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Effects of oxygenated substituents on the [4+2] cycloaddition of singlet oxygen in the photooxygenation of water-soluble naphthyl ethers

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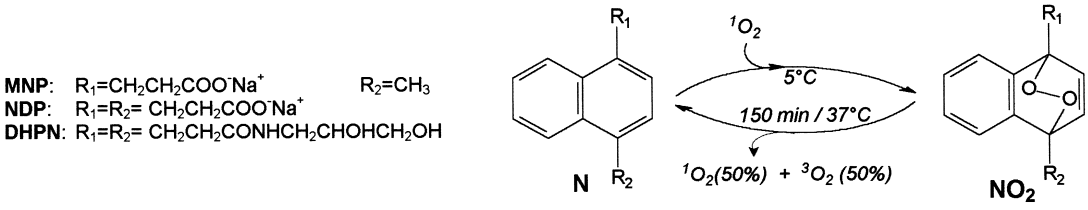
Abstract

Water-soluble ethers **2** and **5** undergo [4+2] cycloaddition of singlet oxygen to afford endoperoxides. Compound 2 is extremely reactive ($k_r+k_q=2.0\times10^8$ M^{-1}/s^{-1} in D_2O) due to the mesomeric interactions between oxygen and the naphthalene ring. However, the unstable endoperoxide was immediately and quantitatively decomposed into the aldehyde ester **6**. When a methylene linker separates the oxygen from the aromatic core (**5**), photooxidation leads to a mixture of 1,4 and 5,8-endoperoxides.

Water-soluble naphthalene endoperoxides NO_2 are used in the biological media to generate pure singlet oxygen ($^1O_2$) free from other reactive oxygen species.[1] The thermolysis of NO_2 at 37°C gives back N and oxygen, 50% of which is in a singlet state.[1] Knowledge of the kinetics of this reaction allows calculation of the time (150 min), necessary to release more than 99% of trapped $^1O_2$ (Scheme 1).



Scheme 1.

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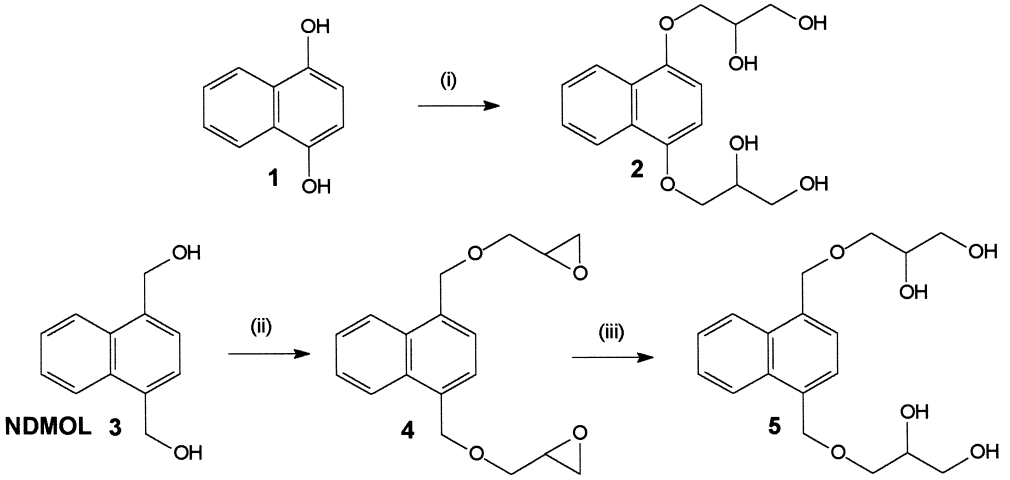
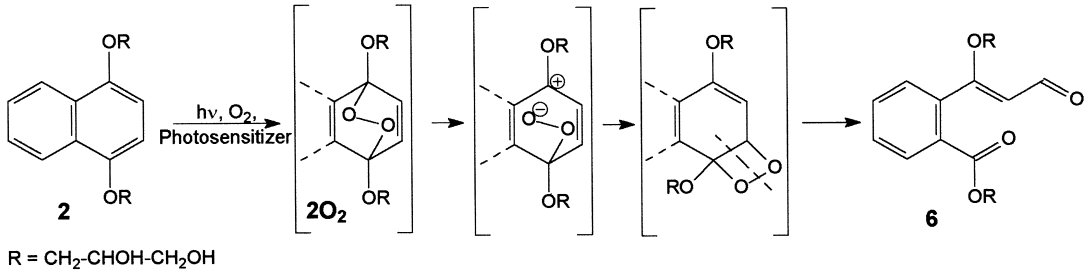
The two compounds generally used for biological assays are **MNPO$_2$**[2] and **NDPO$_2$**[3] but these anionic derivatives are unable to cross lipidic membranes. To avoid this drawback we recently synthesized a non-ionic naphthalene carrier of singlet oxygen **DHPNO$_2$**,[1a] which efficiently releases $^1O_2$ inside the cell. However, although its water-solubility is sufficient ($>10^{-2}$ M) the synthesis of this endoperoxide is a difficult step due to the poor reactivity of $^1O_2$ towards **DHPN**. In a recent article[4] we showed that [4+2] cycloaddition of singlet oxygen on 1,4-disubstituted naphthalene depends on both the inductive effects and the steric hindrance of side chains. Thus, in order to obtain non-ionic carriers of $^1O_2$ more reactive than **DHPN**, we grafted the 2,3-dihydroxypropanoxy group on the side chains to get the required water-solubility. The activation of the naphthalene core was achieved thanks to electron-releasing[5,6] groups, either by the resonance effect of the oxygen atom when the solubilizing group was directly attached to the aromatic ring (**2**) or by the inductive effect of the CH_2 group when a methylene linker separates the ring from the oxygen (**5**). Finally, the diethers of glycerol **2**[7] and **5**[7] were prepared by reaction of 3-chloro-1,2-propanediol[8] or epichlorohydrin[9–11] with parent alcohols **1** or **3**, respectively (Scheme 2)



Scheme 2. (i) 3-Chloro-1,2-propanediol, NaOH, H_2O, 25°C, 24 h, 40%; (ii) epichlorohydrin, NaOH, H_2O, $(n\text{-}C_4H_9)_4N^+$ HSO_4^-; reflux, 24 h, 33%; (iii) H_2SO_4, H_2O, THF, 51%

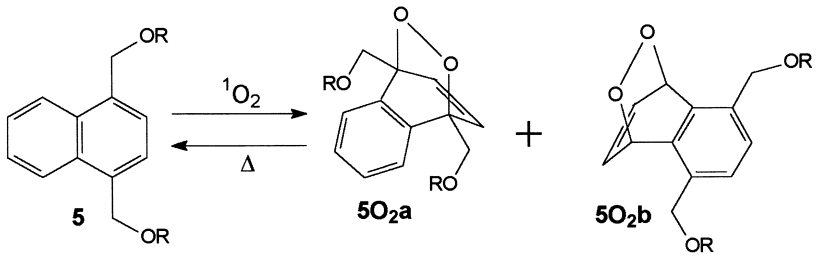
Photooxygenation of **2** (10 mg) in water (3 ml) at 5°C using methylene blue (2×10^{-5} M) as sensitizer with a 250 W sodium vapor lamp was completed within 30 min. Involvement of singlet oxygen in the reaction was confirmed by a faster disappearance (2 min) of **2** in deuterated water where the lifetime of $^1O_2$ (65 μs) is 15 times greater than in H_2O (4.4 μs). However, NMR spectroscopy on the crude products showed 50% of the aldehyde ester **6**[12] but no detectable amount of the expected endoperoxide **2O$_2$**. ^{1}H chemical shifts at the aldehydic (9.33 ppm, d, 8 Hz) and olefinic (5.98 ppm, d, 8 Hz) protons of **6** are in agreement with the spectral values reported for the aldehyde ester obtained from 1,4-dimethoxynaphthalene: (9.2 ppm, d, 8 Hz) and (5.7 ppm, d, 8 Hz),[13] respectively. The opening of the oxygenated cycle is confirmed by ^{13}C DEPT NMR as four tertiary and two quaternary aromatic carbons appeared between 128 and 136 ppm. The signals of the aldehyde (194.3 ppm) and ester (180.6 ppm) groups are assigned from both their characteristic positions and low intensities.

A similar aldehyde ester was already obtained by Rigaudy[13] during direct photooxidation of 1,4-dimethoxynaphthalene in benzene. These authors pointed out the formation of the isolable diacetal 1,4-endoperoxide, which can give back the diether or decompose to the aldehyde ester due to the presence of acid species[13] or with the solvent.[5] Photooxidation of **2** in less polar solvent such as methanol and ethanol where no reaction by electron transfer occurs, gave the aldehyde ester but no trace of the endoperoxide. These experiments have shown that the rate of disappearance of **2** was not temperature-dependent and slower in alcohols (complete consumption of **2** in 7 h) than in water. In methanol, **6** is obtained quantitatively as the sole oxidation product and remains stable for several days at room temperature in the reaction mixture. The formation of **6** (Scheme 3) results from the preliminary formation of hydroperoxide anion from the endoperoxide of **2**, leading to the dioxetane which is then decomposed to **6**.[13b]



Scheme 3.

Prolonged photooxidation (12 h) of **5** in water (H_2O) left the starting naphthalene unchanged. Similar results were observed by using the catalytic system H_2O_2/Na_2MoO_4[14] as a chemical source of $^1O_2$. Both experiments outline the poor reactivity of this diether towards singlet oxygen, even in water which is known to accelerate [4+2] cycloaddition.[15,16] In order to minimize the physical quenching of $^1O_2$ by OH bonds of water, we oxidized **5** in D_2O. Reversed-phase HPLC monitoring showed a 71% maximal conversion in 3 h and the formation of two hydrophilic compounds with shorter elution times. Both derivatives behaved as naphthalene endoperoxides since, after warming of the solution (37°C, 5 h), they were converted back into **5**. NMR analysis of the reaction mixture indicates that besides the expected 1,4-endoperoxide **5O$_2$a**[12] (57%), the regioisomer 5,8-endoperoxide **5O$_2$b** was also formed in minor quantity (14%). The structure of **5O$_2$b** was confirmed by the characteristic ^{1}H chemical shifts in D_2O[4] of the protons attached to the rings [6.23 (dd, J = 3.8 Hz, 2H), 7.12 (dd, J = 3.8 Hz, 2H), 7.35 (s, 2H)] (Scheme 4).



Scheme 4.

Thermolysis of the major endoperoxide **$5O_2$a** into **5** was monitored by HPLC and UV spectrophotometry and followed a first-order kinetics with a rate constant $k = 2.45 \times 10^{-4}/s^{-1}$ leading to the half-time of decomposition ($t_{1/2} = 47$ min). The kinetics of decomposition of **$5O_2$a** shows that this endoperoxide would be suitable to carry $^1O_2$ in biological media since 99% of stored oxygen is released within 5 h at 37°C. However, current $^1O_2$ carriers (**$MNPO_2$**, **$NDPO_2$** and **$DHPNO_2$**) require only 2 h 30 to release the same percentage of singlet oxygen (Table 1). The greater stability of the diether **$5O_2$a** may be compared to the one of the parent diol **$3O_2$** ($t_{1/2} = 70$ min). Adam pointed out a nucleophilic association of the OH functionality of derivative naphthyl alcohol from **3** and singlet oxygen during [4+2] cycloaddition.[17] Thus, a possible explanation for the relative stability of **$5O_2$a** and **$3O_2$** could result from the interaction between the oxygen of the side chain and the peroxide bridge.

Quenching by solvent $^1O_2 + \text{solvent} \xrightarrow{k_d} {}^3O_2$ (1)

Physical quenching $^1O_2 + \mathbf{N} \xrightarrow{k_q} {}^3O_2 + \mathbf{N}$ (2)

Chemical reaction $^1O_2 + \mathbf{N} \xrightarrow{k_r} \mathbf{NO_2}$ (3)

Phosphorescence $^1O_2 \xrightarrow{k_p} {}^3O_2 + h\nu$ (4)

Table 1
Overall $^1O_2$ quenching rate constant in D_2O for naphthalene compounds and half-time of decomposition at 37°C for corresponding endoperoxides

	NDP	**MNP**	**DHPN**	**NDMOL**	**5**	**2**
$(k_r + k_q)x10^{-6}$ $M^{-1}.s^{-1}$	2.8	7.0	1.0	0.4	0.1	200
$t_{1/2}$ (min)	22	22	22	70	47	

The kinetics of $^1O_2$ decay during the photooxygenation of a substrate **N** can be described by reactions (**1**) to (**3**). Using $^1O_2$ phosphorescence detection (**4**), we have measured the rate constant (k_r+k_q) of **2** and **5** in D_2O by laser flash photolysis.[16] As expected, the high reactivity of **2**, due to the mesomeric effect of the oxygen directly attached at the cycle, is characterized by a rate constant (k_r+$k_q = 200 \times 10^6$ M^{-1}/s^{-1}) which is 50 times greater than for fairly reactive subtrates such as **MNP** (k_r+$k_q = 7.0 \times 10^6$ M^{-1}/s^{-1}) or **NDP** (k_r+$k_q = 2.8 \times 10^6$ M^{-1}/s^{-1}).[4] But the fast oxidation of **2** leads to the aldehyde ester **6** rather than the endoperoxide **$2O_2$**. When the oxygen is separated by a methylene linker from the aromatic cycle the electron-withdrawing effect of the ether group overlaps the electron-releasing effect of the CH_2 group.

The fact that both aromatic rings compete for singlet oxygen to give the two regioisomeric endoperoxides **$5O_2$a** and **$5O_2$b**, proves that the electronic density is not much higher in the disubstituted cycle, contrary to our expectation. Moreover, steric hindrance induced by side chains contributes to steer the incoming singlet oxygen to the non-substituted cycle. Finally, it can be supposed that all bulkier ethers derived from **3** will be unable to react with singlet oxygen

since the electron-accepting atom of oxygen in the benzylic position will limit the rate constant (k_r+k_q) to a value lower than 0.4×10^6 M^{-1}/s^{-1}.

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7. Compound **2**: ^{1}H NMR (300 MHz CD_3OD) δ 3.70–3.83 (m, 4H), 4.05–4.20 (m, 6H), 6.80 (s, 2H), 7.48 (dd, J = 6.6, 3.3 Hz, 2H), 8.25 (dd, J = 6.6, 3.3 Hz, 2H) ppm; ^{13}C NMR (300 MHz, DMSO d6) δ 62.84 (d), 70.15 (d), 105.08 (s), 121.95 (s), 125.98 (d), 148.27 (s); mass (*m*/*z*) 308 (M^+), 331 (MNa^+). Compound **5**: ^{1}H NMR (300 MHz, DMSO d6) δ 3.25–3.70 (m, 10H), 4.93 (s, 2H), 7.51 (s, 2H), 7.58 (dd, J = 9.9, 3.3 Hz, 2H), 8.13 (dd, J = 9.9, 3.3 Hz, 2H) ppm; ^{13}C NMR (300 MHz, CD_3OD) δ 63.22, 70.67, 70.89, 72.11, 124.64, 125.57, 125.98, 131.49, 134.29 ppm; mass (*m*/*z*) 337 (MH^+), 359 (MNa^+), 375 (MK^+).
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12. Compound **6**: ^{1}H NMR (300 MHz, CD_3OD) δ 3.75–3.82 (m, 4H), 4.08–4.18 (m, 2H), 4.23–4.40 (m, 2H), 4.45–4.60 (m, 2H), 5.97 (d, J = 8.1 Hz, 1H), 7.70–7.72 (m, 1H), 7.84–7.91 (m, 2H), 8.28–8.31 (m, 1H), 9.32 (d, J = 8.1 Hz, 1H) ppm; ^{13}C NMR (300 MHz, CD_3OD) δ 64.21 (d), 68.04 (s), 71.34 (s), 72.99 (s), 107.92 (s),131.96 (s), 132.18 (s), 132.47 (s), 133.47 (s), 135.58 (s), 167.78 (s), 181.66 (s), 194.31 (s); mass (*m*/*z*) 341 (MH^+), 363 (MNa^+). Compound **5O2a**: ^{1}H NMR (300 MHz, D_2O) δ 7.02 (s, 2H), 7.36–7.50 (m, 4H) ppm; ^{13}C NMR (300 MHz, D_2O) δ 64.81, 72.72, 73.62, 75.17, 84.07, 123.64, 129.83, 138.37, 139.80 ppm.
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