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A kinetic study on the inhibitory action of sympathomimetic drugs towards photogenerated oxygen active species. The case of phenylephrine

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Abstract

Kinetics and mechanism of the aerobic Riboflavin (Rf, vitamin B2) sensitized photodegradation of Phenylephrine (Phen), a phenolamine belonging to the sympathomimetic drugs family, has been studied in water, employing continuous photolysis, polarographic detection of oxygen uptake, steady-state and time-resolved fluorescence spectroscopy, time-resolved IR-phosphorescence and laser flash photolysis. Results indicate the formation of a weak dark complex Rf–Phen, with an apparent association constant of $5.5 \pm 0.5\ M^{-1}$, only detectable at Phen concentrations much higher than those employed in the photochemical experiments. Under irradiation, an intricate mechanism of competitive reactions operates. Phen quenches excited singlet and triplet states of Rf, with rate constants of 3.33 ± 0.08 and $1.60 \pm 0.03 \times 10^9\ M^{-1}\ s^{-1}$, respectively. With the sympathomimetic drug in a concentration similar to that of dissolved molecular oxygen in water, Phen and oxygen competitively quench triplet excited Rf, generating superoxide radical anion and singlet molecular oxygen ($O_2(^1\Delta_g)$) by processes initiated by electron- and energy-transfer mechanisms respectively. As a global result, the photodegradation of the vitamin, a known process taking place from its excited triplet state, is retarded, whereas the phenolamine, practically unreactive towards these oxidative species, behaves as a highly efficient physical deactivator of $O_2(^1\Delta_g)$. The phenolamine structure in Phen appears as an excellent scavenger of activated oxygen species, comparatively superior, in kinetic terms, to some commercial phenolic antioxidants.

Keywords: Phenylephrine; Photo-oxidation; Riboflavin; Singlet molecular oxygen; Superoxide radical anion

1. Introduction

Light-promoted-degradation is being increasingly investigated in substrates of relevance in biology and medicine [1–5]. Sympathomimetic drugs (SD), belong to this class of biologically active and commercially valuable substrates. SD consist of a series of compounds with properties resembling the neurotransmitters epinephrine, norepinephrine, and dopamine [6].

Since SD are transparent to daylight, their decomposition due to direct environmental irradiation can be disregarded. Nevertheless, during elaboration, storage, or in vivo, after medicinal administration of the drugs, in the presence of photosensitising substances they might be able to absorb visible light and generate potentially aggressive species. These species can be transient entities consisting of the electronically excited states of a photosensitiser or some of the so called oxygen active species (OAS), generated from these excited states. A particularly interesting daylight-absorber sensitiser is Vitamin B2 (Riboflavin, Rf, see Scheme 1) which is a natural compound present in most living organisms [7]. The

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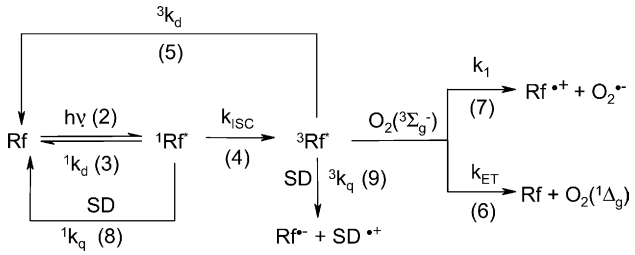
usual mechanism of action of this sensitiser is rather complex, in many cases with the concurrent involvement of the oxidative species singlet molecular oxygen ($O_2(^1\Delta_g)$) and superoxide radical anion ($O_2^{\bullet-}$) which are produced with quantum yields of 0.49 and 0.009, respectively [8]. In the presence of interacting species such as SD, the mentioned mechanism could be summarised as follows:

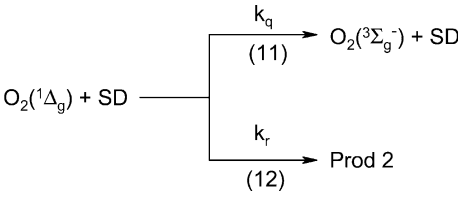
$$Rf + SD \overset{K_{ass}}{\rightleftharpoons} [Rf \cdots SD] \quad (1)$$



Process (1) represents the association Rf–SD, a kind of dark interaction which has been repeatedly reported for couples of Rf with different types of substrates [2,9–11]. Upon absorption of a photon, Rf excited singlet state (^{1}Rf*) is generated (2). It can decay to ground state (3) or, through an intersystem crossing Process (4), it can produce excited triplet Rf (^{3}Rf*). The last species can also decay to ground state Rf (5) or can be quenched by ground state oxygen dissolved in the solution ($O_2(^3\Sigma_g^-)$), generating OAS. That is, singlet molecular oxygen ($O_2(^1\Delta_g)$) (6) and superoxide radical anion ($O_2^{\bullet-}$) are produced by an energy transfer process and by electron transfer to oxygen, respectively (7). Besides, the transient species (^{1}Rf*) and (^{3}Rf*) can also interact with SD (Reactions (8) and (9)).

The interaction of OAS with pharmaceutical products is particularly important since, as a result of the photo-damage, the drug can degrade, either decreasing its original therapeutic activity or even worse, modifying its specific effects and/or eventually generating toxic products (Reactions (10)–(12)).

$$O_2^{\bullet-} + SD \underset{(10)}{\overset{k_{10}}{\rightarrow}} \text{Prod 1}$$



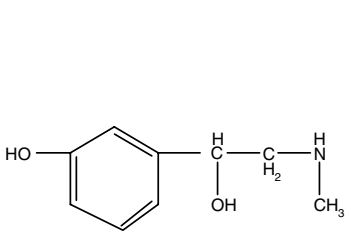
Nevertheless, a positive effect that can arise from the interaction of the drug with some photogenerated oxidative species is the eventual scavenging of the oxygenated species (Reactions (10)–(12)). In this context, the prevalence of the physical Process (11) is a desirable possibility since the final result is the elimination of the oxidative species without considerable loss of the scavenger.

In this paper we present a kinetic and mechanistic study on the behaviour of the SD derivative Phenylephrine (Phen, see Scheme 1) in the presence of molecular or radical species produced through daylight-promoted Rf–sensitised processes. Phen is a phenolamine and it is well known that several compounds with phenol-like structures are susceptible to degradation by reacting with environmentally-photogenerated oxidative species [12,13].

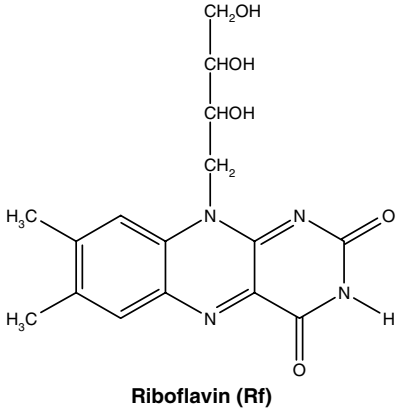
2. Materials and methods

2.1. Materials

Riboflavin (Rf), deuterium oxide 99.9% (D_2O), L-Tryptophan (Trp), Trolox and L-Phenylephrine Hydrochloride (Phen) were purchased from Sigma Chem. Co. Rose Bengal (RB), and furfuryl alcohol (FFA) were from Aldrich. All these chemicals were used



Phenylephrine (Phen)



Riboflavin (Rf)

Scheme 1. Chemical structures of Phenylephrine (Phen) and Riboflavin (Rf).