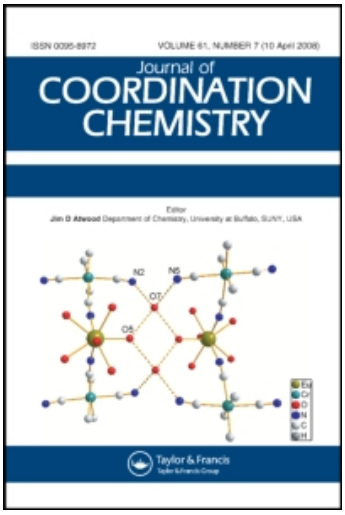

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MIXED LIGAND COMPLEXES OF PLATINUM(II) WITH α-AMINO ACIDS AND PURINES AND PYRIMIDINES

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The synthesis and characterization of mixed ligand complexes of platinum(II) with amino acids as primary ligands and purine and pyrimidine bases as secondary ligands are reported. The interaction of platinum(II) glycine and alanine complexes with purine and pyrimidine, carried out in a 1 : 1 ratio resulted in the formation of mixed ligand complexes. In these complexes adenine and guanine are coordinated to the metal ion through $N_{(7)}$ whereas hypoxanthine acts as a bridging ligand coordinating through $N_{(3)}$ and $N_{(9)}$. The pyrimidines are coordinated to the metal ion through $N_{(3)}$. In all the mixed ligand complexes the amino acids behave as monodentate ligands coordinating through amino nitrogen.

INTRODUCTION

The discovery of *cis*$[Pt(NH_3)_2Cl_2]$ as an effective anti-tumour drug[1] has led to the preparation of a large number of Pt(II) complexes.[2] Since *cis* compounds have more anti-tumour activity than trans compounds,[3] efforts are being made to synthesize various Pt(II) complexes with *cis* geometry. It is postulated that the activity of these compounds are related to their ability to interact with DNA. Several models involving the formation of platinum bridged covalent cross links have also been proposed.[4] From these models it has been proposed that *cis* dichlorodiamineplatinum(II) chelates to the purine and pyrmidine bases usually through nitrogen or oxygen.

In this paper we report the synthesis of mixed ligand complexes of platinum(II) with amino acids as primary ligands and purine and pyrimidine bases as secondary ligands. For this purpose the amino acids taken are glycine and alanine. The secondary ligands are adenine, guanine, hypoxanthine cytosine and uracil.

EXPERIMENTAL

The purines, pyrimidines and amino acids were obtained from Sigma chemicals and were used without further purification. Dihydrogen hexachloroplatinate(IV) was purchased from Alfa Ventron (USA), potassium tetrachloroplatinate(II) was prepared by the published procedure.[8] Potassium dichloroglycinatoplatinate(II)[9] and potassium alaninatodichloroplatinate(II)[10] were also prepared by the published procedures. The IR spectra were recorded on a Perkin Elmer spectrophotometer (337), and the ^1H NMR spectra on Jeol 100 MHz. The U.V. spectra were recorded on Beckman (Model DB) spectrophotometer. Micro analysis was performed at CSIRO (Australia). Percentage of chlorine was estimated by Schoringmer method.

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1. Cis-Dichloroadenineglycineplatinum(II) hydrate
2. Cis-Dichloroglycineguanineplatinum(II) hydrate
3. Tetrachloroglycine-μ-hypoxanthinediplatinum(II)

Potassium dichloroglycinatoplatinate(II) (0.5 mM, 0.20 gms) was dissolved in 15 ml of water and to this a solution of adenine (0.5 mM, 0.06 gms) or guanine (0.5 mM, 0.076 gms) or hypoxanthine (0.5 mM, 0.069 gms) in acidic aqueous medium was added. The resulting solution was stirred for six hours at room temperature in the case of adenine and at 60–70° in case of guanine, when a yellow and a dark brown precipitate was obtained respectively. In the case of hypoxanthine refluxing was carried out at 110° for 5 hours, when a yellow precipitate was obtained. These complexes were filtered, washed with water, acetone and dried.

4. Cis-Dichlorocytosineglycineplatinum(II)
5. Cis-Dichloroglycineuracilplatinum(II)

Potassium dichloroglycinatoplatinate(II) (0.5 mM, 0.20 gms) was dissolved in water and to this a solution of cytosine (0.5 mM, 0.056 gms) or uracil (0.5 mM, 0.057 gms) dissolved in basic aqueous medium was added. The resulting solution was refluxed in the case of cytosine or stirred at room temperature in the case of uracil for four hours. The solution was concentrated and the pH of the solution was brought to about 5–6 with 0.1 N HCl, when a brown complex was obtained. It was filtered washed with water, acetone and dried.

6. Cis-Dichloroadeninealanineplatinum(II)
7. Cis-Dichloroalaninequanineplatinum(II)
8. Tetrachlorodialinine-μ-hypoxanthinediplatinum(II)

Potassium dichloroalaninatoplantinate(II) (0.5 mM, 0.216 gms) was dissolved in 15 ml of water to this a solution of adenine (0.5 mM, 0.068 gms) or guanine (0.5 mM, 0.078 gms) or hypoxanthine (0.5 mM, 0.069 gms) dissolved in acidic aqueous medium was added. The resulting solution was refluxed for eight, ten and five hours when a light yellow, a light brown and a pale yellow precipitate was obtained, respectively.

9. Cis-Dichloroalaninecytosineplatinum(II)
10. Chlorobiscytosinealanineplatinum(II) chloride dihydrate

Potassium dichloroalaninatoplatinate(II) (0.5 mM, 0.216 gms) was dissolved in 10 ml of water and to this a solution of cytosine in 1:1 ratio (0.5 mM, 0.056 gms) or in 1 : 2 ratio (1 mM, 0.115 gms) dissolved in basic aqueous medium was added. The resulting solution was refluxed for six hours in both the cases. The pH of the solution was brought down to 5. On concentration a reddish brown or light pink precipitate was obtained. The precipitate was filtered, washed with ethanol, acetone and dried.

RESULTS AND DISCUSSIONS

The ir spectra of $K[Pt(Gly)Cl_2]$ and $K[Pt(Ala)Cl_2]$exhibit a strong NH_2 deformation band at 1580 cm^{-1}. The C=O antisymmetric stretching mode is observed as strong bands around 1700 cm^{-1} and 1660 cm^{-1} respectively in the two complexes. Medium bands corresponding to N-H stretching is observed at 3400 cm^{-1} and 3250 cm^{-1} respectively. The C-N stretching frequency of the coordinate amino acid is observed around 1210 cm^{-1}. The M-Cl stretching

frequencies corresponding to *cis* chlorides are observed around 320 to 350 cm^{-1} as strong bands. The M-N stretching mode is exhibited around 550 cm^{-1}.

The ir spectra of adenine, guanine and cytosine exhibit a strong absorption band around 1600 cm^{-1} assigned to NH_2 deformation mode. This peak is not shifted to a noticeable extent in these complexes indicating that the NH_2 group is not involved in coordination. The C=C stretching frequency of purines and pyrimidines are observed around 1450 cm^{-1} and 1400 cm^{-1} respectively. This peak is observed around 1480 cm^{-1} for purine complexes and around 1420 cm^{-1} in the pyrimidine complexes. The C=N stretching frequency of the ligands are observed around 1300 cm^{-1} which is shifted to a higher frequency by about 70 cm^{-1} in all the complexes indicating the involvement of ring nitrogens in coordination. The C=O stretching frequency of the ligands (hypoxanthine, guanine, cytosine and uracil) is observed around 1670 cm^{-1}. This peak is not shifted to a noticeable extent in all the complexes indicating that this group is not involved in coordination. In the mixed ligand complexes the C=O anti-symmetric stretching frequency of the carboxyl group of glycine and alanine are present around 1700 cm^{-1} and 1640 cm^{-1} respectively. All complexes exhibit two M-Cl stretching frequencies around 300–360 cm^{-1} corresponding to the presence of *cis* chlorides. The M-N stretching frequencies of coordinated glycine or alanine and purine or pyrimidine is observed as a broad band in the region 500–550 cm^{-1} and could not be separately assigned due to the overlap of these frequencies.

The nmr spectrum of $K[Pt(Gly)Cl_2]$[11] shows a peak at 3.76 ppm which may be assigned to $-CH_2$ of the coordinated glycine. This peak is observed around 3.6 to 4.0 ppm in the mixed ligand complexes.

The nmr spectrum of free adenine exhibits two singlets around 8.2 ppm and 8.32 ppm for $C_{(2)}H$ and $C_{(8)}H$ protons respectively. The nmr spectrum of adenine complex$_{(1)}$ show $C_{(2)}H$ around 8.1 ppm and $C_{(8)}H$ protons at 9.01 ppm. The $C_{(8)}H$ protons are thus shifted to a greater extent as compared to the $C_{(2)}H$ protons indicating $N_{(7)}$ of adenine as the binding site in the complex.

The nmr spectrum of free guanine exhibits a singlet around 7.6 ppm which is assigned to $C_{(8)}H$ protons. In the mixed ligand guanine complex(2) this peak is shifted to 8.2 ppm indicating $N_{(7)}$ as the coordination site in the complex.

The nmr spectrum of free hypoxanthine exhibits two singlets around 7.87 ppm and 8.08 for $C_{(2)}H$ and $C_{(8)}H$ protons respectively. The nmr spectrum of complex *3* exhibits $C_{(2)}H$ protons around 8.16 ppm and $C_{(8)}H$ protons around 8.3 ppm. Here both $C_{(2)}H$ and $C_{(8}H$ protons are shifted to the same extent which indicates that hypoxanthine acts as a bridging ligand in the complex coordinating through $N_{(3)}$ and $N_{(9)}$.

The nmr spectrum of free cytosine exhibits two singlets around 5.8 and 5.67 ppm which are assigned to $C_{(5)}H$ and $C_{(6)}H$ protons, respectively. These peaks are present around 7.2 ppm and 7.77 ppm in complex *4*. The $C_{(5)}H$ protons is thus shifted to a greater extent than $C_{(6)}H$ protons indicating $N_{(3)}$ as the binding site.

The nmr spectrum of free uracil exhibits two singlets around 5.71 ppm and 7.6 ppm for $C_{(5)}H$ and $C_{(6)}H$ protons respectively. These peaks are exhibited in complex *5* at 4.9 ppm and 7.4 ppm respectively. The $C_{(5)}H$ proton is thus shifted to a greater extent than $C_{(6)}H$ proton indicating $N_{(3)}$ as the coordinating site in the complex.

The nmr spectrum of $K[Pt(Ala)Cl_2]$[11] exhibits singlets at 3.83 ppm and 1.48 ppm, respectively which may be assigned to $-CH_2$ and $-CH_3$ protons of the coordinated alanine. In all the complexes the $-CH_2$ protons are observed around 3.7 to 3.9 ppm and $-CH_3$ protons around 1.5 to 1.7 ppm.

In analogy to bonding of adenine in other complexes, $N_{(7)}$ of adenine is the binding site in complex *6*, similar to the corresponding glycine complex (*1*). Complex *7* exhibits a peak around 8.11 ppm which may be assigned to $C_{(8)}H$ protons of guanine, since this peak is shifted downfield corresponding to free guanine in the complex.

TABLE I
Analytical data

Sl. No.	Complex	% Carbon		% Hydrogen		% Nitrogen		% Chlorine	
		Cal.	Found	Cal.	Found	Cal.	Found	Cal.	Found
1.	Cis-$[Pt(GlyH)(Gu)Cl_2]H_2O$	16.80	17.00	2.11	2.30	16.32	17.00	14.80	14.31
2.	Cis-$[Pt(GlyH)(Gu)Cl_2]H_2O$	16.20	15.70	2.30	2.20	13.80	13.80	13.80	13.22
3.	$[Pt_2(GlyH)_2(HyPO)Cl_4]$	12.08	12.62	1.60	1.45	10.35	10.76	17.68	17.35
4.	Cis-$[Pt(GlyH)(Cyt)Cl_2]$	15.91	15.50	2.20	1.90	12.30	12.30	15.66	16.01
5.	Cis-$[Pt(GlyH)(Ura)Cl_2]$	15.90	15.31	1.70	1.55	9.21	8.66	15.09	15.60
6.	Cis-$[Pt(AlaH)(Ade)Cl_2]$	19.50	20.69	2.46	2.87	17.13	17.45	14.55	14.48
7.	Cis-$[Pt(AlaH)(Gu)Cl_2]H_2O$	18.24	18.60	2.68	2.71	16.02	16.52	12.60	12.05
8.	$[Pt_2(AlaH)_2(HyPO)Cl_4]$	16.90	16.61	2.19	1.85	9.92	10.15	16.70	16.20
9.	Cis-$[Pt(AlaH)(Cyt)Cl_2]$	18.01	17.90	2.59	2.36	12.01	12.51	13.40	13.10
10.	$[Pt(AlaH)(Cyt)_2Cl]ClH_2O$	22.16	22.09	3.21	3.24	16.45	16.11	11.57	11.48

Complex *8* is a dimer with hypoxanthane as a bridging group coordinating through $N_{(3)}$ and $N_{(9)}$ similar to that of the corresponding glycine complex (*3*).

The nmr spectrum of complex *9* exhibits two peaks at 5.0 ppm and 7.55 ppm which may be assigned to $C_{(5)}H$ and $C_{(6)}H$ protons. As the $C_{(5)}$ proton is shifted to a greater extent, $N_{(3)}$ is proposed as the binding site.

In the nmr spectrum of complex *10* two peaks are observed at 4.8 and 4.79 ppm which may be assigned to $C_{(5)}H$ and $C_{(6)}H$ protons. The $C_{(5)}H$ proton is shifted to a greater extent than the $C_{(6)}H$ proton indicating $N_{(3)}$ as the binding site.

In the mixed ligand complexes of glycine the methylene protons undergo an upfield shift in the case of adenine and guanine complexes and a downfield shift in the case of pyrimidine complexes. In the hypoxanthine complex where hypoxanthine coordinates as a bridging bidentate group, there is a down field shift in the $-CH_2$ protons of glycine. Thus the $-CH_2$ protons seems to be sensitive to the change in the basicities of the purine and pyrimidine ligand. More basic purine ligands cause an up field shift in the $-CH_2$ frequency of coordinated amino acid corresponding to a greater shielding of the $-CH_2$ protons and the less basic pyrimidines show a downfield shift corresponding to the deshielding of $-CH_2$ protons by a removal of electron density from the $-NH_2$ group of glycine.

For alanine complexes, however, there seems to be an upfield shift in the $-CH_2$ protons of alanine for both the purine and pyrimidine complexes. This may be due to the higher basicity of alanine as compared to glycine. The methyl protons of alanine undergo a downfield shift in all the complexes indicating the drift of electron density from the methyl group in the mixed ligand complexes. (See Table II.)

The mixed ligand complexes of Pt(II) have a C_s symmetry and besides the ligational bands they also exhibit d-d transitions in the range 327 nm to 390 nm. The electronic spectra of all the complexes also exhibit a band around 267–275 nm assigned to $\pi^* \leftarrow \pi$ transition of the purine or pyrimidine ligand.

In neutral solution *cis* dichloroglycinatoplatinate(II) complex has a chelated structure with glycine coordinated to Pt(II) through amino and carboxylate (complex 1). In the presence of acid the carboxylate group gets protonated and is lifted from the coordination position of the

TABLE II
^1H NMR Spectra of the complexes

Complex no.	Complex	Purine		Pyrimidine		Amino acid	
		$C_{(2)}H$	$C_{(8)}H$	$C_{(5)}H$	$C_{(6)}H$	CH_2	CH_3
	$K[Pt(Gly)Cl_2]$					3.76	
	Adenine	8.20	8.32				
1.	$Cis\text{-}[Pt(GlyH)(Ade)Cl_2]H_2O$	8.10	9.01			3.71	
	Guanine		7.68				
2.	$Cis\text{-}[Pt(GlyH)(Gua)Cl_2]H_2O$		8.2			3.60	
	Hypoxanthine	7.87	8.08				
3.	$[Pt_2(GlyH)_2(Hyp)Cl_4]$	8.16	8.3			4.0	
	Cytosine			5.88	7.67		
4.	$Cis\text{-}[Pt(GlyH)(Cyt)Cl_2]$			5.20	7.80	3.80	
	Uracil			5.71	7.60		
5.	$Cis\text{-}[Pt(GlyH)(Ura)Cl_2]$			4.9	7.61	3.80	
	$K[Pt(AlaH)Cl_2]$					3.83	1.48
7.	$Cis\text{-}[Pt(AlaH)(Gua)Cl_2]H_2O$		8.11			3.83	1.71
9.	$Cis\text{-}[Pt(AlaH)(Cyt)Cl_2]$			4.9	7.55	3.74	1.48
10.	$[Pt(AlaH)(Cyt)_2Cl]ClH_2O$			4.8	7.49	3.76	1.51

Solvent D_2O/NaOD: (δ values are given in parts per million).

TABLE III
Electronic spectra of the complexes

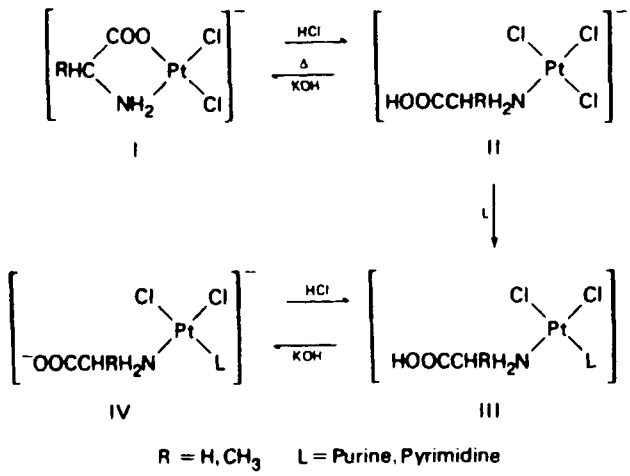
Complex no.	Complex	λ_{max}	ϵ_{max}
1.	Cis-[Pt(GlyH)(Ade)Cl_2]H_2O	345	691
		370	400
2.	Cis-[Pt(GlyH)(Gu)Cl_2]H_2O	345	710
3.	[Pt_2(GlyH)(Hypo)Cl_4]	390	490
		335	272
4.	Cis-[Pt(GlyH)(Cyt)Cl_2]	338	530
		385	412
5.	Cis-[Pt(GlyH)(Ura)Cl_2]	336	393
7.	Cis-[Pt(AlaH)(Gua)Cl_2]	322	245
8.	[Pt_2(AlaH)(Hypo)Cl_4]	338	345
9.	Cis-[Pt(AlaH)(Cyt)Cl_2]	330	250
		354	207
10.	[Pt(AlaH)$(Cyt)_2$Cl]Cl.H_2O	327	581
		344	454

metal ion (common complex II)[12]. The reaction is reversible and the carboxylate group form a chelate on the addition of the base (see Scheme I).

In the presence of purine or pyrimidine bases one of the trans chlorides position on Pt(II) is substituted by these bases, thus act as monodentate ligands coordinating through $N_{(7)}$ in case of purine bases or $N_{(3)}$ in case of pyrimidine bases to form the mixed ligand complex III. The complexes are neutral and insoluble in water at pH = 7. Addition of a base to complex III results in the dissociation of a proton from the carboxylate group to form an anionic complex IV species which is soluble in water. Addition of acid to complex IV reforms the insoluble complex III species by the protonation of the carboxylate group.

The addition of acid to complex I cleaves the chelate ring at the carboxylate position rather than the NH_2 group[15]. This is because of the strong coordination of the soft Pt(II) with the soft-HN_2 compared to the hard carboxylate oxygen which prefers a proton over Pt(II). In the presence of purine or pyrimidine bases, the amino acids are preferentially coordinated

SCHEME I



R = H, CH_3 L = Purine, Pyrimidine

through the $-NH_2$ rather than the carboxylate group.[13–15] Thus glycine or alanine remain as a monodentate ligand in the mixed ligand complexes coordinated through $-NH_2$ with a free carboxylate group. This reaction may have some biological significance where a Pt(II) complex can combine with a peptide $-NH_2$ rather than the carboxyl group.

Alanine complexes are less soluble than the corresponding glycine complexes because of the presence of a hydrophobic methyl group on alanine. Guanine complexes are more soluble than adenine complexes due to the presence of the polar C—Ō group which may be present in an enol form in the basic solution.

REFERENCES

1. B. Rosenberg, L. Van Camp, J. E. Troska and V. H Mansour, *Nature (London)*, **222**, 385 (1969).
2. (a) A. Terzis, N. Hadjiliades, R. Rivert and T. Theophanides, *Inorganica. Chim. Acta.*, **12**, L5 (1975); (b) P. C. Kong, D. Iyansenye and F. D. Rochon, *Bioinorganic. Chem. Acta.*, **16**, 67 (1976).
3. P. Brodkes, P. A. Planther (Ed), *Chemotherapy of cancer*, Elsevier, Amsterdam (1964), pp. 32–43.
4. B. Rosenberg and L. Van Camp, *Cancer Res.* **30**, 1977 (1970).
5. E. Sletten and N. Floogsted, *Acta. Cryst.*, **B33**, 1633 (1977).
6. E. Sletten, *Acta. Cryst.* **B30**, 1961 (1974).
7. T. J. Kistenmacher, D. J. Sozalda and L. G. Marzilli, *Acta. Cryst.*, **B31**, 2416 (1975).
8. H. L. Grube, *Handbook of Preparative Inorganic Chemistry*, G. Brauer, ed., Vol. 2, Academic Press, New York, 1965, pp. 1571.
9. L. E. Erikson, J. W. McDonald, J. K. Howie and R. P. Clow, *J. Amer. Chem. Soc.* **90**, 6391 (1968).
10. H. Leily and K. Fickon, *Ber.*, **45**, 377 (1912).
11. L. E. Erikson, J. W. McDonald, J. K. Howie and R. P. Clow, *J. Amer. Chem. Soc.*, **90**, 6394 (1968).
12. J. Fujila, K. Konya and K. Nakamoto., *Inorg. Chem.*, **9**, 2794 (1970).
13. C. H. Langford and H. B. Gray, *Ligand substitution processes*, W. A. Benjamin, New York, 1965, Chapter 2.
14. F. Basolo and R. G. Pearson, *Mechanism of Inorganic Reactions*, Wiley, New York, 1967, Chapter 5.
15. Hans. C. Freeman, *Inorganic Biochemistry*, G. I. Eichorn, (Ed), Vol. 1, Elsevier, Amsterdam., 1973, pp 126.