



PS6.9 — TH

M.L. VITOLO

J. WEBB

G.T. HEFTER

B.W. CLARE

School of Mathematical and Physical Sciences

Murdoch University

Perth WA 6150

Australia

P. WILAIRAT

C. SANGMA

Faculty of Science

Department of Chemistry

Mahidol University

Bangkok

Thailand

PYRIDOXAL ISONICOTINOYL

HYDRAZONE:

A PROMISING AGENT FOR CHELATION THERAPY OF IRON OVERLOAD

The chemistry of pyridoxal isonicotinoyl hydrazone (PIH) has been investigated with emphasis on the chemical characteristics pertinent to the assessment of its value as a biological iron chelator. In acidic environments, PIH is remarkably stable, with a decomposition of $\leq 3\%$ after 72 hr at pH 2, 37°C. The acid dissociation constants of the several ionisable groups present in PIH have been determined by potentiometric titration and the formation of the iron complexes studied by potentiometry and UV-Vis spectrophotometry. The systems are quite complex due to the number of dissociable protons in both the free and coordinated ligands, the high affinity of these compounds towards iron(III) and the formation of sparingly soluble species at pH 5.

At pH 7.4, $[\text{Fe}^{3+}] = 10^{-6} \text{ M}$ and a 1000-fold excess of ligand, PIH has a pM value of 27.7 which, when compared to 25.6 for transferrin, indicates that PIH is thermodynamically capable of removing iron from transferrin.

The distribution of the complex species as a function of pH shows that in each case a significant fraction is present as the electrically neutral Fe(L)(HL) at pH 7.4. A model of the coordina-

tion geometry of this species, supported by spectroscopic data, is proposed.

The affinity of PIH for iron(II) is significantly lower than for iron(III), as indicated by a formation constant of 7.0 for $[\text{Fe(II)(HL)}_2]$ compared to 12.47 for $[\text{Fe(III)(HL)}_2]$.

PIH therefore possesses many chemical features desirable in an effective iron chelating drug. Furthermore, this chelating agent has been reported to be effective in several cellular and animal bioassays and is currently a highly promising pharmacological agent for the treatment of iron overload.



_ PS6.10 — TH

J. WEBB

School of Mathematical and Physical Sciences

Murdoch University

Perth WA 6150

Australia

E. DELHAIZE

J.F. LONERAGAN

School of Environmental and Life Sciences

Murdoch University

Perth WA 6150

Australia

ASCORBATE OXIDASE, DIAMINE OXIDASE AND THEIR USE IN DIAGNOSIS OF COPPER DEFICIENCY IN PLANTS

Copper deficiency in soils and crops is a cause of concern in many agricultural industries. In general, copper deficiency leads to significant decreases in crop yield and plant fertility. However, it is often difficult to diagnose deficiency without complex laboratory procedures and at a sufficiently early stage in the plant's growth to allow remedial measures to be adopted, *e.g.* by including copper compounds in fertiliser. Analysis of the range of copper compounds present in plants,

as a function of copper supply, has revealed that several enzymes are particularly sensitive to copper deficiency and can act as an early warning signal of deficiency. These enzymes include ascorbate oxidase and diamine oxidase. Their assays have been shown to be at least as sensitive and indeed more reliable than atomic absorption analysis of copper content. In a simplified assay, ascorbate oxidase activity has been used to provide a field test that is quick, reliable and robust.



_PS6.11 — TU

ARGYRIOS VARSAMIDIS

GUY BERTHON

Centre de Technologie Biomédicale INSERM SC 13

Laboratoire de Chimie Bioinorganique

Université Paul Sabatier

38, rue des Trente-six ponts, 31400 Toulouse
France

MALATE AS A POTENTIAL AGENT TO PROMOTE HISTAMINE CATABOLISM

The most of the histamine present in the human body is stored in mast cells in tissues and in basophils in blood [1]. Its release from these sites may be triggered by immune reactions involving IgE antigens, or may directly result from non immunological stimuli such as the incorporation of so-called "histamine liberator" substances inside the membrane of the storage cells [1,2].

When localized, this release will lead to slight disorders like itching, redness and skin edema. When generalized, it may cause profound changes to the cardiovascular system and induce anaphylactic — or anaphylactoid, depending on the respective type of stimuli above — shock [1-3]. Concerning this, the demonstration of a close correlation between the plasma concentration of histamine and the seriousness of the symptoms

observed constituted an important breakthrough in the understanding of the physiological action of this mediator [4-6].

It has been known for a long time that histamine undergoes a rapid destruction in tissues [3]. It thus appears that increasing its rate of diffusion from blood into the environmental tissues may help alleviate its toxic effects. However, account being taken of the complexity of the system of labile equilibria characterizing the species potentially involved, it is impossible to discriminate the predominant forms under which histamine is present in blood plasma on an experimental basis.

A series of studies was thus devoted to the simulation of the distribution of histamine in this biofluid [7-11], which led to the following conclusions: (i) the most important fraction of histamine (about 99%) is constituted by its electrically charged mono- and di-protonated forms, and as such is not likely to passively diffuse through cell membranes, (ii) about 1% of histamine remains free, but its molecular form is highly polar [3], which also makes its passive diffusion unlikely, (iii) a small fraction whose percentage is inferior to 1% represents the binary and ternary metal complexes of histamine [11]. In the normal state, more than 70% of this fraction consists of the electrically neutral zinc-histamine-cysteinate complex, the majority of the remainder involving charged ternary copper complexes.

The hypothesis was thus put forward that zinc could indirectly favour histamine diffusion from plasma to tissues, hence its catabolism rate, whereas copper would in contrary exert an antagonistic effect [11]. This interpretation of the simulation results is in line with the roles previously attributed to zinc and copper in the evolution of the pharmacological effects of histamine in mice [12]. Subsequently, applications of the principles of the hypothesis above were developed using the aforementioned blood plasma simulation model [13,14]. Firstly, an attempt was made at increasing the concentration of the naturally occurring zinc-histamine-cysteinate complex by raising that of cysteine, but this proved unsuccessful [11]. A second study used aspartate and glutamate as successive partner ligands for zinc and histamine, but the increase of the neutral complexed fraction of histamine due to each of these two ligands was