Improvement of a Biomimetic Porphyrin Catalytic System by Addition of Acids

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The conditions of the use of the manganese/porphyrin/imidazole system needed to be improved in order to obtain larger amounts of models of metabolites. An increase of the oxidation yields and a better preservation of this catalytic system have been obtained on the examples of various alkanes, by an acid addition in the reaction mixture. Three manganoporphyrins were checked for evaluation of the reaction. These results were extended to molecules of therapeutical interest such as ibuprofen and phenylbutazone.

Key words porphyrin catalyst; oxidation; metabolite; imidazole cocatalyst; acidic medium

Biomimetic catalytic systems of cytochrome P 450 enzymes present at least two interests: they allow the catalysis of selective oxidations in organic synthesis, and the prediction and the preparation of models of metabolites of biological interest. Cytochromes P 450 catalyse both alkane hydroxylation and alkene epoxidation in the presence of an oxygen atom donor. Unfortunately, in the case of alkane oxidation by biomimetic systems, yields remained medium and it was necessary to improve the reaction conditions.[1)]

Amongst the oxygen atom donors, hydrogen peroxide is particularly convenient for hydrocarbon mono oxygenation: reaction yields are good and the technique is simple to implement. As the use of hydrogen peroxide is only compatible with second-generation metalloporphyrins,[2)] we chose the most robust and efficient one: Mn(TDCPP)Cl; [TDCPP stands for tetrakis-(2,6-dichlorophenyl)porphyrin] (Chart 1; $R_1=R_3=Cl$; $R_2=H$).

A nitrogen base cocatalyst being necessary, imidazole appeared to give the best oxidation yields.[3)] Under these conditions, there was a competition between alkane oxidation and imidazole oxidation. These effects have been shown in the case of alkene oxidation.[4,5)] Destructive oxidation of imidazole became negligible in presence of oxidant or alkene excesses. These conditions have been transposed to alkane hydroxylation without description of their effects on the cocatalyst.[7)]

Oxidation of Ethylbenzene in the Presence of an Excess of Hydrogen Peroxide In order to establish the behaviour of the cocatalyst and to avoid its destruction, we decided to study what occured under these reaction conditions (excess of oxidative agent: hydrogen peroxide, 200 mmol) on an example of saturated hydrocarbon: ethylbenzene (40 mmol). All experiments were realized in the presence of 1 mmol of Mn(TDCPP)Cl (Chart 2).

The results are summarized in Table 1 (experiments A—C). Oxidation yields have been determined on isolated oxidation products, and not by gas or liquid chromatography analysis, in order to finalize a method for the preparation of large amounts of models of metabolites.

When imidazole (24 mmol) was added dropwise in the reaction mixture silmutaneously to hydrogen peroxide in order to prevent any decrease of the cocatalyst amount in the medium, the reaction yield increased significantly (40 to 60%, experiments A and B). The results were even better when greater amounts of imidazole (44 mmol) were used (85%, experiment C), but the reaction time had to be doubled. We observed a significant destruction of imidazole in the presence of an excess of oxidizing agent (200 mmol), (experiments A—C): less than 25% of the starting imidazole were then recovered at the end of the reactions. Oxidation yields depended upon the amount of imidazole in the medium. When imidazole (24 mmol) was added dropwise during 1 h (experiment B), or when greater amounts of imidazole (44 mmol) were used (experiment C), oxidation yields increased, respectively to 60 and 85%. The increase of imidazole amounts introduced in the reaction medium was related to an increase (experiment C compared to experiment B) of the degradation of both catalyst (21%) and cocatalyst (89% in). Meanwhile, the ratio between alcohol and ketone remained the same (about 0.8).

These results showed clearly that imidazole degradation was a limiting factor of alkane oxidation. Besides, the solution consisting in adding imidazole, as soon as its destruction

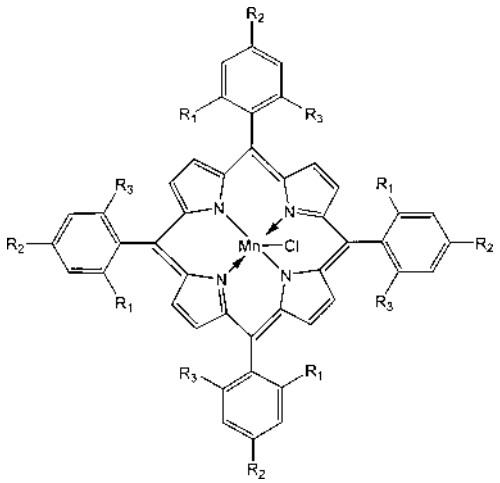

Chart 1

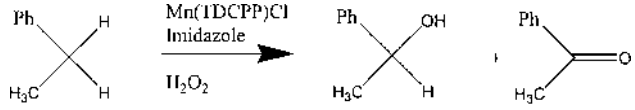

Chart 2

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went on, was limited by the concomitant degradation of the porphyrin catalyst. We meant to study operative conditions allowing to maintain a good stability of imidazole in order to prevent both its oxidation, and the degradation of the catalyst.

Oxidation of Ethylbenzene under Stoichiometric Conditions The reaction was performed in stoichiometric conditions, so far as alkane or hydrogen peroxide were concerned, in order to minimize eventual interactions of an excess of these compounds with the oxidative process. Nevertheless under these stoichiometric conditions, the yields (15%) were much lower than those observed in the presence of an excess of hydrogen peroxide. In order to avoid *N*-oxide formation from imidazole, we decided to add various acids to the medium: HCl and H_2SO_4 as strong acids (Fig. 1), formic acid and acetic acid as weak acids (Fig. 2). The reaction evolution was followed on the basis of the oxidation yield and of Mn(TDCPP)Cl destruction.

In the case of weak acids (Fig. 2), the best results were obtained when 7 to 8 acid equivalents were added. The results were similar wether formic acid or acetic acid were used. The yields (28%) were then higher than in the case of strong acids (Fig. 1; 20%) and varied more gradually about this value.

Oxidation of Ethylbenzene in the Presence of an Excess of Oxidative Agent and of Formic Acid The use of weak acids appeared to be the most efficient process to use. These results were still valid when an oxidant excess was used. In presence of 7 equivalents of formic acid, oxidative yield improved without excessive catalyst degradation (18%, Table 1, experiment D). This allowed to obtain a reaction yield (80%, Table 1, experiment D) similar to the rate obtained by adding an extra quantity of imidazole during the reaction (85%, Table 1, experiment C). The improvement of experiment D consisted in the preservation of the catalyst from its degradation (82% Mn(TDCPP)Cl regenerated in experiment D *versus* 63% in experiment C). The reaction time had also an influence on the reaction yield, which in acid presence, increased until 4 h (80%, Table 1, experiment D), and then remained unchanged.

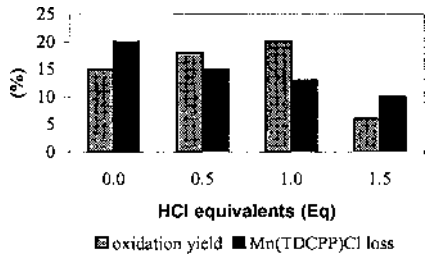

Fig. 1. Influence of the Presence of a Strong Acid upon the Reaction

Role of Acid When the reaction was performed without catalyst or cocatalyst, but in the presence of an excess of weak acid, the yields were very low (Table 1, experiments E and F). This observation proved that the acid was not alone a catalyst of the reaction, but that it helped the catalysts in their action. As regards imidazole, its destruction was complete, when it was treated in the absence of substrate, by hydrogen peroxide and of Mn(TDCPP)Cl. On the other hand, when formic acid was added in the reaction medium, 73% of imidazole was intact at the end of reaction time. This imidazole protection by a weak acid could be explained by a reversible protonation of the nitrogen atom making less available the electron pair.

In one case, the nature of an oxidized imidazole derivative could be isolated, when the experiment was realized in the presence of both formic and phenylacetic acids. It resulted from the oxidation of the three carbon atoms into carbonyl groups, leading to parabanic acid (Chart 3). The low value of the yield (9%) showed that the protection of imidazole nitrogen atoms by acids was effective.

Extension to Other Hydrocarbons In order to test the

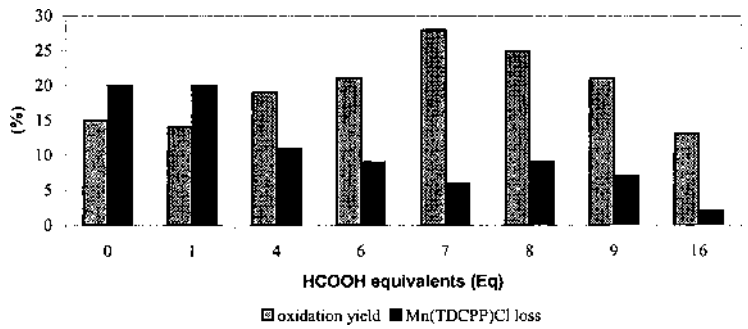

Fig. 2. Influence of the Presence of a Weak Acid Upon the Reaction

Table 1. Experiments in the Presence of an Excess of Oxidative Agent

Conditions	A	B	C	D	E	F
Imidazole (mmol)	24	24[a)]	44[a)]	24	0	24
Formic acid (mmol)	0	0	0	168	168	168
Time (h)	2	2	4	4	4	4
Yield (%)	40	60	85	80	3	0
Ratio (alkohol/ketone)	0.9	0.8	0.8	0.8	nc	—
Regenerated Mn(TDCPP)Cl (mmol)	0.78	0.80	0.63	0.82	0.95	—
Degraded imidazole (mmol (%))	20.4 (85)	18.5 (77)	34.8 (79)	nc	—	0 (0)

Conditions A to E, Mn(TDCPP)Cl (1 mmol)/H_2O_2 (200 mmol)/ethylbenzene (40 mmol); condition F, without Mn(TDCPP)Cl. *a*) Added dropwise. nc: not calculated.

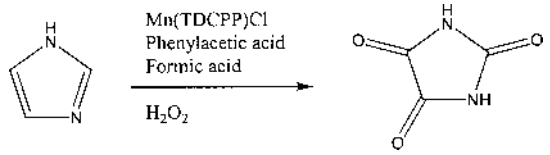

Chart 3

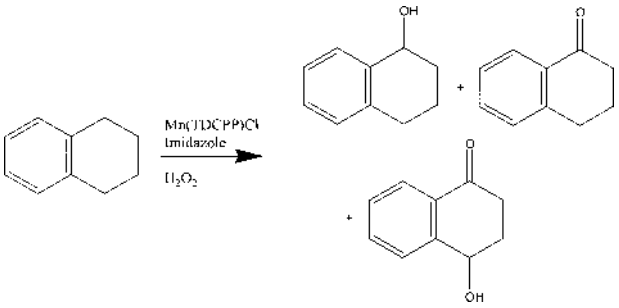

Chart 4

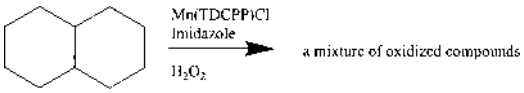

Chart 5

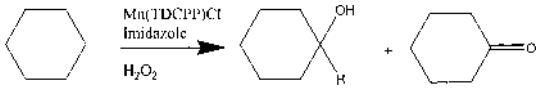

Chart 6

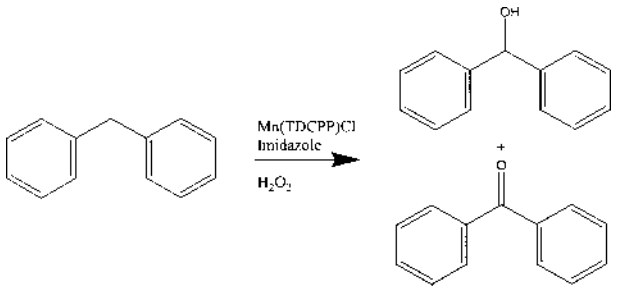

Chart 7

validity of the process with other hydrocarbons, we chose various compounds: tetraline (Chart 4) which presents methylene groups in α-position to the benzene ring like ethylbenzene, decaline (Chart 5) for its structural relation to tetraline, cyclohexane (Chart 6) which can be considered as a part of decaline and diphenylmethane (Chart 7) which is a more bulky substrate.

In the cases of the most reactive compounds (tetraline, decaline, cyclohexane), addition of formic acid significatively improved oxidation yields and the protection of the porphyrinic catalyst (Table 3). In spite of steric hindrance, in the case of diphenylmethane, addition of formic acid allowed to obtain oxidized compound with weak yield (15%), the catalyst being protected from degradation (90%).

Evaluation of Other Porphyrin Catalytic Systems To extend these results, two other manganoporphyrins were tested: Mn(TPP)Cl and Mn(TMP)Cl. Both of them were different from Mn(TDCPP)Cl so far as the substituents of the phenyl group were concerned. For Mn(TPP)Cl, the nucleus was unsubstituted (Chart 1; $R_1=R_2=R_3=H$) [TPP stands for tetrakisphenylporphyrin], and for Mn(TMP)Cl the nucleus was substituted by three methyl groups (Chart 1; $R_1=R_2=R_3=CH_3$) [TMP stands for tetrakismesitylporphyrin]. In the case of alkenes oxidation, these porphyrins had already proved to be less efficient than Mn(TDCPP)Cl.

Table 2. Evaluation of Other Catalysts

	Oxidation yields without formic acid (%)	Oxidation yields with formic acid (%)	Regenerated catalyst without formic acid (%)	Regenerated catalyst with formic acid (%)
Mn(TPP)Cl	<1	2	0	81
Mn(TMP)Cl	11	7	47	76

Conditions: Mn(TPP)Cl or Mn(TMP)Cl (1 mmol)/H_2O_2 (200 mmol)/ethylbenzene (40 mmol)/imidazole (24 mmol).

Table 3. Extension to Other Hydrocarbons

	Oxidation yields without formic acid (%)	Oxidation yields with formic acid (%)	Regenerated catalyst without formic acid (%)	Regenerated catalyst with formic acid (%)
Tetraline	81	92	75	93
Decaline	59	75	72	91
Cyclohexane	50	58	79	85

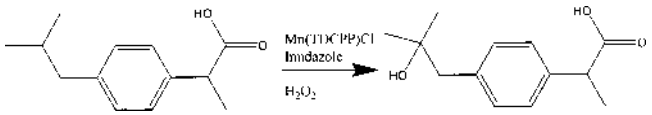

Chart 8

In both cases, addition of formic acid succeeded in protecting the manganoporphyrin from degradation (Table 2). For Mn(TPP)Cl the percentage of regenarated catalyst increased in acidic medium from 0 to 81 and for Mn(TMP)Cl, it increased from 47 to 76.

Unfortunately, the weak efficience of these two catalysts did not allow to increase oxidation yields (Table 2).

Application to Antiflammatory Agents In order to apply this methodology to medicinal compounds, we chose two antiflammatory agents as example of structures of therapeutical interest, ibuprofen and phenylbutazone. Concerning ibuprofen, hydroxylation occurred on the tertiary isobutyl carbon (Chart 8). The hydroxy metabolite was obtained in 15% yield. *In vivo*, this regioselective oxidation was the major biodegradation pathway.[8,9] For phenylbutazone, the oxidation of this molecule had already been achieved.[10] According to the metabolic or the degradation pathways, several products of oxidized phenylbutazone has been isolated.[10,11] Some of them were of particular interest because of their deleterious effects. When phenylbutazone was oxidized by the biomimetic manganese/porphyrine/imidazole catalytic system under acidic conditions, only the 4-hydroxy compound (Chart 9) which may be involved in allergic reactions[12,13] was isolated with a very good yield (90%).

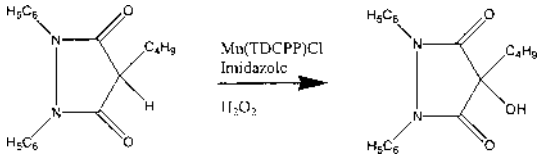

Chart 9

In conclusion, oxidative conditions applied to alkenes were not ideally transposable to alkanes or alkyl groups. The destructive oxidation of the cocatalyst, which was a limiting factor of the reaction, did not allow to obtain good yields while maintaining an appreciable catalyst regeneration.

Addition of formic acid improved the efficiency of the oxidation of alcanes or alkyl chains using Mn(TDCPP)Cl/hydrogen peroxide/imidazole biomimetic system as catalyst. Under acidic conditions, the cocatalyst appeared to be more stable and the catalyst loss remained negligible. The hydroxylation yields have been improved by acid addition, observation which tends to impair that imidazole acts as a basic catalyst. With these improvements, the reaction became quantitatively efficient to prepare sufficient amounts of models of metabolites.

The use of other porphyrin catalysts confirmed the interest of addition of formic acid but showed that Mn(TDCPP)Cl was a better choice.

Experimental

Mn(TDCPP)Cl and Mn(TPP)Cl were prepared according to the respective cited procedures.[6,14—16] Mn(TMP)Cl was obtained as previously described.[16] All oxidized compounds were identified by ^{1}H-NMR and mass spectrometry. Oxidized products of ethylbenzene, tetraline, cyclohexane and diphenylmethane were known compounds.

Oxidation Using Mn(TDCPP)Cl/Imidazole Catalytic System. General Procedure for Oxidation of Ehtylbenzene in the Presence of an Excess of Hydrogen Peroxide Hydrogen peroxide (30% in water, 200 mmol) was diluted in acetonitrile (1/9, v/v), and was added dropwise (during half of the total time of the reaction) at room temperature, to a solution of Mn(TDCPP)Cl (1 mmol for experiments A—C), imidazole (24 mmol for experiments A and B, 44 mmol for C), ethylbenzene (40 mmol) in 400 ml of dichloromethane/acetonitrile (1/1, v/v). The mixture was stirred at room temperature for 2 h (experiments A and B) or 4 h (experiment C). The solvent was evaporated under reduced pressure, and the residual oil was chromatographed (solid phase: SiO_2, solvents: cyclohexane/acetone (9/1, v/v)) to give 1-phenylethanol and acetophenone. Yields are mentionned in Table 1 for every experiment (A—C).

General Procedure for Oxidation of Ehtylbenzene in Stoichiometric Conditions The same general procedure was used, but hydrogen peroxide (100 mmol) and ethylbenzene (100 mmol) were substituted to the previous values. Strong acids volumes used for experimental results indicated in Fig. 1 were 1.05 ml (0.5 eq), 2.10 ml (1.0 eq), 3.20 ml (1.5 eq) in the case of hydrochloric acid (35% water solution), and 0.35 ml (0.5 eq), 0.70 ml (1.0 eq), 1.05 ml (1.5 eq) in the case of sulfuric acid (93% water solution). For weak acids, results indicated in Fig. 2 were obtained with 0.90 ml (1 eq), 3.60 ml (4 eq), 5.40 ml (6 eq), 6.30 ml (7 eq), 7.20 ml (8 eq), 8.10 ml (9 eq), 14.40 ml (16 eq) in the case of formic acid, and 1.40 ml (1 eq), 7.60 ml (4 eq), 8.20 ml (6 eq), 9.60 ml (7 eq), 10.10 ml (8 eq), 12.30 ml (9 eq), 21.90 ml (16 eq) in the case of acetic acid. Reaction time was 4 h. Oxidation yields are respectively mentionned in Figs. 1 and 2.

General Procedure for Oxidation of Ehtylbenzene in the Presence of an Excess of Hydrogen Peroxide and of Formic Acid The same procedure for oxidation of ehtylbenzene in the presence of an excess of hydrogen peroxide (*vide supra*) was used, but eventually (experiments D and F) the amount of imidazole (24 mmol) was substituted to the previous values and formic acid (168 mmol) was added in the medium. Yields are also mentioned in Table 1 for every experiment (D—F).

General Procedure for Oxidation of Tetraline, Decaline, Cyclohexane, Diphenylmethane, Ibuprofen and Phenylbutazone Hydrogen peroxide (30% in water, 200 mmol) was diluted in acetonitrile (1/9, v/v), and was added dropwise (during 2 h) at room temperature, to a solution of Mn(TDCPP)Cl (1 mmol), imidazole (24 mmol), substrate (40 mmol) and formic acid (168 mmol) in 400 ml of dichloromethane/acetonitrile (1/1, v/v). The mixture was stirred at room temperature for 4 h. Evaporation of the solvent under reduced pressure afforded a residual oil which was chromatographed (SiO_2). In the case of ibuprofen and phenylbutazone, the quantities of all reagents and solvents were divided by ten.

1,2,3,4-Tetrahydronaphtalen-1-ol, 4-hydroxy-3,4-dihydronaphtalen-1(2*H*)-one and 3,4-dihydronaphtalen-1(2*H*)-one were respectively obtained in 61% (4-hydroxy-3,4-dihydronaphtalen-1(2*H*)-one) and 31% (3,4-dihydronaphtalen-1(2*H*)-one) yields under acidic conditions (*versus* 48% of hydroxy-compounds and 33% of 3,4-dihydronaphtalen-1(2*H*)-one) yields without acid). The solvent for the chromatography was cyclohexane/acetone (8/2, v/v). A mixture of oxidized compounds of decaline (separating by GC/MS but not isolated) was obtained in 75% yield. Cyclohexanol and cyclohexanone were respectively obtained in 44 and 14% yields under acidic conditions (*versus* 38 and 12% yields without acid). The solvent for the chromatography was chloroform. Diphenylmethanol and benzophenone were respectively obtained in 8 and 7% yields under acidic conditions. The solvent for the chromatography was cyclohexane/acetone (9/1, v/v). 2-[4-(2-Hydroxy-2-methylpropyl)phenyl]propanoic acid was obtained in 15% yield under acidic conditions. The solvent for the chromatography was dichloromethane/diethyl ether (1/1, v/v). mp 122 °C. NMR ($CDCl_3$) δ: 1.15 (6H, s, 2×CH_3), 1.43 (3H, d, CH_3), 2.67 (2H, s, CH_2), 3.64 (1H, q, CH_2), 7.15 (4H, m, phenyl). MS *m/z* (relative intensity): 222 ($M^{+\cdot}$, 3), 207 (5), 177 (5), 164 (74), 162 (38), 159 (8), 119 (100), 115 (14), 105(11), 91 (92), 77 (8), 59 (67). 4-Butyl-4-hydroxy-1,2-diphenylpyrazolidine-3,5-dione was obtained in 90% yield under acidic conditions. The solvent for the chromatography was dichloromethane/cyclohexane (1/1, v/v). mp 128 °C. NMR ($CDCl_3$) δ: 0.77 (3H, t, CH_3), 1.29 (4H, m, 2×CH_2), 1.95 (2H, t, CH_2), 4.67 (1H, s, OH), 7.15 (10H, m, 2×Phenyl). MS *m/z* (relative intensity): 324 ($M^{+\cdot}$, 95), 183 (100), 120 (17), 93 (20), 77 (86), 57 (29).

Oxidation Using Mn(TPP)Cl or Mn(TMP)Cl/Imidazole Catalytic System Hydrogen peroxide (30% in water, 200 mmol) was diluted in acetonitrile (1/9, v/v), and was added dropwise (during 2 h) at room temperature, to a solution of Mn(TPP)Cl or Mn(TMP)Cl (1 mmol), imidazole (24 mmol), ethylbenzene (40 mmol) and formic acid (168 mmol) in 400 ml of dichloromethane/acetonitrile (1/1, v/v). The mixture was stirred at room temperature for 4 h. The solvent was evaporated under reduced pressure, and the residual oil was chromatographed (solid phase: SiO_2, solvents: cyclohexane/acetone (9/1, v/v)) to give 1-phenylethanol and acetophenone. Yields are mentionned in Table 2 for every experiment.

Regeneration of Manganoporphyrin Catalyst When the oxidated compounds were isolated, the solid phase of chromatography was washed by acetone. Then, the catalyst was regenerated by eluting with ethanol. Ethanol solution was concentrated under reduced pressure to 50 ml. Fifty milliliters of water was added, and the residue was filtered to recover manganoporphyrin which was dried and weighed.

Regeneration of Imidazole Isolation of oxidized compounds and regeneration of imidazole was not performed in the same experiment because imidazole could not be separated in the conditions of isolation of oxidized compounds.

When the oxidative reaction was complete, the medium was neutralized with sodium carbonate, and the solvent was evaporated under reduced pressure. The mixture was diluted in dichloromethane and extracted with water. The aqueous solution was dried in a dessiccator, the residue was diluted in dichloromethane and was filtered. The organic solution was evaporated under reduced pressure to recover imidazole which was idendified and quantified.

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References

1) Meunier B., *Bull. Soc. Chim. Fr.*, **4**, 578—594 (1986).
2) Mansuy D., Battioni P., "Metalloporphyrins Catalyzed Oxidations," ed. by Sheldon R. A. Dekker, New York, **17**, 99—132 (1994).
3) Battioni P., Bartoli J.-F., Leduc P., Fontecave M., Mansuy D., *J. Chem. Soc., Chem. Commun.*, **1987**, 791—792.
4) Renaud J. P., Battioni P., Bartoli J. F., Mansuy D., *J. Chem. Soc., Chem. Commun.*, **1985**, 888—889.
5) Rocha Gonsalves A., Johnstone R. A. W., Pereira M., Shaw J., *J. Chem. Soc. Perkin Trans. 1*, **1991**, 645—649.

6) Lindsey J. S., Hsu M. C., Schreiman I. C., *Tetrahedron Lett.*, **27**, 4969—4970 (1986).
7) Battioni P., Renaud J. F., Bartoli J. F., Reina-Artiles M., Fort M., Mansuy D., *J. Am. Chem. Soc.*, **110**, 8462—8470 (1988).
8) Baillie T. A., Adams W. J., Kaiser D. G., Olanoff L. S., Halstead G. W., Harpoothian H., Van Giessen G. J., *J. Pharm. Exp. Ther.*, **249**, 517—523 (1989).
9) Sanins S. M., Adams W. J., Kaiser D. G., Halstead G. W., Baillie T. W., *Drug. Metab. Dispos.*, **18**, 523—527 (1990).
10) Gupta R. N., *J. Chromatogr.*, **530**, 160—163 (1990).
11) Fabre H., Hussam-Eddine N., Mandrou N., *J. Pharm. Sci.*, **73**, 1706—1709 (1984).
12) Alexander D. M., Mathew G. E. A., Wilson J. B., *Xenobiotica*, **15**, 123—128 (1985).
13) Bundgaard H., *Arch. Pharm. Chem.*, **6**, 223—225 (1978).
14) Kinh-Botulinsky M., Meunier B., *Inorg. Chem.*, **27**, 209—210 (1988).
15) Van Der Made A. W., Hoppenbrower E. J. H., Nolte R. J. M., Drenth W., *Rech. Trav. Chim. Pays Bas*, **107**, 15—16 (1988).
16) Lindsey J. S., Wagner R. W., *J. Org. Chem.*, **54**, 827—836 (1989).