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Structural, morphological and biological investigations of some transition metal–5-Fluorouracil–amino acid mixed ligand complexes

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ABSTRACT

Mixed ligand complexes (**1a**–**1c**) of type MAB (where M = Ni(II)/Cu(II)/Zn(II); A = 5-FU; B = phe) were isolated in their solid state and characterized by various physico-chemical and spectral techniques. Thermal studies (TG/DTA) on the synthesized mixed ligand complexes (**1a**–**1c**) show an initial loss of coordinated water molecule followed by decomposition of the organic residue. XRD and SEM analyses suggest the microcrystalline and homogeneous morphology for MAB complexes. The *in vitro* antimicrobial, antioxidant, nuclease cleavage and binding interactions of the free ligand(A) and its mixed ligand systems were studied. Further, the 3D molecular modeling and analysis of Cu(II)–5-FU(A)–phe(B) mixed ligand complex has been undertaken. In addition, the complex formation equilibria were also studied pH-metrically in aqueous medium (I = 0.15 M) for Cu(II) ion with 5-Fluorouracil (5-FU; A) and some bioactive amino acid ligands(B) *viz*., glycine(gly), L-alanine(ala), L-valine(val) and L-phenylalanine(phe). The calculated stabilization parameters $\Delta\log K$, $\log X$, $\log X'$ and % *R.S.* indicate that mixed ligand systems have higher stabilities than their binary counterparts. Thermodynamic parameters ($\Delta^{\ddagger}G$, $\Delta^{\ddagger}H$ and $\Delta^{\ddagger}S$) have also been determined from the stability constants at 300, 310, 320 and 330 ± 0.1 K. The complexation behavior has been studied by means of spectrophotometry at different pH. The biological studies of the mixed ligand systems show moderate activities.

1. Introduction

The significance of coordination behavior of transition metal(II) ions covers up the analytical, environmental, electrochemical and biological chemistry [1]. In the living organisms, coordination of transition metal(II) ions plays a vital part in bioaccumulation and detoxification in the course of chelation therapy. The functional groups of pyrimidines and amino acids have interactions with metal(II) ions to uphold their functionalities [1]. Moreover, the formed heterocyclic structured chelates generate a relation between the chelation therapy and stability constants as mixed chelation occurs in bio fluids *in vivo*. Ni(II)/Cu(II)/Zn(II) metal ions have a momentous function in complexation with pyrimidines and amino acids in living systems which take steps as model for metal-pyrimidine-amino acid equilibria occurring in enzymatic process [1].

Pyrimidine bases are crucial ingredients of nucleic acids, enzymes and co-factors which are required for the appropriate functioning of cells and tissues [2]. Ionization of the pyrimidine moiety in DNA will modify its coding belongings in polymerase interceded replication, consequential in a base substitution mutation [3]. Halo substitution at the fifth position of pyrimidine considerably changes the electronic characters and biological properties of that moiety [4]. 5-Fluorouracil is a type of antimetabolite, it has been employed for antitumor chemotherapy in rectum [5], breast, colon, ovarian, liver, gastrointestinal, head, neck [6] and skin [7] that wields the cytotoxic effect by inhibiting cellular DNA replication [8,9]. It is effectual in the treatment of Bowen's disease [10].

The nickel(II) ion acts as a co-factor structural constituent of a number of specific metalloenzymes in human. Its insufficiency falls in the basis of some diminished action of certain liver enzymes like glucose-6-phosphatase [11]. Copper(II) ion is the thirdmost abundant in human and is indispensable for aerobic metabolism. It can be found as a structural component of a large number of enzymes [12,13]. It plays a vital part in biological systems. Copper(II) complexes have been found to be active as potential cancer inhibitors [13]. Zinc is concerned in several characteristics of cellular metabolism [14]. It is found either at the active sites

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or as structural components of a good number of enzymes and is necessary for normal growth and development of brain, central nervous system [15–18]. Zinc containing enzymes *viz.*, carbonic anhydrase and carboxypeptidase are essential in the processes of CO_2 regulation and digestion of proteins respectively [19–21].

The amino acids like glycine(gly), L-alanine(ala), L-valine(val) and L-phenylalanine(phe) in the form of mixed ligand species partake well in transamination, decarboxylation and metabolism in human [22] and are used as reagents in biology, pharmacy, industry and laboratory [23]. Many drugs and drug precursors containing amino acid moieties are found to have therapeutic activities [24]. Mixed ligand species of amino acids are also involved in the exchange and transport mechanism of trace metal ions in the human body [25]. The stability of mixed ligand–amino acid species depends on the chelate formation, the size [26] and basicity of amino acids which in turn depend on the interactions of metal(II) ions with amino and carboxyl groups.

A substantial attempt has been dedicated to facilitate the dynamic forces that guide the complexation behavior of metal(II) ions in biological systems. In a sequel to our continuation [27–30], in this work MAB (where M = Ni(II)/Cu(II)/Zn(II); A = 5-FU; B = phe) type of mixed ligand complexes (**1a**–**1c**) were isolated in their solid state and characterized by various physico-chemical and spectral techniques. The coordination environment and the stability constants of mixed ligand complexes formed in solutions have also been discussed. Additionally, we have analyzed the formation equilibria of binary and ternary mixed ligand species of Cu(II) metal ion with 5-FU(A) as a primary ligand and some amino acid ligands *viz.*, glycine(gly), L-alanine(ala), L-valine(val) and L-phenylalanine(phe) as secondary ligands.

2. Experimental

2.1. Materials and reagents

All the chemicals were of extra pure Sigma Aldrich and Fluka (Puriss) products and were used without further purification. Solvents used for the physical measurements were of AR grade and purified by standard methods [31]. Carbonate free sodium hydroxide (NaOH) solution (0.3 M) was prepared from a Titrisol solution (ClNa) (Merck) and its concentration was standardized against standard potassium hydrogen phthalate ($C_8H_5KO_4$) solution by means of the appropriate Gran titrations [32]. Nickel(II) perchlorate: $Ni(ClO_4)_2$ solution was prepared and estimated as described earlier [27–30]. Doubly distilled CO_2 free water (H_2O) with specific conductance equal to ($1.81 \pm 0.1\ \Lambda^{-1}\ cm^{-1}$) was used for the preparation of all solutions. Further, 2,2-diphenyl-1-picryl-hydrazyl (DPPH: $C_{18}H_{12}N_5O_6$) and ascorbic acid (AA: $C_6H_8O_6$) were purchased from Sigma Aldrich. DNA was purchased from Genie (Bangalore, India). Agarose (molecular biology grade: $C_{24}H_{38}O_{19}$) and ethidium bromide (EB: $C_{21}H_{20}BrN_3$) were obtained from Sigma (USA). The structure of primary and secondary ligands is given in Fig. 1.

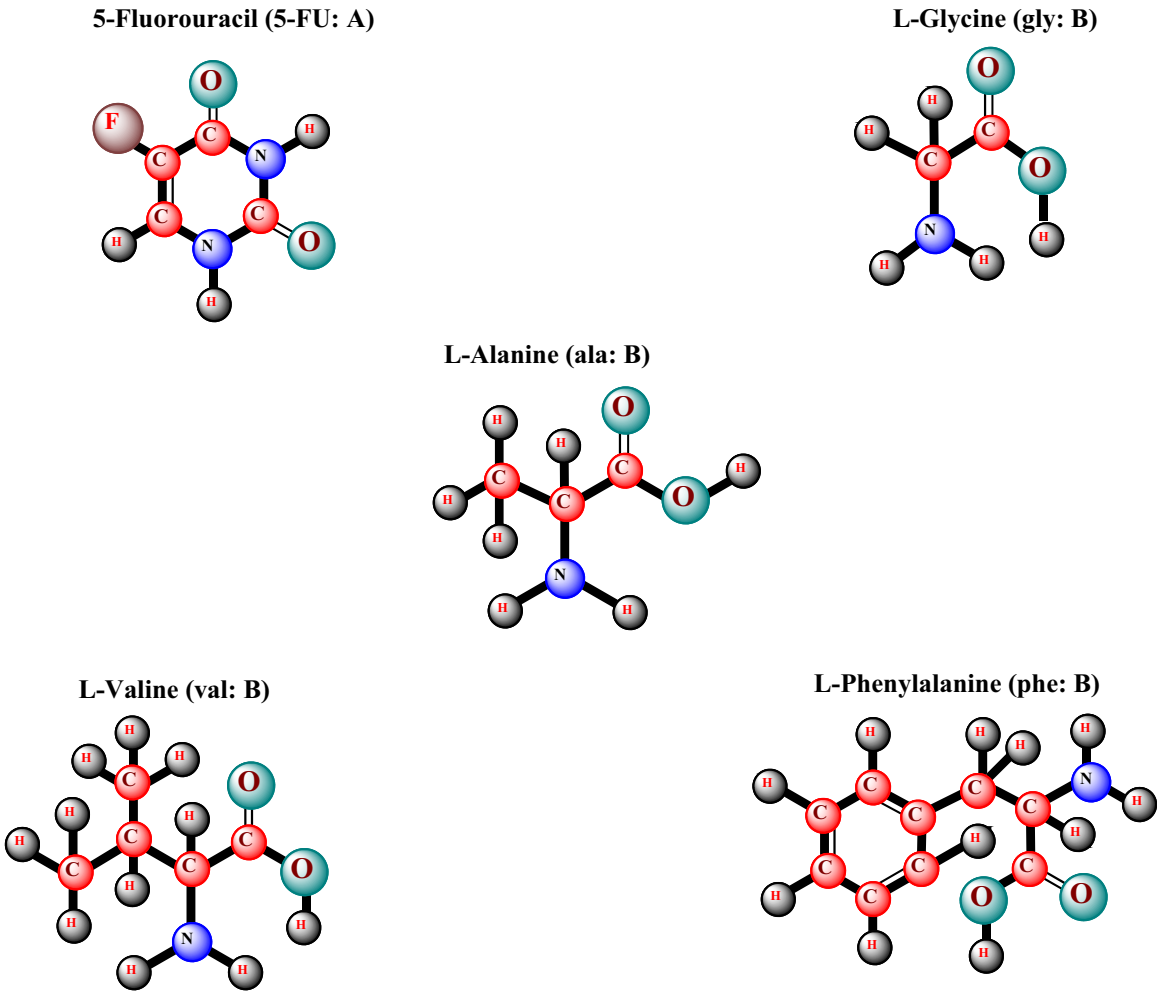

Fig. 1. Structure of primary(A) and secondary(B) ligands.