Sulfite: Cytochrome c Oxidoreductase

INHIBITION BY POLYMERS OF CYTOCHROME c*

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SUMMARY

The sulfite:cytochrome c oxidoreductase (EC 1.8.7.1) of bovine liver has been partially purified by a simple procedure. The preparations obtained gave no spectral evidence of heme components and had very little ability to transfer electrons to oxygen while being very active with cytochrome c. The response of the enzyme to changes in the concentrations of sulfite or of cytochrome c was that to be expected for a ping-pong mechanism. $K_s$ for sulfite under the conditions used was $2.2 \times 10^{-5}$ M. Anions, both monovalent and divalent, were inhibitory; none were competitive with respect to sulfite. Sulfate was competitive with respect to cytochrome c. $K_s$ for sulfite was $3.5 \times 10^{-3}$ M. $K_s$ for ferricytochrome c in the absence of inhibitory anions was calculated to be $2.1 \times 10^{-3}$ M. Bubbling solutions of ferricytochrome c with nitrogen or otherwise exposing them to gas-liquid, liquid-liquid, or solid-liquid interfaces was found to generate polymers of cytochrome c. The higher polymers of cytochrome c, were found to be potent inhibitors of the sulfite:cytochrome c oxidoreductase, competitive with respect to cytochrome c. The inhibition observed varied as the 2.56th power of the concentration of the polymerized cytochrome c. Ferrocytochrome c was resistant to the formation of polymers when exposed to interfaces. Yeast ferricytochrome c was unique among the ferricytochromes c tested in also being resistant to polymerization when exposed to interfaces.

The existence of enzymes capable of catalyzing the oxidation of sulfite has been observed in mammalian (1-4), plant (5-7), and bacterial (8) material. The existence of a free radical chain mechanism for the aerobic oxidation of sulfite (9-11) and the ease with which this chain reaction can be initiated, may readily lead to confusing experimental results. Thus, early observations that hypoxanthine was a cofactor for the enzymic oxidation of sulfite (12) were subsequently explained (13, 14) on the basis of the ability of trace amounts of xanthine oxidase, when acting upon its substrates, to initiate the sulfite-oxygen chain reaction. This chain reaction has been used as a sensitive chemical detector for reactive radicals, generated in the catalytic cycles of a variety of oxidative enzymes (13, 15-19) and as the basis of a sensitive manometric actinometer (20). The sulfite-oxygen chain reaction can be avoided by working at low concentrations of sulfite or in the presence of compounds capable of scavenging those radicals which propagate the chain reaction or by using assay methods which do not depend upon the consumption of oxygen.

A recent report of the partial purification of a sulfite:cytochrome c oxidoreductase (EC 1.8.7.1) from Thiodacillus novelli (8) and the observation that a deficiency of this enzyme in man can be associated with fatal physiological disturbances (21), led us to a reinvestigation of the sulfite-oxidizing enzyme found in bovine liver. During the course of these studies, it was observed that bubbling solutions of ferricytochrome c with nitrogen gas, generated a potent inhibitor of the sulfite:cytochrome c oxidoreductase. This inhibitor was competitive with respect to cytochrome c. The present report documents this effect, establishes the nature of the inhibitor so generated, and presents additional data on the mammalian sulfite:cytochrome c oxidoreductase.

EXPERIMENTAL PROCEDURE

Cytochromes c from horse and bovine hearts (types III, V, and VI) were purchased from Sigma. Cytochromes c from hearts of sheep, pig, kangaroo, rabbit, and chicken and cytochrome c from yeast were generously provided by Dr. E. Margoliash of the Abbott Laboratories. Bovine liver was obtained at a local abattoir, chilled promptly, and stored frozen until used to prepare acetone powders. Milk xanthine oxidase was obtained from the Worthington Biochemical Corporation (Freehold, New Jersey) and was purified as already described (22). TPNH:cytochrome c oxidoreductase (EC 1.6.2.3), which had been prepared from pig liver microsomes by the method of Masters et al.

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chloride containing 1 X 10^{-4} M solutions of horse heart ferricytochrome c: and 1.5 X 10^{-5} M cytochrome c oxidoreductase. Reaction mixtures contained the indicated concentrations of these reagents in a total volume of 30.0 ml buffered at pH 8.5 by 0.10 M Tris chloride containing 0.05 M Tris base. The pH of this ammonium sulfate-Tris solution was 7.8 at 25°C, when measured after dilution with 1.5 volumes of water. After the solution was stirred at 0°C for 15 min, the precipitate was collected by centrifugation and was dissolved in sufficient water to give a conductivity of 18 mmho per cm² at 25°C, which is approximately the conductivity of 2.5% saturated ammonium sulfate. It was then applied to a column (2.5 x 25 cm) of DE-32 which had been equilibrated at 4°C with 2.5% saturated ammonium sulfate solution adjusted to pH 7.8 with Tris base. The column was then washed with this solution until a peak of inactive protein was eluted. A gradient of ammonium sulfate (2.5 to 10% saturated) neutralized to pH 7.8 with Tris was then applied in a total volume of 1.2 liters. Fractions (15 ml) were collected at a flow rate of 100 ml per hour. Active fractions were pooled, and the enzyme was precipitated by addition of an equal volume of neutral saturated ammonium sulfate. The precipitate was collected by centrifugation, dissolved in a minimal volume of 0.01 M potassium phosphate buffer at pH 7.8 which contained 1 X 10^{-4} M EDTA, and stored frozen. It was stable in the freezer for several months. The specific activity of this material ranged from 200 to 400 units per mg which may be compared with the value of 880 achieved by MacLeod et al. (4).

The enzyme was routinely assayed at 25°C in 0.10 M Tris-chloride-10^{-4} M EDTA at pH 8.5 in terms of the rate of reduction of cytochrome c by 10^{-4} M sulfite. Concentrations of cytochrome c were calculated with published extinction coefficients (24). The oxidation of sulfite by dissolved oxygen was followed at 210 mp. The molar extinction coefficient of sulfite at this wave length and at pH 7.8 in 0.010 M phosphate was 2.8 X 10^{4}. All assays were corrected for small nonenzymic rates. Changes of absorbance as a function of time were followed with a Gilford model 2000 or with a Cary model 15 spectrophotometer. In both cases, cell compartments were thermostatted at 25°C, and the instruments were operated at maximum sensitivity so that a full scale deflection corresponded to an absorbance change of 0.10. When greater sensitivity was required, cuvettes with a path length of 10.0 cm were used.

**RESULTS**

**Kinetic Behavior**—The response of the enzymic reaction to variation of the concentration of sulfite and of cytochrome c was that to be expected of a ping-pong (25) mechanism. This is illustrated in Fig. 1. Parallel lines were similarly obtained when reciprocal velocity was plotted as a function of reciprocal sulfite concentration at several fixed concentrations of cytochrome c. The ordinate intercepts of the lines in Fig. 1 were plotted as a function of the reciprocal of the sulfite concentration as shown in Fig. 2. From the data shown in Figs. 1 and 2, Kₘ for sulfite was found to be 2.2 X 10^{-4} M whereas Kₛ for cytochrome c was 3.1 X 10^{-7} M. The buffer used in obtaining these results contained 0.03 M chloride. One may infer that sulfite, in reducing the enzyme, is converted to sulfate and that the reduced enzyme in turn reduced ferricytochrome c. It follows that one or more groups on the enzyme are capable of being alternately reduced by sulfite and reoxidized by ferricytochrome c.

**Inhibition by Anions**—The high affinity exhibited by the enzyme for its anionic substrate suggested that other inorganic anions might act as inhibitors of the enzyme-catalyzed reaction. Anions, both monovalent and divalent, inhibited the sulfite:cytochrome c oxidoreductase. Since all of the anions investigated were inhibitory, to some degree, it was not possible to contrive a buffered assay medium free of inhibitory anions. This problem was circumvented and quantitative data were...
obtained by performing the kinetic analyses at two levels of each anion \((I_1\) and \(I_2\)) in Tris buffer of constant pH. Thus, in the case of sulfate, 0.010 M Tris was adjusted to pH 8.5 with sulfuric acid and \(I_1\) was \(3 \times 10^{-1} \text{ M}\). The level of sulfate was then raised at will without changing the pH by adding sodium sulfate. The constancy of the pH was checked with the glass electrode. Graphing of the data obtained at the different anion concentrations on reciprocal coordinates gave lines with slopes \((S_1\) and \(S_2\)) that could be used to compute \(K_i\) for the anion and with ordinate intercepts \((Y_1\) and \(Y_2\)) could be used to compute \(K'_i\). Thus

\[
K_i = \frac{(S_1)(I_2) - (S_2)(I_1)}{(S_2) - (S_1)}
\]

and

\[
K'_i = \frac{(Y_1)(I_2) - (Y_2)(I_1)}{(I_2) - (I_1)}
\]

\(K_i\) is the dissociation constant of the enzyme-anion complex and \(K'_i\), is the dissociation constant of the enzyme-substrate-anion complex. Fig. 3 presents the results of an investigation of the effects of sulfate performed in 0.010 M Tris buffer containing \(10^{-4} \text{ M}\) EDTA at pH 8.5 and 25°. The points on Line 1 were obtained in the presence of 0.0030 M sulfate, whereas the points on Line 2 were obtained in the presence of 0.030 M sulfate. \(K_i\) for sulfate was found to be 0.011 M and \(K'_i\), to be 0.012 M. Line 3 is a calculated line which represents the inferred behavior of the enzyme in the complete absence of sulfate. From Line 3, \(K_i\) for sulfate in the absence of inhibitory ions was calculated to be \(3 \times 10^{-5} \text{ M}\). It is apparent that sulfate is an effective inhibitor but is not competitive with respect to sulfite.

Fig. 4 presents the results of a similar experiment performed with a monovalent anion, in this case, fluoride. The points on Line 1 were obtained in the presence of 0.015 M fluoride while the points on Line 2 were obtained in the presence of 0.115 M fluoride. \(K_i\) was calculated to be 0.075 M and \(K'_i\), to be 0.065 M. Once again Line 3 is calculated and represents the behavior of the enzyme in the absence of fluoride. Table I summarizes the results obtained in this manner with several anions. Divalent anions were more effective inhibitors than monovalent anions. None of the anions tested were competitive with respect to sulfite.

Several other anions were found to be inhibitory. Thus, when present at 0.10 M, in a standard assay mixture containing 1 \(\times 10^{-4} \text{ M}\) ferricytochrome c, cacodylate, arsenite, nitrate, and selenite caused 70, 72, 80, and 94% inhibition, respectively. Sufficient data were not collected to permit calculation of reliable inhibition constants for these anions.

The possibility that anions were competing with cytochrome c was considered. The extremely low \(K_i\), for cytochrome c made the usual (26) kinetic analysis very difficult even in cells with a 10.0-cm light path. Thus, as already noted, \(K_i\), for cytochrome c was \(3.1 \times 10^{-7} \text{ M}\) in the presence of 0.031 M chloride. At pH 8.5 and at 25° in 0.010 M Tris containing 1 \(\times 10^{-4} \text{ M}\) EDTA, 0.030 M sulfate, and 8 \(\times 10^{-6} \text{ M}\) sulfite, \(K_i\), for cytochrome c was \(2.1 \times 10^{-7} \text{ M}\). Under the same conditions, but in the presence of only 2.1 \(\times 10^{-3} \text{ M}\) sulfate, the \(K_i\), for cytochrome c was too low to be measured by initial velocity methods. The time course of the complete enzymic reduction of 5 \(\times 10^{-7} \text{ M}\) cytochrome c was followed and the results were graphed on the basis

**Table I**

<table>
<thead>
<tr>
<th>Ion</th>
<th>(K_i) (M)</th>
<th>(K'_i) (M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoride</td>
<td>0.075</td>
<td>0.065</td>
</tr>
<tr>
<td>Chloride</td>
<td>0.086</td>
<td>0.161</td>
</tr>
<tr>
<td>Sulfate</td>
<td>0.0108</td>
<td>0.0124</td>
</tr>
<tr>
<td>Phosphate</td>
<td>0.0093</td>
<td>0.010</td>
</tr>
</tbody>
</table>
of an integrated rate equation (27–31)

\[
\frac{1}{t} \ln \left( \frac{S_0}{S_t} \right) = -\frac{1}{K_\text{s}} \frac{S_0 - S_t}{t} + \frac{V_\text{m}}{K_\text{s}}
\]

where \( S_0 \) and \( S_t \) are the substrate concentrations present in the reaction mixture at zero time and at some later time, respectively. Fig. 5 illustrates the result of this treatment of the data. \( K_\text{s} \) for cytochrome \( c \) was \( 3.5 \times 10^{-4} \) M. Thus, decreasing the concentration of sulfate from 0.030 M to 0.0021 M decreased \( K_\text{s} \) for cytochrome \( c \) from \( 2.1 \times 10^{-1} \) M to \( 3.5 \times 10^{-5} \) M. From this change, \( K_\text{s} \) for sulfate was calculated to be 0.0035 M. \( V_\text{m} \) was not changed significantly by changing the concentration of sulfate. Hence, sulfate inhibition was competitive with respect to cytochrome \( c \) but not with respect to sulfite. This result is consistent with the expectations for a ping-pong mechanism (25). Whether or not other anions would be competitive with respect to cytochrome \( c \) was not investigated.

Inhibition by Polymers of Ferricytochrome \( c \)—In the course of rendering solutions of cytochrome \( c \) anaerobic by means of bubbling with nitrogen gas, it was discovered that bubbling solutions of ferricytochrome \( c \) generated a potent inhibitor of the sulfite:cytochrome \( c \) oxidoreductase. This inhibitor could also be generated by shaking solutions of ferricytochrome \( c \) with carbon tetrachloride or by lyophilizing solutions of ferricytochrome \( c \) which contained 0.25 M ammonium acetate. Apparently, exposure to gas liquid, liquid liquid, or solid liquid interfaces generated the inhibitor from cytochrome \( c \). Formation of the inhibitor under these circumstances could be prevented by the inclusion of 0.6 mg per ml of bovine serum albumin in the cytochrome \( c \) solutions. Reduction of ferricytochrome \( c \) with dithionite also prevented the formation of the inhibitor although once formed, it was not destroyed by dithionite. Reoxidation of ferrocytochrome \( c \) with ferricyanide fully restored its ability to give rise to the inhibitor. The inhibitor was more heat labile than was the parent cytochrome \( c \) and a bubbled solution of ferricytochrome \( c \) could be completely freed of the inhibitor by heating it to 80° for 5 min. The inhibitor could then be generated once again by bubbling the cooled solution. The inhibitor was stable to freezing and thawing. Purification of ferricytochrome \( c \) by ion exchange chromatography (32) did not diminish its ability to serve as a source of the inhibitor. The formation of the inhibitor was profoundly temperature dependent. Thus, shaking solutions of ferricytochrome \( c \) for 30 sec at 25° in the presence of an equal volume of carbon tetrachloride produced large amounts of the inhibitor whereas shaking at 0° produced no detectable inhibitor. The inhibitor was macromolecular as deduced from its complete exclusion by Bio-Gel P-4. Ferricytochromes \( c \) prepared from heart muscle of several species were tested for their ability to generate the inhibitor. Cytochromes from horse, cattle, sheep, pig, kangaroo, rabbit, and chicken were found to serve as sources of the inhibitor. Yeast cytochrome \( c \) was unique among those tested in not generating the inhibitor when shaken with carbon tetrachloride.

The known propensity of ferricytochrome \( c \) for the formation of polymers under denaturing conditions such as treatment with trichloroacetic acid (32–35), shaking with ethanol (35), boiling (33), and even lyophilization (36) suggested that the inhibitor was a polymer of cytochrome \( c \). Cytochrome \( c \) polymers have been separated by ion exchange chromatography (34, 35) and by gel exclusion chromatography (37, 38). Horse heart cytochrome \( c \) (123 mg) was dissolved in 25 ml of 0.25 M ammonium acetate, shell frozen, and lyophilized. The residue was taken up in approximately 8 ml of 0.10 M Tris-chloride buffer at pH 8.5 which contained 1 \( \times \) 10^{-4} M EDTA. This solution, which contained 1.34 \( \times \) 10^{-4} M total cytochrome \( c \) produced 47% inhibition of a standard sulfite:cytochrome \( c \) oxidoreductase assay, when tested at a level of 1 \( \mu \)l of the inhibitor solution in 3.0 ml of the assay mixture. Three milliliters of this solution of lyophilized cytochrome \( c \) were placed on a column (2.5 \( \times \) 44 cm) of Sephadex G-75 which had been equilibrated at 4° with 0.10 M Tris-chloride pH 8.0 containing 1.0 M NaCl. A flow rate of 16 ml per hour was applied and 1.0-ml fractions were collected. All fractions were assayed for total content of cytochrome \( c \) at 409 nm and for the ability of 30-\( \mu \)l aliquots to inhibit the standard

\[ \text{Fig. 6. Gel exclusion chromatography on Sephadex G-75 of cytochrome } c \text{ modified by lyophilization from 0.25 M ammonium acetate.} \]

\[ \text{Fig. 5. Time course of the enzymic reduction of cytochrome } c \text{ by sulfite.} \]

\[ \text{Fig. 5. Time course of the enzymic reduction of cytochrome } c \text{ by sulfite.} \]
a final demonstration that the inhibitory factor and the poly-
mer. Its content of inhibitor and its behavior on Sephadex G-75
inhibitory factor generated by bubbling and was observed to
depolymerize essentially all of the cytochrome c polymers. As shown in Fig. 7, the inhibitor was competitive with

\[ v = \frac{V_m}{1 + \frac{K_i}{S} \left(1 + \frac{I}{K_i}\right)} \]

The value of \( n \) was obtained by graphing the data according to the work of Johnson, Eyring, and Williams (39). This is illustrated in Fig. 8. The value of \( n \) obtained from the slopes of the lines in Fig. 8 was 2.56. Applying this value of \( n \) to the data, one may calculate a concentration-independent value of \( K_i \).

Inhibition of Other Enzyme Systems by Polymeric Cytochrome c—Studies of the role of oxygen in the reduction of cytochrome c by the xanthine oxidase system had involved bubbling the solution of ferri-cytochrome c with nitrogen (40). Generation of an inhibitory species as a consequence of bubbling was not noted at that time. It appeared likely, therefore, that polymers of cytochrome c would not inhibit the reduction of cytochrome c by xanthine oxidase plus xanthine. This was tested under the conditions of the standard sulfite:cytochrome c oxidoreductase assay except that \( 1 \times 10^{-5} M \) xanthine replaced sulfite and milk xanthine oxidase was used as the enzyme. Polymeric cytochrome c was without effect in the xanthine oxidase system. In contrast, the TPNH:cytochrome c reductase purified from liver micro-
somes (20) was inhibited by cytochrome c polymers. It was assayed at pH 8.5 and at 25° in 0.010 M Tris-chloride containing
$10^{-4}$ M EDTA, $2 \times 10^{-4}$ M TPNH, and $2.3 \times 10^{-5}$ M cytochrome c. Its sensitivity to polymeric cytochrome c was approximately half that seen with the sulfite:cytochrome c oxidoreductase.

**Role of Oxygen**—The sulfite:cytochrome c oxidoreductase did not effectively transfer electrons to oxygen. Indeed, its turnover number with oxygen as the sole electron acceptor was less than $3\%$ as great as its turnover number with saturating amounts of ferrixytochrome c. Furthermore, oxygen was not required for the reduction of cytochrome c. Thus, anaerobic conditions were achieved in Thunberg cuvettes by alternately evacuating them with nitrogen which had been passed over hot, colloidal copper (41). Care was taken to avoid bubbling the solution of cytochrome c. Cuore was taken to avoid bubbling the solution of cytochrome c. Cytochrome c reduction was not influenced by this procedure.

**Discussion**

The sulfite:cytochrome c oxidoreductase exhibits ping-pong (25) kinetics. This implies the existence of a prosthetic group which can be alternately reduced by sulfite and reoxidized by cytochrome c. Furthermore, the stoichiometry of the reaction demands that this prosthetic group accept a pair of electrons from sulfite and then give up 1 electron to each of 2 molecules of ferrixytochrome c. The nature of this prosthetic group remains unknown. An earlier report (4) indicated that the enzyme was capable of utilizing oxygen as electron acceptor and contained a heme component which was alternately reduced by sulfite and reoxidized by oxygen. This is not the case with the present preparations of the enzyme which do not transfer electrons to oxygen and which give no spectral evidence of a heme component. It appears likely that the earlier preparations of the enzyme (4) may have contained, as an impurity, an autoxidizable hemoprotein such as the P-420 of microsomes (42). The reported localization of the sulfite-oxidizing activity in microsomes and its spectrum (4) support this suggestion. The sulfite-oxidizing enzymes of T. novellus (8) and of human tissues (21) were similarly unable effectively to utilize oxygen as an electron acceptor and required cytochrome c.

Anions, both monovalent and divalent, were effective inhibitors of the enzyme. None of the anions tested were competitive with respect to sulfite. Sulfate was found to be competitive with respect to cytochrome c which is in accord with the expectations of a ping-pong mechanism. Whether other anions might also compete with cytochrome c is a point of considerable interest which has not yet been explored.

These inhibitory anions could act by association with the enzyme or with the ferrixytochrome c. The data in hand do not allow a distinction between these two possibilities. The $K_s$ for cytochrome c in the complete absence of anions, which may be calculated from the data obtained at two levels of sulfate, is remarkably low, being $2.1 \times 10^{-4}$ M.

Bubbling solutions of ferrioxytochrome c or otherwise exposing them to interfaces was found to generate a potent inhibitor which was competitive with respect to cytochrome c. This inhibitor was shown to be a polymer of cytochrome c. It seems likely that the generation of polymers depends upon unfolding of the cytochrome c followed by a polymerization of the unfolded molecules. This is supported by the observation that bubbling ferrioxytochrome c produced a "head" of foam at least 10 times more copious than did an identical rate of bubbling of ferroxytochrome c. Evidently the ferrixytochrome c undergoes surface denaturation much more readily than does ferroxytochrome c, which did not generate polymers when bubbled.

There is a large body of evidence (43) which suggests that ferroxytochrome c has a more compact or more stable structure than does ferrioxytochrome c. The variety of denaturing conditions which gave rise to the inhibitor is also in accord with this suggestion. The inability of yeast ferrixytochrome c and of horse heart ferroxytochrome c to give rise to inhibitor accords with their known resistance to polymer formation (4). The sulfite:cytochrome c oxidoreductase was very sensitive to polymeric cytochrome c as was the TPNH:cytochrome c reductase, whereas the xanthine oxidase system was unaffected by the polymer. This indicates that cytochrome c reduction by the mediator enzymes occurs by a fundamentally different mechanism than by the latter enzyme. The requirement for oxygen as a mediator of cytochrome c reduction in the latter case but not in the former is also indicative of this difference.

The observation that inhibition was an exponential function ($n = 2.56$) of the inhibitor concentration, could have been due to the existence of multiple, interacting binding sites for the inhibitory polymer on the enzyme. This, however, seems very unlikely because the inhibition was strictly competitive with respect to monomeric cytochrome c and the saturation curve for monomeric cytochrome c was hyperbolic ($n = 1$).

It seems more reasonable to suppose that an interconversion of inhibitory high polymers and noninhibitory oligomers of cytochrome c forms the basis of the observed exponential relationship. However, additional experimental work must be done before such an explanation can be considered fully satisfactory. It is likely that inhibition of the sulfite:cytochrome c oxidoreductase could be used as a sensitive index of the state of polymerization of cytochrome c and could thus facilitate careful studies of the interconversions of the monomeric and polymeric forms of cytochrome c. Glogolin and Singer (36) studied the reduction of cytochrome c by the $\beta$-lactic cytochrome c reductase and by other enzymes and noted that the method of preparation of the cytochrome c used markedly affected the kinetic parameters of the enzymes under consideration. They concluded that the differences were due to variable contents of modified or denatured cytochrome c. In the light of present results it is probable that the enzymes they studied were also susceptible to inhibition by polymeric cytochrome c.

**References**


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*E. Margolinsh, personal communication.*
Sulfite: Cytochrome c Oxidoreductase: INHIBITION BY POLYMERS OF CYTOCHROME c
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