Use of 2-methyl-1-phenylpropan-2-yl hydroperoxide (MPPH) as a mechanistic probe for the heterolytic *versus* homolytic O–O bond cleavage of *tert*-alkyl hydroperoxide by iron(III) porphyrin complex

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The mechanism of the O–O bond cleavage of *tert*-alkyl hydroperoxide by iron(III) porphyrin complexes has been studied using 2-methyl-1-phenylpropan-2-yl hydroperoxide (MPPH) as a mechanistic probe; the hydroperoxide O–O bond is cleaved both heterolytically and homolytically and partitioning between the two pathways significantly depends on the reaction conditions such as the pH of the reaction solutions and the nature of porphyrin and axial ligands.

The reactions of iron(III) porphyrin complexes with alkyl hydroperoxides have been intensively studied as biomimetic models for heme-containing enzymes such as cytochromes P-450, peroxidases and catalases, with the intention of elucidating the mechanism of O–O bond activation and the structure of reactive intermediates.[1] Traylor *et al.* proposed that the O–O bond of hydroperoxides is heterolytically cleaved by the iron porphyrins, giving the formation of a high-valent iron oxo porphyrin cation radical intermediate **1** (Scheme 1, pathway A).[2] In contrast, Bruice *et al.*[3] and others[4] provided evidence that the initial step of the hydroperoxide O–O bond cleavage is homolysis, resulting in the formation of a ferryl–oxo complex, **2**, and an alkoxyl radical (Scheme 1, pathway B). Despite the intensive study for the last two decades, the nature of the O–O bond cleavage of ROOH by the iron(III) porphyrin complexes has been controversial and still remains unclear.

In recent years, 2-methyl-1-phenylpropan-2-yl hydroperoxide (MPPH) has been shown to be an excellent mechanistic probe capable of distinguishing between free alkoxyl radical chemistry and radical-free (enzyme mimetic) chemistry in non-porphyrin iron(III) complex-catalyzed oxidations of hydrocarbons by *tert*-alkyl hydroperoxides.[5] When the O–O bond of MPPH is cleaved homolytically by the iron complexes, an alkoxyl radical (MPPO·) is generated [eqn. (1)]. Then, the

$$Fe^{III} + PhCH_2CMe_2OOH \xrightarrow{\text{homolysis}} Fe^{IV}{=}O + PhCH_2CMe_2O^{\bullet} + H^+ \quad (1)$$
(MPPH) (MPPO•)

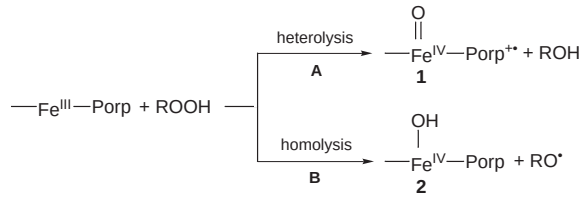
alkoxyl radical undergoes an extremely rapid β-scission, giving PhCHO and $PhCH_2OH$ [eqn. (2)].[5] In contrast, heterolytic

$$PhCH_2CMe_2O^{\bullet} \xrightarrow{-Me_2CO} PhCH_2^{\bullet} \xrightarrow{+O_2} \longrightarrow PhCHO + PhCH_2OH \quad (2)$$
(MPPO•)

reduction of MPPH by the iron complexes yields an alcohol (MPPOH) [eqn. (3)]. Therefore, the mechanism of the O–O

$$Fe^{III} + PhCH_2CMe_2OOH \xrightarrow{\text{heterolysis}} Fe^{V}{=}O + PhCH_2CMe_2OH \quad (3)$$
(MPPOH)

bond cleavage of *tert*-alkyl hydroperoxides can be determined by analyzing the products derived from the decomposition of MPPH by iron complexes. Another mechanistic probe often used to interpret the mechanism of the O–O bond cleavage of ROOH by iron(III) porphyrin complexes is to analyze the products yielded in the epoxidation of olefins such as (*Z*)-stilbene.[6] When **2** is formed *via* homolysis (Scheme 1, pathway B), **2** affords a low yield of epoxide products with a loss of stereospecificity.[7] In contrast, **1**, which is generated *via* heterolysis (Scheme 1, pathway A), is capable of epoxidizing olefins stereospecifically. We therefore studied iron(III) porphyrin complex-catalyzed olefin epoxidation reactions using the aforementioned two mechanistic probes (*i.e.* MPPH as an oxidant and (*Z*)-stilbene as a substrate), in order to clarify the mechanism of the O–O bond cleavage of *tert*-alkyl hydroperoxides by iron(III) porphyrin complexes.



Scheme 1

The catalytic epoxidation of (*Z*)-stilbene by MPPH was carried out in the presence of water-soluble iron(III) porphyrin complexes in buffered H_2O–MeOH–MeCN solutions.† Among the tested iron porphyrins (see Fig. 1), $Fe(TDFPPS)^{3-}$ showed the greatest reactivity for giving a high yield of *cis*-stilbene oxide with a trace amount of *trans*-stilbene oxide, whereas other iron porphyrins gave a small amount of *cis*-stilbene oxide (*vide infra*). Fig. 2 shows the result of product studies obtained in the (*Z*)-stilbene epoxidation by $Fe(TDFPPS)^{3-}$ and MPPH at pH 3–8. The epoxidation reaction was found to depend on the pH of the reaction solutions[8] and the yield of *cis*-stilbene oxide formed was higher at low pH values, as we have observed previously.[9] Interestingly, the amounts of *cis*-stilbene oxide and MPPOH yielded in the reactions were similar, demonstrating that the reaction of $Fe(TDFPPS)^{3-}$ and MPPH involves heterolysis of the hydroperoxide to generate $(TDFPPS)^{+\cdot}Fe^{IV}{=}O$ as a reactive intermediate responsible for the (*Z*)-stilbene epoxidation. In addition to the heterolysis of MPPH by $Fe(TDFPPS)^{3-}$,

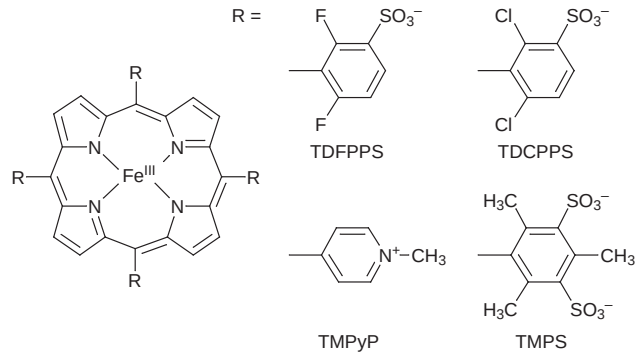


Fig. 1 Structures and abbreviated names of iron(III) porphyrin complexes used in this study.‡

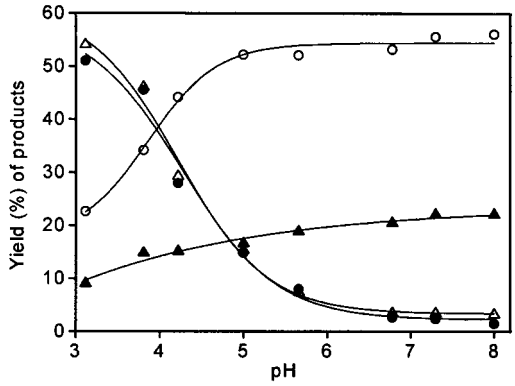


Fig. 2 Plot of the percent yield of products (●, *cis*-stilbene oxide; △, MPPOH; ▲, $PhCH_2OH$; ○, PhCHO) *vs.* pH of reaction solutions for the catalytic epoxidation of (*Z*)-stilbene by $Fe(TDFPPS)^{3-}$ and MPPH. The percent yields are calculated on the basis of MPPH used. See footnote † for detailed experimental procedures.

homolysis of MPPH took place concurrently even at low pH values, as demonstrated by the observation of the formation of PhCHO and $PhCH_2OH$ [eqn. (2)]. As the pH of the reaction solution increased, the yields of *cis*-stilbene oxide and MPPOH products decreased and the amounts of the PhCHO and $PhCH_2OH$ increased. These results indicate that the O–O bond cleavage of MPPH was shifted from heterolysis to homolysis as the pH of the reaction solutions increased.

In addition to the pH effect on hydroperoxide O–O bond cleavage, we found that there are other important factors that control the type of O–O bond cleavage of *tert*-alkyl hydroperoxides. As shown in Table 1, the O–O bond cleavage was significantly affected by the porphyrin ligands bound to iron and the general trend appeared to be that more electronegatively-substituted iron porphyrins gave a high percentage of heterolysis, whereas homolysis prevailed in the reactions with less electronegatively-substituted iron porphyrins. This result is consistent with the observation that electron-deficient iron porphyrins are effective catalysts in the epoxidation of olefins by H_2O_2 and ROOH.[10] We also found, by studying the epoxidation of (*Z*)-stilbene with $Fe(TDFPPS)^{3-}$ and MPPH in the presence of imidazoles, that there is a significant axial ligand effect on the ratio of the heterolytic and homolytic O–O bond cleavage of *tert*-alkyl hydroperoxides.[4b,11,12] Interestingly, the presence of imidazoles such as 5-chloro-1-methylimidazole and 1-phenylimidazole increased the yields of *cis*-stilbene oxide and MPPOH products, whereas 1-methylimidazole and 1,2-dimethylimidazole did not alter the ratio of heterolysis to homolysis significantly (data not shown), indicating that the nature of the axial ligand bound to iron is another important factor determining the type of the hydroperoxide O–O bond cleavage.[11–13]

In summary, we demonstrated unambiguously that the O–O bond of *tert*-alkyl hydroperoxides is cleaved both heterolytically and homolytically,[11] depending on the reaction conditions such as pH and the electronic nature of the porphyrin and axial ligands. These results rationalize the long-standing dichotomy of the interpretations for the O–O bond cleavage mechanism of ROOH by iron(III) porphyrin complexes, mainly suggested by Traylor[2] and Bruice[3] and co-workers.

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Table 1 Product yields formed in the epoxidation of (*Z*)-stilbene by MPPH catalyzed by iron porphyrin complexes at pH 3.2[a]

	Yields (%)[b]			
Iron porphyrins	*cis*-Stilbene oxide	MPPOH	$PhCH_2OH$	PhCHO
$Fe(TDFPPS)^{3-}$	51	54	8	21
$Fe(TDCPPS)^{3-}$[c]	33	38	12	41
$Fe(TMPyP)^{5+}$	2	7	14	59
$Fe(TMPS)^{7-}$[c]	12	19	18	44

[a] See footnote † for detailed reaction procedures. [b] Based on MPPH used. [c] Reactions were run for 8 h.

Notes and references

† MPPH was prepared according to literature procedures[5] and the purity of MPPH was determined to be 100% by NMR. In a typical reaction, MPPH (4 mM, introduced as a 0.2 M solution in MeOH) was added to a reaction solution containing $Fe(TDFPPS)^{3-}$ (0.04 mM, introduced as 0.01 M solution in H_2O) and (*Z*)-stilbene (6 mM, introduced as 0.3 M solution in MeOH) in a solvent mixture (5 mL) of buffered H_2O (2.5 mL)–MeOH (1.0 mL)–MeCN (1.5 mL) in order to make the reaction mixture homogeneous. Reactions at pH 3 were performed in formate buffer (0.1 M), at pH 4–5 in acetate buffer (0.1 M), and at pH 6–8 in phosphate buffer (0.1 M), and the pH was adjusted by adding either HCl (3 M) or NaOH (3 M) solutions as necessary. The reaction mixture was stirred in air for 4 h at 25 °C, and then analyzed by *Orom Vintage 2000* HPLC equipped with a variable wavelength UV-200 detector. Detection was made at 215 and 254 nm.
‡ All iron(III) porphyrin complexes used in this study were obtained from Mid-Century Chemical. Abbreviations used: TDFPPS, [*meso*-tetrakis(2,6-difluoro-3-sulfonatophenyl)porphyrin; TDCPPS, *meso*-tetrakis(2,6-dichloro-3-sulfonatophenyl)porphyrin; TMPyP, *meso*-tetrakis(*N*-methylpyridin-4-ylium)porphyrin; TMPS, *meso*-tetrakis(2,5-disulfonatomesityl)-porphyrin.

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