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Primary processes of photodecomposition of 2-(5′-nitro-2′-furanyl)ethenyl-4-{*N*-[4′-(*N*,*N*-diethylamino)-1′-methylbutyl] carbamoyl} quinoline

Effect of oxygen and compound concentration

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Abstract

The study of the kinetics of photodecomposition of 2-(5′-nitro-2′-furanyl)ethenyl-4-{*N*-[4′-(*N*,*N*-diethylamino)-1′-methylbutyl] carbamoyl} quinoline (Quinifuryl, Q) was studied using steady-state and time resolved absorption spectroscopy. We detected the formation of the Q triplet state, which is characterized by the absorption maximum at 550 nm, triplet state energy $E_T = 18{,}200 \pm 500\,\mathrm{cm}^{-1}$ and a decay constant $k_0 = 1.8 \times 10^4\,\mathrm{s}^{-1}$. This triplet state is quenched by Q molecules in its ground state with the constant $k_{q1} = 2.6 \times 10^8\,\mathrm{M}^{-1}\,\mathrm{s}^{-1}$ and by molecular oxygen with the constant $k_{q2} = 2.0 \times 10^9\,\mathrm{M}^{-1}\,\mathrm{s}^{-1}$. The initial rate of Q photodecomposition under continuous irradiation by visible light (V_i) increases when the Q concentration is increased. In air and oxygen saturated solutions V_i is linearly proportional to Q concentration and does not depend on the O_2 concentration. Our kinetic model of the process supposed two ways of Q photodecomposition: the reaction between Q molecules in triplet and ground states and the photodecomposition directly from the Q singlet excited state.

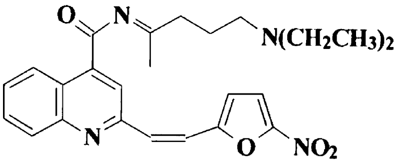
Keywords: Phototherapy; Nitrofurane derivatives; Photobleaching; Quinifuryl; Triplet state; Quenching by oxygen

1. Introduction

Quinifuryl (Q), 2-(5′-nitro-2′-furanyl)ethenyl-4-{*N*-[4′-(*N*,*N*-diethylamino)-1′-methylbutyl] carbamoyl} quinoline, is one of a family of 5-nitrofuran-ethenyl-quinoline drugs (NFEQ) that was synthesized in the early 1970s by Dr. N.M. Sukhova (Institute of Organic Synthesis, Latvian Academy of Sciences, Riga, Latvia) in a search for antitumor agents. Indeed, these compounds have shown significant toxicity toward various lines of cancer cells [1]. Q possessed the highest cytotoxic activity among these compounds [1,2] and showed radiosensitizing activity in vitro [2]. The compound is in clinical use as antiseptic for the treatment of wounds and burns [3].

Due to the presence of the developed system of conjugated π-electrons in its structure, Q possesses an intense optical absorption in the spectral region $350 < \lambda < 450$ nm (ε_{396} nm $= 2.47 \times 10^4\,\mathrm{M}^{-1}\,\mathrm{cm}^{-1}$ at pH 7.0 [1,2]). After photoirradiation, Q becomes colorless, demonstrating photodecomposition of its chromophore. Recently, we observed significant increase in toxicity of Q toward various lines of cancer cells under illumination with light in the above spectral region (manuscript in preparation) [4]. We believe that this effect is due to the formation of some reactive species in the course of the Q photodecomposition. However, the detailed mechanism of the compound photodecomposition is not clear yet. In the present work we report on the study of the Q photodecomposition in aqueous solutions as a function of Q and oxygen concentrations.

2. Materials and methods



This Quinifuryl was obtained from Dr. N.M. Sukhova.

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The compound was dissolved in phosphate buffer (5 mM $NaH_2PO_4 + 2.5$ mM Na_2HPO_4), pH 6.8, using Mili-Q quality water and irradiated in the spectral range from 350 to 450 nm using a tungsten lamp (150 W) and a glass filter (5–57 KOPP color glass filter). A standard quartz 1 cm cuvette with water was used as a thermal filter to prevent collateral heat effects. The intensity of irradiation of the sample was 22 mW cm^{-2}, as measured by a Spectra-Physics 407A radiometer. The concentration of Q in solutions under irradiation was from 7 to 70 μM. The photolysis was performed in standard quartz cuvettes with optical lengths 2 and 10 mm, so that the initial absorbance at the $\lambda_{max} = 396$ nm was below 0.35. The optical absorption spectra were monitored with the DU 650 Beckman spectrophotometer.

The flash-photolysis experiments were performed in a standard quartz 1 cm cuvette. The Q excited states were produced by short light pulses (10 ns) of the third harmonic (355 nm) of Nd:YAG laser SL400 spectron laser system. The excited state absorption spectra and decay profiles were monitored in the spectral region $450 \leq \lambda \leq 750$ nm using a standard registration system.

To study the oxygen effect, the samples were deoxygenated by bubbling nitrogen through the solution and for comparison some samples were deoxygenated with a vacuum pump.

All experiments were run at room temperature (24 °C).

3. Results and discussion

The Q absorption spectra at pH 7.0 are presented on Fig. 1a. Under continuous irradiation in the range 350–450 nm, occurred the photobleaching of Q showing photodecomposition of its chromophore (Fig. 1a). The removal of air increased the rate of photodecomposition (Fig. 1b).

The excitation of deairated Q aqueous solutions by a laser pulse at 355 nm induces the formation of short-lived Q species characterized by absorption in the region from 450 to 700 nm with the maximum centered at 550 nm (Fig. 2a) A short-lived product with a similar spectrum was also observed in dioxane (Fig. 2a). The profile of the decay of this absorption is mono-exponential (Fig. 2b).

$$\Delta D = \Delta D_0 \exp(-k_1 t) \tag{1}$$

The decay constant k_1 increases with increase of the initial Q concentration ($[Q]_i$), demonstrating the quenching of this excited state by Q in the ground state. Two constants were determined (Fig. 3) using the following equation:

$$k_1 = k_0 + k_{q1}[Q]_i \tag{2}$$

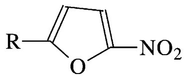
where $k_0 = 1.8 \times 10^4\ s^{-1}$ determined as a limit value at infinite dilution $[Q]_i \rightarrow 0$; and the self-quenching constant $k_{q1} = 2.6 \times 10^8\ M^{-1}\ s^{-1}$.

The observed short-lived species is quenched by molecular oxygen

$$k_2 = k_1 + k_{q2}[O_2] \tag{3}$$

with $k_{q2} = 2.0 \times 10^9\ M^{-1}\ s^{-1}$.

The formation of the triplet excited states from the photoexcitation of nitrofuran derivatives



has been described [5]. The self-quenching and the quenching by molecular oxygen are typical processes for the triplet states. Thus, we should associate the observed short-lived

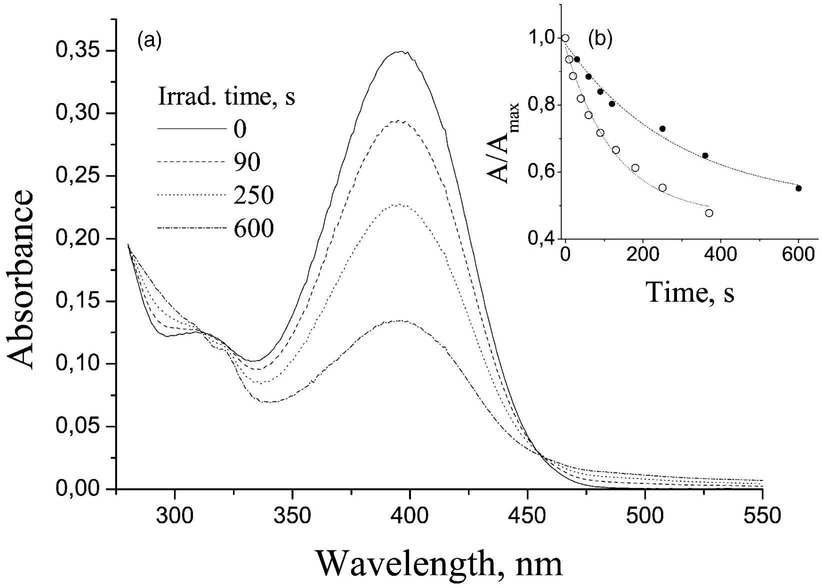


Fig. 1. (a) The absorption spectra of Q aqueous solution as a function of the irradiation time. The concentration $[Q] = 1.4 \times 10^{-5}$ M. (b) Normalized Quinifuryl absorbance at 396 nm as a function of the irradiation time in air saturated (●) and deairated (○) solutions.

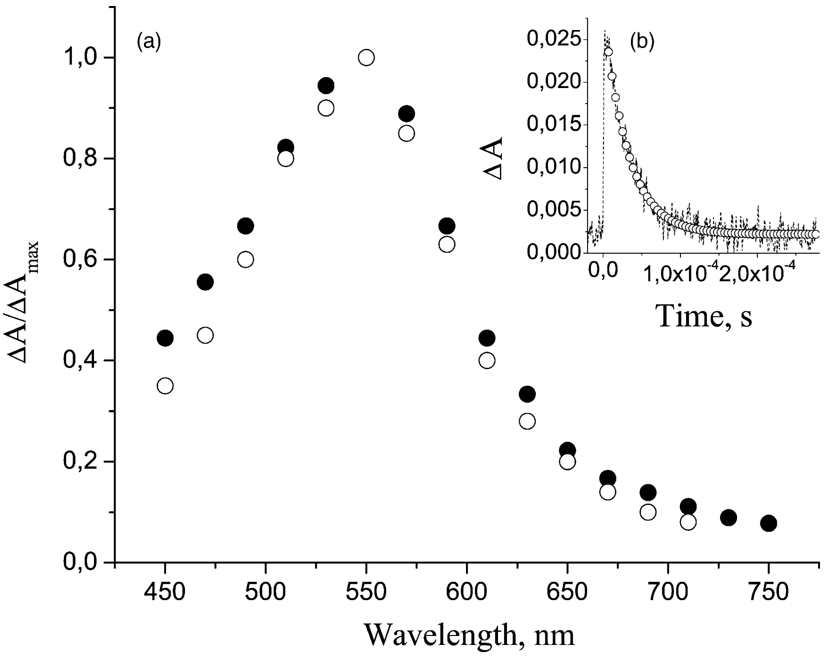


Fig. 2. (a) Normalized Quinifuryl triplet–triplet absorption spectra in water (●) and in dioxane (○) solutions. (b) Decay profiles of the Q triplet state in the aqueous deaerated solution.

species with excited triplet states of Q. Indeed, the experiments done in dioxane have shown that acceptors of the triplet energy quench these species; the quenching constant is dependent on the level of the triplet state energy of acceptor (Table 1). The formation of acceptor triplet states due to the energy transfer from Q triplet state was also observed. The energy of the Q triplet state determined from these experiments is $E_T = 18200 \pm 500\,\mathrm{cm}^{-1}$.

Based on our results, one may consider the scheme of the Q phototransformations as follows:

(0) $Q(S_0) + h\nu \rightarrow Q^*(S_1)$.
(1) $Q^*(S_1) \xrightarrow{k_{IC}} Q(S_0)$.
(2) $Q^*(S_1) \xrightarrow{k_T} Q^*(T_1)$.
(3) $Q^*(T_1) \xrightarrow{k_0} Q(S_0)$.

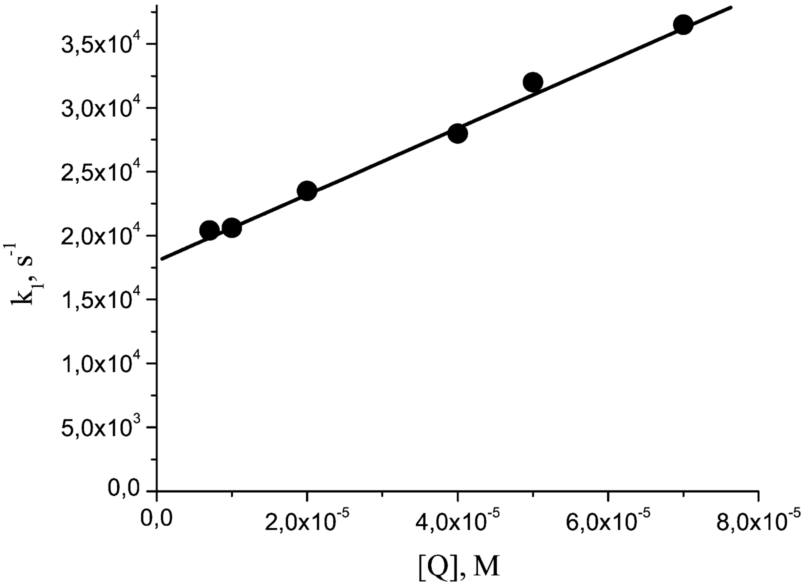


Fig. 3. The constant of decay of Quinifuryl triplet state (k_1) as a function of the Q concentration.

Table 1
The quenching constants of Quinifuryl triplet state by the triplet energy acceptors

Compound	E_T (cm^{-1})	$k_q \times 10^{-9}$ (M^{-1} s^{-1})
Naphthacene	10250	2.7 ± 0.4
Azulene	12000	2.5 ± 0.4
9,10-Dibromoanthracene	14112	1.3 ± 0.2
Eosine	15000	1.2 ± 0.2
Acridine orange	17390	2.0 ± 0.3
1,2-Benzpyrene	18480	$(4.2 \pm 0.9) \times 10^{-2}$
Fluorenone	18860	$<10^{-4}$
Naphtalene	21300	$<10^{-4}$
9H-fluorene	23750	$<10^{-4}$

(4) $Q^*(T_1) + Q(S_0) \xrightarrow{k_{q1}}$ Products 1 (we suppose that this reaction is partly responsible for Q photodecomposition).

(5) $Q^*(T_1) + O_2 \xrightarrow{k_{q2}} Q(S_0) + O_2{}^*(^1\Delta_g)$ (probably this quenching is accompanied by the formation of O_2 excited state (“singlet oxygen”)).

The kinetic scheme of the process is described by the following equations:

$$\frac{d[Q(S_0)]}{dt} = -\beta + k_{IC}[Q^*(S_1)] + (k_0 + k_{q2}[O_2])[Q^*(T_1)] \tag{4}$$

$$\frac{d[Q^*(S_1)]}{dt} = \beta - (k_{IC} + k_T)[Q^*(S_1)] \tag{5}$$

$$\frac{d[Q^*(T_1)]}{dt} = k_T[Q^*(S_1)] - (k_0 + k_{q1}[Q(S_0)] + k_{q2}[O_2])[Q^*(T_1)] \tag{6}$$

where

$$\beta = \left(\int_{\lambda_i}^{\lambda_f} I(\lambda)\{1 - \exp(-2.3A_0)\}\, d\lambda\right)$$

is a factor which is determined by initial light absorption in the region $\lambda_i = 350\,\text{nm} \leq \lambda \leq \lambda_f = 450\,\text{nm}$, $I(\lambda)$ is the intensity of the light, $A_0 = \varepsilon(\lambda)[Q(S_0)]l$ is the initial absorbance of the sample.

If A_0 is <1 we can write in the first approximation

$$\beta = 2.3l[Q(S_0)]\int_{\lambda_i}^{\lambda_f} I(\lambda)\varepsilon(\lambda)\, d\lambda = \beta_1[Q(S_0)] \tag{7}$$

where

$$\beta_1 = 2.3l\int_{\lambda_i}^{\lambda_f} I(\lambda)\varepsilon(\lambda)\, d\lambda$$

depends just on the irradiation conditions.

Since the characteristic times of Q photodecomposition under continuous irradiation are much longer than the lifetimes of the excited states $Q^*(S_1)$ and $Q^*(T_1)$ we should write

$$\frac{d[Q^*(S_1)]}{dt} = 0 \quad \text{and} \quad \frac{d[Q^*(T_1)]}{dt} = 0 \tag{8}$$

Combining (4)–(8) we can write the initial rate of the photodecomposition as

$$V_i = \left(\frac{d[Q(S_0)]}{dt}\right)_{t\to 0} = -\beta_1 \frac{k_T k_{q1}[Q(S_0)]^2}{(k_{IC} + k_T)(k_0 + k_{q1}[Q(S_0)] + k_{q2}[O_2])} \tag{9}$$

Taking into consideration that in air saturated aqueous media the oxygen concentration is $[O_2] \cong 3 \times 10^{-4}$ M at 24 °C, we should expect that, at the Q concentration range $7.0 < [Q] < 70.0\,\mu$M, the V_i value in the air saturated solutions should be 12–30 times less than the value in deairated solutions. However, the observed reduction appeared only two to six times less. Moreover, in oxygen saturated solutions ($[O_2 \cong 1.5 \times 10^{-3}$ M) we should expect a five-fold reduction of V_i compared with that in the air saturated solutions, while we actually observed the same value of V_i in the air and oxygen saturated solutions (Fig. 4).

This discrepancy would be resolved if one supposed that Q may also be decomposed directly from its singlet excited state $Q^*(S_1)$.

(6) $Q^*(S_1) \xrightarrow{k_X} Q(S_0)$

In this case Eqs. (5) and (9) should be rewritten as

$$\frac{d[Q^*(S_1)]}{dt} = \beta - (k_{IC} + k_T + k_X)[Q^*(S_1)] \tag{5a}$$

$$V_i = \left(\frac{d[Q(S_0)]}{dt}\right)_{t\to 0} = -\frac{\beta_1}{k_{IC} + k_T + k_X} \times \left(\frac{k_T k_{q1}[Q(S_0)]}{(k_0 + k_{q1}[Q(S_0)] + k_{q2}[O_2])} + k_X\right)[Q(S_0)] \tag{9a}$$

If $k_{q2}[O_2] > k_0, k_{q1}[Q(S_0)]$ and $k_X > (k_T k_{q1}[Q(S_0)]/k_{q2}[O_2])$, V_i is independent of $[O_2]$. This situation occurs both in air and in oxygen saturated solutions. Moreover, in these solutions V_i should possess a linear dependence on $[Q(S_0)]$. The experiment confirms this assumption (Fig. 4).

Two ways of phototransformation of nitrocompounds has been described [6]. The first is direct photoionization with formation of a hydrated electron, which is, in the consequence, bound to the molecule in the ground state, producing a nitrogen oxide radical

$$RNO_2 + \xrightarrow{h\nu} RNO_2{}^{\bullet} + e_h{}^{\bullet -}$$

$$RNO_2 + e_h{}^{\bullet -} \rightarrow RNO_2{}^{\bullet -}$$

The second way is electron transfer from an electron donor to the nitrocompound in its triplet excited state

$$RNO_2{}^*(T_1) + D \rightarrow RNO_2{}^{\bullet -} + D^{\bullet +}$$

Finally, the nitrogen oxide radical is also produced.

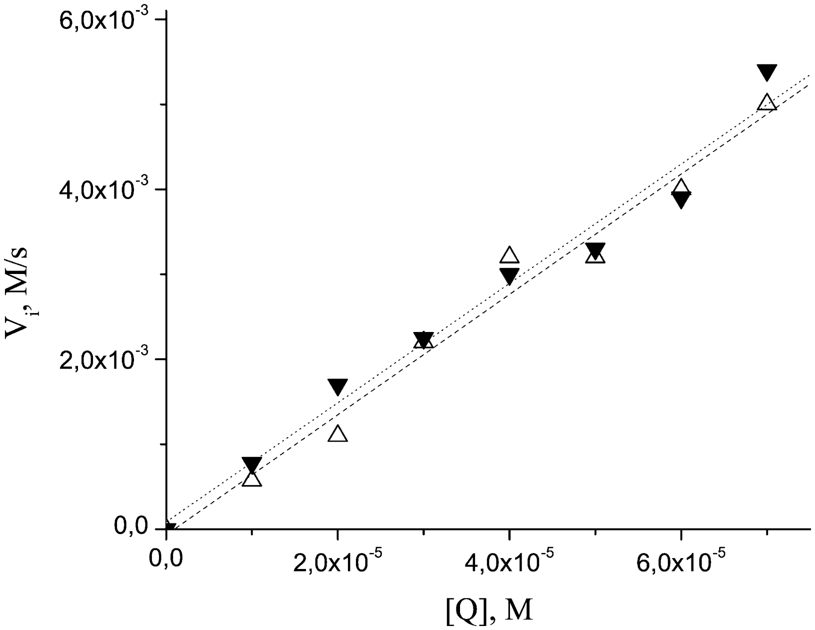


Fig. 4. The initial rate of Quinifuryl photodecomposition (V_i) as a function of Q initial concentration ($[Q]_i$) in air saturated (△) and oxygen saturated (▼) solutions.

We suppose that both ways occur also for the photodecomposition of Q, producing a nitrogen oxide radical. In this case the Q molecule in the ground state should play the role of the electron donor in the reaction with the $Q^*(T_1)$ state. To confirm this hypothesis we have performed a series of experiments with electron donors (ascorbic acid, hydroquinone, 1,7-dioxynaphthaline, aniline) and with epinephrine. The results are to be published soon.

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