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Note

The preparation and crystal and molecular structure of the complex *cis*-$PtCl_2$(razoxane)

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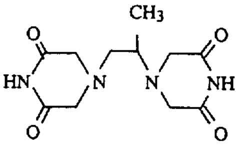
Abstract

Treatment of $K_2[PtCl_4]$ with the anti-cancer drug razoxane (3,5-dioxopiperazin-1-yl-propane) in aqueous HCl solution gave the water-insoluble complex *cis*-$PtCl_2$(razoxane), which is the first metal complex of razoxane to have been isolated. The crystal and molecular structure of the complex confirms that razoxane is present as a bidentate ligand, Pt–N = 2.095(11) and 2.080(9) Å, and was not hydrolysed during complex formation as was previously observed in the presence of other metal ions. This is also one of the few examples in which platinum is bonded to a ligand via tertiary nitrogen atoms only. The presence in the complex of two *cis* chloride ligands, Pt–Cl = 2.299(4) and 2.277(3) Å, and square planar geometry around the metal ion is also confirmed. Intermolecular hydrogen bonding between an imide oxygen atom of each molecule and an imide NH group of another results in a sheet-like 'zig-zag' structure. Crystal data for *cis*-$PtCl_2$(razoxane): monoclinic, space group $P2_1/c$, $a = 9.165(2)$, $b = 16.573(3)$, $c = 10.984(2)$ Å, $\beta = 114.60(3)°$, $Z = 4$, $R = 0.0341$, $R_w = 0.0385$. © 1998 Elsevier Science S.A.

Keywords: Platinum(II) complexes; Bidentate razoxane ligands; Crystal structures

1. Introduction

The toxic side effects of cisplatin pose severe limitations on its clinical use and much effort has been expended in finding analogues of lower toxicity and with improved effectiveness [1]. This effort has led to the development of second generation platinum drugs which are either in clinical use or at advanced stages of clinical development. We decided to attempt the synthesis of cisplatin analogues containing bis(3,5-dioxopiperazin-l-yl)alkanes. These compounds display antitumour activity of their own and the propane derivative, razoxane, (**I**), has been used clinically in association with radiotherapy in the treatment of sarcomas [2–5]. However because of its side effects it is no longer widely used. The drug was originally designed on the basis that it would enter tumour cells and undergo hydrolytic metabolism to a chelating agent which would inhibit metalloenzymes necessary for tumour cell growth [2]. We have previously described the formation and coordination properties of these hydrolysis products [6,7] and in this paper we report the synthesis and characterisation by X-ray crystallography of *cis*-$PtCl_2$(razoxane), the first metal complex of razoxane to have been synthesised and one of the few which contains platinum bonded to a ligand via tertiary nitrogen donor atoms only.



(I)

2. Experimental

2.1. Synthesis

Razoxane was prepared by heating 1,2-diaminopropanetetraacetic acid (45 g, 0.15 mol) and formamide (120 ml, 3 mol) under reduced pressure at 100–120°C for 5 h as previously described [8]. The title complex was prepared by the addition with stirring of a solution of razoxane (150 mg, 6×10^{-4} mol) in HCl (5 ml, 1 mol dm^{-3}) to a solution of

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$K_2[PtCl_4]$ (0.25 g, 6×10^{-4} mol) in deionised water (20 ml). The resulting pale orange solution was then placed over $CaCl_2$ in a vacuum desiccator. After a period of 24 h a large crop of yellow crystals was obtained. Yield: 0.2 g (64%). *Anal.* Found: C, 24.9; H, 3.2; N, 10.6; Cl, 13.5%. Calc. for $C_{11}H_{16}N_4O_4Cl_2Pt$: C, 24.7; H, 3.0; N, 10.5; Cl, 13.3%. IR bands at 3400 (broad), 3220 (strong), 1735 (strong, broad) cm^{-1}.

2.2. X-ray structure determination

X-ray crystallographic data were obtained on a Nonius CAD4 diffractometer using Mo Kα radiation at ambient temperature. Crystallographic data and details of data collection and refinement are given in Table 1. All hydrogen atoms were located in the difference Fourier synthesis and included in the refinement using the riding model approximation with fixed U_{iso} equal to 0.04 Å^2. The molecular structure of the complex is shown in Fig. 1 with the atom numbering scheme used and key bond distances and angles. Table 2 lists the atomic coordinates for non-hydrogen atoms and Table 3 lists selected bond lengths and angles, as well as the most relevant torsion angles.

Table 1
Crystal data and measurement conditions for *cis*-$PtCl_2$(razoxane)

Formula	$C_{11}H_{16}N_4O_4Cl_2Pt$
Formula weight	534.3
Crystal dimensions (mm)	$0.05\times0.1\times0.05$
Colour, habit	yellow, prism
Crystal system	monoclinic
Space group	$P2_1/c$
a (Å)	9.165(2)
b (Å)	16.573(3)
c (Å)	10.984(2)
β (°)	114.60(3)
V (Å^3)	1516.9(5)
Z	4
D_c (g cm^{-3})	2.339
$F(000)$	1016
λ(Mo Kα) (Å)	0.71073
μ(Mo Kα) (mm^{-1})	9.625
Temperature (K)	293
Scan type	ω–$5/3\theta$
Scan speed (°min^{-1})	variable 1.50–8.00° in ω
Scan range (ω) (°)	1.80 plus Kα separation
Reflections collected	3495
Independent reflections	3294 ($R_{int}=5.35\%$)
Observed reflections	1806 ($I>3\sigma(I)$)
Absorption correction	semi-empirical, based on azimuthal scans measured for 15 reflections
Solution	direct methods
Refinement method	full-matrix least-squares
Weighting scheme	unit weight
No. parameters refined	199
R	0.0341
R_w	0.0385
Goodness of fit	3.92
$\Delta\rho$, max., min. (e Å^{-3})	1.14, −1.08
System used	SHELXTL PLUS

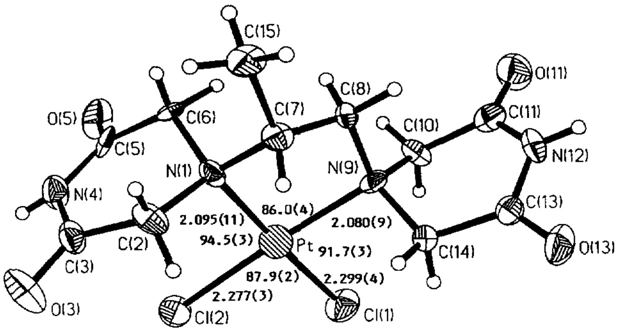

Fig. 1. Molecular structure of *cis*-$PtCl_2$(razoxane) with atom numbering scheme and selected bond lengths (Å) and angles (°) around Pt are shown. Thermal ellipsoids of non-hydrogen atoms are drawn at the 50% probability level.

Table 2
Atomic coordinates ($\times10^4$) and equivalent isotropic displacement coefficients (Å$^2\times10^3$) for *cis*-$PtCl_2$(razoxane)

Atom	x	y	z	U_{eq} [a]
Pt	7332(1)	2646(1)	1779(1)	23(1)
Cl(1)	9374(4)	2307(2)	1177(4)	41(1)
Cl(2)	6697(4)	1312(2)	1652(4)	42(2)
O(3)	4342(14)	1139(6)	3463(10)	47(5)
O(5)	2551(10)	2204(6)	−694(9)	42(4)
O(11)	8739(13)	5547(6)	351(11)	50(5)
O(13)	11482(11)	4808(6)	4694(10)	40(4)
N(1)	5486(11)	3007(5)	2313(9)	23(3)
N(4)	3222(12)	1689(6)	1381(10)	31(4)
N(9)	8031(11)	3851(5)	2028(9)	21(3)
N(12)	9991(15)	5230(7)	2575(14)	40(4)
C(2)	5257(15)	2446(7)	3266(11)	28(5)
C(3)	4265(15)	1695(7)	2708(13)	31(5)
C(5)	3209(13)	2275(8)	474(13)	30(5)
C(6)	3926(12)	3081(7)	1083(12)	26(4)
C(7)	6052(14)	3828(7)	2998(12)	25(5)
C(8)	6741(13)	4299(6)	2251(12)	25(4)
C(10)	8328(16)	4224(7)	909(12)	27(5)
C(11)	8994(15)	5058(8)	1231(14)	34(5)
C(13)	10429(14)	4659(7)	3581(14)	26(5)
C(14)	9574(14)	3862(7)	3262(13)	27(5)
C(15)	4718(16)	4316(8)	3187(14)	34(5)

[a] Equivalent isotropic U defined as one third of the trace of the orthogonalised U_{ij} tensor.

3. Results and discussion

Reaction of $K_2[PtCl_4]$ with razoxane in aqueous HCl solution (a soluble source of razoxane) gave the complex *cis*-$PtCl_2$(razoxane) for which satisfactory microanalysis was obtained. The IR spectrum of the complex in the CO stretching region contains an intense, broad band at 1735 cm^{-1} and is similar to that of the free ligand.

The crystal and molecular structure of the complex obtained by X-ray diffraction (Fig. 1) confirms the presence of bidentate razoxane which is coordinated via the tertiary nitrogen atoms with the coordination sphere of the metal ion being completed by two *cis* chloride ligands. As is almost invariably the case with complexes of platinum(II), the

Table 3
Selected bond lengths (Å) and bond and torsion angles (°) for *cis*-$PtCl_2$ (razoxane)

Pt–Cl(1)	2.299(4)	Pt–N(1)	2.095(11)
Pt–Cl(2)	2.277(3)	Pt–N(9)	2.080(9)
Cl(1)–Pt–Cl(2)	87.9(2)	C(6)–N(1)–C(7)	111.6(8)
Cl(1)–Pt–N(1)	177.6(3)	C(3)–N(4)–C(5)	123.5(10)
Cl(2)–Pt–N(1)	94.5(3)	Pt–N(9)–C(8)	106.0(7)
Cl(1)–Pt–N(9)	91.7(3)	Pt–N(9)–C(10)	116.0(7)
Cl(2)–Pt–N(9)	176.1(2)	C(8)–N(9)–C(10)	110.8(9)
N(1)–Pt–N(9)	86.0(4)	Pt–N(9)–C(14)	104.7(6)
Pt–N(1)–C(2)	112.8(7)	C(8)–N(9)–C(14)	111.0(10)
Pt–N(1)–C(6)	110.3(8)	C(10)–N(9)–C(14)	108.2(10)
Pt–N(1)–C(7)	104.1(8)	C(11)–N(12)–C(13)	123.1(11)
C(2)–N(1)–C(7)	109.2(9)		
C(6)–N(1)–C(2)–C(3)	40.6	C(10)–N(9)–C(8)–C(7)	161.4
C(7)–N(1)–C(2)–C(3)	162.7	C(14)–N(9)–C(8)–C(7)	−78.4
C(5)–N(4)–C(3)–C(2)	10.8	N(1)–C(7)–C(8)–N(9)	−53.3
N(1)–C(2)–C(3)–N(4)	−20.7	C(15)–C(7)–C(8)–N(9)	−179.4
C(3)–N(4)–C(5)–C(6)	−23.0	C(8)–N(9)–C(10)–C(11)	65.3
C(2)–N(1)–C(6)–C(5)	−51.9	C(14) N(9) C(10) C(11)	−56.5
C(7)–N(1)–C(6)–C(5)	−172.6	C(13)–N(12)–C(11)–C(10)	3.0
N(4)–C(5)–C(6)–N(1)	44.4	N(9)–C(10)–C(11)–N(12)	32.2
C(2)–N(1)–C(7)–C(8)	162.8	C(11)–N(12)–C(13)–C(14)	−10.9
C(2)–N(1)–C(7)–C(15)	−73.1	C(8)–N(9)–C(14)–C(13)	−72.4
C(6)–N(1)–C(7)–C(8)	−76.8	C(10)–N(9)–C(14)–C(13)	49.4
C(6)–N(1)–C(7)–C(15)	47.4	N(12)–C(13)–C(14)–N(9)	−16.9

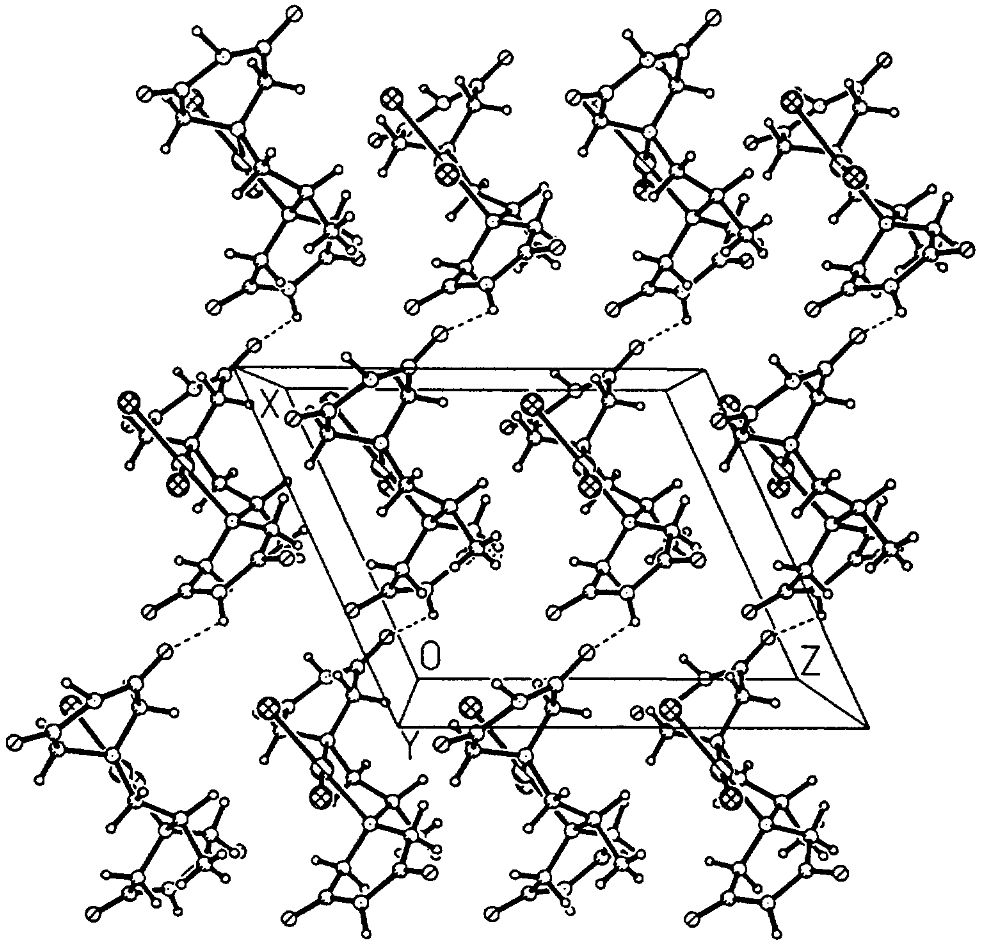

Fig. 2. Molecular packing of *cis*-$PtCl_2$(razoxane) with hydrogen bonds represented by dashed lines.

geometry around the metal ion is square planar [9] with atom deviations from planarity around the platinum being no greater than 0.04 Å and deviations from ideal 90° bond angles being no greater than 4.5°. The slight decrease to 86.0(4)° in the N(1)–Pt–N(9) bond angle may be attributed to a chelate effect.

The Pt–Cl bond distances of 2.299(4) and 2.277(3) Å are similar to those found in other complexes of platinum(II) such as *cis*-$[Pt(NH_3)_2Cl_2]$, $K[Pt(NH_3)Cl_3]\cdot H_2O$ and $[PtCl_4]^{2-}$ for which Pt–Cl distances of 2.328(9) and 2.333(9) [10] 2.300–2.311 [11] and 2.281–2.309 Å [12] respectively have been reported. In the complex PtCl(HL) where H_2L is the diamide derived from EDTA, i.e. $[CH_2N(CH_2COOH)CH_2CONH_2]_2$, the Pt–Cl bond distance is 2.287(1) Å [6]. The Pt–N bond distances of 2.095(11) and 2.080(9) Å obtained for *cis*-$PtCl_2$(razoxane) are similar to those previously observed for platinum(II)–nitrogen bonds [6,13–17]. In the aforementioned complex PtCl(HL), which like the title complex contains tertiary amine donor atoms, the Pt–N bond distances are 2.073(4) and 2.014(4) Å, the shorter distance being due to the fact that the nitrogen in question, unlike the nitrogens in the present complex, is part of two chelate rings, which causes contraction of the metal–nitrogen bond distance. Amongst the many other reported Pt–N distances in complexes of the type *cis*-$PtCl_2$(N-donor)$_2$ are 2.08(3) Å in *cis*-$PtCl_2(GlyOH)_2$ [15] 2.07(3) and 2.14(3) Å in *cis*-$PtCl_2(GlyOH)_2\cdot H_2O$ [15] 2.03 Å in *cis*-$PtCl_2$(L-MetOH) [16] and 2.037(5) and 2.050(5) Å in *cis*-$PtCl_2(NH_2Me)_2$ [17].

The structure of free razoxane has been reported in the racemic triclinic and optically active monoclinic crystal forms [18]. By necessity the central alkane bridge of the ligand in the platinum complex reported herein has a cisoid conformation with an N(1)C(7)C(8)N(9) torsion angle of 53.3°. This is the conformation also reported for the moiety in the racemic crystal of free razoxane for which the corresponding torsion angle is equal to 55.5°. In the complex the mean planes of the carbon atoms of the two piperazine rings are almost parallel (the dihedral angle is equal to 2.8°), whereas in the racemic modification of free razoxane the planes are inclined to each other by 71°. An almost parallel arrangement of the mean piperazine planes is also observed in the optically active modification which, in contrast to the platinum complex and the racemic crystal, features a transoid conformation of the central NCCN moiety.

The packing diagram of the complex, Fig. 2, shows that the complex molecules are linked by weak intermolecular hydrogen bonds involving an imide carbonyl group of one molecule and an imide NH group of another $(-1+x, 0.5-y, -0.5+z)$ resulting in a sheet-like, 'zig-zag' structure in which the N···O distances are 3.11(1) Å and N–H···O angles are 158°.

We have previously reported that razoxane undergoes facile base-promoted ring opening reactions in the presence of metal ions such as copper(II). At 25° and at pH values as low as 5 hydrolysis of one of the imide rings is observed [19] while at higher temperatures hydrolysis of both imide groups occurs [7]. The absence of hydrolysis in the present case may be due to a combination of the acidic reaction conditions and the insolubility of the title complex.

4. Supplementary material

Full lists of bond lengths and angles and hydrogen atom coordinates are available from the Cambridge Crystallographic Data Centre.

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References

[1] N. Farrell, Transition Metal Complexes as Drugs and Chemotherapeutic Agents, Kluwer, Dordrecht, 1989.
[2] A.M. Creighton, K. Hellmann and S. Whitecross, Nature, 222 (1969) 384.
[3] M.T. Bakowski, Cancer Treatment Rev., 3 (1976) 95.
[4] K.M. Dawson, Biochem. Pharm., 24 (1975) 224.
[5] J.E.F. Reynolds (ed.), Martindale, The Extra Pharmacopoeia, 31st edn., Royal Pharmaceutical Society, London 1996, p. 597.
[6] K.B. Nolan, L.P. Ryan, C.J. Campbell, P. McArdle, D. Cunningham and T. Higgins, Met. Based Drugs, 1 (1994) 321.
[7] N. NicDaeid, K.B. Nolan and L.P. Ryan, J. Chem. Soc., Dalton Trans., (1991) 2301.
[8] A.M. Creighton, UK Patent 1 234 935 (1972).
[9] D.M. Roundhill, in R.D. Gillard, J.A. McCleverty and G. Wilkinson (eds.), Comprehensive Coordination Chemistry, Vol. 5, Pergamon, Oxford, 1987, Ch. 52.
[10] G.H.W. Milburn and M.J. Truter, J. Chem. Soc. A, (1966) 1609.
[11] Y.P. Jeannin and D.R. Russell, Inorg. Chem., 9 (1970) 778.
[12] C.J. Campbell, A. Castineiras and K.B. Nolan, Inorg. Chim. Acta, 245 (1996) 247.
[13] V. Pavone, A. Lombardi, B. Di Blasio, E. Benedetti and C. Pedone, Inorg. Chim. Acta, 153 (1988) 171.
[14] A. Lombardi, O. Maglio, E. Benedetti, B. Di Blasio, M. Saviano, F. Nastri, C. Pedone and V. Pavone, Inorg. Chim. Acta, 196 (1992) 241.
[15] I.A. Baidina, N.V. Podberezskaya and S.V. Borisov, Zh. Strukt. Khim., 22 (1981) 185.
[16] H.C. Freeman and M.L. Golomb, J. Chem. Soc., Chem. Commun., (1970) 1523.
[17] L. Brammer, J.M. Charnock, P.L. Goggin, R.J. Goodfellow, T.F. Koetzle and A.G. Orpen, J. Chem. Soc., Chem. Commun., (1987) 443.
[18] A. Hempel, N. Camerman and A. Camerman, J. Am. Chem. Soc., 104 (1982) 3453.
[19] K.B. Nolan, T. Murphy, R.D. Hermanns, H. Rahoo and A.M. Creighton, Inorg. Chim. Acta, 168 (1990) 283.