A Unique Fourfold Intramolecular Hydrogen Bonding Stabilises the Structure of *trans*-Bis(2-amino-5,7-dimethyl[1,2,4]triazolo[1,5-*a*]pyrimidine-N^3)-aquatrichlororuthenium(III) Monohydrate

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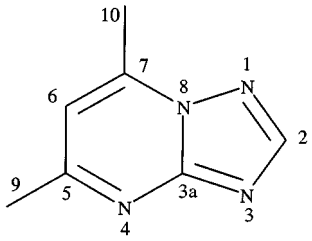
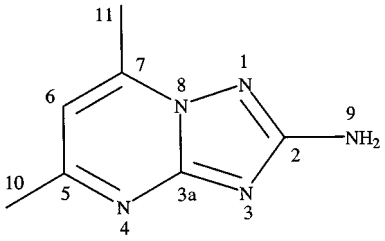
The X-ray structure of the potential antitumour complex *trans*-[$RuCl_3(H_2O)(admtp)_2$] · H_2O (admtp = 2-amino-5,7-dimethyl[1,2,4]triazolo[1,5-*a*]pyrimidine) shows unique and very interesting intramolecular hydrogen-bonding properties with the non-bridgehead pyrimidinic nitrogen atom of admtp acting as hydrogen acceptor and the amino group acting as hydrogen donor.

In the search for new chemotherapeutic antitumour agents, ruthenium(III) complexes of the type *trans*-(LH)[$RuCl_4(L)_2$] (where L is an aromatic N-heterocycle like imidazole or indazole and HL the protonated heterocycle) have shown promising activity in preclinical tests against different (platinum-resistant) tumour models.[1] As yet no clear structure−activity relationship has been reported for ruthenium(III) complexes, like for platinum compounds;[2] therefore, the hydrolysis properties[3] and DNA binding[4] are important factors to analyse. In vivo the ionic *trans*-(LH)[$RuCl_4(L)_2$] complexes with bicyclic ligands like indazole appear to be prodrugs that hydrolyze rapidly to form relatively stable neutral complexes of the type *trans*-[$RuCl_3(H_2O)(L)_2$].[5] However, the consecutive extracellular and intracellular reactions of these monoaquatrichlororuthenium(III) complexes that finally lead to the antitumour activity, and the role of the heterocyclic ligands therein, are not yet understood[3,6] and are currently under investigation.

Recently, we have reported the synthesis and characterisation of the neutral trichlororuthenium(III) complex *trans*-[$RuCl_3(H_2O)(dmtp)_2$] · H_2O, in which the azapurine 5,7-dimethyl[1,2,4]triazolo[1,5-*a*]pyrimidine (dmtp) (Scheme 1), is coordinated to the ruthenium(III) centre through the N(3) nitrogen atom of the triazole moiety, whilst the pyrimidinic (N4) nitrogen atoms of both coordinated ligands are involved in intramolecular hydrogen bonds with the two hydrogen atoms of the coordinated water molecule.[7] The hydrogen-bonding interactions of the dmtp suggested the possibility of fine-tuning in the investigations of the hydrolysis reactions and hydrolysis products of ruthenium(III) antitumour complexes, on use of heterocyclic ligands with the capacity to form intramolecular donor and/or acceptor hydrogen bonds.



dmtp



admtp

Scheme 1

In the past two decades several triazolopyrimidines have been used to synthesise complexes with different metals and purposes,[8,9] and recently a platinum complex with two triazolopyrimidine ligands has been reported which has interesting antimour activity.[9c] To our knowledge, the 2-amino-5,7-dimethyl[1,2,4]triazolo[1,5-*a*]pyrimidine,[10] (admtp) (Scheme 1), has not been reported yet as a ligand for metal coordination. We now present the synthesis and characterisation of a ruthenium complex, in which admtp acts as a monodentate ligand with unique intramolecular hydrogen-bonding properties, and its possible role in the search for a structure−activity relationship of antitumour-active ruthenium(III) complexes is discussed.

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The new neutral monoaquatrichlororuthenium(III) compound *trans*-[$RuCl_3(H_2O)(admtp)_2$] · H_2O (**1**) was synthesised by a procedure analogous to *trans*-[$RuCl_3(H_2O)(dmtp)_2$] · H_2O[7] (**2**) and characterised by elemental analysis, and NMR and IR spectroscopy. The crystal structure of **1** (Figure 1) was determined by X-ray diffraction analysis and shows a six-coordinated ruthenium(III) ion with three chloride ions in a *mer* configuration, two admtp molecules, coordinated by their N(3) nitrogen atoms, in a parallel "face-to-face" *trans* orientation, and a water molecule coordinated in the plane of the chloride ions and lying in between the pyrimidinic rings of the two admtp ligands. The Ru−N, Ru−Cl, and Ru−O bond lengths are comparable with those found in related complexes, like *trans*-[$RuCl_3(H_2O)(dmtp)_2$][7] and *trans*-[$RuCl_3(H_2O)(1\text{-MeInd})_2$][5] which also display a quasi-octahedral stereochemistry with two *trans*-located heterocyclic ligands.

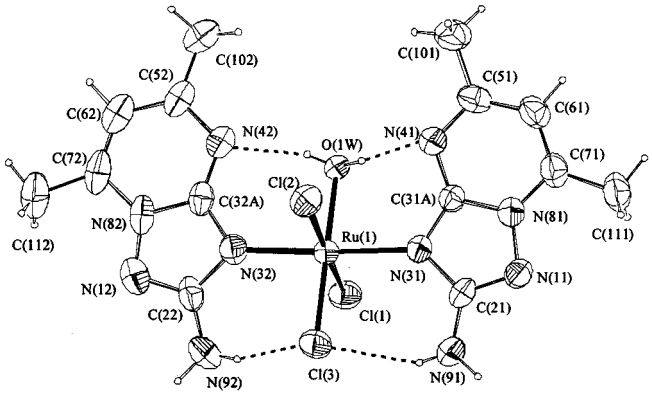

Figure 1. X-ray structure and numbering scheme of **1** with the thermal ellipsoids drawn at a 50% probability level (PLATON); intramolecular hydrogen bondings are indicated with dotted lines; the crystal water is omitted for clarity; selected metal−ligand bond lengths [A] and angles [°]: Ru(1)−N(31) 2.117(4), Ru(1)−N(32) 2.131(5), Ru(1)−O(1W) 2.098(4), Ru(1)−Cl(1) 2.339(2), Ru(1)−Cl(2) 2.348(2), Ru(1)−Cl(3) 2.358(2), N(32)−Ru(1)−N(31) 175.7(2), Cl(1)−Ru(1)−Cl(2) 175.08(5), Cl(3)−Ru(1)−O(1W) 176.5(1); donor···acceptor (D···A) and hydrogen···acceptor (H···A) distances [A], and donor−hydrogen···acceptor (D−H···A) angles [°] of the intramolecular hydrogen bonds: O(1W)−H(1WA)···N(41) 2.650(6), 1.81(9), and 154(8); O(1W)−H(1WB)···N(42) 2.662(6), 1.95(7), and 165(8); Cl(3)···H(91A)−N(91) 3.126(6), 2.51(6), and 141(6); Cl(3)···H(92A)−N(92) 3.077(7), 2.35(10), and 155(10)

The most striking feature of the structure of **1** is that a fourfold intramolecular hydrogen-bond system is present. In addition to the hydrogen-bonding acceptor properties of the pyrimidinic N(4) nitrogen atoms to the coordinated water hydrogen atoms, the amino groups of the two admtp ligands are both involved as hydrogen donors in intramolecular hydrogen bonding to the chloride ion Cl(3) lying *trans* to the coordinated water molecule. This special hydrogen bonding is probably also the origin of the elongated Ru(1)−Cl(3) distance (2.358 Å), which is slightly longer than the other two ruthenium−chloride bonds (2.339 and 2.348 Å). It is more difficult to draw conclusions about differences in the stability of the coordinated water molecule from the crystallographic data of **1** and **2** as the water molecule in the former is also involved in intermolecular hydrogen bonds.

Double intramolecular hydrogen bonding of heterocyclic ligands with both hydrogen atoms of a coordinated water molecule has been observed before for metal complexes,[7,9a,11a] and also double intramolecular hydrogen bonding of N−H groups with one coordinated halide ion is not an unknown feature for coordination compounds. However, the combination of (intramolecular) hydrogen-accepting and hydrogen-donating bonds of one ligand in a coordination compound, like in this case for admtp [via the N(4) nitrogen atom and the amine moiety, respectively] is to our knowledge unique.[11b] As both admtp ligands in **1** bind in a similar way, complex **1** is an as yet unique example of a coordination compound in which four square-planar coordinated monodentate ligands, linked to each other by a fourfold intramolecular hydrogen bond, form a pseudo-chelating tetradentate ligand which is organised by the heterocyclic ligand.

Due to the (non-symmetric) intermolecular hydrogen bonds of the two amino groups and the two water molecules in the crystal structure of **1** no twofold symmetry is present. However, it is likely that in solution **1** does have a twofold symmetry, in agreement with the single set of admtp signals found in NMR. Time-dependent UV/Vis absorption, NMR, and conductivity measurements of **1** in coordinating solvents (Solv), like DMSO and acetonitrile, indicate the formation of complexes of the type *trans*-[$RuCl_3(Solv)(admtp)_2$]. This type of reactions is related to those seen in the *trans*-[$RuCl_3(H_2O)(dmtp)_2$] · H_2O chemistry[7] and will be published in detail in a full paper. Preliminary results indicate that the solvolysis of **1**, in acetonitrile for example, is slightly faster than that of **2**, but still much slower than in analogous complexes that do not have double intramolecular hydrogen bonds that can stabilise the coordinated water molecule.[12] Although the water-substitution reactions are not directly correlated to in vivo reactions of this type of ruthenium complexes, these results do indicate that the ruthenium−ligand properties have been slightly changed by a small modification of the ligand.

As hydrolysis properties play a key role in the antitumour mechanism of chemotherapeutic platinum complexes, it is useful to study these properties of ruthenium complexes, too. The structure of complex **1** indicates that the use of the triazolopyrimidine admtp offers the possibility to stabilise, isolate, and study the first hydrolysis product of antitumour-active ruthenium(III) complexes of the type *trans*-(LH)[$RuCl_4(L)_2$]. Furthermore, the intramolecular hydrogen bonds of admtp are likely to influence hydrolysis properties through interactions with incoming (water molecules), as well as with leaving ligands (chloride ions). Also the consecutive in vivo reactions of the aquated ruthenium species, in which the water molecules are thought to be substituted by DNA bases, are likely to be influenced by the presence of hydrogen-donating as well as hydrogen-accepting moieties of the heterocyclic ligands. Finally, the amine group of the ligand admtp is also interesting for its potential intermolecular hydrogen-bonding properties, which for antitumour-active platinum compounds have been proven to be a crucial factor for the in vivo DNA binding and

distortion that finally lead to cell death.[2]

In summary, the hydrogen-bonded stabilised structure of *trans*-[$RuCl_3(H_2O)(admtp)_2$] proves the possibility to design and synthesise new ruthenium complexes with specific ligands that can fine-tune the chemical and physical properties of potential antiumour complexes via multiple intramolecular hydrogen bondings. The easy synthesis and interesting hydrogen-bonding properties of admtp give it promise as a useful ligand for the synthesis of complexes with other transition metals in different fields of coordination chemistry, too. Although the amine group of the admtp is not as reactive as a primary amine, due to the delocalisation of the electron pair in the triazolopyrimidine ring system,[10] it is a useful functional group for the design and synthesis of other triazolopyrimidine derivatives that might also be successful ligands.

Experimental Section

General: NMR: Bruker WM 300 MHz spectrometer. For [D_6]acetone as solvent, δ_H = 2.06 at 295 K. ^{1}H-NMR data of **1** were obtained using an inversion recovery pulse sequence, *π-τ-π/2-acquisition*, with τ (the variable delay time between the inversion and the acquisition pulse, respectively) in the order of 100 ms. The ^{1}H-NMR signals of **1** could be identified as the paramagnetically shifted and broadened signals with relaxation times in the order of ms.

***trans*-[$RuCl_3(H_2O)(admtp)_2$] · H_2O (1):** The ligand 2-amino-5,7-dimethyl[1,2,4]triazolo[1,5-*a*]pyrimidine (admtp) was prepared by a method slightly different method from the one by Kreutzberger[10] by condensation of 3,5-diamino-1,2,4-triazole (Aldrich) with a small excess of 2,4-pentanedione (Merck) in boiling ethylene glycol. After gentle heating at 75°C for 3 h of a ruthenium(III) chloride solution (5 mmol in 50 mL 1 M HCl) with admtp (15 mmol in 50 mL of ethanol), *trans*-[$RuCl_3(H_2O)(admtp)_2$] · H_2O was obtained as a brick-red powder; recrystallisation from acetone/water (5:1) yielded orange-red prismatic crystals. — $C_{14}H_{22}Cl_3N_8O_2Ru$ (569.8): calcd. C 29.50, H 3.86, N 24.58, Cl 18.67; found: C 29.52, H 3.86, N 24.58, Cl 18.6. − The effective magnetic moment, μ_{eff}, of the complex was determined to be 1.9 Bohr magneton at 20°C. − ^{1}H NMR ([D_6]acetone): δ (peak width at half height) = +1.4 (20 Hz) [H(61/62)], +4.7 (35 Hz) and −3.5 (15 Hz) [CH_3(101/102) and CH_3(111/112)], and +53 (2000 Hz) [coordinated H_2O].

X-ray Crystallographic Study of 1: $C_{14}H_{20}Cl_3N_{10}ORu \cdot H_2O$; M = 569.823; monoclinic, space group $P2_1/c$; a = 8.292(5), b = 26.289(5), c = 10.175(5) Å, β = 97.16(2)°; V = 2201(2) Å^3; Z = 4; $D_{calcd.}$ = 1.720 g cm^{-3}; graphite-monochromated Cu-K_α radiation (λ = 1.54178 Å); μ = 9.421 mm^{-1}; T = 293 K. Data were collected with a Siemens AED and corrected for Lorentz and polarisation effects: 4150 unique data in the range 6° < θ < 70°. Refinement on F^2 values of all data with SHELXL96.[13] Final $R1 = \Sigma ||F_o| - |F_c||/\Sigma|F_o| = 0.0566$ for 3140 $F_o > 4\sigma(F_o)$ and 0.0689 for all data, $wR2 = [\Sigma w(F_o^2 - F_c^2)^2/\Sigma wF_o^4]^{1/2} = 0.1605$, $\Sigma = [\Sigma w(F_o^2 - F_c^2)^2/(n - p)]^2 = 1.073$ for 303 parameters. Residual electron density extrema are 2.49 and −1.5 eÅ^{-3}. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC-103269. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: int. code + 44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

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