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^{18}O-Tracer Studies of Fe(II)-Induced Decomposition of 1,2,4-Trioxolanes (Ozonides) Derived from Cyclopentenes and Indenes. Inner-Sphere Electron Transfer Reduction of the Peroxide Linkage

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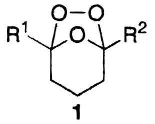
Abstract: Fe(II)-induced decomposition of 1,2,4-trioxolanes (ozonides) **1** and **2** is studied in detail. The inner-sphere electron transfer reduction, which is sensitive to steric effects, is proposed to be a reasonable mechanism for the peroxide decomposition, i.e., the selective generation of one of the two possible Fe(III)-complexed oxy radicals. The fate of the oxy radical species is revealed in detail by using ^{18}O-tracer studies in the reduction of ^{18}O-labeled ozonides **1a** and **2a**, in which the ethereal oxygens are labeled by ^{18}O atom (^{18}O, 77%) and also by the reduction in the presence of $H_2{}^{18}O$ (^{18}O, 10%). The results of the ^{18}O-tracer studies are consistent with the regioselective generation of the Fe(III)-complexed oxy radical species.

Introduction

The chemistry of endoperoxides as active oxygen sources has attracted considerable attention in connection with their biological activity. Thus, the metal-induced decomposition of the peroxide linkage has been well investigated in the past three decades.[1] The decomposition mechanism can be rationalized by the electron transfer reduction[2] of the electrophilic peroxy bond (Scheme 1).

For example, Co(II)- or Ru(II)-induced decomposition of endoperoxides has been explained by the inner-sphere one-electron transfer process, proved by the lack of a well-defined correlation with the oxidation potential of the metal and also by the effect of the steric circumstances around the peroxide linkage on the reaction pathways.[3] Fe(II)-induced decomposition[4,5] of endoperoxides has also been studied in connection with their antimalarial activity.[6,7]

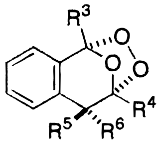
In conjunction with our interest[8] in the synthesis of isolable 1,2,4-trioxolanes[9] (ozonides) **1** and **2**, derived from the ozonolysis of cyclopentenes and indenes, we have decided to examine the Fe(II)-induced decomposition of a wide variety of ozonides (**1**, **2)** in detail. If the inner-sphere electron transfer reduction is the preferred process for the ozonide reduction too, a significant difference in the steric circumstances[10,11] around the peroxide linkage would result in the regioselective generation of one of the two possible Fe(III)-complexed oxy radicals, which in turn leads to the substituent-dependent product selectivity. To elucidate the fate of the oxy radicals, we have also examined the ^{18}O-isotope labeling studies.



1

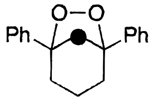
	R1	R2
a	Ph	Ph
b	Ph	Mes
c	H	Ph

(Mes = mesityl)



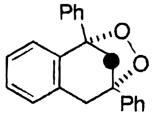
2

	R3	R4	R5	R6
a	Ph	Ph	H	H
b	Ph	H	H	H
c	Ph	H	CH3	CH3
exo-**d**	Ph	H	CH3	H
endo-**d**	Ph	H	H	CH3
e	H	Ph	H	H
f	H	Ph	-(CH2)4-	



^{18}O-**1a**

(●; ^{18}O)



^{18}O-**2a**

Results and Discussion

Fe(II)-Induced Decomposition of Ozonides 1a−c Derived from the Cyclopentenes. The reductions of ozonides **1a**−**c**

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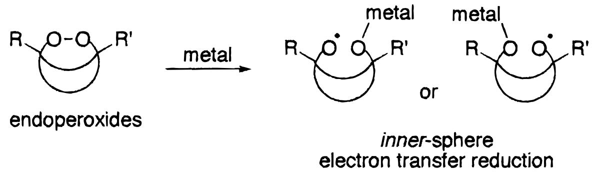
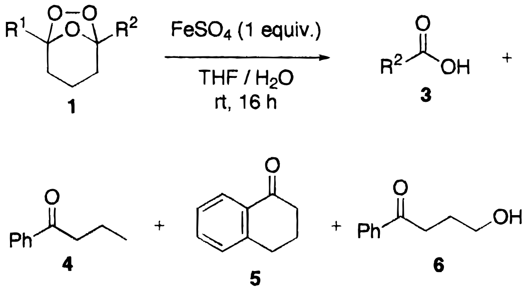
Scheme 1. Metal-Induced Reduction of Endoperoxides, Inner-Sphere Electron Transfer Mechanism



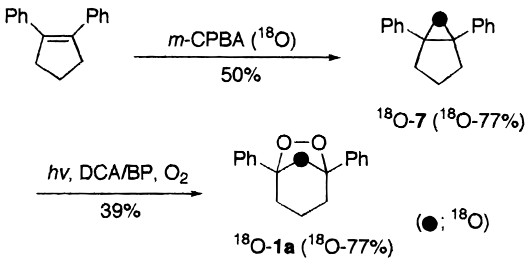
were examined in the presence of stoichiometric amounts of $Fe(II)SO_4$ in THF/H_2O (1/1) under an argon atmosphere for typically 16 h (eq 1). The reactions proceeded cleanly, giving the decomposition products **3**−**6** in high yields (eq 1 and Table 1).



(1)

From the reaction of the symmetrical ozonide **1a** ($R^1 = R^2$ = Ph), benzoic acid **3a** (R^2 = Ph) was obtained quantitatively together with ketones **4**−**6** (entry 1 in Table 1). Interestingly, the reduction of the unsymmetrical ozonides **1b** (R^1 = Ph, R^2 = mesityl) and **1c** (R^1 = H, R^2 = Ph) resulted in the selective formation of one of the two possible carboxylic acids (entries 2 and 3). Namely, **3b** (R^2 = mesityl) from **1b** and **3a** from **1c** were obtained in high yields, respectively. In the case of the reaction of the ozonide **1b**, the ketones **4**−**6** were also formed in similar yields observed for the reduction of **1a** (compare entries 1 and 2). For the ozonide **1c**, although 1-butanal was detected by ^{1}H NMR (270 MHz) of the crude reaction mixture, only benzoic acid **3a** could be isolated.

To verify the mechanism for the production of **3**−**6**, isotope labeling studies were performed in the reduction of the ozonide **1a**. First of all, the ^{18}O-tracer experiments were examined by using the ^{18}O-labeled ozonide ^{18}O-**1a** (^{18}O, 77%),[12] in which the ethereal oxygen was labeled by ^{18}O atom (eq 2). The labeled ozonide ^{18}O-**1a** was prepared by an electron transfer photooxygenation[13] of the ^{18}O-labeled epoxide ^{18}O-**7** (^{18}O-77%), which was prepared by the epoxidation of 1,2-diphenylcyclopentene by using ^{18}O-labeled *m*-CPBA as depicted in eq 2 (see Experimental Section).



(2)

The ^{18}O content (%) of the epoxide ^{18}O-**7** was calculated from the relative mass peak intensities of 236 (M^+) and 238 ($M + 2^+$), comparing with those of the unlabeled epoxide **7** (see Table 3). The ^{18}O contents (%) reported below were determined by a similar method.

By the careful mass spectroscopic analyses of the products **3**−**6** formed in the reduction of the ozonide ^{18}O-**1a** (^{18}O, 77%), interestingly, only benzoic acid **3a** was found to contain almost the same amount of ^{18}O-atom (^{18}O, 76%; entry 4). Other products **4**−**6** did not contain ^{18}O atom derived from the ethereal oxygen of the ozonide ^{18}O-**1a**. Next, the Fe(II)-induced decomposition of the ozonide **1a** was performed in the presence of ^{18}O-labeled H_2O (^{18}O, 10%; entry 5). As expected, the ^{18}O content of benzoic acid **3a** did not exceed the natural amount of ^{18}O-atom (ca. 0.2%). However, products **4**−**6** did contain ^{18}O-atom from $H_2{}^{18}O$: **4** (^{18}O, 9.3%); **5** (^{18}O, 7.7%); **6** (^{18}O, 6.0%) (entry 5). In the keto-alcohol **6**, only the carbonyl oxygen contained external ^{18}O atom (^{18}O, 6.0%), proved by the following mass spectroscopic evidence: (1) no (M + 4) peak in the mass spectra was observed; (2) the fragment peak (C_6H_5-CO^+, 105) did contain the similar amounts of ^{18}O atom (^{18}O-4.9%). These results clearly suggest that the carbonyl oxygens

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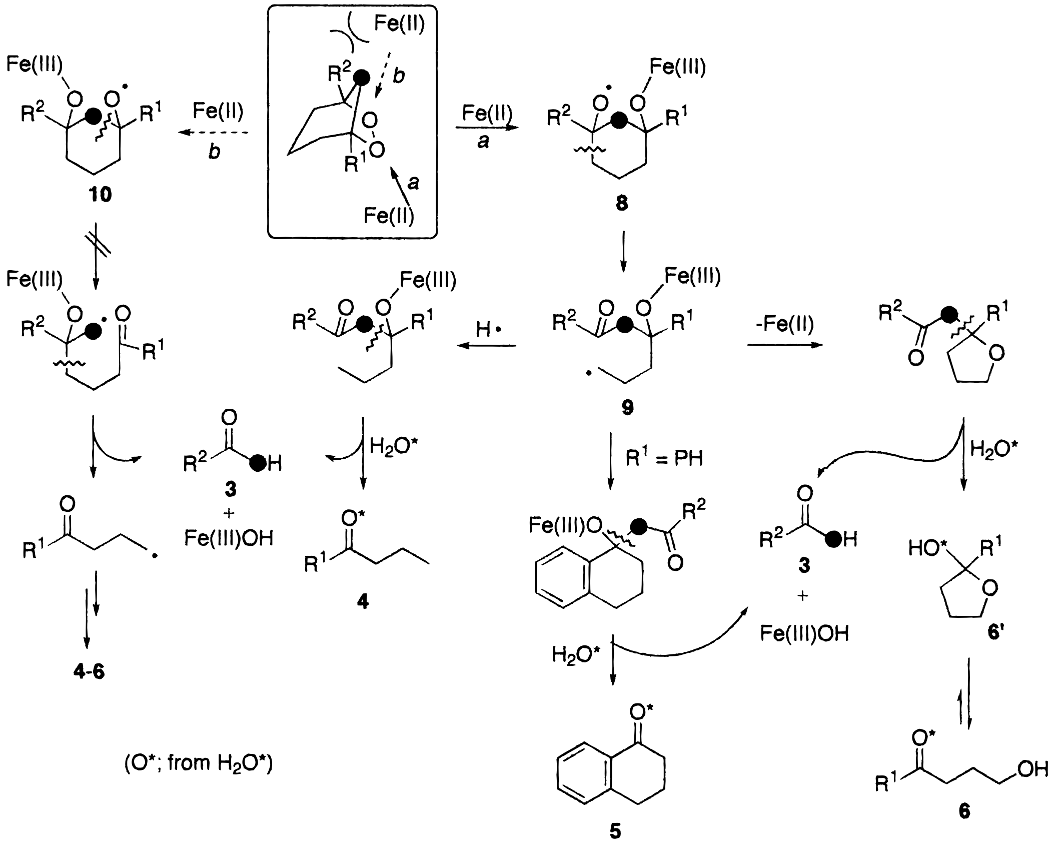
Table 1. Fe(II)-Induced Decomposition of Ozonides 1a−c and ^{18}O-1a[a]

	ozonide	products and yields (%)[b]			
1	**1a**	**3a** (98)	**4** (33)	**5** (19)	**6** (7)
2	**1b**	**3b** (81)	**4** (26)	**5** (13)	**6** (9)
3[c]	**1c**	**3a** (79)			
4	^{18}O-**1a** (^{18}O, 77%)[d]	^{18}O-**3a** (93; ^{18}O, 76%)[d]	**4** (29)	**5** (16)	**6** (9)
5[e]	**1a**	**3a** (94)	^{18}O-**4** (31; ^{18}O, 9.3%)[d]	^{18}O-**5** (21; ^{18}O, 7.7%)[d]	^{18}O-**6** (8; ^{18}O, 6.0%)[d]

[a] Fe(II)SO$_4$ (1 equiv) induced decomposition of ozonides **1a**−**c** in THF/H_2O (1/1) were run at room temperature (ca. 20 °C) for 16 h. [b] Isolated yields after column chromatography (SiO$_2$). [c] The other products and yields were not determined, although 1-butanal was detected by ^{1}H NMR (270 MHz) analysis. [d] ^{18}O contents (%) were calculated by the mass spectroscopic analyses (see Table 3), error ± 0.5%. [e] The reaction was performed in THF/$H_2$18O (^{18}O, 10%).

Scheme 2



in the products **4**−**6** are mainly derived from H_2O used as a solvent for the reduction. Finally, to clarify the origin of the terminal hydrogen atom for the formation of butyrophenone **4**, the reduction of the ozonide **1a** was run in THF/D_2O. As a result, the deuterium isotope was not detected in the ketone **4**. Thus, the origin of the terminal hydrogen in **4** may be THF used as a cosolvent.

As mentioned above, it should be noted that one of the two possible carboxylic acids **3** was selectively produced from the unsymmetrically substituted ozonides **1b**,**c**. This implies the regioselective formation of oxy radical species **8** by the inner-sphere electron transfer reduction rather than the relative stability of the oxy radical species **8** and **10** (Scheme 2).[14] To understand the regioselective formation of the oxy radical, molecular orbital calculations (PM3 method)[15] were performed for the ozonide **1c** (Figure 1).

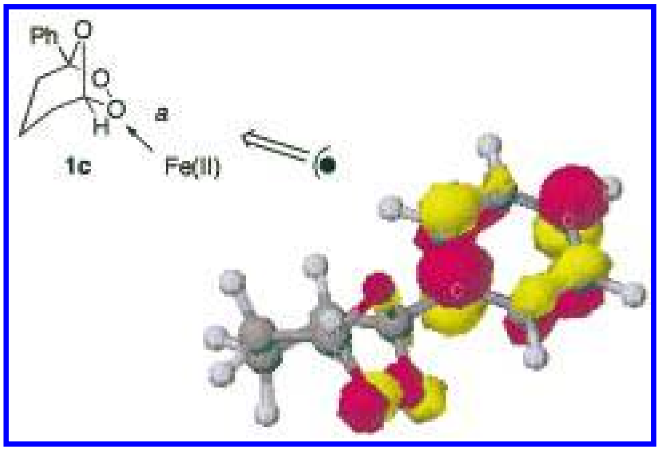


Figure 1. LUMO of the ozonide **1c**, calculated by PM3 method, showing the large coefficient at the peroxide linkage (O−O σ* orbital)

As visualized in Figure 1, the LUMO was found to be located largely at the peroxide linkage (O−O σ* orbital). Therefore, it is reasonable to expect that the nuclephilic Fe(II) species can attack the peroxidic oxygen from the less hindered direction of the antibonding orbital (a in Figure 1 and Scheme 2); in other words, the difference in the steric crowding around the antibonding orbital plays an important role in generating regiose-

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(14) Recently, such an equilibration between two Fe(III)-complexed oxy radicals derived from Artemisinin (1,2,4-trioxane derivatives) was postulated by Wu et al.: Wu, W.-M.; Wu, Y.; Wu, Y.-L.; Yao, Z.-J.; Zhao, C.-M.; Li, Y.; Shan, F. *J. Am. Chem. Soc.* **1998**, *120*, 3316.

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lectively one of the two possible Fe(III)-complexed oxy radicals **8** and **10** (a or b in Scheme 2).[16]

On the basis of the above-mentioned experimental data and the MO consideration, the mechanism for the Fe(II)-induced decomposition of ozonides **1a**−**c** is summarized as shown in Scheme 2. The nucleophilic Fe(II) species attack the ozonide **1** from the less hindered side (a) of the electrophilic O−O σ^* orbital to generate exclusively the oxy radical **8** (inner-sphere electron transfer, steric hindrance $R^2 > R^1$ in Figure 1 and Scheme 2). After the selective C−C bond scission, the resulting carbon-centered radical **9** would produce the observed products **3**−**6**. The formation of butyrophenone **4** can be rationalized by the hydrogen atom abstraction and the successive elimination of the carboxylic acid **3**. The ^{18}O-tracer experiments strongly suggest that this hydrolysis occurs selectively at the acetal carbon. The competitive radical cyclizations in **9** to either the phenyl ring or the O−Fe(III) bond[20] would give the ketone **5** and the keto alcohol **6**, respectively (Scheme 2).

Alternatively, products **3**−**6** may be produced from the alkoxy radical species **10** (generated from the b attack, the dotted arrow in Scheme 2) by the successive C−O and C−C bond scissions. However, this mechanism can be reasonably excluded from the following reasons. (1) The selective bond scission of the C−O bond in **10** is unlikely, because in general the C−C bond cleavage is the preferred process due to the generation of the thermodynamically stable carbon-centered radical.[21] (2) The generated ketones **4**−**6** from the b route should not contain any ^{18}O atom from H_2O. In reality, the products isolated in the reaction did contain substantial amounts of ^{18}O atom from $H_2{}^{18}O$ used as a cosolvent.

On the basis of our detailed study, the inner-sphere electron transfer is the most likely decomposition process of the peroxide linkage of ozonides **1a**−**c** by Fe(II). To test if this hypothesis is correct or not, we next conducted the similar Fe(II)-induced decomposition of ozonides **2** derived from indene derivatives.

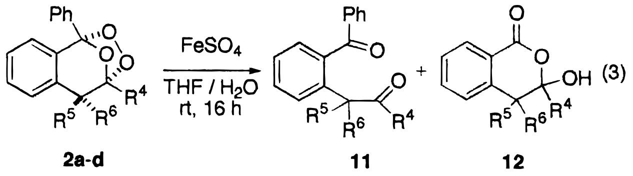

Table 2. Fe(II)-Induced Decomposition of Ozonides 2a−d[a]

	ozonide	products and yields (%)[b]	
1	**2a**	**11a** (93)	**12a** (4)
2	**2b**	**11b** (93)	**12b** (3)
3	**2c**	**11c** (73)	**12c** (14)
4	*exo*-**2d**	**11d** (87)	**12d** (11)
5	*endo*-**2d**	**11d** (85)	**12d** (8)
6	^{18}O-**2a** (^{18}O, 77%)[c]	^{18}O-**11a** (94; ^{18}O, 39%)[c]	^{18}O-**12a** (2)[d]

[a] Fe(II)SO$_4$ (1 equiv) induced decomposition of ozonides **2a**−**d** in THF/H_2O (1/1) were run at room temperature (ca. 20 °C) for 16 h. [b] Isolated yields after column chromatography (SiO$_2$). [c] ^{18}O contents (%) were calculated by the mass spectroscopic analyses (see Table 3), error ± 0.5%. [d] The ^{18}O contents (%) was not determined.

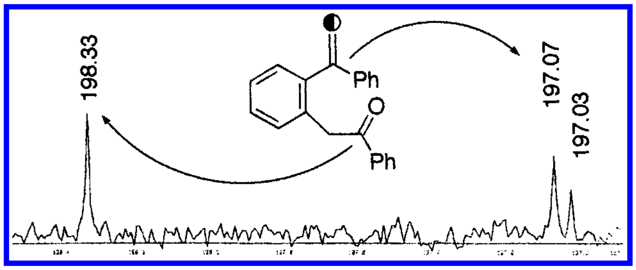

Figure 2. ^{13}C NMR (150 MHz in CDCl$_3$) signals of the carbonyl carbons in ^{18}O-**11a** (^{18}O, 39%) showing ^{18}O atom exists in the carbonyl carbon of the benzophenone moiety

Fe(II)-Induced Decomposition of Ozonides 2a−**d Derived from 3-Phenyl Indenes.** First, the reaction of ozonides **2a**−**d** ($R^3 = $ Ph) derived from 3-phenyl indenes with Fe(II) species is shown (eq 3 and Table 2). From all of the reductions of ozonides **2a**−**d**, the corresponding diketones **11** and lactones **12** were obtained (entries 1−5). To clarify the reaction process, ^{18}O-tracer experiments were also performed for the case of the ozonide **2a** ($R^3 = R^4 = $ Ph, $R^5 = R^6 = $ H) (entry 6 in Table 2). The ozonide ^{18}O-**2a** (^{18}O-77%)[22] was prepared in a way similar to that for ^{18}O-**1a** (see eq 2). The reduction showed that the ^{18}O-labeled diketone ^{18}O-**11a** (^{18}O, 39%; mass spectroscopic analysis) was obtained in a similar yield to the unlabeled case. To identify which oxygen in the diketone **11a** contains ^{18}O atom, the highly resolved ^{13}C NMR (150 MHz) analysis was performed (Figure 2). In the carbonyl carbon region, only three signals, δ 197.03, 197.07, 198.33, which correspond to one ^{18}O-labeled carbonyl carbon and two unlabeled carbonyl carbons, were detected. Judging from the chemical shifts, the two signals which appear very close ($\Delta\delta = 0.04$ ppm) and at higher fields were assigned to the carbonyl carbon of the benzophenone moiety.[23,24] Thus, only the oxygen of the benzophenone moiety was confirmed to be labeled.

The reduction of the ozonide **2a** was also performed in ^{18}O-labeled H_2O (^{18}O, 10%). After the isolation of the diketone **11a**, the careful mass spectroscopic analysis was examined, which indicated the uptake of a small but significant amount of ^{18}O atom in **11a** (^{18}O, 1.2%). The unlabeled diketone **11a** was treated with Fe(III) in THF/H_2O (^{18}O, 10%). After being stirred for 24 h, the recovered diketone **11a** did contain a similar amount of ^{18}O atom (^{18}O, 1.1%).

The worthwhile results of the ^{18}O-tracer studies mentioned above are summarized as follows. (1) A drop in the ^{18}O content in the diketone **11a** (^{18}O, 39%) was observed when the labeled ozonide **2a** (^{18}O, 77%) was used for the reaction. (2) Only the carbonyl oxygen of the benzophenone moiety in **11a** was labeled by ^{18}O atom. (3) When the reduction was conducted in the presence of $H_2{}^{18}O$ (^{18}O, 10%), the isolated diketone **11a** was found to contain ^{18}O atom (^{18}O, 1.2%). (4) In the presence of Fe(III), it was possible for the oxygen atom of the unlabeled product **11a** to exchange with the external oxygen atom.

The mechanism for the Fe(II)-induced decomposition of ozonides **2a**−**d** is shown in Scheme 3. The nucleophilic Fe(II)

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(16) Nucleophilic attack toward O−O σ^* orbital in 1,2-dioxetanes was extensively investigated by Adam.[17−19]

(17) Adam, W.; Heil, M.; Voerckel, V. *J. Org. Chem.* **1992**, *57*, 2680.

(18) Adam, W.; Heil, M. *Chem. Ber.* **1992**, *125*, 235.

(19) Adam, W.; Heil, M. *J. Am. Chem. Soc.* **1992**, *114*, 5591.

(20) The mechanism was also postulated in ref 5k.

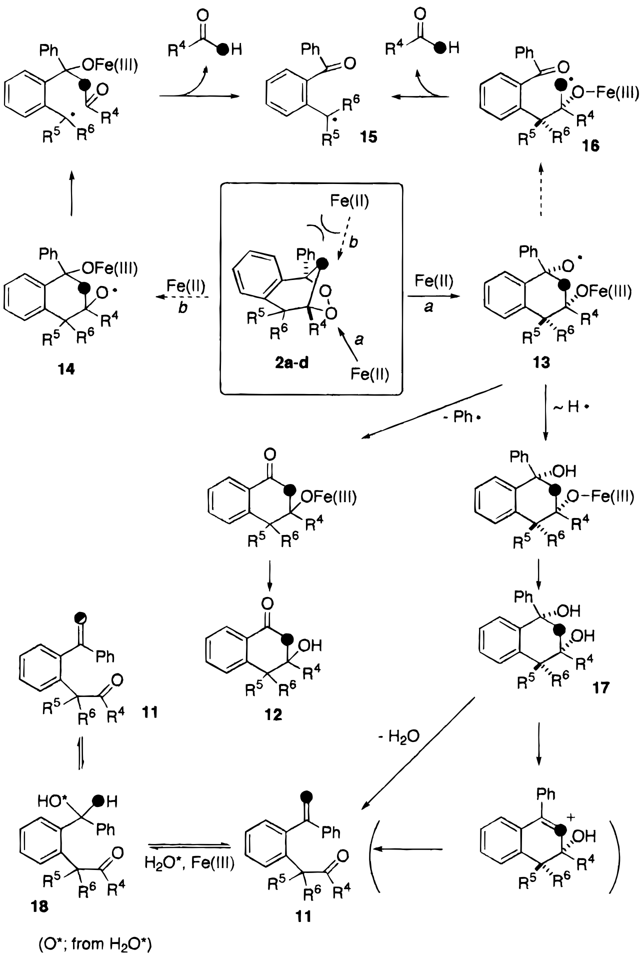
(21) Examples for the selective C−C bond cleavage from oxy radical species: (a) Schreiber, S. L. *J. Am. Chem. Soc.* **1980**, *102*, 6165. (b) Cardinale, G.; Grimmelikhuysen, J. C.; Laan, J. A. M.; Ward, J. P. *Tetrahedron Lett.* **1984**, *40*, 1881. (C) Cardinale, G.; Laan, J. A. M.; Ward, J. P. *Tetrahedron Lett.* **1985**, *41*, 2899. (d) Cardinale, G.; Laan, J. A. M.; Ward, J. P. *Tetrahedron* **1985**, *41*, 6051. (e) McCullough, K. J.; Motomura, Y.; Masuyama, A.; Nojima, M. *Chem. Commun.* **1998**, 1173.

(22) The ^{18}O content (%) of the ozonide **2a** was estimated from that of the epoxide ^{18}O-**7**, since the 2,3-diphenylindene epoxide, which was prepared by using ^{18}O-*m*-CPBA used for the preparation of ^{18}O-**7**, could not be isolated due to the instability on silica gel.

(23) An upfield shift (ca. 0.04 ppm) in the ^{13}C NMR spectrum by ^{18}O-isotopic substitution, see: Risley, J. M.; Etten, R. L. V. *J. Am. Chem. Soc.* **1979**, *101*, 252.

(24) ^{13}C NMR (150 MHz, CDCl$_3$) $\delta_{CO} = 196.58$ ppm (benzophenone); $\delta_{CO} = 197.95$ ppm (acetophenone).

Scheme 3



attack from the less hindered side of the O−O σ^* orbital (a attack, steric effect Ph > R^4) occurs to generate the Fe(III)-complexed oxy radicals **13a**−**d**, selectively. In the case of the ozonide **2a** (R^4 = Ph), at first sight there is no significant difference of the steric circumstances around the two peroxide oxygens. However, as can be seen in the PM3-optimized structure of the ozonide **2a** (Figure 3), the nucleophilic attack of Fe(II) from the b side of the O−O σ^* orbitals can be suppressed by the perpendicularly locked conformation of the phenyl ring (R^3). On the other hand, the a side is relatively less hindered due to the flexible conformation of the phenyl ring (R^4). Thus, in the case of the ozonide **2a**, the Fe(II) attack from the a side is the preferred process giving the alkoxy radical **13a** (Scheme 3). The structure of the products **11** and **12** indicates that the fates of the alkoxy radical **13** are Ph$^{\bullet}$ elimination or hydrogen abstraction, giving lactone **12** and hemiacetal **17**, respectively. The position of the labeled oxygen and the drop of the ^{18}O content in the diketone **11a** suggest the intervention of the hemiacetal **18**. The possibility of such a mechanism is supported by the fact that the recovered **11a** did contain the ^{18}O atom when the nonlabeled **11a** was treated with H$_2$^{18}O in the presence of Fe(III) species, as mention above.

If the regioisomeric alkoxy radical **14** were generated by the b side attack of Fe(II), the fast C−C bond cleavage might have occurred to give the carbon radical **15**. In reality, we could not detect even trace amounts of products derived from the radical **15**. Thus, the intervention of the alkoxy radical **14** in the ozonide **2a**−**d** reduction is unlikely. Next, we have examined the reduction of ozonides **2e**,**f**, in which the b side is relatively less hindered.

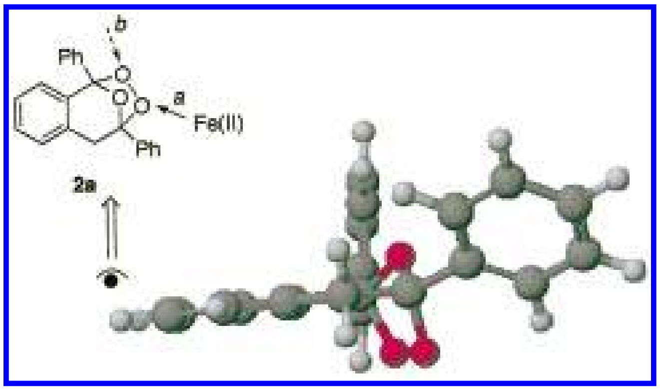
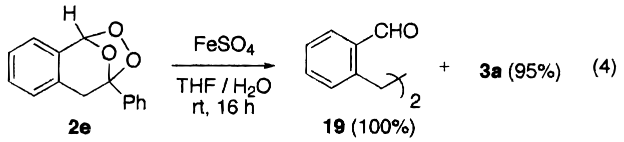
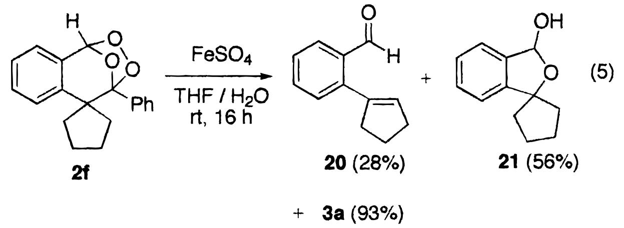


Figure 3. PM3-optimized structure of ozonide **2a**, showing that one side (b) of the O−O σ^* orbital is blocked by the perpendicularly locked conformation of the phenyl ring (R^3)

Fe(II)-Induced Decomposition of Ozonides 2e,f Derived from 2-Phenyl Indenes. The reductive decomposition of ozonides **2e**,**f** derived from 2-phenyl indenes was examined in a similar way (eqs 4 and 5). In both cases, benzoic acid **3a** was





obtained in high yields. In the case of the ozonide **2e** (R^3 = R^5 = R^6 = H, R^4 = Ph), the dimer **19** was quantitatively obtained together with benzoic acid **3a** (eq 4). On the other hand, for the reduction of the ozonide **2f** (R^3 = H, R^4 = Ph, R,^{5} R^6 = −(CH$_2$)$_4$−), the aldehyde **20** (15%), and the alcohol **21** (53%) were isolated without formation of a radical dimer (eq 5). The **20**/**21** product ratio did not change after the prolonged reaction time (up to 48 h). Thus, the possibility of the chemical transformation from the alcohol **21** to the aldehyde **20** under the reaction conditions was excluded.[25]

To understand the detail of the transformation, the ^{18}O-tracer study for the reduction of the ozonide **2f** was examined in THF/H$_2$^{18}O (^{18}O, 10%) (eq 6). No incorporation of the external ^{18}O

$$\mathbf{2f} \xrightarrow[\text{THF / H}_2{}^{18}\text{O, rt, 16 h}]{\text{FeSO}_4} {}^{18}\text{O-}\mathbf{20}\ (24\%,\ {}^{18}\text{O-}4.3\%),\ {}^{18}\text{O-}\mathbf{21}\ (54\%),\ \mathbf{3a}\ (93\%) \tag{6}$$

atom in benzoic acid **3a** was identified by the mass spectroscopic analysis. In the aldehyde **20**, however, 4.3% of ^{18}O atom was labeled (Table 3). Interestingly, in the case of the alcohol **21** a small (M + 4) peak was observed (see Table 4).

The mass spectroscopic data in Table 4 clearly suggest that two oxygens in **21** were derived from the external oxygen atom. Fortunately, the peak intensities of the mass fragments M$_1$$^+$ (161, M−CHO) and M$_2$$^+$ (105, PhCHO) were strong and easily

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[25] The alcohol **21** did not converted to the aldehyde **20** by treatment with silica gel.

Table 3. Mass Spectral Data for Natural and ^{18}O-Labeled Samples and the ^{18}O Contents (%)[a]

	relative peak intensity[c]						
	natural sample			^{18}O-labeled sample			^{18}O contents[b]
compound	M	M + 1	M + 2	M	M + 1	M + 2	(%)
7	100	21.4	2.34	26.5	7.91	100	77
3a	100	9.14	0.82	30.2	4.85	100	76
4	100	12.2	0.69	100	13.1	11.1	9.3
5	100	13.2	1.27	100	13.5	9.84	7.7
6	100	14.9	1.74	100	21.3	8.38	6.0
$PhCO^+$ (105) in **6**	100	9.20	0.98	100	9.15	6.21	4.9
11a	100	24.5	3.28	100	27.9	72.9	39[d]
				100	25.1	4.59	1.2[e]
				100	24.8	4.51	1.1[f]
20	100	14.5	1.18	100	17.0	5.70	4.3

[a] Mass (EI, 70 eV) spectroscopic data were measured by using a JEOL JNS-BX-303-HF spectrometer. [b] ^{18}O contents (%) = $[(M + 2)/(M + (M + 2))_{labeled} - (M + 2)/(M + (M + 2))_{natural}] \times 100$. [c] Average values, after three trials. The highest peak was normalized to 100% as a standard. [d] The ^{18}O content (%) was for **11a** obtained in the Fe(II)-induced reduction of ^{18}O-**2a** (^{18}O, 77%). [e] The value was for **11a** obtained from the reduction of **2a** in $H_2{}^{18}O$(^{18}O, 10%). [f] The value was for the recovered **11a**, after the nonlabeled **11a** was treated with Fe(III) in $H_2{}^{18}O$ (^{18}O, 10%).

observed, thereby making accurate calculations of the respective ^{18}O contents (%) in the two fragments feasible (Table 4). The 9.0% ^{18}O in the $M_1{}^+$ fragment (M−CHO) and 5.0% ^{18}O in the $M_2{}^+$ fragment (PhCHO) were calculated from the method stated in Table 3. It should be noted that only in the case of the reduction of the ozonide **2f** was there no need for the stoichiometric amounts of Fe(II). Namely, 0.5 equiv of Fe(II) was enough to decompose the ozonide **2f**, although for the other cases ca. 1 equiv of Fe(II) was indispensable for the completion of the ozonide decomposition.

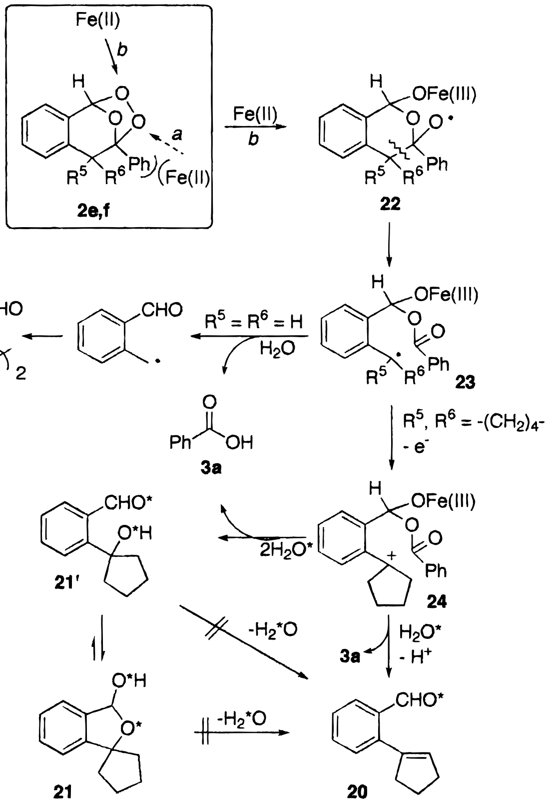
On the basis of the above-mentioned experimental results, the reaction mechanism of ozonides **2e,f** with Fe(II) species is shown in Scheme 4.

The inner-sphere reduction of peroxide linkage occurs from the direction (b) of the less hindered O−O σ^* orbital to give the oxy radical **22** (steric hindrance Ph > H). In the case of the ozonide **2e** ($R^5 = R^6 = H$), the resulting carbon radical **23e** derived from the fast C−C bond cleavage of the oxy radical **22e** can dimerize to give quantitatively the dialdehyde **19** together with benzoic acid **3a**. Thus, stoichiometric amounts of Fe(II) were needed. In contrast, only monomeric products **20** and **21** were obtained from the ozonide **2f**. Furthermore, a catalytic amount of Fe(II) was enough to realize complete decomposition of the ozonide **2f**. These results may suggest that the carbon radical **23f** derived from the ozonide **2f** ($R^5 = R^6 = -(CH_2)_4-$) may be oxidized by Fe(III) or the ozonide **2f** itself to give the cation **24**. The resulting carbocation **24** can be trapped or deprotonated to give the alcohol **21′**, which can be equilibrated with the aldehyde **20**. The intervention of the carbocation intermediate **24** was strongly supported by the fact that the $M_1{}^+$ fragment (161, M^+−CHO) contained ^{18}O atom (^{18}O, 9.0%) when $H_2{}^{18}O$ (^{18}O, 10%) was used as a solvent.

Summary

The reaction of a wide variety of 1,2,4-trioxolanes (ozonides) **1** and **2** with $Fe(II)SO_4$ has been explored in detail. We have found that the electrophilic peroxy bond in the ozonides was actually reactive to Fe(II) species to afford the decomposition products. The notable substituent effects around the peroxide linkage on the product distributions observed in our experiments strongly suggest that the inner-sphere electron transfer reduction by Fe(II) species is a reasonable mechanism for the ozonide decomposition to generate regioselectively one of the two possible Fe(III)-complexed oxy radical species. The regioselective generation of oxy radical species was proved by the ^{18}O-tracer studies.

Scheme 4



Experimental Section

General. ^1H and ^{13}C NMR spectra were recorded on JEOL JNM-EX-270 or Varian UNITY INOVA-600 spectrometers. ^1H NMR (270 MHz) chemical shifts were reported in ppm (δ) using residual $CHCl_3$ (δ 7.26) in $CDCl_3$. ^{13}C NMR (68 or 150 MHz) chemical shifts were reported in ppm (δ) relative to the internal standard $CDCl_3$ (δ 77.00). IR spectra were recorded on a Hitachi 260-30 spectrophotometer. Mass spectroscopic data were obtained by using a JEOL JNS-BX 303-HF mass spectrometer.

^{18}O Analysis. All ^{18}O contents (%) were calculated from the relative mass peak intensities of M^+ and $(M + 2)^+$, corrected for natural abundance. The mass spectroscopic data (relative intensities) were collected in Tables 3 and 4 as the averages of three measurements, error ±~0.5%. Since all the products have strong parent peaks, it was easy to determine accurately the ^{18}O contents (%) by using the following equation:

$$^{18}O\ \text{content (\%)} = [(M + 2)/(M + (M + 2))_{\text{labeled}} - (M + 2)/(M + (M + 2))_{\text{natural}}] \times 100$$

Synthesis of Ozonides 1a−c and 2a−h. Ozonides **1 and 2**, except for **1b**, were prepared by the usual ozonolysis procedure of the corresponding alkenes as reported in our previous work.[8] Since the mesityl-substituted ozonide **1b** could not be obtained by the usual ozonolysis, the ozonide **1b** was prepared by an electron transfer photooxygenation[13] of the acid-labile 1-mesityl-5-phenyl-6-oxabicyclo-[3.1.0]hexane, followed by the epoxidation of 1-phenyl-2-mesitylcyclopentene.[26] Spectroscopic data for **1b** are as follows.

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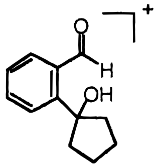
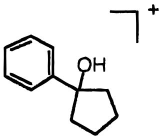
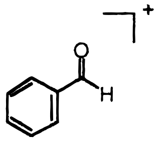
(26) Curtin, D. Y.; Bender, P. E.; Hetzel, D. S. *J. Org. Chem.* **1971**, *36*, 565.

Table 4. Mass Spectroscopic Data for 21 and Its Fragment Species[a]

structure of molecular ions	natural sample			labeled sample					^{18}O contents[b] (%)
	M	M + 1	M + 2	M	M + 1	M + 2	M + 3	M + 4	
 $M = 190$	100	13.3	0.75	100	15.2	11.5	1.17	0.20	
 M_1 (M - CHO) = 161	100	13.2	1.42	100	15.7	11.6			9.0
 $M_2 = 105$	100	13.2	2.95	100	13.7	7.95			5.0

[a] Mass (EI, 70 eV) spectroscopic data were measured by using a JEOL JNS-BX-303-HF spectrometer. [b] ^{18}O contents (%) = $[(M + 2)/(M + (M + 2))_{labeled} - (M + 2)/(M + (M + 2))_{natural}] \times 100$.

*1-Mesityl-5-phenyl-6,7,8-trioxabicyclo[3.2.1]octane (**1b**).* ^1H NMR (270 MHz, $CDCl_3$) δ 1.91−1.98 (m, 1 H), 2.09−2.33 (m, 4 H), 2.25 (s, 3 H), 2.47−2.58 (m, 1 H), 2.49 (s, 6 H), 6.85 (s, 2 H), 7.35−7.40 (m, 3 H), 7.53−7.58 (m, 2 H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 17.59, 20.60, 22.90, 33.25, 33.37, 108.41, 113.71, 125.68, 128.23, 129.16, 130.46, 132.33, 135.62, 136.51, 137.47. Anal. Calcd for $C_{20}H_{22}O_3$: C, 77.39; H, 7.14. Found: C, 76.99; H, 7.04.

Synthesis of ^{18}O-Labeled Ozonides 1a and 2a. ^{18}O-labeled ozonide **1a** and **2a** were prepared by an electron transfer photooxygenation[13] of the corresponding ^{18}O-labeled epoxides, which were prepared by the epoxidation of the alkenes by using ^{18}O-labeled *m*-CPBA. ^{18}O-labeled *m*-CPBA was prepared from *m*-chlorobenzoyl chloride and ^{18}O-labeled hydrogen peroxide.[27] Total yields of ^{18}O-**1a** and **2a** from the alkenes were 20% (123 mg) and 6% (58 mg), respectively. The contents (%) of ^{18}O-atom in ozonides **1a** and **2a** were estimated from the content (%) calculated for the epoxide ^{18}O-**7**; see Table 3.

Reaction of Ozonides 1 and 2 with $FeSO_4$•$7H_2O$, a General Procedure. To a stirred solution of ozonide (typically 1 mmol) in degassed THF (20 mL) was added a degassed solution of $FeSO_4$ in distilled water (10 mL) under argon atmosphere at room temperature (ca. 20 °C). The neutral products were separated by using column chromatography on silica gel. The acidic products were extracted from the reaction mixture by aq $NaHCO_3$, and then the acids were obtained by Et_2O after the acidification of the aqueous solution. The products and yields were reported in the text. Except for the commercially available compounds **3a**, **4**, and **5**, the known compounds **3b**,[28] **6**,[29] **11a**−**d**,[8] **12b**,[30] **19**,[31] and **20**[32]were characterized by the comparison of the ^1H and ^{13}C NMR with those of the authentic samples reported previously. The spectroscopic data for the new compounds, **12a**,**c**,**d** and **21**, obtained in this study are as follows.

*3,4-Dihydro-3-hydroxy-3-phenyl-1H-2-benzopyran-1-one (**12a**).* White powder; mp 162−163 °C; ^1H NMR (270 MHz, $CDCl_3$) δ 4.70 (s, 2 H), 7.25−7.27 (m, 1 H), 7.36−7.60 (m, 5 H), 8.00−8.12 (m, 3 H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 46.05, 127.33, 128.15, 129.25, 129.66, 131.48, 132.22, 133.33, 133.89, 134.16, 138.63, 170.27, 200.05; IR (KBr) 3500, 1700, 1580, 1420, 1310, 1280, 760 cm^{-1}; Anal. Calcd for $C_{15}H_{12}O_3$: C, 74.99; H, 5.03. Found: C, 74.92; H, 5.10.

*3,4-Dihydro-4,4-dimethyl-3-hydroxy-1H-2-benzopyran-1-one (**12c**).* An oil; ^1H NMR (270 MHz, $CDCl_3$) δ 1.37 (s, 3 H), 1.42 (s, 3 H), 5.35 (d, J = 4.0 Hz, 1 H, OH), 5.53 (d, J = 4.0 Hz, 1 H), 7.35−7.43 (m, 2 H), 7.59−7.65 (m, 1 H), 8.08−8.11 (m, 1 H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 21.96, 26.74, 38.33, 102.12, 123.27, 124.76, 127.12, 130.15, 134.61, 146.56, 165.43; IR (liquid film) 3400, 2950, 1710, 1260, 980 cm^{-1}; HRMS (EI) calcd for $C_{11}H_{12}O_3$ 192.0786, found 192.0787.

*3,4-Dihydro-3-hydroxy-4-methyl-1H-2-benzopyran-1-one (**12d**).* White powder; mp 51−52 °C; 1H NMR (270 MHz, $CDCl_3$) δ 1.39 (d, J = 7.0 Hz, 3 H), 3.14−3.36 (m, 1 H), 5.70−5.82 (m, 1 H), 7.31−7.94 (m, 3 H), 8.07−8.12 (m, 1 H); IR (KBr) 3350, 2950, 1710, 1280, 960 cm^{-1}. Anal. Calcd for $C_{10}H_{10}O_3$: C, 67.41; H, 5.66. Found: C, 67.29; 5.45.

*1,3-Dihydro-1-hydroxy-3-spiro-1′-cyclopentylisobenzofuran (**21**).* White powder; mp 95−96 °C; ^1H NMR (270 MHz, $CDCl_3$) δ 1.83−2.15 (m, 8 H), 3.56 (d, J = 7.6 Hz, 1 H), 6.41 (d, J = 7.6 Hz, 1 H), 7.16−7.72 (m, 4 H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 24.87, 40.86, 95.69, 99.64, 120.56, 122.70, 127.78, 129.45, 139.21, 145.59; IR (KBr) 3200, 2950, 1460, 1000 cm^{-1}; HRMS (EI) calcd for $C_{12}H_{14}O_2$ (M^+) 190.0994, found 190.0997. Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.58; H, 7.49.

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