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Structural and thermal studies of a 5-fluorouracil complex of copper

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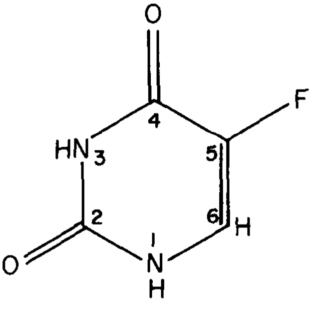
Abstract

A green compound of 5-fluorouracil with copper has been prepared in aqueous alkaline solution. The metal complex (characterised by elemental analyses, and vibrational and electronic spectra) has the molecular formula $Cu(C_4H_2O_2N_2F)(OH)(H_2O)_2$ and has a polymeric octahedral structure. The thermal behaviour of this complex has been studied by thermogravimetry and differential thermal analyses. The copper complex decomposes to give a compound of empirical formula $CuO \cdot H_2O$.

INTRODUCTION

5-Fluorouracil is a water soluble, fluoronated pyrimidine which has many applications in the treatment of human malignancies [1].



Structure 1. 5-Fluorouracil ($C_4H_3O_2N_2F$).

5-Flourouracil (Structure 1) is structurally similar to thymine and is thus readily inserted into DNA, in place of thymine, during replication. This can cause transition mutations and ultimately "thymineless death" of the cancerous cell.

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Some mutagenic agents show increased performance when administered as metal complexes [2]. In some particular instances, divalent copper ions when complexed with anti-cancer agents provide an additional mechanism with regard to anti-inflammatory properties [3]. The metal–ligand bonding sites may be of importance when considering the mechanism of action.

This paper describes an investigation into a green copper–5-fluorouracil complex which was prepared from aqueous alkaline solution. Spectral studies have been used to characterise the copper complex and to interpret the type of co-ordination which takes place to the copper ion. In addition, results obtained from the thermal analysis studies of 5-fluorouracil and the copper complex are reported.

EXPERIMENTAL

Preparation of the copper complex

1 mmol of 5-fluorouracil was dissolved in the minimum volume of water by heating. A solution containing 1 mmol of hydrated copper hydrate in water was then added to the hot solution. The resultant solution was reduced to half the original volume by evaporation. The green copper complex was precipitated by adding NaOH to bring the pH of the solution within the 6–7 range. The precipitate was filtered, washed several times with water and finally with ether, before drying in an oven at 60°C.

Apparatus and measurements

The concentration of the metal ion was obtained using a Perkin–Elmer 373 atomic absorption spectrophotometer and the carbon, hydrogen and nitrogen analyses was obtained using a Carlo Erba elemental analyser.

The IR spectra were obtained using KBr discs (4000–600 $\mathrm{cm^{-1}}$) and polyethylene discs (600–200 $\mathrm{cm^{-1}}$) with a Perkin–Elmer IR spectrophotometer model 598.

The electronic spectra were obtained using a Beckmann Acta MIV spectrophotometer as solid diffuse reflectance spectra.

The thermal analysis studies were carried out on a Stanton–Redcroft model STA 1500 thermobalance. The TG and DTA curves were obtained at a heating rate of 10°C $\mathrm{min^{-1}}$. The 20–800°C range was studied.

RESULTS AND DISCUSSION

The elemental analysis for the copper ion, carbon, nitrogen and hydrogen contents of the copper complex are shown in Table 1. The results indicate an empirical formula of $\mathrm{CuC_4H_7N_2O_5F}$.

TABLE 1

Elemental analysis (%) of the copper compound

Compound		Copper	Carbon	Nitrogen	Hydrogen
$Cu(C_4H_7N_2O_5F)$	Theory	25.76	19.48	11.36	2.85
	Found	25.02	19.13	10.62	2.97

A broad band was observed at 14.084 cm^{-1} in the electronic spectrum of the copper complex. This indicates that the copper atoms are in an octahedral environment [4] and corresponds to the d–d transition $^2E_g(D) \rightarrow {}^2T_{2g}(D)$.

Some characteristic IR data of 5-flourouracil and the copper complex are presented in Table 2. Several absorption bands are observed in the region 3500–3000 cm^{-1}. This indicates the presence of hydrogen bonding in the free ligand. In the copper complex, a band at 3400 cm^{-1} shows that water molecules are bonded to copper [5]. This is confirmed by the presence of a $\nu(Cu-O)_{water}$ band. The $N_{(1)}$–H band disappears on complexation, owing to the removal of the proton by sodium hydroxide. The nitrogen atom then bonds to a copper atom. This is confirmed by the presence of a $\nu(Cu-N)$ band in the IR spectrum of the complex [6]. The $N_{(3)}$–H band is unchanged on complexation, indicating that this nitrogen atom is not bonded to a copper atom. Further metal co-ordination is indicated through $C_{(4)}$=O, as $\nu(C_{(4)}=O)$ moves to a lower wavenumber on complexation [7]. A $\nu(Cu-O)$ band is also detected. $C_{(2)}$=O is not

TABLE 2

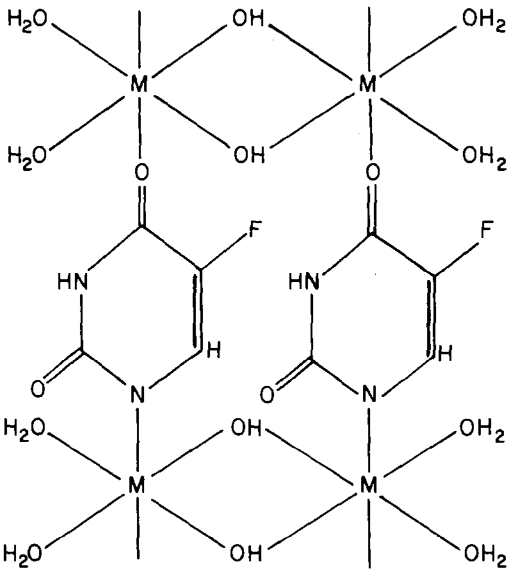
Infrared spectra (4000–200 cm^{-1})[a]

Assignment	Compound	
	5-Fluorouracil	Copper complex
Hydrogen bonding	3500–3000	–
$\nu(O-H)_{water}$	–	3400(w)
$\nu(Cu-O)_{water}$	–	308(w)
$\nu(N-H)$	3130(m)	3020(w)
$\delta(N_{(1)}-H)$	1499(m)	–
$\delta(N_{(3)}-H)$	1429(sh)	1430(m)
$\nu(Cu-N_{(1)})$	–	250(m)
$\nu(C_{(4)}=O)$	1660(s)	1575(s)
$\nu(C_{(2)}=O)$	1725(s)	1725(s)
$\nu(Cu-O)$	–	278(w)
(OH) bridging	–	920(m)

[a] Key: (s) = strong; (m) = medium; (w) = weak; (sh) = shoulder. ν = stretching; δ = bending.

involved in bonding as $\nu(C_{(2)}{=}O)$ shows no change in wavenumber on complexation. A band at 920 cm^{-1} in the complex indicates the presence of bridging OH groups [8].

The poor solubility of the copper complex in polar and non-polar solvents indicates that it has a polymeric structure. From spectral data it is deduced that bridging occurs through OH groups as well as through $N_{(1)}$–H and $C_{(4)}{=}O$ groups of 5-fluorouracil as shown in Structure 2. The molecular formula for the complex is $Cu(C_4H_2N_2O_2F)(OH)(H_2O)_2$.



Structure 2. $Cu(C_4H_2N_2O_2F)(OH)(H_2O)_2$.

The TG and DTA traces for 5-fluorouracil, Fig. 1, show that it is thermally stable in the range 20–240°C. Its pyrolytic decomposition starts

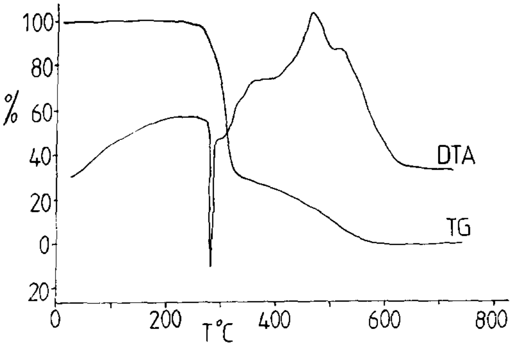


Fig. 1. TG and DTA traces for 5-fluourouracil.

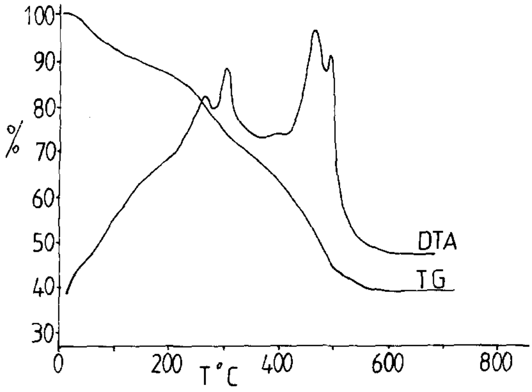


Fig. 2. TG and DTA traces for the copper complex with 5-flourouracil.

at 240°C and finishes at 618°C with the total elimination of the sample. The DTA trace of 5-fluorouracil shows an endothermic peak at 281°C corresponding to fusion. Liquid 4-fluorouracil decomposes immediately, resulting in an exothermic peak. The TG and DTA traces for the copper complex, Fig. 2, show that it undergoes exothermic reactions to give a compound of empirical formula $CuO \cdot H_2O$ (calculated, 39.7%; found, 38.8%).

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