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MIXED NEUTRAL COMPOUNDS OF PALLADIUM(II) AND PLATINUM(II) CHELATED BY DIOLATO(2−) AND DI-IMINE LIGANDS

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Abstract—The synthesis and characterization are described for compounds abbreviated (a) **1–5**: [Pd(phen)(OO)], where OO = the dianion from 1,2-ethanediol (**1**), (+)-1,2-propanediol (**2**), (±)-2,3-butanediol (**3**), (−)-1,2-butanediol (**4**), catechol (**5**); (b) the sulphur analogue (**6**) [Pd(phen)(SCH_2CH_2S)], from ethane-1,2-dithiol; (c) the platinum analogue (**7**) [Pt(phen)(OCH_2CH_2O)]; (d) the 2,2′-bipyridyl analogue (**8**), [Pd(bipy)(OCH_2CH_2O)] (phen = 1,10-phenanthroline and bipy = 2,2′-bipyridyl).

A recent report[1] of compounds [Pd(malonate)(en)] (en = 1,2-diaminoethane) and [Pd(malonate)$(N)_2$], where N = unidentate N-heterocycles like N-methylimidazole prompts us to describe briefly our work[2] on the related compounds **1–8** shown in Scheme 1. Since the advent[3] of treatment of tumours by "*cis* platin", *cis*-[$Pt(NH_3)_2Cl_2$], efforts have been made both to synthesize other anti-tumour agents of analogous structure [Pt(NN)XY] and to understand the mode of action of such species.

Under the first heading are such compounds as *cis*-dichloro-2,2′-bipyridylplatinum(II), [Pt(bipy)Cl_2], which shows[4] no anti-tumour activity and complexes containing the [$Pt(bipy)^{2+}$] fragment with amino acids (alanine and methionine) which turn out to have[5] lower inhibitory doses than [$Pt(NH_3)_2Cl_2$], and under the second heading are studies of the binding between platinum-containing drugs and the DNA helix.[6]

The suggestion was made[7] that the presence of a chiral diamine element, NN, say (+)-1,2-diaminocyclohexane rather than its enantiomer in a potential anti-tumour agent might have a beneficial effect on specificity. Experiment suggests[8] that there is in fact an absence of chiral recognition. However, there seem to be no studies in which the potential drug had "leaving group"[6] chirality in the XY moiety of [Pt(NN)XY], a property of obvious potential relevance to the transport of drugs to, into and within the cell. We therefore made a few compounds containing racemic and optically active chelated diols, as their dianions, giving neutral complex compounds, as in the equation:

$$[Pd(NN)(OH)_3]^- + {}^-OCHRCHR'O^- \rightarrow [Pd(NN)(OCHRCHR'O)] + 3OH^-.$$

Stable crystalline products were produced by reacting strongly alkaline solutions of ML_{aq}^{2+} (M = palladium or platinum, L = 1,10-phenanthroline or 2,2′-bipyridyl, forming $ML(OH)_3^-$) with the appropriate diol.

As an example of the present syntheses, shaking a dilute aqueous solution of [Pd(phen)$(OH)_3]^-$ with a few drops of ethane-1,2-diol leads to an immediate colour change to a paler yellow, followed by formation of pale lemon–yellow, needle-shaped crystals over a few minutes. All the compounds described below were prepared by such combination of diimine complex and diol. The compounds synthesized are listed in Scheme 1. All were characterized by nuclear resonance spectroscopy, elemental and thermogravimetric analysis, IR spectroscopy and where applicable, circular dichroism (C.D.) spectroscopy.

Compounds **1, 2, 3** and **4** show an interesting solubility in water: 1—insoluble, 2—soluble, 3—insoluble, 4—soluble, possibly due to differences in lattice energies of the four solids.

Compounds **2** and **4** were prepared using resolved

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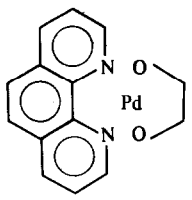

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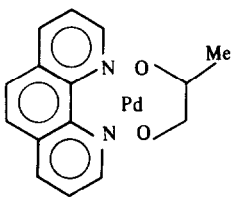

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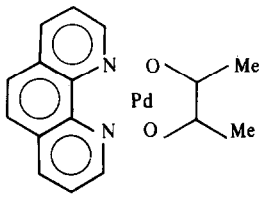

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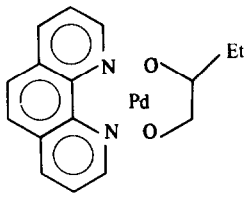

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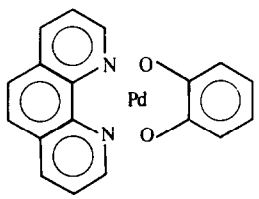

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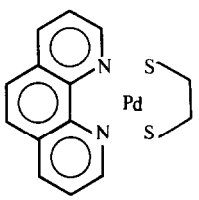

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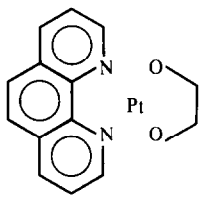

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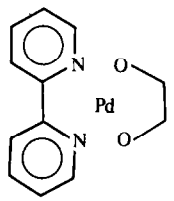

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Scheme 1. Structures of the compounds **1–8**.

chiral diols and circular dichroism spectra are shown in Table 1. It is quite clear from the essentially enantiomeric circular dichroism spectra of the two complex compounds in Table 1 [Pd(phen)(diolate)], that the (−)1,2-diolata-butane ion generates in the $[Pd(phen)]^{2+}$ chromophore of **4** chirality opposite to that generated in **2** by (+)-1,2-diolatopropane. These two diolate di-imines (and hence their parent diols) have opposite configurations. The present method of deducing relative configurations by coupling the diol chirality to the remarkably stable $[Pd(phen)]^{2+}$ chromophore should be general for optically active 1,2-diols, for which satisfactory chromophores are lacking. (Although the recent examples[9] of the use of dimeric carboxylates of dimolybdenum, dirhodium and diruthenium as "Cottonogenic derivatives" for 1,2-diols by Snatzke and his colleagues seem very promising.)

Table 1. Circular dichroism spectra of [Pd(phen)(OCHRCHRO)] **2** and **4**

2		**4**	
λ	$\Delta\varepsilon^a$	$\Delta\varepsilon^a$	λ
530	0	0	530
455	−13	+24	450
410	0	0	412
360	+51	−98	357
312	0	0	312
308	−85	+160	310
299	0	0	299

[a] The $\Delta\varepsilon$ values are estimates, because both powdered products contained a small amount (<5%) of unreacted diol: the diols are colourless and hence have no visible or near UV C.D. spectra before complexation.

In the context of stereoselective effects in drugs containing chiral ligands, the recent work[10] of Totani at the Shionogi laboratories is noteworthy. Compounds containing α-hydroxyacidates [e.g. (glycolato-O,O′)diammineplatinum(II)] have been made and evaluated in chemotherapy.

Compound **5**, a deep red microcrystalline powder, is insoluble in water, but dissolved in dimethylsulphoxide to give a deep violet solution. Its red colour is probably produced by intramolecular conjugation of the π-systems of the heterocycle with those of the benzene ring, since the DMSO solution is violet, whereas the isolated unconjugated N_2PdO_2 chromophore should be yellow. In the $Pt(bipy)Cl_2$ case, the red solid dimorph gives a yellow solution, where the non-conjugated N_2PtCl_2 chromophore is present.

Compound **6** (in which the oxygen atoms are replaced by sulphur) was formed by adding drops of ethane-1,2-dithiol to a dilute alkaline solution of $Pd(phen)(OH)_2 \cdot 3H_2O$. The reaction was rapid, with formation of an orange–yellow water-insoluble powder.

EXPERIMENTAL

$Pd(phen)Cl_2$ and the analogous compounds $Pt(bipy)Cl_2$ etc. were made by dissolving

Table 2. Elemental analyses for $[M(LL)X]nH_2O$

Serial number		LL[a]	X	n	Formula	Found (%) C	H	N	Required (%) C	H	N
—	Pd	P	Cl_2		$C_{12}H_8Cl_2N_2Pd$	39.9	2.2	9.0	40.3	2.2	7.9
—	Pd	P	$(OH)_2$	3	$C_{12}H_{16}N_2O_5Pd$	38.6	3.7	6.9	38.5	4.3	7.4
1	Pd	P	eg		$C_{14}H_{12}N_2O_2Pd$	48.3	4.3	8.4	48.6	3.5	8.1
2	Pd	P	pn[b]		$C_{15}H_{14}N_2O_2Pd$	50.0	4.1	7.4	50.0	4.0	7.8
3	Pd	P	2,3-bn		$C_{16}H_{16}N_2O_2Pd$	50.8	4.7	7.4	51.3	4.3	7.5
4	Pd	P	1,2-bn[b]		$C_{16}H_{16}N_2O_2Pd$	51.6	4.6	7.3	51.3	4.3	7.5
5	Pd	P	cat	3[c]	$C_{18}H_{18}N_2O_5Pd$	48.9	5.7	6.2	48.2	5.6	6.3
6	Pd	P	dithiol		$C_{14}H_{12}N_2PdS_2$	43.1	3.9	7.1	44.4	3.2	7.7
—	Pd	B	Cl_2		$C_{10}H_8Cl_2N_2Pd$	36.4	2.5	7.9	36.0	2.4	8.4
—	Pd	B	$(OH)_2$	4	$C_{10}H_{18}N_2O_6Pd$	32.4	4.2	7.6	32.6	4.8	7.6
8	Pd	B	eg		$C_{12}H_{12}N_2O_2Pd$	45.2	4.1	9.0	44.7	3.7	8.7
—	Pt	P	Cl_2		$C_{12}H_8Cl_2N_2Pt$	33.8	2.1	6.1	32.3	1.8	6.3
—	Pt	P	$(OH)_2$	3	$C_{12}H_{16}N_2O_5Pt$	31.1	2.2	6.0	30.9	2.5	6.0
7	Pt	P	eg		$C_{14}H_{12}N_2O_2Pt$	35.7	3.0	6.4	36.2	2.7	6.4
—	Pt	B	Cl_2[d]		$C_{10}H_8Cl_2N_2Pt$	28.6	1.6	7.0	28.4	1.9	6.6

[a] B = 2,2′-bipyridyl, P = 1,10-phenanthroline.

[b] Elemental analysis in these cases does not reveal that the powders contain a little unreacted diol: this can be seen microscopically as colourless crystals and from proton magnetic resonance, where its amount is estimated as less than 5%: an assumed 5% has however been used to calculate the values of molar circular dichroism for 2 and 4 in Table 1.

[c] The deep red trihydrate became black on dehydration (over warm silica gel); the anhydrous black crystals reverted to the red trihydrate under hot water.

[d] This well-known compound (yellow dimorph) was used to check analytical procedures.

K_2MCl_4(M = palladium or platinum) in 2 M HCl and adding an ethanolic solution of the ligand with rapid stirring. After digesting the precipitate by boiling for 1–2 h, the pale yellow or pale tan-coloured finely divided product was collected at the pump, washed with water, then ethanol (thoroughly to remove any unreacted ligand), acetone and diethyl ether, and dried at 100°C. Yields were all quantitative within experimental error.

$Pd(phen)(OH)_2 \cdot 3H_2O$ was prepared by suspending $Pd(phen)Cl_2$ (0.182 g) in distilled water (100 cm^3) containing NaOH (0.1 g). The mixture was heated (hot plate stirrer) until the solid dissolved, giving a lemon–yellow colour. The solution was cooled and poured through an Amberlite resin IRA 400 anion exchange column prepared in the OH^- form by washing with 0.05 M NaOH solution. The eluate solution was reduced in volume (rotary evaporator) until a yellow powder began to precipitate, after which the flask was removed and allowed to cool. $Pt(phen)(OH)_2 \cdot 3H_2O$, $Pd(bipy)(OH)_2 \cdot 3H_2O$ and $Pt(bipy)(OH)_2 \cdot 3H_2O$ were prepared by (*mutatis mutandis*) the above procedure.

Yields for the step $MLCl_2 \rightarrow ML(OH)_2$ were low in all cases. We assume that the presence of some ML^{2+}_{aq} as $ML(OH)_3^-$ in the very alkaline conditions led to some interaction with the anion exchange resin.

1,2 - *ethanediolato* - 1,10 - *phenanthrolinepalladium* (*II*), **1**

This was prepared by dissolving $Pd(phen)(OH)_2 \cdot 3H_2O$ (0.2 g) in water (50 cm^3) containing NaOH (0.1 g) and adding dropwise ethane-1,2-diol (0.2 g). Crystals of the desired product formed in a few minutes and were collected and washed carefully with ice-cold distilled water. (Compounds **3** and **8** were made in the same way.)

Compound **1** had IR adsorption at : 230, 260, 370, 445, 615, 720, 855, 880, 890, 1050, 1110, 1150, 1230, 1360s, 1430, 1515, 1660, 2820, 3400b. Compound **1** had ^1H resonance at: δ2.62, 8.13m, 8.31, 8.96.

S(+)1,2 - *propanediolato* - 1,10 - *phenanthroline-palladium*(II), **2**

This was prepared by dissolving $Pd(phen)(OH)_2 \cdot 3H_2O$ (0.2 g) in water (50 cm^3) containing NaOH (0.1 g) and adding S(+)1,2-propanediol (0.2 g) with rapid shaking and stirring. The solution was warmed on a steam bath for several hours and allowed to cool. Reduction of volume of the resultant pale yellow solution to approximately 1/10th of the original led to precipitation of a finely divided pale yellow product which was

evidently contaminated with small amounts of the diol. Compound **4** was made by an adaptation of this method.

Compound **2** had IR absorption (measurements were made from 625 cm^{-1}) at: 640b, 680s, 710s, 840s, 850s, 865s, 920, 990, 1050, 1080, 1150, 1220, 1280, 1350, 3400b. Compound **2** had ^1H resonance at: δ1.07d, 3.49m, 3.87q, 7.63, 7.82m, 8.22d, 8.47m.

Catecholato-1,10-*phenanthrolinepalladium*(II), **5**

This was prepared by dissolving Pd(phen)$(OH)_2 \cdot 3H_2O$ (0.2 g) in distilled water containing NaOH (0.1 g) and adding a solution of catechol in distilled water (0.25 g in 5 cm^3). An immediate precipitation of deep red product occurred. This was collected on a fine sintered glass crucible (Grade 4) and washed with large quantities of water to remove NaOH and excess diol.

Compound **5** had IR absorption at: 230, 340s, 390, 440, 460, 535, 560, 580, 605, 635, 665, 715, 730, 755, 800, 845, 860, 885, 905, 965, 990, 1020s, 1040, 1095s, 1120, 1155, 1200, 1260s, 1355, 1415, 1435, 1480, 1530, 1570, 1585, 1805, 1635, 1660, 3060, 3305b. Compound **5** had ^1H resonance at: δ6.22q, 6.38q, 8.10q, 8.28, 8.95.

1,2 - *ethanedithiolato* - 1,10 - *phenanthrolinepalladium*(II), **6**

This was produced immediately on adding 1,2-ethanedithiol (0. 1g) dropwise to a solution of Pd(phen)$(OH)_2 \cdot 3H_2O$ (0.2 g) in distilled water (50 cm^3) containing NaOH (0.1 g). The orange–yellow finely divided precipitate was collected at the pump and washed with large amounts of cold distilled water to remove the unreacted thiol (smell!).

Compound **6** had IR absorption at: 230, 250, 350, 360, 430, 455, 500, 620, 650, 660, 715s, 735, 765, 840s, 875, 1100, 1140, 1220, 1240, 1275s, 1355s, 1410, 1415s, 1500, 1510s, 2600, 1625, 1660, 2720, 2880s, 2900, 3040, 3380b. Compound **6** had ^1H resonance at: δ2.63, 8.05q, 8.23, 8.57d, 8.90d, 9.07.

1,2 - *ethanediolate* - 1,10 - *phenanthrolineplatinum* (II), **7**

This was made by the same method as the palladium analogue, **1** above, modified by heating the reacting solution on the steam bath for 24 h. Acicular yellow crystals were produced on cooling to room temperature.

Compound 8 had IR bands at: 280, 420, 480, 490, 545, 610, 725, 770, 895s, 1025, 1060s, 1110, 1160, 1225, 1255, 1360, 1450, 1470, 1495, 1565, 1600, 1665, 2350b, 2820, 3360b. Compound **8** had ^1H resonance at: δ2.52, 8.36t, 8.66m.

IR spectra were measured using Nujol mulls: the numbers appended to each compound are in order of frequency (cm^{-1}), s, strong; b, broad. Proton magnetic resonance spectra (δ-values relative to TMS) were obtained in DMSO solution, with TMS reference, except for compound **2**, measured in D_2O, with TSS reference.

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