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Note

Dye-sensitized Photo-oxygenation of Nitrofurazone by Singlet Oxygen

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Dye-sensitized photo-oxygenation of nitrofurazone by singlet oxygen has been carried out under various reaction conditions, including changes in solvents and sensitizers. The product has been isolated and characterized by elemental analysis, physical, chemical and spectral data. A suitable mechanism has been proposed for the formation of photoproduct. To confirm the participation of singlet oxygen in the reaction, singlet oxygen scavengers have been used in the photo-oxygenation reaction.

INTRODUCTION

Nitrofurazone is commonly used in the treatment of different infections such as Gram positive and Gram negative organisms including *E. Coli* and *Aerobacter*. It is a drug of choice in trichomoniasis. Unfortunately, no attention has been given to the photo-oxygenation of nitrofurazone by singlet molecular oxygen, which has been found to be an active oxidizing species for a number of organic compounds¹ of biological importance. Singlet oxygen is an active oxidant *in vivo* and also nitrofurazone may be attacked by this species. Therefore, the purpose of the present work is to elucidate the role of singlet molecular oxygen in the oxidation of nitrofurazone.

EXPERIMENTAL

0.5 g of nitrofurazone was dissolved in 40 ml of slightly alkaline methanol. A few drops of methylene blue solution were added to the solution so that the concentration of the methylene blue in the reaction mixture was $\sim 1.0 \times 10^{-5}$ M. The solution was then exposed to a tungsten lamp kept at a distance of 20 cm from the lower surface of the reaction flask. Oxygen gas was continuously bubbled through the solution. The progress of the reaction was monitored with thin layer chromatography (tlc) at regular intervals using the solvent system - *n*-butanol : ethanol : water = 27:3:10 (v/v). After 60 minutes of irradiation, it was observed that the TLC of the solution showed two spots, one for the original substrate nitrofurazone ($R_f = 0.26$) and the other for the product ($R_f = 0.48$). The reaction was allowed to proceed to completion. The light source was

removed, when the tlc plate showed only one spot, namely the product. The solution was then decolourized with activated animal charcoal and the decolourized solution was allowed to evaporate. A solid product was contained and was crystallized from alcohol.

Microanalyser (Carbo Erba-1106) was used for the estimation of carbon, hydrogen and nitrogen. UV, IR, NMR and mass spectral data were obtained from Shimadzu-UV 240 Shimadzu-IR-440, 90MHz FT-FX 600 JEOL and JEOL JMS DX-300 spectrometers, respectively.

RESULTS

The effect of the nature of solvent on the photo-oxygenation of nitrofurazone was studied using different solvents. However, the amount of substrate could not be maintained constant because of the varying solubility in different solvents. Therefore, only relative product yields were determined.

TABLE I
Effect of solvents

Solvent	Life time ⁶⁻⁷ μ S	Dielectric constant ϵ_r	Yield of the product %	Time of initiation minutes
Water	2	80.1	20.0	75.0
Acetone	42	20.7	40.0	40.0
Dioxane	32	2.2	32.0	50.0
Pyridine	17	12.3	25.0	56.0
Ethanol	19	24.5	30.0	55.0
Methanol	11	32.7	25.0	60.0

Methylene blue = 1.0×10^{-5} M, time of irradiation = 120 minutes

Dye-sensitized photo-oxygenation of nitrofurazone was also carried out in the presence of various photosensitizers, all other factors being identical. The effect of triplet energies of sensitizers on product yield was measured. The results are reported in Table II.

TABLE II
Effect of triplet energies

Sensitizer	Triplet ⁸⁻¹⁰ energies kcal/mol	Yield of the product %	Time of initiation minutes
Methylene blue	34.0	25.0	60.0
Eosin-Y	43.2-46.0	20.0	75.0
Rose Bengal	37.5-42.2	22.0	70.0
Thionine	48.0	17.0	80.0
Riboflavin	57.8	13.0	100.0

[Dye] = 1.0×10^{-5} M; time of irradiation = 120 minutes

The effect of various singlet molecular oxygen scavengers on the photoproduct yield are given in Table III.

The crystallized product was identified by elemental analysis, physical, chemical and spectral data.

- (i) *m.p.* = 37.38 °C
- (ii) *Analysis*; Found C = 42.23%, H = 2.10%, N = 10.02%
Calculated C = 42.55%, H = 2.13%, N = 9.93%.
- (iii) The product was positive for the -CHO group.^{16a}
- (iv) The product was positive for the -NO₂ group.^{16b}
- (v) The product was positive for furfural.^{16c}
- (vi) The absorption band at 276 nm is characteristic of the nitro group whereas the bands at 225 and 332 nm indicate the presence of an aldehyde group.
- (vii) The IR band at 2948-2898 cm⁻¹ is due to aliphatic C-H stretching vibrations, whereas the presence of a band at 1465 cm⁻¹ may be attributed to C-H bending vibrations. The bands at 1695 and 1665 cm⁻¹ indicate the presence of an α,β -unsaturated aldehyde.¹⁷ A weak band at 1410 cm⁻¹ is due to C-N bending vibrations. The absorption bands at 1648 and 1610 cm⁻¹ may be assigned to an aldehyde group attached to a diene.¹⁸ The presence of a nitro group is clearly indicated by bands at 1525 and 1342 cm⁻¹.¹⁹ The 1210 and 700 cm⁻¹ bands may be attributed to C-O stretching and C-C-N skeleton deformation vibrations, respectively.
- (viii) The pair of doublets centered at 3.04 and 2.82 σ indicates that the two protons are present in similar environments. The signal at 0.20 σ clearly indicates an aldehyde proton.
- (ix) The molecular ion peak of the product was obtained at $m/e = 141$. It lost a fragment to give a peak at $m/e = 95$, whereas the base peak was obtained at $m/e = 113$ after the loss of a CO fragment. The loss of an aldehyde group give rise to fragments at $m/e = 112$ and 29. The fragment at $m/e = 46$ may be due to NO₂⁺.

TABLE III

Effect of singlet molecular oxygen scavengers

Scavenger ¹¹⁻¹⁵	Product yield %
-	25.0
Nickel chloride	0.2
Cobalt chloride	0.2
β -carotene	Nil
DABCO	0.1
α -Tocopherol	Nil

[Methylene blue] = 1.0×10^{-5} M, time of irradiation = 120 minutes,
[Scavengers] = 1.0×10^{-5} M

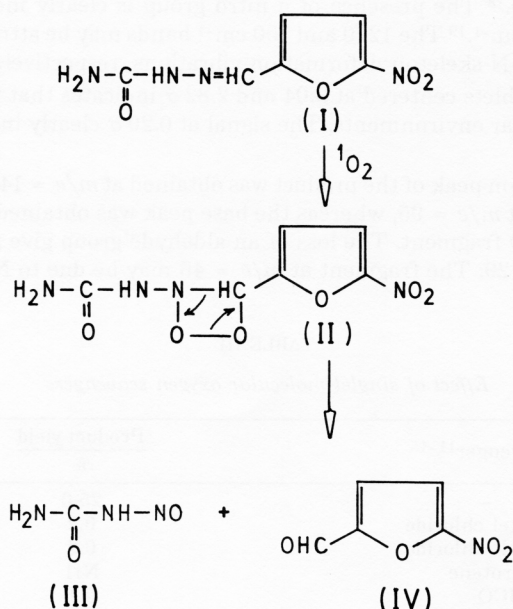
DISCUSSION

On the basis of the above experimental observations, the following tentative mechanism has been proposed for the photooxygenation of nitrofurazone by singlet molecular oxygen.

In the first step, singlet molecular oxygen attacks the -N=CH bond of nitrofurazone (I) to produce a dioxetane derivative (II). The dioxetane then dissociates to give products (III) and (IV). Product (III) is unstable and cannot be isolated; however, product (IV) has been isolated and characterized.

The yield of the product in different solvents was observed to be higher in non-polar solvents. This may be attributed to the longer life-time of singlet molecular oxygen in the non-polar solvents. The product yield as a function of the triplet energies of sensitizers was observed to be highest in methylene blue and lowest in riboflavin. This may be due to the fact that methylene blue has a lower triplet energy and generates singlet oxygen ($^1\Delta_g$) whereas lesser amounts of $^1\Delta_g$ O_2 are generated in the presence of riboflavin because of its higher triplet energy. The $^1\Delta_g$ state of singlet oxygen has longer life than the $^1\Sigma_g$ state of O_2 . Dyes with higher triplet energies generate $^1\Sigma_g$ in preference to $^1\Delta_g$.

The effect of singlet molecular oxygen scavengers on product yield confirms that singlet oxygen is the active oxidizing species in the photo-oxygenation of nitrofurazone.



Mechanism of photooxygenation of nitrofurazone

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SAŽETAK

Bojom-senzibilizirana fotooksidacija nitrofurazona singletnim kisikom

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Bojom senzibilizirana fotooksidacija nitrofurazona provedena je pod raznim uvjetima, uključujući i promjene u otapalima i senzibilizatorima. Produkt je izoliran i karakteriziran na temelju elementne analize, fizikalnih, kemijskih i spektroskopskih podataka. Pretpostavljen je odgovarajući mehanizam nastajanja fotoprodukta. Da bi se potvrdilo sudjelovanje singletnog kisika u reakciji fotooksidacije korišteni su hvatači singletnog kisika.