

A novel 18-membered metallacrown containing a double-azathiacrown

Wei Luo · Xu-zhuo Sun · Kai Hu · Zhen-ping Ji · Gong-zhen Cheng ·
Xiang-gao Meng

Received: 23 August 2007 / Accepted: 17 October 2007 / Published online: 29 November 2007
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Abstract A new type of 18-metallacrown-6, $[\text{Fe}_6(\text{H}_2\text{O})_6\text{L}_6]$ ($\text{L} = 1\text{-(2-hydroxy-benzoyl)-thiosemicarbazide}$), has been prepared and characterized. The backbone of this metal-organic assembly is the double-azathiacrown, which is formed by six repeating units of the five-membered rings $[\text{Fe}-\text{S}-\text{C}-\text{N}-\text{N}]$. It is the first metal complex containing a double-azathiacrown. Due to the meridional coordination of the ligand to the Fe^{3+} ion, the ligand enforces the stereochemistry of the Fe^{3+} ions as a propeller configuration with alternating Λ/Δ forms. Antibacterial screening data showed that the metallacrown has strong antimicrobial activity against *Escherichia coli* and *Staphylococcus aureus*.

Introduction

In 1989, Pecoraro reported the first metallacrowns as a new class of inorganic recognition agents [1–3]. They have two types of structures. The first type is cyclic with interlinked $[\text{M}-\text{N}-\text{O}]$ repeat units as 9-MC-3 [1, 3, 4], 12-MC-4 [5–7], 15-MC-5 [8–10], one metal ion could be coordinated in the center of the ring. Another type of metallacrown has $[\text{M}-\text{N}-\text{N}]$ repeat units, and they cannot encapsulate metal ions in the cavity of the ring. The dihydrazide derivative template ligands (Fig. 1a) were

used to synthesize the second type of metallacrowns, the rings of the metallacrowns were expanded from 15-MC-5 to 18-MC-6 [11–15], 24-MC-8 [16, 17], 30-MC-10 [18, 19], 36-MC-12 [20, 21], even to 60-MC-20 [22].

In this article, we report a new pentadentate ligand 1-(2-hydroxy-benzoyl)-thiosemicarbazide (**1**) (H_3L) and a novel iron(III) 18-metallacrown-6 compound, $[\text{Fe}_6(\text{H}_2\text{O})_6\text{L}_6]$ (**2**). The binding mode of the deprotonated L^{3-} is shown in Fig. 1b.

In previous studies, with an attempt to examine the mode of binding to metal ions and possible antagonistic or synergic effects, antibacterial screening data showed that 15-MC-5 and 12-MC-4 metallacrowns are more active than the simple manganese herbicide or carboxylate complexes [23, 24]. But those metallacrowns studied are the type of hydroxamic acids, whereas our interest is focused on salicylhydrazide derivatives. In our former reports [15, 25], the metallacrowns containing salicylhydrazides have shown effective antimicrobial activity.

Experimental section

Materials and methods

All reagents were of the best commercial grade and were used as received. ^1H -NMR and ^{13}C -NMR spectra were recorded on a Varian Mercury 300 MHz NMR spectrometer at 25 °C. Chemical shifts were referenced to the residual solvent peak. IR spectra were recorded on AVATAR 360 FT-IR spectrophotometer. Melting points were obtained with a digital melting-point apparatus, TP Micro Printer S-X6. Elemental analyses were performed on a Perkin–Elmer 2400 CHN elemental analytical instrument. Cyclic voltammetry (CV) studies were performed on Eco Chemie Autolab

W. Luo · X.-z. Sun · K. Hu · Z.-p. Ji · G.-z. Cheng (✉)
College of Chemistry and Molecular Sciences, Wuhan
University, Wuhan, Hubei 430072, P.R. China
e-mail: gzcheng@chem.whu.edu.cn

X.-g. Meng
College of Chemistry and Material Science, South-Central
University for Nationalities, Wuhan, Hubei 430074, P.R. China

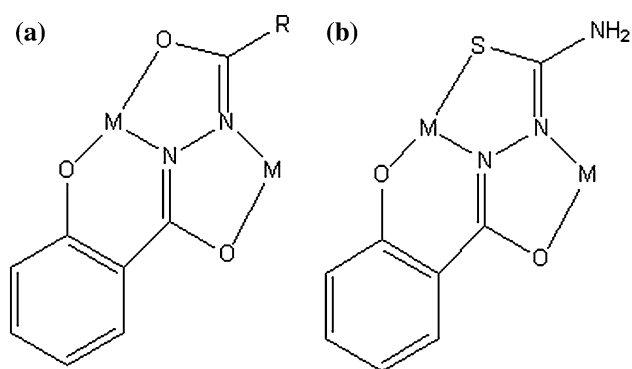


Fig. 1 (a) The binding sites of the template ligands to form the second type of metallacrown (b) The binding sites of the new ligand in our work

Electrochemical analyzer. The experiments were carried out in a three-electrode cell with a platinum electrode, a glass-carbon electrode as the working electrode, and a Ag/AgCl electrode saturated with KCl as the reference electrode. The supporting electrolyte was tetrabutylammonium perchlorate (tbap) recrystallized twice from ethanol and dried under vacuum. Pure nitrogen was insufflated in the solution of the compound to remove the oxygen. All electrochemical measurements were carried out at room temperature. The antimicrobial activity of the complexes was assessed by their ability to inhibit the growth of *S. Aureus*, *E. Coli*, *B. Subtilis*, and *P. Vulgaris* in Mueller–Hinton broth medium. The minimum inhibitory concentration in $\mu\text{g/ml}$ against the four bacteria species was measured. The bacteria concentration was $5 \times (10^5 - 10^6)$ cfu/ml and concentrations of 1,600, 800, 400, 200, 100, 50, and 25 $\mu\text{g/ml}$ of the complexes in DMF were tested. The solvent showed no antimicrobial action.

Synthesis of the ligand 1

Salicylhydrazide (3.04 g, 0.02 mol) in concentrated HCl (2 g) and 30 ml water, was heated 2 h on a water bath with KSCN (2.5 g, 0.025 mol), then cooled, the product was filtered and recrystallized from hot water (yield 3.88 g, 92.1%), mp 201–202 °C. Anal. found: C, 45.6; H, 4.1; N, 19.8%. $\text{C}_8\text{H}_9\text{N}_3\text{O}_2\text{S}$ calcd.: C, 45.5; H, 4.2; N, 19.9%; $^1\text{H-NMR}$ (600 MHz, $\text{DMSO-}d_6$, 25°C), δ = 11.90 (s, 1 H, Ar–OH), 10.57 (s, 1 H), 9.45 (s, 1 H) (both amide NH's); 7.97 (s, 1H, Ar); 7.83 (d, 1 H, Ar); 7.72(s, 1H, Ar); 7.433(t, 1H, Ar); 6.927(s, 2H, $-\text{NH}_2$) ppm. $^{13}\text{C-NMR}$ (150.9 MHz, $\text{DMSO-}d_6$, 25 °C), δ = 182.5, 169.28, 160.20, 134.74, 129.49, 119.96, 119.40, 117.82 ppm.

Synthesis of compound 2

H_3L (21.1 mg, 0.1 mmol) was dissolved in 20 ml DMF, and 40.4 mg (0.1 mmol) of iron(III) nitrate nonahydrate was added. The mixture was stirred for 10 min with the color of the mixture changing to dark brown, then filtered. After slow evaporation of the mother liquor over several weeks, dark brown crystals suitable for X-ray diffraction were obtained. Yield: 1.29 g, 76.5%. IR (KBr pellet, cm^{-1}): H–OH, 3,410 m, broad, C=N–C=N, 1,600 s, (C–O)phenolic, 1,560 s, N–C=O, 1,480 vs, Fe–O, 657 m, Fe–N, 560 m.

X-ray crystallography

A crystal of the title compound **2** with dimensions of $0.20 \times 0.10 \times 0.10$ mm was mounted in a glass capillary with the mother liquor to prevent the loss of the structural solvents during X-ray diffraction data collection. The data were recorded on a Siemens Smart CCD area detector diffractometer with graphite-monochromated Mo K α radiation (λ = 0.71073 Å), the scan mode being ω . It crystallizes in the trigonal system and space group *R*-3. $a = b = 18.8277(13)$ Å, $c = 31.774(5)$ Å, $\alpha = \beta = 90^\circ$, $\gamma = 120^\circ$. From a total of 26,365 reflections corrected by SADABS in the $1.79 \leq \theta \leq 25.49$ range, 4,036 were independent with $R_{\text{int}} = 0.0797$. The crystals diffracted poorly, with a relatively low percentage observed intensities above the threshold $2\sigma(I)$ within the 1.79 – 25.49° θ range. The noncoordinated solvent molecules are severely disordered which could not be modeled by discrete atoms in the compound. Correspondingly, the contribution of the solvent to the diffraction pattern was subtracted using SQUEEZE procedure of the PLATON [26]. The structure was solved by direct methods using SHELX-86 and refined by full-matrix least-squares calculations with SHELX-97 giving a final R_1 value of 0.0668 and ωR_2 of 0.1740. All non-hydrogen atoms were refined with anisotropic thermal parameters. All hydrogen atoms were located in calculated positions and/or in the positions from difference Fourier map.

Results and discussion

IR spectroscopy

In the IR spectra, the ligand **1** shows stretching bands attributed to C=O, C=S, C=N, C–OH(phenolic), and $\text{N}_2\text{–H}$ at 1,613, 1,225, 1,159, 1,105, and 3,199 cm^{-1} , respectively

[27]. In addition, a strong band found at $1,541\text{ cm}^{-1}$ is assigned to $\text{C}=\text{N}-\text{N}=\text{C}$ group [27–29]. In the compound **2**, the absence of the N_2-H , the weakness of the $\text{C}=\text{O}$ and $\text{C}=\text{N}$ stretching vibration bands is consistent with the deprotonation of the CONH groups and coordination to the $\text{Fe}(\text{III})$ ion. The deprotonation and coordination are also confirmed by the band at 657 cm^{-1} , attributed to $\text{Fe}-\text{O}$ linkages, and the band at 560 cm^{-1} , assigned to $\text{Fe}-\text{N}$ linkages. The broad band at $3,410\text{ cm}^{-1}$ is reasonably assigned to OH stretching vibrations, and the band is attributable to coordinated H_2O molecules [30].

Crystal structure

A diagram of the crystal structure of compound **2** is presented in Fig. 2. The deprotonated ligand acts as a trianionic pentadentate ligand; one phenolate oxygen atom, one hydrazinic nitrogen atom, and the sulfur atom are bonded to one Fe^{3+} cation, and the other hydrazinic nitrogen atom plus the carbonyl oxygen atom are chelated to an adjacent Fe^{3+} in a back-to-back fashion. The remaining coordination site of Fe^{3+} cation is satisfied by the oxygen atom of the water molecule. Therefore, the pentadentate ligand is not only bridging the ring metal ions,

but also forcing the stereochemistry of all Fe^{3+} cations into a propeller configuration with alternating Λ/Δ stereochemistry as $\Delta\Lambda\Delta$ or $\Lambda\Delta\Lambda$ forms. Three water groups coordinated at the metal centers with Λ configuration are found on one face of the metallacrown and the other three water groups coordinated to the other metal centers with Δ configuration are found on the other face of the metallacrown. The two faces of the disc-shaped hexanuclear ring have opposite chiralities to each other. This organization results in an 18-membered hexanuclear core ring system with a $[\text{Fe}-\text{N}-\text{N}]$ repeat unit. The possible ring strain in a planar conformation can be released by the puckering of the macrocyclic ring, which can be considered as a thermodynamically more stable structure than the strained planar conformation [20]. The approximate dimensions of the oval-shaped cavity are about $4.560\text{ \AA}$ in diameter at the entrance, $9.908\text{ \AA}$ at its diameter at the center of the cavity. It is also observed that all the atoms in the ligand are almost coplanar and the metal ions in the 18-membered ring are in a chair conformation. All iron(III) ions in compound **2** are in a severely distorted octahedral $\text{FeN}_2\text{O}_3\text{S}$ environment. The equatorial plane is formed by two diazine nitrogen atoms [$\text{N}(2)$, $\text{N}(2e)$], an acyl oxygen atom [$\text{O}(1)$], a water oxygen atom [$\text{O}(3)$], the sulfur atom [$\text{S}(1)$], and the phenolate oxygen atom [$\text{O}(2e)$] are in the axial

Fig. 2 Ortep diagram of compound **2** (solvent molecules and all hydrogen atoms have been omitted for clarity)

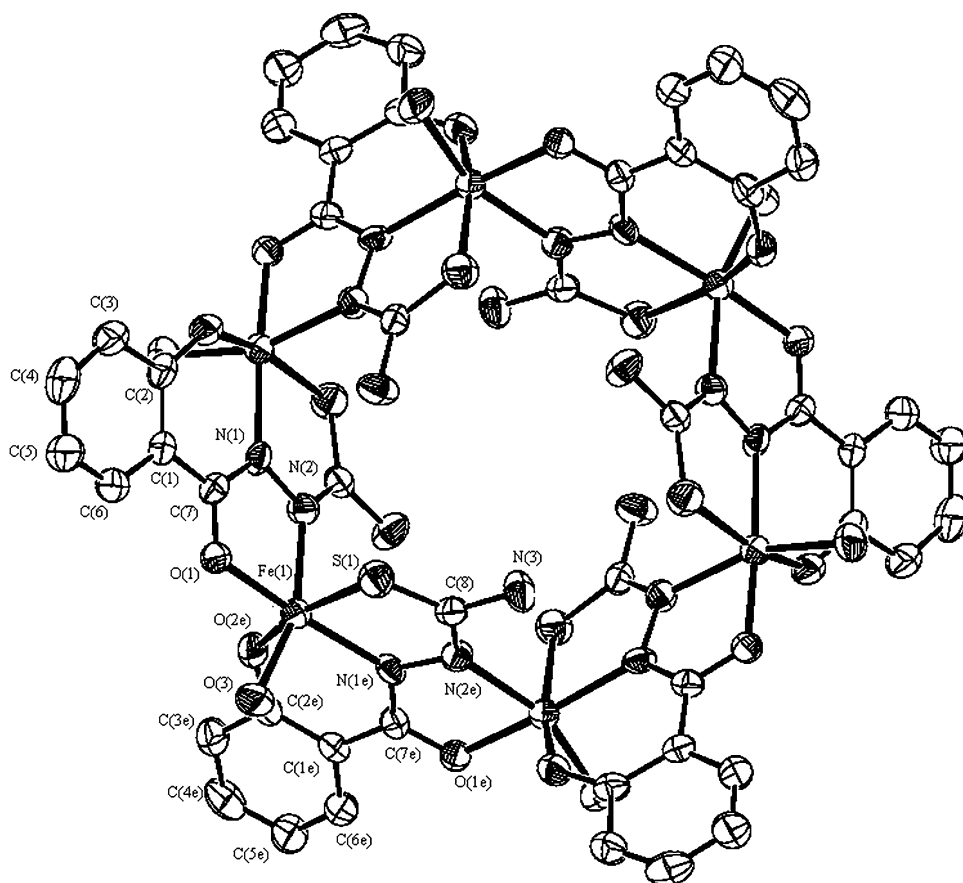
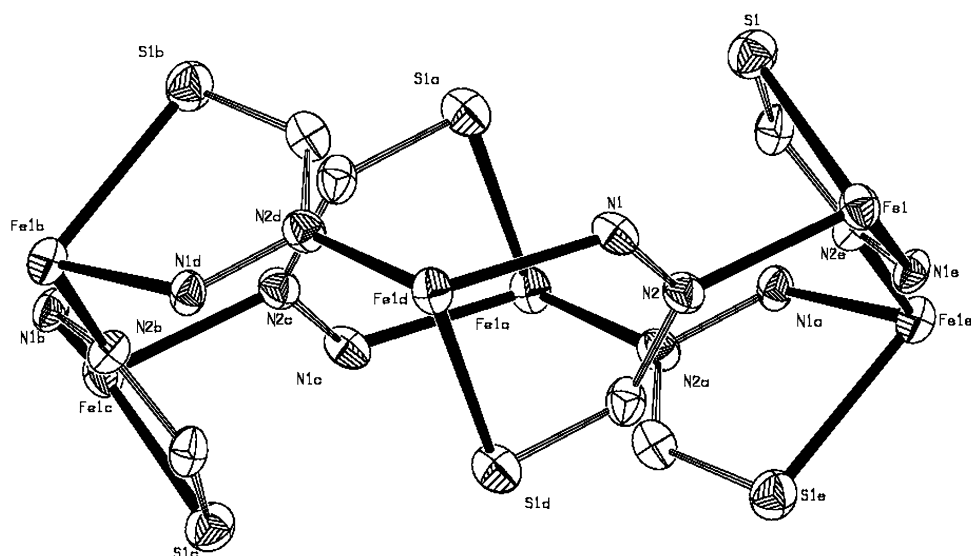


Fig. 3 The double-azathiacrown in the metallacrown with carbon atoms not marked



coordination sites. The bond distances Fe–N (diazine), Fe–O (phenolate), Fe–O (acyl), Fe–O (H₂O) Fe–S are 2.091(4), 2.103(4), 1.890(3), 1.985(3), 2.074(3), 2.3941(17) Å, respectively. The diameter of the metallacrown is 19.57 Å. In the Ni₆ metallacrown [Ni₆(SCH₂CH₂OH)₁₂] [31], The six nickel atoms approximately form a hexagon, with Ni–Ni separations in the range of 2.9010–2.9378 Å. Two μ_2 -S from one ligand are connected to adjacent nickel atoms with one above and the other below the Ni₆ plane to form double crowns. The 18-membered hexanuclear metallacrown is in a puckered conformation, linked by six five-membered Fe–S–C–N–N rings. Three sulfur atoms stay in one side of the Fe₆N₁₂ ring, leaving the other three sulfur atoms in the other side of the ring to form a double-azathiacrown (Fig. 3).

The S...S...S interatomic angles in the double-azathiacrown are 60° (Table 1), the neighboring Fe...Fe interatomic distances alternate between 5.01 and 5.02 Å,

The Fe...Fe...Fe interatomic angle is 117.6° which is quite close to the value for interior angles in an *n*-hexagon (120°). This type of metal complex with double-azathiacrown is to our knowledge, the first of its kind.

Cyclic voltammetry suggested that the title compound is electrochemically inactive in DMF in the range +1.5 to –1.5 V, which is consistent with the conjecture and conclusions in the earlier literature with other small ring metallacrowns [6, 23, 32]. The absence of any redox activity of the compound indicates that the hexanuclear iron(III) ions in this double-azathiacrown ring are redox stable. Notably, this ligand can stabilize trivalent iron ions in DMF.

Antimicrobial activity

Minimum inhibitory concentration of the ligand and compound **2** against *S. aureus*, *E. coli*, *B. Subtilis*, and *P. vulgaris* are listed in Table 2.

As can be seen clearly from the table, both compounds do not indicate specificity against Gram-positive or Gram-negative bacteria, although it is generally expected that a much greater number would be active against Gram-positive than Gram-negative bacteria [33]. The free ligand shows relatively weak effects against the tested micro-organisms, while compound **2**

Table 1 Selected bond lengths (Å) and angles (°) for **2**

Bond lengths			
Fe(1)–O(2) ^{#1}	1.890(3)	Fe(1)–O(1)	1.985(3)
Fe(1)–O(3)	2.073(3)	Fe(1)–N(1) ^{#1}	2.091(4)
Fe(1)–N(2)	2.103(4)	Fe(1)–S(1)	2.3941(17)
N(1)–Fe(1) ^{#2}	2.091(4)	O(2)–Fe(1) ^{#2}	1.890
Bond angles			
O(2) ^{#1} –Fe(1)–O(1)	102.47(14)	O(2)–Fe(1)–O(3)	90.48(17)
O(1)–Fe(1)–O(3)	84.74(14)	O(2) ^{#1} –Fe(1)–N(1) ^{#1}	87.79(14)
O(1)–Fe(1)–N(1) ^{#1}	169.61(14)	O(3)–Fe(1)–N(1) ^{#1}	93.66(14)
O(2) ^{#1} –Fe(1)–N(2)	91.34(15)	O(1)–Fe(1)–N(2)	74.44(14)
O(3)–Fe(1)–N(2)	158.99(15)	N(1) ^{#1} –Fe(1)–N(2)	107.32
O(2) ^{#1} –Fe(1)–S(1)	166.49(11)	O(1)–Fe(1)–S(1)	90.91(11)
O(3)–Fe(1)–S(1)	92.58(14)	N(1) ^{#1} –Fe(1)–S(1)	78.90(11)

Symmetry transformations used to generate equivalent atoms:
^{#1} x – y, x, – z ^{#2} y, – x + y, – z

Table 2 Minimum inhibitory concentration (MIC) of the compounds **1** and **2** in µg/ml

Micro-organism	Compound	
	1	2
<i>S. aureus</i> (Gram+)	1,600	50
<i>E. coli</i> (Gram–)	800	50
<i>P. vulgaris</i> (Gram–)	800	400
<i>B. subtilis</i> (Gram+)	400	200

shows more potent antimicrobial activity, especially against *E. coli* and *S. aureus*. Similar anti-microbial activities (MIC = 50–100 µg/ml) have been previously reported for other small ring metallacrowns [23, 24]. However, it is risky to attempt to correlate the activities of these compounds to the size of the rings in their structures.

In conclusion, we synthesized a new type of 18-metallacrown-6 using a new ligand 1-(2-hydroxy-benzoyl)-thiosemicarbazide. The backbone of this type of metallacrown is a double-azathiacrown, which is formed by six repeating units of five-membered rings [Fe–S–C–N–N]. It is the first metal cluster containing a double-azathiacrown. Antibacterial screening data showed that the metallacrown has strong antimicrobial activity against *E. coli* and *S. aureus*.

Supplementary material

Further details of the crystal structure investigation may be obtained from the Cambridge Crystallographic Data Centre, Postal Address: CCDC, 12 Union Road, CAMBRIDGE CB12 1EZ, UK. Telephone: (44) 01223 762910 Facsimile: (44) 01223 336033; E-mail: deposit@ccdc.cam.ac.uk on quoting the depository number CCDC 640627.

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