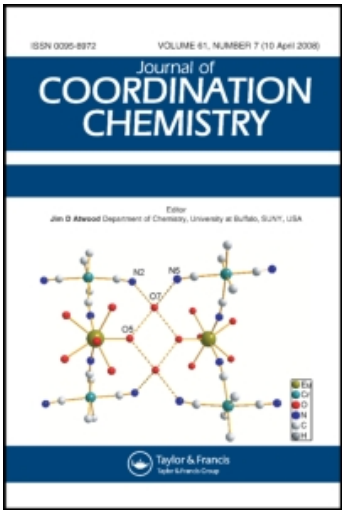

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An anticancer metallobenzylmalonate: crystal structure and anticancer activity of a palladium complex of 2,2'-bipyridine and benzylmalonate

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An anticancer metallobenzylmalonate: crystal structure and anticancer activity of a palladium complex of 2,2′-bipyridine and benzylmalonate

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The novel metallobenzylmalonate $[Pd(bipy)(bmal)] \cdot 2H_2O$ (bipy = 2,2′-bipyridyl, bmal = benzylmalonate) has been synthesized and structurally characterized by element analyses, electronic spectroscopy, electrophoresis and single-crystal X-ray diffraction. The complex is orthorhombic, space group $Pna2_1$, with $a = 7.637(2)$, $b = 13.018(4)$, $c = 20.961(7)$ Å, $V = 2083.8(12)$ Å^3, $Z = 4$. Pd(1) is four coordinated by two nitrogen atoms from the bipy ligand and two oxygen atoms from bmal with square planar geometry. In the lattice, π–π stacking and hydrogen bonding are the main intermolecular interactions and propitious for non-covalent insertion into DNA molecules. Electronic spectra confirm that the main reaction mode of the compound with DNA is non-covalent. Electrophoresis shows the cleavage of both supercoiled and circular DNA to form small molecular fragments under the action of the complex. The complex shows excellent anti-cancer activity towards lung cancer AGZY-83a.

Keywords: Palladium; Bipyridyl; Benzylmalonate; Crystal structure; DNA binding; Electrophoresis; Anti-cancer activity

1. Introduction

Platinum complexes such as *cis*-DDP (*cis*-diaminedichloroplatinum(II) or *cis*-platin) are subject to intense research as therapeutic agents [1, 2]. Because of the similar coordination modes and chemical properties of palladium(II) and platinum(II), the anticancer activity of palladium complexes has also drawn broad attention. In some systems, palladium complexes have greater activity than platinum analogues [3, 4]. More recently, research on the inhibition of lung cancer cell AGZY-83a and interaction of DNA with palladium(II) complexes has been reported [5–9]. We are interested not

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only in the interaction mechanism with DNA but also in designing new molecules as efficient drugs. We report herein the syntheses and crystal structure of a novel palladium complex containing benzylmalonate and 2,2′-bipyridine, its interaction with DNA and its activity towards AGZY-83a. To the best of our knowledge, the bioactivity of palladium complexes that contain benzylmalonate as a ligand has not yet been described.

2. Experimental

2.1. *Reagents and methods*

$PdCl_2$ and 2,2′-bipyridine (bpy) were of reagent grade and used without further purification. The benzylmalonic acid (bmal) used was a biochemical reagent. Elemental analyses (C,H,N) were performed on a Perkin-Elmer2400 CHN instrument. Pd was determined using a Leaman ICP spectrometer.

2.2. *Synthesis of [Pd(bipy)(bmal)] · 2H$_2$O (1)*

Aqueous solutions of $PdCl_2$, benzylmalonic acid and 2,2′-bipyridine in ethanol were mixed at a 1 :1 : 1 mol ratio and pH kept at 6.7 with stirring for 2 h at room temperature. After filtering, the clear solution was left to stand at room temperature (about 20°C). Seven days later, the yellow crystals that had formed were collected (yield: 27%, based on Pd). Anal. Calcd for $C_{20}H_{21}N_2O_{6.50}Pd$(%): C, 48.1; H, 4.2; N, 5.6; Pd, 21.3. Found: C, 47.9; H, 4.3; N, 5.4; Pd, 21.6.

2.3. *X-ray crystallography*

The crystal structure of **1** was determined by single-crystal X-ray diffraction. A suitable single crystal of dimensions $0.24 \times 0.22 \times 0.20\,mm^3$ was mounted in a glass fibre capillary. Data were collected on a Bruker Smart 100 CCD X-ray single-crystal diffractometer with Mo-Kα radiation ($\lambda = 0.71073$ Å) at 293(2) K in the range of $1.84 < \theta < 26.42^\circ$ with the ω-scan technique. The structure was solved by direct methods using SHELXL 97 [10, 11] and refined by full-matrix least-squares methods on F^2. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were located from different Fourier maps. Structure solution and refinement based on 3796 independent reflections with $I > 2\sigma(I)$ and 281 parameters gave $R_1 = 0.0527$, $wR_2 = 0.0990$. Crystal data and structure refinement details are summarized in the table 1 and selected bond lengths and angles are given in table 2.

3. Result and discussion

3.1. *Crystal structure of [Pd(bipy)(bmal)] · 2H$_2$O (1)*

Complex **1** contains one crystallographically independent palladium atom, as shown in figure 1. Pd(1) is four coordinated by two nitrogen atoms from the bipy ligand and two oxygen atoms from the bmal ligand, with square planar geometry. As usual, the

Table 1. Summary of crystallographic data for **1**.

Empirical formula	$C_{20}H_{21}N_2O_{6.50}Pd$
Formula weight	499.79
Crystal system, space group	Orthorhombic, $Pna2_1$
Unit cell dimensions (Å)	$a = 7.637(2)$ $b = 13.018(4)$ $c = 20.961(7)$
V, Z	2083.8(12) Å^3, 4
Crystal size (mm^3)	$0.24 \times 0.22 \times 0.20$
θ range for data collection (°)	$1.84 < \theta < 26.42$
Limiting indices	$-9 \le h \le 6$, $-13 \le k \le 16$, $-26 \le l \le 20$
Reflections collected/unique	9272/3796 [R(int) = 0.0641]
Completeness	99.7%
Data/restraints/parameters	3796/1/281
Goodness-of-fit on F^2	1.003
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0527$, $wR_2 = 0.0990$
R indices (all data)	$R_1 = 0.0942$, $wR_2 = 0.1118$
Largest diff. peak and hole (e Å^{-3})	0.796 and −0.480

Table 2. Selected bond lengths (Å) and angles (°).

Pd(1)–O(1)	1.986(5)	Pd(1)–N(1)	1.992(7)
Pd(1)–N(2)	1.997(6)	Pd(1)–O(3)	1.997(6)
O(1)–C(19)	1.298(10)	O(2)–C(19)	1.219(8)
O(3)–C(20)	1.288(9)	O(4)–C(20)	1.226(9)
N(1)–C(1)	1.340(11)	N(1)–C(5)	1.354(10)
N(2)–C(10)	1.307(13)	N(2)–C(6)	1.355(10)
O(1)–Pd(1)–N(1)	93.0(3)	O(1)–Pd(1)–N(2)	173.1(3)
N(1)–Pd(1)–N(2)	80.6(3)	O(1)–Pd(1)–O(3)	91.5(2)
N(1)–Pd(1)–O(3)	174.3(2)	N(2)–Pd(1)–O(3)	94.7(2)
C(19)–O(1)–Pd(1)	120.1(5)	C(20)–O(3)–Pd(1)	120.4(5)
C(1)–N(1)–Pd(1)	123.7(6)	C(5)–N(1)–Pd(1)	115.5(5)
C(10)–N(2)–Pd(1)	126.7(8)	C(6)–N(2)–Pd(1)	114.8(5)

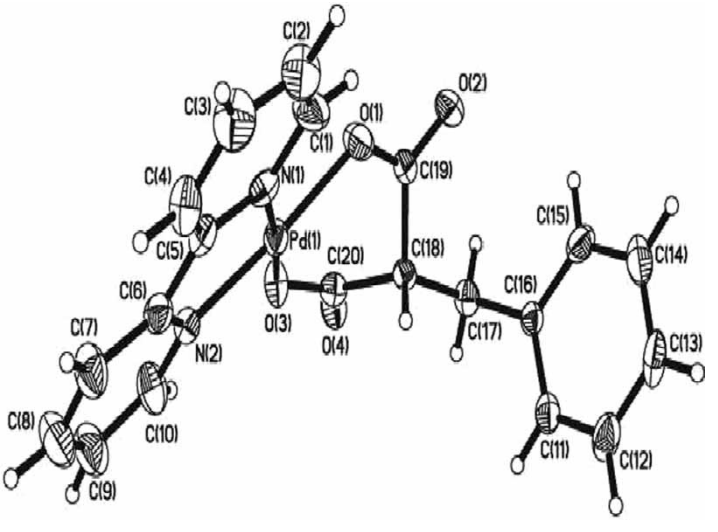

Figure 1. The structure of [Pd(bipy)(bmal)] · $2H_2O$ showing the atom numbering scheme.

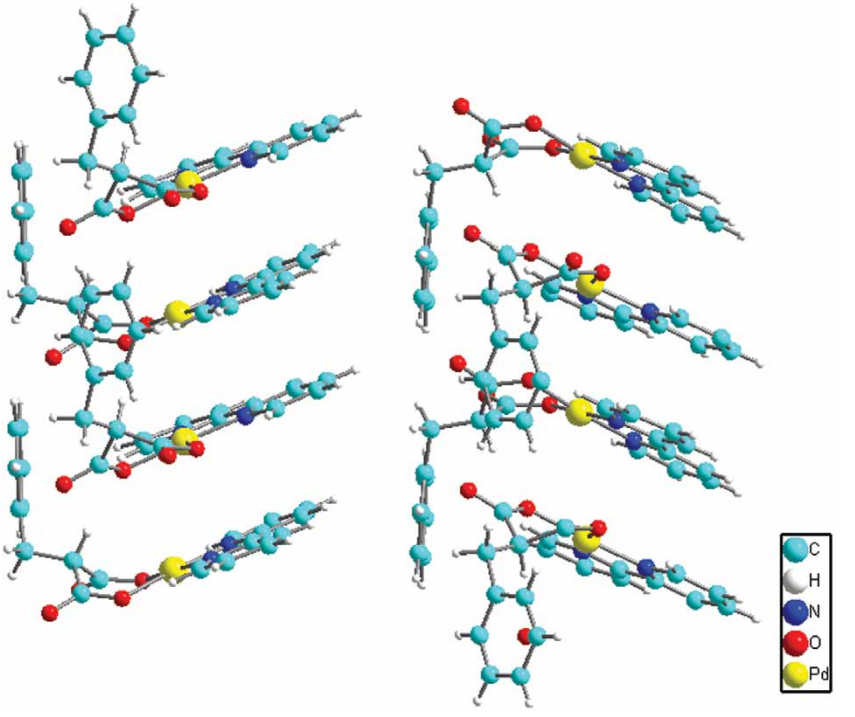

Figure 2. View of the 1D chain formed through π–π stacking interactions and the packing arrangement of [Pd(bipy)(bmal)]·$2H_2O$ along the *b* axis.

carboxy group of bmal adopts a unidentate coordination mode. Pd–O bond lengths are 1.986 and 1.997 Å, and the Pd–N distances are 1.992 and 1.997 Å. The N–Pd–N(O) bond angles are in the range 80.6–174.3°.

The structurally interesting feature of complex **1** is the π–π stacking mode as shown in figure 2. The bipy ligand often adopts π–π stacking modes for structural stabilization [12–17]. Because the aromatic rings of bipy and bmal are nearly orthogonal, bmal does not participate in the stacking. Stacking of bipy ligands of adjacent molecules forms a distorted 1D and bmal ligands form a helical arrangement along the 2_1 axis. Adjacent 1D chains are not parallel, as shown as figure 2. Furthermore, there are strong hydrogen bonds arising from O atoms of bmal and water molecules (O2···O5 2.752 Å, O3···O7 2.692 Å, O6···O5 2.650 Å, O6···O7 2.747 Å; O5, O6 and O7 are from water molecules). Hydrogen bonds connect the 1D chains into a 3D framework. The connection of π–π stacking and hydrogen bonding may be propitious for non-covalent insertion into DNA.

3.2. *Electronic spectra*

Figure 3 shows the electronic spectrum of solution involving reaction of **1** and sperm DNA. The absorbance maximum of the complex is at 258 nm ($\pi \rightarrow \pi^*$). A hypochromic red shift of the absorption maximum occurs with increasing DNA concentration. This is similar to the case of the reaction of related Pd bipy complexes and calf thymus

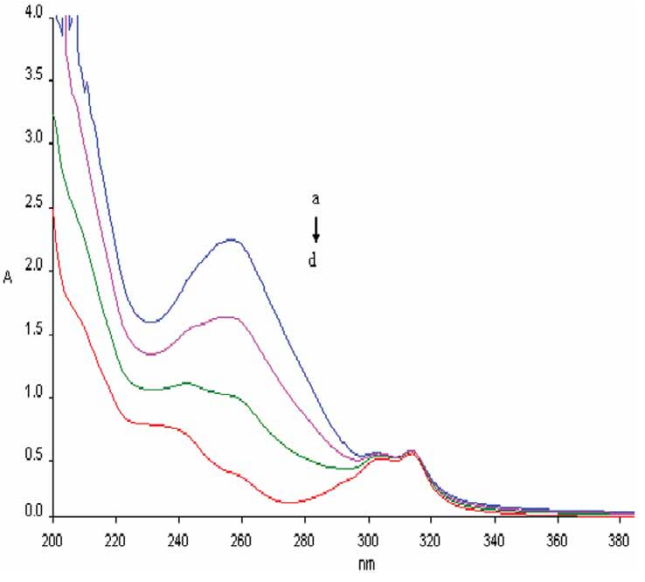

Figure 3. Electronic spectra of DNA and **1** at a: $C_M = 6.8 \times 10^{-5}\,mol\,L^{-1}$; b: $C_{DNA} = 1.2 \times 10^{-4}\,mol\,L^{-1}$ + a; c: $C_{DNA} = 2.4 \times 10^{-4}\,mol\,L^{-1}$ + a; d: $C_{DNA} = 3.6 \times 10^{-4}\,mol\,L^{-1}$ + a.

DNA [14]. The main reaction mode of the compound with DNA is thought to be non-covalent insertion.

3.3. *Electrophoresis*

Electrophoresis runs of pBR322 plasmid DNA incubated with different concentrations of **1** for 1 h are shown in figure 4. Pure pBR322 plasmid DNA gives two bands corresponding to supercoiled form (I) and nicked circular form (II) (lane l) in which form (I) predominates [15]. When the concentration of the complex was further increased, the two DNA bands become narrow and the band intensity is found to decrease gradually (lanes 2–4). This is considered to be due to cleavage of both supercoiled and circular DNA to form small molecular fragments. When the concentration is low, electrophoretic mobility of the bands is found to decrease slightly with increasing concentration of complex, believed to be due to the intercalation of the complex with DNA, thus increasing its molecular mass.

3.4. *Anti-cancer activity*

Tumor inhibition of the compound towards the lung cancer cell line AGZY-83a at concentrations 6.1, 12.2, 24.4, 48.8 and 97.6 $\mu g\,mL^{-1}$ is 5.9, 11.7, 21.1, 53.1 and 88.9%, respectively. There is a linear relation between the concentration and the extent of tumor-inhibition with an IC_{50} calculated by least-squares method of 55.4 $\mu g\,mL^{-1}$. The complex has strong anti-cancer activity.

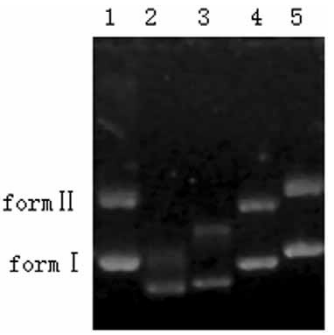

Figure 4. Electrophoresis runs showing photoactivated cleavage of pBR322 DNA in the presence of the complex. Lane 1: $C_{DNA} = 1.23 \times 10^{-4}\,\mu g\,mL^{-1}$; lane 2: $C_{DNA} = 1.23 \times 10^{-4}\,\mu g\,mL^{-1} + \mathbf{1} = 3.0 \times 10^{-3}\,mol\,L^{-1}$; lane 3: $C_{DNA} = 1.23 \times 10^{-4}\,\mu g\,mL^{-1} + \mathbf{1} = 1.5 \times 10^{-3}\,mol\,L^{-1}$; lane 4: $C_{DNA} = 1.23 \times 10^{-4}\,\mu g\,mL^{-1} + \mathbf{1} = 7.5 \times 10^{-4}\,mol\,L^{-1}$; lane 5: $C_{DNA} = 1.23 \times 10^{-4}\,\mu g\,mL^{-1} + \mathbf{1} = 3.75 \times 10^{-4}\,mol\,L^{-1}$.

Supplementary data

Crystallographic data (excluding structure factors) for the structure have been deposited with Cambridge Crystallographic Data Centre as supplementary publication CCDC 252835. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44 1223 336033 or E-mail: deposit@ccdc.cam.ac.uk).

References

[1] G. Admiraal, M. Alink, C. Actona, F.J. Dijt, C.J. Garderen, R.A. Graa, J. Reedijk. *J. Am. Chem.*, **114**, 930 (1992).
[2] M.A. Elizondo-Riojas, J. Kozelka. *Inorg. Chim. Acta*, **297**, 417 (2000).
[3] R. Mital, G.M. Shah, T.S. Srivastava, R.K. Bhattacharya. *Life Sci.*, **50**, 781 (1992).
[4] L. Tusek-Bozic, A. Furlani, V. Scarcia, E.D. Clercq, J. Balzarini. *J. Inorg. Biochem.*, **72**, 201 (1998).
[5] E.J. Gao, Q.T. Liu. *Acta Chim. Sina.*, **60**, 674 (2002).
[6] E.J. Gao, S.M. Zhao, Q.T Liu, R. Xu. *Acta Chim. Sin.*, **62**, 593 (2004).
[7] E.J. Gao, S.M. Zhao, Q.T. Liu. *Chin. J. Inorg. Chem.*, **20**, 191 (2004).
[8] W. Guan, J.Y. Sun, X.D. Zhang, Q.T Liu. *Chem. J. Chin. Univ.*, **19**, 5 (1998).
[9] E.J. Gao, D. Zhang, Q.T. Liu. *Acta Chim. Sin.*, **61**, 1834 (2003).
[10] G.M. Sheldrick. *SHELXS 97. Program for Crystal Structure Solution*, University of Göttingen, Germany (1997).
[11] G.M. Sheldrick. *SHELXS 97. Program for Crystal Structure Refinement*, University of Göttingen, Germany (1997).
[12] D.K. Chand, M. Fujita, K. Biradha, S. Sakamoto, K. Yamaguchi. *J. Chem. Soc., Dalton Trans.*, 2750 (2003).
[13] K. Umakoshi, Y. Yamauchi, K. Nakamiya, T. Kojima, M. Yamasaki, H. Kawano, M. Onishi. *Inorg. Chem.*, **42**, 3907 (2002).
[14] B. Milani, A. Marson, E. Zangrando, G. Mestroni, J.M. Ernsting, C.J. Elsevier. *Inorg. Chim. Acta*, **327**, 188 (2002).
[15] M. Sabat, M. Jezowska, H. Kozlowski. *Inorg. Chem. Acta*, **37**, 511 (1997).
[16] M. Cusumano, M.L.D. Pietro, A. Giannetto. *J. Chem. Soc., Chem. Comm.*, 2527 (1996).
[17] I. Kazuhiko, T. Mate, K.U. Mohamed, N. Kou, S. Shiori. *J. Inorg. Biochem.*, **91**, 437 (2002).