Comments on Inorganic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713455155

Anti-Inflammatory Compounds as Ligands in Metal Complexes as Revealed in X-Ray Structural Studies

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To cite this Article Cini, Renzo(2000) 'Anti-Inflammatory Compounds as Ligands in Metal Complexes as Revealed in X-Ray Structural Studies', Comments on Inorganic Chemistry, 22: 3, 151 — 186
To link to this Article: DOI: 10.1080/02603590008050867
URL: http://dx.doi.org/10.1080/02603590008050867

Anti-Inflammatory Compounds as Ligands in Metal Complexes as Revealed in X-Ray Structural Studies

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(Received December 13, 1999)

The papers which report on the crystal structures of the metal complexes containing anti-inflammatory drugs used to cure humans and other animals are critically reviewed and analyzed to search for the major structural-characteristics both for the coordination spheres and the ligand moieties. Even though this is not an exhaustive review, it appears that metal complexes of non-steroidal anti-inflammatory drugs (NSAID) only, have been reported thus far. The total number of compounds structurally characterized via diffraction techniques is small (ca. 20). Five of the complexes contain piroxicam (H_2pir, see list of abbreviations) and almost fifteen of them are based on drugs from the carboxylic acid family: indomethacin (Hindo), tolmetin (Htol), naproxen (Hnap), diclofenac (Hdic) and aspirin (Hasp). The metals studied are also few in number, Cu(II) being the more frequently encountered; other metals are Cd(II), Pt(II) and Sn(IV). Some of the articles reviewed include the syntheses and the physico-chemical characterizations of other complexes whose molecular structures are inferred from spectroscopic techniques. Some complexes of H_2pir with Fe(II), Co(II), Ni(II), and Zn(II) and a complex of ibuprofen (Hibu)

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Comments Inorg. Chem.
2000, Vol. 22, No. 3-4, pp. 151-186
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with Cu(II) have been partially characterized in this way. The preponderance of Cu(II) complexes stems from the long-known anti-inflammatory superoxide dismutase (SOD) like activity shown by several Cu(II) inorganic and coordination compounds. $[M^{II}(Hpir)_2(dmf)_2]$ (M: Cu, Cd) are pseudo-octahedral neutral complexes of the monoanionic piroxicam ($Hpir^-$) drug in the ZZZ conformation. The Cu(II) derivatives have a high oxygen radical scavenger activity as measured through the luminescence technique by using stimulated human neutrophils from healthy subjects. The peripheral parts of the complex molecules are mostly hydrophobic in character. The $[Pt^{II}Cl_2(H_2pir)L]$ (L: dmso, C_2H_4) complexes contain the neutral ligand molecule H_2pir in the EZE conformation, coordinated through the pyridyl nitrogen atom only. The Pt-N linkage is greatly weakened by the high trans influence of the S-DMSO and η^2-C_2H_4ligands. The molecular structure of the polymeric $[Sn^{IV}(pir)(bu)_2]_n$ compound has two n-bu groups and a doubly deprotonated tridentate pir^{2-} ligand (ZZE) per Sn center. The donor atoms from pir^{2-} are the enolate oxygen and the amidate nitrogen. The pyridyl nitrogen is also weakly bound to the Sn^{IV} atom. The amidic oxygen atom forms a weak link to the Sn^{IV} atom from a different coordination unit. The Pt and Sn compound are of potential anti-inflammatory and anti-tumor interest because of the presence of the piroxicam and of the $PtCl_2$ and $Sn(bu)_2$ reactive moieties. The complexes from the carboxylic acid family usually have the formula $[Cu^{II}{}_2L_4L'_2]$ (L: $indo^-$; L': dmf, H_2O, nmp, dma, dmso. L: tol^-, nap^-; L': dmso. L: dic^-; L': ac, dmf) and $[Cu_2(asp)_4]$, and are neutral binuclear molecules which show a high peripheral hydrophobicity. The $indo^-$, tol^-, nap^-, dic^- and asp^- derivatives have a chemical inertness, at least as regards the $[Cu_2L_4]$ coordination core, in some solution conditions (e.g. biological buffers, HEPES (*N*-2-hydroxyethylpiperazine-*N'*-2-ethanesulfonic acid) and TES (*N*-tris(hydroxymethyl-2-aminoethanesulfonic acid)). The compounds can exert a SOD-like activity once the apical positions on Cu(II) are made free by dissociation of L'. Both the piroxicam and the carboxylic acid family molecule conformations have been analyzed (the metal-bound and the free forms). Molecular orbital investigations at semi-empirical levels have been initiated for some of the ligands in this article, with the aim of searching for fast and easily accessible ways to compute reliable conformations, charges and energetics; I hope that all laboratories will find these methods to be useful in subsequent analyses of drug-metal and drug-enzyme interactions.

Keywords: *Anti-inflammatory; Inflammation; Complexes; Copper; Platinum; Tin; Structure; X-Ray; Neutron; Diffraction*

Abbreviations: ac, acetone, aca, acetaldehyde, bu, n-butyl, buOH, n-butyl alcohol, dma, N,N-dimethylacetamide, etac, ethylacetate, etOH, ethyl alcohol, dmf, N,N-dimethylformamide, dmso, dimethylsulfoxide, FDA, Food and Drug Administration (U.S.A.), Hasp, acetylsalicylic acid, Hdic, diclofenac, 2-[(2,6-dichlorophenyl)amino]-phenyl-acetic acid, Hibu, ibuprofen, α-methyl-4-(2-methylpropyl)benzene-acetic acid, Hindo, indomethacin, 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indole-3-acetic acid, H_2mel, meloxicam, 4-hydroxy-2-methyl-*N*-(5-methyl-2-thiazolyl)-2*H*-1,2-benzothiazine-3-carboxamide-1,1-dioxide, Hnap, naproxen, 6-methoxy-α-methyl-2-naphthalene-acetic acid, H_2pends, penicillamine disulfide, H_2pir, piroxicam, 4-hydroxy-2-methyl-*N*-2-pyridyl-2*H*-1,2-benzothiazine-3-carboxamide-1,1-dioxide, Htol, tolmetin, 1-methyl-5-(p-toluolyl)-1*H*-pyrrole-2-acetic acid, ipOH, isopropyl alcohol, meOH, methyl alcohol, MM, molecular mechanics, MO, molecular orbital, Nmp, N-methylpyrrolidone, py, pyridine

I. INTRODUCTION

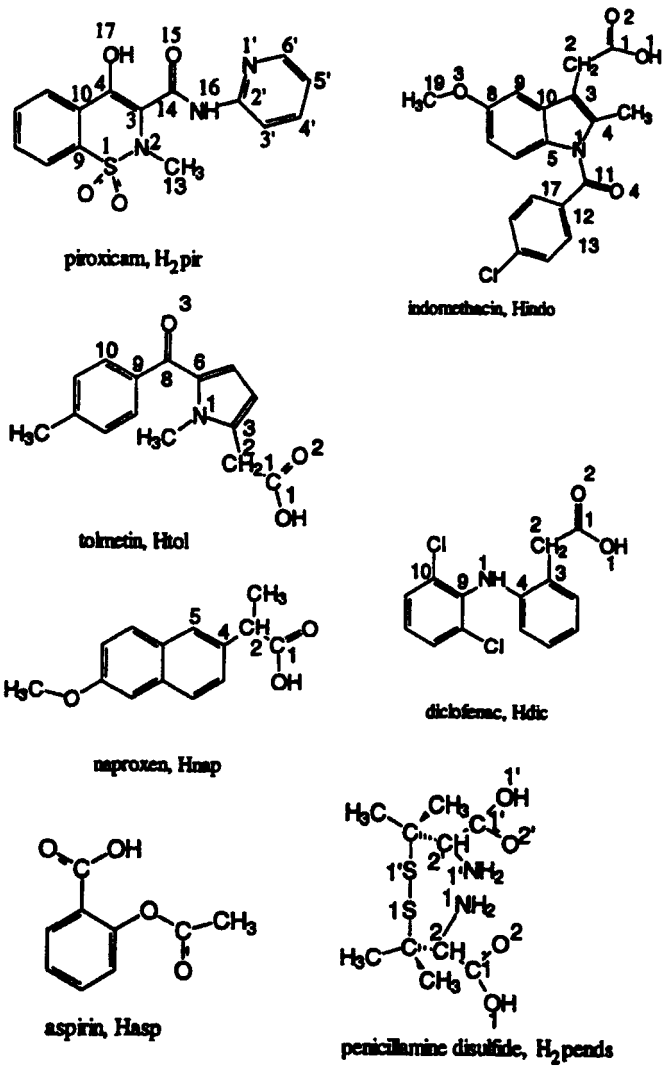
The synthesis of metal complexes of active drugs as ligands is a field of increasing interest for inorganic, pharmaceutical and medicinal chemistry.[1–6] The goal is to prepare compounds with better pharmacological activity than that of the free ligands. This result can come from one or more of several contributions such as: (a) synergistic effects of the ligand and the coordination residue once the complex is decomposed in the biological environment, (b) an intrinsic high activity of the complex itself, (c) a protection from the enzymatic degradations of the drug once it is firmly linked to a metal center, (d) the neutralization of overall negative charges on the drug molecule upon complex formation, (e) the tuning of the hydrophobicity/hydrophilicity in a manner allowing a better solubility in the biological fluids, and finally (f) a superior transport process through the cell membranes. Combined therapies are nowadays very often administered in many diseases with the aim of increasing efficacy and circumventing drug resistance.[3,7] Different active functions can be successfully combined in the same molecule through coordination chemistry. In fact, several active molecules can be added to the same metal center. From this latter they can be released in several steps. Moreover, the coordination residues can exert their own effects; for instance, anti-tumoral and anti-bacterial activities are expected in the cases the central atoms are Pt(II), Pt(IV), Ru(II), Ru(III), Rh(II), Rh(III), Bi(III), Sb(III), Sb(V), Ag(I), and Au(I).[2–4]

Inflammation or flogosis is "a protective response of tissues affected by disease or injury, and characterized by redness, localized heat, swelling, pain, and possibly impaired function of the affected part."[8a] Rheumatic diseases are usually deeply related to inflammation. The clinics of rheumatology are the places in which most research is devoted to cure inflammatory diseases. Most of the anti-inflammatory drugs are also anti-rheumatic drugs. Furthermore, tissues which neighbor tumors are often inflamed, and the mutagenic and carcinogenic mechanisms can be connected with inflammatory factors.[8b]

Metal ions are connected in several ways with inflammatory diseases. For instance, rheumatoid arthritis, which is an inflammatory disease that causes the progressive erosion of the articular cartilage is often treated by chrysotherapy. This consists in the administration of gold-based drugs such as myochrysin, sanochrysin, allochrysine, salganol, auronofin, etc.[3a] Interestingly, auronofin and analogues derivatives also

have anti-tumor activity; whereas salganol and analogues inhibits reverse transcriptase *in vitro*.[3a] As a second example it is worth noting that Zn(II) has been tested as an anti-inflammatory agent, and that Zn(II) at 80–200μM has a near total inhibition of Scl-70/Topoisomerase I, a DNA unwinding enzyme essential for gene transcription and for selective activation of gene clusters required for the coding of dermal collagene.[9] A collagen overproduction brings to the series of human disorders known as scleroderma.[8a,10] As other examples of metal-inflammation relationships, the superoxide scavenger activity of the Cu(II)/Zn(II)-superoxide dismutase (CuZn-SOD),[11] the anti-inflammatory activity of $[Cu_2(indo)_4(dmf)_2]$[6] and related molecules which act as drugs in dogs, and of various other Cu(II)[5] as well as Mn(II)[12] complexes, must be mentioned. Oxygen radicals are thought to be mediators of several diseases such as neuronal apoptosis, cancer, and acquired immuno-deficiency. While the anti-inflammatory activity exerted by gold drugs seems to pass through a proteasic / histocompatibility complex (HC) formation / immune system (T-cell)-HC interaction mechanism,[3a] non-steroidal anti-inflammatory drugs (NSAIDs) are believed to act mostly by receptorial mechanisms at the level of the arachidonic acid cascade.[13a] In fact, a characteristic of the NSAIDs is their ability to inhibit the cyclooxygenase (COX) activity of prostaglandin (PG) endoperoxide synthase.[13a,b,c] In this way the production of PGH2, PGE2, which act as mediators of inflammation, is prevented. However, NSAIDs are usually the cause of damage to the gastro-intestinal tract and to the kidneys, when administered for a long period.[14] In this regard, it was found that there were two isoforms of COX, namely COX1 and COX2.[15,16] It has been proposed that the gastro-intestinal and renal toxicity is due to inhibition of COX1, while the anti-inflammatory activity is due to inhibition of COX2. Therefore, the search for selective inhibitors for COX2 is a field of investigation at the present time.[16a] The highest selectivity toward COX2 found in a work on several oxicam NSAIDs showed that meloxicam has the better COX2/COX1 selectivity profile, while piroxicam has the second position in that list of anti-inflammatory agents.[13c] The X-ray structures of indomethacin-COX1 and -COX2 complexes have been reported.[16b–f] Recent papers and review articles related to the field of COX2/COX1 selectivity and to new drugs approved by FDA are listed in Refs 17.

In this review, attention is focused on the metal complexes of the NSAID family (to my knowledge no metal-steroidal anti-inflammatory



SCHEME 1.1 Structural formulae for the anti-inflammatory drugs discussed in the review. The numbering of the atoms used throughout the manuscript is also shown. The conformations of some of the ligands here represented can eventually be described as follows: H_2pir, EZZ (O(17)-C(4)-C(3)-C(14)(O(15))-N(16)(H) C(2')-N(1')); Hindo, Z (C(5)-N(1)-C(11)-O(4)); Htol, Z(N(1)-C(6)-C(8)- O(3))

drug (SAID) complexes have been characterized via diffraction techniques). With the aim of discussing accurate structural data, only the articles devoted to single crystal diffraction studies have been analyzed. The analysis brings structural information relevant to the drug which can help in the modeling of drug-enzyme interaction. The active drugs reported in the articles reviewed here, together with their structural formulas, are listed in Scheme 1.1.

II. SYNTHESIS OF THE ANTI-INFLAMMATORY DRUG – METAL COMPLEXES

A list of anti-inflammatory drug – metal complexes, together with selected information relevant to their synthesis, is reported in Table II.1.

TABLE II.1 Crystalline anti-inflammatory drug-metal compounds discussed in this review

compound	*preparation medium*	*ref.*
$[Cu(Hpir)_2(dmf)_2]$	meOH, dmf	18g
$[Cd(Hpir)_2(dmf)_2]$	meOH, dmf	18g
$[PtCl_2(H_2pir)(dmso)]$	dmso, n-buOH, C_6H_5Cl	18e
$[PtCl_2(H_2pir)(C_2H_4)]\cdot 0.5C_6H_6$	etOH, C_6H_6	18a
$[Sn(pir)(bu)_2]_n$	meOH, CH_3CN	19b
$[Cu_2(indo)_4(dmf)_2]\cdot 1.6dmf$	dmf, etOH	6
$[Cu_2(indo)_4(H_2O)_2]\cdot 1\ 5H_2O$[a]	etOH	6
$[Cu_2(indo)_4(nmp)_2]$[a]	nmp, etOH	6
$[Cu_2(indo)_4(dma)_2]$[a]	dma, etOH	6
$[Cu_2(indo)_4(dmso)_2]$	etOH, dmso	20
$[Cu_2(tol)_4(dmso)_2]$	meOH, dmso	19g
$[Cu_2(nap)_4(dmso)_2]$	meOH, dmso	19g
$[Cu(nap)_2(py)_2(H_2O)]$	dmso, py	19f
$[Mg(H_2O)_6](dic)_2\cdot 2H_2O$	H_2O/etac	21a

compound	*preparation medium*	*ref.*
$[Cu_2(dic)_4(ac)_2]\cdot aca$	H_2O/ac/aca	21b
$[Cu_2(dic)_4(dmf)_2]$	dmf	19d
$[Cd_2(dic)_4(etOH)_2(H_2O)]_n$	H_2O/etOH	19e
$KH(asp)_2$	H_2O/etOH	22a
$RbH(asp)_2$	H_2O/EtOH	22b
$KH(asp)_2$[b]	H_2O/etOH	23
$[Cu_2(asp)_4]$	H_2O/etOH	24
$[Cu_2(pends)_2(H_2O)_2]\cdot 7H_2O$	ipOH, H_2O	25

a. Compounds were characterized via X-ray powder diffraction analysis only; the space group and the molecular structures were not reported.
b. Compound was characterized via single crystal neutron diffraction analysis.

II.1. Synthetic procedures

Crystalline metal complexes of the anti-inflammatory drugs were usually obtained on mixing alcoholic, hydro-alcoholic or aqueous solutions of the ligands (the active drugs) and alcoholic or aqueous solutions of the starting metal compounds. The crystal growth procedures were carried out from different media which include H_2O, meOH, etOH, dmso, dmf, C_6H_5Cl, C_6H_6, py, dma and ipOH. The main features of the preparation and crystal growth of the complexes are summarized below.

$[M^{II}(H_2pir)_2(dmf)_2]$ (M: Cu, Cd).[18g] Microcrystalline solids whose formula is $M^{II}(H_2pir)_2(H_2O)_2$ were first obtained on mixing hot solutions of H_2pir and $[Cu^{II}_2(OOCCH_3)_4(H_2O)_2]$ (2:1 molar ratio), in methanol. The crude products were recrystallized from dmf (when the solvent for recrystallization was dmso, the corresponding $[M^{II}(H_2pir)_2(dmso)_2]$ complexes were obtained). Single crystals suitable for X-ray diffraction analysis were prepared by cooling to room temperature hot dmf solutions (80°C) of the pure compounds.

$[Pt^{II}Cl_2(H_2pir)(dmso)]$.[18e]A mixture of $K_2[Pt^{II}Cl_4]$ and dmso was stirred at 25°C for 0.5 h. The white precipitate (KCl) was filtered off and the clear solution was added to a solution of H_2pir in dmso (Pt:H_2pir molar ratio, 1:1). The mixture was stirred at 110°C for 0.5 h and then an excess of n-buOH was added under stirring and heating. A yellow crys-

talline powder precipitated. The mixture was cooled to 25°C. The solid was removed on a filter and washed with dmso, n-buOH and diethyl-ether. X-ray diffraction quality single crystals were obtained on cooling hot solutions (refluxing) of the pure compounds in chlorobenzene, to 25°C.

$[Pt^{II}Cl_2(H_2pir)(C_2H_4)]$.[18a] The crystalline organometallic complex was prepared on mixing dilute ethanol solutions of H_2pir and $K[Pt^{II}Cl_3(C_2H_4)]\cdot H_2O$ at 25°C. A pale yellow solid precipitated within a few minutes. The mixture was stirred for 8 h. It is important to work at temperatures below 25°C; otherwise, the yield decreases significantly. The solid collected by filtration was rinsed with etOH and diethyl ether and then dried. The crystalline compound is slightly soluble in boiling benzene. X-ray diffraction quality single crystals of *trans*-$[Pt^{II}Cl_2(H_2pir)(C_2H_4)]\cdot 0.5C_6H_6$ were produced by cooling to 25°C and concentrating hot (50°C) benzene solutions of the crude product.

$[Sn^{IV}(pir)(bu)_2]_n$.[19b] A suspension of H_2pir in methanol was treated with KOH 0.1 M (1:2 molar ratio) until complete dissolution of the drug. The resulting mixture was stirred while a solution of $Sn(bu)_2Cl_2$ (1:1 molar ratio) in methanol was added. The metal complex was precipitated from the solution by adding water and was separated by filtration as a white powder. Crystals of $[Sn^{IV}(pir)(bu)_2]_n$ suitable for X-ray diffraction analysis were obtained by slowly evaporating a clear solution of the metal compound in a methanol-acetonitrile mixture.

$[Cu^{II}_2(tol)_4(dmso)_2]$ and $[Cu^{II}_2(nap)_4(dmso)_2]$.[19g] The sodium salt of the ligand (Na^+ tol^- or Na^+ nap^-) and $CuCl_2\cdot 2H_2O$ were mixed (2:1 molar ratio) in the medium meOH/dmso (3:4, v:v). The mixture was heated for 1 h. The by-product (NaCl) was precipitated by adding dichloromethane and removed by filtration. The clear solution produced green crystals suitable for X-ray diffraction analysis by slow evaporation at room temperature.

$[Cu^{II}(nap)_2(py)_2(H_2O)]$.[19f] The sodium salt of the ligand (Na^+ nap^-), $Cu^{II}Cl_2\cdot 2H_2O$ (2:1 molar ratio) and dmso were mixed. The mixture was heated for 1 h, cooled to 25°C, and then filtered. The clear filtrate was treated with py (excess). Blue microcrystals formed overnight. Crystals suitable for X-ray diffraction analysis were obtained from a solution of the pure complex in py/dmso/CH_2Cl_2 (4:1:1, v:v).

$[Cu^{II}_2(dic)_4(dmf)_2]$.[19d] A solid whose formula is $Cu^{II}(dic)_2(H_2O)$ was first prepared by mixing meOH solutions of Na^+ dic^- and $Cu^{II}Cl_2$ (2:1

molar ratio). The precipitate was collected by filtration, washed with H_2O/meOH (1:5) and then dried in vacuo. Green crystals of $[Cu^{II}_2(dic)_4(dmf)_2]$ suitable for X-ray diffraction were prepared from dmf solutions of $Cu^{II}(dic)_2(H_2O)$.

$[Cd^{II}_2(dic)_4(etOH)_2(H_2O)]_n$.[19e] A powder whose formula is $Cd^{II}(dic)_2(H_2O)$ was prepared by mixing aqueous solution of Na^+ dic^- and $Cd^{II}Cl_2$ (2:1 molar ratio). The pH was adjusted at 6.5 by adding KOH 0.1M and the mixture was stirred for ca. 4 h, at room temperature. The powder was filtered, washed with H_2O and dried over silica gel. Colorless single crystals of $[Cd^{II}_2(dic)_4(etOH)_2(H_2O)]_n$ suitable for X-ray diffraction were obtained by evaporating ethanolic solutions of $Cd^{II}(dic)_2(H_2O)$.

$[Mg^{II}(H_2O)_6](dic)_2 \cdot H_2O$.[21a] A crystalline powder which contains Mg^{2+} and dic^- in a 1:2 molar ratio was prepared by mixing aqueous solutions of $Mg^{II}Cl_2$ and Na^+ dic^- (1:2). Colorless single crystals of $[Mg^{II}(H_2O)_6](dic)_2 \cdot H_2O$ were prepared by evaporating ethylacetate solutions of the microcrystalline $Mg^{II}(dic)_2$ powder.

$[Cu^{II}_2(dic)_4(ac)_2] \cdot aca$.[21b] Two aqueous solutions of $Cu^{II}(NO_3)_2$ and Na^+ dic^-, respectively, were mixed. The green microcrystalline powder obtained from the mother solution after "several minutes"[21b] was filtered and dissolved in ac/aca. Grey-blue crystals of $[Cu^{II}_2(dic)_4(ac)_2] \cdot aca$ suitable for X-ray analysis formed by slowly evaporating the solvent. It has to be noted that the authors of the work reports that ac was used for recrystallization of the crude product. No explanation was given for the presence of aca in the crystals. I assume that aca came from the solvent as an inpurity.

$[Cu^{II}_2(indo)_4L_2]$ (L: dmf, H_2O, nmp, dma).[6] The following method is that relevant to the dmf derivative. The analogous compounds were obtained by similar procedures. A warm dmf solution of Hindo was added to a dmf solution of $[Cu^{II}_2(OOCCH_3)_4(H_2O)_2]$ (2:1 molar ratio). The mixture was heated to 80°C. An excess of etOH was then added to the mixture with stirring. The deep green solution was set aside for one day; it produced a microcrystalline green powder. Single crystals suitable for X-ray diffraction analysis of $[Cu^{II}_2(indo)_4(dmf)_2] \cdot 1.6dmf$ were obtained by dissolving the powder in dmf/etOH (1:4), and then concentrating the solution by evaporation.

$[Cu^{II}_2(indo)_4(dmso)_2]$.[20] A solution of Hindo in H_2O/etOH (1:1, v/v) was treated with $Cu^{II}O$ dust (Cu:Hindo molar ratio, 1:2). The suspension was heated at reflux for 1h. The solid collected by filtration was

recrystallized three times from dmso. Single crystals suitable for X-ray diffraction were obtained by cooling the hot dmso solution.

$KH(asp)_2$,[22a,23] $RbH(asp)_2$.[22b]Colorless crystals of $MH(asp)_2$ suitable for diffraction techniques were made by warming an H_2O/etOH (1:1 v/v) solution of Hasp and MOH (2:1 molar ratio). The crystals of $MH(asp)_2$ form first. Crystals of Hasp can sometimes grow upon further evaporation of the mother liquor.

$[Cu^{II}_2(asp)_4]$.[24a,b] Hasp and Cu(II)-salicylate tetrahydrate (2:1 molar ratio) were mixed in a H_2O/etOH (1:1 v/v) medium. The mixture was heated at 50°C. Dark-blue prisms of $[Cu^{II}_2(asp)_4]$, suitable for X-ray analysis, formed on cooling.

$[Cu^{II}_2(pends)(H_2O)_2]\cdot 7H_2O$.[25] Two aqueous solutions of H_2pends and $Cu^{II}Cl_2\cdot 2H_2O$, respectively (Cu:H_2pends molar ratio, 1:1), were mixed. A stoichiometric amount of $NaHCO_3$was added as a neutralizing agent for the H_2pends molecules. The carbon dioxide by-product was removed under vacuum; then the mixture was filtered. The clear solution, diluted with water and then with ipOH, was placed in a refrigerator, and single crystals of the complex formed.

$Cu^{II}(pends)\cdot nH_2O$, n = 3,5.[26] A different procedure for preparing Cu(II)-pends crystalline compounds was also reported. H_2pends was first dissolved in water. An equivalent amount of freshly prepared cupric hydroxide was added to the solution. The resulting deep blue mixture was filtered and allowed to evaporate at room temperature. Large blue crystals formed; on standing in air the crystals lost water.

II.2. General aspects of the syntheses

The preparations of the metal-drug derivatives were mostly aimed at linking Cu(II) ions to the anti-inflammatory agents. The main reason for the preponderance of Cu(II)complexes is because these species can exert SOD-like activity (see, for instance, Ref. 18d). Other metals studied were Pt(II) and Sn(IV). The choice of these elements is related to the well-known cytostatic and anti-cancer activity of some of their complexes. So, the preparations of Pt(II)- and Sn(IV)-anti-inflammatory drug complexes can generate potential anti-inflammatory and anti-cancer agents. Metal ions such as Cd(II), Ni(II), Co(II) and Fe(II) were investigated and reported in the papers reviewed (see, for instance, Ref. 18g) mainly for purposes of comparison at the level of coordination and

structural chemistry or because some of these metal ions play important roles in several biological systems.

The syntheses usually produced crystalline powders which precipitated from the mother liquor. The recrystallization procedures (which were performed from a variety of solvents such as dmf, ac, dmso, benzene, etOH, dma, or nmp, depending on the compound) sometimes changed only slightly the composition of the initial crystalline material, by substituting the weakly bound ligands or by inserting co-crystallized molecules from the solvent. This suggests that the metal-drug molecule frameworks remain intact in a high percentage in solution. The published data confirm the hypothesis (see, for instance, Refs. 6, 18d, 18g).

III. STRUCTURES OF THE ANTI-INFLAMMATORY DRUG-METAL COMPLEXES

III.1. The Piroxicam Derivatives

III.1.1. The coordination spheres

$[M^{II}(H_2pir)_2(dmf)_2]$ (M: Cu, Cd).[18g] These species were the first oxicam-metal compounds to be characterized via X-ray diffraction. The coordination sphere is pseudo-octahedral for both the compounds (Figure 3.1.1.1 for the Cd(II) derivative) with the metal-coordination to amide O(15) (see Scheme 1.1 for the numbering) and pyridyl N(1′) atoms. Oxygen atoms from two dmf molecules occupy the axial positions. The Cu(II) derivative shows the typical axial elongation. The selected geometrical parameters relevant to the atoms of the coordination spheres of the metal-piroxicam complexes are listed in Table III.1.1.1. The M-O(15) and M-N(1′) bond distances are 1.92(1) and 2.05(1), and 2.194(3) and 2.276(4) Å, for the Cu(II) and the Cd(II) derivatives, respectively.

$[PtCl_2(H_2pir)(dmso)]$.[18e] The platinum center has the usual square-planar geometry, being linked to two trans chlorides, to the S atom from dmso and to the N(1′) atom of neutral H_2pir (EZE) (Figure 3.1.1.2). The Pt-N, Pt-Cl and Pt-S bond lengths are 2.06(1), 2.300(4) and 2.217(4) Å, respectively.

TABLE III.1.1.1 Selected geometrical parameters for the coordination spheres of the metal-piroxicam complexes[a]

parameter	$[M^{II}(Hpir)_2(dmf)_2]$[18g]		$[Sn^{IV}(pir)(bu)_2]_n$[19b]	
	Cu	*Cd*		
lengths (Å)				
M-O(17)			2.083(3)	2.073(3)
M-O(15)	1.92(1)	2.194(3)	3.020(5)[b]	2.611(5)[b]
M-N(1′)	2.05(1)	2.276(4)	2.426(4)	2.479(4)
M-N(16)			2.135(3)	2.176(3)
M-O(5)	2.43(1)	2.386(3)		
angles (°)				
O(17)-M-N(16)			83 9(2)	83 6(2)
O(17)-M-O(15)			86.3(2)	76.3(2)
O(15)-M-N(1′)	90.2(5)	82.7(1)		
O(15)-M-O(5)	91.8(4)	94.1(1)		
N(1′)-M-N(16)			57.7(2)	56.8(2)
N(1′)-M-O(5)	90.8(4)	88.2(1)		

[a]Numbering is that reported in Scheme I.1. The atom O(5) for the $[M^{II}(Hpir)_2(dmf)_2]$ complexes is the oxygen from dmf. Pt-N(1′) bond distances for $[Pt^{II}Cl_2(H_2pir)L]$ are: L = dmso, 2 08(1), 2.05(1) Å;[18e] L = C_2H_4, 2.093(6) Å.[18a]
[b]These values are relevant linkages between the Sn(IV) center and a second molecule of pir^{2-}.

$[PtCl_2(H_2pir)(C_2H_4)]\cdot 0.5C_6H_6$.[18a] The metal center is linked to two trans chloride anions, to the η^2-C_2H_4ligand and to the N(1′) atom from neutral H_2pir (EZE) (Figure 3.1.1.3). The bond lengths relevant to the metal-donor linkages are dominated by the large trans influence exerted by C_2H_4 on the Pt-N(1′) bond (2.093(6) Å), which is even longer than that found for the dmso analogue. The Pt-Cl bond lengths have normal values (2.295(3) Å, average). The Pt-C bond distances are 2.15(1) and 2.18(1) Å, in agreement with the corresponding value for the Zeise's salt.[27]

$[Sn^{IV}(pir)(bu)_2]_n$.[19b] The compound is polymeric with two n-bu residues and a doubly deprotonated piroxicam (pir^{2-}) ligand per Sn center

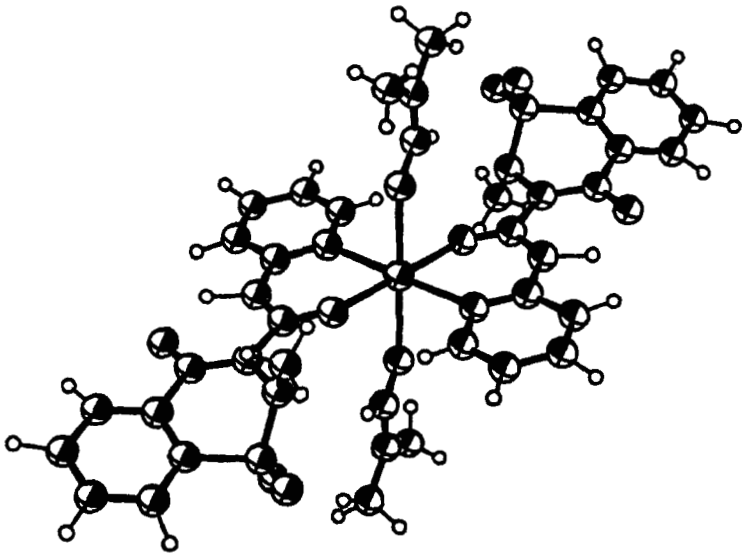


FIGURE 3.1.1.1 Ortep-style drawing for the $[Cd^{II}(Hpir)_2(dmf)_2]$ molecule. The numbering of the atoms of the drug-ligand is given in Scheme 1.1

(Figure 3.1.1.4). There are two similar independent molecules in the asymmetric unit. The pir^{2-} dianions behave as tridentate through the enolic oxygen, the pyridyl and the amidate nitrogen atoms, so that the coordination geometry can be described as pseudo-square-pyramidal. However, each center also has a weak interaction to the oxygen atom from a neighboring ketonic function. By taking into account this weak interaction, the geometry of the coordination sphere is highly distorted-octahedral. The Sn-N(1′) bond lengths (2.427(3), 2.478(3) Å) are very long when compared to Sn-N(16) (2.135(3), 2.176(3) Å), in agreement with a large strain effect from the four-membered chelate ring. The authors claim that the existence of Sn-N bonds longer than 2.39 Å suggests possible antitumor activity on the basis of the reasoning by Crow et al.[28] The Sn-C and Sn-O(17) bond distances (average, 2.120(5) and 2.078(3) Å) are normal for Sn(IV)-alkyl and Sn(IV)-enolate linkages. The Sn-O(amidate) contact distances to other pir^{2-} ligands are 3.019(4) and 2.611(2) Å, respectively, in agreement with covalent bonding inter-

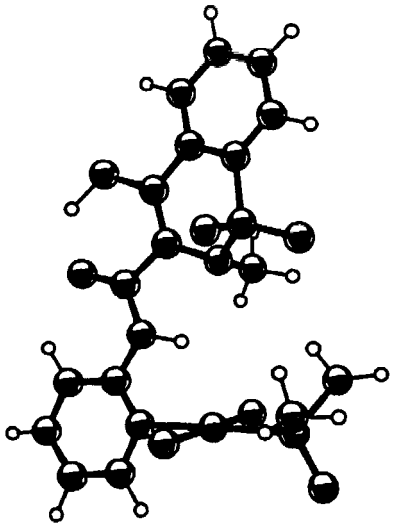


FIGURE 3.1.1.2 Ortep-style drawing for one of the complex molecules in the asymmetric unit of $[Pt^{II}Cl_2(H_2pir)(dmso)]$

actions, even though weak (sum of the Van der Waals radii, 3.7 Å).[29] The pir^{2-} tridentate ligands have the ZZE conformation which must be compared to those for the Cu(II)- and Cd(II)-$Hpir^-$ (ZZZ), and Pt(II)-H_2pir (EZE) derivatives.

III.1.2. The piroxicam ligand

Selected geometrical parameters relevant to the free (three forms, neutral,[30] zwitterionic,[31] and anionic[32]) and metal-bound drug molecules are discussed below. The drug components in $[M^{II}(Hpir)_2(dmf)_2]$ are deprotonated at O(17) and have the ZZZ (see Scheme 1.1 for EZZ) conformation around the O(17)-C(4)-C(3)-C(14)(O(15))-N(16)-C(2′)-N(1′) chain. The free neutral H_2pir molecule has been reported as EZE at the solid state.[30] A comparison carried out on the basis of the values for all the complexes and the free drug molecules reveals that the bond distances and bond angles more sensitive to the protonation and metal-lig-

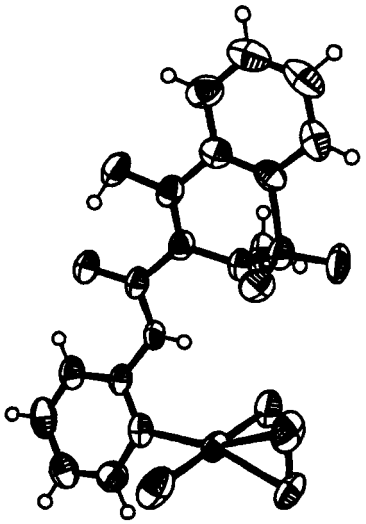


FIGURE 3.1.1.3 Structure of $[Pt^{II}Cl_2(H_2pir)(C_2H_4)]$

and bond formation are those of the O(17)-C(4)-C(3)-C(14)(O(15))-N(16)-C(2')-N(1') grouping. The O(17)-C(4) bond distance is larger in all the O(17)-protonated molecules, being 1.341(4) Å in the free neutral ligand, and 1.276(6) and 1.25(2) in the Cd(II) and Cu(II) derivatives, respectively. The C(3)-C(4) bond length is enlarged but not much influenced by the metal coordination to O(15) and N(1') in $[M^{II}(Hpir)_2(dmf)_2]$ (1.397(7) Å, Cd(II); 1.42(2), Cu(II)), when compared to the free H_2pir molecule (1.369(4) Å). The C(3)-C(14) bond length is shortened upon coordination by six times the estimated standard deviation (esd) for the Cd(II) derivative. The C(14)-N(16) bond is somewhat lengthened (five times esd) in the Cd(II) derivative when compared to the neutral free form. The structure of the zwitterionic form of the free drug H_2pir^{+-} has been reported as ZZZ[31] and strictly resembles the structure of the $Hpir^-$ ligand found in the $[M^{II}(Hpir)_2(dmf)_2]$ complexes, as regards most of the bond distances. Bond length differences between the zwitterionic H_2pir^{+-} and metal-bound $Hpir^-$ molecules occur at the level of the pyridyl ligand. In fact, the N(1')-C(2') and

C(2')-C(3') bond distances are 1.333(6) and 1.413(7) Å for the Cd(II) derivative, and 1.389(7) and 1.342(6) Å for H_2pir^{+-}.

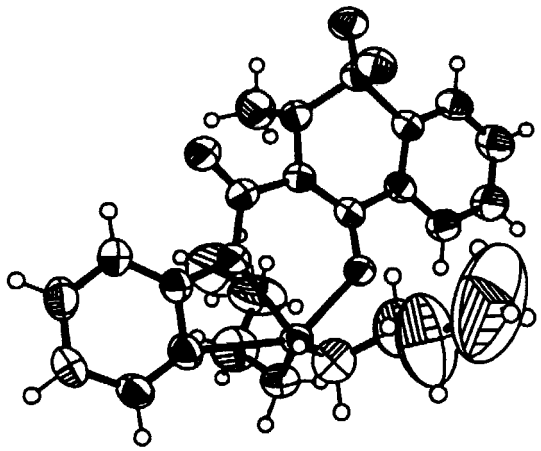


FIGURE 3.1.1.4 Structure of one of the two complex molecules in the asymmetric unit of $[Sn^{IV}(pir)(bu)_2]_n$

The conformation of the metal-bound ($Hpir^-$) and free (H_2pir) piroxicam molecules deserves a deeper analysis to search for the effects caused by the metal ligation. The $Hpir^-$ ligand of $[M^{II}(Hpir)_2(dmf)_2]$ has some similarities with both free anionic $Hpir^{-}$[32] and zwitterionic H_2pir^{+-}.[31] Significant differences between the ligand and free $Hpir^-$ occur at the level of the benzo-thiazine system (which is far from the donor atoms), in particular for the C(10)-C(9)-S(1)-N(2) (τ_{10}) angle, which is higher for the Cd(II)-bound $Hpir^-$ molecule for ~5° than for free $Hpir^-$. The difference between the C(4)-C(3)-C(14)-N(16) (ω'_4) angles is ~9°; whereas that relevant to C(14)-N(16)-C(2')-N(1') (ω_{14}) angles is very large: ~160°. This latter difference is especially due to the metal ligation at the O(15) and N(1') atoms, the chelation causing the large rotation of the pyridyl system around the N(16)-C(2') vector. When the conformation of the $Hpir^-$ ligand of $[M^{II}(Hpir)_2(dmf)_2]$ is compared to that of the zwitterionic molecule, some differences are found for the τ_{10} angle (~4°, on average), for the O(15)-C(14)-N(16)-C(2') (ω_{15}) angle (~8°, average), whereas the difference relevant to the

ω_{14} angle is very small. The deprotonated forms at O(17) both for the free and metal-bound molecules (but not for the zwitterionic form) have a flatter geometry around the N(2) atom as estimated from the values of the S(1)-N(2)-C(13)-C(3) torsion angles. The O-S-O bond angle is almost the same for all the free and metal bound molecules and range 117.2–119.5°. Therefore, the conformation of the benzo-thiazine system is sensitive to the metal-ligation to O(15) and N(1′) (which are far apart from the ring). The effects of the metal-chelation through the O(15) and N(1′) atoms appear to be similar to the protonation of $Hpir^-$ at N(1′). The complex molecules $[M^{II}(Hpir)_2(dmf)_2]$ are stabilized by an intramolecular hydrogen bond, N(16)-H···O(17) (N···O, 2.581(8) Å; N-H···O, 124(2)°, for the Cd(II) derivative).

The intermolecular interactions consist of hydrophobic stacking-type contacts between two N(16)-pyridyl systems. The overlapping region is very small and is relevant to the edges of the rings and the C(2′)-N(16) bond. The shortest contact distance is that between C(3′) and N(16) (-x, -y+1, -z) (3.37(1) Å, Cd(II)). The oxygen atoms from the $>SO_2$ grouping have weak intermolecular interactions with some CH functions. For instance, C(6)-H (x, 0.5-y, 0.5+z) interacts with O(2) (C···O, 3.37(1) Å; C-H···O, 127(3)°, Cd(II)). No other significant intermolecular interaction could be revealed for the $[M(Hpir)_2(dmf)_2]$ complexes.

The bond lengths relevant to the ligand H_2tp molecules for $[PtCl_2(H_2pir)(dmso)]$ are very similar to those of free H_2pir in agreement with the same protonation status and the same EZE conformation. The metal coordination to N(1′) causes some alteration of the C(14)/N(1′) fragment; for instance, the C(14)-N(16) bond length in the complex (1.394(17) Å on average) seems to be closer to the relevant value of the zwitterionic form (1.385(6) Å) than to that of the neutral H_2pir uncomplexed form (1.353(4) Å). The drug molecule is stabilized by a strong intramolecular hydrogen bond between O(17)H and O(15) (O···O), 2.59(1) Å). Intermolecular hydrogen bonds are weak and involve the O(17) and O(15) atoms (O···O), 3.27(2) Å). There are no stacking interactions between the drug molecules.

The H_2pir molecule for $[Pt^{II}Cl_2(H_2pir)(C_2H_4)]$ deviates significantly from coplanarity around the C(2′)-N(16) bond (ω_{14}, −151.1°). This deviation must be compared to that for $[Cu^{II}(pir)_2(dmf)_2]$ (ω_{14}, 11°) and for $[Pt^{II}Cl_2(H_2pir)(dmso)]$ (ω_{14}, −179.6, −167.2°). The intramolecular O(17)-H···O(15) hydrogen bond is strong (O···O, 2.638(6) Å), as usually found for the EZE conformation of H_2pir. A weak intermolecular hydro-

gen bond exists between O(17) and O(11) (O···O), 3.086(8) Å). Some stacking interaction takes place between the benzo and the pyridyl rings, the angle between the least-squares planes being 19°.

The comparative analysis of the bond lengths for $[Sn^{IV}(pir)(bu)_2]_n$ shows that the O(17)-C(4) vector is significantly longer than for free O(17)-deprotonated $Hpir^-$ molecules (ca. 0.03–0.04Å) owing to the Sn-O(17) interaction. Interestingly, the replacement of Sn for the proton at N(16) does not change appreciably the N(16)-C(14) and the N(16)-C(2′) bond distances. Also, Sn coordination to N(1′) does not alter the pyridyl ring bond lengths. On the contrary, the value of the N(1′)-C(2′)-N(16) bond angle is very sensitive to the formation of the Sn-N(16)-C(2′)-N(1′) four-membered chelate ring and decreases to 108.4 °(average) from the idealized value of 120°. Each polymeric chain of Sn(2) is weakly hydrogen bonded to neighboring chains of Sn(1) by C(13)-H···O(2) (0.5-x, y-0.5, 0.5-z) (C···O, 3.52(1) Å).

III.1.3. Molecular modeling analysis for free piroxicam at different protonation status

A molecular orbital (MO) calculation was carried out in this reviewing work at various semiempirical levels through the HyperChem 5.1 package,[33] for the H_2pir, $Hpir^-$ and pir^{2-} and zwitterionic H_2pir^{+-} molecules. The methods were MNDO, MNDO/d, INDO, CNDO, AM1, PM3 and ZINDO/1.[34] The geometry optimizations through only the ZINDO/1 method reproduced the structures for the different forms of the drug molecule at an acceptable degree of accuracy, when compared to the solid state structures. The most stable conformation in the gas phase was the EZE-type, some 27.15 kcal more stable than the ZZZ-type. In fact, optimization of the EZE- and the ZZZ-type structures in a periodic box filled by water molecules (12x10x28 $Å^3$, 96 H_2O), using the atomic charges computed from the ZINDO/1-type molecular orbital method for the isolated molecule (cutoff radii: 1 Å, inner; 5Å, outer) produced a ZZZ-type minimum energy structure some 7.00 kcal more stable than the EZE-type conformation. This analysis confirms that the molecular mechanics (MM) geometry optimizations carried out for the isolated molecules of the oxicam family drugs[18d] and that ZINDO/1 semi-empirical MO methods applied to isolated and to solution phases are valid tools for producing reliable geometrical parameters. However, the relative energies for the different conformations of each form

depends on the treatment of the electrostatic contribution and of the solvent. Neglecting the electrostatic contribution at the MM level reproduces well the influence of the solvent at least for water, as regard as the values of the relative energies. Furthermore, the MO analysis suggests that the ZINDO/1 method is a proper approach for quickly estimating the values for the total energy of different conformations and the atomic charges of oxicam-type molecules.

As the pharmaceutical activity of the oxicams and other NSAID drugs is thought to pass through the inhibition of the COXs enzymes, the molecular recognition ability of the drug molecule in all its forms, as well as that of the metal-bound drug molecules should be carefully analyzed in further accurate experimental and theoretical studies. The estimation of reliable geometries, energetics and electrostatics is preliminary to this analysis.

III.2. The Carboxylic Acid Family Derivatives

$[Cu^{II}_2(indo)_4(dmf)_2]\cdot 1.6dmf$.[6] The structure consists of the $Cu^{II}_2(OOCR)_4$ core unit usually found in several Cu(II)-carboxylate species. The dmf molecules are the apical ligands (through the oxygen donor) for each metal center (Figure 3.2.1). Two free independent dmf molecules are co-crystallized with the complex molecules. The Cu-Cu distance is 2.630(1) Å, slightly shorter than the value for $[Cu^{II}_2(OAc)_4(H_2O)_2]$[36] (2.616(1) Å), and much longer than the shortest Cu-Cu contact in metallic copper (2.55 Å).[35] The geometry around each Cu(II) atom is octahedral with the common axial elongations for a d^9 electronic configuration. The four equatorial oxygen donors have normal bond distances to Cu(II) (1.947(4)-1.967(4) Å), whereas the oxygen atom from dmf is 2.143(5) Å away from Cu(II). The apical Cu-O(water) bond length for $[Cu^{II}_2(OAc)_4(H_2O)_2]$ is 2.156(3) Å.[36]

The indole and chlorobenzyl systems extend away from the coordination core, and the aromatic systems are not coplanar with the COO^- groups. The C(1)-C(2)-C(3)-C(10) (ω_1) torsion angles are –61.6 and 69.1° for the two independent residues. The chlorobenzyl systems are not coplanar with the indole rings; the C(5)-N(1)-C(11)-O(4) (ω_2) and C(17)-C(12)-C(11)-O(4) (ω_3) torsion angles being 143.3 (Z-type conformation) and 21.9(E), and –143.1 and –142.2 for the two independent residues, respectively. This shows that a significant rotational flexibility

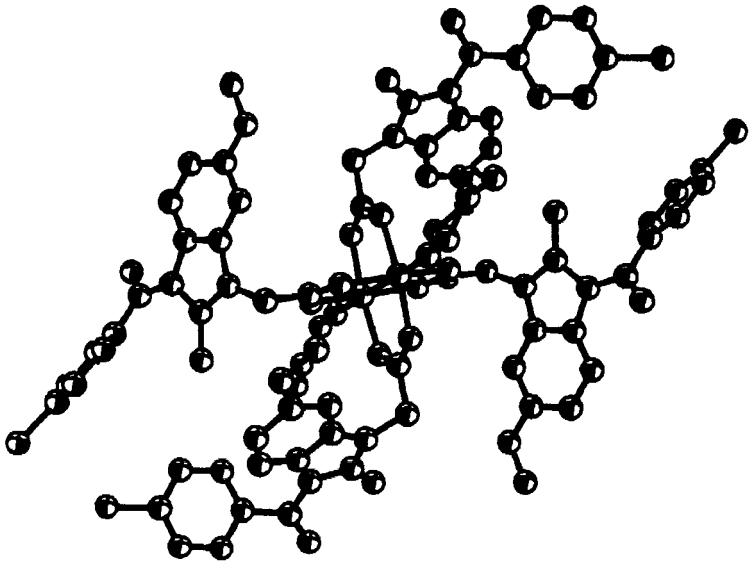


FIGURE 3.2.1 The complex molecule of $[Cu^{II}_2(indo)_4(dmf)_2]\cdot 1.6dmf$

of the groups around the N(1)-C(11) and C(11)-C(12) vectors exists. The dimers do not have any remarkably short intermolecular contact in the crystal. Therefore, intermolecular forces do not cause the difference relevant to the conformation of the aromatic systems of the indo$^-$ ligand. The indo-ligands have in general almost the same bond lengths and bond angles as the free Hindo ligand.[37] Some differences are as follows. The C(1)-C(2)-C(3) bond angle is 112.5(6)° for free Hindo and 110.6(6)° and 113.9(6)° for the Cu(II) complex. The C(5)-N(1)-C(11) angle is 126.7(8)° for free Hindo and 128.2(8)° and 123.1(6)° for the complex. The differences can be related to the type of conformation of the C(5)-N(1)-C(11)-O(4) grouping. It is Z- type for the structure of free Hindo and Z- and E-type in the two independent indo$^-$ ligands of the Cu(II) complex. The E-type indo$^-$ ligands has, as expected, the largest deviations from free Z-type Hindo molecule. The values of the ω_1, ω_2 and ω_3 torsion angles for free Hindo are −79.4, 145.5, 135.3°, again closest to the Z-type indo- ligand.

An MO calculation at the level of the ZINDO/1 and MNDO/d semi-empirical methods through HyperChem 5.1[33] has been performed to simulate the conformation of indo$^-$. MNDO/d only reproduced at an acceptable degree of accuracy the structure of the indo$^-$ anion. An optimized structure has the torsion angles ω_1, −85.2°; ω_2, −126.5°; ω_3, −125.2° (it is Z-type around N(1)-C(11)). The orientation of the CH_3O group around the C(8)-O(3) vector is not well reproduced by theory (the torsion angle C(9)-C(8)-O(3)-C(19) is ~0° for all the Hindo and indo$^-$ structures found at the solid state, whereas it is 82.6° for the computed indo$^-$ ion).

The work by Weder et al.[6] reports that the complexes $[Cu^{II}_2(indo)_4L_2]$ for L = H_2O, dma and nmp, have structures similar to that of the dmf species, at the solid state. The paper reports also that the binuclear structure is maintained in buffer solutions and that the structure is important in allowing the transport of the drug through the biological membranes.[6]

$[Cu^{II}_2(indo)_4(dmso)_2]$.[20] The structure of this compound was refined to a low degree of accuracy (conventional R factor, 13%), precluding a detailed description of the geometry of the indo$^-$ ligand in this case. The crystallographic space group is P(-1) as it is for the dmf derivative, and even the cell parameters of the two compounds are very similar. The main features of the two independent indo$^-$ molecules are also similar in the two crystals, and again the E- and Z-type conformations are shown by indo$^-$ in the dmso derivative. The study reports that the $[Cu^{II}_2(indo)_4(dmso)_2]$ complex has superoxide scavenger activity in dmso/water and acetonitrile/water, and that $[Cu^{II}_2(indo)_4]$ is present in rat serum after administration of Hindo in vivo.

$[Cu^{II}_2(tol)_4(dmso)_2]$.[19g] The structure consists of dimers in which the four carboxylate groups from the tol$^-$ anions bridge the copper centers; the apical coordination positions are occupied by O-dmso molecules (Figure 3.2.2). The Cu-Cu bond distance is 2.662(1) Å. The Cu-O(carboxylate) bond lengths range 1.961(3)-1.973(2) Å. The conformation of the tol$^-$ molecule around the N(1)-C(6)-C(8)-O(3) torsion angle (ω_2, −16.0°) is E-type for both the independent ligand molecules, whereas the six-membered aromatic ring is significantly twisted with respect to the O(3)-C(8)-C(9)-C(10) torsion angle (ω_3, 39.5, −24.6°). The orientation around C(1)-C(2)-C(3)-N(1) (ω_1, −73.4, −83.5°) is gauche. The C(1)-C(2)-C(3) bond angles are 116.8° and 113.2° for the two tol$^-$ ligands. All the bond lengths and angles for tol$^-$ have normal values.

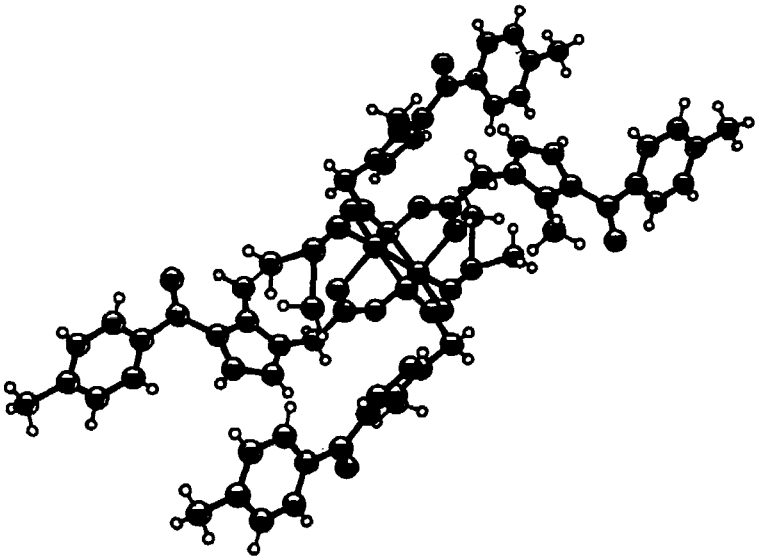


FIGURE 3.2.2 Structure of $[Cu^{II}_2(tol)_4(dmso)_2]$

The neutral complex molecules have a highly hydrophobic external surface. The O(3) atoms have intramolecular hydrogen bonds to C(7) (shortest C···O, 2.83(1) Å) and weak intermolecular hydrogen bonds to several carbon atoms (shortest C···O, 3.14(1) Å). No significant intermolecular stacking interaction is operating in the solid state structure. A MO geometry optimization at the semiempirical MNDO/d level for tol^- brought to a minimum energy structure with the E-type conformation (ω_2, 37.2°; ω_3, 73.8°). The computed C(1)-C(2)-C(3) angle is 113.5°.

$[Cu^{II}_2(nap)_4(dmso)_2]$.[19g] The structure (Figure 3.2.3) consists of $Cu^{II}_2(OOCR)_4$ dimers whose apical positions are occupied by the oxygen atoms from dmso. The Cu-Cu inter-atomic distance (2.629(1) Å) is somewhat shorter than that for the tol^- derivative. The Cu-O(carboxylato) bond distances are in the range 1.958(3)-1.995(2) Å. The ligand nap^- has an asymmetry at C(2) and adopt the S-configuration for all the molecules in the crystal, as found for the free Hnap ligand.[38] Both Hnap and $[Cu^{II}_2(nap)_4(dmso)_2]$ crystallize in the polar P21 space group. The C(1)-C(2)-C(4) bond angles range from 111.2–113.3°. The orientation

around the C(2)-C(4) vector is gauche, the C(1)-C(2)-C(4)-C(5) torsion angle being in the range (ω_1, 46.8–98.7°) for the four independent nap$^-$ anions in the complex and being −70.7° for the free Hnap ligand. The complex molecule has multiple C-H···π intramolecular interaction between the protons and the π-systems of the naphthalene rings, for vicinal nap$^-$ moieties. Weak O(3)···H-C interactions link the complex molecules. No intra- and inter-molecular stacking interaction could be detected. MO geometry optimization at the semiempirical MNDO/d level for the nap$^-$ molecule, by starting from the structure of one of the nap$^-$ units found for the $[Cu^{II}_2(nap)_4(dmso)_2]$ complex was carried out. It reproduced well the experimental structure: ω_1, −76.3; C(1)-C(2)-C(4), 110.5°.

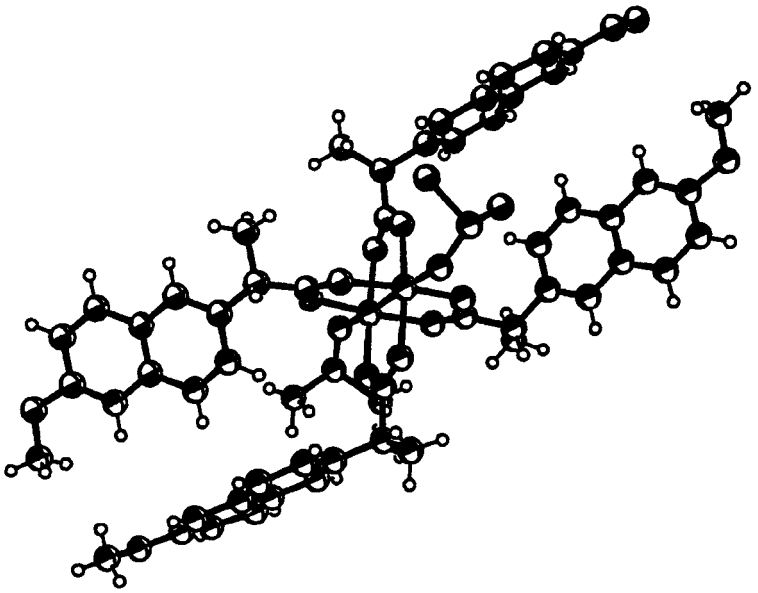


FIGURE 3.2.3 A view of the $[Cu^{II}_2(nap)_4(dmso)_2]$ molecule

$[Cu^{II}(nap)_2(py)_2(H_2O)]$.[19f] The metal center is five coordinate and is part of a distorted square-planar coordination polyhedron (Figure 3.2.4). The two carboxylato groups of the nap$^-$ ligands behave as unidentate.

The Cu-O(carboxylato) bond distances average 1.945(3) Å, whereas the Cu-N bond lengths are 2.021(3) and 2.063(3) Å. The apical donor O(water) is, as usual, farther from the metal center (2.202(4) Å) when compared to the equatorial ones. The free carboxylato-oxygen atoms lie below the basal plane (opposite to the OH_2 ligand) and are 3.134(4) Å far from the metal center. The Cu-O(OH_2) group is disordered; two positions were refined for Cu (0.80 and 0.20 occupancy, respectively). The distances reported above are relevant to the atoms with the highest occupancy. The C-O(donor) distances are 1.217(8) and 1.251(8) Å for the two nap$^-$ ligands, whereas the C-O(terminal) distances are 1.248(8) and 1.209(8) Å. The difference between the distances is in agreement with the intramolecular C-H···O interaction which involves one of the O(t) atoms. This complex molecule is far less hydrophobic than $[Cu^{II}_2(nap)_4(dmso)_2]$ because of the presence of a H_2O ligand. In fact, at least two $(H_2O)O\cdots O(t)$ intermolecular hydrogen bonds exist (O···O, 2.66(1) and 2.76(1) Å). The nap$^-$ ligand molecules have the usual S-configuration. The conformation around the C(1)-C(2)-C(4)-C(5) torsion angle is gauche (ω_1, −78.1° and 73.5°). No significant inter-molecular stacking interaction could be revealed from the analysis of the packing scheme. However, an intramolecular π-interaction exists between a py ring and one of the naphthalene systems. This is in agreement with the following: the narrow C(1)-C(2)-C(8) angle for one of the nap$^-$ ligand (106.5(7)°) when compared to the other (112.8(7)°); the short contact distances (3.43(1)Å, the shortest) between some of the C-atoms of the two moieties; and the coplanarity of the two aromatic systems.

$[Mg^{II}(H_2O)_6](dic)_2{\cdot}2H_2O$.[21a] The structure contains two $[Mg^{II}(H_2O)_6]^{2+}$ cations located at the inversion center, two dic$^-$ anions and two free water molecules in general positions (Figure 3.2.5). There are no direct linking interactions between Mg(II) and dic$^-$. Therefore, this compound is not an inner-sphere metal complex of an anti-inflammatory drug; notwithstanding, it was included in this review article for comparison purposes relevant to the conformation of the dic$^-$ anion. Each metal cation is linked to six water molecules (octahedral coordination). The Mg-O distances range from 2.048(3)-2.076(3) Å, and the angles at metal are close to the idealized values. Both the dic$^-$ anions have the two aromatic systems significantly tilted with respect to each other; the C(3)-C(4)-N(1)-C(9) (ω_2) and C(4)-N(1)-C(9)-C(10) (ω_3) torsion angles being 166.1°, −166.4°, (anti-trans [39]) and 126.9°, −118.5° (anti-clinal). The C(1)-C(2)-C(3)-C(4) (ω_1) torsion angle is 63.9° and

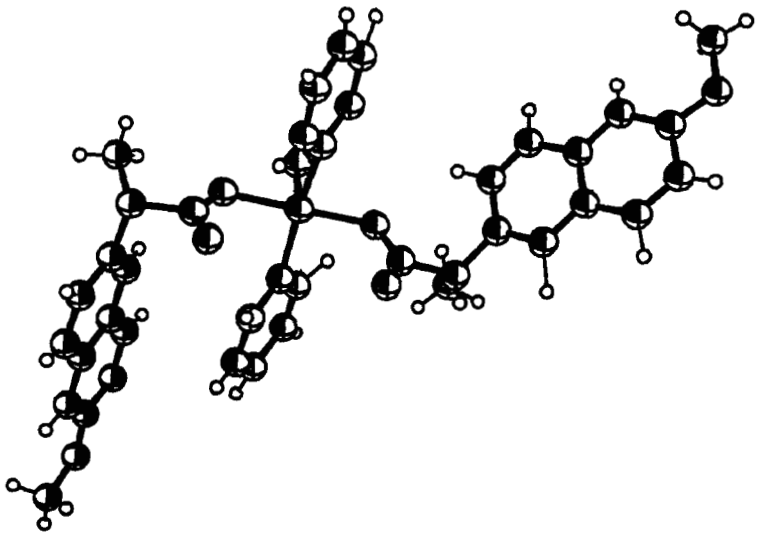


FIGURE 3.2.4 Molecular structure of $[Cu^{II}(nap)_2(py)_2(H_2O)]$

−79.2° (gauche) and the O(1)-C(1)-C(2)-C(3) torsion angle is 0.3° and 73.1°, in the two molecules. The C(4)-N(1)-C(9) bond angle (123.3° and 122.4°) is more rigid than C(1)-C(2)-C(3) (111.1° and 115.6°). All the C-O bond distances are almost identical and average 1.258(4) Å.

The $[Mg^{II}(H_2O)_6]^{2+}$ion, the carboxylate groups and the free water molecules are involved in a network of hydrogen bonds. The N(1) atom has intramolecular hydrogen bonds to O(1) (N···O, 2.898(6), 2.940(6) Å) and to Cl(1) (Cl···O, 2.989(4), 2.969(4) Å). Weak intermolecular C-H···Cl and C-H···O(water) hydrogen bonds involve all the four chlorine atoms of dic^-. The geometry of the dic^- anion is well reproduced at the semi-empirical MO MNDO/d level. The selected computed torsion angles are: ω_2, −157.4°; ω_3, −113.3°; ω_1, −95.1°. The computed C-O(carboxylate) distances are 1.259 Å. A series of papers which report on the structure of Hdic[40]and various dic^- salts with organic counter-ions, i.e.: 1-(2-hydroxyethyl)pyrrolidinium,[41] tris(2-hydroxyethyl)ammonium,[42] N-(2-hydroxyethyl)-piperidinium, -morpholinium,-piperazinium,[43] appeared recently.

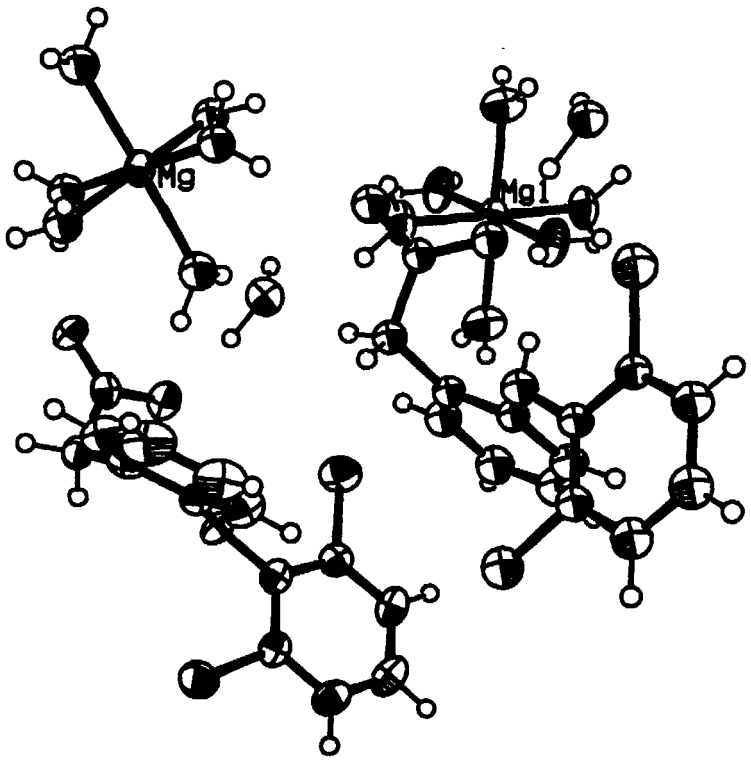


FIGURE 3.2.5 Crystal structure of $[Mg^{II}(H_2O)_6](dic)_2 \cdot 2H_2O$. Two symmetry-related $[Mg^{II}(H_2O)_6]^{2+}$ cations are pictured

$[Cu^{II}_2(dic)_4(ac)_2] \cdot (aca)$,[21b] $[Cu^{II}_2(dic)_4(dmf)_2]$.[19d] The structures have the usual dimeric $Cu^{II}_2(OOCR)_4$ core (Figure 3.2.6). The Cu-Cu distance is 2.610(1) Å and the Cu-O(carboxylato) distances average 1.964(4) Å for the ac derivative. The two apical positions are occupied by the oxygen atoms from two ac molecules (Cu-O, 2.177(5) Å). The conformation of the dic^- molecules around the C(4)-N(1) and N(1)-C(9) vectors, as argued from the values of the ω_2(-163.8, −159.0°) and ω_3 (-115.0, −128.1°) torsion angles, can be described as anti-trans anti-clinal, for the ac derivative. Bond lengths and bond angles for the dic^- ligand are in perfect agreement with those discussed above for the

$[Mg^{II}(H_2O)_6](dic)_2 \cdot 2H_2O$ compound. The Cu(II) complex is much more hydrophobic when compared to the Mg(II) derivative. In fact, the O(carboxylato) atoms are involved in intramolecular N-H···O and (ac)C-H···O hydrogen bonds, and the N(1) atom has the intramolecular interaction to O(1) and Cl(1), but no significant intermolecular hydrogen bonding and stacking interaction could be found.

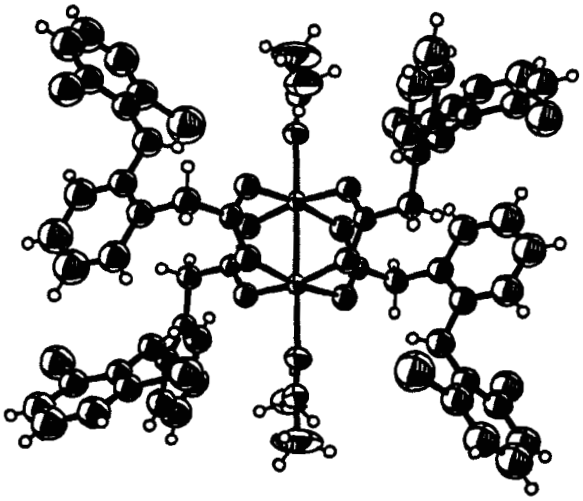


FIGURE 3.2.6 Ortep-style diagram for the molecule $[Cu^{II}_2(dic)_4(ac)_2]$

The dmf derivative crystallizes in a different space group ($P2_{1/n}$) as compared to the ac derivative (P(-1)). The Cu-Cu and Cu-O(carboxylato) distances are 2.6265(8) and 1.969(2) Å. The conformation of the two independent dic^- moieties is similar to that described above for the Mg(II)-and Cu(II)-ac derivatives.

$[Cd^{II}_2(dic)_4(etOH)_2(H_2O)]_n$.[19e] The complex is polymeric, and the coordination geometry for the two independent metal atoms is highly distorted. Cd(1) is hexa-coordinated by the oxygen atoms (Cd-O, 2.407(7), 2.321(7) Å) from a bridging carboxylato to Cd(2), by two oxygen atoms (Cd-O, 2.26(1) Å average) from two etOH (cis to each other), by an oxygen atom (Cd-O, 2.25(1) Å) from a second bridging carboxy-

lato to another Cd(2) center, and from a water molecule (Figure 3.2.7). Cd(2) has a penta-coordination to the two oxygen atoms (Cd-O, 2.505(8), 2.282(8) Å) from a carboxylato, and to one oxygen atom (Cd-O, 2.28(1), 2.17(1), 2.17(1)) each from three bridging carboxylato to Cd(1). Cd(2) has a sixth very weak interaction to an oxygen from a bridging carboxylato (2.76(1) Å). The conformation of dic$^-$ around the ω_2 angle is anti-trans (-166, -166, -174, -162°) in the four independent molecules, whereas the conformation for the ω_3 angle is anti-clinal (-118, -118, -122, -125°). The analysis reported above for the dic$^-$ derivative shows that the flexibility of the dic$^-$/Hdic molecules around the C(4)-N(1) and N(1)-C(9) vectors is restricted to a rather narrow range. It has been reported that the proper conformation adopted by diclofenac to inhibit COXs and to affect rat adjuvant arthritis consists of a twisting of the two aromatic rings of some 58–69°, as found for the structures of the metal-dic$^-$ complexes.[44]

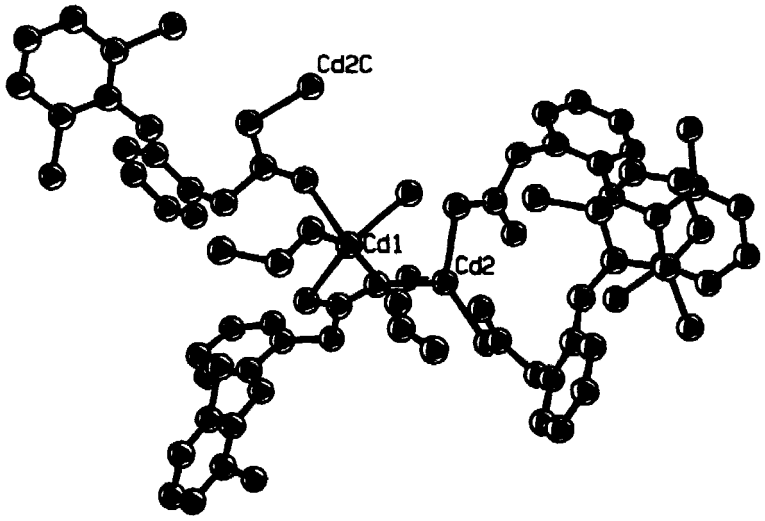


FIGURE 3.2.7 A fragment of the polymeric molecule $[Cd^{II}_2(dic)_4(etOH)_2(H_2O)]_n$

$KH(asp)_2$,[22,23] $RbH(asp)_2$.[22b]The results from the neutron diffraction analysis[23] only are discussed here since the X-ray diffraction analyses[22,22b] do not have a high degree of accuracy. The K^+ cation is surrounded by six oxygen atoms, four from the carboxylate groups

(K-O, 2.748(3) Å, average) and two from the acetyl group (K-O, 2.832(3) Å) (Figure 3.2.8). The hydrogen di-aspirinate system $H(asp)^{2-}$ is held together by an O-H···O (O···O, 2.449(2) Å) interaction which involves two carboxylate groups. The C=O and C-O(H) (carboxylate) bond distances are 1.216(2) and 1.283(3)Å. All other bond distances have normal values. The carboxylate group is tilted with respect to the aromatic ring, and the ω_1 (O–C(O)–C–C) and ω_3 ((CH_3)C–O–C–C) torsion angles are −146.6(4) and 66.3(4)°. The MO computations at the semi-empirical MNDO/d level for the asp^- molecule produce an optimized structure which agrees well with the structure in the solid state for the hydrogen di-aspirinate.

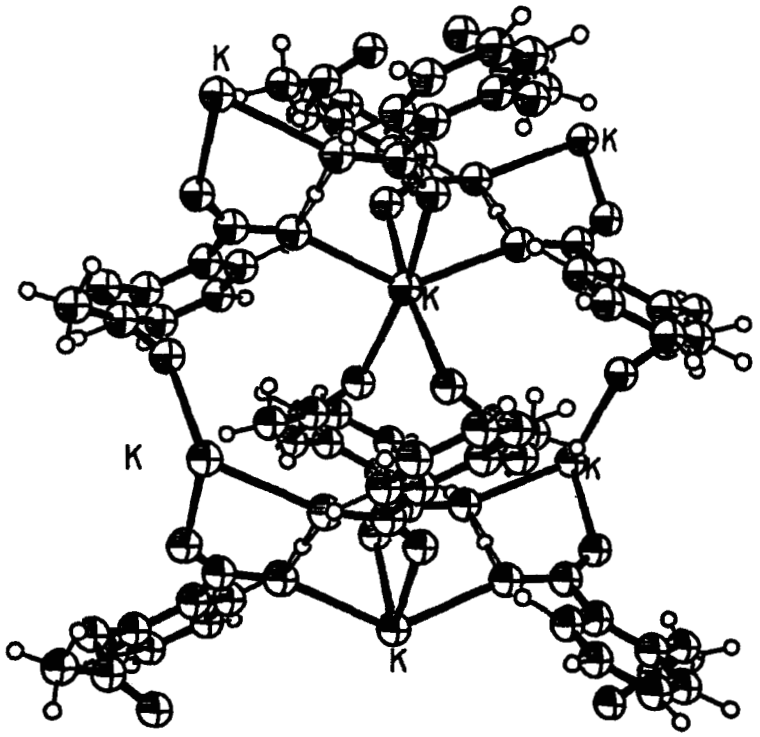


FIGURE 3.2.8 A view of the crystal structure of $KH(asp)_2$. The hydrogen bonds that bridge the Hasp and asp^- molecules are indicated by dashed lines

$[Cu^{II}_2(asp)_4]$.[24] The crystal structure of the compound consists of binuclear units, whose geometry is similar to that reported for most of the dimeric Cu(II)-carboxylates (see above) $[Cu^{II}_2(O_2CR)_4L_2]$, where L is a monodentate ligand. In the structure of $[Cu^{II}_2(asp)_4]$ the positions of the L ligands are occupied by two O(acetyl) atoms from adjacent units, so that polymeric chains are present within the crystal (Figure 3.2.9). The polymeric chains are almost parallel to each other. Each Cu(II) center has the usual distorted octahedral coordination geometry, which consists of four oxygen atoms at the equatorial positions (at 1.963(8) Å, average), and a Cu(II) atom (at 2.617(3) Å) and an O(acetyl) atom (at 2.241(8) Å) at the apical positions. The conformation of the asp^- ligand is similar to that found for $KH(asp)_2$. The ω_1 torsion angle is -47.4°, -176.7° for the two independent asp^- units, whereas the ω_3 angle is 102.7° and 77.9°. This shows that large rotations of the carboxylate group around the C(1)-C(2) vector can occur. Analysis of the crystal packing around the aspirinate groups does not reveal any remarkable interaction.

III.3. The Penicillamine Derivative

$[Cu^{II}_2(pends)_2(H_2O)_2]\cdot 7H_2O$.[25] The complex molecules consist of two Cu(II) ions bridged by two $pends^{2-}$ anions which act as ligands through the N(1) and O(1) and N(1′) and O(1′) (see Scheme 1.1for the numbering) atoms at the equatorial positions of a square pyramid, and by two water molecules which occupy the apical positions (Figure 3.3.1). The Cu-N and Cu-O bond distances average 2.00(2) and 1.96(2) Å. The Cu-O(water) bond distances are 2.48(1) and 2.38(1) Å. Both the metal ions have an S atom from the S_2 bridge at a long distance (3.04(1) and 3.14(1) Å) and trans to a water. The S-S bond lengths average 2.04(1) Å and the two S_2groups are buried inside the dimer to allow the Cu···S interactions. Disulfide complexation with Cu(II) is not frequent and almost all of the compounds that could be retrieved from the Crystallographic Structure Database at Cambridge under the search "disulfide and copper" are relevant to Cu(I) complexes. The S-S bond distances found for $[Cu^{II}_2(pends)_2(H_2O)_2]$ agree with the values of 2.063(7) Å reported for polymeric bis (diethyldisulfide)iodinecopper(I).[45] The C-S-S-C torsion angles for the two $pends^{2-}$ anions are -101.6° and -103.5°, in agreement with other disulfide metal complexes (e.g., 95.6°

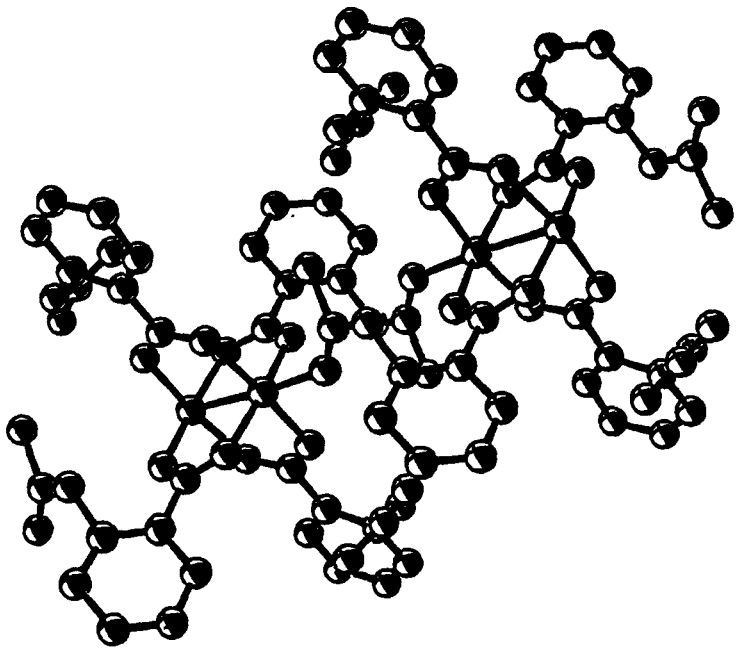


FIGURE 3.2.9 Molecular structure of $[Cu^{II}_2(asp)_4]$

for the diethyldisulfide-Cu(I) complex).[45] The dimeric units are connected by a network of hydrogen bonds involving water molecules, carboxylate oxygen atoms and nitrogen atoms. Even though several methyl groups are distributed at the external surface of the dimer, the molecule is relatively hydrophilic.

IV. CONCLUSION

Analysis of the structures of the metal-complexes with NSAIDs both from the oxicam and the carboxylic acid family reveals that in the case of Cu(II) the formation of stable chelates prevails. The Sn(IV) center, for the only tin-complex reported so far, is also strongly chelated by the

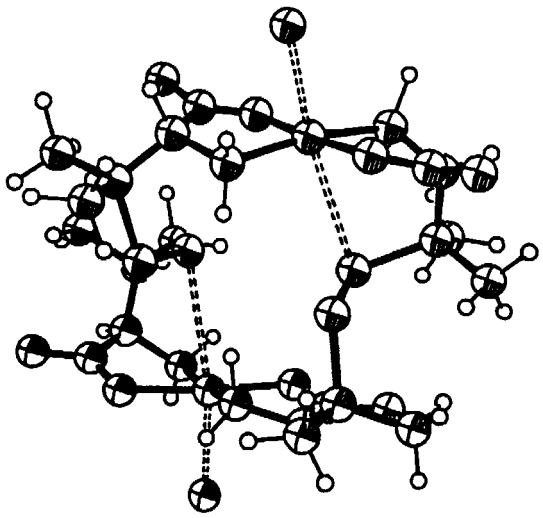


FIGURE 3.3.1 Ortep-style representation of the complex molecule $[Cu^{II}_2(pends)_2(H_2O)_2]$

drug molecule. The two Pt(II) complexes, instead, are linked by monodentate drug molecules. On the basis of physico-chemical data, most of the compounds maintain their structures in the solution phase. Some of the Cu(II) complexes have shown oxygen radical scavenger activity in vitro,[18d,20] whereas certain others are clinically used to treat animals.[6,46] The SOD-like activity exerted by the Cu(II) complexes or by some of their Cu(II)-containing metabolites, added to the COXs-enzyme inhibitory activity by the released ligands or by the complexes themselves, can explain the beneficial effects on the organisms. The metal-piroxicam and metal-carboxylic acid family drug complexes so far characterized are usually highly hydrophobic neutral molecules. This property should facilitate passage of the complex molecule through the membranes. The weakly apically bound ligands of most of the Cu(II) complexes can easily dissociate and the O_2^- radicals can interact with the metal via the free sites: in this way the SOD-like activity is readily rationalized. The Pt(II) and Sn(IV) complexes discussed above are potential anti-cancer agents because some interaction between the metal center and the nucleic acid molecules can occur after the complex has entered the cell and at least one of the donor ligands has dissociated.

The field of metal complexes containing anti-inflammatory compounds as ligands is potentially vast but almost untouched; this field deserves greater attention by inorganic chemists, biochemists and pharmacologists. At least the following work remains to be done: (1) the synthesis and the physico-chemical characterization of many metal complexes with several metal ions such as Cu(II), Mn(II), Fe(II), Co(II), Zn(II), Ru(II,III), Rh(II,III), Pd(II), Pt(II,IV), Au(I,III), Sn(IV), etc. and with several drugs, especially those of the last generation recently approved by FDA having the proper COXs selectivity (see, for instance, Refs. 12, 17); (2) the synthesis of properly designed metal-mixed ligand complexes with at least two different drug molecules (e.g., the coordination of anti-inflammatory drug molecules to metal-anticancer drug compounds of the type reported in Refs. 1a, 18b,c,f); (3) the investigation through theoretical tools of the possible interactions the complexes can have with those bio-molecules which are reasonable targets (with the aim of predicting enzyme-inhibitory effects, conformational alterations, scavenging activity against oxygen radicals, and cytostatic activity; see, for instance Refs. 6, 18d, 19a,c); (4) the investigation of the decay of the complexes and the analysis of the interactions between the metal-containing fragments and the bio-molecules; (5) the performance of in-vitro studies on cell lines and of in-vivo tests for activity, toxicity, drug resistance, etc. Of course, studies in the field mandate a high level of interdisciplinary effort, but there is ample opportunity for even small research groups oriented toward medicinal inorganic chemistry.

Acknowledgements

Università di Siena, Ministero della Università e della Ricerca Scientifica e Tecnologica (MURST) and Consiglio Nazionale delle Ricerche (CNR) are acknowledged for funding.

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