Reactivity of an Iron(III) Complex of Gallic Acid

S. ARIF KAZMI*, M. SAQIB QURESHI and ZAHIDA MAQSOOD
Department of Chemistry, University of Karachi, Karachi-32, Pakistan
(Received November 17, 1986)

Abstract

Gallic acid (3,4,5-trihydroxybenzoic acid) is the end product of hydrolysis of tea tannins which are believed to be responsible for the lowered iron absorption resulting from excessive tea ingestion. Gallic acid forms a 3:1 complex with iron in the pH range 4–6. This complex is reduced by ascorbate. The second-order rate constants at 30 °C at pH 4.4, 5.0 and 5.4 are 40, 21.5 and 9.4 $M^{-1} s^{-1}$, respectively. Activation parameters are $\Delta H^{\ddagger} = 17.6$ kcal mol^{-1} and $\Delta S^{\ddagger} = 6.4$ cal deg^{-1} mol^{-1} at pH = 5.0. Preliminary studies of substitution of gallic acid by tenfold excess of other ligands gave the following results for $t_{1/2}$: EDTA, 10 h at pH = 5; acetohydroxamic acid, ~2 days at pH = 5; desferrioxamine B, 6 s at pH = 5 and 2 min at pH = 7.

Introduction

Gallic acid (3,4,5-trihydroxybenzoic acid) is a constituent of tea leaves. It is also found condensed with other polyphenol compounds in the form of tannin or tannic acid. These compounds, while very important for the flavour and taste of tea, happen to be potent chelators of metal ions including Fe^{3+} (Fig. 1). Most of these compounds, under a variety of conditions, hydrolyse to give gallic acid [1]. In fact catechols (compounds containing two adjacent hydroxyl groups on a benzene ring) have been used as a biological iron transport system. Thus enterobactin, which is a triester of catechol, is used by a number of enteric bacteria to solubilize and transport iron under conditions of low iron stress [2].

The presence of polyphenolic material in tea is thus ominous from the point of view of bioavailability of iron, *i.e.*, iron complexed by these polyphenolic compounds is likely to be excreted unabsorbed. Thus it is possible that heavy tea drinkers risk anaemia. In fact it has already been demonstrated that iron absorption is reduced by tea ingestion [3]. Fortunately, however, the polyphenols have a preference for iron in the +3 oxidation state and consequently if such conditions were to prevail which would keep iron in the +2 state, iron bioavailability should not be adversely affected by tea ingestion. It has been demonstrated that ascorbic acid, a moderate reducing agent, reverses the impaired iron absorption caused by tea ingestion [4].

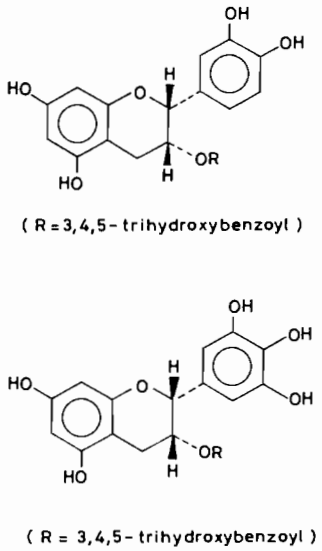


Fig. 1. Condensed polyphenols commonly found in tea leaves.

The observations of refs. 3 and 4 are empirical and no attempt to elucidate the molecular basis of these observations was made. We have now undertaken a detailed study of the interaction of Fe^{3+} with tannic acid and its simplest constituent, gallic acid [5]. We report here the kinetics of reduction of the Fe(III) complex of gallic acid when the two are mixed in the ratio of 1:3 (metal:ligand) in acetate buffer of pH 4.4, 5.0 and 5.4. Also of importance is the abstraction of the Fe^{3+} from this complex by biological and other important chelators. Thus we also report here the ligand exchange kinetics of the complex I by EDTA (ethylene diamine tetraacetic acid), acetohydroxamic acid and desferrioxamine B – a microbial iron chelator of hydroxamic variety.

*Author to whom correspondence should be addressed.

0020-1693/87/$3.50

Experimental

All chemicals used were of reagent grade quality and no purification was made before their use. $Fe(NO_3)_3 \cdot 9H_2O$ was obtained from Reidel-de-Hass; gallic acid was obtained from EGA-Chemie. Acetohydroxamic acid was obtained from Aldrich, whereas desferrioxamine B (as its mesylate) was gift of Ciba-Geigy. Values of pH were measured on an Orion 301A pH meter. All solutions were made in acetate/acetic acid buffers of the desired pH. The ionic strength was kept at 0.2 M. Standard techniques to exclude air were used and the solutions of the Fe^{3+} complex as well as that of ascorbic acid were used within a few hours of their preparation.

Kinetics were followed spectrophotometrically on a Beckman DU 25 spectrophotometer by following the disappearance of the ferric trigallate complex ($Fe^{III}(GA)_3$) using the 560 mm peak. Pseudo-first-order conditions were used with the reducing agent or the substituting ligand in large excess. Plots of $\ln(A - A_\alpha)$ *versus* t were linear for better than 90% of the reaction. The slopes of these plots gave $-k_{obs}$ values which in turn were measured for at least 4 different concentrations of the reagent at each given pH and temperature.

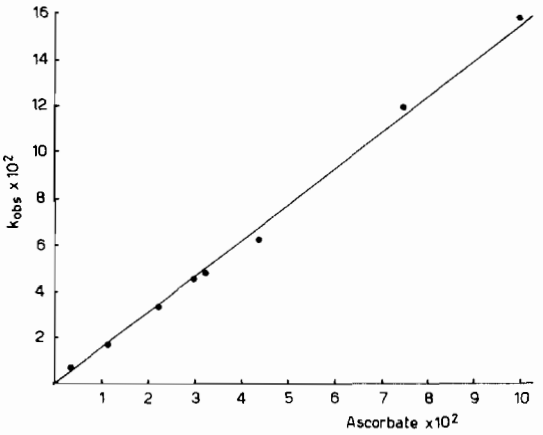


Fig. 2. A plot of k_{obs} *vs.* [ascorbate] at 30 °C.

TABLE I. Variation of Rate Constants for Reduction of Fe(III) Complex of Gallic Acid by Ascorbate at Different pH at 30 °C

pH	k_2 (M^{-1} s^{-1})
4.4	40
5.0	21.5
5.4	9.4

Results and Discussion

Reduction by Ascorbate

The reduction was found to be first-order in both the complex concentration (as evidenced by the linear plots of $\ln(A - A_\alpha)$ *versus* t as well as in the ascorbate concentration. A plot of k_{obs} *versus* [ascorbate] (Fig. 2) is linear with zero intercept. The slope of this plot is k_2 in the equation:

$$Fe^{III}(GA)_3 + \text{ascorbate} \longrightarrow Fe^{II}(GA)_3 + \text{dehydroascorbate} \qquad k_2$$

and

$$\text{rate} = -\frac{d[Fe^{III}(GA)_3]}{dt} = k_2[Fe^{III}(GA)_3][\text{ascorbate}]$$

Table I gives the values of k_2 at pH 4.4, 5.0 and 5.4 at 30 °C.

The variation of rate constant with pH may be ascribed to two factors: (i) the reducing ability of ascorbate and (ii) the equilibrium between the species $Fe^{III}(GA)_3$ and its partially hydrolysed products. The fact that the rate constant increases as the pH decreases points to the second factor, *i.e.*, the bis species predominates at low pH (see Scheme 1).

The first pK_a of ascorbate is 3.95 [6] which is more than one unit separate from the mean pH of this study. Thus, although it would be expected that an increase in pH will cause an increase in the rate of reduction by ascorbate, this effect would be a minor one in this pH range.

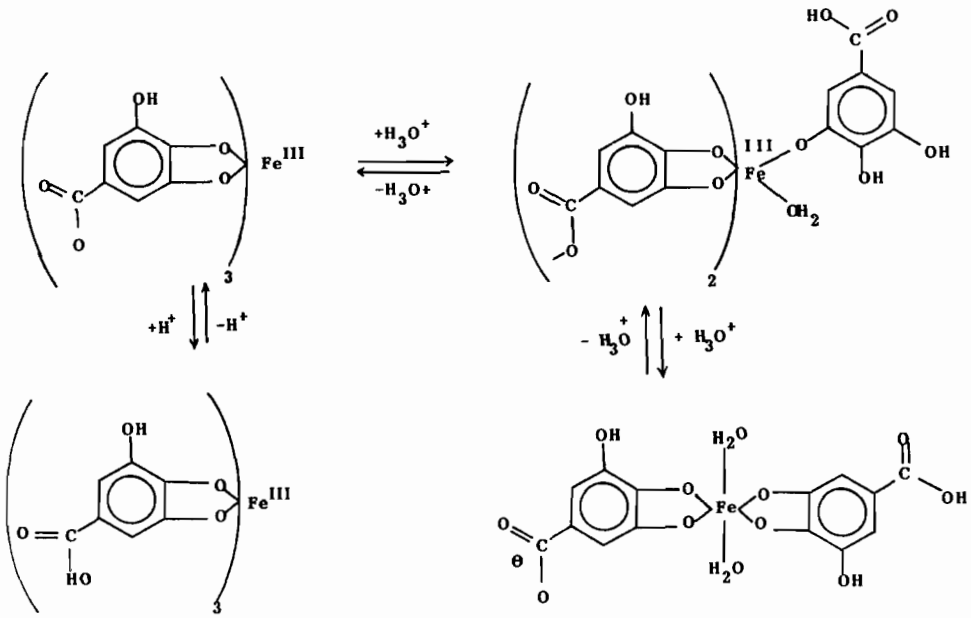
A partial hydrolysis of the tris(gallate)iron(III) complex, on the other hand, is likely to contribute significantly to a decrease in rate constants with an increase in pH (Table I). Similar effects have been demonstrated by Kazmi *et al.* in the case of reduction of ferrichrome [7], and by Kazmi in the case of reduction of tris(acetohydroxomate)iron(III) by ascorbate [8].

However, since the effect of pH on the reducing ability of ascorbate cannot be ignored, it is not feasible to attempt to isolate the rate constant into acid independent and acid dependent terms for the reduction of tris(gallate) and bis(gallate) complexes, respectively.

A temperature dependence study at pH 5 gave a plot of $\ln(k/T)$ *versus* T^{-1} as shown in Fig. 3. This yielded $\Delta H^{\ddagger} = 17.6$ kcal mol^{-1} and $\Delta S^{\ddagger} = 6.4$ cal deg^{-1} mol^{-1} for the reduction of this complex by ascorbate.

Substitution by Other Ligands

Gallic acid can be substituted by other ligands at a variety of rates. Our results in this regard are pre-



Scheme 1.

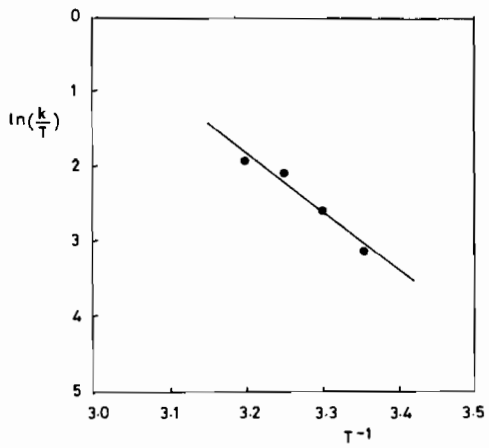


Fig. 3. Arrhenius plot of reduction of iron(III) complex of gallic acid by ascorbate at pH = 5.

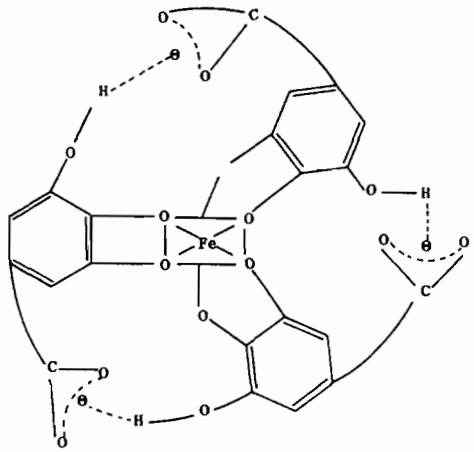


Fig. 4. Proposed structure of freshly prepared complex of iron(III) with gallic acid.

TABLE II. $t_{1/2}$ Values

Substituting ligand	pH	$t_{1/2}$ (s)
EDTA	5.0	3.6×10^4
Acetohydroxamic acid	5.0	1.73×10^5
Deferrioxamine B	5.0	6.0
Desferrioxamine B	7.0	1.2×10^2

liminary at this stage and no rate laws have been worked out nor are mechanisms postulated. However, in Table II, we report the $t_{1/2}$ values of the rate of disappearance of the 560 nm peak by different ligands when they were used in tenfold excess over the complex. Further studies on substitution are underway.

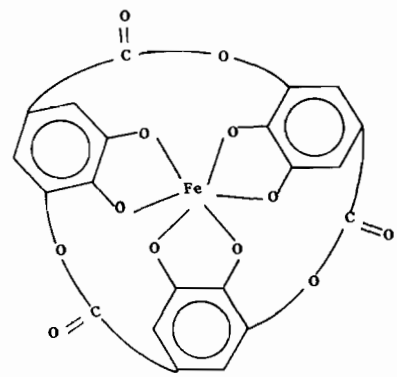


Fig. 5. Proposed structure of iron(III) complex with gallic acid after esterification of gallic acid residues.

Rearrangement of the Complex

All the kinetic data discussed above are for freshly prepared complex. However, when the complex is subject to prolonged standing, interesting changes appear in both its spectrum as well as its reactivity towards ascorbate. If left standing for several hours, the λ_{max} shifts to a longer wavelength. At the same time the rate of reduction by ascorbate is slowed down by an order of magnitude or more. The reduced product, instead of being colourless (as in the case of the freshly prepared complex), is now pale yellow. These observations are currently being analysed more carefully in our laboratory. We put forward a tentative hypothesis to explain these observations. The freshly prepared complex is a tris(bidentate) complex of iron where the free hydroxyl group of one ligand is hydrogen bonded to the carboxylate group of the adjacent ligand (Fig. 4). However upon prolonged standing, there is an esterification of these bonds so that we now have a cyclic triester as a hexadentate ligand (Fig. 5). The E° of this complex would be considerably more negative and the rate of reduction slower than that of a tris(bidentate)catechol complex. Analogy for such a difference in E° values of a cyclic hexadentate catechol complex and tris-(catechol) complexes of iron(III) exists in the literature [9].

References

1 'Encyclopedia of Chemical Technology', McGraw Hill, New York, Vol. 19, 1969, pp. 743–755.
2 J. B. Neilands, 'Microbial Iron Metabolism', Academic Press, New York, 1974.
3 D. D. Miller and B. R. Sehricker, in C. Kies (ed.), 'Nutritional Bioavailability of Iron', ACS Symp. Ser., Vol. 203, 1982, pp. 11–27.
4 L. Rossander, L. Hallberg and E. Bjor-Rasmussen, *Am. J. Clin. Nutr., 32*, 2484 (1979).
5 (a) R. Rehmat, *M.Sc. Thesis*, University of Karachi, 1986; (b) Z. Maqsood, University of Karachi, unpublished results.
6 M. Kimura, M. Yamamoto and S. Yanabe, *J. Chem. Soc., Dalton Trans.*, 423 (1982).
7 S. Arif Kazmi, A. Lee Shorter and J. V. McArdle, *Inorg. Chem., 23*, 4332 (1984).
8 S. Arif Kazmi, *188th Meeting of the American Chemical Society*, Philadelphia, Pa., August 26–31, 1984, Abstract INOR 150.
9 W. R. Harris, C. J. Carrano, S. R. Cooper, S. R. Sofen, A. E. Avdeef, J. V. McArdle and K. N. Raymond, *J. Am. Chem. Soc., 101*, 6097 (1979).