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Hemin-Catalyzed Addition Reactions of Thiophenols to Styrene

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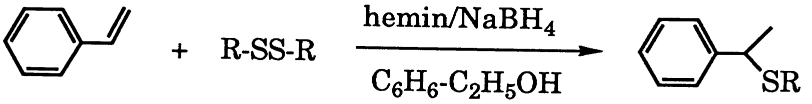
Hemin promotes the Markovnikov-type addition reactions of thiols (origins of the thiols are their disulfide derivatives) to styrene in benzene-ethanol (1:1) containing $NaBH_4$. The plausible reaction mechanism has been discussed.

Metalloporphyrins have been studied extensively to mimic the cytochrome P-450 function.1) The reactions studied in most model systems, however, have been limited to epoxidation and hydroxylation of alkenes using iodosylbenzene and alkyl hydroperoxides as oxidizing agents. In order to use molecular oxygen, porphinatoiron(III) should be reduced to porphinatoiron(II) prior to form activated dioxygen. Tabushi and Koga2) have succeeded oxygenation of cyclohexene using 5,10,15,20-tetraphenylporphinatomanganese(III) (TPPMn(III)) as a catalyst and $NaBH_4$ as a reducing agent. Later the tetrahydroborate anion (BH_4^-) has been confirmed to activate molecular oxygen in oxidation reactions of alkenes which are catalyzed by metalloporphyrines.3) In the TPPFe(III)-catalyzed oxygenation of styrene in methanolic benzene containing $NaBH_4$ and tetramethylammonium hydroxide, a Markovnikov-type addition of H_2O to styrene formally occurs.3c) In the present study, we found a new type addition reaction of thiophenol to styrene which is catalyzed by hemin in anaerobic benzene-ethanol containing $NaBH_4$. We report herein the preliminary results and the plausible reaction mechanism of the following reactions:



(1)

$R = C_6H_5-, C_2H_5-, CH_3-$

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A mixture of 0.153 mmol of hemin, 3.06 mmol of $NaBH_4$, and 1.53 mmol of diphenyl disulfide was placed in a 30 ml flask and the reaction atmosphere was replaced by nitrogen. Styrene (1.53 mmol) in 8 ml of benzene-ethanol (1:1) was added into the flask by using a syringe and the mixture was stirred for 24 h at room temperature. After the reaction, the solvent was evaporated and the residue was extracted by hexane. The insoluble solids were filtrated and hexane was evaporated from the filtrate. The oily residue was chromatographed on silica gel with a benzene-hexane mixture. The structure of the product was determined by means of ^1H and ^{13}C NMR, IR, and mass spectroscopy. The only product isolated was phenyl 1-phenylethyl sulfide (36% yield). Diethyl disulfide and dimethyl disulfide also provided the Markovnikov-type adducts of corresponding thiols in the 23 and 22% yields, respectively. The IR spectrum indicated that hemin is converted to its disodium salt.

Table 1 shows the results on the reactions of styrene with diphenyl disulfide in organic solvents containing $NaBH_4$ and hemin or TPPFe(III)Cl at room temperature. The yields of phenyl 1-phenylethyl sulfide were determined by means of gas chromatography using biphenyl as an internal standard.

Table 1. Porphinatoiron(III)-Catalyzed Reactions of Styrene with Diphenyl Disulfide in Organic Solvents Containing $NaBH_4$[a)]

Run	Catalyst	Solvent[b)]	Reaction time/h	Yield/%[c)]
1	Hemin	A	24	47 (89)
2	TPPFe(III)	A	24	19 (22)
3	None	A	6	0.6 (100)
4	Hemin	A	6	38 (83)
5	Hemin	B	6	14 (82)
6	Hemin	C	8	7 (34)
7	Hemin	D	6	8 (24)
8	Hemin	E	6	1 (8)

a) $[NaBH_4] = 0.38$ M (1 M = 1 mol dm^{-3}), [styrene] = [diphenyl disulfide] = 0.19 M, [porphyrin] = 0.019 M.

b) A: C_6H_6-C_2H_5OH (1:1), B: C_6H_6-2-Propanol (1:1), C: C_6H_6-CH_3CN (1:1), D: C_2H_5OH, E: C_6H_6-C_2H_5OH-pyridine (4:4:1).

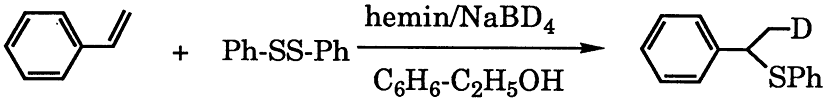
c) The values in parentheses are the yields of the thiophenol adduct based on the consumed styrene.

Although porphinatoiron(III) is not essential (see Run 3), the addition reaction is greatly accelerated by hemin. TPPFe(III) shows a poor catalytic effect compared with hemin (Run

2). Fe(III)EDTA, Co(II)salen, and $Ru(III)(bpy)_3Cl_2$ do not act as the catalysts under the similar conditions. Pyridine strongly inhibits the reaction (Run 8).

The yield of phenyl 1-phenylethyl sulfide (2%) was significantly reduced when thiophenol itself was used in place of diphenyl disulfide.[4)] No addition reaction was occurred between styrene and phenol under the similar conditions.

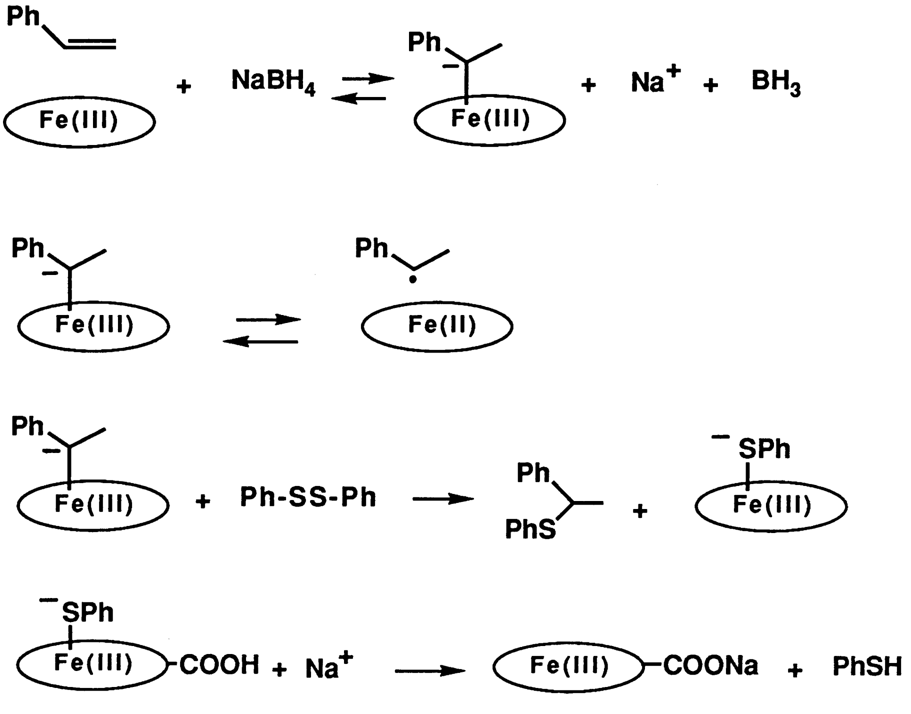
In order to clarify the reaction mechanism, the deuterium incorporation was examined by using $NaBD_4$ and C_2H_5OD. The product was analyzed by means of ^1H NMR and mass spectroscopy. When $NaBD_4$ was used, phenyl 1-phenyl-2-deuterioethyl sulfide was the only product which could be isolated:



(2)

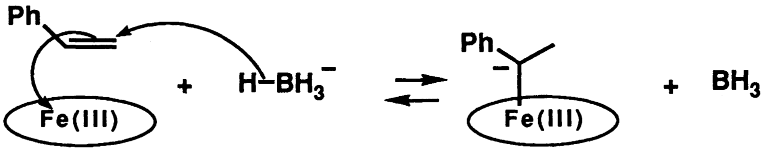
No hydrogen transfer from the protic solvent was observed.

On the basis of these findings, we assumed the following scheme as a plausible reaction mechanism:



Scheme 1.

A point of this mechanism may be the hydride transfer from BH_4^- to styrene to form secondary carbanion. In general, alkenes cannot be reduced by BH_4^-. Probably the transition state of this reaction is stabilized by interacting with hemin:



(3)

Recently, we found that styrene and *trans*-stilbene are reduced to ethylbenzene and bibenzyl, respectively, by $NaBH_4$ in protic solvents containing hemin.5) This strongly supports the formation of the carbanion of styrene stabilized by hemin. It has been known that carbanion-porphynatoiron(III) complexes are formed during the haloalkane metabolism catalyzed by cytochrome P-450.6) Detailed study on the reaction mechanism is now in progress.

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4) The reaction was carried out under the following conditions: [styrene] = 0.19 M, $[C_6H_5SH]$ = $[NaBH_4]$ = 0.38 M, [hemin] = 0.019 M. The yield of phenyl 1-phenylethyl sulfide was 11% when the hemin-catalyzed reaction of styrene with thiophenol was carried out in the presence of NaH (0.38 M) and 18-crown-6 (0.38 M).

5) The details will be published in the near future.

6) H. H. Ruf, H. Ahr, W. Nastainczyk, V. Ullrich, D. Mansuy, J.-P. Battioni, R. Montiel-Montoya, and A. Trautwein, *Biochemistry*, **23**, 5300 (1984) and references cited therein.

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