Anticancer Agents

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Dinuclear Ruthenium(II) Triple-Stranded Helicates: Luminescent Supramolecular Cylinders That Bind and Coil DNA and Exhibit Activity against Cancer Cell Lines**

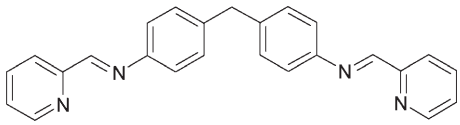
*Gabriel I. Pascu, Anna C. G. Hotze, Carlos Sanchez-Cano, Benson M. Kariuki, and Michael J. Hannon**

Synthetic agents that bind to DNA and affect its processing are attractive targets in molecular design. Small molecules can regulate specific gene expression[1] and remain at the forefront of clinical application as anticancer and antiviral drugs.[2] Clinical drugs can intercalate (anthracycline antibiotics),[3] minor groove bind (berenil),[4] or form coordination bonds to DNA (cisplatin).[5] To create different spectra of activity and circumvent cross-resistance, it is important to explore drugs that interact with DNA in new and distinct ways.

We have previously described synthetic metallo-supramolecular cylinders of a similar size and shape to protein zinc fingers. These tetracationic cylinders contain three bis(pyridylimine) ligand strands wrapped in a helical fashion about two iron(II) centers. The cylinders not only can bind strongly and noncovalently in the major groove of DNA, inducing dramatic and unprecedented intramolecular DNA coiling in natural polymeric DNAs,[2,6] but also can bind at the heart of Y-shaped DNA junctions, an unparalleled and hitherto unexpected mode of DNA recognition.[7]

Combining these striking DNA binding features with the fact that ruthenium compounds represent a new and promising class of anticancer drugs[8–10] led to the aim of developing a triple-stranded ruthenium cylinder that would be one of the few noncovalent DNA recognition metal compounds studied for its biological activity. This design was still more attractive because of the potential for luminescence (from MLCT states),[11] which might be used to probe the DNA binding. We describe herein the synthesis of the luminescent ruthenium(II) triple-stranded helicate of ligand L (Scheme 1) and explore its DNA binding and activity against cancer cells.

Although the synthesis of triple-stranded helicates with labile first-row transition metals is well established,[12] the synthesis of triple-stranded helicates with an inert metal such as ruthenium(II) represents a considerable challenge and prior to this work had not been achieved. Coordinate bond formation with labile metals is reversible and the assembly is under thermodynamic control. With inert metals this is not the case and the metals and ligands can become trapped in alternative polymeric structures that are not pathways to the assembly of the helicate; in illustration we note that of the three isomeric dinuclear double-stranded unsaturated ruthenium(II) helicates we recently described, none has the correct conformation at any of their metal centers needed for triple-helicate formation.[13] It is striking that, despite the great interest in the photophysical and redox properties of ruthenium(II) tris(diimine) centers,[14] no diruthenium(II) triple-stranded helicate has been prepared.[15]



Scheme 1. Ligand L.

To try to prepare the triple-stranded diruthenium(II) complex, we initially explored different ruthenium starting materials ($[\{Ru(cod)Cl_2\}_n]$, $RuCl_3$, and $[Ru(CH_3CN)_6](PF_6)_2$; cod = 1,5-cyclooctodiene), which we heated under reflux with the ligand in a variety of organic solvents (such as different alcohols, ethylene glycol, acetonitrile, acetone) for various reaction times (days to weeks). In all cases we obtained mixtures (polymers?) from which the desired product could not be separated nor identified in the crude by ESI-MS or NMR spectroscopy. However, by refluxing a highly crystalline sample of *cis*-$[Ru(dmso)_4Cl_2]$ (dmso = dimethylsulfoxide) with L in ethylene glycol under N_2 for several days we obtained a more promising, dark-orange solution. Pouring this solution into a methanolic solution of ammonium hexafluorophosphate gave an orange-brown precipitate, and the ESI mass spectrum for this crude product showed peaks with a correct isotopic distribution for $[Ru_2L_3]^{4+}$ and $[Ru_2L_3](PF_6)_2^{2+}$ species along with other unidentified species. The ^{1}H NMR spectrum of the crude product showed only very broad peaks due to the presence of several species and perhaps also of Ru^{III} compounds, which could be formed during the reaction.

Purification of the triple-stranded cylinder was achieved by column chromatography on neutral alumina with the solvent mixture $CH_3CN/H_2O/KNO_{3(aq)}$ (20:1:1). The product eluted as an orange band, and two columns were usually

[*] G. I. Pascu, Dr. A. C. G. Hotze, C. Sanchez-Cano, Dr. B. M. Kariuki, Prof. M. J. Hannon
School of Chemistry
University of Birmingham
Edgbaston, Birmingham, B15 2TT (UK)
Fax: (+44) 121-414-7871
E-mail: m.j.hannon@bham.ac.uk

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Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

required for the purification. Following reprecipitation with NH_4PF_6, the $[Ru_2L_3](PF_6)_4$ compound was recrystallized (twice) from acetonitrile by slow diffusion of diethyl ether at 4 °C to afford small red-orange crystals. The yield of $[Ru_2L_3]^{4+}$ of analytical purity is very low (around 1%), although this is unsurprising in view of the competing reaction pathways, the need for extensive purification, and the relatively low yields associated with the syntheses of even straightforward ruthenium(II) compounds.

Larger crystals suitable for X-ray diffraction could be obtained by slow diffusion of benzene into a solution of the complex in acetonitrile, and the crystal structure is shown in Figure 1.[16] As expected, the crystal structure reveals the

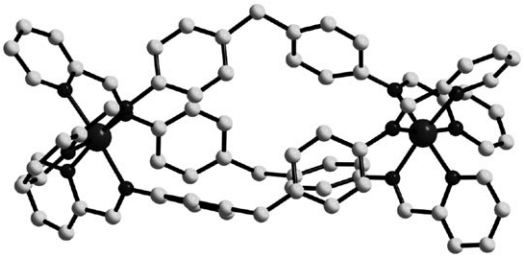

Figure 1. Structure of $[Ru_2L_3]^{4+}$ cation. Ru large black spheres, N small black spheres, C small gray spheres. Hydrogen atoms, anions, and cocrystallized solvent molecules are omitted for clarity.

cation to be a dinuclear triple-stranded helicate with two metal centers bound to three pyridylimine ligands. The structure is analogous to that of the corresponding iron(II) and nickel(II) cylinders.[17] Although the metal–nitrogen bonds (Ru–N 2.02–2.08 Å) are longer than those for the first-row metals, this difference has relatively little effect on the overall structure (see the Supporting Information): the cylinder has a length of approximately 1.8 nm and a diameter of approximately 1.0 nm. The intermetallic separation within the cylinder is 11.3 Å (compared with 11.4 Å in the Fe^{II} analogue). The phenylene rings at the center of the cylinder are stacked together through face–edge π interactions (CH···π). There are two sets of rings, each containing three rings each drawn from a different strand. Each ring acts as a CH H-bond donor to one ring and uses its π system as the H-bond acceptor to the other ring in the group of three (centroid···centroid 4.9–5.1 Å; H···centroid 2.9–3.0 Å). This interaction is an important contributor to the structure of the cylinder, in that it imparts rigidity down the length of the structure and arranges the π surfaces on the surface of the cylinder.

The red-orange color of the compound is characteristic for a RuN_6 chromophore and the UV/Vis absorption spectrum reveals an MLCT band centered at 485 nm ($\varepsilon = 16900\ M^{-1}cm^{-1}$). As anticipated, the compound is luminescent; excitation at the wavelength of this MLCT band leads to an emission centered at 705 nm (Figure 2). The MLCT band of the cylinder was unperturbed upon addition of DNA, which confirms that the cylinder structure is not destroyed or perturbed.

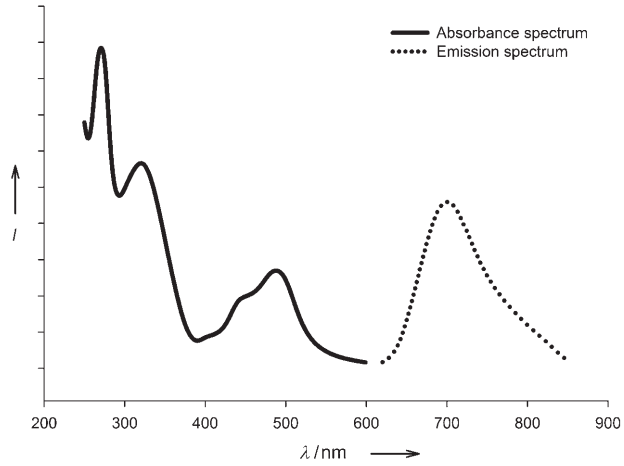

Figure 2. Absorption (solid line) and emission (dotted line) spectra ($\lambda_{ex} = 480$ nm) for $[Ru_2L_3](PF_6)_4$ in MeCN (298 K).

To explore the binding of this cylinder to DNA, we first used circular dichroism spectroscopy. Titration of the racemic ruthenium(II) cylinder into calf-thymus DNA (500 μM ct-DNA; 20 mM NaCl; 1 mM sodium cacodylate) led to a strong induced MLCT CD signal indicating binding (Figure 3). Importantly, the characteristic DNA CD signal below 300 nm confirms that a B-DNA conformation is retained throughout the titration.

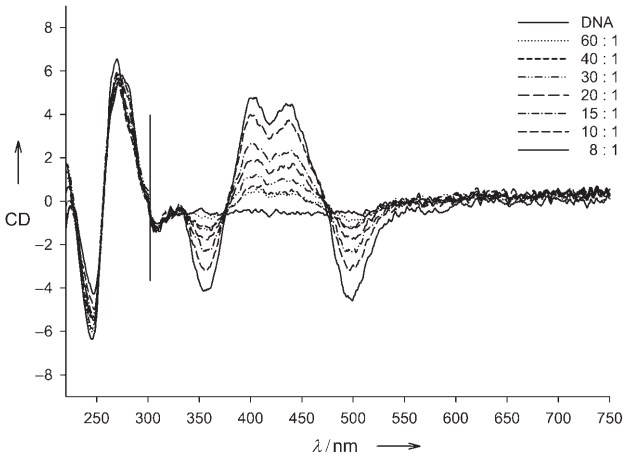

Figure 3. CD spectra of ct-DNA (500 μM, 20 mM NaCl, 1 mM aqueous sodium cacodylate buffer) in the presence of $[Ru_2L_3]^{4+}$. Pathlength 1 mm (220–300 nm), 1 cm (300–750 nm). Mixing ratios are indicated as DNA bases to cylinder.

Flow-linear dichroism experiments were also performed under the same conditions. In this experiment, long, polymeric DNA is oriented by viscous drag in a Couette cell and then the orientation of the chromophores is probed by plane-polarized light. The technique allows two features to be probed: 1) Whether the cylinder binds to the DNA in a specific orientation(s); the cylinders are themselves too small to be oriented by the viscous drag, but will nevertheless become oriented if they are bound in a specific orientation to DNA that is long enough to become oriented. 2) DNA coiling

or kinking effects; these effects reduce the length of the DNA and thus the extent of its orientation in the experiment. This second feature renders flow-linear dichroism a very powerful tool for assessing DNA coiling induced by supramolecular cylinders.[6]

Linear dichroism spectra are shown in Figure 4. The strong positive LD signals that appear in the cylinder MLCT area of the spectrum demonstrate that the cylinder binds to

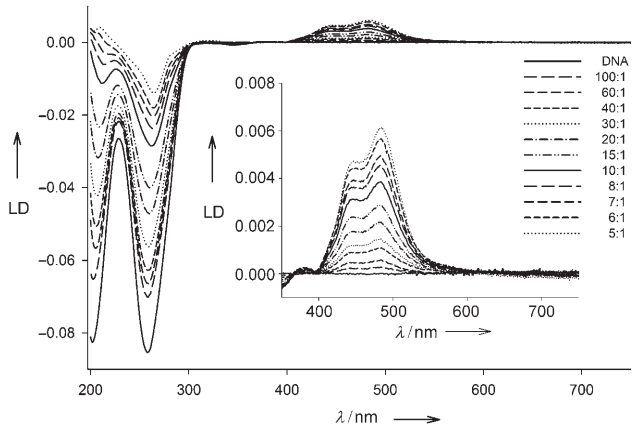

Figure 4. LD spectra of ct-DNA (500 μM, 20 mM NaCl, 1 mM sodium cacodylate buffer) in the presence of $[Ru_2L_3]^{4+}$. Mixing ratios are indicated as DNA bases to cylinder.

calf-thymus DNA in a specific orientation(s) and not merely randomly. The magnitude of the (negative) LD signal at 260 nm attributable to the DNA bases decreases rapidly, which is consistent with the loss of DNA orientation caused by bending or coiling of the DNA by the cylinder. The ruthenium(II) cylinder has a very similar bending/coiling effect on DNA as the corresponding iron(II) cylinder (see the Supporting Information).[6] Although this is entirely expected, it provides additional confirmation that these coiling effects are a consequence solely of the cylinder structure and not of other constituent parts (such as iron(II)).

Having established that the cylinder binds ct-DNA and has similar effects on the DNA structure as its iron(II) analogue, we turned to examine the photoresponse of the cylinder to DNA. Successive additions of ct-DNA to the ruthenium cylinder induce both an enhancement in the intensity of the emission from the ruthenium cylinder and also a blue shift (8 nm) in the emission maximum (Figure 5). This enhancement in the luminescence occurs very rapidly, and no kinetic processes were observed under our experimental conditions. By a ratio of around 4:1 DNA bases/complex the emission intensity has almost doubled; no further enhancement is observed at higher loadings. This emission enhancement is more striking than that for $[Ru(bpy)_3]^{2+}$, which shows little or no enhancement upon binding to DNA,[18] but less dramatic than the classic "light-switch" $[Ru(phen)_2(dppz)]^{2+}$ complexes.[19] Rather, the enhancement is comparable with that for $[Ru(phen)_3]^{2+}$.[20]

To explore the potential anticancer activity of this new ruthenium cylinder, its cytotoxicity was evaluated on human breast cancer HBL-100 and T47D cells. IC_{50} data are reported

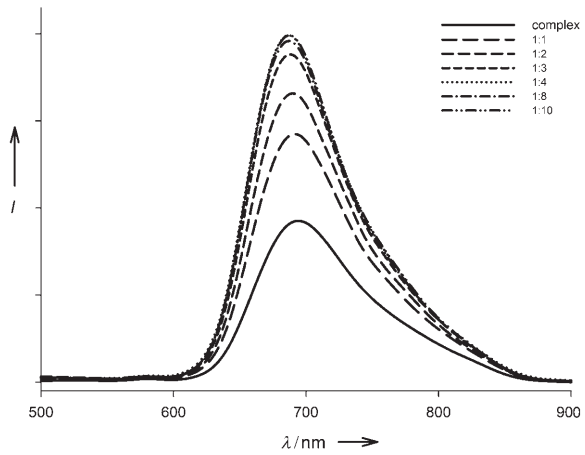

Figure 5. Fluorescence response ($\lambda_{ex} = 485$ nm) of $[Ru_2L_3]Cl_4$ (25 μM complex; 20 mM NaCl; 1 mM aqueous sodium cacodylate buffer) towards calf-thymus DNA. Mixing ratio of metal complex to DNA base is indicated in the graph.

in Table 1. The compound does show cytotoxic activity against these cells; the activities are only 2–5 times lower than those of cisplatin. Indeed the activity is quite striking in view of the noncovalent nature of its interaction with DNA. Interestingly, the compound did not display significant cytotoxicity against human ovarian carcinoma SKOV-3 cells.

Table 1: IC_{50} values (in μM) in breast cancer cell lines.

	HBL100	T47D
$[Ru_2L_3](PF_6)_4$	22	53
cisplatin	4.9	28

A number of ruthenium compounds have attracted interest as antitumor agents.[8–10] Two such compounds (NAMI-A[8] and KP1019[9]) are currently in clinical trials. Like cisplatin, all have chloride ligands that can be replaced to allow coordinative binding to biomolecules. We have previously incorporated such centers within a cylinder design to create unsaturated dinuclear double helicates with high anticancer activity.[13] The cylinder herein is different from these agents in that it is a saturated helicate with no potential for coordinative DNA binding.

The anticancer activity of noncovalent DNA-binding metallodrugs has not been widely studied. Lincoln and Nordén report similar IC_{50} values to those herein[21] for a dinuclear threading metallo-intercalator. The simple tris-(chelate) complex $[Ru(bpy)_3]^{2+}$ (a groove binder) is reported to be inactive, but some related azopyridine- and thiosemicarbazone-containing compounds that can potentially (partially) intercalate DNA do display some activity.[22] Farrell and co-workers recently described a trinuclear platinum compound that binds noncovalently to the phosphate backbone of DNA.[23] This synthetic agent has parallels with the cylinders in that it has an unprecedented mode of binding to DNA. It also shows good activity in cell lines.[24]

Our studies on noncovalent DNA-binding cylinders herein and elsewhere,[6,25] together with the few previous reports detailed above,[22–24] suggest that metallodrugs that bind to DNA by noncovalent interactions, and particularly those with novel DNA-binding modes, have considerable potential as anticancer agents. Since new mechanisms and types of activity are most likely to be discovered by moving away from cisplatin-type paradigms, noncovalent metallodrug designs could prove a fertile ground for discovery.

In summary, we present herein for the first time a diruthenium triple-stranded helicate and demonstrate that it binds and coils DNA. The associated photoresponse makes this compound a valuable addition to the class of DNA-binding supramolecular cylinders, but equally important is the high compound stability that the inert ruthenium(II) centers confer. This stability allows the activity in cells to be unequivocally ascribed to the cylinder and not to its constituent components. Excitingly, the activity of the compound in cell lines is only 2–5 times lower than that of cisplatin even though it has a completely different structure and mode of interaction with DNA. Further detailed DNA-binding and biological studies on these and other cylinders are in progress to understand the activity of these agents more fully.

Experimental Section

$[Ru_2L_3](PF_6)_4$: Ligand L (0.565 g 1.5 mmol) was added dropwise to a stirred, nitrogen-purged solution of *cis*-$[Ru(dmso)_4Cl_2]$ (0.484 g, 1 mmol) in ethylene glycol. The resulting beige-tan reaction mixture was refluxed for 5 days, after which a dark-orange solution was formed. The reaction mixture was cooled to room temperature, filtered through celite, poured into a methanolic solution of concentrated NH_4PF_6, and kept overnight at 4 °C. The resulting precipitate (1.5 g) was filtered, washed with cold methanol/diethyl ether, and dried in vacuo. A small batch of compound (50 mg) was chromatographed on 50 g of neutral alumina Brockman I (Fisher) using as mobile phase a mixture of CH_3CN, H_2O, and KNO_3 (saturated, aqueous) in a ratio of 20:1:1. The compound eluted from the column as a second, orange band. The solution was reduced in volume in vacuo, and the orange material was redissolved in CH_3OH and filtered to remove excess KNO_3. Reprecipitation with NH_4PF_6 afforded an orange compound that was recrystallized from acetonitrile/diethyl ether at 4 °C (1 mg, yield 1% with respect to starting materials). Scaling up the column procedure proved to be unsuccessful, and so multiple small-scale purifications were necessary. Crystals suitable for X-ray diffraction measurements were obtained by slow diffusion of benzene into a solution of complex in acetonitrile. The corresponding chloride complex was obtained by anion metathesis. ^{1}H NMR, $[Ru_2L_3](PF_6)_4$ (400 MHz, CD_3CN, 25 °C): $\delta = 8.71$ (s, 1H, H_{im}), 8.45 (d, $J = 7.7$ Hz, 1H, H3), 8.29 (td, $J = 7.7$, 1.2 Hz, 1H, H4), 7.72 (ddd, $J = 9.0$, 7.2, 1.2 Hz, 1H, H5), 7.65 (d, $J = 5.2$ Hz, 1H, H6), 6.96 (d, $J = 6.5$ Hz, 2H, H_{Ph}), 5.71 (d, $J = 8.2$ Hz, 2H, H_{Ph}), 4.02 ppm (s, 1H, CH_2 spacer); $[Ru_2L_3]Cl_4$ (500 MHz, MeOD, 27 °C): $\delta = 8.98$ (s, 1H, H_{im}), 8.58 (d, $J = 7.7$ Hz,1H, H3), 8.38 (td, $J = 7.7$, 1.1 Hz, 1H, H4), 7.82 (ddd, $J = 8.8$, 6.9, 1.1 Hz, 1H, H5), 7.78 (d, $J =$ 5.1 Hz, 1H, H6), 7.05 (d, $J = 6.9$ Hz, 2H, H_{Ph}), 5.76 (d, $J = 8.4$ Hz, 2H, H_{Ph}), 4.06 ppm (s, 1H, CH_2 spacer); ESI-MS (CH_3CN): m/z (%): 333.1 (100, $[Ru_2L_3]^{4+}$), 492.5 (33, $\{[Ru_2L_3][PF_6]\}^{3+}$), 811.3 (10, $\{[Ru_2L_3][PF_6]_2\}^{2+}$); UV/Vis ($CH_3CN$): λ_{max} [nm] (ε [$M^{-1}cm^{-1}$]): 485 (24200), 445 (17600), 320 (45500), 270 (71300); UV/Vis (H_2O): λ_{max} [nm] (ε [$M^{-1}cm^{-1}$]): 485 (16900), 445 (11800), 320 (25700), 270 (55400); IR (KBr): $\tilde{\nu} = 1591$ (s), 1503 (s), 1386 (m), 1241 (m), 1180 (m), 1160 (m), 1105 (m), 1068 (m), 826 (vs), 787 (s), 649 (m) cm^{-1}.

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