Binuclear Complexes

A Highly Flexible Dinuclear Ruthenium(II)–Platinum(II) Complex: Crystal Structure and Binding to 9-Ethylguanine**

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Polynuclear platinum complexes represent a novel class of anticancer agents.[1,2] It is believed they can overcome both acquired and intrinsic resistance to the antitumor drug cisplatin, because they are capable of forming a completely different range of DNA adducts compared to cisplatin and its analogues. Chain length and flexibility, hydrogen-bonding capacity and charge of the linker, and the geometry of the chloro ligand to the linker chain emerge as the major factors in designing polynuclear platinum antitumor drugs. A challenging extension of the polynuclear concept is to introduce a different metal in one of the coordination sites to achieve selective specificity and reactivity at each metal center. Ruthenium as the second metal appears to be promising because ruthenium compounds are also known for their antitumor activity.[3] This field of heteropolynuclear ruthenium–platinum anticancer complexes is relatively unexplored and only a few, rather rigid compounds have been studied so far.[4] These complexes consist of a ruthenium(II) cationic species as a light-absorbing unit linked to a reactive platinum center through a short, rigid polyazine bridging ligand. Conversely, it would be interesting to develop nonrigid heterodinuclear compounds of greater length that are capable of engaging in delocalized long-range DNA interactions, since the excellent cytotoxicity of polynuclear platinum complexes is thought to be a consequence of the formation of long-range inter- and intrastrand DNA adducts.[1] Just a single example,[5] that is, $[\{cis\text{-}RuCl_2(Me_2SO)_3\}H_2N(CH_2)_4NH_2\{cis\text{-}PtCl_2(NH_3)\}]$, has been published, but the complex has been found to be too reactive for use as a DNA-binding probe, because of its light sensitivity and fast hydrolysis.

Herein, the X-ray diffraction structure of the highly flexible heterodinuclear ruthenium(II)–platinum(II) complex $[(tpy)Ru(dtdeg)PtCl]Cl_3$ (**1**) (tpy = 2,2′:6′,2″-terpyridine, dtdeg = bis[4′-(2,2′:6′,2″-terpyridyl)]-diethyleneglycol ether) is presented. Uniquely, a long and flexible bridging terpyridine ligand[6] (dtdeg) has been used to link the two metal moieties. The design and subsequent development of the dinuclear complex have been inspired by the cytotoxic mononuclear platinum complex $[Pt(tpy)Cl]Cl\cdot 2H_2O$, which can both intercalate and coordinate to DNA.[7] Moreover, substitution-inert ruthenium polypyridyl complexes are known to be able to bind to DNA in a noncovalent mode, such as electrostatic or surface binding, or partial intercalation.[8] It is thought that the ruthenium moiety of **1** increases the DNA affinity by its 2+ charge, thereby directing the complex to its target. Subsequently, both metal moieties can exert the DNA-binding features of their parental mononuclear complexes. As a first step in evaluating the DNA interactions of **1**, reactions with the DNA model base 9-ethylguanine have been performed.

Complex **1** was synthesized in high yield by refluxing a mixture of $[(tpy)Ru(dtdeg)]Cl_2$ and $[Pt(cod)Cl_2]$ (cod = 1,5-cyclooctadiene) in MeOH (see Supporting Information). Red plate-shaped crystals of **1** were obtained by slow precipitation of the reaction mixture with diethyl ether. Despite the great length and flexibility of the linker, the crystal structure[9] was elucidated (Figure 1) and confirmed unambiguously the molecular structure of **1**. Notably, no crystal structures of heterodinuclear ruthenium–platinum complexes, in which the two metal moieties are linked by a long and flexible bridging ligand, are included in the January 2004 update of the Cambridge Structural Database. In this unique crystal

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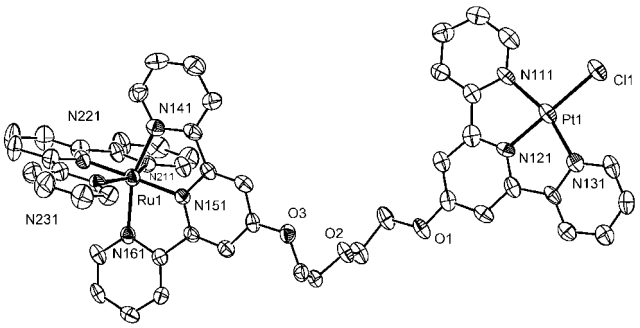

Figure 1. Displacement ellipsoid (50% probability) plot of the structure of **1**. Counterions and solvent molecules are not shown. Hydrogen atoms are also omitted for clarity. Bond lengths and angles are in agreement with literature data for parental cationic mononuclear complexes:[13,18] N-Ru-N bite angles vary from 78.58(19) to 80.10(19)°, N-Pt-N bite angles are 80.50(19) and 81.62(19)°, the Ru-N bond distances lie in the range 1.965(5)–2.078(5) Å, the Pt-N distances lie in the range 1.939(5)–2.025(5) Å, and the Pt-Cl distance is 2.3054(15) Å.

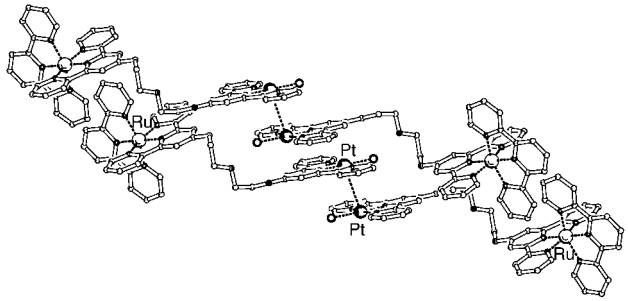

Figure 2. View of the packing of the crystal structure of **1** in which alternating short and long Pt···Pt distances are displayed by the platinum units. A short intermolecular Pt1···Pt1 [2−*x*,−*y*,−*z*] distance (dashed lines) of 3.4935(7) Å is observed between two platinum terpyridine units that are exactly oriented in a head-to-tail fashion. The long intermolecular Pt1···Pt1 [1−*x*,−*y*,−*z*] distance is caused by a lateral shift of one Pt-tpy unit with respect to the short Pt1···Pt1 [2−*x*,−*y*,−*z*] vector.

structure, the intramolecular Ru···Pt distance is 14.547(3) Å. For comparison, the intramolecular Ru···Pt distance in the crystal structure[10] of $[Ru(bpy)_2(\mu\text{-}2,3\text{-}dpp)PtCl_2](PF_6)_2$ (bpy = 2,2′-bipyridine), in which dpp is the short and rigid bridging ligand 2,3-bis(2-pyridyl)pyrazine, is 6.7 Å. Given that the diethyleneglycol ether linker of **1** is somewhat folded in the crystal structure, the length over which both metal moieties can interact with DNA might even be larger. Long-range binding from the minor to the major groove of the DNA over the phosphate backbone has been shown to be possible[11] for the trinuclear platinum compound $[\{trans\text{-}PtCl(NH_3)_2\}_2\mu\text{-}\{H_2N(CH_2)_6NH_2\}_2Pt(NH_3)_2](NO_3)_4$ (BBR3464) bound to a self-complementary DNA octamer 5′-d(ATG*TACAT)$_2$-3′. The two *trans*-$\{PtCl(NH_3)_2\}$ units coordinate in the major groove at the N7 positions of guanine residues on opposite DNA strands, whereas the central tetraamine linker is located in or close to the minor groove. Considering the length of the linker of **1**, either intercalative binding or coordination of the platinum moiety of **1** might occur in the major groove of the DNA after pre-association, which is largely stabilized by electrostatic forces upon binding of the 2+ charged ruthenium unit in the minor groove.

Surprisingly, the crystal structure of **1** also shows intermolecular stacking interactions between the platinum moieties despite the linked, rather bulky ruthenium units (Figure 2). The platinum units stack in a head-to-tail fashion with alternating short and long Pt···Pt distances of 3.4935(7) and 6.7337(12) Å, respectively, because the packing of the crystal structure of **1** is such that chains of alternating platinum units related by inversion symmetry are situated in between the ruthenium units. A continuous π–π ring-stacking interaction is displayed along the Pt–tpy chain, with the perpendicular distances of the center of geometry of one ring to the least-squares plane of the other ring being approximately 3.38 and 3.45 Å for the short and long pair, respectively (see the Supporting Information). The short Pt···Pt distance of 3.49 Å might even allow weak d_z^2-d_z^2 interactions.[12] Indeed, aggregation through weak bonding interactions into metal-bound d^8-d^8 pairs in an infinite π–π stack has been reported for the perchlorate salt of the parental mononuclear $[Pt(tpy)Cl]^+$ ion.[13] Studies to examine the Pt–Pt interactions of **1** have not been undertaken yet. Nonetheless, the self-stacking interactions imply that the platinum unit of **1** is able to intercalate in the DNA, thereby aiding coordination. Although intercalation is initially more feasible, coordination has been determined to be the thermodynamically more favorable mode of binding for mononuclear platinum terpyridine complexes containing a fourth labile ligand.[14]

Mononuclear platinum terpyridine complexes are known to coordinate preferentially to the DNA base guanine.[15] Studies performed with the DNA model base 9-ethylguanine (9egua) prove that the platinum unit of **1** is able to coordinate to 9egua through N7 (see Supporting Information for data of the adduct $[(tpy)Ru(dtdeg)Pt(9egua)](PF_6)_4$ (**2**)), which agrees with previously reported data.[16] Apparently, coordination of platinum to 9egua is not hindered at all by the dangling ruthenium unit. However, although the platinum moiety of **1** possibly displays the DNA interactions inherent to its parental mononuclear complex, preliminary experiments on the cisplatin-sensitive cell lines A2780 (human ovarian cancer) and L1210/0 (mouse leukemia) and their cisplatin-resistant derivatives A2780cisR and L1210/2 indicate that **1** is not as cytotoxic[17] as $[Pt(tpy)Cl]Cl\cdot 2H_2O$. The lower cytotoxicity of **1** might be explained by the fact that the ruthenium moiety of **1** can only display electrostatic DNA interactions, just like its mononuclear counterpart.[8] Consequently, the ruthenium unit linked to the platinum moiety can easily be removed from DNA by repair proteins. Hence, the ruthenium unit is currently being modified to enable coordination of ruthenium to the DNA.

In summary, the first crystal structure of a highly flexible heterodinuclear ruthenium–platinum complex and its coordination to the DNA model base 9-ethylguanine is presented. The results suggest that the platinum moiety is able to both intercalate and coordinate to the DNA without being hindered by the ruthenium unit, which simultaneously allows for additional electrostatic binding to the DNA. Despite the relatively low cytotoxicity of the presented

complex, it is a unique example of a new series of potentially antitumor-active complexes of which variation of the terminal tpy ligand of the ruthenium unit offers great possibilities to improve noncovalent DNA-binding modes as well as DNA-coordination abilities. In view of the relatively long intramolecular ruthenium–platinum separation of 14.5 Å found for **1**, this approach can lead to compounds able to form delocalized long-range DNA adducts, thereby bestowing antitumor activity onto this new series of heterodinuclear ruthenium–platinum complexes.

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[9] Crystal data for **1**·8 CH_3OH: $C_{57}H_{63}Cl_4N_9O_{11}PtRu$, $M_r = 1496.20$, red plate-shaped crystal ($0.03 \times 0.13 \times 0.30$ mm), triclinic, space group $P\bar{1}$, $a = 8.8396(12)$, $b = 15.961(2)$, $c = 23.548(4)$ Å, $\alpha = 75.031(13)$, $\beta = 88.528(13)$, $\gamma = 78.975(17)°$, $V = 3149.4(8)$ Å^3, $Z = 2$, $\rho_{calcd} = 1.578$ g cm^{-3}, $\mu(Mo_{K\alpha}) = 2.804$ mm^{-1}. A total of 53838 reflections were measured (11287 independent, $R_{int} = 0.1061$, $\theta_{max} = 25.35°$, $T = 150$ K, $Mo_{K\alpha}$ radiation, graphite monochromator, $\lambda = 0.71073$) on a Nonius Kappa CCD diffractometer on a rotating anode; data were corrected for absorption using PLATON/MULABS, T range 0.741–0.929. The structure was solved by automated direct methods (SHELXS86). Full-matrix least-squares refinement of 577 parameters on F^2 (SHELXL-97) resulted in a final $R1$ value of 0.0470, w$R2 = 0.0927$, $S = 0.898$. H atoms were introduced on calculated positions. A volume of 1257 Å^3 per unit cell is filled with disordered methanol solvent molecules in which the chloride counterions are positioned as well. Disorder models of solvent and counterions suggest the presence of three chloride ions per ruthenium–platinum complex, one of which is disordered over two positions. However, these models proved to be unstable upon refinement. By using the PLATON/SQUEEZE method, a total of 379 e$^-$ was found in the disordered region, which corresponds to about eight methanol molecules per ruthenium–platinum complex. CCDC-230794 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).
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