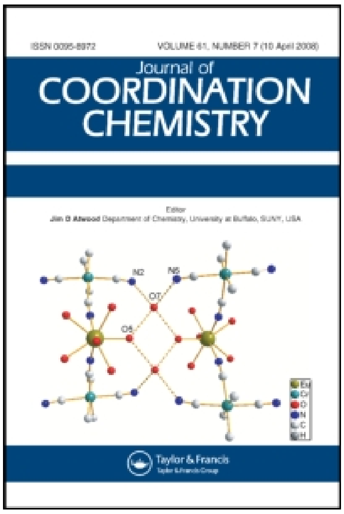

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COMPLEXES OF COBALT(II), NICKEL(II) AND ZINC(II) AZIDES AND THIOCYANATES WITH MEPIRIZOLE, AN ANTI-INFLAMMATORY AGENT

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The synthesis and characterization of thiocyanate and azide derivatives of metal complexes of mepirizole [4-methoxy-2-(5-methoxy-3-methyl-pyrazol-1-yl)-6-methylpyrimidine, hereinafter L] with cobalt(II), nickel(II) and zinc(II) is reported. Spectroscopic and magnetic results for $ML_2(NCS)_2$ (M = Co, Ni) biscomplexes indicate isolated MN_6 chromophores and a *cis*-octahedral arrangement around the M(II) ion. Also for the ML $(N_3)_2$ (M = Co, Ni) compounds, an essentially octahedral environment is inferred from the spectroscopic data, thus requiring polymerization through azido bridges. Finally, for both zinc derivatives a distorted tetrahedral environment around the metal atom is suggested.

Keywords: Pyrimidino-pyrazole, mepirizole, complexes, synthesis

INTRODUCTION

The chemistry of pyrimidine-pyrazoles and related heterocyclic systems is the subject of study in view of the role played by such compounds in several biological processes. Moreover, their biological activity seems to be related to their ability to interact with a trace metal ion.[1–4] We have undertaken a study of the interaction between pyrimidino-pyrazole derivatives and trace metal ions. In earlier work[5–7] we reported the synthesis and characterization of several metal complexes of mepirizole [4-methoxy-2-(5-methoxy-3-methyl-pyrazol-1-yl)-6-methylpyrimidine, hereinafter L], a biologically active compound used as an anti-inflammatory agent.[8] In previous structural studies[9–11] we have shown that mepirizole acts as a bidentate ligand through two nitrogen atoms (Figure 1), with significant steric hindrance in the formation of metallic complexes.

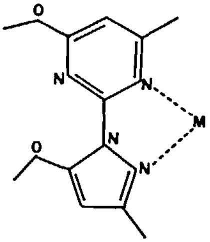

FIGURE 1 Schematic view of the mepirizole ligand showing its usual coordination mode.

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In this paper we report the synthesis and characterization of thiocyanate and azide (two coordinating anions) derivatives of complexes of mepirizole with cobalt(II), nickel(II) and zinc(II).

EXPERIMENTAL

Preparation of the Complexes

The complexes were prepared as follows. Solutions of L (2 mmoles for the MLX_2 complexes) in ethanol (25 cm^3) were added with stirring to aqueous solutions of the appropriate metal nitrate (2 mmoles in 25 cm^3). To the resulting solutions was added a solution of the respective potassium or sodium pseudohalide salt (4 mmoles) in H_2O (25 cm^3). The powders which formed in each case were separated by filtration, washed with a water:ethanol mixture and dried in a desiccator over silica gel.

Analysis

Metal contents were determined by atomic absorption. Solid samples were previously heated in conc. H_2SO_4. C, H, and N were determined separately. Analytical data are given in Table I.

TABLE I
Analytical data for the complexes.

	%C		%N		%H		%M		Λ_M^a
Compound	calc.	found	calc.	found	calc.	found	calc.	found	(Ω^{-1} cm^2 mol^{-1})
(*1*) $CoL_2(NCS)_2$	44.9	44.1	21.7	21.5	4.4	4.6	9.3	9.4	14
(*2*) $NiL_2(NCS)_2$	44.8	44.6	21.8	21.7	4.4	4.3	10.1	10.1	50
(*3*) $ZnL_2(NCS)_2$	37.5	37.7	20.2	20.0	3.3	3.4	15.7	15.3	14(17)
(*4*) $CoL_2(N_3)_2$	35.0	35.6	37.1	36.4	3.7	3.5	15.3	15.6	[b]
(*5*) $NiL(N_3)_2$	35.0	35.4	37.1	36.9	3.7	3.6	15.6	14.9	[b]
(*6*) $ZnL(N_3)_2$	34.4	34.8	36.5	36.1	3.7	3.7	17.3	17.8	30(26)

[a] In *ca* 10^{-3} M in nitromethane (values in parentheses correspond to DMSO solution). [b] Insufficiently soluble for determination

Physical Measurements

I.r. spectra (KBr pellets) were recorded on a Pye-Unicam SP 2000 spectrophotometer. Electronic spectra were measured using a Perkin Elmer Lambda 9 spectrophotometer. X-ray powder diffraction patterns were obtained by means of a Siemens Kristalloflex 810 diffractometer using CuKα radiation. Magnetic moments at room temperature were carried out using a Gouy balance with $[Ni(en)_3]S_2O_3$ as calibrant. Diamagnetic corrections were applied using Pascal's constants.[12] A value of $X = -88 \cdot 10^{-6}$ cm^3 $mole^{-1}$ was measured for the mepirizole. ^1H NMR spectra were recorded in DMSO-d_6 on a Hitachi PE R-24 spectrometer using $CHCl_3$ as external standard. The molar conductances in solution were measured using a Radiometer CDC 304 electrode in conjunction with a Radiometer CDMD 83 conductivity bridge.

RESULTS AND DISCUSSION

As shown in Table I, the analytical data correspond with the assigned molecular formulae. All the isolated solids are crystalline powders and from their X-ray diffraction patterns the isostructural nature of the cobalt(II) and nickel(II) thiocyanate derivatives can be established. Attempts to isolate compounds of formula $ML(NCS)_2$ (M = Ni, Co) were unsuccesful.

Assignments of the more relevant i.r. spectral bands in the complexes are listed in Table II. The strong band centered at *ca* 1600 cm^{-1} assigned in the free ligand to $\nu(CN)$ is shifted to higher energy ($\Delta\nu = 15 \pm 5\,cm^{-1}$) in the metal complexes, indicating the expected nitrogen atom participation in coordination.[5,13] Furthermore, several bands in the 1500–500 cm^{-1} region, which are assigned in the free ligand to characteristic vibrations of both pyrimidine and pyrazole systems are shifted in the complexes, supporting the preceding argument.[14] The metal–nitrogen vibrations, which must occur below 400 cm^{-1}, are not assigned. The absorptions due to M–N(mepirizole) and M–N(pseudohalide) bonds are expected to be rather close to each other and probably coupled. Moreover, mepirizole exhibits several vibrations in this i.r. region (380, 335 and 280 cm^{-1}) which interfere with the assignment.

TABLE II
Relevant i.r. (cm^{-1}) data for the complexes.[a]

Compound	$\nu(X)$	$\nu'(X)$	$\delta(X)$
$CoL_2(NCS)_2$	2081, 2068	800	480
$NiL_2(NCS)_2$	2092, 2082	798	480
$ZnL(NCS)_2$	2085	787	479
$CoL(N_3)_2$	2105, 2060	1335	602
$NiL(N_3)_2$	2090, 2050	1333	601
$ZnL(N_3)_2$	2066	1334	610

[a] X = NCS, N_3; $\nu = \nu(CN)$ or $\nu_{as}(NNN)$; $\nu' = \nu(CS)$ or $\nu_s(NNN)$.

Cobalt(II) and Nickel(II) Complexes

The molar conductance values (Table I) of the thiocyanate derivatives are lower than those expected for 1:1 electrolytes in nitromethane[15] suggesting a non-ionic character for the complexes. In accordance with the literature[16–18] the position of the assignable bands to NCS groups ($\nu(CN)$, $\nu(CS)$ and $\delta(NCS)$) suggests that thiocyanate acts as a monodentate terminal N-bonded ligand. Moreover, the splitting of the $\nu(CN)$ band may be interpreted as evidence for a *cis*-octahedral arrangement,[19] as could be expected from steric hindrances imposed by repulsion between the methyl groups of the mepirizole molecules.

Electronic spectral data for both cobalt(II) and nickel(II) bis-complexes are consistent with an octahedral environment for the metal atoms. Fitting the experimental wavenumber values to energy level diagrams for octahedral d^7 and d^8 systems, respectively, leads to the set of crystal field parameters included in Table III. In particular, for the cobalt(II) complex, the ν_2/ν_1 ratio (2.01) and the D_q value, close to $\nu_2 - \nu_1/10$, supports the bands assignments.[20,21] The crystal field parameters fall in the usual range for MN_6 (M = Co, Ni) chromophores.[20] The application of rule of averaged environment to the $NiL_2(NCS)_2$ compound (MN_4N_2 chromophore) affords $D_q = 1035\,cm^{-1}$, taking $D_q = 960\,cm^{-1}$ for $Ni(NCS)_6$[22] and $1070\,cm^{-1}$ for the NiL_3,[6] in excellent agreement with the experimental data. Moreover, the room temperature μ_{eff} values as well as the isostructural nature of the ML_2 $(NCS)_2$ complexes are in good agreement with the above suggestions. For the Ni(II) ion it is possible to estimate the spin-orbit coupling constant (λ) from the equation[23] $\mu_{eff} = \mu_{s,o}\,(1\text{–}4\lambda/10D_q)$. The obtained value, $\lambda = -248\,cm^{-1}$, is considerably reduced from the free ion value ($\lambda_o = -324\,cm^{-1}$). We attribute this reduction to the covalency of the Ni–N bonds, in good agreement with the calculated B′ parameter.

TABLE III
Visible spectral analysis and magnetic data for the Ni(II) and Co(II) complexes.

Complex[a]	Exp. energies (cm^{-1}) and assignment				C.F. param (cm^{-1})		
Ni(II) complexes	$^3T_{2g}$	^1E_g	$^3T_{1g}$	$^3T_{1g}(P)$	D_q	B	μ(BM)
$NiL_2(NCS)_2$ solid	10400	12900	16500	26950	1040	820	3.11
$NiL_2(NCS)_2$ soln.	10400(6)	12850sh	16400(8)	27200(11)	1040	820	
$NiL(N_3)_2$ solid	8300	11900	14500	23100	830	860	2.73
Co(II) complexes	$^4T_{2g}$	$^4A_{2g}$	$^4T_{1g}$	$^2A_{2g}$			
$CoL_2(NCS)_2$ solid	9100	18500	20100	21500	910	795	4.59
$CoL(N_3)_2$ solid	6900	13400	18000	19400	795	830	4.98
	$^4E''(F)$	$^4E'$	$^4A_2$	$^4E''(P)$			
$CoL_2(NCS)_2$ soln.	5500(15)	13200(18)	16600(92)	18600(98)			
				19700sh			
				21100sh			

[a] For the complexes in solution the extinction coefficients ($M^{-1}\,cm^{-1}$) are given in parentheses; sh = shoulder.

Both bis-complexes behave differently in a solution of nitromethane, a non-donor solvent with low dielectric constant. The nickel derivative is soluble without any change from its characteristic blue colour. The close similarity of the solid and solution spectra (Table III) implies that octahedral stereochemistry is retained in solution. This fact, as well as the low molar conductance value, supports the existence of $[NiL_2(NCS)_2]$ species in solution. On the other hand, in the corresponding bis-complex of cobalt(II) an appreciable change from the pink colour of the solid state to violet in solution is observed. At first, an *octahedral–tetrahedral* equilibrium implying the loss of either a molecule of mepirizole or the two pseudohalide groups might be invoked, as shown below.

$$CoL_2X_2 \leftrightarrow CoL_2 + 2X^- \text{ or } CoL_2X_2 \leftrightarrow CoLX_2 + L$$

However, the electronic absorption spectrum seems inconsistent with either a tetrahedral or octahedral coordination environment for the Co(II) ion, but is similar to those reported for cobalt(II) high spin trigonal bypiramidal complexes.[24–26] In accordance with these arguments we assign a five-coordinate structure to the complex in solution with a formal D_{3h} symmetry and a $^4A_2$ ground state. Two possible equilibria can then be proposed as an explanation for the existence of pentacoordinated complexes in nitromethane, as shown below.

$$\begin{array}{ccc} & (1) & (2) \\ [CoL_2(NCS)]^+ + NCS^- & \leftrightarrow [CoL_2(NCS)_2] & \leftrightarrow [CoL^2L^1(NCS)_2] \end{array}$$

The first must be rejected on the basis of the very low conductivity recorded (indeed, the bis-complex behaves in solution as a non-electrolyte). Thus the existence of a neutral species with a molecule of mepirizole acting as bidentate (L^2) and the other as monodentate (L^1) is suggested.

With regard to the azide derivatives, the position of the bands assignable to azide groups in the i.r. spectra of the compounds (*4*) and (*5*) is compatible with the existence of monocoordinated and/or μ-1,1 (end-on) bridging azide.[17,27] Unfortunately, the best defined feature of these spectra (ν_{as}) cannot be used as an unambiguous diagnostic for the coordination mode of the N_3 groups. On the other hand, the more significant ν_s and δ vibrations are located in regions overlapped by several mepirizole bands. The suggested mode of coordination of the azide groups above must be considered as tentative and the existence of μ-1,3 (end-to-end) bridging groups can not be discounted.

The electronic spectrum of the $NiL(N_3)_2$ compound may be satisfactorily interpreted in terms of a roughly octahedral environment for the nickel(II) ion. The triple-triplet transitions are assigned to the strongest bands in the electronic spectrum (Table III), and the ν_2/ν_1 ratio (1.74) suggests a pseudo-octahedral stereochemistry for the metal atom with an appreciable degree of tetragonal distorsion.[28] The diffuse reflectance spectrum of the cobalt(II) azide derivative displays two main absorptions at *ca* 7000 and 18000 cm^{-1}, with several shoulders at lower and higher wavenumbers on the latter. These features also suggest an essentially octahedral stereochemistry for the cobalt atom. As is the case with the thiocyanate derivative, the ν_2/ν_1 ratio is close to 2, supporting the band assignment.

In view of the molecular formulae, the coordination number six would imply a polymeric arrangement for both complexes, thus requiring the existence of N_3 bridging groups. Another fact supporting a polymeric structure is the poor solubility of these complexes in all common solvents. The D_q values are consistent with the existence of $MN_2N'_4$ chromophores (where two N atoms belong to a mepirizole molecule and the four N′ atoms to azide groups). Applying the rule of average environment gives a value of $D_q = 710\,cm^{-1}$ for the N_3 group, in good agreement with the position of azide in the spectrochemical series.[20] The room temperature μ_{eff} value of the $CoL(N_3)_2$ complex is consistent, as is the electronic spectral data, with high-spin six-coordinated cobalt(II) ions. However, in the $NiL(N_3)_2$ compound, μ_{eff} is slightly lower than that expected for magnetically isolated nickel(II) ions in an octahedral environment ($\mu_{s,o} = 2.83$). This anomalous value suggests an antiferromagnetic interaction between the nickel(II) ions.

Zinc Complexes

With regard to the ZnL $(NCS)_2$ compound, its i.r. spectrum is consistent with the existence of monodentate terminal N-bonded thiocyanate as occurs in the cobalt(II) and nickel(II) bis-complexes. However, no conclusive information can be obtained from the i.r. spectrum concerning the coordination mode of the azide ion in

$ZnL(N_3)_2$. Both derivatives are soluble in several solvents and the measured conductivity values in nitromethane and dimethylsulfoxide support a non-ionic character in the solid state. These results lead us to propose the existence of essentially isolated $ZnLX_2$ entities with a tetrahedral environment around the metal atom.

The ^1H NMR spectrum of mepirizole in DMSO-d_6 shows six resonances assigned as is shown in Table IV, in good agreement with the literature.[13,29] The spectra of both $ZnLX_2$ complexes are very similar to that obtained for the free ligand, with slight shifts of the resonance lines to higher δ values, especially in the azide derivative. This fact may be attributed to the interaction between the zinc(II) ions and the mepirizole molecule which modifies the magnetic environment of the ligand in solution, *via* coordination.

TABLE IV
^1H-NMR data for mepirizole and the $ZnLX_2$ ($X = NCS$ or N_3) compounds in DMSO-d_6. Chemical shifts (δ) and complexation shifts ($\Delta\delta$) are in ppm from TMS.

Compound	H(A)[a]	H(B)	$CH_3O(A)$	$CH_3O(B)$	$CH_3(A)$	$CH_3(B)$
L (mepirizole)	6.45	5.50	3.75	3.70	2.20	2.00
$ZnL(NCS)_2$	6.53	5.71	3.78	3.78	2.30	2.13
$\Delta\delta$	+0.08	+0.21	+0.03	+0.08	+0.10	+0.13
$ZnL(N_3)_2$	6.70	5.85	3.88	3.88	2.38	2.15
$\Delta\delta$	+0.25	+0.35	+0.13	+0.18	+0.18	+0.15

[a] A and B refer to the pyrimidine and pyrazole ring, respectively.

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