First evidence of the formation of 5,8-endoperoxide from the oxidation of 1,4-disubstituted naphthalene by singlet oxygen

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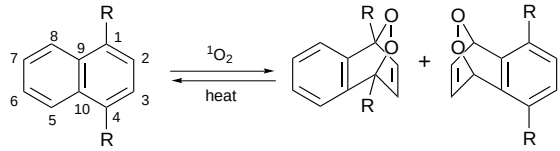
Bulky water-soluble 1,4-disubstituted naphthalenes react with singlet oxygen giving the usual 1,4- and the unexpected 5,8-endoperoxides and showing that the regioselectivity of the [4 + 2] cycloaddition of singlet oxygen depends on the steric hindrance of the substrate.

In contrast to anthracene and higher members of the acene series,[1] naphthalene does not react with singlet oxygen ($^1O_2$) to form the 1,4-endoperoxide.[2] However, the naphthalene 1,4-endoperoxide **2a** has been obtained indirectly in three steps from 1,6-imino[10]annulene.[3] When electron-donating substituents are introduced on the 1,4 positions of the naphthalene core, $^1O_2$ readily reacts leading regiospecifically to 1,4-endoperoxides.[4–6] 5,8-Endoperoxides have been solely observed when at least one additional methyl group was placed on the 6,7[7] or 8 positions[8,9] of the naphthalene core. In the course of our work on water-soluble carriers of $^1O_2$,[6,10] we have discovered that the photooxidation of the bulky non-ionic water-soluble 1,4-disubstituted naphthalene, *N*,*N*′,*N*″,*N*‴-tetrakis(2,3-dihydroxypropyl)2,2′-(naphthalene-1,4-diyldimethyl)bis(malonamide) **1b** (Scheme 1) leads to the simultaneous formation of the 1,4- and 5,8-endoperoxides (**2b** and **3b**). This example clearly shows that in addition to electronic effects, the steric hindrance of the substituents can modify the regioselectivity of the [4 + 2] cycloaddition of singlet oxygen on polycyclic aromatic hydrocarbons.

NMR and HPLC analysis of **1b**†‡ after dye-sensitized photooxygenation§ at −5 °C in D_2O–CD_3OD (77 : 13) showed a 50% conversion in 2 h, and indicated that, beside the usual 1,4-endoperoxide **2b**, the unexpected 5,8-endoperoxide **3b** was also formed, with a time-independent ratio equal to 78 : 22 (Table 1). All spectra showed that the malonamide side chains remained unchanged during oxidation and the symmetry of each spectrum suggested that no other products of oxidation with lower symmetry, such as hydroperoxides, were formed.



a R = H
b R = $CH_2CH[CONHCH_2CH(OH)CH_2(OH)]_2$
c R = $CH_2CH_2CO_2Na$
d R = $CH_2CH(CO_2Na)_2$

Scheme 1

Table 1 Product distribution after photooxidation of **1b**

Solvent	*T*/°C	*t*/h	Conversion (%)	Regioselectivity **2b** : **3b**
D_2O–CD_3OD (77 : 13)	−5	2	50	78 : 22
H_2O–MeOH (77 : 13)	−5	2	3	100 : (< 1)
D_2O	25	1	26	69 : 31
	50	1	40	(< 1) : 100
CD_3OD	25	2	20	80 : 20

^{1}H and ^{13}C NMR chemical shift assignments for **2b**¶ were in agreement with the spectral data of other 1,4-naphthalene endoperoxides such as **2c**.[10] The structure of the endoperoxide **3b**‖ was confirmed by comparison with **2b.** Thus, **3b** has four quaternary carbons in the aromatic region, in positions 1, 4, 9 and 10 (d, J = 139.2 and 133.5 Hz) whereas **2b** has only two carbons of this type, C^9 and C^{10} (d, J = 142.2 Hz). Another telling difference was observed for the carbons supporting the peroxide bridge, which were the tertiary carbons C^5 and C^8 (d, J = 75.7 Hz) for **3b** compared to the quaternary carbons C^1 and C^4 (d, J = 83.4 Hz) for **2b**.

When the oxidation of **1b** was run over 2 h in H_2O–MeOH (77 : 13) instead of deuterated solvents, **2b** was formed with a 13 times lower yield (3% compared to 39%), and the concentration of **3b** became too small to be measurable. This lower yield was expected since the lifetime of $^1O_2$ is 15 times shorter in H_2O than in D_2O. Chemical oxidation of **1b** by a chemical source of $^1O_2$ (H_2O_2–MoO_4^{2-}),[10] also led to the formation of **2b** and **3b**, confirming the involvement of singlet oxygen in the formation of both endoperoxides (Table 1).

Warming of the solutions of pure **2b** and **3b** obtained by semi-preparative HPLC indicated that both endoperoxides decompose giving the starting naphthalene **1b** and oxygen (Scheme 1) according to first order kinetics (Table 2). Comparison of the half-lives of decomposition ($t_{1/2}$) clearly showed the greater stability of **3b** since no significant decomposition occurred at 5 °C, and it was found to be ten times more stable than **2b** at 25 and 37 °C. On the contrary, **2b** was particularly thermolabile since its half-life at 37 °C ($t_{1/2}$ = 7 min) is three times shorter than that of other 1,4-endoperoxides such as **2c**. This phenomenon seems to be general, in fact we observed similar half-lives for other bulky 1,4-disubstituted endoperoxides such as **2d** ($t_{1/2}$ = 5 min at 37 °C). The poor stability of these 1,4-endoperoxides could result from the steric hindrance induced by the bulky substituents R in the 'butterfly' structure **2**, which would favour dissociation into the starting naphthalene derivative and oxygen.

$$\mathbf{1} + {}^1O_2 \xrightarrow{k_{r2}} \mathbf{2} \quad (1)$$

$$\mathbf{1} + {}^1O_2 \xrightarrow{k_{r3}} \mathbf{3} \quad (2)$$

Table 2 Half-lives ($t_{1/2}$) of dissociation at 5, 25 and 37 °C for endoperoxides **2b**, **3b**, **2c** and **2d**, and rate constant (k_r) of their formation at −5 °C

	$t_{1/2}$/min			$k_A/10^4$ M^{-1} s^{-1}
	5 °C	25 °C	37 °C	(D_2O–CD_3OD = 77 : 13)
2b	540	30	7	3
3b	stable	300	70	1
2c	stable	113	23	142
2d	208	18	5	44

The rate constants, k_{r2} [eqn. (1)] and k_{r3} [eqn. (2)], for the chemical quenching of $^1O_2$ by **1b** were estimated by comparison with the well known $^1O_2$ acceptor **1c**[11] (Table 2). Thus, they were separately photooxidized in deuterated water at −5 °C under the same conditions. The kinetics of the disappearance of the starting materials indicated that **1b** ($k_{r2} + k_{r3} = 4 \times 10^4$ M^{-1} s^{-1}) is about 13 times less reactive than **1c** ($k_r^{NDP} = 142 \times 10^4$ M^{-1} s^{-1}). The constant regioselectivity observed at this temperature permits us to determine the contribution of each pathway: $k_{r2} = 3 \times 10^4$ M^{-1} s^{-1} and $k_{r3} = 1 \times 10^4$ M^{-1} s^{-1}. The poor reactivity of **1b** towards $^1O_2$ could be explained by the electron-withdrawing effect of the amide function, which decreases the electronic density on the 1,4-positions of the naphthalene core, compared to the slight electron-donating effect of the sodium carboxylate functions of **1c**. However, since these groups are separated from the binding site by an ethylene linkage, it appears more likely that the difference of reactivity is mainly a consequence of the steric hindrance due to the side chains.[6]

To strengthen this hypothesis, we oxidized the tetra-(sodium carboxylate) **1d** which is more bulky than **1c**, but which exhibits a greater electronic density on the naphthalene ring due to the presence of four sodium carboxylate functions instead of two. Actually, the reactivity of **1d** towards $^1O_2$ is three times lower than that of **1c**. This result confirms the predominating contribution of steric hindrance over the electron-donating effects of the side chains of **1b** and **1d**.

It is noteworthy that the formation of the 5,8-endoperoxide **3b** is straightforward only when the oxidation of **1b** is carried out in deuterated water. Thus, in deuterated methanol, only 4% is obtained after 150 min at 25 °C (compared to 33% in deuterated water). This result seems astonishing if we refer to the lifetime of $^1O_2$, which is 3.5 times longer in CD_3OD (τ_Δ = 230 μs) than in D_2O (τ_Δ = 65 μs). In fact, contrary to a generally accepted principle, it was reported recently that the rate constants of singlet oxygen [4 + 2] cycloadditions (k_r) are strongly solvent-dependent. In particular, it was shown that highly structured solvents such as formamide and water considerably increase the reactivity of conjugated dienes and polycyclic aromatic derivatives.[2,12] Thus, the finding that **1b** exhibits a 15-fold higher rate constant in D_2O than in CH_3OD is just a further example of this accelerating effect.

Finally, it appears that the formation of the unusual 5,8-endoperoxide by reaction of $^1O_2$ with 1,4-disubstituted naphthalene is possible only when a number of stringent requirements are met: (i) substituents must be a little electron-donating to increase the electronic density of the whole naphthalene core; (ii) they must be very bulky to make difficult the approach of $^1O_2$ to the crowded ring and to impair the formation of the resulting butterfly structure; (iii) the peroxidation must be carried out in D_2O in order to benefit from the rate-accelerating effect of water on the [4 + 2] cycloaddition of $^1O_2$ and from the enhancement of $^1O_2$ lifetime in deuterated solvents; (iv) a gentle warming of the reaction medium increases the ratio of 5,8- to 1,4-endoperoxides with oxidation time because of the greater thermolability of the 1,4-endoperoxide, which dissociates as it is forms whereas the 5,8-endoperoxide remains unchanged.

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Footnotes and References

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† High performance liquid chromatographic analyses (HPLC) were carried out with Waters pumps Model 600 with a reversed-phase column (Nova Pack RP 18, 25 cm) using 15 to 50% MeOH over 20 min at 0.7 ml/min and UV detection at 200 nm.

‡ *Synthesis* of **1b**: A solution of tetraethyl 2,2′-(naphthalene-1,4-diyldimethyl)bis(malonate) (ref. 11) (2 g, 4.2 mmol) and 3-aminopropane-1,2-diol (5.6 g, 73.3 mmol) in MeOH (30 ml) was stirred overnight under reflux. After evaporation of the solvent, acetone was added to the residue and the resulting suspension was filtered. The white precipitate was recristallised from MeOH (50%); mp = 195 °C; δ_H (300 MHz, D_2O) 8.10 (dd, $J_{5,6} = J_{5,7} = 3.15$, 2 H, H^5), 7.64 (dd, $J_{5,6} = J_{5,8} = 3.15$, 2 H, H^6), 7.26 (s, 2 H, H^2); δ_C (300 MHz, D_2O) 174.3 (s, CO), 136.0 and 134.4 (s, C^1, C^9), 129.9, 129.3 and 127.1 (s, C^2, C^5, C^6), 72.5 [d, CH(OH)], 65.9 [d, CH_2(OH)], 57.2 [$CH(C)_3$], 44.4 (d, CH_2N), 35.3 (s, Ar-CH_2); *m/z* 675 (MNa^+), 663 (MH^+).

§ *Photooxidation of* **1b** *into* **2b** *and* **3b**. A solution of **1b** (30 mg) and Methylene Blue (1.6×10^{-5} M in 1 ml of deuterated water was irradiated with a sodium lamp (150 W) under continuous bubbling of oxygen at constant temperature. During the reaction, some Methylene Blue was periodically added to compensate for its fading. HPLC analysis showed the ratio of each product.

‖ *Selected data* for δ_H (300 MHz, D_2O) 7.38 (m, 4 H, H^5, H^6), 6.87 (s, 2 H, H^2); δ_C (300 MHz, D_2O) 174.2 (CO), 142.2 (C^9), 140.5 (C^2), 130.3 (C^6), 123.6 (C^5), 83.4 (C^1), 72.5 [CH(OH)], 65.6 [CH_2(OH)], 51.1 [$CH(C)_3$], 44.3 (CH_2N), 31.9 (CH_2C^1).

** *Selected data* for **3b**: δ_H (300 MHz, D_2O) 7.15 (s, 2 H, H^2), 7.06 (dd, $J_{5,6} = J_{6,8} = 3.15$, 2 H, H^6), 6.10 (dd, $J_{4,5} = J_{5,7} = 3.15$, 2 H, H^5); δ_C (300 MHz, D_2O) 173.6 (CO), 139.2 (C^9), 138.1 (C^6), 133.5 (C^1), 131.5 (C^2), 75.7 (C^5), 72.5 [CH(OH)], 65.6 [CH_2(OH)], 58.0 [$CH(C)_3$], 44.3 (CH_2N), 33.2 (CH_2C^1).

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