Dinuclear and Mononuclear Platinum(II) and Palladium(II) Complexes with Modified 2,2′-Dipyridylamine Ligands Featuring a Cisplatin Analogous Structure Motif

Sarah Fakih, Wing Chau Tung, Dirk Eierhoff, Christian Mock, and Bernt Krebs*

Münster, Institut für Anorganische und Analytische Chemie der Westfälischen Wilhelms-Universität

Received January 11th, 2005.

Dedicated to Professor Gerd Becker on the Occasion of his 65th Birthday

Abstract. In modern cancer therapy the clinical application of platinum-based drugs is more and more limited by the occurrence of intrinsic or acquired resistances. In this context the potential use of dinuclear platinum complexes in chemotherapy is increasingly relevant. The novel complexes $Pd(Bzdpa)Cl_2$, $Pd_2(C_4H_8(dpa)_2)Cl_4$, and $Pt_2(C_4H_8(dpa)_2)Cl_4$ allow a direct comparison of mono- and dinuclear palladium and platinum complexes respectively deriving from a 2,2′-dipyridylamine (Hdpa) ligand system. They were characterized by single crystal X-ray analysis as well as infrared spectroscopy and elemental analysis. The cisplatin analogous mononuclear palladium complex $Pd(Bzdpa)Cl_2$ (**1**) (Bzdpa: (2,2′-dipyridylbenzyl)amine) belongs to a range of 2,2′-dipyridylamine-based compounds which were extensively studied in our laboratories. **1** crystallizes in the orthorhombic space group $Pna2_1$ with a = 13.722(3), b = 13.457(3), c = 9.483(2), V = 1751.1(6) Å^3, and Z = 4. The metal binding motif of **1** was expanded by a flexible butyl-linker to form the tetradentate $C_4H_8(dpa)_2$ ligand. The resulting isotypic dinuclear complexes $Pd_2(C_4H_8(dpa)_2)Cl_4{\cdot}2CH_3CN$ (**2**) and $Pt_2(C_4H_8(dpa)_2)Cl_4{\cdot}2CH_3CN$ (**3**) crystallize in the triclinic space group $P\bar{1}$ with a = 7.8427(2), b = 8.7940(2), c = 11.7645 (3), α = 79.219(2)°, β = 84.033(2)°, γ = 87.744(2)°, V = 792.58(3) Å^3 (**2**) and a = 7.831(5), b = 8.814(5), c = 11.817(5), α = 79.271(5)°, β = 83.571(5)°, γ = 88.063(5)°, V = 796.3(8) Å^3 (**3**), both with one centrosymmetrical molecule in the unit cell.

Keywords: Platinum; Palladium; 2,2′-Dipyridylamine ligands

Introduction

Chemotherapy with the clinically available platinum-based anticancer drugs is restricted by several drawbacks. Next to the occurrence of severe side effects such as ototoxicity [1], neurotoxicity [2, 3], and nephrotoxicity [4−6] intrinsic or acquired resistances of the tumor cells strongly limit the application of cytostatic platinum compounds. The introduction of so called third generation platinum complexes aims at improved compounds with new structural features leading to altered and possibly advanced functional properties. In this context multinuclear platinum complexes became increasingly relevant in order to circumvent cellular resistance [7−9]. With the compound BBR 3464 the first trinuclear platinum complex entered human clinical trials and is presently undergoing phase II studies [10]. BBR 3464 has superior cytostatic activity in tumor cell lines and xenografts poorly responsive to cisplatin [11, 12].

The bifunctional DNA binding of multinuclear platinum complexes is characterized by the formation of long range intrastrand and interstrand cross-links [13−17]. Due to the flexibility of the bridging groups within most of the multinuclear complexes a large number of different DNA adducts can be formed. Significantly, the DNA kink characteristically induced by cisplatin and its mononuclear analogues cannot be observed [16]. Thus a fundamentally different mode of action of multinuclear platinum complexes is postulated on the basis of a different nuclear processing of the DNA adducts. For BBR 3464 and other dinuclear complexes *Brabec* et. al could show that as a result of the lacking DNA bending the bifunctional DNA adducts do not attract HMG domain proteins which strongly mediate the shielding of cisplatin-induced DNA lesions [18, 19]. The nature of the bridging group is thus of crucial importance for the extent, geometry and intracellular processing of the DNA distortion.

Highly flexible compounds have been realized by using alkyl linkers of various lengths or different alkyldiamine linkers [20−22]. In these complexes the coordinating platinum unit is implemented into the whole molecule as cis- or transplatin in which one ligand is exchanged by the corresponding linker. Here we report the first dinuclear platinum complex deriving from an aromatic 2,2′-dipyridylamine (Hdpa) metal binding unit. Mononuclear complexes with a 2,2′-dipyridylamine ligand system, their reactions with model nucleobases and cytotoxicity have been extensively studied in our group [23−25]. The systematic research on this type of compounds included the substitution of platinum by its homologue palladium for structural investigation purposes. Because of the lanthanoid contraction their ionic radii are nearly the same. Although their kinetic behavior is quite different, they show a similar coordinative behavior.

Our functional investigations which were exclusively carried out on the platinum complexes proved that the steri-

* Prof. Dr. Bernt Krebs
Inst. f. Anorg. u. Analyt. Chemie der Universität
Corrensstr. 36
D-48149 Münster
Fax: +49 (0)251/8338366
e-mail: krebs@uni-muenster.de

cally not demanding 2,2′-dipyridylamine unit provides a favorable structural feature for an unhindered DNA-complex interaction [26] leading to significant cytostatic activity in the range of cisplatin in several tumor cell lines [27, 28]. The platinum homologue of the presented palladium complex Pd(Bzdpa)Cl_2 (**1**) has accordingly been functionally investigated using the cisplatin resistant malignant human glioma cell line U251 [29]. The combination of two Hdpa units by a flexible butyl-linker resulted in the two presented dinuclear isotypic complexes $Pd_2(C_4H_8(dpa)_2)Cl_4$ and $Pt_2(C_4H_8(dpa)_2)Cl_4$. The bridging alkyl chain offers a wide operating range for DNA binding and enables an optimized adjustment of the molecule to the DNA topology.

Experimental

General methods

All starting materials were obtained from commercial sources (Aldrich, Fluka, Merck) and used as received. Elemental analyses were performed on an ELEMENTAR VARIO EL III instrument. IR spectra were obtained on a Bruker Fourier-Transform IFS 48 spectrometer (4000−400 cm^{-1}) from KBr pellets of the newly synthesized compounds. FIR spectroscopy of the complexes was performed on a Bruker IF 113v spectrometer (400−80 cm^{-1}). NMR spectra were recorded on a BRUKER AMX 300 NMR spectrometer.

Due to a low crystal yield analytical measurements (elemental analyses, IR) of the metal complexes were exclusively carried out on the amorphous complex powder. Insufficient solubility of the complexes in any solvent or solvent mixture strongly limited NMR studies, which are therefore not separately discussed.

Syntheses

Synthesis of the ligands

(2,2′-Dipyridyl)benzylamine (Bzdpa)

To a suspension of 5.20 g potassium hydroxide in 30 ml of DMSO 3.42 g (0.02 mol) 2,2′-dipyridylamine were added. The suspension was stirred at room temperature over night and 2.30 ml (0.02 mol, 2.53 g) benzyl chloride were added subsequently. After stirring for another hour the reaction was quenched with 30 ml of water. The precipitated crude product was collected, washed with water and dried in vacuum. For purification the Bzdpa ligand was then dissolved in hot *n*-hexane and precipitated again as a yellow crystalline powder after cooling of the solution.

Yield: 2.30 g (8.80 mmol; 44.0 %)

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 5.43 (s, 2H, CH_2), 6.93 (m, 2H, CH_{Py}), 7.24 (m, 5H, CH_{ar}), 7.66 (m, 2H, CH_{Py}), 8.28 (d, 2H, CH_{Py})

1,4-*N*,*N*′-Di-(2,2′-dipyridylamine)butane ($C_4H_8(dpa)_2$)

To a suspension of 5.20 g potassium hydroxide in 30 ml of DMSO 3.42 g (0.02 mol) 2,2′-dipyridylamine were added. The suspension was stirred at room temperature over night and 1.32 ml (0.01 mol, 3.10 g) 1,4-diiodobutane were added subsequently. After stirring for another 5 hours the reaction was quenched with 70 ml of water and the solution repeatedly extracted with diethylether (4 x 30 ml). The combined organic extracts were dried over $MgSO_4$. The solvent was removed in vacuum to yield $C_4H_8(dpa)_2$ as a yellow powder.

Yield: 2.41 g (6.08 mmol; 60.8 %)

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.76 (m, 4H, CH_2), 4.20 (m, 4H, CH_2-N), 6.79 (dd, 4H, CH_{Py}), 7.03 (dt, 4H, CH_{Py}), 7.45 (ddd, 4H, CH_{Py}), 8.30 (ddd, 4H, CH_{Py})

Synthesis of the complexes

Pd(Bzdpa)Cl_2, $Pd_2(C_4H_8(dpa)_2)Cl_4$

0.326 g (1 mmol) $K_2[PdCl_4]$ were dissolved in 50 ml of water and stirred for 10 min. The respective ligand was dissolved in a small amount of ethanol and added to the light brown solution (mononuclear complex: 1 mmol, dinuclear complex: 0.5 mmol). The reaction mixture was stirred overnight at room temperature. The resulting precipitates were collected, washed with water and dried in vacuum. Diffusion of diethyl ether into a solution of complex **1** in DMF yielded pale yellow single crystals after three weeks at ambient temperature. Single crystals of compound **2** were obtained by diffusion of diethyl ether into a solution of the complex in acetonitrile/methanol after one week at ambient temperature.

Pd(Bzdpa)Cl_2: Yellow powder. Yield: 377 mg (0.86 mmol, 86 %). $[C_{17}H_{15}Cl_2N_3Pd]$ (M_r = 438.7 g/mol): C: 46.41 (calc. 46.54); H: 3.53 (3.44); N: 9.54 (9.58) %

IR (KBr, 4000−400 cm^{-1}): 3083 w, 3037 w, 1599 s, 1487 s, 1459 s, 1445 s, 1345 m, 1265 m, 1228 m, 1144 m, 1053 w, 1003 w, 915 w, 878 w, 790 s, 773 s, 698 s, 528 m, 502 w, 448 w, 435 w

FIR (PE, 400−80 cm^{-1}): 393 m, 339 s, 302 m, 243 w, 199 w, 169 m, 120 m

$Pd_2(C_4H_8(dpa)_2)Cl_4$: Light orange powder. Yield: 170 mg (0.23 mmol, 23 %). $[C_{24}H_{24}Cl_4N_6Pd_2]$ (M_r = 751.1 g/mol): C: 37.97 (calc. 38.38); H: 3.13 (3.22); N: 11.27 (11.19) %

IR (KBr, 4000−400 cm^{-1}): 3081 br, 3055 w, 3008 w, 2940 m, 1574 s, 1469 s, 1424 s, 1378 m, 1317 w, 1273 s, 1183 s, 1148 w, 1080 w, 988 m, 865 m, 775 s, 737 w, 609 w, 531 w

FIR (PE, 400−80 cm^{-1}): 431 s, 409 s, 341 m, 330 m, 225 w, 143 m, 129 m, 92 m

$Pt_2(C_4H_8(dpa)_2)Cl_4$

0.415 g (1 mmol) $K_2[PtCl_4]$ were dissolved in 50 ml of water. After stirring the solution for 10 min 0.200 g $C_4H_8(dpa)_2$ (0.5 mmol) were dissolved in a small amount of ethanol and added to the red solution. The reaction mixture was stirred overnight at 50 °C. The resulting precipitate was collected, washed with water and dried in vacuum. Diffusion of diethyl ether into a solution of the complex in acetonitrile yielded pale yellow single crystals of compound **3** after one week at ambient temperature.

$Pt_2(C_4H_8(dpa)_2)Cl_4$: Yellow powder. Yield: 490 mg (0.53 mmol, 53 %). $[C_{24}H_{24}Cl_4N_6Pt_2]$ (M_r = 928.5 g/mol): C: 30.94 (calc. 31.05); H: 2.72 (2.61); N: 8.97 (9.05) %

IR (KBr, 4000−400 cm^{-1}): 3078 w, 3008 w, 2948 w, 2856 w, 1637 w, 1577 s, 1520 w, 1469 s, 1436 s, 1385 m, 1302 m, 1184 s, 1156 m, 1079 m, 988 m, 956 w, 865 m, 777 s, 738 m, 639 w, 608 w, 532 w, 509 w

FIR (PE, 400−80 cm^{-1}): 433 m, 410 s, 335 s, 227 w, 135 m, 91 w

Single crystal structure analyses

The unit cell data and diffraction intensities of **1** were collected on a SIEMENS-P3 diffractometer with graphite monochromated Mo-K_α radiation (λ = 0.71073 Å) at 293 K, intensity data of compound **2** and **3** on a BRUKER AXS SMART 6000 with monochromated Cu-K_α radiation (Göbel mirror, λ = 1.54178 Å) at 110 K. The complete data collection parameters and details of the structure solutions and refinements are summarized in Table 1. The structure of **1** was solved by direct methods (SHELXS 97 [30]) while the structure of **2** was determined by Patterson synthesis (SHELXS 97 [30]). The structure of compound **3** was solved by

Table 1 Crystal data and structure refinement for **1**−**3**

		1	**2**	**3**
Empirical formula		$C_{17}H_{15}Cl_2N_3Pd$	$C_{28}H_{30}Cl_4N_8Pd_2$	$C_{28}H_{30}Cl_4N_8Pt_2$
Formula weight, g/mol		438.62	833.20	1010.57
Crystal color and shape		pale yellow cuboids	yellow plates	pale yellow cuboids
Crystal system		orthorhombic	triclinic	triclinic
Space group		*Pna*2$_1$ (No.33)	*P*-1 (No.2)	*P*-1 (No.2)
Unit cell dimensions	*a*	13.722(3) Å	7.8427(2) Å	7.831(5) Å
	b	13.457(3) Å	8.7940(2) Å	8.814(5) Å
	c	9.483(2) Å	11.7645(3) Å	11.817(5) Å
	α	90°	79.219(2)°	79.271(5)°
	β	90°	84.033(2)°	83.571(5)°
	γ	90°	87.744(2)°	88.063(5)°
Volume, Å^3		1751.1(6)	792.58(3)	796.3(8)
Formula units/cell		4	1	1
D_c, g/cm^3		1.664	1.746	2.107
Diffractometer (wavelength, Å)		SIEMENS-P3 (Mo-Kα, λ=0.71073)	BRUKER AXS SMART 6000 (Cu-Kα, λ=1.54187)	BRUKER AXS SMART 6000 (Cu-Kα, λ=1.54187)
Monochromator		Graphite	Göbel mirror	Göbel mirror
Temperature, K		293(2)	110(2)	110(2)
Absorption coefficient, mm^{-1}		1.366	12.526	9.144
Data collection range		4.24° < 2θ < 53.96°	7.68° < 2θ < 142.58°	3.52° < 2θ < 51.80°
Indices		−17 ≤ h ≤ 17 −17 ≤ k ≤ 17 −10 ≤ l ≤ 12	−9 ≤ h ≤ 8 −10 ≤ k ≤ 9 −14 ≤ l ≤ 14	−8 ≤ h ≤ 7 −9 ≤ k ≤ 10 −13 ≤ l ≤ 13
Reflections collected		7731	4650	4549
Independent reflections		2368	2658	2644
Program for structure solution		SHELXS-97	SHELXS-97	SIR 97
Program for structure refinement			SHELXL-97, Full matrix on F^2	
Goodness-of-fit on F^2		0.997	1.034	1.019
Final R values (I>2σ(I))		R1 = 0.0320, *w*R2 = 0.0775[a]	R1 = 0.0425, *w*R2 = 0.1099[b]	R1 = 0.0624, *w*R2 = 0.1606[c]
Final R value (all data)		R1 = 0.0359, *w*R2 = 0.0761[a]	R1 = 0.0450, *w*R2 = 0.1114[b]	R1 = 0.0688, *w*R2 = 0.1635[c]
$(\Delta/\rho)_{max}$; $(\Delta/\rho)_{min}$, e$^-$ Å^{-3}		0.0385; −1.226	1.102; −1.126	3.455; −3.099

$w = 1/[\sigma^2(F_o^2) + (xP)^2 + yP]$, $P = (F_o^2 + 2F_c^2)/3$; [a] x = 0.0551, y = 0; [b] x = 0.0834, y = 0; [c] x = 0.1201, y = 0.

SIR 97 [31]. All structures were refined in full-matrix least-squares methods on F_o^2 using the program SHELXL 97 [32]. Anisotropic displacement parameters were used to refine the positions of all non-hydrogen atoms. Hydrogen atoms were placed at calculated positions according to a riding model with group isotropic temperature factors. The residual value wR_2 in Table 1 is defined as $[w(F_o^2 - F_c^2)^2 / w(F_o^2)^2]^{1/2}$. Selected bond lengths and angles are reported in Tables 2 and 3. Atomic coordinates, thermal parameters, and all bond lengths and angles have been deposited with the Cambridge Crystallographic Data Center (CCDC). Copies of the data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html or on application to the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, Fax: (international) + 44 -1223/336-033; e-mail: deposit@ccdc.cam.ac.uk on full quoting the journal citation and deposition number CCDC 144494 (**1**), CCDC 265544 (**2**), CCDC 265543 (**3**).

Results and Discussion

Crystal structure of Pd(Bzdpa)Cl$_2$ (1)

The mononuclear palladium complex **1** crystallizes in the space group *Pna*2$_1$ (No. 33) with four neutral Pd(Bzdpa)Cl$_2$ complex molecules in the orthorhombic unit cell. The structure of **1** is presented in Figure 1 with thermal ellipsoids (50 % probability). Figure 2 shows the unit cell of the complex.

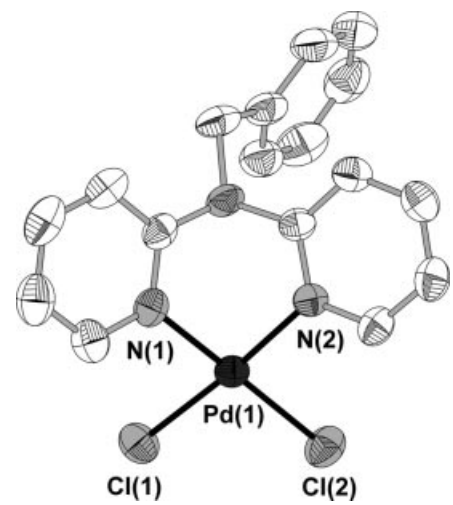

Fig. 1 Ellipsoid plot of **1** (50 % probability); hydrogen atoms omitted for clarity

The metal center of **1** is coordinated by a N_2Cl_2 donor set provided by the two aromatic pyridine systems and two chlorine ions in *cis*-position to complete the first coordination sphere. A square-planar coordination is generated from which the centered palladium ion deviates only by

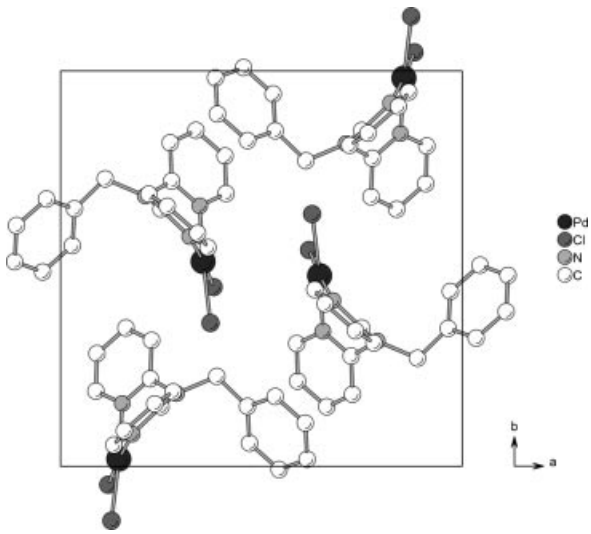

Fig. 2 Unit cell of **1**, view along [001]

0.003 Å. Together with the bidentate Bzdpa ligand the palladium atom closes a six membered chelate ring adopting a boat conformation. The planes through the heterocyclic rings of the ligand include a dihedral angle of 55.8° which corresponds to commonly observed values for 2,2′-dipyridiylamine-based ligand systems. All bond lengths and angles are well within expected ranges. Selected values are reported in Table 2. The packing of the neutral complex molecules in the crystal structure results in a shortest intermolecular metal-metal distance of 6.212(1) Å (Pd(1)···Pd(1b); b = −1−x, 1−y, −0.5+z), thus indicating no intermetallic interactions.

Table 2 Selected bond lengths [Å] and angles [°] in **1**

atoms	bond length	atoms	angles
Pd(1)-Cl(1)	2.312(1)	Cl(1)-Pd(1)-Cl(2)	90.5(1)
Pd(1)-Cl(2)	2.314(1)	Cl(1)-Pd(1)-N(1)	90.7(1)
Pd(1)-N(1)	2.045(4)	Cl(2)-Pd(1)-N(2)	92.2(1)
Pd(1)-N(2)	2.057(4)	N(1)-Pd(1)-N(2)	86.8(2)

Crystal structures of $Pd_2(C_4H_8(dpa)_2)Cl_4{\cdot}2CH_3CN$ (2) and $Pt_2(C_4H_8(dpa)_2)Cl_4{\cdot}2CH_3CN$ (3)

The isotypic compounds **2** and **3** crystallize in the triclinic space group $P\bar{1}$ (No. 2) with a dinuclear neutral complex molecule and two acetonitrile molecules in each unit cell. The structure of the complex molecule in **2** is presented in Figure 3 with thermal ellipsoids (50 % probability). Figure 4 displays the unit cell of **2**.

The $C_4H_8(dpa)_2$ ligand derives from 2,2′-dipyridylamine by substitution of the hydrogen at the bridging amine. The dipyridyl units coordinate the particular metal centers via their two nitrogen donor atoms. Two chloride ions in *cis*-position complete the coordination sphere resulting in a square-planar coordination around the metal cations. The

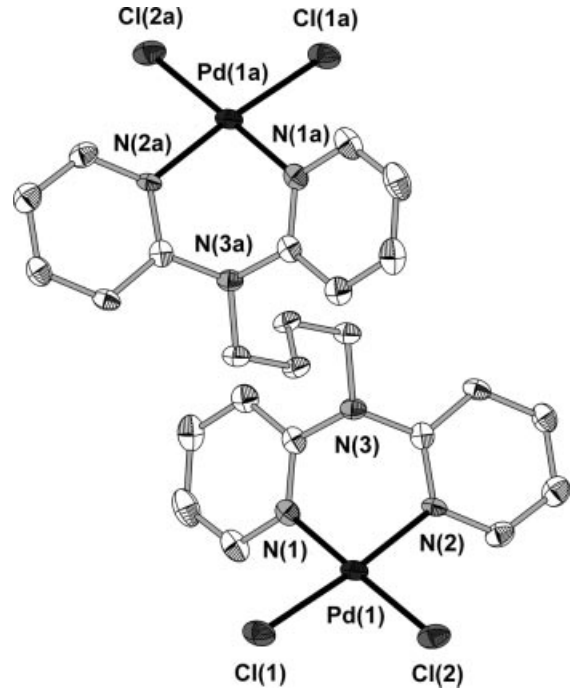

Fig. 3 Ellipsoid plot of **2** (50 % probability); hydrogen atoms omitted for clarity

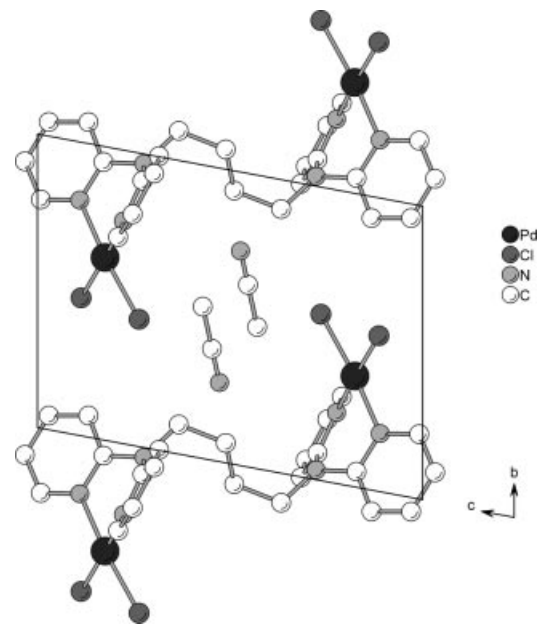

Fig. 4 Unit cell of **2**, view along [100]

palladium atoms as well as the platinum atoms deviate only marginally from the planes through the first coordination spheres (0.010 Å in **2** and 0.001 Å in **3**) not distorting the virtually ideal square-planar structure. Each metal center closes a six membered chelate ring which adopts a distinct boat conformation. Within the structures of both dinuclear complexes an inversion center is located in the middle of the bridging butyl chain generating one half of each mol-

ecule. The planes through the heterocyclic aromatic ring systems of the coordinating $C_4H_8(dpa)_2$ ligand form a dihedral angle of 52.7° in **2** and 53.5° in **3**. All bond lengths and angles are well within the expected ranges. Selected values are reported in Table 3. The intramolecular metal-metal distances amount in **2** to 9.172(1) Å and in **3** to 9.180(3) Å. The shortest intermolecular metal-metal distance for the palladium complex is 4.27(1) Å and for the platinum complex 4.33(1) Å (M(1)···M(1b); b = 1−x, 1−y, 2−z; M = Pd, Pt). Intermetallic interactions can thus be excluded.

Table 3 Selected bond lengths [Å] and angles [°] in **2** and **3**

2	bond length	**3**	bond length
Pd(1)-Cl(1)	2.292(1)	Pt(1)-Cl(1)	2.292(3)
Pd(1)-Cl(2)	2.297(1)	Pt(1)-Cl(2)	2.312(4)
Pd(1)-N(1)	2.017(4)	Pt(1)-N(1)	2.004(9)
Pd(1)-N(2)	2.023(4)	Pt(1)-N(2)	1.999(9)
2	angles	**3**	angles
Cl(1)-Pd(1)-Cl(2)	91.2(1)	Cl(1)-Pt(1)-Cl(2)	90.7(1)
Cl(1)-Pd(1)-N(1)	90.6(1)	Cl(1)-Pt(1)-N(1)	91.1(3)
Cl(2)-Pd(1)-N(2)	91.9(1)	Cl(2)-Pt(1)-N(2)	91.8(3)
N(1)-Pd(1)-N(2)	86.5(2)	N(1)-Pt(1)-N(2)	86.4(4)

The potential use of dinuclear platinum complexes in cancer chemotherapy is expected to offer important advantages over the clinically applied mononuclear compounds. A more efficient DNA interaction of two DNA-bound platinum centers is not only believed to result in a higher cytostatic activity but to overcome intrinsic or acquired resistances of tumor cells towards platinum chemotherapeutics. The presented structures show the extension of well investigated and highly cytostatic mononuclear 2,2′-dipyridylamine metal complexes to their dinuclear correspondents. The mononuclear 2,2′-dipyridylamine compounds tightly fit into the DNA structure due to a lack of sterical hindrance of the flat aromatic systems around the metal center. Variable extensions of the ligand system at the bridging secondary amine strongly influence the cytostatic activity of the compound by introducing electronic interactions of different alkyl groups or intercalation effects through additional aromatic ring systems as it is shown in complex **1**. However, the operating range of these mononuclear compounds is limited to only one selective DNA lesion. Consequently, the introduction of a second metal binding unit which can also interfere with the DNA will significantly enhance the cytotoxic effect. To optimize the DNA binding capacity of two 2,2′-dipyridylamine units the butyl-linker in the complex molecules in **2** and **3** was chosen to cover a wide range of the duplex and to be highly flexible in order to adapt to the DNA structure. In contrast to the selective intrastrand cross-link of the mononuclear complex the dinuclear platinum compound is expected to adopt preferred long range intra- and interstrand cross-linking modes, thus leading to a more efficient DNA distortion.

Acknowledgements. The authors would like to thank the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie (FCI) for financial support and the W.C. HERAEUS GmbH for substantial support of their work. *S. F.* thanks the International Graduate College "Template Directed Chemical Synthesis" for a graduate fellowship and *W. C. T.* gratefully acknowledges a research fellowship from the Erasmus-Program. *D. E.* would like to thank the Westfälische Wilhelms-Universität for a graduate fellowship.

References

[1] S. D. Schaefer, J. D. Post, L. G. Close, C. G. Wright, *Cancer* **1985**, *56*, 1934.
[2] D. Screnci, M. J. McKeage, *J. Inorg. Biochem.* **1999**, *77*, 105.
[3] D. S. Alberts, J. K. Noel, *Anti-Cancer Drugs* **1995**, *3*, 369.
[4] M. P. Goren, R. K. Wright, M. E. Horowitz, *Cancer Chemother. Pharmacol.* **1986**, *18*, 69.
[5] M. P. Goren, R. K. Wright, M. E. Horowitz, C. B. Pratt, *Am. J. Clin. Pathol.* **1986**, *6*, 780.
[6] J. T. Hartmann, C. Kollmannsberger, L. Kanz, C. Bokemeyer, *Int. J. Cancer* **1999**, *83*, 866.
[7] B. A. J. Jansen, J. Brouwer, J. Reedijk, *J. Inorg. Biochem.* **2002**, *89*, 197.
[8] S. Komeda, M. Lutz, A. L. Spek, M. Chikuma, J. Reedijk, *Inorg. Chem.* **2000**, *39*, 4230.
[9] S. Komeda, G. V. Kalayda, M. Lutz, A. L. Spek, Y. Yamanaka, T. Sato, M. Chikuma, J. Reedijk, *J. Med. Chem.* **2003**, *46*, 1210.
[10] D. I. Jodrell, T. R. J. Evans, W. Steward, D. Cameron, J. Prendiville, C. Aschele, C. Noberasco, M. Lind, J. Carmicheal, N. Dobbs, G. Camboni, B. Gatti, F. De Braud, *Eur. J. Cancer* **2004**, *40*, 1872.
[11] A. Riccardi, D. Meco, C. Ferlini, T. Servidei, G. Carelli, G. Segni, C. Manzotti, R. Riccardi, *Cancer Chemother. Pharmacol.* **2001**, *47*, 498.
[12] P. Perego, L. Gatti, C. Caserini, R. Supino, D. Colangelo, R. Leone, S. Spinelli, N. Farrell, F. Zunino, *J. Inorg. Biochem.* **1999**, *77*, 59.
[13] J. W. Cox, S. Berners-Price, M. S. Davies, Y. Qu, N. Farrell, *J. Am. Chem. Soc.* **2001**, *123*, 1316.
[14] Y. Qu, N. J. Scarsdale, M.-C. Tran, N. Farrell, *J. Inorg. Biochem.* **2004**, *98*, 1585.
[15] S. Berners-Price, M. S. Davies, J. W. Cox, D. S. Thomas, N. Farrell, *Chem. Eur. J.* **2003**, *9*, 713.
[16] J. Kasparkova, K. J. Mellish, Y. Qu, V. Brabec, N. Farrell, *Biochem.* **1996**, *35*, 16705.
[17] Y. Zou, B. van Houten, N. Farrell, *Biochem.* **1994**, *33*, 5404.
[18] J. Kasparkova, N. Farrell, V. Brabec, *J. Biol. Chem.* **2000**, *275*, 15789.
[19] J. Zehnulova, J. Kasparkova, N. Farrell, V. Brabec, *J. Biol. Chem.* **2001**, *276*, 22191.
[20] B. A. J. Jansen, J. van der Zwan, H. den Dulk, J. Brouwer, J. Reedijk, *J. Med. Chem.* **2001**, *44*, 245.
[21] A. Hegmans, Y. Qu, L. R. Kelland, J. D. Roberts, N. Farrell, *Inorg. Chem.* **2001**, *40*, 6108.
[22] B. A. J. Jansen, J. van der Zwan, J. Reedijk, H. den Dulk, J. Brouwer, *Eur. J. Inorg. Chem.* **1999**, 1429.
[23] M. J. Rauterkus, S. Fakih, C. Mock, I. Puscasu, B. Krebs, *Inorg. Chim. Acta* **2003**, *350*, 355.
[24] I. Puscasu, C. Mock, M. J. Rauterkus, A. Röndigs, G. Tallen, S. B. Gangopadhyay, J. E. A. Wolff, B. Krebs, *Z. Anorg. Allg. Chem.* **2001**, *627*, 1292.
[25] C. Mock, I. Puscasu, M. J. Rauterkus, G. Tallen, J. E. A. Wolff, B. Krebs, *Inorg. Chim. Acta* **2001**, *319*, 109.

[26] M. J. Bloemink, H. Engelking, S. Karentzopoulos, B. Krebs, J. Reedijk, *Inorg. Chem.* **1996**, *35*, 619.
[27] S. B. Gangopadhyay, A. Röndigs, B. Kangarloo, B. Krebs, J. E. A. Wolff, *Anticancer Res.* **2001**, *21*, 2039.
[28] G. Tallen, C. Mock, S. B. Gangopadhyay, B. Kangarloo, B. Krebs, J. E. A. Wolff, *Anticancer Res.* **2000**, *20*, 445.
[29] N. Möller, B. S. Kangarloo, I. Puscasu, C. Mock, B. Krebs, J. E. A. Wolff, *Anticancer Res.* **2000**, *20*, 4435.
[30] G. M. Sheldrick, *SHELXS-97 Programm zur Lösung von Kristallstrukturen*, Universität Göttingen, **1997**.
[31] A. Altomare, M. C. Burla, M. Camalli, G. Cascarano, C. Giacovazzo, A. Gagliardi, A. G. G. Moliterni, G. Polidori, R. Spagna, *SIR 97*, Release 1.02, Roma, Bari, Perugia, **1997**.
[32] G. M. Sheldrick, *SHELXL-97 Programm zur Verfeinerung von Kristallstrukturen*, Universität Göttingen, **1997**.

