Sterically restrictive metal complexes. The synthesis and structural characterization of (1,2-bis(6-methylpyridin-2-yl)ethane-*N,N'*)-(malonato)palladium(II) trihydrate. Proton NMR binding studies to cytosine and guanine derivatives

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Abstract

Two different routes for the preparation of the bidentate ligand 1,2-bis(6-methylpyridin-2-yl)ethane (bmpe) have been explored and are described. 1:1 coordination of this ligand with palladium(II) and the isolation of crystals of the complex as the malonate trihydrate has allowed the crystal and molecular structure to be determined. The compound crystallizes in space group $P2_1/n$ with $a=12.946(1)$, $b=7.431(1)$, $c=20.483(2)$ Å, $\beta=91.941(3)°$, $Z=4$. The structural analysis reveals that the 6-methyl groups of the bidentate bmpe ligand both project over one side of the square-plane, effectively blocking it off. The interaction of the $Pd(bmpe)^{2+}$ complex cation with cytosine and guanine derivatives has been investigated by proton NMR spectroscopy.

Introduction

The nature of the binding of a metal complex to a nucleic acid may be strongly influenced by steric factors. Structural studies on model systems for the interaction of the cisplatinum antitumour drugs with DNA demonstrate that, in some cases, intramolecular steric effects may even be determinative of the molecular conformation of the adduct [1]; although difficulties remain in deducing to what extent correlations arising from model systems can be carried over with fidelity to a metal–nucleic acid complex.

Recent studies on the mechanism of the cytotoxicity of the anticancer compound *cis*-diamminedichloroplatinum(II) (cisplatin) and its active analogs suggest that their mode of action may be related to the recognition by a key cellular protein of a structural motif on the DNA induced by metal coordination [2]. Uniquely distorted DNA and RNA conformations have also been implicated as being important in ribozymes [3] and in genetic signalling [4]. Thus the manipulation of the steric parameters involved in the binding of metal species to nucleic acids may hold promise for the rational design of distortions in nucleic acids and may provide a means for the control of various biological functions related to nucleic acid topology.

For the cisplatinum systems, such steric demands are dictated by the bulk on the coordinated amine and by the DNA-base exocyclic groups which are contiguous to the metal binding site [5]. Thus there is scope for influencing the molecular conformation of an adduct by a judicious design of the metal complex via the coordinated ammine or other appropriate 'carrier ligands' [6]. In addition, since the aforementioned exocyclic functional groups vary with DNA base type, there is also the possibility of manipulating site specificity. This may be brought about, for example, by selectively precluding coordination at a particular base site. Such reagents would have obvious applications as biological probes [7].

An important mode of coordination for cisplatinum derivatives to DNA is an intrastrand crosslinkage be-

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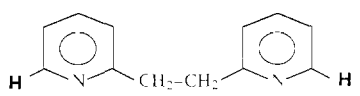
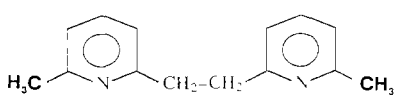
tween the N(7) positions of adjacent guanines. Up to 60% of cisplatin DNA adducts may be of this type [8]. Crystal structure analyses of systems modelling the guanine[N(7)]–Pt–guanine[N(7)] intrastrand crosslinkage reveal that in the majority of cases the bases are arranged in the head-to-tail (HT) conformation [5]. In only four cases has a head-to-head (HH) conformation be found [9], and these are of a fortuitous nature. An HH conformation has also been demonstrated in several complexes involving di- and trinucleotides [10, 11]. In the latter cases the HH conformation is dictated by the polymeric nature of the nucleotide ligand. The predominance of the HT conformation in the crystal structures of simple model systems has allowed the flexibility of this adduct to be systematically examined [12]; although the biological relevance of this geometry is not considered by some researchers to be as important as HH; this being the orientation of the bases in the nucleic acids themselves (albeit prior to any disruptive influence). A specific goal of our research is to develop metal complexes which sterically enforce head-to-head (HH) conformations of *cis* bis-coordinated 6-oxopurine bases, nucleosides and nucleotides. This would then allow the flexibility of the HH adduct to be explored further and to be manipulated by rational design of the carrier ligand.

It has been realized for some time that a coordinated ligand which selectively blocks off one side of a square-plane, has the potential for enforcing an HH geometry of *cis* bis-coordinated 6-oxo purines. Reedijk and co-workers [13] employed the ligand 1,2-bis(pyridin-2-yl)ethane, bpe, Fig. 1(a), in an attempt to achieve this goal. It was confirmed by these workers via an X-ray analysis of the complex $Pt(bpe)(9\text{-MeHX})_2(NO_3)_2$, 9-MeHX = 9-methylhypoxanthine, that even though the bpe ligand provides different environments above and below the platinum coordination plane (by pitching the hydrogen atoms *ortho* to the pyridinyl nitrogens over one side of the coordination plane whilst maintaining the rigid ethylene bridge on the other side) it does



(a) bpe



(b) bmpe

Fig. 1. The ligands 1,2-bis(pyridine-2-yl)ethane, bpe (a) and 1,2-bis(6-methylpyridin-2-yl)ethane, bmpe (b) The protons and the methyl substituents *ortho* to the ring nitrogens in bpe and bmpe, respectively, are highlighted

not influence the N(7)-coordinated 9-MeHX ligands enough to force them into an HH arrangement. In order to further investigate the possibility of achieving an enforced HH configuration and influencing its geometry sterically (by further ligand modification) we have synthesized, by two different routes, the ligand 1,2-bis(6-methylpyridin-2-yl)ethane, bmpe, Fig. 1(b). When coordinated to a square-planar metal centre, the presence in bmpe of the bulky methyl groups adjacent to the pyridinyl donor nitrogens compared to just hydrogen atoms in bpe, should result in an even greater obstruction of one side of the plane in bmpe compounds compared to bpe. This additional bulk might be sufficient to enforce the required HH coordination upon subsequent reaction of the $M(bmpe)^{2+}$ moiety with two equivalents of an N(7)-coordinated 6-oxopurine ligand. Thus we have synthesized and characterized by X-ray analysis the 1·1 complex of the bidentate bmpe ligand with palladium(II) as the malonate trihydrate and we have investigated, both by attempting to isolate complexes and by proton NMR spectroscopy, the coordinating ability of the $Pd(bmpe)^{2+}$ moiety towards 9-ethylguanine (9-EtG), guanosine (Guo), the disodium salt of guanosine 5′-monophosphate ($GMPNa_2$) and 1-methyl cytosine (1-MeC).

Experimental

K_2PdCl_4 was supplied by Aldrich; 9-EtG, guanosine, $GMPNa_2$ and 1-MeC were supplied by Sigma. The ligand bmpe was synthesized in our laboratories by procedures described in this paper. Common chemicals were obtained from other scientific supply houses.

Synthesis of 1,2-bis(6-methylpyridin-2-yl)ethane, bmpe

Method 1. This method followed a procedure similar to the preparation of 1,2-bis(pyridin-2-yl)ethane (bpe) reported by Campbell and Teague [14]. To a solution of 2,6-lutidine (29 ml; 0.25 mol) in dry THF (120 ml) at −30 °C was added n-butyl lithium (100 ml of a 0.25 M solution in hexane; 0 25 mol). The resulting bright orange–red solution was then left to stir for 1 h while the temperature rose to ambient. The solution was stirred rapidly while bromine (22 g; 0.138 mol) was added dropwise over 1 h at −40 °C. After stirring for an additional 1 h, the mixture was treated with water (50 ml) and 6 N HCl (50 ml). The two layers were separated, the aqueous layer made alkaline with NaOH and extracted with chloroform (3 × 20 ml) The combined chloroform extracts were then dried. The residue, after solvent removal, was distilled. The desired product (b.p. 124–128 °C/5 mm Hg) was obtained as a colourless liquid which solidified on standing to an off-white solid, 9.6 g (36% yield). The identity and purity of the product

was confirmed by proton NMR and by gas chromatography/mass spectroscopy.

Method 2. This method is a slight modification of the procedure of Bass *et al.* [15]. A solution of t-butyl peroxide (6 g) in 2,6-lutidine (100 g), under nitrogen, was heated under reflux in an oil bath for 72 h. The low boiling point products and the excess 2,6-lutidine were removed by distillation through a fractionating column. The residue was distilled under reduced pressure to give 4.66 g (53% yield) of an off-white solid. This material was recrystallized from absolute light petroleum (40–60 °C) and its identity and purity confirmed by proton NMR and FT-IR. The crystals melted over the range 49–50 °C; literature value, 50–54 °C.

Preparation of Pd(bmpe)Cl_2

Method 1. Pd(bmpe)Cl_2 was prepared by reacting [Pd(benzonitrile)$_2Cl_2$] with bmpe in acetonitrile in a reaction analogous to that used to prepare several Pd(II) diimine complexes [16]. *Anal.* Found: C, 42.97; H, 4.35; N, 7.14; Pd, 27.1. Calc. for $C_{14}H_{16}Cl_2PdN_2$: C, 43.16; H, 4.14; N, 7.19; Pd, 27.3%.

Method 2. To a solution of 0.4 g of K_2PtCl_4 (1.2 mmol) in 5 ml of deionized water was added a solution of 0.26 g (1.2 mmol) of bmpe in 2 ml of acetone. A yellow precipitate formed immediately. The resulting mixture was stirred overnight, the precipitate filtered, and washed with water, ice-cold ethanol and ether, and dried in a dessicator over silica gel. The yield was 0.44 g (92%). *Anal.* Found: C, 43.0; H, 4.3; N, 7.3. Calc.: as given in Method 1.

Preparation of Pd(bmpe)(malonato)·3H_2O

To a stirred suspension of Pd(bmpe)Cl_2 in a dark bottle was added 1.95 equiv. of $AgNO_3$ as a concentrated solution in water. The mixture was stirred at a temperature of 60 °C for 2 h. The AgCl was filtered off over celite giving a pale yellow filtrate which is assumed to contain the diaquo species. To this solution was added a small excess of sodium malonate in a minimum amount of water. A slightly lighter yellow solution resulted which was reduced in volume at 70 °C and allowed to cool slowly. Yellow needles suitable for X-ray analysis were harvested and air dried. Drying over silica gel *in vacuo* caused the crystals to deteriorate; this is reflected in the analytical figures which correspond to the anhydrous compound. *Anal.* Found: C, 48.2; H, 4.7; N, 6.9. Calc. for $C_{17}H_{18}PdN_2O_4$: C, 48.5; H, 4.3; N, 6.7%.

Crystallography

Crystallographic data for [Pd(bmpe)(mal)]·3H_2O are given in Table 1. The diffraction data were collected on a Huber four-circle diffractometer in a $\theta/2\theta$ scan mode using graphite-crystal monochromated Mo Kα radiation. The unit cell parameters were obtained from least-squares refinement on the setting angles of 37 reflections ($10 < 2\theta < 20°$). Of 5548 reflections ($h, k, \pm l$) collected to $2\theta_{max}$ of 57°, 4215 were considered observed with $I \geq 3\sigma(I)$. The space group $P2_1/n$ was assigned on the basis of systematic absences ($0k0$, k odd absent, and $h0l$, $h+l$ odd absent). The structure was solved by direct phasing and Fourier methods. Ligand hydrogen atoms were included in calculated positions after confirming their presence in difference Fourier maps. In particular, the geometry of the methyl groups was checked to confirm they were not disordered. The hydrogen atoms of the water molecules were located in a difference Fourier map. All hydrogen atoms were assigned fixed thermal parameters and ligand hydrogen atom positions were updated after each cycle of refinement to maintain geometry. Positional and anisotropic thermal parameters for the non-hydrogen atoms were refined using full-matrix least-squares. Atomic scattering factors and anomalous dispersion parameters were from International Tables for X-ray Crystallography. Crystallographic programs included in the UCLA crystallographic computing package include modified versions of the following: REDUCE (Coppens, Becker, Blessing and Broach), peak profile analysis, Lorenz and polarization corrections; MULTAN (Main), direct methods, Fourier analysis and map searching; ORFLS (Busing, Martin and Levy), structure factor calculations and least-squares refinement; ORFFE (Busing, Martin and Levy), distances, angles and error calculations; ABSORB (Coppens, Edwards and Hamilton), absorption corrections; ORTEP-II (Johnson), figure plotting; HYDROGEN (Trueblood) calculation of hydrogen atom positions. All calculations were performed using DEC VAX computers. Fractional coordinates of the non-hydrogen atoms are given in Table 2.

TABLE 1 Crystallographic data for Pd(bmpe)(malonato)·3H_2O

Formula	$C_{17}H_{24}N_2O_7Pd$
Formula weight	474.79
a (Å)	12.946(1)
b (Å)	7.431(1)
c (Å)	20.483(2)
β (°)	91.941(3)
V (Å^3)	1969.4
Z	4
Space group	$P2_1/n$ (No. 14)
T (°C)	22
λ (Å)	0 71069
ρ_{calc} (g/cm^3)	1.60
μ(Mo Kα) (cm^{-1})	9 66
Transmission coefficient	0.826–0.872
R^a	0.027
$R_w{}^b$	0.038

$^aR = \Sigma||F_o| - |F_c||/\Sigma|F_o|$. $^bR_w = (\Sigma||F_o| - |F_c||^2/\Sigma w|F_o|^2)^{1/2}$.

TABLE 2 Atomic coordinates and equivalent isotropic temperature factors for Pd(bmpe)(malonato) $3H_2O$

Atom	x	y	z	$U^a \times 10^4$
Pd	0.23946(1)	0.17648(2)	0.56415(1)	284(1)
O(1)	0.0965(1)	0.0965(3)	0.5848(1)	386(9)
O(2)	0.3016(1)	−0.0244(3)	0.6174(1)	436(10)
O(3)	−0.0100(2)	−0.0425(3)	0.6482(1)	590(13)
O(4)	0.3142(2)	−0.1662(4)	0.7107(1)	805(18)
O(5)	−0.1326(2)	0 0136(3)	0.7533(1)	660(15)
O(6)	0.5318(2)	−0.1384(4)	0 7231(2)	1020(23)
O(7)	0.6735(2)	0 1427(4)	0 7149(2)	884(20)
N(1)	0.3827(1)	0.2367(3)	0 5355(1)	308(10)
N(2)	0.1841(1)	0.3859(3)	0 5094(1)	335(10)
C(1)	0.4041(2)	0.1890(3)	0.4734(1)	373(13)
C(2)	0 5032(2)	0.2090(4)	0 4505(1)	482(16)
C(3)	0.5806(2)	0 2777(4)	0.4920(2)	540(18)
C(4)	0.5571(2)	0 3251(4)	0.5548(2)	485(16)
C(5)	0 4574(2)	0 3042(3)	0.5759(1)	380(13)
C(6)	0 4287(2)	0 3577(5)	0.6440(1)	546(18)
C(7)	0.3158(2)	0 1065(4)	0.4335(1)	493(16)
C(8)	0 2367(3)	0 2364(5)	0.4059(1)	564(18)
C(9)	0 1947(2)	0 3916(4)	0.4438(1)	409(13)
C(10)	0 1635(2)	0 5438(5)	0 4091(2)	582(19)
C(11)	0.1194(3)	0 6865(4)	0 4395(2)	630(21)
C(12)	0 1059(2)	0.6776(4)	0 5057(2)	562(19)
C(13)	0 1402(2)	0.5276(4)	0 5406(1)	423(14)
C(14)	0.1306(2)	0 5206(4)	0 6135(2)	564(18)
C(15)	0 0767(2)	0 0176(3)	0.6385(1)	383(13)
C(16)	0 1604(2)	−0 0006(4)	0 6918(1)	472(15)
C(17)	0.2656(2)	−0 0701(4)	0 6726(1)	433(15)

$U_{eq} = [1/(6\pi^2)]\Sigma\Sigma\beta_{ij}a_i a_j$

Description of the structure

The Pd(bmpe)(malonato) complex is shown, together with the labelling of the atoms, in Fig. 2. The coordination geometry about Pd(II) is square-planar within experimental error; the four equatorial positions are occupied by the nitrogen atoms of the bidentate bmpe ligand (labelled N(1) and N(2)) and by the oxygen donors of the bidentate malonate anion (labelled O(1) and O(2)). The bmpe ligand forms a boat-like seven-membered chelate ring and the two pyridine moieties of this ligand are twisted from the square-plane with angles of 66.2 and 73.0°. These angles compare well with 67.9° for both pyridine moieties in $Pt(dmdap)(bpe)Cl_2 \cdot H_2O$ [17] and the 62 5 and 69.4° reported for the pyridine moieties in the complex $Pt(bpe)(9\text{-MeHX})_2(NO_3)_2$ [13] (the asymmetry observed in the latter may be attributed to the bulk of the two coordinated 9-methylhypoxanthine ligands). The similarity in these angles between the coordinated bpe and bmpe systems reflects the rigidity of ligands of this type. Consistent with the observations of Reedijk and co-workers for the bpe system [13], we also observe distinct chemical shifts for the ethylene bridge protons in our NMR studies of the $Pd(bmpe)^{2+}$ system in solution. This is further evidence for the rigidity of the seven-membered chelate ring.

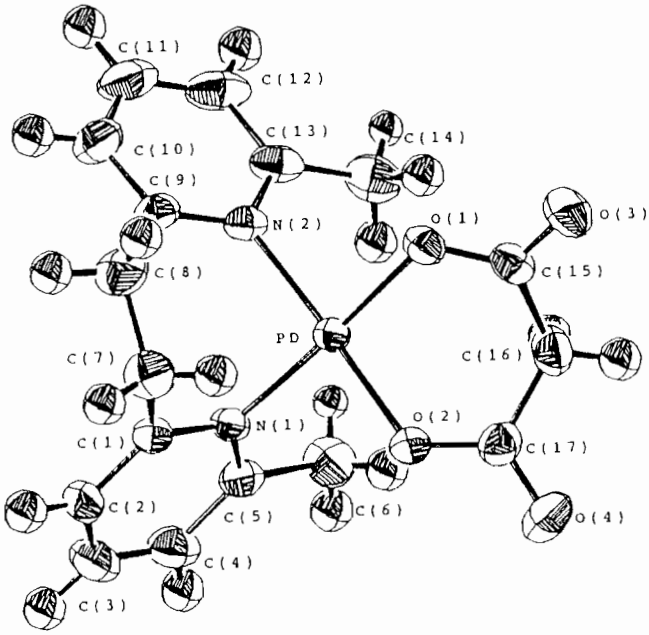


Fig 2. View of the Pd(bmpe)(mal) molecule perpendicular to the coordination plane together with the atom numbering scheme Anisotropic ellipsoids represent 50% probability boundaries. H atoms are represented as spheres of arbitrary radii

In the title compound, the bidentate coordination of the malonate to the palladium may be compared with its coordination to other metals [18]. Generally, the coordinated malonate ligand displays a high degree of conformational flexibility and can adopt a variety of conformations including chair, boat, envelope, or flattened with distortions towards 'skewboat' configurations In the present case the palladium–malonate ring exhibits a boat conformation. Bond lengths and angles are consistent with those observed in other malonato complexes [18].

An interesting feature of the structure is the intramolecular approach of one of the ethylene bridge protons to the palladium atom, Fig. 3(a) and (b). The H(7a) to Pd distance of 2.436(5) Å (Pd–H(7a)–C(7) angle 109.0(3)°) is considerably shorter than the sum of the van der Waals radii ($r_H + r_{Pd} = 1.2 + 1.9 = 3.1$ Å) [19], and it is tempting to assume a weak attractive interaction. Agostic intramolecular interactions of the kind C–H–Pd have been reported in a number of structures [20–22]. Those representing a 'strong' interaction have H to Pd distances under 2 Å (e.g. 1.874 Å [23]), whereas the 'weaker' interactions are between 2.5 and 3.0 Å (e.g. 2.57 and 2.84 Å [20], 2.84 Å [21], 2.98 Å [22]). Only one structure [22] has a contact involving a methylene bridge, the other structures [20, 21, 23] involve α-hydrogens of phenyl rings. The presence of such an attractive interaction in the title complex

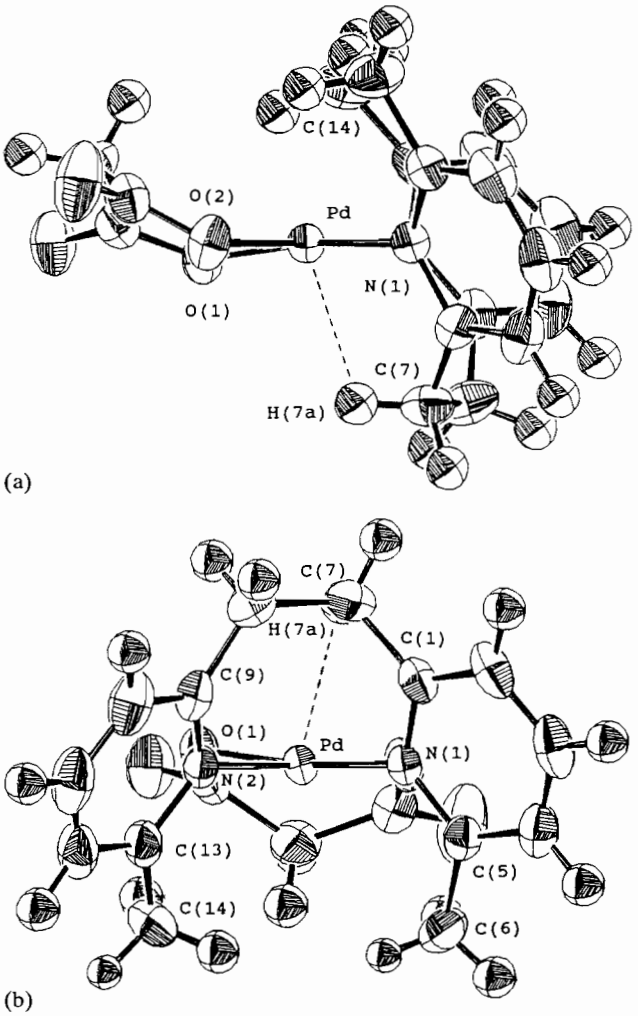


Fig. 3. (a) A side view and (b) an end view of the Pd(bmpe)(mal) molecule

could contribute to the asymmetry in the dihedral angles between the pyridine moieties and the coordination plane (66.2 and 73.0°).

Selected bond distances and angles for the complex are given in Table 3. Bond lengths and angles associated with the coordination plane are typical of those reported in related systems. We do note however, a slight downward distortion of the Pd–O(1) bond away from the bulk of the C(14) methyl substituent, Fig. 3(a) and (b). This is reflected in the N(1)–Pd–O(1) angle of 173.7(7)°. The influence of the bulk of the C(14) methyl substituent is also reflected in the angles at N(2) which are consistent with a 'pushing-down' effect on the Pd–O(1) bond. A compendium of the angles around both N(1) and N(2), and a comparison with the corresponding angles in $Pt(bpe)(9\text{-}MeHX)_2(NO_3)_2$ are given Table 4. Other bond lengths and angles in the complex have expected values within experimental error.

Side and end views of the complex, which are presented in Fig. 3(a) and (b), respectively, clearly show

TABLE 3 Molecular geometry for Pd(bmpe)(malonato) $3H_2O$ bond lengths (Å), bond angles (°)

Primary coordination sphere about the Pd atom			
Pd–N(1)	2.013(2)	Pd–O(1)	2.003(2)
Pd–N(2)	2.034(2)	Pd–O(2)	2.002(2)
N(1)–Pd–N(2)	88.90(8)	N(2)–Pd–O(2)	176.96(7)
N(1)–Pd–O(2)	88.14(8)	N(2)–Pd–O(1)	91.86(8)
N(1)–Pd–O(1)	173.76(7)	O(1)–Pd–O(2)	91.16(7)
1,2-Bis(6-methylpyridin-2-yl)ethane ligand			
N(1)–C(5)	1.348(3)	C(5)–C(6)	1.509(4)
N(1)–C(1)	1.358(3)	C(7)–C(8)	1.504(4)
N(2)–C(9)	1.356(3)	C(8)–C(9)	1.502(4)
N(2)–C(13)	1.366(3)	C(9)–C(10)	1.389(4)
C(1)–C(2)	1.389(4)	C(10)–C(11)	1.365(5)
C(1)–C(7)	1 512(4)	C(11)–C(12)	1.375(5)
C(2)–C(3)	1 389(5)	C(12)–C(13)	1.389(4)
C(3)–C(4)	1 378(5)	C(13)–C(14)	1.503(4)
C(4)–C(5)	1.384(4)		
C(5)–N(1)–C(1)	120.48(22)	N(1)–C(5)–C(6)	118.13(23)
C(5)–N(1)–Pd	123 54(17)	C(4)–C(5)–C(6)	121.38(26)
C(1)–N(1)–Pd	115.70(17)	C(8)–C(7)–C(1)	115.83(26)
C(9)–N(2)–C(13)	119 83(23)	C(9)–C(8)–C(7)	123 53(23)
C(9)–N(2)–Pd	121 61(17)	N(2)–C(9)–C(10)	119.69(27)
C(13)–N(2)–Pd	118 47(18)	N(2)–C(9)–C(8)	122.59(24)
N(1)–C(1)–C(2)	120.56(26)	C(10)–C(9)–C(8)	117.70(27)
N(1)–C(1)–C(7)	115.94(22)	C(11)–C(10)–C(9)	121.22(30)
C(2)–C(1)–C(7)	123 43(25)	C(10)–C(11)–C(12)	118.81(27)
C(1)–C(2)–C(3)	119 22(26)	C(11)–C(12)–C(13)	119.81(28)
C(4)–C(3)–C(2)	119.20(26)	N(2)–C(13)–C(12)	120 59(27)
C(3)–C(4)–C(5)	120.05(28)	N(2)–C(13)–C(14)	119 20(24)
N(1)–C(5)–C(4)	120.49(26)	C(12)–C(13)–C(14)	120.21(27)
The malonato ligand			
O(1)–C(15)	1 280(3)	O(4)–C(17)	1.217(3)
O(2)–C(17)	1 283(3)	C(15)–C(16)	1.518(4)
O(3)–C(15)	1.230(3)	C(16)–C(17)	1.521(4)
C(15)–O(1)–Pd	122.08(16)	C(15)–C(16)–C(17)	117.91(22)
C(17)–O(2)–Pd	121.79(17)	O(4)–C(17)–O(2)	121.66(28)
O(3)–C(15)–O(1)	121 02(25)	O(4)–C(17)–C(16)	118.78(26)
O(3)–C(!5)–C(16)	118 97(24)	O(2)–C(17)–C(16)	119 55(23)
O(1)–C(15)–C(16)	120.00(22)		

TABLE 4. A compendium of the angles (°) around N(1) and N(2) in $Pd(bmpe)(mal)\cdot 3H_2O$ and the corresponding angles in $Pt(bpe)(9\text{-}MeHX)_2(NO_3)_2$

Angle	Pd(bmpe)-(mal)·$3H_2O$	Pt(bpe)-$(9\text{-}MeHX)_2(NO_3)_2$
Pd–N(1)–C(5)	123 54(17)	120.2(8)
Pd–N(1)–C(1)	115.70(17)	119.7(8)
Pd–N(2)–C(13)	118.47(18)	115.1(7)
Pd–N(2)–C(9)	121 61(17)	124.8(8)

both of the methyl substituents of the bmpe ligand projecting to approximately the same extent over one side of the coordination plane, effectively blocking it off. Thus, as anticipated, the methyl substituents *ortho* to the pyridinyl nitrogens of the bmpe ligand project preferentially over one side of the coordination plane

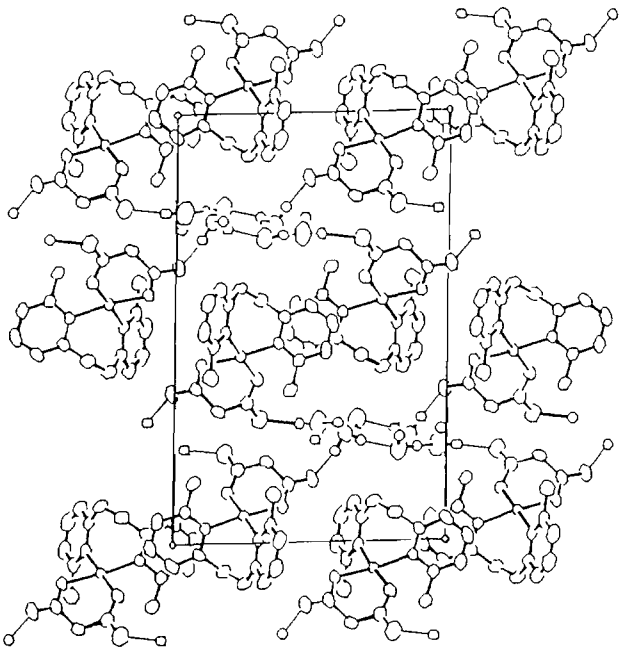


Fig. 4. The unit cell contents for Pd(bmpe)(mal) $3H_2O$ (*a*, to the right; *b*, to the viewer).

TABLE 5 hydrogen bonding distances (Å) within Pd(bmpe)-(malonato) $3H_2O$

–O–H---	---O–	Distance
O(5)	O(3)	2.749(3)
O(6)	O(4)	2 828(4)
O(7)	O(6)	2 789(5)
O(5)[a]	O(7)	2 776(4)
O(7)[b]	O(5)	2.885(4)

Equivalent positions: [a] $x+1, y, z$; [b] $\frac{1}{2}-x, y-\frac{1}{2}, \frac{3}{2}-z$

in the same way as the *ortho* hydrogen atoms of the bpe ligand in $Pt(bpe)(9\text{-}MeHX)_2(NO_3)_2$. As in the reported bpe system the ethylene bridge also projects to some extent over the other side of the plane, Fig. 3(a), and this is also expected to influence the coordinating properties of the $Pd(bmpe)^{2+}$ cation.

The unit cell contents is depicted in Fig. 4. Intermolecular contacts less than 3.2 Å are listed in Table 5. The three water molecules of crystallization $H_2O(5)$, $H_2O(6)$ and $H_2O(7)$ are all involved in a hydrogen bonding network with each other and with the uncoordinated oxygen atoms, O(3) and O(4), of the malonato ligand. The bmpe pyridine ring systems of adjacent molecules stack in a head-to-tail fashion at distances of approx. 3.4 Å apart.

Proton NMR results

All reagents used in the NMR experiments were of the highest purity. In D_2O medium, a stock solution of $Pd(bmpe)(D_2O)_2^{2+}$ was prepared as described previously for the diaquo species. An appropriate amount of this solution was mixed with two equivalents each of 1-MeC, Guo and 5'-$GMPNa_2$. The pHs of these solutions were 6.6, 5.5 and 6.5, respectively (pD values may be obtained by adding 0.4 to the pHs). Similarly, $Pd(bmpe)Cl_2$ was dissolved in Me_2SO-d_6 and combined with two equivalents of 9-EtG. All solutions had been standing for at least 24 h before their proton NMR spectra were recorded. The spectra were recorded on a Bruker WB AMX300 (300 MHz) spectrometer at 25 °C. All chemical shifts are reported downfield from DSS (2,2-dimethyl-2-silapentane-5-sulfonate) for the samples in D_2O, and downfield from TMS (tetramethylsilane) for the sample in DMSO-d_6. Spectra were also recorded under the same conditions for all of the free (potential) ligands. Evidence for coordination of the palladium complex to the N(7) position of the guanine base was monitored by observing the chemical shift of the H(8) resonance in the presence and absence of metal complex. Evidence for coordination to the N(3) position of the cytosine moiety was monitored by observing the chemical shifts for the H(5) and H(6) resonances in the presence and absence of metal complex. Results are summarized in Tables 6 and 7.

Coordination by Pt(II) or Pd(II) to the N(7) position of guanine is expected to result in a downfield shift for the H(8) resonance of at least 0.4 ppm compared to the free ligand [24]. Similarly, coordination to the N(3) position of cytosine is expected to result in a downfield shift for the H(5) and H(6) resonances of

TABLE 6. H(8) proton chemical shifts (δ) for guanine derivatives in the absence and presence of $Pd(bmpe)^{2+}$

	9-EtG[a]	Guo	5'-$GMPNa_2$
Free guanine derivative	7.70	7.98	8 20
Guanine derivative (2 equiv.) + $Pd(bmpe)^{2+}$	7 70	8.03	8.23
Difference in shift	0.00	+0 05	+0.03

[a]Downfield from TMS in Me_2SO-d_6. Other values are from DSS in D_2O

TABLE 7 H(5) and H(6) chemical shifts (δ) for 1-methylcytosine in the absence and presence of $Pd(bmpe)^{2+}$

	H(5)	H(6)
Free 1-methylcytosine	5.94	7.55
1-methylcytosine (2 equiv.) + $Pd(bmpe)^{2+}$	5.87	7.51
Difference in shift	−0 07	−0.04

All values are downfield from DSS in D_2O Values are averages of the doublet signals for H(5) and H(6)

at least 0.2 ppm [1]. The results summarized in Tables 6 and 7 show that the observed differences in the chemical shift values in the presence and absence of metal complex are considerably less in magnitude than what would be expected if binding had occurred and, in the case of the 1-methylcytosine signals, are in the opposite direction (upfield) than expected. Therefore, we conclude that binding of the $Pd(bmpe)^{2+}$ moiety to the N(7) and N(3) positions of guanine and cytosine, respectively, does not occur in any of these experiments under these conditions. This is consistent with our inability to isolate any complexes preparatively.

Discussion

To our knowledge, this is the first structural characterization of a coordination compound with the bmpe ligand. As expected, bmpe introduces an asymmetric environment with respect to the coordination plane in the same way as bpe [13]. Thus by replacing the hydrogen atoms *ortho* to the donor nitrogen atoms in the bpe ligand with methyl substituents, Fig. 1, we have succeeded in building up the bulk preferentially on one side of the coordination plane, Fig. 3(a). Attempts to introduce N(7)-bound 6-oxo purine ligands and N(3)-bound 1-methylcytosine into the coordination sphere by reacting the $Pd(bmpe)^{2+}$ moiety with two equivalents of the appropriate nucleoligand have not been successful, as evidenced by proton NMR studies and by our inability to isolate any 1:2 complexes preparatively. This is in contrast to the reported reaction of two equivalents of 9-methylhypoxanthine (9-MeHX) with $Pt(bpe)(H_2O)_2^{2+}$ which results in the ready isolation of $[Pt(bpe)(9\text{-}MeHX)_2](NO_3)_2$ [13]. Those workers have characterized that complex by X-ray crystallography and have demonstrated the bases to be coordinated in an HT arrangement via the N(7) positions. Thus it is surprising, when $Pd(bmpe)(H_2O_2^{2+}$ is exposed to two equivalents of a 6-oxopurine derivative, that at least one such ligand is not introduced into the coordination sphere with the 6-oxo moiety on the same side of the coordination plane as the ethylene bridge. This arrangement is readily accommodated for one of the two 9-MeHXs in the aforementioned $[Pt(bmpe)(9\text{-}MeHX)_2](NO_3)_2$ complex and there is no evidence to suggest that the ethylene bridge is significantly more obstructive in the $Pd(bmpe)^{2+}$ moiety than in the $Pt(bpe)^{2+}$ moiety, see Table 8. Indeed, it is remarkable how rigid ligands of this type appear to be. We have noted, however, the slight distortion in the molecule attributed to a 'pushing down' of one of the methyl substituents onto part of the coordination plane. This is reflected in the distortion of the square-plane itself and in the angles at the N(2) atom of the bmpe ligand.

TABLE 8. A comparison of the geometric parameters associated with the projection of the ethylene bridge across the coordination plane in $Pd(bmpe)(mal)\cdot 3H_2O$ and $Pt(bpe)(9\text{-}MeHX)_2(NO_3)_2$ Values for the latter compound are given in parentheses

Contacts	Distance (Å)	Δ (Å)
C(8)–Pd (C(11)–Pt)	2 906 (3 028)	0 122
C(7)–Pd (C(31)–Pt)	3.270 (3 327)	0 057
C(8)–O(1) (C(11)–N(27))	3 893 (4.150)	0.257
C(7)–O(2) (C(31)–N(17))	4.204 (4 420)	0 216

This effect may be visualized in Fig. 3(a) and (b). Further details of these distortions are discussed under a previous heading. Although one must attribute the complete hindering of nucleobase binding in the bmpe system to the influence of the steric bulk of the exocyclic methyl substituents, we are not convinced that the subtle change in coordination geometry as described above, by itself, could have such a dramatic effect on the relative coordinating abilities of the bpe and bmpe systems. Investigations are continuing into other factors which could be operative.

Supplementary material

Further details of the crystal structure investigation are available on request from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK, on quoting the full journal citation.

Information available from the authors upon request includes GC-MS peaks (with $m/z > 3\%$) for bmpe, proton NMR data for bmpe, and FT-IR data for bmpe, Pd(bmpe)malonate and $Pd(bmpe)Cl_2$.

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References

1 J.D. Orbell, L.G. Marzilli and T.J. Kistenmacher, *J. Am. Chem. Soc.*, *103* (1981) 5126.

2 P.M. Pil and S.J Lippard, *Science, 256* (1992) 234.
3 T.R. Cech, *Science, 236* (1987) 1532.
4 J. Haseloff and W.L. Gerlach, *Nature (London), 334* (1988) 585.
5 T.J Kistenmacher, J.D Orbell and L.G. Marzilli, in S J. Lippard (ed.), *Platinum, Gold and Other Metal Chemotherapeutic Agents,* Vol. 209, ACS Symposium Series, Washington, DC, 1983, p. 191.
6 (a) Y Kidani, *Yakugaku Zasshi, 105* (1985) 909; (b) G Trovo and B. Longato, *Inorg Chim. Acta, 192* (1992) 13.
7 A.M. Pyle and J.K. Barton, in S J. Lippard (ed.), *Progress in Inorganic Chemistry: Bioinorganic Chemistry,* Vol. 38, Wiley, New York, 1990, p. 413
8 B Lippert, in S.J. Lippard (ed.), *Progress in Inorganic Chemistry,* Vol. 37, Wiley, New York, 1989, p 3.
9 H. Schollhorn, G. Raudaschl-Sieber, G. Muller, U Thewalt and B. Lippert, *J. Am Chem Soc, 107* (1985) 5932
10 S.E Sherman, D Gibson, A H.-J Wang and S.J Lippard, *J. Am Chem Soc, 110* (1988) 7368.
11 G. Admiraal, J.L. van der Veer, R.A.G. de Graaf, J H J den Hartog and J. Reedijk, *J Am Chem Soc, 109* (1987) 592
12 J.D. Orbell, K. Wilkowski, B. de Castro, L.G. Marzilli and T.J Kistenmacher, *Inorg. Chem., 21* (1982) 813.
13 A.T.M. Marcelis, H. Korte. B Krebs and J. Reedijk, *Inorg Chem, 21* (1982) 4059.
14 P.G. Campbell and P C. Teague, *J. Am Chem Soc, 76* (1954) 1371.
15 K C. Bass, B. McIntosh and A.G Osborne, *Spectrosc. Lett, 18* (1985) 35.
16 G R. Newkome, V.K. Gupta, H C.R Taylor and F.R. Fronczek, *Organometallics, 3* (1984) 1549.
17 W.K. Kleibohmer, B. Krebs, A.J.M. Marcelis, J. Reedijk and J.L. van der Veer, *Inorg Chim Acta, 75* (1983) 45
18 C.G van Kralingen, J. Reedijk and A.L. Spek, *Inorg Chem, 19* (1980) 1481, and refs therein.
19 L. Pauling, *The Nature of The Chemical Bond,* Cornell University Press, Ithaca, NY, 2nd edn., 1944, p. 80.
20 N A. Bailey and R Mason, *J Chem Soc A,* (1968) 2594
21 G.R. Clark and J D. Orbell, *J. Organomet Chem, 215* (1981) 121.
22 G. Minghetti, M A. Cinella, A L. Bandini, G. Banditelli, F. Demartin and M. Manaserro, *J Organomet Chem, 215* (1986) 387
23 R.K. Brown, J.M Williams, A.J Schultz, G.D Ittel and R.L Harlow, *J Am Chem Soc., 102* (1980) 981.
24 J D Orbell, M R. Taylor, S.L. Birch, S.E. Lawton, L.M. Vilkins and L.J. Keefe, *Inorg Chim Acta, 152* (1988) 125.