Biomimetic Aromatic Hydroxylation of Selected Diphenylmethane Derivatives[1)]

Biomimetische aromatische Hydroxylierung ausgewählter Diphenylmethanderivate

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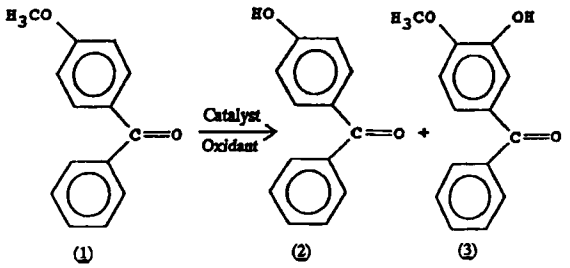
Many oxidation systems using iron or manganese porphyrins as catalysts and various oxygen atom donors have been reported to mimic cytochrome P-450-dependent monooxygenases[1-3]. Such systems are very efficient for epoxidation of alkenes and reasonably for alkane hydroxylation. Few authors also reported about the activity to hydroxylate aromatic rings. In these cases low yields were found for hydroxylation of anisole, benzene, naphthalene, and toluene[4-7]. Biomimetic systems based on metalloporphyrin catalysts can be used for preparative oxidation of some substrates and appear particularly useful for the preparation of oxidized metabolites of drugs or other xenobiotics.

The aim of our investigations is the development of a model which is able to afford potential metabolites and possibly predicts the metabolism of drugs with diphenylmethane structure. Various substituted porphyrins were compared as catalysts for the oxygenation of 4-methoxybenzophenone (**1**) by H_2O_2, iodosobenzene (PhIO), pentafluoroiodosobenzene (PhF_5IO)[8], or NaOCl. Two reactions were expected to take place: *O*-demethylation and aromatic hydroxylation. Further we investigated the influence of different N-bases on the qualitative and quantitative results of aromatic hydroxylation.

Results and Discussion

The reaction of 4-methoxybenzophenone (**1**) shown in Scheme 1 affords 4-hydroxybenzophenone (**2**) and 3-hydroxy-4-methoxybenzophenone (**3**).



Scheme 1

We used *meso*-tetraphenylporphyrins (TPP) bearing no halogen substituent, chlorine substituents at the *ortho*-positions of the phenyl rings (TDCPP) and additional bromine substituents on all pyrrole rings ($TDCBr_8P$), fluorine substituents at all positions of the phenyl rings (TPFPP), 4-methoxy- (MOPP), 3,5-di-(trifluoromethyl)-(DTFMPP), or 2-trifluoromethyl-*meso*-tetraphenylporphyrin (TFMPP)[9]. The efficacy of these porphyrins was compared in presence of imidazole (Table 1).

Table 1: Oxygenation of 4-methoxybenzophenone by various oxidants and porphyrins in presence of imidazole.

Oxidant	Catalyst	Yields (%)[1)]		
		2	**3**	Total
H_2O_2	Co(MOPP)Cl	6.4	–	6.4
	Fe(TPFPP)Cl	19.0	0.6	19.6
	Mn(MOPP)Cl	16.0	–	16.0
	Mn(TPP)Cl	18.4	<0.5	18.4
	Mn(TDCPP)Cl	20.0	<0.5	20.0
	Mn(TPFPP)Cl	21.2	36.5	57.7
	$Mn(TDCPBr_8P)Cl$	25.2	20.4	45.6
	Mn(DTFMPP)Cl	22.7	<0.5	22.7
	Mn(TFMPP)Cl	21.1	–	21.1
	Zn(TDCPP)Cl	18.9	–	18.9
PhIO	Fe(TPFPP)Cl	19.4	1.4	20.8
	Mn(TPP)Cl	1.0	<0.5	1.0
	Mn(TDCPP)Cl	30.0	<0.5	30.0
	Mn(TPFPP)Cl	36.8	1.6	38.4
	$Mn(TDCBr_8P)Cl$	42.8	<0.5	42.8
PhF_5IO	Fe(TPFPP)Cl	19.8	2.4	22.2
	Mn(TPP)Cl	1.5	<0.5	1.5
	Mn(TDCPP)Cl	35.4	1.0	36.4
	Mn(TPFPP)Cl	38.1	2.6	40.7
	$Mn(TDCPBr_8P)Cl$	45.4	0.8	46.2
NaOCl	Fe(TPFPP)Cl	23.5	–	23.5
	Mn(TPP)Cl	19.7	–	19.7
	Mn(TDCPP)Cl	22.2	–	22.2
	Mn(TPFPP)Cl	23.8	–	23.8
	$Mn(TDCPBr_8P)Cl$	23.2	–	23.2

[1)] Yields based on oxidant.

There are some catalysts which are not able to form 3-hydroxy-4-methoxybenzophenone (**3**) (Table 1). We obtained low yields of (**3**) with most catalysts, whereas O-demethylation rates are in part sufficient. MnTPPCl generates only low rates of 4-hydroxybenzophenone (**2**) in the system with both PhIO and PhF_5IO, because it is almost completely destroyed by these oxidants. Therefore, we investigated the stability of all catalysts listed in Table1 toward the oxidants under the same conditions as in the biomimetic reaction. Porphyrins can be destroyed by oxidation at the *meso*-position or at the β-position of the pyrrole ring and by irreversible formation of μ-oxo-dimers[10]. The oxidative attack can be decreased by sterically hindering and/or electron-withdrawing substituents at the phenyl ring or the β-pyrrole position. H_2O_2 and NaOCl caused less oxidative degradation than PhIO as well as PhF_5IO. Polyhalogenated porphyrins are more stable than unsubstituted ones. These results are helpful for the interpre-

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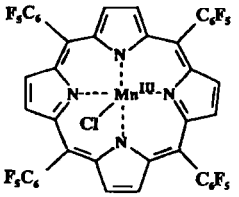
tation of the different rates of oxygenation. So it is not surprising that Mn(TPFPP)Cl (Scheme 2), one of the most resistent catalysts, and H_2O_2 lead to the best yields.



Scheme 2: Manganese(III) *meso*-tetrakis(pentafluorophenyl)porphyrin chloride: Mn(TPFPP)Cl.

Table 2 shows that the system Mn(TPFPP)Cl/H_2O_2 without N-base does not lead to aromatic hydroxylation, but *O*-demethylation takes place. We obtained highest yields of **2** and **3** with pyridine.

Table 2: Influence of various N-bases on the oxidation of 4-methoxybenzophenone by H_2O_2 and Mn(TPFPP)Cl.

N-base	Yields (%)		
	2	3	Total
Imidazole	21.2	36.5	57.7
Pyridine	19.8	50.1	69.9
Pyrimidine	28.1	–	28.1
Pyrazole	30.6	14.8	45.4
No base	25.8	–	25.8

The change of the molar ratio substrate: oxidant does not essentially improve the yield of products. But the rate of oxygenation can possibly be increased by continuous addition of oxidant.

The best system consisting of Mn(TPFPP)Cl/H_2O_2/pyridine was used to oxygenate 4-methoxybenzilic acid, benzophenone, and benzilic acid as shown in Table 3.

Table 3: Oxygenation of various substrates with the system: Mn(TPFPP)Cl/H_2O_2/pyridine

Substrate	Products
4-Methoxybenzophenone	**2**, **3**
4-Methoxybenzilic acid	4-Hydroxyhenzilic acid, 3-Hydroxy-4-methoxybenzilic acid, **2**, **3**
Benzophenone	3-Hydroxybenzophenone, **2**
Benzilic acid	2-Hydroxybenzilic acid, 4-Hydroxybenzilic acid, 2-Hydroxybenzophenone, **2**

We found **2** and **3** using 4-methoxybenzilic acid instead of 4-methoxybenzophenone and in addition we detected 4-hydroxybenzilic acid and 3-hydroxy-4-methoxybenzilic acid. Benzophenone is monohydroxylated in *meta*- or *para*-position, whereas benzilic acid yields *ortho*- or *para*-hydroxylated benzilic acids and the corresponding benzophenones. Therefore, we assume that the oxygenation takes place before the ketone is formed. The formation of benzophenone from benzilic acid is a well known reaction in aqueous solution, which also happens in absence of catalysts[11]. It appears as metabolite of some drugs derived from benzilic acid, too[12].

In conclusion, the system Mn-polyhalogenated porphyrin/H_2O_2/pyridine was found to give the best yields for aromatic ring hydroxylation of diphenylmethane derivatives. Therefore, this system may be employed to obtain metabolites of xenobiotics derived from hydroxylation of their aromatic rings, but it is necessary to improve the yield of hydroxylated products and to get more information about the mechanism of aromatic hydroxylation.

Experimental Part

Acetonitrile, dichlormethane and authentic samples of 4-methoxybenzophenone (**1**), benzophenone, 4-hydroxybenzophenone (**2**), 2-hydroxybenzophenone, and benzilic acid: Aldrich Chemie. 4-Methoxybenzilic acid and 4-hydroxybenzilic acid were prepared according to ref.[12] and porphyrins according to ref.[9]. The reference substance 3-hydroxy-4-methoxybenzophenone (**3**) was prepared according to ref.[13]. On the basis of UV-, mass-, and ^{1}H-NMR-spectroscopic data the substance corresponds in all respects with the compound described in ref.[14].

Conditions for oxygenation: substrate: oxidant: catalyst: N-base = 700:10:1:10 in CH_2Cl_2 : CH_3CN (1:1) 24 h at 20°C (catalyst concentration: 2.5 μ mol/ml). Products were directly identified from the mixture and yields were determined by HPLC, in comparison with authentic samples using calibration curves. HPLC analyses were performed with a Lichrograph HPLC-system (Merck-Hitachi) with Diode Array Detector and a Lichrospher 100 RP-18 (5μm) column (length 10 cm; diameter 4 mm). Benzophenones were detected at 250 nm, benzilic acids at 275 nm. HPLC was carried out with an acetonitrile: water gradient (benzophenones) and acetonitrile: 0.05 M ammonium acetate buffer with 0.5 vol.-% $HClO_4$ pH = 2 (40:60) (benzilic acids) mobile phase at a flow rate of 1.0 ml/min.

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