

Synthesis and crystal structure of the bis-calcimycin anion–Ni²⁺ complex

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Abstract

The X-ray structure of [Ni(calcimycin)₂] complex shows two essentially identical conformations of the two calcimycin ligands in the dimeric association, in this ionophore family. In the title complex, the nickel (II) cation has a distorted O₄N₂ octahedral coordination environment.

Keywords: Calcimycin, nickel (II) cation, complex

Introduction

Since its discovery, calcimycin I (Fig. 1), a carboxylic polyether antibiotic with calcium carrier properties, has attracted considerable attention in biology as a tool for the study of calcium second messenger in living systems.¹⁻² Its non-fluorescent 4-bromo derivative was subsequently described and found suitable for the same application in the presence of fluorescent probes.³

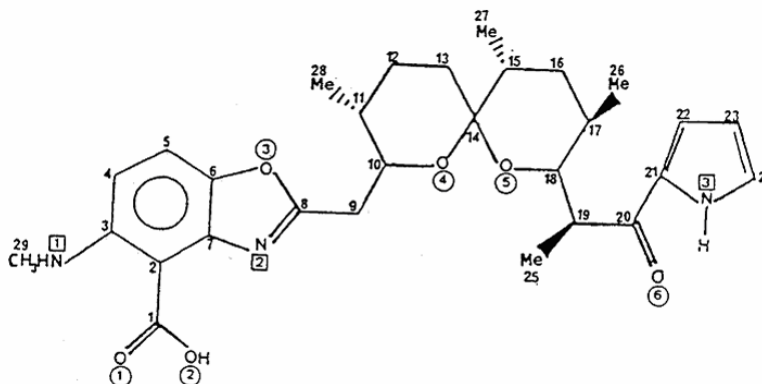


Figure 1. Calcimycin-acid formula showing carbon and oxygen numbering scheme.

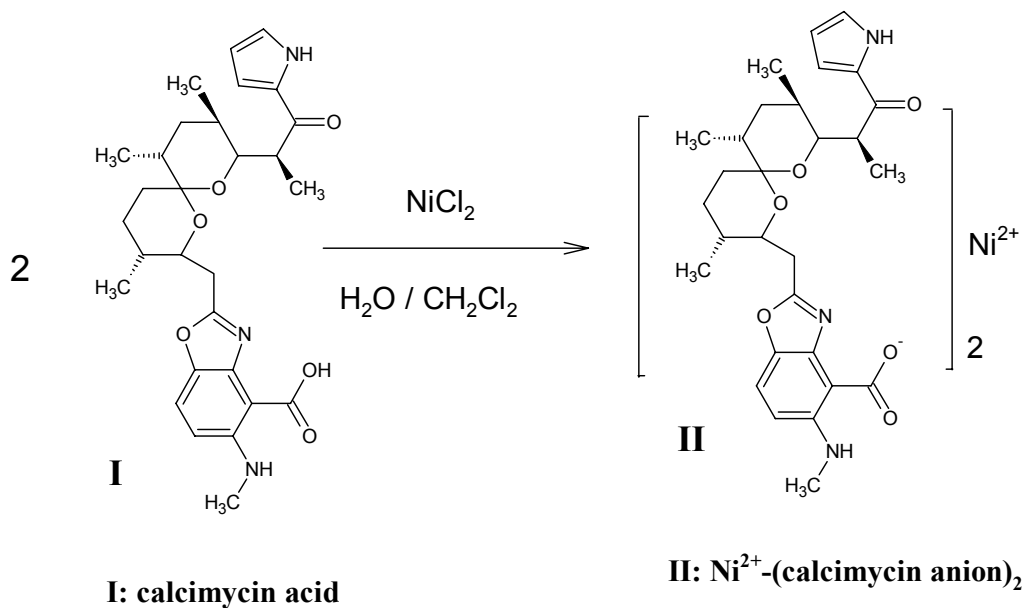
Erdahl and colleagues^{4a} recently showed that 4-bromo derivative of compound (**I**) transports Zn^{2+} and Mn^{2+} with high selectivity over Ca^{2+} in phospholipid vesicles, and they made interesting findings concerning the stoichiometry of species involved in the transport. However, information on the structure of cation complexes with this natural ligand was lacking.

We recently undertook the preparation of crystalline adducts of (**I**) with various divalent cations suitable for X-ray analysis. Here we report the crystal structure obtained for a cation of topical biological interest, Ni^{2+} , which reveals unusual features.

Results and Discussion

Synthesis of bis-calcimycin anion– Ni^{2+} complex

To obtain the complex, we used a ($\text{H}_2\text{O} / \text{CH}_2\text{Cl}_2$) biphasic system in which the free calcimycin acid dissolved in the organic layer was stirred with an aqueous NiCl_2 solution at pH superior of 10.



Scheme 1. Synthesis of the $[\text{Ni}(\text{calcimycin anion})_2]$ complex (**II**).

^1H and ^{13}C NMR data

^1H and ^{13}C NMR data of calcimycin acid as free ligand were acquired as previously described^{4b} using either Bruker 300 or AX 400 spectrometers. Chemical shifts are referred to tetramethylsilane (Figures 2 and 4).

It will be difficult to elucidate the correct coordination of nickel from ^1H and ^{13}C NMR data of compound **II**. By comparison with the ^1H and ^{13}C NMR data of free ligand **I**. The hydrogen

and carbon signals of complex (II) are wide. Undoubtedly this resulting complex is slightly paramagnetic (Figures 3 and 5).

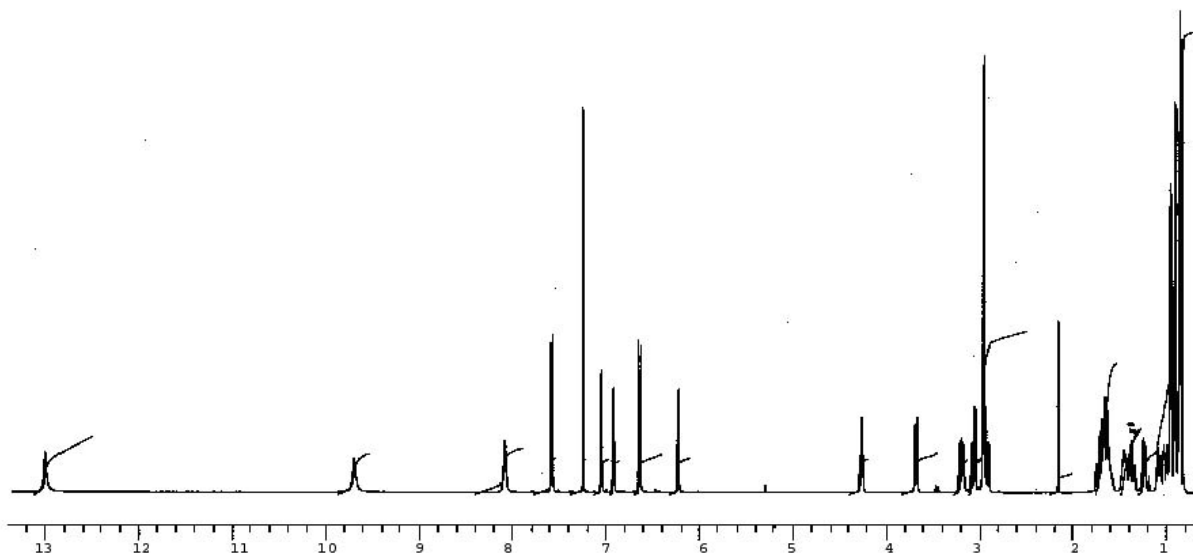


Figure 2. ¹H NMR spectrum of calcimycin acid.

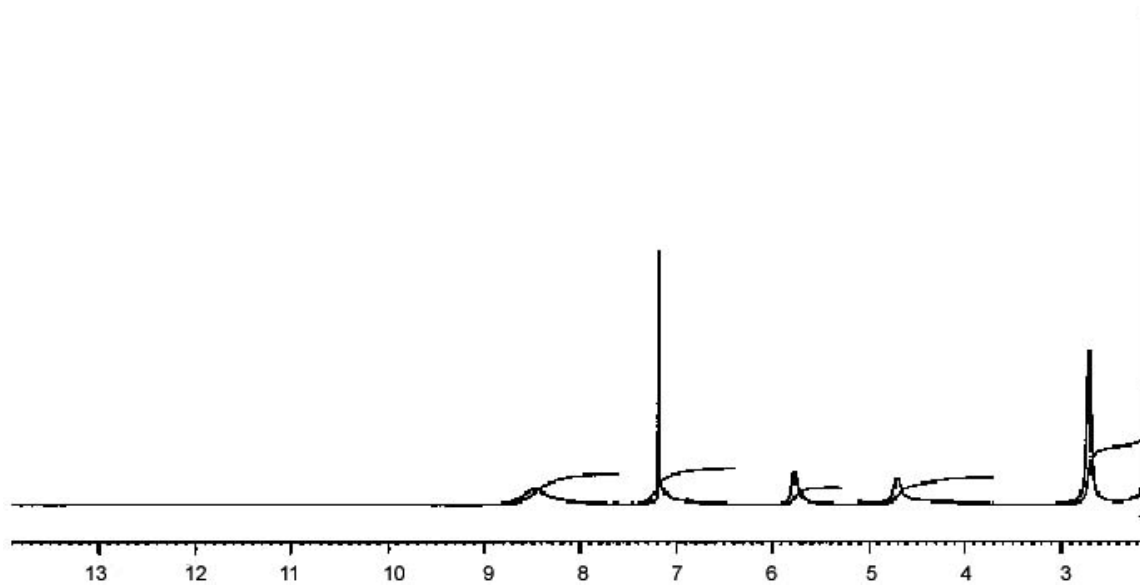


Figure 3. ¹H NMR spectrum of [Ni(calcimycin anion)₂] complex.

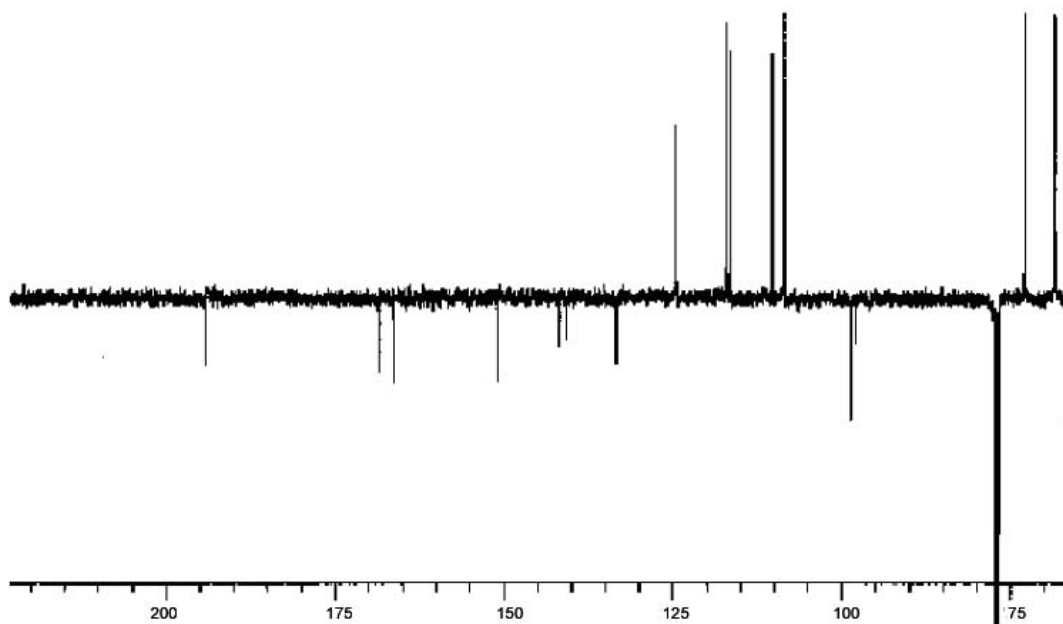


Figure 4. ¹³C NMR spectrum of calcimycin acid.

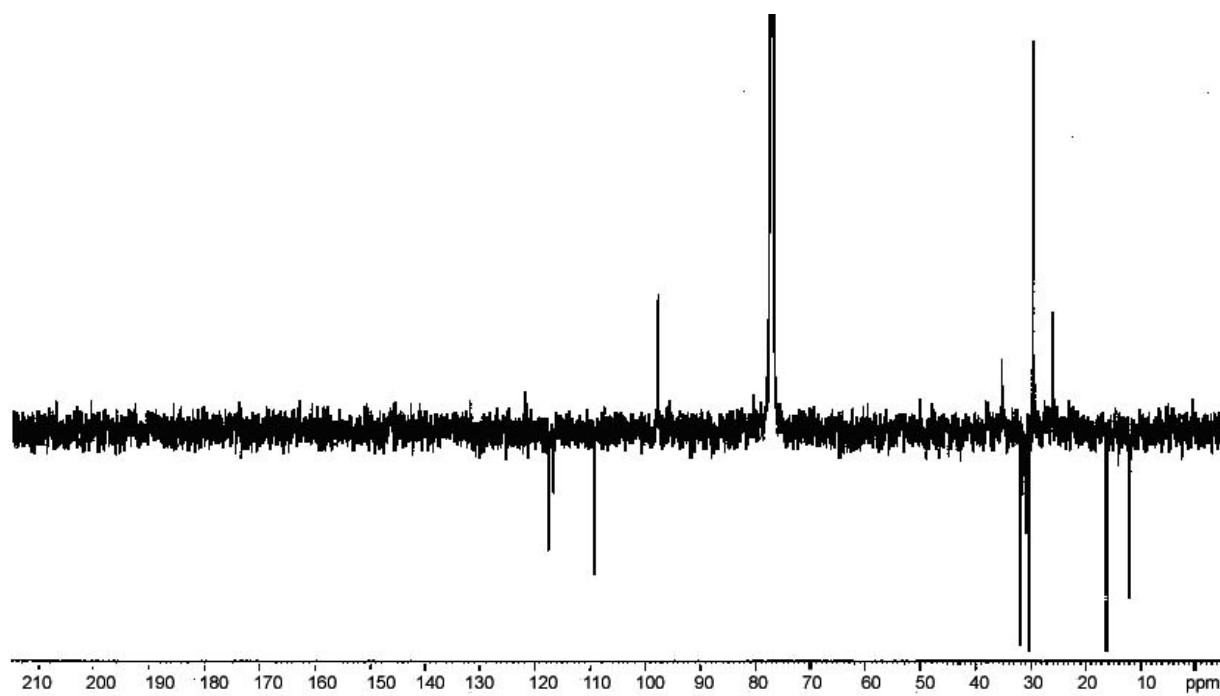


Figure 5. ¹³C NMR spectrum of [Ni(calcimycin anion)₂] complex.

Crystallographic structure analysis

The crystal structure determination by X-ray diffraction was consistent with the neutral dicarboxylate complex $[\text{Ni}(\text{calcimycin})_2]$ (Fig. 6). The nickel atom occupied the centre of a slightly distorted octahedron (Table 2).

The two ligands show very similar conformations, bind the nickel through the same groups and are related by pseudo-twofold symmetry.

Coordinations of Ni were provided by O2, N2, O6 of the first calcimycin ligand; L1, and correspondingly by O8, N5 and O12 of the second ligand, L2 of L2. Note that the ligands are tridentate (Figure 6). Octahedral arrangements of the same type of ligand were recently described for Zn(II) complexes containing more simple aromatic moieties with nitrogen and carboxylate coordinating sites, but no such unsymmetrically bound ligand with a bidentate/ tridentate arrangement has been described.⁵ The specific conformation adopted by L1 and L2 did not permit the two head-to-tail intermolecular chelations observed in the well-known calcimycin dimeric complexes⁶⁻⁸ described for Ca^{2+} , Mg^{2+} and Fe^{2+} . Two intermolecular hydrogen chelation remained for Ni—O2...N6 of pyrrol and Ni—O8...N3 of pyrrol rings.

Also, the 3-aminomethyl substituent which was NH-chelated with the carboxylate group for Calcimycin⁶⁻⁸ was moved out of the aromatic plane owing to the presence of the bulky carboxylate groups in the C7 of L1 or C31 position of L2, and the existing intramolecular hydrogen bonding was thus suppressed.

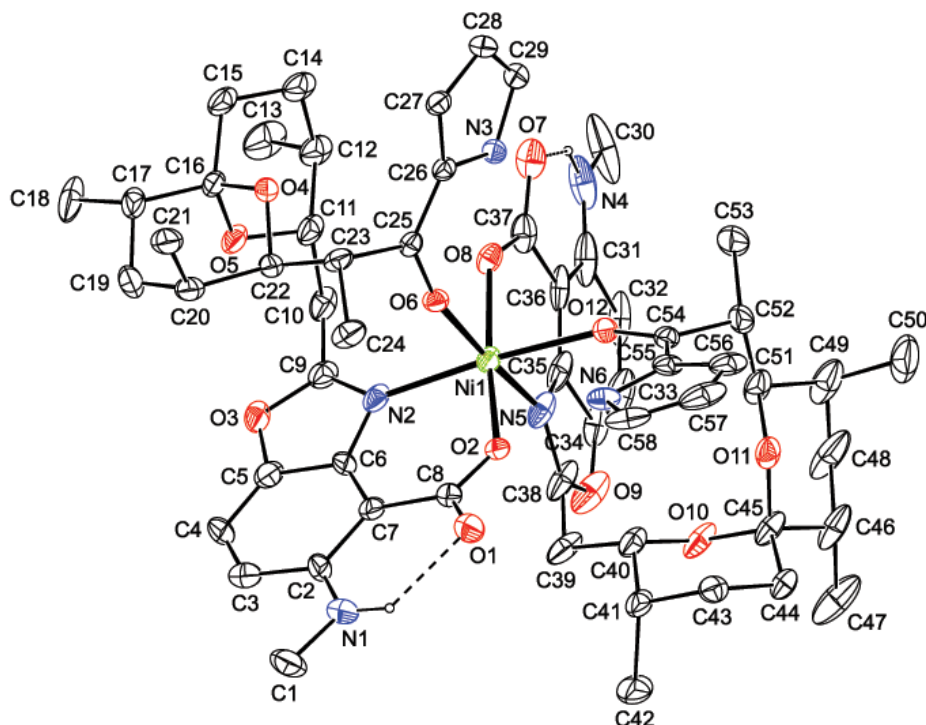


Figure 6. ORTEP drawing of $[\text{Ni}(\text{calcimycin})_2]$ crystal structure showing the very similar conformations in the ligands and intramolecular N—H...O bonds. H atoms have been omitted for clarity. Displacement ellipsoids are drawn at the 10% probability level.

Table 1. Crystal and experimental data

Formula: $C_{58}H_{70}N_6NiO_{12}$

Formula weight = 1101.91
Crystal system: orthorhombic
Space group: $P2_12_12_1$ (No. 19); $Z = 4$
 $a = 14.8944(18)$ Å
 $b = 17.075(2)$ Å
 $c = 23.386(3)$ Å
 $V = 5947.5(12)$ Å³
 $D_x = 1.231$ g cm⁻³
 $\mu(MoK_\alpha) = 0.39$ cm⁻¹
 $T = 293(2)$ K
 $F(0\ 0\ 0) = 2336$
Crystal size = 0.12 x 0.13 x 0.36 mm
Radiation: MoK α
 $R_1 [I \geq 2\sigma(I)] = 0.075$
 $wR_2 (F^2) = 0.259$
 $\theta_{max} = 28.5^\circ$
 $h = 19 \rightarrow 19$; $k = -22 \rightarrow 22$; $l = -31 \rightarrow 31$
No. of reflections measured = 61727
No. of independent reflections = 14862
No. of observed data with $[I \geq 2\sigma(I)] = 6471$
No. of parameters = 695
 $S = 1.01$
 $(\Delta/\sigma)_{max} = 0.001$
 $(\Delta\rho)_{max} = 0.33$ eÅ⁻³
 $(\Delta\rho)_{min} = -0.33$ eÅ⁻³
Extinction correction: SHELXL
Extinction coefficient : 0.0004(2)
Measurements: Bruker SMART APEX-II CCD diffractometer⁹
Absorption correction: multi-scan (SADABS)¹⁰
Structure determination: *SIR97*¹¹
Refinement: full matrix least-squares SHELXL-97¹²
CCDC 663241 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Table 2. Selected bond lengths (Å) and angles (°)

N2—Ni1	2.087(6)	C25—O6	1.242(7)
N5—Ni1	2.040(7)	C26—N3	1.388(7)
O2—Ni1	1.978(5)	C29—N3	1.355(9)
O6—Ni1	2.110(4)	C30—N4	1.481(12)
O8—Ni1	1.968(5)	C31—N4	1.351(19)
O12—Ni1	2.134(4)	C34—O9	1.266(14)
C1—N1	1.444(11)	C35—N5	1.264(14)
C2—N1	1.381(12)	C37—O8	1.243(9)
C5—O3	1.444(12)	C37—O7	1.286(12)
C6—N2	1.425(10)	C38—O9	1.274(12)
C8—O1	1.219(10)	C38—N5	1.305(11)
C8—O2	1.327(9)	C40—O10	1.447(11)
C9—N2	1.279(10)	C45—O10	1.397(10)
C9—O3	1.343(10)	C45—O11	1.463(10)
C11—O5	1.421(10)	C51—O11	1.432(9)
C16—O4	1.416(9)	C54—O12	1.237(7)
C16—O5	1.443(9)	C55—N6	1.379(10)
C22—O4	1.441(9)	C58—N6	1.394(11)
C9—N2—Ni1	133.5(7)	O2—Ni1—N2	87.1(3)
C6—N2—Ni1	120.6(5)	N5—Ni1—N2	97.0(2)
C38—N5—Ni1	135.6(9)	O8—Ni1—O6	86.70(16)
C8—O2—Ni1	136.9(5)	O2—Ni1—O6	85.75(18)
C25—O6—Ni1	157.6(4)	N5—Ni1—O6	176.4(3)
C37—O8—Ni1	133.9(6)	N2—Ni1—O6	84.45(19)
C54—O12—Ni1	155.3(4)	O8—Ni1—O12	84.71(17)
O8—Ni1—O2	168.4(2)	O2—Ni1—O12	87.28(17)
O8—Ni1—N5	89.8(3)	N5—Ni1—O12	83.2(2)
O2—Ni1—N5	97.6(3)	N2—Ni1—O12	174.4(3)
O8—Ni1—N2	100.9(3)	O6—Ni1—O12	95.73(17)

Table 3. Hydrogen-bonding geometry

D—H...A	D—H (Å)	H...A (Å)	D...A (Å)	D—H...A (°)
N1—H1...O1	0.86	1.96	2.605(11)	131
N4—H4A...O7	0.86	1.91	2.606(15)	137

Interestingly, for both L1 and L2 the ketopyrrole arm adopted the preferential orientation already observed in the solid⁶⁻⁸ and liquid state¹³ for calcimycin with the characteristic antiperiplanar position of H atoms.

All these observations suggest that in the complex formation, a 2...1 (L1-Ni⁺) association occurs followed by the simultaneous approach of the two ligands L1 and L2. The latter is able to displace the remaining water ligand by its ketone function to give a final 2...1 supramolecular association. This may be related to the transport experiments in vesicles.⁴ We could suppose that Ni²⁺ is transported, in part, as a 2...1 and 1...1 complexes in a pH-dependent stoichiometry.

Conclusions

In conclusion, we describe here what is to our knowledge the first Nickel complex structure obtained with calcimycin. Furthermore, the Ni²⁺ complex studied shows an unusual supramolecular scaffold compared with known calcimycin Ca²⁺, Mg²⁺ and Fe²⁺ dimeric arrangements and with other described carboxylate zinc complexes. As recently stated,¹⁴ zinc homeostasis studies in higher animals and humans have proved difficult. This work may therefore help gain a better understanding of the difference in mechanism of cellular transport of zinc and nickel through biological membranes.

Acknowledgements

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Experimental Section

Preparation. A solution of calcimycin free acid (2 mmol) in CH₂Cl₂ (20 mL) was stirred with aqueous solution of NiCl₂·6H₂O (50 mL). The pH of (H₂O / CH₂Cl₂) solution containing organic ligand and metallic precursor was adjusted to *ca.* 10.5 by addition of tetrabutylammonium hydroxide. The mixture was stirred at 20°C for 4 h under atmospheric pressure in the dark. The organic layer was then dried over anhydrous Na₂SO₄, filtered and evaporated. The solid residue was dissolved in MeOH and the solvent was left to evaporate at 20 °C for 2 week in the dark. Pale green crystals obtained proved suitable for X-ray analysis.

Crystal structure analysis

The crystal structure of the title compound has been determined at room temperature. Data were collected using a Bruker SMART APEX-II CCD diffractometer system, using graphite-

monochromated MoK α radiation. Molecules crystallize in the orthorhombic space group P 2₁ 2₁ 2₁.

The crystallographic details are given in Table 1. The structure was solved by direct methods by using SIR-97 program¹¹ and refined by least-squares on F_{obs}² in SHELXL-97 program.¹² All H atoms bonded to C and N were inserted at calculated positions and refined using a riding model. The isotropic displacement parameters for H atoms were assigned $U_{\text{iso}}(\text{H}) = 1.2U_{\text{eq}}$ or $1.5U_{\text{eq}}$ (carrier atom). A displacement ellipsoid plot with the atomic numbering scheme of the title compound is shown in Figure 2; with selected bond angles and hydrogen-bond parameters in Tables 2 and 3.

The structure shows an approximately octahedral coordination pattern for the Ni^{II} atom. The mean Ni—N and Ni—O distances are 2.0635 (7) and 2.0475(5) Å. These distances in agreement with values reported previously for Ni^{II} complexes.¹⁵ The Flack parameter is 0.01 (2), thus the absolute configuration is determined reliably.¹⁶ The piperidine rings adopts a chair conformation and 3,4-dihydro-2H-pyrrole rings are planar. The molecular structure of the title compound is stabilized by intramolecular N—H...O intermolecular interactions (Table 3).

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