CHAPTER EIGHT

Arene Ruthenium Complexes in Supramolecular Chemistry

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Abstract

For many years, the use of arene ruthenium complexes in catalysis and bioinorganic chemistry has showed great promises due to their chemical properties, but opportunities remain in supramolecular chemistry where arene ruthenium units are still poorly exploited. The strength of coordination bonds offers limitless possibilities in the field of supramolecular chemistry. The choice of the ligand can fine-tune the stability of the complex, thus setting up its application. Robust complexes are required for repetitive processes (catalysis, sensing, host–guest chemistry), or when the initial complex needs to be recovered or reused. However, for a single or highly specific task (drug delivery, bioimaging, metal-based drug) decomplexation (decomposition) can also be acceptable and even beneficial. In this chapter, all kinds of systems involving arene ruthenium complexes are discussed and illustrated with selected examples. The purpose of this chapter is not to provide a comprehensive review showing all arene ruthenium complexes that can be found in the literature, but mostly to highlight some of the new directions followed by these versatile complexes in supramolecular chemistry.

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1. INTRODUCTION

Half-sandwich complexes, also commonly named piano-stool complexes, are extensively used in catalysis,[1] and they possess interesting biological properties.[2] Several transition metals can form half-sandwich complexes, and among them, the arene ruthenium derivatives are probably the most studied examples.[3] The popularity of arene ruthenium complexes can be associated with their relative stability in solution, and their facility to be synthesized and handled.[4] Accordingly, starting arene ruthenium materials are either commercially available or easy to prepare. Common starting materials include the dinuclear arene ruthenium complexes $[(arene)RuCl_2]_2$ (Fig. 1), in which the arene ligands are benzene (bzn), toluene (tol), *p*-cymene (cym), or hexamethylbenzene (hmb). Then, mononuclear half-sandwich complexes are obtained by rupture of the chlorido bridges upon addition of donor ligands (Scheme 1). This simple strategy is certainly the most common access to mononuclear arene ruthenium complexes.

The η^6-arene ligand, especially the electron-rich hmb, is strongly attached to the ruthenium atom, thus being relatively inert to decomplexation. However, other arenes can be used to alter this relative coordination stability. Introduction of electron-withdrawing groups on

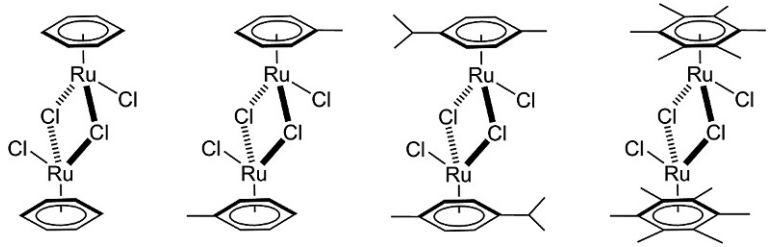
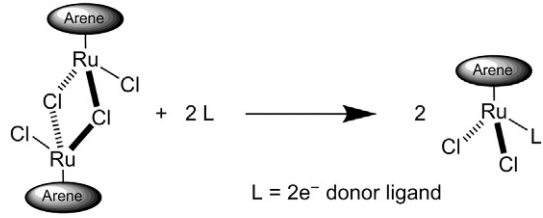


Fig. 1 Commercially available arene ruthenium complexes.



Scheme 1 Typical synthesis of mononuclear arene ruthenium complexes.

the arene can facilitate its displacement,[5] while arenes with higher electron-donating ability can in principle replace the initially coordinated electron-poor arene.[6] On the other hand, the presence of functional groups at the periphery of the arene ligand can modify the physical properties of the complex (solubility, reactivity, redox potential).[7] As the η^6-arene occupies half of the coordination sites of the octahedral metal center, three remaining sites are available for the insertion of various ligands. These other ligands can be mono-, bi-, or tridentate, and have C-, N-, O-, S-, or P-donor groups.

Therefore, the ability of introducing all kinds of ligands (Scheme 1) coupled to the facial arrangement of the arene ligand accounts for the attractiveness of using arene ruthenium complexes to design supramolecular assemblies (Fig. 2). The 90° angles found between the remaining three coordination sites offer endless possibilities, and by selecting the appropriate ligands (connectors, spacers, bridges), all kinds of geometric shapes can be obtained, including two- and three-dimensional assemblies. Moreover, the length of the connectors modulates the distance between the ruthenium atoms, and accordingly the size of the assemblies, which can generate interstices in the metal-based assemblies and therefore can theoretically allow the accommodation of guest molecules.

The coordination strength of the ligands plays an important role in the stability of the system and consequently to their chemical behavior in solution. For catalysis, weak coordination of at least one ligand is essential to allow a substrate to come and go and to interact with the metal during the catalytic cycle, while for protecting a guest molecule or for trapping chemicals, the metal-based assembly needs to resist to external attacks (solvent, light, acid, base, water, etc.). Overall, the choice of the ligands will dictate not only the shape of the assembly but also the nature of the supramolecular assembly and its possible application. Therefore, this chapter will mainly focus on the following applications: catalysis, crystal engineering, interaction with guest molecules (sensing, transport, protection, host–guest chemistry), and liquid-crystalline materials. They all have in common the presence of arene ruthenium units in their supramolecular system.

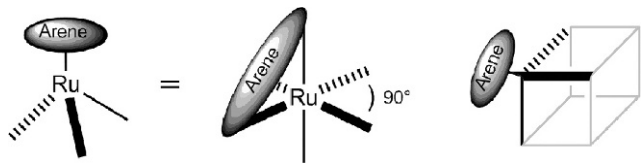


Fig. 2 Half-sandwich complexes as building blocks in supramolecular chemistry.

2. CATALYSIS

Standard catalytic cycles involving arene ruthenium complexes imply the coordination of a substrate by ligand substitution, followed by the transformation of the substrate, and the release of the corresponding product (Fig. 3). This concept is universal to metal-based Lewis acid catalysts,[8] and for arene ruthenium complexes, the ruthenium acts as the electron-pair acceptor. Therefore, in this section, traditional catalyses comprising arene ruthenium complexes will not be discussed; only examples in which additional supramolecular aspects are involved will be covered and illustrated.

In life, enzymatic processes remain the most successful catalytic systems. These natural catalysts offer several advantages.[9] They operate in aqueous media, show high catalytic efficiency, and possess tremendous selectivity for specific substrates. However, this high specificity somehow hampers their use in industrial processes, since limited stability under harsh catalytic conditions can also diminish their attractiveness. Therefore, combining the robustness and versatility of arene ruthenium complexes with an enzymatic scaffold has attracted a lot of attention, and has been the subject of several research projects.

The first X-ray structure analysis of an arene ruthenium complex coordinated to an enzyme was published by Sadler in 2004.[10] The structure

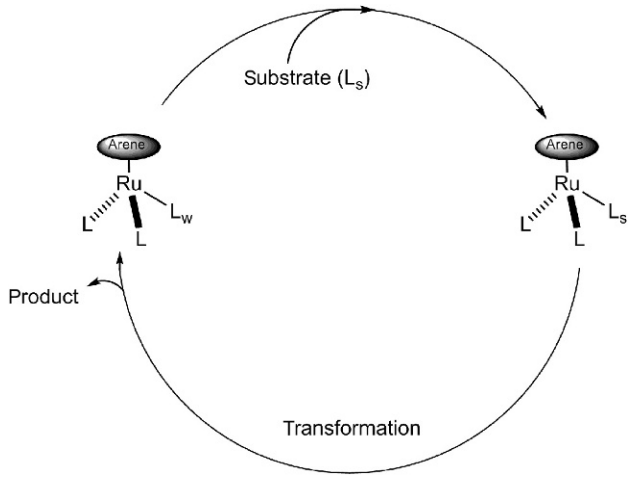


Fig. 3 Schematic representation of a standard catalytic cycle involving arene ruthenium complexes (L_w = weak coordinated ligand).

shows a diaqua *p*-cymene ruthenium unit being *N*-bonded to a histidine residue (His15) of the hen egg white lysozyme. The complex was situated at the periphery of the enzyme, and potentially accessible for additional interactions with substrates. Despite this promising result, the use of arene ruthenium enzyme systems for catalytic reactions started a few years later.

Based on the very strong biotin binding affinity for the tetrameric protein streptavidin, Ward and coworkers have developed several biotin-derived half-sandwich complexes. These artificial metalloenzymes show good catalytic activity for various reactions.[11] For example, when inserted in streptavidin, the arene ruthenium derivatives (Fig. 4) become excellent enantioselective catalysts for the reduction of ketones.[12] Fine-tuning of the arene–protein interactions by genetic optimization allows enantiodiscrimination between the *R* and *S* isomers, thus providing both enantioenriched alcohols in high yield and high enantiomeric excess (up to 97% ee).

In view to mimic the Fe–Ni active site of hydrogenase, Ogo and coworkers have prepared from $[(\text{hexamethylbenzene})\text{Ru}(\text{H}_2\text{O})_3]^{2+}$ and NiL (L = *N,N*′-dimethyl-*N,N*′-bis(2-marcaptoethyl)-1,3-propanediamine) a mixed arene ruthenium nickel complex of the general formula $[(\text{hexamethylbenzene})\text{Ru}(\text{H}_2\text{O})\text{NiL}]^{2+}$, which after activation has generated a hydrido derivative (Fig. 5).[13] This enzymatic-like dinuclear complex showed an interesting pH-dependent catalytic activity in water.

Functionalization of the arene unit was used to design arene ruthenium complexes for site-specific and covalent anchoring to papaya proteinase I (papain). Chloroacetamide and maleimide groups were attached to the

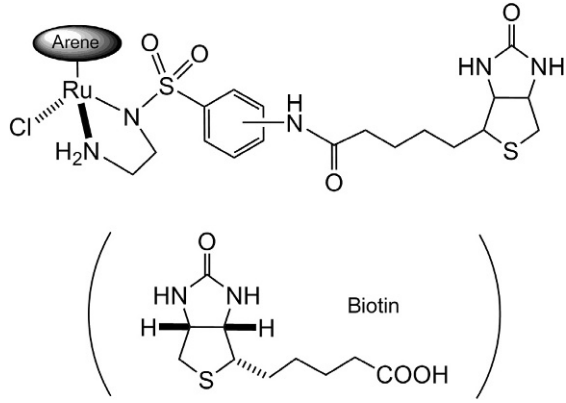


Fig. 4 Molecular structure of biotin-derived arene ruthenium complexes.[12]

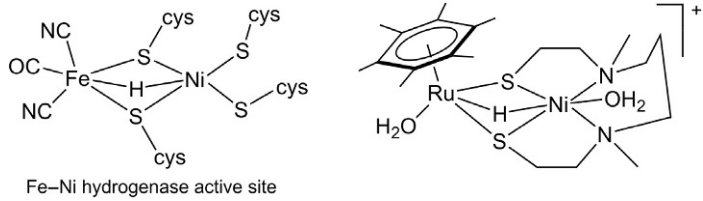


Fig. 5 Dinuclear arene ruthenium nickel complex developed by Ogo to mimic the Fe–Ni active site of hydrogenase.[13]

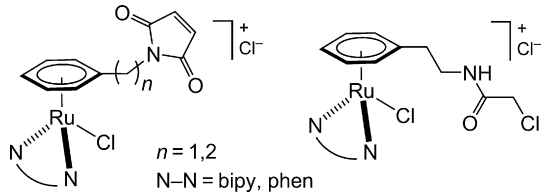


Fig. 6 Molecular structures of maleimide and chloroacetamide arene ruthenium complexes (bipy = 2,2′-bipyridine, phen = phenanthroline) for interactions with papaya proteinase I.[14]

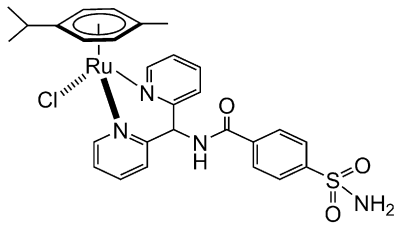


Fig. 7 Molecular structure of an arene ruthenium complex incorporating a sulfonamide-derived ligand able to interact with human carbonic anhydrase II.[15]

arene moiety to generate complexes with special affinity for papain (Fig. 6).[14] The catalytic activity of the complex in water for Diels–Alder reactions was increased by two orders of magnitude when the complex was embedded in the protein scaffold.

A bispyridyl-based derivative incorporating an acyl sulfonamide group has been coordinated to arene ruthenium units (Fig. 7).[15] The sulfonamide-derived arene ruthenium complex interacts with human carbonic anhydrase II through the sulfonamide moiety. The functionalized complex sits in the binding site of the protein, as revealed by single-crystal X-ray structure analysis.

The coenzyme NAD^+/NADH (NAD = nicotinamide adenine dinucleotide) is involved in many cellular redox reactions, and in recent years, it was

shown that organometallic complexes can interfere with NAD^+/NADH hydride transfer reactions.[16] The group of Sadler has intensively studied the catalytic activity of arene ruthenium complexes in the reduction of NAD^+.[17] The ethylene diamine (en) complexes (arene)$RuCl_2$(en) (arene = *p*-cymene, hexamethylbenzene) catalyze the reduction of NAD^+ by formate in water under physiological conditions. However, it was later observed that the same complexes are also excellent catalysts to perform the reverse reaction, namely, the transfer of hydride from NADH to arene ruthenium complexes.[18] An increase of activity for the transfer hydrogenation of NAD^+ to give NADH in the presence of formate was obtained when a sulfonamide group was added to the ethylene diamine ligand (Fig. 8), confirming the potential of arene ruthenium complexes in intracellular catalysis.

Another biological reaction that can be catalytically induced in living cells by arene ruthenium complexes is the oxidation of glutathione (GSH) to its oxidized form glutathione, GSSG.[19] This oxidation reaction of thiols is possibly correlated to the anticancer activity of several arene ruthenium complexes.[20] Indeed, an increase of the GSSG/GSH ratio indicates oxidative stress in cells, thus leading to protein, lipid, and DNA damages, and ultimately to apoptosis. The dithiolato- and trithiolato-bridged arene ruthenium complexes (Fig. 9) developed by Süss-Fink are so far the most cytotoxic arene ruthenium complexes that are also active catalysts in

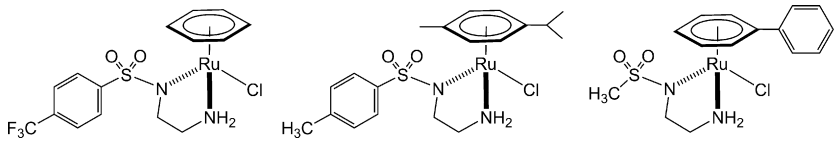


Fig. 8 Molecular structures of catalytically active arene ruthenium complexes developed by Sadler.[17,18]

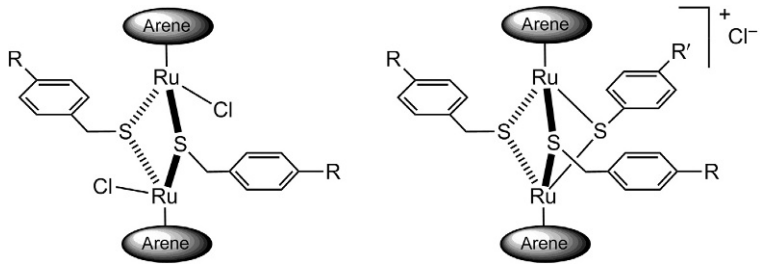


Fig. 9 General structures of the neutral dithiolato- and cationic trithiolato-bridged arene ruthenium complexes developed by Süss-Fink.[21]

the oxidation of GSH.[21] The IC_{50} values observed for some of these derivatives (up to 30 nM) are among the most cytotoxic arene ruthenium compounds reported to date.

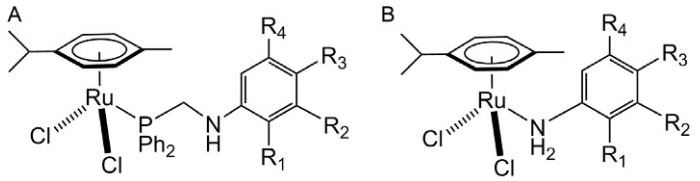
3. CRYSTALLINE NETWORKS

For decades, crystalline structures of arene ruthenium complexes have been determined by single-crystal X-ray structure analysis. In many cases, interesting packing (network) arrangements involving intermolecular interactions have been observed. Yet, these supramolecular assemblies in the solid state were neither designed nor obtained in a controlled manner; they were serendipitous. However, in recent years, some research groups have taken the challenge to use arene ruthenium complexes as building blocks in crystal engineering to design two- and three-dimensional networks.

Indeed, in the solid state, accumulation of weak interactions can generate relatively robust two- and three-dimensional assemblies. Therefore, inspired from the field of metal-organic framework (MOF), arene ruthenium units have now been used to prepare periodic porous materials. Like MOFs, these supramolecular assemblies can find applications in catalysis, biomedical imaging, optoelectronics, drug delivery, and in separation technology. With such applications in mind, the design of crystalline supramolecular assemblies involving arene ruthenium units is growing rapidly.

Among the first examples of crystal engineering with arene ruthenium units, we can mention a series of two- and three-dimensional assemblies obtained from arene ruthenium complexes of the general formula (*p*-cymene)$RuCl_2(PPh_2R)$ (R = amino-benzoic acid group).[22] The presence of the arene ligand and the halogens on the ruthenium atom, as well as the carboxylic acid functional group at the periphery of the phosphine ligand has allowed multiple intermolecular interactions (Fig. 10A). In aprotic solvents, the carboxylic acid moiety formed with a neighboring complex a head-to-tail dimer, while in the presence of protic solvents (methanol, water) extended hydrogen-bonded systems are observed. These hydrogen-bonded systems involved the carboxylic acid group, the halogens of the complex, as well as solvent molecules.

Using arene ruthenium complexes of amino-benzoic acid derivatives (Fig. 10B), Bacchi and Pelagatti have generated several two- and three-dimensional motifs.[23] The nature of the solvent used to initiate crystallization of the complexes influences greatly the packing arrangement within the crystals. In some cases, solvent molecules disrupt the dimeric benzoic acid



R_1 = COOH; R_2, R_3, R_4 = H
R_2 = COOH; R_1, R_3, R_4 = H
R_3 = COOH; R_1, R_2, R_4 = H
R_4 = COOH; R_1 = OCH_3; R_2, R_3 = H
R_1, R_4 = COOH; R_2, R_3 = H
R_1 = COOH; R_3 = OH; R_2, R_4 = H
R_2 = OH; R_3 = COOH; R_1, R_4 = H

R_3 = COOH; R_1, R_2, R_4 = H
R_3 = COOH; R_1 = OH; R_2, R_4 = H
R_4 = COOH; R_1 = OH; R_2, R_3 = H
R_3 = CH═CHCOOH; R_1, R_2, R_4 = H
R_3 = $(CH_2)_2$COOH; R_1, R_2, R_4 = H
R_3 = $(CH_2)_3$COOH; R_1, R_2, R_4 = H
R_2, R_4 = COOH; R_1, R_3 = H
R_3 = $CONH_2$; R_1, R_2, R_4 = H
R_3 = CONHPh; R_1, R_2, R_4 = H

Fig. 10 Molecular structures of arene ruthenium complexes incorporating a diphenylphosphine amino-benzoic acid ligand (A) or an amino-benzoic acid ligand (B).[22,23]

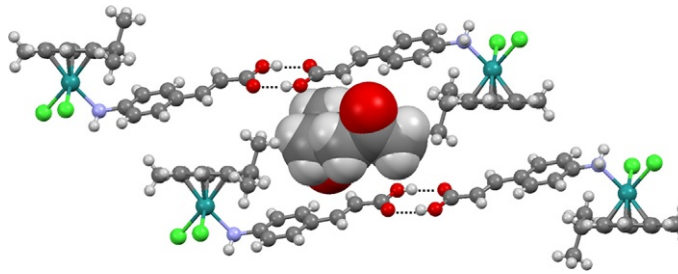


Fig. 11 Solvent molecules (acetone, space-filling model) trapped between two arene ruthenium amino-benzoic acid dimers.[23]

pairing to generate voids between the arene ruthenium units. These voids can accommodate guest molecules (Fig. 11), thus offering the possibility to use these porous materials as hosts for volatile guests. Recently, analogous interactions and packing arrangements were obtained with arene ruthenium complexes incorporating amino-derived ligands.[24]

In view to obtain stronger assemblies in the solid state, bispyridyl linkers were used to mimic and replace the supramolecular benzoic acid dimers (Fig. 12).[25] The large planar aromatic surface of some of these bispyridyl linkers has allowed crystals to absorb vapors of toluene and *p*-xylene at room temperature. In less than 1 h, an increase of about 20%–25% of the weight of the solid was observed, which corresponds to a host/guest ratio of more or less 1/3. Interestingly, when soaked in tetrahydrofuran (THF), crystals obtained with a bis-diphenylphosphine linker have kept their crystallinity despite insertion of 1.5 equiv. of THF in the crystals. The process is fully

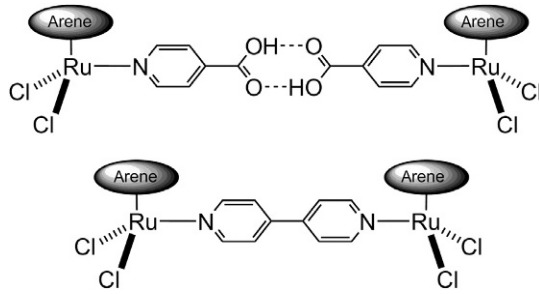


Fig. 12 Supramolecular arene ruthenium isonicotinic acid dimer (*top*) and covalent analog obtained with 4,4′-bipyridine (*bottom*).[25]

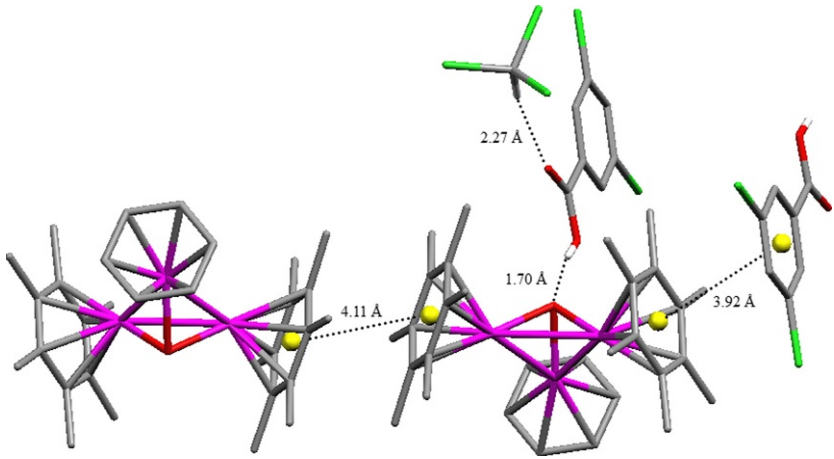


Fig. 13 Main interactions involved in the crystalline packing of $[H_3Ru_3(C_6H_6)(C_6Me_6)_2(O)][BF_4]\cdots 3,5\text{-}Cl_2C_6H_3COOH\cdots CHCl_3$.[26]

reversible, and the THF molecules can also be replaced by aromatic guest compounds (benzene, toluene, *p*-xylene), demonstrating a great potential of these systems in host–guest chemistry and separation technology.

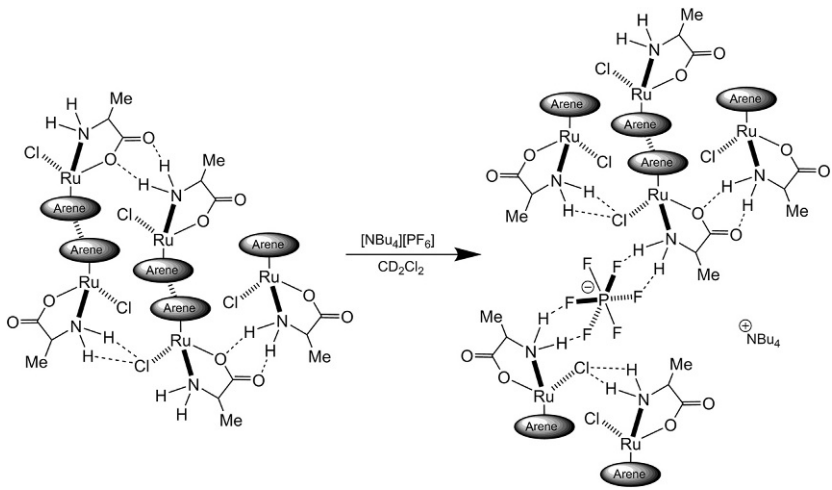
Exploiting the hydrophobic cavity of a trinuclear arene ruthenium cluster cation ($[H_3Ru_3(C_6H_6)(C_6Me_6)_2(O)]^+$), several supramolecular assemblies have been prepared and characterized, using aromatic carboxylic acid derivatives as guest compounds and linkers.[26] These systems show in the solid state a combination of hydrogen bonding between the carboxylic acid group and the oxo-bridging ligand of the cluster, π-stacking between the arene ligands and the aromatic part of the guests, as well as ionic intermolecular interactions from the chloroform solvate for example (Fig. 13) or the tetrafluoroborate anions. Overall, these systems form between all the

different components (cation, anion, guest, solvent) of the crystalline material, a compact environment. Interestingly, the weak host–guest (cluster-carboxylic acid) interaction persists in solution as demonstrated by cold-spray ionization mass spectrometry.

4. ASSEMBLIES IN SOLUTION

Interactions similar to those observed in the solid state (hydrogen bond, π–π stacking, Van der Waals, ionic, electrostatic, etc.) can also occur in solution. However, the weakness of these interactions makes the characterization and observation of the supramolecular assemblies (dimer, aggregate, polymer, host–guest, etc.) in solution more challenging. Moreover, the choice of the solvent can either favor or disfavor the interactions, as well as the concentration of the arene ruthenium complex, thus complicating such studies. Nevertheless, arene ruthenium complexes have shown interesting aggregation behavior in solution.

Aggregation of mononuclear *p*-cymene ruthenium complexes incorporating amino-acetate chelating ligand (AA^-) has been studied in solution by nuclear Overhauser effect spectroscopy.[27] The study shows that the aggregates, which are initially composed of multiple (*p*-cymene)RuCl(AA^-) complexes, doubled in size when $[NBu_4][PF_6]$ or KPF_6 salts are added to a CD_2Cl_2 solution of the complex (Scheme 2). This observation suggests



Scheme 2 Formation of supra-anionic aggregates upon addition of $[NBu_4][PF_6]$ to a dichloromethane-d_2 solution of (*p*-cymene)RuCl(AA^-) (AA^- = methylamino acetate).[27]

that two neutral aggregates bind an anion to form supra-anionic species in solution, thus accounting for the presence of larger aggregates.

Advanced NMR spectroscopy was also used to characterize a series of arene ruthenium metalla-assemblies held together by hydrogen bonds.[28] The metalla-rectangles were obtained by self-pairing of 2-ureido-4-[1H]-pyrimidinone (UPy) units (Fig. 14). The cationic assemblies are stable in aprotic solvents, and the simplicity of preparation paves the way for the preparation of more complexed systems.

Introduction of linear bidentate ligands to replace the UPy self-pairing dimer in these arene ruthenium metalla-rectangles increases the stability of the assemblies and therefore allows other applications. Sensing is one of these applications, which deals with systems (host) that can interact in solution with substrates (guest). If the host–guest interaction can be translated into a stimulus that can be observed (measured) spectroscopically (UV–vis, fluorescence, ^{1}H NMR), a sensor is generated.[29] Such stimuli-responsive interactions are relatively easy to obtain; however, the challenges remain in the specificity and sensitivity of the sensor for the substrate: both qualities being essentials for the development of valuable sensors.

Exploiting these concepts, two arene ruthenium metalla-rectangles with extended π-electron aromatic connectors (*N,N′*-bis[4-(pyridin-4-ylethynyl)phenyl]terephthalamide) have been synthesized and characterized.[30] The tetranuclear complexes show interactions with C_{60} and C_{70}.

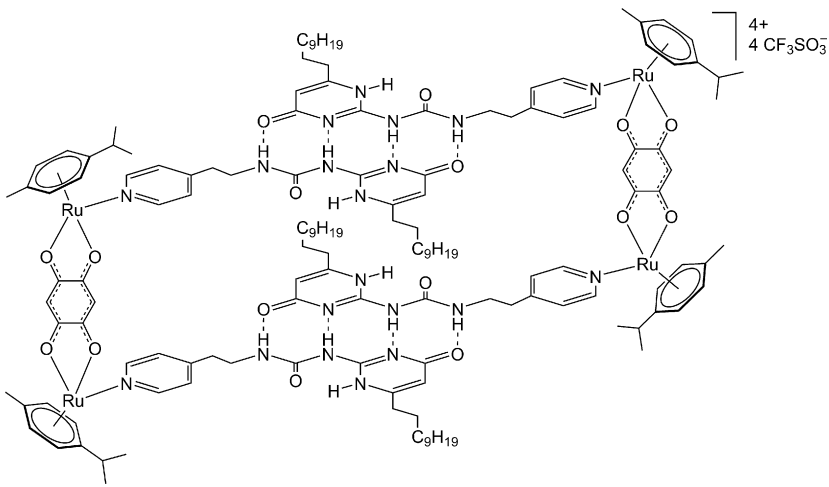


Fig. 14 An arene ruthenium metalla-rectangle showing a combination of coordination and hydrogen-bonded interactions.[28]

The shape and size of the tetranuclear assemblies suggest that C_{60} and C_{70} sit in the cavity of the metalla-rectangles, where the guests are surrounded by the two polyaromatic connectors (Fig. 15).

Analogous arene ruthenium assemblies with planar trispyridyl panels have been used to prepare metalla-prisms and metalla-cubes (Fig. 16).[31] These large assemblies possess a hydrophobic cavity capable to accommodate planar molecules.[32] Among guest compounds encapsulated in the cavity of the metalla-prisms, it was showed that nitroaromatic derivatives can fit perfectly in such assemblies.[33] Nitroaromatics are often encountered in explosive devices, which make them valuable targets in safety regulations and counter-terrorism measures. In that study, the highest fluorescence quenching efficiency was observed for picric acid. Similarly, the electron deficiency of picric acid was used to interact strongly with tetranuclear

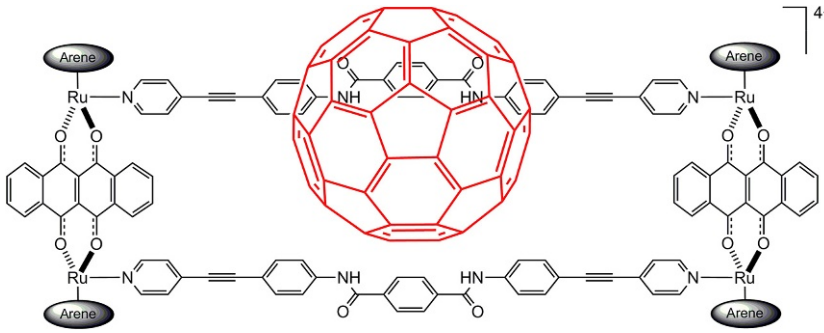


Fig. 15 Fullerene sitting in the cavity of an arene ruthenium metalla-rectangle.[30]

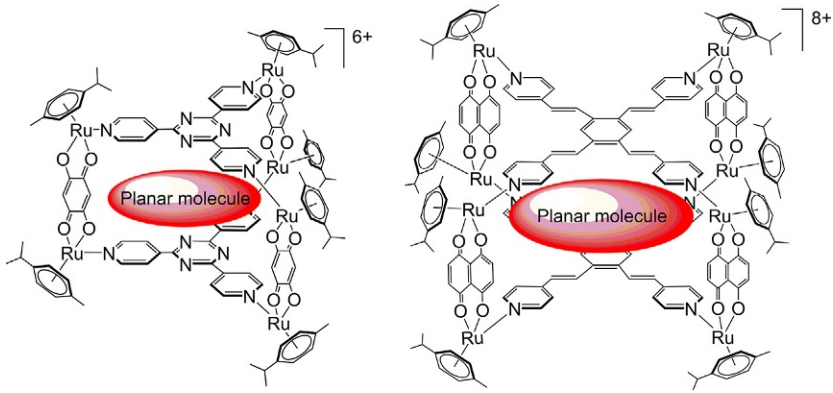


Fig. 16 Standard arene ruthenium metalla-prism and metalla-cube with a hydrophobic cavity large enough to accommodate planar molecules.[31]

and octanuclear arene ruthenium systems, incorporating electron-rich tetrapyridyl tetrathiafulvene panels.[34]

The nature of the host–guest interaction can also be modulated by the size of the assembly and of its cavity. It was shown that moving from pyrazine, to 4,4′-bipyridine, to 1,2-di(4-pyridyl)ethylene, the interaction of anthracene, pyrene, perylene, and coronene with a series of tetranuclear arene ruthenium complexes was either absent, outside the cavity, or in the cavity (Fig. 17).[35] The different interactions were studied in solution by multiple ^{1}H NMR experiments, including ROESY and DOSY.

Bioimaging is another application that can be foreseen for arene ruthenium complexes. As demonstrated by Sadler and coworkers, fluorescent labeling of mononuclear arene ruthenium complexes is relatively easy to achieve, and can potentially provide valuable answers regarding the biological behavior of arene ruthenium complexes.[36] The fluorescent-labeled complex was synthesized by reacting the dinuclear *p*-cymene ruthenium complex $[(p\text{-cymene})RuCl_2]_2$ with ethylenediamine-derived ligands containing the fluorescent moiety (Fig. 18).

Fluorescent molecules can also be encapsulated in the hydrophobic cavity of arene ruthenium metalla-prisms. These host–guest systems have been used to evidence the drug delivery efficiency of metalla-prisms (Fig. 19A).[37]

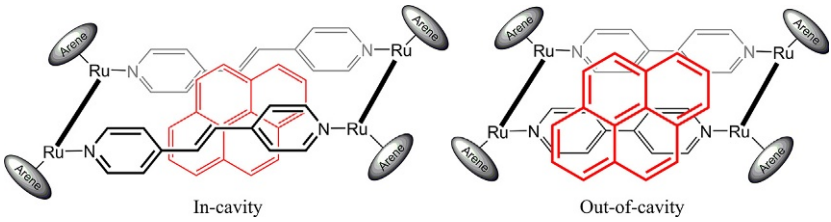


Fig. 17 In- and out-of-cavity interactions of pyrene with arene ruthenium metallacycles.[35]

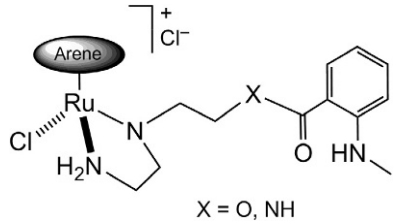


Fig. 18 Fluorescent labeling of arene ruthenium complexes by functionalization of ethylenediamine-derived ligands.[36]

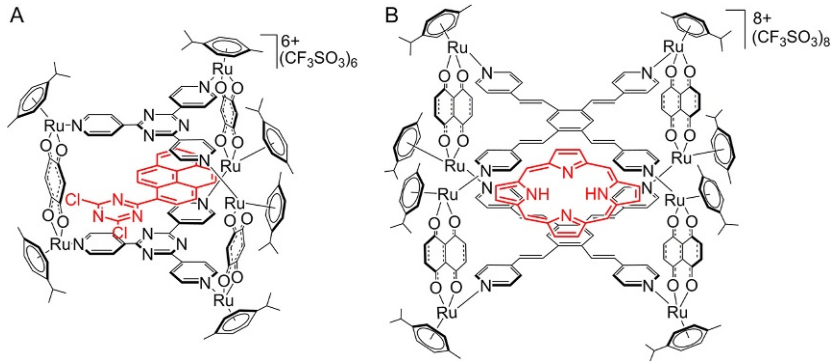


Fig. 19 Arene ruthenium metalla-prism and metalla-cube encapsulating fluorescent molecules.[37,38]

Accumulation in cells of the fluorescent guest compound 1-(4,6-dichloro-1,3,5-triazin-2-yl)pyrene was monitored by flow cytometry and fluorescent microscopy showing that the uptake of the guest was significantly increased as compared to the guest alone, thus confirming the drug delivery potential of these metalla-assemblies.

Porphin is another photo-responsive molecule that can be trapped inside the cavity of arene ruthenium metalla-assemblies and transported into cells (Fig. 19B).[38] Again, fluorescent microscopy was used to confirm the accumulation of porphin in cells after the internalization of the host–guest system. The presence of porphin molecules offered the possibility to kill cancerous cells by triggering a photoreactive response of porphin upon irradiation. Such photodynamic treatment of cancers by porphyrin derivatives is already in the clinic and shows great promises.[39]

These selected examples show how arene ruthenium complexes can be useful platforms to develop stimuli-responsive molecules for applications in host–guest chemistry and other fields.

5. INTERACTIONS WITH DNA AND PROTEINS

Considering that cisplatin, undeniably the most successful metal-based drug in the clinic, intercalates DNA to trigger the proliferation of cancers.[40] It was initially postulated that the main mode of action of arene ruthenium complexes was also interaction with DNA.[41] However, even if several arene ruthenium complexes can indeed interact with DNA, it is now clear that other mechanisms and other targets are used by arene ruthenium complexes

to kill cancer cells.[42] The arene ligand, the nature of the auxiliary ligands, the overall charge of the complex, the lipophilicity, the size, as well as other aspects can play important roles in the biological activity of arene ruthenium complexes. In this section, we will focus on selected complexes that are known to interact with DNA and proteins.

Arene ruthenium complexes with planar aromatic auxiliary ligands have shown intercalation in double-stranded DNA. The hexamethylbenzene ruthenium complex (Fig. 20) with dppz *N,N*-chelating ligand (dppz = dipyridophenazine) formed a 1:1 system with calf thymus DNA.[43] The high ΔT_m value (T_m = melting temperature) suggests specific dipolar major groove binding between the dipyridyl moiety of dppz and nucleobases.

Several other mononuclear arene ruthenium complexes can interact with DNA, either by intercalation when they possess large planar aromatic appendages[44] like the dppz derivative as previously shown, or by coordination-binding of nucleobases upon ligand exchange. In this second family of DNA binders, the N7 of guanine is generally the preferred coordination site, followed by the other nitrogenous bases and the other nitrogen atoms of guanine.[45]

Targeting oncogenic DNA is an elegant strategy to limit toxicity and drug resistance of metal-based drugs. Among cancer-related DNA structures, the G-quadruplex has received a great deal of attention. Stabilization of G-quadruplex DNA can hamper the proliferation and growth of tumor cells.[46] The structure of G-quadruplex shows series of guanine tetrads stacked on top of each other, which is further stabilized by the presence of cations (K^+, Na^+) between these tetrads. Therefore, planar aromatic compounds and guanine binders can in principle interact with G-quadruplexes. Indeed, it has been shown that the coordination of four arene ruthenium units to

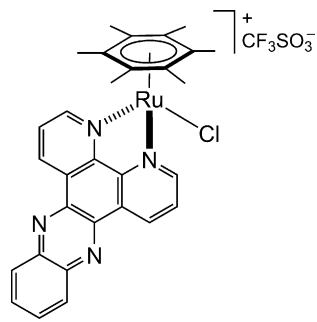


Fig. 20 Arene ruthenium complex showing intercalation to CT DNA.[43]

the tetrapyridylporphyrin core generates good G-quadruplex DNA stabilizers (Fig. 21A).[47] Similarly, the mononuclear arene ruthenium complex incorporating phenanthroline-derived ligand was able to interact with *c-myc* G-quadruplex DNA in a groove binding mode (Fig. 21B).[48] These examples confirm that arene ruthenium complexes are an interesting scaffold to design DNA binders.

Like for sensing, tetranuclear arene ruthenium metalla-assemblies can interact with DNA and proteins. The components (connectors, arenes, linkers), the size, and the overall charge of the assemblies can influence the affinity of these supramolecular compounds for biomolecules. The bowl-shape tetranuclear arene ruthenium system $[(p\text{-cymene})_4Ru_4(oxonato)_2(bpy)_2]^{4+}$ (bpy = 4,4′-bipyridine) binds DNA,[49] while larger arene ruthenium metalla-rectangles interact with proteins.[50]

Ethacrynic acid is a known GST inhibitor (GST = glutathione transferase), and it has been conjugated to arene ruthenium complexes in multiple ways (Fig. 22). The ethacrynic acid moiety has been, for example, grafted to the arene ligand,[51] or to an imidazole-derived ligand.[52] In both cases, the

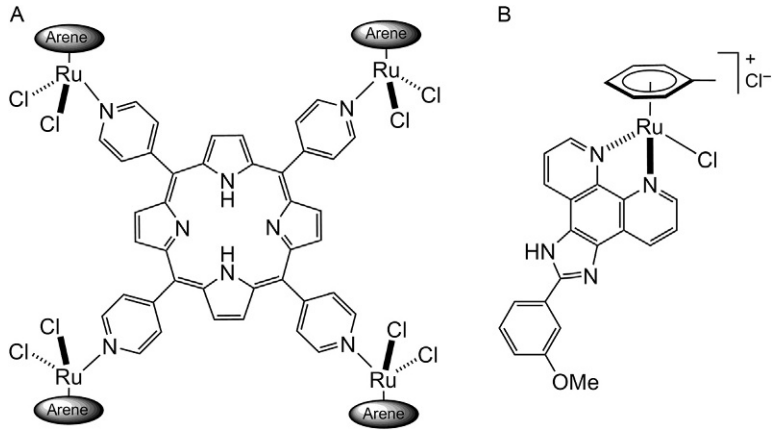


Fig. 21 Arene ruthenium complexes that can stabilize G-quadruplexes.[47,48]

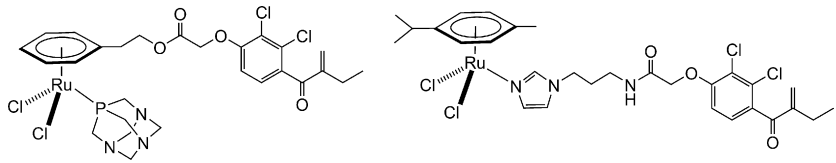


Fig. 22 Arene ruthenium complexes incorporating an ethacrynic acid group.[51,52]

bioconjugate complex showed excellent antiproliferative activity on cancer cells and appeared to be inhibitors to GST.

Involved in DNA transcription and mitosis, the enzyme type II topoisomerase (Topo II) is a potential target for cancer treatment, and finding Topo II inhibitors remains an active field of research. Several arene ruthenium complexes have been identified as inhibitors of Topo II, for example, the thiomaltol-based mononuclear arene ruthenium complex (Fig. 23A)[53] or the dinuclear complex $[Ru(tptz)(PPh_3)Cl_2\{(arene)RuCl\}]^+$ (tptz = 2,4,6-tris(2-pyridyl)-1,3,5-triazine) (Fig. 23B).[54]

Plectin is another protein that can be targeted by arene ruthenium complexes. Plectin is found in mammalian cells, and participates to the formation of the cytoskeleton. In a recent study, it was observed that the arene ruthenium pyridinecarbothioamide complexes (Fig. 24) selectively target plectin, thus causing cell death by G0/G1 arrest.[55] The *p*-cymene derivative showed anticancer activity against primary tumors and in invasive melanomas after oral administration to mouse implanted with murine colon carcinoma tumor model.

Considering the huge number of proteins in a single cell, it is quite obvious that all arene ruthenium complexes can in principle interact with some of them. However, the difficulty remains in having high selectivity for a

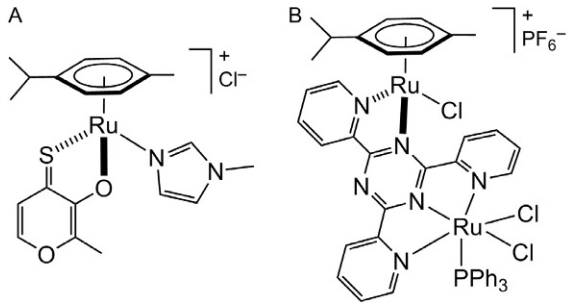


Fig. 23 Two arene ruthenium complexes that can inhibit type II topoisomerase.[53,54]

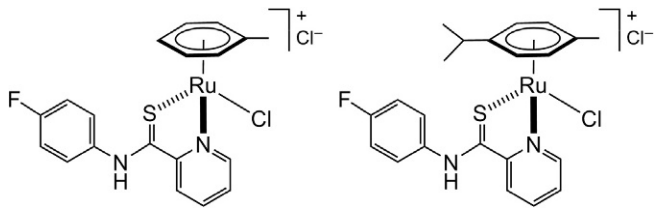


Fig. 24 Arene ruthenium complexes that can target the plectin protein.[55]

specific protein, to avoid undesired biological responses. Therefore, publications dealing with new arene ruthenium–protein interacting systems will keep coming at a regular pace, and should bring new applications for arene ruthenium complexes.

6. LIQUID CRYSTALS

Metallomesogens, a combination of metal ions and mesogens, offer great perspectives in designing innovative liquid-crystalline materials.[56] The only example of metallomesogen containing arene ruthenium complexes comes from our group.[57] A three-component system involving pyrenyl-functionalized poly(arylester) dendrimers, cationic arene ruthenium metallacycle, and dodecyl sulfate anions has showed interesting liquid-crystalline properties (Fig. 25). The pyrenyl-functionalized dendrimers exhibit a smectic A-like phase, while in the presence of the arene ruthenium metallacycle and the anions the supramolecular systems self-organize into cubic phases. The facility to modify and interchange the different components in these systems suggests that this is only the beginning

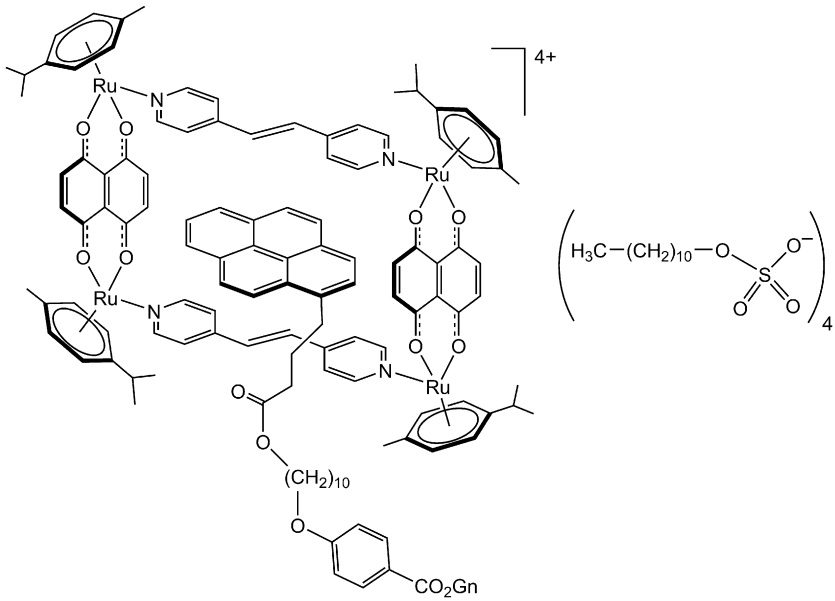


Fig. 25 Three components, arene ruthenium metallacycle, pyrenyl-functionalized poly(arylester) dendrimer, and dodecyl sulfate, showing liquid-crystalline properties.

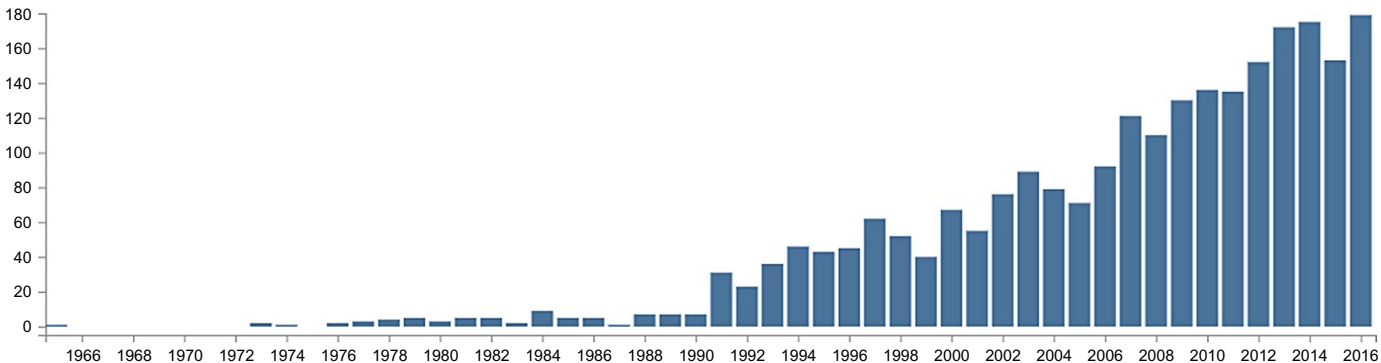


Fig. 26 Publications per year (1950–2016) with *arene ruthenium* as topic (Clarivate Analytics, Web of Science Core Collection, June 2017).

and that more arene ruthenium containing supramolecular liquid-crystalline systems will appear soon.

7. CONCLUSION

Since the discovery of benzene ruthenium dichloride, 50 years ago,[58] the field of arene ruthenium complexes remains a fertile soil. These complexes can be used as catalysts, or as metal-based drugs, and now they start playing an important role in supramolecular chemistry. As illustrated in this review, applications are already starting to emerge, and for those with creativity and imagination, arene ruthenium complexes can still offer amazing opportunities. Therefore, the future of arene ruthenium complexes in supramolecular chemistry looks good and soon it will further increase the number of publications dealing with arene ruthenium (Fig. 26), which has been growing rapidly in the last 30 years.

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