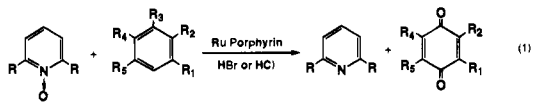
Selective Quinone Formation by Aromatic Oxidation with Heteroaromatic *N*-Oxide Catalyzed by Ruthenium Porphyrin

Tsunehiko Higuchi, Chika Satake, and Masaaki Hirobe*

Faculty of Pharmaceutical Sciences
University of Tokyo
7-3-1 Hongo, Bunkyo-ku, Tokyo 113, Japan

Received April 10, 1995
Revised Manuscript Received June 19, 1995

Oxidative functionalization of unactivated hydrocarbons is a key area of metalloporphyrin chemistry from the viewpoints of the model study of cytochrome P-450 and utilization of hydrocarbon resources. A large number of oxidation systems using metalloporphyrins have been reported for alkane hydroxylation,[1] but little is known about the oxidation of aromatic rings catalyzed by metalloporphyrins.[1a] In most cases, the product yields based on the aromatic compounds used are too low for synthetic purposes. We have already revealed that ruthenium porphyrins effectively catalyze P-450-type oxidations of olefins, sulfides, alkanes and alcohols in the presence of heteroaromatic *N*-oxides.[2] In particular, this catalytic system efficiently oxidizes unactivated alkanes to afford alcohols and/or ketones in high yields with extremely high turnover numbers (up to 10^5 times), in the presence of HCl or HBr.[2d,e] Therefore, this highly reactive Ru(Por)−*N*-oxide system was also expected to effectively oxidize rather unreactive aromatic compounds. We describe here efficient and selective quinone formation from aromatic compounds with the Ru(Por)−2,6-disubstituted pyridine *N*-oxide system in the presence of acid (eq 1).



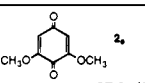
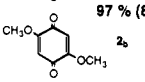
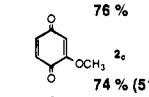
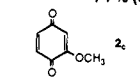
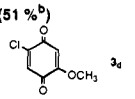
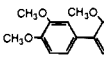
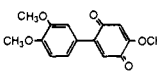
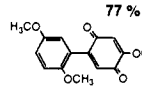
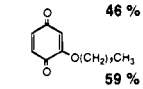
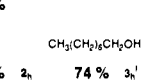
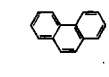
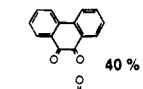
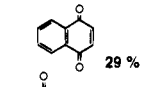
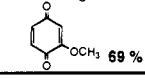
(1)

Oxidation of various arenes was examined with 2,6-dichloropyridine *N*-oxide catalyzed by Ru(Por) in the presence of hydrogen halide. Alkoxybenzene derivatives were oxidized to afford mainly *p*-benzoquinones in yields that greatly depended upon the structure of the substrates (Table 1). This *p*-quinone selectivity in product formation was independent of the amount of the oxidant used. Compound $\mathbf{1_a}$ gave the best result ($\mathbf{2_a}$: yield 97%). The turnover number of Ru(Por) reached 33 000 in the case of $\mathbf{1_a}$. *m*-Dimethoxybenzene (abbreviated as *m*-DMB) ($\mathbf{1_c}$) was converted into 2-methoxy-*p*-benzoquinone ($\mathbf{2_c}$) in good yield (run 3). In contrast, *o*-DMB ($\mathbf{1_d}$) afforded $\mathbf{2_c}$ and the chlorinated quinone $\mathbf{3_d}$ in low yield (recovered $\mathbf{1_d}$: 45%) (run 4), and *p*-DMB ($\mathbf{1_e}$) gave almost no product (run 5). Competitive oxidation of *o*- and *m*-DMB showed the latter to be ca. 10× more reactive than the former. The reaction rate of *m*-DMB was much higher than that of *o*-DMB in the oxidizing system. Therefore, the chemoselectivity of the oxidizing system was examined by using compounds $\mathbf{1_f}$ and $\mathbf{1_g}$, which possess both *m*-DMB and *o*-DMB or *p*-DMB structure, as substrates. In the case of $\mathbf{1_f}$, 2-methoxy-5-(3,4-dimethoxyphenyl)-*p*-benzoquinone ($\mathbf{2_f}$) was afforded in high yield as a single product (run 6). The oxidation of $\mathbf{1_g}$ gave an analogous result ($\mathbf{2_g}$) (run 7). This type of selectivity is unique among oxidizing reagents commonly used in quinone synthesis.[3] For example, cerium(IV) ammonium nitrate (CAN) preferentially oxidizes *p*-dimethoxybenzene structures.[3] Our attempt to oxidize $\mathbf{1_f}$ and $\mathbf{1_g}$ with CAN resulted in the formation of a complex mixture of products, respectively. The only isolable product in the CAN oxidation of $\mathbf{1_g}$ was 2-(2,4-dimethoxyphenyl)-*p*-benzoquinone (yield 8%) as was expected.

Anisole afforded $\mathbf{2_c}$ and *p*-benzoquinone in low yields. The reaction system could oxidize phenanthrene ($\mathbf{1_l}$) to give 9,10-phenanthroquinone ($\mathbf{2_l}$). Naphthalene ($\mathbf{1_j}$) afforded 1,4-naphthoquinone ($\mathbf{2_j}$). Benzene was inert. In the absence of acid, almost no oxidation of *m*-DMB occurred.

Several experiments were carried out to examine the mechanism. We determined the one-electron oxidation potential of dimethoxybenzenes (DMBs) in dichloromethane by cyclic voltammetry, in order to examine the correlation between the potential and the reactivity of DMBs. These compounds gave

Table 1. Oxidation of Aromatic Compounds by the Ruthenium Porphyrin−2,6-Dichloropyridine *N*-Oxide System

Run	Substrate	Catalyst and Additive	Product (Isolated yield)
1[a]	 $\mathbf{1_a}$	Ru(TPP)CO HBr	 $\mathbf{2_a}$ 97 % (89 %)
2	 $\mathbf{1_b}$	Ru(TMP)CO HBr	 $\mathbf{2_b}$ 76 %
3	 $\mathbf{1_c}$	Ru(TMP)CO HBr	 $\mathbf{2_c}$ 74 % (51 %[b])
4	 $\mathbf{1_d}$	Ru(TMP)(O)$_2$ HCl	 $\mathbf{2_c}$ 11 %  $\mathbf{3_d}$ 11 %
5	 $\mathbf{1_e}$	Ru(TMP)CO HBr	None
6[c]	 $\mathbf{1_f}$	Ru(TMP)CO HBr	 $\mathbf{2_f}$ 77 %
7	 $\mathbf{1_g}$	Ru(TMP)CO HBr	 $\mathbf{2_g}$ 46 %
8	 $\mathbf{1_h}$	Ru(TMP)CO HBr	 59 % $\mathbf{2_h}$  74 % $\mathbf{3_h}$[f]
9[d]	 $\mathbf{1_i}$	Ru(TMP)CO HBr	 40 % $\mathbf{2_i}$
10	 $\mathbf{1_j}$	Ru(TMP)CO HBr	 29 % $\mathbf{2_j}$
11[e]	 $\mathbf{1_k}$	Ru(TMP)CO HBr	 69 % $\mathbf{2_e}$

Reaction conditions: substrate (1 mmol), Ru(por) (2 μmol), 2,6-dichloropyridine *N*-oxide (2.4 mmol), 47% HBr or 36% HCl (30 μL); molecular sieves 4A (300 mg) and benzene (2 mL) at 40 °C under an Ar atmosphere overnight, unless otherwise noted. Yields are based on the substrate used. [a] 0.5 μmol of Ru(TPP)CO was used. The yield in parentheses was obtained in the reaction in which 0.05 μmol of catalyst was used. [b] The yield with 2,6-lutidine *N*-oxide as oxidant. [c] Room temperature for 45 h. [d] 3.6 mmol of 2,6-dichloropyridine *N*-oxide was used. [e] Compound $\mathbf{1_j}$ was slowly added over 5 h to the reaction system. The scale of this reaction was 1.5 times larger than usual. [f] The yield of compound $\mathbf{3_h}$ was determined by GLC.

(1) For recent reviews see: (a) Ortiz de Montellano, P. R., Ed. *Cytochrome P-450*; Plenum: New York, 1986. (b) Meunier, B. *Chem. Rev.* **1992**, *92*, 1411.

(2) (a) Higuchi, T.; Ohtake, H.; Hirobe, M. *Tetrahedron Lett.* **1989**, *30*, 6545−6549. (b) *Ibid.* **1991**, *32*, 7435. (c) Ohtake, H.; Higuchi, T.; Hirobe, M. *Ibid.* **1992**, *33*, 2521. (d) *Idem. J. Am. Chem. Soc.* **1992**, *114*, 10660−10662. (e) *Idem. Heterocycles* **1995**, *40*, 867.

(3) For recent reviews see: (a) Dudfield, P. J. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 7, Chapters 2.10 and 2.11.

(4) These differences in the localization of electron density on carbon among *o*-, *m*-, and *p*-DMB were supported by the results obtained from AM1 calculations for these compounds.

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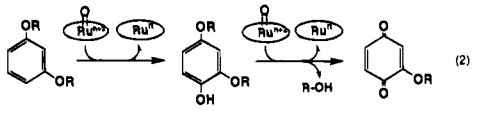
clear and reversible cyclic voltammograms. The order of $E_{1/2}$ was as follows: *m*-DMB (1.6 V vs SCE, Pt electrode, 0.1 M Bu_4NClO_4) > *o*-DMB (1.5 V) > *p*-DMB (1.4 V). *p*-DMB should be oxidized most effectively if one-electron oxidation of the aromatic ring is an important process in the quinone formation as electrochemical oxidation and CAN oxidation. Therefore, these data suggest that the reaction mechanism does not involve one-electron abstraction from the aromatic ring as a rate-determining step. Methoxy-*p*-benzoquinone formation from DMB is highly likely to be a multistep reaction, since it is a four-electron oxidation process. There might therefore be a trace amount of a highly oxidizable intermediate in the reaction mixture. As the result of careful investigation by GC/MS, 2,4-dimethoxyphenol was detected in a reaction solution with *m*-DMB as the substrate, and *m*-methoxyphenol was not detected. When ^{18}O-labeled 2,6-dichloropyridine *N*-oxide was used, 1.2 ^{18}O atoms per quinone molecule were incorporated into $\mathbf{2_c}$ and 1 ^{18}O atom was incorporated into formed 2,4-dimethoxyphenol in the oxidation of *m*-DMB.[5] Considerable ^{18}O incorporation (40%) into $\mathbf{2_c}$ occurred in the oxidation of *m*-DMB using normal *N*-oxide in the presence of $H_2{}^{18}O$, probably because of ready O atom exchange between the keto groups and $H_2{}^{18}O$. Therefore, these results provide evidence that at least one O atom of the quinone originates from the *N*-oxide. The oxidation of 4-deuterio-1,3-dimethoxybenzene with the oxidizing system gave an equimolar mixture of 5-deuterio-2-methoxybenzoquinone and 2-methoxybenzoquinone, and 6-deuterio-2-methoxy-*p*-benzoquinone, which should be formed via NIH shift, was not detected. 1-(Trideuteriomethoxy)-3-methoxybenzene afforded a 1:1 mixture of 2-methoxy-*p*-benzoquinone and 2-(trideuteriomethoxy)-*p*-benzoquinone, and a small amount of 2-(trideuteriomethoxy)-4-methoxyphenol. This result indicates that no isotope effect occurred, and therefore it does not seem likely that hydrogen abstraction from the methoxy group is a key reaction. The oxidation of $\mathbf{1_h}$ with our system afforded $\mathbf{2_h}$ and an almost equal amount of *n*-octyl alcohol ($\mathbf{3_h}$), with trace amounts of octanal and octanoic acid. Further, 2,4-dimethoxyphenol ($\mathbf{1_k}$) was oxidized to give $\mathbf{2_c}$ in 69% yield by slow addition of the phenol to the oxidizing system (Table 1, run 11). These results provide strong evidence that 2,4-dimethoxyphenol is an intermediate in the oxidation of *m*-DMB. Thus, we believe the mechanism of the reaction is as shown in eq 2. The Ru(Por)−*N*-oxide system seems to be



(2)

one of the most efficient of the catalytic systems which hydroxylate aromatic rings, because the ratio of hydroxylated molecules to Ru(Por) exceeds 10^4. The 4-carbon of *m*-DMB is highly electron-rich because both methoxy groups donate electrons to this position. *o*-DMB and *p*-DMB do not have a carbon with such highly localized electron density as *m*-DMB since only one methoxy group contributes.[4] It is therefore likely that the active species of the oxidizing system preferentially attacks the most electron-rich carbon on the aromatic ring. It is highly probable that the reactivity of the active intermediate toward an aromatic ring depends largely on the electron density on a carbon of the ring, considering the high chemoselectivity of the system. Recently several reports about a lignin peroxidase (LP) model using a water-soluble iron or manganese porphyrin−oxidant couple have appeared.[6] It is known that methoxybenzenes with lower oxidation potentials are oxidized more easily by LP.[7] Hence, the Ru(Por)−*N*-oxide system exhibits a tendency different from that of LP in chemoselectivity. The reactivity of the system appears to resemble that of P-450 rather than that of LP.

We have shown that the ruthenium porphyrin−heteroaromatic *N*-oxide system selectively converts aromatic compounds to quinones in the presence of HBr or HCl. Many quinone-type compounds have interesting biological activities, and some are potential anticancer drugs, because quinones often have selective cytotoxicities arising from their active oxygen-producing ability.[8] Further, arenes are metabolized *in vivo* by cytochrome P-450 to form quinones in addition to phenolic compounds.[9] Our reaction system should be useful to prepare these biologically active quinones and metabolites.

Acknowledgment. This work was supported by a Scientific Research Grant from the Ministry of Education, Science and Culture, Japan.

Supporting Information Available: Text giving the details of the experimental procedure and characterization data for all reaction products (3 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

JA9511432

(5) In this experiment, HCl-saturated benzene was used as an additive instead of concentrated hydrochloric acid plus molecular sieves 4A, in order to avoid participation of normal H_2O.

(6) (a) Labat, G.; Meunier, B. *J. Org. Chem.* **1989**, *54*, 5008. (b) Artaud, I.; Ben-Aziza, K.; Chopard, C.; Mansuy, D. *J. Chem. Soc., Chem. Commun.* **1991**, 31.

(7) Kersten, *Biochem. J.* **1990**, *268*, 475.

(8) (a) Ohtsuka, H.; Komiya, T.; Fujioka, S.; Goto, M.; Hiramatsu, Y.; Fujimura, H. *Yakugaku Zasshi* **1981**, *101*, 1108. (b) Hayashi, S.; Ueki, H.; Aoki, H.; Tanaka, K.; Fujimoto, J.; Katsukawa, K.; Mori, M. *Chem. Pharm. Bull.* **1963**, *11*, 948. (c) Misra, H. P.; Fridovich, I. *J. Biol. Chem.* **1972**, *247*, 188. (d) For a review see: Sinha, B. K. *Chem.-Biol. Interact.* **1989**, *69*, 293−317.

(9) (a) Slaughter, D. E.; Hanzlik, R. P. *Chem. Res. Toxicol.* **1991**, *4*, 349. (b) For a review see: Monks, T. J.; Hanzlik, R. P.; Cohen, G. M.; Ross, D.; Graham, D. G. *Toxicol. Appl. Pharmacol.* **1992**, *112*, 2.