Thiazolidine-2-carboxylic Acid, an Adduct of Cysteamine and Glyoxylate, as a Substrate for D-Amino Acid Oxidase

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A mixture of cysteamine and glyoxylate, proposed by Hamilton et al. to form the physiological substrate of hog kidney D-amino acid oxidase (Hamilton, G. A., Buckthai, D. J., Mortensen, R. M., and Zerby, K. W. (1979) Proc. Natl. Acad. Sci. U. S. A. 76, 2825-2829), was confirmed to act as a good substrate for the pure enzyme. As proposed by those workers, it was shown that the actual substrate is thiazolidine-2-carboxylic acid, formed from cysteamine and glyoxylate with a second order rate constant of 84 min⁻¹ M⁻¹ at 37 °C, pH 7.5. Steady state kinetic analyses reveal that thiazolidine-2-carboxylic acid is a better substrate at pH 8.5 than at pH 7.5. At both pH values, the catalytic turnover number is similar to that obtained with D-proline. D-Amino acid oxidase is rapidly reduced by thiazolidine-2-carboxylic acid to form a reduced enzyme-imino acid complex, as is typical with D-amino acid oxidase substrates. The product of oxidation was shown by NMR to be Δ₂-thiazolidine-2-carboxylic acid. Racemic thiazolidine-2-carboxylic acid is completely oxidized by the enzyme. The directly measured rate of isomerization of L-thiazolidine-2-carboxylic acid to the D-isomer was compared to the rate of oxidation of the L-isomer by D-amino acid oxidase. Their identity over the range of temperature from 2-30 °C established that the apparent activity with the L-amino acid can be explained quantitatively by the rapid, prior isomerization to D-thiazolidine-2-carboxylic acid.

The flavoprotein D-amino acid oxidase was first detected in hog kidney nearly 50 years ago (1). It has been studied extensively since then, and many of the details of its mechanism have been worked out. The enzyme first oxidizes its D-amino acid substrate to the corresponding α-imino acid, probably through a carbanion mechanism, forming a reduced enzyme-imino acid complex (2-4). This then transfers its electrons to oxygen, producing hydrogen peroxide and oxidized enzyme-imino acid. The α-imino acid finally dissociates from the oxidized enzyme in the rate-limiting step (2, 5-7). With cyclic amino acids such as D-proline, the α-imino acid is the final product; with noncyclic amino acids the α-imino acid rearranges to the corresponding α-keto acid, the more common final product.

Despite this detailed knowledge of the mechanism, the physiological role of D-amino acid oxidase remains unknown. The enzyme is known to be specific for D-amino acids (except for very low reported activity with L-proline and L-3,4-dehydropoline (8)), yet the low level of these found in mammalian tissues does not seem to justify the large amount of D-amino acid oxidase present there.

Recently, Hamilton et al. proposed that the true substrate might be an adduct formed between glyoxylate and one of several physiological amines (9). Among the amines they tested, one, cysteamine, when combined with glyoxylate, was particularly active as a substrate for D-amino acid oxidase. They proposed that the actual substrate oxidized was thiazolidine-2-carboxylic acid, formed as in Scheme 1. They also reported that such a mixture was a better substrate at pH 7.4, a pH in the physiological range, than at pH 8.3, a more common pH for the study of D-amino acid oxidase.

![Scheme 1](http://www.jbc.org/)

Because of the importance that discovery of the physiological substrate of D-amino oxidase would have, we examined the reaction of the cysteamine-glyoxylate adduct with D-amino acid oxidase in some detail. In this paper we address ourselves to the following aspects of the problem: 1) Do cysteamine and glyoxylate react to form a substrate for D-amino acid oxidase under physiological conditions, and what is the product of this reaction? 2) How good a substrate for D-amino acid oxidase is this reaction product? 3) Is D-amino acid oxidase specific for only the D-isomer of this product? Our results provide substantial evidence for the proposal of Hamilton et al. (9) that the true substrate is thiazolidine-2-carboxylic acid and that it is oxidized enzymically to thiazoline-2-carboxylic acid. It has been shown, in addition, that the enzyme flavin is reduced extremely rapidly by D-thiazolidine-2-carboxylic acid but only slowly by the L-isomer. These results indicate that D-thiazolidine-2-carboxylic acid behaves as a normal substrate for the enzyme, with reaction properties very similar to those documented previously with D-proline (2, 5).

**EXPERIMENTAL PROCEDURES**

*Materials—Cysteamine, glyoxylate, and deuterium oxide were obtained from Aldrich Chemical Co. D-Cysteine, L-proline methyl ester, (+)- and (−)-tartarate, and porcine liver esterase, type I, were obtained from Sigma. The esterase was free of any racemase activity when measured with either D-proline or L-proline methyl ester. D-Proline was from Calbiochem; DL-proline was from Nutritional Biochemicals. All other chemicals were of the highest quality commercially available.*

D-Amino acid oxidase was purified from hog kidney using a modification of previous methods. The homogenization and heat/ammonium sulfate steps were as described by Jenkins et al. (10). The pellet obtained this way was then further purified by calcium phosphate
and DEAE-Sephadex chromatography as previously described (11). 

Steady State Kinetics—Steady state kinetic analysis of d-amino acid oxidase with most amino acid substrates results in a series of apparently parallel lines; this is consistent with Equation (5), with $\phi_{A0}$ being very small. This type of

$$c = \phi_0 + \phi_0 + \phi_{A0}$$

pattern was also obtained with a mixture of cysteamine and glyoxylate as substrate (Fig. 2A). To ensure that the substrate was the cysteamine-glyoxylate adduct, 0.75 mM glyoxylate and 0.5 mM cysteamine, measured as free thiol, were allowed to react for 2 h at 25 °C, pH 8.5, before being diluted and used for assays. Authentic thiazolidine-2-carboxylic acid, the expected result of such a reaction, also gave a pattern of parallel lines (Fig. 2B). A summary of the results at both pH 7.5 and pH 8.5, as well as the results with D-proline and D-thiazolidine-4-carboxylic acid, are given in Table I. The kinetics with d-thiazolidine-4-carboxylic acid at pH 7.5 was the only instance where converging lines were seen (data not shown).

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**D-Amino Acid Oxidase Substrates**

The results with the cysteamine-glyoxylate mixture and with thiazolidine-2-carboxylic acid showed nearly identical $\phi_0$ and $\phi_0$ values at both pH values, only differing slightly in their $\phi_{A0}$ values. Indeed, the limited solubility of oxygen made it impossible to measure $\phi_0$ accurately, so the values obtained with thiazolidine-2-carboxylic acid and with the cysteamine-glyoxylate mixture cannot be considered meaningfully different.

**Reaction of Cysteamine with Glyoxylate**—The rate of the reaction of cysteamine with glyoxylate was measured at 37 °C, in 0.1 M sodium phosphate, pH 7.5, to simulate physiological conditions. The assay followed the loss of the cysteamine thiol, since Scheme 1 predicts that this would be the final step in the reaction. A direct plot of the observed rate versus the concentration of the varied substrate, glyoxylate, gave a straight line with a zero intercept (Fig. 1). The second order rate constant calculated from these results was 84 min⁻¹ M⁻¹. More extensive measurements at 25 °C, varying the glyoxylate concentration from 1 mM to 0.1 M, showed no evidence of either a non-zero intercept or a limiting rate at high glyoxylate concentrations.

These results are consistent with an irreversible reaction in which ring closure is more rapid than formation of the Schiff's base between cysteamine and glyoxylate. In all cases the reaction showed complete and monophasic disappearance of free thiol, again indicating that formation of adduct is essentially irreversible. Finally, the rate of ring opening was measured directly by incubating a large excess of 5,5'-dithiobis-(2-nitrobenzolic acid) with authentic thiazolidine-2-carboxylic acid. The observed rate, which was very slow, was however directly dependent on 5,5'-dithiobis-(2-nitrobenzolic acid) concentration, consistent with Scheme 1, and with ring closure being of the order of 10⁶ times faster than ring opening.

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acetyl charge transfer complex; the imino acid then slowly dissociates (2). This same pattern was found with thiazolidine-2-carboxylic acid. The rapid reduction had a limiting rate of 326 s⁻¹ and a $K_d$ of 5.6 mm (Fig. 3). The charge transfer complex had an extinction coefficient of approximately 2000 cm⁻¹ M⁻¹ at 600 nm and was similar in shape to that seen with D-proline (2); it decayed to free reduced enzyme at a rate of 5.8 min⁻¹.

Identification of the Product of Oxidation of Thiazolidine-2-carboxylic Acid—The expected product from oxidation of thiazolidine-2-carboxylic acid by D-amino acid oxidase is $\Delta^2$-thiazoline-2-carboxylic acid. That this is indeed the product was shown by the proton NMR spectra of the substrate and product (Fig. 4). The product spectrum showed the expected loss of the $\alpha$-hydrogen signal at 5.3 $\delta$. Also, the triplets from the 4- and 5-carbon hydrogens were shifted downfield, as expected from the formation of an adjacent double bond.

$$\Delta^2\text{-thiazoline-2-carboxylic acid}$$

Finally, the product was unstable in acid, in agreement with the known behavior of thiazolines (17). Two results indicated that thiazolidine-2-carboxylic acid and the cysteamine-glyoxylate mixture gave the same product. First, the ultraviolet spectra of the products from both substrates showed maxima at 268 nm and minima at 242 nm. Second, the visible spectra of a-amino acid oxidase during aerobic turnover with both substrates were identical; this is typically the spectrum of the oxidized enzyme-imino acid complex.

Utilization of L-Thiazolidine-2-carboxylic Acid by D-Amino Acid Oxidase—We next determined the stoichiometry of oxygen consumption during the oxidation of thiazolidine-2-carboxylic acid by D-amino acid oxidase. As shown in Fig. 5, complete oxidation required an equinolar amount of oxygen, even though the thiazolidine-2-carboxylic acid used was racemic, based on its lack of optical activity. This result thus suggested that both D- and L-thiazolidine-2-carboxylic acids are good substrates, contrary to the known stereospecificity of D-amino acid oxidase.

To determine if L-thiazolidine-2-carboxylic acid actually is

![Double reciprocal plot of reductive half-reaction data for thiazolidine-2-carboxylic acid at 19 °C in 20 mM sodium pyrophosphate, pH 8.5.](http://www.jbc.org/)

**FIG. 3.** Double reciprocal plot of reductive half-reaction data for thiazolidine-2-carboxylic acid at 19 °C in 20 mM sodium pyrophosphate, pH 8.5. Substrate was mixed anaerobically with enzyme and the reaction followed at 450 nm. The concentration of adduct was calculated assuming that all of the cysteamine was converted to the adduct.

| Substrate | $1/\phi_0$ | $\phi_0$ | $K_a$ | $K_m$ |
|-----------|-----------|-----------|-------|-------|
| pH 8.5    |           |           |       |       |
| D-thiazolidine-2-carboxylic acid | 5,000 | 1.11 x 10⁻² | 8.7 x 10⁻³ | 5.5 | 4.4 |
| cysteamine/glyoxylate* | 4,000 | 1.0 x 10⁻² | 8.4 x 10⁻³ | 4.8 | 3.3 |
| D-Proline | 10,000 | 2.3 x 10⁻² | 2.4 x 10⁻³ | 2.4 |
| D-thiazolidine-4-carboxylic acid | 200 | 1.3 x 10⁻² | 4.7 x 10⁻³ | 0.26 x 0.87 |
| pH 7.5    |           |           |       |       |
| D-thiazolidine-2-carboxylic acid | 2,500 | 7.75 x 10⁻² | 6.0 x 10⁻² | 1.9 | 1.5 |
| cysteamine/glyoxylate* | 2,200 | 7.4 x 10⁻² | 6.5 x 10⁻³ | 1.6 | 1.4 |
| D-Proline | 2,800 | 7.7 x 10⁻² | 2.0 x 10⁻³ | 0.22 | 0.59 |
| D-thiazolidine-4-carboxylic acid | 230 | 5.6 x 10⁻³ | 3.3 x 10⁻³ | 0.13 | 0.25 |

*Produced by incubating 0.5 mM cysteamine and 0.75 mM glyoxylate for 2 h at 25 °C; pH 8.5, before diluting for assays.
Fig. 4. Proton NMR spectra in deuterium oxide of thiazolidine-2-carboxylic acid before (A) and after (B) oxidation by D-amino acid oxidase. The product was prepared as described under "Experimental Procedures." A sample of thiazolidine-2-carboxylic acid to which no D-amino acid oxidase had been added was treated identically to obtain spectrum A.

![Proton NMR spectra](image)

Fig. 5. Stoichiometry of oxygen consumption during oxidation of thiazolidine-2-carboxylic acid at 19°C in 20 mM sodium pyrophosphate, pH 8.5. A 3-ml solution of 1 mM DL-proline (---) or 1 mM DL-thiazolidine-2-carboxylic acid (----) was equilibrated with oxygen in the chamber of the oxygen electrode. D-Amino acid oxidase was then added at t₀ to a final concentration of 5.6 μM.

A substrate for D-amino acid oxidase, we synthesized and resolved the relatively stable D- and L-ethyl esters. Attempts to hydrolyze these chemically were unsuccessful; in strong base thiazolidine-2-carboxylic acid was destroyed, while in strong acid the ester racemized faster than it hydrolyzed. We therefore used pig liver esterase, which hydrolyzed the esters quite rapidly. However, upon hydrolysis the free amino acids then racemized. The possibility that the esterase had amino acid racemase activity was tested using L-proline methyl ester. Upon addition of the esterase, there was a rapid decrease in optical activity, corresponding to the difference between L-proline methyl ester and L-proline; no further change was detected. Moreover, in all of the following experiments, the observed rates were independent of esterase concentration, showing that the racemization was not enzyme-catalyzed and that hydrolysis of the esters was not rate-limiting.

To measure the rate of racemization, it was necessary to generate the free D- or L-amino acid from the ester in situ by mixing with esterase in the polarimeter, and then observing the loss of optical activity due to racemization of the amino acid. The esters themselves racemize under the conditions used, but only over a period of days; by making up the solutions immediately before use we were able to minimize this. At 20°C in 0.1 M sodium pyrophosphate, pH 8.5, both D- and L-thiazolidine-2-carboxylic acids lost optical activity with a half-time of 3.3 min. This is approximately the rate required to explain the results of Fig. 5 by isomerization of L-thiazolidine-2-carboxylic acid to the D-amino acid, which is then oxidized by D-amino acid oxidase. That the product of hydrolysis by esterase was thiazolidine-2-carboxylic acid was confirmed by thin layer chromatography on silica gel plates in butanol/acetic acid/water (12:3:5) using authentic thiazolidine-2-carboxylic acid as a standard.

To determine if all the activity with L-thiazolidine-2-carboxylic acid could be explained by isomerization, we compared the rate of oxidation of the L-amino acid with the directly measured rate of isomerization as a function of temperature. For temperatures above 15°C the rate of oxidation was measured with the oxygen electrode. A sample of either the D- or L-ester was incubated with esterase for 5 min at 4°C, at which temperature racemization is very slow. An aliquot was then injected into the chamber of the oxygen electrode, which already contained D-amino acid oxidase, to give a final concentration of 100 or 133 μM amino acid. As shown in Fig. 6, at 15°C use of the D-ester resulted in rapid consumption of some 80–90% of the substrate, followed by slow consumption of the remainder; the second phase can be explained by isomerization of some D-amino acid to L-amino acid during the experiment. The same experiment with the L-ester gave a small burst, due to the presence of some D-amino acid, followed by logarithmic consumption of the remaining substrate (Fig. 6). The first order rate constant determined from such a trace was used for comparison with the measured isomerization rate.

At temperatures below 15°C, the rate of reduction of D-amino acid oxidase was used to measure the rate of oxidation of the substrate. Ten to twenty μM D-amino acid oxidase was combined with esterase in the main chamber of an anaerobic spectrophotometer cuvette containing either D- or L-thiazolidine-2-carboxylic acid ethyl ester in the sidearm. The amount of ester was ±10 times that of the D-amino acid oxidase after mixing. The cuvette was made anaerobic and the ester tipped in. The reduction, followed at 455 nm, was slow with the L-ester and too rapid to observe with the D-ester, even at 2°C (Fig. 7). Instead, with the D-ester only the slow breakdown of the reduced enzyme-amino acid complex was seen. No reduction was observed in the absence of the esterase.

An Arrhenius plot of the results from both the aerobic and anaerobic measurements of oxidation rate and from the direct measurement of loss of optical activity are shown in Fig. 8. All the results lie on the same line, justifying the conclusion that the oxidation of L-thiazolidine-2-carboxylic acid by D-amino acid oxidase was identical to that of the L-amino acid.

![Arrhenius plot](image)
A further problem arises in that D-amino acid oxidase is located in peroxisomes (21). The concentration of free glyoxylate in peroxisomes is probably much lower than 5 μM, since peroxisomes also contain L-hydroxy acid oxidase, for which glyoxylate is a substrate (21). Any reaction between glyoxylate and cysteamine would therefore have to occur in the cytosol, with the adduct entering the peroxisome before oxidation by D-amino acid oxidase could occur. It is at least as likely that it would instead be oxidized by mitochondrial proline oxidase, which is active on both L-proline and L-thiazolidine-4-carboxylic acid (22).

Whatever its physiological significance, it seems certain that the actual substrate formed by cysteamine and glyoxylate is thiazolidine-2-carboxylic acid, as proposed by Hamilton et al. (9). It is the major product of the reaction of cysteamine and glyoxylate at neutral or basic pH (23, 13). The possibility that a side reaction forms the actual substrate is ruled out by the similarity of the steady state kinetic parameters obtained with thiazolidine-2-carboxylic acid and the cysteamine-glyoxylate mixture, and the fact that they both give the same product upon oxidation by D-amino acid oxidase.

Examination of the results in Table I and Fig. 3 suggests that thiazolidine-2-carboxylic acid could best be described as a proline analog as far as its kinetics with D-amino acid oxidase are concerned. Both are more active at pH 8.5 than at pH 7.5, and both show higher turnover numbers than is usual for D-amino acid oxidase substrates. It is interesting that D-thiazolidine-4-carboxylic acid, which might be expected to follow this pattern, has a low turnover number, as well as a greatly reduced reactivity of the reduced enzyme-imino acid complex with oxygen, as reflected in the φ₀ parameter. In terms of catalytic efficiency, often measured by kcat/Km or 1/φₐ, both thiazolidine-2-carboxylic acid and D-thiazolidine-4-carboxylic acid are better substrates than D-proline at pH 8.5, especially since the kinetics with thiazolidine-2-carboxylic acid were done with a racemic mixture.

The most unexpected result from these studies was that L-thiazolidine-2-carboxylic acid was apparently almost as good a substrate as the D-isomer. D-Amino acid oxidase is generally thought to have absolute specificity for D-amino acids, although L-proline, L-dehydroproline, and L-thiazolidine-4-carboxylic acid have been reported to be very poor substrates (8). In none of these cases, however, was the L-isomer oxidized at an appreciable rate by D-amino acid oxidase. For that reason we investigated in some detail the possibility that the high apparent activity with L-thiazolidine-2-carboxylic acid could be explained by rapid isomerization to the D-amino acid, the actual substrate. The close agreement between the measured isomerization rate and the rate of reaction with D-amino acid oxidase over a range of temperatures confirms that all activity with L-thiazolidine-2-carboxylic acid can be quantitatively accounted for in this way.

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