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Oxidation of Thiols.
I. Kinetics and Mechanism of Oxidation of β-Hydroxy-α-thiobenzoyl-*p*-methoxy-styrene by Hexacyanoferrate(III) in Neutral and Weakly Alkaline Medium

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The oxidation of β-hydroxy-α-thiobenzoyl-p-methoxy-styrene by hexacyanoferrate(III) follows the rate law (i)

$$Rate = \left(\frac{k_o'}{[H^+]} + k_2[Fe(CN)_6^{3-}]_T + \frac{k_3[Fe(CN)_6^{3-}]_T}{[H^+]}\right) \times (RSH)_T \qquad (i)$$

The two pathways showing first order in $[Fe(CN)_6^{3-}]_T$ are believed to proceed by an outer-sphere mechanism, with the acid-independent route involving the thiol form RSH, and in the acid-dependent route the thiolate ion, RS^- was encountered. The pathway independent of $[Fe(CN)_6^{3-}]$ proceeds via the formation of an intermediate $[(CN)_5Fe(CNSR)]^{4-}$ in which a sulphur–carbon bond is probably formed between the thiolate ion and a coordinated cyano-ligand. No copper(II) ions catalysis was observed.

Introduction

Hexacyanoferrate(III) has been successfully used in the quantitative determination of thiols and in the preparation of their oxidation products [1]. In some cases, it is preferred to other oxidizing agents. Thus, in the synthesis of mesoionic oxidation products of diphenylthiocarbazones, hexacyanoferrate(III) is preferred to iodine, amyl nitrite, hydrogen peroxide and permanganate [2]. Its successful application is attributed to the fact that it yields a stable reduction product by the gain of a single electron. Furthermore, it was thought that the inert nature of hexacyanoferrate(III) would preclude the formation of complexes with thiols or disulphides.

There are, however, conflicting reports on the type of mechanism employed by hexacyanoferrate(III) in its oxidation of thiols and other substrates [3–5]. Both inner and outer-sphere mechanisms have been proposed. Evidence for an inner-sphere mechanism is usually derived from the inhibition of the reaction rate caused by addition of cyanide [3], but this has lately been criticized [6]. In the oxidation of sulphite, in addition to reported inner- and outer-sphere mechanism [7, 8], Murray has proposed the formation of a complex between the reactants without invoking the loss of a cyanide from the inert $Fe(CN)_6^{3-}$ [9].

An important source of confusion in oxidations by hexacyanoferrate(III) arises from neglect of catalysis by trace amounts of copper as reported by Wilson *et al.* in the oxidation of cysteine and related thiols [4].

In the present investigation the oxidation of β-hydroxy-α-thiobenzoyl-*p*-methoxy-styrene (I) by hexacyanoferrate(III) in 50% ethanol–water mixture is reported.

Experimental

Materials and Reagents

The compound β-hydroxy-α-thiobenzoyl-*p*-methoxystyrene (I) was prepared as reported and its purity was determined from its m.p. and uv–visible spectrum [10]. Potassium hexacyanoferrate(III) was recrystallized and dried. A stock solution was prepared by weight and standardized spectrophotometrically (ϵ = 1030 M^{-1} cm^{-1} at 420 nm). Phosphate sodium hydroxide buffer solutions were made up from stock solutions of KH_2PO_4 and NaOH of known concentrations prepared from reagent grade chemicals. Freshly distilled ethanol was always used. Sodium cyanide was prepared by weight.

Instruments

The acid dissociation constant of compound (I) as well as the stoichiometry of its reaction with $[Fe(CN)_6^{3-}]$ were determined using a Unicam Sp 8000 spectrophotometer.

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TABLE I. Stoichiometric Results[a].

$[RSH]_{initial} \times 10^5$	$[Fe(CN)_6^{3-}]_{added} \times 10^5$	Absorbance	$[RSH]_{consumed}/[Fe(CN)_6^{3-}]_{added}$
3.77	0	0.63	0
2.75	1	0.46	1.02
2.25	1.5	0.375	1.01
1.73	2.0	0.29	1.04
0.808	3	0.135	0.99

[a] I = 0.08M, pH = 7.7, T °C = 25.

A radiometer pH meter (type 63) equipped with a combined glass electrode type GK 2311c was used in measuring the pH of solutions in both acid dissociation constant determination as well as in kinetic runs. Kinetic runs were performed with a Unicam SP 700 spectrophotometer equipped with thermostated cell-holders.

Determination of the Acid Dissociation Constant of Compound (I)

The change in the uv–visible spectrum of compound (I) was recorded with change in the pH of the solution. In a typical experiment, 25 ml of the thiol in ethanol–water mixture was transferred to a titration vessel and successive portions of 0.05 ml or less of NaOH of suitable concentration were added. The pH of the solution was read after each addition and the spectrum of the solution recorded. The titration was repeated twice. The pH meter readings were calibrated prior to titration against a standard radiometer buffer at pH's 4.01 ± 0.01 and 7.01 ± 0.01. The pH meter readings (B) in 50% ethanol–water solutions were converted to $[H^+]$ by means of the widely used relation

$$-\log [H^+] = B + \log U$$

where U, a correlation factor, is reported to be –0.35 [11].

Kinetic Measurements

All kinetic runs were performed under pseudo first order conditions with $[Fe(CN)_6^{3-}]$ in large excess (more than tenfold) over that of compound (I). An indented flask was used as a reaction vessel. The ethanolic solution of compound (I) and buffer was added to one compartment, and in the other, hexacyanoferrate(III), buffer and potassium chloride (to adjust ionic strength) solutions were added. The flask was kept in a thermostat, controlled at 25 °C for about 20 minutes, before the reactants were thoroughly mixed and an aliquot quickly transferred to a 1 cm quartz cell which was kept in the thermostated cell-holder of the spectrophotometer. The change in absorbance as function of time was followed at 440 nm where the magnitude of change in absorbance was found to be reasonable. The pH of each reaction solution was then measured.

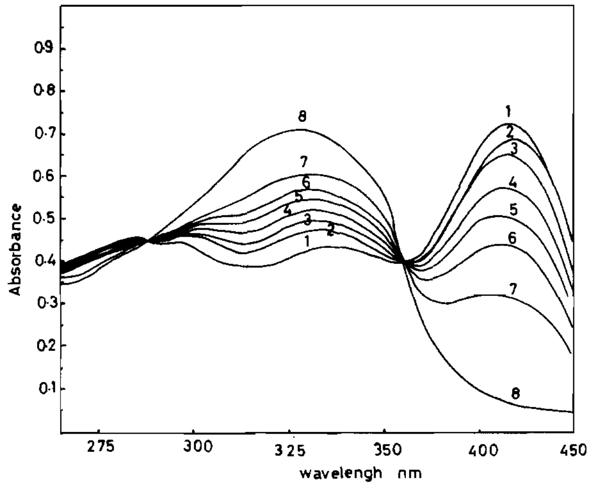


Figure 1. Effect of time on the absorption spectrum of an equimolar solution of $Fe(CN)_6^{3-}$ and compound (I). Curve 1 was recorded immediately after mixing and curve 8 after 100 minutes.

Results

Stoichiometry and Product

The stoichiometry of the reaction was verified by observing the change in absorbance of compound (I) in 50% ethanol–water mixture when increasing amounts of hexacyanoferrate(III) were added. Table I shows that the ratio of compound (I) consumed to hexacyanoferrate(III) added is close to 1:1. The stoichiometric equation may then be represented by eq. 1:

$$2RSH + 2\,Fe(CN)_6^{3-} \longrightarrow RSSR + 2\,Fe(CN)_6^{4-} + 2\,H^+ \qquad (1)$$

The reaction product was identified by mixing equimolar concentrations of compound (I) in ethanol (12..5 ml) and hexacyanoferrate(III) in water (12.5 ml) at pH 7.7 and then observing the change in the

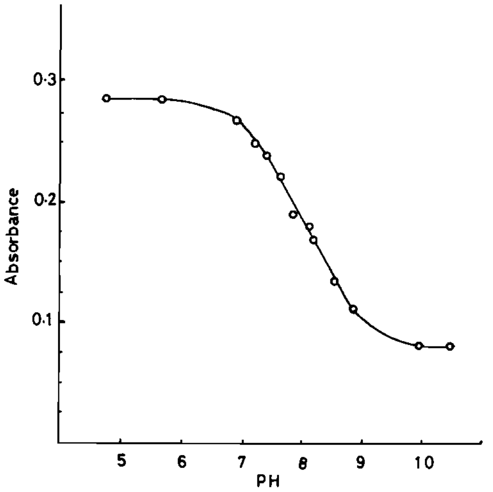


Figure 2. Dependence of absorbance at 428 nm of compound (I) on pH.

spectrum over the range 250–450 nm with time. Figure 1 shows that the peak at 417 nm, characteristic of compound (I) at this pH, decreases in intensity until it completely disappears. However, at the second peak (λ = 338 nm) the absorbance increases with time with a shift in λ_{max}. At completion of the reaction λ_{max} is shifted to 327 nm, and this wavelength corresponds to λ_{max} of an authentic sample of the disulphide in 50% ethanol–water which has been isolated and analysed [10]. This shows that the disulphide is the only oxidation product.

Acid Dissociation Constant

The absorbance at λ = 428 nm (where compound (I) has a maximum absorption) is plotted against pH as shown in Figure 2. The pK_a value (7.93) was calculated by applying the equation [12]

$$pK_a = pH + \log\frac{A_x - A_a}{A_\mu - A_x}$$

where A_x is the absorbance at pH_x, A_a is the absorbance of the anion and A_μ is that of unionized form of compound (I).

Kinetics

Plots of $\log(A_t - A_\infty)$ *vs.* time, where A_t and A_∞ correspond to absorbances at time t and infinity respectively, obeyed first order kinetics to beyond 90% of reaction. The magnitude of the pseudo first order rate constant, k_{obs} sec^{-1}, is obtained from the slopes X2.303 and is independent of the concentration of compound (I), as shown in Table II. It is, however, worth mentioning that at low $[Fe(CN)_6^{3-}]$ an induction period was observed.

The variation of k_{obs} on $[Fe(CN)_6^{3-}]$ at different pH values is shown in Figure 3. The dependence, at all pH values, can be described by eq. 2:

TABLE II. Order with Respect to $[RSH]_T$[a].

$[RSH]_T \times 10^5$	$k_{obs} \times 10^3$
4.4	2.35
3.4	2.32
2.4	2.30
1.4	2.28

[a] $[Fe(CN)_6^{3-}]_T = 1 \times 10^{-3}$ *M*; pH = 7.06; I = 0.08 *M*; T 25 °C.

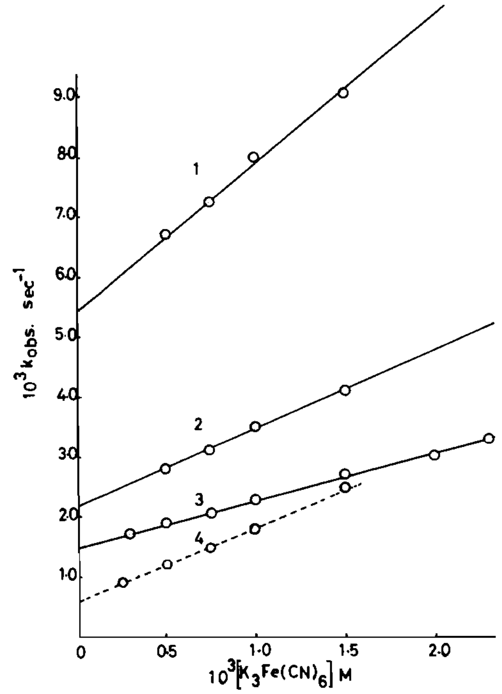


Figure 3. Plot of k_{obs} against $[Fe(CN)_6^{3-}]$, [RSH] = 2.4 × 10^{-5} *M*, I = 0.08 *M*, temp. 25 °C; 1, pH = 7.62; 2, pH = 7.25; 3, pH = 7.06; 4, pH = 7.19; 4, $[CN^-]$ = 2.4 × 10^{-4} *M*.

$$k_{obs} = k_o + k_1 [Fe(CN)_6^{3-}] \tag{2}$$

where k_o and k_1 correspond to the intercept and the slope respectively. From Figure 3 both k_o and k_1 are acid dependent; and from plots of k_o *vs.* $1/[H^+]$ and k_1 *vs.* $1/[H^+]$ as shown in Figures 4 and 5, these dependences are described by eqs. 3 and 4 respectively:

$$k_o = k_o'/[H^+] \tag{3}$$

$$k_1 = k_2 + k_3/[H^+] \tag{4}$$

k_o', k_2 and k_3 have values of 1.28 × 10^{-10} *M* sec^{-1}, 0.2 M^{-1} sec^{-1} and 6.0 × 10^{-8} M^{-2} sec^{-1} respectively at 25 °C. The overall rate equation at fixed $[H^+]$ is described by eq. 5:

TABLE III. Kinetic Data in Presence of Added Cu^{2+} or EDTA[a].

$[Fe(CN)_6^{3-}] \times 10^3$	pH	$[Cu^{2+}]$	$[EDTA] \times 10^4$	$k_{obs} \times 10^3$
0.5	7.06		1	1.85
0.5			0	1.92
0.75			1	2.1
0.75			0	2.05
1.00			1	2.25
1.00			0	2.30
1.500			1	2.85
1.500			0	2.70
1.00	7.19	0		2.8
1.00		5×10^{-8}		2.9
1.00		2.6×10^{-7}		2.85
1.00		5×10^{-7}		2.72
1.00		1×10^{-6}		2.75
1.00		2×10^{-6}		2.8
1.00		3×10^{-6}		2.8

[a] $I = 0.08\,M$; $[RSH]_T = 2.4 \times 10^{-5}$; T °C = 25.

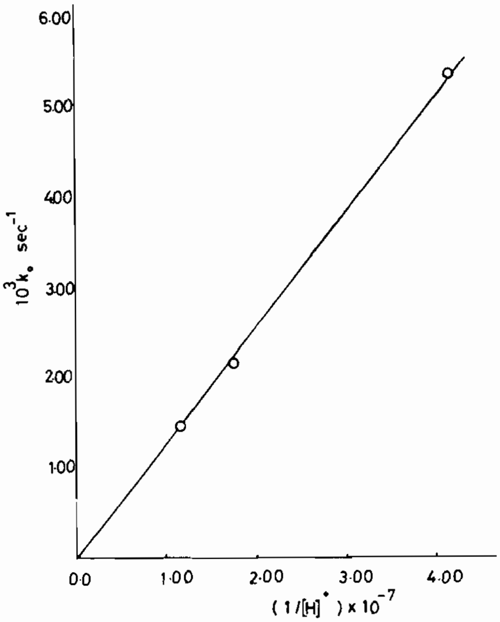


Figure 4. Dependence of k_o on $1/[H^+]$, $[RSH] = 2.4 \times 10^{-5}$, $I = 0.08\,M$, temp. 25 °C.

$$\text{Rate} = \left(\frac{k_o'}{[H^+]} + k_2[Fe(CN)_6^{3-}]_T + \frac{k_3[Fe(CN)_6^{3-}]_T}{[H^+]} \right) [RSH]_T \qquad (5)$$

where $[Fe(CN)_6^{3-}]_T$ and $[RSH]_T$ represent total hexacyanoferrate(III) and compound (I) concentrations respectively.

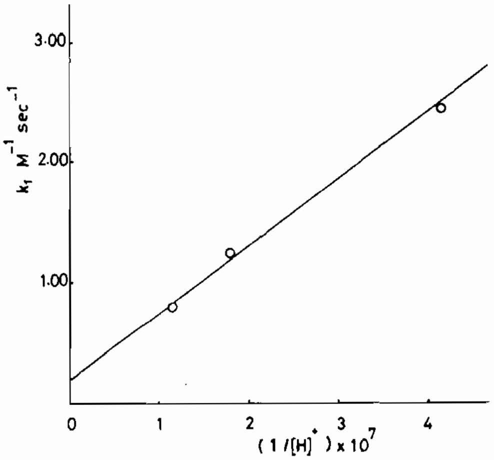


Figure 5. Dependence of k_1 on $1/[H^+]$, $[RSH] = 2.4 \times 10^{-5}$, $I = 0.08\,M$, temp. 25 °C.

Kinetics of the Reaction in Presence of EDTA

The effect of EDTA on the reaction rate was studied by varying the concentration of EDTA over the range 10^{-7}–10^{-4} M. The results in Table III show that the rate constant is not affected by EDTA. The concentration of EDTA used is far in excess of any copper ion impurity that may be present to catalyse oxidation by $Fe(CN)_6^{3-}$ as reported [4]. Indeed the deliberate addition of varying concentrations of Cu^{2+} ions, where other conditions were maintained, showed no appreciable effect on the reaction rate over the $[Cu^{2+}]$ range 5.0×10^{-8}–3.0×10^{-6} M (Table III).

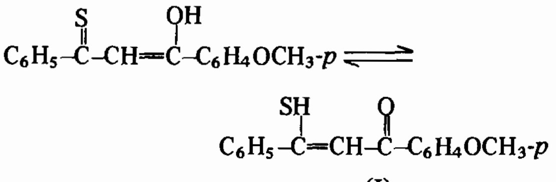
Kinetics of the Reaction in Presence of Cyanide

The addition of equal volumes of an aqueous solution of cyanide (4×10^{-4} M) and an ethanolic solution of compound (I) (5×10^{-5} M), shifted the peak at 428 nm to 394 nm. However, the peak at 335 nm has completely disappeared and a new band appeared at 280 nm. The observed spectrum in presence of cyanide ion is identical to that of the completely ionized form of compound (I) even though the pH of the solution was 6.5.

The effect of cyanide on the reaction rate was studied by varying ($Fe(CN)_6^{3-}$) in presence of cyanide ion (2.0 × 10^{-4} *M*), the other factors being constant. Figure 3 shows that the addition of cyanide ions inhibits both the hexacyanoferrate(III) dependent and independent paths. Thus, k_o takes the values 2.0 × 10^{-3} and 5.5 × 10^{-4} sec^{-1} in absence and presence of cyanide ions respectively, at pH 7.19 and 25.0 °C. The magnitudes of k_1 are 1.07 and 1.25 M^{-1} sec^{-1} in absence and presence of cyanide ion respectively, at the above conditions. Although the value of k_1 in presence of cyanide ions is higher than in their absence, this value is much lower than it should be, compared to the value of k_1 obtained for completely ionized form of compound (I)

Discussion

β-Hydroxy-α-thiobenzoylstyrene derivatives have been shown, by both chemical and physical evidence, to exist as enethiol, thione–enol or as an equilibrium mixture of thione–enol–enethiol tautomers [10, 13]



$$C_6H_5\text{-}\overset{\overset{S}{\|}}{C}\text{-}CH{=}\overset{\overset{OH}{|}}{C}\text{-}C_6H_4OCH_3\text{-}p \rightleftharpoons C_6H_5\text{-}\overset{\overset{SH}{|}}{C}{=}CH\text{-}\overset{\overset{O}{\|}}{C}\text{-}C_6H_4OCH_3\text{-}p$$

(I)

In their reactions with diazomethane, the S-methyl derivatives were obtained. Further, their reactions with the corresponding aroylphenylacetylene to give (E, Z)-β,β′-di(α-aroylstyryl) sulphides, and their oxidation with sodium nitrite/sodium hydrogen sulphate to give the disulphide, indicated that enethiol form is the active tautomer. Accordingly, the β-hydroxy-α-thiobenzoyl-*p*-methoxystyrene may be represented, in its oxidation reaction with hexacyanoferrate(III), as RSH. The disulphide, being the product of oxidation, is consistent with this representation.

The kinetics of the reaction indicate three pathways, which could be described by this scheme

$$RSH + OH^- \rightleftharpoons RS^- + H_2O \quad K_1 \qquad (6)$$

$$RS^- + Fe(CN)_6^{3-} \xrightarrow{k_7} RS\cdot + Fe(CN)_6^{4-} \qquad (7)$$

$$RSH + Fe(CN)_6^{3-} \xrightarrow{k_8} RS\cdot + Fe(CN)_6^{4-} + H^+ \quad (8)$$

$$RS^- + Fe(CN)_6^{3-} \rightleftharpoons [Fe(CN)_6SR] \quad K_2 \quad (9)$$

$$[Fe(CN)_6SR] \xrightarrow{k_{10}} RS\cdot + Fe(CN)_6^{4-} \qquad (10)$$

$$2\,RS\cdot \longrightarrow RSSR \qquad (11)$$

If the total thiol $[RSH]_T$ = [RSH] + $[RS^-]$, and thus neglecting the $[RS^-]$ associated with $[Fe(CN)_6^{3-}]$, we obtain eq. 12

$$[RS^-] = \frac{[RSH]_T}{1 + \dfrac{1}{k_1[OH^-]}} \qquad (12)$$

The rate law will then be given by eq. 13

$$\text{Rate} = \left(k_7[Fe(CN)_6^{3-}]_T + \frac{k_8[Fe(CN)_6^{3-}]_T}{k_1[OH^-]} + \frac{k_{10}K_2[Fe(CN)_6^{3-}]_T}{1 + K_2[Fe(CN)_6^{3-}]}\right)\left(\frac{[RSH]_T}{1 + \dfrac{1}{K_1[OH]^-}}\right) \qquad (13)$$

$K_2[Fe(CN)_6^{3-}] \gg 1$, and since $1/K_1[OH^-] \gg 1$, over the pH range employed, eq. 13 will take the form of eq. 14.

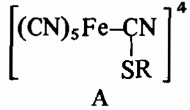
$$\text{Rate} = ((k_7K_1[OH^-] + k_8)[Fe(CN)_6^{3-}]_T + k_{10}K_1[OH^-])[RSH]_T \qquad (14)$$

or the form of eq. 15

$$\text{Rate} = \left\{\left(\frac{k_7K_1K_w}{[H]^+} + k_8\right)[Fe(CN)_6^{3-}]_T + \frac{k_{10}K_1K_w}{[H]^+}\right\}[RSH]_T \qquad (15)$$

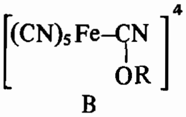
which are similar to the experimentally determined rate equation. By comparing eqs. 5 and 15 we obtain $k_o' = k_{10}K_1K_w$, $k_2 = k_8$ and $k_3 = k_7K_1K_w$. The magnitudes of the true rate constants, k_{10} and k_7, are calculated by substituting the values of K_1 and K_w, as 5.3 × 10^{11} sec^{-1} and 2.5 × 10^{14} M^{-1} sec^{-1} and are unusually high.

The proposed reaction scheme suggests that both reactions 7 and 8 proceed via an outer-sphere mechanism. However, the pathway described by reactions 9 and 10 involves the formation of an intermediate which is supported by the induction period observed at low $[Fe(CN)_6^{3-}]$. The intermediate may be formed either by attack of a thiolate ion on coordinated cyalo-ligand (A) or by attack of the carbonyl oxygen of compound (I) on a cyano-ligand of hexacyanoferrate(III) to form the intermediate (B)



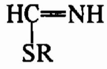
$$\left[(CN)_5Fe\text{-}\underset{\underset{SR}{|}}{C}N\right]^{4-}$$

A



$$\left[(CN)_5Fe\text{-}\underset{\underset{OR}{|}}{C}N\right]^{4-}$$

B

The interaction between thiolate and cyanide ion has been reported [6], and that of carbonyl oxygen with cyanide ions is well known. The intermediate (A) may be preferred to (B) as the two centres involved in the electron-transfer will be much closer in (A) than in (B). This, in fact, is in agreement with the high value calculated for k_{10}. This is also in agreement with formation of a sulphur–carbon bond, with the cyano-ligand bonded to the metal centre via the carbon atom, proposed for the $Fe(CN)_6^{3-}$–SO_3^{2-} reaction [9]. The reaction pathway independent of $[Fe(CN)_6^{3-}]$ cannot be explained by inner-sphere mechanism as the rate of loss of a cyano-ligand from this complex is negligibly small at the employed pH values. Furthermore, if the loss of a coordinated cyano-ligand is rate-determining, the magnitude of k_0 would have decreased, not increased, with increasing pH values as this step is acid catalysed [14]. The inhibition of the reaction rate by added cyanide ion most likely results from the interaction RSH + HCN →  $H\underset{SR}{C}{=}NH$ rather than from the suppression of the reaction

$$Fe(CN)_6^{3-} \rightleftharpoons Fe(CN)_5^{2-} + CN^-$$

The oxidation of compound (I) by hexacyanoferrate(III) is not catalysed by Cu^{2+} ions as evidenced by experiments carried out in presence of EDTA or deliberately added Cu^{2+} ions.

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