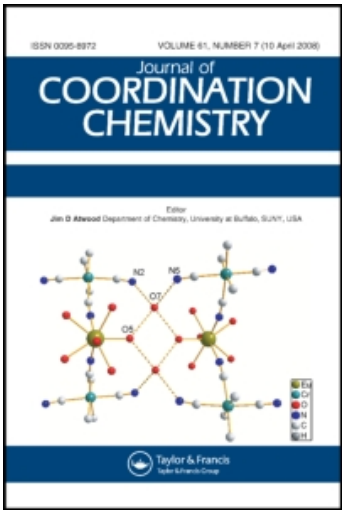


Journal of Coordination Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713455674

Hydrothermal synthesis, crystal structure and antibacterial studies of nickel(II) and manganese(II) complexes with ciprofloxacin

Liang-Cai Yu[ab]; Zhen-Feng Chen[a]; Hong Liang[ab]; Chun-Shan Zhou[b]; Hoong-Kun Fun[c]
[a] College of Chemistry & Chemical Engineering of Guangxi Normal University, Guilin 541004, P.R. China [b] College of Chemistry & Chemical Engineering of Central-South University, Changsha 410012, P.R. China [c] X-ray Crystallography Unit, School of Physics, Universiti Sains Malaysia, Penang, Malaysia

To cite this Article Yu, Liang-Cai , Chen, Zhen-Feng , Liang, Hong , Zhou, Chun-Shan and Fun, Hoong-Kun(2006) 'Hydrothermal synthesis, crystal structure and antibacterial studies of nickel(II) and manganese(II) complexes with ciprofloxacin', Journal of Coordination Chemistry, 59: 9, 953 — 959
To link to this Article: DOI: 10.1080/00958970500438136
URL: http://dx.doi.org/10.1080/00958970500438136

Journal of Coordination Chemistry
Vol. 59, No. 9, 15 June 2006, 953–959

Taylor & Francis
Taylor & Francis Group

Hydrothermal synthesis, crystal structure and antibacterial studies of nickel(II) and manganese(II) complexes with ciprofloxacin

LIANG-CAI YU†‡, ZHEN-FENG CHEN†, HONG LIANG*†‡, CHUN-SHAN ZHOU‡ and HOONG-KUN FUN§

†College of Chemistry & Chemical Engineering of Guangxi Normal University, Guilin 541004, P.R. China
‡College of Chemistry & Chemical Engineering of Central-South University, Changsha 410012, P.R. China
§X-ray Crystallography Unit, School of Physics, Universiti Sains Malaysia, 11800 USM, Penang, Malaysia

(*Received 5 April 2005; in final form 19 July 2005*)

Hydrothermal treatments of ciprofloxacin with $Ni(NO_3)_2 \cdot 6H_2O$ and $Mn(ClO_4)_2 \cdot 6H_2O$ yield two metal complexes: $[Ni(H\text{-}cip)_2(H_2O)_2](NO_3)_2 \cdot 2H_2O$ (**1**) and $[Mn(H\text{-}cip)_2(H_2O)_2](ClO_4)_2 \cdot 2H_2O$ (**2**), confirmed by elemental analysis, IR and single crystal X-ray diffraction analyses. Complexes **1** and **2** were screened for antibacterial activity against *Staphylococcus aureas*, *E. coli*, *Pseudomonas aeruginos* and *Candidaalbicans*.

Keywords: Nickel(II); Manganese(II); Ciprofloxacin; Hydrothermal synthesis; Crystal structure; Antibacterial activity

1. Introduction

Quinolone represents a large family of synthetic antibacterial agents, which inhibit two important bacterial enzymes, viz., DNA gyrase and topoisomerases and are characterized by a broad-spectrum antibacterial activity [1–3]. The most active representatives of this class of compounds, designated as ''fluoroquinolones'', include norfloxacin, ofloxacin, enoxacin, perfloxacin and ciprofloxacin [H-cip = 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinoline carboxylic acid]. Many drugs possess modified pharmacological and toxicological properties when administered in the form of metallic complexes. Recently, studies on the biological activity of quinolone-based metal complexes have appeared [4, 5]. In the last few years,

*Corresponding author. Email: chenzfgxnu@yahoo.com

Journal of Coordination Chemistry
ISSN 0095-8972 print: ISSN 1029-0389 online © 2006 Taylor & Francis
DOI: 10.1080/00958970500438136

we have studied the structural and chemical behavior of several complexes of norfloxacin with magnesium, calcium [6], zinc [7], copper [8], manganese [9], iron [10], lead [11], vanadium [12] and silver [13] ions. Till now, the reports on the crystal structures of ciprofloxacin directly chelated to transition metals are rare [14–20]. As a continuation of our work on metal interactions with 4-quinolone derivatives, we report here the syntheses, crystal structures of two metal complexes, $[Ni(H\text{-}cip)_2(H_2O)_2](NO_3)_2 \cdot 2H_2O$ (**1**) and $[Mn(H\text{-}cip)_2(H_2O)_2](ClO_4)_2 \cdot 2H_2O$ (**2**), and their activity against certain bacteria.

2. Experimental

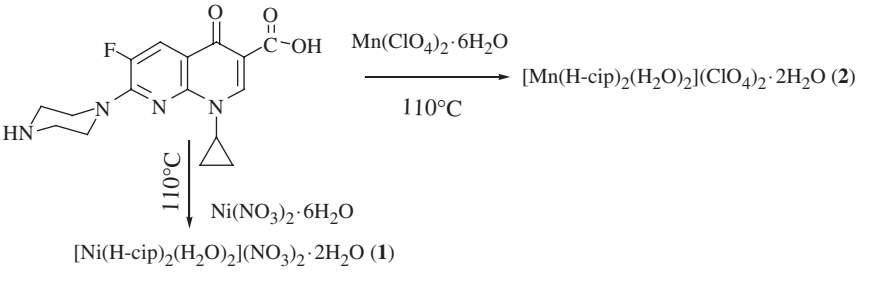
2.1. *Materials and physical measurements*

Ciprofloxacin was purchased from Fluka. All reagents used were of analytical grade. Elemental analyses were performed on a Perkin-Elmer analyzer model 240II. IR spectra were recorded as KBr discs on a Perkin-Elmer spectrophotometer (Model Spectrum One FT-IR) in the 4000–400 cm^{-1} region.

2.2. *Synthesis of the complexes*

The green block crystalline **1** and light yellow block crystalline **2** were obtained by the hydrothermal reactions of ciprofloxacin with $Ni(NO_3)_2 \cdot 6H_2O$, $Mn(ClO_4)_2 \cdot 6H_2O$, respectively (scheme 1).

2.2.1. $[Ni(H\text{-}cip)_2(H_2O)_2](NO_3)_2 \cdot 2H_2O$ (1). 0.2 mmol $Ni(NO_3)_2(6H_2O$ and 0.4 mmol of ciprofloxacin were thoroughly mixed, then placed in thick-walled Pyrex tubes (ca. 20 cm long). After addition of 0.5 mL of ethanol and 1.5 mL of H_2O, the tube was frozen with liquid N_2, evacuated under vacuum and sealed with a torch. The tube was heated at 110°C for one day to give green block crystals. Yield: 50%. (Found: C, 44.61; H, 4.76; N, 12.34. $C_{34}H_{44}F_2N_8O_{16}Ni$ Calcd: C, 44.51; H, 4.83; N, 12.21%.) IR (KBr, cm^{-1}): 3458(w), 3272(m), 3085(m), 2903(w), 2502(w), 1619(s), 1561(s), 1546(m), 1492(s), 1451(s), 1417(m), 1399(m), 1384(s), 1356(w), 1336(w), 1304(s), 1275(s), 1257(m), 1200(w), 1179(w), 1147(w), 1133(w), 1110(m), 1035(w), 945(m), 933(w), 916(w), 899(m), 839(w), 819(m), 791(w), 748(m), 711(w), 661(w), 629(w), 572(w), 541(w), 507(w).



Scheme 1. The reaction conditions of **1** and **2**.

2.2.2. $[Mn(H\text{-}cip)_2(H_2O)_2](ClO_4)_2\cdot 2H_2O$ (2). Complex **2** was prepared by the same procedure as **1** except that $Mn(ClO_4)_2\cdot 6H_2O$ was used. Yellow block crystals of **2** were obtained. Yield: 50%. (Found: C, 41.42; H, 4.56; N, 8.57. $C_{34}H_{44}Cl_2F_2N_6O_{18}Mn$ Calcd: C, 41.31; H, 4.49; N, 8.50%.) IR (KBr, cm^{-1}): 3462(m), 3075(w), 2975(w), 2840(w), 2522(w), 1624(s), 1560(s), 1490(s), 1453(m), 1397(m), 1387(m), 1356(w), 1336(w), 1300(s), 1276(s), 1224(w), 1180(w), 1147(w), 1112(m), 1088(s), 1027(w), 943(m), 921(w), 894(w), 862(w), 837(w), 820(m), 791(w), 741(m), 713(w), 663(w), 626(m), 568(w), 553(w), 541(w), 505(w), 478(w), 442(w), 411(w).

2.3. *X-ray structural determination*

Crystals of dimensions ca. $0.40\times 0.22\times 0.20$ mm for complex **1** and $0.50\times 0.40\times 0.16$ mm for complex **2** were selected and mounted on a Bruker Smart CCD diffractometer with graphite monochromatized Mo-$K\alpha$ radiation ($\lambda = 0.71073$ Å). Diffraction data were collected using ω–2θ scans at room temperature (293 K). LP correction was applied to the data. The crystal data and refinement details are summarized in table 1.

Both structures were solved by direct methods using the SHELXS-97 program. Refinement on F^2 was performed using SHELXL-97 by full-matrix least-squares with anisotropic thermal parameters for all non-hydrogen atoms [21, 22]. All hydrogen atom positions were fixed geometrically at calculated distances and allowed to ride on

Table 1. Crystal data and details of structural determination of **1** and **2**.

Complex	**1**	**2**
Empirical formula	$C_{34}H_{44}F_2N_8NiO_{16}$	$C_{34}H_{44}Cl_2F_2MnN_6O_{18}$
Crystal system	Triclinic	Triclinic
Space group	$P\bar{1}$	$P\bar{1}$
a (Å)	9.2845(18)	9.9838(8)
b (Å)	10.040(2)	10.0330(8)
c (Å)	11.935(2)	12.5201(10)
α (°)	76.633(3)	74.4470(10)
β (°)	77.992(4)	75.0540(10)
γ (°)	63.766(3)	62.2030(10)
V (Å^3)	963.8(3)	1055.70(15)
Z	1	1
Calculated density (Mg m^{-3})	1.581	1.555
F(0 0 0)	478	511
μ (Mo-$K\alpha$) (mm^{-1})	0.599	0.530
θ range (°)	2.29 to 28.27	2.33 to 28.27
Limiting indices	$-7\le h\le 12$, $-13\le k\le 13$, $-15\le l\le 15$	$-13\le h\le 12$, $-9\le k\le 13$, $-14\le l\le 16$
Total reflections	6131	6596
Independent reflections	4541 [R(int) = 0.0143]	4935 [R(int) = 0.0126]
Data/restraints/parameters	4541/0/365	4935/0/358
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Weighting scheme	$w = 1/[\sigma^2(F_o^2)+(0.0831P)^2+0.6985P]$ $P=(F_o^2+2F_c^2)/3$	$w = 1/[\sigma^2(F_o^2)+(0.0443P)^2+0.4722P]$ $P=(F_o^2+2F_c^2)/3$
Final R indices ($I > 2\sigma(I)$)	0.0427, 0.0977	0.0500, 0.1422
R indices (all data)	0.0524, 0.1025	0.0582, 0.1512
Goodness-of-fit on F^2	1.097	1.060
Largest difference peak and hole (e Å^{-3})	0.538 and −0.366	0.691 and −0.454

Table 2. Selected bond lengths (Å) and bond angles (°) for $[Ni(H\text{-}cip)_2(H_2O)_2](NO_3)_2 \cdot 2H_2O$ (**1**).

Ni(1)–O(1)	2.0161(14)	Ni(1)–O(1W)	2.084(2)
Ni(1)–O(2)	2.0207(14)		
O1–Ni1–O1	180.0(1)	O1–Ni1–O1	180.0(1)
O1–Ni1–O2	88.45(6)	O1–Ni1–O1W	91.80(7)
O1–Ni1–O1W	88.20(7)	O2–Ni1–O1W	90.40(8)
O2–Ni1–O1W	90.40(8)		

Table 3. Selected bond lengths (Å) and bond angles (°) for $[Mn(H\text{-}cip)_2(H_2O)_2](ClO_4)_2 \cdot 2H_2O$ (**2**).

Mn1–O2	2.1195(16)	Mn1–O1	2.1469(15)
Mn1–O1W	2.195(2)		
O2–Mn1–O2	180.000(1)	O2–Mn1–O1	82.93(6)
O2–Mn1–O1W	89.40(9)	O2–Mn1–O1W	89.40(9)
O2–Mn1–O1W	89.40(9)	O2–Mn1–O1W	90.60(9)
O1–Mn1–O1W	90.06(8)	O1–Mn1–O1W	89.94(8)

Table 4. Comparative *in vitro* activities of three tested compounds against four bacteria.[a]

	Final concentrations of the tested substances ($\mu g\,mL^{-1}$)								
	Ciprofloxacin			**1**			**2**		
	0.5	0.25	0.125	0.5	0.25	0.125	0.5	0.25	0.125
Staphylococcus aureas	23	21	19	–	–	–	22	20	19
E. coli	36	33	31	17	11	–	34	31	29
Pseudomonas aeruginos	27	24	21	–	–	–	27	25	23
Candidaalbicans	12	10	9	11	10	8	10	9	7

[a] "–" denoting that the complexes have no antibacterial activity. **1** = $[Ni(H\text{-}cip)_2(H_2O)_2](NO_3)_2 \cdot 2H_2O$, **2** = $[Mn(H\text{-}cip)_2(H_2O)_2](ClO_4)_2 \cdot 2H_2O$.

the parent carbon atoms. Selected bond lengths and angles are presented in tables 2 and 3, respectively.

2.3.1. Antibacterial tests. The complexes were suspended into distilled water, and the orbicular filter scrip method was used for testing all samples. The process is similar to that of antibacterial tests of bismuth(III)-quinolone against *Helicobacter pylori* and some other bacteria [23, 24].

All tested strains (*Streptococcus haemolyticus*, *Straphyloccus aureus*, *Escherichia coli* and *Pseudomonas aeruginosa*) were freshly isolated from clinical material and dissolved in 15 mL of sterilized agar culture media at 40°C, and were incoculated to sterilized culture dish. After being stirred to homodisperse, kept horizontal, and cooled, the culture medium of strains were obtained.

The suspensions of the complexes and orbicular filter scrip with diameter of 6 mm were sterilized at 120°C and under high pressure. The minimum of suspensions were dropped in filter scrip, and put into a culture dish containing culture medium of strains after drying at room temperature. Then the culture dish was placed into a culture box at 37°C for 18 h. The results showed the average ranges (mm) of inhibiting bacteria and are listed in table 4.

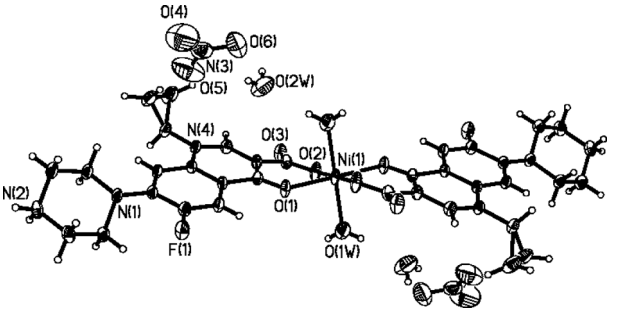


Figure 1. ORTEP view of $[Ni(cip)_2(H_2O)_2](NO_3)_2 \cdot 2H_2O$ (**1**). The thermal ellipsoids are drawn at 50% probability level.

3. Result and discussion

3.1. *Crystal structure of $[Ni(H\text{-}cip)_2(H_2O)_2](NO_3)_2 \cdot 2H_2O$ (1)*

The molecular structure is shown in figure 1. Similar to $Zn(H\text{-}Norf) \cdot (NO_3) \cdot 2H_2O$ [7], the crystal structure of **1** is mononuclear, with Ni^{2+} in a distorted octahedral coordination environment with an equatorial plane composed of four O atoms, two from the quinolone ring and the other two from carboxylate forming a stable six-membered chelate ring, and two water molecules occupying apical positions. Due to two hydrogen atoms attached to N2, the protonated N atom of the piperidyl ring has no coordination capacity, H-cip is a typical zwitterion in **1**. The NO_3^- remains uncoordinated as counterion. The bond distances of Ni1–O1 and Ni1–O2 are very close, 2.0161 and 2.0207 Å, respectively; the bond distance of Ni1–O1W is 2.084 Å, slightly longer than that of Ni1–O1. The angles O1–Ni1–O2 and O1–Ni1–O1W vary from 88.2 to 91.8°, slight deviation from the normal value of 90°. Bond distances and angles of ciprofloxacin ligand are within normal ranges [25]. Hydrogen bonds weave **1** into a very complicated network, all possible donor hydrogens participate actively, lattice water, aqua ligands, the protonated amino group, and the uncoordinated carboxylate O atoms.

3.2. *Crystal structure of $[Mn(H\text{-}cip)_2(H_2O)_2](ClO_4)_2 \cdot 2H_2O$ (2)*

The crystal structure of **2** is very similar to that of **1**. The environment around Mn(II) in **2** is also a slightly distorted octahedron (figure 2). Two ClO_4^- anions remained uncoordinated. The apical positions are occupied by two water molecules, resulting in a monomer. H-cip is a typical zwitterion in **2**. The geometric parameters involved in coordination environment of Mn(II) are comparable to those of $[Mn(H\text{-}Norf)_2 \cdot H_2O](ClO_4)_2$ [9].

3.3. *Spectroscopic properties*

The IR spectra show two very strong peaks at 1619 and 1492 cm^{-1}, for **1**, and two very strong peaks at 1624 and 1490 cm^{-1}, for **2**, indicating that the carboxylic acid of ciprofloxacin is deprotonated and coordinates to the metal ions due to the absence of a strong ν(COOH) band above 1700 cm^{-1} for free ciprofloxacin [25]. A strong and broad peak at 1304 cm^{-1} for **1** indicates the presence of uncoordinated NO_3^-

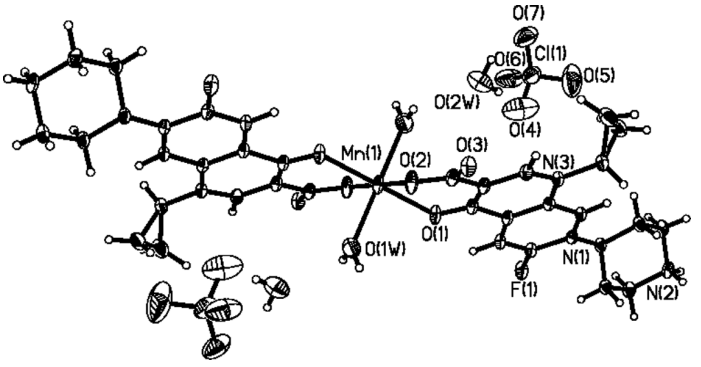


Figure 2. ORTEP view of $[Mn(cip)_2(H_2O)_2](ClO_4)_2 \cdot 2H_2O$ (**2**). The thermal ellipsoids are drawn at 50% probability level.

anion in **1**, and a similar peak at $1088\,cm^{-1}$ for **2** indicates the presence of uncoordinated ClO_4^- anion in **2**.

3.4. *Antibacterial activities*

As shown in table 4, the activity of compound **2** was similar to that of ciprofloxacin; **2** exhibits almost the same antibacterial abilities as ciprofloxacin against *Staphylococcus aureas*, *E. coli*, *Candidaalbicans*. Nevertheless, **2** showed stronger activity than ciprofloxacin against *Pseudomonas aeruginos* at lower concentration. Similar to $Ni(cip)_2 \cdot 10H_2O$ [15], **1** is significantly less active than ciprofloxacin, and even inactive against *Staphylococcus aureas* and *Pseudomonas aeruginos*. It is difficult to compare these results for the antibacterial activity with those reported by other authors because of the different methodology and strains assayed. In general, the action mechanism proposed that the transition metal complex with quinolones interferes with the transport of substrates and ions through the cell membrane resulting in antibacterial activity [16]. The synergistic enhancement of the ligand activity upon metal coordination from increased liposolubility of the ligand may contribute to the facile transport into the bacterial cell [14]. The better activity of complex **2** than **1** may be related to the Irving-Williams series of the stability of transition metal complexes. However, at this stage it is impossible to find a simple explanation for the antibacterial effect of metal-ciprofloxacin complexes and further studies will be needed to elucidate this phenomenon [16].

Supplementary material

Crystallographic data for the structures of **1** and **2** have been deposited with the Cambridge Crystallographic Data Center and assigned No. CCDC245755 and CCD245756, respectively.

Acknowledgements

The authors thank the National Natural Science Foundation of China (No. 20361002, 30460153), the Youth Science Foundation of Guangxi (No. 0135002), the Natural

Science Foundation of Guangxi (No. 0229003), and the Support Program for 100 Young and Middle-aged Disciplinary Leaders in Guangxi Higher Education Institutions of the People's Republic of China, and the Teaching and Research Award Program for Outstanding Young Teachers in Higher Education Institutions of Chinese Ministry of Education as well as supported by Program for New Century Excellent Talents in University of Chinese Ministry of Education (NCET-04-0836).

References

[1] M. Gellet, K. Mizuuchi, M.H. O'Dea, H.A. Nash. *Proc. Natl. Acad. Sci., USA*, **73**, 3872 (1976).
[2] T.D. Gootz, J.F. Larrent, J.A. Suteliffe. *Antimicrob. Agent Chemother.*, **34**, 8 (1990).
[3] K. Hoshino, A. Kitamura, I. Morrissey, K. Sato, J. Kato, H. Ikeda. *Antimicrob. Agents Chemother.*, **38**, 2623 (1994).
[4] M. Ruíz, L. Perelló, R. Ortiñeiras, C. Maichle-Mössmer, E. Cantó. *J. Inorg. Biochem.*, **59**, 801 (1995).
[5] M. Ruíz, L. Perelló, J. Server-Carrió, R. Ortiz, S. García-Granda, M.R. Díaz, E. Cantó. *J. Inorg. Biochem.*, **69**, 231 (1998).
[6] Z.-F. Chen, R.-G. Xiong, J.-L. Zuo, Z. Guo, X.-Z. You, H.-K. Fun. *J. Chem. Soc., Dalton Trans.*, 4013 (2001).
[7] Z.-F. Chen, R.-G. Xiong, J. Zhang, X.-T. Chen, Z.-L. Xue, X.-Z. You. *Inorg. Chem.*, **40**, 4075 (2001).
[8] Z.-F. Chen, B.-Q. Li, Y.-R. Xie, R.-G. Xiong, X.-Z. You, X.-L. Feng. *Inorg. Chem. Commun.*, **4**, 36 (2001).
[9] L.-Z. Wang, Z.-F. Chen, X.-S. Wang, Y.-H. Li, R.-G. Xiong, X.-Z. You. *Chinese J. Inorg. Chem.*, **18**, 1185 (2002).
[10] Z.-R. Qu, H. Zhang, L.-X. Xing, X.-S. Wang, Z.-F. Chen, Z. Yu, R.-G. Xiong, X.-Z. You. *Eur. J. Inorg. Chem.*, 2920 (2003).
[11] Z.-F. Chen, H.-L. Zou, H. Liang, Y. Li, R.-G. Xiong, X.-Z. You. *Appl. Organometal. Chem.*, **17**, 883 (2003).
[12] Z.-F. Chen, H. Liang, H.-M. Hu, Y. Li, R.-G. Xiong, X.-Z. You. *Inorg. Chem. Commun.*, **6**, 241 (2003).
[13] Y.-X. Li, Z.-F. Chen, R.-G. Xiong, Z. Xue, H.-X. Ju, X.-Z. You. *Inorg. Chem. Commun.*, **6**, 819 (2003).
[14] D.K. Saha, S. Padhye, C.E. Anson, A.K. Powell. *Inorg. Chem. Commun.*, **5**, 1022 (2002).
[15] M.P. López-Grea, R. Ortiz, L. Perelló, J. Latorre, M. Liu-González, S. García-Granda, M. Pérez-Priede, E. Cantón. *J. Inorg. Biochem.*, **92**, 65 (2002).
[16] I. Turel, A. Golobič, A. Klavžar, B. Philar, P. Buglyó, E. Tolis, D. Rehder, K. Sepčić. *J. Inorg. Bichem.*, **95**, 199 (2003).
[17] I. Turel, L. Golič, O.L.R. Ramirez. *Acta Chim. Slov.*, **46**, 203 (1999).
[18] S.C. Wallis, L.R. Gahan, B.G. Charles, T.W. Hambley, P.A. Duckworth. *J. Inorg. Biochem.*, **62**, 1 (1996).
[19] S.C. Wallis, L.R. Gahan, B. Charles, T.W. Hambley. *Polyhedron*, **14**, 2835 (1995).
[20] I. Turel. *Coord. Chem. Rev.*, **232**, 27 (2002).
[21] G.M. Sheldrick. *SHELXS-97*, *Program Used to Solve Structure*, Göttingen University, Göttingen (1997).
[22] G. M. Sheldrick. *SHELXl-97*, *Program Used to Refine Structure*, Göttingen University, Göttingen (1997).
[23] I. Turel, L. Golič, P. Bukovec, M. Gubina. *J. Inorg. Biochem.*, **71**, 53 (1998).
[24] Z.-F. Chen, S.-M. Shi, R.-X. Hu, M. Zhang, H. Liang, Z.-Y. Zhou. *Chinese J. Chem.*, **21**, 1059 (2003).
[25] I. Turel, P. Bukovec, M. Quirós. *Int. J. Pharm.*, **152**, 59 (1997).