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Chromium(III) complexes of Asparagine preparation and exploration of its viability as supplement for chromium deficiency in humans.

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Abstract: Chromium (III) is biologically active ingredient found in food and known to enhance the efficiency of insulin which in turn controls the blood sugar and depression in natural health. Chromium deficiency in humans is rare which contribute to the development of diabetes and metabolic syndrome and even mild deficiency can produce problems in blood sugar metabolism leading to other symptoms such as anxiety or fatigue. Adequate dietary chromium helps to maintain insulin sensitivity which can be obtained from different sources of food or commercially available supplements such as chromium picolinate and chromium polynicotinate. In the present paper, the preparation and characterization of products formed by the interaction of chromium(VI) as oxidant with asparagine and exploring their viability as chromium supplement is being reported.

Key words: Chromium deficiency ,Diabetes, Chromium(III)-Asparagine comlexes Ditertiary butyl chromate, Supplement, Chromium(VI) oxidant, Microwave.

INTRODUCTION

Asparagine has the credit of being the first amino acid to be isolated. It was isolated from asparagus in 1806 by French chemist Louis Nicolas Vauquelin and Pierre Jean Robiquet[1]. It is a non-essential amino acid which may be enzymatically synthesized in the body from the precursor oxaloacetate.

On the other hand, chromium (III) is known to enhance the action of insulin, a hormone critical to metabolism and storage of carbohydrate, fat and protein in body[2]. Diets rich in sugar can increase chromium excretion in the urine[3]. Infection, acute exercise, pregnancy lactation & stressful status increases chromium losses and can lead to deficiency[4]. This deficiency can be made up by taking it from food source, but most of the food provide only small amount (less than 2 microgram) of chromium. Few supplements to cure chromium deficiency available in the market are chromium picolinate, chromium polynicotinate[5] etc.

In the present work, we have taken asparagine as organic substrate in water as solvent to be treated with ditertiary butyl chromate in order to prepare some variant of chromium (III) which can function as supplement for chromium defiency. Ditertiary butyl chromate[6] is one of the best option as chromium(VI) based oxidants among the large number of variants available like dipyridine chromium (VI) oxide[7], chromium trioxide 3,5-dimethyl pyrozole complex[8], pyridinium fluoro chromate[9], benzylmethyl ammonium flurochromate[10], etc. due to its docility, versatility and efficiency. A large number of papers have come up dealing with the oxidation of organic substrates by ditertiary butyl chromate[11,12] under ordinary stirring and heating conditions. However, the increasing

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use of microwave as energy source has prompted not only its application in the organic synthetic work, but the revision of the old methods too. This is in accordance with the principles of clean and green chemistry[13]. The preparation of asparagine variant of chromium (III) as reported in the paper is a part of project undertaken by the authors with the caption "*preparation and characterization of complexes of chromium with biologically active organic ligands*" under which a large number of products of amino acids and carbohydrates have been prepared[14] by microwave irradiation.

MATERIAL & METHODS

The chemicals were all A.R grade. Freshly prepared solutions were used. The experimental method used in the present work consists of mainly

(i) Preparation of Ditertiary butyl chromate : The oxidant was prepared by dissolving accurately weighed amount of dry and powdered chromium trioxide in calculated volume of tertiary butyl alcohol at room temperature. Care was taken to avoid bigger pieces of CrO3 as this may cause explosive reaction leading to fire.

(ii) Preparation of solution of Asparagine: Accurately weighed amounts of pure asparagine required for a particular substrate : oxidant molar ratio were dissolved in 50 ml of water. The substrate: oxidant molar ratio which led to positive results were 1:2, 2:3, 1:1, 2:1 and 3:1. For 1:2 molar ratio the weight of Asparagine and CrO3 were 1.5 gm and 2 gm respectively. Similarly, other solutions were made with the calculated quantity of asparagine and chromium trioxide.

(iii) Reaction between Asparagine solution & oxidant: The two solutions as prepared in (i) and (ii) were mixed carefully and stirred on a mechanical stirrer for several minutes before subjecting to microwave irradiation. The wattage, period of irradiating and standing for different substrate:oxidant ratios are tabulated in **table-1**. The solid products of different colours and compositions were obtained which were washed several times with acetone to remove any impurities and collected in air tight bottles as samples AS-12, AS-23, AS-11, AS-21 and AS-31

(iv) Characterization of the products: The products were characterized by elemental analysis by "Elemental analyser- Heraeus Vario EL III Carlo Erba 1108", FTIR curves obtained by "Fourier Transform Infrared Spectrometer – Shimadzu 8201 PC" and DTA-TGA thermogravimetric mass loss pattern. The solubility of the products in different solvents was also tested.

RESULTS & DISCUSSION

The reaction conditions in **table-1** show that the formation of compounds/complexes of chromium with asparagine is very difficult. The same is observed in cases of other amino acids too, as explored by the authors of this paper[14] and others[15]. However, enzymatically asparagine is oxidised to asparatic acid in presence of asparaginase and then into oxaloacetic acid which is an important member of citric acid cycle. Asparagine is also a precursor to acrylamide when carbohydrate containing food stuff is fried in presence of reducing sugar[16,17].The chemical oxidation of asparagine under microwave condition leads to different products including nitro derivatives also as mentioned in **table-2**.The degradative oxidation of the substrate takes place when the ratio of oxidant is more as substantiated by the presence of smaller fragments in case of AS-12 and AS-23. The formation of ammonia in higher ratio of oxidant is supported by its presence in AS-12 and AS-23 as ligand[15]. This is not observed in other cases where the extent of oxidation is less. The extent of degradative oxidation increases as the proportion of oxidant is raised. This is also supported by the observation that unoxidised asparagine is associated with AS-11, AS-21 and AS-31 whereas highly oxidised fragment HCOOH is present in AS-12 where the ratio of oxidant is more. Again, the solubility of the products in water is more in those cases when asparagine itself is present as ligands. The number of water molecules in the products AS-12 and AS-23 is more whereas it is less in products AS-11, AS-21 and AS-31. This may be due to the fact that greater extent of oxidation leads to the formation of smaller organic moiety and greater number of water molecules.

The strikingly different colour of AS-31 along with its greater solubility in water and presence of only amino acids and water as ligands makes it much different from other products. The presence of amino acids in the form of ion is not a remote possibility and thus the assumption that one carboxylic group is present as carboxylate ion supports the plus three state of chromium in the sample. On the basis of above facts, we can very well consider the potentiality of AS-31 as food supplement for chromium deficiency if it clears the sorption[18] and other biological tests.

Table-1 (Reaction Conditions)

Sample Code	Solvent	S:O ratio	Stirring	Irradiation	Left
AS-12	Water	1:2	10 min	1 min (180W) + 4 min (450 W)	42 days
AS-23	Water	2:3	15 min	4 min (450 W)	42 days
AS-11	Water	1:1	50 min	2 min (180W) + 3 min (270W) + 10 min (360W) + 10 min (450W)	45 days
AS-21	Water	2:1	57 min	3 min (180W) + 2 min (270W) + 8 min (360W) + 6 min (450W)	30 days
AS-31	Water	3:1	70 min	5 min (270W) + 20 min (360W) + 4 min (450W) + 4 min (540W)	45 days

Table-2 (Product Characterisation)

Sample Code	Colour	Solubility in water	Empirical Formula	Formulation
AS-12	Deep brown	Partially soluble	$C_{10}H_{27}O_{30}N_4Cr_2$	$Cr_2O_3.3HOOC.CH.NO_2COOH.HCOOH.NH_3.7H_2O$ ($C_{10}H_{28}O_{30}N_4Cr_2$)
AS-23	Brown	Partially soluble	$C_{10}H_{28}O_{26}N_4Cr_2$	$Cr_2O_3.HOOCCH_2CH.NH_2COOH.2(COOH.CH.NO_2.COOH).NH_3.7H_2O.$ ($C_{10}H_{30}O_{26}N_4Cr_2$)
AS-11	Brown	Soluble	$C_6H_{16}O_{11}N_3Cr$	$CrO_2.H_2N.CO.CH_2.CH.NH_2.COOH.NO_2CH_2COOH.2H_2O.$ ($C_6H_{15}O_{11}N_3Cr$)
AS-21	Light brown	Soluble	$C_{11}H_{26}O_{14}N_5Cr$	$CrO_2.2H_2NCOCH_2CHNH_2COOH.CH_3CHNO_2COOH.2H_2O$ ($C_{11}H_{25}O_{14}N_5Cr$)
AS-31	Mustard yellow	Soluble	$C_{13}H_{37}O_{15}N_6Cr$	$CrO.2H_2NCOCH_2CHNH_2COOH.COOHCHNH_2COOH.NH_2CH_2COOH.2H_2O$ ($C_{13}H_{30}O_{15}N_6Cr$)

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