Helical Structures

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Dinuclear Double-Stranded Metallosupramolecular Ruthenium Complexes: Potential Anticancer Drugs**

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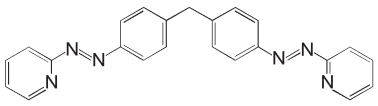
Platinum metallodrugs are among the most effective clinical agents for the treatment of cancer, and three such agents (cisplatin, carboplatin, and oxaliplatin) are in widespread use. These agents are believed to act by binding to DNA and to have similar molecular-level actions.[1] Clinical problems include acquired cisplatin resistance the limited spectrum of cancers that can be treated. To address these issues, alternative metallodrug designs that are distinct from cisplatin and have different molecular-level interactions are being explored. Recently, some ruthenium compounds have been shown to have antitumor[2–4] and antimetastatic[5] actions; two such compounds are currently in clinical trials and have a different spectrum of activity to the platinum drugs.[2,5] Polynuclear drugs in which the metal centers are linked by an alkyl chain have also been designed.[6–8] Some of these show very high activity and overcome both acquired and intrinsic cisplatin resistance as a result of their ability to form long-range inter- and intrastrand DNA cross-links.[6]

Rather than using a flexible alkyl chain to link the metal centers, we were interested in exploring whether activity could be obtained by positioning the metal centers within a more-rigid metallosupramolecular architecture. The architecture would impose the relative spatial positions of the two metal centers and the ligands, and their structural conformations might afford additional effects. Our reasoning was informed by our observations that the external surfaces of metallosupramolecular helicates can impart unprecedented noncovalent DNA-binding properties, such as the recognition of unusual DNA junction structures and remarkable intramolecular DNA coiling effects.[9,10]

In most helicates (such as those used in our previous DNA-binding studies[9,10]), the metal centers are fully coordinated by the helical ligands; these are termed "saturated"[11] helicates. The focus of our design herein is on "unsaturated"[12] helicates, in which there are vacant coordination sites that offer the additional possibility of the metal center interacting directly with DNA. We selected ruthenium, rather than platinum, as our metal center of choice for its higher coordination number and because mononuclear azopyridine ruthenium(II) complexes with two vacant coordination sites have been shown to exhibit cytotoxic activity.[3] There are only a few previous reports of helicates based on ruthenium, and their properties have not been explored.[13] We describe herein three isomeric dinuclear unsaturated ruthenium(II) complexes each with a different double-stranded supramolecular architecture and report their activity in cell lines, thus presenting the first direct biomedical application of metallosupramolecular helical arrays.

The investigated complexes $[Ru_2Cl_4L_2]$ are based on a dinucleating bisazopyridine ligand with a di(4-phenyl)methane spacer (Scheme 1), which is the azo analogue of the bispyridylimine ligand systems[9] whose DNA binding we have previously described. The related mononuclear complexes $[RuCl_2(azpy)_2]$ (azpy = 2-phenylazopyridine) have five possible geometric isomers (three *cis* and two *trans*).[3] Of these, two of the isomers (*cis*–α and *trans*–γ) show the highest cytotoxicities. As shown below, the steric constraints inherent in our bisazopyridine-ligand design are such that these configurations at the metal center are favored in a dinuclear double-stranded array.



Scheme 1. The bisazopyridine ligand (L).

The dinuclear double-stranded ruthenium complexes were synthesized from $[RuCl_2(dmso)_4]$ (dmso = dimethyl

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sulfoxide) and the bisazopyridine ligand (L) in acetone (see the Experimental Section). The crude product that precipitated from the reaction was purified using column chromatography. NMR spectroscopic analysis of the green main product confirmed a single species of high symmetry (a single set of pyridinyl and phenyl resonances), and ESI-mass-spectrometric analysis indicated the desired dinuclear double-stranded formulation. The compound was recrystallized by slow diffusion of diethyl ether into a solution of the product in $CHCl_3$, thus resulting in needle-shaped crystals that proved suitable for X-ray diffraction studies.[14] The molecular structure reveals the compound to be the isomer in which the chlorine ligands at both ruthenium centers are in a *trans* configuration (Figure 1). The constraints of the ligand

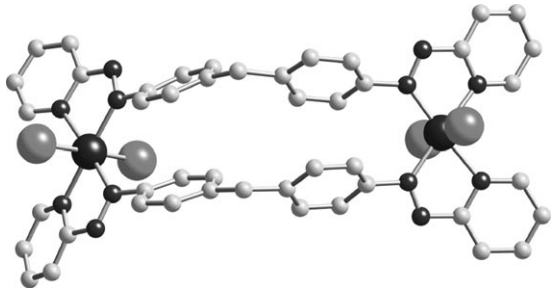

Figure 1. Structure of the metallocyclophane *trans*/*trans* isomer **1**. Hydrogen atoms are omitted for clarity.

structure and the dinuclear double-stranded formulation mean that the pyridine nitrogen atoms and the azo nitrogen atoms are both in *cis* configurations. In accordance with literature nomenclature,[3] this structure is the γγ isomer. The double-stranded compound is not helical, but rather a metallocyclophane. However, this structure is very different from the metallocyclophane box-type architecture seen when this type of ligand system interacts with tetrahedral metal ions.[15] In that system, the ligands are disposed on opposite sides of the metal–metal axis, whereas the ligands are placed side-by-side in this structure. Therefore, the phenyl rings of one strand are located above the rings of the other strand at a distance (centroid–centroid distance: 3.6 Å) and orientation (offset coplanar) consistent with face–face π-stacking interactions. The side-by-side ligand arrangement gives the structure an overall arc shape (see the Supporting Information). The intramolecular Ru−Ru separation is 12.2 Å, which is similar, though slightly longer, than in the related triple-stranded helical dinickel(II) complex (11.6 Å)[16] and the double-stranded helical copper(I) complex (11.1 Å).[15]

Careful column chromatography allowed the isolation of a second green–blue isomer from the reaction mixture. The NMR spectroscopic analysis showed lower symmetry (two sets of pyridinyl and phenyl resonances), and the ESI-mass-spectroscopic analysis indicated the desired dinuclear double-stranded formulation. This isomer was recrystallized by slow diffusion of diethyl ether into a solution of the product in $CHCl_3$. An X-ray diffraction study[14] revealed this species to be the *trans*/*cis*-$[Ru_2Cl_4L_2]$ (**2**) compound (Figure 2). The *trans* metal center is in the γ conformation, as in **1**, whereas

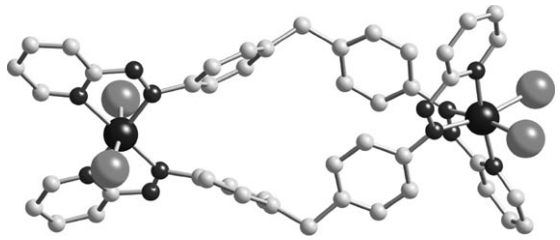

Figure 2. Structure of the double-helical *trans*/*cis* isomer **2.** Hydrogen atoms are omitted for clarity.

the other ruthenium center has the chlorine ligands in a *cis* configuration, the pyridine nitrogen atoms *trans*, and the azo nitrogen atoms *cis*, which corresponds to the α configuration. The two ligand strands are wrapped about the metal–metal axis in a helical fashion. This compound is in fact a completely new class of helical complex, in that it has a dinuclear double-helical structure, but the chiral twist is induced by just one of the two metal centers (the *cis*–α center). Proton–proton interactions between the pyridine units do lead to a small chiral twist at the *trans* center (similar to the distortions observed in palladium bipyridine complexes),[17] but to a first approximation the ligands are coplanar at the *trans* center.[18] The intramolecular Ru−Ru distance of 12.5 Å is similar to that in the *trans*/*trans* isomer.

We have, on one occasion, observed conversion of a sample of **2** into a third isomer **3** on standing in a solution of $CHCl_3$. The conversion was revealed by a dramatic color change from green–blue to blue. NMR spectroscopic analysis confirmed a single species of high symmetry (a single set of pyridinyl and phenyl resonances), and the ESI-mass-spectrometric analysis again indicated a dinuclear double-stranded formulation. This sample was recrystallized by diffusion of diethyl ether into a solution of the product in $CHCl_3$, and a few crystals were isolated and an X-ray structural determination undertaken.[14]

The molecular structure of **3** shows the two chlorine ligands on both ruthenium centers to be in a *cis* configuration (Figure 3). These *cis* ruthenium(II) centers have the same α configuration as that seen for the *cis* center in **2**. The two ligand strands are again wrapped about each other in a double-helical fashion. This structure thus has a more conventional unsaturated double-helical structure with both

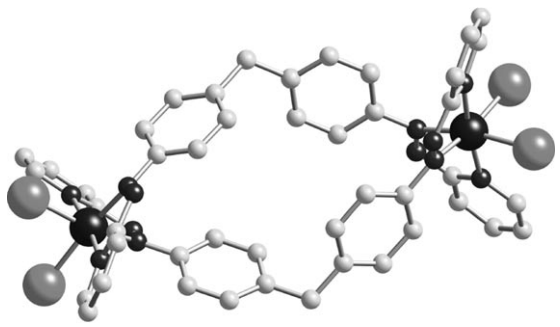

Figure 3. Structure of the double-helical *cis*/*cis* isomer **3.** Hydrogen atoms are omitted for clarity.

metal centers of the same chirality. As would be expected, the two centers cause more extensive ligand wrapping in **3** than **2**. The intramolecular Ru···Ru separation of 12.1 Å is again similar to that in the other isomers.

In these three isomers, only the *cis*–α and *trans*–γ configurations of the metal centers are observed. The azo nitrogen atoms must lie *cis* to create a dinuclear double-stranded array, and this requirement decreases the number of potential configurations to *cis*–α, *cis*–β, or *trans*–γ. Although dinuclear double-stranded species are likely to be intermediates in the assembly of triple-stranded helicates, the addition of a third ligand strand to the three isomers characterized herein would require considerable rearrangement (at the metal center and of ligands) to generate *cis*–β configurations. The diphenylmethane spacer units of the two ligand strands would be forced closer in space by the *cis*–β configuration: previous unsaturated helicates also contain *cis*–α configurations.[12]

In view of the cytotoxicity of the mononuclear counterparts, these dinuclear compounds have been tested on human-breast-tumor HBL100 and T47D cell lines. Two isomers have been tested (the third isomer was not available in suitable quantities), and the IC_{50} data are shown in Table 1. Both

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

	HBL100	T47D
cisplatin	4.9	28.3
1	0.16	0.29
2	5.1	6.7

compounds are very active against these cell lines: The *cis*/*trans* isomer **2** has similar activity to cisplatin in the HBL100 cell lines and better activity in the T47D cell lines, whereas the *trans*/*trans* isomer **1** shows extremely high activity, with approximately 30 times more potency than cisplatin in the HBL100 cell lines and 100 times more in the T47D cell lines. The activity is in the same range as the mononuclear counterparts tested on other cell lines. Interestingly, mononuclear $[RuCl_2(azpy)_2]$ shows higher activity for the γ isomer (0.02–0.2 μM in a panel of cell lines, but different from those herein) than the α isomer (0.06–0.5 μM).[3] The same trend is seen herein as the *trans*/*trans* species being more active than the *cis*/*trans* isomer.

The isomeric dinuclear $[Ru_2Cl_4L_2]$ complexes reported herein are among the first, and to date the most promising, dinuclear ruthenium anticancer agents. The IC_{50} values compare very favorably with those of previously reported dinuclear ruthenium complexes. The dinuclear complexes derived from the new antitumour metastasis inhibitor A (NAMI-A) do not show direct cytotoxicity[19] (just as NAMI-A does not). Compounds in which two $[Ru(phen)_2dppz]^{2+}$ (dppz = dipyridophenazine, phen = phenyl) moieties are joined through long alkane linkers show IC_{50} values that range from 8 to 45 μM,[7] whereas a bisruthenium organometallic compound has a reported IC_{50} value of 5 μM.[8]

In summary, the three compounds reported herein represent a new set of dinuclear coordination isomers, each of which have quite different supramolecular architectures. The three isomers comprise an arc-shaped nonhelical metallocyclophane, an unsaturated conventional double helicate, and a new type of double helicate, in which just one of the two metal centers is responsible for imparting helicity to the ligand strands. The ability to isolate a range of different architectures of the same nuclearity from a single metal–ligand combination makes this a particularly remarkable system. Moreover, these compounds are the first compounds to bridge the fields of metallosupramolecular architecture and anticancer drug design. The initial cell-line experiments indicate that the compounds show very good activity. Further biological studies are in progress to fully understand the activity and DNA binding of this new class of complex.

Experimental Section

trans/*trans*-$[Ru_2Cl_4L_2]$ (**1**): A mixture of $[RuCl_2(dmso)_4]$ (0.150 g, 0.31 mmol) and the bispyridylazo ligand L (0.117 g, 0.31 mmol) in acetone (75 mL) was heated under reflux for 16 h. The green precipitate that formed was isolated by filtration and washed with a little acetone and diethyl ether to afford 110 mg of the crude product, which consisted of the desired product and insoluble polymeric material. The filtrate was reduced to half volume and treated with diethyl ether to afford a second precipitate, which was isolated, washed with diethyl ether, and purified as below to afford **2**. The first precipitate was purified by column chromatography on alumina with dichloromethane/acetonitrile (1:1) as the eluent. The first fraction was collected, and NMR spectroscopy showed a single compound **1** (yield = 10 mg). (3%) ESI MS: *m*/*z* 1097 $[Ru_2Cl_3L_2(MeOH)]^+$, 1143 $[Ru_2Cl_3L_2(dmso)]^+$, 1065 $[Ru_2Cl_3L_2]^+$; ^{1}H NMR (500 MHz, [D$_6$]DMSO): $\delta = 9.07$ (1H, d, $J = 5.6$ Hz, 6py), 8.76 (1H, d, $J = 7.7$ Hz, 3py), 8.43 (1H, t, $J = 7.7$ Hz, 4py), 8.04 (1H, br t, $J = 6.0$ Hz, 5py), 7.24 (2H, d, $J = 8.2$ Hz, Ph^a), (2H, d, $J = 8.4$ Hz, Ph^b), 4.32 ppm (2H, s, CH_2); UV/Vis ($CHCl_3$) λ_{max}: 642, 430, 304 nm.

trans/*cis*-$[Ru_2Cl_4L_2]$ (**2**): The second precipitate (18 mg), obtained from the filtrate of **1**, was purified by column chromatography on alumina with acetonitrile/dichloromethane (1:3) as the eluent. The second fraction was collected, and NMR spectroscopy showed a single compound **2** (yield = 3 mg). (1% with respect to starting materials) ESI MS: *m*/*z* 1097 $[Ru_2Cl_3L_2(MeOH)]^+$, 1143 $[Ru_2Cl_3L_2(dmso)]^+$, 1065 $[Ru_2Cl_3L_2]^+$; ^{1}H NMR (500 MHz, [D$_6$]DMSO; prime numbering is used for the *cis*–α segment): $\delta = 9.59$ (1H, d, $J = 5.6$ Hz, 6py′), 9.15 (1H, d, $J = 5.6$ Hz, 6py), 8.76 (1H, d, $J = 7.8$ Hz, 3py′), 8.67 (1H, d, $J = 7.6$ Hz, 3py), 8.40 (1H, t, $J = 7.7$ Hz, 4py), 8.36 (1H, t, $J = 7.8$ Hz, 4py′), 8.0 (2H, m, 5py + 5py′), 7.95 (2H, d, $J = 8.5$ Hz, Ph^a), 7.12 (2H, d, $J = 8.5$ Hz, Ph^b), 6.43 (2H, d, $J = 8.5$ Hz, Ph$^{b\prime}$), 6.25 (2H, d, $J = 8.5$ Hz, Ph$^{a\prime}$), 3.84 (1H, d, $J = 16.0$ Hz, CH_2), 3.79 ppm (1H, d, $J = 16.0$ Hz, CH_2); UV/Vis ($CHCl_3$) λ_{max}: 601, 389, 349 nm.

cis/*cis*-$[Ru_2Cl_4L_2]$ (**3**): An sample of **2** in $CDCl_3$ in an NMR tube changed color from green–blue to blue on standing. ESI MS: *m*/*z* 1125 $[Ru_2L_2Cl_4 + Na]^+$, 1148 $[Ru_2L_2Cl_4 + 2Na]^+$, 1099 $[Ru_2L_2Cl_3(MeOH)]^+$; ^{1}H NMR (500 MHz, [D$_6$]DMSO): $\delta = 9.35$ (1H, d, $J = 5.9$ Hz, 6py), 8.76 (1H, d, $J = 8.4$ Hz, 3py), 8.30 (1H, t, $J = 7.7$ Hz, 4py), 7.85 (1H, br t, $J = 7.0$ Hz, 5py), 6.68 (2H, d, $J = 8.4$ Hz, Ph^b), 6.46 (2H, d, $J = 8.6$ Hz, Ph^a), 3.72 ppm (2H, s, CH_2).

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[14] a) Crystal data for **1** (*trans*/*trans*): $C_{46}H_{36}Cl_4N_{12}Ru_2 \cdot 2\,CHCl_3 \cdot 2\,H_2O$; $M_r = 1375.58$; $T = 296(2)$ K, $\lambda = 1.54178$ Å; monoclinic; space group $C2/c$, $a = 34.6167(11)$, $b = 11.2147(4)$, $c = 15.9881(5)$ Å, $\beta = 91.166(2)°$; $V = 6205.5(4)$ Å^3; $Z = 4$; Dc = 1.472 Mg m^{-3}; $\mu = 8.278$ mm^{-1}; crystal size $= 0.50 \times 0.04 \times 0.04$ mm^3; θ range for data collection: 4.97–70.64°; 19343 reflections collected; 5638 reflections unique ($R_{int} = 0.077$); absorption correction: semiempirical from equivalents; max. and min. transmission: 0.733 and 0.104; 337 parameters; final R indices: ($I > 2\sigma(I)$): $R1 = 0.0580$, $wR2 = 0.1530$; largest diff. peak and hole: 0.968 and −0.771 e Å^{-3}; riding model for hydrogen atoms except those for disordered water positions, which are not included. b) Crystal data for **2** (*trans*/*cis*): $C_{46}H_{36}Cl_4N_{12}Ru_2 \cdot 4.5\,CHCl_3$; $M_r = 1637.9$; $T = 200(2)$ K; $\lambda = 1.54178$ Å; triclinic; space group $P\bar{1}$, $a = 13.5414(5)$, $b = 20.8960(6)$, $c = 24.5813(9)$ Å, $\alpha = 94.338(2)$, $\beta = 94.386(2)$, $\gamma = 95.160(2)°$; $V = 6883.2(4)$ Å^3; $Z = 4$; Dc = 1.581 Mg m^{-3}; $\mu = 10.161$ mm^{-1}; crystal size $= 0.24 \times 0.24 \times 0.06$ mm^3; θ range for data collection: 2.68–60.88°; 35195 reflections collected; 16611 reflections unique ($R_{int} = 0.121$); absorption correction: semiempirical from equivalents; max. and min. transmission: 0.958 and 0.069; 1428 parameters; final R indices: ($I > 2\sigma(I)$): $R1 = 0.0795$, $wR2 = 0.1985$; largest diff. peak and hole: 1.77 and −1.20 e Å^{-3}; riding model for hydrogen atoms. Solvent positions are disordered, ADPs and geometry were restrained (366 restraints). c) Crystal data for **3** (*cic*–*cis*): $C_{46}H_{36}Cl_4N_{12}Ru_2 \cdot 2.5\,CHCl_3 \cdot 5\,H_2O$; $M_r = 1481.75$; $T = 200(2)$ K, $\lambda = 1.54178$ Å; monoclinic; space group $C2/c$, $a = 16.5258(5)$, $b = 17.4447(5)$, $c = 25.3085(8)$ Å, $\beta = 105.3280(10)°$; $V = 7036.6(4)$ Å^3; $Z = 4$; Dc = 1.399 Mg m^{-3}; $\mu = 7.887$ mm^{-1}; crystal size $= 0.30 \times 0.28 \times 0.14$ mm^3; θ range for data collection: 3.62–70.59°; 22137 reflections collected; 6099 reflections unique ($R_{int} = 0.071$); absorption correction: semiempirical from equivalents; max. and min. transmission: 0.8798 and 0.1027; 438 parameters; final R indices: ($I > 2\sigma(I)$): $R1 = 0.0773$, $wR2 = 0.2362$; largest diff. peak and hole: 1.65 and −1.44 e Å^{-3}; riding model for hydrogen atoms. Solvent/water positions are disordered, ADPs and geometry were restrained (60 restraints), water hydrogen atoms for disordered water positions were not included in the refinement. d) Data were recorded on a Bruker Smart 6000 CCD diffractometer using $Cu_{K\alpha}$ radiation. Structure solution was by direct methods using SIR92 (A. Altomare, G. Cascarano, C. Giacovazzo, A. Guagliardi, *J. Appl. Crystallogr.* **1993**, *26*, 343 – 350) and refinement was by full-matrix least-squares on F^2 using SHELXL97 (G. M. Sheldrick, SHELX97, Program for Crystal Structure refinement, University of Göttingen, Germany, **1997**). CCDC-603390–603392 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.

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[18] In fact, in the crystal structure, the twist at the *trans* center is of the opposite helicity to that of the *cis* center, but the twist is so small that it does not affect the double-helical wrapping of the two ligands; the same effect is seen in the *trans*/*trans* isomer, in which the two *trans* centers have the same helicity but do not induce ligand–strand helical wrapping.

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