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Iron(II) Complex with 1,3-Bis(2-benzimidazyl)-2-thiapropane as a Model Compound for Lipoxygenase

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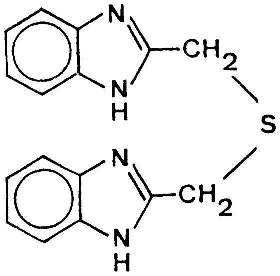
Iron(II) complex with 1,3-bis(2-benzimidazyl)-2-thiapropane is stable in air in both the solid and the solution states. This complex is oxidized to Fe(III) state by 13(S)-hydroperoxy-9Z,11E-octadecadienoic acid, and the Fe(III) species is readily reduced to Fe(II) state by phenidone. This suggests the presence of thioether group in the coordination sphere of native lipoxygenase.

Lipoxygenase(linoleate:oxygen oxidoreductase, EC 1.13.11.12) is a non-heme iron dioxygenase which catalyzes the dioxygenation of polysaturated fatty acids containing a 1Z,4Z-pentadiene system.$^{1)}$ Interest in the mechanism of lipoxygenase has been stimulated these last years by the discovery of the implication of lipoxygenases in the biosynthesis of leukotrienes which have an important role in inflammation and immediate hypersensitivity.$^{2)}$ A still unsolved mechanistic question is whether lipoxygenation proceeds via free-radical or organoiron intermediate formed during rate-limiting C-H bond cleavage,$^{3,4)}$ and it seems necessary to prepare a suitable model compound for the elucidation of the above question.

Native lipoxygenase-1 from soybean is colorless(Fe^{2+}) and virtually ESR-silent. Addition of an equivalent amount of 13(S)-hydroperoxy-9Z,11E-octadecadienoic acid(13(S)-HPOD) yields an active yellow enzyme species and ESR signal around g=6, stemming from high spin Fe(III).$^{1)}$ Iron is directly bound to the polypeptide backbone and does not bind with dioxygne molecule,$^{5)}$ but little is known about the actual coordination sphere. The study on the mechanism of inactivation of lipoxygenase has suggested the formation of stoichiometric amount of methionine sulfoxide,$^{6)}$ and thus we have initiated to prepare the iron(II) complexes with ligands containing a thioether group. In this article we wish to report that iron(II) complex with 1,3-bis(2-benzimidazyl)-2-thiapropane exhibits the properties similar to those observed for native lipoxygenases.



Chemical structure of (L)

The ligand used in this study(abbreviated as (L)) was prepared according to the published method.[7)] The iron(II) complex was obtained as colorless prisms from the reaction mixture(methanol) of ligand and $FeCl_2 \cdot 4H_2O$ under an aerobic condition. Analytical data[8)] is consistent with the formula, $Fe(L)Cl_2$. The magnetic moments of the complex are 5.06 and 5.06 μ_B at 294.6 and 81.5 K, respectively,[9)] indicating that this complex is a high-spin Fe(II) complex. As shown in Fig. 1, $Fe(L)Cl_2$ is ESR-silent at 77 K(dmso-methanol). When 13(S)-HPOD was added to the colorless solution of $Fe(L)Cl_2$, the solution turned yellow. This yellow species is ESR-detectable (cf. Fig. 1), and the presence of signals at g=4.3 — 7 demonstrates that oxidation of Fe(II) state to Fe(III) one proceeds in this step. The addition of phenidone to the yellow solution led to the disappearance of the ESR signal(trace C in Fig. 1), which should be due to the reduction of the Fe(III) state to Fe(II) state.[10)] These phenomena are very similar to those observed for the native lipoxygenases,[1,10)] and suggest the presence of thioether group in the coordination sphere of lipoxygenases.

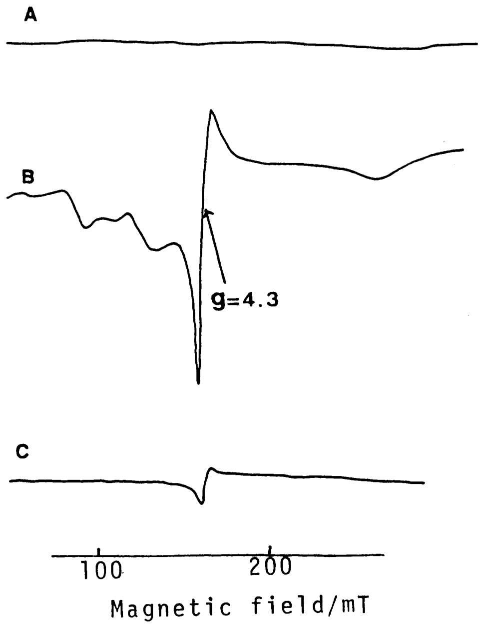


Fig. 1. ESR spectra(dmso-methanol ; [Fe]$\approx$5x10^{-3} mol dm^{-3}, 77 K)

A: $Fe(L)Cl_2$

B: $Fe(L)Cl_2$+13(S)-HPOD

C: solution B + phenidone

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