Note

Synthesis, characterization and X-ray crystal structure of ethylenediamine(orotato)palladium(II)

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(Received December 20, 1993; revised February 25, 1994)

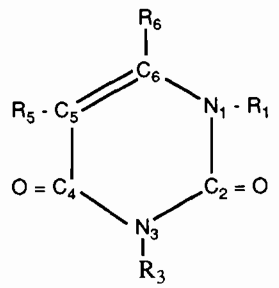
Abstract

Reaction of the hydrolysis product of dichloroethylenediaminepalladium(II) with orotic acid methyl ester in aqueous or methanol–water media gives an orotic acid complex: $[Pd(C_5H_2N_2O_4)(C_2H_8N_2)](H_2O)_{0.5}$. The complex was characterized by UV, ^1H NMR and X-ray diffraction. The compound crystallizes in the space group $P1$, $a = 9.742(1)$, $b = 10.535(1)$, $c = 11.113(1)$ Å, $\alpha = 100.60(1)$, $\beta = 103.165(7)$, $\gamma = 109.22(1)°$, $V = 1006.2(2)$ Å^3, $Z = 2$. It appears that during the reaction process hydrolysis of the ester function arises and that the compound obtained is a complex of orotic acid.

Key words: Crystal structures; Palladium complexes; Orotato complexes; Bidentate amine complexes

Introduction

The ligating properties of uracil and thymine with platinum or palladium have been extensively studied over recent years with the purpose of obtaining a better understanding of the coordinating properties of the *cis*-diammineplatinum(II) residue [1]. As a result, it has become evident that there is a versatility of the uracilato** fragment to coordinate via N_1 or/and via N_3. A large variety of complexes are formed with uracil under its neutral, monoanionic and dianionic forms [2, 3]. The versatility of uracils as ligands arises mainly from their many tautomeric forms and their tendency to deprotonation which vary with pH. By contrast orotic acid which is a substituted uracil coordinates exclusively via N_1 and the carboxylate group. The only exception known so far is the copper(II) complex of 5-NO_2-orotic acid which coordinates via the N_1 and N_3 nitrogen [4].



$R_1 = R_3 = R_5 = R_6 = H$, Uracil
$R_1 = Me$, $R_3 = R_5 = R_6 = H$, 1-Methyluracil
$R_1 = R_3 = R_5 = H$, $R_6 = COOH$, Orotic acid

Fig. 1. Numbering scheme of orotic acid ($R_1 = R_2 = H$).

We have recently shown that palladium complexes of orotic acid may exhibit significant antitumor activity [5]. With the view to obtaining new complexes for medical purposes, since N_3 is the second deprotonation site of orotic acid, we attempted to obtain complexes where N_3 rather than N_1 is the coordination site. 5-NO_2-orotic acid complexes copper(II) at N_3 but with platinum and palladium only N_1 complexes are obtained. The use of the orotic acid methyl ester derivative which prevents stabilization of N_1 complexes may perhaps allow N_3 complexes to be obtained.

Reaction of orotic acid methyl ester with $enPdCl_2$ yielded pale yellow crystals characterized by spectroscopic techniques and X-ray analysis.

Experimental

Synthesis

The ethylenediaminepalladium(II) hydrolysis product was prepared from 216 mg of $enPdCl_2$ (0.9 mmol) and 310 mg of $AgNO_3$ (1.8 mmol) in 7 ml of water in the dark. The mixture was stirred overnight. After removing AgCl by centrifugation and filtration, an equivalent amount of orotic acid methyl ester in a minimum amount of hot water was added. On standing at room temperature the solution rapidly yielded pale yellow crystals.

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**The nomenclature and numbering scheme of uracils and substituted forms are shown in Fig. 1.

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SSDI 0020-1693(94)03970-Y

Anal. Found: C, 25.57; H, 3.37; N, 17.08; O, 22.57. Calc. for $[Pd(C_5H_2N_2O_4)(C_2H_8N_2)]_2(H_2O)$: C, 25.51; H, 3.36; N, 17.00; O, 21.84%.

Physical measurements

UV spectra were recorded on a Perkin-Elmer Lambda 15 spectrometer in aqueous solutions. NMR spectra were recorded on a Bruker AC 200 FT spectrometer in dmso-d_6.

Crystallography

Cell parameters and diffracted intensities were measured at room temperature on a STOE STADI 4 diffractometer with monochromated Mo Kα radiation ($\lambda = 0.71069$ Å). Data were corrected for Lorentz and polarization effects and for absorption [6]. The structure was solved by direct methods (MULTRAN 87 [7]). Atomic scattering factor and anomalous dispersion terms were obtained from the International Tables for X-ray Crystallography [8]. All coordinates of the hydrogen atoms were observed and refined. All calculations were performed with the XTAL 3.2 program [9].

$[Pd(C_5H_2N_2O_4)(C_2H_8N_2)](H_2O)_{0.5}$, $M = 339.6$, triclinic, $P1$, $a = 9.742(1)$, $b = 10.535(1)$, $c = 11.113(1)$ Å, $\alpha = 100.60(1)$, $\beta = 103.165(7)$, $\gamma = 109.22(1)°$, $V = 1006.2(2)$ Å^3, $Z = 2$, $F(000) = 652$, μ(Mo Kα) $= 1.831$ mm^{-1}. $R = 2.1$, $R_w = 2.0\%$.

For experimental data and refinement conditions see 'Supplementary material'. Selected bond lengths and bond angles are listed in Table 1.

TABLE 1. Selected interatomic distances (Å) and bond angles (°) with e.s.d.s in parentheses

	1	**2**
Metal environment		
Pd–O1	2.012(3)	2.013(3)
Pd–N1	2.011(4)	1.991(5)
Pd–N01	2.024(4)	2.019(4)
Pd–N02	2.026(5)	2.020(6)
O1–Pd–N1	81.6(2)	81.9(2)
O1–Pd–N02	94.3(2)	95.0(2)
N1–Pd–N01	101.3(2)	100.0(2)
N01–Pd–N02	82.9(2)	83.2(2)
Ligand (orotic)		
O1–C5	1.294(7)	1.300(7)
O2–C5	1.218(6)	1.212(7)
C5–C1	1.518(9)	1.517(8)
O3–C2	1.221(6)	1.230(6)
O4–C3	1.233(7)	1.233(7)
C1–N1	1.355(6)	1.370(6)
N1–C2	1.377(8)	1.367(8)
C2–N2	1.388(7)	1.389(7)
N2–C3	1.387(6)	1.367(6)
C3–C4	1.430(9)	1.438(9)
C4–C1	1.353(8)	1.341(8)
Pd–O1–C5	115.2(4)	114.7(4)
Pd–N1–C1	113.0(4)	114.2(4)
O1–C5–C1	115.1(4)	115.8(5)
C1–N1–C2	118.9(5)	118.7(5)
N1–C2–N2	116.1(4)	116.2(4)
C2–N2–C3	127.2(5)	127.0(5)
N2–C3–C4	113.3(5)	114.2(5)
C3–C4–C1	119.3(5)	118.5(5)
C4–C1–N1	125.1(5)	125.2(5)
C4–C1–C5	120.5(5)	121.6(5)
C1–C5–O2	122.0(5)	121.7(5)
Hydrogen bonds		
N022···O21x, y, z	3.091(8)	
N21···O42$x, y+1, z-1$	2.848(6)	
N22···O41$x, y-1, z+1$	2.851(7)	
O01···O22$x, y+1, z$	2.819(6)	
O01···O21$x-1, y, z$	2.776(6)	

Results and discussion

From the UV data characterizing the methylated (N_1 or/and N_3) orotic acids [10], uracils [11, 12], and their related anions, one may note that the spectrum of the N_1 substituted derivatives is blue shifted with respect to the N_3 substituted ones.

In the case previously mentioned of the nickel(II) [13] and copper(II) [14] complexes, the observed bathochromic shift may be related to the predominance of the N_3H form and to the concomitant coordination of the metal to N_1 that is evidenced by structural determination. The relationship between the UV data and the coordination sites is further supported by the marked change suffered by the UV spectra of 3-methyl orotic acid upon complexation by nickel(II) which unambiguously occurs at N_1 [15]. The absorbance of a complex in a range above 310 nm may be due to a N_1 complexation and thus infers the existence of a N_3H tautomer (or of a substituted N_3), since the absorbance in the 280–290 nm range may infer a N_3 complexation.

In a previous work [16], we succeeded in isolating three complexes of orotic acid and orotic acid methyl ester with palladium: [enPd(orotato)], $[Pd(orotato)_2]K_4$ and $[Pd(orotic\ acid\ methyl\ ester)_4]K_2$. On the basis of analytical and UV data, it may be inferred that in [enPd(orotato)] the palladium is likely bonded to N_1 and COO^- whereas in $[Pd(orotato)_2]K_4$ all the potential sites of coordination of orotic acid, N_1, N_3 and the carboxylate group participate in the complexation of the metal.

With $[Pd(orotic\ acid\ methyl\ ester)_4]K_2$, two absorption bands are observed at 285 and 320 nm, respectively. We assumed that, as in the case of uracil platinum complexes [1–3], two types of compounds involving N_1 and N_3 bonded ligands are simultaneously present. Another possibility would imply that two types of mono deprotonated ligands are bonded to the same palladium center.

For the complex obtained in the present work, complexation induced a significant bathochromic shift in the maximum absorbance wavelength ($\lambda_{max}=316$ nm) with respect to the free dianion. This effect would be in good agreement with a coordination mode involving N_1 and the carboxylate group suggesting that during the reaction process hydrolysis of the ester function arises and that the compound obtained is a complex of orotic acid and not of the orotic acid methyl ester. The ^1H NMR spectra of the complex points out the disappearance of the methyl-ester group.

X-ray crystal structure evidenced that the orotic acid methyl ester was demethylated during the coordination process. The comparatively slow hydrolysis of methyl orotate has been accelerated by the metal. The same complex is obtained when the reaction process is conducted in a mixture water/methanol to try to prevent hydrolysis.

An ORTEP representation of the complex is shown in Fig. 2. The palladium orotato complex consists of two crystallographically independent molecules labelled **1** and **2**. Orotic acid coordinates to the palladium atom by chelating through the deprotonated N_1 and the carboxylic oxygen to form a five-membered ring. Although it has been postulated according to UV spectroscopic results that orotic acid deprotonates first at the N_3 site the coordination at N_1 is much more favored due to chelate formation. This is the case, as previously mentioned, of all the known complexes of orotic acid [17] (except the copper(II) complex of 5-NO_2-orotic acid [4]). The deviations from the Pd coordination plane are very small (maximum distance for N = 0.05 Å). The bond angles around the metal atom indicate a distorted geometry, the O1–Pd–N1 having a rather small value of 81.6(2) in **1** and 81.9(2) in **2** because of the steric hindrance arising from coordination to orotic acid directly to ring N and adjacent carboxylate atom. Similarly the angle N01–Pd–N02 is small due to the strain imposed by the bidentate ethylenediamine ligand. It is in good agreement with the angle (83.6°) found in $[Pd(en)_2]^{2+}$ [18]. The pyrimidine ring deviates only very slightly from planarity. The dihedral angles between the pyrimidine ring and coordination ring planes are 10.1(2) and 4.7(2)° in **1** and **2**, respectively. The bond distances and bond angles are those expected for a metal complex of orotic acid.

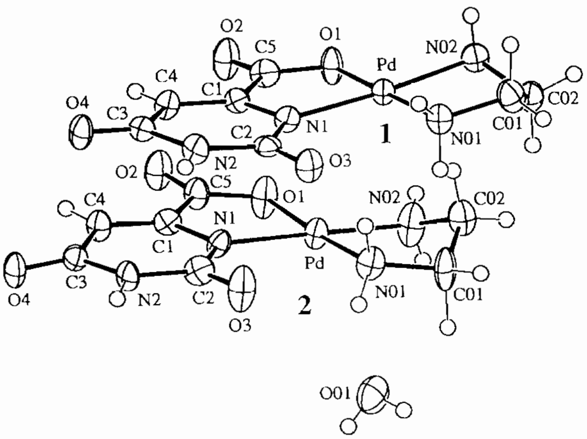

Fig. 2. ORTEP representation of $[Pd(C_5H_2N_2O_4)(C_2H_8N_2)]_2(H_2O)$ with atomic labels. Ellipsoids are represented with 50% probability.

The crystal structure is dominated by an extensive array of hydrogen bonds involving all hydrogen atoms bound to non-carbon atoms and those of the water molecule (Table 1).

Supplementary material

Tables of experimental data and refinement conditions, complete distances, bond angles, atomic coordinates and equivalent isotropic displacement parameters are available from the authors on request.

References

1 B. Lippert, *Inorg. Chem., 20* (1981) 4326.
2 R. Pfab, P. Jandik and B. Lippert, *Inorg. Chim. Acta, 66* (1982) 193.
3 B. Lippert, in S.J. Lippard (ed.), *Platinum, Gold and other Metal Chemotherapic Agents: Chemistry and Biochemistry,* Symposium Series, No. 209, 1983, p. 147.
4 P. Arrizabalaga, P. Castan and F. Dahan, *Inorg. Chem., 22* (1983) 2245.
5 P. Castan, E. Colacio-Rodriguez, A.L. Beauchamp, S. Cros and S. Wimmer, *J. Inorg. Biochem., 38* (1990) 225.
6 E. Blanc, D. Scharzenbach and H.D. Flack, *J. Appl. Crystallogr., 24* (1991) 1035.
7 P. Mains, S.J. Fiske, S.E. Hull, L. Lessinger, G. Germain, J.-P. Declercq and M.M. Woolfson, *MULTRAN,* a system of computer programs for the automatic solution of crystal structures from X-ray diffraction data, Universities of York, UK and Louvain-la-Neuve, Belgium, 1987.
8 *International Tables for X-ray Crystallography*, Kynoch, Birmingham, UK, 1974.
9 S.R. Hall and J.M. Stewart (eds.), XTAL 3.2 User's Manual, Universities of Western Australia and Maryland.
10 J.J. Fox, N. Yung and I. Wenpen, *Biochim. Biophys. Acta, 23* (1957) 295.
11 K. Inagaki and Y. Kidani, *Bioinorg. Chem., 9* (1978) 157.
12 K. Nakanishi, N. Suzuki and F. Yamazaki, *Bull. Chem. Soc. Jpn., 34* (1961) 53.
13 M. Sabat, D. Zglinska and B. Jezowska-Trzebiatowska, *Acta Crystallogr., Sect. B, 36* (1980) 1187.
14 I. Mutikainen and P. Lumme, *Acta Crystallogr., Sect. B, 36* (1980) 2233.
15 D. Lalart, J. Guillerez, G. Dodin and J.-E. Dubois, *J. Chem. Soc., Perkin Trans. II,* (1981) 1057.
16 P. Arrizabalaga, P. Castan and J.P. Laurent, *J. Inorg. Biochem., 20* (1984) 215.
17 I. Mutikainen, *Ann. Acad. Sci. Fenn., 217* (1988) 1, and refs. therein.
18 J.R. Wiesner and E.C. Lingafelter, *Inorg. Chem., 5* (1966) 1770.