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Reaction of 4,7-dimethylbenzofurazan with singlet oxygen

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Abstract—4,7-Dimethylbenzofurazan (**1**) was transformed by $^1O_2$ produced by irradiation of C_{60} into 4,7-dimethylbenzofurazan 4,7-endoperoxide (**2**) in $CDCl_3$ or CD_2Cl_2 at 0°C in excellent yields. The endoperoxide decomposed back to **1** at room temperature. When tetramethylethylene (TME) was added to the decomposing endoperoxide at 37°C, the hydroperoxide from reaction of TME with $^1O_2$ was detected. The rate constant for the reaction of $^1O_2$ with **1** was determined by the quenching of $^1O_2$ luminescence to be 4.8×10^3 M^{-1} s^{-1}. © 2001 Published by Elsevier Science Ltd.

Benzofurazan derivatives have numerous pharmacological and industrial applications.[1] Reactions of benzofuroxans with active methylene compounds have been reported to lead to the corresponding quinoxaline 1,4-dioxides catalyzed by silica gel or molecular sieves[2–5] and their antibacterial activity has been determined.[6] The toxicity of benzofurazans in *Escherichia coli* has been reported to be caused by an increase in intracellular flux of superoxide on aerobic incubation.[7–10] Superoxide production was confirmed using the cytochrome *c* reduction method and ESR spectra.

Singlet oxygen ($^1O_2$) is useful in organic synthesis and has important biological reactivity. $^1O_2$ is a toxic species which oxidizes DNA, lipids and proteins in vivo. Reactivity of $^1O_2$ toward guanine and in many other reactions has been reported.[11–13] This paper shows that 4,7-dimethylbenzofurazan[13] (**1**) reacts with $^1O_2$ to give an endoperoxide.

Photosensitized oxygenation of **1** was carried out in 5 mm NMR tubes with Buckminsterfullerene (C_{60}) as photosensitizer and a 300-W Xenon lamp as the light source under oxygen. C_{60} produces $^1O_2$ by energy transfer.[14] Oxygen was continuously bubbled during irradiation, and a filter was used to cut off wavelengths below 550 nm. As a general procedure, a solution of 7.4 mg (0.05 mmol) of **1** and 0.05 mg of C_{60} dissolved in 0.5 mL of $CDCl_3$ or CD_2Cl_2 was irradiated. The formation of 4,7-dimethylbenzofurazan 4,7-endoperoxide (**2**) was detected by ^1H, ^{13}C NMR and FAB mass spectroscopy. After 12 hours photoreaction in $CDCl_3$, the yield of **2** was 93% as calculated by ^1H NMR integration. No other signal except **1** was detected. Product **2** showed resonances (^1H NMR, δ, ppm, CD_2Cl_2) at 1.97 (6H, 4-CH_3 and 7-CH_3), 6.76 (2H, 5-H and 6-H). ^{13}C NMR (δ, ppm, CD_2Cl_2): 15.3 (4-CH_3 and 7-CH_3), 77.1 (C_4 and C_7), 138.0 (C_5 and C_6), 155.4 (C_8 and C_9). FAB low-resolution mass spectrum (m/z): 181 (M+1), 165 (M+1–16), 149 (M+1–32). FAB high-resolution mass spectrum (m/z): 181.0613 (calcd for $C_8H_9N_2O_3$: 181.0617).

Starting material **1** showed resonances (^1H NMR, δ, ppm, CD_2Cl_2) at 2.58 (6H, 4-CH_3 and 7-CH_3), 7.03 (2H, 5-H and 6-H). ^{13}C NMR (δ, ppm, CD_2Cl_2): 16.9 (4-CH_3 and 7-CH_3), 124.3 (C_4 and C_7), 129.7 (C_5 and C_6), 150.4 (C_8 and C_9).

To measure singlet oxygen reaction rate, **1** at various concentrations was dissolved in benzene containing 1×10^{-5} M 5,10,15,20-tetraphenyl-21*H*,23*H*-porphine (TPP) as sensitizer. Direct measurement of total removal of $^1O_2$ by substrates was made by measuring the decay of $^1O_2$ by its luminescence at 1268 nm. Sensitizer was excited with either the second (532 nm) or third (355 nm) harmonic of a Quanta-Ray (DCR-2) Nd:YAG laser. The laser pulse was filtered to remove any fundamental from the laser using a 355/532 nm pass 1060 nm reflecting mirror. The 355 nm pulse was also filtered with a 355 nm pass/532 nm reflecting mirror. Samples were irradiated in a 1 cm quartz cell.

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Results

4,7-Dimethylbenzofurazan **1** was transformed by $^1O_2$ produced by irradiation of with C_{60} into 4,7-dimethylbenzofurazan 4,7-endoperoxide (**2**) in $CDCl_3$ or CD_2Cl_2 at 0°C in excellent yields. The structure of **2** was shown by NMR and high resolution mass spectroscopy. Benzofurazan and 5,6-dimethylbenzofurazan did not react with $^1O_2$ at 0°C.

The endoperoxide decomposed back to **1** at room temperature, the only organic product detectable by ^1H, ^{13}C NMR and TLC. The reaction was complete (100% **1**) in 28 hours at room temperature. When tetramethylethylene (TME) was added to the endoperoxide at 37°C, the corresponding hydroperoxide from reaction of $^1O_2$ with TME was detected by NMR. From the amount of hydroperoxide formed, the yield of singlet oxygen from the decomposition was 26%.

Formation of the corresponding hydroperoxide results from the decomposition of **2** to produce $^1O_2$ and **1**. The conversion of **2** to the starting material on heating is similar to many other endoperoxides[15] and is further evidence of the endoperoxide structure (Scheme 1).

The rate constant for the reaction of $^1O_2$ with **1** was determined from its luminescence decay. The plot of $1/\tau$ versus [**1**] (Fig. 1) gives a k_r value of 4.8×10^3 M^{-1} s^{-1}.

The production of endoperoxide **2** requires C_{60}, O_2 and light and was detected directly by NMR and MS. The rate constant of the reaction is one of the slowest ever reported, only 4.8×10^3 M^{-1} s^{-1}. This is undoubtedly due to the low electron density in the diene ring caused by the electron poor furazan substituent.

To our knowledge, this is the first direct observation of endoperoxide formation from a benzofurazan. The endoperoxide is stable at low temperature. On warming, **2** lost $^1O_2$ to regenerate the starting benzofurazan. Many other heterocyclic endoperoxides decompose to give singlet oxygen: for example, an 8-methyl guanosine endoperoxide does this below room temperature.[16]

Acknowledgements

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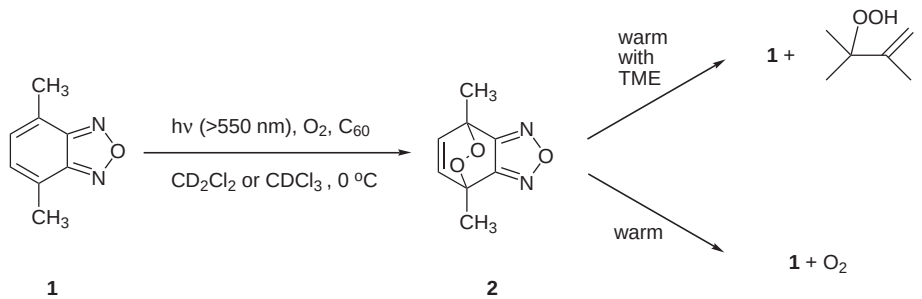

Scheme 1.

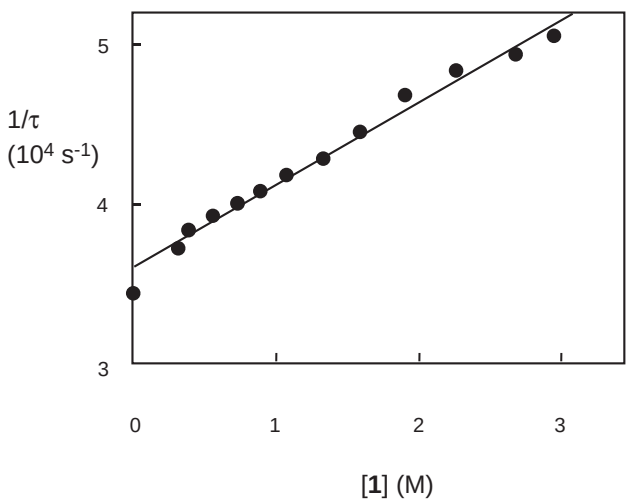

Figure 1. Luminescence quenching of singlet oxygen by 4,7-dimethylbenzofurazan (**1**) in benzene; τ is $^1O_2$ lifetime. The plot of $1/\tau$ and [**1**] has a slope of k_r for the reaction of **1** and $^1O_2$.

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