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Platinum(II) Complexes of Pyrimidine-derived Ligands

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Abstract

A series of new Pt(II) complexes of hydrazinouracils were synthesized and studied. The complexes have the general formula $[Pt_2L_2^-Cl_2]nH_2O$, where L^- is a deprotonated molecule of a ligand, n = 1–3 and there are two bridging chloride ions. The ligands are bonded through the amino group of the hydrazine residue and the nitrogen atom of the pyrimidine cycle. From ^1H NMR data it is concluded that the preferred type of coordination is Pt–N(3), hydrazine chelation, which is characteristic for solid complexes. Although the participation of the N(1) atom in formation on the polynuclear complexes is possible, it may be that N(1) coordination occurs only in solutions.

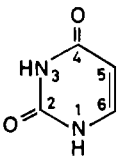
Introduction

Pyrimidine derivatives play a dominant role in many biological systems, the ring system being present in, for example, nucleic acids, several vitamins, coenzymes, *etc.* and provide potential binding sites for metal ions.

On the other hand, the remarkable antitumour activity of *cis*-dichlorodiammineplatinum(II) [1] and related species has stimulated research in the design and synthesis of a considerable number of 'model metal complexes' [2] with ligands taking part in the building-up of many biological systems.

In connection with this, the complex compounds of Pt(II) with a range of pyrimidines and their derivatives [3–9], being of interest as potential antitumour drugs, are the object of a great number of investigations. It is noteworthy that small variations in the ligands can produce remarkable differences in antitumour activity [10].

In the present work we report the synthesis and spectroscopic identification of 7 new Pt(II) complexes of the general formula $(PtL^-Cl)_2nH_2O$, where L^- is a deprotonated molecule of one of the following ligands: 2-hydrazinouracil (2-HDUra), 2-hydrazino-6-methyluracil (2-HDMeUra), 4-hydrazinouracil (4-HDUra), 4-hydrazino-6-methyluracil (4-HDMeUra), 6-hydrazinouracil (6-HDUra) or 2-hydrazino-6-azathymine (2-HDAzaThy), 2-thio-4-hydrazino-6-azathymine (2-Thio-4-HDAzaThy) and n-1, 2 or 3, which are derivatives of uracil (I) and 6-azathymine (II), respectively.



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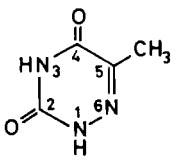

II

Experimental

Preparation and Characterization of the Complexes

The hydrazinopyrimidines were synthesized and purified as described in [11]. All other reagents used were of AR grade.

The complexes were synthesized by heating, on the boiling water bath, a mixture of 1 mmol of K_2PtCl_4 and 1 mmol* of the corresponding ligand in

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*1 mmol of ligand is equal to: 0.126 g 2OHDUra, 0.126 g 4-HDUra, 0.141 g 2-HDAzaThy, 0.140 g 2-HDMeUra, 0.140 g 4-HDMeUra, 0.172 g 2-Thio-4-HDAzaThy and 0.142 g 6-HDUra.

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TABLE I. Analytical Data and Some Important Properties of the Pt(II) Complexes.

Complex Number	Complex	Colour	Yield %	%C[a]	%H	%N	%Cl	%Pt	Λ_M mho cm^{-2} mol^{-1}
1	$[Pt(2\text{-}HDUra^-)^bCl]_2 \cdot 3H_2O$	bright brown	61	12.07(12.54)	2.30(2.09)	13.89(14.64)	9.54(9.28)	50.83(50.98)	40
2	$[Pt(2\text{-}HDAzaThy^-)Cl]_2 \cdot H_2O$	yellow-green	69	12.58(12.64)	1.56(1.84)	16.99(18.42)	8.72(9.35)	51.29(51.31)	23
3	$[Pt(2\text{-}HDMeUra^-)Cl]_2 \cdot H_2O$	yellow-green	64	16.33(15.85)	1.91(2.11)	15.30(14.79)	9.40(9.37)	50.86(51.52)	14
4	$[Pt(4\text{-}HDUra^-)Cl]_2 \cdot H_2O$	green	75	13.10(12.86)	1.90(1.87)	15.32(15.01)	9.51(9.50)	51.58(52.20)	40
5	$[Pt(4\text{-}HDMeUra^-)Cl]_2 \cdot H_2O$	green	66	15.77(15.85)	2.04(2.11)	14.60(14.79)	9.12(9.37)	51.60(51.52)	10.6
6	$[Pt(2\text{-}Thio\text{-}4\text{-}HDAzaThy^-)Cl]_2 \cdot 2H_2O$	bright brown	64	11.64(11.86)	2.33(1.97)	17.98(17.30)	8.20(8.77)	47.72(48.20)	11
7	$[Pt(6\text{-}HDUra^-)Cl]_2 \cdot 2H_2O$	brown	58	11.97(12.32)	2.10(1.80)	14.90(14.37)	9.45(9.11)	50.50(50.06)	–

[a]Calculated values in parentheses. [b]$2HDUra^-$ = deprotonized molecule of the ligand.

TABLE II. Infrared and Electronic Spectral Data of the Pt(II) Complexes.

Complex Number	Free Ligand and Their Complex	Electronic Spectral Data, nm (ϵ)	Infrared Spectral Data, cm^{-1}						
			$\nu_{C=O}$	ν_{NH}		ν_{OH}	ν_{Pt-Cl}	ν_{Pt-N} (ring)	ν_{Pt-N} (hydrazine residue)
	2-HDUra	290sh	1670	3300	3220				
1	$[Pt(2\text{-}HDUra^-)Cl]_2 \cdot 3H_2O$	650(2250) 410sh	1680sh	3160	3080	3420br	336br	250br	480
	2-HDAzaThy	248(7400)	1670	3310	3210				
2	$[Pt(2\text{-}HDAzaThy)Cl]_2 \cdot H_2O$	670(3150)	1620br	3150br		3430br	336; 326	250br	472
	2-HDMeUra	233(13000) 293(11500)	1650	3320	3220				
3	$[Pt(2\text{-}HDMeUra^-)Cl]_2 \cdot H_2O$	640(2700)	1650	3180	3080	3420br	336; 328sh	250br	470
	4-HDUra	260(11200)	1650	3320	3220				
4	$[Pt(4\text{-}HDUra^-)Cl]_2 \cdot 2H_2O$	680(6600)	1640	3200	3080	3415br	330br	250br	476
	4-HDMeUra	262(8600)	1660	3320	3220				
5	$[Pt(4\text{-}HDMeUra^-)Cl]_2 \cdot H_2O$	660(2800)	1650	3200	3100	3440br	320; 315sh	260br	465
	2-Thio-4-HDAzaThy	270(11400)		3290	3190				
6	$[Pt(2\text{-}Thio\text{-}4\text{-}HDAzaThy^-)Cl]_2 \cdot 2H_2O$	450sh		3170	3080sh	3440br	336; 326sh	248br	465
	6-HDUra	268(9000)	1710 1640	3310	3180				
7	$[Pt(6\text{-}HDUra^-)Cl]_2 \cdot 2H_2O$	480sh 700sh	1710sh 1640	3170br	3080sh	3430br	338br	250v,br	470

aqueous solution. After 30 min the sediments were filtered, washed with water and alcohol and dried over P_2O_5. The complexes are not soluble in water and reasonably soluble in DMF and DMSO.

The elemental analyses for C, H, N and Cl were performed according to standard microanalytical procedures. The platinum content in the complexes was determined gravimetrically, as metallic platinum.

Physical Measurements

The molar conductivity was measured in DMF solution at 21 °C on a Wheatstone bridge arrangement with a glass cell containing platinum electrodes.

The electronic spectra of solutions were recorded on a Specord UV–Vis spectrophotometer.

The IR spectra were recorded for solids in KBr pellets (4000–500 cm^{-1} region) and in suspensions in nujol (500–100 cm^{-1} region) on a Perkin-Elmer 180 spectrophotometer.

The ^1H NMR spectra were measured on a Jeol JNM-PS 100 spectrophotometer operating in CW and FT pulse mode. Dimethylsulfoxide-d_6 as obtained from IBJ Swierk (Poland) was used as solvent for NMR studies. Chemical shifts were related to the highest peak of DMSO.

Results and Discussion

The complexes of the hydrazinopyrimidines were obtained, at a ratio of 1:1 metal:ligand, as yellow-green, green and brown solids. The complexes obtained represent nonelectrolytes of the type $(PtL^-Cl)_2nH_2O$, n = 1, 2 or 3. The results of the elemental analysis are summarized in Table I. The data of molar electroconductivity, shown in the same Table, indicate the non-electrolyte character of the complexes.

In the FIR spectra all the studied complexes show two close bands in the range 315–338 cm^{-1}, which are connected with ν_{Pt-Cl} stretching frequency. In a few cases only one wide band is observed or the long-wave band occurs as a shoulder on the short-wave band (Table II).

The third and fourth coordination sites of the Pt(II) ion are occupied by ligand donors. It can be seen from Table II that the ν_{N-H} stretching frequency is shifted by 120–140 cm^{-1} towards lower energy, indicating NH_2 group coordination. Additionally a ν_{Pt-N} (hydrazine residue) stretching band was observed at 462–478 cm^{-1}. The band at 250–260 cm^{-1} is consistent with the $\nu_{Pt-N(ring)}$ stretching mode, *i.e.* the second donor is a nitrogen atom of the pyrimidine cycle. These data are in agreement with previous results of Saha *et al.* for the 2-hydrazino-4,6-dimethylpyrimidine complex with Pt(II) [9]. The broad band in the range 3440–3420 cm^{-1} is due to ν_{O-H}.

With the exception of the platinum complex of 2-HDAzaThy, no essential changes for $\nu_{C=O}$ stretching frequencies are observed indicating that the exocyclic oxygen atom takes no part in coordination (Table II). From the IR spectra it cannot be judged which of the nitrogens of individual ligands are used as donors. 2-Hydrazinopyrimidines are ambivalent chelating ligands because they have two nitrogen donors at the 1 and 3 positions in the pyrimidine ring, while 4-hydrazinopyrimidines have only one chelation possibility, *i.e.* via the hydrazine residue and N_3.

The ^1H NMR spectrum recorded for the complex of 2-HDMeUra (see Table III, complex 3) immediately after dissolution shows only one signal of the $CH_3(6)$ group at −0.46 ppm, close to the free ligand signal (Δ = 0.04 ppm). This small change in chemical shift excludes the coordination of the neighbouring N(1) nitrogen donor, because such a type of coordination results in greater chemical shift differences [5, 6]. The spectrum of complex 3 is time dependent. In the course of time new signals appear at −0.36 ppm and −0.54 ppm. The intensity of the signal at −0.36 ppm increases with time, simultaneously with a decrease in intensity of resonance at −0.46 ppm.

The observed isomerization may be consistent with the equilibrium between di ↔ mononuclear complexes and/or N(1), hydrazine ↔ N(3), hydrazine chelates isomerization. This second type of reaction seems to be more possible because of distinct differences in chemical shifts between species.

It should be noted also that two forms of ligand were observed for 2-HDMeUra. The signals at 2.88 and −0.50 ppm (Table III) of higher intensity than the 3.18, −0.44 ppm pair were assigned to the keto form, predominating in DMSO solution, and the second pair of resonances was attributed to the enol form.

Thus the methyl group signal at −0.46 ppm corresponds to Pt–N(3), hydrazine coordination mode, existing in the solid state, while the resonance at −0.36 ppm, shifted downfield by 0.14 ppm (in relation to the keto form of the free ligand) is consistent with Pt–N(1), hydrazine chelation. The third CH_3 peak (at −0.54 ppm) was assigned to free ligand, because of the probable dissociative mechanism of isomerization.

No isomerization was observed for complexes of 2-HDUra and 2-HDAzaThy (Table III, complexes 1 and 2).

The small coordination shift for complex 1 indicates that 2-HDUra coordinates to the Pt(II) ion through the N(3) and hydrazine nitrogens. The ^1H NMR spectrum of complex 2 is the simplest among the 2-hydrazino derivatives in spite of the introduc-

TABLE III. ^{1}H NMR Data of the Pt(II) Complexes.

Ligand	Chemical shifts for free ligand				Complex Number	Chemical shifts for platinum complex[a]							Assignment
	H(5)	H(6)	CH_3(5)	CH_3(6)		H(5)	(Δ)	H(6)	(Δ)	CH_3(5)	(Δ)	CH_3(6) (Δ)	
2-HDUra	3.04[d]	5.04[d]	–	–	1	2.95[b]	(−0.09)	5.14[b]	(0.10)	–		–	Pt–N(3)
2-HDAzaThy	–	–	−0.48	–	2					−0.44	(0.04)	–	Pt–N(3)
2-HDMeUra	2.88[e]	–	–	−0.50[e]	3	2.80[c]	(−0.08)					−0.36 (0.14)	Pt–N(1)
	3.18[f]	–	–	−0.44[f]								−0.46 (0.04)	Pt–N(3)
												−0.54 (−0.04)	free ligand
4-HDUra	3.04[d]	4.64[d]			4	3.54[b]	(0.50)	5.18[b]	(0.54)				Pt–N(1)
						4.12[b]	(1.08)	4.90[b]	(0.26)				Pt–N(3)
4-HDMeUra	2.84			−0.54	5	3.40	(0.56)					−0.42 (0.12)	Pt–N(1)
						3.95	(1.11)					−0.42 (0.12)	Pt–N(3)
2-Thio-4-HDAzaThy			−0.54		6					−0.44	(0.10)		Pt–N(3)

[a]Coordination shift defined as: $\Delta = \delta_{complex} - \delta_{free\ ligand}$ is shown in parenthesis. [b]Not well resolved doublet. [c]Broad signal. [d]Doublet, $J_{5,6} = 8$ Hz. [e]Keto form. [f]Enol form. The ratio of concentrations of keto to enol form of ligand is higher than 5.

tion of the third nitrogen into the ring, being the sixth potential donor for the Pt(II) ion. For the same complex the singlet of CH_3(5), shifted downfield by 0.04 ppm, is not informative for the structure of complex, but a slight change in chemical shift of the methyl group proves that N(6) is not a donor for Pt(II) [5, 6].

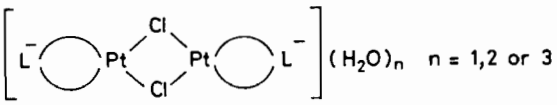
In the ^{1}H NMR spectra of Pt(II) complexes with 4-hydrazino derivatives (Table III, complexes 4, 5, 6) more distinct coordination shifts occur than for the complexes of 2-hydrazino derivatives. Two spectra were observed for complexes 4 and 5. The first of them is characterized by the H(5) signal shifted by 0.5–0.6 ppm downfield, while the second one contains the H(5) signal shifted more markedly downfield (~1.0 ppm). In the spectrum of complex 4 the pair of signals at 4.12 and 4.90 ppm was attributed to Pt–N(3), hydrazine chelate, while the pair of resonances at 3.54 and 5.18 ppm are consistent with the participation of N(1) in coordination, because of the great coordination shift of the H(6) proton (Table III). Amine nitrogen takes part in coordination for both types of complex. Coordination through N(1) and amine nitrogens leads to the formation of polynuclear complexes.

^{1}H NMR signals of the CH_3 group at positions 6 and 5 are not sensitive to coordination of Pt(II), N(1) (complex 5) or hydrazine nitrogen (complex 6). In both cases the coordination shift is equal to 0.12 ppm.

The ^{1}H NMR spectrum of complex 6 consists of only one narrow CH_3 resonance suggesting only one coordination mode, *i.e.* Pt–N(3), hydrazine chelation.

No ^{1}H NMR spectrum has been obtained for the complex of 6-HDUra because of the low solubility of the compound.

From the elemental analysis, IR and ^{1}H NMR data the following general structure of the studied complexes was derived **(III)**:



III

The origin of the bands in 315–338 cm^{-1} in the FIR spectra was confirmed in the following way. In addition to the complex of Pt(II) with 2-hydrazinopyrimidine prepared as described in Experimental, two Pt(II) complexes with this ligand were prepared starting from *cis*-$Pt(NH_3)_2Cl_2$ and from *cis*-$[Pt(NH_3)_2(H_2O)_2](NO_3)_2$. Analytical data for these show no chloride and the FIR spectra do not contain the bands in the 315–338 cm^{-1} region. But it is known that when the chloride ions are bridged in the platinum complexes, ν_{Pt-Cl} is reduced and is in

the ranges 335–310 cm^{-1} and 295–250 cm^{-1} [12]. In the complexes described in the present work, it is also possible that in the region ~250 cm^{-1}, there exists a band for ν_{Pt-Cl} together with the one for the Pt–N (ring), which could explain the type of band indicated in the same region (broad, with centre 250 cm^{-1}).

The investigated ligands are isomers in relation to the position of the hydrazine residue. For 2-HDUra, 2-HDAzaThy and 2-HDMeUra the hydrazine residue is at position (2) in the pyrimidine ring, and for 4-HDUra, 4-HDMeUra and 2-Thio-4-HDAzaThy at position (4), while for 6-HDUra it is at position (6). All of the studied pyrimidine derivatives are very complex as ligands, because they provide 5–6 potential donors. As is seen from the IR and ^1H NMR spectra only nitrogens are donors for the studied platinum complexes. The preferred type of coordination is Pt–N(3), hydrazine chelation, which is characteristic for solid complexes. Besides the discussed case of the Pt(II) complex with 2-HDMeUra, Pt–N(1) coordination is also observed for 4-HDUra and 4-HDMeUra solutions. This may be due to the long time period required to take the spectra (the FT method was used because of the weak solubility of complexes 4 and 5). Although the participation of the N(1) atom in the formation of polynuclear complexes is possible, it may be that N(1) coordination occurs only in solutions. In such situations only Pt–N(3), hydrazine chelation occurs for complexes of 4-HDUra and 4-HDMeUra in the solid state as is the case for 2-Thio-4-HDAzaThy.

The hydrazine residue consists of two nitrogen atoms, but the participation of imine nitrogen in chelate formation is doubtful since in such a case a 4-membered chelate ring would be formed. Chelate formation through exocyclic oxygen and ring nitrogen is excluded for the same reason and on the basis of the data presented above.

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