Inorganica Chimica Acta, 55 (1981) L57–L59

Synthesis of Potential Platinum(II) Anti-tumor Complexes: Complexes containing Bidentate Pyridyl and Imidazolyl Donors

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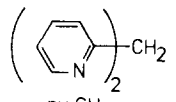
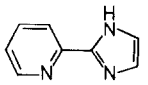
Received January 16, 1981

The complexes *cis*-PtL_2Cl_2 (L = pyridine [1, 2], imidazole [3, 4] and N-methylimidazole [4–6]) have been studied as potential anti-tumor drugs, and complexes of the related polydentate ligands 2,2′-bipyridyl and 2,2′:6′,2″-terpyridyl have been investigated as intercalating agents for DNA [7]. We report here the synthesis of complexes of some related bidentate ligands containing pyridyl rings connected by a carbon atom, di-2-pyridylmethane (py_2CH_2) and py_2CEt_2, and containing both pyridyl and imidazolyl rings, (2,2′-pyridyl)imidazole (pyIm) and py-NMeIm.



py_2CH_2



pyIm

The ligands py_2CH_2 and py_2CEt_2 were chosen because of their close relationship to pyridine and 2,2′-bipyridyl; pyIm and py-NMeIm were chosen as these bidentates are expected to be coplanar with the $PtCl_2$ group, in contrast to *cis*-PtL_2Cl_2 (L = pyridine [8], HIm and NMeIm [6]). In addition pyIm has a proton that may become involved in hydrogen bonding, a factor which may be important in interaction of Pt(II) complexes with DNA [9].

Preliminary screening of the complexes, together with *cis*-PtL_2Cl_2 (L_2 = 2,2′-bipyridyl; L = NH_3, pyridine), *in vitro* with L1210 mouse leukemia cells indicate that the complexes have $I.D._{50}$ values (concentration of complex required to inhibit growth by 50%) higher than that of clinically useful [10] *cis*-$Pt(NH_3)_2Cl_2$, except for $Pt(pyIm)Cl_2 \cdot H_2O$ which has the same $I.D._{50}$ values as *cis*-$Pt(NH_3)_2Cl_2$.

Experimental

Platinum sponge (Matthey Garrett, Sydney) was converted to K_2PtCl_4 as described [11]. The ligands py_2CH_2, pyIm, py-NMeIm, and py_2CEt_2 were prepared previously [12]. As all of the complexes were prepared in a similar manner the preparation of $Pt(pyIm)Cl_2 \cdot H_2O$ is given as an example. Infrared spectra (4000–400 cm^{-1}) in Nujol and hexachlorobutadiene mulls, and far infrared spectra (600–200 cm^{-1}) in Nujol mulls between polyethylene plates were recorded with a Perkin-Elmer 577 spectrometer; maximum errors are considered to be *ca.* 4 cm^{-1}. Conductivities were measured with a Philips PW 9504/00 conductivity meter in dimethylformamide. Microanalyses were carried out by the Australian Microanalytical Service, Melbourne, and are recorded in Table I.

cis-Dichloro[2(2′-pyridyl)imidazole]platinum(II) Monohydrate

A solution of pyIm (0.3 g, 2.07 mmol) in 1 *M* hydrochloric acid was added to a filtered solution

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TABLE I. Analytical Data for the Complexes.

Complex	Found %			Calcd. %		
	C	H	Cl	C	H	Cl
$Pt(py_2CH_2)Cl_2$	30.2	2.5	16.4	30.3	2.3	16.3
$Pt(py_2CEt_2)Cl_2$	36.2	3.7	14.2	36.6	3.7	14.4
$Pt(pyIm)Cl_2 \cdot H_2O$[a]	22.4	1.9	16.9	22.4	2.1	16.5
$Pt(py\text{-}NMeIm)Cl_2$	25.6	2.4	16.9	25.4	2.1	16.7

[a]Found: N, 9.6; Calcd. 9.8%. Drying at *ca.* 110 °C for 2 hours over P_2O_5 in a vacuum gave $Pt(pyIm) \cdot ca.\ 0.5H_2O$. Found: C, 22.9; H, 1.9; Cl, 16.9; N, 10.1. Calcd. C, 22.9; H, 1.9; Cl, 16.9; N, 10.0%.

TABLE II. Platinum–Chlorine Stretching Frequencies[a] and Conductance Data.[b]

Complex	ν_{as} (cm^{-1})	ν_{s} (cm^{-1})	Molar Conductance (ohm^{-1} cm^2 mol^{-1})
$Pt(py_2CH_2)Cl_2$	342 s	329 s	1.0
$Pt(py_2CEt_2)Cl_2$	339 w	328 w	2.4
$Pt(pyIm)Cl_2 \cdot H_2O$[c]	3.43 w	329 s (sh,b)	6.7
$Pt(py\text{-}NMeIm)Cl_2$[d]	342 m	330 m	1.2

[a]Nujol mulls; s, strong; m, medium; w, weak; sh, shoulder; b, broad; v, very. [b]In dimethylformamide at 10^{-3} *M*. [c]ν(OH) 3530 m(vb). [d]An absorption at 356 m is assumed to be a ligand mode, shifted from 369 w in the free ligand.

of K_2PtCl_4 (0.08 g, 1.93 mmol) in water. The resulting solution was stirred at ambient temperature for 2 hr and a yellow powder collected by filtration and washed with water (0.6 g, 74%). For complexes of py_2CH_2 and py_2CEt_2 the dihydrochloride salt of the ligand was dissolved in water and added to an aqueous solution of K_2PtCl_4.

Procedure for Studies of Growth Inhibition

Complexes were dissolved in dimethylsulphoxide at concentrations such that 0.005 ml of solution when added to 2 ml of culture medium gave the required drug concentration. Cultures were assessed using a Coulter counter 48 hrs after drug additions; 0.005 ml of dimethylsulphoxide in 2 ml of medium had no effect on cell growth.

TABLE III. 50% Inhibitory Dose ($I.D._{50}$) for *cis*-PtL_2Cl_2 Complexes.[a]

L_2	$I.D._{50}$[b] ($mol\ l^{-1}$)
py_2CH_2	1.0×10^{-5}
py_2CEt_2	3.5×10^{-6}
pyIm[c]	1.0×10^{-6}
py-NMeIm	[d]
2,2'-bipyridyl	6.0×10^{-6}
$(NH_3)_2$	1.0×10^{-6}
$(pyridine)_2$	7.0×10^{-6}

[a]Cultures of L1210 mouse leukemia cells. [b]Concentration of complex, in dimethylsulphoxide, required to inhibit growth L1210 cells by 50%. [c]Monohydrate. [d]Insufficiently soluble to obtain concentrations $>2 \times 10^{-6}$ mol l^{-1}.

Results and Discussion

The complexes precipitated as yellow powders on reaction of the ligands with an acidic aqueous solution of K_2PtCl_4. The complexes gave satisfactory microanalyses (Table I), and all of the complexes are insoluble in water but form non-conducting solutions in dimethylformamide (Table II), consistent with absence of ionic salts, *e.g.* Magnus type salts, as impurities.

Infrared spectra indicate that pyridine ring vibrations are shifted in the usual manner observed on coordination [13, 14], *e.g.* the band at 405 cm^{-1} [14] for pyridine is raised on coordination [13, 14] and similar shifts occur for the ligands studied here. Thus, bands at 403 w (py_2CH_2), 403 m (py_2CEt_2), 400 m (pyIm), and 403 w cm^{-1} (py–NMeIm) occur at 453 m or 437 w(b), 456 w and/or 446 w, 430 w, and 431 w cm^{-1}, respectively, in the complexes. Platinum–chlorine stretching modes are readily identified in the range 343–328 cm^{-1} for the complexes by comparison with spectra of the ligands and *cis*-PtL_2Cl_2 (L = pyridine [15], imidazole [3], N-methylimidazole [6], and L2 = 2,2'-bipyridyl [16]) which have these modes in the range 345–320 cm^{-1} (Table II).

Preliminary screening of the complexes, including the 2,2'-bipyridyl complex and *cis*-PtL_2Cl_2 (L = NH_3, pyridine), on cultures of L1210 mouse leukemia cells has been carried out (Table III) [17]. Results were obtained over a range of concentrations required to give 10–90% inhibition of growth, and the expected sigmoidal curves (percent growth *vs.* concentration) were obtained. The complex *cis*-Pt(pyridine)$_2Cl_2$ gave an $I.D._{50}$ value higher than that of *cis*-$Pt(NH_3)_2Cl_2$, consistent with earlier studies showing that this complex has lower activity than *cis*-$Pt(NH_3)_2Cl_2$ against Ehrlich ascites and Sarcoma 180 tumors in mice [1, 2]. The complex $Pt(pyIm)Cl_2 \cdot H_2O$ gave an $I.D._{50}$ value similar to that of *cis*-$Pt(NH_3)_2Cl_2$, and below values for the other complexes. These results suggest that further testing with tumor bearing animals is warranted for $Pt(pyIm)Cl_2 \cdot H_2O$.

Acknowledgements

We thank the Australian Research Grants Committee for financial support, the Education Department for a Studentship (E.A.S.), and we thank Ian A. G. Roos and Janette E. Sutton (Chemotherapy Unit, The Cancer Institute, Melbourne, Victoria, Australia) for *in vitro* testing with L1210 mouse leukemia cells (Table III).

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