(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.

1 S. K. Carter, in 'Bleomycin Status and New Developments', S. K. Carter, S. T. Crooke and H. Umezawa (eds.), Academic Press, New York (1978).
2 E. A. Sausville, R. W. Stein, J. Peisach and S. B. Horwitz, *Biochemistry, 17*, 2746 (1978).
3 J. C. Dabrowiak, in 'Metal Ions in Biological Systems', E. Sigel (ed.), Vol. 11, p. 305 (1980).

V11

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

J. KOBE, P. BUKOVEC and Z. MEIĆ

Edvard Kardelj University, Department of Chemistry, Ljubljana, Murnikova 6, Boris Kidrič Institute of Chemistry, Hajdrihova 19, 61000 Ljubljana, Yugoslavia and Rudjer Bošković Institute, P.O.B. 1016, 41001 Zagreb, Yugoslavia

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:

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

1 L. G. Marzilli, *Adv. Inorg. Biochem., 3*, 47 (1981).
2 P. Bukovec, L. Golič, B. Orel and J. Kobe, *J. Carbohydrates, Nucleotides, Nucleosides, 8*, 1–17 (1981).

V12

Metal Ion Interaction with Inducers of Reverse Transformation of Cancer Cells

M. KUBIAK, T. TATAROWSKI, T. GŁOWIAK, H. KOZŁOWSKI

Institute of Chemistry, University of Wrocław, 50-383 Wrocław, Poland

and M. GOSÁLVEZ

Clinica Puerta de Hierro, National Center of Medical Research, Madrid-35, Spain

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].

The use of methanol solutions makes possible the observation of the direct metal AT interaction before ligand decomposition. The X-ray and spectroscopic studies have shown that in both ligands the major coordination site is a heterocyclic nitrogen (for TP see also [6]).

This similarity in metal ion binding by the heterocyclic nitrogen donor of both ligands and their possible chemical analogues could play a critical role in complex formation in a lipid environment.

1 M. Gosálvez, Abstract, 13th International Cancer Congress, Seattle, 1982.
2 A. Brugarolas and M. Gosálvez, *Res. Results in Cancer Research, 80,* 346 (1982) and references therein.
3 M. Gosálvez, 'The Zipper Mechanism', S. L. Malbar (ed.), Editores, Madrid (1982).
4 T. Głowiak, M. Kubiak, T. Tatarowski, H. Kozłowski and M. Gosálvez, *Inorg. Chim. Acta,* submitted for publication.
5 M. Kubiak and T. Głowiak, T. Tatarowski and H. Kozłowski, (unpublished results).
6 Z. X. Huang, P. May, D. R. Williams and M. Gosálvez, *Inorg. Chim. Acta, 56,* 41 (1981).

V13

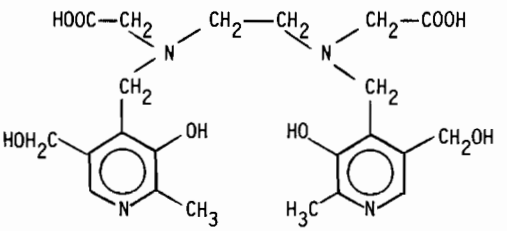
PLED – A New Chelating Ligand for the Treatment of β-Thalassemia

ARTHUR E. MARTELL and RAMUNAS J. MOTEKAITIS

Department of Chemistry, Texas A&M University, College Station, Tex. 77843, U.S.A.

The structure of EDTA has been modified by replacing two acetate groups with *o*-hydroxybenzyl groups, producing N,N′-bis-*o*-hydroxybenzylethylenediamine-N,N′-diacetic acid (HBED) [1] which has a very high affinity for the Fe(III) ion. Previously, an analogous ligand, ethylenebis-*o*-hydroxybenzylglycine (EHPG) had also been reported to have high selectivity for Fe(III) [2]. This paper describes a new ligand analogous to HBED, with pyridine rings derived from vitamin B_6. This ligand, N,N′-dipyridoxylethylenediamine-N,N′-diacetic acid, PLED *1*, has lower pK's than do HBED and EHPG. The corresponding protonation constants of these three ligands, and of EDTA, are presented in Table I. The stability constants of the chelates of PLED with Fe^{3+} and Ga^{3+} are considerably lower than those of HBED and EHPG, and lower than expected on the basis of ligand basicity perhaps because of the steric factors arising from the substituents on the pyridoxyl rings. The much higher stability of the Cu(II) chelate relative to those of EHPG and HBED was unexpected, but the lower coordination requirement of Cu(II) would probably tend to minimize steric repulsions.

PLED, HBED, and EHPG, and their esters have proved to be effective in test animals for the removal of iron overload [4], thus demonstrating the effectiveness of aromatic hydroxyl groups in the design of chelating agents having specificity for Fe(III). The lower stability constant of PLED for Fe(III) is partially compensated for by lower basicity of its donor groups, thus increasing its relative effectiveness at physiological pH. The application of this ligand to the treatment of β-thalassemia is made somewhat attractive by the relatively low toxicity of the pyridoxyl rings.



1 PLED, H_4L

1 F. L'Eplattenier, I. Murase and A. E. Martell, *J. Am. Chem. Soc., 89,* 837 (1967).
2 A. E. Frost, H. H. Freedman, S. J. Westerback and A. E. Martell, *J. Am. Chem. Soc., 80,* 530 (1958).
3 A. E. Martell and R. M. Smith, 'Critical Stability Constants', Vols. 1 & V, Plenum, New York, 1974, 1982.
4 A. E. Martell and R. J. Motekaitis, to be published.

TABLE I. Protonation Constants and Stability Constants of N,N′-Dipyridoxylethylenediamine-N,N′-diacetic Acid (PLED) and Related Ligands.

Equilibrium Quotient	PLED	HBED [1]	EHPG [2]	EDTA [3]
[HL]/[L][H]	11.08	12.46	11.68	10.17
$[H_2L]/[HL][H]$	9.95	11.00	10.24	6.11
$[H_3L]/[H_2L][H]$	8.57	8.32	8.64	2.68
$[H_4L]/[H_3L][H]$	6.26	4.64	6.32	1.95
[CuL]/[Cu][L]	26.48	21.38	23.94	18.70
[FeL]/[Fe][L]	29.80	39.57	33.9	25.0
[GaL]/[Ga][L]	30.45	39.57	33.6	21.0