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Synthesis and characterization of ruthenium(II) complexes with the new ligand 2-phenylazopyridine-5-sulfonic acid (Hsazpy): in search for new anticancer agents

Anna C. G. Hotze,†[a] Huub Kooijman,[b] Anthony L. Spek,[b] Jaap G. Haasnoot[a] and Jan Reedijk*[a]

[a] *Leiden Institute of Chemistry, Gorlaeus Laboratories, Leiden University, P.O. Box 9502, 2300 RA, Leiden, The Netherlands. E-mail: reedijk@chem.leidenuniv.nl; Fax: +31-715274671*

[b] *Bijvoet Center for Biomolecular Research, Crystal and Structural Chemistry, Utrecht University, Padualaan 8, 3584 CH, Utrecht, The Netherlands*

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Isomers of dichlorobis(2-phenylazopyridine)ruthenium(II) [$Ru(azpy)_2Cl_2$], especially the so-called α isomer, display remarkably high cytotoxicities against human tumor cell lines. Unfortunately, the parent [$Ru(azpy)_2Cl_2$] compounds are poorly water-soluble. In this paper the synthesis and characterization of the new water-soluble ligand 2-phenylazopyridine-5-sulfonic acid (Hsazpy) is described. Use of this ligand in reaction with $RuCl_3$ gave two isomers, which were isolated as α- and β-[$NEt_4]_2[Ru(sazpy)_2Cl_2$]. The compounds have been fully characterized by (2D) NMR spectroscopy. The molecular structure of the α isomer of [$NEt_4]_2[Ru(sazpy)_2Cl_2]\cdot 2H_2O$ has been determined by single-crystal structure analysis. The packing in the crystal structure of α-[$NEt_4]_2[Ru(sazpy)_2Cl_2]\cdot 2H_2O$ shows an interesting hydrogen-bonding pattern in which two water molecules are involved. One water molecule bridges between a Cl ligand and a SO_3^- group within one ruthenium moiety, the other water molecule forms a bridge between two SO_3^- groups from two different ruthenium centers, resulting in a chain-like structure. Preliminary evaluation of the cytotoxicity by means of the IC_{50} value in A2780 cell line classifies α-[$NEt_4]_2[Ru(sazpy)_2Cl_2$] as non-toxic, but this does not rule out other anticancer activities.

Introduction

Since the discovery of the antitumor activity of cisplatin (*cis*-diaminedichloroplatinum(II), *cis*-[$PtCl_2(NH_3)_2$], many other metal complexes have been investigated for their possible application as antitumor drugs.[1–3] At present several ruthenium complexes are known for their cytotoxic or antitumor activity.[1] For example, complexes such as *trans*-[(H_2ind)-$[Ru^{III}Cl_4(Hind)_2]$ (Hind = indazole), *mer*-[Ru(terpy)Cl_3] (terpy = 2,2′:6′,6″-terpyridine), and [$Ru^{IV}(H_2chd)Cl_2$] (chd = 1,2-cyclohexanediamine tetraacetate) have been reported to be highly antitumor-active.[1] Recently, some Ru(II) arene complexes have also been reported, which show *in vitro* inhibition of cancer cell growth and *in vivo* antitumor activity.[4,5]

The isomeric dichlorobis(2-phenylazopyridine)ruthenium(II) compounds are under renewed investigation due to their shown cytotoxicity for several human tumor cell lines.[6] As the ligand 2-phenylazopyridine is an asymmetric ligand, the moiety [$Ru(azpy)_2Cl_2$] can in theory exist in 5 different isomeric forms of which three isomers are the most common ones (see Fig. 1).[7,8] The so-called α-isomer (α indicating the coordinating chlorides, the pyridine nitrogens and azo nitrogens in mutual cis, trans and cis orientations) of the dichlorobis(2-phenylazopyridine)ruthenium(II) complexes, α-[$Ru(azpy)_2Cl_2$], has shown a remarkable high *in vitro* cytotoxicity.[6] Unfortunately, this compound is not water-soluble (one of the requirements for further biological testing). Recently, the water-soluble compound α-[$Ru(azpy)_2(NO_3)_2$] has been developed, but its cytotoxicity compared to the dichloro analog was decreased by approximately a factor of 10.[9] In addition, replacing the Cl ligands of α-[$Ru(azpy)_2Cl_2$] by carboxylate ligands resulted in water-soluble compounds, but these complexes are also less cytotoxic than the parent dichloro complex.[10] For this reason it was attempted to increase the water solubility of α-[$Ru(azpy)_2Cl_2$] by replacing the azpy ligand by a water-soluble derivative. Water-soluble azpy ligands (Fig. 2) containing, for example NH_2, NO_2, OH or COOH substituents, are known in the literature, but only derivatives of bis(2-phenylazopyridine)-ruthenium(II) compounds with NH_2 and NO_2 substituents on the azpy ligand have been reported.[11,12] As it is known that sulfonic acid groups attached to polypyridyl ligands increase the water solubility, the new ligand 2-phenylazopyridine-5-sulfonic acid (Hsazpy, shown in Fig. 2) has been synthesized and used for the synthesis of the corresponding dichlorobis-(Hsazpy)ruthenium(II) complexes. The only previous example

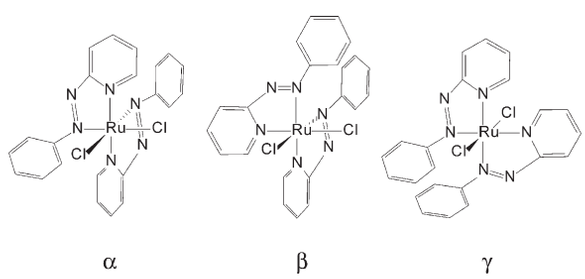

Fig. 1 Schematic representation of the three most common isomers of the [$Ru(azpy)_2Cl_2$] complexes: the α isomer with the coordinating pairs N_{py} trans, N_{azo} cis and Cl cis (left), the β isomer with the coordinating pairs N_{py} cis, N_{azo} cis and Cl cis (middle) and the γ isomer with the coordination pairs N_{py} cis, N_{azo} cis and Cl trans (right).

† Current address: Bijvoet Center for Biomolecular Research, Crystal and Structural Chemistry, Utrecht University, Padualaan 8, 3584 CH, Utrecht, The Netherlands.

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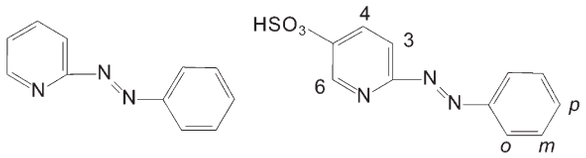

Fig. 2 Schematic representation of the 2-phenylazopyridine (azpy) and 2-phenylazopyridine-5-sulfonic acid (Hsazpy) ligands, with numbering used for the NMR assignments.

of a molecular structure for a sulfonic acid group attached to a polypyridyl ligand containing the azo functionality has been reported in the case of a nickel compound.[13]

Two isomers, α- and β-$[NEt_4]_2[Ru(sazpy)_2Cl_2]$ (sazpy is the anionic form of the 2-phenylazopyridine-5-sulfonic acid ligand), have been obtained pure and have been characterized by NMR spectroscopy. The molecular structure of α-$[NEt_4]_2[Ru(sazpy)_2Cl_2]$ has been determined by single-crystal X-ray diffraction analysis.

Results and discussion

Synthetic considerations and general information

Upon reaction of $RuCl_3$ and azpy in methanol the γ isomer of $[Ru(azpy)_2Cl_2]$ is easily obtained as this isomer precipitates as the main product (containing also small amounts of the δ isomer).[7,8,14,15] The α and β isomers are also formed, but remain in solution.[7,8,14] Synthetic procedures have been developed to convert the γ-$[Ru(azpy)_2Cl_2]$ isomer into the corresponding α and β isomers.[7,8,14]

Unfortunately, after reaction of $RuCl_3$ and the ligand Hsazpy the crude mixture consists of three isomers of $[Ru(Hsazpy)_2Cl_2]$ in a ratio of α:β:γ = 1:1.2:0.13, which all remain in solution (the isomers have been identified by NMR, *vide infra*). To separate and purify this crude mixture several column materials and solvents have been tried, but in most of the cases the compounds remained on top of the column, probably due to interaction of the compounds with the column material. Using a basic alumina column and eluting first only with methanol a green fraction, most likely the γ isomer, separated from the α and β isomers. However, this isomer was not obtained in quantities sufficient enough to allow its isolation and characterization. The mixture of α and β isomers could be obtained from the column by eluting with a tetraethylammonium chloride solution. Fractional recrystallization finally allowed separation of the α and β isomers. Sulfonic acids are easily ionized, which makes it difficult, but not impossible, to observe neutral sulfonic acids rather than the anionic form.[16] The IR spectrum of 2-phenylazopyridine-5-sulfonic acid shows a signal at 2625 cm^{-1}, assigned to the $\nu(SO_3H)$ vibration. Important to note is the fact that by using basic alumina, the sulfonic acid group of the ligand is ionized and the compound was isolated with the counter ions $[NEt_4]^+$, as shown in the crystal structure (*vide infra*). The absence of the O–H vibration in the IR spectrum of α-$[NEt_4]_2[Ru(sazpy)_2Cl_2]$ confirms the ionization of the sulfonic acid group. As anticipated the compound α-$[NEt_4]_2[Ru(sazpy)_2Cl_2]$ shows a good water solubility (>1 mg ml^{-1}).

X-Ray structure determination

A projection of the molecular structure of α-$[NEt_4]_2[Ru(sazpy)_2Cl_2]$ (**2**) is shown in Fig. 3 and selected bond distances and angles are listed in Table 1. If the coordination pairs Cl, N_{py} and N_{azo} are considered in that order, the configuration of **2** is cis, trans, cis (α = ctc). The presence of two $[NEt_4]^+$ ions indicates the sazpy ligand to be ionized. The structure contains further two lattice water molecules per ruthenium

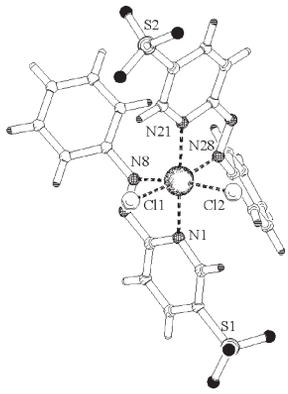

Fig. 3 Molecular structure of **2**.

molecule. The Ru–N_{py} and Ru–N_{azo} distances are comparable to those in similar structures.[9,17] The angle Cl(1)–Ru–Cl(2) [90.93(9)°] is also similar to this angle in the related α-$[Ru(azpy)_2Cl_2]$ (89.44°). The bite angles N(1)–Ru–N(8) and N(21)–Ru–N(28) of respectively 77.3(3)° and 77.0(3)° reveal a considerable distortion of the octahedron, as was found for the complexes α-$[Ru(azpy)_2Cl_2]$ and α-$[Ru(azpy)_2(NO_3)_2]$.[9,17]

The co-crystallized water molecules contribute to an interesting hydrogen-bonding pattern. One of the water molecules bridges between two sulfonate groups of two ruthenium centers, forming an infinite chain-like structure parallel to the crystallographic *b* axis; [O(40)–H(40A)···O(1) (x, $1+y$, z) with D···A = 2.841(13) Å and O(40)–H(40B)···O(3) ($1-x$, $\frac{1}{2}+y$, $1-z$) with D···A = 2.963(13) Å]. The other water molecule forms a bridge between a Cl^- ligand and the SO_3^- group [O(50)–H(50A)···O(6) ($x-1$, y, z) with D···A = 2.867(12) Å and O(50)–H(50B)···Cl(1) ($x-1$, y, z) with D···A = 3.357(10) Å] within one ruthenium complex (see Fig. 4).

NMR characterization

The ^1H NMR spectrum in acetone-d_6 of the crude product obtained from the reaction mixture directly after the reaction of $RuCl_3$ and Hsazpy shows three singlets at low field, at 10.17, 10.10 and 9.82 ppm. It is known that the different isomers of $[Ru(azpy)_2Cl_2]$ show distinct signals in NMR and especially the H6 signal is used to recognize the particular isomer.[15] In general, the H6 resonances of the $[Ru(azpy)_2Cl_2]$ isomers appear at lowest field compared to the other pyridine resonances. Moreover, from the synthesis of the $[Ru(azpy)_2Cl_2]$ isomers from $RuCl_3$ and azpy it is known that the α, β and γ isomers appear as main isomers and the δ isomer only accounts for 5%. Consequently, the three clearly separated singlets at 10.17, 10.10 and 9.82 ppm, present in the ^1H NMR

Table 1 Selected bond distances (Å) and angles (°) of **2**

Ru(1)–Cl(1)	2.410(2)	Cl(1)–Ru(1)–Cl(2)	90.93(9)
Ru(1)–Cl(2)	2.393(2)	Cl(1)–Ru(1)–N(1)	89.2(3)
Ru(1)–N(1)	2.032(7)	Cl(1)–Ru(1)–N(8)	88.0(2)
Ru(1)–N(8)	2.011(7)	Cl(1)–Ru(1)–N(21)	94.0(3)
Ru(1)–N(21)	2.057(7)	Cl(1)–Ru(1)–N(28)	171.0(2)
Ru(1)–N(28)	1.981(7)	Cl(2)–Ru(1)–N(1)	95.3(3)
S(1)–O(1)	1.447(8)	Cl(2)–Ru(1)–N(8)	172.5(2)
S(1)–O(2)	1.430(8)	Cl(2)–Ru(1)–N(21)	84.4(3)
S(1)–O(3)	1.432(8)	Cl(2)–Ru(1)–N(28)	88.3(2)
S(1)–C(5)	1.790(10)	N(1)–Ru(1)–N(8)	77.3(3)
S(2)–O(4)	1.433(8)	N(1)–Ru(1)–N(21)	176.8(3)
S(2)–O(5)	1.450(10)	N(1)–Ru(1)–N(28)	99.8(3)
S(2)–O(6)	1.465(9)	N(8)–Ru(1)–N(21)	103.1(3)
N(7)–N(8)	1.287(10)	N(8)–Ru(1)–N(28)	94.0(3)
N(27)–N(28)	1.287(12)	N(21)–Ru(1)–N(28)	77.0(3)

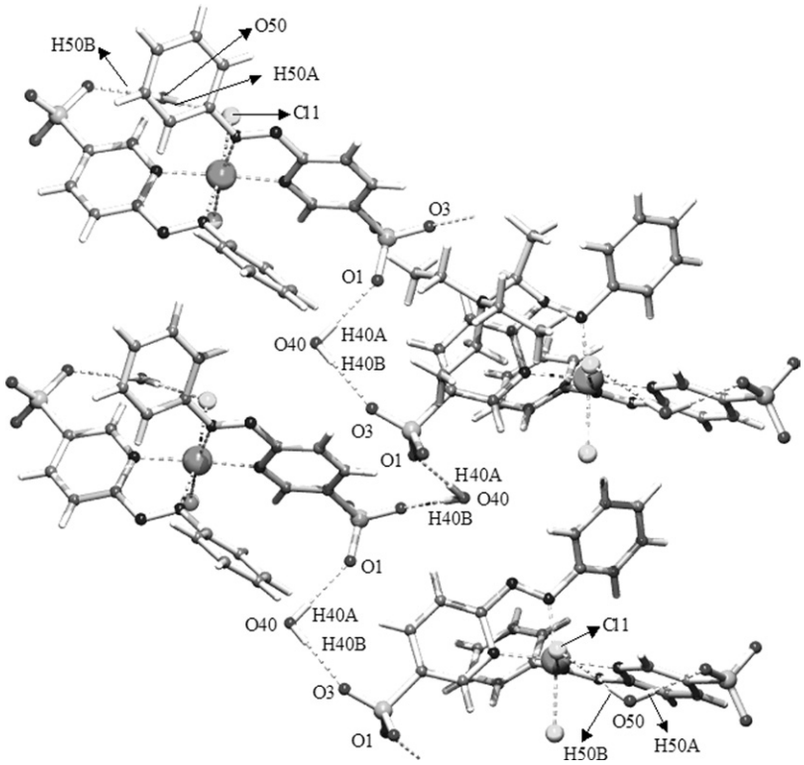

Fig. 4 Hydrogen-bonding pattern in the crystal lattice of α-$[NEt_4]_2[Ru(sazpy)_2Cl_2]\cdot 2H_2O$. One of the water molecules bridges two sulfonate groups of two ruthenium centers, forming an infinite chain-like structure, parallel to the crystallographic *b* axis. The other water molecule forms a bridge between a Cl ligand and the SO_3^- group within one ruthenium complex.

spectrum of the crude reaction mixture $[Ru(Hsazpy)_2Cl_2]$, are assumed to correspond to the H6 resonances of the α, β and γ isomers of $[Ru(Hsazpy)_2Cl_2]$. The identification of the three isomers in NMR has been done by NMR spectroscopy of several recrystallized fractions containing the three isomers in different ratios and using the NMR spectra of the pure α- and β-$[NEt_4]_2[Ru(sazpy)_2Cl_2]$ (*vide infra*). As stated above, the γ isomer could not be isolated and characterized.

The ^{1}H NMR spectra of α- and β-$[NEt_4]_2[Ru(sazpy)_2Cl_2]$ are depicted in Fig. 5. The α isomer shows only one set of signals due to the C_2 axis present in the compound. Three signals are observed belonging to the pyridine H6 (doublet with small ^4J coupling), H3 and H4 atoms and three phenyl signals for the ortho, meta and para resonances. 2D COSY NMR and 2D NOESY NMR spectroscopy has been used to assign all signals. In the case of α-$[NEt_4]_2[Ru(sazpy)_2Cl_2]$ NOESY NMR shows a strong NOE cross peak between the H6 and ortho hydrogen resonances. It has already been mentioned that this H6-ortho NOE cross peak indicates the α isomer of the $[Ru(azpy)_2Cl_2]$ complexes.[9,15] Moreover, the α configuration has been unambiguously proven by the X-ray structure determination (*vide supra*). The ^{1}H NMR spectrum of β-$[NEt_4]_2[Ru(sazpy)_2Cl_2]$ shows twice the number of signals, as this isomer has no C_2 axis, which results in two inequivalent azpy ligands. From all 5 theoretically possible isomers only the beta isomer has no C_2 axis; so already from this ^{1}H NMR spectrum the configuration has been proven. The appearance of the NOE cross peak between the two ortho resonances provides further evidence for the β configuration, as this NOE interaction is also observed in the case[15] of β-$[Ru(azpy)_2Cl_2]$. The NOE cross peak between the H6 and H6′ resonances, which has also been used to indicate the β isomer, is not observed in the 2D NOESY spectrum of β-$[NEt_4]_2[Ru(sazpy)_2Cl_2]$, probably because these H6 resonances are somewhat broadened. The origin for this broadening is not clear as yet.

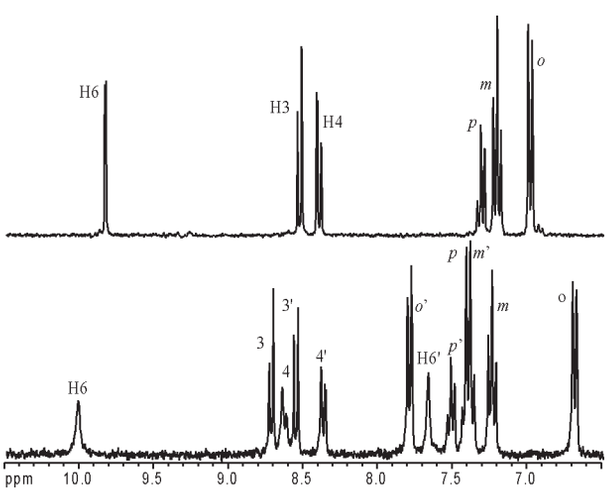

Fig. 5 ^{1}H NMR spectra of the (upper) α and (lower) β isomers of $[NEt_4]_2[Ru(sazpy)_2Cl_2]$ in MeOD.

Cytotoxicity

The cytotoxicity of α-$[NEt_4]_2[Ru(sazpy)_2Cl_2]$ has been determined and compared with the activity of the related and highly cytotoxic α-$[Ru(azpy)_2Cl_2]$. The cytotoxicity has been evaluated by means of IC_{50} values (the concentration of the drug required to reduce cellular growth by 50%) in the human ovarium carcinoma cell lines A2780 and A2780CisR (a cisplatin-resistant cell line). The IC_{50} values of α-$[NEt_4]_2[Ru(sazpy)_2Cl_2]$ in A2780 and A2780CisR are respectively 112 and 149 μM which, in comparison to the IC_{50} value of *ca.* 0.9 μM in both cell lines for α-$[Ru(azpy)_2Cl_2]$, classifies the compound as non-cytotoxic. Cytotoxicity data are not the only parameter to identify a potential anticancer agent, as for example the first ruthenium compound in clinical trials, NAMI-A, is also devoid of any cytotoxic effect, but appears to be a promising

antimetastatic agent.[18] So additional biological experiments are required for understanding the origin for the activity, or absence of activity, of bis(2-phenylazopyridine) ruthenium(II) complexes and its derivatives.

Concluding remarks

In this work the synthesis and characterization of the new water-soluble ligand 2-phenylazopyridine-5-sulfonic acid (Hsazpy) and the corresponding ruthenium(II) compounds, isolated as $[NEt_4]_2[Ru(sazpy)Cl_2]$ salts, have been described. The α and β isomers have been obtained pure and have been characterized by NMR spectroscopy, which showed once more the usefulness of NMR for the characterization of isomeric azpy-like complexes. The packing in the crystal structure of α-$[NEt_4]_2[Ru(sazpy)_2Cl_2]$ showed the incorporation of two water molecules, one forming a bridge between two acceptors within the Ru moiety, the other linking the Ru moieties into an infinite chain parallel to the crystallographic *b* axis. The IC_{50} values of α-$[NEt_4]_2[Ru(sazpy)_2Cl_2]$ against the human ovarium carcinoma cell lines A2780 and A2780cisR exceed 100 μM, which identifies the compound as being non-cytotoxic. For a better understanding of the reason for the absence of cytotoxicity for these compounds, more biological experiments are required.

Experimental

General

^{1}H NMR spectra were recorded on a Bruker 300 DPX spectrometer. Spectra were recorded in MeOD and calibrated on the residual solvent peak. Elemental analyses (C, H and N) were carried out on a Perkin Elmer 2400 CHNS analyzer. Mass spectra were obtained by the chemical services of the Gorlaeus Laboratories with a Finnigan MAT 900 instrument equipped with an electrospray ionization (ESI) interface.

Hydrated $RuCl_3$ was used as received from Johnson and Matthey, Inc. Basic aluminium oxide (alumina Woelm B Super I) was used. The synthesis of 2-aminopyridine-5-sulfonic acid was performed as described in the literature.[19] The synthesis of the ligand 2-phenylazopyridine-5-sulfonic acid from nitrosobenzene and 2-aminopyridine-5-sulfonic acid was performed as a modification of the synthesis of 2-phenylazopyridine.[8]

The synthesis of the crude mixture of isomers of the dichlorobis(2-phenylazopyridine-5-sulfonic acid)ruthenium(II) complexes was done analogously to the synthesis of the crude product of the $[Ru(azpy)_2Cl_2]$ complexes, as described in the literature.[7,8] The isolation of the pure isomers required more complicated purification steps than described for the $[Ru(azpy)_2Cl_2]$ complexes and will be discussed below.

Syntheses

2-Phenylazopyridine-5-sulfonic acid (Hsazpy), 1. 2-Aminopyridine-5-sulfonic acid (5.0 g, 0.029 mol) was added to a solution of 13.5 g NaOH in 13.5 ml of water containing 1.8 ml of benzene. The solution was heated up to 100 °C and nitrosobenzene (3.2 g, 0.030 mol) was added over a 20 min period. The mixture was stirred and heated under reflux for 30 min. The mixture was cooled in ice and the precipitate was isolated by filtration. The compound was dissolved in diluted hydrochloric acid (1:1), a black residue was filtrated and benzene was added to the filtrate in order to dissolve unreacted nitrosobenzene. A precipitate was formed in the water layer, which was collected by filtration. Yield 1.05 g (14%). ESI-MS: m/z 264 $[M+H]^+$. IR (CsI): $\nu(SO_2$–OH), 2625, $\nu(SO_3$ asym stretch) 1216, $\nu(SO_3$ sym stretch) 1042. ^{1}H NMR (300 MHz, MeOD): δ 9.10 (d, H6), 8.88 (d, H4), 8.35 (d, H3), 8.14 (d, *o*), 7.21 (m, $m+p$).

$[NEt_4][Ru(sazpy)_2Cl_2]\cdot 2H_2O$. $RuCl_3\cdot 3H_2O$ (0.187 g, 0.72 mmol) was dissolved in 21 ml of methanol and N_2 gas was bubbled through for 15 min. The ligand 2-phenylazopyridine-5-sulfonic acid (0.42 g, 1.6 mmol) dissolved in 25 ml of methanol was added and the mixture was heated under reflux for 16 h. The solution was concentrated and purified over alumina (basic alumina, diameter 2 cm, length 17 cm). The first green fraction was separated by eluting with methanol, but not isolated. A blue fraction remained on top. By eluting with a tetraethylammonium chloride solution in methanol the blue fraction was obtained. The solution was concentrated by rotary evaporation and diethyl ether (1:1) was added slowly dropwise. After standing for 48 h blue crystals of α-$[NEt_4]_2[Ru(sazpy)_2Cl_2]$ appeared, suitable for X-ray analysis. Yield 48 mg (8%). From the filtrate a second blue fraction was isolated, which after slow re-crystallization from methanol–ether resulted in pure β-$[NEt_4]_2[Ru(sazpy)_2Cl_2]$.

α-[N(Et)$_4$]$_2$[Ru(sazpy)$_2$Cl$_2$], **2**. Anal. calcd. for $RuC_{38}H_{56}N_8O_6S_2Cl_2\cdot 2H_2O$: C, 46.0; H, 6.09; N 11.28, Cl 7.14, S 6.46; found: C, 46.2; H, 5.92; N 11.05, Cl 7.22, S 6.99. IR (CsI): ν (SO_3 asym stretch) 1231, 1219; (SO_3 sym stretch) 1040, 1024. ^{1}H NMR (300 MHz, MeOD): δ 9.84 (d, H6), 8.56 (d, H3), 8.43 (d, H4), 7.33 (t, *p*), 7.21 (t, *m*), 7.00 (d, *o*).

β-[N(Et)$_4$]$_2$[Ru(sazpy)$_2$Cl$_2$]. This isomer was only obtained in a sufficient amount to characterize by NMR spectroscopy. ^{1}H NMR (300 MHz, MeOD): δ 10.02 (s, H6), 8.74 (d, H3), 8.65 (d, H4), 8.57 (d, H3′), 8.39 (d, H4′), 7.81 (d, *o*′), 7.67 (s, H6′), 7.52 (t, *p*′), 7.42 (m, *p*), 7.39 (m, *m*′), 7.24 (t, *m*), 6.70 (d, *o*).

Structure determination

Crystal data for **2**. $[C_{22}H_{16}Cl_2N_6O_6RuS_2][C_8H_{20}N]\cdot 2H_2O$, $M_r = 993.05$, black plate-shaped crystal ($0.05\times 0.20\times 0.25$ mm^3), monoclinic, space group $P2_1$ (no. 4) with $a = 9.3614(12)$, $b = 9.8737(12)$, $c = 24.449(4)$ Å, $\beta = 90.81(3)°$, $U = 2259.6(5)$ Å^3, $Z = 2$, $D_c = 1.4596(3)$ g cm^{-3}, $F(000) = 1036$, μ(Mo Kα) = 0.615 mm^{-1}, 20733 reflections measured, 8023 independent, $R_{int} = 0.0582$, $1.00° < \theta < 25.26°$, $T = 150$ K, Mo Kα radiation, graphite monochromator, $\lambda = 0.71073$ Å, Nonius Kappa CCD diffractometer on a rotating anode, no absorption correction. The structure was solved by automated direct methods.[20] The measured crystal turned out to be a pseudo-merohedral twin. The twin operation is a 2-fold rotation axis parallel to the *a* axis. The crystal was also an inversion twin, leading to a total of 4 components, related by symmetry operations 1, 2, *m* and $\bar{1}$ with respect to the *a* axis. Since β is close to 90° a refinement model[21] of complete overlap of the twin components led to satisfactory results. The ratio in which the four components 1, 2, *m* and $\bar{1}$ were present refined to 0.28(4):0.15(3):0.42(5):0.15(4). The water hydrogen atoms were placed at calculated positions corresponding to ideal H-bond geometry. Refinement of 535 parameters converged at a final wR_2 value of 0.1348, $R_1 = 0.0577$ [for 7131 reflections with $F_o > 4\sigma(F_o)$], $S = 1.057$, $-1.08 < \Delta\rho < 1.36$ e Å^{-3}.‡

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‡ CCDC reference numbers 228185 . See http://www.rsc.org/suppdata/nj/b3/b313746e/ for crystallographic data in .cif or other electronic format.

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References

1 M. J. Clarke, *Coord. Chem. Rev.*, 2002, **232**, 69.
2 J. Reedijk, *Proc. Natl. Acad. Sci. U. S. A*, 2003, **100**, 3611.
3 E. Wong and C. M. Giandomenico, *Chem. Rev.*, 1999, **99**, 2451.
4 R. E. Aird, J. Cummings, A. A. Ritchie, M. Muir, R. E. Morris, H. Chen, P. J. Sadler and D. I. Jodrell, *Brit. J. Cancer*, 2002, **86**, 1652.
5 R. E. Morris, R. E. Aird, P.D. Murdoch, H. M. Chen, J. Cummings, N. D. Hughes, S. Parsons, A. Parkin, G. Boyd, D. I. Jodrell and P. J. Sadler, *J. Med. Chem.*, 2001, **44**, 3616.
6 A. H. Velders, H. Kooijman, A. L. Spek, J. G. Haasnoot, D. de Vos and J. Reedijk, *Inorg. Chem.*, 2000, **39**, 2966.
7 S. Goswami, A. R. Chakravarty and A. Chakravorty, *Inorg. Chem.*, 1981, **20**, 2246.
8 R. A. Krause and K. Krause, *Inorg. Chem.*, 1980, **19**, 2600.
9 A. C. G. Hotze, A. H. Velders, F. Ugozzoli, M. Biagini-Cingi, A. M. Manotti-Lanfredi, J. G. Haasnoot and J. Reedijk, *Inorg. Chem.*, 2000, **39**, 3838.
10 A. C. G. Hotze, M. Bacac, A. H. Velders, B. A. J. Jansen, H. Kooijman, A. L. Spek, J. G. Haasnoot and J. Reedijk, *J. Med. Chem.*, 2003, **46**, 1743.
11 R. A. Krause and K. Krause, *Inorg. Chem.*, 1984, **23**, 2195.
12 A. K. Mahapatra, B. K. Ghosh, S. Goswami and A. Chakravorty, *J. Indian Chem. Soc.*, 1986, **63**, 101.
13 H. Huang, F. Kai, Y. Asai, M. Hirohata and M. Nakamura, *Bull. Chem. Soc. Jpn.*, 1991, **64**, 2464.
14 T. Bao, K. Krause and R. A. Krause, *Inorg. Chem.*, 1988, **27**, 759.
15 A. H. Velders, K. van der Schilden, A. C. G. Hotze, J. Reedijk, H. Kooijman and A. L. Spek, *J. Chem. Soc., Dalton Trans.*, 2003, 448.
16 G. Socrates, *Infrared Characteristic Group Frequencies*, John Wiley & Sons, New York, 1980.
17 A. Seal and S. Ray, *Acta Crystallogr., Sect. C*, 1984, **40**, 929.
18 G. Sava, A. Bergamo, S. Zorzet, B. Gava, C. Casarsa, M. Coccietto, A. Furlani, V. Scarcia, B. Serli, E. Iengo, E. Alessio and G. Mestroni, *Eur. J. Cancer*, 2002, **38**, 427.
19 M. A. Tchitchibabine and M. Vialatout, *Bull. Soc. Chim. Fr.*, 1939, **6**, 736.
20 G. M. Sheldrick, *SHELXS-86, Program for crystal structure determination,*University of Göttingen, Germany, 1986.
21 G. M. Sheldrick, *SHELXL-97, Program for refinement of crystal structures*, University of Göttingen, Germany, 1997.