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Thermal decomposition processes of Boc-*p*-fluoro-phenylalanine, Boc-*p*-iodo-phenylalanine and complex of *p*-iodo-phenylalanine and copper

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Abstract

The thermal decomposition process of non-natural amino acid *tert*-butoxycarbonyl-*p*-fluoro-phenylalanine ($FC_6H_4CH_2CH[NHCOOC(CH_3)_3]COOH$, the so-called Boc-*p*-fluoro-phenylalanine) is slightly different from that of its iodo analogue ($IC_6H_4CH_2CH[NHCOOC(CH_3)_3]COOH$, Boc-*p*-iodo-phenylalanine) The dehydration reaction of the two non-natural amino acids is intramolecular, but not intermolecular. The complex of copper has been prepared through a solid–liquid reaction between the powder of Boc-*p*-iodo-phenylalanine and the aqueous solution of copper nitrate. The chemical and thermal analysis and the infrared spectra show that the new compound is the complex of *p*-iodo-phenylalanine and copper with crystal water $[Cu(IC_6H_4CH_2CHNH_2COO)_2]\cdot 0.5H_2O$. The iodine atom in the organic ligand may also be coordinated directly to the copper ion in crystals of the new complex.

Keywords: Non-natural amino acids; Complex of copper; Solid–liquid reaction; Thermal decomposition; Infrared spectra

1. Introduction

The number of non-natural amino acids is now more than that of natural amino acids. A lot of non-natural amino acids and complexes of non-natural amino acids with metal ions have been used in many fields such as medicine and biochemistry [1–5]. Therefore, the synthesis of new non-natural amino acids, and the complexes of non-natural amino acids with various metal ions, especially the essential metal ions for life, and the investigation of their physical or chemical properties such as thermal stability is important. The *tert*-butoxycarbonyl-*p*-halo-phenylalanine (the so-called Boc-*p*-halo-phenylalanine, $XC_6H_4CH_2CH[NHCOOC(CH_3)_3]COOH$) is a non-natural amino acid. As Fig. 1(a) shows, Boc-*p*-halo-phenylalanine has both a free carboxyl group and an ester which is similar to a urethane [6]. Because of rather low solubility of Boc-*p*-iodo-phenylalanine in water, its complex cannot be synthesized by a conventional method, hence, we have attempted to synthesize the complex of Boc-*p*-iodo-phenylalanine with copper by a solid–liquid reaction. The results of thermal analysis of the two non-natural amino acids and the synthesis, thermal decomposition and infrared spectra of the new complex are reported.

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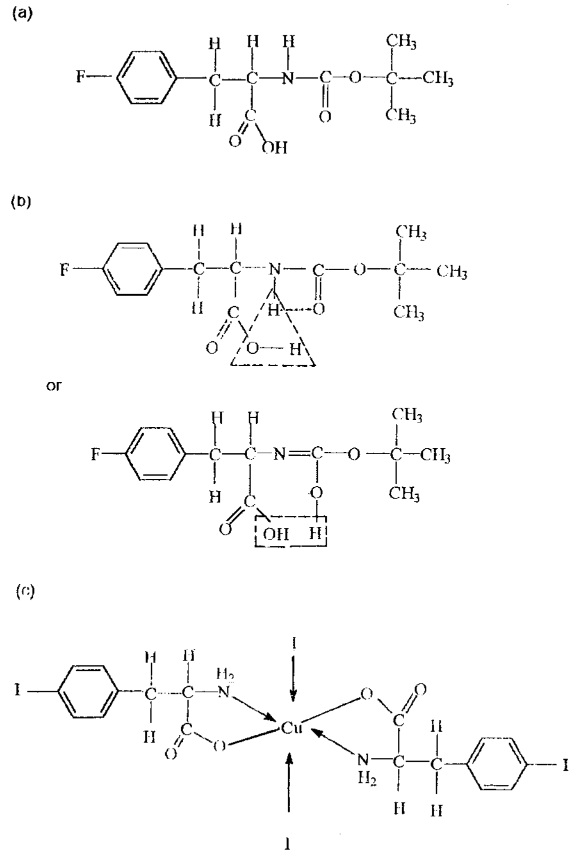

Fig. 1. Molecular structures of Boc-*p*-fluoro-phenylalanine, intramolecular hydrogen bond and coordination structure of complex of *p*-iodo-phenylalanine with Cu: (a) structure of Boc-*p*-fluoro-phenylalanine molecule; (b) intramolecular hydrogen bond; (c) coordination structure of complex.

Table 1
Results of elemental analysis of the product

Element	Cu	C	H	N	O	I
Calculated (%)	9.74	33.12	2.93	4.29	11.03	38.88
Found (%)	9.92	33.03	2.72	4.42	–	–

2. Experimental

All the chemicals used in the synthesis experiments were of analytical reagent grade. Boc-*p*-fluoro-phenylalanine and Boc-*p*-iodo-phenylalanine were dextrotatory stereoisomers from Shanghai ACI Biotech. First, a 0.1 M aqueous solution of copper nitrate was prepared. Then, the white powder of Boc-*p*-iodo-phenylalanine was added to the solution of copper nitrate, when the colour of the solid surface changed to blue indicating that a reaction had occurred. During the reaction the lumps of powder were broken up with a glass rod. The solid–liquid reaction was conducted at room temperature and the holding time was about 5 days. The product was washed repeatedly with the distilled water and collected by filtration. Finally, the product was dried in a vacuum desiccator over phosphorus pentoxide for about a week. The product was a light blue crystalline compound.

The content of C, H and N in the product was determined by an elemental analyzer and that of Cu by EDTA titration. The results are shown in Table 1.

Thermal studies were done with an LCT-1 differential thermal balance in air, with a heating rate of 10°C min^{-1}. The reference was α-Al_2O_3. The sample mass was 11.90 mg for Boc-*p*-fluoro-phenylalanine, 11.60 mg for Boc-*p*-iodo-phenylalanine and 9.02 mg for the complex. The thermogravimetric and differential thermal analysis curves are shown in Fig. 2. The data and the possible thermal decomposition reactions are summarized in Table 2.

The infrared spectra of Boc-*p*-iodo-phenylalanine and the complex in the range of 2000–4000 cm^{-1} were recorded by an FT infrared spectrometer and KBr-disc method. The infrared spectra are shown in Fig. 3.

3. Results and discussion

The first weight loss of Boc-*p*-fluoro-phenylalanine in Fig. 2(a) is observed at about 140°C. This is attributable to dehydration of the molecule and corresponds to a small endothermic peak in differential analysis curve. The weight loss shows the loss of one molecule of water per molecule of starting material indicating an intramolecular dehydration, not an intermolecular dehydration as in many common amino acids. As Fig. 1(b) shows, the dehydration reaction may occur more easily in the region of an intermolecular hydrogen bond. Evidence, for an intramolecular hydrogen bond can be observed in the infrared spectrum.

The second weight loss corresponds to the elimination of the fluorine atom. The differential analysis

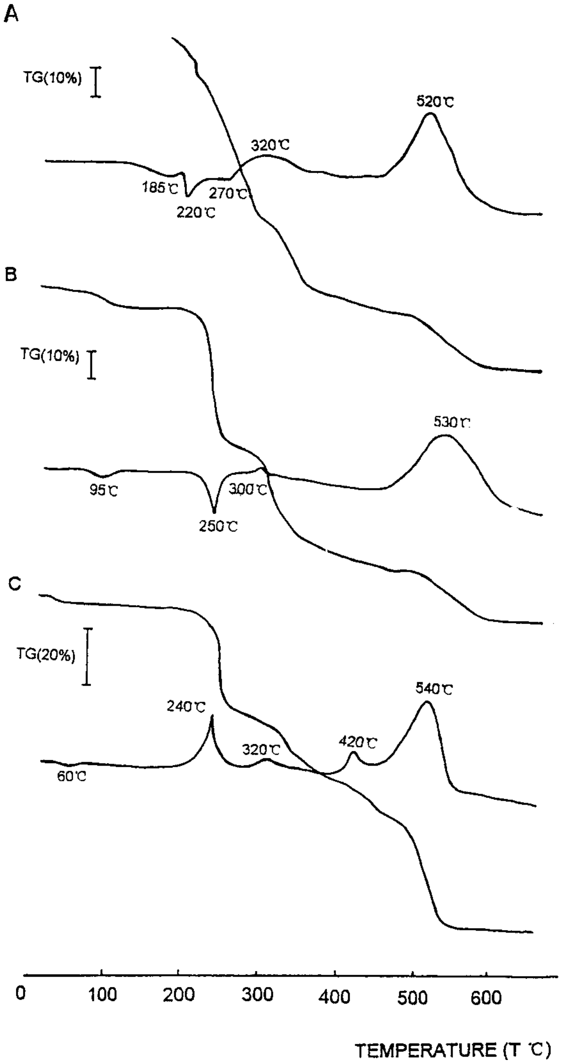

Fig. 2. The thermogravimetric and differential thermal analysis curves of Boc-*p*-fluoro-phenylalanine, Boc-*p*-iodo-phenylalanine and the complex of *p*-iodo-phenylalanine and copper: (a) Boc-*p*-fluoro-phenylalanine; (b) Boc-*p*-iodo-phenylalanine; (c) complex of *p*-iodo-phenylalanine and copper.

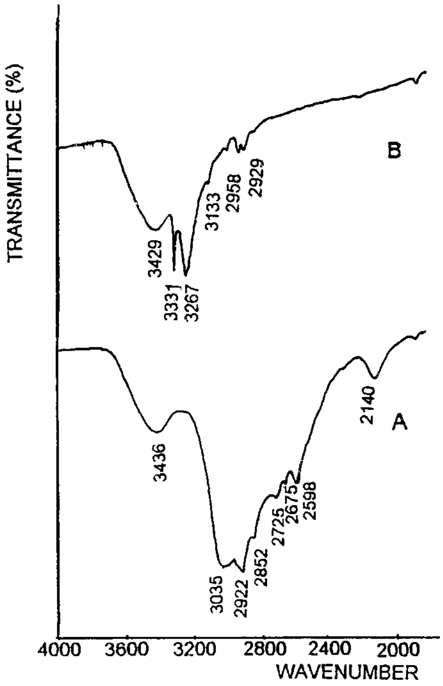

Fig. 3. The infrared spectra of Boc-*p*-iodo-phenylalanine and the complex of *p*-iodo-phenylalanine and copper ion: (a) Boc-*p*-iodo-phenylalanine; (b) complex of *p*-iodo-phenylalanine and copper.

curve also shows the endothermic reaction in this step, because the cleavage of the bond between the F and C atom is endothermic.

At about 270°C, the thermogravimetric curve shows a larger weight loss. This may be due to the pyrolytic elimination of carbonyl group and benzyl group, very similar to Hofmann degradation [6]. The α-C atom in amino acid bonds not only with the C atom in methylene from benzyl group, but also with the N atom in amide and the C atom in carboxylic group. The bond between the α-C atom and the C atom in methylene of benzyl group or the C atom in carboxylic group will become weaker due to an adjacent inductive effect. This will make the pyrolytic elimination of the benzyl and carbonyl group from the molecule to occur more easily. The percentage weight loss is close to the expected one. The elimination reaction is indicated by an endothermic peak in the differential analysis curve.

Next, an exothermic peak (about 320°C) appears in the differential analysis curve and the most possible reaction is the oxidation and pyrolytic elimination of OCN group. The calculated percentage weight loss is slightly smaller than the experimental one.

Over about 350°C, a wide endothermic peak can be observed in differential analysis curve. It is attributable to the pyrolytic elimination of methoxy group (OCH_3).

Table 2
Thermal decomposition results for Boc-*p*-fluoro-phenylalanine, Boc-*p*-iodo-phenylalanine and complex of *p*-iodo-phenylalanine and copper

Reaction	Peak in DTA (°C)	Weight loss (%) in TG	
		$W_{\mathrm{experimental}}$	$W_{\mathrm{theoretical}}$
Boc-*p*-fluoro-phenylalanine			
$FC_6H_4CH_2CH[NHCOOC(CH_3)_3]COOH$			
↓ $-H_2O$	185 Endo	6.7	6.4
$FC_6H_4CH_2CHCOONCOC(CH_3)_3$			
↓ $-F$	220 Endo	6.7	6.7
$–C_6H_4CH_2CHCOONCOC(CH_3)_3$			
↓ $-C_6H_4$, CHCO	270 Endo	40.5	41.3
$–CH_2ONCOC(CH_3)_3$			
↓ $-NCO$	320 Exo	15.8	14.8
$–CH_2OC(CH_3)_3$			
↓ $-CH_2O$	– Endo	11.8	10.6
$–C(CH_3)_3$			
↓	520 Exo	18.6	20.1
CO_2+H_2O			
Boc-*p*-iodo-phenylalanine			
$IC_6H_4CH_2CH[NHCOOC(CH_3)_3]COOH$			
↓ $-H_2O$	95 Endo	4.3	4.6
$IC_6H_4CH_2CHCOONCOC(CH_3)_3$			
↓ $-I$, CO	250 Endo	40.0	39.6
$–C_6H_4CH_2CHONCOC(CH_3)_3$			
↓ $-C_6H_4$, CHONC	300 Exo	33.6	33.5
$–CH_2OC(CH_3)_3$			
↓ $-CH_2O$	– Endo	7.7	7.7
$–C(CH_3)_3$			
↓	530 Exo	14.6	14.6
$CO_2 + H_2O$			
Complex of *p*-iodo-phenylalanine and copper[a]			
$Cu(IC_6H_4CH_2CHNH_2COO)_2{\cdot}0.5H_2O$			
↓ $-0.5H_2O$	50 Endo	1.3	1.4
$Cu(IC_6H_4CH_2CHNH_2COO)_2$			
↓ $-C_6H_4$	240 Exo	24.2	23.3
$Cu(ICH_2CHNH_2COO)_2$			
↓ −d.p.	320 Exo	6.6	5.2
$Cu(ICH_2CHNHCO)_2$			
↓ −d.p.	420 Exo	15.7	16.8
$Cu(OI)_2$			
↓ −d.p.	540 Exo	39.4	41.3
CuO			

[a] d.p. is the thermal decomposition product.

Finally, the residue will be oxidized or burned up at about 500°C, hence, there is a very large exothermic peak in differential analysis curve.

The thermogravimetric and differential thermal analysis curve of Boc-*p*-iodo-phenylalanine is slightly different from that of Boc-*p*-fluoro-phenylalanine below 350°C.

The first weight loss of Boc-*p*-iodo-phenylalanine at about 80°C is also from the intramolecular dehydration. We cannot explain why the dehydration temperature of Boc-*p*-iodo-phenylalanine is much lower than that of Boc-fluoro-phenylalanine.

Next, there is a weight loss at about 250°C and an endothermic peak in differential analysis curve is attributable to the elimination of iodine atom and decarboxylation of the amino acid.

At about 300°C, the sample loses the benzyl group and the OCN group as indicated by the percentage weight loss.

When the temperature is higher than 350°C, the thermal decomposition process of Boc-*p*-iodo-phenylalanine is very similar to that of Boc-*p*-fluoro-phenylalanine.

From the results of elemental analyzes in Table 1, one can determine that the composition of the complex obtained by a solid–liquid reaction is $CuC_{18}H_{19}N_2O_{4.5}I_2$. This means that the complex is not that of Boc-*p*-iodo-phenylalanine with copper. The most likely formula is $[Cu(IC_6H_4CH_2CHNH_2COO)_2]\cdot 0.5H_2O$ in agreement with the experimentally determined contents of C, H and N and Cu and the infrared spectra.

As Fig. 2(c) shows, the thermal decomposition process of the new complex is quite different from that of Boc-*p*-iodo-phenylalanine. First, there is a dehydration process of the complex at about 50°C corresponding to loss of half a molecule of crystal water. The lower dehydration temperature could indicate that the water molecule is not in the inner coordination sphere of the Cu ion, but an interstitial one.

Next the complex loses the phenyl group from the organic ligand at about 240°C as indicated by the percentage weight loss (24.2%) and the corresponding exothermic peak in the differential analysis curve. In contrast to the original amino acid, the copper complex does not lose iodine at this stage (a large weight loss and an endothermic peak would be expected for this). It is suggested that the iodine is not lost at this stage because, as Fig. 1(c) shows, the iodine atom is coordinated to the Cu ion of a neighboring molecule in the crystal. Due to the formation of coordination bond between the iodine and the Cu ion, the bond between the iodine and the C atom of benzene ring becomes weaker, resulting in the phenyl groups being eliminated more easily than the iodine.

At about 320°C, the degradation reaction may occur in the region of carboxylic and amino group in the complex, consequently, the amide can be formed after loss of an O atom and a H atom, very similar to Hofmann rearrangement.

At about 400°C, the amide and another organic group will be oxidized and lost, together, and copper oxoiodate will be formed. This is an exothermic reaction and corresponds to an exothermic peak in the differential analysis curve.

Over 500°C, the copper oxoiodate will lose two iodine atoms and an oxygen atom, consequently becoming copper(II) oxide.

At temperatures higher than 550°C, the weight of the residue remains constant. The experimental percentage weight of the residue was 12.7% and the theoretical percentage weight of CuO in the copper complex of *p*-iodo-phenylalanine with half a crystal water is 12.2%. CuO is very stable below 1000°C [7].

Fig. 3 shows that the infrared spectrum of the complex is appreciably different from that of Boc-*p*-iodo-phenylalanine in the range of 2000–4000 cm^{-1}. Comparison of spectra gives evidence for the formation of coordination bonds between the organic ligand and Cu ion. There are the carboxylic group, *sec* amide group, methyl group and an intramolecular hydrogen bond in Boc-*p*-iodo-phenylalanine. Generally, there are several characteristic absorption bands with a weaker intensity in the range 3000–2500 cm^{-1} of infrared spectra of aliphatic carboxyl acid [8]. So, we can assign the weaker absorption bands at 2725, 2675 and 2598 cm^{-1} in the infrared spectrum of Boc *p*-iodo-phenylalanine to the characteristic ones from carboxylic group. The absorption band at 3050 cm^{-1} may be the first overtone band (at 3070 cm^{-1}) from bending vibration of the N–H bond in *sec* amide [8]. The frequencies of asymmetric and symmetric stretching vibrations of the C–H bond in methyl group are expected at 2970 and 2870 cm^{-1}, respectively [8]. Hence, the absorption bands at 2922 and 2832 cm^{-1} may be from the asymmetric and symmetric stretching vibration of the C–H bond in methyl groups, but, the positions of the two absorption bands shift slightly to the lower frequency region due to inductive effect from adjacent O atom and amide group. The absorption band at 3436 cm^{-1} may be from the stretching vibration of the O–H bond with an intramolecular hydrogen bond [8]. The above absorption bands, except that (at 3436 cm^{-1}), disappear in the infrared spectrum of the complex. This indicates that there is no free carboxyl acid, no *sec* amide group, and no methyl group in the complex. Absorption bands at 3331 and 3267 cm^{-1} appear in the infrared spectrum of complex, which are characteristic of the stretching vibrations of the N–H bond in complexes of amino acid and metal ion (for example, there are two such absorption bands at 3320 and 3260 cm^{-1} in the infrared spectrum of the complex of glycine and Cu) [9]. Thus, we can assign the absorption band at 3331 cm^{-1} to the asymmetric stretching vibration (ν_{as}) of the N–H bond and that at 3267 cm^{-1} to the symmetric stretching vibration (ν_s) of the N–H bond in amino group of the new complex. The relationship between the frequencies of the symmetric and asymmetric stretching vibration of the N–H bond in amino group has been suggested as $\nu_s = 345.5 + 0.876\nu_{as}$ [10]. If ν_{as} is 3331 cm^{-1}, the calculated ν_s by this formula will be 3263 cm^{-1} which is very close to the experimentally determined ν_s (3267 cm^{-1}). This demonstrates the assignments for the two absorption bands. The fact that the characteristic absorption bands of the various stretching vibrations of free carboxyl acid, *sec* amide and methyl group disappear in the infrared spectrum of the new complex is consistent with the formation of a complex of amino acid and Cu. We have noted that there also is an absorption band at 3429 cm^{-1} in the infrared spectrum of the complex. In the crystal of the complex of glycine and Ni with crystal water, only one of the two O atoms from carboxyl group is coordinated directly to the Ni ion and another O atom takes part in the formation of intermolecular hydrogen bond with the H atom from crystal water [9]. There may be a similar coordination structure in the crystal of copper complex of *p*-iodo-phenylalanine. So, the absorption band at 3429 cm^{-1} in the Infrared spectrum of complex may be attributed to the existence of crystal water. The strength of O–H bond stretching vibration in the molecule with intermolecular hydrogen bond may be slightly different from that in the molecule with intramolecular hydrogen bond, hence, the position of the absorption band (3429 cm^{-1}) in the infrared spectrum of the complex will be slightly different from that (3436 cm^{-1}) in the infrared spectrum of Boc-*p*-iodo-phenylalanine. Thus, the infrared spectra gives evidence for the formation of coordination bond between the organic ligand and the Cu ion and for the existence of hydrogen bond in the new complex.

The fact that the compound obtained by a solid–liquid reaction is the complex of *p*-iodo-phenylalanine with Cu, but not that of Boc-*p*-iodo-phenylalanine with Cu, indicates that Boc-*p*-iodo-phenylalanine has been hydrolyzed during in the reaction, losing a *tert*-butyl formate group $(CH_3)_3COOC$– and becoming *p*-iodo-phenylalanine.

4. Conclusions

The thermal decomposition process of Boc-*p*-iodo-phenylalanine is slightly different from that of Boc-*p*-fluoro-phenylalanine below 340°C. The dehydration reaction in this kind of non-natural amino acids is intramolecular. The compound obtained through a solid–liquid reaction between the solid powder of Boc-*p*-iodo-phenylalanine and the aqueous solution of copper nitrate is the complex of *p*-iodo-phenylalanine and Cu with crystal water and the formula is $Cu(IC_6H_4CH_2CHNH_2COO)_2 \cdot 0.5H_2O$. The thermal decomposition process of the complex is considerably different from that of Boc-*p*-iodo-phenylalanine. The iodine atom may be coordinated directly to the Cu ion in the lattice.

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