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Journal of Molecular Structure 789 (2006) 147–151

Journal of MOLECULAR STRUCTURE

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Transition metal(II) complexes of vitamin B13 with monodentate orotate(1−) ligands

Dursun Ali Köse [a], Birgül Zümreoglu-Karan [a,*], Onur Şahin [b], Orhan Büyükgüngör [b]

[a] *Department of Chemistry, Hacettepe University, Beytepe Campus, 06532 Ankara, Turkey*
[b] *Faculty of Arts and Sciences, Department of Physics, Ondokuz Mayıs University, Samsun, Turkey*

Received 16 November 2005; accepted 20 December 2005
Available online 20 February 2006

Abstract

The formation of bisorotate(1−) complexes of the type $[M(C_5H_3N_2O_4)_2(H_2O)_4]\cdot nH_2O$ (M = Co, Ni, Zn and $n=2$, 4) was achieved by the reaction of ammonium orotate with the corresponding M(II) ions. The crystal structure of $[Co(C_5H_3N_2O_4)_2(H_2O)_4]\cdot 2H_2O$ was determined by single crystal X-ray diffraction analysis. Each Co(II) ion in the monomeric $Co(C_5H_3N_2O_4)_2(H_2O)_4$ units adapts a slightly distorted octahedral geometry comprised of two monodentate orotate anions and four H_2O ligands. Columnar packing of pyrimidine rings along the *c* axis leads to the formation of layers that propagate parallel to the *b* axis and the adjacent layers are linked by hydrogen bonds forming a 3D lattice. Complexes of nickel and zinc were assumed to contain monodentate bound orotate ligands as well on the basis of physical and spectroscopic data.

Keywords: Vitamin B13; Orotic Acid; Orotate Complexes; Monodentate coordination

1. Introduction

Orotic acid (Vitamin B13, uracil carboxylic acid, $C_5H_4N_2O_4$) plays a key role in the biosynthesis of pyrimidine bases of nucleic acids [1]. Some metal compounds of the acid itself and derivatives have successful applications in curing syndromes related with metal ion deficiencies [2] and promising applications as therapeutic agents for cancer [3]. The biocoordination chemistry of vitamin B13 therefore demands a better understanding regarding its interactions with metal ions.

The orotic acid molecule (H_3Or) has a multidentate nature (Fig. 1). The most potential coordination sites in the pH range of 5–9 are the carboxylic oxygen and the adjacent pyrimidine nitrogen atom (N1), for the formation of a stable chelate ring. In very alkaline solutions, deprotonation occurs from (N1) and coordination through the other sites becomes available as well due to the existence of different tautomeric forms [4–6 and the references therein]. The literature lists several reports on mononuclear and polynuclear orotato complexes.

The crystal structures of mononuclear Ni [7,8], Mg [9], Co [10], Zn [11] complexes have been described where orotate dianions $(HOr)^{2-}$ act as bidentate ligands. In polymeric complexes, $(HOr)^{2-}$ acts as a polydentate ligand and bridges the metal ions forming 1D-polymeric chains with Ca [12], Cd [13], Mn [5], Cu [14], Ni [15,16] or 2D-layer structures in mixed metal complexes where the layers are interconnected with hydrogen bonds to form the final network structures [17].

Relatively little information is available regarding the compounds with orotate monoanion, $(H_2Or)^{1-}$. Crystal studies with Mg [18], Zn [19] and Ni [20] have showed that aquated metal cations interact with the $(H_2Or)^{1-}$ counter ions through hydrogen bonds. In these isotopic compounds, the orotate monoanion does not enter the inner coordination sphere of the metal. Here we report the synthesis and characterization of complexes of the type $[M(H_2Or)_2(H_2O)_4]\cdot nH_2O$ (M = Co(**1**), Ni(**2**), Zn(**3**) and $n=2$, 4) where bis-coordinated orotate monoanions bind monodentately.

2. Experimental

2.1. Synthesis

Because of the low solubility of orotic acid in water and also the difficulty in controlling the extent of ionization in alkaline medium, the ammonium salt was used in all experiments as the source of the orotate monoanion. Ammonium orotate

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* Corresponding author. Tel.: +90 312 2977951; fax: +90 312 2992163.
E-mail address: bkaran@hacettepe.edu.tr (B. Zümreoglu-Karan).

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doi:10.1016/j.molstruc.2005.12.030

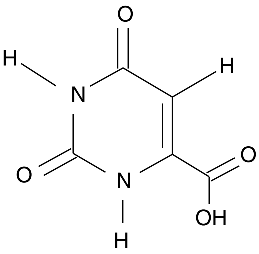

Fig. 1. Orotic acid.

monohydrate (m.p. = 350.5 °C) was prepared from anhydrous orotic acid (Fluka) according to the procedure described by Solbakk [21]. To a solution of $M(NO_3)_2 \cdot nH_2O$ (Aldrich), a warm solution of $NH_4H_2Or \cdot H_2O$ was added in a 1:2 molar ratio. The precipitates obtained in about 3 weeks at room temperature were separated by filtration and dried in a desiccator. The yields were found around 65% based on the metal. The compounds have low solubility in water and in common organic solvents. The Co compound dissolves better upon gentle heating.

Found: C, 25.53; H, 4.06; N, 11.59. Calc. For $C_{10}H_8N_4O_{10}Co$: C, 25.16; H, 3.77; N, 11.74. Found: C, 25.59; H, 4.03; N, 11.59. Calc. For $C_{10}H_8N_4O_{10}Ni$: C, 25.16; H, 3.77; N, 11.74. Found: C, 23.48; H, 4.72; N, 10.78. Calc. For $C_{10}H_8N_4O_{10}Zn$: C, 23.12; H, 4.24; N, 10.79.

2.2. Characterization

Carbon, hydrogen and nitrogen analyses were performed using a LECO CHNS 932 instrument. FTIR spectra were recorded in KBr matrix on a MATTSON 1000 FTIR spectrophotometer. Thermal gravimetric analyses were performed in flowing nitrogen atmosphere (10 mL min^{-1}) using a Schimadzu DTG-60 instrument.

2.3. Crystallography

The green crystals of the Ni complex were found to be of twin nature and those of the Zn complex gradually transformed amorphous as noted previously for Mg- and Zn-bis[orotate(1−)] phases [19]. A red single crystal of the cobalt complex, $[Co(H_2Or)_2(H_2O)_4] \cdot 2H_2O$, suitable for data collection was mounted on a glass fiber and data collection was performed on a STOE IPDS II diffractometer with graphite monochromated Mo Kα radiation at 296 K. Details of crystal data, data collection and refinement are given in Table 1.

The structure was solved by direct methods using SHELXS-97 [22] and refined by full-matrix least-squares methods on F^2 using SHELXL-97 [23] from within the WINGX [24,25] suitable of software. All non-hydrogen atoms were refined with anisotropic parameters. Hydrogen atoms bonded to carbon and nitrogen were placed in calculated positions (C–H = 0.93 Å and N–H = 0.86 Å) and refined using riding model with U = 1.2 U of the parent atom for CH and NH. The H atoms of water were refined with fixed O–H = 0.83 Å (U = 1.5 U of the parent atom). Molecular drawing was obtained using ORTEP-III [26].

Table 1
Crystal data of $[Co(H_2Or)_2(H_2O)_4] \cdot 2H_2O$ and structure refinement

Empirical formula	$C_{10}H_{18}CoN_4O_{14}$
Formula weight	477.21
Temperature (K)	296
Wavelength (Å)	0.71073
Crystal system	Monoclinic
Space group	$P2_1/c$
Unit cell dimensions	
a (Å)	9.7205(8)
b (Å)	12.4541(7)
c (Å)	7.1266(6)
β	96.520(6)
Volume (Å^3)	857.17(11)
Z	2
Calculated density (mg/m^{-3})	1.849
Absorption coefficient (mm^{-1})	1.090
$F(000)$	490
Crystal size (mm)	0.320×0.213×0.080
θ range for data collection	2.11–15.99
Index ranges	$-11<h<11$, $-15<k<15$, $-8<l<8$
Independent reflection	1681
Measurement reflection	11,630
Absorption correction	Integration
Refinement method	Full-matrix least-squares on F^2
Goodness-of-fit on F^2	1.144
Final R indices [$I>2\sigma(I)$]	$R_1=0.047$
R indices (all data)	$R_1=0.051$
Largest diff. peak and hole	1.72 and −0.51 e Å^{-3}

Geometric calculations were performed on Platon [27]. Selected geometric parameters and hydrogen-bonding geometry parameters are listed in Table 2.

3. Results and discussion

The compounds were found to be pure and formulated as $Co(C_5H_3N_2O_4)_2(H_2O)_4 \cdot 2H_2O$ (**1**), $Ni(C_5H_3N_2O_4)_2(H_2O)_4 \cdot 2H_2O$ (**2**) and $Zn(C_5H_3N_2O_4)_2(H_2O)_4 \cdot 4H_2O$ (**3**) based on microanalytical, spectroscopic and thermo-analytical results.

3.1. FTIR spectra

The FTIR spectra of the compounds exhibited characteristic features in the OH, ketone/carboxylate and NH regions. The spectrum of the Zn compound differed slightly from those of the Co and Ni compounds due to the presence of a higher amount of lattice water leading to different hydrogen bonding interactions with the coordinated water and orotate anions. The assignments proposed were discussed considering previous assignments for similar molecules (Table 3).

Table 2
Selected geometric parameters (Å, °)

O1–Co1	2.090(3)
O2–Co1	2.133(3)
O3–Co1	2.063(2)
H1B···O7	1.87(2)
O3–Co1–O1	85.09(11)
O3–Co1–O2	90.92(11)
O1–Co1–O2	92.95(12)

Table 3
Some important IR frequencies of orotic acid, ammonium orotate and prepared compounds

Assignment	H_3Or[a]	$NH_4H_2Or\cdot H_2O$	**1**	**2**	**3**
ν(N1–H)	3160 sh	3230 sb	Unresolved	3212 sh	3198 sb
$\nu(O–H)_{acid}$	2500 b	–	–	–	–
$\nu(C=O)_{acid}$	1729 vs	1741 vs	1701 vs	1752 vs	1696 vs
ν(C2=O)	1719 vs				
ν(C4=O) + ν(ring)	1700 vs	1675 vs			
ν(C=C)	1653 vs				
$\nu_{asym}(COO^-)$	–	1636 vs	1639 vs	1641 vs	1615 s
Ring	1500–1590	1480 sh	1473 m	1475 m	1492 m
δ(N1–H)	1435 sb	1430 sh	1407 m	1409 m	Unresolved
$\nu_{sym}(COO^-)$	–	1365 s	1375 s	1378 s	1380 s
$\Delta(\nu_a-\nu_s)$		271	262	263	235

Abbreviations: b: broad, m: medium, s: strong, sb: strong broad, sh: shoulder, vs: very strong.

[a] From Ref. [28].

In the 3500–2500 cm^{-1} region, the O–H stretching bands of coordinated water overlapped with the N–H bands of orotate ions and their involvement in hydrogen bonding produced a band broadening. The carboxylate group and the ν_{CO} stretches of the carbonyl groups exhibited strong bonds in the region 1750–1700 cm^{-1}. These strong bands were shifted and broadened with respect to free orotic acid. The FTIR spectral assignments of several transition metal orotate complexes have been comprehensively discussed by Maistralis et al. [6]. The authors stated that involvement of N(1) in coordination to the metal reduces the electron density in the C(2)=O band leading to a downward shift of related frequencies. No such assignment was possible in our case and moreover the differences between the asymmetric and symmetric stretches of the carboxylate groups of the three complexes, $\Delta\nu > 200$ cm^{-1}, suggest a monodentate binding of the carboxylate group to the metal ion [29]. Another important band in distinguishing the mono- or bidentate coordination of the orotate ligand is the ν(N1–H) and δN(1)–H vibrations that are observed around 3200 and 1430 cm^{-1}, respectively, in H_3Or and NH_4H_2Or. These bands disappear in the complexes of orotate(2−) ligands or change position for many bidentate orotate(1−) complexes due to the participation of the N(1) atom in coordination [6]. For the compound $[UO_2(H_2Or)_2(H_2O)_3\cdot 2H_2O]$ [30], in which two orotic acid moieties are bonded monodentate through the carboxylate oxygens, the position of the δ(N1–H) remains the same while ν(N1–H) shifts to higher wave numbers with respect to nonionized orotic acid. The complexes **1**, **2** and **3** exhibited a similar shift for ν(N1–H) but a downward shift for δ(N1–H) was observed due to strong hydrogen bonding between N(1)–H and lattice water molecules.

3.2. Thermogravimetric analysis

Thermogravimetric analysis of the compounds has been conducted in the 40–900 °C temperature range under nitrogen and the results are given in Table 4. The observed mass losses for the dehydration and decomposition steps agree well with calculated values. The loss of lattice water and coordinated water for the cobalt and nickel complexes was observed in an overlapped pattern below 150 °C. Dehydration of the zinc complex proceeded in two distinct steps corresponding to the loss of 6 mol of water at 109 °C, 1 mol of water at 229 °C and 1 mol of water at 302 °C. The difference in the dehydration behavior of **3** is possibly due to different hydrogen bonding interactions in a different crystal structure arising from the presence of a higher amount of lattice water. The anhydrous forms of **1** and **2** are relatively stable showing a plateau in the range 200–250 °C while for **3** decomposition immediately starts following the final dehydration step. The overall weight loss in the range 250–600 °C corresponds to the loss of organic matter in the form of H_2O, CO/CO_2 and NO/NO_2 in several consecutive steps to give the metal oxide residue around 600 °C.

3.3. Structural description of complex 1

The structure of complex **1** was determined by X-ray crystallography, and a thermal ellipsoid drawing is provided in

Table 4
Thermogravimetric decomposition data

	Dehydration		Decomposition		Total mass loss (%)[a]
	DTG peak temperature (°C)	Mass loss (%)[a]	Onset temperature (°C)	DTG peak temperature (°C)	
$NH_4H_2Or\cdot H_2O$	114	10 (9.4)	≅250	273 + 352	100 (100)
1	143	23 (22.6)	≅250	341 + 470	84 (84)
2	147	23.5 (22.6)	≅250	335 + 511	79 at 525 °C (85.4)
3	109 229 302	23 2.7 2.7 (28)	≅250	359 + 479	82 (84)

[a] Values in parentheses refer to calculated mass losses.

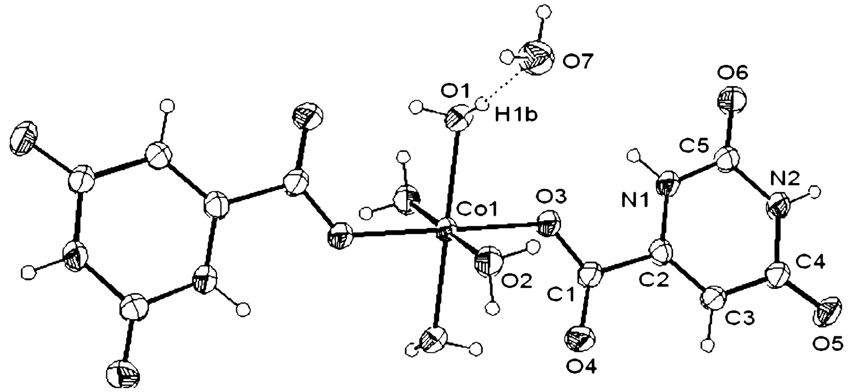

Fig. 2. Representative unit in the crystal structure of $[Co(H_2Or)_2(H_2O)_4]\cdot 2H_2O$ with atomic numbering.

Fig. 2. Although the crystals were suitable for X-ray analysis, the overall quality of the crystals was poor.

The compound consists of neutral $Co(H_2Or)_2(H_2O)_4$ units which are bonded to each other by hydrogen bonds through the lattice. Each Co atom lies on a crystallographic inversion center and is coordinated to six oxygens belonging to two orotate and four aqua ligands. The polyhedron of six oxygen atoms is a distorted octahedron with two orotate ligands at 2.063(2) Å, via their carboxylate oxygens, and two H_2O ligands at 2.133(3) Å in the equatorial plane. The two axial ligands at 2.090(3) Å are significantly bent by ca. 5° where the O3–Co–O1 angle is 85.09(11)° and the O3–Co–O1i is 94.91(11)°. Like the molecule in the crystal of free orotic acid, the orotate ligand occurs in the keto form [31]. The value of the C2–N1–C5 angle (122.5(3)°) is nearly equal to that in free orotic acid (122.7(2)°) indicating that N1 is not involved in complexation with the metal. On the other hand, the lengthening in the C1–C2 bond (1.522(5) Å) and the shortening in the C1–O3 bond (1.263(4) Å) relative to those in the free orotic acid (1.498(4) and 1.306(3) Å, respectively) indicate the participation of the carboxylate group in coordination. The complex contains also crystallization water. Co(II) ions are arranged in polymeric chains where the lattice water molecules act as bridges by making strong hydrogen bonds with coordinated water (H1(B)···O(7) = 1.87 Å) thus aligning the molecules in a zigzag fashion forming layers that propagate parallel to the *b* axis (Fig. 3). The pyrimidine rings are nearly planar and pack along the *c* axis in a columnar mode. There are also hydrogen bonds in which the pyrimidine ring is a donor and oxygen from the lattice molecule is an acceptor. The adjacent layers are linked by hydrogen bonding forming a 3D lattice.

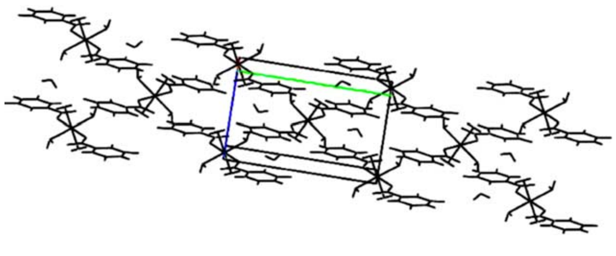

Fig. 3. Perspective view of **1**.

4. Conclusion

The complexes described in this article demonstrate the monofunctional binding property of the orotate ligand. Physical and spectroscopic data suggest that the metal center in the cobalt complex is a distorted octahedron formed by the coordination of the carboxylate oxygens of the orotate ligands and four aqua ligands. The Ni and Zn complexes could not be characterized crystallographically because of the unavailability of suitable crystals. However, based on IR spectroscopy, compositional and thermal analysis, they were assumed to contain monodentate bound orotate ligands as well.

5. Supplementary material

Crystallographic data for **1** have been deposited at the Cambridge Crystallographic Data Centre, CCDC, with deposition number 284789.

Acknowledgements

This work was supported by the Turkish Scientific and Technical Research Council through the project TBAG 2236. The authors wish to acknowledge the Faculty of Arts and Sciences, Ondokuz Mayıs University, Turkey, for the use of the Stoe IPDS-II diffractometer (purchased under grant no. F279 of the University Research Fund).

References

[1] A. Lehninger, Principles of Biochemistry, Worth Publishers, New York, 1970, p. 661.
[2] H. Schmidbaur, H.G. Classen, J. Helbig, Angew. Chem. 102 (1990) 1122.
[3] P. Castan, E. Colacio-Rodrigez, A.E. Beauchamp, S. Cros, S. Wimmer, J. Inorg. Biochem. 38 (1990) 225.
[4] Br.E. Doody, E.R. Tucci, R. Scruggs, N.C. Li, J. Inorg. Nucl. Chem. 28 (1996) 883.
[5] F. Nepveu, N. Gaultier, N. Korber, J. Jaud, P. Castan, J. Chem. Soc., Dalton Trans. (1995) 4005.
[6] G. Maistralis, A. Koutsodimou, N. Katsaros, Transition Met. Chem. 25 (2000) 166.
[7] M. Sabat, D. Zglinska, B. Jezowska-Trzebiatowska, Acta Crystallogr. B36 (1980) 1187.

[8] A.Q. Wu, L.Z. Cai, G.H. Guo, F.K. Zheng, G.C. Guo, E.G. Mao, J.S. Huang, Chin. J. Inorg. Chem. 19 (2003) 879.
[9] I. Mutakainen, R. Hämäläinen, M. Klinga, O. Orama, U. Turpeinen, Acta Crystallogr. C52 (1996) 2480.
[10] H. İçbudak, H. Ölmez, O.Z. Yeşilel, F. Arslan, P. Naumov, G. Javanowski, A.R. İbrahim, A. Umsan, H.-K. Fun, S. Chantrapromma, S.W. Ng, J. Mol. Struct. 657 (2003) 225.
[11] A. Karipides, B. Thomas, Acta Crystallogr. C42 (1986) 1705.
[12] I. Mutakainen, Recl. Trav. Chim. Pays-Bas 106 (1987) 438.
[13] I. Mutakainen, Inorg. Chim. Acta 136 (1987) 155.
[14] T.T.B. Ha, A.M. Larsonneur-Galibert, P. Castan, J. Jaud, J. Chem. Crystallogr. 29 (1999) 565.
[15] M.J. Plater, M.R.St.J. Foreman, J.M. Skakle, R.A. Howie, Inorg. Chim. Acta 332 (2002) 135.
[16] D. Sun, R. Cao, Y. Liang, M. Hong, Y. Zhao, J. Weng, Aust. J. Chem. 55 (2002) 681.
[17] D. Sun, R. Cao, Y. Liang, M. Hong, Chem. Lett. (2001) 878.
[18] M. Lutz, Acta Crystallogr. E57 (2001) m103.
[19] O. Kumberger, J. Riede, H. Schmidbaur, Z. Naturforsch. 48b (1993) 961.
[20] L.R. Falvello, D. Ferrer, T. Soler, M. Tomas, Acta Crystallogr. C59 (2003) m149.
[21] J. Solbakk, Acta Chem. Scand. 25 (1971) 3006.
[22] G.M. Sheldrick, SHELXS-97—A Program for Automatic Solution of Crystal Structures, University of Gottingen, Germany, 1997.
[23] G.M. Sheldrick, SHELXL-97—A Program for Crystal Structure Refinement, University of Gottingen, Germany, 1997.
[24] L.J. Farrugia, WINGX—A Windows Program for Crystal Structure Analysis, University of Glasgow, 1998.
[25] L.J. Farrugia, J. Appl. Crystallogr. 32 (1999) 837–838.
[26] L.J. Farrugia, Appl. Crystallogr. 30 (1997) 565.
[27] A.L. Spek, PLATON—A Multipurpose Crystallographic Tool, Utrecht University, Utrecht, The Netherlands, 2005.
[28] A. Hernanz, F. Billes, I. Bratu, R. Navarro, BioPolymers 57 (2000) 187.
[29] K. Nakamoto, Infrared and Raman Spectra of Inorganic and Coordination Compounds, fifth ed., Wiley Interscience, New York, 1997, pp. 59–62.
[30] D. Mentzafos, N. Katsaros, A. Terzis, Acta Crystallogr. C43 (1987) 1905.
[31] F. Takusagawa, A. Shimada, Bull. Chem. Soc. Jpn. 46 (1973) 2011.