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STELEOSELECTIVE REDUCTION OF RACEMIC N-HYDROXYAMINO ACIDS BY OPTICALLY ACTIVE THIOLS-IRON(II)

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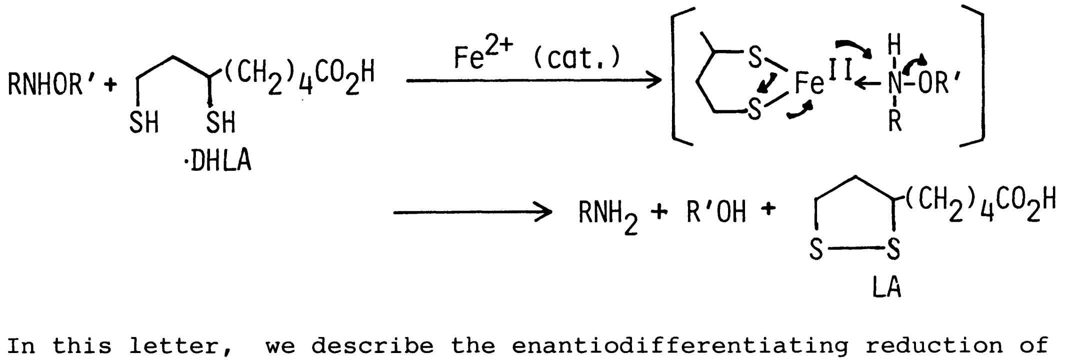
Kinetic resolution of racemic N-hydroxyamino acids by the reduction with optically active thiols and a catalytic amount of ferrous ion gave optically active amino acids presumably through enantiodifferentiating coordination of substrates to thiol-Fe(II) complexes.

In living systems many reactions catalyzed by metalloenzymes proceed with substrate specificity and stereoselectivity. These catalytic properties of metalloenzymes almost derive from the properties of the metal complexes formed with ligands of apoenzymes and substrates.[1)]

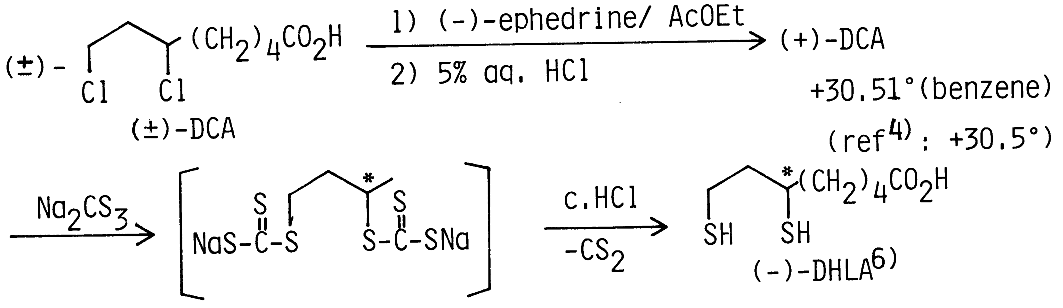
We have already reported[2)] that hydroxylamines are reduced by dihydrolipoic acid (DHLA) in the presence of a catalytic amount of ferrous ion under weakly alkaline conditions as shown in Eq. 1. We have further reported[3)] the selective reduction of substituted nitrobenzenes, isoxazolidines, and isoxazoles by dihydolipoamide-Fe(II).



(1)

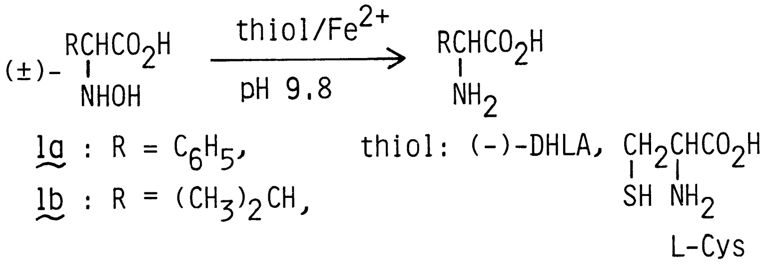
In this letter, we describe the enantiodifferentiating reduction of racemic N-hydroxyamino acids by optically active thiol-Fe(II) systems, which might have some similarities to the functions of metalloenzymes.

Optically active dihydrolipoic acid ((-)-DHLA) was prepared by the optical resolution of racemic 6,8-dichlorooctanoic acid (DCA) with (-)-ephedrin,[4] trithiocarbonylation[5] of the (+)-DCA, followed by the hydrolysis of the resulting bis(trithiocarbonate).[6]



(2)

The kinetic resolution of racemic N-hydroxyamino acids (1a,b)[7] was carried out by the reduction with 0.5 equiv.of optically active thiol, (-)-DHLA or L-cysteine (L-Cys), in the presence of ferrous ammonium sulfate in 0.1 M carbonate buffer (pH 9.8).



$$(\pm)\text{-}\underset{\text{NHOH}}{\text{RCHCO}_2\text{H}} \xrightarrow[\text{pH 9.8}]{\text{thiol/Fe}^{2+}} \underset{\text{NH}_2}{\text{RCHCO}_2\text{H}} \qquad (3)$$

1a : R = C_6H_5,

1b : R = $(CH_3)_2CH$,

thiol: (-)-DHLA, $\underset{\text{SH}\ \ \text{NH}_2}{\text{CH}_2\text{CHCO}_2\text{H}}$

L-Cys

Table 1. Reduction of 1 by optically active thiol-Fe(II)[a]

Substrate	M	Thiol	M	Conditions Temp/°C	Time/h	Yield/%[b]	$[\alpha]_D^{25}$/°	O.p./%[c]
1a	0.1	(-)-DHLA	0.05	1	72	29.5	+9.75	6.2(L)
1b	0.16	(-)-DHLA	0.08	5	120	25.5	+4.40	15.5(L)
1b	0.1	L-Cys	0.1	1	20	45.5	-17.42	61.6(D)

a) Reduction was carried out with 0.5 equiv. of thiols and 0.04 equiv. of Fe^{2+} in 0.1 M carbonate buffer (pH 9.8) under argon. Products were obtained by purification with an anion exchange resin and further recrystallization.

b) Yields were estimated on the basis of substrates.

c) L-Val: $[\alpha]_D^{25}$ +28.3°(5 M HCl), L-phenylglycine: $[\alpha]_D^{25}$ +156.4°(5 M HCl).

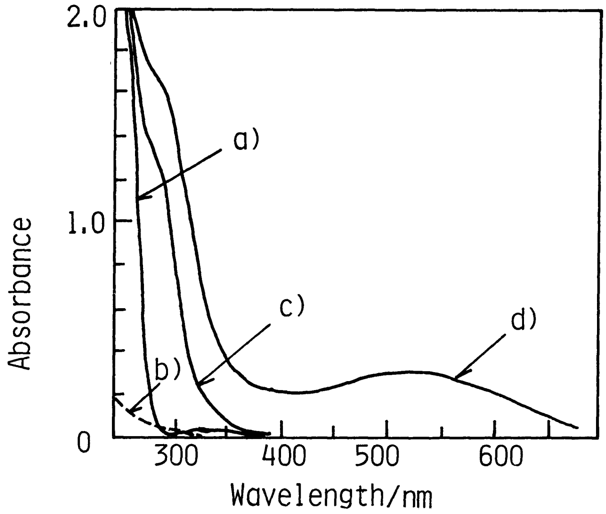


Fig. 1. Electronic spectra of an L-Cys-Fe(II) complex: a) L-Cys, b) Fe^{2+}, c) L-Cys and Fe^{2+}, d) L-Cys, Fe^{2+}, and **1b**; [L-Cys] = 2.8×10^{-3}M, [Fe^{2+}] = 8×10^{-4}M, [1b]= 5×10^{-4}M.

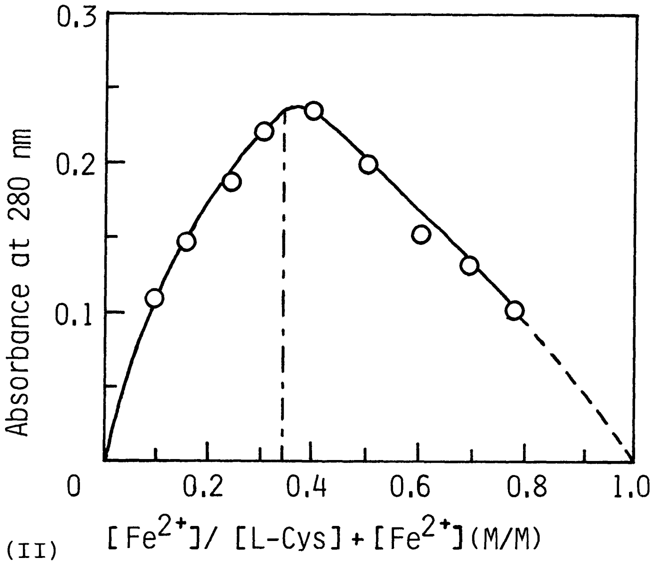
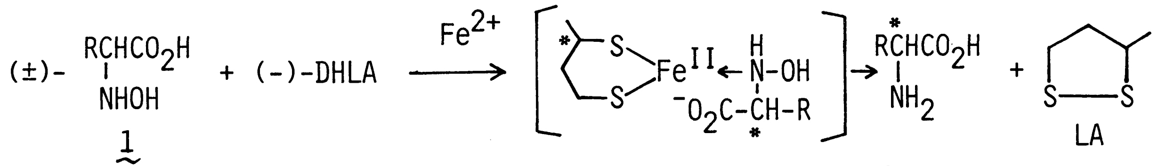


Fig. 2. Continuous variation curve: [L-Cys] + [Fe^{2+}] = 4.7×10^{-3}M.

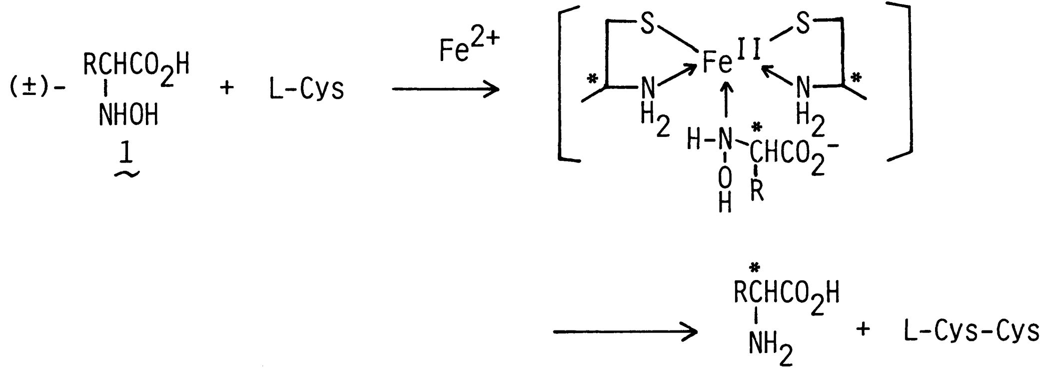
Optically active amino acids were obtained by the reduction of racemic substrates (**1a**,**b**) as summarized in Table 1. In case of L-Cys a good result was obtained in the reduction of **1b** to give optically active valine in higher chemical and optical yields, accompanied by the formation of L-cystine as precipitates.

As described earlier in Eq. 1, the reduction of hydroxylamines by the DHLA-Fe(II) system proceeded by the electron transfer in the mixed ferrous complex. The complex formation of L-Cys with ferrous ion was also suggested from Fig. 1, where the electronic spectrum of L-Cys (Fig. 1-a) changed to a new spectrum (Fig. 1-c) in the presence of ferrous ion, which was further changed to another spectrum (Fig. 1-d) by adding a substrate **1b**. The composition of the complex was examined by the continuous variation method (Fig. 2) by plotting the absorbance at 280 nm in Fig. 1-c, and a 2:1 complex was found to be formed from L-Cys and ferrous ion.

From these results, the stereoselective reduction of N-hydroxyamino acids by (-)-DHLA or L-Cys in the presence of ferrous ion was suggested to be derived from the enantiodifferentiating complex formation of substrates to the optically active thiol-Fe(II) complexes, followed by the electron transfer in the complexes, which might resulted in the difference of reduction rate of the enantiomers. Higher selectivity was obtained by the coordination of the substrate to a 2:1 complex of L-Cys and ferrous ion which had presumably a higher stereoregulation (Eq. 5).



(4)



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References

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6) (-)-DHLA: bp 144-145 °C (0.2 mmHg)(lit,[8] bp 169-172 °C(1 mmHg));$[\alpha]_D^{25}$ -12.28° (MeOH)(lit,[4] $[\alpha]_D^{25}$ -8.8°). Other analytical data were identical with those of the racemic DHLA.

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