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Synthesis and Characterization of Mixed Ligand Complexes of Copper with Nalidixic Acid and (N–N) Donors. Crystal Structure of $[Cu(Phen)(Nal)(H_2O)]NO_3 \cdot 3H_2O$

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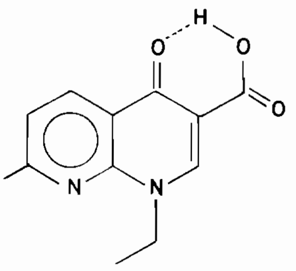
Abstract

The synthesis of two new mixed ligand complexes of Cu(II), $[Cu(Phen)(Nal)]^+$ and $[Cu(Bipy)(Nal)]^+$, is presented (Nal = nalidixate). The results obtained confirm those suggested in a previous paper: the nalidixic acid (I) binds to metal ions by the 3-carboxylate and 4-oxo groups in the solid state. The complex $[Cu(Phen)(Nal)(H_2O)]NO_3 \cdot 3H_2O$ is triclinic with $a = 16.654(3)$, $b = 11.130(2)$, $c = 7.918(2)$ Å, $\alpha = 98.53(2)$, $\beta = 112.12(2)$, $\gamma = 89.94(2)°$, $V = 1342.2(8)$ Å^3, $P\bar{1}$, $D_x = 1.551$ g cm^{-3}, $Z = 2$, $F(000) = 650$, $\lambda(\text{Mo K}\alpha) = 0.71069$ Å, $\mu(\text{Mo K}\alpha) = 9.20$ cm^{-1}, 288 K.

Introduction

Nalidixic acid (HNal) (I) is a monoprotic acid with pK_a reported values between 5.9 and 6.2 [1]. It is absorbed in the gastrointestinal tube and is employed as a drug in the control of several gram (–) infections. It has been proved that this compound inhibits the replication of DNA [2]. Two different modes of action have been suggested: (a) by inhibition of the DNA-gyrase which is probably a metalloenzyme [2, 3], and (b) by interaction with the DNA molecule by an intermediate that acts as a carrier of nalidixic acid; such an intermediate is probably a copper or iron complex (structure I) [4, 5].



I

In a previous paper [6] the isolation and characterization of a range of complexes of nalidixic acid with some metal ions has been reported. Such compounds were found to have a 2:1 HNal:metal ratio when the metal ion had an oxidation state of II, and a 3:1 ratio when its oxidation state was III. Unfortunately those compounds were found to be basically insoluble in water or any common solvent.

Studies of $M(Nal)_n$ complexes in the solid state [6] suggest that such complexes are formed by the 3-carboxylate group with no interaction of the keto group, with the formation of a four-membered ring. Other studies of solution chemistry of nalidixic acid and metal ions have been reported, and those authors have suggested that the coordination mode is by the 4-oxo and 3-carboxylate groups, but no definitive evidence has been shown [1c, 1d].

In order to enhance the knowledge of the behaviour of nalidixic acid as a complexing agent in biological tissues, we have been working with other ligands to obtain mixed ligand complexes of copper, that will be used as models and as materials for biological testing. Those ligands are 1,10-phenanthroline (Phen) and 2,2′-bipyridine (Bipy). Both ligands and their metal complexes are interesting from the point of view of biological activity [7, 8]. Such a type of system will also help to prepare a model of

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TABLE I. Elemental Analysis and Conductivity of [Cu(N–N)(Nal)]X Complexes

Compound[a]	Analysis (%)						Cm[b]
	Found			Calculated			
	C	H	Cu	C	H	Cu	
[Cu(Phen)(Nal)]NO_3	51.42	3.70	11.09	51.93	3.80	11.44	182
[Cu(Phen)(Nal)]Cl			12.02			11.90	177
[Cu(Bipy)(Nal)]NO_3			12.02			11.90	181
[Cu(Bipy)(Nal)Cl]$\cdot 2H_2O$	49.88	4.39	12.66	50.58	4.49	12.16	91

[a] All complexes were dried at 100 °C over 12 h before the analysis. [b] Cm: Molar conductivity in water solutions 10^{-3} M.

the copper carrier of nalidixic acid in its binding to DNA, as was previously mentioned [4, 5].

Experimental

Nalidixic acid was obtained from commercial pharmaceutical products, used by government medical centers, by extraction with chloroform in a soxhlet, and was treated with activated carbon and crystallized.

Complex [Cu(N–N)(Nal)]X, where X = Cl^-, NO_3^-

In 10 ml of distilled water, 1 mmol of the corresponding copper salt was dissolved and 1 mmol of the (N–N) ligand (1,10-phenanthroline or 2,2′-bipyridine) dissolved in 5 ml of ethanol was added. To this mixture was added a nalidixate (Nal) solution prepared by dissolving 1 mmol of nalidixic acid in 70 ml of water containing 1 mmol of NaOH; its pH was adjusted to 7.0–7.5 with HCl or HNO_3. The resulting blue solution was then concentrated and cooled overnight. The crystalline product was filtered off, and for studies other than crystal structure, the products were dried at 100 °C over 12 h under vacuum. The complexes obtained are listed in Table I.

Single Crystal of [Cu(Phen)(Nal)(H_2O)]$NO_3\cdot 3H_2O$

Blue prismatic crystals were grown by slow evaporation of a water solution, prepared by redissolving the obtained product. A specimen of 0.1 X 0.1 X 0.15 mm was selected and mounted on a Philips PW-1100 four-cycle diffractometer. Unit cell parameters were determined from 25 reflections ($4 \leqslant \theta \leqslant 12°$) and refined by the least-squares method. Intensities were collected with graphite monochromatized Mo Kα radiation, using the ω-scan technique, with a scan width of 0.8° and a scan speed of 0.03° s^{-1}. 3586 independent reflections were measured in the range. 4117 intensities were collected over the range $2 \leqslant \theta \leqslant 25°$, 4059 of which were assumed as observed applying the condition $I \geqslant 2.5\sigma(I)$. Three reflections were measured every 2 h as orientation and intensity control; significant intensity decay was not observed. Lorentz polarization, but no absorption, corrections were made.

The structure was solved by direct methods, using the MULTAN84 system of computer programs [9] and refined by full-matrix least-squares, using the SHELX76 program [10]. The function minimized was $\Sigma w \| F_o| - |F_c \|^2$, where $w = (\sigma^2(F_o) + 0.047|F_o|^2)^{-1}$, f, f', f'' were taken from the International Tables of X-ray Crystallography [11]. Twenty-six H atoms were located from a difference synthesis and refined with an overall isotropic temperature factor and the remaining atoms were found anisotropically. The final R value was 0.047 (wR = 0.055) for all observed reflections. The final atomic coordinates are listed in Table IV.

Job's Method

For Job's method [12] we considered Cu(Phen) or Cu(Bipy) as the metal ion and Nal^- as the ligand. Solutions (5 mM) of Cu(Phen) or Cu(Bipy) (as nitrates) and 5 mM solutions of NaNal were mixed in varying ratios to produce the mol fractions indicated in Fig. 5.

The determination of copper was made by complexometry with α,α'-biquinoline [13] and the results are given in Table I.

Instruments

The infrared spectra were carried out on a 567 Perkin-Elmer spectrophotometer as KBr pellets. The electronic spectra were obtained in a UV–Vis Perkin-Elmer spectrophotometer, model Lambda 4B. The measurements of conductivity were made on a Beckman Instruments conductivity bridge, model RC 12C-1P serial 55584. The thermogravimetric analyses (TGA) were carried out at the 'Centro de Investigaciones en Química Inorgánica' with a heating rate of 10 °C/min and a temperature range of 25–500 °C, in an air atmosphere.

Results and Discussion

Nalidixic acid was employed as the anionic form in order to increase its solubility (its sodium salt was prepared immediately before use). The copper complexes prepared are listed in Table I together with the conductivity, elemental and copper analyses.

These results are in agreement with the minimal formula proposed, given conductivities corresponding to 1:1, with the exception of [Cu(Bipy)(Nal)(H_2O)]-Cl, which was found to have a low value that suggests that the chloride ion is coordinated and in solution exhibits the equilibrium:

$$[\mathrm{Cu(Bipy)(Nal)(H_2O)}]\,\mathrm{Cl} \rightleftharpoons [\mathrm{Cu(Bipy)(Nal)(H_2O)_2}]^+ + \mathrm{Cl}^-$$

When dissolved, these compounds probably keep the same structure as in the solid state, or perhaps they obtain another water molecule in the coordination sphere, given the very symmetrical structure that is reflected in the electronic spectra (see Fig. 1); the exception is [Cu(Bipy)(Nal)Cl(H_2O)], which probably has the chloride ion coordinated in the position of one water molecule, even in solution.

In the visible region, the d–d transition band for the [Cu(Phen)(Nal)]X complex appears centered at 632 nm for both anions (Cl^-, NO_3^-), indicating that in solution they are not coordinated (see Table II and Fig. 1). In the case of the [Cu(Bipy)(Nal)]Cl complex, the spectra are different in shape and position, indicating that the chloride ion is coordinated; this is in agreement with the conductivity result. In the UV region, all the compounds show bands that correspond to nalidixic acid and the (N–N) ligand (see Fig. 2 and Table II).

The solid state infrared spectra of the complexes showed bands corresponding to both ligands. In the region of 1800–1300 cm^{-1}, the bands corresponding to the 4-oxo and to the 3-carboxylate groups appear, as reported in a previous paper [6]. These results suggest that the behaviour of the nalidixate ion should be the same as in $Cu(Nal)_2$. In the region of 600–1000 cm^{-1}, it is possible to see bands of nalidixate and (N–N) ligands (see Fig. 3).

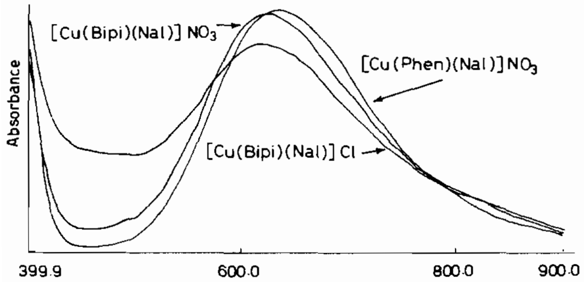

Fig. 1. Electronic spectra (Visible) of [Cu(N–N)(Nal)]X complexes (N–N is 1,10-phenanthroline or 2,2′-bipyridine).

TABLE II. UV/Vis Absorption Wavelengths

	UV				Vis
	λ1	λ2	λ3	λ4	ν
HNal	334.1	257.5	215.1	194.4	
[Cu(Phen)(Nal)]NO_3	317.0	271.8[a]	257.6	204.4	632.7
[Cu(Phen)(Nal)]Cl	317.9	271.8[a]	257.5	205.8	634.2
[Cu(Bipy)(Nal)]NO_3	310.7	249.7		197.3	626.7
[Cu(Bipy)(Nal)]Cl	310.7	249.8	233.7	195.9	618.3

[a]These bonds correspond to Phen ligand; in the case of Bipy complexes the bands overlap with those of nalidixate ligand (see Fig. 2).

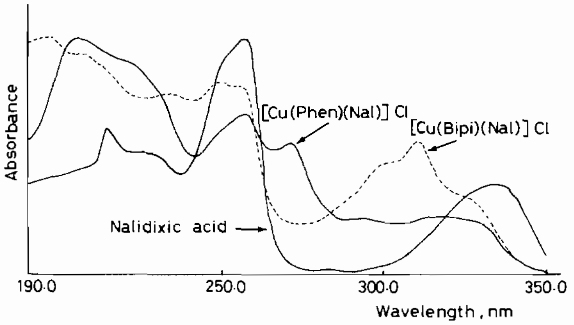

Fig. 2. Electronic spectra (UV) of [Cu(N–N)(Nal)]X complexes (N–N is 1,10-phenathroline or 2,2′-bipyridine).

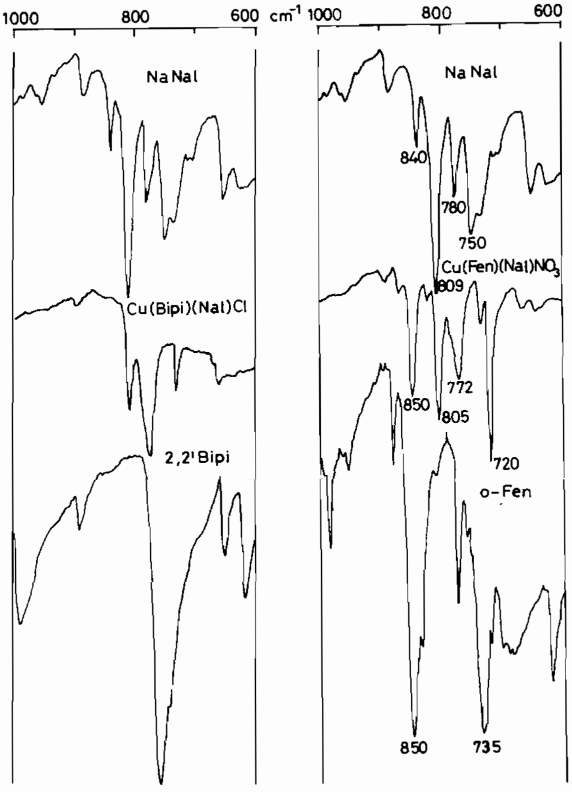

Fig. 3. Infrared spectra (1000–600 cm^{-1}) of [Cu(N–N)-(Nal)]X.

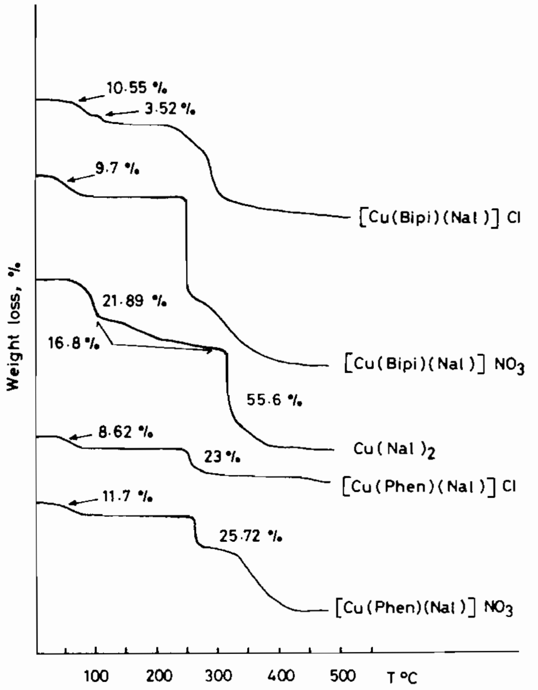

Fig. 4. Thermograms of Cu(II) complexes (not in scale).

TGA studies showed that it is possible to obtain the anhydrous complexes by heating to 110 °C for a short period (see Fig. 4). Observing the behaviour of these complexes (electronic and IR spectra, conductivity, TGA) they probably have a similar structure to [Cu(Phen)(Nal)(H$_2$O)]NO$_3$·3H$_2$O (discussed below) with the exception of the [Cu(Bipy)(Nal)Cl] complex, which also presents differences in its thermogram, showing a smaller stability interval ($T <$ 200 °C against $T <$ 240–270 °C). Besides, if the TGA of Cu(Nal)$_2$ is compared with those of the new complexes, (Cu(Nal)$_2$ has no thermal stability at temperatures above 90 °C), such a difference is important and reveals that the mixed complexes are thermally more stable.

The behaviour of the NO$_3^-$ complexes in solution (for Bipy and Phen ligands) was analysed using Job's method. This confirmed the stoichiometric ratios of these complexes in solution, resulting in agreement with the other results (see Fig. 5). This study was possible due to the fact that in solution Cu(Phen) or Cu(Bipy) exist practically without any dissociation, and because the stability constants of Cu(N–N) and Cu(N–N)$_2$ are sufficiently separate ($\Delta \log K = 2.4$ for Phen, and $\Delta \log K = 2.7$ for Bipy) [14] given solutions with 88.8% of [Cu(Phen)] (91.8% [Cu(Bipy)]) under stoichiometric conditions.

All the complexes give crystals when prepared, but only the complex [Cu(Phen)(Nal)]NO$_3$ (water omitted) yields a single crystal suitable for X-ray measurements. Its structure is shown in Figs. 6 and 7,

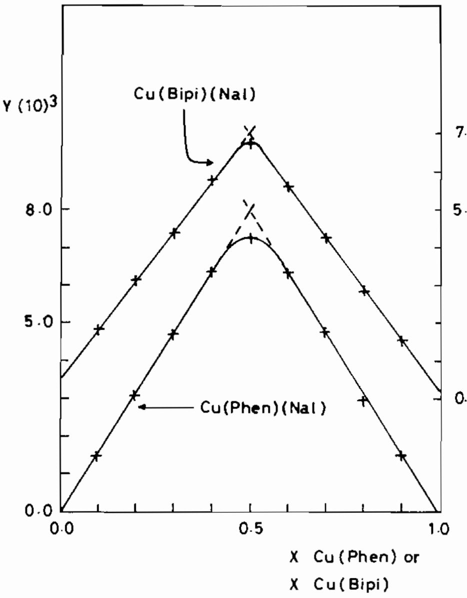

Fig. 5. Job's Method of [Cu(N–N)(Nal)]NO$_3$ complexes (X = mole fraction; $Y = A_{\text{obs}} - (1 - x)A_{[\text{Cu(N–N)}]}$).

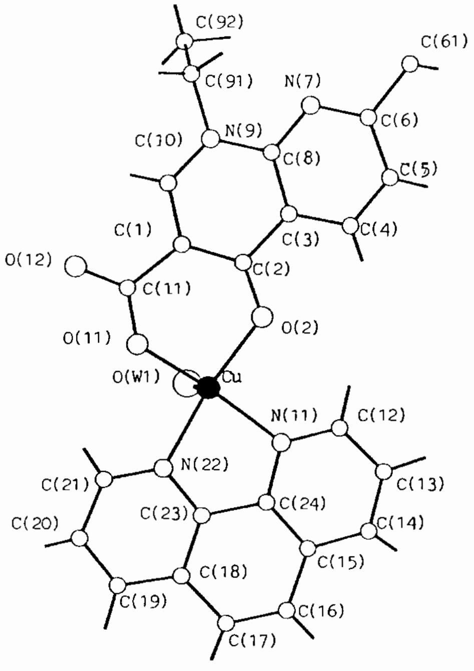

Fig. 6. Crystal structure of [Cu(Phen)(Nal)(H$_2$O)]NO$_3$·3H$_2$O.

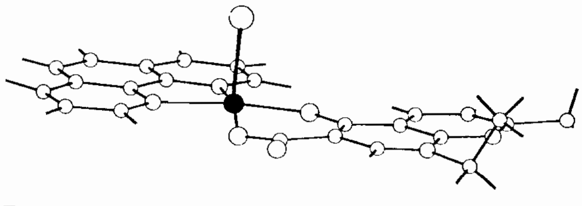

Fig. 7. Perpendicular view of [Cu(Phen)(Nal)(H$_2$O)]NO$_3$·3H$_2$O.

TABLE III. Final Atomic Coordinates[a,b] ($\times 10^4$) of [Cu(Phen)(Nal)(H_2O)]$NO_3 \cdot 3H_2O$ ($B_{eq} = (8\pi^2/3)U_{ij}a_i^*a_j^*a_ia_j$) (Cu $\times 10^5$)

	x/a	y/b	z/c	B_{eq}
Cu	−4684(2)	72163(3)	86953(4)	2.65(2)
C(1)	1351(2)	7798(2)	12219(4)	2.63(11)
C(2)	1249(2)	6710(2)	10997(4)	2.65(10)
C(3)	1994(2)	5965(2)	11375(4)	2.56(10)
C(4)	1978(2)	4855(3)	10268(4)	3.05(11)
C(5)	2715(2)	4232(2)	10669(4)	3.29(12)
C(6)	3469(2)	4701(3)	12164(4)	3.32(12)
N(7)	3491(1)	5726(2)	13276(3)	3.02(10)
C(8)	2772(2)	6342(2)	12898(4)	2.64(11)
N(9)	2801(1)	7403(2)	14069(3)	2.90(9)
C(10)	2125(2)	8093(2)	13707(4)	2.91(11)
C(11)	641(2)	8663(2)	12122(4)	2.98(11)
O(11)	−129(1)	8366(2)	10928(3)	3.69(9)
O(12)	820(1)	9602(2)	13248(3)	4.64(11)
O(2)	565(1)	6320(2)	9569(3)	3.23(8)
C(61)	4311(2)	4078(3)	12584(5)	4.67(16)
C(91)	3602(2)	7786(3)	15773(4)	3.88(13)
C(92)	4295(2)	8387(3)	15346(5)	5.19(16)
N(11)	−1036(1)	5863(2)	6600(3)	2.55(9)
C(12)	−711(2)	4843(3)	6089(4)	3.10(12)
C(13)	−1188(2)	4018(3)	4551(4)	3.61(13)
C(14)	−2025(2)	4203(3)	3520(4)	3.62(13)
C(15)	−2397(2)	5263(3)	4009(4)	3.06(11)
C(16)	−3268(2)	5563(3)	3013(4)	3.84(13)
C(17)	−3586(2)	6597(3)	3592(4)	3.80(13)
C(18)	−3062(2)	7423(3)	5194(4)	3.25(12)
C(19)	−3342(2)	8501(3)	5924(5)	3.92(14)
C(20)	−2803(2)	9204(3)	7474(5)	3.95(14)
C(21)	−1953(2)	8868(3)	8355(4)	3.44(13)
N(22)	−1663(1)	7854(2)	7732(3)	2.80(9)
C(23)	−2207(2)	7149(2)	6186(4)	2.72(11)
C(24)	−1877(2)	6049(2)	5556(3)	2.50(10)
Ow(1)	20(2)	8341(2)	7059(3)	3.44(9)
Ow(2)	−1748(2)	11243(3)	11904(5)	5.77(13)
Ow(3)	−1012(2)	7538(3)	13224(4)	6.83(16)
Ow(4)	−2342(2)	9338(4)	12959(5)	7.66(19)
Ow(5)	−3996(2)	8869(4)	10291(6)	7.68(19)
N(31)	4032(2)	7903(3)	20622(4)	4.13(12)
O(32)	4398(2)	6996(4)	20388(5)	8.19(18)
O(33)	3262(2)	7821(3)	20400(4)	6.99(16)
O(34)	4443(3)	8894(3)	21172(6)	9.28(22)

[a] H atoms are omitted. [b] Values in parentheses refer to the e.s.d. of the least significant digit.

TABLE IV. Bond Lengths[a,b] for [Cu(Phen)(Nal)(H_2O)]$^+$ Cation

Bond	Length	Bond	Length
O(11)–Cu	1.914(2)	O(12)–C(11)	1.225(3)
O(2)–Cu	1.934(2)	C(92)–C(91)	1.502(6)
N(11)–Cu	1.999(2)	C(12)–N(11)	1.331(4)
N(22)–Cu	2.014(2)	C(24)–N(11)	1.366(3)
Ow(1)–Cu	2.277(3)	C(13)–C(12)	1.378(4)
C(2)–C(1)	1.400(4)	C(14)–C(13)	1.358(4)
C(10)–C(1)	1.380(3)	C(15)–C(14)	1.403(4)
C(11)–C(1)	1.510(4)	C(16)–C(15)	1.433(4)
C(3)–C(2)	1.452(4)	C(24)–C(15)	1.378(3)
O(2)–C(2)	1.284(3)	C(17)–C(16)	1.357(5)
C(4)–C(3)	1.399(4)	C(18)–C(17)	1.428(4)
C(8)–C(3)	1.408(3)	C(19)–C(18)	1.409(5)
C(5)–C(4)	1.363(4)	C(23)–C(18)	1.403(4)
C(6)–C(5)	1.397(3)	C(20)–C(19)	1.345(4)
N(7)–C(6)	1.325(4)	C(21)–C(20)	1.401(4)
C(61)–C(6)	1.508(5)	N(22)–C(21)	1.328(4)
C(8)–N(7)	1.335(3)	C(23)–N(22)	1.348(3)
N(9)–C(8)	1.378(3)	C(24)–C(23)	1.440(4)
C(10)–N(9)	1.326(4)	O(32)–N(31)	1.207(5)
C(91)–N(9)	1.503(3)	O(33)–N(31)	1.229(4)
O(11)–C(11)	1.282(3)	O(34)–N(31)	1.228(4)

[a] The bonds formed with H atoms are omitted. [b] Values in parentheses refer to the e.s.d. of the least significant digit.

its atomic coordinates, bond lengths and angles are listed in Tables III, IV and V, respectively. In this compound the Cu ion displays a distorted square-pyramidal coordination, being linked to two N atoms of the Phen ligand, two O atoms of the nalidixate ligand and a water molecule in the apical site. O(2), O(11), N(11), N(22) atoms are in a puckered plane with deviations from the mean plane equal to +0.043(2) and +0.040(2) Å. The Cu ion is 0.185(1) Å out of this plane. The small difference between the Cu–O bond lengths (Cu–O(11): 1.914(2) Å, Cu–O(2): 1.934(2) Å) is assigned to the different electronegative character of two O atoms which are in different functional groups. The two basal ligands are planar with a dihedral angle between them equal to 0.5(2)°. The main differences between the geometrical values of nalidixate ligand and the values for the free acid [15] are in C(1)–C(2), C(2)–O(2), C(1)–C(11) and C(11)–O(11) bond lengths. In particular, it is important to notice that in the complex the 4-oxo group (C(2)–O(2)) and the C(11)–O(11) bond, that correspond to the carboxylate group coordinated to metal ion, become equivalent, with bond lengths of 1.284(3) and 1.282(3) (nalidixic acid values are 1.254(3) and 1.323(3), respectively). This fact produces a lengthening in C(1)–C(11) and a shortening in C(1)–C(2) bond lengths because of the different electronic delocalization of the charge in the chelate ring formed.

This change in the charge distribution causes the moiety formed by the 4-oxo and 3-carboxylate groups to behave similarly to a substituted acetylacetonate, with unsymmetrical carboxyl groups, given (as was mentioned above) a small difference in the metal–oxygen bond lengths.

Such a charge distribution could also explain the results given by Barba and co-workers [6] for nalidixate complexes, who observed (for EPR and Mössbauer spectrometry) a highly symmetrical

TABLE V. Bond Angles for $[Cu(Phen)(Nal)(H_2O)]^+$ Cation

O(2)–Cu–O(11)	93.8(1)	O(12)–C(11)–O(11)	122.5(3)
N(11)–Cu–O(11)	165.6(1)	C(11)–O(11)–Cu	127.7(2)
N(11)–Cu–O(2)	90.6(1)	C(2)–O(2)–Cu	124.4(2)
N(22)–Cu–O(11)	91.8(1)	C(92)–C(91)–N(9)	111.9(3)
N(22)–Cu–O(2)	169.4(1)	C(12)–N(11)–Cu	129.5(2)
N(22)–Cu–N(11)	81.9(1)	C(24)–N(11)–Cu	113.3(2)
Ow(1)–Cu–O(11)	97.6(1)	C(24)–N(11)–C(12)	117.1(2)
Ow(1)–Cu–O(2)	95.7(1)	C(13)–C(12)–N(11)	122.0(2)
Ow(1)–Cu–N(11)	95.6(1)	C(14)–C(13)–C(12)	120.7(3)
Ow(1)–Cu–N(22)	92.5(1)	C(15)–C(14)–C(13)	119.3(2)
C(10)–C(1)–C(2)	119.6(2)	C(16)–C(15)–C(14)	124.3(2)
C(11)–C(1)–C(2)	124.6(2)	C(24)–C(15)–C(14)	116.6(2)
C(11)–C(1)–C(10)	115.6(2)	C(24)–C(15)–C(16)	119.2(3)
C(3)–C(2)–C(1)	116.5(2)	C(17)–C(16)–C(15)	120.8(2)
O(2)–C(2)–C(1)	126.2(2)	C(18)–C(17)–C(16)	121.1(2)
O(2)–C(2)–C(3)	117.3(2)	C(19)–C(18)–C(17)	125.2(2)
C(4)–C(3)–C(2)	122.3(2)	C(23)–C(18)–C(17)	119.0(3)
C(8)–C(3)–C(2)	120.6(2)	C(23)–C(18)–C(19)	115.8(2)
C(8)–C(3)–C(4)	117.1(2)	C(20)–C(19)–C(18)	120.6(3)
C(5)–C(4)–C(3)	118.8(2)	C(21)–C(20)–C(19)	119.6(3)
C(6)–C(5)–C(4)	120.2(3)	N(22)–C(21)–C(20)	122.0(2)
N(7)–C(6)–C(5)	122.1(3)	C(21)–N(22)–Cu	129.2(2)
C(61)–C(6)–C(5)	121.7(3)	C(23)–N(22)–Cu	112.6(2)
C(61)–C(6)–N(7)	116.1(2)	C(23)–N(22)–C(21)	118.1(2)
C(8)–N(7)–N(6)	118.2(2)	N(22)–C(23)–C(18)	123.9(3)
N(7)–C(8)–C(3)	123.5(2)	C(24)–C(23)–C(18)	119.3(2)
N(9)–C(8)–C(3)	118.8(2)	C(24)–C(23)–N(22)	116.9(2)
N(9)–C(8)–N(7)	117.7(2)	C(15)–C(24)–N(11)	124.2(2)
C(10)–N(9)–C(8)	120.6(2)	C(23)–C(24)–N(11)	115.1(2)
C(91)–N(9)–C(8)	119.9(2)	C(23)–C(24)–C(15)	120.6(2)
C(91)–N(9)–C(10)	119.5(2)	O(33)–N(31)–O(32)	119.7(3)
N(9)–C(10)–C(1)	123.8(2)	O(34)–N(31)–O(32)	119.6(3)
O(11)–C(11)–C(1)	119.1(2)	O(34)–N(31)–O(33)	120.5(3)
O(12)–C(11)–C(1)	118.3(2)		

environment, reflecting small distortions of the ideal geometries of $Fe(Nal)_3$ and $Mn(Nal)_2$ complexes. We suggest that some of those complexes could have a form of linkage between the metal ion and nalidixic acid, similar to those reported here.

In conclusion, under the experimental conditions employed, new mixed complexes of Cu(II) have been isolated, which showed stability in the solid state and in solution. The behaviour of nalidixic acid as a ligand has been established definitively: NalH acts as a ligand by forming a chelate ring of six members, with the participation of 4-oxo and 3-carboxylate groups. This difference of coordination with those suggested by Barba and co-workers [6], is probably due to the influence of the (N–N) ligands, that make the metal center less hard, but it is also possible that, depending on the metal ion in the $M(Nal)_n$ complexes, the ligand can have different coordination modes. To probe this we carried out some ^{13}C NMR studies that showed such behaviour [16].

The possibility that the mode of action of nalidixic acid as a drug is through a copper carrier, has been shown with these results. Perhaps the copper Nal carrier is a soluble protein complex that can be modelled by the complexes reported here. With this idea, these complexes are currently being tested for biological activity.

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