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A [24-MC-6] Zinc Metallacoronate with a Nonsteroidal Antiinflammatory Drug as the Constructing Ligand

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Supporting Information

ABSTRACT: The interaction of $ZnCl_2$ with 2-dipyridylketonoxime (=Hpko) and flufenamic acid (=Hfluf) in a basic methanolic solution leads to the formation of a hexanuclear 24-membered metallacoronate, $[Zn_6(OH)_2(pko)_4(fluf)_6]$ (**1**), with a [Zn−O−C−O] repeat unit and a nonsteroidal antiinflammatory drug as the constructing ligand. Compound **1** retains its structure in a dimethyl sulfoxide solution, as shown by ^1H NMR spectroscopy and molar conductance.

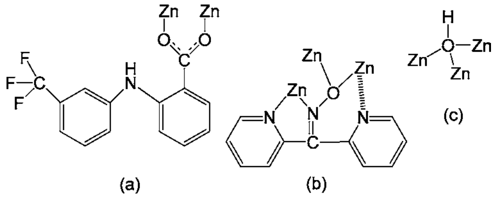
It has been remarked that the attention of coordination chemists is increasingly directed toward polynuclear systems. Among them, metallacrowns are a class of complexes that could be considered as molecular recognition agents.[1] The nature of inorganic molecular recognition agents allows them not only to function as cation or anion recognition agents but also to selectively bind zwitterionic compounds, recognizing the cation and anion simultaneously. The cavity size of metallacrowns compares well to that of organic crown ethers. [9-MC-3], [12-MC-4], [15-MC-5], inverse [12-MC-4], [12-MC-6], [16-MC-8], [18-MC-6], up to [60-MC-20] with metal ions $V^{V}O$, Mn^{III}, Fe^{III}, Co^{II}, Co^{III}, Ni^{II}, Cu^{II}, Zn^{II}, Ag^{I}, Pd^{II}, and Au^{I} are the most characteristic examples reported to date.[2−5] For the [24-MC-6] motif, there are examples with different types of repeat units constructing the metallamacrocycle molecule. For $[M−N−C−O]_6$ (M = Cu^{II}, Co^{II}), the repeat unit is the ligand 6-methyl-2-hydroxypyridine, which provides two N−C−O bridges between the metal ions.[6] For aza[24-MC-6] metallacrowns with [M−N−C−N] (M = Ag^{I}, Cu^{II}) connectivity, pyrimidine or pyridine derivatives have been used as constructing ligands.[7] A [24-MC-6] complex with [−M−S−C−N−] (M = Rh^{III}) connectivity has also been produced with the ligand 6-purinethione riboside,[8a] while 24-MC-6 macrocycles with $[Pd^{II}−S−S−S]$[8b] or $[Sn^{IV}−O−P−O]$[8c] repeat units have also been reported. The [24-MC-6] metallacoronates consist of a $[Cu^{II}−O−C−O]$ repeat unit with glycinato or tricarboxylato ligands.[8d]

For zinc metallacrowns, two structural motifs have been reported so far, regular and inverse. For the regular motif, the metallacrown ring shows the repeat pattern [−O−N−M−], with the O atoms oriented toward the center of the cavity.[2d] For the inverse motif, while the repeat pattern [−O−N−M−] remains the same, now the metal atoms are oriented toward the center of the cavity.[2e] The regular metallacrown binds cations in a central cavity, while the inverse metallacrown can bind anions.

Zinc complexes with drugs showing antibacterial/antimicrobial, anticonvulsant, antidiabetic, antiinflammatory, and antiproliferative/antitumor activity have already been reported in the literature.[9] Our recent studies have been focused on the coordination chemistry of carboxylate-containing antiinflammatory or antimicrobial drugs with diverse metal ions (Co^{2+}, Ni^{2+}, Cu^{2+}, and Zn^{2+}) in an attempt to examine their mode of binding and possible biological relevance.[10]

In this paper, we report the synthesis, characterization, and crystal structure of a hexanuclear 24-membered metallacoronate, $[Zn_6(OH)_2(pko)_4(fluf)_6]$ (**1**; Hpko = 2-dipyridylketonoxime). Compound **1** is a particularly interesting molecule because it is the only example of a zinc metallacoronate with a [Zn−O−C−O] repeat unit with a nonsteroidal antiinflammatory drug (NSAID), flufenamic acid (=Hfluf; Scheme 1a), constructing the metallacoronate ring.

Scheme 1. Coordination Modes of Binding of (a) a Bidentate Mode for the fluf Ligand, (b) Two Modes, Such as Tetradentate or Pentadentate, for the pko Ligand, and (c) a Tridentate Mode for the Hydroxyl Ion



X-ray diffraction analysis revealed that compound **1** consists of six Zn atoms bridged by six flufenamato ligands via the carboxylato moieties, creating a 24-membered metallacoronate ring with a [Zn−O−C−O] repeat unit (Figure 1a). Four deprotonated pko^- ligands and two OH^- ions act as bridging ligands, stabilizing the six Zn^{II} atoms in a distorted trigonal-antiprismatic arrangement. Zn_1, Zn_3, and Zn_5 possess the vertices of one trigonal base (base 1), while Zn_2, Zn_4, and Zn_6 lie on the vertices of the second almost parallel antiprismatic trigonal base (base 2; the angle between two basal planes is

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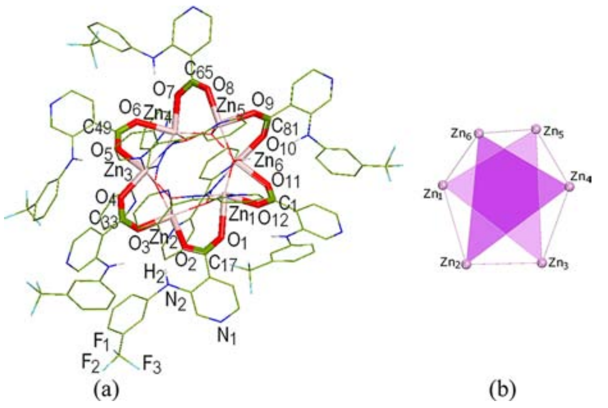

Figure 1. (a) Diagram of the crystal structure of compound **1** with only the metallacoronate atoms labeled (O, red; N, blue; F, cyan; Zn, pink; C, olive) and a constructing fluf ligand. (b) Overlapping diagram of two parallel levels of the trigonal-antiprismatic arrangement of six Zn atoms.

6.73°) at an average distance (centroid Zn_2−Zn_4−Zn_6 to centroid Zn_1−Zn_3−Zn_5 distance) of 1.954 Å (Figure 1b). Each Zn^{II} ion is in a slightly distorted octahedral geometry, with axial angles around Zn^{II} ions varying between 157.1(2)° and 175.0(2)°. Two pko ligands, one from each side of the trigonal-antiprismatic bases in a trans arrangement, act in a pentadentate deprotonated mode, with the oximato group bridging three Zn^{II} atoms (Scheme 1b). For one side, these atoms are Zn_3 and Zn_5 from one trigonal base and the third Zn_4 from the antiprismatic base. The pyridyl N atoms of this ligand are bound to the Zn_3 and Zn_5 atoms. The oximato groups of the trans analogue pentadentate pko ligand at the other side of the prism bridge Zn_6 and Zn_2 atoms from this trigonal base and Zn_1 from the antiprismatic one. The N atoms of the pyridyl groups from this ligand are bound to the Zn_6 and Zn_2 atoms. The other two pko ligands lie also above and below the trigonal bases of the antiprism in an approximate trans arrangement and act in a tetradentate fashion. The oximato group of one ligand bridges Zn_1 and Zn_3 from one base and Zn_2 from the other, and the N atom from one pyridyl ring is bound to Zn_1. The oximato group of the trans analogue tetradentate pko ligand bridges the Zn_2 and Zn_4 atoms from its own side and Zn_3 from the antiprismatic one, and the N atom from one pyridyl group of this ligand is bound to Zn_4. The two μ_3-OH^- atoms also bridge three Zn^{II} atoms each, which are those forming the third edge of each trigonal base, Zn_1···Zn_5 and Zn_4···Zn_6, and the corresponding Zn_6 and Zn_3 atoms from the antiprismatic base for each edge. The average Zn^{II}−N_{pko}/O_{pko} bond distance of the pko ligand is 2.120 Å.

The six carboxylato groups of the fluf ligands bridge the six Zn^{II} ions, creating a 24-membered metallacoronate ring in which each carboxylato group acts in a bidentate mode bridging two Zn^{II} atoms. Three carboxylato groups bridge Zn_2 and Zn_3, Zn_4 and Zn_5, and Zn_6 and Zn_1, respectively, in a symmetrical fashion [Zn_2−O_3 = 2.091(4) Å, Zn_3−O_4 = 2.058(4) Å, Zn_4−O_7 = 2.066(4) Å, Zn_5−O_8 = 2.082(4) Å, Zn_6−O_{11} = 2.162(4) Å, and Zn_1−O_{12} = 2.043(4) Å], while the three other bridge Zn_1 and Zn_2, Zn_3 and Zn_4, and Zn_5 and Zn_6, respectively, in an unsymmetrical fashion [Zn_1−O_1 = 2.381(4) Å, Zn_2−O_2 = 2.060(4) Å, Zn_3−O_5 = 2.057(4) Å, Zn_4−O_6 = 2.261(4) Å, Zn_5−O_9 = 2.043(4) Å, and Zn_6−O_{10} = 2.103(5) Å]. The Zn···Zn separation by each carboxylato bridging ligand varies between 3.010 and 3.649 Å, while the O···O carboxylato bite distance varies from 2.223 to 2.252 Å. The fluf ligands are stabilized close to the central [Zn−O−C−O] repeat unit through six intramolecular hydrogen-bonding interactions between the NH and O−C−O groups with N···O interatomic distances in the range 2.571−2.695 Å. Further stabilization is provided by weak π−π interactions between the pyridyl rings belonging to tetradentate and tridentate pko ligands. The pyridyl rings are almost parallel with angles between the planes in the range 4.9−19.8° and the average distance between the planes in the range 3.159−3.568 Å.

Wheel structures with six metal ions and a [18-MC-6] motif have been reported for Cu^{II} 2f, Co^{III},[5a] Mn^{III},[5b,c] Fe^{III},[5d] Au^{I},[4f] or Ga^{III} 6f metal ions with a [18-MC_{M-N-O}-6] or [18-MC_{M-N-N}-6] metallacrown ring, while there are many examples of the [12-MC-6] motif with a [−M−O−], [−M−S−], or [−M−Cl−] repeat unit.[3] For the [24-MC-6] motif, there are only a few examples, while for carboxylato bridging ligands as the constructing groups, they are limited just to two copper clusters with glycinato or aminotricarboxylato ligands.[4i] For zinc metallacrowns with six metal ions, there is only one example with a [12-MC-6] motif with a [−M−O−] repeat unit.[4a] The present compound, **1**, is the first zinc example with a [24-MC-6] motif.

In order to confirm that compound **1** retains its structure in solution, we have studied ^1H NMR spectroscopy in dimethyl sulfoxide (DMSO)-d_6 and molar conductance in DMSO (Figure 2). Both studies revealed that there is no dissociation in solution. In ^1H NMR spectra (Figures S1−S3 in the Supporting Information), all of the protons associated with the antiinflammatory ligand confirm that the fluf ligand is bound to Zn^{II} atoms without any protons associated with the free drug, while the absence of the oxime proton (N−O−H) of Hpko supports the deprotonated mode of pko ligands.[11] The molar conductance ($\Lambda_M \leq 6$ mho cm^2 mol^{-1}) in DMSO is also strong evidence of nondissociation of the metallacoronate compound in solution.

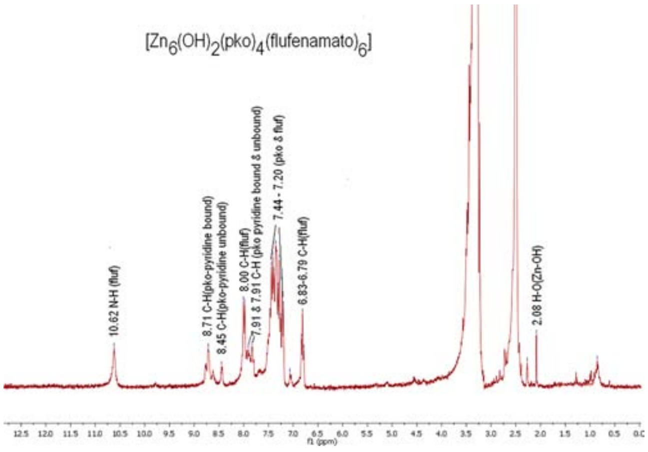

Figure 2. ^1H NMR spectrum of **1** in DMSO-d_6.

The hexanuclear 24-membered metallacoronate **1** with a [Zn−O−C−O] repeat unit and a NSAID as the constructing ligand is the first example of a zinc(II) metallacrown of the type [24-$MC_{Zn^{II}-O-C-O(fluf)}$-6]. Compound **1** retains its structure in a DMSO-d_6 solution, as shown by ^1H NMR spectroscopy and molar conductance measurements. It might be considered a potential new molecule in guest−host chemistry.

Compound **1** was prepared by mixing Hpko (0.6 mmol, 0.120 g), $ZnCl_2$ (0.9 mmol, 0.123 g), Hfluf (0.9 mmol, 0.253 g), and KOH (1.5 mmol, 0.084 g) in a methanolic solution (15 mL) under stirring. Upon slow evaporation in the presence of diethyl ether, pale-yellow prismatic crystals were isolated after 2 weeks. Yield: 45%.

Crystals of **1** have been structurally characterized with the formula $C_{123.3}H_{87.7}F_{18}N_{24}O_{19.55}Zn_6$ (fw = 2952.61). Anal. Calcd for **1**: C, 50.07; H, 2.95; N, 11.25. Found: C, 50.16; H, 2.99; N, 11.39. Crystal data for $\mathbf{1}\cdot 1.3\mathrm{MeOH}\cdot 0.25\mathrm{H_2O}$: M_r = 2952.61, monoclinic, space group $P2_1/a$, a = 22.1436(4) Å, b = 21.9303(4) Å, c = 27.7426(5) Å, β = 108.583(1)°, V = 12769.8(4) $Å^3$, Z = 4; d_{calc} = 1.536 mg m^{-3}; $6.71 < \theta < 63.00$; crystal dimensions (mm), 0.10 × 0.10 × 0.49; μ = 2.128 mm^{-1}; T = 148(2) K; 20244 used of 92132 reflections collected [R_{int} = 0.0593]. A total of 20244 reflections and 1733 parameters were used for the full-matrix, least-squares refinement of F^2, R1 = 0.0843 [14245 reflections with $I > 2\sigma(I)$], R1 = 0.1093 (all data); wR2 = 0.2303 [14245 reflections with $I > 2\sigma(I)$], wR2 = 0.2598 (all data). All non-H atoms were refined anisotropically, with the H atoms placed at calculated positions as riding on bonded atoms. Solvate molecules were refined isotropically with partial occupancy. CCDC 882881 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB21EZ, U.K.; fax (+44) 1223-336-033 or e-maildeposit@ccde.cam.ac.uk).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Molar conductance measurements and ^{1}H NMR spectra (Figures S1−S3). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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