Effective Trap of Zwitterionic Intermediate during Oxygenation of Electron-Rich Naphthalenes with Singlet Oxygen by the Intramolecular Alcohol

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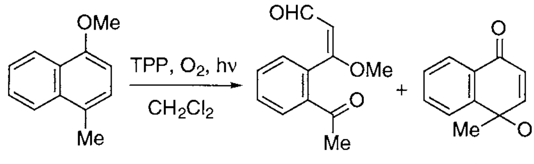
The presence of a zwitterionic intermediate during the oxygenation of electron-rich naphthalenes with singlet oxygen is clarified by the clean and efficient formation of hydroperoxide *via* nucleophilic addition of the intramolecular alcohol to the intermediate and by its stereochemical analysis using an optically active linker of the alcohol.

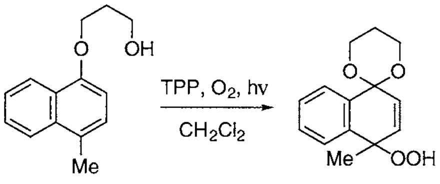
During the oxygenation of electron-rich 1,3-dienes with singlet oxygen,[1] [2+2] cycloaddition predominantly proceeds to yield dioxetanes *via* a zwitterionic intermediate, while oxygenation of usual 1,3-dienes mainly affords endoperoxides.[2,3] Various types of mechanisms[2,3] have been proposed for the singlet oxygenation which includes a concerted mechanism, stepwise mechanism *via* zwitterion, *etc.* Generally, the product distribution is widely affected by the change in the mechanism of the oxygenation.[2,3] In contrast to the well-documented mechanism for the singlet oxygenation of the 1,3-dienes,[2] the singlet oxygenation of arenes has hardly been discussed in mechanistic aspects[4,5] until recently. The simple formation of endoperoxides[3] in the oxygenation of arenes partially causes the difficulty of mechanistic discussion based on the product distribution. In the case of electron-rich naphthalenes, however, rearranged products have been obtained during the singlet oxygenation.[6,7] The cause of the unusual reactivity of the electron-rich naphthalenes has been unknown and the mechanism has not been established due to the complicated rearranged products.[7] If the zwitterionic intermediate is derived from the electron-rich naphthalenes, the intermediate would be nucleophilically trapped[8] to suppress the complicated rearrangement.

This study reports that the intramolecular alcoholic function in naphthalene derivatives through a proper length of linker efficiently traps the zwitterionic intermediate to quantitatively yield a hydroperoxide with cyclic acetal. The clean and simple oxygenation provides an opportunity to gain a more comprehensive and confirmative understanding of the oxygenation mechanism of electron-rich naphthalenes with singlet oxygen.

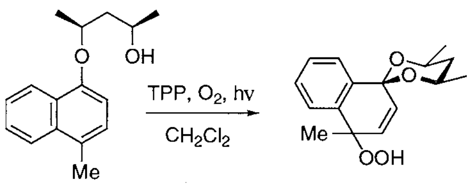
Singlet oxygen was generated by the photoirradiation of tetraphenylporphine (TPP) in oxygen saturated dichloromethane with a high-pressure mercury lamp (300 W) through the $BiCl_3$ solution filter transmitting $\lambda > 350$ nm. Photooxygenation of 1-methoxy-4-methylnaphthalene with singlet oxygen for 110 min gave a complicated mixture containing **1** (16%) and **2** (19%) with 77% conversion (eq 1). During the irradiation for 65 min under the same conditions except for the naphthalene having an intramolecular alcohol, **3**, the oxygenation readily proceeded to give the hydroperoxide **4** with 91% isolated yield (eq 2). Such a quantitative oxygenation due to the intramolecular alcohol may be ascribed to trapping of the zwitterionic intermediate or unstable 1,4-endoperoxide. The nucleophilic substitution of an endoperoxide by methanol has been reported in the oxygenation of furanes.[9] It is, however, quite difficult to distinguish these two modes; the addition to the zwitterionic intermediate and the substitution of the endoperoxide, unless a transient formation of the endoperoxide is detected. To further analyze the reaction mechanism, a stereochemical analysis was employed as follows. The stereochemically pure substrates **5**[10] were prepared *via* the Mitsunobu reaction with enantiomeric pure diols and the corresponding naphthols. The oxygenation of **5a** also readily proceeded to give the hydroperoxide **6a** as a single diastereomer with 73% isolated yield (eq 3). The relative stereochemistry of the hydroperoxide **6a** was determined as that produced by the *si*-face attack of the intramolecular alcohol to the naphthalene ring based on the NOE signal between the olefin proton and the methine protons. The preference of the *si*-attack may be due to the steric repulsion between the *peri*-proton of the naphthalene core and the cyclic acetal moiety. The cyclic acetal formation causes the disappearance of chirality of the linker. Thus, the stereodifferentiation of the oxygenation at C-4 of the naphthalene ring can be determined by the enantiomer ratio of the product. In order to determine the enantiomer ratio, the hydroperoxide **6** was reduced to the alcohol **7** by triphenylphosphine, followed by the elimination of the acetal moiety from **7** under acidic conditions to give **9** (Scheme 1). Typically, **7a** was generated with 99% yield by the reduction of **6a** and the following step from **7a** gave **9a** with 86% yield. The enantiomer ratio was determined by HPLC



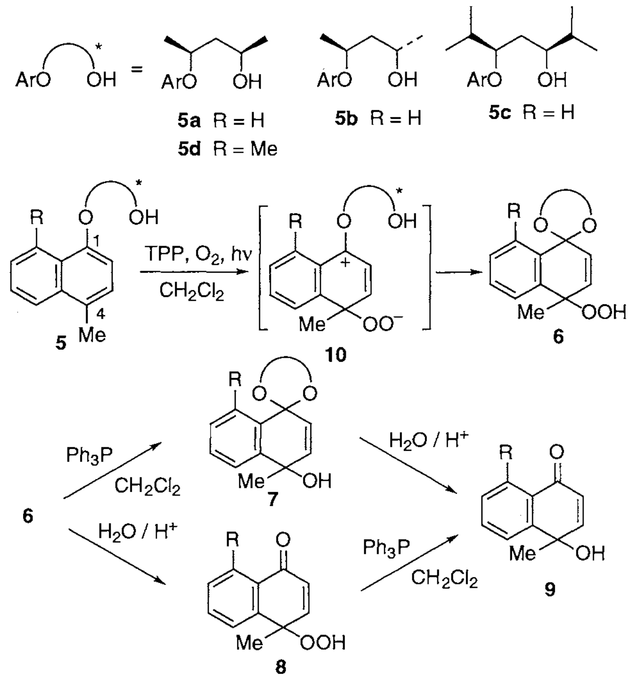
1 (16%) **2** (19%) (1)



3 **4** (2)



5a **6a** (3)



Scheme 1.

with a chiral column (DAICEL CHIRALCEL AD) for **7a** and **9a** as 66:34 and 65:35, respectively. The other pathway *via* **8a** also gave the same enantiomer ratio within experimental error. These results indicate that the following treatments from the hydroperoxide **6a** proceed without epimerisation. The enationmer ratio caused by the oxygenation at C-4 of the naphthalene ring is 2:1 in contrast to the complete diastereoface differentiating formation of the cyclic acetal at C-1. Such disagreement between the stereodifferentiation at C-1 and that at C-4 can not be explained by the concerted substitution of the endoperoxide by the intramolecular alcohol. Thus, the intramolecular alcohol nucleophilically attacks the zwitterionic intermediate **10**.

Table 1. Oxygenation of naphthalene derivatives **5** with singlet oxygen[a]

Entry	Substrate **5**	Temp/°C	Yield/%[b]	e.r.[c]	o.r.[d]
1	**a**	rt	72	66:34	(–)
2	**a**	-50	82	65:35	(–)
3[e]	**a**	rt	72	66:34	(–)
4[f]	**a**	rt	63	50:50	
5	**b**	rt	71[g]	68:32[h]	(–)
6	**c**	rt	77	66:34[i]	(–)
7	**d**	rt	76[j]	63:37[i]	(–)
8	**d**	-50	62[j]	62:38[i]	(–)

[a] In dicholoromethane unless otherwise noted. [b] Yield from **5** to **7** unless otherwise noted. [c] Enantiomer ratio of **7**. [d] Direction of optically rotation of **9**. [e] In benzene. [f] In a mixture of dichloromethane and 2-propanol (1:1). [g] Yield from **5** to **8**. [h] Diastereomer ratio of **6b** determined from ^{1}H nmr. [i] Enantiomer ratio of **9**. [j] Yield from **5** to **9**.

To gain more information about the stereodifferentiating addition at C-4, various conditions and substrates were employed as shown in Table 1. During the oxygenation of **5a** with singlet oxygen at room temperature, definite π-facial differentiation was observed for benzene (entry 3) as well as that in dichloromethane (entry 1), whereas the stereodifferentiation significantly dropped when 2-propanol was added to the solution (entry 4). Lowering the temperature led to no change in the stereodifferentiation of the oxygenation of **5a** in dichloromethane (entry 2). The enantiomer ratio's independence from the reaction temperature in the oxygenation was also observed in the oxygenation of **5e** (entries 7, 8). The oxygenation of the 4-methylnaphthalene derivatives with various side chains of the intramolecular alcohol (**5b**-**c**) gave a similar enantiomer ratio and the same stereochemistry as that obtained from **5a**. Especially, the preferential formation of the product with negative optical rotation from the epimer (**5b**) of **5a** indicates that the stereogenic centre at the ether is strongly responsible for stereochemsitry of newly formed chiral centre at C-4.

Such stereodifferentiating addition at C-4 may be caused by coordination of the singlet oxygen with the intramolecular alcohol. The coordination effect of intramolecular alcohols to singlet oxygen has been proposed by W. Adam and M. Prein[4,11,12] on the basis of the π-facial differentiating [4 + 2] cycloaddition of singlet oxygen to naphthyl alcohols with up to 90% de. The significant decrease in the enantiomer ratio by the addition of 2-propanol into the solution (entry 4) may be due to the inhibition of the coordination of singlet oxygen with the intramolecular alcohol by 2-propanol.

References and Notes

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