Characterization of a Mononuclear Copper Carboxylate Complex: Bis(acetylsalicylato)bis(pyridine)copper(II)

FREDERICK T. GREENAWAY

Department of Chemistry, Clark University, Worcester, Mass. 01610, U.S.A.

ABBAS PEZESHK

Department of Chemistry, The University of Iowa, Iowa City, Iowa 52242, U.S.A.

A. WALLACE CORDES, MARK C. NOBLE

Department of Chemistry, University of Arkansas, Fayetteville, Ark. 72701, U.S.A.

and JOHN R. J. SORENSON

Department of Biopharmaceutical Sciences, University of Arkansas for Medical Sciences, Little Rock, Ark. 72205, U.S.A.

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Abstract

The preparation, spectral properties, and crystal structure of a mononuclear copper(II) complex of acetylsalicylate and pyridine are reported. The complex exists as bis(acetylsalicylato)bis(pyridine)copper(II) both in the solid state and in chloroform solution. The crystal is monoclinic, space group $P2_1/n$, with a = 17.823(5), b = 10.903(4), c = 6.598(2) Å, β = 95.74(2)°. The final refinement used 1472 observed reflections and gave an R of 0.046. The copper atom is surrounded by four atoms in a *trans* square planar arrangement with two short Cu–O distances of 1.949(3) Å and two Cu–N distances of 2.003(4) Å. Two longer Cu–O distances of 2.623(3) Å are made with the remaining oxygen atoms of the aspirin carboxylate groups.

Introduction

Salicylic acid and its derivatives have been used for treatment of inflammatory diseases for many years. In 1951 Reid *et al.* [1] and later Chenoweth [2] suggested that the biological activity of acetylsalicylic acid (aspirin) was due to its ability to form metal complexes. In 1976 it was suggested that the active form of this drug was a copper complex, formed *in vivo* [3]. The copper(II) complex of aspirin has been found to be more effective than aspirin as an antiinflammatory agent and, in addition, has antiulcer activity which further distinguishes it from aspirin, which is ulcerogenic [4]. Recently Kollbrunner and Lederle [5] claimed that Cu_2asp_4 (asp = 'aspirinate' = acetylsalicylate) is effective in treatment of rheumatoid disorders. This complex has also been found to reduce seizures in an animal model of seizure [6] and to decrease the rate of tumor growth as well as increase survival in two animal models of cancer [7]. Other copper(II) aspirinate complexes, including a copper–aspirinate–pyridine complex, have also been found to be effective antiinflammatory, anticancer and anticonvulsant agents [6–8].

Few spectroscopic studies of copper(II) complexes of acetylsalicylic acid have been reported. X-ray analysis of copper aspirinate demonstrated that it contains binuclear units with bridging carboxylate groups [9], similar to that of copper acetate and many other carboxylates [10–12]. Ternary complexes of the general type $Cu(asp)_2L_2$ where L = DMF or DMSO, have been reported [13]. Based on magnetic moments and electronic and infrared spectra, it has been shown that these binuclear complexes have structures analogous to that of $[Cu(acetate)_2(H_2O)]_2$ and other carboxylate solvates [10–12].

Although the pyridine solvate of copper aspirinate has been reported to have a variety of pharmacologic effects [6–8], its structure has not been fully characterized. It has been reported both as being monomeric [8] and dimeric [6, 13], but no definitive structural studies have been reported. Dimeric $[Cu(carboxylate)_2(substituted\ pyridine)]_2$ complexes are well known [10–18] and monomeric $Cu(carboxylate)_2(substituted\ pyridine)_2$ complexes have been reported for a variety of carboxylates including salicylic acid [10–25] but not aspirin. We are reporting the crystal structure and the EPR, infrared and UV-visible spectroscopic properties of the mononuclear pyridine solvate of copper aspirinate, $Cu(asp)_2py_2$.

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TABLE I. Crystallographic Data.

A. *Crystal Data*	
Formula	$CuC_{28}H_{24}O_8N_2$
Formula weight	580.05
Space group	$P2_1/n$
a, Å	17.82(1)
b, Å	10.903(7)
c, Å	6.598(4)
B, degrees	95.74(5)
V, Å^3	1276
Z	2
d_{calc}, g cm^{-3}	1.510
Crystal size, mm	0.10 X 0.14 X 0.30
$\mu(MoK_\alpha)$, cm^{-1}	8.848
Abs. corr. range	0.865–0.926
B. *Data Collection*	
Data collection instrument	Enraf-Nonius CAD-4
Radiation	MoK_α, graphite monochromator
Scan method	$\theta-2\theta$
Scan width	$\Delta\theta = (1.00 + 0.35 \tan\theta)°$
Scan speed range	4–20° min^{-1}
Data collection range (2θ)	4–60°
Total data collected	3894
R_F for dupl. data merge	0.027
Standard refl. variation	5.0%
No. obs. unique data $F_o^2 \geq 3\sigma(F_o^2)$	1472
No. parameters refined	178
Weights	counting statistics, p = 0.03
Final diff. map max.	0.33 eÅ^{-3}
R[a]	0.046
Rw[b]	0.046
Goodness-of-fit[c]	1.26
Largest shift/esd, final cycle	<0.01

[a] $R = (|\Delta F|/|F_o|)$. [b] $R_w = (w\Delta F^2/wF_o^2)^{1/2}$. [c] GOF = $[w\Delta F^2/(N_o - N_v)]^{1/2}$.

Experimental

Nujol mulls of complexes were used to obtain infrared spectra in the 4000 to 600 cm^{-1} region with a Beckman Acculab 4 spectrophotometer. Ultraviolet-visible spectra of chloroform solutions were recorded in the 200–800 nm region with a Shimadzu Model 200 spectrophotometer. EPR spectra were obtained with a Varian E-9 spectrophotometer operating at 9.1 GHz with 100 kHz modulation. The microwave frequency was measured using a Hewlett-Packard microwave frequency counter and the magnetic field was calibrated using a Magnion NMR-type gaussmeter. Table I gives the details of the X-ray data collection, the crystal data set, and the refinement results. Twenty five reflections were used for the unit cell determination. The absorption correction was made on the basis of psi scans. The structure was solved by direct methods; in the final full-matrix least-squares refinement hydrogen atoms were constrained to idealized positions (C–H = 0.95 Å) with isotropic thermal parameters of 5.0 Å^2. Elemental analyses were performed by M.H.W. Laboratories, Phoenix, Arizona.

Synthesis of Bis(acetylsalicylato)bis(pyridine)copper-(II)

$Cu(asp)_2py_2$ was prepared by adding 2 gm of $Cu_2(asp)_4$ [3] to 50 ml of warm (50 °C) pyridine. The mixture was stirred at 50 °C for 15 minutes and then set aside. After two days the purple crystalline product was filtered, washed with 95% ethanol and

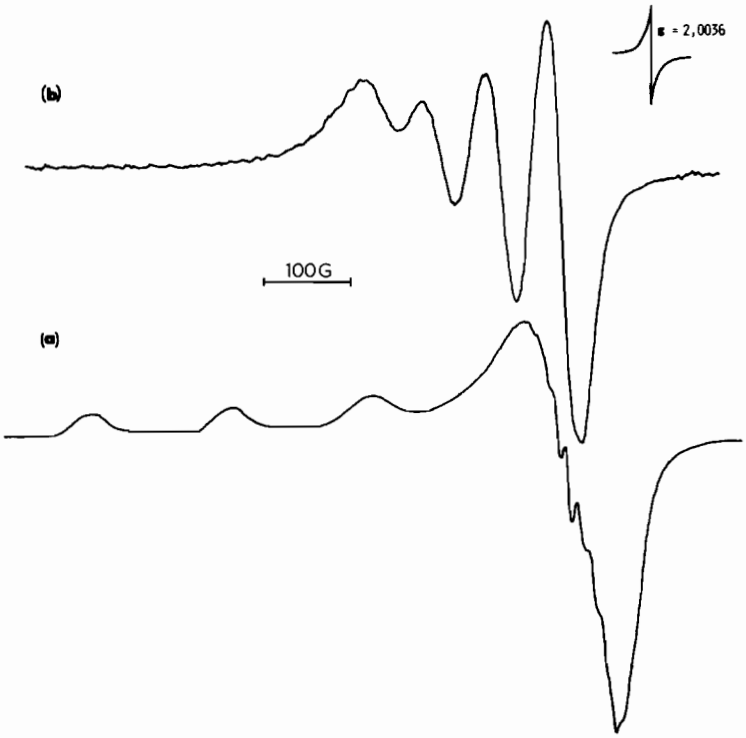

Fig. 1. X-band EPR spectra of $Cu(asp)_2py_2$ in chloroform solution at (a) 110 K, (b) 300 K.

ether, and air-dried. *Anal.* Calcd. for ($CuC_{28}H_{24}N_2O_8$): C, 57.98; H, 4.17; N, 4.83. Found: C, 57.90; H, 4.20; N, 4.64%.

Results and Discussion

Infrared absorption spectra for $Cu_2(asp)_4$ and its pyridine adduct, $Cu(asp)_2py_2$, contain a single antisymmetric carboxylate stretch at 1620 and 1603 cm^{-1} and a single symmetric stretch at 1410 or 1405 cm^{-1}, respectively. In addition, the infrared spectrum of the pyridine adduct shows absorptions at 1075, 1058, and 1025 cm^{-1}, characteristic of the pyridine ring vibrations. These absorptions are shifted towards higher frequencies as compared to the corresponding absorptions of non-bonded pyridine which occur at 1067, 1029, and 989 cm^{-1}, as expected for pyridine bound to a copper atom. X-ray analysis of $Cu_2(asp)_4$ revealed two types of acetoxy carbonyl groups [9]. One of these is weakly bonded to a copper atom of a neighboring $Cu_2(asp)_4$ molecule, while the other is not. As a consequence, the infrared spectrum of $Cu_2(asp)_4$ shows two different carbonyl stretching frequencies [13]. The infrared spectrum of $Cu(asp)_2py_2$ shows only one band at 1748 cm^{-1}, consistent with its structure (*vide infra*).

The electronic spectra for the pyridine adduct in chloroform solution exhibits a low energy absorption band at 725 nm (ϵ_M = 230) due to the copper d–d transition. The complex is purple rather than blue as in the dimeric $Cu_2(asp)_4$ which has a d–d transition at 650 nm [13]. It also lacks the charge transfer band near 400 nm characteristic of dimeric complexes [10–18]. The d–d band was not split as has been observed in other monomeric carboxylate-pyridine complexes of Cu(II) [23, 24]. In the UV region, the complex shows five bands, at 285 (ϵ_M = 5000), 265 (ϵ_M = 11000), 259 (ϵ_M = 13300), 253 (ϵ_M = 14500), and 241 (ϵ_M = 15300) nm, which have been assigned to acetylsalicylate and pyridine π–π^* transitions.

EPR spectra of $Cu(asp)_2py_2$ in frozen (110 K) and liquid (300 K) chloroform solutions, Fig. 1, show well resolved superhyperfine structure due to two equivalent nitrogen atoms, and the EPR parameters ($g_\parallel$ = 2.284, g_{iso} = 2.137, $A_\parallel(Cu)$ = 0.0174 cm^{-1}, $A_{iso}(Cu)$ = 0.0071 cm^{-1}, $A_\perp(N)$ = 0.0016 cm^{-1}) indicate square planar coordination by two nitrogen and two oxygen atoms with zero charge on the CuN_2O_2 moiety [26]. EPR spectra of Cu(II) complexes are insensitive to the axial ligands. EPR spectra of $Cu(salicylate)_2py_2$ were very similar ($g_\parallel$ = 2.299, $A_\parallel(Cu)$ = 0.0170 cm^{-1}, $A_\parallel(N)$ = 0.0010 cm^{-1}, $A_\perp(N)$ = 0.0016 cm^{-1}) indicating essentially identical structures for the two compounds. Spectra determined in DMSO were similar except for an increase in linewidth. In pyridine solution, EPR spectra show that the complexes dissociate to give $Cupy_6^{2+}$. Solid state EPR spectra of these two complexes show little

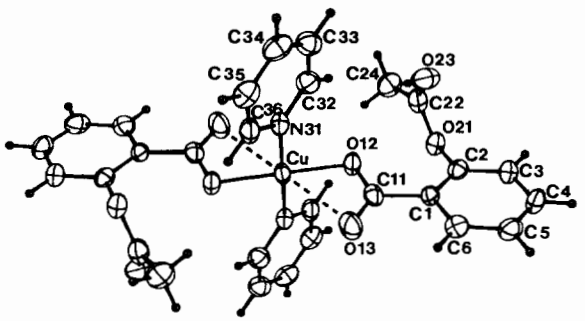

Fig. 2. ORTEP drawing of the monomer $Cu(asp)_2py_2$ showing the atomic labelling system used. Thermal ellipsoids are drawn at the 50% probability level.

TABLE II. Bond Distances in Angstroms.[a]

Atom 1	Atom 2	Distance
Cu	O12	1.949(3)
Cu	O13	2.623(3)
Cu	N31	2.003(4)
O12	C11	1.278(4)
O13	C11	1.226(5)
O21	C2	1.401(7)
O21	C22	1.350(6)
O23	C22	1.187(7)
N31	C32	1.335(5)
N31	C36	1.326(5)
C1	C2	1.393(6)
C1	C6	1.381(7)
C1	C11	1.515(5)
C2	C3	1.372(6)
C3	C4	1.371(7)
C4	C5	1.374(6)
C5	C6	1.382(7)
C22	C24	1.481(7)
C32	C33	1.372(6)
C33	C34	1.379(7)
C34	C35	1.380(7)
C35	C36	1.373(6)

[a]Numbers in parentheses are estimated standard deviations in the least significant digits.

resolution due to dipole–dipole interactions between copper atoms of neighboring molecules. EPR spectra for $Cu(salicylate)_2py_2$ have been previously reported [19] for DMF solutions. However, the $g_{\|}$ value of 2.401 shows that the complex had decomposed with the formation of $Cu(DMF)_6^{2+}$.

As shown in Fig. 2, $Cu(asp)_2py_2$ consists of a single copper atom bonded in a *trans* square planar arrangement to the nitrogen atoms of two pyridine molecules and one carboxylate oxygen atom from each of two aspirinate anions. The two other carboxylate oxygen atoms are weakly bonded to the copper and the direction of the Cu–O bonds lie at 34.8° from the normal to the CuO_2N_2 plane. The copper atom lies on a crystallographic center of symmetry.

TABLE III. Bond Angles in Degrees.[a]

Atom 1	Atom 2	Atom 3	Angle
O12	Cu	N31	89.6(1)
O13	Cu	N31	89.0(1)
O12	Cu	O13	55.2(1)
C11	O13	Cu	75.7(2)
Cu	O12	C11	105.9(2)
C2	O21	C22	116.9(4)
Cu	N31	C32	121.7(3)
Cu	N31	C36	120.7(3)
C32	N31	C36	117.6(3)
C2	C1	C6	117.0(4)
C2	C1	C11	124.7(4)
C6	C1	C11	118.3(4)
O21	C2	C1	120.9(5)
O21	C2	C3	117.3(5)
C1	C2	C3	121.7(5)
C2	C3	C4	120.1(5)
C3	C4	C5	119.7(4)
C4	C5	C6	119.9(4)
C1	C6	C5	121.6(5)
O12	C11	O13	123.1(3)
O12	C11	C1	117.9(3)
O13	C11	C1	118.9(4)
O21	C22	O23	123.9(5)
O21	C22	C24	110.6(4)
O23	C22	C24	125.5(4)
N31	C32	C33	123.0(4)
C32	C33	C34	119.2(4)
C33	C34	C35	117.7(4)
C34	C35	C36	119.4(4)
N31	C36	C35	123.0(4)

[a]Numbers in parentheses are estimated standard deviations in the least significant digits.

Bond distances and angles are listed in Tables II and III and fractional atomic coordinates in Table IV. The Cu–N distance is 2.003(4) Å for pyridine coordination. The aspirinate anion is bonded to copper by one oxygen atom of the carboxylate group with a Cu–O distance of 1.949 Å and by the other with a Cu–O distance of 2.623(3) Å. The in-plane O–Cu–N angle is 89.6(1) degrees and the out-of-plane O–Cu–N angle is 89.0(1) degrees but because of the small bite of the carboxylate group the angle between the short Cu–O bond and the long Cu–O bond is only 55.2 degrees. The oxygen atom which is most strongly bonded to the copper atom has a C–O bond distance which is longer, 1.278(4) Å, than the other C–O bond, 1.226(5) Å, of the carboxylate unit. These bond lengths are quite similar to those of other monomeric carboxylate pyridine complexes of copper(II) [21, 22].

There have been many studies directed at investigating the reasons for preference for dimer formation over monomer formation [10–25] in

TABLE IV. Fractional Positional Parameters.[a]

Atom	*x*	*y*	*z*	*B* (Å^2)
Cu	0.000	0.000	0.000	2.24(1)
O12	−0.0513(2)	0.1563(3)	−0.0757(5)	2.59(7)
N31	0.0886(2)	0.0555(3)	−0.1402(6)	2.42(8)
C11	−0.0346(2)	0.2270(4)	0.0731(7)	2.5(1)
C32	0.0801(3)	0.1144(4)	−0.3185(7)	2.9(1)
C36	0.1584(3)	0.0320(4)	−0.0604(7)	3.0(1)
O13	0.0069(2)	0.1986(3)	0.2253(5)	4.01(9)
O21	−0.1145(2)	0.3395(3)	−0.2991(5)	2.68(7)
O23	−0.2143(2)	0.2366(3)	−0.2064(6)	3.98(8)
C1	−0.0683(2)	0.3546(4)	0.0594(7)	2.14(9)
C2	−0.1073(2)	0.4045(4)	−0.1150(7)	2.29(9)
C3	−0.1355(3)	0.5216(4)	−0.1178(8)	3.1(1)
C4	−0.1257(3)	0.5930(4)	0.0540(8)	3.4(1)
C5	−0.0881(3)	0.5463(5)	0.2290(8)	3.4(1)
C6	−0.0592(3)	0.4286(5)	0.2300(8)	3.2(1)
C22	−0.1674(3)	0.2506(5)	−0.3198(8)	3.0(1)
C24	−0.1587(3)	0.1751(5)	−0.5027(8)	4.1(1)
C33	0.1397(3)	0.1520(5)	−0.4193(7)	3.2(1)
C34	0.2122(3)	0.1294(5)	−0.3342(8)	3.5(1)
C35	0.2210(3)	0.0678(5)	−0.1505(8)	3.2(1)

[a]Numbers in parentheses are estimated standard deviations in the least significant figure. Anisotropically refined atoms are given in the form of the isotropic equivalent thermal parameter, $B(Å^2)$, defined as: $(4/3)^*[a^{2*}B(1,1) + b^{2*}B(2,2) + c^{2*}B(3,3) + ab(\cos \text{gamma})^*B(1,2) + ac(\cos \text{beta})^*B(1,3) + bc(\cos \text{alpha})^*B(2,3)]$.

Cu(II)–carboxylate solvate complexes. Halogenation of the carboxylate favors monomeric structures [12] which is apparently related to electronic effects on the acidity of the carboxylate. There is also a preference for monomer formation with basic solvents such as pyridine and its derivatives, when compared to less basic solvents such as water, DMSO or DMF. Although there has been no systematic study of the relationship between steric effects and monomer formation, they appear to be less important than electronic effects as is shown by our finding that both salicylate and acetylsalicylate form monomeric compounds with pyridine [27]. To our knowledge, this is the first report of the crystal structure of a monomeric Cu(carboxylate)$_2$L$_2$ complex where the carboxylate is not halogenated.

Supplementary Material

The following supplementary material (16 pages) has been stored with the editors.

Table S1. Values of 10^*F_{obs} and 10^*F_{calc}.

Table S2. General Temperature Factor Expressions.

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