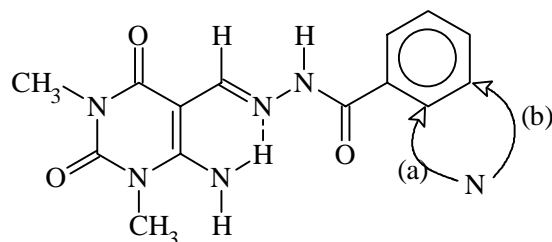


Ni(II), Cu(II), Zn(II) AND Cd(II) COMPLEXES WITH DINEGATIVE N,N,O-TRIDENTATE URACIL-DERIVED HYDRAZONES**Francisco Hueso-Ureña, Nuria A. Illán-Cabeza, Miguel N. Moreno-Carretero* and Antonio L. Peñas-Chamorro***Departamento de Química Inorgánica y Orgánica, Universidad de Jaén, 23071-Jaén, Spain**Received 9.10.2000***Abstract**

The synthesis and spectroscopic characterization of complexes of Ni^{II}, Cu^{II}, Zn^{II} and Cd^{II} containing hydrazones derived from 6-amino-5-formyl-1,3-dimethyluracil and nicotinic and isonicotinic acid hydrazides are reported. In all cases, the complexes appear to be monomeric and four-coordinated, with three binding sites occupied by the dinegative tridentate ligand, which makes two five- and six-membered chelate rings and the fourth position occupied by either water or ammonia. The coordination of the organic ligand takes place through the deprotonated N6 atom from the 6-amino group, the N51 azomethine atom and the O52 oxygen from the hydrazide moiety. Experimental data indicate that neither carbonyl oxygen atoms from the uracil ring nor the endocyclic nitrogen atom from pyridine are involved in the coordination to the metal.

Keywords: Complexes, hydrazones, Schiff bases, nicotinic acid, uracil**Introduction**

Biological activity of complexes derived from hydrazones has been widely studied and contrasted, acting in processes such as antibacterial, antitumoral, antiviral, antimalarial and antituberculosis effects.¹ A lot of complexes derived from hydrazones such as thiosemicarbazones have been reported;²⁻⁵ compounds of this type have a great biological activity as antitumoral and antiviral agents. They usually show an N,N,S coordinating mode. However, there are very little information about O,N,O or N,N,O hydrazone compounds in bibliography.



In order to increase the knowledge about the coordination and bioinorganic chemistry of these compounds,⁶⁻¹⁴ two new hydrazone ligands (see Fig. 1) derived from 6-amino-5-formyl-1,3-dimethyluracil and nicotinoyl and isonicotinoyl hydrazides have been synthesized. The molecular structure of both ligands has been designed in a way that the activity of hydrazones with the uracil derivatives one has been tried to join with. Thus, the coordinating capacity through both the azomethinic nitrogen and carbonylic oxygen atoms of hydrazones has been enhanced with two new basic atoms (O4 and N6) available for metal ligation from the five-substituted uracil derivative. Furthermore, the presence of uracil ring may contribute to the resulting compounds with an structural analogy with the species found in biological systems, being this fact useful to their potential pharmacologic applications due to the azomethinic bond may be hydrolyzed in the acid pH of cancer cells, liberating the uracil derivative, which may act as an efficient alkylating or antimetabolite drug.

Experimental

Apparatus: C, H, N and S microanalyses were performed on a Fisons EA1108 apparatus. Conductivity measurements have been carried out using 10^{-3} M freshly prepared DMF solutions on a Hanna HI8820 instrument. IR spectra were measured on Perkin-Elmer FT-IR 1760-X (KBr pellets, 4000 - 400 cm^{-1}) and FT-IR Bruker Vector-22 spectrophotometer (polyethylene pellets, 600 - 220 cm^{-1}). ^{13}C and ^1H -NMR spectra were recorded using a Bruker AM-300 apparatus (DMSO- d_6 solutions). Electronic spectra (diffuse reflectance, 240 - 1500 nm) were recorded on a Perkin-Elmer UV/VIS/NIR

Lambda-19 machine using a BaSO₄ pellet as reference. EPR spectra were obtained in the X-band at room temperature on a Bruker ESP 300E spectrometer, with a microwave frequency of 9.79 GHz and a modulation frequency of 100 kHz. Magnetic susceptibility measurements (70–290 K) were carried out on a Manics DSM-8 system.

Synthetic procedures: Commercial grade chemicals were used without further purification. The Schiff bases were prepared by reacting equimolar amounts (10 mmol) of 6-amino-5-formyl-1,3-dimethyluracil with nicotinoyl hydrazide (H₂NDO·H₂O) and isonicotinoyl hydrazide (H₂INDO) in EtOH medium (*ca.* 100 cm³) containing a few drops of glacial AcOH; after stirring the resulting solution for several hours, the Schiff bases were filtered off, washed with EtOH and Et₂O and air dried (yields *ca.* 80%). Characterizational data were as follows: H₂NDO·H₂O; Found: C, 50.2; H, 4.9; N, 26.8. C₁₃H₁₅N₆O_{3.5} calcd.: C, 50.1; H, 4.8; N, 27.0%. ¹³C{¹H}-n.m.r.: 29.3 (C1), 27.5 (C3), 150.1 (C2), 153.5 (C4), 82.7 (C5), 160.0 (C6), 146.8 (C51), 160.9 (C52), 129.2 (C1 py), 147.8 (C2 py), 123.8 (C4 py), 136.0 (C5 py), 151.2 (C6 py); ¹H-n.m.r.: 3.12 and 3.35 (N-CH₃), 8.68 (H51), 8.23 and 9.90 (C6-NH₂), 11.88 (H52); 9.08 (H2 py, singlet), 7.59 (H4 py, double doublet), 8.31 (H5 py, multiplet), 8.76 (H6 py, doublet). H₂INDO; Found: C, 51.2; H, 4.5; N, 27.4. C₁₃H₁₄N₆O₃ calcd.: C, 51.6; H, 4.6, N, 27.8%. ¹³C{¹H}-n.m.r.: 29.4 (C1), 27.6 (C3), 150.2 (C2), 153.6 (C4), 82.8 (C5), 160.2 (C6), 147.4 (C51), 161.0 (C52), 140.3 (C1 py), 121.4 (C2 and C6 py), 150.2 (C3 and C5 py); ¹H-n.m.r.: 3.15 and 3.27 (N-CH₃), 8.73 (H51), 8.22 (C6-NH₂), 9.92 (H52); 7.81 (H2 and H6 py, doublet), 7.45 (H3 and H5 py, doublet). The structure of ligands is depicted in the Fig. 1.

Preparation of the complexes: The complexes were synthesized by reacting 0.5 mmol of ligand (H₂NDO·H₂O or H₂INDO) with 0.5 mmol of Ni(NO₃)₂·6H₂O, Cu(NO₃)₂·3H₂O, Zn(NO₃)₂·6H₂O and CdCl₂·2H₂O, respectively, in 50 ml of conc. aqueous NH₃, with the exception of Cu(NDO)·2H₂O (H₂O, 40 cm³). In all the cases, a suspension of the reaction product was obtained which was heated and stirred for about one hour and left to cool at room temperature before getting filtered off. The solids were washed with EtOH and Et₂O and air dried: Ni(NDO)·2H₂O·NH₃ (orange, Λ_M=10

Table 1. Selected infrared data (cm⁻¹)

Compound	$\nu(\text{N-H})$	$\nu(\text{C=O})$	$\nu(\text{N-N})$	Amide II	$\nu(\text{M-N})$
H ₂ NDO	3350, 3323	1701, 1676 1662	953	1543	-
Ni(NDO)·2H ₂ O·NH ₃	3540, 3461 3386, 3291	1682	963	1554	436
Cu(NDO)·2H ₂ O	3467, 3377	1700	966	1547	440
Zn(NDO)·1''H ₂ O·1''NH ₃	3376, 3333 3235	1669	978	1552	371
Cd(NDO)·2''H ₂ O·NH ₃	3494, 3340	1667	973	1547	431
H ₂ INDO	3418, 3297	1703, 1682	971	1552	-
Ni(INDO)·H ₂ O·''NH ₃	3437, 3396 3289	1700	972	1514	457
Cu(INDO)·2H ₂ O·NH ₃	3335	1698	965	1540	434

ohm⁻¹·cm²·mol⁻¹), found: C, 38.2; H, 4.3; N, 23.4%. NiC₁₃H₁₉N₇O₅ calcd.: C, 37.9; H, 4.6; N, 23.8. Cu(NDO)·2H₂O (grey, $\Lambda_M=5$ ohm⁻¹·cm²·mol⁻¹), found: C, 38.8; H, 3.6; N, 21.3%. CuC₁₃H₁₆N₆O₅ calcd.: C, 39.0; H, 4.0; N, 21.0%. Zn(NDO)·1''H₂O·1''NH₃ (yellow, $\Lambda_M=2$ ohm⁻¹·cm²·mol⁻¹), found: C, 36.9; H, 4.7; N, 25.0%. ZnC₁₃H_{19.5}N_{7.5}O_{4.5} calcd.: C, 37.3; H, 4.7; N, 25.1%. Cd(NDO)·2''H₂O·NH₃ (yellow, $\Lambda_M=2$ ohm⁻¹·cm²·mol⁻¹), found: C, 32.5; H, 3.8; N, 20.3%. CdC₁₃H₂₀N₇O_{5.5} calcd.: C, 32.9; H, 4.2; N, 20.6%. Cu(INDO)·2H₂O·NH₃ (brown, $\Lambda_M=13$ ohm⁻¹·cm²·mol⁻¹), found: C, 38.3; H, 4.3; N, 23.1%. CuC₁₃H₁₉N₇O₅ calcd.: C, 37.4; H, 4.6; N, 23.5%. Ni(INDO)·H₂O·''NH₃ (orange, $\Lambda_M=30$ ohm⁻¹·cm²·mol⁻¹), found: C, 40.2; H, 4.4; N, 23.7%. NiC₁₃H_{15.5}N_{6.5}O₄ calcd.: C, 40.5; H, 4.1; N, 23.6%. N.m.r. data of Zn(NDO)·1''H₂O·1''NH₃ complex display the following signals: ¹³C{¹H}-n.m.r.: 27.7 (C1), 27.0 (C3), 150.5 (C2), 155.5 (C4), 83.5 (C5), 161.6 (C6), 151.2 (C51), 163.9 (C52); ¹H-n.m.r.: 3.14 and 3.32 (N-CH₃), 8.85 (H51), 6.12 (H6). It was not possible to record the Cd(NDO)·2''H₂O·NH₃ spectra due to the low solubility in DMSO of this complex.

Results and discussion

The conductivity values have clearly shown the non-electrolyte character of the complexes. In all the complexes, the presence of water and/or ammonia molecules has

been corroborated from the thermal studies. The pyrolytic degradation in the t.g. plots begins around 70°C due to the loss of the water and/or ammonia molecules. Each of these molecules causes an endothermic effect, being the NH₃ ones at higher temperature since they must be coordinated to the metal because of their greater basicity if it is compared with the water ones. The pyrolytic degradations finish between 400 and 600°C, leaving as final residue the metallic oxide, which was corroborated by infrared spectroscopy.

To carry out a comparative study of the IR spectra of the complexes and the free ligands is very difficult, due to the great number of bands; only general remarks can be made. The most interesting features are listed in Table 1. There is a general displacement due to the coordination process. The $\nu(\text{N-H})$ bands are displaced to upper wavenumber due to the coordination and the double deprotonation, because the two lost hydrogen to make the dianion are from 6-amino group (which becomes to an imino group)^{6,7,9} and the hydrazone nitrogen atom.¹² So, bands of groups involved in the coordination are displaced too. As it has been found from X-ray diffraction studies,¹² the more feasible predominant tautomeric form of the dinegative ligand in these complexes is the enolate one. The amide II band is displaced to lower wavenumber in the H₂INDO complexes due to the electronic delocalization, but in the H₂NDO ones, this displacement is to upper wavenumber; so, at least from the IR spectral point of view, it is not clear the predominant tautomeric form of these complexes. The $\nu(\text{N-N})$ bands are displaced to upper wavenumber, being this shift very characteristic for several hydrazone ligands coordinated through the azomethine nitrogen atom.^{15,16} In the 600-200 cm⁻¹ range, the bands associated to M-N and terminal M-X vibrations have been assigned, and are in good accordance with the data found in the literature.¹⁷ On comparing the NMR spectra of Zn(NDO)·1'H₂O·1'NH₃ complex with those of free ligand, weak shifts (< 2 ppm) of the signals assigned to the C1 and C3 (downfield) and C2, C5 and C6 atoms (upfield) are observed; so, a stronger displacement is found in the C4 (upfield, 2 ppm). The C4 and C6 signals are equally modified, so it is not clear which of them is the metal binding site; however, we have characterized the similar complex [Pd₄(TSDO)₄]-4H₂O·2DMF,⁹ whose ligand contains the same monodeprotonated uracil moiety, in which an analog

displacement is observed, but the crystallographic studies have clearly shown that the coordination takes place through the N6 atom. On the other hand, we have pointed out that when the 6-aminouracil derived ligand is not deprotonated, the coordination is established through the O4,⁸ so the deprotonation seems to be a decisive fact to assign the coordination pattern in these molecules. The signals assigned to the hydrogen attached to the N(6) atom display a strong change because the initial amino group becomes into an imino group as consequence of the deprotonation. So, it does not appear the H52 signal, due to its deprotonation. The shifts of the C(51), C(52) and H51 signals are in accordance to the loss of electronic density of the ligand through the M-L bonds. In the pyridine moiety there is long distance coupling between hydrogen atoms, which causes the presence of double doublets (H4 and H6) and doublets (H2).

The electronic spectra of the copper(II) complexes show a single broad and poorly defined asymmetric band around 17500 cm⁻¹ and the spectra of nickel(II) complexes show a band around 20000 cm⁻¹. These results are consistent with square-planar structures, since the four lower orbitals are often so close together in energy, that individual transitions therefrom to the upper *d* level cannot be distinguished - hence the single absorption band.¹⁸

The nickel(II) complexes showed a diamagnetic behaviour consistent with square-planar environment around the metal ion. Magnetic susceptibilities at different temperatures of the copper(II) compounds have been fitted to the Curie-Weiss law ($1/\chi_m = (T-\theta)/C$): Cu(NDO)·2H₂O: C=0.239(6) cgsu·K·mol⁻¹, $\theta=39(8)$ K, $\mu_{\text{eff}}=1.72(5)$ BM; Cu(INDO)·2H₂O·NH₃: C=0.257(7) cgsu·K·mol⁻¹, $\theta=36(8)$ K, $\mu_{\text{eff}}=1.87(2)$ BM. The effective magnetic moments are in accordance with diluted monomeric units¹⁹ although the slightly high θ value could indicate antiferromagnetic interactions between the metal atoms. Both copper(II) complexes display rhombic EPR powder spectra with $g_1=2.05$, $g_2=2.07$, $g_3=2.14$ (Cu(NDO)·2H₂O) and $g_1=2.03$, $g_2=2.05$, $g_3=2.17$ (Cu(INDO)·2H₂O·NH₃) respectively.²⁰

From these data, square-planar structures may be proposed for the nickel(II) and copper(II) complexes with the tridentate ligand and the fourth coordination position occupied by either an ammonia or water molecule, as depicted in fig. 2; a similar

structure has been observed from single-crystal X-ray diffraction studies for the related compounds aqua-[6-amino-1,3-dimethyl-uracilato-benzoylhydrazone(2-)-N⁶,N⁵¹,O⁵²]-copper(II) hydrate¹² and several O-nitrito⁶ and halide-complexes with monodeprotonated *N,N,Z*-tridentate hydrazones (*Z* = S or O) derived from 6-amino-5-formyl-1,3-dimethyluracil.¹³ A similar structure but tetrahedral may be suggested for the zinc(II) and cadmium(II) complexes.

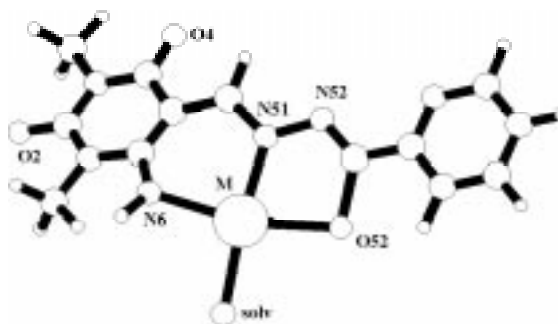


Figure 2. Computer-generated square-planar structure proposed for the nickel(II) and copper(II) complexes (solv = NH₃ or H₂O). The two hydrogen lost to make the dianion are from N6 and N52 atoms.

Acknowledgements

The authors are indebted to Dirección General de Enseñanza Superior e Investigación Científica (MEC, Spain) (project PB97-0786-C03-03) and Consejería de Educación y Ciencia (Junta de Andalucía, research group FQM-273).

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Povzetek

Opisana je sinteza in spektroskopska karakterizacija kompleksov Ni(II), Cu(II), Zn(II) in Cd(II) s hidrazonom 6-amino-5-formil-1,3-dimetiluracila ter hidrazidoma nikotinske in izonikotinske kisline.