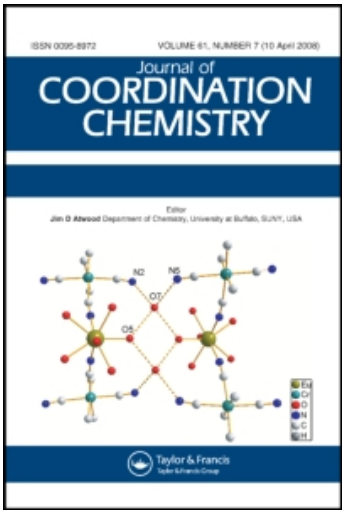

Journal of Coordination Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713455674

Crystal structures and antibacterial activities of two enoxacin based compounds

Liang-Cai Yu[a]; Zi-Long Tang[a]; Pin-Gui Yi[a]; Sheng-Li Liu[a]; Xia Li[a]
[a] College of Chemistry & Chemical Engineering of Hunan University of Science and Technology, Xiangtan 411201, P.R. China

To cite this Article Yu, Liang-Cai , Tang, Zi-Long , Yi, Pin-Gui , Liu, Sheng-Li and Li, Xia(2009) 'Crystal structures and antibacterial activities of two enoxacin based compounds', Journal of Coordination Chemistry, 62: 6, 903 — 910
To link to this Article: DOI: 10.1080/00958970802366308
URL: http://dx.doi.org/10.1080/00958970802366308

Journal of Coordination Chemistry
Vol. 62, No. 6, 20 March 2009, 903–910

Taylor & Francis
Taylor & Francis Group

Crystal structures and antibacterial activities of two enoxacin based compounds

LIANG-CAI YU*, ZI-LONG TANG, PIN-GUI YI, SHENG-LI LIU and XIA LI

College of Chemistry & Chemical Engineering of Hunan University of Science and Technology, Xiangtan 411201, P.R. China

(*Received 16 May 2007; in final form 9 June 2008*)

Hydrothermal reactions of $Cu(ClO_4)_2 \cdot 6H_2O$ and $Cu(SO_4)_2 \cdot 5H_2O$ with enoxacin yielded two compounds, $(H_2\text{-Eno}) \cdot ClO_4$ (**1**) and $[Cu(H\text{-Eno}) \cdot (H_2O)_2 \cdot SO_4] \cdot 2H_2O$ (**2**). Their solid-state structures have been characterized by elemental analysis, IR spectroscopy and single crystal X-ray diffraction analyses. Compounds **1** and **2** were screened for antibacterial activity against *Staphylococcus aureas*, *Escherichia coli*, *Pseudomonas aeruginos* and *Candida albicans*.

Keywords: Enoxacin; Crystal structure; Hydrothermal syntheses; Copper complex; Enoxacin perchlorate

1. Introduction

The quinolones are a group of synthetic antibacterial agents structurally related to nalidixic acid, which is very active against aerobic Gram-negative microorganisms, but less active against Gram-positive microorganisms [1]. They are extremely useful for the treatment of a variety of infections, including urinary tract infections, soft tissue infections, respiratory infections, bone-joint infections, sexually transmitted diseases, prostatitis, acute bronchitis and sinusitis [1]. The most active representatives of this class of compounds, designated as ''fluoroquinolones,'' include ciprofloxacin, norfloxacin, enoxacin and perfloxacin. Enoxacin based organic compounds have been prepared [2, 3] and the metal complexes with quinolones have been extensively reported [4–22]. Cu(II) complexes are effective in induction of cytotoxicity of quinolones against *leukemia in vitro*, whereas Mg(II) complex was not effective. In previous papers, we have described the syntheses and crystal structures of four metal complexes of the fluoroquinolone class [23–25]; reports on crystal structures of enoxacin chelated to transition metals are rare. In order to continue our work on metal interactions with 4-quinolone derivatives, we report here the syntheses and crystal structures of $(H_2\text{-Eno}) \cdot ClO_4$ (**1**) and $[Cu(H\text{-Eno}) \cdot (H_2O)_2 \cdot SO_4] \cdot 2H_2O$ (**2**), and their activity against certain bacteria.

*Corresponding author. Email: ylcphd@gmail.com

Journal of Coordination Chemistry
ISSN 0095-8972 print/ISSN 1029-0389 online © 2009 Taylor & Francis
DOI: 10.1080/00958970802366308

2. Experimental

2.1. *Materials and apparatus*

Enoxacin was purchased from Fluka, and all other chemicals were purchased and used as received without purification. All solvents were of analytical grade. C, H and N data were obtained using an American PE 2400 II CHNS/O elemental analyzer. Infrared spectra were measured as KBr pellets using a Nicolet 5DXB system.

2.1.1. (H_2-Eno)·ClO_4 (1). Samples of enoxacin (1 mmol, 0.3350 g) and $Cu(ClO_4)_2$ (0.5 mmol, 0.132 g) were thoroughly mixed and placed in an autoclave. After addition of 5 mL of EtOH and 15 mL of H_2O, the pH was adjusted to 5.0 with $HClO_4$ and the autoclave was heated to 110°C for 3 days to give pale yellow crystals of **1**. Anal. Calcd for C_{15} $H_{18}ClFN_4O_7$: C, 42.78; H, 4.28; N, 13.31. Found: C, 42.82; H, 4.31; N, 13.28. IR data: (KBr pellet, cm^{-1}), 3449(s), 2935(s), 2785(m), 2455(m), 2346(m), 1725(s), 1631(s), 1582(m), 1556(m), 1467(s), 1425(s), 1373(s), 1354(s), 1267(s), 1243(m), 1207(m), 1117(s), 1077(s), 1020(s), 966(m), 937(m), 904(m), 861(w), 807(s), 744(m), 680(m), 625(s), 570(m), 497(m), 470(m).

2.1.2. [Cu(H-Eno)·$(H_2O)_2$·SO_4]·$2H_2O$ (2). An aqueous mixture (15 mL) containing enoxacin (1 mmol) and $Cu(SO_4)_2 \cdot 5H_2O$ (1 mmol) was placed in a Teflon-lined stainless steel vessel (25 mL). Ethanol (5.0 mL) was added to the mixture, and the pH of the solution was adjusted to 7.0. The vessel was sealed and heated to 110°C for 4 days. Upon cooling to room temperature, blue, block-shaped crystals of **3** were obtained. Anal. Calcd for $C_{15}H_{22}CuFN_4O_{11}S$: C, 32.78; H, 4.00; N, 10.20. Found: C, 32.92; H, 4.03; N, 9.89. IR data: (KBr pellet, cm^{-1}), 3409(s), 1634(s), 1575(m), 1554(m), 1524(w), 1479(s), 1455(s), 1368(m), 1316(w), 1280(m), 1120(s), 1090(s), 950(m), 811(m), 794(w), 774(w), 750(w), 730(w), 618(w), 516(w).

2.2. *Crystal structure determination and antibacterial tests*

Structure determinations and antibacterial studies were done by the procedures in the preceding manuscript. The H atoms of lattice of water molecules in **2** cannot be located. The absolute structure parameter of **2** is −0.017(16). For the crystal data, see table 1.

3. Results and discussion

3.1. *Spectroscopic properties*

The IR spectrum of **1** shows a strong peak at 1725 cm^{-1} indicating that the carboxylic acid of the quinolone is protonated and a strong and broad peak at 1090 cm^{-1} indicates the presence of uncoordinated ClO_4^-. For **2**, two very strong peaks at 1634 and 1479 cm^{-1} indicate deprotonated carboxylic acid of quinolone coordinated to copper (due to the absence of a strong ν(COOH) band at 1725 cm^{-1} for enoxacin), and a peak at 1280 cm^{-1} for **2** indicates the presence of coordinated SO_4^{2-}.

Table 1. Summary of crystallographic data for **1** and **2**.

Parameter	**1**	**2**
Empirical formula	$C_{15}H_{18}ClFN_4O_7$	$C_{15}H_{22}CuFN_4O_{11}S$
Formula weight	420.78	548.97
Crystal system	Triclinic	Monoclinic
Space group	$P\bar{1}$	Cc
Crystal size (mm^3)	$0.22 \times 0.21 \times 0.19$	$0.50 \times 0.16 \times 0.06$
V ($Å^3$)	888.93(8)	2024.7(3)
Z	2	4
T(K)	296(2)	296(2)
2θ range for data collection (°)	4.06–52.02	3.82–52.02
Units of dimensions (Å, °)		
a	7.1246(4)	13.0892(6)
b	10.1965(5)	21.3679(8)
c	12.5661(7)	7.3735(8)
α	79.481(4)	90
β	82.201(4)	100.9590(10)
γ	87.122(4)	90
Data/restraints/parameters	3477/0/255	3206/4/309
Reflections collected/unique	7874/3477	6032/3206
Max shift (Su)	0.000	0.002
Final R indices [$I > 2\sigma(I)$]	0.0434, 0.1184	0.0521, 0.1307
R indices (all data)	0.0565, 0.1287	0.0533, 0.1319
Completeness	99.4%	98.5%
D_{Calcd} ($mg\,m^{-3}$)	1.572	1.801
F(000)	436	1128
Absorption coefficient (mm^{-1})	0.274	1.262
Max. and Min. transmission	0.9497, 0.9421	0.9281, 0.5711
Index ranges	$-8 \le h \le 8$, $-12 \le k \le 12$, $-15 \le l \le 15$	$-13 \le h \le 15$, $-15 \le k \le 25$, $-8 \le l \le 8$
Largest diff. peak and hole ($e\,Å^{-3}$)	0.254, −0.305	0.767, −0.645
Goodness-of-fit on F^2	1.062	1.070

3.2. *Crystal structures*

1 is composed of a cation involving a protonated quinolone and perchlorate anion (see figure 1). The bicyclic naphthyridine system is essentially planar, whereas the piperazine ring has a chair conformation. H_2-Eno is a cation with two hydrogens attached to N4 which are clearly seen in the ΔF maps; the carboxyl group is protonated. The ethyl group plane (C10, C11 and N1) is almost orthogonal to the mean plane of the naphthyridine system with a dihedral angle of 81.6°. All bond distances and angles within the rigid quinolone ring system and in the piperazine ring are listed in table 2. The hydrogen bond O2–H2A···O1 involving the carboxyl OH group and the naphthyridine oxo atom forms a six-membered pseudo-ring within the cation. The piperazine NH functions as the hydrogen-bond donor to the carboxyl O linking neighboring cations in the crystal structure; it also participates in hydrogen bonds with ClO_4^- (see table 3). Interionic hydrogen bonds link the residues in the structure of **1** into a 3D network; the crystal packing of **1** is also stabilized by π–π stacking (3.562 Å) of the naphthyridine (see figure 2).

2 is composed of $[Cu(H\text{-}Eno)\cdot(H_2O)_2\cdot SO_4]$ and uncoordinated water. The coordination environment around copper(II) is slightly distorted square pyramidal. In the equatorial plane, Cu^{2+} is coordinated by four oxygens, two from one enoxacin

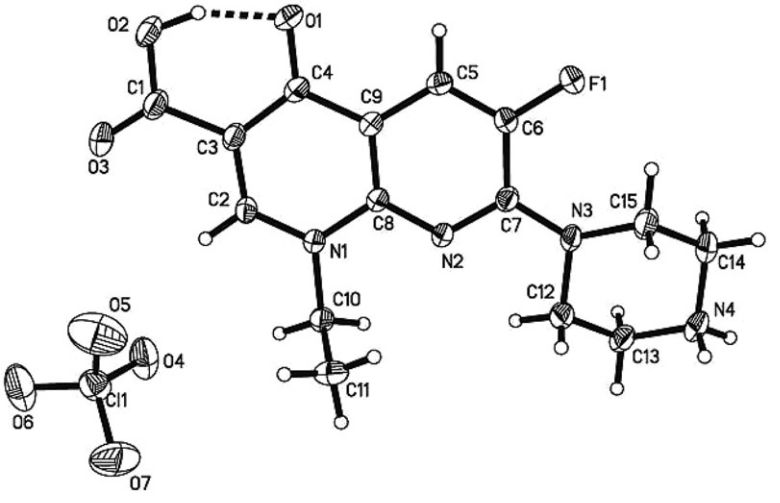

Figure 1. Thermal ellipsoid plot of **1**. The thermal ellipsoids are drawn at 30% probability.

Table 2. Selected bond lengths (°) and angles (Å) for **1** and **2**.

1			
C(1)–O(3)	1.204(3)	C(1)–O(2)	1.319(3)
C(1)–C(3)	1.490(3)	C(2)–N(1)	1.341(2)
C(2)–C(3)	1.368(3)	C(3)–C(4)	1.422(3)
C(4)–O(1)	1.282(2)	C(4)–C(9)	1.437(3)
C(9)–C(8)	1.399(3)	C(5)–C(6)	1.346(3)
C(5)–C(9)	1.404(3)	C(6)–F(1)	1.354(2)
C(6)–C(7)	1.428(3)	C(7)–N(2)	1.332(2)
C(7)–N(3)	1.366(2)	C(8)–N(2)	1.334(2)
C(8)–N(1)	1.389(2)	C(8)–C(9)	1.399(3)
C(10)–N(1)	1.489(2)	C(10)–C(11)	1.505(3)
C(12)–N(3)	1.467(3)	C(12)–C(13)	1.502(3)
O(3)–C(1)–O(2)	121.12(19)	C(2)-C(3)–C(4)	119.94(17)
O(1)–C(4)–C(9)	120.99(18)	C(5)–C(6)–F(1)	118.68(18)
N(1)–C(8)–C(9)	119.95(16)	N(1)–C(10)–C(11)	112.01(17)
C(7)–N(2)–C(8)	119.75(16)	O(7)–Cl(1)–O(4)	111.63(16)
2			
Cu(1)–O(2)	1.914(4)	Cu(1)–O(3)	1.927(4)
Cu(1)–O(4)	2.252(4)	Cu(1)–O(5)	1.956(4)
Cu(1)–O(6)	1.982(4)	O(6)–S(1)	1.503(4)
O(7)–S(1)	1.467(5)	O(8)–S(1)	1.443(5)
O(9)–S(1)	1.444(5)	O(1)–C(1)	1.237(7)
O(2)–C(1)	1.274(7)		
O(2)–Cu(1)–O(3)	93.13(16)	O(2)–Cu(1)–O(5)	173.4(2)
O(3)–Cu(1)–O(5)	88.03(17)	O(2)–Cu(1)–O(6)	86.02(16)
O(3)–Cu(1)–O(6)	168.18(18)	O(5)–Cu(1)–O(6)	91.51(18)
O(2)–Cu(1)–O(4)	91.96(17)	O(3)–Cu(1)–O(4)	102.13(17)
O(5)–Cu(1)–O(4)	94.12(19)	O(6)–Cu(1)–O(4)	89.69(18)
C(1)–O(2)–Cu(1)	130.3(4)	C(3)–O(3)–Cu(1)	126.0(3)
S(1)–O(6)–Cu(1)	124.5(3)	O(1)–C(1)–O(2)	121.8(5)

[Cu(1)–O(2) = 1.914(4) Å, Cu(1)–O(3) = 1.927(4) Å], one from SO_4^{2-} [Cu(1)–O(6) = 1.982(4) Å] and the remaining from one water [Cu(1)–O(5) = 1.956(4) Å]. The apical water molecule is coordinated at a longer distance [Cu(1)–O(4) = 2.252(4) Å] (see figure 3 and table 2). Bond lengths of O(7)–S(1), O(8)–S(1) and O(9)–S(1) are very

Table 3. Hydrogen bonds for **1**.

D–H···A	d(D–H)	d(H···A)	d(D···A)	∠(DHA)
O(2)–H(2A)···O(1)	0.82	1.68	2.448(2)	154.6
N(4)–H(4B)···O(4)#1	0.90	2.50	2.976(3)	113.6
N(4)–H(4B)···O(6)#1	0.90	1.99	2.878(3)	170.5
N(4)–H(4B)···Cl(1)#1	0.90	2.75	3.511(2)	142.9
N(4)–H(4A)···O(3)#2	0.90	2.59	3.343(3)	141.3
N(4)–H(4A)···O(2)#2	0.90	1.96	2.833(2)	162.1

Symmetry transformations used to generate equivalent atoms: #1 $x, y, z-1$; #2 $x+1, y, z-1$.

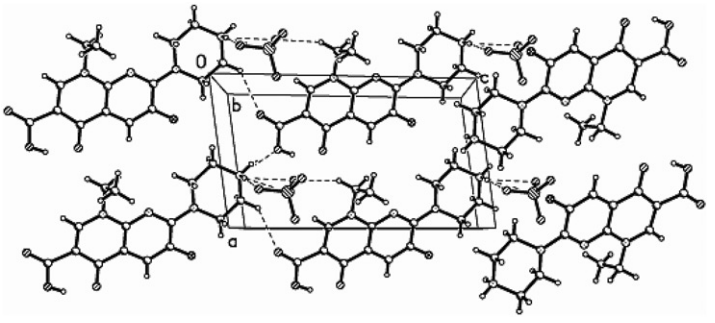

Figure 2. Crystal packing view of **1** along the b axis.

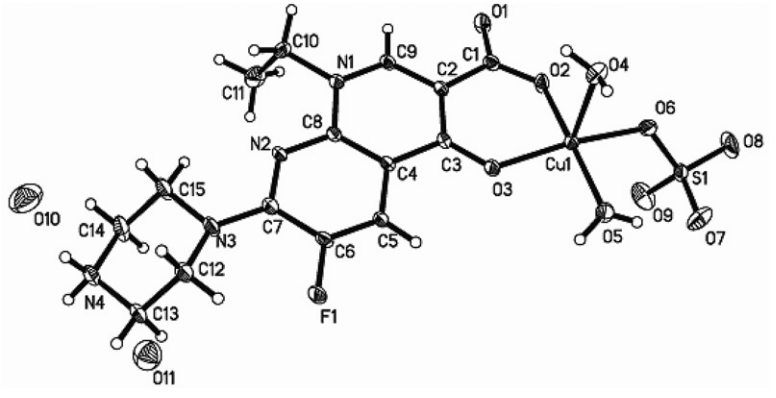

Figure 3. Thermal ellipsoid plot of **2**. The thermal ellipsoids are drawn at 30% probability.

close [1.467(5), 1.443(5) and 1.444(5) Å, respectively] and slightly shorter than that of O(6)–S(1) [1.503(4) Å]. The difference in the S–O bond distances of SO_4^{2-} confirms formation of a bond between SO_4^{2-} and copper. Differences in carboxylate distances O(1)–C(1) and O(2)–C(1) [1.274(7) and 1.237(7) Å] confirm a bond between carboxylate and copper; these bond lengths are virtually identical in the uncoordinated enoxacin ligand. The bond angles O(2)–Cu(1)–O(3), O(5)–Cu(1)–O(6), O(3)–Cu(1)–O(5), O(2)–Cu(1)–O(6), O(5)–Cu(1)–O(6), O(2)–Cu(1)–O(4), O(5)–Cu(1)–O(4) and O(6)–Cu(1)–O(4) vary from 86.02(16)° to 94.12(19)°. As in other reported compounds [2–4],

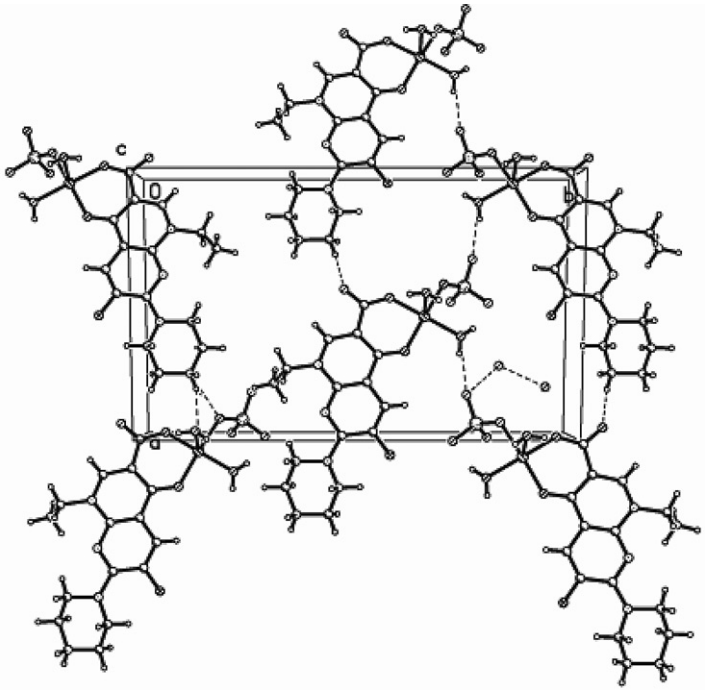

Figure 4. Crystal packing view of **2** along the c axis.

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

	Final concentrations of the tested substances ($\mu g\,mL^{-1}$)								
	Enoxacin			**1**			**2**		
	0.50	0.25	0.125	0.50	0.25	0.125	0.50	0.25	0.125
Staphylococcus aureas	23	21	19	24	22	20	23	20	19
Escherichia coli	36	33	31	37	33	32	34	32	29
Pseudomonas aeruginos	27	24	21	28	25	22	28	25	23
Candida albicans	12	10	9	13	12	10	11	9	8

enoxacin (H-Eno) is in zwitterionic form with two hydrogens attached to N4. Hydrogen bonds weave **2** into a very complicated 3-D network, all possible hydrogen donors participate actively, lattice water, coordinated water, the uncoordinated carboxylate O atoms, and the uncoordinated O atoms of SO_4^{2-}, see figure 4.

3.3. *Antibacterial activities*

As shown in table 4, the activity of **2** was similar to that of enoxacin, displaying almost the same antibacterial abilities as enoxacin against *Staphylococcus aureas*, *Escherichia coli* and *Candida albicans*; **2** showed stronger antibacterial activities against *pseudomonas aeruginos* at any concentration. Compound **1** is more soluble than

enoxacin and proves to be more bioactive against the four bacteria. It is difficult to compare these results for the antibacterial activities with those reported by other authors because of the different methodology and strains assayed. Generally, the mechanism of action is proposed that the transition metal complex with quinolones interferes with the transport of substrates and ions through the cell membrane, resulting in antibacterial activity [26]. 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 [27]. The increased activity of **1** and **2** with respect to enoxacin may be related to the different solubility. However, at this stage it as impossible to find a simple explanation for the antibacterial effect of metal-ciprofloxacin complexes and further studies will be needed to elucidate this phenomenon.

Supplementary material

Crystallographic data for **1** and **2** were deposited to the Cambridge Crystallographic Data Centre with deposition numbers CCDC 646906 and 630546, respectively.

Acknowledgement

This work was supported by the Doctor Foundation of Hunan University of Science and Technology (E55106).

References

[1] O. Paulsen. *Drugs Today*, **23**, 269 (1987).
[2] M. Parvez, S. Arayne, N. Sultana, A.Z. Siddiqic. *Acta Crystallogr., Sect. C*, **60**, o281 (2004).
[3] L. Yoon, K.M. Park, K.M. Bark, M.S. Yang, S.S. Lee. *Anal. Sci.*, **19**, x11 (2003).
[4] N. Jiménez-Garrido, L. Perelló, R. Ortiz, G. Alzuet, M. González-Alvarez, E. Cantón, M. Liu-González, S. García-Granda, M. Pérez-Priede. *J. Inorg. Biochem.*, **99**, 677 (2005).
[5] F. Gao, P. Yang, J. Xie, H. Wang. *J. Inorg. Biochem.*, **60**, 61 (1995).
[6] M. Ruiz, L. Perelló, J.S. Carrió, R. Ortiz, S.G. Grand, M.R. Díaz, E. Cantón. *J. Inorg. Biochem.*, **69**, 231 (1998).
[7] G.C. Crumplin, J.T. Smith. *Antimicrob. Agents Chemother.*, **8**, 251 (1985).
[8] D.I. Annear. *J. Antimicrob. Chemother.*, **10**, 260 (1982).
[9] E. Cantón, M.T. Jimenez, M.S. Ramón, M. Gobernado. *J. Chemother.*, **3**, 65 (1991).
[10] E. Cantón, M.S. Romón, M.T. Jimenez, J.P. Martinez. *Chemotherapy*, **39**, 394 (1993).
[11] Z.F. Chen, R.G. Xiong, J.L. Zuo, Z. Guo, X.Z. You, H.K. Fun. *J. Chem. Soc., Dalton Trans.*, 4013 (2001).
[12] Z.-F. Chen, R.-G. Xiong, J. Zhang, X.-T. Chen, Z.-L. Xue, X.-Z. You. *Inorg. Chem.*, **40**, 4075 (2001).
[13] Z.F. Chen, B.Q. Li, Y.R. Xie, R.G. Xiong, X.Z. You, X.L. Feng. *Inorg. Chem. Commun.*, **4**, 36 (2001).
[14] 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).
[15] 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).
[16] Z.F. Chen, H.L. Zou, H. Liang, Y. Li, R.G. Xiong, X.Z. You. *Appl. Organomet. Chem.*, **17**, 883 (2003).
[17] Z.F. Chen, H. Liang, H.M. Hu, Y. Li, R.G. Xiong, X.Z. You. *Inorg. Chem. Commun.*, **6**, 241 (2003).
[18] Y.X. Li, Z.F. Chen, R.G. Xiong, Z. Xue, H.X. Ju, X.Z. You. *Inorg. Chem. Commun.*, **6**, 819 (2003).

[19] D.K. Saha, S. Padhye, C.E. Anson, A.K. Powell. *Inorg. Chem. Commun.*, **5**, 1022 (2002).
[20] S.C. Wallis, L.R. Gahan, B.G. Charles, T.W. Hambley, P.A. Duckworth. *J. Inorg. Biochem.*, **62**, 1 (1996).
[21] S.C. Wallis, L.R. Gahan, B. Charles, T.W. Hambley. *Polyhedron*, **14**, 2835 (1995).
[22] I. Turel. *Coord. Chem. Rev.*, **232**, 27 (2002).
[23] L.C. Yu, Z.F. Chen, L. Hong, C.S. Zhou, H.K. Fun. *J. Coord. Chem.*, **59**, 953 (2006).
[24] L.C. Yu, Z.F. Chen, C.S. Zhou, L. Hong, Y. Li. *J. Coord. Chem.*, **58**, 1681 (2005).
[25] Z.F. Chen, L.C. Yu, M. Zhang, T. Yuan, H. Liang, H.K. Fun, Y. Zhang. *J. Coord. Chem.*, **60**, 219 (2007).
[26] I. Turel, A. Golbič, A. Klavžar, B. Philar, P. Buglyó, E. Tolis, D. Rehder, K. Sepčić. *J. Inorg. Biochem.*, **95**, 199 (2003).
[27] D.K. Saha, S. Padhye, C.E. Anson, A.K. Powell. *Inorg. Chem. Commun.*, **5**, 1022 (2002).