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Coordination Chemistry Reviews
196 (2000) 3–30

COORDINATION CHEMISTRY REVIEWS

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Coordination chemistry of some biologically active ligands

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Received 3 December 1998; received in revised form 12 March 1999; accepted 30 April 1999

Contents

Abstract

We have been interested in the coordination behaviour of biologically active ligands containing N and O donor atoms towards metal ions and boron. Structural and spectroscopic studies have been carried out. Also, the stability, chemical structure and behaviour of some of the coordination compounds in solution have been studied and their effect on photosynthetic activities investigated.

Keywords: 2-Guanidinobenzimidazole; Quinic acid; *N*-carboxymethylpseudoephedrine; Iminodiacetic acid esters; Quinolones; Metal ions

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0010-8545/00/$ - see front matter
PII: S0010-8545(99)00153-8

1. Introduction

Metal ions play a vital role in a vast number of widely different biological processes. The interaction of these ions with biologically active ligands, for example in drugs, is a subject of considerable interest. Some of the biologically active compounds act via chelation [1], but for most of them little is known about how metal binding influences their activity. Therefore we have been interested in studying the complexing ability of biologically active ligands.

Here, we discuss the coordination chemistry of 2-guanidinobenzimidazole, quinic acid, *N*-carboxymethylpseudoephedrine, iminodiacetic acid esters, nalidixic acid, cinoxacin and oxolonic acid towards essential and toxic metal ions and towards boron.

Benzimidazoles are active components involved in a great variety of biological processes. Some of its derivatives are the active components of fungicides, bactericides, among others [2]. 2-Guanidinobenzimidazole also contains the guanidine group that contributes to the activity of several antibiotics [3].

Quinic acid (quin) is a natural product involved in the metabolism of plants; polyglycols may act as metal carriers, therefore the study of the interaction of quin with metal ions will provide very useful information in this respect. We also report here the effect of some of these coordination compounds on photosynthetic activities, where it is evident that the metal ions present in the coordination compounds modify the effect that the ligand itself has on photosynthesis.

N-carboxymethylpseudoephedrine and iminodiacetic acid esters are *N*-substituted glycine derivatives that may act as polydentate ligands. Their coordination compounds are used as models for understanding the different conformations stabilised by the metal ions interacting with biologically relevant molecules.

Quinolones are widely used drugs for the treatment of renal infections; their interaction with metal ions may be a relevant factor for their pharmacological activity.

2. 2-Guanidinobenzimidazole compounds

2-Guanidinobenzimidazole (2gb, Fig. 1) and some of its derivatives show biolog-

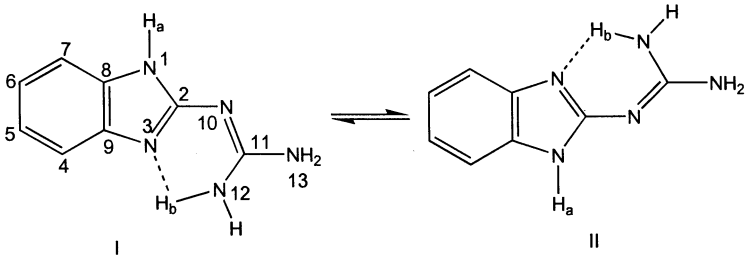

Fig. 1. 2-Guanidinobenzimidazole.

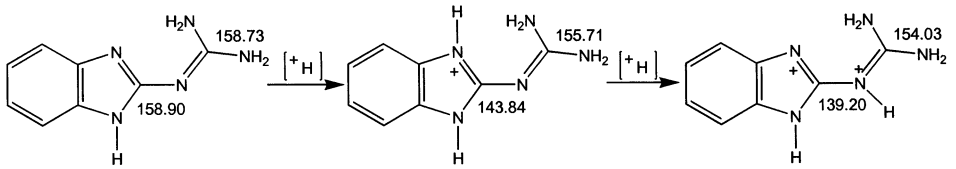

Fig. 2. Protonation of 2-guanidinobenzimidazole.

ical properties, for example, as blocking agents of the skin sodium channels. Also, 2gb interacts through the guanidine group with the outward-facing channel entrance forming a labile complex and through the pyrazolic fraction to the receptor site [4,5]; however the structures of the 2gb complexes with Na^+, K^+ have not been established. 2gb diminishes gastric acid secretion [6], and also shows hypoglycemic [7] and hypotensive [8] properties.

2-Guanidinobenzimidazole is a polyfunctional planar molecule with a delocalised π electronic system, with five nitrogen atoms which may act as basic centres and five labile N–H bonds. The molecule may present several tautomers and conformers. Its structure and dynamical behaviour have been studied in solution by ^{1}H- [9], ^{13}C- [9,10] and ^{15}N- [11] NMR. The equivalent conformers **I** and **II** are the principal contributors to the molecular structure of this molecule in solution; they are in equilibrium and stabilised by intramolecular hydrogen bonds [9]. In the solid state X-ray diffraction [12] reveals widely used intramolecular hydrogen bonding, which gives rise to a six membered ring, Fig. 1.

The protonation, coordination and methylation sites of 2gb were investigated using NMR and X-ray diffraction studies. In order to get information about the Lewis basic sites in this molecule, reactions of 2gb with acids, borane-THF, methyl iodide and metallic ions were performed. The imidazolic proton substitution and the blockage of the lone pair of N-3 add information about the N–H tautomeric equilibrium of 2gb and the preferred sites for coordination or alkylation.

Andrade-López et al. [13] showed that 2gb has an open structure without an intramolecular hydrogen bond in DMSO or DMF. The imidazolic N-3 is the preferred basic site in solution for protonation (Fig. 2), methylation and coordination and not N-10 as was suggested from semiempirical calculations [1]. Under strong acidic conditions, diprotonation occurs at N-3 and N-10.

Some N-protonated, N-methylated, N-borane adducts and tin, nickel and zinc heterocyclic compounds depicted in Fig. 3 were prepared [13]. Several research groups have investigated the coordination behaviour of 2gb towards metal ions, such as Cr(III), Hg(II), Pd(II), V(IV), Ni(II), Co(II) and Cu(II) [14–22].

More recently a systematic study was carried out where a structural study using data from X-ray crystallographic determinations was presented [23]. Coordination compounds derived of 2-guanidinobenzimidazole (2gb), containing Co(II), Ni(II), Cu(II) and Zn(II) were synthesised and characterised, namely $[Co(2gb)Cl_2(H_2O)_2]\cdot 5H_2O$, $[Co(2gb)_2Cl_2]\cdot 3H_2O$, $[Co(2gb)_2(H_2O)_2](NO_3)_2\cdot 4H_2O$, $[Co(2gb)_2(H_2O)_2]\cdot(OAc)_2$, $[Ni(2gb)_2]Cl_2\cdot H_2O$, $[Ni(2gb)_2]Br_2\cdot 3H_2O$, $[Ni(2gb)_2](NO_3)_2$,

$[Ni(2gb)_2](OAc)_2$, $[Cu(2gb)Cl_2]$, $[Cu(2gb)Br_2]$, $[Cu(2gb)_2]Br_2{\cdot}2H_2O$, $[Cu(2gb)_2](NO_3)_2{\cdot}H_2O$, $[Cu(2gb)_2](OAc)_2{\cdot}H_2O$, $[Zn(2gb)Cl_2]{\cdot}H_2O$ and $[Zn(2gb)Br_2]{\cdot}H_2O$.

The ligand has several isomers some of which are probably involved in coordination towards metal ions. Theoretical calculations were performed to identify the more probable isomers, shown in Fig. 4, and the possible structures of the coordination compounds in order to verify that the experimental proposed structures were stable. Two different types of coordination compounds were found. In the first type, the ligand coordinates as a chelate through the imidazole N(3) and the guanidine N(12), which is the case for most of the complexes. Compounds that contained only one ligand in the coordination sphere yield either compounds with tetrahedral geometry (copper and zinc) or octahedral (cobalt). With two chelating 2gb units a square-planar geometry was stabilised (nickel and copper). The second type of coordination behaviour was observed for the cobalt compounds, where the ligand coordinates as a monodentate through the imidazole N(3) and the structure is tetrahedral (Fig. 5) [23]. The square planar nickel(II) coordination compounds showed paramagnetic behaviour and from their EPR spectra the presence of a free radical was suggested [24].

The ability of 2gb to form diamagnetic complexes by coordination with acidic boron atoms such as boron difluoride, boron diphenyl and borodihydroxyphenyl was investigated, and studied by NMR techniques [13]. The results showed that 2gb gives stable borate heterocycles with a delocalised π electronic system. The reactions of 2gb with diphenyl borinic and phenyl boronic acids yield diphenyl-(2-guanidinobenzimidazole-*N*,*N*′)borate and hydroxy-phenyl-(2-guanidinobenzimidazole-*N*,*N*′)borate respectively, Fig. 6. The reaction of 2gb with BF_3–OEt_2 afforded the BF_2 heterocycle plus the protonated tetrafluroborate derivative as shown in Fig. 7. A dynamic exchange of N–H protons was observed with preferred protonation at N-12. Two spirane compounds were obtained by the reaction of two equivalents of

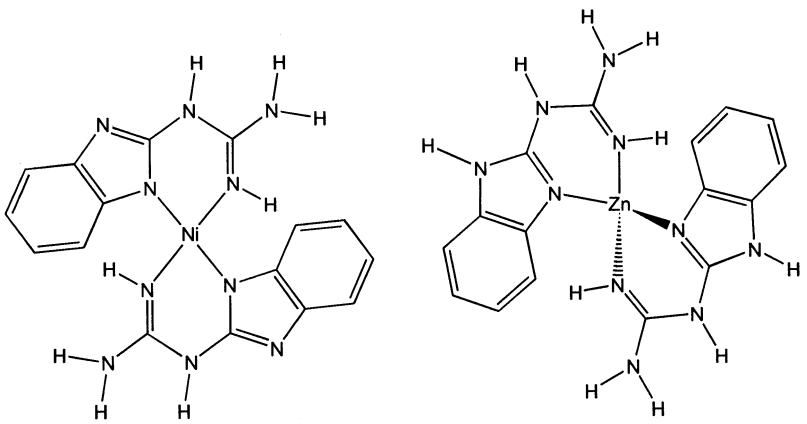

Fig. 3. 2-Guanidinobenzimidazole coordination compounds with nickel(II) and zinc(II).

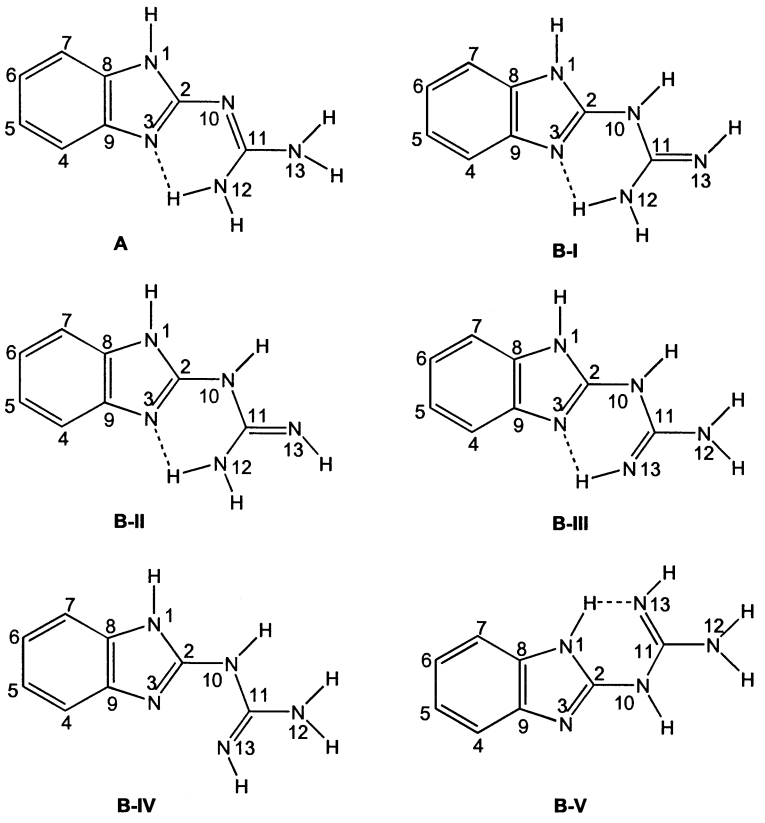

Fig. 4. Isomers of 2-guanidinobenzimidazole.

2gb with one of borane (Fig. 8) or two equivalents of 2gb with one of 1,3,2-benzothiazaborole (Fig. 9).

The reactivity of 2gb towards organometallic tin complexes and to $SnCl_4$ has also been investigated [25]. The organotin compounds used were: R_2SnCl_2 (R = Me, Bu, Ph) and R_3SnCl (R = Bu, Ph). The structures of the compounds were investigated by ^{1}H-, ^{13}C-, ^{119}Sn-, ^{15}N-NMR, mass spectrometry, IR spectroscopy and elemental analyses. The NMR data suggest pentacoordinated (products from the reactions with R_3SnCl) or hexacoordinated tin atoms (products from reactions with R_2SnCl_2 or $SnCl_4$) see Fig. 10. In all cases 2gb acts a bidentate ligand.

The effect on photosynthesis of metal salts containing metal ions in oxidation state (II) such as Cu, Zn, Cd has previously been investigated [26,27]. Barba-Behrens et al. [28] studied the effect of transition metal ion coordination compounds on photosynthesis. Co(II) quinic acid compounds behave as decouplers on photosynthesis, while nickel(II) salts and their coordination compounds with ethyl-5-methylimidazole-4-carboxylate (emizco), behave as Hill reaction inhibitors [29]. The effect of Cr(III) and Co(III) coordination compounds on the thylakoids

embedded proteins was investigated [30]. $[Cr(2gb)_3]Cl(ZnCl_4)$, $[Cr(2gb)_3]Cl_3$ and $[Co(2gb)_3]Cl_3$ were synthesised and characterised. Their chemical structures and the oxidation state of the metal centres remained unchanged in solution. The effect of these compounds and of $CrCl_3$ and $[Co(NH_3)_6]Cl_3$ on photosynthesis was investigated. The coordination compounds inhibit ATP synthesis, and electron flow (basal, phosphorylating and uncoupled) behaving as Hill reaction inhibitors. The target for $[Cr(2gb)_3]Cl(ZnCl_4)$ is located at the Q_B level. On the other hand, the interaction sites of $[Cr(2gb)_3]Cl_3$ and $[Co(2gb)_3]Cl_3$ are located in the span from P_{680} to Q_A at the b_6f complex. Neither $CrCl_3$ nor $[Co(NH_3)_6]Cl_3$ inhibited photosynthe-

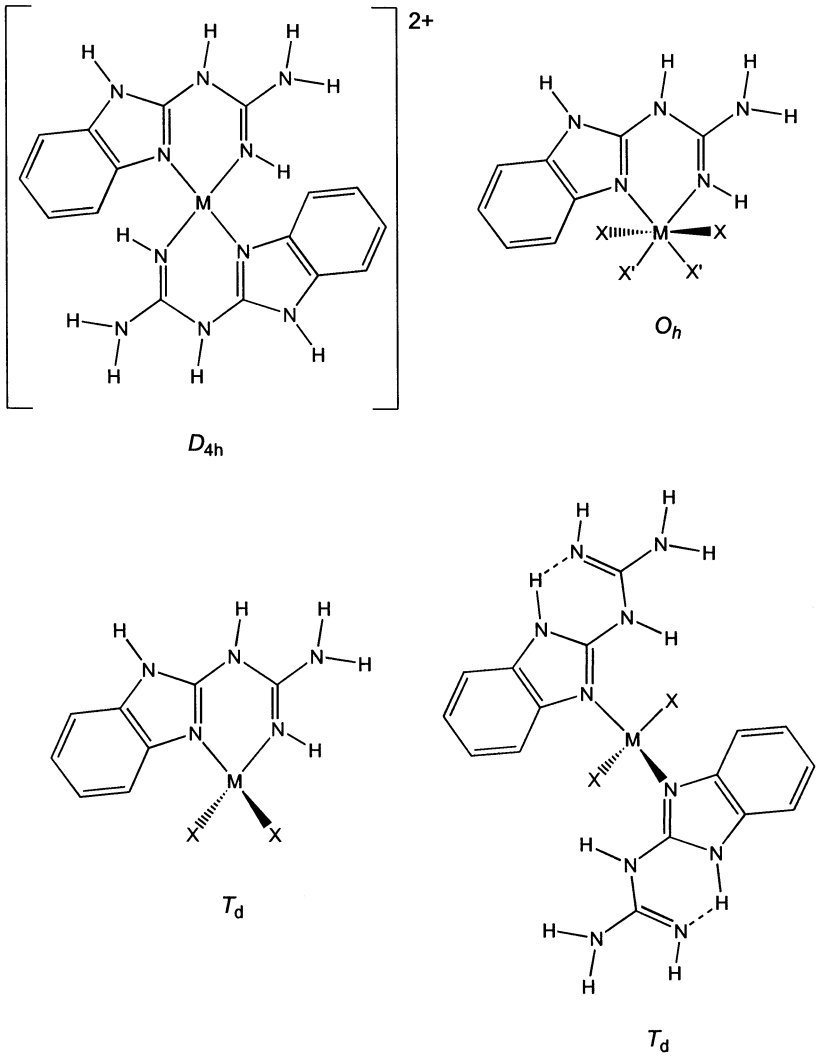

Fig. 5. Coordination compounds of 2-guanidinobenzimidazole with transition metal ions.

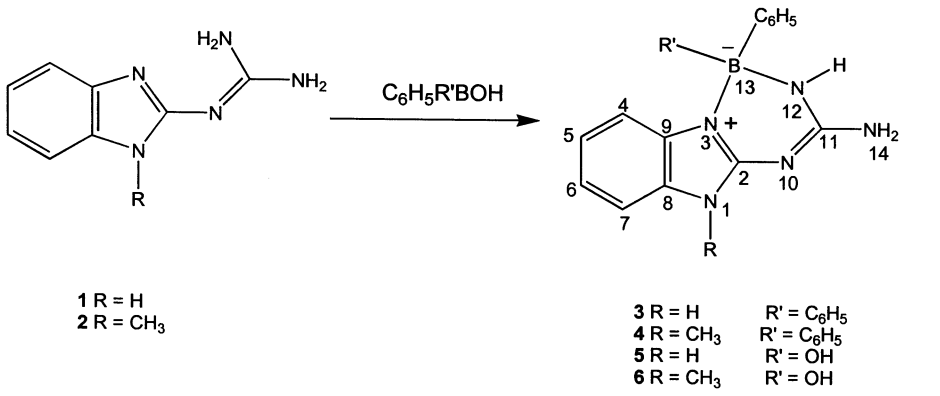

Fig. 6. Reactions of 2-guanidinobenzimidazole with phenylboronic acids.

sis. The 100% inhibition on PSII of $[Cr(2gb)_3]Cl(ZnCl_4)$ is explained in terms of a synergystic effect between the 2gb-chromium(III) coordination compound (Fig. 11) and the $ZnCl_4^{2-}$ anion [30].

3. Quinic acid compounds

Quinic acid (Fig. 12) is a natural metabolite closely related to shikimic acid [31]. Free quinic acid is widely found in the plant kingdom. It is known that cyclic polyols act as calcium carriers in biological systems, such compounds could therefore also be effective carriers for other metal ions, due to the formation of coordination compound [32]. It is also a very useful chiral raw material for total synthesis of complex molecules and chiral reagents for asymmetric synthesis [33,34]. Its relevance is based on its four chiral centres and the five functional groups. There has been an interest in preparing boron [35] and metallic derivatives [36] of quinic acid in order to study their structures, reactivity, spectroscopy, and their role in plant biology. The reactivity of diols and triols present in glycosides with boron containing reagents has been of interest in the chemistry of carbohydrates [37,38]. Reacting 1,2-diols or 1,3-diols with boron derivatives may prepare cyclic boronic

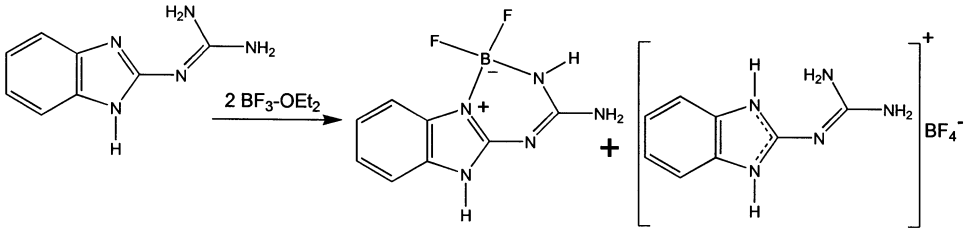

Fig. 7. Reactions of 2-guanidinobenzimidazole with BF_3–OEt_2.

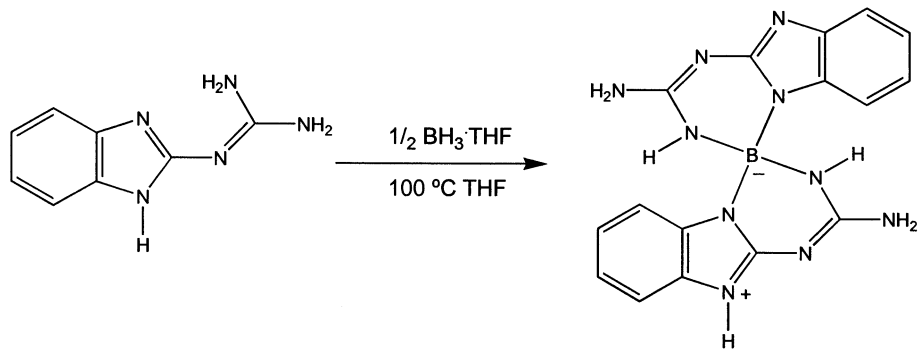

Fig. 8. Reactions of 2-guanidinobenzimidazole with borane.

esters. Quinic acid was reacted with boric acid in basic aqueous solution and the reaction followed by ^{11}B- and ^{13}C-NMR spectroscopies, where spirane compounds were obtained (Fig. 13) [39].

Bello-Ramírez et al. [40] reacted quinic acid with BH_3–THF or phenylboronic acid in different stoichiometries. The reaction of quinic acid with one equivalent of BH_3–THF affords the dioxaborolane, where equilibrium between the two species shown in Fig. 14 is presented. However with two equivalents of BH_3–THF a bis-dioxaborolane was isolated (Fig. 15).

Several groups have investigated the coordinating behaviour of quinic acid toward metal ions, lanthanides [41], indium [42], nickel(II) and cobalt(II) [43], praseodymium [44] and terbium [45]. There is an interaction between quinic acid and the metal ions through the α-hydroxyacid group in C-1, some stability constants are reported. It is proposed that quinic acid coordinates as a bidentate or tridentate ligand towards terbium(III), depending on the ligand to metal ratio and on the pH of the solution.

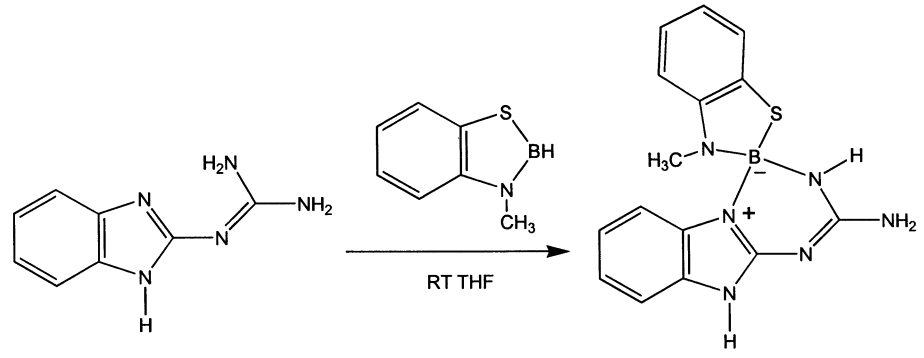

Fig. 9. Reactions of 2-guanidinobenzimidazole with 1,3,2-benzothiazaborole.

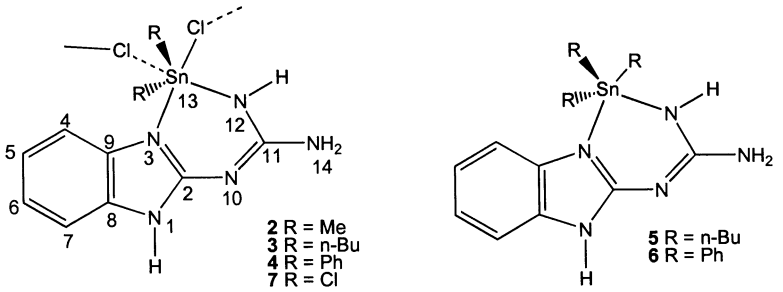

Fig. 10. 2-Guanidinobenzimidazole organotin compounds.

Griffith et al. [46] prepared and characterised a quinic acid compound with Mo(VI), and its structure (Fig. 16) was established by X-ray crystallography, ^{13}C- and ^{105}Mo-NMR spectroscopy. Later, two osmium(VI) complexes with quinic acid: $[OsO_2(py)_2(quin)]$ and $K[OsO_2(quin)]$ (where py = pyridine, quin = quinic acid) were also isolated (Fig. 17) [47]. Hata synthesised and characterised [48] a platinum(II) complex containing quinic acid and 1*R*,2*R*-cyclohexandiamine as ligands. The X-ray diffraction study of (1*R*,3*R*,4*R*,5*R*)-(−)-quinate(1*R*,2*R*-cyclohexandiamine)platinum(II) shows that quinic acid is bound to the platinum(II) metal centre through the α-hydroxyacid group, indicating that this is the most reactive group of the ligand towards metal atoms (Fig. 18).

Barba-Behrens et al. [49] synthesised the compounds: $[Cu(quin)Cl(H_2O)]_n\cdot(H_2O)_n$, $[Ni(quin)Cl(H_2O)]_n\cdot(2H_2O)_n$, $[Co(quin)Cl(H_2O)]_n\cdot(2H_2O)_n$, $[Cu(quin)(NO_3)(H_2O)]_n\cdot$

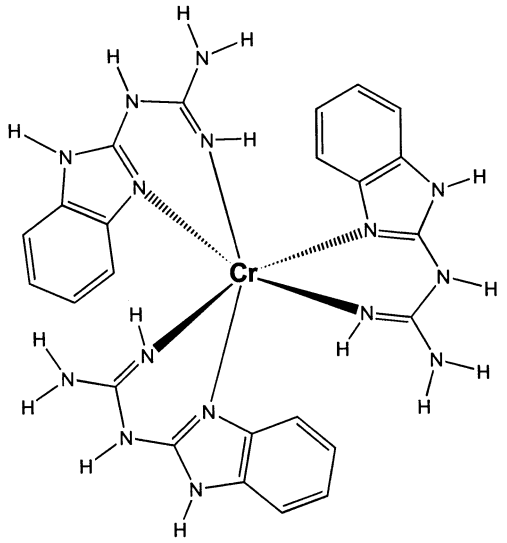

Fig. 11. 2-Guanidinobenzimidazole chromium(III) cation.

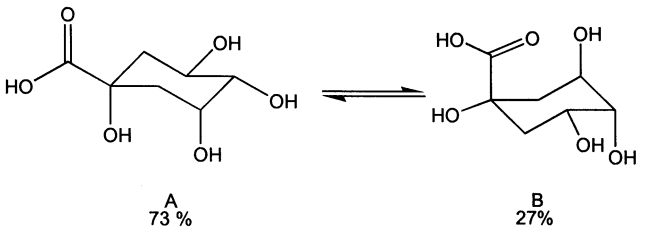

Fig. 12. Quinic acid in solution.

$(2H_2O)_n$, $[Cu(quin)(AcO)(H_2O)]_n\cdot(2H_2O)_n$, $[Cu(quin)H_2O]_2\cdot 2H_2O$, $[Cu(quin)_2]_2$, $[Zn(quin)_2]_2$,·$[Cd(quin)_2]_2$ and $[Hg(quin)_2]_2\cdot 4H_2O$. All compounds were characterised by IR and UV spectroscopies, additionally the compounds containing Zn(II)

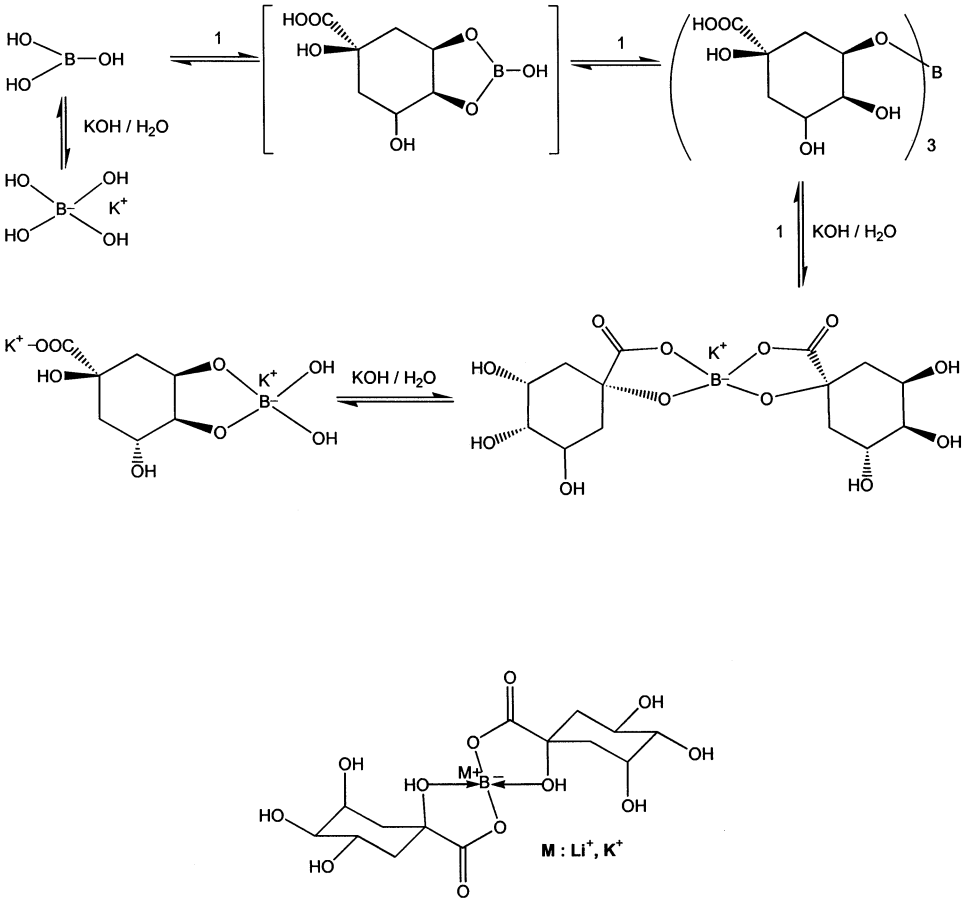

Fig. 13. Reactions of quinic acid with boric acid in basic aqueous solution.

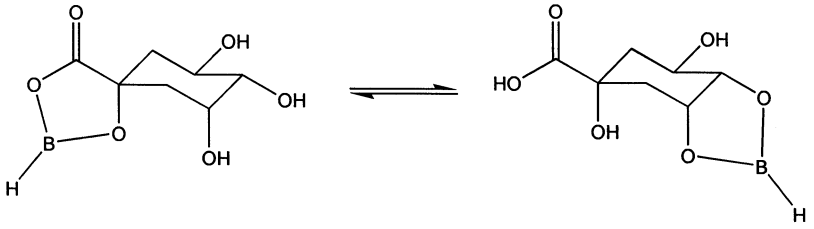

Fig. 14. Reaction product of quinic acid with one equivalent of BH_3–THF.

and Cd(II) were analysed by NMR and some of the copper compounds by X-ray crystallography. Due to the polyfunctionality of quinic acid diverse structures were obtained, some of them polymeric, or dimeric, while the Zn, Cd and Hg compounds were spiranes (Fig. 19). In $[Cu(quin)Cl(H_2O)]_n \cdot (H_2O)_n$ the copper has a distorted octahedral structure; it is a chiral centre with six different substituents and an optically active ligand. Only one stereoisomer (OC-6-25Δ) of the 30 possible was observed in the crystal (Fig. 20). $[Cu(quin)(NO_3)(H_2O)]_n \cdot (2H_2O)_n$ (Fig. 21) was also polymeric, the hexacoordinated Cu atom was a chiral centre(OC-6-53C) and only one stereoisomer was observed. It was bonded to three quinic acid ligands in three different coordination modes and each quinic acid was in turn bonded to three different Cu atoms. Each chain was linked to another two chains giving a net structure. $[Cu(quin)H_2O]_2 \cdot 2H_2O$ was a dimer with two square pyramidal Cu atoms. Two apical water molecules were found in a *cis* arrangement. Each quinic acid ligand was bonded to two Cu atoms that were linked by two oxygen bridges and each Cu atom was bonded to two quinic acid moieties (Fig. 22).

Quinic acid is an intermediate in the pathway of the synthesis of aromatic amino acids in plants. Barba-Behrens et al. have studied the uncoupling properties of quinic acid. Its uncoupling properties are most interesting, since most uncouplers are lipid soluble, possess a dissociable proton and a structure that allows for large charge delocalisation; however some uncouplers can be very soluble in water and have no dissociable proton and still be powerful uncouplers. In order to gain further insight into the uncoupling properties of quinic acid the influence of metal ions on its mode of uncoupling action was studied [49,28]. Quinic acid behaves as non-classical decoupler on photophosphorylation. The effect on photosynthetic

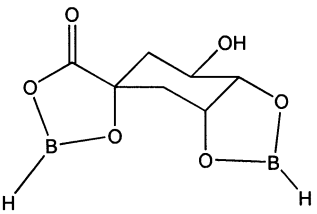

Fig. 15. Reaction product of quinic acid with two equivalents of BH_3–THF.

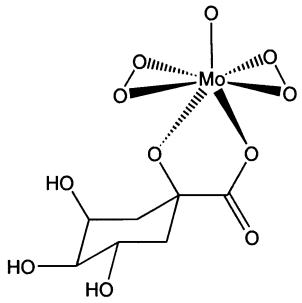

Fig. 16. Quinic acid coordination compound Mo(VI).

activities of M(quin)X(H_2O) (M^{2+} = Co, Ni, X^- = Cl) and M(quin)$_2$ (M^{2+} = Co, Zn, Cd) was studied [27]. The compounds [Co(quin)Cl(H_2O)]$_n$·(2H_2O)$_n$, [Co-(quin)$_2$]$_2$, [Ni(quin)Cl(H_2O)]$_n$·(2H_2O)$_n$, [Zn(quin)$_2$]$_2$, [Cd(quin)$_2$]$_2$, behave as non-classical decouplers. These compounds are stable in buffered aqueous solution, as indicated by UV-vis absorption spectroscopy. The effect of metal salts on photo-synthesis was assayed: cobalt chloride has a very mild effect as a decoupler, the other metal chlorides (nickel, zinc and cadmium) do not behave as decouplers on freshly lysed chloroplasts. With these results it is proposed that quinic acid may present uncoupling properties in vivo. This activity is important in the regulation of energy metabolism in plants [28].

Codd et al. reported the synthesis, characterisation and crystal structure of the first mixed-valence V(V)–V(IV)–V(V) trinuclear complex [50]. In $(NH_4)_2$-{[$V^V(O)_2$]$_2$[V^{IV}(O)](μ-(−)-quinato(3−))$_2$}·H_2O each trianion of quinic acid (1(*R*),3(*R*),4(*R*),5(*R*)-tetrahydroxycyclohexanecarboxylic acid) coordinates to all three vanadium ions. The ligand acts as a 2-hydroxylate chelate toward one V(V) ion and as a monodentate alcoholate toward the other V(V) ion. The alcoholate donors form a 1,3-diolato chelate and act as bridging groups between the central V(IV) ion and the outer V(V) ions. The geometry about all of the five-coordinate vanadium ions tends more toward an idealised square pyramid than towards a trigonal bipyramid, with the central V(IV) ion [V(O)(OR′)$_2$(OR″)$_2$]$^{2-}$ having the most square-pyramidal character (Fig. 23). The greater degree of trigonal character found in the coordination sphere of the V(V) centres [V(O)$_2$(O_2CR)(OR′)(OR″)]$^{2-}$ compared to the V(IV) centre, approximates the geometry of the active site of V(V)

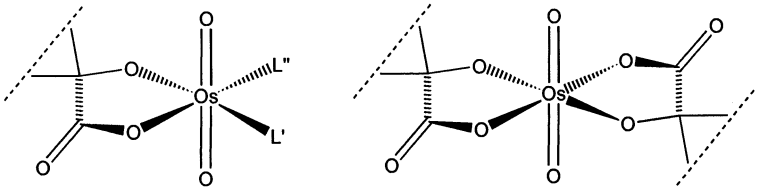

Fig. 17. Quinic acid coordination compounds with Os(VI).

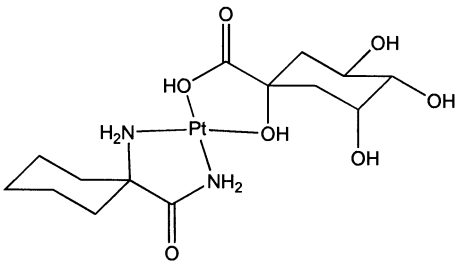

Fig. 18. Quinic acid coordination compounds with Pt(II).

inhibitor complexes of enzymes, including ATPases and RNases. The EPR spectrum ($g_{iso} = 1.9725$, $A_{iso} = 99.3 \times 10^{-4}$ cm^{-1}) is typical of a localised V(IV) system showing that the complex is a trapped-valence system. This is supported by a bond valence sum analysis (BVSA). The electronic spectrum shows a weak broad transition between 900 and 1000 nm, which is assigned to the intervalence transition of the complex.

The stability and ligand exchange reactions of chromium(IV) carboxylato complexes in aqueous solutions were investigated by Codd et al. [51]. The quantitative in situ generation of a range of Cr(IV) carboxylato complexes in aqueous media was achieved by a combination of the newly-developed Cr(IV) ligand exchange chemistry together with the existing methods of reduction of Cr(VI) or Cr(V) complexes. The reactions Cr(VI) + As(III) and Cr(V) + V(IV) in buffer solutions of the corresponding ligands were used for generation of Cr(IV) complexes with 2-hydroxy-2-methylbutanoate (hmba), 2-ethyl-2-hydroxybutanoate (ehba), and (−)-quinate (qa) ligands. Addition of oxalate (ox), malonate (mal), or 2-picolinate (pic) to the generated Cr(IV) complexes led to the quantitative formation of the new Cr(IV) species. The spectral and chemical properties of these Cr(IV) complexes were described for the first time (except for the known Cr(IV)-ehba complexes). From UV-vis and CD spectroscopic data, Cr(IV) appears to form mainly *bis*-chelated oxo complexes, in excess ligand. Fig. 24 shows the assigned structure for the Cr(IV)–quinate complex. The stability curves of the Cr(IV) compounds as a function of pH exhibit a bell-shape. The regions of maximum stability and maximal

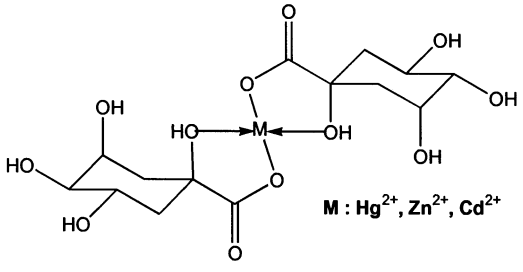

Fig. 19. Spiranic compounds of quinic acid.

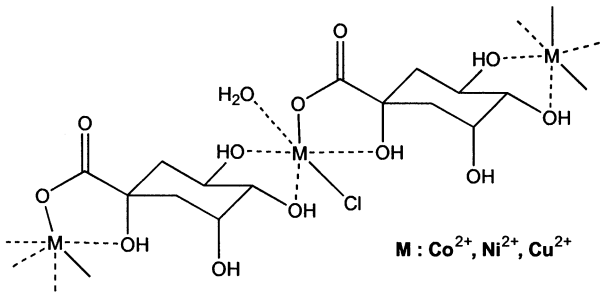

Fig. 20. Coordination compounds of quinic acid with transition metal ions.

half-lives ($[Cr(IV)]_0 = 0.1$ mM; 25°C) are as follows: pH approximately 3 and approximately 30 min for Cr(IV)–hmba and Cr(IV)–ehba; pH approximately 5 and approximately 1.5 h for Cr(IV)-ox; pH approximately 5 and approximately 1.5 min for Cr(IV)–mal; pH approximately 5 and approximately 20 min for Cr(IV)–pic; pH approximately 6 and approximately 1 h for Cr(IV)–qa. The stabilities of the Cr(IV) complexes were compared with those of the corresponding Cr(V) complexes (studied by EPR spectroscopy). The results are discussed in terms of the

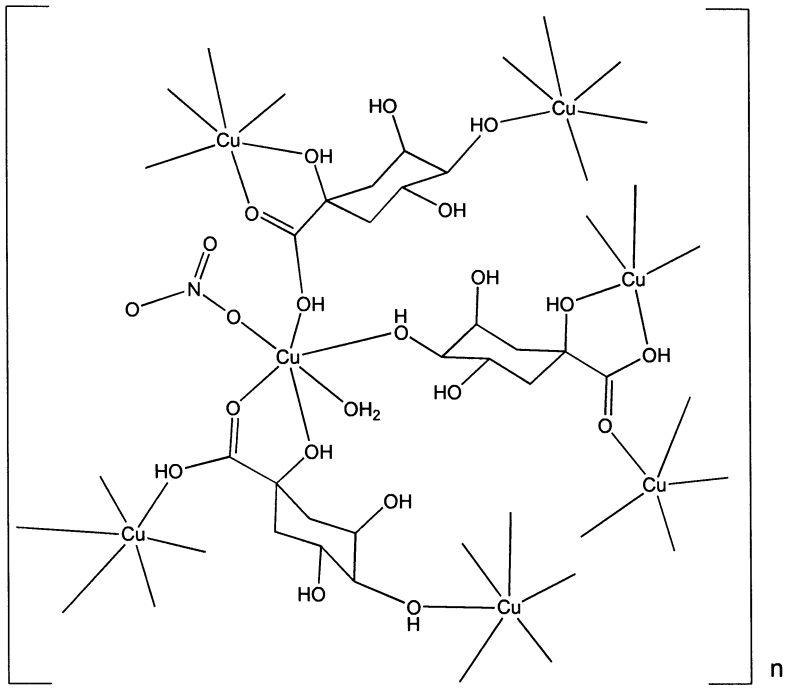

Fig. 21. Net structure of polymeric $[Cu(quin)(NO_3)(H_2O)]_n \cdot (2H_2O)_n$.

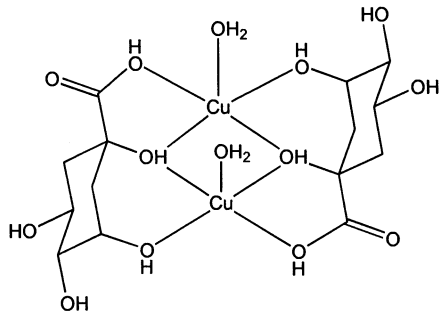

Fig. 22. Structure of dimeric $[Cu(quin)(H_2O)]_2 \cdot 2H_2O$.

possible roles of Cr(IV) and Cr(V) complexes as DNA-damaging agents in Cr-induced genotoxicities.

4. Coordination compounds with amino acid derivatives

4.1. N-carboxymethylpseudoephedrine

Most naturally occurring metal ions are bound to proteins. The question of the nature and extent of metal ion–protein interaction is therefore a most important one and has been the subject of extensive work using amides; amino acids and small peptides as model compounds [52–54]. The binding of metal ions may control the conformation of biological molecules and so affect their chemical and biological properties. In this context, there has been interest in the chemistry of coordination compounds derived from N-substituted glycine ligands, which may act as tridentate molecules. These tridentate molecules may have a strong preference for facial or meridional coordination, or both geometries could be stabilised.

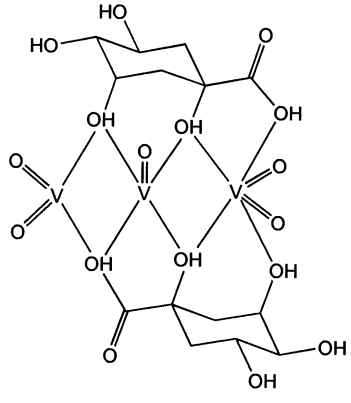

Fig. 23. V(V)–V(IV)–V(V) trinuclear quinic acid complex.

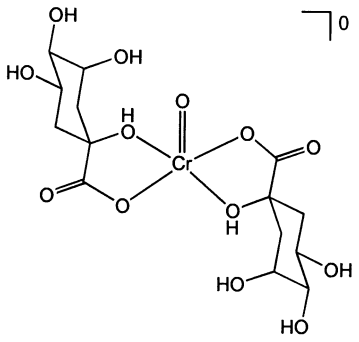

Fig. 24. Cr(IV) quinic acid complex.

The reaction of secondary and aromatic primary amines with aqueous glyoxal yields a complex mixture of products [55–57]. *N*-[2-hydroxy-1(*R*)-methyl-2(*R*)-phenylethyl]-*N*-methylglycine (*N*-carboxymethyl-pseudoephedrine, Hcpe) has been synthesised by reacting ephedrine with glyoxal and ethanol and characterised by Farfán et al. [58], as shown in Fig. 25.

The reaction between phenylboronic acid and *N*-alkyl-*N*-(ethyl-2-hydroxy)-aminoacetic acids leads stereoselectively to stable bi-cyclic esters containing chiral boron and nitrogen atoms [59]. The presence of carboxylic groups produces boron bi-cycles of great stability as has been observed in organyl boronic esters derived from iminodiacetic esters [56,57]. The formation of bi-cyclic structures can be demonstrated easily by spectroscopic methods. The reaction of *N*-(2-hydroxyethyl)-*N*-methylglicine with phenylboronic acid is shown in Fig. 26. Two isomers were detected by NMR spectroscopy, however only one isomer was isolated [59].

Farfán et al. [60] have reported the synthesis of bi-cyclic organoboron compounds, where ring closure between the nitrogen and boron atoms occurs under asymmetric induction, through the reactions of optically active *N*-methyl-*N*-(1-methyl-2-phenyl)glycines with 4-bromophenylboronic acid or with 1,4-phenyldiboronic acid. The reaction products are shown in Fig. 27. The same type of compounds had previously been derived from diethanolamines [61], phenolamines

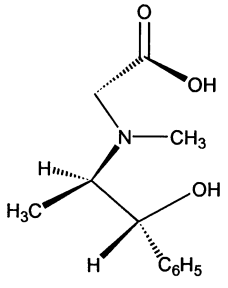

Fig. 25. *N*-carboxymethylpseudoephedrine.

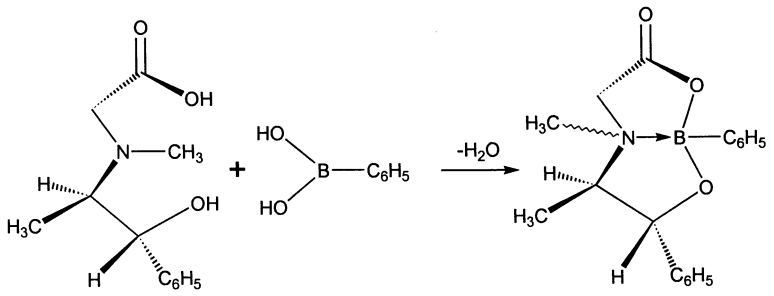

Fig. 26. Reaction of *N*-carboxymethylpseudoephedrine with phenylboronic acid.

[62], iminodiacetic acid [63] and *N*-alkyl-*N*-(hydroxyethyl)glycine [59]. Bi-clyclic boron compounds are of interest since they present cytotoxic activity [64–66] and have also found application in a technique known as boron neutron therapy used for the treatment of certain brain tumours [67].

N-[2-hydroxy-1(*R*)-methyl-2(*R*)-phenylethyl]-*N*-methylglycine (*N*-carboxymethylpseudo-ephedrine, Hcpe) with copper(II), cobalt(II) and cadmium(II) have been prepared and characterised [68]. Crystal structures of copper and cadmium complexes were obtained. In the compound $[Cu(cpse)_2]\cdot H_2O$, two cpse are coordinated in a tridentate mode giving place to an *fac*-*RS*-octahedral geometry (Fig. 28). The monomeric compound $[Cd(cpse)_2(H_2O)]$ has an uncommon seven-coordinate geometry with one cpse bonded in a similar arrangement to that of the copper(II) compound, with an oxygen atom from the carboxylate group in an apical position. The second cpse molecule is coordinated with all three atoms in the equatorial plane, the remaining axial position of the distorted pentagonal bipyramid being occupied by a water molecule (Fig. 28). As for the latter complex, the metal centre of $[Cd(cpse)Cl(H_2O)]\cdot H_2O\cdot$dmso (dmso = dimethyl sulfoxide) presents a distorted pentagonal–bipyramidal geometry where the apical positions are occupied by a water molecule and a chloride ion. The tridentate cpse ligand lies in the equatorial plane and the coordination sphere is completed by a chelating carboxylic group from another cpse ligand. Each carboxylate group of cpse is bridging two different cadmium atoms, forming a zigzag chain in a polymeric structure (Fig. 29).

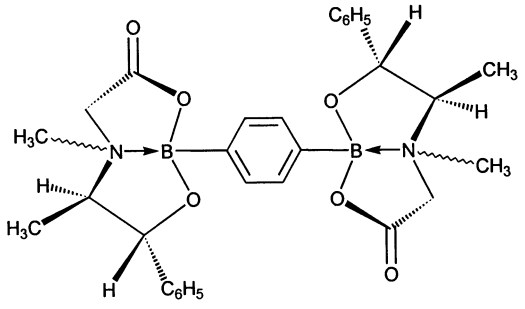

Fig. 27. Reaction of *N*-carboxymethylpseudoephedrine with 1,4-phenyldiboronic acid.

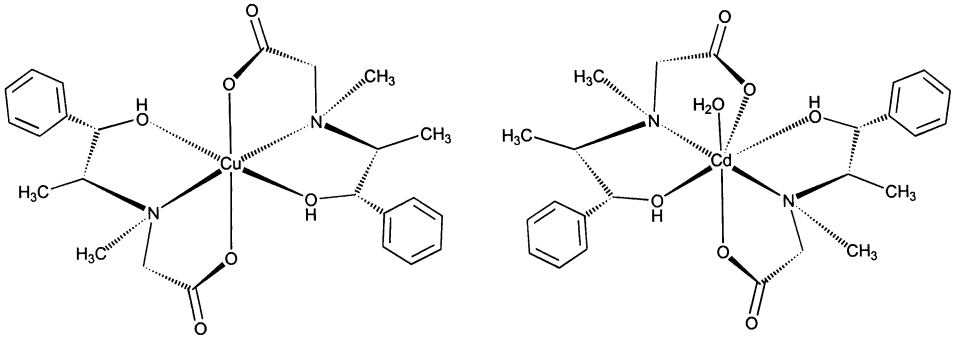

Fig. 28. Coordination compound of *N*-carboxymethylpseudoephedrine with Cu(II) and Cd(II).

Mancilla [69] reacted R_2SnO, where R = Me, *n*-Bu, *t*-Bu and Ph, with *N*-[2-hydroxy-1(*R*)-methyl-2(*R*)-phenylethyl]-*N*-methylglycine. Out of the several possible diastereomers (Fig. 30), the more abundant isomers obtained were those which have the CH_3–N and CH_3–C in *trans* position. The compounds were characterised by ^{1}H-, ^{13}C-NMR, IR and mass spectrometry.

4.2. Esters of iminodiacetic acid

Iminodiacetate (ida) is a tridentate ligand that forms coordination compounds where the metal ion is bound to one or two ligands in an octahedral arrangement via meridional or facial coordination [70,71]. This ligand is used as chelating agent in materials for detection and removal of trace elements from biological fluids and enzyme systems [72]. Copper–imidazole–iminodiacetate and related complexes have been used as structural models for some copper-proteins [73–75]. The dimethylester of iminodiacetic acid ($NH(CH_2CO_2CH_3)_2$) reacts with $CuCl_2{\cdot}H_2O$ and $ZnCl_2$ in aqueous ethanol to yield [Cu(idae)Cl(H_2O)] and [Zn(idae)Cl(H_2O)], respectively (idae = *O*-ethyliminodiacetato). In both compounds the original ligand is monohydrolysed and transesterified by ethanol [76,77]. When the reaction was carried out in methanol the corresponding methylmonoester copper compound, [Cu(idam)Cl(H_2O)] (idam = *O*-methyliminodiacetato), was the product. The X-ray diffraction structure of [Cu(idae)Cl(H_2O)] was obtained. The copper(II) atom is in

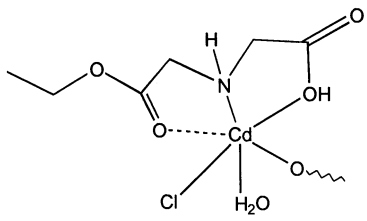

Fig. 29. Zig-zag chain in polymeric structure of [Cd(cpse)Cl(H_2O)]·H_2O·dmso.

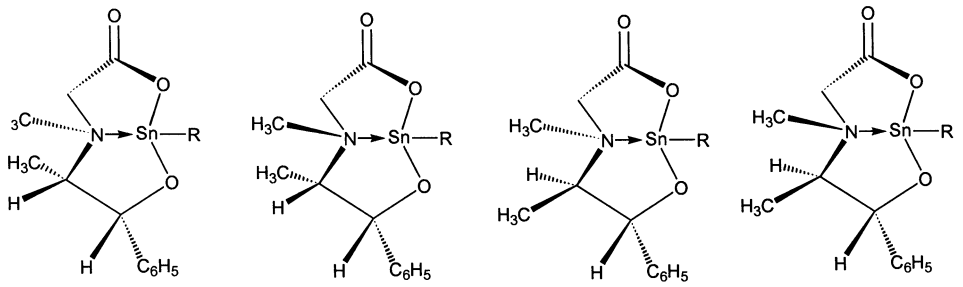

Fig. 30. Possible diastereomers of the reaction of R_2SnO.

a distorted octahedral geometry, with a *fac* coordination of the ligand. A chloride ion, water molecule and carboxylate oxygen from another molecule complete the coordination sphere, as shown in Fig. 31. The compound presents a monodimensional zigzag chains structure where the carboxylate oxygen of one ligand bridges two adjacent copper atoms, Fig. 31. The chirality of the N and Cu atoms alternates in the chains. The zinc compound was characterised by TGA, IR, and ^{13}C-NMR spectroscopic methods, and presented a similar structure to [Cu(idae)Cl(H_2O)] [77].

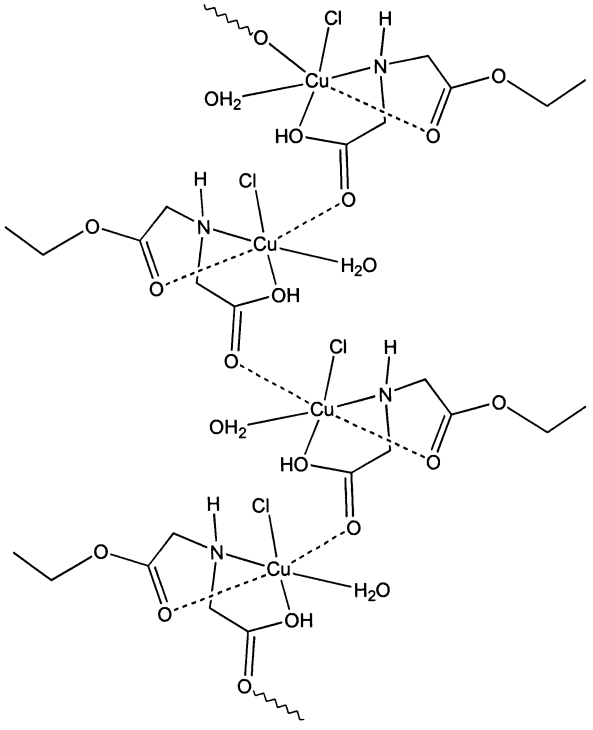

Fig. 31. Structure of [Cu(idae)Cl(H_2O)].

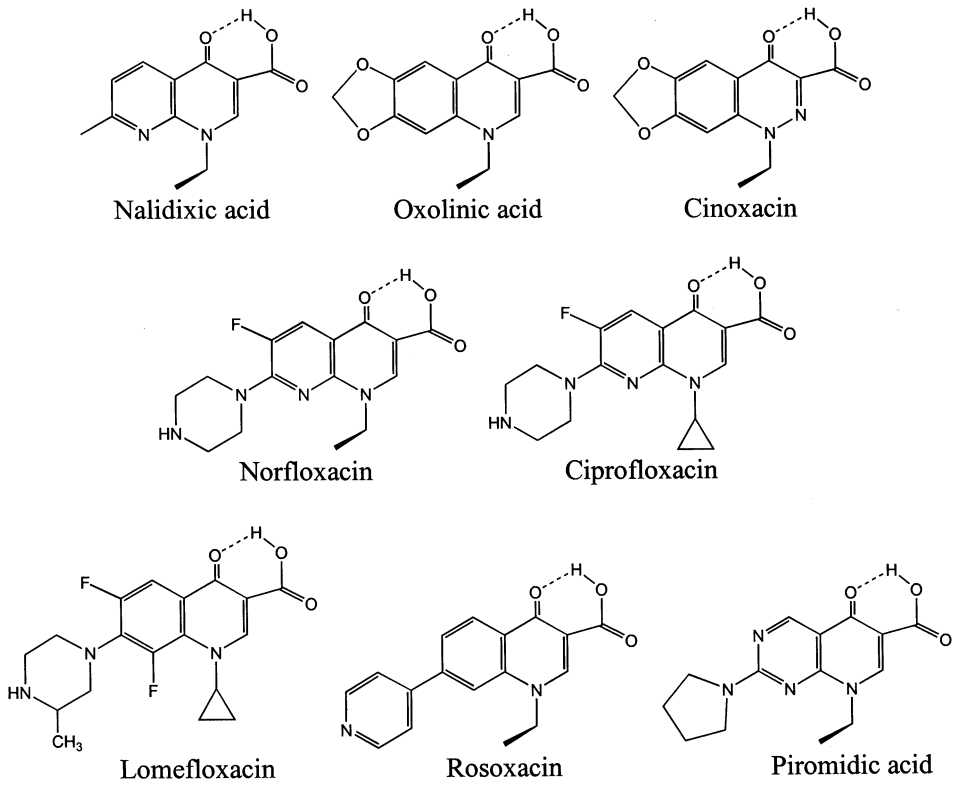

Fig. 32. Some drugs of the 4-quinolone family.

The interaction of vanadate with iminodiacetic acid derivatives caused the reduction of V(V) to V(IV) [72], contrary to what has been previously reported by Crans [78], who studied this interaction by ^{51}V-NMR. Guevara et al. studied the kinetics of the reduction reaction of V(V) to V(IV). The reaction was first order with respect to vanadate ($k_{obs} = 1.57 \times 10^{-4}$ min^{-1}), and was inhibited by the addition of *N*-donors, such as imidazole or pyridine [79].

5. Compounds containing quinolone antibiotics

There has been a tremendous growth of drugs from the 4-quinolone family. It began with the discovery of nalidixic acid 35 years ago. Since then, the exponential growth of this family has produced more than 10 000 analogues. Some are shown in Fig. 32.

The complexation of nalidixic acid (Fig. 32) has been the subject of research of several groups. Timmers [79] determined the ionisation constants and some divalent cation dissociation constants of nalidixic and oxolinic acids, both specific inhibitors

of bacterial DNA replication. The carboxylic pK'_a values are 6.1 and 6.9 at 25°C for nalidixic and oxolinic acids. These values indicate that intramolecular hydrogen bonding stabilises the un-ionised form of these compounds in aqueous solution. Both compounds bind divalent cations; the divalent cation dissociation constants for oxolinic acid are somewhat smaller than those for nalidixic acid. Both compounds may act by forming a complex in situ with a divalent cation in a metalloprotein involved in DNA replication.

Cole et al. [80] determined the formation constants for nalidixic acid complexation with proton, Cu(II), Mg(II), and GMP–copper(II). Use of these data (together with the corresponding published constants for Ca, Fe(II), Mn(II) and Zn(II)) supports the hypothesis that the drug acts at a site other than extracellular. Complex formation between nalidixic acid, metal ion, and DNA (at guanosine residues) may be involved in its antibacterial activity.

Barba-Behrens et al. [81] reported the preparation and spectral properties of a range of complexes of nalidixic acid (Hnal) with Cr, Mn, Fe, Ni, Cu, Zn, Mg, Ca, Cd, Hg and Pd. Most of the compounds formed by the divalent metal ions had a 2:1 Hnal:metal ratio, and some are polymeric. Complexes in which the carboxylate group of Hnal functions as a chelate were isolated with Cu(II), Pd(II), Fe(III) and Cr(III).

The complex-forming properties of drugs may be important both for their optimal biological activity and for alterations in the levels of endogenous ligands. Sykora [82] used the Mellor–Maley rule for prediction of the stability constants of drug complexes with metal ions of Mn, Fe, Co, Ni, Cu and Zn. Predictions for the complexes of tetracyclines, nalidixic acid and methicillin were based on the known complex-forming behaviour of ethylene diamine, dipyridyl and dithizone, respectively. These models allow estimation of complex stability for various metals from measurements with a single ligand. However, the models do not allow prediction of all biological aspects, such as formation of insoluble complexes altering drug absorption and other undesirable side effects.

Mendoza-Díaz reports that the nalidixate ion exhibits the capability to act as a chelate towards Cu^{2+} ions in aqueous solution, as detected by ^{13}C-NMR [83]. The site of binding depends upon the nature of the other ligands present in solution. In the absence of added ligands, chelation via the 3-carboxylate group is observed, while interaction with $[Cu(phen)]^{2+}$ (phen = 1,10-phenanthroline) is via chelation with both the 3-carboxylate and 4-oxo groups.

The complexation behaviour of nalidixic acid (Hnal) with Fe(III) in aqueous solution under various conditions was examined [84]. A yellow water soluble complex formed in acidic medium (pH 3.0), at 25°C and ionic strength of $\mu = 0.3$. This 1:2 (Fe(III):Hnal) complex exhibits an absorbance maximum at $\lambda = 419$ nm, has an apparent molar absorptivity $\varepsilon = 3.09 \times 10^3$ dm^3 mol^{-1} cm^{-1}, involving Sandell's sensitivity of 18.1 ng cm^{-2} per 0.001 absorption unit, while its formation constant, which was determined spectrophotometrically at 25°, was $K_f = 4.7 \times 10^7$. The above-mentioned Fe(III)–Hnal complex was applied afterwards to the determination of traces of Fe(III). The calibration graph is rectilinear at 0.5–40.0 ppm of Fe(III) and the corresponding regression line equation is $A = 5.3 \times 10^{-2}\ C \pm 1.2 \times$

10^{-2} with a correlation coefficient of 0.9997 ($N = 11$). Except for Ce(IV), common cations like Cu(II), Zn(II), Ca(II), Mg(II), Co(II), Ni(II), Mn(II), Al(III) and La(III) do not interfere with the determination. A statistical comparison of the results obtained by the suggested procedure with those derived from the thiocyanate method showed no significant difference.

Nalidixic acid has been extensively used against Gram-negative bacteria in urinary tract infections and in some gastrointestinal infection caused by Shigella and other bacteria [85]. Anaya-Velázquez et al. investigated the in vitro activity of the antibacterial agent nalidixic acid (Hnal) and its iron(III) complex (Fenal) against *Entamoeba histolytica* HM1 strain trophozoites in axenic or monoxenic (associated with *Clostridium symbosium*) cultures [85]. Using a dilution test with TYI-S-33 medium, this protozoan was found to be susceptible to both drugs, but Fenal showed amoebicidal activity only at concentrations higher than those used with Hnal.

Maeng et al. [86] studied the metallodrug formation of nalidixic acid, the first member of the quinolone antibiotics, with heavy metal ions such as Cu^{2+} and Tb^{3+} by a UV-spectrophotometric titration method. They also investigated the effect of the nalidixic acid–metal complex on the growth of both gram negative (*Escherichia coli* K1100) and gram positive (*Bacillus subtilis* KCTC1210) bacteria. The complex was more effective in the inhibition of the growth than nalidixic acid alone without the metal. The antibiotic effect of the metallodrug may result from the inhibition of DNA synthesis of the bacteria.

Djurdjevic et al. [87] studied the complexation equilibrium between cadmium(II) ion and nalidixic acid by pH-metric and spectral (UV and fluorimetric) measurements. The experimental data obtained by pH titration in 0.1 M KCl medium, at 298 K, were explained by the formation of the following complexes and their respective stability constants, log ($\beta \pm \sigma$): $[Cd(nal)]^+$ (5.48 ± 0.10) and [Cd(OH)nal], (-2.35 ± 0.12).

Mendoza-Díaz [88] reported the synthesis and characterisation of a series of mixed complexes of the type $[Zn(N–N)(nal)(X)]\cdot nH_2O$ (where N–N is either 1,10-phenanthroline (phen) or 2,2′-bipyridine (bipy); nal is the anion of the antibiotic nalidixic acid and X could be a nitrate or chloride anion). Using ^{13}C-NMR studies, it was concluded that the complexes have trigonal bipyramid geometry, Fig. 33. The nalidixate anion is coordinated through one oxygen atom of the 3-carboxylate and one of the 4-oxo group.

Ramírez-Ramírez et al. [89] reported the alteration of bacterial DNA structure and/or associated functions in vivo by $[Cu(phen)(nal)]^+$, a metal complex of the type $[Cu(phen)(antib)]^+$ (where antib is a quinolone or a fluoroquinolone). This was demonstrated by the induction of a *recA–lacZ* fusion integrated at the *amyE* locus of a recombinant *Bacillus subtilis* strain. Using the same approach, nalidixic acid induced 14% of the β-galactosidase levels of $[Cu(phen)(nal)]^+$. On the other hand, none of the other components, i.e. Cu, phen or $[Cu(phen)_2]^{2+}$ significantly activated the *recA*-directed β-galactosidase activity, suggesting that the intact structure of the complex be required to reach maximum levels of induction. Results of in vitro experiments demonstrated that under reductive conditions $[Cu(phen)(nal)]^+$

behaves as a powerful nuclease capable of degrading plasmid DNA; this activity was stronger than that of the chemical nuclease $[Cu(phen)_2]^{2+}$. The nuclease activity putatively occurred by a mechanism involving hydroxyl radicals since the reaction was partially inhibited by catalase. These results support the hypothesis that the mechanism of action of quinolones could be mediated by a transition metal ion such as Cu.

Alvarez et al. [90] undertook a systematic study of the nature of quinolone metal complexes formed by electrospray ionisation and laser desorption/ion–molecule reactions to evaluate the analytical utility of metal complexation as an alternative to conventional ionisation via protonation.

Studies of complexation equilibrium of the antibiotic anions nalidixate and cinoxacinate with $[Cu(phen)]^{2+}$ and $[Cu(bipy)]^{2+}$ were carried out by Mendoza-Díaz et al. [91]. These studies indicate that the stability of this type of complex is strongly related to the metal environment. A correlation between the stability constants, determined here, with the sigma donation character of the ligand is proposed. This study shows that the stability constant for the reaction between the quinolones and the moiety $[Cu(N–N)]^{2+}$ is dependent on the diamine coordinated to the metal ion. These results suggest that inside the living cell, a possible interaction with some metal ions will be strongly controlled by the type of ligand bound to the cation.

Perello [92] prepared the compounds $Na[Co(cx)_3]\cdot 10H_2O$, $[Ni_2(cx)_3]ClO_4\cdot 8H_2O$, and $[Cu(cx)_2H_2O]$ (Hcx = cinoxacin) and studied their thermal behaviour by thermogravimetry, and IR spectroscopy. The complexes decompose in two steps: dehydration and decomposition of the anhydrous complexes to metal or metal oxide. The activation energies of the dehydration processes were determined and the water molecules are concluded to interact weakly with the metallic ion.

The thermal behaviour of complexes of cinoxacin with Co(II), Zn(II) and Cd(II) was studied using TG and DSC [93]. The complexes decompose in two steps: dehydration and pyrolytic decomposition. Dehydration enthalpies have been calculated from the DSC curves.

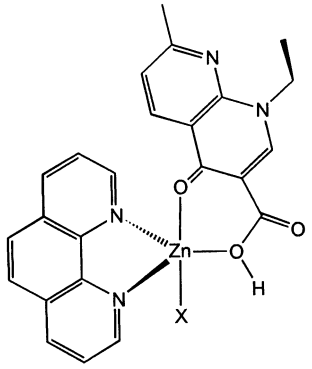

Fig. 33. Mixed complexes of zinc(II): $[Zn(N–N)(nal)(X)]\cdot nH_2O$.

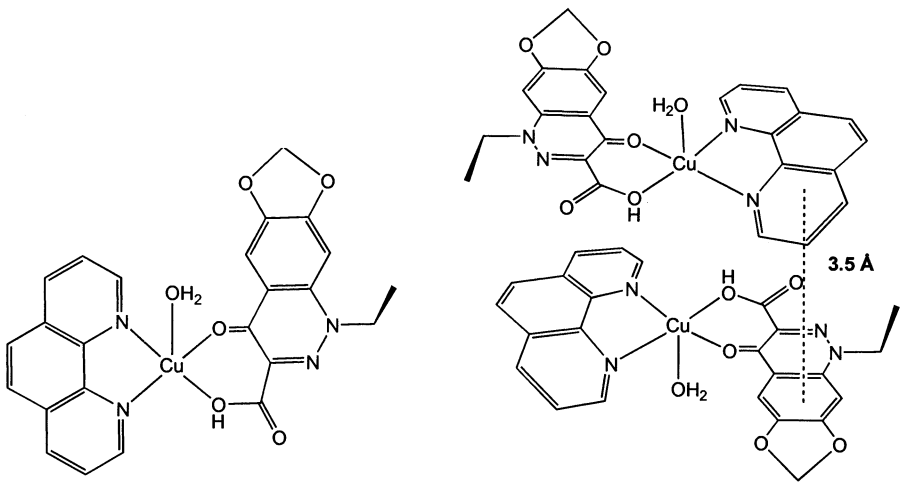

Fig. 34. Structure of $[Cu(phen)(cx)(H_2O)]\cdot NO_3\cdot H_2O$.

The stability constants of metal complexes of several pyridonecarboxylic acid drugs (ofloxacin, norfloxacin and lomefloxacin) were determined by potentiometry and spectrophotometry [94]. The stability values of the aluminium, magnesium and calcium complexes lie in the sequence $Ca < Mg \cong Al$. The stability constants of lomefloxacin complexed with divalent transition metal ions were determined and these values follow the Irving–Williams series ($Mn < Fe < Co < Ni < Cu < Zn$). The stability constants of metal complexes for several pyridonecarboxylic acids synthesised were also determined and compared with those for pyridonecarboxylic acid drugs. The stability constants of these compounds gradually increased with an increasing pK_a value of the carboxyl group of pyridonecarboxylic acid. In the case of aluminium complexes, the complexes Al(OH)L and $Al(OH)_2L$ were formed under weak acidic conditions and the dissociation constants for the hydrolysis of the aluminium complexes were determined. The participation of the carboxyl group and the carbonyl group in the chelating reaction was confirmed by the measurement of ^{13}C-NMR of the aluminium complex and the magnesium complex. These results suggest that when pyridonecarboxylic acids are administered with metallic containing aluminium hydroxide and magnesium oxide, aluminium complexes AlL, Al(OH)L or $Al(OH)_2L$ are formed and the adsorption of the drugs is reduced.

The crystal structures of cinoxacin [95] and rosoxacin [96] and piromidic acid [97] were determined. The central fused rings are nearly planar and the *N*-ethyl substituent adopts a similar conformation as in oxolinic and nalidixic acids, as can be seen in Fig. 32.

Mendoza-Díaz et al. [98] reported the synthesis of eight new mixed-ligand complexes of Cu(II) of the type [Cu(N–N)(ant)]X, where N–N is 1,10-phenanthroline or 2,2′-bipyridine, ant is the anion of cinoxacin (cx) or oxolinic acid (oxo), both drugs of the quinolone family. The crystal structure of $[Cu(phen)(cx)(H_2O)]\cdot$

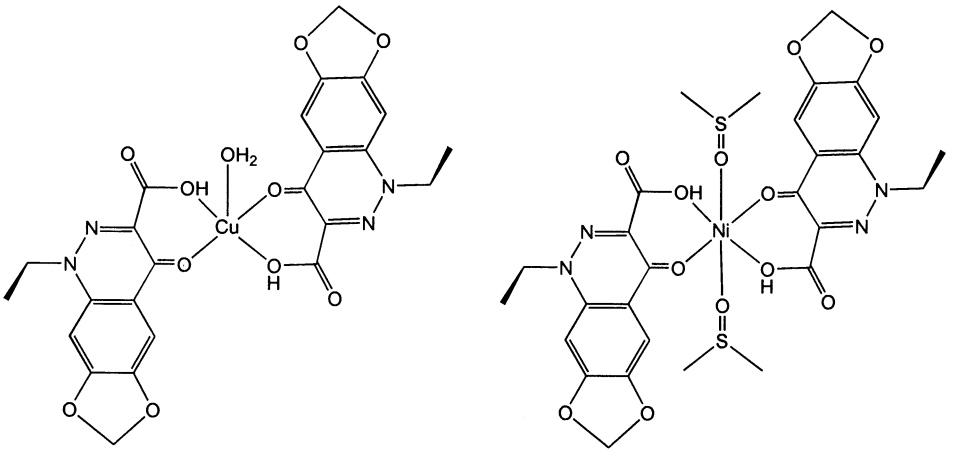

Fig. 35. Structures of $[Cu(cx)_2(H_2O)]\cdot 3H_2O$ and $[Ni(cx)_2(dmso)_2]\cdot 4H_2O$

$NO_3\cdot H_2O$ (Fig. 34) is presented and discussed. These results together with those previously reported for the complex $[Cu(phen)(nal)(H_2O)]NO_3\cdot 3H_2O$ and preliminary crystal data for $[Cu(bipy)(oxo)]NO_3\cdot H_2O$ suggest that all the quinolone type drugs behave as ligands in a similar way, under equivalent conditions.

The interaction of cobalt(II), nickel(II), copper(II), and zinc(II) with cinoxacin has been studied at metal/ligand ratios of 1:1–1:3 by means of pH-metric, spectrophotometric and EPR methods [99]. The formation constants have been determined and the stereochemistry for the metal ions in the species present in aqueous solutions (37 ± 0.1°C and $I = 0.1$ mol dm^{-3}) is discussed. In all the studied systems, complexes with different stoichiometric ratios, in which cinoxacin acts both as neutral and deprotonated ligand are formed. The anomalous sequence of the stepwise stability constants observed for cobalt(II) and nickel(II) systems suggests changes in stereochemistry when $Cocx_2$ and $Nicx_2$ are formed. A $[Zncx_2]^+$ species has not yet been detected. The stepwise stability constants for Cu(II) suggest the preferential formation of a $[Cucx_2]^+$ monocomplex. The $[Cu(cx)_2H_2O]\cdot 3H_2O$ is five coordinate and the $[Ni(cx)_2(dmso)_2]\cdot 4H_2O$ contains six-coordinated Ni(II), as shown in Fig. 35 [99].

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