Isolation of an Oxomanganese(v) Porphyrin Intermediate in the Reaction of a Manganese(iii) Porphyrin Complex and H_2O_2 in Aqueous Solution

Wonwoo Nam,*[a] Inwoo Kim,[a] Mi Hee Lim,[a] Hye Jin Choi,[a] Je Seung Lee,[b] and Ho G. Jang[b]

Abstract: The reaction of $[Mn(TF_4TMAP)](CF_3SO_3)_5$ (TF_4TMAP = *meso*-tetrakis(2,3,5,6-tetrafluoro-*N*,*N*,*N*-trimethyl-4-aniliniumyl)porphinato dianion) with H_2O_2 (2 equiv) at pH 10.5 and 0 °C yielded an oxomanganese(v) porphyrin complex **1** in aqueous solution, whereas an oxomanganese(iv) porphyrin complex **2** was generated in the reactions of *tert*-alkyl hydroperoxides such as *tert*-butyl hydroperoxide and 2-methyl-1-phenyl-2-propyl hydroperoxide. Complex **1** was capable of epoxidizing olefins and exchanging its oxygen with $H_2{}^{18}O$, whereas **2** did not epoxidize olefins. From the reactions of $[Mn(TF_4TMAP)]^{5+}$ with various oxidants in the pH range 3–11, the O–O bond cleavage of hydroperoxides was found to be sensitive to the hydroperoxide substituent and the pH of the reaction solution. Whereas the O–O bond of hydroperoxides containing an electron-donating *tert*-alkyl group is cleaved homolytically, an electron-withdrawing substituent such as an acyl group in *m*-chloroperoxybenzoic acid (*m*-CPBA) facilitates O–O bond heterolysis. The mechanism of the O–O bond cleavage of H_2O_2 depends on the pH of the reaction solution: O–O bond homolysis prevails at low pH and O–O bond heterolysis becomes a predominant pathway at high pH. The effect of pH on ^{18}O incorporation from $H_2{}^{18}O$ into oxygenated products was examined over a wide pH range, by carrying out the epoxidation of carbamazepine (CBZ) with $[Mn(TF_4TMAP)]^{5+}$ and $KHSO_5$ in buffered $H_2{}^{18}O$ solutions. A high proportion of ^{18}O was incorporated into the CBZ-10,11-oxide product at all pH values but this proportion was not affected significantly by the pH of the reaction solution.

Keywords: enzyme mimetics · epoxidation · heme proteins · O–O activation · porphyrinoids

Introduction

An important objective in research aimed at understanding biological oxygenation reactions by heme-containing monooxygenase enzymes is to elucidate the nature of the reactive intermediates and the mechanism of formation of high-valent metal oxo porphyrin intermediates.[1, 2] Model studies using synthetic iron(iii) porphyrin complexes have been fruitful in affording a mechanistic insight into the enzymatic reactions and developing biomimetic oxygenation reactions.[3] Some high-valent oxoiron(iv) porphyrin cation radicals have been isolated and characterized, and the reactivities of the oxoiron(iv) porphyrins in a variety of oxygenation reactions have been investigated.[4] As a result of intensive studies of the formation of high-valent oxoiron(iv) porphyrin intermediates in the reactions of iron(iii) porphyrin complexes and hydroperoxides, O–O bond heterolysis and homolysis have been proposed.[5]

Although synthetic manganese(iii) porphyrin complexes have shown promise as versatile catalysts in the oxygenation of hydrocarbons,[6] only recently has the key oxomanganese(v) porphyrin intermediate been isolated and well characterized spectroscopically.[7] Groves and co-workers generated an oxomanganese(v) porphyrin complex in the reaction of a water-soluble manganese(iii) *meso*-tetrakis(*N*-methyl-2-pyridyl)porphyrin [Mn^{III}TM-2-PyP] with artificial oxidants such as *m*-chloroperoxybenzoic acid (*m*-CPBA), HSO_5^- (oxone), and OCl^- at room temperature in aqueous solution.[7b] An analogous oxomanganese(v) complex with a corrole ligand was also synthesized and characterized by Gross and coworkers, and the catalytic activity of the oxomanganese(v) corrole intermediate was investigated in oxygenation reactions.[8] Thus elucidation of the chemistry of the long-sought high-valent oxomanganese(v) intermediates began by isolation and characterization of the oxomanganese(v) complexes of porphyrin and corrole ligands.[9]

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  0947-6539/02/0809-2067 $ 20.00+.50/0

Since the oxomanganese(v) porphyrin complexes are generated by heterolytic O–O cleavage of hydroperoxides by manganese(iii) porphyrin complexes, an understanding of the mechanism of hydroperoxide O–O bond cleavage is crucial in designing better catalysts in manganese(iii) porphyrin complex catalyzed oxygenation reactions. Although the mechanism of O–O bond cleavage of peracids such as *m*-CPBA has been well established,[10] the exact nature of O–O bond cleavage of biologically relevant hydroperoxides such as hydrogen peroxide (H_2O_2) and alkyl hydroperoxides (ROOH) has been less clearly understood. In the present study, we report the isolation of an oxomanganese(v) porphyrin intermediate in the reaction of a biologically important oxidant, H_2O_2, in buffered aqueous solution. The oxomanganese(v) porphyrin complex was demonstrated to be a reactive epoxidizing intermediate in the catalytic epoxidation of olefins by H_2O_2. Some mechanistic aspects such as the pH dependence of the O–O bond cleavage of various hydroperoxides by the manganese(iii) porphyrin complex and the oxygen exchange between the oxomanganese(v) porphyrin intermediate and ^{18}O-labeled water, $H_2{}^{18}O$, are discussed.

Results and Discussion

Addition of H_2O_2 (2 equiv) to a reaction solution containing $[Mn(TF_4TMAP)](CF_3SO_3)_5$ ((TF_4TMAP = *meso*-tetrakis-(2,3,5,6-tetrafluoro-*N*,*N*,*N*-trimethyl-4-aniliniumyl)porphinato dianion; see Supporting Information, Figure S1) at pH 10.5 and 0 °C caused immediate generation of a new species **1** with a strong and sharp Soret band at 427 nm (Figure 1).[11] The formation of **1** was also observed in the reactions of $[Mn(TF_4TMAP)]^{5+}$ with other oxidants such as *m*-CPBA, $KHSO_5$, NaOCl, and iodosylbenzene (PhIO) under identical reaction conditions.[7a, b] Interestingly, when *tert*-alkyl hydroperoxides such as *tert*-butyl hydroperoxide (*t*BuOOH) and 2-methyl-1-phenyl-2-propyl hydroperoxide (MPPH)[12] were used as terminal oxidants, the formation of another intermediate **2** with a broad and weak Soret band at 417 nm was observed at pH 10.5 and 0 °C (Figure 1).[7b, 13] While the X-band EPR of **2** showed a strong and broad resonance at $g_\perp \approx 4$ and a weak signal at $g_\parallel \approx 2$ (see Supporting Information, Figure S2), **1** was EPR-silent.[7b] On the basis of the UV/Vis and EPR spectral features of **1** and **2**, we suggest that **1**, generated in the reactions of H_2O_2 and other single oxygen atom donors, is an oxomanganese(v) porphyrin complex and **2**, formed in the reactions of *tert*-alkyl hydroperoxides, is an oxomanganese(iv) porphyrin complex (vide infra).

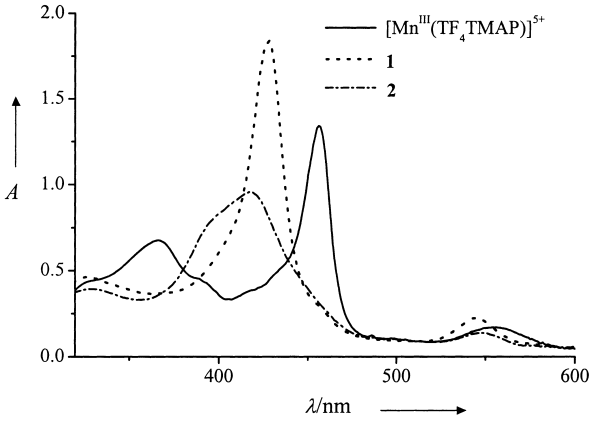

Figure 1. UV/Vis spectra of $[Mn(TF_4TMAP)]^{5+}$, **1**, and **2**. Reaction conditions: ROOH (4×10^{-2} mM, dissolved in 0.05 mL H_2O) was injected into a 1 cm UV cuvette containing a reaction solution of $[Mn(TF_4TMAP)]^{5+}$ (2×10^{-2} mM) in 50 mM borate buffer (3 mL, pH 10.5) at 0 °C.

The reactivity of the intermediates **1** and **2** was then examined in olefin epoxidation reactions, by generating the intermediates and using them directly in reactivity studies. When an olefin substrate such as carbamazepine (CBZ)[7d, 14] was added to a reaction solution containing **1** generated in the reaction of $[Mn(TF_4TMAP)]^{5+}$ with a stoichiometric amount of H_2O_2, the intermediate **1** reverted to the starting manganese(iii) porphyrin complex with clear isosbestic points at 394, 442, and 555 nm and with a half-life of 47 s (Figure 2).[15] HPLC analysis of the resulting solution revealed that a good

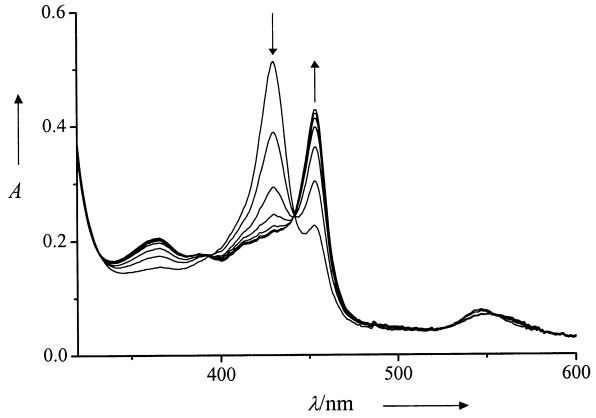

Figure 2. UV/Vis spectral changes upon addition of CBZ (2.1 mM, dissolved in 0.1 mL CH_3CN) into a 0.1 cm UV cuvette containing a solution of **1** generated in the reaction of $[Mn(TF_4TMAP)]^{5+}$ (7×10^{-2} mM) and H_2O_2 (7×10^{-2} mM) in a solvent mixture of 50 mM borate buffer (0.5 mL, pH 10.5) and CH_3CN (0.05 mL) at 0 °C. Scan interval: 45 s (first scan was immediately after the addition of CBZ).

yield (55 ± 10% based on the amount of **1** formed) of CBZ-10,11-oxide was obtained, demonstrating that **1** is capable of oxidizing the olefin to give the epoxide product. Furthermore, when a stoichiometric amount of H_2O_2 was added to a reaction solution containing $[Mn(TF_4TMAP)]^{5+}$ and CBZ, **1** was formed immediately upon addition of H_2O_2 to the reaction mixture and then decayed back to the starting $[Mn^{III}(TF_4TMAP)]^{5+}$ complex (see Supporting Information, Figure S3). HPLC analysis of the reaction mixture revealed a yield of 60 ± 10% CBZ-10,11-oxide (based on the amount of H_2O_2 added). Significantly, when the latter reaction was performed with $H_2{}^{16}O_2$ in buffered ^{18}O-labeled water ($H_2{}^{18}O$) solution,[16] 45% of the oxygen in the CBZ-10,11-oxide product came from the labeled water (Scheme 1)[7d, 14a, 14b, 17] These results demonstrate that **1** is generated as a reactive species in the catalytic epoxidation of olefins by $[Mn^{III}(TF_4TMAP)]^{5+}$ and H_2O_2 and that the oxygen atom

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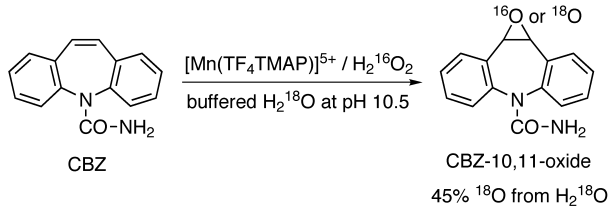
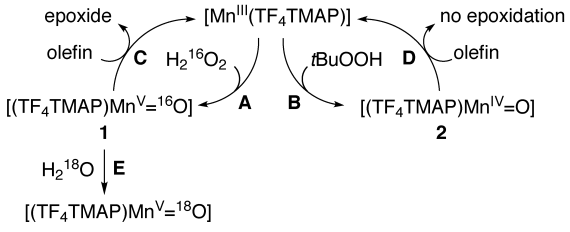


Scheme 1. Labeled water, $H_2{}^{18}O$, experiment.

bound to **1** is exchanged with that of labeled water via "oxo–hydroxo tautomerism" as suggested by Meunier and co-workers, resulting in ^{18}O incorporation from $H_2{}^{18}O$ into the oxide product.[14a, 17a] To ensure that the oxygen atom in the oxide product does not come from molecular oxygen (O_2) by an autoxidation reaction, the catalytic epoxidation of CBZ by $[Mn^{III}(TF_4TMAP)]^{5+}$ was performed with ^{18}O-labeled hydrogen peroxide ($H_2{}^{18}O_2$) in buffered $H_2{}^{18}O$ solution.[18] The percentage of ^{18}O ($97 \pm 2\%$) in the CBZ-10,11-oxide product demonstrated that all the oxygen present in the oxide product is derived from either H_2O_2 or H_2O, with essentially no oxygen incorporation from air.

As we have observed formation of another intermediate **2** in the reactions of *tert*-alkyl hydroperoxides such as *t*BuOOH and MPPH, the reactivity of **2** was also examined in the CBZ epoxidation. When CBZ was added to a reaction solution containing **2** generated in the reaction of *t*BuOOH, the UV/Vis spectrum of the reaction solution did not change for 2 h, and HPLC analysis of the reaction mixture did not show the formation of CBZ-10,11-oxide. In addition, when *t*BuOOH was used as a terminal oxidant in the catalytic epoxidation of CBZ by $[Mn(TF_4TMAP)]^{5+}$, the intermediate **2** formed upon the addition of *t*BuOOH to the $[Mn(TF_4TMAP)]^{5+}$ solution did not show any UV/Vis spectral changes, and HPLC analysis of the resulting solution revealed no CBZ-10,11-oxide product formation. These results demonstrate that **2** does not oxidize olefins under our reaction conditions. The unreactivity of an oxomanganese(IV) porphyrin complex [oxoMn^{IV}TM-2-PyP] toward olefin epoxidation in aqueous solution has also been reported by Groves and co-workers.[7b] Scheme 2 summarizes the above results: the UV/Vis and EPR spectral features and reactivities of **1** and **2** clearly indicate that **1**, generated in the H_2O_2 reaction, is an oxomanganese(V) porphyrin complex (pathway **A**) and **2**, formed in the reactions of *tert*-alkyl hydroperoxides such as *t*BuOOH and MPPH, is an oxomanganese(IV) porphyrin complex (pathway **B**). The complex **1** epoxidizes olefins (pathway **C**) and readily exchanges its oxygen with $H_2{}^{18}O$ (pathway **E**), where-



Scheme 2. Schematic summary of the reactions of $[Mn(TF_4TMAP)]^{5+}$ with H_2O_2 and *t*BuOOH at pH 10.5 and 0 °C.

as **2** does not epoxidize olefins (pathway **D**). Furthermore, the successful isolation of **1** in the H_2O_2 reaction implies that a catalase reaction between **1** and H_2O_2 does not occur under these reaction conditions.[19]

The pH dependence of $[Mn(TF_4TMAP)]^{5+}$ reactions with various oxidants has been investigated for the catalytic epoxidation of *cis*-stilbene in the pH range 3–11 at room temperature.[12c, 20] Whereas the *cis*-stilbene oxide yields were high and independent of pH in the reactions of *m*-CPBA and $KHSO_5$, the oxide product yields in the H_2O_2 reaction varied depending on the pH of the buffer solution (Figure 3). In the

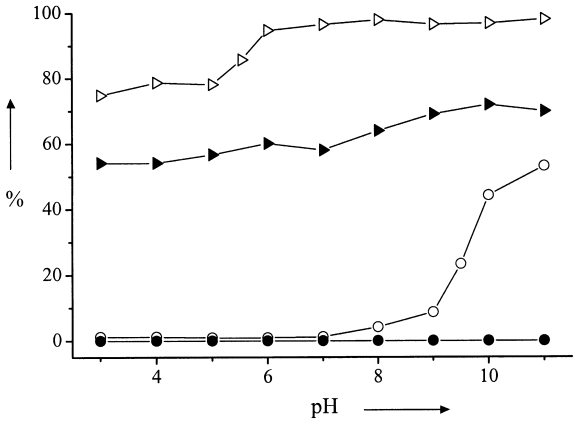


Figure 3. Yields (%, based on oxidants added) of *cis*-stilbene oxide versus pH of reaction solution for the catalytic epoxidations of *cis*-stilbene by H_2O_2 (○), *t*BuOOH (●), *m*-CPBA (▲), and $KHSO_5$ (△). No *trans*-stilbene oxide and benzaldehyde, or only trace amounts, were formed in any of the reactions, which were run at least in triplicate, and the data reported represent the average of these reactions. See the Experimental Section for detailed reaction procedures.

latter reaction, no *cis*-stilbene oxide formation was observed at low pH values (below pH 7), but the oxide yield gradually increased as the reaction solution became basic. In the *t*BuOOH reaction, *cis*-stilbene oxide formation was not detected over the entire pH range. These results suggest that hydroperoxide O–O bond cleavage is sensitive to the hydroperoxide substituent.[5a] The O–O bond of hydroperoxides containing an electron-donating *tert*-alkyl group tends to be cleaved homolytically, resulting in the generation of **2** and no epoxide formation (Scheme 2, pathways **B** and **D**). In contrast, an electron-withdrawing substituent such as an acyl group in *m*-CPBA facilitates O–O bond heterolysis, resulting in the formation of **1** and yielding the epoxide product. The pH dependence of the H_2O_2 reaction may imply that the mechanism of HO–OH bond cleavage depends on the pH of the reaction solution, with O–O bond homolysis prevailing at low pH and O–O bond heterolysis becoming a predominant pathway as the pH of the reaction solution increases.[21, 22] It is interesting that an opposite trend was observed in iron(III) porphyrin complex mediated O–O bond cleavage of H_2O_2 in aqueous solution, in which O–O bond heterolysis predominates at low pH, whereas O–O bond homolysis prevails at high pH.[12c, 14b, 22]

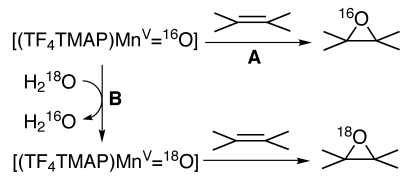
Since the oxide yields in the $KHSO_5$ reaction were high and independent of pH, we have examined the effect of pH on the

extent of incorporation of ^{18}O from $H_2{}^{18}O$ into oxygenated products over a wide pH range,[17a] by epoxidation of CBZ with $[Mn(TF_4TMAP)]^{5+}$ and $KHSO_5$ in buffered $H_2{}^{18}O$ solutions. Some of the oxygen in the CBZ-10,11-oxide was derived from ^{18}O-labeled water (Table 1), indicating the involvement of **1** as a common reactive species over the entire pH range. In addition, the amounts of ^{18}O incorporated into the oxide product did not differ greatly at different pH values, implying that the oxygen exchange between **1** and $H_2{}^{18}O$ (Scheme 3, pathway **B**) may not be affected significantly by the pH of the reaction solution. However, the oxygen exchange between **1** and $H_2{}^{18}O$ (Scheme 3, pathway **B**) is competing with the oxygen transfer from **1** to organic substrate (Scheme 3, pathway **A**).[7d, 17b] Therefore, another factor that may influence the degree of ^{18}O incorporation in $H_2{}^{18}O$ experiments is the effect of pH on the rate of oxygen transfer from **1** to olefins (Scheme 3, pathway **A**). Consequently, to elucidate the effect of pH on the oxygen exchange between **1** and $H_2{}^{18}O$, the effect of pH on the rate of oxygen transfer from **1** to olefins should be determined as well; this is under active investigation in this laboratory.

Table 1. ^{18}O [%][a] incorporated from $H_2{}^{18}O$ into CBZ-10,11-oxide in the catalytic epoxidation of CBZ by $[Mn(TF_4TMAP)]^{5+}$ and $KHSO_5$ at different pH values.[b]

pH	3	5	7	9	10.5
^{18}O incorporated [%][a]	26 ± 4	28 ± 4	37 ± 5	36 ± 5	35 ± 5
CBZ converted to CBZ-10,11-oxide [%]	45	60	50	50	50

[a] Calculated on the basis of the mass balance of oxygen derived from $H_2{}^{18}O$. [b] All reactions were run at least in duplicate, and the data reported represent the average of these reactions. See the Experimental Section for detailed reaction procedures. It had been demonstrated previously that oxygen exchange between $KHSO_5$ and $H_2{}^{18}O$, and between CBZ-10,11-oxide-[^{16}O] and $H_2{}^{18}O$, did not occur.[7d, 14a, 14b]



Scheme 3. Competition between oxygen exchange and oxygen transfer for the reaction of **1**.

Experimental Section

Materials: $[Mn(TF_4TMAP)](CF_3SO_3)_5$ was purchased from Mid-Century Chemicals. All chemicals obtained from Aldrich Chemical Co. were of the highest purity available and were used without further purification unless otherwise indicated. H_2O_2 (30% aqueous), *t*BuOOH (70% aqueous), *m*-CPBA, and $KHSO_5$ (oxone) were purchased from Aldrich. *m*-CPBA was purified by washing with phosphate buffer (pH 7.4) followed by water and then dried under reduced pressure. PhIO was prepared from iodobenzene diacetate by a literature method.[23] $H_2{}^{18}O$ (95% ^{18}O-enriched) and $H_2{}^{18}O_2$ (90% ^{18}O-enriched, 2% solution in $H_2{}^{16}O$) were obtained from Aldrich and ICON Isotopes, respectively. CBZ-10,11-oxide was prepared by a literature method.[14a] Water used in all the experiments was distilled and deionized (Millipore, Milli-Q).

Instrumentation: Product analyses were performed on a Dionex Summit HPLC System equipped with a variable-wavelength UVD-170S detector. Products were separated on a Waters Symmetry C_{18} reverse-phase column (4.6 mm × 250 mm), and detected at 215 and 254 nm. Low-temperature UV/Vis spectra were recorded on a Hewlett Packard 8453 spectrophotometer equipped with an Optostat variable-temperature liquid-nitrogen cryostat (Oxford Instruments). EPR spectra were obtained on a JEOL JES-FA200 spectrometer.

Catalytic epoxidation of *cis*-stilbene: In a typical reaction, oxidant (2 mM H_2O_2, 2 mM *m*-CPBA, 2 mM $KHSO_5$, and 4 mM *t*BuOOH) was added to a reaction solution containing $[Mn(TF_4TMAP)]^{5+}$ (4×10^{-2} mM) and *cis*-stilbene (6 mM) in a solvent mixture (5 mL) of buffered H_2O (2.5 mL)/CH_3OH (1.0 mL)/CH_3CN (1.5 mL) to make the reaction mixture homogeneous. Reactions were performed at pH 3–4 in formate buffer (0.1 M), at pH 5–6 in acetate buffer (0.1 M), at pH 7–9 in phosphate buffer (0.1 M), and at pH 10–11 in borate buffer (0.05 M), and the pH of the reaction solutions was adjusted by adding either HCl (3 N) or NaOH (3 N) solutions whenever necessary. The reaction mixture was stirred in air for 1 h (H_2O_2, *m*CPBA, and $KHSO_5$) or 4 h (*t*BuOOH) at 25 °C, and then analyzed by HPLC. Products were separated on a Waters Symmetry C_{18} reverse-phase column (4.6 mm × 250 mm), and product yields were determined by comparison with standard curves of known authentic samples.

$H_2{}^{18}O$ experiments with CBZ: Reactions were run in buffered ^{18}O-labeled water solutions (0.15 mL, 85% ^{18}O-enriched) containing $[Mn(TF_4TMAP)]^{5+}$ (7×10^{-2} mM) and CBZ (3.6×10^{-1} mM). Oxone (0.7 mM in 0.1 M pH 3 formate buffer, 1 mM in 0.1 M pH 5 acetate buffer and pH 7 phosphate buffer, 1.6 mM in 0.1 M pH 9 phosphate buffer, 2 mM in 0.1 M pH 10.5 borate buffer) was added to the reaction solution, which was stirred for 40 min at room temperature, then taken to dryness in a Speed-Vac. After addition of CH_3CN (0.1 mL) to the residue, followed by filtration, the filtrate was analyzed by the electronic impact method at 70 eV with a VG70-VSEQ mass spectrometer (VG Analytical). ^{16}O and ^{18}O compositions in CBZ-10,11-oxide were determined from the relative abundances of mass peaks at *m*/*z* 252 (^{16}O) and 254 (^{18}O).[7d, 14]

The conversion of CBZ and the yield of CBZ-10,11-oxide were determined by carrying out the reactions in buffered $H_2{}^{16}O$ solutions under identical conditions. The reaction mixture was analyzed directly by HPLC. CBZ and its oxide derivative were separated on a Waters Symmetry C_{18} column; the detection was made at 215 nm.

Acknowledgement

This work was supported by the Korea Science and Engineering Foundation (R03–2001–00028), Ewha Womans University (2000), CCSR at Ewha Womans University, and the Korea Research Foundation (DP0270). I.K. and J.S.L. hold a Research Fellowship (Brain Korea 21 Program).

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Received: October 31, 2001 [F3646]