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Preparation of a new ruthenium(II) building block for the synthesis of mixed-metal complexes

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Abstract—A new tris(dimine)ruthenium(II) complex containing a free flexible tail on one ligand, available for the coordination of a second metal, has been synthesised.

The field of bioinorganic chemistry has been rapidly developing and offers enormous potential for medicinal chemistry and real opportunities to the pharmaceutical industry. The worldwide success of the square-planar platinum(II) complex *cis*-diamminedichloroplatinum (*cis*platin) as a leading anti-cancer drug,[1] has boosted research into the development of new metallo-drugs.

Over recent years, the field has expanded further, and is now looking at the possibility of using transition-metal ions other than platinum.[2] Using different metals would give possibilities such as having additional co-ordination sites, different oxidation states and ligand affinities, as well as providing the opportunity for photodynamic therapy.[3] More recently, research groups have started looking at the possibility of coupling different metal complexes with different activities and modes of action with the purpose of synergising their effect and developing more effective chemotherapeutic agents.[4,5]

A new ruthenium(II) building block, with potential DNA photocleavage properties and a long flexible arm side chain available for binding another biologically active metal complex, has now been designed (Fig. 1). Based on the literature,[6] a ruthenium complex containing different didentate ligands was prepared. The ligands, 1,4,5,8-tetra-azaphenanthrene (tap, **2**) and a tetraazatriphenylene derivative (tatpd, **3**), were chosen because they are commonly used for Ru(II) photocleavage agents.[7] Bridging ligand **3** synthesised from 1,10-phenanthroline-5,6-dione **4** (Fig. 2) possesses a long and flexible tail, which would enable the two metals to perform their biological function independently. The successful synthesis of complex **1**, is described in this paper.

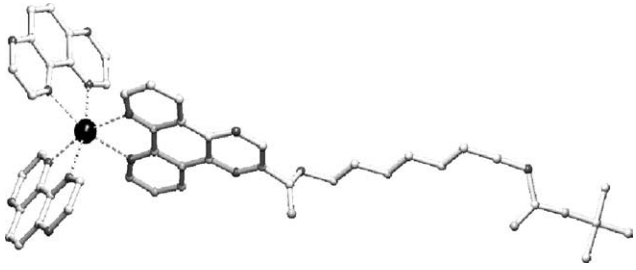

Figure 1. Spartan generated model of $[Ru(tap)_2(tatpd)]^{2+}$ **1**.

The synthesis of $[Ru(tap)_2(tatpd)]^{2+}$ **1** required the preparation of 1,4,5,8-tetra-azaphenanthrene **2**, 1,10-phenanthroline-5,6-dione **4** and the diamino-propionic acid derivative **8**, which was necessary for the synthesis of the bridging ligand. 1,4,5,8-Tetra-azaphenanthrene was synthesised in four steps from the commercially available 4-nitro-1,2-phenylenediamine, as described by Nasielski-Hinkens et al.[8] 1,10-Phenanthroline-5,6-dione **4** was prepared from the commercially available 1,10-phenanthroline according to a literature procedure by Nordén and co-workers.[9] The diamino-propionic acid derivative was prepared as shown in Scheme 1 and is described below.

Scheme 1 summarises the three-step synthesis of 2,3-diamino-*N*-(7-*tert*-butoxycarbonylaminoheptyl)-propionamide **8**. *N*,*N*′-Di-trifluoroacetyl-2,3-diaminopropionic acid **6**, prepared from 2,3-diaminopropionic acid

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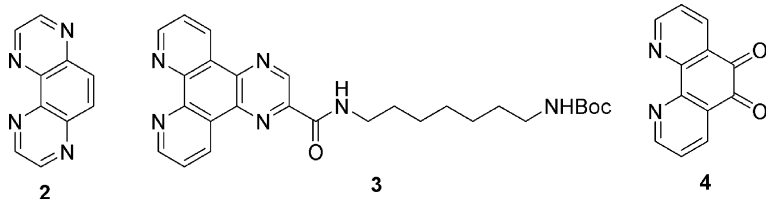
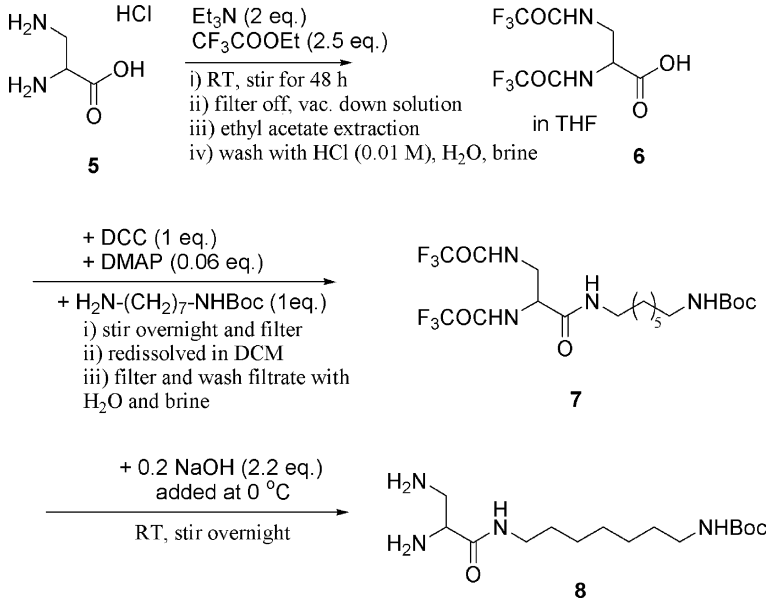


Figure 2. 1,4,5,8-tetra-azaphenanthrene (tap, **2**), tetra-azatriphenylene derivative (tatpd, **3**) and 1,10-phenanthroline-5,6-dione (phen-dione, **4**).



Scheme 1. Reaction scheme for the preparation of 2,3-diamino-*N*-(7-*tert*-butoxycarbonylaminoheptyl)-propionamide **8**.

monohydrochloride **5**, according to a slightly modified literature procedure by Rinken[10] (i.e., the addition of 2 equiv of triethylamine to quench both acids in solution) was coupled to *N*-*tert*-butoxycarbonyl-1,7-heptanediamine, previously prepared following a method by Krapcho et al.,[11] as described by van der Tol et al.[12] using 1,3-dicyclohexylcarbodiimide (DCC) rather than 1,1′-carbonyldiimidazole (CDI) as coupling reagent. The hydrolysis of the trifluoroacetamides in basic media as described by Rauter et al.[13] afforded the desired intermediate, 2,3-diamino- *N*-(7-*tert*-butoxycarbonyl-aminoheptyl)propionamide **8**. Two pathways were considered for the synthesis of complex **1**: (i) the synthesis of ligand **3** followed by its coordination to $[Ru(tap)_2Cl_2]$ **9** or (ii) the condensation of $[Ru(tap)_2(phen\text{-}dione)]^{2+}$ **10** with the diamino derivative **8**. The latter pathway was chosen because of its expected simplicity.

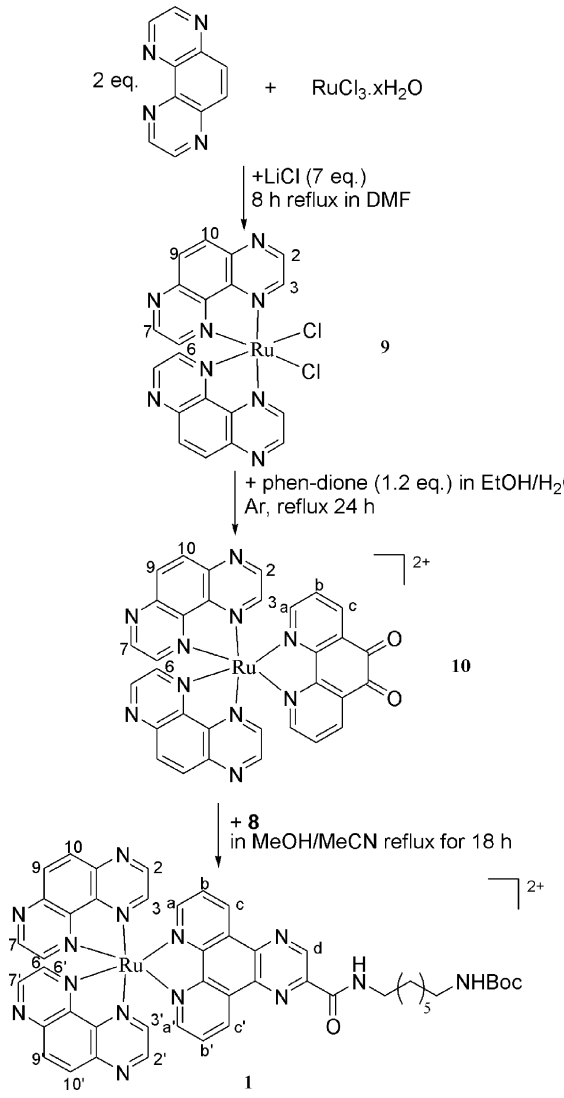
The desired ruthenium(II) complex, **1**, was obtained after a three-step synthesis as shown in Scheme 2. The first step was the synthesis of *cis*-$[Ru(tap)_2Cl_2]$ **9**, followed by the addition of the didentate ligand **4** to yield $[Ru(tap)_2(phen\text{-}dione)]^{2+}$ **10** and finally the formation of the tetra-azatriphenylene derivative tail.

1D and 2D ^1H NMR spectra of each complex were recorded on a Bruker 600 MHz instrument. It proved necessary to measure COSY and NOESY ^1H–^1H NMR spectra in order to assign the different aromatic protons. The labelling of the protons is shown in Scheme 2.

Synthesis of 2,3-diamino-*N*-(7-*tert*-butoxycarbonyl-aminoheptyl)-propionamide 8

To a solution of 0.7 g 2,3-diaminopropionic acid monohydrochloride **5** in 25 ml methanol was added 1.4 ml (2 equiv) triethylamine and 1.48 ml (2.5 equiv) ethyl trifluoroacetate. The resulting mixture was stirred at room temperature for 48 h. The solution was filtered and rotary evaporated. The residue was extracted with ethyl acetate and subsequently washed with 50 ml 0.01 M hydrochloric acid, 50 ml water and 50 ml brine. The organic phase was rotary evaporated to yield the desired compound **6** (66%). ^1H NMR (MeOH-d_4, 300 MHz): δ 4.71 (1H, t, $J = 3.5$ Hz, CH), 3.78 (2H, m, CH_2).

To a solution of 1.16 g *N*,*N*′-di-trifluoroacetyl-2,3-diaminopropionic acid **6** in 25 ml THF were added 0.71 g (1 equiv) 1,3-dicyclohexylcarbodiimide and 0.025 g (0.06 equiv) dimethylaminopyridine. The resulting solution was stirred at room temperature for 1 h. Then 0.8 g (1 equiv) *N*-*tert*-butoxycarbonyl-1,7-heptane-



Scheme 2. Reaction scheme for the synthesis of the new ruthenium(II) complex **1**.

diamine, previously prepared following a method by Krapcho et al.[11] were added, and the mixture allowed to stir overnight at room temperature. The solution was filtered from the precipitate and rotary evaporated. The residue was extracted with 50 ml dichloromethane and subsequently washed with 50 ml 0.01 M hydrochloric acid, 50 ml water and 50 ml brine. Evaporation of the organic phase yielded **7** (25%) as a yellow powder. ^{1}H NMR (MeOH-d_4, 300 MHz): δ 4.63 (1H, t, $J = 6.4$ Hz, CH), 3.78 (2H, d, $J = 5.7$ Hz, CF_3CONH–CH_2), 3.18 (2H, m, CH_2–NHBoc), 3.00 (2H, t, $J = 6.9$ Hz, CH_2NHCO), 1.42 (4H, m, CH_2–CH_2–NHBoc+CH_2–CH_2–NH–CO, +9H, s, Boc), 1.33 (6H, m, $(CH_2)_3$); ESI-MS: m/z 508.4 (M+H).

To a solution of 0.45 g of compound **7** in 20 ml methanol was added dropwise 9.8 ml 0.2 M aqueous solution of NaOH at 0 °C. The solution was allowed to warm to room temperature and stirred overnight. Then methanol was removed in vacuo, and the product was extracted with $CHCl_3$/MeOH (9:1). Evaporation of the organic phase to dryness yielded **8** (45%) as a white powder. ^{1}H NMR (D_2O, 300 MHz): δ 3.30 (1H, m, CH), 3.08 (2H, t, $J = 6.6$ Hz, CH_2–NHBoc), 2.92 (2H, t, $J = 6.5$ Hz, CH_2–NHCO), 2.70 (2H, m, H_2N–CH_2), 1.30 (13H, m, Boc+CH_2–CH_2–NHBoc+CH_2–CH_2–NH–CO), 1.19 (6H, s, br, $(CH_2)_3$); ESI-MS: m/z 317.0 (M+H), 338.9 (M+Na).

Synthesis of *cis*-[Ru(tap)$_2$Cl$_2$] 9

The *cis*-[Ru(tap)$_2$Cl$_2$] complex **9** was prepared following a method by Sullivan et al. for the synthesis of *cis*-(bpy)$_2$RuCl$_2$.[14]

$RuCl_3 \cdot 3H_2O$ (261 mg, 1.0 mmol), LiCl (296 mg, 7 mmol) and the tap ligand **2** (364 mg, 2 mmol) were refluxed in DMF (20 ml) for 8 h. After the reaction mixture had been cooled to room temperature, acetone was added and the resulting mixture was left at 0 °C overnight. The dark purple mixture obtained was then filtered, yielding, after washing with diethyl ether, a dark purple powder (82%). ^{1}H NMR (DMSO-d_6, 600 MHz): δ 10.17 (2H, d, $J = 2.6$ Hz, H-3), 9.46 (2H, d, $J = 2.6$ Hz, H-2), 8.61 (2H, d, $J = 9.3$ Hz, H-9/10), 8.61 (2H, d, $J = 3.1$ Hz, H-7), 8.48 (2H, d, $J = 9.3$ Hz, H-9/10), 8.28 (2H, d, $J = 3.1$ Hz, H-6).

Synthesis of [Ru(tap)$_2$(phen-dione)](PF$_6$)$_2$ 10

The [Ru(tap)$_2$(phen-dione)](PF$_6$)$_2$ complex **10** was synthesised, combining different published methods,[15,16] by adding 1,10-phenanthroline-5,6-dione **4** (210 mg, 1.2 mmol) to a suspension of *cis*-[Ru(tap)$_2$Cl$_2$] complex **9** (536 mg, 1 mmol) in 120 ml of EtOH/H_2O (1:1). The suspension was refluxed under Ar for 24 h. The resulting brown reaction mixture was allowed to cool, filtered, then the filtrate concentrated under vacuum and upon the addition of a saturated ethanolic solution of NH_4PF_6, [Ru(tap)$_2$(phen-dione)](PF$_6$)$_2$ was precipitated as a brown powder. Further purification was achieved by dissolving the complex in the minimum amount of MeCN, and after filtration, precipitating the desired complex (30%) by the slow addition of diethyl ether. ^{1}H NMR (MeCN-d_3, 600 MHz): δ 9.13 (2H, d, $J = 2.8$ Hz, H-2), 8.91 (2H, d, $J = 2.6$ Hz, H-7), 8.63 (2H, d, $J = 9.4$ Hz, H-9/10), 8.60 (2H, d, $J = 9.4$ Hz, H-9/10), 8.57 (2H, d, $J = 7.8$ Hz, H_c), 8.40 (2H, d, $J = 2.8$ Hz, H-3), 8.12 (2H, d, $J = 2.6$ Hz, H-6), 7.98 (2H, d, $J = 5.7$, H_a), 7.56 (2H, dd, $J = 5.7$, 7.8 Hz, H_b); ESI-MS: $m/z = 337.9$ ($[M^{2+}]_{calcd} = 337.8$).

Synthesis of [Ru(tap)$_2$(tatpd)](PF$_6$)$_2$ 1

Complex **1** was prepared by adding 2,3-diamino-*N*-(7-*tert*-butoxycarbonylaminoheptyl)propionamide **8** (78 mg, 0.25 mmol) in 3 ml of MeOH to a MeCN solution (5 ml) of [Ru(tap)$_2$(phen-dione)](PF$_6$)$_2$ **10** (160 mg, 0.16 mmol). The resulting solution was heated at reflux for 18 h before being evaporated to dryness. The desired compound was obtained after purification using an alumina

N column, using at first MeCN as eluent followed by 10:1 MeOH/NH_4OH eluent. The MeOH fraction was taken to dryness and the product was obtained as a dark brown oil. ^1H NMR (MeCN-d_3, 600 MHz): δ 9.88 (1H, s, H_d), 9.87 (1H, d, $J = 8.6$ Hz, $H_{c/c'}$), 9.6 (1H, d, $J = 8.3$ Hz, $H_{c/c'}$), 9.0 (4H, m, H2,7,2′,7′), 8.6 (4H, m, H9,10,9′,10′), 8.27 (4H, m, H3,6,3′,6′), 7.91 (1H, dd, $J = 8.6$, 8.3 Hz, $H_{a/a'}$), 7.90 (1H, dd, $J = 8.6$, 8.3 Hz, $H_{a/a'}$), 5.25 (1H, s, br, CO–*NH*), 3.52 (2H, t, $J = 6.5$ Hz, *CH*$_2$–NHBoc), 2.97 (2H, m, *CH*$_2$–NHCO), 1.37 (19H, m, $(CH_2)_5$+Boc); ESI-MS: $m/z = 954.5$, 477.2 ($[M^+]_{calcd} = 954.1$, $[M^{2+}]_{calcd} = 477.0$).

In this paper, the synthesis of a new ruthenium(II) building block has been presented. The long flexible side arm on the third ligand, was designed to give maximum freedom at both ends of the bridge, allowing the ruthenium side of the molecule to bind within the DNA groove without restricting the rest of the dinuclear complex. The coordination of a second metal is expected to be a straightforward procedure after deprotection of the free primary amine under acidic conditions. Studies with metals such as Pt and Zn are ongoing.

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