Journal of Thermal Analysis and Calorimetry, Vol. 63 (2001) 787–795

THE THERMAL STABILITY OF CIPROFLOXACIN COMPLEXES WITH MAGNESIUM(II), ZINC(II) AND COBALT(II)

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(Received April 17, 2000; in revised form September 4, 2000)

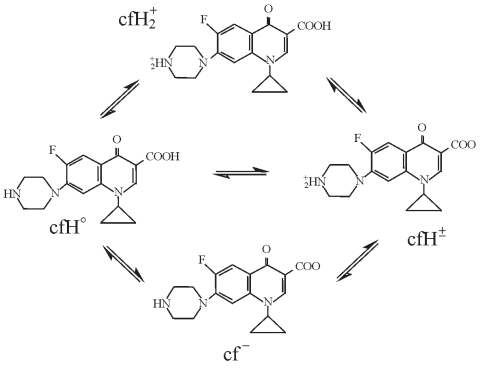
Abstract

The thermal behaviour of Mg(II), Zn(II) and Co(II) compounds of ciprofloxacin was studied by thermogravimetry (TG) and differential thermal analysis (DTA) in order to determine or to confirm some structural characteristics of substances. The complexes decompose in two steps: dehydration and pyrolytic decomposition of the anhydrous complexes to form metal oxide or metal fluoride. The dehydration process of one magnesium(II) compound takes place in two steps suggesting a marked difference in the bonding of water molecules. The different bonding mode of the ciprofloxacin molecules in both magnesium compounds leads to different residues of the thermal decompositions.

Keywords: ciprofloxacin, DTA, metal complexes, quinolones, TG

Introduction

Ciprofloxacin (abbreviation cfH, 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinoline carboxylic acid) is a synthetic fluoroquinolone antibacterial agent with broad spectrum of activity [1]. The protolytic scheme of ciprofloxacin is:



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1418–2874/2001/ $ 5.00

Akadémiai Kiadó, Budapest
Kluwer Academic Publishers, Dordrecht

Co-administration of quinolones with drugs that contain metal ions reduces their bioavailability significantly, probably due to metal ion–drug complexation [2–4]. Many authors [5–22] have studied the interactions of quinolones and metal ions.

The ability of ciprofloxacin to form metal complexes is very sensitive to the pH value of the solution. The quinolone binds extensively to the metal only at high solution pH values (i.e. 7 and more). The very low solubility of ciprofloxacin in the pH region 5 to 10 leads to difficulty in the isolation of the metal complexes with ciprofloxacin. As the metal complexes are even less soluble than ciprofloxacin, the preparation of single crystals of the complexes, suitable for X-ray structure analysis, is almost impossible.

We have decided to compare the thermal behaviour of the following compounds: two ionic compounds $(cfH_2)_2[Mg(H_2O)_6](SO_4)_2{\cdot}6H_2O$ (compound I) and $(cfH_2)_2[ZnCl_4]{\cdot}2H_2O$ (compound III) and three coordination compounds $[Mg(cf)_2(H_2O)_2]{\cdot}2H_2O$ (compound II), $[Zn(cf)_2]{\cdot}3H_2O$ (compound IV) and $[Co(cf)_2]{\cdot}3H_2O$ (compound V).

Metal complexes with quinolones are of great importance for potential pharmacological use. TG analysis is a very powerful method for the characterization of these compounds and can be used as fingerprints for repeated syntheses.

Experimental

Methods

Analysis of carbon, hydrogen and nitrogen was carried out on a Perkin Elmer 2400 CHN microanalyser.

Thermogravimetric (TG) measurements were carried out in a dynamic air atmosphere using Perkin Elmer TGA7 Thermoanalyser in a temperature range from 25 to 800°C. Platinum crucibles (diameter 8 mm) were used. The heating rate was 5 K min^{-1} and the sample masses were from 2.6 mg (due to the limited availability of monocrystals) up to 14.0 mg (when powdered samples were used). Seven-point calibration was performed on TG apparatus using ferromagnetic standards (alumel, nickel, nicoseal, perkalloy, trafoperm and iron), the seventh known temperature was room temperature (22°C).

Differential thermal analyses (DTA) data were recorded on Perkin Elmer DTA 7 instrument in alumina crucible. The empty alumina crucible was used as a reference. The heating rate was 5 K min^{-1} and the sample masses were from 2.2 to 18.0 mg. Before the measurements two point calibration was performed, using onset melting temperatures of aluminium and gold.

Powder diffraction data were recorded with a Guinier 620 camera equipped with Guinier monochromator 615 with CuK_α radiation. Sodium chloride was used as an internal standard. Micro Powder Diffraction Search/Match (μ-PDSM), Fein-Marquart Associates Inc., was used for data processing.

Preparations of the compounds

The samples of ciprofloxacin and ciprofloxacin·HCl·H_2O were kindly provided by Krka Pharmaceutical factory (laboratory samples). $ZnSO_4\cdot7H_2O$ (Laphema Skopje), $CoCl_2\cdot6H_2O$ (Kemika Zagreb), $MgSO_4\cdot7H_2O$ (Kemika Zagreb), NaOH (Kemika Zagreb), HCl (Kemika Zagreb) and $ZnCl_2$ (Carlo Erba) were used for the syntheses. All reagents were analytical reagent grade. The solutions were prepared with twice-distilled water.

The magnesium and zinc compounds of ciprofloxacin (compound I, compound II, compound III and compound IV) were prepared as reported elsewhere [11, 23–24]. Compounds I and III were prepared from the water solution of ciprofloxacin·HCl and $MgSO_4$ ($ZnSO_4$ respectively) at pH 1, meanwhile compounds II and IV were isolated from the saturated solution of ciprofloxacin·HCl at pH 8, when $MgSO_4\cdot7H_2O$ ($ZnSO_4\cdot7H_2O$ respectively) was added in molar ratio quinolone:metal=2:1.

Compound V was prepared from the saturated aqueous solution of ciprofloxacin·HCl at pH 8 (the pH value was adjusted with 0.10 M NaOH). $CoCl_2\cdot6H_2O$ was added to obtain molar ratio cfH:Co(II)=2:1. The solution was stirred and a pale rose precipitate appeared after one day. The precipitate was removed by filtration, washed with ethanol and dried at 60°C for 5 h. The product was insoluble in water and organic solvents and decomposed in dilute solutions of all strong acids. All trials to pre-

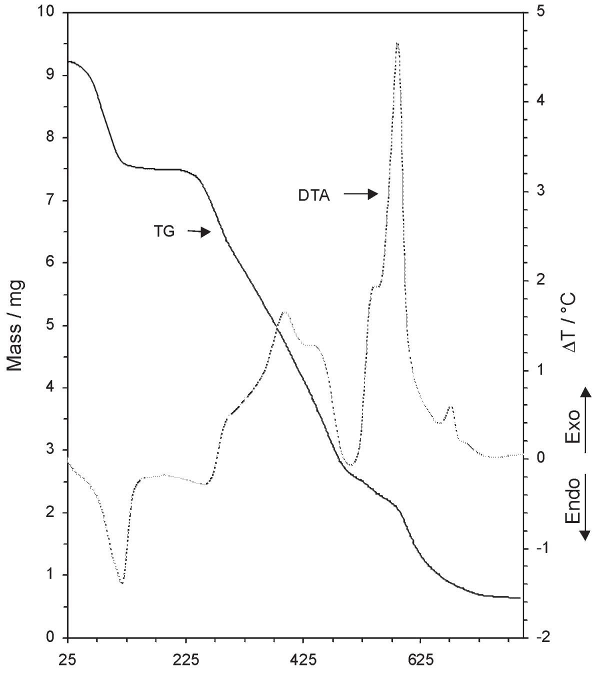

Fig. 1 TG and DTA curves of $(cfH_2)_2[Mg(H_2O)_6](SO_4)_2\cdot6H_2O$

pare single crystals failed. Elemental analysis of the compound V gave: C 52.99, H 4.98, N 10.68%. Calculated for $C_{34}H_{40}N_6F_2O_9Co$: C 52.78, H 5.22, N 10.86%.

Compound V is isostructural with compound IV, proved by powder diffraction analysis.

Results and discussion

The thermal behaviour of the isolated complexes consists of two major processes: dehydration of hydrated compounds and decomposition of the anhydrous complexes.

Thermal analysis of $(cfH_2)_2[Mg(H_2O)_6](SO_4)_2\cdot 6H_2O$ *(compound I)*

The crystal structure of the compound has been previously published [11]. The magnesium(II) ion is coordinated with six water molecules. The ciprofloxacin molecule is protonated at the terminal N atom of the piperazine residue and is not bonded to the magnesium(II) ion. There are also two sulphate(VI) ions and six water molecules in the unit cell.

The TG and DTA curves of compound I are presented in Fig. 1. The dehydration process ends at 135°C. In the DTA curve a strong endothermic peak at 120°C shows the maximum of dehydration process. The mass loss in the temperature range 25–135°C (18.87%) is lower than the calculated value for the loss of twelve water

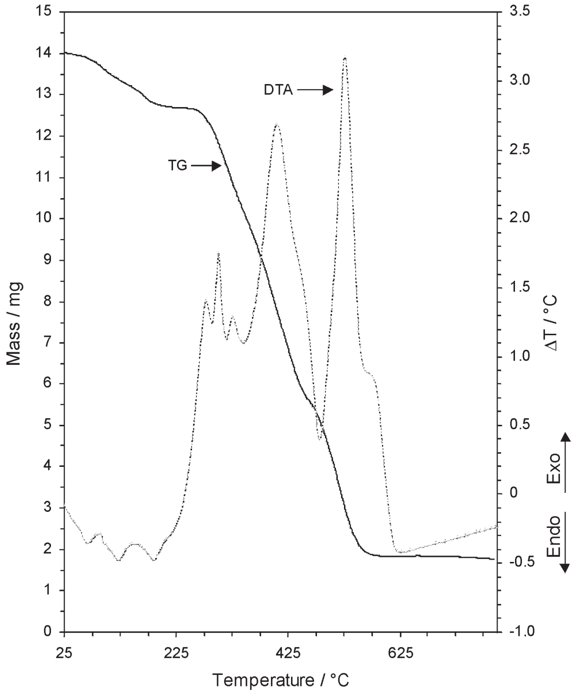

Fig. 2 TG and DTA curves of $[Mg(cf)_2(H_2O)_2]\cdot 2H_2O$

molecules per molecule of the compound (19.70%). The single crystals of the compound slowly became opaque, probably due to loss of crystal water. This may explain the slight discrepancy in experimental and calculated dehydration values. The dehydration occurs in a single step, which is surprising as there are two types of water molecules in the crystal unit. In the crystal structure six water molecules are bound to the metal ion and six water molecules are lying between the distinct layers and participate in the hydrogen-bonding network [11]. The bond lengths Mg–O (water) are 2.04 to 2.06 Å, which are in the range of the middle strong bonds Mg–O [25]. The participation of lattice water molecules in the hydrogen-bonding network probably strengthens the binding of them that much that the dehydration of these molecules occurs at higher temperature and coincides with the temperature of the dehydration of the water molecules bound to the metal ion.

The pyrolysis of the compound I begins at 230 and ends at 740°C. It takes place in several clearly defined steps with exothermal maximum at 585°C. The product of the thermal decomposition of the complex is MgO confirmed by powder diffraction analysis. The mass loss in the temperature range 25–740°C is 97.98% (calculated 96.33%). Because of the low mass of the sample (~5 mg), such discrepancy is in the range of the accuracy of the method.

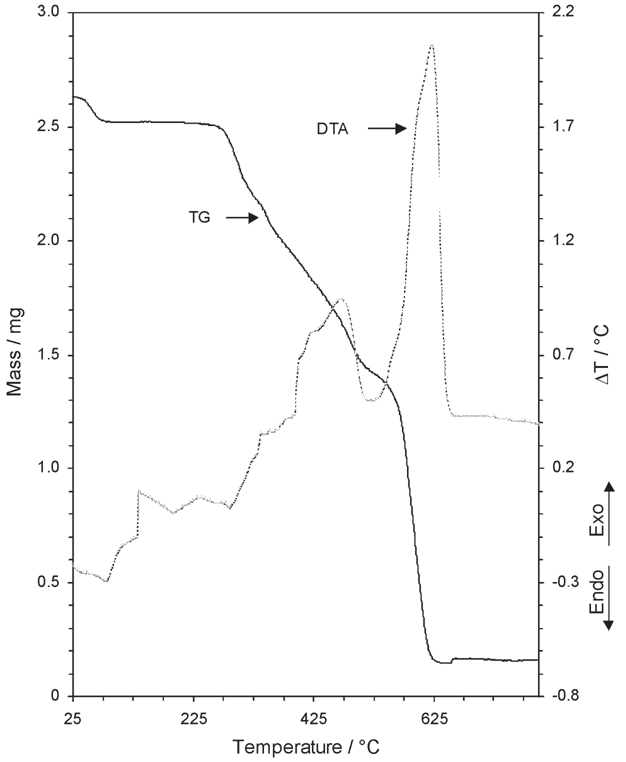

Fig. 3 TG and DTA curves of $(cfH_2)_2[ZnCl_4]\cdot 2H_2O$

Thermal analysis of $[Mg(cf)_2(H_2O)_2]\cdot 2H_2O$ *(compound II)*

All attempts to prepare single crystals of the compound failed. The structure was proposed from the results of the thermal and other analysis [23]. In contrast with compound I a bonding of quinolone to Mg(II) ion is proposed in compound II. Mg(II) ion is coordinated with six oxygens. Four of them are from the two ciprofloxacinate ions. Another two oxygens are contributed from the two water molecules. Each of the ciprofloxacinate ions is bound through the pyridone oxygen and one of the carboxylic oxygen atoms. Another two water molecules are presumably included in the crystal structure as lattice water.

The TG and DTA curves of the compound II (Fig. 2) are quite different from the TG and DTA curves of the compound I. The dehydration process of the compound II takes place in two poorly defined steps suggesting a marked difference in the bonding of the water molecules between these two compounds. The process ends at a much higher temperature than for compound I. The observed mass change in the temperature range from 25 to 220°C (9.76%) is in fair agreement with the calculated value of 9.52% corresponding to the loss of four water molecules per molecule of substance. DTA curve of the compound II shows three clearly defined small endothermic processes in the temperature range 25 to 225°C, which are not clearly observed in the TG trace. The maximum of the first process is at 65°C and probably belongs to the removal of moisture. The second and the third process have their maxima at 120 and 185°C and are due to removal of the two types of differently bonded water molecules. The mode of the dehydration process proves our presumption about different binding of water molecules. In comparison with the compound I, the coordinated water molecules in the compound II are probably more strongly bound to the metal ion, leading to a much higher temperature of the dehydration process of that molecules.

The pyrolysis starts at 250 and ends at 600°C. The product of the thermal decomposition of the compound II is not MgO as seen with compound I, but MgF_2 as a result of the considerably different path of the pyrolysis. In the compound $(cfH_2)_2[Mg(H_2O)_6](SO_4)_2\cdot 6H_2O$ magnesium is included in $[Mg(H_2O)_6]^{2+}$ ion and thermal decomposition gives MgO. In compound $[Mg(cf)_2(H_2O)_2]\cdot 2H_2O$ magnesium is bonded to the ciprofloxacinate ion which results in quite different decomposition reaction giving MgF_2. This phenomenon clearly shows the different bonding mode of ciprofloxacin molecules in both compounds.

Thermal analysis of $(cfH_2)_2[ZnCl_4]\cdot 2H_2O$ *(compound III)*

The crystal structure of the compound III has been published [24]. Its structure is ionic, consisting of a tetrachlorozincate(II) ion, two protonated ciprofloxacin molecules and two lattice water molecules.

The TG and DTA curve of compound III are presented in Fig. 3. The product of the thermal decomposition of complex is ZnO confirmed by powder diffraction analysis. Dehydration of the compound ends at 80°C and takes place in one step which is in agreement with only one type of water molecules present in crystal structure. The maximum of the process occurs at 75°C. The experimental value of mass loss from

25 to 90°C (4.40%) is in fair agreement with the calculated value for the loss of two water molecules (3.97%). As mentioned previously the hygroscopy of the complexes is a frequent problem when dealing with thermal and elemental analysis of such compounds. In comparison with the compound I the dehydration process ends at quite lower temperature demonstrating weaker connection of lattice water molecules in the hydrogen-bonding network.

The pyrolysis of compound III begins at 220 and ends at 645°C. The mass loss in the temperature range 25–645°C is 94.37% (calculated 91.04%). It is known [26] that zinc oxide sublimes at higher temperatures. The experimental value 6.97% (theoretical 7.20%) of zinc in the compound III, determined by complexometric titration [24], also suggests that zinc oxide was probably lost by sublimation at TG measurement.

A sharp exothermal peak is noticed at 132°C in the DTA curve of compound III. The exothermal process could be ascribed to the crystallisation of the anhydrous complex.

Thermal analysis of [Zn(cf)$_2$]·3H$_2$O (compound IV)

Compound IV and compound V are isostructural. Zinc(II) ion (cobalt(II) ion respectively) is coordinated with four oxygens of the two ciprofloxacinate ions. Each cipro-

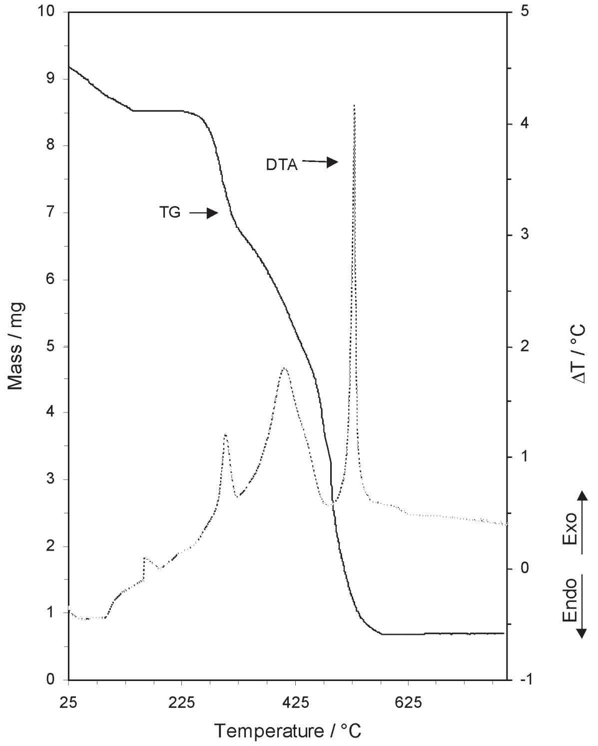

Fig. 4 TG and DTA curves of [Zn(cf)$_2$]·3H$_2$O

floxacinate ion donates two oxygens, one from the pyridone and one from the carboxylic group [24]. Three water molecules are included in structure as lattice water.

Dehydration of compound IV ends at 110°C (Fig. 4). The observed mass change at that process (7.12%) is in fair agreement with calculated one (6.93%). The DTA curve for dehydration reaction is not split proving that all water molecules are bonded equally in contrast to similar magnesium(II) complex with ciprofloxacin (compound II) where quinolone is bonded to the metal ion, too. We suppose that only lattice water is included in the structure of compound. In DTG curve of complex IV the identical sharp rise as in DTA curve of complex III is observed at 160°C, ascribed to the crystallisation of the anhydrous complex.

The pyrolysis begins at 240 and ends at 590°C. The product of the thermal decomposition is ZnO. The total mass loss is 92.4% and corresponds to 5.13% of zinc in sample (theoretical 8.38%). The reason for this discrepancy is the same as in compound III i.e. sublimation.

Thermal analysis of [Co(cf)$_2$]·3H$_2$O (compound V)

Although the compound V is isostructural with the compound IV, the TG and DTA curves of the compounds are quite different (Fig. 5). The dehydration of compound V takes place in a single step, observed as a small endothermic process in DTA curve with its end at 135°C. The observed mass change (7.14%) is in good agreement with

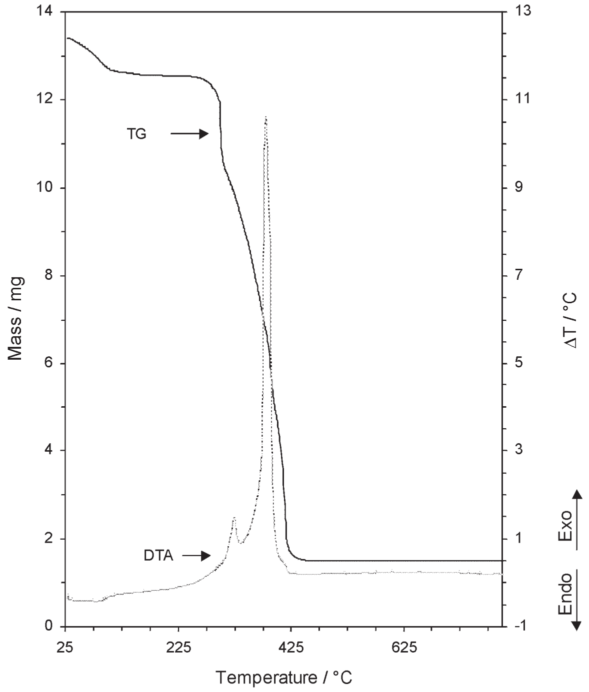

Fig. 5 TG and DTA curves of [Co(cf)$_2$]·3H$_2$O

the calculated value of 6.97%, corresponding to the loss of three water molecules per mole of substance. Due to the higher endset temperature for the dehydration process of the compound IV and V in comparison with the compound III, the stronger inclusion of lattice water molecules in the hydrogen-bonding network is proposed in the former ones.

The pyrolysis of the compound V ends at much lower temperatures than compound IV. The process of pyrolysis starts at 260 and ends at 460°C and is observed as two sharp exothermic peaks in DTA. The Co_3O_4 is determined as residue of thermal decomposition. The sample contains 7.16% of cobalt and is in good agreement with the calculated value of 7.62%.

References

1 H. Koga, A. Itoh, S. Murayama, S. Suzue and T. Irikura, J. Med. Chem., 23 (1980) 1358.
2 B. M. Lomaestro and G. R. Bailie, Ann. Pharmacother., 25 (1991) 1249.
3 A. O. Okhamafe, J. O. Akerele and C. S. Chukuka, Int. J. Pharm., 68 (1991) 11.
4 R. E. Polk, Am. J. Med., 87 (1989) 76.
5 N. C. Baenziger, Acta Cryst. C, 42 (1986) 1505.
6 C. Chulvi. M. C. Muñoz, L. Perelló, R. Ortiz, M. I. Arriortua, J. Via, K. Urtiaga, J. M. Amigó and L. E. Ochando, J. Inorg. Biochem., 42 (1991) 133.
7 G. M. Diaz, L. M. R. Martinez-Aquilera and R. P. Alfonso, Inorg. Chim. Acta, 138 (1987) 41.
8 P. B. Issopoulos, Acta Pharm. Yugosl., 39 (1988) 267.
9 M. Ruiz, R. Ortiz and L. Parello, Inorg. Chimica Acta, 217 (1994) 149.
10 G. M. Diaz and J. Ireta-Moreno, J. Inorg. Biochem., 54 (1994) 235.
11 I. Turel, I. Leban, M. Zupančič, P. Bukovec and K. Gruber, Acta Cryst. C, 52 (1996) 2443.
12 F. Gao, P. Yang, J. Xie and H. Wang, J. Inorg. Biochem., 60 (1995) 61.
13 I. Turel, K. Gruber, I. Leban and N. Bukovec, J. Inorg. Biochem., 61 (1996) 197.
14 S. C. Wallis, L. R. Gahan, B. G. Charles, T. W. Hambley and P. A. Duckworth, J. Inorg. Biochem., 62 (1996) 1.
15 I. Turel, N. Bukovec and E. Farkas, Polyhedron, 15 (1996) 269.
16 I. Turel and P. Bukovec, Thermochim. Acta, 287 (1996) 311.
17 I. Turel, I. Leban, G. Klintschar, N. Bukovec and S. Zaral, J. Inorg. Biochem., 66 (1997) 77.
18 I. Turel, I. Leban and N. Bukovec, J. Inorg. Biochem., 66 (1997) 241.
19 G. Mendoza-Diaz, R. Perez-Alonso and R. Moreno-Esparza, J. Inorg. Biochem., 64 (1996) 207.
20 M. Ruiz, L. Perelló, R. Ortiz, A. Castiñeiras, C. Maichle-Mössmer and E. Cantón, J. Inorg. Biochem., 59 (1995) 801.
21 I. Turel, A. Šonc, M. Zupančič, K. Sepčić and T. Turk, Metal-Based Drugs, 7 (2000) 101.
22 S. E. Castillo-Blum and E. Barba-Behrens, Coord. Chem. Rev., 196 (2000) 3.
23 M. Zupančič and P. Bukovec, Acta Pharm., 46 (1996) 221.
24 M. Zupančič, I. Turel, P. Bukovec, A. J. P. White and D. J. Williams, submitted for publication in Croatia Chemica Acta.
25 Fachinformationszentrum Karlsruhe, Inorganic Crystal Structure Database, FIZ Karlsruhe and Gmelin-Institut 1990, release 1999.
26 F. A. Cotton and G. Wilkinson, Advanced Inorganic Chemistry, John Wiley and Sons, New York, 5th edition, 1988, Chap. 16.