TABLE I. Stability Constants and Spectral Data of Complexes I and II.

	log β													
		Spectral data												
I	16.7	Ab λ(nm)		304			400			512				
		ε		8300			2400			6700				
		CD λ(nm)	230	260	300	350	380	430	490	540				
		Δε	−26.5	−8.8	−18	+4	+5.5	+1.7	−6	+8.5				
II	12.2	Ab λ(nm)			316			420		540				
		ε			9400			3000sh		6000				
		CD λ(nm)		260	305					570	605			
		Δε		+16.4	+2					+4.5	+6.2			

ions are present in all biological processes involving the nucleic acid and since DNA seems to be the target for adriamycin action, the occurrence of metal-adriamycin complexes inside the cell may play a crucial role in chemotherapeutic action.

Several recent observations have focused attention on the interaction of adriamycin and Cu(II) in the absence and in the presence of DNA [2–5]. In this communication we report the results of a detailed potentiometric and spectroscopic investigation which was undertaken to characterize accurately Cu(II)–adriamycin complexes, their stability constants and their effect on DNA.

The addition of Cu(II) to Adr at 1:1 molar ratio yields a first complex (I) at pH 5.8 and a second one (II) at pH 7.2. Using the results of potentiometric titrations these complexes can be formulated as $Cu(AdH)_2$(I) and Cu(Ad)(II). AdH and Ad stand for Adr in which the 1,4-dihydroxianthraquinone moiety is half deprotonated and fully deprotonated respectively. Absorption, CD data and the stability constants of both complexes are reported in Table I. The visible CD spectrum of complex I is of the couplet type indicating stacking of Adr due to the presence of Cu(II). Resonance Raman spectroscopy measurements indicate that coordination takes place through quinone and phenolate oxygens as shown by the shifting of the corresponding CO stretching Raman bands (carbonyl and phenolic).

When DNA is added to Adr at pH 7.4 (HEPES 0.05 *M*) precipitation of a DNA·Adr complex occurs, with a molar ratio of one nucleotide per Adr, if the Adr concentration is higher than 100 μM. When DNA is added to complexes I or II a Cu·Adr·ADN species precipitates. In this case, however, an Adr concentration lower than 20 μM has to be reached to prevent precipitation.

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V10

Fe(III)·Bleomycin–DNA system. Evidence of Fe(III) to DNA Coordination

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Bleomycin (BLM) are a family of glycopeptide antibiotics clinically prescribed for the treatment of selected neoplastic diseases [1]. This drug, which both chelates metal ions and binds to DNA, induces a degradation of DNA in a reaction that has been shown to depend, *in vitro*, on the presence of Fe(II) and molecular oxygen [2]. At the end of the reaction Fe(III)·BLM and degraded DNA are obtained.

In this communication we report evidence suggesting that in the BLM·Fe(III)–DNA system, Fe(III) is directly bound to DNA.

In Fe(III)·BLM complex four nitrogens, from the secondary amine, the pyrimidine ring, a peptide bond, and the histidine imidazole coordinate to Fe(III) as the basal planar donor; at pH 7 the two axial positions (hereafter labelled A and B) are occupied by the α amino nitrogen and probably an oxygen atom of a glucide, respectively [3]; the complex is then in a low spin form. At pH 4 the α amino nitrogen is no longer bound in A (being presumably superseded by a water molecule) and the metal is therefore in the high spin form.

The following experiments suggest that position A can be occupied by different types of ligands and particularly by DNA.

(i) at pH 4 by addition of DNA, Fe(III)·BLM is converted into a low spin species which rapidly decays. On the other hand, the addition of ligands (L) such as N_3^-, SCN^-, $S_2O_3^{--}$ to Fe(III)·BLM yields brightly colored complexes in the low spin form.

(ii) at pH 7 the same colored complexes BLM·Fe(III)·L are obtained by addition of an excess of L. The addition of DNA to these complexes gives rise to the release of L and an BLM·Fe(III)·DNA complex is obtained.

These experiments strongly suggest that the various ligands: the α amino group of BLM, N_3^-, SCN^-, $S_2O_3^{--}$ or ADN are competing ligands for the apical position A.

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V11

Metal Ion Interaction with Ribavirin (1-β-D-ribufuranosyl-1,2,4-triazole-3-carboxamide)

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The antitumor agent cis $Pt^{II}(NH_3)_2Cl_2$ is known to interact with guanine with possible binding to the 6-oxo group, promoting deprotonation on N(1) [1]. N(4)–O(7)–Cu(II)-ribavirin chelate has been demonstrated [2] in a solid state and these particular binding sites were assumed also for other ribavirin–Me(II) interactions in solution.

Even a single crystal-X-ray analysis assumed a conformation of ribavirin strikingly similar to guanosine [2]. This resemblance prompted further studies of ribavirin Pt(II) complexes as Pt(II) complexes are convenient to compare solid state and solution properties of these chelates. The binding of the paramagnetic Cu^{++} ion to ribavirin in solution was located mainly on N(5) by ^1H and ^{13}C line broadening and T_1 relaxation times and did not support any binding on exocyclic oxygen O(7).

The role of the carboxamide group in metal binding to ribavirin is thus not completely clear. Pt(II)-complexing will be discussed in order to clarify this question, as well as ^{14}N relaxation of the carboxamide nitrogen. In this case, the indirect measurement of ^{14}N relaxation rates is possible. $T_{1\rho}$ (spin-locking method) eliminates effects on proton relaxation other than proton–nitrogen scalar coupling. Thus T_{1N} and A (^{14}N-coupling) of amino protons will be evaluated from the following equation:

$$\frac{1}{T_{1\rho}(\text{obs})} - \frac{1}{T_1} = \frac{2}{3}A^2 \frac{T_{1N}}{1 + \omega_1^2 T_{1N}^2}$$

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V12

Metal Ion Interaction with Inducers of Reverse Transformation of Cancer Cells

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Gosálvez, based on a theoretical hypothesis of the function of the plasma membrane, designed three heterocycles as possible inducers of reverse transformation of cancer cells to normal phenotype [1]. Two of these compounds (thiaproline, TP, and 2-amino-1,3-thiazoline, AT) have been taken to the anticancer clinics and have shown, preliminarily, an antitumor activity [2].

Both ligands are believed to bind in the lipid environment a zinc ion linked to a protein complex of the membrane, which would be the origin of macrofilaments [3].

In this communication the NMR, spectroscopic and X-ray results for the Cu(II), Cd(II) and Zn(II) complexes with the above mentioned ligands are discussed to establish possible binding modes of these ligands with metal ions.

Both ligands are unstable in aqueous solution at $pH > 6$ and their decomposition is additionally promoted by the presence of metal ions [4].

In acidic solution the AT ligand does not interact directly with the studied metal ions, but it acts as cation ATH^+.

The protonation site, established by X-ray technique, is the heterocyclic nitrogen which appears to be quite a basic donor.

The most 'destructive' metal ion seems to be the cupric ion, which due to the redox reaction leads to several different decomposition products of AT, including SO_4^{2-} and $[NH_2\text{-}CH\text{=}NH_2]^+Cl^-$ [5].