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Note

Metal complexes of salicylhydroxamic acid and *O*-acetylsalicylhydroxamic acid

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Abstract

The salicylhydroxamic acid (H_2Sha) complexes, $Ni(HSha)_2 \cdot 2H_2O$, $Cu(HSha)_2 \cdot 2H_2O$, $Zn(HSha)_2 \cdot 1.5H_2O$ and $Fe(Sha)_3 \cdot 2H_2O$, in which the ligand is coordinated to the metal through the hydroxamate group have been synthesised. Acetylation of salicylhydroxamic acid with acetyl chloride in pyridine gave *O*-acetylsalicylhydroxamic acid (H_2Sha-OAc) in which the hydroxamate oxygen is acetylated and from which the complexes $Ni(HSha\text{-}OAc)_2 \cdot H_2O$ and Zn(Sha-OAc) were prepared. In the zinc complex the ligand is coordinated to the metal through the phenolate oxygen and the deprotonated nitrogen of the acetylhydroxamic group, the latter being an extremely rare type of coordination in the case of this metal ion. Attempted preparation of iron(III) and copper(II) complexes resulted in deacetylation of the ligand and the formation of salicylhydroxamate complexes. © 1997 Elsevier Science S.A.

Keywords: Salicylhydroxamic acid complexes; *O*-Acetylsalicylhydroxamic acid complexes; Nickel complexes; Copper complexes; Zinc complexes; Iron complexes

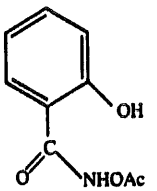
1. Introduction

The biological and medical importance of hydroxamic acids is now well recognised due to their involvement in processes such as microbial iron transport [1], inhibition of the nickel-dependent urease enzymes [2,3], the zinc-dependent matrix metalloproteinases [4,5], the haem-dependent prostaglandin-H synthase [6], and others [7,8]. This activity is largely due to the ability of hydroxamic acids to form very stable metal chelates.

The chelating properties of a wide range of hydroxamic acids in the solution and solid states have been studied [9–14]. Invariably in chelates of simple hydroxamic acids the ligands behave as (O,O) donors thus forming five-membered ring complexes. However, if the ligand contains other complexing sites adjacent to the hydroxamate group a range of coordination possibilities exists depending on the metal ion involved, the pH of the reaction solution and other factors. Hence, for example, anions of α-aminohydroxamic acids, $NH_2CH(R)CON'HO'H$, may act as (N,N'), (N,O') or (O,O') donors where N' and O' are deprotonated NH or OH groups, respectively [9–11]. Another example of such a ligand is salicylhydroxamic acid, H_2Sha.

Recently the complex $Ni_2(Sha)(HSha)(Pyr)_4OAc$, which contains bidentate salicylhydroxamate ligands with bridging hydroxamate oxygen atoms, has been crystallographically characterised [12]. In this complex the phenolic oxygens (O^- in Sha, OH in HSha) are not complexed to the metal. Several 1:1 metal complexes of salicylhydroxamic acid have also been prepared but the structures have not been reported [13].

In this note we describe the preparation, characterisation and likely structures of salicylhydroxamate complexes of iron(III), nickel(II), copper(II) and zinc(II). We also report on complexes of *O*-acetylsalicylhydroxamic acid (I), a ligand obtained by acetylation of H_2Sha.



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2. Experimental

2.1. H_2Sha

H_2Sha was obtained from Aldrich and used without further purification. IR (KBr disc): 1630, 1360, 1250, 1030, 750 cm^{-1}.

2.2. H_2Sha-OAc

H_2Sha (5 g, 32.7 mmol) was dissolved in pyridine (15 ml) with stirring to give an orange coloured solution which was cooled to 0°C. Acetyl chloride (2.4 ml, 34 mmol) was then added slowly via a syringe and the resulting solution was stirred at 0°C for 30 min and at room temperature for a further 2 h [15]. After the addition of ethyl acetate (30 ml) the solution was washed with 5% HCl (3×30 ml), saturated sodium chloride solution (3×40 ml) and dried over $MgSO_4$. The solvent was removed on a rotary evaporator resulting in a cream coloured solid which was recrystallised from ethyl acetate. The product was filtered and dried. Yield: 1.7 g, 27%. *Anal.* Found: C, 55.5; H, 4.6; N, 7.3. Calc. for $C_8H_9NO_4$: C, 55.4; H, 4.7; N, 7.2%. IR (KBr disc): 1805, 1795, 1650, 1620, 1200 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.45 (s, 3H, CH_3), 7–8 (m, 4H, ArH).

2.3. $Ni(HSha)_2 \cdot 2H_2O$

Solid $NiCl_2 \cdot 6H_2O$ (0.78 g, 3.2 mmol) was dissolved in a hot (80°C) aqueous solution (45 ml) of H_2Sha (1 g, 6.53 mmol). The pH of the resulting solution was raised to 5.5 using 0.1 M NaOH solution whereupon a copious pale green precipitate was obtained. After standing at room temperature for several hours this was suction filtered, washed with warm water and dried over P_2O_5 in vacuo. Yield: 0.8 g, 62%. *Anal.* Found: C, 41.6; H, 3.7; N, 7.0; Ni, 14.0. Calc. for $C_{14}H_{12}N_2O_6Ni \cdot 2H_2O$: C, 42.1; H, 4.0; N, 7.0; Ni, 14.7%. IR (KBr disc): 1610, 1375, 1250, 1030, 750 cm^{-1}.

2.4. $Cu(HSha)_2 \cdot 2H_2O$

This was prepared as above using $CuCl_2 \cdot 2H_2O$ (0.28 g, 1.63 mmol) and H_2Sha (0.5 g, 3.26 mmol). Yield: 0.28 g, 42.4%; pale green precipitate. *Anal.* Found: C, 41.3; H, 4.0; N, 6.7; Cu, 15.3. Calc. for $C_{14}H_{12}N_2O_6Cu \cdot 2H_2O$: C, 41.6; H, 4.0; N, 6.9; Cu, 15.7%. IR (KBr disc): 1610, 1390, 1270, 1045, 750 cm^{-1}.

2.5. $Zn(HSha)_2 \cdot 1.5H_2O$

This was prepared as above using $ZnCl_2$ (0.45 g, 3.27 mmol) and H_2Sha (1 g, 6.53 mmol). Yield: 0.74 g, 56%; white precipitate. *Anal.* Found: C, 42.9; H, 3.7; N, 7.1; Zn, 15.3. Calc. for $C_{14}H_{12}N_2O_6Zn \cdot 1.5H_2O$: C, 42.4; H, 3.8; N, 7.1; Zn, 16.5%. IR (KBr disc): 1610, 1370, 1240, 1030, 755 cm^{-1}.

2.6. $Fe(HSha)_3 \cdot 2H_2O$

This was prepared as above using $FeCl_3 \cdot 2H_2O$ (0.59 g, 2.18 mmol) and H_2Sha (1 g, 6.53 mmol). Yield: 0.8 g, 69%; maroon precipitate. *Anal.* Found: C, 45.4; H, 3.8; N, 7.6; Fe 10.6. Calc. for $C_{21}H_{18}N_3O_9Fe \cdot 2H_2O$: C, 46.0; H, 4.0; N, 7.7; Fe, 10.2%. IR (KBr disc): 1610, 1370, 1260, 1040, 750 cm^{-1}.

2.7. $Ni(HSha\text{-}OAc)_2 \cdot H_2O$

Solid $NiCl_2 \cdot 6H_2O$ (0.12 g, 0.51 mmol) was dissolved in a hot (60°C) aqueous solution (20 ml) of H_2Sha-OAc (0.2 g, 1.03 mmol). The pH of the resulting solution was raised to 5.5 using 0.1 M NaOH solution whereupon a pale green precipitate was obtained. After standing at room temperature for several hours this was suction filtered, washed with warm water and dried over P_2O_5 in vacuo. Yield: 0.08 g, 16.8%. *Anal.* Found: C, 46.4; H, 3.5; N, 6.0; Ni, 13.6. Calc. for $C_{18}H_{16}N_2O_8Ni \cdot H_2O$: C, 46.5; H, 3.9; N, 6.0; Ni, 12.6%. IR (KBr disc): 1680, 1620, 1160 cm^{-1}.

2.8. $Zn(Sha\text{-}OAc) \cdot H_2O$

This was prepared as above using $ZnCl_2$ (0.07 g, 0.51 mmol) and H_2Sha-OAc (0.2 g, 1.03 mmol). Yield: 0.07 g, 50%; white precipitate. *Anal.* Found: C, 39.2; H, 3.3; N, 5.0; Zn, 23.1. Calc. for $C_9H_7NO_4Zn \cdot H_2O$: C, 39.1; H, 3.3; N, 5.1; Zn, 23.6%. IR (KBr disc): 1690, 1610, 1585, 1540 cm^{-1}.

2.9. $Zn(Sha\text{-}OAc)$

This was prepared as above using $ZnCl_2$ (0.07 g, 0.51 mmol) and H_2Sha-OAc (0.2 g, 1.03 mmol) dissolved in ethanol (20 ml). The pH was adjusted to 5.5 using 0.1 M NaOH solution (aqueous). Yield: 0.09 g, 34%; white precipitate. *Anal.* Found: C, 41.6; H, 2.8; N, 5.3; Zn, 23.5. Calc. for $C_9H_7NO_4Zn$: C, 41.8; H, 2.7; N, 5.4; Zn, 25.2%. IR (KBr disc): 1700, 1610, 1580 cm^{-1}.

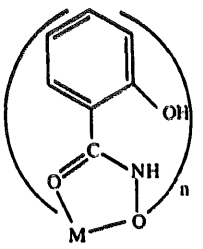
2.10. $Cu(HSha\text{-}OAc)_2$ and $Fe(HSha\text{-}OAc)_3$

The attempted synthesis of $Cu(HSha\text{-}OAc)_2$ and $Fe(HSha\text{-}OAc)_3$ by the above method resulted in deacetylation and formation of $Cu(HSha)_2 \cdot 2H_2O$ and $Fe(HSha)_3 \cdot 2H_2O$ the preparations of which, from the metal chlorides and H_2Sha, are described above. This was confirmed by the disappearance of the ν(CO) acetyl absorptions in the IR spectra and by microanalysis. *Anal.* Found: C, 42.3; H, 4.1; N, 7.0; Cu, 15.0. Calc. for $C_{14}H_{12}N_2O_6Cu \cdot 2H_2O$: C, 41.6; H, 4.0; N, 6.9; Cu, 15.7%. Found: C, 46.4; H, 4.2; N, 7.4; Fe, 10.8. Calc. for $C_{21}H_{18}N_3O_9Fe \cdot 2H_2O$: C, 46.0; H, 4.0; N, 7.7; Fe, 10.2%. IR (KBr disc): bands identical to $Cu(HSha)_2 \cdot 2H_2O$ and $Fe(HSha)_3 \cdot 2H_2O$.

3. Results and discussion

Acetylation of H_2Sha with acetyl chloride (1:1) in pyridine resulted in acetylation of the hydroxamic acid group. The IR spectrum of the product has strong absorption bands of similar intensities at 1805 and 1795 cm^{-1} due to the C=O stretch of the acetyl group. The spectrum in this region is strikingly similar to that of an anhydride which shows symmetrical and unsymmetrical C=O stretching bands around 1800 cm^{-1} [16]. If acetylation of the phenolic group rather than the hydroxamic acid group had occurred a broad absorption around 1740 cm^{-1} similar to that observed in the IR spectrum of *O*-acetylsalicylic acid (aspirin) would have been expected. The product also shows strong bands at 1650 and 1620 cm^{-1} due to the C=O stretch of the hydroxamate group [10]. The C–O stretch of the ester occurs as a prominent band at 1200 cm^{-1}.

Addition of metal chlorides to hot aqueous solutions of H_2Sha in 1:2 mole ratios or 1:3 in the case of iron followed by pH adjustment to 5.5 resulted in precipitates of composition $M(HSha)_2 \cdot 2H_2O$ and $Fe(HSha)_3 \cdot 2H_2O$. Good microanalysis results were obtained for all complexes. However despite repeated attempts, crystals for X-ray structure investigations could not be obtained for any of the complexes. Furthermore the insolubility of the complexes in common solvents did not permit spectroscopic investigations in solution. However the microanalysis results indicate that the ligands in the complexes are monoanions resulting from hydroxamic acid group or phenolic group ionization. The C=O stretch of the hydroxamate group for each complex was shifted by about 20 cm^{-1} to lower wavenumber relative to the ligand. This could indicate hydroxamate group coordination [10], as shown in structure **II**, or coordination via the phenolate and the carbonyl group. The structure shown in **II** is chosen on the basis of it being by far the most likely

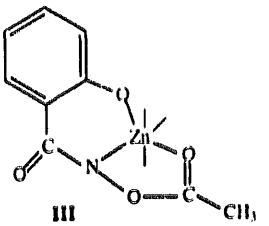


n=2, M=Ni, Cu and Zn
n=3, M=Fe.

II

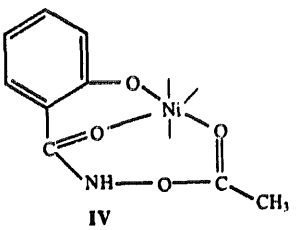
structure for the iron(III) complex. The affinity of iron(III) for hydroxamate ligands is well established [14,17], and the structure shown in **II** for the iron complex is much more likely than the alternative structure involving coordination by the phenolate oxygen and hydroxamic acid carbonyl group. Since the IR spectra of the other complexes are similar to the iron(III) complex in the hydroxamate C=O region it is assumed that the coordination of the ligand is the same as shown in structure **II** (the complexes may also be polymeric involving phenolic OH or hydroxamate O^- bridging groups [12]). The IR spectra of the complexes show bands at 1370–1390 and 1240–1270 cm^{-1} due to interaction between O–H bending and C–O stretching vibrations, respectively [16].

Reaction of $NiCl_2 \cdot 6H_2O$ or $ZnCl_2$ with the acetylated derivative H_2Sha-OAc at pH 5.5 gave the products $Ni(HSha\text{-}OAc)_2 \cdot H_2O$ and $Zn(Sha\text{-}OAc) \cdot H_2O$ in aqueous solution or Zn(Sha-OAc) in ethanol. The products gave satisfactory microanalysis. In the zinc(II) complexes the ligand is a dianion which necessarily implies phenolic group and –CONH– group ionisation and coordination to the metal by the resulting O^- and N^- sites. The IR spectra of the complexes show marked changes relative to the free ligand. The acetyl C=O stretching band is shifted by over 100 cm^{-1} to lower wavenumbers indicating coordination of the carbonyl oxygen to the metal. On the basis of the above it may be concluded that the ligand is coordinated to the metal ion as shown in structure **III**. The coordination polyhedron around the zinc is completed by a water ligand or by a donor atom from a neighbouring complex molecule functioning as a bridging ligand. Coordination of deprotonated hydroxamate nitrogen to zinc(II) has not previously been observed and is indeed extremely rare in the case of the related amidate nitrogen (i.e. deprotonated amide group) having only been observed in the case of some histidine containing peptides such as Gly-His and β-Ala-His [18–20]. Therefore structure **III** represents a novel type of coordination for this metal ion and may be due to the presence of the electron-withdrawing $-OC(O)CH_3$ group which enhances the acidity of the attached CONH group sufficiently to permit deprotonation in the presence of zinc(II).

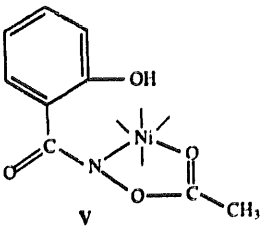


III

In the complex $Ni(HSha\text{-}OAc)_2 \cdot H_2O$ the ligands are monoanions. The C=O stretch of the acetyl group in this complex is 120 cm^{-1} lower than the free ligand indicating coordination of this group to the metal. Possible structures of the nickel(II) complex are shown in **IV** and **V** in which only one of the two ligands is shown. Although the preparative procedures for the nickel and zinc complexes were very similar the fact that different types of products were obtained is surprising.



IV



V

Complex formation between iron(III), copper(II) and H_2Sha-OAc resulted in deacetylation and the formation of the same products as with H_2Sha (structure **II**). The cleavage of the acetyl group was confirmed by the disappearance of its C=O stretching band in the IR spectra and by microanalysis.

Acknowledgements

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