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THERMAL AND PHOTOCHEMICAL BEHAVIOUR OF Zn(II) COMPLEXES OF SOME CEPHALOSPORINS

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Abstract

Zn(II) complexes of some cephalosporin antibiotics namely cephalexin, cephapirin, cefamandole, cefuroxime, cefotaxime and ceftazidime were synthesised and characterized. The stoichiometrics and the mode of bonding of the complexes were deduced from their elemental analysis, IR and electronic spectroscopies. Thermal stabilities and the photochemical behaviour of the complexes were studied. The Zn(II) complex of cephalexin exhibited a high light sensitivity. The remaining Zn(II) complexes behaved similarly to their free antibiotics, upon irradiation.

Keywords: cephalosporins, photochemical behaviour, thermal stability, Zn(II) complexes

Introduction

Most pharmaceuticals contain electron donor groups likely to bind metal ions occurring naturally [1, 2]. Among these, cephalosporin antibiotics have long been known to behave as relatively efficient chelating agents [3, 4]. They are the most important class of drugs against infectious diseases caused by bacteria [5, 6] and their interactions in human body were recently studied [7]. Zinc is biologically one of the most important metals and is apparently necessary to all forms of life. The zinc content of white blood cells in human leukemia patients is reduced to 10% of the normal amount [8]. Thermal stability of drugs is the aim of many invesigations [9, 10], which can be in the study of preformulation of drugs and also as a parameter in the studies of pharmaceutical equivalence. In this context, and in continuation of our program on investigating thermal properties of coordination compounds [11–13] the present work reports on synthesis, together with thermal and photochemical studies of Zn(II) complexes of some cephalosporins. It is to be noted that the prepared complexes and those previously reported on Cu(II) and Cd(II) with such antibiotics [14] constitute a continuous series of complexes.

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Experimental

All chemicals were of analytical grade. Cephalexin (CID, Egypt) and the sodium salts of cephapirin (Bristol–Myers Squibb Co., New York), cefamandole (Eli Lilly Italia, S.P.A), cefuroxime, ceftazidime (Glaxo Wellcome, UK) and cefotaxime (Pharrco-Pharmaceutical, A. R. E.) were used as purchased. The structures of the antibiotics under investigation are given in Table 1.

Synthesis of Zn(II) complexes

The complexes were prepared by mixing the sodium salts of the antibiotics dissolved in minimum amount of distilled water (~10 mL) with an aqueous solution of $ZnCl_2$ in the molar ratios (metal:ligand) 1:1 (for cephalexin and cephapirin), 1:2 (for cefamandole, cefuroxime and cefotaxime) and 2:1 (for ceftazidime). The complexes precipitated immediately, the precipitates were filtered off, washed with 1–2 mL distilled water, acetone and diethyl ether, and finally dried under vacuum. The complexes are white or creamy. The carbon, hydrogen, nitrogen and sulfur contents of the solid complexes were determined by an Elementar Analysensysteme GmbH Vario EL analyzer.

Physical measurements

The infrared spectra were recorded as KBr pellets on a 470 Shimadzu infrared spectrophotometer. The electronic spectra were done in DMF solution on a UV-2101 PC Shimadzu spectrophotometer. The thermal studies were carried out in dynamic air (40 mL min^{-1}) on a DuPont 2000 thermal analyzer. Detailed working conditions include: heating rate of 10°C min^{-1}, temperature range from ambient to 700°C, sample mass of about 5 mg and using a flat-boat platinum crucible. The photolyses were performed on Osram HBO 200 w/2 lamp as light source. Monochromatic light was obtained using the Schott IL interference filter 298 nm. Irradiations were carried out in solutions of DMF in 1 cm spectrophotometer cells at room temperature. Progress of the photolysis was monitored by the above mentioned spectrophotometer.

Results and discussion

The complexes of Zn(II) were prepared from the following antibiotics: cephalexin, cephapirin, cefamandole, cefuroxime, cefotaxime and ceftazidime (Table 1). These complexes are readily precipitated from aqueous solutions by the interaction of the above mentioned antibiotics and the respective $ZnCl_2$. The following Eqs (1)–(3) correspond to the three stoichiometries of the complexes, namely 1:1, 1:2 and 2:1 (M:L):

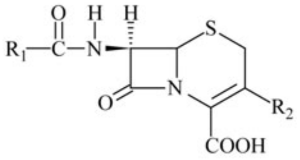
$$\mathrm{NaABT+ZnCl_2 \rightarrow [ZnCl(ABT)]+NaCl} \qquad (1)$$

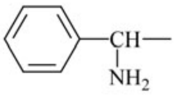
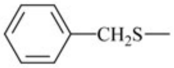
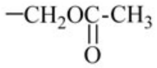
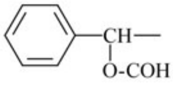
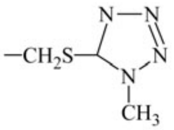
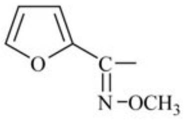
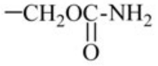
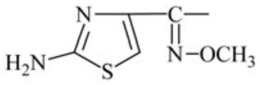
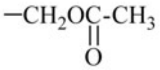
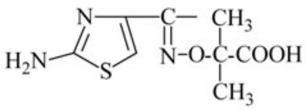
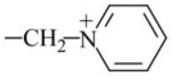
$$\mathrm{2NaABT+ZnCl_2 \rightarrow [ZnCl(ABT)_2]+2NaCl} \qquad (2)$$

$$\mathrm{Na_2ABT+2ZnCl_2 \rightarrow [Zn_2Cl_2(ABT)]+2NaCl} \qquad (3)$$

where ABT=antibiotic.

Table 1 Name, notation and structure of the antibiotics under investigation



Name	Notation	R$_1$	R$_2$
Cephalexin (Keflex)	CEX		$-CH_3$
Cephapirin (Cefadyl)	CEP		 $-CH_2O\underset{\overset{\|}{O}}{C}-CH_3$
Cefamandole (Mandol)	CML		
Cefuroxime (Zinacef)	CRX		 $-CH_2O\underset{\overset{\|}{O}}{C}-NH_2$
Cefotaxime (Claforan)	CTX		 $-CH_2O\underset{\overset{\|}{O}}{C}-CH_3$
Ceftazidime (Fortaz)	CFZ		

The complexes are fairly soluble in DMF and DMSO, and are not soluble in alcohol, acetone, chloroform and ether. The analytical data, colour and decomposition points of the complexes are presented in Table 2.

Table 2 Color, elemental analyses and decomposition temperature of the complexes

Complex	Color	Found (calcd.)/%				Dec. p./ °C
		C	H	N	S	
$[ZnCl(CEX)(H_2O)]\cdot 2H_2O$	creamy	40.00 (39.65)	4.80 (4.37)	8.68 (8.68)	6.90 (6.62)	360
$[ZnCl(CEP)(H_2O)]\cdot 2H_2O$	white	37.09 (36.51)	3.10 (3.60)	8.06 (7.51)	12.00 (11.46)	285
$[Zn(CML)_2)]\cdot 3H_2O$	creamy	41.28 (41.55)	3.57 (3.67)	14.85 (15.30)	11.39 (11.67)	244
$[Zn(CRX)_2)]\cdot 3H_2O$	creamy	40.17 (39.78)	3.45 (3.75)	11.80 (11.59)	6.82 (6.64)	260
$[Zn(CTX)_2)]\cdot 3H_2O$	creamy	37.13 (37.39)	3.60 (3.73)	13.14 (13.62)	11.98 (12.47)	358
$[Zn_2Cl_2(CFZ)(H_2O)]\cdot 3H_2O$	creamy	32.01 (32.30)	3.20 (3.45)	9.89 (10.27)	8.20 (7.84)	305

Electronic spectra

The electronic absorption spectra of complexes were recorded in DMF and listed in Table 3. The complexes exhibited an intense band in the region 37.037–36.036 cm^{-1}, which is attributed to a π–π^* transition of the antibiotics moiety, and an additional shoulder in the region 33.112–33.444 cm^{-1} assignable to intraligand charge transfer transition. Owing to the d^{10}-configuration of Zn(II), no *d–d* transition could be observed and therefore the stereochemistry around Zn(II) in its complexes cannot be determined from ultraviolet and visible spectra. However, comparing the spectra of Zn(II) complexes and those of similar environments, a tetrahedral structure is suggested for the present Zn(II) complexes.

IR spectra

The IR spectra of the complexes are given in Table 3. The general feature of the IR spectra is the shift of $\upsilon_a(COO)^-$ of the carboxylate group which absorbs in the region 1570–1610 cm^{-1} towards lower frequency compared to the ligands [15, 16]. The frequency difference ($\Delta\upsilon$) between $\upsilon_a(COO)^-$ and $\upsilon_s(COO)^-$ lies in the range 185–230 cm^{-1}, typical of monodentate coordination of the carboxyl group [17, 18]. The υ(NC) absorption appears for the studied complexes in the region 1430–1480 cm^{-1}. This band is appreciably red shifted to a lower frequency if compared with that of the free ligands, giving an evidence for coordination of Zn(II) through the nitrogen adjacent to the carboxylate group. Bands located at 3250–3450 cm^{-1} for all the complexes

Table 3 IR and electronic spectral data of the complexes

Complex	IR/cm^{-1}								Assignment
	υ(NH)+ +υ(OH)·H_2O	$\upsilon_a(CO_2^-)$	$\upsilon_s(CO_2^-)$	$\Delta\upsilon$	υ(NC)	$\rho_r(H_2O)$	$\rho_w(H_2O)$	υ_{max}	
$[ZnCl(CEX)(H_2O)]\cdot 2H_2O$	3250, 3440	1580	1390	185	1430	845	530	33.444 37.453	IL-charge transfer π–π^* transition
$[ZnCl(CEP)(H_2O)]\cdot 2H_2O$	3250, 3450	1576	1380	190	1480	760	540	24.875 36.764	IL-charge transfer π–π^* transition
$[Zn(CML)_2]\cdot 3H_2O$	3260, 3400	1590	1390	200	1460	–	–	36.563	π–π^* transition
$[Zn(CRX)_2]\cdot 3H_2O$	3270, 3420	1605	1410	195	1480	–	–	28.368 36.036	IL-charge transfer π–π^* transition
$[Zn(CTX)_2]\cdot 3H_2O$	3200, 3350	1610	1380	230	1440	–	–	33.222 36.900	IL-charge transfer π–π^* transition
$[Zn_2Cl_2(CFZ)(H_2O)]\cdot 3H_2O$	3250, 3510	1605	1390	215	1460	825	520	33.112 37.037	IL-charge transfer π–π^* transition

are ascribed to υ(NH) and υ(OH)H_2O, respectively. The rocking and wagging vibrations of H_2O can be assigned to the bands at 760–845 and 520–540 cm^{-1}, respectively.

For the $[Zn_2Cl_2(CFZ)H_2O]\cdot 3H_2O$ complex in which two Zn(II) ions are coordinated to the ligand, one metal ion is attached to the carboxylate group and the adjacent nitrogen atom; $\upsilon_{as}(CO_2)^-$, $\upsilon_s(CO_2)^-$ and υ(NC) are lying in the above frequency ranges. The other metal ion coordinates to the nitrogen atom of the group –C=N–O (which is manifested by the shift of υ(C=N) band from 1690 cm^{-1} in the ligand [19, 20] to 1655 cm^{-1} in the complex) and the sulphur of the thiazolyl ring which exhibits a band at 680 cm^{-1} attributed to υ(C–S–C). This band is lowered in frequency relative to the free ligand (690 cm^{-1}), suggesting the involvement of the thiazolyl ring sulphur in bonding to the metal [21].

Thermal behaviour

The TA-curves of the Zn(II) complexes exhibit several thermal events i.e. three, four or six decomposition steps. The first step for all the complexes represents a dehydration step. The decomposition of the anhydrous complexes commences in the temperature range 106–170°C. $ZnCO_3$ or $ZnSO_4$ were detected from mass loss considerations to be formed as intermediates. The end products were confirmed to be ZnO or ZnS. In the following are the detailed thermal decompositions of the complexes.

The TA curve of $[ZnCl(CEX)H_2O]\cdot 2H_2O$ complex exhibits several thermal events (Fig. 1). The DTG curve shows six overlapping maxima corresponding to overlapping steps in the TG curve; however, the first and second steps are well defined maxima. The first step (29–143°C) corresponds closely to liberation of two water molecules (calc. 7.5, found 9.0%). The second step is a slow step (168–289°C) (22.7%). Afterwards a continuous decomposition sets in with varying decomposition rate unil 600°C. The residue mass after the final decomposition is in agreement with the formation of ZnS (calc. 20.2, found 21.0%).

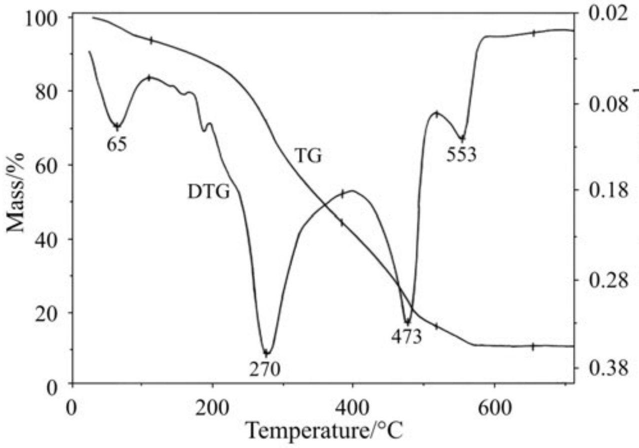


Fig. 1 TG and DTG TA curves of $[ZnCl(CEX)(H_2O)]\cdot H_2O$

The pyrolysis curve of $[ZnCl(CEP)(H_2O)]\cdot 2H_2O$ shows three steps of decomposition at 40–145, 150–263 and 263–518°C. The first step is commensurate with the release of two water molecules (calc. 6.4%, found 6.8%). The second step is accompanied by a mass loss of 30.2%. Afterwards a progressive decomposition sets in until 518°C where a constant mass was achieved indicating the formation of ZnS (calc. 17.4%, found, 17.5%).

The stepwise course of the TA curve of $[Zn(CML)_2]\cdot 3H_2O$ complex is characterized by four steps in the temperature ranges 50–122, 122–260, 260–416 and 510–561°C. The first step in the decomposition sequence represents the release of three water molecules (calc. 4.9, found 5.4%). The second (34.6%) and third (24.4%) steps are strongly overlapped. The fourth step (25.0%) corresponds to the formation of $ZnCO_3$ (calc. 11.4, found 10.6%).

The TA curve of $[Zn(CRX)_2]\cdot 3H_2O$ complex is composed of four steps at 45–124, 130–238, 276–480 and 520–561°C. The dehydration occurs at the first step where evolution of three water molecules takes place (calc. 5.5, found 5.9%). In the second, third and fourth stages, the organic part of the anhydrous complex undergoes a stepwise decomposition. ZnO is the final product (calc. 8.9, found 9.1%).

$[Zn(CTX)_2]\cdot 3H_2O$ complex decomposes in four overlapping steps (Fig. 2). The first step involves evolution of three water molecules in the temperature range 30–106°C (calc. 5.3, found 6.2%). Afterwards a continuous decomposition sets in with three overlapping steps. In the temperature range 381–519°C an intermediate of $ZnSO_4$ may be formed (calc. 15.7, found 16.2%). The end product is ZnS (calc. 9.5, found 10.2%).

The TA curve of $[Zn_2Cl_2(CFZ)H_2O]\cdot 3H_2O$ complex consists of four steps at 28–136, 156–358, 358–506 and 525–676°C (Fig. 3). The first step is consistent with the elimination of $3H_2O$+2HCl (calc. 17.6, found 17.0%). The second step (35.9%) is a slow step. The third step corresponds to the intermediate $ZnCO_3$ (calc. 30.6, found 31.1%). The fourth step is a slow step (12.4%) leading to the formation of ZnO (calc. 19.8, found 18.7%) as the final product.

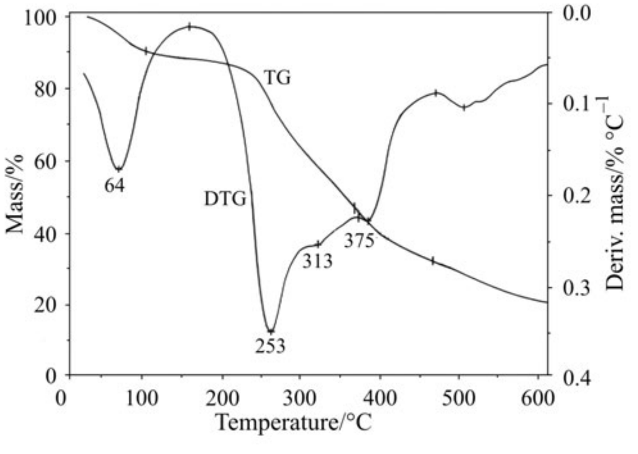


Fig. 2 TG and DTG TA curves of $[Zn(CTX)_2]\cdot 3H_2O$

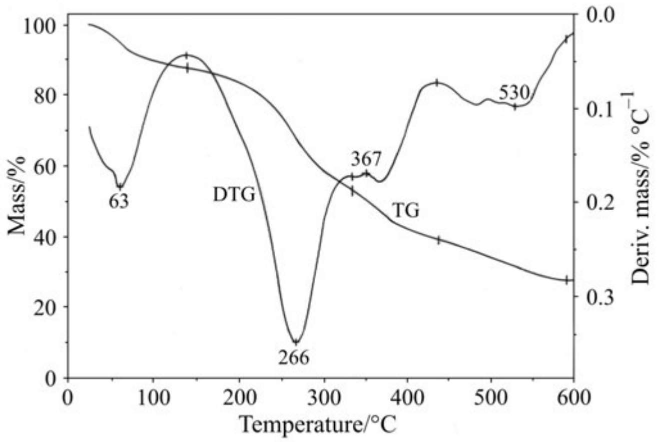
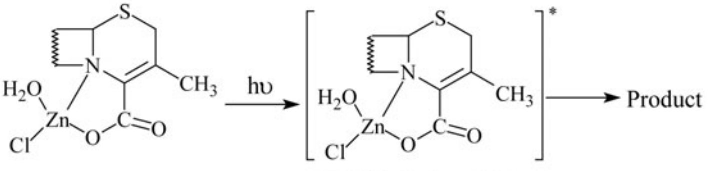


Fig. 3 TG and DTG TA curves of $[Zn_2Cl_2(CFZ)(H_2O)]\cdot3H_2O$

Photolyses of Zn(II) complexes

The $[ZnCl(CEX)(H_2O)]\cdot2H_2O$ complex shows a high light sensitivity as indicated from the spectral changes during irradiating its solution in DMF with light of λ_{irr}=298 nm. The absorbance at 300–270 nm decreases with some increase at 370 nm (Fig. 4). The photoreaction is rather clean as indicated by the presence of a sharp isosbestic point at 346 nm. It seems that the active excited state reached by the light absorption is of the intraligand charge transfer type (ILCT) [22]. The following mechanism accounts for the observed behaviour:



ILCT – Exicted State

The photochemical behaviour of $[Zn(CML)_2]\cdot3H_2O$ seems to be similar to that of its free cefamandole [14]. The observed results (Fig. 5) show that this complex undergoes two competitive processes. One is the photodecomposition as indicated by the decreases in the absorbance at 273 nm. The other is the intramolecular hydrogen abstraction in the ligand molecule, leading to formation of a photocyclisation product of long wavelength absorption, as shown from the increase in the absorbance at 333 nm. For the remaining Zn(II) complexes, it is observed that their photochemical behaviour is similar to that of their free cephalosporins [14].

Unfortunately, a correlation between the thermal and photochemical behaviour of the studied complexes could not be found. This may be attributed to the difference in mechanisms controlling the two processes.

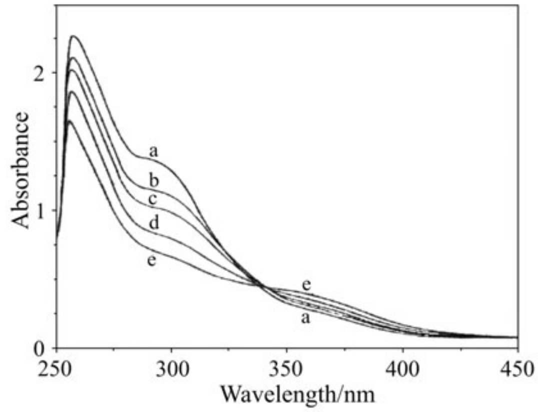


Fig. 4 Spectral changes during the photolysis of [ZnCl(CEX)(H_2O)]·H_2O in DMF at *a*=0, *b*=6, *c*=10, *d*=20 and *e*=40 min irradiation time (λ_{ex}=298 nm; 1 cm cell)

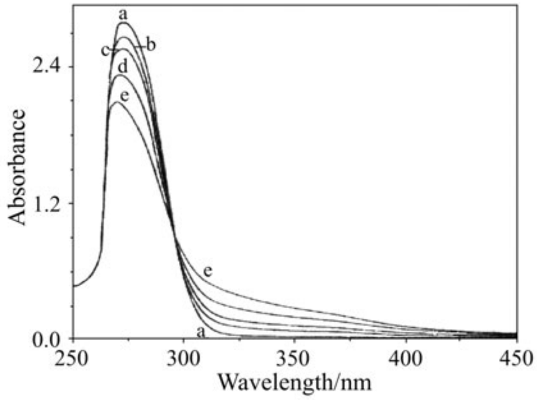


Fig. 5 Spectral changes during the photolysis of [Zn($CML)_2$]·$3H_2O$ in DMF at *a*=0, *b*=10, *c*=20, *d*=40 and *e*=70 min irradiation time (λ_{ex}=298 nm; 1 cm cell)

References

1 a) D. R. Williams, Proc. Summer Comput. Simul. Cont., 2 (1984) 92.
b) S. Odake, K. Nakahashi, T. Morikawa, S. Takebe and K. Kobashi, Chem. Pharm. Bull., 40 (1992) 2764.
2 a) M. M. Shoukry, E. M. Shoukry and S. M. El-Medani, Monatshefte für Chemie, 126 (1995) 909.
b) F. Grams, M. Crimmin, L. Hinnes, P. Huxley, M. Pieper, H. Tschesche and W. Bode, Biochemistry, 34 (1995) 14012.
c) A. A. M. Aly, A. Strasser and A. Vogler, Inorg. Chem. Acta, 336 (2002) 91.
3 M. M. Shoukry, W. M. Hosny, A. Abd Razik and R. A. Mohamed, Talanta, 44 (1997) 2109.
4 M. S. Iqbal, A. R. Ahmad, M. Sabir and S. M. Asad, J. Pharm. Pharmacol., 51 (1999) 371.
5 a) A. Gringauz ‘Introduction to Medicinal Chemistry’ Wiley-VCH, Inc., New York 1997, p. 216.
b) W. Druckheimer, J. Blumbach, R. Lattrell and K. H. Sheunemann, Angew. Chem. Internat.

Edit. in Eng., 24 (1985) 180.
c) F. A. Jung, W. R. Pilgrim, J. P. Poyser and P. J. Siret, 'Topics in Antibiotic Chemistry', 1 (1980) 4.

6 M. J. Schwaber, C. S. Graham, B. E. Sands, H. S. Gold and Y. Carmelia, Antimicrob. Agents Chemother., 47 (2003) 1882.

7 a) M. Takeda, E. Babu, S. Narikawa and H. Endou, Euro. J. Pharm., 438 (2002) 137.
b) S. Khamdang, M. Takeda, E. Babu, R. Noshiro, M.L. Onozato, A. Tojo, A. Enomoto, X. L. Huang, S. Narikawa and N. Anzai, P. Piyachaturawat and H. Endou, Euro. J. Pharm., 465 (2003) 1.

8 H. A. Harper 'Review of Physiological Chemistry' 15th Ed., Lange Medical Publ., California 1975, p. 441.

9 N. A. B. de Souza, F. S. de Souza, I. D. Bas[iacute]lio Jr, A. C. D. Medeiros, E. J. Oliveira, A. F. O. Santos and R. O. Macedo, J. Therm. Anal. Cal., 72 (2003) 535.

10 A. P. B. Gomes, F. S. Souza and R. O. Macedo, J. Therm. Anal. Cal., 72 (2003) 545.

11 A. I. El-Said, A. A. M. Aly and A. S. A. Zidan, J. Thermal Anal., 37 (1991) 2473.

12 A. A. M. Aly, A. S. A. Zidan and A. I. El-Said, J. Thermal Anal., 37 (1991) 627.

13 A. S. A. Zidan, A. I. El-Said, M. S. El-Meligy, A. A. M. Aly and O. F. Mohammed, J. Therm. Anal. Cal., 62 (2000) 665.

14 a) A. H. Osman, N. A. El-Maali, A. A. M. Aly and G. A. A. El-Hazmi, Synth. React. Inorg. Met.-Org. Chem., 32 (2002) 763.
b) A. H. Osman, A. A. M. Aly, N. A. El-Maali and G. A. A. El-Hazmi, Synth. React. Inorg. Met.-Org. Chem., 32 (2002) 1289.

15 L. P. Morrelli, 'Analytical Profiles of Drug Substances' Acad. Press., 4 (1975) 21.

16 A. M. Abdel-Mawgoud, Synth. React. Inorg. Met.-Org. Chem., 28 (1998) 555.

17 K. Nakamoto, 'Infrared and Raman Spectra of Inorganic and Coordination Compounds' 3rd Edn., Wiley, New York 1978, p. 232.

18 G. Wang, Synth. React. Inorg. Met.-Org. Chem., 30 (2000) 601.

19 T. J. Wozniak and J. R. Hicks, 'Analytical Profiles of Drug Substances' Acad. Press, 20 (1991) 209.

20 M. Tumer, B. Evodan, H. Koseyin, S. Serin and M. Y. Nutku, Synth. React. Inorg. Met.-Org. Chem., 28 (1998) 529.

21 R. C. Maurya and P. Sharma, Indian J. Chem., 38A (1999) 509.

22 a) H. Kunkely and A. Vogler, Chem. Phys. Lett., 304 (1999) 187.
b) H. Kunkely and A. Vogler, Inorg. Chem. Comm., 3 (2000) 645.