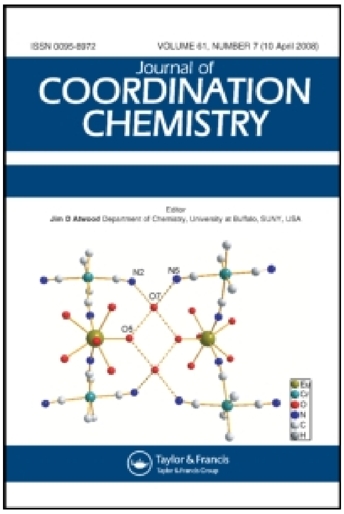

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Synthesis and characterization of transition metal-vitamin B13 complexes mixed with a co-vitamin

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Synthesis and characterization of transition metal-vitamin B13 complexes mixed with a co-vitamin

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The synthesis and structural characterization of mixed vitamin-metal complexes are reported. A complex bearing two vitamins (B3 and B13) on the same metal centre, nicotinamide(orotato)nickel(II) pentahydrate, has been prepared and characterised by single-crystal X-ray diffraction methods. A complex of Cr(III) with vitamins C and B13, bis(ascorbato)orotatochromium(III) dihydrate, has been isolated and its nature investigated by means IR, ^{13}C NMR, API-ES and thermogravimetric measurements. Theoretical calculations have been performed to propose a structure in accord with results obtained.

Keywords: Vitamin B3; Nicotinamide; Vitamin B13; Orotic acid; Vitamin C; Ascorbic acid; Nickel(II); Chromium(III); X-ray structure

1. Introduction

The use of coordination compounds as pharmaceutical agents represents one of the most successful applications of bioinorganic chemistry after the discovery of the antitumor activity of cis-diamminedichloroplatinum(II) [1]. Attempts to generate new complexes with enhanced biological activities usually involves the synthesis of derivatives of compounds known to be active. Among biological ligands, heterocyclic compounds are of special importance since many vitamins and drugs belong to this class [2, 3]. The vitamin B family is structurally based on nitrogen heterocycles. All B vitamins are essential in converting carbohydrates to glucose, and breakdown of fats and proteins. Orotic acid (**1**) is a quasi-B vitamin commonly known as vitamin B13. It helps with the production of genetic material and is an intermediate in pyrimidine metabolism [4]. The literature lists many reports on mononuclear [5–10] and polymeric [11–16] orotate complexes. Nicotinamide (**2**) is a form of vitamin B3 and is an important component of several enzymes [17]. Besides the usual complexes with metal ions, a number of mixed

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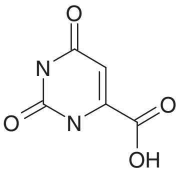
ligand nicotinamide complexes has been reported [18–22]. Nicotinamide complexation appears to be a useful approach to increase the solubility of physiologically useful systems [23]. Vitamin C (*L*-ascorbic acid, **3**) is a very important of all vitamins with a range of activities [24]. The molecule contains a lactone ring, enolic and alcoholic oxygens. Many solutions studies but relatively fewer structural studies are known regarding its complexation with metal ions [25, and references therein].



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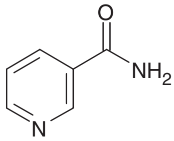

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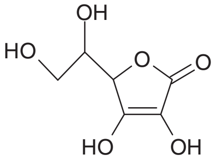

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Some metal compounds of these vitamins and their derivatives have applications in curing certain syndromes involving metal ion and vitamin deficiencies and have promising applications as anti-cancer agents [25, 26]. Having in mind that the functions of B vitamins are synergistic, ternary combinations of two different vitamins with a metal might be of both scientific and pharmacological interest. The present paper reports the crystal structure of a new complex bearing two vitamins (B3 and B13) on the same metal centre, nicotinamide(orotato)nickel(II) pentahydrate. Synthetic and structural studies on the formation of a Cr(III) complex with vitamins B13 and C are also reported.

2. Experimental

Abbreviations: H_2A, ascorbic acid ($C_6H_8O_6$); NA, nicotinamide ($C_6H_6N_2O$); H_3Or, orotic acid ($C_5H_4N_2O_4$) H_2Or, orate monoanion $[C_5H_3N_2O_4]^-$; HOr, orotate dianion $[C_5H_2N_2O_4]^{2-}$; en: ethylenediamine; phen: 1,10-phenanthroline; DACH: diaminocyclohexane.

2.1. *Materials and methods*

HA (Merck), NA (Merck), anhydrous H_3Or (Fluka), $NiSO_4 \cdot 6H_2O$ (Merck), $Cr_2(SO_4)_3 \cdot 15H_2O$ (BDH Chemicals Ltd.) and $BaSO_4 \cdot 8H_2O$ (BDH Chemicals Ltd.) were used as received. $NH_4H_2Or \cdot H_2O$ (m.p. = 350.5°C) was prepared from H_3Or according to the procedure described by Solbakk [27]. C, H and N analyses were performed using a Leco CHNS 932 instrument. FTIR spectra were collected on a Mattson 1000 instrument (KBr matrix). ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance DPX-400 spectrometer using D_2O as solvent and TMS as reference. Thermogravimetric analyses were performed in flowing nitrogen atmosphere ($10\,cm^3\,min^{-1}$) using a Schimadzu DTG-60 instrument. API/ES mass spectra were recorded on a Agilent 100 LC/MSD spectrometer. Theoretical calculations were carried out at the unrestricted Hartree-Fock level (UHF) using the PM3D model in SPARTAN'02 [28]. Calculations were carried out for various coordination modes with complete geometry optimization at precise level and conformers located at minima were characterized by the calculations of vibrational frequencies.

2.2. *Synthesis of nicotinamide(orotato)nickel(II) pentahydrate*

To a stirred solution of $NiSO_4 \cdot 6H_2O$, a warm solution of NH_4H_2Or and NA were added in 1 : 2 : 2 mole ratio. Green crystals suitable for crystallographic analysis were produced in about 3–4 weeks. The crystals were collected and dried at room temperature. Anal. Calcd for $C_{11}H_{18}N_4NiO_{10}$ (%): C, 31.06; H, 4.24; N, 13.17. Found: C, 30.78; H, 4.74; N, 12.95.

2.3. *Synthesis of bis(ascorbato)orotatochromium(III) dihydrate*

The experiments were conducted under nitrogen in deoxygenated, deionized water as a requirement of vitamin C chemistry [29]. All attempts to prepare ternary transition metal(II) complexes with vitamins B13 and C resulted in the formation of bis(orotate) complexes of the corresponding metals. With M(III) ions, the best result was obtained by the following reaction route.

To an aqueous chromium(III) sulfate solution was added a warm NH_4H_2Or solution in 1 : 4 mole ratio. To this solution, a $Ba(HA)_2$ solution (prepared separately by reacting $Ba(OH)_2$ with H_2A in 3 : 6 mole ratio) was added. The resulting solution was kept overnight for completion of $BaSO_4$ precipitation and then filtered through a G4 filter. The green filtrate was concentrated to 1/3 of its original volume under vacuum and the product rapidly precipitated by adding cold acetone. It was filtered off, washed and dried under vacuum. Anal. Calcd for $C_{17}H_{21}N_2O_{20}Cr$ (%): C, 34.28; H, 3.19; N, 4.70. Found: C, 33.90; H, 4.14; N, 5.58.

2.4. *Crystallography*

A green crystal of the nickel complex was mounted on a glass fibre and data collection performed on a STOE IPDS II diffractometer with graphite-monochromated Mo-Kα radiation at 100 K. Details of crystal data, data collection and refinement are given in table 1. The structure was solved by direct methods using SHELXS-97 [30] and refined by full-matrix least-squares methods on F^2 using SHELXL-97 [31] from the WINGX [32, 33] suite 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 = 0.88–0.93 and N–H = 0.78–0.89 Å) and refined using a riding model with $U = 1.2$ times that of the parent atom. H atoms of water molecules were refined with fixed O–H = 0.83 Å ($U = 1.5$ times that of the parent atom). Molecular drawing was performed using ORTEP-III [34]. Geometric calculations were performed using PLATON [35]. Atomic coordinates and equivalent isotropic displacement parameters are listed in table 2.

3. Results and discussion

3.1. *Nicotinamide(orotato)nickel(II) pentahydrate*

The reaction of aquated Ni(II) with NA and H_2Or resulted in the compound formulated as $Ni(NA)(HOr)(H_2O)_5$. Though an initial ratio of Ni : NA : H_2Or = 1 : 2 : 2 was used,

Table 1. Crystal data for nicotinamide(orotato)nickel(II) pentahydrate and structure refinement details.

Empirical formula	$C_{11}H_{18}N_4NiO_{10}$
Formula weight	424.98
Temperature (K)	100
Wavelength (Å)	0.71073
Crystal system	Triclinic
Space group	$P\bar{1}$
Unit cell dimensions (Å, °)	$a = 7.1262(6)$
	$b = 10.1469(8)$
	$c = 12.6454(10)$
	$\alpha = 69.375(6)$
	$\beta = 75.268(6)$
	$\gamma = 77.906(6)$
V ($Å^3$)	820.34(12)
Z	2
Calculated density ($Mg\,m^{-3}$)	1.720
Absorption coefficient (mm^{-1})	1.246
$F(000)$	440.0
Crystal size (mm^3)	0.120 × 0.127 × 0.140
θ range for data collection (°)	2.16 to 25.99
Index ranges	$-8 < h < 8$, $-12 < k < 12$, $-15 < l < 15$
Independent reflections	3232
Measured reflections	11,209
Absorption correction	Integration
Refinement method	Full-matrix least-squares on F^2
Goodness-of-fit on F^2	1.023
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.029$
R indices (all data)	$R_1 = 0.037$
Largest diff. peak and hole ($e\,Å^{-3}$)	0.681 and −0.431

Table 2. Selected geometric parameters(Å, °) for the nickel complex.

N1–Ni1	2.0773(18)	H1B···O9	1.957(18)
N2–Ni1	2.0481(17)	H3A···O6	1.868(17)
O1–Ni1	2.0685(16)	H10A···O7	1.842(18)
O2–Ni1	2.1045(16)		
O3–Ni1	2.0774(14)		
O4–Ni1	2.0733(14)		
N2–Ni1–O1	91.84(7)	N2–Ni1–O4	80.21(6)
O1–Ni1–O4	90.44(6)	N2–Ni1–N1	175.60(7)
O1–Ni1–N1	90.36(7)	O4–Ni1–N1	95.96(6)
N2–Ni1–O3	93.76(6)	O1–Ni1–O3	88.03(6)
O4–Ni1–O3	173.73(6)	N1–Ni1–O3	90.13(6)
N2–Ni1–O2	88.58(6)	O1–Ni1–O2	179.39(6)
O4–Ni1–O2	90.07(6)	N1–Ni1–O2	89.25(6)
O3–Ni1–O2	91.50(6)		

the final stoichiometry was Ni : NA : HOr = 1 : 1 : 1, presumably because of steric factors. In the alkaline medium generated by excess NA, H_2Or is deprotonated to HOr^-. The product is stable under atmospheric conditions and is slightly soluble in water.

IR bands in the 3500–2500 cm^{-1} region are due to the O–H stretches of coordinated water overlapped with N–H and C–H stretches of the organic ligands.

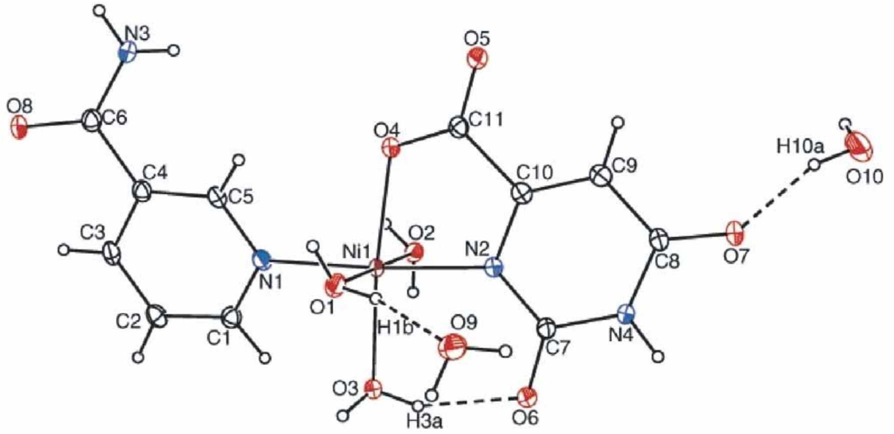

Figure 1. The structure of $Ni(NA)(HOr) \cdot 5H_2O$ with the atom numbering scheme.

Broadening in this region indicates the involvement of O–H and N–H groups in hydrogen bonding. Overlap of carboxylate and carbonyl stretches with ring modes of the heterocycles and water bending modes complicates precise assignments between 1700 and 1500 cm^{-1} but the positions of carboxylate, carbonyl and ring modes of HOr and NA suggests interactions of these groups with Ni(II) [9, 36]. The strong band at 1386 cm^{-1} may be assigned to C–N stretching of the amide group and the shift with respect to the corresponding peak (1395 cm^{-1}) in the spectrum of free NA may be due to the involvement of amide hydrogens in hydrogen bonding. C–C stretches of the pyridine ring appear as medium intensity peaks at 1204 and 1129 cm^{-1}. The 1000–500 cm^{-1} region covers a number of bands corresponding to ring stretching, deformation and lattice vibrations.

The structure analysis shows Ni(II) lying in a distorted octahedron formed by the coordination of the pyridinic nitrogen atom of NA (N1), the chelating HOr ligand (through carboxylate oxygen (O4) and deprotonated ring nitrogen (N2) atoms) and three water molecules (O1, O2, O3) (figure 1). Pyrimidine rings of both HOr and NA ligands are slightly distorted from planarity. Equatorial H_2O ligands *trans* to each other make an O1–Ni(1)–O2 angle of 179.39(6)° where O2 positions itself at a slightly farther distance from Ni(1). The other two equatorial and axial bonds deviate from linearity with N2–Ni(1)–N1 = 175.60(7) and O4–Ni(1)–O3 = 173.73(6)°, distorting the octahedral geometry. The unit cell contains four lattice water molecules and monomeric units are bonded to each other by intermolecular hydrogen bonds between the carboxylate oxygen of the orotate ligand of one unit and the donor H_2O ligand on the other, forming 2D layers. The layers are stacked by hydrogen bonds between the amide oxygen from one layer and the coordinated H_2O from the next such that the arrangement of *quasi* octahedral Ni(II) ions is parallel to the *a* axis. There are also intramolecular hydrogen bonds between ligand H_2O (H3a) and the nearest exocyclic oxygen (O6) of orotate. The geometries of the hydrogen bonds are very close to linear. Lattice water molecules stabilize the structure also with hydrogen bonds by playing the role both of acceptors from ligand water molecules and of donors to the exocyclic oxygen atoms.

3.2. *Metal complexes of vitamin B13 mixed with vitamin C*

Though vitamins C and B13 on their own have been shown to form genuine complexes with biorelevant metals, a mixed complex of both has not yet been reported to the authors' knowledge. All our efforts aimed towards the preparation of mixed complexes of vitamins B13 and C with M(II) ions resulted in the isolation of simple orotate complexes. It is known that the stabilities of ascorbate complexes are weak due to the delocalization of the negative charge on HA and formation constants of the 1 : 1 complexes are in the range of 10^1–$10^{3.6}$ at 25°C, as reported by Martell [37]. On the other hand, values for orotate complexes are around 10^6–10^7 at this temperature [38]. Regardless of the order of adding reagents, reactions between M(II), HA and H_2Or proceeded with eventual precipitation of the thermodynamically more favorable orotate complexes in a few weeks. Transfer of HA ligands into solution was obvious from the progressive colour change of the solution to brown, due to the decomposition of ascorbate with time. The idea of blocking some coordination sites by neutral chelating amine ligands (en, phen, DACH; $M:\text{amine}:H_2Or = 1:1:1$ or $1:2:1$) to prepare cationic complexes with HA counterions yielded neutral, mixed complexes of amine and HOr ligands.

A number of experiments was also carried out with M(III) ions. Reactions between Ln(III), H_2Or and HA ions yielded pure lanthanoid orotate complexes. With Cr(III), a compound was obtained as described in the experimental section, which can best be formulated as $Cr(HA)_2(H_2Or)\cdot 2H_2O$ on the basis of analytical data. The synthetic procedure was repetaed twice and comparable microanalytical results were obtained, indicating the same formula. The following results have been interpreted to propose a structure for the compound.

The observed mass loss for the removal of two moles of water (6.5%) agrees well with the theoretical value (6.1%). A clear plateau was not reached after complete dehydration. Decomposition of the anhydrous species started at ca 150°C, right after the dehydration process. This low temperature behavior with respect to bis(orotate) [10] and chromium(III) ascorbate complexes [39] suggests a thermally less stable structure arising possibly from the relatively weak co-complexation tendencies of HA and H_2Or ligands. Total mass loss at 500°C (74.3%) agrees with the final formation of Cr_2O_3 (74.4%).

The FTIR spectrum represents a superposition of the spectra of orotate [9, 10] and ascorbate complexes [39]. A broad and strong band in the 3700–2700 cm^{-1} region was observed with poor resolution due to the overlap of ν(OH) of water molecules with the OH, CH and NH stretches of the organic ligands. The 2000–1000 cm^{-1} region shows characteristic features of the ligands. Strong bands observed in the corresponding pure complexes around 1730 [ν_a(C=O) of HA and H_2Or], 1700 [$\nu_a(COO^-)$ of H_2Or] and 1630 cm^{-1} [ν_a(C=O) + ν_a(C=C) of HA] were merged and broadened into two groups around 1731 and 1631 cm^{-1}. The $\nu_s(COO^-)$ mode at 1363 cm^{-1} showed a shoulder around 1380 cm^{-1}, corresponding to $\nu_a(C_3O^-)$ of HA. The pattern in the range 1150–1020 cm^{-1} is typical of metal ascorbate complexes [40].

^{13}C NMR spectra of $Cr(HA)_2(H_2Or)\cdot 2H_2O$, measured over long periods in D_2O exhibited eleven distinct resonances corresponding to HA and H_2Or ligands. Table 3 lists measured NMR data for the compound and related published data for comparison. Like the FTIR bands, the observed chemical shifts represent a superposition of the ^{13}C NMR spectra of orotate and ascorbate compounds. Due to

Table 3. ^{13}C NMR data for $Cr(HA)_2(H_2Or) \cdot 2H_2O$ and related compounds [δ (ppm)].

NaHA [25]	NH_4H_2Or	$Cr(HA)_2(H_2Or) \cdot 2H_2O$
63.46(C6)		62.92
70.46(C5)		69.88
79.28(C4)		78.43
	102.42(C5)	101.69
113.85(C2)		114.53
	149.89(C6)	148.68
	154.00(C2)	152.57
	166.43(C7)	166.73
	169.40(C4)	169.70
176.34(C3)		175.99
178.30(C1)		176.39

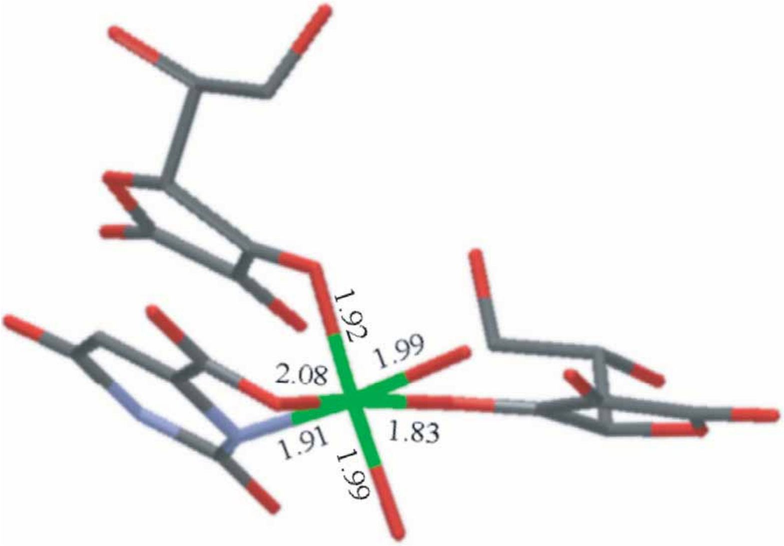

Figure 2. Calculated structure of $Cr(HA)_2(H_2Or) \cdot 2H_2O$ (bond distances in Å).

the insoluble nature of orotate complexes, no satisfactory NMR data are available in the literature. Nevertheless, the fact that the spectrum of NH_4H_2Or remains almost unchanged on complexation with Cr(III) verifies the earlier findings that the ^{13}C chemical shifts of orotic salt solutions are not affected by the addition of paramagnetic transition metal ions [9]. On the other hand, the chemical shift corresponding to C(2) of HA refers to monodentate binding of the ascorbate ligand [25]. The position of the C(2) resonance retains or shows a small upfield shift with respect to free H_2A (114.1 ppm, pH = 7) if binding to the metal is as for alkaline and alkaline earth salts. In order to propose a structure that correlates with experimental observations, PM3 calculations have been performed for various coordination modes of the ligands. The structure given in figure 2, where two ascorbate ligands bind as monodentates *via* O(3), H_2Or chelates through its carboxylate oxygen and the adjacent ring nitrogen and two H_2O ligands complete octahedral coordination around Cr(III), was found to be more stable than others.

API/ES mass spectrometry gave no evidence for the parent molecule (*m*/*z* 595) but fragments resulting from the successive losses from the coordination sphere were detected providing further support to the proposed structure. Degradation of HA groups by removal of the side chain ($CH_2OHCHOHC$–, *m*/*z* 73) followed by CO_2 (*m*/*z* 44) elimination were typically observed as previously noted for chromium ascorbate complexes [39]. The base peak in the spectrum corresponds to protonated free ascorbic acid (*m*/*z* $177 = H_2A + H^+$).

4. Conclusions

A mixed complex of nickel with vitamins B13 and B3 was obtained and crystallographically defined. On the other hand, competitive binding of the vitamins B13 and C in the coordination sphere of M(II) ions resulted in the eventual formation of thermodynamically favourable M(II)–orotate complexes by ousting HA ligands. A compound of Cr(III) with vitamins B13 and C was obtained where the two ascorbate ligands bind monodentately and orotate in a chelating mode, as suggested by spectroscopic and computational studies. In addition to binary transition metal-vitamin complexes, ternary combinations with different vitamins can also be used for medication. This gives a real impetus to carry out more detailed studies to elucidate the therapeutic role of multivitamin-metal complexes. Preparations of various other metal/vitamin(1)/vitamin(2) combinations are in progress.

Supplementary material

Crystallographic data for $Ni(NA)(HOr) \cdot 5H_2O$ have been deposited at the Cambridge Crystallographic Data Centre, CCDC, with deposition number 28433. ^{13}C NMR and mass spectra of $Cr(HA)_2(H_2Or) \cdot 2H_2O$ can be supplied from the corresponding author upon request.

Acknowledgements

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