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Metal Complexes of the Virus-Inhibitor 3,4-Dihydro-1-phenyl-1*H*-[1,4]-oxazino[4,3-a]benzimidazole

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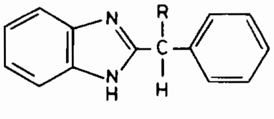
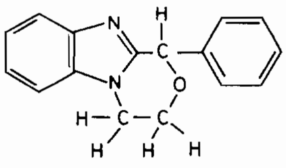
Complexes of the title ligand with cobalt(II) and nickel(II) salts have been prepared and characterised. The complexes are readily formed in solvents such as ethanol and acetone, with coordination taking place through the imidazole nitrogen (N 10). Electronic and infrared spectra and magnetic properties are reported for the complexes, which are mostly tetrahedral with ML_2X_2 stoichiometry.

Introduction

Substituted imidazoles and benzimidazoles show a variety of biological activity in a wide range of organisms. In particular, benzimidazoles with hydroxy- and alkoxy-benzyl substituents in the 2-position show antiviral action [1] and it has been suggested that the ability to complex metal ions may be important in this activity. We have previously shown that 2-α-hydroxybenzyl-benzimidazole (I, R = OH) chelates well with metal ions [2]. When the hydroxyl group is replaced by an ether, antiviral activity is retained, though the ability to chelate is expected to be reduced. We report here the reaction of cobalt(II) and nickel(II) ions with 3,4-Dihydro-1-phenyl-1*H*-[1,4]oxazino[4,3-a]benzimidazole(II) which shows anti-viral activity comparable with that of I, but which, for steric reasons, cannot be involved in chelation.



I



II

Experimental

*Preparation of 3,4-Dihydro-1-phenyl-1*H*-[1,4]oxazino[4,3-a]benzimidazole*

This was made using the method of O'Sullivan and Wallis [3], scaled up considerably to obtain the large quantity required. The hydrogenation stage was very slow (3 weeks were required for completion) and the overall yield was less than 5%. M.p., 160 °C (lit. 161–162°).

Preparation of Complexes

Acetone solutions of the cyclic ether (II) and the metal salt in the appropriate molar ratio were mixed with stirring. The complexes precipitated either immediately, on standing for a few days, or on reduction of the volume. In some cases it was necessary to dehydrate the solutions with dimethoxypropane. For the nickel thiocyanate complex ethanol was used instead of acetone. Analytical results are given in Table I.

Physical Measurements

Reflectance spectra were obtained with a Beckman DK 2A spectrometer, solution electronic spectra with a Unicam SP 1800, and infrared spectra with a Unicam SP3-300 spectrometer. Magnetic moments were measured at room temperature on a conventional Gouy balance.

X-ray powder patterns were obtained with a Philips PW 1050 vertical diffractometer.

Results

The cyclic ether ligand II (= L) coordinates readily to cobalt(II) and nickel(II) ions, even in the presence of reasonably polar solvents. Most of the cobalt(II) complexes appear to have essentially tetrahedral

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TABLE I. Analytical Results for the Complexes.

Complex	Found			Calculated		
	C	H	N	C	H	N
CoL_2Cl_2	60.83	4.55	9.56	60.97	4.48	8.89
CoL_2Br_2	53.18	4.06	7.85	53.43	3.92	7.79
CoL_2I_2	47.17	3.66	6.90	47.26	3.47	6.89
$CoL_2(NCS)_2$	60.13	4.06	12.25	60.44	4.18	12.44
$CoL_2(NO_3)_2$	56.39	4.26	12.48	56.23	4.13	12.30
$CoL_4(ClO_4)_2$	61.12	4.16	8.85	61.20	4.49	8.90
$CoL_4(ClO_4)_2 \cdot H_2O$	60.38	4.88	9.19	60.19	4.58	8.77
$CoL_4(BF_4)_2$	62.26	4.98	9.08	62.31	4.58	9.08
NiL_2Cl_2	61.21	5.03	9.20	60.99	4.48	8.89
NiL_2Br_2	54.08	4.04	8.25	53.45	3.92	7.80
$NiL_2(NCS)_2$	60.56	4.19	12.46	60.46	4.18	12.44
NiL_2I_2	46.70	3.51	6.78	47.24	3.47	6.89
$NiL_2(NO_3)_2$acetone	56.75	4.74	11.59	56.70	4.62	11.34
$NiL(NO_3)_2(H_2O)_2$	40.37	3.56	12.00	40.97	3.86	11.94

TABLE II. Reflectance Spectra and Magnetic Moments of the Complexes.

Complex	μ_{eff}	Band Maxima (cm^{-1})
CoL_2Cl_2	4.55	5970, 6970, 8970, 15,750, 16,950sh
CoL_2Br_2	4.55	5880, 6760, 8400, 15,300, 16,700sh
CoL_2I_2	4.66	~5700sh, 6540, 7970, 14,500, 15,400, 16,300
$CoL_2(NCS)_2$	4.39	~8070br, 16,100, ~17,400sh
$CoL_2(NO_3)_2$	4.49	8470, 9430, 13,900, 18500
$CoL_4(ClO_4)_2$		~7600br, 16,000, 17,700
$CoL_4(ClO_4)_2 \cdot H_2O$		~7600br, ~9400sh, ~16,700sh, 17,700, ~18,400sh
$CoL_4(BF_4)_2$		~7600br, ~9400sh, ~15,900sh, ~16,700sh, 17,700, ~18,500
NiL_2Cl_2	3.68	6100, 7580, 10,310, ~15,900sh, 18,200
NiL_2Br_2	3.43	6060, 6900, 10,000, ~11,500sh, ~15,400sh, 17,240
NiL_2I_2	3.64	6670, 9620, ~10,600sh, 14,300, ~16,100sh
$NiL_2(NCS)_2$	diamag.	11,500vw, 18,900
$NiL_2(NO_3)_2ac$[a]	3.24	8700, 15,400, 24,100
$NiL(NO_3)_2 \cdot 2H_2O$		8770, 15,200, 23,800

[a] ac = acetone.

geometry, as shown by their electronic spectra and magnetic moments (Table II). The spectra of the halides are generally similar to those of other benzimidazole complexes [4, 5] though the ligand fields are slightly weaker. They are, however, much stronger than in CoO_2X_2 tetrahedra and there is no reason to doubt that the expected mode of coordination through the tertiary nitrogen atom is present.

The difference in ligand field from the 2-methylbenzimidazole complexes is most marked in the iodide, where steric constraints are expected to be greatest. It is shown particularly in the position of the highest-energy component of $\nu_2[^4A_2 \rightarrow {}^4T_1(F)]$ which in complexes of pyridine-type ligands is the most sensitive to steric effects [6]. The iodide also shows the smallest spread of the components of ν_2, implying that the distortion from tetrahedral symmetry is least here. It appears that the Co–N bonds may lengthen in order to accommodate the bulky iodide ions.

TABLE III. Infrared Spectra (200–400 cm^{-1}) of the Cyclic Ether and Its Complexes.

Compound	ν(M–X)	Ligand Bands
L		345m, ~310wbr, series vw bands 240–290
CoL_2Cl_2	333s, 307s	364m, 350m, 278w, 242w
CoL_2Br_2	250s, br	363m, 315w, 305w, 280w, ~210w
CoL_2I_2	235ms, 215s	366m, 348w, 328w, 310w, 287m, 276m, 268w, 246m
$CoL_4(BF_4)_2$		357m, 335wsh, 320vw, 308w, 290sh, 280m, ~250wsh, 240m
NiL_2Cl_2	330s, 297s	358m, 280sh, 270sh, 238w, 224vw, 207vw
NiL_2Br_2	250s,br	364m, 352m, 304w, ~284sh, ~275sh, 237sh, ~224sh
NiL_2I_2	236m, 209s	364m, 345sh, 330sh, 308w, 287mw, 276mw, 268w, 244sh

Solution spectra of these complexes in acetone are very similar in the visible region to those of the solids, with molar extinction coefficients of 530, 750 and 620 for the chloro, bromo and iodo-complexes respectively. The fact that the value for the iodo complex is lower than for the bromo, may indicate some decomposition in solution, though Beer's Law was obeyed in the concentration range 6.3×10^{-5} to 5×10^{-4} *M*. The molar conductance of 9.3 mho cm^{-1} in nitrobenzene indicates some dissociation in this solvent too.

The crystal field is also unusually weak in $CoL_4(ClO_4)_2$, with Δ about 4,400 cm^{-1} compared with the 5000 cm^{-1} normally found for benzimidazole. The ν_2 band is at even lower energy than in the $Co(NCS)_4^{2-}$ ion, whereas in $CoL_2(NCS)_2$, where the crowding must be much reduced, ν_2 is at higher energy than in $Co(NCS)_4^{2-}$. The complex $CoL_4(ClO_4)_2$ was difficult to prepare in a pure state, and it is likely that the bulk of the ligand makes it difficult to accommodate four molecules round the metal ion, so that unusually long bonds are necessary.

Attempts to prepare $CoL_4(ClO_4)_2$ tended to yield samples which analysed as $CoL_4(ClO_4)_2 \cdot H_2O$ and which showed broad, weak absorption at about 3400 cm^{-1}. Their electronic spectra also differed in detail from that of the anhydrous complex (Table II), whilst retaining a similar overall appearance. The ν_3 band is at appreciably higher energy for the hydrate, while ν_2 is unchanged except that a weak shoulder appears on the high energy side. The water molecule seems to perturb the chromophore in some way, though whether it is coordinated is not clear.

The only other complex containing four mol of ligand is $CoL_4(BF_4)_2$. This anhydrous salt is formed much more readily than $CoL_4(ClO_4)_2$. Its electronic spectrum is very similar to that of $CoL_4(ClO_4)_2 \cdot H_2O$, and the B–F stretching vibration appears as a broad, split band with components at 1040 and 1100 cm^{-1}. Again, it seems that there is some perturbation of the CoN_4 tetrahedron.

The nickel halides form complexes NiL_2X_2, which also appear, from their electronic spectra (Table II) to have essentially tetrahedral structures. Their magnetic moments are high at room temperature, implying that the splitting of the ground state is rather small. However, the band intensities which show $\nu_2(^3T_1 \rightarrow {}^3A_2)$ as relatively strong, indicate that there is considerable distortion from true T_d symmetry.

The chloro- and bromo-complexes dissolve in acetone to give deep blue solutions with spectra similar to those of the solids, and molar extinction coefficients of 82 and 136 respectively. The iodo-complex, however, gives a golden-yellow solution showing only an intense band centred at 370 nm, and the molar conductance of 25.1 ohm^{-1} cm^{-1} in nitrobenzene shows considerable dissociation in this solvent.

A full X-ray structure determination was carried out on the chloride. Details will be published elsewhere, but the coordination geometry may be summarised as a tetrahedron, somewhat distorted towards a square, with Ni–N and Ni–Cl bond lengths of about 2.0 and 2.2 Å respectively, which are in the range expected for such bonds. However, the splitting of the $\nu_1(^3T_1 \rightarrow {}^3T_2)$ band, which is quite pronounced in the chloride, is somewhat reduced in the bromide, and is not detected in the iodide. Also, the iodide appears from X-ray powder patterns to be isomorphous with CoL_2I_2, whereas the chloride and bromide are clearly different.

The complex $CoL_2(NO_3)_2$ is similar to Co(2-methylbenzimidazole)$_2(NO_3)_2$, which is considered to have a very distorted octahedral structure with chelating nitrate ions. With nickel nitrate no unsolvated complex could be prepared, the compound $NiL_2(NO_3)_2 \cdot$ acetone crystallising from the acetone solution. Although the infrared spectrum suggests that the acetone is not coordinated, since ν(C=O) is at about 1710 cm^{-1}, attempts to remove the solvent by heating *in vacuo* resulted in complete decomposition of the complex. Solution of the compound in chloroform followed by slow evaporation yielded $NiL(NO_3)_2 \cdot 2H_2O$, which retained the water after prolonged heating *in vacuo*.

The compound $NiL_2(NCS)_2$ is red and diamagnetic, and presumably contains the metal ion in an essentially planar environment. The electronic spectrum indicates that the NCS^- is -N bonded, but the C≡N stretch at 2100 cm^{-1} is much higher than that (2065 cm^{-1}) in the tetrahedral cobalt complex. Anomalously high values of ν(C≡N) have been reported in other planar nickel(II) complexes [7].

In the 200–330 cm^{-1} region, all the halo-complexes show bands which from their strength and anion-dependence may be assigned as metal–halide stretches (Table III). Assignment of metal–nitrogen stretches is more difficult because the ligand itself has some very weak bands in the range 240–290 cm^{-1}, which are most reasonably attributed to this cause. In addition, $CoL_4(BF_4)_2$ and the two iodides have a medium-intensity band near 240 cm^{-1}, which could possibly be due to ν(M–N), but which may also be a ligand mode.

The changes in higher energy ligand bands on coordination were small, involving mainly broadening and splitting of bands. Intensity at 1500 cm^{-1}. was greater in the complexes, while the strong, sharp 1090 cm^{-1} band, presumably due to the ether grouping was slightly lowered and normally split. It seems likely that the conformation of the ligand is the same in all the complexes, so that found [8] for NiL_2Cl_2 may be taken as representative.

Acknowledgements

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