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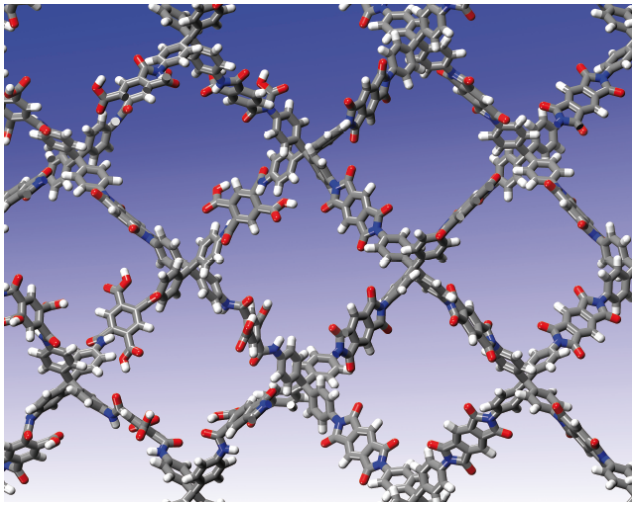

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Molecular architecture of redox-active half-sandwich Ru(II) cyclic assemblies. Interactions with biomolecules and anticancer activity†‡

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Tetranuclear cationic open boxes non-covalently bind DNA major groove. By contrast, they covalently bind cysteine after ligand exchange reactions. In addition, these systems exhibit potent antitumour activity circumventing cisplatin resistance.

Introduction

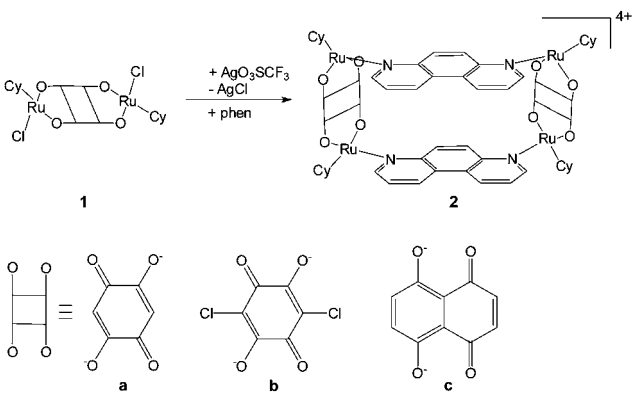
In recent years, the self assembly process between transition metal ions and organic linkers to give discrete supramolecular boxes has been widely investigated. The versatility of these molecular cages has been exploited to generate confined cavities in which selective molecular recognition processes take place,[1] leading to applications ranging from sensing,[2] stabilisation of reactive species[3] to vectors for drug delivery.[4] Traditionally, metal fragments providing 90° coordination geometries in combination with linear organic spacers have been used to form square and rectangular architectures.[5] Recently, metal complexes with octahedral geometry have been employed as building blocks for the construction of novel supramolecular boxes with different properties.[6] For this purpose, blocking chelating ligands are necessary to control the accessibility to the coordination sites of the octahedral metal centre in order to favour the formation of cyclic polynuclear systems. In this regard, arene ruthenium complexes (arene = benzene, toluene, *p*-cymene, hexamethylbenzene) have been extensively used to generate supramolecular assemblies.[7–9]

On the other hand, a large number of compounds containing metals other than platinum[10] have been investigated in the search for anticancer agents overcoming the high toxicity and spontaneous or acquired resistance to Pt-based drugs.[11] It should be highlighted that the improvement of the activity of these metal anticancer compounds lies in the fine-tuning of their biological activity and mechanism of action by the appropriate choice of the metal, its oxidation state and of the ligands.[12,13] In this context, ruthenium compounds and, in particular, ruthenium-arene organometallic complexes have recently shown a high potential for the development of metal-based anticancer drugs[10,14] as they exhibit interesting features, such us robustness, low toxicity and combine a good balance of hydrophilicity and hydrophobicity, which is a key issue for their transport in biological media.[4] In this regard, we have previously reported on the formation of a series of robust half-sandwich Ru(II) assemblies able to give non-covalent interactions with DNA and exhibiting a selective cytotoxic activity towards ovarian A2780R cancer cell lines with acquired resistance to cisplatin.[9]

Moreover, the cathepsin B enzyme activity inhibition exhibited by some Ru and Pd compounds, related to their binding to the cysteine residues of the enzyme active site, also correlates with their enhanced cytotoxicity.[15] In addition, it has been shown that certain types of tumour cells expose unusually high levels of negatively charged phospholipids at their surface.[16] Finally, it has also been proven that the incorporation of a redox active functionality on an antitumour drug increases its toxicity towards tumour cells.[17]

Taking into account the above considerations, our group is interested in the design of novel cationic metallacycles using Ru-*p*-cymene building blocks connected through organic spacers of different lengths and shapes and incorporating a redox function in order to investigate the possible synergistic effect of this additional feature in the citotoxic properties of these systems.

In this communication, we report that the arene ruthenium dinuclear systems $[(Cy)_2Ru_2(\mu\text{-}OO,O'O'\text{-}L)Cl_2]$ (Cy: *p*-cymene; phen: 4,7-phenanthroline; **1a**: 1,4-benzoquinone-2,5-diolato (dhbq); **1b**: 2,5-dichloro-*p*-benzoquinone-3,6-diolato (chloranilato); **1c**: 1,4-naphtoquinone-5,8-diolato (dhnq)) can be employed to build metallarectangles of the general formula $[(Cy)_4Ru_4(\mu\text{-}OO,O'O'\text{-}L)_2(\mu\text{-phen})_2](CF_3SO_3)_4$ (**2a–c**) (Scheme 1). These compounds have been structurally characterised and their electrochemical behaviour,



Scheme 1 Reaction of formation of the $[(Cy)_4Ru_4(\mu\text{-}OO,O'O'\text{-}L)_2(\mu\text{-phen})_2](CF_3SO_3)_4$ (**2a–c**) cyclic assemblies.

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† Electronic supplementary information (ESI) available: Detailed experimental methods, elemental analysis and ^{1}H NMR spectra of **2a–c** complexes, UV-vis, CD and fluorescence spectra exhibiting the interaction of **1a**, **1c**, **2a** and **2c** with ct-DNA and ^{1}H NMR spectra showing the interaction of **2a–c** with cysteine. CCDC reference number 764877. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c002411b

‡ Rotation freedom about the Ru-(phen) make it possible the cyclic system to adopt additional conformations.

reactivity towards bio-relevant species and *in vitro* anticancer activity have been studied in order to establish if there is a relation among their structural features, robustness, redox activity and cytotoxicity.

Results and discussion

Synthesis and characterization of the cyclic assemblies

The dinuclear complexes $[(Cy)_2Ru_2(\mu\text{-}OO,O'O'\text{-}L)Cl_2]$ (**1a**: 1,4-benzoquinone-2,5-diolato (dhbq); **1b**: 2,5-dichloro-*p*-benzoquinone-3,6-diolato (chloranilato); **1c**: 1,4-naftoquinone-5,8-diolato (dhnq)) have been obtained following literature methods.[9,18] Removal of the chloride ligands of **1a–c** by treatment with $AgCF_3SO_3$ leads to the formation of the corresponding $[(Cy)_4Ru_4(\mu\text{-}OO,O'O'\text{-}L)_2(CF_3SO_3)_2]$ species (**1′a–c**), which upon posterior reaction with the *N*,*N*′-donor 4,7-phenanthroline bent spacer yields the tetranuclear metallacycles $[(Cy)_4Ru_4(\mu\text{-}OO,O'O'\text{-}L)_2(\mu\text{-phen})_2](CF_3SO_3)_4$ (phen: 4,7-phenanthroline; **2a**: dhbq; **2b**: chloranilato; **2c**: dhnq). These tetranuclear systems have been studied by ^{1}H NMR spectroscopy and the X-ray crystal structure of **2a** has been determined. ^{1}H NMR spectra for **2a–c** in both DMSO-d_6 and D_2O remain unaltered at least for two weeks, which is indicative of the robustness of these species in both solvents.

The single-crystal X-ray diffraction analysis showed that compound **2a** crystallizes in the $P2_1$ space group and is composed of rectangular tetranuclear $[(Cy)_4Ru_4(dhbq)_2(phen)_2]^{4+}$ cationic open boxes (Fig. 1) of approximate dimensions 8.0 × 15.0 × 17.0 Å. The ruthenium metal centres, coordinated to one *p*-cymene ring, are bridged by the dianionic 1,4-benzoquinone-2,5-diolato ligands and the neutral *N*,*N*′-phen linkers, which show *OO*,*O*′*O*′-exotetradentate and N^4,N^7-exobidentate coordination modes, respectively. The open box adopts a cone conformation, thereby creating a vase-like cavity suitable for molecular recognition processes. Indeed, the wider entrance of the cone hosts one non-coordinated 4,7-phen molecule, whose shortest atom-atom contacts with the 1,4-benzoquinone-2,5-diolato and 4,7-phen ligands situated in the cavity walls are 3.18 and 3.39 Å, respectively. The tetranuclear coordination rectangles stack along the *b*-axis to build supramolecular zig-zag chains supported by π–π interactions established between the *p*-cymene moieties of adjacent assemblies (ESI, Fig. S1).† The presence of hosted phen moieties inside the cavities is also supported by elemental analysis and ^{1}H NMR spectroscopy (see supporting information). It should be noted that for **2c**, the elemental analysis and ^{1}H NMR integrals account for four phen molecules encapsulated in the metallarectangle cage. This fact should be related to the lengthened dimensions and extended aromaticity of the 1,4-naphtoquinone-5,8-diolato bridges and a probable *trans* disposition of the 4,7-phen moieties which permit to host two pairs of stacked phen moieties above and below the Ru_4 plane.

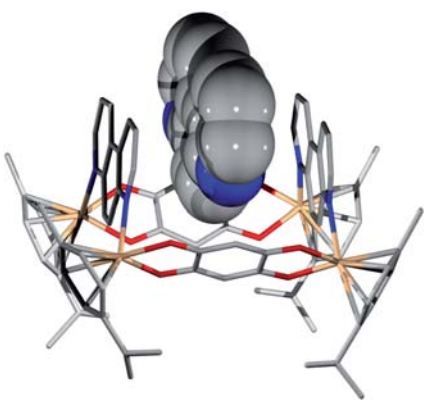

Fig. 1 Crystal structure of the supramolecular assembly $[(Cy)_2Ru_4(1,4\text{-benzoquinone-2,5-diolato})_2(phen)_2]^{4+}$ (**2a**). C (grey), N (blue), O (red), Ru (orange). H-atoms have been omitted for clarity.

Reactivity and host–guest chemistry of the Ru(II) assemblies towards bio-relevant species

The study of the interaction of these systems with DNA and their possible significant effects on DNA structure is of great importance as DNA is thought to be the primary cellular target for Ru(II) complexes,[19,13] as for many metal-based anticancer drugs. To gain additional insight into the potential modes of interaction, we have studied the binding of the dinuclear and tetranuclear complexes to adenosine monophosphate (AMP) as a model of DNA, by means of ^{1}H NMR spectroscopy in aqueous solution at pH 7.0. The experiments show that the chloride ligands in **1a–c** exchange with the mononucleotide within two hours, which is in agreement with related mononuclear [(Cy)RuLCl] systems.[13] Indeed, in the case of the dinuclear **1a** and **1c** species, the addition of AMP is responsible for an important upfield shift (−0.4 ppm) of the signals of the aromatic protons of benzoquinone and naphtoquinone units. On the other hand, only a slight upfield shift of the ^{1}H NMR signals is observed upon addition of AMP to solutions of **2a–c**, indicating the robustness of the assemblies and that the interaction of the mononucleotide takes probably place at the external surface of the cage through π–π, anion-π and electrostatic interactions. This result is expected as the π–π stacking between the free phen included inside the cavity and the phen ligands situated in the walls is very strong (in the case of **2a**, is close to ideal, with interplanar distances and dihedral angles of 3.82–4.02 Å and 5.20–6.31°) avoiding a possible exchange and, as a consequence, the incorporation of the AMP inside the receptor.

On the other hand, the ability of **1a**, **2a**, **1c** and **2c** to interact with calf-thymus ct-DNA has been examined by means of biophysical methods (UV-vis, circular dichroism (CD) and competitive binding essays with ethidium bromide (EB)) (Fig. 2, ESI Fig. S3, S4 and S5).† Of particular interest are the EB competitive studies, which show that the strength of the interaction follows the trend **1a** < **1c** ∼ **2c** < **2a**. This trend is further confirmed by the CD measurements showing the largest ellipticity diminution for the **2a** system, which might be related to a probable DNA coiling induced by the supramolecular binding of **2a** to the DNA major groove in a similar way to Hannon's metallacylinders (Fig. 2).[20] The ability of **2a** to interact with DNA and to induce conformational changes is a probable result of a mixture of electrostatic interactions with polyanionic DNA and size and shape complementarity of this system with the DNA major groove.

Finally, reactions with sulfur containing biomolecules (*i.e.* amino acids, proteins) appear to play an important role in the biological chemistry of soft metal based metallodrugs, as such interactions can be responsible for drug inactivation/activation processes and/or the drug delivery mechanism.[13,15] Taking it into account, we have studied the interaction of **1a–c** and **2a–c** systems with the S-donor amino acid L-cysteine. Indeed, ^{1}H NMR studies show that incubation of **1a–c** and **2a–c** with 4 equiv. of cysteine at 37 °C and at pH 7.4, leads to

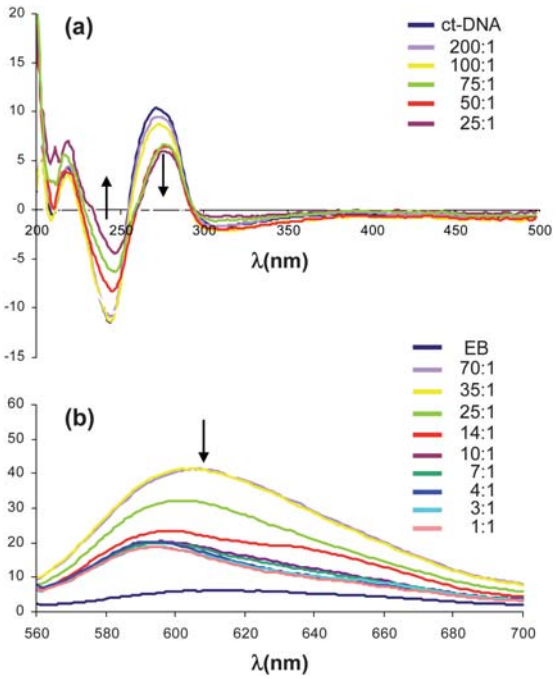

Fig. 2 (a) CD spectra of the titration of ct-DNA (150 μM) with $[(Cy)_2Ru_4(1,4\text{-benzoquinone-2,5-diolato})_2(phen)_2](CF_3SO_3)_4$ (**2a**). (b) Competitive binding assays: fluorescence spectra of intercalated ethidium bromide (5 μM) in DNA (4 μM) upon addition of increasing amounts of **2a** in 1mM sodium cacodylate buffer and 20 mM NaCl.

rapid ligand exchange reactions of chloride and phen ligands for **1a–c** and **2a–c** sets of compounds (ESI, Fig. S6).†

Redox properties

Compounds **1a–c** and **2a–c** have been studied by cyclic voltammetry. The redox response of the dinuclear **1a–b** species has been previously described by Therrien *et al.*[8] It should be noted that **1c** behaves in a similar way displaying two reversible reduction peaks at −0.85 and −1.9 V. Like in the case of the dinuclear compounds, the response of the tetraruthenium complexes **2a–b** is analogous to their related metallacycles $[(Cy)_4Ru_4(dhbq)_2(bpy)_2](CF_3SO_3)_4$ and $[(Cy)_4Ru_4(chloranilato)_2(bpy)_2](CF_3SO_3)_4$[8] and only a slight shift of the waves to less negative potentials (< 0.1 V) is observed. Noteworthy, the **2c** system shows three reductions peaks at −0.72, −0.90 and −2.0 V. The first two events are indicative of electronic communication being transmitted through the phen bridges leading to consecutive reduction processes of one dhnq side after the other. This unusual feature is probably related to the extended aromaticity of the phen ligand, which put this system in close relation to the classical pyrazine bridged Creutz-Taube dinuclear Ru systems.[21] It should be noted, however, that the redox activity in our case is ligand centred.

Cytotoxicity studies

Table 1 summarises the antiproliferative activity results of the dinuclear **1a–c** and the tetranuclear **2a–c** species as well as related arene Ru(II) tetranuclear assemblies against the cisplatin sensitive A2780 and cisplatin resistant A2780R ovarian cancer cell lines.

In the case of the A2780 cell line, we have observed that **1b** is inactive whereas **1a**, **2b**, and the previously reported $[(Cy)_4Ru_4(Hoxonato)_2(phen)_2](CF_3SO_3)_4$, $[(Cy)_4Ru_4(Hoxonato)_2(bpy)_2](CF_3SO_3)_4$[9] show moderate activities, in the range of one to two orders of magnitude lower than those exhibited by cisplatin (Table 1). Nevertheless, **2b** is almost thirteen times more potent as an inhibitor than the $[(Cy)_4Ru_4(chloranilato)_2(bpy)_2](CF_3SO_3)_4$ related tetramer reported by Therrien *et al.*[8] It is worth noting that the dinuclear **1c** and tetranuclear **2c** species posses a potent activity, with IC_{50} values of 0.95 and 0.20, respectively. In addition, the cyclic **2a** species, with an IC_{50} value of 0.79, can be considered equipotent to cisplatin and clearly overcomes the performance of the related $[(Cy)_4Ru_4(dhbq)_2(bpy)_2](CF_3SO_3)_4$ system (Table 1).[8] According with these results, the activity of the dinuclear systems is clearly outperformed by the tetranuclear ones. Particularly, **2c** shows the best performance with an activity *ca.* 4 times higher than that of cisplatin in this cancer cell line.

Regarding the behaviour of these systems against A2780R cancer cell line with acquired resistance to cisplatin, the cytotoxic effect of **1a** and **1b** is relatively low. However, **1c**, **2a–c** proved to be more active against human ovarian A2780R cancer cells than cisplatin and the $[(Cy)_4Ru_4(Hoxonato)_2(phen)_2](CF_3SO_3)_4$ and

Table 1 IC_{50}[a] values (in μM) in ovarian A2780 and cisplatin resistant A2780R cancer cell lines and resistance factor RF (IC_{50} cisplatin resistant/IC_{50} cisplatin sensitive)

Compound	A2780[c]	A2780R[c]	RF	Ref.
$[(Cy)_4Ru_4(Hoxonato)_2(bpy)_2]$ $(CF_3SO_3)_4$	19	4.6	0.2	9
$[(Cy)_4Ru_4(Hoxonato)_2(phen)_2]$ $(CF_3SO_3)_4$	15	8.3	0.6	9
$[(Cy)_2Ru_2(dhbq)Cl_2]$ (**1a**)	9.5	24	2.5	b
$[(Cy)_2Ru_2(chloranilato)Cl_2]$ (**1b**)	Inactive	Inactive	—	b
$[(Cy)_2Ru_2(dhnq)Cl_2]$ (**1c**)	0.95	1.09	1.1	b
$[(Cy)_4Ru_4(dhbq)_2(phen)_2](CF_3SO_3)_4$ (**2a**)	0.79	2.40	3.0	b
$[(Cy)_4Ru_4(dhbq)_2(bpy)_2](CF_3SO_3)_4$	66	—	—	8
$[(Cy)_4Ru_4(chloranilato)_2(phen)_2](CF_3SO_3)_4$ (**2b**)	3.30	3.20	1.0	b
$[(Cy)_4Ru_4(chloranilato)_2(bpy)_2](CF_3SO_3)_4$	43	—	—	8
$[(Cy)_4Ru_4(dhnq)_2(phen)_2](CF_3SO_3)_4$ (**2c**)	0.20	0.18	0.9	b
Phen	50	Inactive	—	b
Cisplatin	0.69	4.00	5.6	b

[a] IC_{50}: drug concentration necessary for 50% inhibition of cell viability. [b] This work. H_2dhbq= 2,5-dihydroxy-1,4-benzoquinone; chloranilic= 2,5-dichloro-3,6-dihydroxy-*p*-benzoquinone; H_2dhnq= 5,8-dihydroxy-1,4-naftoquinone. [c] Standard deviations are below 4%.

$[(Cy)_4Ru_4(Hoxonato)_2(bpy)_2](CF_3SO_3)_4$ species previously reported by us.[9] Remarkably, the activities of **1c**, **2a–c** do not significantly diminish compared to the wild-type human ovarian cancer cells. This means that they are apparently able to circumvent the acquired resistance to cisplatin treatment.

In view of these results, it seems that the structural features exhibited by the tetranuclear assemblies are optimal to exert a high toxicity towards these cancer cell lines. Namely, the cationic and hydrophobic/hydrophilic nature of these systems coupled to the presence of highly extended aromatic phen ligands and redox active *OO,O′O′*-exotetradentate organic spacers synergistically increases their cytotoxic behaviour. In this regard, it should be remarked the high performance of the **2c** system which might be related to the additional presence of extended aromaticity in the dhnq *OO,O′O′*-exotetradentate ligand which might favour its non-covalent interaction with polyanionic DNA. In relation to this, it should be noted the unusual behaviour of the dimeric **1c** compound, which also exhibits very low IC_{50} values, as a probable consequence of its capacity to intercalate DNA as envisaged from the competitive binding assays with EB. On the other hand, in the case of **2a–c**, their high activity as anticancer drugs could be related to a combination of the activity of the metallarectangles as vectors of the phen aromatic extended systems. Finally, it should also be noted that the enhanced cytotoxicity of the here reported systems compared to our previously reported $[(Cy)_4Ru_4(Hoxonato)_2L_2](CF_3SO_3)_4$ systems might also correlate with the robustness of the later towards ligand exchange reactions with cysteine.[9]

Conclusions

A series of redox active tetra cationic rectangular ruthenium open boxes have been prepared and characterized by spectroscopic methods, X-ray diffraction and cyclic voltammetry. In addition, we have studied the ligand exchange reactions of these assemblies towards bio-relevant S- and N-donor ligands, their interaction with ct-DNA and screened for *in vitro* anticancer activity against cisplatin sensitive ovarian carcinoma A2780 and cisplatin resistant A2780R cancer cell line.

The results show that the dinuclear systems readily react with S-donor cysteine and N-donor mononucleotides after ligand exchange processes of the labile chloride ligands. At variance, the tetranuclear assemblies only give ligand exchange reactions with cysteine with the concomitant release of the exobidentate phen ligands. On the other hand, the tetranuclear cationic assemblies exhibit a significant higher cytotoxic activity and DNA binding properties than their dinuclear precursors. Of particular interest is their high antitumour activity towards A2780R cell line suggesting the circumvention of resistance to a chemotherapeutic treatment. In this regard, the reactivity of the tetranuclear species towards cysteine, coupled to their redox activity and their ability to non-covalent interact with the DNA double strand appears to synergistically promote the increased cytotoxicity of these systems towards the studied carcinoma.

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