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# Aerobic Oxygenation/Dehydrogenation of Olefins and 1,4-Dihydropyridines Catalyzed by Tris(tetrazolyl enolate)iron(III) Complexes

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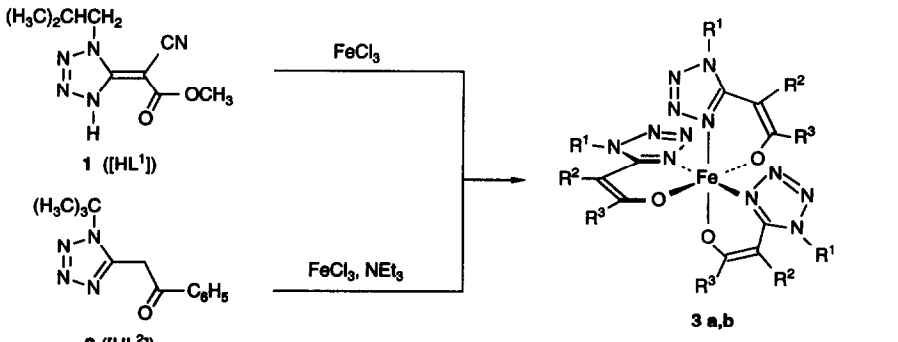
*Keywords: Epoxidation; dehydrogenation; dealkylation; [$FeL_3$]-complexes; catalysis; cytochrome P-450; 1,4-dihydropyridines.*

*Abstract: The catalytic epoxidation of olefins 4 - 7 catalyzed by synthetic metalloporphyrin analogues [$FeL_3$] 3 associated with molecular oxygen in the presence of an electron source (isobutyraldehyde) is described. Furthermore, it is shown, that 4-substituted 1,4-dihydropyridines 12 can be dehydrogenated and dealkylated, respectively, by the same system. The analogy to cytochrome P-450 is obvious.*

Metal catalysis of the oxidation of various organic substrates is of synthetic as well as of biological interest[1,2]. Since the discovery of cytochrome P-450 catalyzed reactions, the unique ability of these enzymes to transfer an O-atom regio- and stereospecifically has been a serious challenge to the organic chemist. Crucial step in simulating P-450 catalyzed reactions is the problematic reductive cleavage of molecular oxygen.

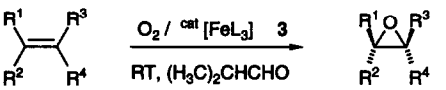
Recent results[3-12], obtained in the field of oxygenation reactions of hydrocarbons (epoxidation and hydroxylation) catalyzed by synthetic metalloporphyrins or tris(1,3-diketonato)iron(III) complexes associated with various oxidants: single-oxygen donors (iodosylbenzene, N-oxides, hydrogen peroxide, potassium hydrogen persulfate, alkylhydroperoxides) or di-oxygen in the presence of an electron source prompt us, to report on our own investigations in this field.

Naturally occurring and synthetically accessible siderophores (iron carriers) contain predominantly bidentate pyrocatechinato- or hydroxamato-ligands and are of special interest because of their high affinity towards trivalent metal ions, especially towards iron(III) ions[13,14]. Upon reaction of the synthetic siderophores **1** and **2** of the tetrazolylenol type in ether with aqueous iron(III) chloride solution, a deep blue colouration of the ether phase suddenly occurs, and after addition of hexane, the corresponding iron(III) complexes **3** separate in the form of deep blue microcrystals. If the hydrochloric acid formed thereby is trapped by addition of triethylamine, yields between 84 and 89% can be achieved.



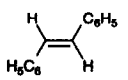
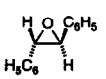
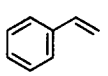
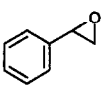
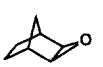
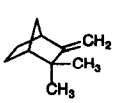
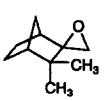
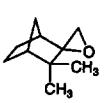

| 3 | $R^1$ | $R^2$ | $R^3$ |
|---|---|---|---|
| a ([FeL$^1_3$]) | $CH_2CH(CH_3)_2$ | CN | $OCH_3$ |
| b ([FeL$^2_3$]) | $C(CH_3)_3$ | H | $C_6H_5$ |

The [$FeL_3$]-complexes **3**, at first prepared by us with a completely different intention, appeared to be also suitable as oxygenation / dehydrogenation catalysts. Like cytochrome P-450, synthetic metalloporphyrins or tris(1,3-diketonato)iron(III) complexes, [$FeL_3$] **3** is capable in catalyzing the epoxidation of the olefins **4** - **7** with combined use of molecular oxygen at atmospheric pressure and an aldehyde at room temperature. The epoxides **8** - **11** are generated in good yields.




**4 - 7** $R^{1-4}$ = H, Alkyl, Aryl **8 - 11**

Table 1. [$FeL_3$]-catalyzed aerobic epoxidation of olefins.

| | olefin | epoxide | catalyst (mol-%) | time [h] | yield [%] |
|---|---|---|---|---|---|
| 4 |  | 8  | **3a** (2) | 8 | 10 |
| | | | **3b** (2) | 12 | 96 |
| 5 |  | 9  | **3b** (2) | 4 | 46 |
| 6 |  | 10  | **3b** (1) | 5 | 85 |
| 7 |  | **11a**  | **3b** (1) | 4 | 87 (**a:b** = 1:1) |
| | | **11b**  | | | |

*General procedure (I):* A solution of 30 mmol olefin **4** - **7**, 0.3 - 0.6 mmol (1.0 - 2.0 mol-%) [$FeL_3$] **3**, prepared according to Lit.[13], and 6.45 g (90 mmol) isobutyraldehyde in 50 ml 1,2-dichloroethane is stirred (turbo stirrer: 5000 tpm) at 20 °C under 1.0 atm of oxygen. After 1 - 2 h, the colour of the solution changes from deep blue to pale red, and oxygen is consumed. Stirring is continued for additional 2 - 10 h, then the reaction mixture is washed with saturated aqueous sodium hydrogen carbonate solution, and, after drying over anhydrous sodium sulfate, the solvent is removed in vacuo. Purification of the residue by column chromatography on silica gel (hexane) affords the epoxides **8** - **11** in excellent yields (determined by GC analysis). For further details see table 1.

4-Substituted 3,5-bis(alkoxycarbonyl)-2,6-dimethyl-1,4-dihydropyridines (e. g. *nifedipine*) are important because of their roles as calcium channel blockers. The major products of cytochrome P-450-catalyzed aerobic dehydrogenation of 4-*aryl*-substituted dihydropyridines are the pyridine derivatives, containing the 4-aryl group. In contrast, 4 *alkyl*-substituted dihydropyridines are dealkylated under equivalent conditions[15].

The biomimetic potential of [$FeL^2_3$]-catalyst **3b**, $O_2$ and isobutyraldehyde has also been studied using dihydropyridines **12** as substrates. The results obtained indicate the formation of products identical to those obtained in the case of *in vivo* metabolism. The dihydropyridines **12a,c** are dehydrogenated to give the pyridines **13** and **14**, respectively, whereas **12b** is dealkylated to yield **14**.

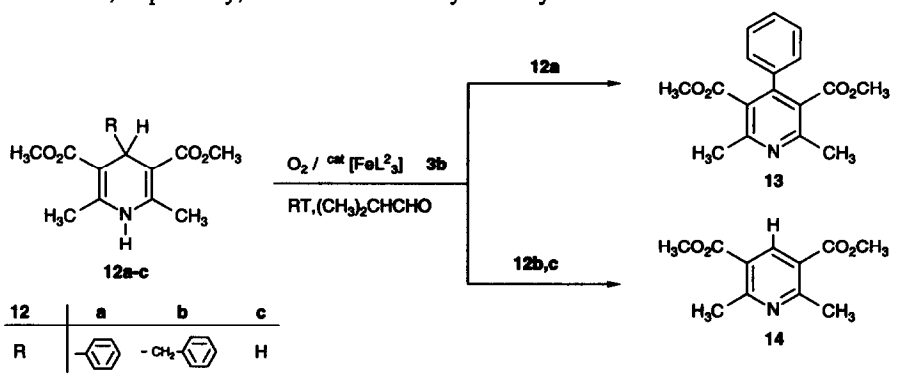



Table 2. [$FeL^2_3$]-catalyzed aerobic dehydrogenation / dealkylation of dihydropyridines.

| 1,4-dihydropyridine | pyridine | catalyst (mol-%) | time [h] | yield [%] |
|---|---|---|---|---|
| **12a** | **13** | **3b** (4) | 7 | 57 |
| **12b** | **14** | **3b** (4) | 72 | 80 |
| **12c** | **14** | **3b** (4) | 72 | 100 |

*General procedure (II)*: See *procedure (I)*: 3.0 mmol dihydropyridine **12**, 0.13 mmol (4.0-mol%) [$FeL^2_3$] **3b**, 0.65 g (9.0 mmol) isobutyraldehyde, 30 ml dichloroethane: The sodium hydrogen carbonate workup is followed by extraction with 30 ml of hydrochloric acid (20%, four times), neutralisation of the

aqueous phase with 26.0 g sodium hydroxide and evaporation of the water. The residue is three times extracted with boiling ethanol, the solvent evaporated and the product crystallized from hexane. For further details see table 2.

In conclusion, the results indicate the usefulness of model porphyrin systems as substitutes for cytochrome P-450. Thus, *in vivo* cytochrome P-450 metabolic processes can easily be mimicked *in vitro*. This allows to study the oxidative metabolism of a large array of endogenous and exogeneous compounds, including drugs and environmental pollutants and may help to reduce the number of laboratory animals.

**Acknowledgements**

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