R5

Comparison (Nature and Biological Activity) between two New Blue Species Involving, respectively, Malonamide and Succinamic Acid as Ligands

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Although the preparation of blue platinum complexes is generally achieved through the reaction of a ligand involving a –HN–CS– group with the hydrolysis products of *cis*-$Pt(NH_3)_2Cl_2$, blue species may be obtained using M_2PtCl_4 as platinum precursors. Two new blue species involving malonamide and succinamic acid have been prepared according to this process.

They display the main characteristics of the blue species, *i.e.*: an absorption near 660 nm in their visible spectrum, a paramagnetic behaviour (EPR signal) and platinum atoms in a nonintegral oxidation state. In both cases, solid state infrared spectroscopy gives evidence of coordination through the deprotonated amido groups.

The two species have been tested for antitumor activity and toxicity using Sarcoma 180 in mice. Examination of test data shows important differences between the two compounds. For instance, malonamide blue does not significantly improve the median survival time (T/C) at doses up to 1100 mg/Kg body w. while a single dose (150 mg/Kg) of the succinamic acid species produces a 189% T/C (10% survivors).

The analytical data and the physico-chemical properties of the two blue species are considered with the aim of suggesting likely explanations of the differences observed in their biological properties.

R6

Syntheses and Properties of Platinum Group Metal Complexes with 1,4-Benzodiazepines as Ligands

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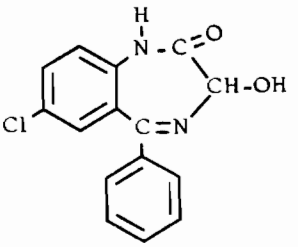
Following our interest in the chemistry of 1,4-benzodiazepines [1–4], we report the results of the study of the derivatives of rhodium(III), iridium(III), palladium(II) and platinum(II) halides with Oxazepam, 7-chloro-1,3-dihydro-5-phenyl-3-hydroxy-2H-1,4-benzodiazepin-2-one [5]:



The study of the stereochemistries and of the chemical reactivity of coordination compounds of benzodiazepines will help to determine what relationship exists between chemical structure and biological activity of these drugs, in the belief that metal complexes of ligands having biological activity are more active than the free ligands.

The obtained complexes, of the type ML_3X_3 (M = Rh, Ir; X = Cl, Br, I) and ML_2X_2 (M = Pd, Pt; X = Cl, Br, I), have been studied and characterized through vibrational and electronic spectra, ^1H and ^{13}C n.m.r. studies, conductivity measurements and magnetic susceptibility data. Furthermore, the complexation effects of the transition metal ions on the conformation of the diazepine ring are discussed.

The results will be discussed in detail and compared with those obtained for other metal complexes with the same ligand and for a long series of benzodiazepines in the free and complexed form.

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R7

NMR and INDO Study of the Ni(II) Complexes of Some Bidentate Ligands

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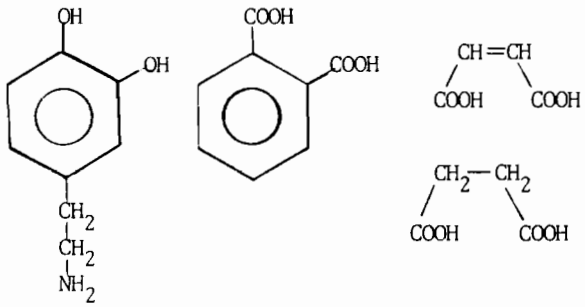
The joint use of NMR spectroscopy and quantum mechanical calculations proved a powerful tool for investigating the conformational and electronic properties of various ligands complexes to paramagnetic metal ions.

It is well known that the spin–lattice relaxation rates cannot often be rationalized in terms of the Solomon-Bloembergen equation, in its original form, because of the important contribution arising from the unpaired spin density onto the ligand molecule [1]. Thus a modified S.B. equation, where both the metal-centered and ligand-centered dipolar contributions are taken into account, must be employed.

In this work the Ni(II) complexes of dopamine [2], a molecule of biological relevance, phthalic acid [3], maleic and succinic acid [4] were examined. The common feature of these differently flexible ligands is a potential bidentate binding site.



From the analysis of the proton and carbon paramagnetic shifts, induced on the nuclei of the different ligands bound to Ni^{2+}, a delocalization mechanism was hypothesized with the aid of an INDO M.O. analysis, performed on suitable radical models of the ligand. The radical model giving hyperfine coupling constants in the best agreement with the experimental shifts was then used to obtain a complexation model. The reliability of the model chosen was tested introducing the metal–nucleus distances in the reduced and modified S.B. equation and verifying whether the calculated total unpaired spin densities and correlation times satisfy the experimental nuclear relaxations.

In the case of ligands having a partially rigid skeleton (dopamine, phthalic and maleic acids) the approach led to a unique complexation model, consistent with the experimental data, while for the more flexible succinic acid the result were not so encouraging.

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R8

Cu(II)–Mn(II)–Imidazole Competing Equilibria. ESR Study.

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The interaction between divalent metal ions and nucleobases is very important in many biochemical reactions [1].

The metal ions affinity toward different ligands is strongly related to the extent of the metal-ligand equilibrium. The aim of this report is to apply the ESR analysis carried out by means of the Mn(II) and Cu(II) paramagnetic probes to study the competion equilibrium of the Me-nucleobases complexes [2–4].

Cu(II)–Imidazole System

The Cu(II)–imidazole interaction is analyzed in terms of the X-band ESR hyperfine structure resolution. Due to the interaction of $S_{Cu} = ½$ with $I_{Cu} = 3/2$ four lines of equal intensity are expected in the presence of imidazole. The Hamiltonian of such an interaction is represented by [5]:

$$\mathcal{H} = \beta_o [g_{\parallel} H_z S_z + g_{\perp}(H_x S_x + H_y S_y)] + \\ + A_{\parallel} I_z S_z + A_{\perp}(I_x S_x + I_y S_y) \qquad (1)$$

The well-resolved hpf structure of the Cu(II)–Imidazole system at low metal ligand molar ratios (Cu(II)/[L] = 1:20) suggests a very strong interaction between the paramagnetic metal ion and the base.

The ESR analysis shows that the following equilibrium:

$$Cu(II)(H_2O)_6 + 4\ Imid \overset{K}{\rightleftarrows} \\ Cu(II)–(Imid)_4(H_2O)_2 + 4H_2O \qquad (2)$$

is pH independent for pH values up to 5.2; in more acidic conditions, the hpf structure reduces and the Cu(II)–H_2O broadline appears (Fig. 1(a) and (b)).

The superhyperfine structure in the Cu(II)–Imid spectrum is absent and the nitrogen atoms interacting with the cupric ions are equivalent. The value of $a_{Cu-N} = 7.45$ mT found, is consistent with a four planar imidazole molecule and two axial water molecules.

Mn(II)–Imidazole System

The presence of different molecular species in a manganous solution can be detected by means of the study of ESR parameters like a, the hyperfine coupling constant and ΔT, linewidth [6]. The ESR