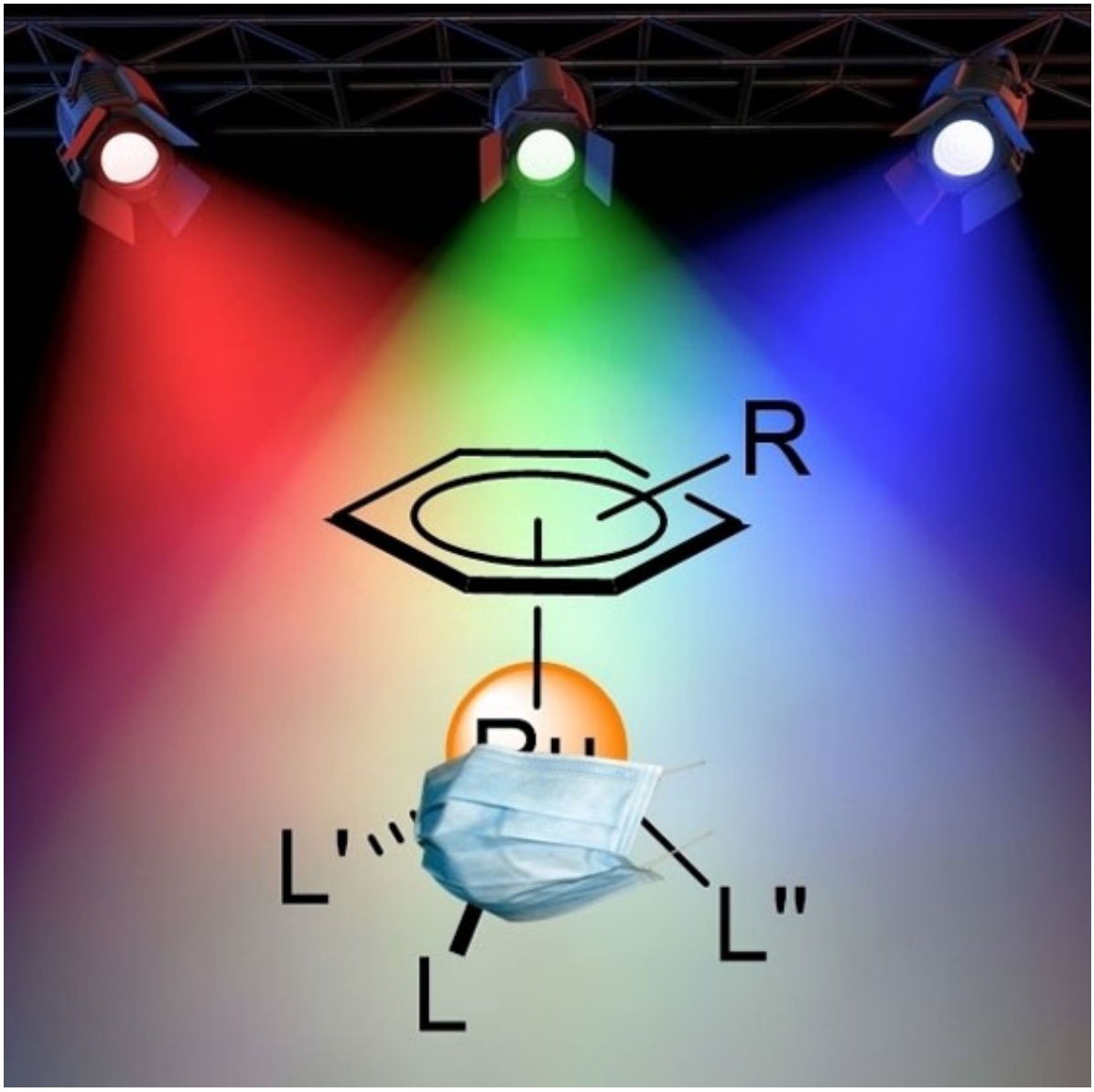
Dedicated to Pierre H. Dixneuf for his exceptional contribution to the development of ruthenium chemistry



Abstract: We have, like many others, contributed to the development and to the popularity of arene ruthenium assemblies. From early on, our research was driven by applications, mainly biological (therapeutic, drug delivery, DNA interactions, photodynamic therapy, imaging). For nearly 15 years, we have focused on the use of arene ruthenium building block as a tool to construct added-value objects. In this account, we want to give the basic reasons behind our choice, and uncover our most successful examples, with an emphasis on the foreseen applications.

Keywords: arene, ruthenium, supramolecular chemistry, metalla-assembly, piano-stool complexes, bioinorganic

1. Introduction

Mononuclear arene ruthenium complexes are particularly famous for their role in catalysis,[1] and for their potential as anticancer agents.[2] In catalysis, several arene ruthenium complexes have been studied, showing excellent catalytic activity for a wide range of transformations, under soft and hard conditions.[3] The versatility and robustness of arene ruthenium catalysts can be associated to the structural and electronic properties of the complexes.

Similarly, the biological activities of arene ruthenium complexes are linked to their intrinsic properties. These complexes possess an amphiphilic nature, having a lipophilic and stable arene ligand as well as labile and water-soluble monodentate ligands.[4] These labile ligands can be exchanged with water or coordinating solvent molecules, thus forming cationic and hydrophilic species in solution. They can also interact with biomolecules, to trigger or inhibit biological processes.[5]

Yet, another field is growing rapidly, in which the characteristics of arene ruthenium complexes are also nicely exploited. Initiated in the 1990s, the self-assemblies of arene ruthenium complexes to form discrete metalla-assemblies have now accessed new dimensions, and the sophistication of these metalla-assemblies has reached an impressive level,[6] providing new perspectives in supramolecular chemistry.

The first example of discrete arene ruthenium metalla-assemblies came from the group of Süss-Fink, which has described in 1997, the stepwise formation of a tetranuclear arene ruthenium rectangle.[7] The synthesis involves the preparation and isolation of a dinuclear clip, the dicationic oxalato complex $[(\eta^6\text{-}p\text{-cymene})_2Ru_2(\mu\text{-}C_2O_4)(CH_3OH)_2]^{2+}$, prior to the addition of 4,4'-bipyridine (bipy). The final step generates the tetranuclear macrocyclic complex of the general formula $[(\eta^6\text{-}p\text{-cymene})_4Ru_4(\mu\text{-}C_2O_4)_2(\mu\text{-bipy})_2]^{4+}$ (Figure 1A), which was isolated as the triflate salt.

Soon after, Severin and his coworkers used a slightly different strategy to prepare a series of trinuclear arene ruthenium metalla-cycles.[8] The one-pot synthesis implied the mixing of 3-hydroxy-2-pyridone with dinuclear arene ruthenium complexes, $[(\eta^6\text{-arene})RuCl_2]_2$, in the presence of a base (Cs_2CO_3 or K_2CO_3). The self-assembly process has generated neutral trinuclear species in solution. These trinuclear complexes, like the benzene derivative $[(\eta^6\text{-benzene})Ru(\mu\text{-}C_5H_3NO_2)]_3$ (Figure 1B), were used as macrocyclic ionophores.

These pioneered works have paved the way to the development of discrete arene ruthenium metalla-assemblies, and the use of arene ruthenium building blocks in supramolecular chemistry. At the time, these research groups were probably unaware that they were witnessing the beginning of a new era. And today, several groups have implemented the synthesis of arene ruthenium-based supramolecular metalla-assemblies in their research projects,[6] showing the effectiveness of the arene ruthenium building blocks.

2. Arene Ruthenium Complexes

The first arene ruthenium complex, $[(\eta^6\text{-benzene})RuCl_2]_2$, was synthesized in Germany in the late 1960s from ruthenium(III) chloride hydrate and 1,3-cyclohexadiene.[9] However, the

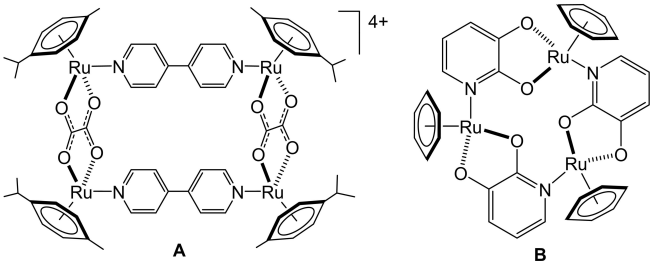


Figure 1. Molecular structures of the first tetranuclear (**A**) and trinuclear (**B**) arene ruthenium metalla-assemblies.[7,8]

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dimeric nature of the organometallic complex was only established in 1972.[10] The dimeric structure shows two terminals and two bridging chloro ligands on the ruthenium (II) atoms, as well as two η^6-coordinated benzene arene-ligands (Figure 2).[11] Monomeric species of the general formula [(η^6-benzene)Ru(L)Cl_2] are easily obtained in solution, either from coordinating solvent molecules, or from Lewis base donor ligands (Scheme 1). The stability of these neutral mononuclear dichloro arene ruthenium complexes depends largely on the coordinating strength of the ligand (L) used.[5]

Following the synthesis and characterization of the benzene derivative [(η^6-benzene)$RuCl_2$]$_2$, other arene ruthenium complexes were prepared.[12] As previously mentioned, dimers are easily transformed in monomeric species by the introduction of coordinating agents (Scheme 1). These mononuclear species, with two chlorides and a monodentate ligand (L), are relatively stable. However, the chloride atoms and L are potentially labiles, and they can be removed and replaced if desired by other ligands (monodentate, bidentate, tridentate). This is a key aspect in the design of arene ruthenium assemblies.

The easiest method to gain access to dinuclear arene ruthenium complexes is by reacting at high temperature ruthenium(III) chloride hydrate with an excess of a dienyl derivative (Scheme 2). However, other methods are also available, using either harsh conditions to exchange the arenes,[13] or microwaves.[14] Consequently, the relative facility to prepare dinuclear arene ruthenium complexes has allowed the synthesis of all kind of derivatives, even some with functionalized arene ligands,[15] thus increasing the attractiveness of arene ruthenium building blocks in supramolecular chemistry.

In such complexes, the ruthenium atom possesses an octahedral geometry in which the arene ligand occupies one face. And because of this arene ligand, the octahedral geometry is often described as pseudo-tetrahedral (Figure 3A). However, the three remaining coordination sites are positioned at ≈90° from each other, not 109.5°. On the other hand, like in tetrahedral geometry, the central atom can be chiral if surrounded by different substituents (Figure 3B). This is a second key aspect in choosing arene ruthenium complexes as building blocks, having a limited number of coordination sites available to be able to control the outcome of the metalla-assembly process.

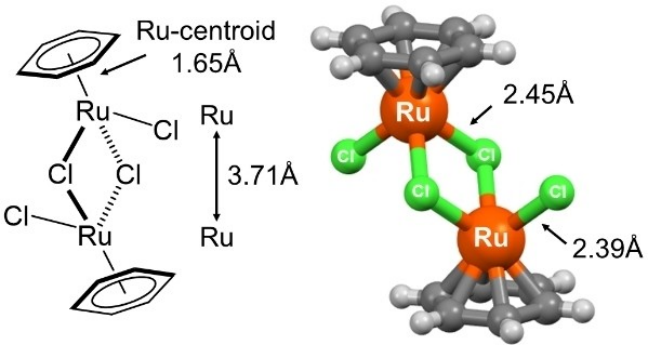
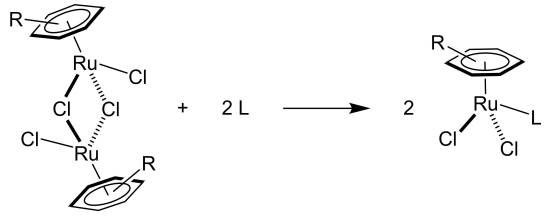
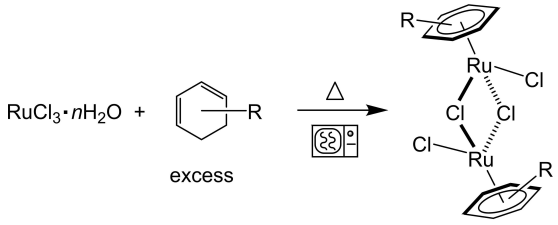


Figure 2. Molecular structure of [(η^6-benzene)$RuCl_2$]$_2$ in the solid state, including selected parametrical data.[11]



Scheme 1. Synthesis of mononuclear arene ruthenium complexes from a monodentate ligand (L).



Scheme 2. Standard synthesis of dinuclear arene ruthenium complexes.

2.1. Synthesis of Arene Ruthenium Metalla-Assemblies

In coordination-driven self-assembly, two approaches are used, a one-pot synthesis or a step-controlled process, both strategies being potentially successful.[16] However, some thinking is needed before taking any decision on the best strategy to use.

After my PhD in Berne Switzerland, and several postdocs around the world, I have in 2005 joint the Institute of Chemistry at the University of Neuchatel within the group of Georg Süss-Fink as a crystallographer. This fruitful collaboration gave me the opportunity to develop my own research interest, the use of arene ruthenium complexes in supramolecular chemistry.

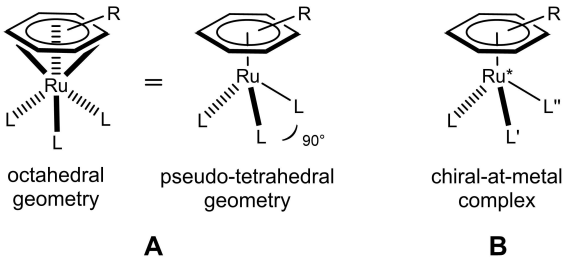
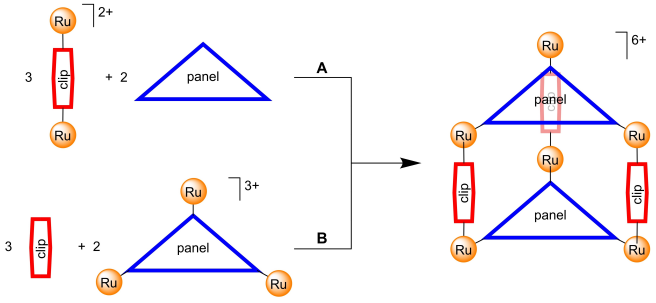


Figure 3. Arene ruthenium complexes as building blocks.

In addition, predicting the outcome is not always trivial, as multiple variables have to be taken into account (denticity of the ligands, directionality, solubility, stability, steric hindrance, kinetics, thermodynamics, second-coordination sphere interactions, etc.). In our group, we have focused our attention on a step-controlled strategy, having pre-organized metal-based entities (metalla-clips or metalla-panels), see Scheme 3.

In this approach, the metalla-clips and metalla-panels can be isolated and characterized, or they can be prepared and reacted in situ without purification. In both cases, the final product remains the same, and all kind of arene ruthenium assemblies have been generated following this approach.[17] Commonly, we have used dinuclear arene ruthenium complexes with tetradentate bridging ligands, including N∩O or



Scheme 3. Step-controlled strategy to form arene ruthenium prisms, from metalla-clips (**A**) or metalla-panels (**B**).

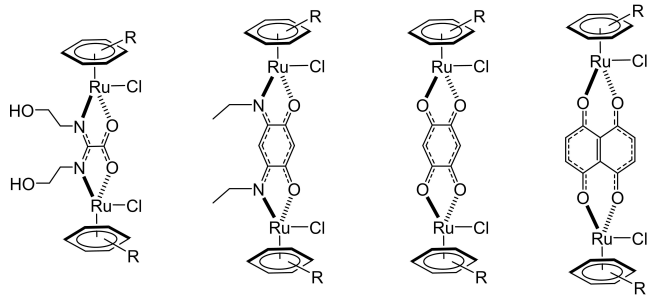


Figure 4. Typical dinuclear arene ruthenium clips.

O∩O derivatives (Figure 4). These bridging ligands form highly stable dinuclear complexes and some of them can be further functionalized. Such robust metalla-clips, where only the remaining monodentate ligands are labile, is another key aspect in our strategy.

In Figure 4, the dinuclear complexes are all represented as *cis* isomers. However, both isomers have been observed, and they usually interchanged rapidly in solution. The kinetics of the *cis-trans* interconversion depend mostly on the nature of the ligands, and it remains an important factor for the formation of discrete metalla-assemblies as only a *cis*-coordination can provide a discrete assembly.[18]

3. Arene Ruthenium Metalla-Assemblies

The use of dinuclear arene ruthenium clips has allowed the construction of two and three dimensional assemblies, from tetranuclear metalla-cycles to prims, and to cubes.[17] As illustrated in Scheme 3, metalla-clips are ideal for preparing prisms from tridentate panels. In this approach, the nature of the multidentate panels dictates the geometry of the assembly, while the metalla-clips modulate the size. Large metalla-clips create cavities between the panels, providing rooms to accommodate guest molecules. According to the apertures left between the clips and panels, the cage-like assembly can act as a carceplex (permanent encapsulation) or a host-guest system. Both behaviors can be useful, depending on the application foreseen, and this will be further discussed in the following sections.

3.1. Macrocyclic Assemblies

Like organic-based macrocyclic molecules,[19] metalla-cycles can find applications in biological, environmental, and chemical sciences. They have the potential to act as host compounds, and to interact with molecules, thus showing sensing, imaging, signaling, transporting, protecting, and other remarkable properties. Such applications have been explored, and some examples will be presented.

In 2009, two distinct tetranuclear arene ruthenium metalla-cycles have showed biological activity,[20,21] the complexes $[(\eta^6\text{-}p\text{-cymene})_4Ru_4(\mu\text{-oxanato})_2(bpy)_2]^{4+}$ (Figure 5A) and $[(\eta^6\text{-}p\text{-cymene})_4Ru_4(\mu\text{-dihydroxybenzoquinonato})_2(bpy)_2]^{4+}$ (Figure 5B). The oxanato derivative interacts with DNA,[21] and both systems possess antiproliferative properties against cancer cell lines. Following these pioneered studies, many other arene ruthenium metalla-cycles have been investigated as DNA and protein binders, as well as anticancer agents.[6]

Other biological applications can be integrated in arene ruthenium metalla-cycles. Introduction of porphyrin-based, anthracene-based or bodipy-derived spacers can generate

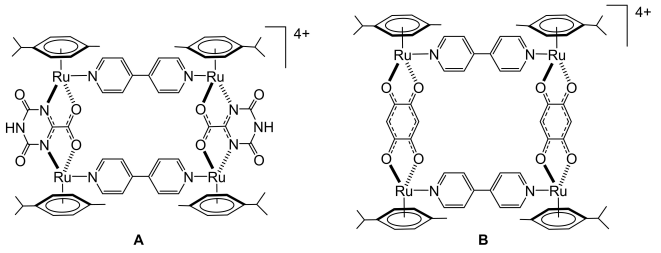


Figure 5. Molecular structures of two tetranuclear arene ruthenium metalla-cycles showing biological activity.[20,21]

metalla-cycles with additional characteristics. Like most arene ruthenium metalla-cycles, a bodipy-based metalla-cycle (Figure 6) has showed interactions with DNA and proteins, as well as antiproliferative activity.[22] Yet, the bodipy units can also provide an opportunity for imaging and tracing, as bodipy dyes are highly fluorescent.[23]

Molecular dyes have also the ability to transfer their photochemical energy to surrounding substrates.[24] This phenomena has been used to treat tumors and skin disorders, and it is called photodynamic therapy (PDT).[25] In such treatment, the photochemical energy absorbed by the photosensitizer is transferred to oxygen, which becomes highly toxic for cells. Therefore, porphyrin-based linkers have been incorporated to arene ruthenium metalla-cycles for PDT applications.[26] Moreover, as the presence of oxygen is crucial for an efficient PDT treatment, anthracene-9,10-endoperoxide functionalized linkers have also been inserted in arene ruthenium metalla-cycles in view to transport oxygen.[27] Both systems were synthesized for increasing the PDT response, but the effectiveness of such strategies remains to be confirmed.

As previously mentioned, these arene ruthenium metalla-cycles interact strongly with DNA. They are positively charged, they have hydrophilic and hydrophobic regions, and depending on the size, they can interact and sit in DNA grooves. Therefore, these systems were further evaluated as

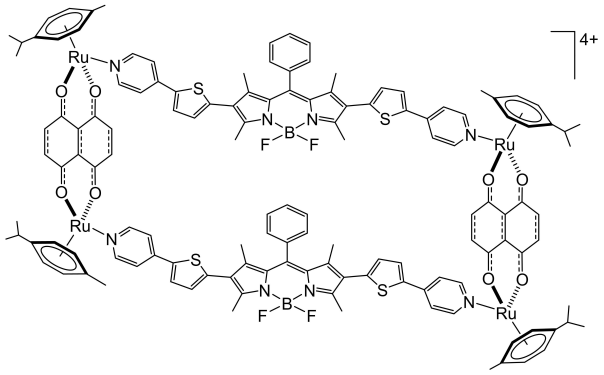


Figure 6. Arene ruthenium metalla-cycle incorporating bodipy dyes.[22]

DNA secondary structure binders.[28] They appear to have the ability to stabilize three-way DNA junctions, as well as G-quadruplex DNA. Indeed, it has been showed that the $[(\eta^6\text{-}p\text{-cymene})_4Ru_4(\mu\text{-dioxidonaphthoquinonato})_2\{bis(ethynyl\text{-}pyridyl)\}_2]^{4+}$ metalla-rectangle (Figure 7) interacts strongly with three-way DNA junctions, thus confirming the affinity of such assemblies for DNA structures.

Other than for biological applications, arene ruthenium metalla-cycles were also used to generate thermotropic liquid-crystalline materials.[29] To introduce mesomorphism to arene ruthenium metalla-cycles, poly(arylester) dendritic side-chains carrying cyanobiphenyl mesogens were attached to bis(pyridyl) linkers (Figure 8). This functionalized metalla-cycle was a rare example of a hierarchical assembly with thermotropic liquid-crystalline properties, and it opened up new perspectives for arene ruthenium metalla-assemblies.

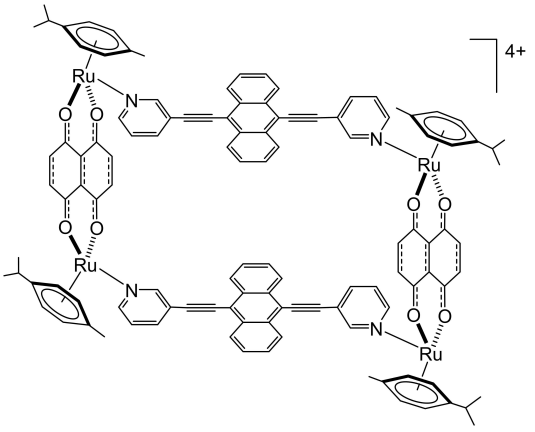


Figure 7. An arene ruthenium metalla-cycle binding three-way DNA junctions.[28]

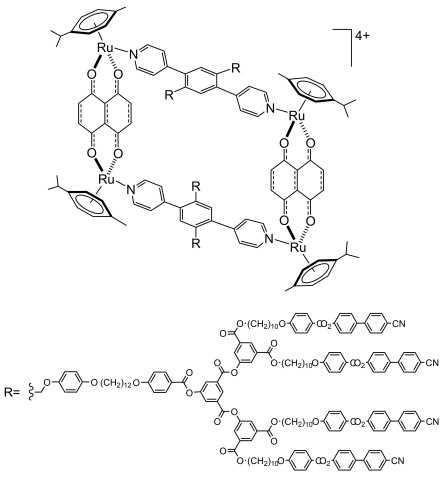


Figure 8. An arene ruthenium metalla-cycle showing liquid-crystalline properties.[29]

3.2. Cage-Like Assemblies

Similar to arene ruthenium metalla-cycles, cage-like assemblies can interact with DNA and proteins. Arene ruthenium metalla-prisms and metalla-cubes have been shown to interact with duplex,[30] three-way junction[28] and G-quadruplex[31] DNA structures. This attraction for amino acids, nucleobases, and other biomolecules, can be either by intermolecular π-stacking or electrostatic interactions, which involved an intact assembly, or by metal-coordination after the loss of one of more ligands. The ratio between these two types of interactions can vary greatly, according to the type of assemblies, the nature of the biomolecule, as well as the chemical environment.

Despite showing strong interactions with DNA structures, the prime target of biologically active arene ruthenium assemblies is probably not DNA.[32] It was demonstrated that in cells, the arene ruthenium metalla-prisms, $[(\eta^6\text{-}p\text{-cymene})_6Ru_6(\mu\text{-dihydroxybenzoquinonato})_3(trispyridyltriazine)_2]^{6+}$, did not reach the nucleus, and appeared to remain in the cytoplasm.[33] Interestingly, the presence of a guest can modify the stability of the assembly,[34] and accordingly, can offer an elegant strategy to control the release of guest molecules.

Various guest molecules have been hosted in the cavity of arene ruthenium assemblies. The first example was a complex-in-a-complex system,[35] in which a square-planar palladium or platinum complex, [M(acetylacetonato)$_2$] (M=Pd, Pt), was inserted in the cationic $[(\eta^6\text{-}p\text{-cymene})_6Ru_6(\mu\text{-dihydroxybenzoquinonato})_3(trispyridyltriazine)_2]^{6+}$ cage-like assembly (Figure 9). This important study showed that the complex-in-a-complex systems were more cytotoxic than the cage alone, suggesting a cooperative effect between the hydrophilic cage and the hydrophobic metal-based guest.

Following this initial study, other guest molecules were encapsulated in the cavity of arene ruthenium assemblies, with some guest being of biological interest. For instance, guest with fluorescence properties were used to study the release process,[36] or to induce photochemical damage after light activation.[37] In general, these host-guest systems have similar features; water solubility of the cage-like assembly, a positive charge, and a lipophilic cavity. Therefore, the hydrophobicity of the guest is important, it ensures a strong encapsulation in the cavity of the host, it avoids a premature release in biological media, and it can even increases the stability of the host-guest system.[34]

The stability of the host-guest system is an interesting aspect to look at, especially when dealing with biological applications. If the system is regarded as a drug delivery vector, it should, after reaching its target, release the guest. On the other hand, if the host-guest system is considered as a cytotoxic agent, it can remain intact, but disassembly can also be essential for attacking cancer cells. Therefore, it is quite challenging to find the perfect stability window, strong enough to transport and reach the target, and still, being able to free the guest molecule at the right time, if necessary. This is why, some arene ruthenium metalla-assemblies have been constructed with stimuli responsive linkers and spacers, to have a degree of control over the releasing mechanism. Different stimulus can be used to achieve this goal, pH, temperature, light, redox processes, etc… all having the same purpose, to have a spatio-temporal switch to trigger the release of the guest.[38]

Introduction of zwitterionic redox-active spacers in arene ruthenium metalla-assemblies was achieved a few years ago.[39] The redox activity of the dinuclear and hexanuclear complexes was quite remarkable, showing a series of reversible and quasi-reversible reduction processes. Interestingly, with coronene inside the cavity of the metalla-prism (Figure 10), the currents of the redox processes were stable, whereas for the empty

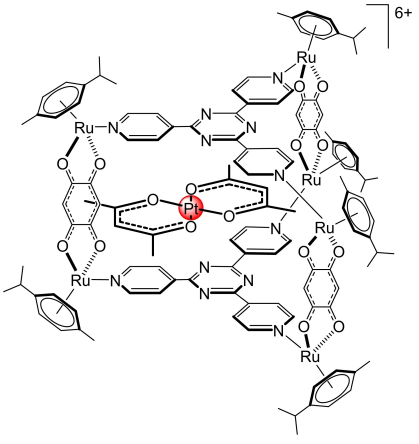


Figure 9. The first complex-in-a-complex arene ruthenium assembly.[35]

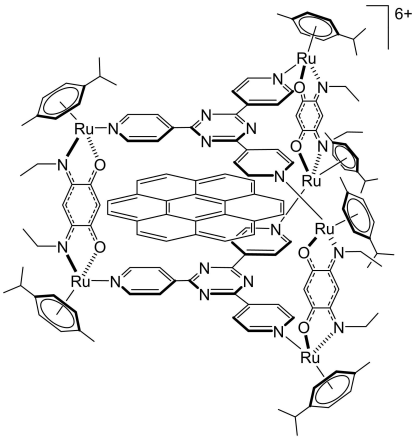


Figure 10. Coronene sitting inside the cavity of a zwitterionic-based arene ruthenium metalla-prism.[39]

metalla-prism, the currents decreased, suggesting stabilization of the redox reactions due to the presence of coronene.

If not for spatio-temporal released of guest molecules, stimuli-responsive building blocks can be introduced within arene ruthenium assemblies to produce other chemical responses. Porphyrin-based metalla-cubes are one example (Figure 11A), in which the porphyrin panels are used as photosensitizers in photodynamic therapy.[26] Such octanuclear assemblies are cytotoxic, but upon irradiation (652 nm, 20 mW/cm^2, 2–20 J/cm^2), they become highly phototoxic, suggesting a dual effect of the arene ruthenium assemblies (chemotherapeutic) and the porphyrinic photosensitizers (PDT).

The phototoxicity of arene ruthenium metalla-prisms and metalla-cubes in which a photosensitizer was added as a guest molecule were also evaluated as PDT agents (Figure 11B).[37] These systems offer also a dual activity, the cytotoxicity of the arene ruthenium assembly, and the phototoxicity of the photosensitizer upon irradiation. Therefore, an additive effect, or a synergetic effect, can in principle be obtained for such hybrid systems. Moreover, additional functional group can be added to the metalla-assembly to develop theranostic agents.[40]

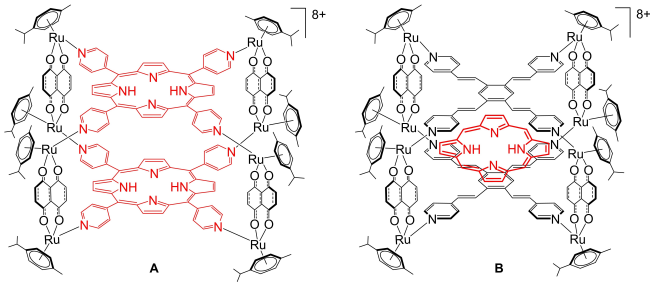


Figure 11. Photosensitizer incorporated (**A**) or encapsulated (**B**) in arene ruthenium metalla-assemblies.[26,37]

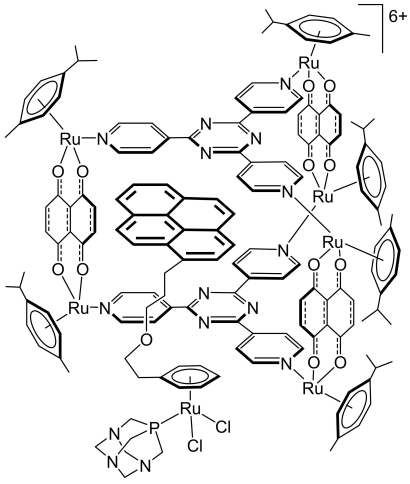


Figure 12. Pyrenyl-functionalized arene ruthenium complex partially encapsulated in an arene ruthenium metalla-prism.[42]

Guest molecules can either be fully encapsulated, or only partially.[41] To have partial encapsulation of a guest molecule, the simplest strategy is to have an amphiphilic derivative, in which a planar aromatic lipophilic entity is linked to a hydrophilic or bulky constituent. The planar aromatic moiety is then located in the cavity of the arene ruthenium assembly, while the other part is hanging out, as illustrated in Figure 12. In this particular case, the arene ligand was functionalized with a pyrenyl unit, thus allowing the arene ruthenium moiety to rest outside the cavity.[42] Therefore, such systems have allowed the addition of biologically active agents,[43] metal-based drugs,[42] as well as mesogenic chains for the preparation of super-large systems,[44] and liquid-crystalline materials.[45]

4. Conclusion

As illustrated in this account, arene ruthenium assemblies offer numerous possibilities. Functional groups can be part of the assembly, attached to building blocks, linked to arene ligands, or associated to guest molecules. Therefore, different combinations are possible, and the properties of arene ruthenium assemblies can be modulated to accomplish various tasks. Biological applications, and to some extend liquid-crystalline properties, remain the top two applications studied so far in our group. However, considering the synthetic flexibility and versatility of these arene ruthenium systems, other applications will certainly be explored in the near future.

Acknowledgements

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