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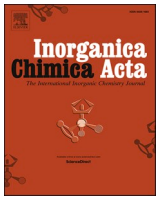

Ibuprofen: A multi-purpose active pharmaceutical ingredient as versatile ligand for zinc(II) and copper(II). Solid state and solution studies

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ABSTRACT

Two new, Zn(II) and Cu(II), complexes of the non-steroidal anti inflammatory drug (NSAID) ibuprofen (HIbu) are reported. Results from their solid state investigation are complemented by potentiometric and ^{1}H NMR studies in view of the role that chelation of these biologically relevant metal ions might play in affecting the Active Pharmaceutical Ingredient (API) biological properties, but also of the use of metallo-ibuprofen drugs. In the solid state, the ibuprofenate anion (Ibu^-) gives rise to 0- and 1-D species, $[Zn(Ibu)_2(H_2O)_2]$ and $[Cu(Ibu)_2]_n$, respectively. The $[Zn(Ibu)_2]$ species is also present in H_2O/EtOH 50 % v/v solution ($pK_w = 14.41(1)$) and starting from pH 4–4.5 coexists in solution with the $[Zn(Ibu)]^+$ one. As for the copper structure, it represents, to the best of our knowledge, the first example of 1-D coordination polymer consisting of copper-ibuprofen dinuclear paddle-wheel units. Interestingly, this crystal phase is the only one obtained irrespective of the different synthetic and crystallization procedures adopted. Potentiometric titrations evidence that copper(II) gives the more stable complexes (also in this case $[Cu(Ibu)_2]$ and $[Cu(Ibu)]^+$ coexist in solution) with respect to the zinc ones. Lastly, in light of the increasing interest around the antibacterial activities of NSAIDs and NSAIDs-containing compounds, the antimicrobial effects of ibuprofen, $[Zn(Ibu)_2(H_2O)_2]$ and $[Cu(Ibu)_2]_n$ were preliminary evaluateted on *Bacillus Subtilis*, chosen as a model of Gram-positive bacteria.

1. Introduction

Ibuprofen (2-(4-Isobutylphenyl)propanoic acid, HIbu hereafter, Scheme 1), which belongs to the class of non-steroidal anti-inflammatory drugs (NSAIDs), is one of the leading analgesic tablets used for relieving pain, such as headache, menstrual cramps, muscle pain, dental pain, but also to reduce fever as well as inflammation [1]. Its anti-inflammatory action is attributed to the slowly reversible inhibition of cyclooxygenase enzymes (COX-1 and COX-2) [2]. In addition, several studies demonstrate that the anti-inflammatory activity of ibuprofen can help as cancer-preventive and as adjuvant in the chemotherapeutic treatment of various cancer cell lines (inflammation contributes to tumor proliferation, metastases formation and spreading) [3,4].

Ibuprofen comprises lipophilic and hydrophilic moieties, it is relatively insoluble in water (for example, solubility in water ranges from 0.140 g/dm^3, at pH 4.5 to 2.300 g/dm^3 at pH 7.5) and exists almost entirely in the anionic form (Ibu^-) at physiological pH. The presence of the ionizable –COOH group is used to overcome the low solubility issue through salification but also to obtain complexes with transition metals showing promising biological activity as anticancer [5] and antibacterial agents [6].

In fact, it has been demostrated that the NSAIDs scaffolds can exhibit great tendency to interact with metal ions, giving metal complexes that show a therapeutic potency greater than that of the free ligands. Amongst the transition metals, zinc and copper are the second and third most abundant trace metals in the human body after iron (2–3 g and

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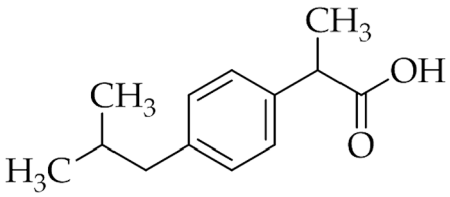


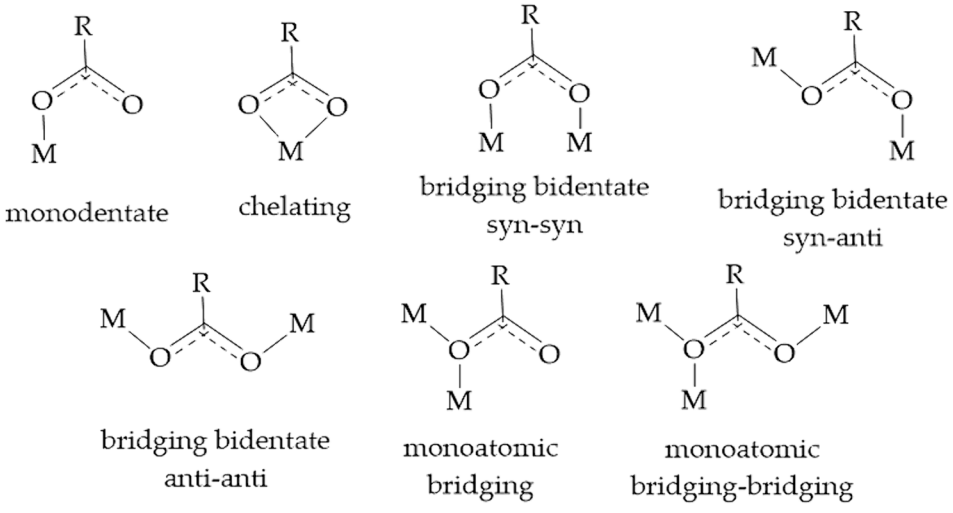
Scheme 1. Schematic drawing of ibuprofen (HIbu) structural formula.

75–100 mg of zinc and copper distributed throughout the body) and play fundamental roles in the organism [7,8]. At the same time numerous zinc and copper complexes act as anticancer agents [9,10]. The dicationic Zn (II) and Cu(II) ions display several coordination number and geometries. As for zinc(II), which has a d^{10} electronic configuration (hence a zero ligand-field stabilization energy), it usually adopts four coordinate tetrahedral (the most common) and five coordinate trigonal pyramidal geometries, with a large variety of ligands providing S, N and O donor atoms. Cu(II) shows a versatile coordination chemistry, exhibiting a wide range of coordination number and geometries (tetra-, penta- and *hexa*-coordination) seldom regular (e.g. Jahn-Teller distortion for six-coordinate systems due to the d^9 electronic configuration). The carboxylate group, which characterizes most of the generally used NSAIDs, may coordinate to metal in different modes; for example, as monodentate, chelating, bridging bidentate (*syn*-syn, *syn*-anti, anti-anti) and monoatomic bridging (alone and with additional bridging) as depicted in Scheme 2 (from left to right, top to bottom) [11]. For example, Guillon et al. [12] reported on three new copper complexes of ibuprofen, which feature the NSAID as monodentate ligand. In all cases the coordination sphere about the metal centre is completed by 2 nitrogen-donor co-ligands in XAWJIR (Cambridge Structural Database, CSD hereafter [13], refcode; Cu(II) exhibits a square-planar geometry) and a further water molecule in XAWJEN and XAWJOX (square-pyramidal geometry). Complexation of NSAIDs as monodentate, bidentate and chelating ligand with Cu(II) [14], Zn(II) [15–21] and Mn(II) [22] can also lead to the formation of coordinative polymeric structures, where in some cases an ancillary ligand is needed to complete the coordination sphere or to allow the polymeric coordination. Whether the drug is encapsulated in the supramolecular structure or forms part of it as a building block, the system must undergo a structural response following a stimulus such as a pH change, a redox reaction, a temperature change, etc., in order to release the drug [23–26]. Given that, due to their interesting structures and properties, including their ability to respond to external stimuli, as is known in many fields, especially for 1D structures [27–29], coordination polymers have been identified as potential drug delivery systems that provide controlled release of the drug in the targeted body environment [30].

Finally, in recent years there has been a general interest around the antibacterial activity of "*old*" non-antibiotics such as NSAIDs, and their complexation with several metals has been demonstrated to improve the therapeutic outcomes if compared to the free drugs, but also to represent a valid strategy to design new drugs with synergistic biologically active ligands [31]. Ibuprofen itself possesses an antimicrobial activity [32], however, notwithstanding this could represent an advantage or, on the other side, introduce additional risks during its usage, this aspect is generally considered as a mere side effect and it is not mentioned in the leaflets of ibuprofene drugs. To establish the antimicrobial effect associated to ibuprofen and to its metal complexes is therefore of great importance and a few studies reported on the antibacterial activities of complexes of this important NSAID with different transition metals [6,31].

As part of our involvement in the study of API (especially NSAID) containing systems [33–40], we thought interesting to study the coordination properties, both in the solid state and in solution, of racemic ibuprofen towards the zinc(II) and copper(II) ions. As for the solution, the coordination properties displayed by APIs in the presence of metal ions of biological relevance are of interest in light of the aforementioned role that chelation might have in affecting/altering their biological properties but also in view of the pharmacological use of metallo-ibuprofen species. In both cases a detailed knowledge of the possible metal complexed species formed in solution at different pH values, including physiological pH is crucial. On the other hand, when dealing with APIs, the knowledge of their solid form property and behaviour (e.g. phase stability, phase transformation, solvation/desolvation processes, etc.), which are strictly related to their molecular and crystal structures, is fundamental.

We report here the results of the solid state study of $[Zn(Ibu)_2(H_2O)_2]$ (**1**) and $[Cu(Ibu)_2]_n$ (**2**) by using a combined experimental (single-crystal and microcrystalline-powder X-ray diffraction, differential scanning calorimetry) and in silico (Mercury [41] and Crystal Explorer 17 [42]) approach, accompanied by data mining (Cambridge Structural Database); potentiometric and ^{1}H NMR studies (in water–ethanol 50 % (v/v) mixture) complete the investigation of the ibuprofen coordination properties towards Cu(II) and Zn(II). Finally, the antimicrobial properties of the synthesized metal complexes and of ibuprofen were also preliminary investigated, through agar diffusion test, against *Bacillus subtilis* (*B. subtilis* in the following) selected as a model of Gram-positive bacteria, and effect of ibuprofen metal complexes are compared to that of the API itself.



Scheme 2. Schematic representation of coordination modes adopted by carboxylate group.

The final aim is to provide new insights on NSAID-based coordination compounds which could have potential pharmacological effects [43].

2. Materials and methods

2.1. Chemicals

All reagents were purchased from Sigma-Aldrich and used as received without further purification.

2.2. Synthesis and crystallization procedures

$[Zn(Ibu)_2(H_2O)_2]$ (1). A solution of ibuprofen sodium salt (NaIbu, 1 mmol, 228 mg) in EtOH (2 mL) was added to 0.5 eq of $ZnCl_2$ (0.5 mmol, 68.2 mg) in H_2O (1 mL) to favor the predominant formation in solution of the complexed species with Ibu^-:Zn^{2+} stoichiometry of 2:1 (*vide infra*). Shortly, the formation of a microcrystalline solid was observed. The mixture was heated at 50 °C under stirring for 1 h. After cooling to r.t., the crystals were filtered and washed with EtOH. The sample was used for SCXRD (Single Crystal X-Ray Diffraction) and, after grinding, for PXRD (Powder X-Ray Riffraction) and DSC (Differential Scanning Calorimetry) measures.

Yield: 115.75 mg (45 % based on the formula $[Zn(Ibu)_2(H_2O)_2]$.

El. An. Calcd for $C_{26}H_{40}ZnO_6$: C, 62.46 %; H, 8.06 % Found: C, 62.31 %; H, 8.46 %.

$[Cu(Ibu)_2]_n$ (2). For the synthesis of crystals of **2** suitable for SCXRD analysis, several procedures were used. In the following we report the ones (P1-P3) that afford single crystals, whose quality was, unfortunately, quite poor (see the "Single-Crystal X-ray Diffraction" paragraph).

P1) The same procedure used to obtain crystals of **1** was used. More in detail: a solution of ibuprofen sodium salt (NaIbu, 1 mmol, 228 mg) in EtOH (2 mL) was added to a solution of $CuCl_2$ (0.5 eq, 0.5 mmol, 67 mg) in H_2O (2 mL), immediately the formation of small crystals was observed. The crystals were filtered and washed with EtOH, part of them were grinded and a PXRD pattern was collected (see Result paragraph), some of the remaining crystals were tested for SCXRD analysis.

Yield: 93.34 mg (40 % based on the formula $[Cu(Ibu)_2]_n$.

El. An. Calcd for $C_{26}H_{36}CuO_4$: C, 66.44 %; H, 7.72 % Found: C, 66.65 %; H, 7.47 %.

P2) A solution of ibuprofen sodium salt (NaIbu, 0.95 mmol, 216 mg) in H_2O (8 mL) was added to a solution of $CuSO_4{\cdot}5H_2O$ (0.5 eq, 0.47 mmol, 118 mg) in H_2O (1 mL), in few minutes the formation of a pale blue powder was observed. The solution was stirred for 30 min, then the powder was filtered and washed with H_2O and then with EtOH. The powder was dissolved in diethyl ether and after the solvent evaporation small crystals of **2** were obtained. As in P1, crystals were filtered, part of them was grinded and a PXRD pattern was collected (see Result paragraph), some of the remaining crystals were tested for SCXRD analysis.

Yield: 90.57 mg (38 % based on the formula $[Cu(Ibu)_2]_n$.

El. An. Calcd for $C_{26}H_{36}CuO_4$: C, 66.44 %; H, 7.72 % Found: C, 66.78 %; H, 7.42 %.

P3) In this case the ibuprofen acid was used instead of the sodium salt. In particular, 206 mg of ibuprofen (HIbu, 1 mmol) were added to a solution of K_2CO_3 (110 mg, 0.8 mmol) in H_2O (80 mL). At this solution, kept under stirring, a solution of 125 mg (0.5 eq, 0.5 mmol) of $CuSO_4{\cdot}5H_2O$ in 10 mL of water, was added. The solution was kept under stirring for half an hour at r.t. A pale blue powder was obtained, which was filtered and washed with H_2O and then with EtOH. The powder was dissolved in diethyl ether and after the slow solvent evaporation small crystals of **2** were obtained. As in P1 procedure, crystals were filtered, part of them were grinded and a PXRD pattern was collected (see Result paragraph), some of the remaining crystals were tested for SCXRD analysis.

Yield: 100.11 mg (42 % based on the formula $[Cu(Ibu)_2]_n$.

El. An. Calcd for $C_{26}H_{36}CuO_4$: C, 66.44 %; H, 7.72 % Found: C, 66.68 %; H, 7.51 %.

2.3. Single crystal X-ray diffraction (SCXRD) data collection and structure solution

$[Zn(Ibu)_2(H_2O)_2]$ (**1**). Single crystal X-ray diffraction data of **1** were collected on a Bruker Apex-II diffractometer equipped with a CCD detector (T = 100 K; Cu–Kα radiation, λ = 1.54184 Å), several crystals were tested and the best one was chosen for the data collection. Data were collected with the APEX2 software [44], while data integration and reduction were performed with the Bruker SAINT software [45]. The crystal structure was solved using the SIR-2004 package [46] and refined by full-matrix least squares against F2 using all data (SHELXL-2018/3) [47]. The isopropyl group of one of the two independent ibuprofen anions is disordered. Such disorder was modelled by introducing two models in the refinement procedure by using the PART instruction (refined occupancy factors: 0.56649 and 0.43351). All the non-hydrogen atoms were refined with anisotropic displacement parameters, while all the hydrogen atoms of the ibuprofenate anions were set in calculated position. Finally, the hydrogen atoms of the two water molecules were found in the Fourier Density Maps, their coordinates were freely refined while their thermal parameter was set in accordance with that of the atoms to which they are bonded.

$[Cu(Ibu)_2]_n$ (**2**). Notwithstanding the different procedures adopted to obtain single crystals suitable for SCXRD measures, the quality of the samples was quite poor. Data reported in the present work refer to the best diffracting sample. Single crystal X-ray diffraction data were collected, at 100 K, by using an Oxford Diffraction XCalibur diffractometer equipped with a CCD area detector. The radiation used was

Table 1
Crystallographic data and refinement parameters of $[Zn(Ibu)_2(H_2O)_2]$ (**1**) and $[Cu(Ibu)_2]_n$ (**2**).

	(**1**)	(**2**)
Empirical formula	$C_{26}H_{38}O_6Zn$	$C_{26}H_{34}O_4Cu$
Formula weight	511.93	474.07
T (K)	100	100
Crystal system, space group	Monoclinic, $P2_1/n$	Monoclinic, $P2_1/c$
Unit cell dimensions (Å, °)	a = 9.7273(6)	a = 5.2543(6)
	b = 5.9482(4), β = 92.905(2)	b = 30.530(3), β = 90.919(11)
	c = 45.204(3)	c = 15.1131(14)
V (Å^3)	2612.1(3)	2424.1(4)
Z, d_{calc}(g/cm^3)	4, 1.302	4, 1.299
μ (mm^{-1})	1.604	0.493
F(000)	1088	1004
Reflections collected/unique/Rint	31,947/5102/0.0544	6212/3168/0.1406
Data/parameters/restrains	5102/338/0	3168/273/6
Final R indices [I > 2σ(I)]	R1 = 0.0519, w$R2$ = 0.1748	R1 = 0.0998, w$R2$ = 0.2066
R indices all data	R1 = 0.0567, w$R2$ = 0.1807	R1 = 0.2088, w$R2$ = 0.2697

Cu–Kα radiation (λ = 1.54184 Å). Data collection and data reduction were carried on with the CrysAlisPro program [48]. Absorption correction was performed with the program SCALE3 ABSPACK multi-scan method [48]. The structure was then solved by using the SIR-2004 and refined by full-matrix least-squares against F2 using all data (SHELX-2018/3). The isopropyl moieties of both ibuprofen anions as well as the aromatic ring of the b-labelled anion (see Fig. 2) are affected by disorder. Such disorder was modelled by introducing two positions for every disordered atom. The occupancy factors were refined to 0.65393/0.34607, 0.54693/0.45307 and 0.58149/0.41851 for the a-labelled ibuprofen isopropyl group, the b-labelled ibuprofen aromatic ring and isopropyl group, respectively. All the non-hydrogen atoms were anisotropically refined. All the hydrogen atoms were set in calculated positions. Geometrical calculations, for both structures, were performed by PARST97 [49] and molecular plots were produced by the program CCDC Mercury (v. 2022.3.0) [41].

In Table 1 crystallographic data and refinement parameters of the two structures are reported.

2.4. Powder X-ray diffraction data collection (PXRD)

Room temperature PXRD measures were carried out by using a Bruker New D8 Da Vinci diffractometer (Cu-Kα1 radiation = 1.54056 Å, 40 kV × 40 mA), equipped with a Bruker LYNXEYE-XE detector, scanning range 2θ = 3–40°, 0.03° increments of 2θ and a counting time of 0.8 s/step.

2.5. Differential scanning calorimetry (DSC)

DSC measures on **1** were performed on a Mettler–Toledo DSC1 Excellence. Measurements were run in aluminium pans with pinhole lids (mass samples range from 2.5 to 3.8 mg). Temperature and enthalpy calibrations were done using indium as a standard. The investigated temperature range was 30–320 °C, and a linear heating rate of 10 °C/min was used. Experiments were performed in air. DSC peaks were analysed using the STARe software [50]. All measurements were performed in triplicate and standard errors were 0.1 °C for temperature and 0.3 kJ/mol for enthalpy.

2.6. In silico studies

The CCDC Mercury software [41] was used to analyze the crystal packing arrangement. CrystalExplorer17 [42] was used to compute Hirshfeld surfaces (HS) and their associated 2D (two-dimensional) fingerprint plots and to calculate the interaction energies of **1** (HF/3-21G and B3LYP/6-31G(d,p) models). [51,52] The strict analogous crystal structure with the enantiopure ibuprofen, $[Zn(S\text{-}Ibu)_2(H_2O)_2]$, was not investigated with CrystalExplorer17 due to the lack of the hydrogen atoms on the water molecules in the reported structure (SUWTAH CSD refcode) [16]; while for **2** the investigation was not carried out due to the disorder which affects the ibuprofenate anions.

Searches in the CSD [14] were performed for the structural fragments depicted in Scheme 3.

2.7. Potentiometric and ^1H NMR studies

Potentiometric measurements were performed in degassed 0.10 M NMe_4Cl H_2O/EtOH 50 % (v/v) solution at 298 ± 0.1 K, by using equipment and methods previously reported [53,54]. Briefly, a combined glass electrode was calibrated as hydrogen concentration probe by titrating known amounts of HCl with CO_2-free NMe_4OH solutions while using an Ag/AgCl electrode in saturated KCl solution as reference electrode. The equivalent point was determined by employing the Gran's method [55], affording to obtain the standard potential E° and the ionic product (pK_w of 14.41 ± 0.01) of the water–ethanol mixed media.

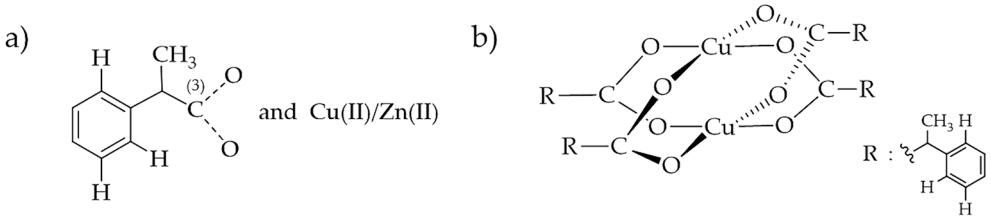
The concentration of ibuprofen (HIbu), the M:HIbu molar ratios (M = Zn(II), Cu(II)) and the pH intervals were chosen to allow the formation of metal complexes with possible different stoichiometries without incurring in the precipitation of insoluble metal complexed species and/or metal hydroxides in the pH range of measurements. To this aim, the binary systems M:HIbu were investigated by using a total HIbu concentration varying from 1×10^{-3} mol/dm^3 to 3×10^{-3} mol/dm^3, with [M] ranging between 0.3[HIbu] and 0.8[HIbu]. The pH intervals examined were 2–7.3 and 2–6 for Zn(II) and Cu(II), respectively; above these values, precipitation occurred in solution precluding the investigation in more alkaline conditions. Each system was studied by performing at least three potentiometric titrations consisting of ca. 100 data points each. The computer program HYPERQUAD [56] was used to determine the equilibrium constants for the formation of metal complexes from e.m.f. data whereas the Hyss program [57] was used to reckon the corresponding distribution diagrams of the species formed in solution at different pH values.

We herein specify that, according to the pKa in the solvent of this study (5.72 ± 0.05) [33], ibuprofen can be present both in its protonated (HIbu) and deprotonated (Ibu^-) forms in the interval of pH of potentiometric measurements.

All the reagent solutions were prepared by using absolute ethanol (99.9 % anhydrous, Sigma Aldrich) and freshly boiled, doubly deionized water. Both were saturated with anhydrous nitrogen prior to use. The NMe_4OH solution was standardized against carbonate free potassium hydrogen phthalate (standard reference material for pH measurement, Sigma Aldrich) and stored under nitrogen atmosphere. The ^1H NMR spectra were collected in D_2O/EtOD 50 % (v/v) solution at 298 ± 0.1 K, on a Bruker 400 MHz spectrometer.

2.8. Antimicrobial studies

The antimicrobial effects of complexes $[Cu(Ibu)_2]_n$ and $[Zn(Ibu)_2(H_2O)_2]$ were assessed by performing agar diffusion tests and were compared to that of ibuprofen [58]. The broth culture of the bacterial strain *B. subtilis* 168 was prepared in LB medium. Agar plates were prepared with LB agar inoculated with 5×10^5 CFU/ml *B. subtilis*. Transition complexes ($[Cu(Ibu)_2]_n$ and $[Zn(Ibu)_2(H_2O)_2]$,) and ibuprofen (sodium salt) were dissolved respectively in DMSO and H_2O and stock solutions were prepared at the concentration of 1 M, 0.1 M, 0.01 M and 0.001 M. 1 μl of each dilution, as well as pure DMSO and water, were spotted on the agar plate. The plates were maintained at room temperature for 2 h to allow diffusion of the compounds into the agar and then incubated at 37 °C for 24 h. Each test was performed in



Scheme 3. Schematic representation of a) copper or zinc complexes containing aryl propionic acid derivatives; b) the paddle-wheel copper-carboxylate structure.

triplicate. The antibacterial effect of the compounds against *B. subtilis* was evaluated by measuring the diameter of the inhibition zones around the spots.

3. Results and discussion

3.1. Synthesis and crystallization procedures

Notwithstanding the different procedures used (P1-P3, see "*Synthesis and crystallization procedures*"), in all cases the quality of single crystals of the copper-ibuprofen species **2** was quite poor for SCXRD data collection. The best set of diffraction data, although not fully satisfactory, was collected by using single crystals obtained from P2.

The PXRD pattern of the microcrystalline samples obtained by using the three different methods reported above are well superimposable (see Fig. S1 in Supplementary data), thus ensuring the consistent isolation of the same crystal form. The good superimposition of the experimental PXRD patterns with the theoretical one obtained from the single crystal data of **2** (see below) indicates that the crystalline phases are the same.

3.2. Molecular and crystal structures from SCXRD and in silico studies

Single crystal X-ray diffraction reveals that the ibuprofenate anion forms a zero-dimensional (0-D) complex with zinc(II), ([Zn(Ibu)$_2$(H$_2$O)$_2$] (**1**)), which crystallizes in the P2$_1$/n space group and a one-dimensional (1-D) coordination polymer with copper(II), ([Cu(Ibu)$_2$]$_n$ (**2**)), P2$_1$/*c* space group.

In Figs. 1 and 2 the ORTEP view of the asymmetric unit (a.u) of **1** and **2**, respectively, are reported [49].

In **1**, the zinc ion exhibits a tetrahedral coordination geometry: the four oxygen atoms are provided by two water molecules and two carboxylates from two homochiral ibuprofen anions (Fig. S2, left). Bond distances and angles are within the expected range (see Table S1).

The two crystallographically independent ibuprofen anions, which are almost superimposable except for the isopropyl groups (which is disordered in the Ibu anion labelled as B, see Fig. 1) are U shaped (based on the relative orientation of the methyl and isopropyl groups). As a whole, the zinc complex well superimposes with that found in the enantiopure [Zn(S-Ibu)$_2$(H$_2$O)$_2$] compound (SUWTAH CSD refcode, Fig. S2, right) [16]. Each carboxylate oxygen atom not involved in the metal coordination is H-bonded by the water molecules from a contiguous metal complex originating a $R_2^2(12)$ motif, according to the graph-set notation (intermolecular contacts are listed in Table 2) [59].

As a result, homochiral chains originate which propagate along the *b*-axis direction (Fig. 3, left). Additionally, as shown in Fig. 3 (right), each chain develops along the *a*-axis direction *via* –COO···HOH hydrogen bonds involving the uncoordinated carboxylic oxygen atoms O2A and O2B and a further ring motif of $R_3^2(10)$ type can be recognized. Then, the uncoordinated carboxylic oxygen atoms and both the zinc-coordinated water molecules act as hydrogen bond acceptor and donor at two sites, respectively. Finally, along the c-axis direction there are not significant intermolecular contacts involving the facing isopropyl moieties (Fig. S3).

The intra-chain arrangement in the [Zn(S-Ibu)$_2$(H$_2$O)$_2$] compound [16] is definitely identical (see Fig. S4 in Supplementary data).

The crystal packing of the 0-D complex **1** was further investigated by using the Hirshfeld Surface (HS) analysis (see Supplementary data file for a complete description of results), the related fingerprint plot, given in Fig. S5, presents two sharp spikes characteristic of hydrogen bonds and lateral wings related to CH···π interactions, being the relative contributions to the HS area due to C···H (CH···π), O···H and H···H 11.0 %, 15.8 % and 72.9 %, respectively.

Results from interaction energies calculations (HF/3-21G and B3LYP/6-31G(d,p) models, Fig. 4) show that the most significant interaction in energetic terms (-220.5 and −198.3 kJ/mol, respectively) is between the two metal complexes doubly bonded which describe the $R_2^2(12)$ motif involving the water molecules and the uncoordinated carboxylic oxygen atom (O1w-H1w2···O2A^1 and O2w-H2w1···O2B^1; ^{1} = x,y + 1,z). Accordingly, the interaction energies between singly bound metal complexes (O1w-H1w1···O2A^2 and O2w-H2w2···O2B^3; ^{2} = −x + 3/2,y + 1/2,−z + 3/2, ^{3} = −x + 1/2,y + 1/2,−z + 3/2) are about half with respect to the previous one (−86.2, −91.8, HF/3-21G model; −82.0, −87.2 B3LYP/6-31G model).

In **2**, there are two crystallographically independent ibuprofenate anions which mainly differ for the relative orientation of the carboxylate group with respect to the phenyl ring [60]. The ordered Ibu anion adopts a Z shape, based on the relative orientation of the methyl and isopropyl groups. The 1-D coordination chains of **2** consist of dinuclear paddle-wheel units [Cu$_2$(Ibu)$_4$], in which each carboxylate oxygen atom is involved in the metal coordination with a lone pair (Fig. 5, left). Units are linked along the *a*-axis direction via the second lone pair of the oxygen atom labelled O2B which binds the copper ions of adjacent paddle-wheel units (Fig. 5, right). This is the kind of structure usually expected for anhydrous copper (II) carboxylates [14]. The copper ion has a square pyramidal geometry (see Table S1 in Supplementary data for distances and angles), with the copper ion 0.168(2) Å distant from the mean plane described by the equatorial donors. The four carboxylate oxygen atoms in equatorial position are definitely closer to the metal (distances range from 1.932(7) to 1.998(7) Å) with respect to the apical oxygen donor (2.242(7) Å), being O2B the carboxylate oxygen atom responsible for the extension of the paddle-wheel motif in an infinite chain long the *a*-axis. The intra- and inter- paddle-wheel Cu···Cu distances are 2.580(2) and 3.260(2) Å, respectively. The resulting crystal packing is shown in Fig. 6.

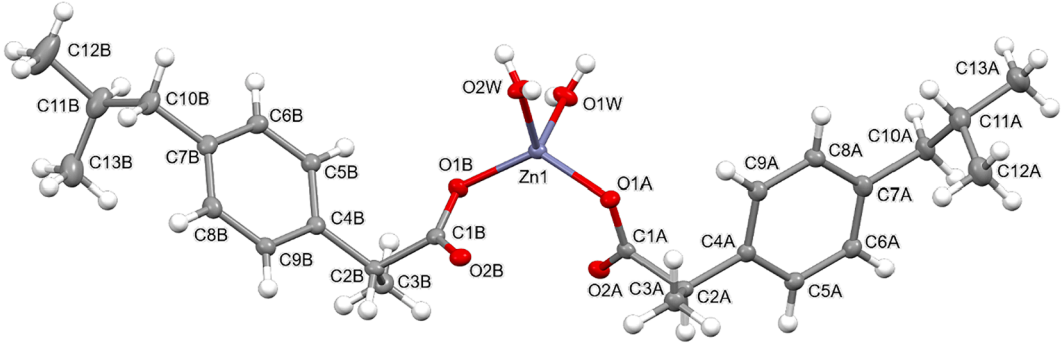


Fig. 1. ORTEP view (30% ellipsoid probability) of the asymmetric unit of [Zn(Ibu)$_2$(H$_2$O)$_2$] (**1**). For sack of clarity only the most populated model of the disordered moiety is shown.

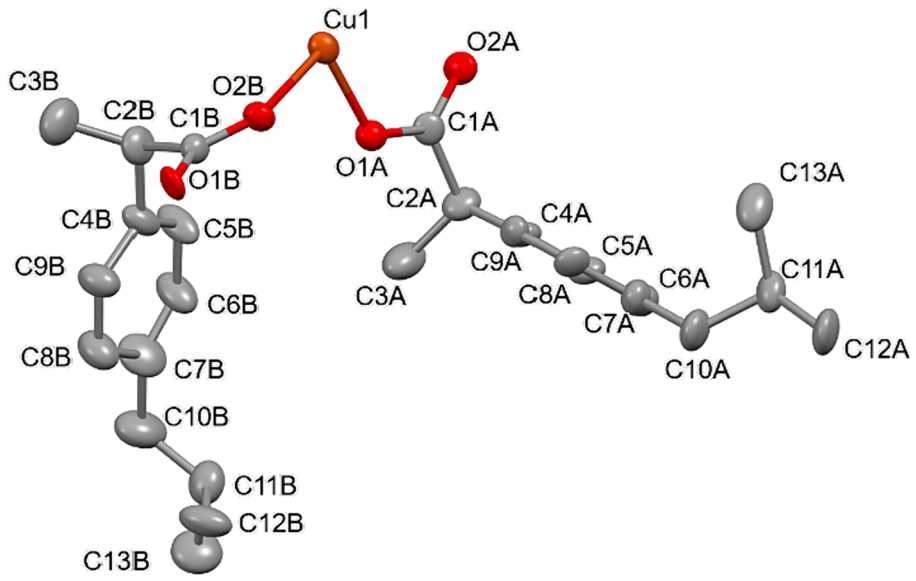


Fig. 2. ORTEP view (30% ellipsoid probability) of the asymmetric unit of $[Cu(Ibu)_2]_n$. For sack of clarity only the most populated model of the disordered moieties are shown and the hydrogen atoms have been omitted.

Table 2
H-bond interactions in the crystal packings of $[ZnIbu)_2(H_2O)_2]$ (**1**).

D-H···A	D···A (Å)	H···A (Å)	D-H···A (°)
O1w-H1w2···O2A[1]	2.656(2)	1.86(4)	171(4)
O2w-H2w1···O2B[1]	2.657(2)	1.85(4)	171(4)
O1w-H1w1···O2A[2]	2.689(2)	1.99(4)	162(4)
O2w-H2w2···O2B[3]	2.692(2)	2.00(4)	162(4)

[1] x, y + 1, z; [2] −x + 3/2, y + 1/2, −z + 3/2; [3] −x + 1/2, y + 1/2, −z + 3/2.

3.3. Comparison with solid state literature data

A CSD search for the molecular fragment sketched in Scheme 3 (fragment a), including zinc and copper ions, gives 76 hits; 28 of them contain Ibu^- bound to the metal center, most of them are zinc complexes (20 vs 8). In all the ibuprofen-based complexes, except for the [Zn(S-Ibu)$_2$(H$_2$O)$_2$] compound (SUWTAH CSD refcode) [16], the metal ion coordination sphere is completed by ancillary ligands, most of them providing nitrogen atoms as donors, and solvent molecules.

The analysis of the deposited structures revels that in most of the cases, the ibuprofen acts as monodentate ligand (Scheme 2) as found in **1** and in SUWTAH. Few zinc complexes featuring a chelate (SUWSUA, GETNUS, ZERZOP, KAKDIN and KAKDUZ CSD refcodes) binding mode and only one in which the two coordinated ibuprofenate anions show a different coordination mode: monodentate and chelate (OMAKUL CSD refcodes) [16,18,20,21,61].

Finally, there are several examples of structures featuring the ibuprofenate acting as bridging bidentate *syn*-syn ligand both towards zinc (MUJFUV, NETJAB CSD refcodes) and copper (SUCVOE, WIKSAL, WIKSEP and COMBEM01 CSD refcodes) ions [62–66]. The resulting dinuclear species are characterized by a pyramidal paddle-wheel coordination about the metal ions. In the resulting 0-D structures, the four Ibu^- anions are anchored to the two metal centers through both the oxygen atoms, being only one of the lone pairs involved in the metal coordination. The square pyramidal geometry about the metal ion being completed by an ancillary ligand which in NETJAB [63], for example, is the amifampridine drug, thus realizing a dual drug metal complex.

To the best of our knowledge, the crystal structure of **2**, here reported, is the first example of 1-D coordination polymer consisting of copper-ibuprofen dinuclear paddle-wheel units. Moreover, only few crystal structures (16 hits, only one of them has a polymeric structure [14]) featuring the dinuclear copper fragment sketched in Scheme 3 (fragment b) have been found in the CSD.

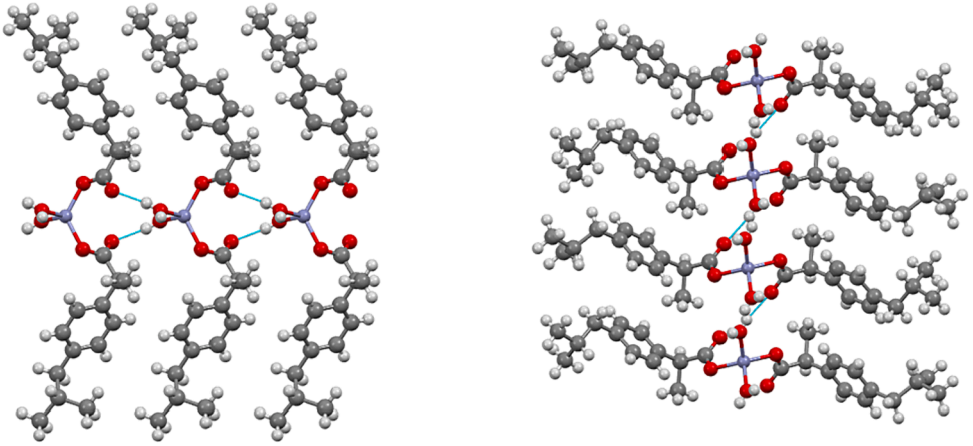


Fig. 3. Left: view (along *a*) of the $R_2^2(12)$ motif which originates a $[Zn(Ibu)_2(H_2O)_2]_n$ chain extending along the *b*-axis direction. Right: view (along *b*) of the [Zn(Ibu)$_2$(H$_2$O)$_2$]$_n$ chain extending along the *a*-axis direction.

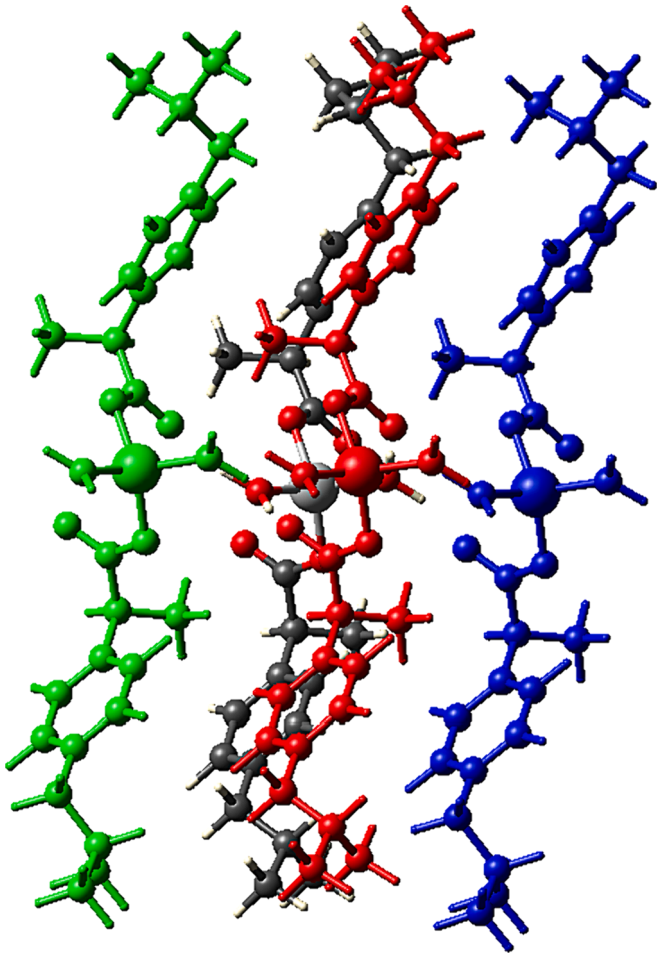


Fig. 4. The Zn(II) metal complex (grey) and the neighboring interacting ones (the color code, red, blue and green, refers to decreasing interaction energy).

As for the ibuprofen overall shape, the U shape observed in **1** is definitely the most common in ibuprofen zinc/copper metal complexes in which the carboxylate acts as monodentate ligand and that observed in all the paddle-wheel structures above mentioned at variance with the Z shape found in **2**.

3.4. DSC measurement results

The thermal stability of $[Zn(Ibu)_2(H_2O)_2]$ was tested by DSC measurements. The DSC curve shows an intense broad endothermic peak at about 100 °C (peak = 97.3 °C; extrapolated peak = 98.3 °C) which can be related to the loss of the zinc-coordinated water molecules, followed by a very small one (see Fig. S6 in Supplementary data). The enthalpy value correlated to this intense peak is 152.1 kJ/mol which, normalized with respect to the moles of water eliminated from the crystal lattice, results in a molar enthalpy of 76.1 kJ. Such a value is about 86 % higher than the heat of vaporization of water at 97 °C (40.8 kJ/mol), thus it cannot be only ascribed to the dehydration process [35]. As a consequence, we can speculate that this endothermic event should also be related to the zinc-coordination sphere rearrangement which causes a loss of crystallinity and subsequent amorphization of the sample as testified by the comparison of the PXRD patterns (see Fig. S7 in Supplementary data) collected before and after the dehydration process (dehydration was induced by keeping $[Zn(Ibu)_2(H_2O)_2]$ in oven for half an hour at 110 °C). These findings are in keeping with the role played by the water molecules in constructing the crystal structure of **1** as testified by the interaction energy calculations. Thus, their loss, which requires a significant energy contribution, definitely destroys the crystal packing, hence the molar enthalpy.

3.5. Potentiometric and ^1H NMR studies

The coordination properties of ibuprofen towards Zn(II) and Cu(II) were also investigated in solution through potentiometric measurements, in 0.1 NMe_4Cl 50 % (v/v) water–ethanol mixture, to overcome the scarce solubility of the drug in pure water [67,68]. In this solvent mixture, HIbu fully solubilized and no precipitation occurred in the pH range of potentiometric measurements (pK_w of 14.41 ± 0.01, see also experimental section). Moreover, ethanol is a commonly used cosolvent to increase the drug solubility [69] and, as an example, it has been shown to enhance the ibuprofen permeation in silicone and human skin [70].

Potentiometric investigation evidenced the ability of HIbu to form both the $[MIbu]^+$ and $[M(Ibu)_2]$ species, in analogy to the behavior previously displayed by the drug in the same media with the alkaline earth metal ions Mg(II), Ca(II) and Sr(II) [35]. Table 3 reports the formation constants (Logβ values) determined for complexes of ibuprofen with Cu(II) and Zn(II). As expected, their Logβ values turned out to be significantly higher if compared to the ones of the previously considered

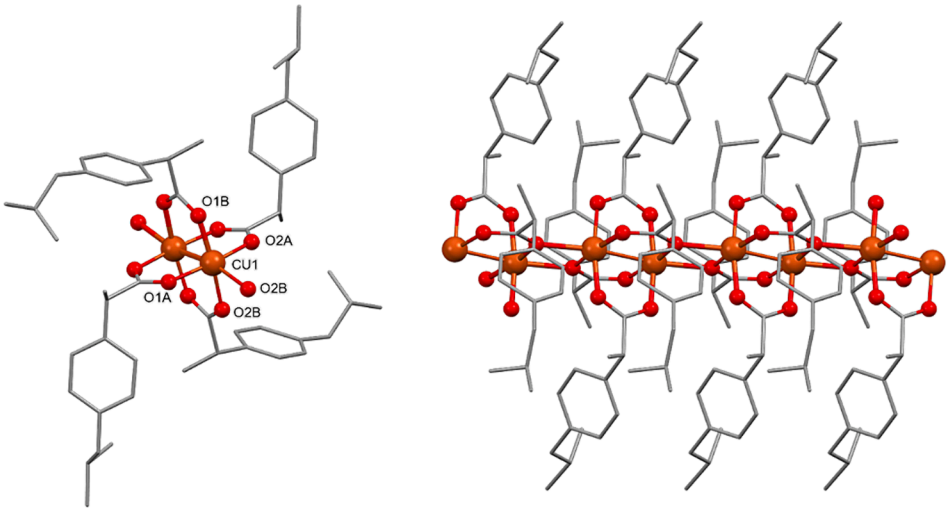


Fig. 5. Left: view of the dinuclear paddle-wheel units $[Cu_2(Ibu)_4]$ and the copper coordination sphere. Right: $[Cu(Ibu)_2]_n$ 1D chain viewed along the c axis. For sake of clarity hydrogen atoms have been omitted.

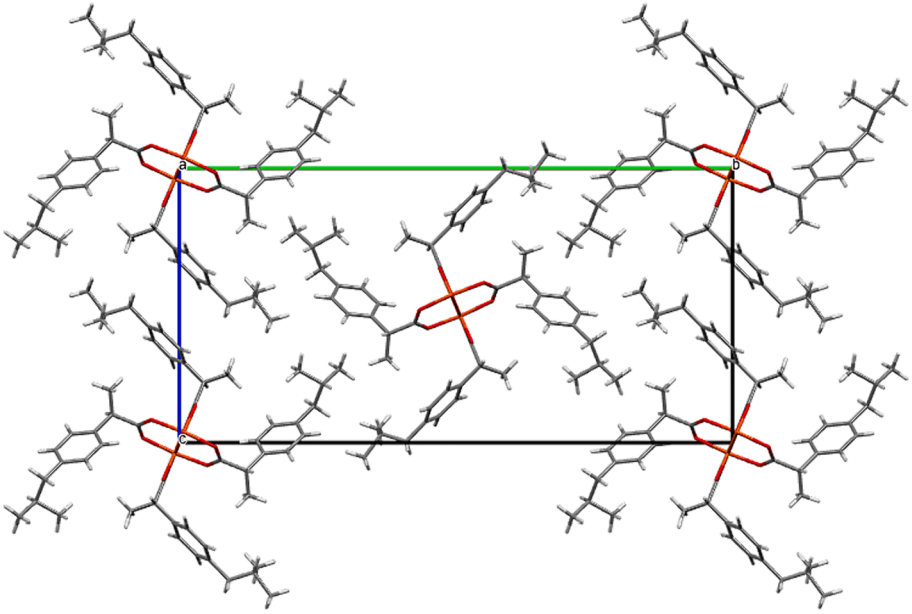


Fig. 6. Crystal packing of $[Cu(Ibu)_2]_n$ viewed along *a*-axis direction.

Table 3
Logarithm of the formation constants for Cu(II)- and Zn(II)-ibuprofen complexes in 0.1 M NMe_4Cl H_2O/EtOH 50 % (v/v) at 298.1 ± 0.1 K.

Reaction	Logβ*
$Cu^{2+} + Ibu^- = [CuIbu]^+$	3.01(5)
$Cu^{2+} + 2Ibu^- = [Cu(Ibu)_2]$	5.98(9)
$Zn^{2+} + Ibu^- = [ZnIbu]^+$	2.53(6)
$Zn^{2+} + 2Ibu^- = [Zn(Ibu)_2]$	4.88(8)

* Values in parenthesis are standard deviations on the last significant figures.

alkaline earth metal ions, up to 2.5 Log units higher, for example, in case of $[M(Ibu)_2]$ species. Among the two transition metals, Cu(II) gave the most stable complexes. As an example, the Logβ values for the equilibrium $M^{2+} + Ibu^- = [MIbu]^+$, were 3.01(5) and 2.53(6) respectively for M = Cu(II) and Zn(II). It can be noted that these values are in line with the ones previously potentiometrically determined for the formation of 1:1 M-Ibu complexes in 0.1 M KNO_3 aqueous solution (3.12 and 2.63 respectively for Cu(II) and Zn(II)) [71,72]; however, no evidence for the formation in solution of 1:2 complexes was provided in these studies, in contrast to this and previous reports [6,73]. As shown in Fig. 7a, where are reported the species present in solution as a function of pH for a system containing HIbu and Zn^{2+} in 1:1 M ratio, the $[ZnIbu]^+$ and $[Zn(Ibu)_2]$ species coexist in solution starting from pH 4–4.5 and reach a maximum around neutral pH, at which they display an overall percentage of formation of about 50 %. No metal complexation was observed below pH 4, as expected considering the competitive protonation of the carboxylate function of the drug. Similar findings were also obtained for the system Cu(II)-HIbu, whose distribution diagram is reported in Fig. S8 (Supplementary data).

The higher stability of Cu(II)- over Zn(II)-Ibu complexes can be also easily appreciated by the selectivity diagram for the system M-HIbu (M = Cu(II), Zn(II) and the biologically relevant Ca(II) and Mg(II)) (Fig. 7b), which shows the preferential binding of ibuprofen to Cu(II) over Zn(II) in a wide range of pH, with an almost negligible percentage of Ca(II) and Mg(II) complexed species.

^{1}H NMR measurements were also performed to further confirm the coexistence of different metal complexed species in solution and to get insights into the nature of the coordination site of ibuprofen involved in metal complexation.

As shown in Fig. 8, where are reported the ^{1}H NMR spectra of a solution of ibuprofen in 50 % (v/v) D_2O-EtOD mixture at pH 6 with increasing amounts of Zn(II), the first addition of the metal (0.25 eq.) determines the appearance of a second, and broad, set of signals which accompanies the primary and more defined spectrum of ibuprofen. This would indicate that, in the presence of an excess of ligand relative to Zn (II), at least two species, slowing exchanging on the NMR time scale, are simultaneously occurring in solution; these species are mainly ascribable to the free drug, and $[Zn(Ibu)_2]$.

With increasing the Zn(II) concentration (0.25–0.75 eq.), along with the above mentioned subspectrum it can be observed a downfield shift of the resonance attributable to the H2 proton of ibuprofen, whereas no other significant shifts neither in the aromatic region nor in the aliphatic one were registered.

This would indicate the formation of a second complexed species likely the one with Zn(II):Ibu^- stoichiometry of 1:1, which coexists with the 1:2 one. It can be also noted that the H2 resonance shifts from 3.59 ppm, in the absence of Zn(II), to 3.67 ppm in the presence of 1 eq. of the metal, with a $\Delta\delta$ ($\delta_{complex} - \delta_{ligand}$) of ~0.08 ppm. Despite being modest, such effect would confirm the interaction between ibuprofen and Zn(II), through, as expected, the carboxylate motif of the drug, in agreement with previous ^{1}H NMR studies on Pd^{2+}-complexes with ibuprofen in EtOD [74] and also with what generally reasoned for the Zn(II) coordination by phenylacetic residues [75].

When ≥1 eq. of Zn(II) is added to the solution, the second set of signal disappears, suggesting the predominance in solution of one complexed form, likely the $[ZnIbu]^+$ species, in these conditions.

Unfortunately, the paramagnetic nature of Cu(II) precluded the same analysis on the Cu(II)-Ibu complexes. However, on the basis of potentiometric studies a similar behavior to the HIbu-Zn(II) system in solution could be envisaged.

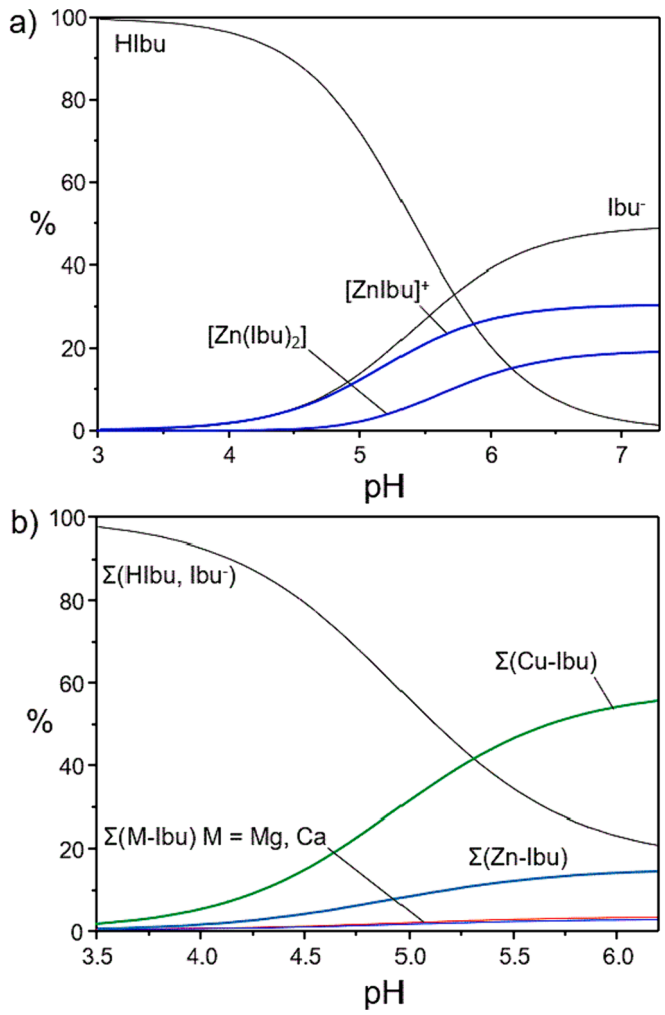


Fig. 7. a) Distribution diagram of the species formed in solution for the system Zn(II)-HIbu in 1:1 M ratio as a function of pH ([HIbu] = 3×10^{-3} M). b) Selectivity diagram for the system M-HIbu (M = Cu(II), Zn(II), Mg(II) and Ca(II)) showing the percentage of the complexed species formed with the different metals as a function of pH. The biologically relevant Mg(II) and Ca(II) were also considered in the construction of the selectivity diagram. Percentages were calculated with respect to ligand concentration ([HIbu] = [M] = 3×10^{-3} M), NMe_4Cl H_2O/EtOH 50 % (v/v) at 298.1 ± 0.1 K.

3.6. Biological studies

The increasing interest on the antimicrobial activity of NSAIDs has prompted us to preliminary investigate the possible effect that complexation with Cu(II) and Zn(II) could have on the antibacterial behaviour of ibuprofen. This was evaluated through agar diffusion tests, by incubating broth cultures of the bacterial strain *B. subtilis* 168, chosen as a model for Gram-positive bacteria, with different concentrations of metal complexes $[Cu(Ibu)_2]_n$ and $[Zn(Ibu)_2(H_2O)_2]$, and ibuprofen (see experimental details section). The antibacterial activities were evaluated through measurements of the inhibition zones around the spotted compounds; the resulting agar plates are shown in Fig. S10 (in Supplementary data), whereas the measurements of inhibition diameters are reported in Fig. 9, and listed in Table 4.

As shown, and in line with previous studies on *B. subtilis*, ibuprofen displayed a modest antimicrobial activity, as it was found to be active only at the highest dose tested (1 M, inhibition zone of 12.7 ± 2.1 mm), without significant effects for lower drug doses. On the contrary, inhibition zones were still present at 1 M, 0.1 M and 0.01 M of both $[Cu(Ibu)_2]_n$ and $[Zn(Ibu)_2(H_2O)_2]$, thus indicating that the copper and zinc ibuprofen complexes possess increased antibacterial activity compared to the parent ibuprofen. This finding is in agreement with the enhanced biological properties reported upon metal complexation for other metal-NSAID complexes [76], and could be tentatively rationalized considering different aspects, such as: i) the favourable role played by the positive charge gathered on metal ions in improving the uptake mechanisms of chelate compounds [77]; ii) possible redox cicles between Cu(II) and Cu(I) oxidation states that lead to reactive radical species and iii) the catalytic role of Zn(II) in various metalloenzymes [78].

4. Conclusions

This paper presents the results of combined solid state and solution studies of the racemic ibuprofen towards zinc(II) and copper(II) ions. In the solid state ibuprofen turns out to be a very versatile ligand, in terms of coordination mode (e.g. monodentate, bridging bidentate and monoatomic bridging-bridging), adopted conformation (U vs Z shaped) and resulting structure dimensionality (zero-dimensional complex vs one-dimensional coordination polymer). Results from the solid state investigation of $[Zn(Ibu)_2(H_2O)_2]$ highlight the role of the coordinated water molecules in building up the crystal lattice: the loss of the water molecules upon heating at about 100 °C is accompanied by a structural rearrangement about the metal ion (DSC results), which results in an amorphization of the solid form (PXRD results). Both results are consistent with the crucial role played by the water molecules in holding up the crystal packing, especially the H-bonded chains extending along the *a*-axis direction, as suggsted by the results from the interaction energy calculations.

As for the copper-ibuprofen system, the crystal structure of $[Cu(Ibu)_2]_n$ is, to the best of our knowledge, the first example of 1-D coordination polymer consisting of copper-ibuprofen dinuclear paddle-wheel units. Moreover, the fact that irrespective of the different synthetic and crystallization procedures the same crystal form is obtained, suggests that the 1-D coordination polymer-based structure is the stable solid form in the experimental condition adopted.

In solution there are not significant differences among the complexed species formed by ibuprofen with zinc(II) and copper(II), as provided by the potentiometric measurements which indicate the formation of both the $[MIbu]^+$ and $[M(Ibu)_2]$ species, being the Cu(II) complexes the more stable. ^{1}H NMR studies on the Zn(II) system, evidence, as expected, the involvement of the carboxylate group in the metal complexation but also confirm the simultaneous formation of $[ZnIbu]^+$ and $[Zn(Ibu)_2]$ species, hinting at the complexity of the system when considering its equilibria in solution.

Lastly, given the growing interest about the antimicrobial activity of NSAIDs, the antimicrobial effects of $[Cu(Ibu)_2]_n$ and $[Zn(Ibu)_2(H_2O)_2]$ were preliminary evaluated on *B. subtilis*, chosen as model of Gram-positive bacteria, and compared to that of ibuprofen. Results showed that the bioactivity of ibuprofen is effectively augmented as a result of metal coordination with Cu(II) and Zn(II); this could be particularly important to discover new perspectives for "*old*" non-antibiotic drugs but also to design new drugs with synergistic biologically active ligands (metal-NSAID complexes).

In conclusion, this paper provides further insights into the coordination ability of the multi-purpose NSAID ibuprofen ligand towards two biological relevant metal ions and highlights its versatility which results in the different solid forms here presented, thus contributing to the NSAID-based metal complexes research field.

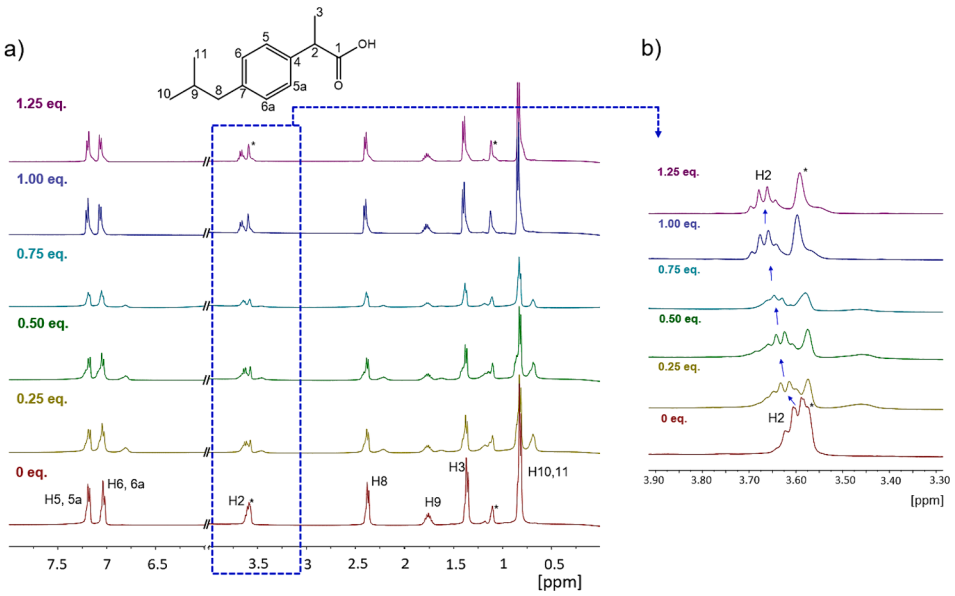


Fig. 8. A)[1]H NMR spectra of ibuprofen in D_2O/EtOD 50 % (v/v) at pH 6 in presence of increasing concentration of Zn(II) and b) magnification of the 3.90–3.30 ppm region. The pale blue arrows highlight the shift underwent by the H2 proton induced by the increasing concentration of zinc, asteriks indicate solvent residual peaks. ([HIbu] = 10 mM, 298.1 ± 0.1 K).

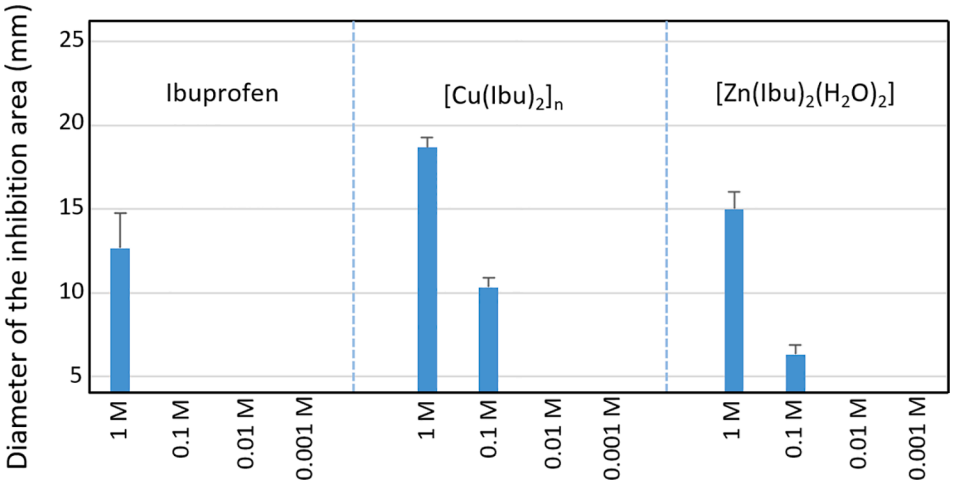


Fig. 9. Antimicrobial activity of ibuprofen and $[Cu(Ibu)_2]_n$ and $[Zn(Ibu)_2(H_2O)_2]$ complexes evaluated *via* agar diffusion tests; diameters of the inhibition areas are reported in nm and are listed in Table 4.

Table 4
Measurements of the diameters of the inhibition areas around the spotted compounds (ibuprofen and the metal complexes $[Cu(Ibu)_2]_n$ and $[Zn(Ibu)_2(H_2O)_2]$ in mm.

	ibuprofen (mm)				$[Cu(Ibu)_2]_n$ (mm)				$[Zn(Ibu)_2(H_2O)_2]$ (mm)			
	1 M	0.1 M	0.01 M	0.001 M	1 M	0.1 M	0.01 M	0.001 M	1 M	0.1 M	0.01 M	0.001 M
	11	0	0	0	18	10	3	0	16	7	1	0
	15	0	0	0	19	11	2	0	14	6	0	0
	12	0	0	0	19	10	0	0	15	6	0	0
mean	12.7	0.0	0.0	0.0	18.7	10.3	1.7	0.0	15	6.3	0.3	0.0
sd	2.1	0.0	0.0	0.0	0.6	0.6	1.5	0.0	1	0.6	0.6	0.0

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Credit authorship contribution statement

Martina Lippi: Conceptualization, Methodology, Validation, Visualization, Writing – review & editing. **Paola Paoli:** Conceptualization, Project administration, Supervision, Writing – original draft, Writing – review & editing. **Luca Conti:** Funding acquisition, Investigation, Supervision, Writing – original draft. **Gina Elena Giacomazzo:** Formal analysis. **Eleonora Macedi:** Investigation, Writing – review & editing. **Jacopo Ceccarelli:** Investigation. **Juliana Morais Missina:** Investigation. **Camilla Fagorzi:** Investigation. **Patrizia Rossi:** Conceptualization, Funding acquisition, Writing – review & editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Patrizia Rossi reports financial support was provided by MUR Ministero Università e Ricerca (ITALY). Luca Conti reports financial support was provided by European Union. Luca Conti reports financial support was provided by Green Economy and Agriculture Centro per la Ricerca s.r.l. Luca Conti reports financial support was provided by MUR Ministero Università e Ricerca (ITALY).

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

CIFs Files can be downloaded, free of charge from the Cambridge Structural Datacenter (https://www.ccdc.cam.ac.uk/structures/; Deposition numbers: 2283934 ($[Zn(Ibu)_2(H_2O)_2]$; **1**) and 2283933 ($[Cu(Ibu)_2]_n$; **2**). Supplementary data to this article can be found online at https://doi.org/10.1016/j.ica.2024.122034.

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