Complexes of 2,4-Diamino-5(3′,4′,5′-trimethoxybenzyl)pyrimidine (Trimethoprim) with Palladium(II)

DIMITRA KOVALA-DEMERTZI* and JOHN M. TSANGARIS

Laboratory of Inorganic Chemistry, University of Ioannina, Ioannina, Greece

(Received April 14, 1986; revised June 10, 1986)

A great deal of interest has been shown in the pyrimidines, due to their biological importance as components of the nucleic acids. Many compounds of therapeutic importance contain the pyrimidine ring system. Substituted 2,4-diamino pyrimidines are widely employed as metabolic inhibitors of pathways leading to the synthesis of proteins and nucleic acids in the chemotherapy of malaria and neoplastic disease [1]. Trimethoprim is a popular member of this class of antifolates and has the unusual property of being bound about 5000 times more strongly to the bacterial *Escherichia coli* reductase than to the equivalent protein from mammalian sources [2]. The interaction of trimethoprim with copper(II) nickel(II), cobalt(II), platinum(II), gold(III) and rhodium(III) leads to products with interesting chemical and structural properties [3, 4]. The coordination of trimethoprim via a NH_2 nitrogen atom was inferred on the basis of IR and visible measurement; in the case of the Co(II) compound no hypothesis on the bonding mode of the aromatic ligand was formulated. Demartin *et al.* have shown by X-ray diffraction methods [5] that in the complex $CoCl_2$ (trimethoprim)$_2$ the coordination site of the trimethoprim molecule is the N_1 of the pyrimidine ring (Fig. 1a). The pyrimidines provide potential binding sites for metal ions and any information on their coordinating properties is important for understanding the role of metal ions in biological systems. This communication describes the synthesis and characterization of some Pd(II) complexes of trimethoprim.

*Author to whom correspondence should be addressed.

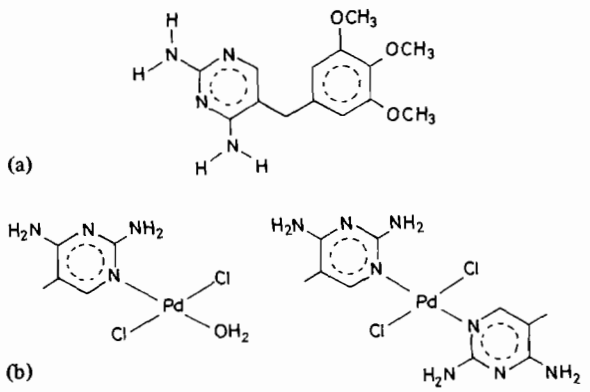

Fig. 1. (a) The structure of trimethoprim. (b) The proposed geometry for the $PdLCl_2 \cdot 2H_2O$ and PdL_2Cl_2 complexes.

Experimental

K_2PdCl_4 was purchased from Fluka Chemical Company. All the solvents and chemicals used were of high purity. Trimethoprim was prepared [6], purified and characterized according to known procedures. The Pd(II) complexes of trimethoprim were prepared by mixing aqueous solutions of the ligand and metal salt, K_2PdCl_4 [2:1, 1:1 molar ratio]. The reaction mixtures were stirred for 24 h at room temperature. In the case of the complex PdL_2Cl_2, the pH of the reaction mixture was maintained in the neutral region. The precipitate formed in each case was washed with cold water, acetone and ether and dried in vacuum over silica gel and redried at 90 °C under vacuum over P_4O_{10}.

The infrared spectra were recorded with a Perkin Elmer 580 spectrophotometer on KBr pellets in the 4000–400 cm^{-1} region and on Nujol mulls supported by polyethylene windows in the 500–200 region. The analyses of the metal ions and halogens were carried out by previously described methods [7]. The Du Pont 951 has been used for thermal analysis: the UV–Vis spectra have been recorded on a Cary 17D model.

Results and Discussion

Analytical and some physicochemical data are given in Table I. The complexes are insoluble in polar solvents and soluble in DMF and DMSO. The one molecule of water is eliminated at *ca.* 220–260 °C; thus, it may be either coordinated or held very strongly in the lattice [8].

The vibrational data and the proposed assignments for the ligand and its complexes are tabulated in Table II. The position and intensity of the NH_2 bands in the complexes are comparable with the bands in the ligand, so we can conclude that the NH_2 groups are not involved in the metal–ligand vibration. All the N–H bands shift to lower frequencies upon deuteriation (NH/ND = 1.3–1.4).

The low frequency spectra of the complexes show two medium intense bands at 550 and 420 cm^{-1}, assignable to the ν(Pd–N) mode. These assignments are in agreement with the literature data. Adeyemo

0020-1693/86/$3.50

TABLE I. Analytical Results, pH of Precipitation, Λ_M Values and Effects of Heat for the Complex $PdLCl_2 \cdot 2H_2O$

Complex	Percentage calculated (percentage found)			pH of Precipitation	Λ_M ($S\ cm^2\ mol^{-1}$)	Removal of water	
	M	Cl	H_2O			Temperature (°C)	Weight loss (%)
$PdLCl_2 \cdot 2H_2O$	21.12 (20.79)	14.08 (13.80)	7.15 (7.00)	2.5	16.89[a]	60–70 220–260	3.5 3.5
PdL_2Cl_2	14.04 (14.80)	9.35 (8.70)		7.1	27.06[a]		

[a]Values of molar conductance for *ca.* 10^{-3} M solutions DMF at 25 °C; the compounds were assumed to be monomeric.

TABLE II. Characteristic IR Bands (cm^{-1}) of the Ligand and its Pd(II) Complexes

Compound	$\nu(NH_2)$	$\nu(ND_2)$	$\delta(NH_2)$	$\delta(ND_2)$	$\rho(NH_2)$	$\rho(ND_2)$	ν(M–N)	δ(M–Cl)	δ(Cl–M–Cl)
Ligand	3470s 3318s	2600s 2320s	1655s 1635s	1150s	1270sh	890m			
$PdLCl_2 \cdot 2H_2O$	3450s 3340s	2580s 2420s	1660sh	1160sh	1270sh	870m	551m 415w	367s	262m
PdL_2Cl_2	3475s 3400s 3340s	2600s 2490s	1660sh	1160sh	1270sh	870m	563w 430w	380s	260m

TABLE III. Electronic Spectral Data of the Ligand and its Pd(II) Complexes

Compound	D.R. energy (cm^{-1})	DMF (ϵ, $cm^{-1}\ M^{-1}$)	Assignment
Trimethoprim		34190(3400)	$n \rightarrow \pi^*$
$PdLCl_2 \cdot 2H_2O$		16190(4)	$^1A_{1g} \rightarrow {}^3A_{2g}$
		18230(9)	$^1A_{1g} \rightarrow {}^3B_{1g}$
	21280		$^1A_{1g} \rightarrow {}^1A_{2g}$
	24100	24845(293)	$^1A_{1g} \rightarrow {}^1B_{1g}$
	27030		$^1A_{1g} \rightarrow {}^1E_g$
		33900(6640)	$n \rightarrow \pi^*$
PdL_2Cl_2		16060(7)	$^1A_{1g} \rightarrow {}^3A_{2g}$
		18050(12)	$^1A_{1g} \rightarrow {}^3B_{1g}$
	21500		$^1A_{1g} \rightarrow {}^1A_{2g}$
	24690	24240(283)	$^1A_{1g} \rightarrow {}^1B_{1g}$
	26670		$^1A_{1g} \rightarrow {}^1E_g$
		34480(11340)	$n \rightarrow \pi^*$

et al. [9] accept the situation of the ν(Pd–N) band in the 500 cm^{-1} region for L = 2,4-dimethyl-6-hydroxypyrimidine. The intense band at 370 cm^{-1} is ascribed to a terminal ν(Pd–Cl) mode and indicates a *trans* configuration [10, 11]. It is therefore concluded from the IR spectroscopy that trimethoprim acts as a unidentate through the endocyclic nitrogen rather than through the nitrogen of the amino group and the complexes exist in the *trans* form (Fig. 1b).

The electronic spectra UV–Vis of the complexes and the ligand and the assignments of the observed bands are given in Table III. The d–d bands are typical for square planar geometry. The very weak bands at 16 000 cm^{-1}, 18 000 cm^{-1} are assigned to d–d spin-forbidden transitions, while the more intense band at 24 500 cm^{-1} is assigned to d–d spin-allowed transition. Spin-forbidden transitions, of Pd(II) complexes will be less intense than those in platinum-(II) complexes because of the lower spin–orbit coupling coefficient [12]. The band at 34 200 cm^{-1} is assigned to $n \rightarrow \pi^*$ transition [13].

The thermal decomposition of the complex $PdLCl_2 \cdot 2H_2O$ is given in Fig. 2. The figure shows the formation of the anhydrous compound $PdLCl_2$ and

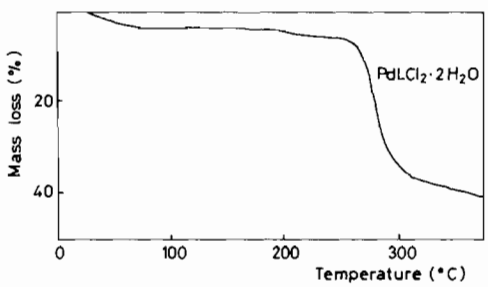

Fig. 2. Thermal decomposition curves of $PdLCl_2$ (heating rate 10 °C/min).

TABLE IV. Thermogravimetric data for $PdLCl_2 \cdot 2H_2O$

Loss of weight (%) $PdLCl_2 \cdot 2H_2O$	Temperature (°C) at heating rate (°C/min)				E_a (kJ/mol)	E_a
	1	5	10	20		
17.5	246.0	264.0	276.0	279.5	191.59	198.08
20.0	249.0	267.0	278.0	282.0	198.86	
22.5	251.5	269.0	280.0	285.0	200.29	
25.0	255.0	271.5	283.0	289.0	201.58	

then the decomposition of the complex where no further refined intermediates can be assigned to the other curve inflections. The activation energy E_a of the $PdLCl_2$ decomposition, calculated by the Flynn and Wall method [14], is 198 kJ/mol (Table IV).

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