

## Fe(III) complexes of D-glucose and D-fructose\*

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**Fe(III)–saccharide complexes of D-glucose and D-fructose have been synthesized from methanol using stoichiometric quantities of sodium salts of the corresponding saccharides. Both the compounds were isolated in the solid state and characterized by various analytical, spectroscopic, magnetic and cyclic voltammetric methods. Both the complexes were found to be stable, in solution, in the pH range 2.5–12.0.**

**Keywords:** complexes, Fe(III), fructose, glucose

### Introduction

Iron–saccharide chemistry is important not only because of its possible involvement in nutritional supplementation studies but also to understand the basic interactions present between iron and saccharides. The formation and stability of several complexes of saccharides and related ligands have been reported in the literature (Charley *et al.* 1963, Saltman 1965, Burger *et al.* 1983, Gorman & Clydesdale 1983, Galdi & Valencia, 1988, Xu & Jordan 1990, Rao *et al.* 1992). Several solution studies performed in making iron complexes of saccharides and other related molecules were hampered due to the formation of polymeric and colloidal materials (Traube & Kuhbier 1932, Bourne *et al.* 1959, Rich *et al.* 1991). In spite of this, there are several reports mentioned in the literature regarding the complex formation between Fe(III) and saccharides, particularly where the reactions were performed in aqueous basic solutions possessing a large excess of saccharides (Charley *et al.* 1963, Davis & Deller 1966, Barker *et al.* 1974, Wolowice & Drabent 1985, Nagy *et al.* 1986, 1989) and other related molecules (Pecsok & Sandera 1955, Dolezal & Langmyhr 1972, Tonkovic *et al.* 1982, 1983, van Duin *et al.* 1989). Structural understanding of these complexes needs further attention. To date crystal-

lographically known saccharide complexes are those of *N*-glycosidic sugars of nickel and molybdenum reported by Yano's group from Japan (Yano 1988). In a systematic study of the understanding of possible interactions between saccharides and transition metals, we have recently synthesized and isolated various soluble, low molecular weight complexes of several early first low transition elements with different monosaccharides (Rao *et al.* 1990, Rao & Kaiwar 1991, 1992, 1993, Kaiwar & Rao 1992). In the present paper we report the synthesis, isolation and characterization of complexes of Fe(III) with D-glucose (D-glc) and D-fructose (D-fru).

### Materials and methods

#### Methods

Absorption spectra were measured on a Shimadzu UV260 spectrophotometer in water, methanol (MeOH) and *N,N*-dimethylformamide (*N,N*-DMF). Fourier transform IR (FTIR) spectra of the compounds were measured on a Nicolet spectrometer in KBr. Electron paramagnetic resonance (EPR) spectra of the solid products were recorded on a Varian ESR112 spectrometer where tetracyanoethylene (TCNE) was used as a field marker ( $g = 2.00277$ ). Mössbauer spectra were measured at room temperature where  $^{57}\text{Co}$  served as a gamma source and elemental iron powder as a reference. Magnetic susceptibility measurements of the solid samples were performed in the temperature range 10–300 K. Cyclic voltammetric studies were performed on a BAS100B electrochemical analyzer using a hanging mercury drop electrode (HMDE) in water at various pH values in the potential range 0 to

\*This paper is dedicated to Professor Richard H. Holm on his 60th birthday.

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−1.6 V at a scan speed of 100 mV s<sup>−1</sup> using 0.1 M Me<sub>4</sub>NCl as the supporting electrolyte and Ag/AgCl as the reference electrode. The pH of the solutions was adjusted using appropriate amounts of either HCl or NaOH.

### Synthesis

Saccharide (D-glc or D-fru), 2.7 g (15 mmol) was taken in 50 ml of MeOH and stirred for 10 min. To this, 0.69 g (30 mmol) of sodium metal was added and stirred until all of it was reacted to form a disodium salt. To this sodium salt, a 25 ml methanolic solution containing 0.811 g (5 mmol) of anhydrous ferric chloride was added to give a brownish yellow precipitate. The reaction mixture was further stirred for about 3 h in order to ensure the completion of the reaction. A solid product was obtained by filtering the reaction mixture through a frit funnel and further washing with ether and drying under vacuum. The solid thus obtained was dissolved in a water:methanol mixture of 2:1 (v/v) ratio and reprecipitated with ethanol so as to remove any free saccharide present. This procedure was repeated three times. Further, the product was purified by treating with methanol followed by hexane by stirring the materials in these solvents. These reactions gave product yields of 83.5 and 89.7% based on the metal, respectively, in the case of D-glc and D-fru.

### Analytical data

**Fe(III)–D-glc complex.** Calculated for C<sub>12</sub>H<sub>23</sub>FeNa<sub>2</sub>O<sub>14</sub>: C, 29.23; H, 4.70; Fe, 11.33; Na, 9.32. Found: C, 29.60; H, 4.69; Fe, 11.32; Na, 9.50.

**Fe(III)–D-fru complex.** Calculated for C<sub>24</sub>H<sub>41</sub>Na<sub>3</sub>Fe<sub>2</sub>O<sub>25</sub> · 2H<sub>2</sub>O: C, 30.46; H, 4.79; Fe, 11.80; Na, 7.29. Found: C, 30.19; H, 4.37; Fe, 12.14; Na, 7.64.

### Absorption data

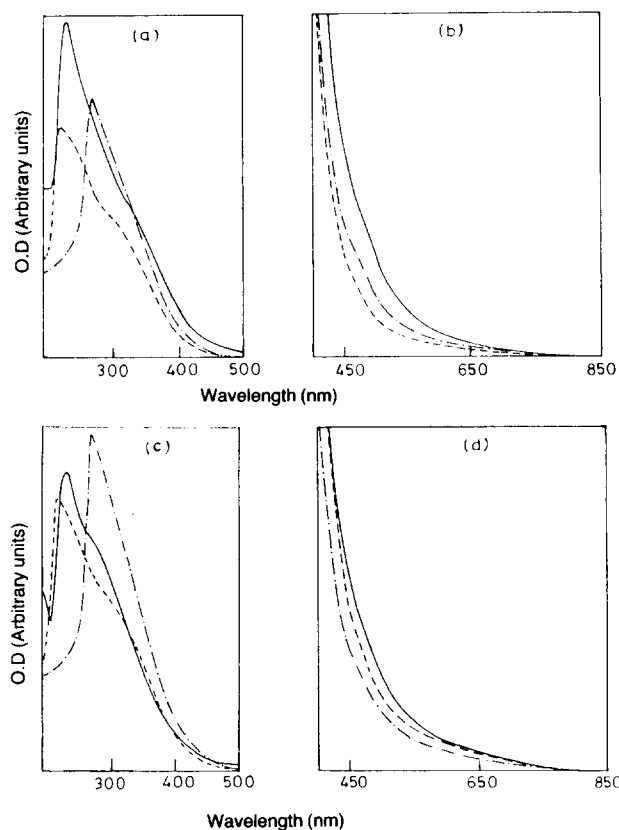
(λ(ε); in H<sub>2</sub>O). Fe(III)–D-glc complex: 225(9464); 260(6919); 320(4464); 470(429); 570(96). Fe(III)–D-fru complex: 225(12 666); 260(6720); 320(6666); 460(505); 590(120).

(λ(ε); in MeOH). Fe(III)–D-glc complex: 209(14528); 250(10977); 300(8071); 360(3445); 470(118); 570(18). Fe(III)–D-fru complex: 208(15 934); 230(15 158); 300(9871); 360(4935); 465(479); 545(176).

(λ(ε), in N,N-DMF). Fe(III)–D-glc complex: 265(10 266); 330(5929); 380(2184); 470(153); 530(44). Fe(III)–D-fru complex: 267(9454); 320(6152); 380(2197); 470(318); 550(105).

## Results and discussion

Both the D-glc and D-fru complexes of Fe(III) are highly soluble in water and can be dissolved in MeOH and N,N-DMF using 18-crown-6 ether. The absorption spectra of both the complexes in aqueous solutions are fully characteristic of the complex formation, and are different from those of the ferric chloride and sodium salts of saccharides. Corresponding absorption data in all three solvents are provided in Materials and methods and the spectra are shown in Figure 1. Furthermore, the spectra are also indicative of the coordination of saccharides through the oxygens of the ligands, including those of the deprotonated ones. A recent EXAFS study provided evidence for direct coordination between iron and oxygens of the ligand (Nagy *et al.* 1989). Changes observed in the absorption spectra in all three solvents suggest the involvement of solvent molecules in the coordination sphere. This further confirms our findings based on IR and elemental analysis that water molecules are involved in these complexes. We have recently reported our prelimin-



**Figure 1.** Absorption spectra of Fe(III) complexes of D-glc (a, b) and D-fru (c, d). —, H<sub>2</sub>O; ---, MeOH; - · -, DMF.

ary results regarding the solution stability of various mono- and disaccharide complexes of Fe(III) (Rao *et al.* 1992). Absorption spectra of both these complexes were measured in the concentration range  $10^{-5}$  to  $10^{-2}$  M and a linear behavior with the absorbance was observed, which speaks for well defined structures.

FTIR spectra of both the complexes are grossly indicative of the breakage of extensive intermolecular hydrogen bonds, otherwise existing in the solid state of the parent ligands (Gritsan *et al.* 1983, Tajmir-Riahi 1988) ( $3300\text{--}3500\text{ cm}^{-1}$ ), upon complex formation resulting in an almost symmetric band at  $3375 \pm 5\text{ cm}^{-1}$  with a small low frequency component as a shoulder at  $3280 \pm 10\text{ cm}^{-1}$ . The rather low OH stretching frequency, observed around  $3375\text{ cm}^{-1}$ , may be envisaged as arising from the interactions through  $\text{Na}^+$  ions, the shoulder at  $3280\text{ cm}^{-1}$  can be assigned to some intermolecular hydrogen bonded species. This region is further overlapped with  $\nu_{\text{OH}}$  of water molecules. All the sharp bands observed in the free ligand spectra and the spectra of sugar adducts of non-transition elements in the region  $840\text{--}1200\text{ cm}^{-1}$  are found to be merged and broadened upon complex formation (Kaiwar & Rao 1992). Yet further evidence for the presence of water molecules may also be derived from the H-O-H bending vibrations observed at  $1603 \pm 10\text{ cm}^{-1}$  in both the complexes studied.

The X-band EPR spectra of both the complexes in the solid state exhibited one sharp band ( $g = 4.168$  and  $4.208$ ;  $\Delta H_{\text{pp}} = 10$  and  $7\text{ mT}$ , respectively, for D-glc and D-fru) and another very broad band ( $g = 2.112$  and  $2.100$ ;  $\Delta H_{\text{pp}} = 62$  and  $60\text{ mT}$ , respectively, for D-glc and D-fru). These spectra were compared with that of  $\text{FeCl}_3$  measured under the same conditions, where there is only one sharp signal present ( $g = 2.009$ ,  $\Delta H_{\text{pp}} = 20\text{ mT}$ ). While the narrow band reflects the presence of isolated high spin Fe(III) centers, the broader one can be assigned to a signal arising from interacting paramagnetic high spin Fe(III) centers. Similar EPR spectral parameters were also reported by Nagy *et al.* (1986) for Fe(III) complexes of sugar-type ligands, where the corresponding complexes were synthesized using high ligand:Fe(III) ratios from strongly alkaline solutions.

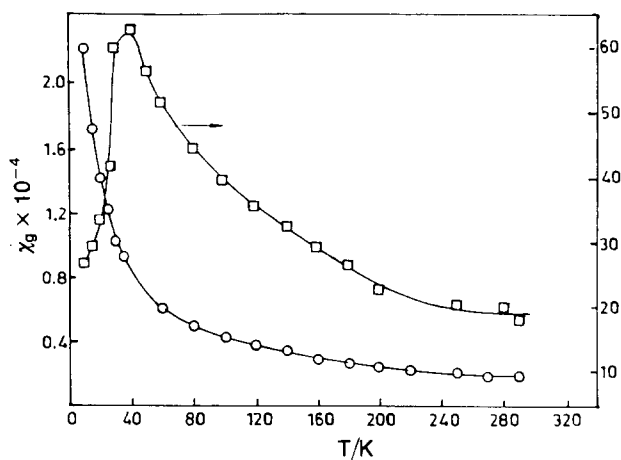
From Mössbauer spectra, the isomer shift values are found to be  $0.319$  and  $0.329\text{ mm s}^{-1}$ , respectively, for D-glc and D-fru, and are indicative of a high spin ferric state. The quadrupole splitting values ( $0.847$  and  $0.895\text{ mm s}^{-1}$ , respectively, for D-glc and D-fru) indicate distorted octahedral metal centers.

Magnetic susceptibility of the D-glc and D-fru

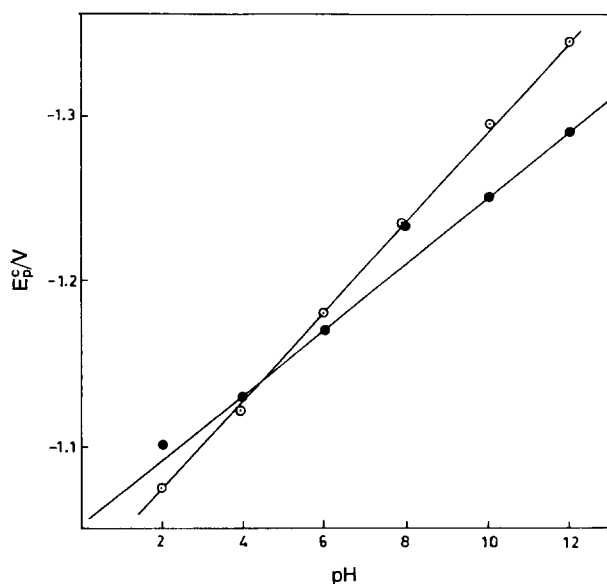
complexes was measured in the temperature range  $10\text{--}300\text{ K}$  and the corresponding  $\chi_g$  versus  $T$  plots are shown in Figure 2. The magnetic moment ( $\mu_{\text{eff}}$ ) showed a decrease of 30% in D-glc and 75% in D-Fru complexes on going from room temperature down to  $10\text{ K}$ . The data is clearly indicative of the presence of antiferromagnetic interaction between iron nuclei in the D-fru complex. The molar susceptibility per iron center ( $\chi_m$ ) has been fitted as per standard formula (Murray 1974, Walker & Poli 1990) in the temperature range  $40\text{--}290\text{ K}$  for the D-fru complex and found to have weak antiferromagnetic coupling with  $J = -4.5\text{ cm}^{-1}$ .

Cyclic voltammetry showed a single reversible cathodic reduction peak for both the complexes at HMDE corresponding to the  $\text{Fe(III)} \rightarrow \text{Fe(II)}$  process. The reduction potentials are found to be shifted to more negative values with an increase in pH. The relation between the cathodic potentials ( $E_p^c$ ) and pH was found to be linear in both cases (Figure 3). From the slopes of these straight lines ( $28$  and  $19\text{ mV pH}^{-1}$  for D-glc and D-fru complexes), the D-glc complex is found to be more susceptible towards pH. The study further implies that there exists substantial changes in the structures of both the complexes. We have recently reported the solution stability of iron-saccharide complexes in the pH range  $2\text{--}12$  based on absorption and cyclic voltammetry studied at glassy carbon and platinum electrodes (Rao *et al.* 1992).

Using this data together with elemental analyses, it has been possible to propose a mono nuclear complex for D-glc and a dinuclear complex for D-fru, having the molecular formulae  $[\text{Na}_2\text{Fe(D-glc)}_2]$



**Figure 2.** Gram susceptibility ( $\chi_g$ ) as a function of temperature (K): (○) D-glc complex (Fe-D-glc) and (□) D-fru complex (Fe-D-Fru).



**Figure 3.**  $E^\circ$  versus pH plots for Fe(III)–D-glc ( $\odot$ ) and Fe(III)–D-fru ( $\bullet$ ) complexes for the Fe(III)  $\rightarrow$  Fe(II) reduction process.

(OH)(H<sub>2</sub>O)] for D-glc and [Na<sub>3</sub>Fe<sub>2</sub>( $\mu$ -O)(D-fru)<sub>4</sub>(H<sub>2</sub>O)<sub>2</sub>] for D-fru complexes.

## Conclusions

Fe(III)–D-glc and Fe(III)–D-fru complexes were synthesized by an entirely different method using stoichiometric quantities of sodium salts of saccharides in methanolic solution, and the products were isolated in the solid state, purified and characterized by various methods. While absorption and IR data indicated complex formation, EPR and Mössbauer spectra indicated the presence of high spin Fe(III) centers in these complexes. Furthermore, the magnetic studies indicated antiferromagnetic interaction in the case of the D-fru complex suggesting a possible di-iron center in this case. All the data along with analytical results favored a mononuclear formula for D-glc and a dinuclear one with a possible  $\mu$ -oxo center in the case of the D-fru complex.

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## References

- Barker SA, Somers PJ, Stevenson J. 1974 Redissolvable ferric–D-fructose and ferric–D-glucose–D-fructose complexes. *Carbohydr Res* **36**, 331–337.
- Bourne EJ, Nery R, Weiger H. 1959 Metal chelates of polyhydroxy compounds. *Chem Ind* 998–999.
- Burger K, Zay I, Nagy GT. 1983 A novel polynuclear iron (III) mixed ligand complex for use in parenteral iron therapy. *Inorg Chim Acta* **80**, 231–235.
- Charley PJ, Sarkar B, Stilt CF, Saltman P. 1963 Chelation of iron by sugars. *Biochim Biophys Acta* **69**, 313–324.
- Davis PS, Deller DJ. 1966 Prediction and demonstration of iron chelating ability of sugars. *Nature* **212**, 404–405.
- Dolezal J, Langmyhr FJ. 1972 Some possibility of redox titrations with iron(II) sulphate in an alkaline mannitol medium. *Anal Chim Acta* **61**, 73–81.
- Galdi M, Valercia ME. 1988 Stability of iron(III) chelates of nutritional interest. *J Food Sci* **53**, 1844–1847.
- Gorman JE, Clydesdale FM. 1983 The behaviour and stability of iron-ascorbate complexes in solution. *J Food Sci* **48**, 1217–1225.
- Gritsan VN, Rano VP, Kachur VG. 1983 Theoretical analysis of hydrogen bonds in carbohydrate crystals. *Carbohydr Res* **112**, 11–21.
- Kaiwar SP, Rao CP. 1992 Soluble complexes of early first row transition metal ions with D-glucose. *Carbohydr Res* **237**, 203–210.
- Murray KS. 1974 Binuclear oxo-bridged iron(III) complexes. *Coord Chem Rev* **12**, 1–35.
- Nagy L, Burger K, Kurti J, Mostafa MA, Koresz L, Kiricsi I. 1986 Iron(III) complexes of sugar type ligands. *Inorg Chim Acta* **124**, 55–59.
- Nagy L, Ohtaki H, Yamaguchi, Nomura M. 1989 EXAFS study of iron(III) complexes of sugar type ligands. *Inorg Chim Acta* **159**, 201–207.
- Pecsok RL, Sandera J. 1955 The gluconate complexes. II. Ferric gluconate system. *J Am Chem Soc* **77**, 1489–1494.
- Rao CP, Kaiwar SP. 1991 Homoleptic glucose complexes of VO<sup>2+</sup> and Cr<sup>3+</sup>. *Inorg Chim Acta* **186**, 11–12.
- Rao CP, Kaiwar SP. 1992 Chromate reduction: reduction of potassium chromate by D-glucose and D-fructose to form chromium (III) saccharide complexes. *Carbohydr Res* **237**, 195–202.
- Rao CP, Kaiwar SP. 1993 Reduction of potassium chromate by D-fructose, D-galactose, D-glucose and L-sorbose. *Carbohydr Res* **244**, 15–25.
- Rao CP, Geetha K, Bandwar RP. 1992 Solution stability of iron saccharide complexes. *BioMed Chem Lett* **2**, 997–1002.
- Rao CP, Sarkar PS, Kaiwar SP, Vasudevan S. 1990 Chromate reductase activity: conversion of Cr (VI) to Cr (III). *Proc Ind Acad Sci (Chem Sci)* **102**, 219–230.
- Rich HW, Hegetschweiler K, Streit HM, Erni I, Schneider W. 1991 Mononuclear, oligonuclear and polynuclear iron(III) complexes with polyalcohols formed in alkaline aqueous media. *Inorg Chim Acta* **187**, 9–15.

- Saltman P. 1965 The role of chelation in iron metabolism. *J Chem Edn* **42**, 682–687.
- Tajmir-Riahi HA. 1988 Interaction of D-glucose with alkaline-earth metal ions. Synthesis, spectroscopic and structural characterization of magnesium(II) and calcium(II) D-glucose adducts and the effect of metal ion binding on anomeric configuration of the sugar. *Carbohydr Res* **183**, 35–46.
- Tonkovic M, Hadzija O, Nagy-Czako I. 1983 Preparation and properties of iron(III) sugar complexes. *Inorg Chim Acta* **80**, 251–254.
- Tonkovic M, Music S, Hadzija O, Nagy-Czako I, Vertes A. 1982 Mossbauer study of iron–sugar complexes. *Acta Chim Acad Sci Hung* **110**, 197–202.
- Traube W, Kuhbier F. 1932 Complex ferric compounds of polyhydric alcohols. *Ber* **65B**, 93–95.
- Van Duin M, Peters JA, Kieboom APG, van Bekkum H. 1989 A general coordination ionization scheme for polyhydroxy carboxylic acids in water. *Recl Trav Chim Pays-Bas* **108**, 57–60.
- Walker JD, Poli R. 1990 Iron trichloride–phosphine adducts with tetrahedral geometry and their reaction with ethanol. Structure magnetic properties of  $[\text{PH}(t\text{-Bu})_3]_2[\text{Fe}_2(\mu\text{-OEt})_2\text{Cl}_6]$ . *Inorg Chem* **29**, 756–761.
- Wolowice S, Drabent K. 1985 Mossbauer study of iron(III) reducing sugar complexes. *J Radioanal Nucl Chem Lett* **95**, 1–12.
- Xu J, Jordan RB. 1990 Kinetics and mechanism of the reaction of aqueous iron with ascorbic acid. *Inorg Chem* **29**, 4180–4184.
- Yano S. 1988 Coordination compounds containing sugars and their derivatives. *Coord Chem Rev* **92**, 113–156.