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Chiral Environment around the Metal Center Observed by the Epoxidation with the Iron Complexes of Bleomycin and the Synthetic Analogue[1)]

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cis-β-Methylstyrene is oxidized either with the Fe(III)-H_2O_2 or with the Fe(II)-O_2 complex systems of bleomycin and the synthetic model ligand PYML-6 to give optically active epoxide, showing that the environment around the iron-nucleus is chiral enough to cause asymmetric epoxidation.

Antitumor antibiotics bleomycins (BLMs) form Fe(II) complex to activate molecular oxygen and induce oxidative cleavage of DNA.[2)] The ultimate active species responsible for the oxidative reaction appear to be closely related to the transient BLM-Fe(III)-O_2^{2-} complex.[3)] Previously, we have reported a synthetic model equivalent to BLM in oxygen activation, namely PYML-6 (Fig. 1), and disclosed that stilbene can be epoxidized with the Fe(III)-H_2O_2 complex system of the synthetic analogue or BLM.[4)] Other groups have also studied oxidation of stilbene, styrene, chalcone, cinnamic acid, cyclohexene, norbornene, and indene using Fe(II), Fe(III), Cu(II), Mn(III), or Zn(III) complexes of BLM in the presence of O_2, C_6H_5IO, or $KHSO_2$ as oxygen donor.[5)] Although the formation of chiral iron chelate was reasonably proposed as shown in Fig. 1, there has been no report on asymmetric induction in the oxidation mediated by BLM-metal complex systems.[3,6)] We now found cis-β-methylstyrene to be affected by the chiral

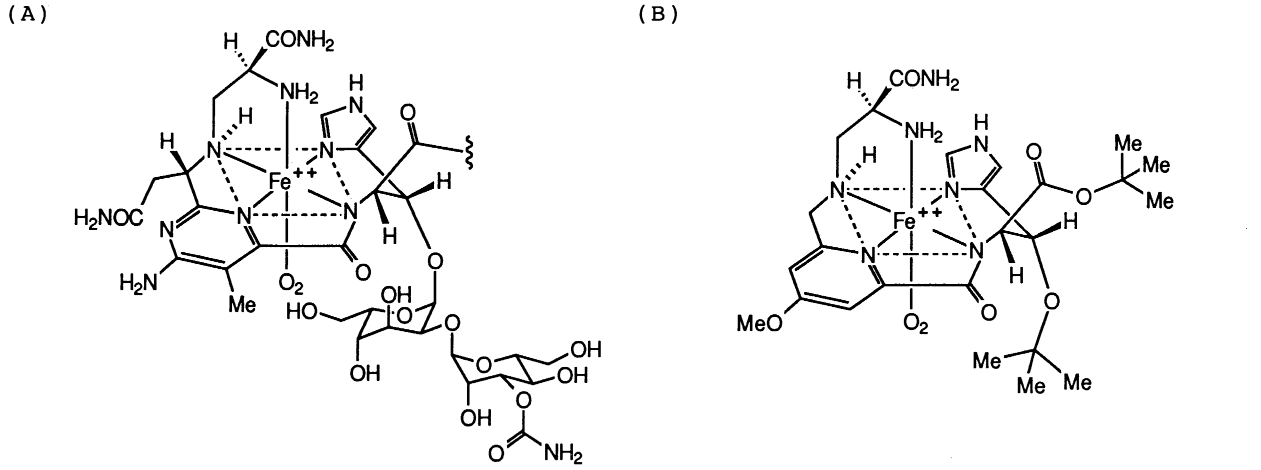
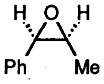
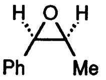
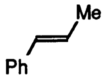
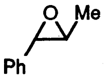
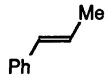
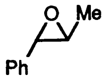


Fig. 1. Proposed structures of the Fe(II)-O_2 complexes of BLM (A) and PYML-6 (B).[2,4)]

Table 1. Epoxidation of cis- and trans-β-methylstyrene with the Fe(III)-H_2O_2 complex systems of BLM B4 and PYML-6

Ligand	Substrate	Product	Yield/% based on H_2O_2	Yield/% based on Ligand	ee (%)
BLM B4			17.2	500	46
PYML-6			7.0	212	45
BLM B4			5.6	169	0
PYML-6			4.3	124	0

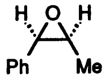
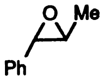
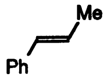
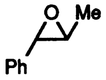
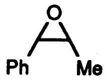
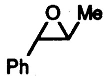
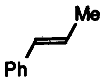
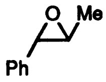
environment of the iron center and describe herein our results on the oxidation reaction mediated either by the Fe(III)-H_2O_2 or by Fe(II)-O_2 complex systems of BLM or PYML-6 to produce optically active epoxide.

Oxidation by the Fe(III)-H_2O_2 system was carried out as follows. A solution of the BLM B4 or PYML-6 Fe(III) complex (1 equiv.), H_2O_2 (1.17 M aqueous solution, 30 equiv.), and β-methylstyrene (90 equiv.) in methanol (2 ml per 1 μmol BLM B4 or PYML-6) was stirred for 2 h under argon atmosphere at room temperature. The solution was partitioned between dichloromethane and water and the organic layer was dried over sodium sulfate and concentrated in vacuo. The residue was purified by silica gel column chromatography eluted with hexane/ether = 50/1 to give epoxide. Retention time on gas chromatography (PEG 20M, 3 mm x 200 cm column, 120 °C) of this product was identical to that of the authentic racemic epoxide prepared by the m-chloroperbenzoic acid oxidation of the substrate olefin.7) The absolute stereochemistry and enantiomeric excess (ee) of this material was determined based on the polarimetric measurement and ^{1}H NMR measurement using chiral shift reagent tris[3-(heptafluoropropylhydroxymethylene)-d-camphonato]europium(III).8)

Oxidation by the Fe(II)-O_2 system in the presence of a reducing agent was carried out as follows. A solution of the PYML-6-Fe(II) complex (1 equiv.), a reducing agent (2-mercaptoethanol or sodium L-ascorbate) (45 equiv.), and β-methylstyrene (90 equiv.) in methanol (1.5 ml per 1 μmol PYML-6) was stirred for 2 h in the air at room temperature. Work-up of the solution and analysis of the product were carried out as described above.

The results summarized in Table 1 indicate that BLM B4-Fe(III)-H_2O_2 and PYML-6-Fe(III)-H_2O_2 both exhibited the same tendency in the substrate specificity and the stereoselectivity in the epoxidation of β-methylstyrene. Catalytic efficiency of BLM B4-Fe(III) was higher than that of PYML-6-Fe(III) and cis-olefin was more reactive than trans-olefin. Whereas the epoxidation of trans-β-methylstyrene resulted in the formation of racemic product, cis-β-methylstyrene was epoxidized stereoselectively to give (-)-cis-

Table 2. Epoxidation of *cis*- and *trans*-β-methylstyrene with the PYML-6-Fe(II)-O_2 complex system

			Yield/% based on		
Reducing agent	Substrate	Product	PYML-6	Reducing agent	ee (%)
2-Mercaptoethanol			87	2	51
			trace		-
		PhCHO	344	7.7	-
2-Mercaptoethanol			104	2.3	0
		PhCHO	334	7.5	-
L-Ascorbate			trace		-
			199	4.5	<5
		PhCHO	142	3.2	-
L-Ascorbate			451	9.8	<5
		PhCHO	101	2.3	-

β-methylstyrene oxide in about 45% ee. *trans*-Epoxide could hardly be observed in the epoxidation of the *cis*-substrate.

Table 2 shows the results of aerobic oxidation with the PYML-6-Fe(II) complex. The result of this reaction largely depends on the choice of the reducing agent. Use of sodium dithionite or sodium borohydride afforded no reaction-products. On the other hand, *cis*- and *trans*-β-methylstyrenes were oxidized with the PYML-6-Fe(II)-O_2-(2-mercaptoethanol) system to give (-)-*cis*-epoxide (51% ee) and racemic *trans*-epoxide, respectively. Major product of this oxidation system was benzaldehyde. Control experiments using (2-mercaptoethanol)-Fe(II)-O_2 system afforded benzaldehyde exclusively, without formation of any epoxide. In contrast, when sodium L-ascorbate was employed as reducing agent, virtually racemic *trans*-epoxide was obtained in addition to benzaldehyde from both cis and trans substrates, suggesting the radical character of the metallocene intermediate.

Metal binding site of BLM has a unique, asymmetrical array of five nitrogen donor atoms including the secondary amino group with locked configuration, and the disaccharide moiety appears to be spatially close to the iron-oxygen site and must play a signifficant role as a steric factor (Fig. 1). It is noteworthy that the displacement of the disaccharide by a t-butyl group in PYML-6 ligand reproduced virtually the same ee value of the epoxide. The observed stereochemical outcome could be explained by assuming that the olefin approaches in such an orientation as to minimize the steric repulsion between the phenyl group and the disaccharide or the t-butyl group.

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