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Short communication

Kinetics of photooxidation of papaverine hydrochloride and its major photooxidation products

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Abstract

HPCE methodology was modified to be used in kinetic experiments on photooxidation reactions of papaverine hydrochloride **1** and its oxidation products (papaverinol **2** and papaveraldine hydrochloride **3**) chloroform solutions exposed to UV_{254} light in aerobic conditions. On photooxygenation of the above compounds is formed the final degradation product, a brown compound X **4**, 2,3,9,10-tetramethoxy-12-oxo-12*H*-indolo[2,1-*a*]isoquinolinylim chloride. The rate of **4** formation from the above compounds can be given as **2** > **3** > **1** > **1** HCl. The photooxidation reactions of **1** and **2** proceed with pseudo first-order kinetics and that reaction for **3** follows zero-order kinetics. The most labile compound is **2** whose half-life time is 2.4 times shorter than that one of **1** HCL. The most stable product is **3** whose half-life time is 31-fold longer than of **2**. The specific quantum yields are equal 0.28, 0.30 and 0.10 for **1** HCl, **2** and **3**, respectively which confirm the above stability pattern of the compounds concerned.

Keywords: HPCE quantification; Photooxidation kinetics; Papaverine hydrochloride; Papaverinol; Papaveraldine hydrochloride; Quantum yield; A brown degradation product X; Rate of its formation

1. Introduction

Papaverine **1** salts (hydrochloride and sulfate), used in medical treatments, are susceptible to oxidation in either aqueous (injections) or especially in nonaqueous solutions, in which the solubility of oxygen is greater, as well as in the solid phase. However, **1** base is more stable if compared to its salts. The salts are oxidized to first a secondary alcohol **2** (papaverinol) and second a ketone **3** (papaveraldine) which have been known for a long time [1,2]. The presence of the above **1** oxidation products did not explain the observation that **1** salts solutions had become brown on their storage for an extended period of time when exposed to an either day- or a sunlight conditions, because they are not brown but only yellowish. However, the brown compound—named "the compound X" was first observed in ageing 4% **1** sulfate aqueous injection solutions as a brown spot on a paper chromatogram [3]. The compound X was later on isolated in a yield approx. 40% from a 2 mg/ml **1** hydrochloride chloroform solution stored for over 1 year at the daylight conditions [4]. The formation of the compound X is faster in a nonaqueous solution, e.g. a chloroform one, because the solubility of oxygen in that solvent is much greater than in water [5–7]. The compound X has been lastly identified with a yet unknown chemical **4**—2,3,9,10-tetramethoxy-12-oxo-12*H*-indolo[2,1-*a*]isoquinolinylium salt (e.g., chloride) [8]. Its synthesis procedure from a **2** chloroform solution exposed to a UV light at 254 nm has been published [7]. However, it is not clear, if it is formed from the **1** salts via either the product **3** or the product **2**.

Therefore, the aim of this paper is to follow kinetics and the quantum yield of photochemical degradation reactions of aerobic chloroform **1** chloride, **2** base and **3** hydrochloride solutions exposed to the UV light at 254 nm to find out which of the above compounds favors their degradation to the brown isoquinolinylium chloride **4**.

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2. Materials and methods

2.1. Materials

Loratadine (IS), lot # 7LTL012, Jelfa SA, Jelenia Góra, Poland; papaverine hydrochloride, mp 219–225 °C dec. (lit. 218–223 °C dec. FP VI), Farm-Impex, Gliwice, Poland; papaveraldine hydrochloride $C_{10}H_{19}NO_5HCl{\cdot}2.5H_2O$, synthesized according to Tsatsas [9], mp 211–212 °C (lit. 210 °C [9]); papaverinol $C_{20}H_{21}NO_5$, synthesized according to Gadamer [10], mp 136–137 °C (lit. 137 °C [2]). All other chemicals were of reagent or HPLC grade.

2.2. Apparatus

Melting points were determined on a Boëtius microscope (VEB Wägetechnik Rapido, Germany) and are not corrected. High Performance Capillary Electrophoresis (CE), model 3D 1 apparatus with diode array UV detector (Agilent Technologies, Waldbronn, Germany) was used for quantification of **1**–**3**. A 3D apparatus was equipped with Chemstation used for instrument control, data acquisition and data analysis. The system was controlled by Windows NT software. A low pressure mercury lamp 254 nm Original Hanau TNN 15/32 (Heraeus, Germany) was used in photo-kinetic experiments.

2.3. CE methodology for quantification of photooxidation processes

An Agilent fused silica capillary of 50 μm i.d. and 72 cm total length was used for separation of **1**–**4**. Background electrolyte (BGE) consisted of 50 mmol/l NaH_2PO_4 and 100 mmol/l H_3PO_4 to receive pH 2.5. A new capillary was flushed with NaOH solutions of concentrations 1, 0.1 (mol/l) and subsequently with demineralized water and BGE for 10, 10, 5 and 8 min, respectively. The temperature of the capillary was maintained by a thermostatic system at 25 °C. The samples were automatically injected using hydrodynamic injection at the anode for 2 s (0.5 psi, 3447.38 Pa). The capillary between subsequent injections was washed with 0.1 mol/l NaOH, water and BGE for 5 min each. All experiments were carried out at the voltage 20.0 kV resulting in the current of 21.0 ± 0.3 μA.

2.4. Calibration curve for *1–4*

About 10 mg/l stock solutions each of the above compounds and an internal standard (IS) were prepared in methanol. Then standard solutions each of 0.05, 0.10, 0.20, 0.50, 1.00 and 2.00 mg/l containing each 2.00 mg/l IS were prepared by dilution with methanol. To 16 mm culture tubes were added 200 μl each of chloroform and of a standard solution, and the mixture was vortexed and the solvent was evaporated out at 60 °C under nitrogen. The residue was reconstituted in a mixture (1:1) of methanol and BGE. The solution was injected onto the capillary as mentioned above. The peak area ratio of an analyte to IS was plotted as a function of four analyzed compound concentrations. In order to calculate precision and accuracy different concentrations of the compound considered were determined within-day and between-days. Every single determination was done in triplicate.

2.5. Kinetics of photooxidation reactions

About 2 mg/ml chloroform solutions each of **1**–**3** were exposed to UV light of 254 nm in 15 ml cylindrical silica cells from the distance of 2.5 cm at ambient temperature and in aerobic conditions. At suitable time intervals 200 μl samples withdrawn were diluted with 200 μl IS stock solution and evaporated to dryness. The residue was further treated according to the above specified procedure. The concentrations of **1** and its degradation products (**2**–**4**) were calculated as a function of time from a suitable electropherogram obtained.

2.6. Measurement of the quantum yield

A uranyl oxalate actinometer was applied to measure the quantum yield of the above photolysis experiment. The uranyl oxalate actinometer itself has a known quantum yield ($\varphi = 0.602$) [11]. An aqueous solution (0.01 mol/l) of the actinometer was palced in the above 15 ml cylindrical cell and exposed to UV_{254} light from the distance 2.5 cm for 10, 20 and 30 min.

The actinometer was titrated with manganate(VII) potassium (0.0930 mol/l) prior and after the irradiation. The results of the titrations (Δc) allow us to calculate the intensity of light absorbed by the substrate according to the following formula:

$$I_a = \frac{\Delta c}{\varphi t} \tag{1}$$

where t denotes the time of irradiation.

2.6.1. Quantum yield of photooxidation reaction of a papaverine hydrochloride solution and its degradation products

About 2 mg/ml chloroform solutions each of papaverine hydrochloride, papaverinol and papaveraldine hydrochloride were exposed to UV_{254} light in cylindrical 15 ml silica cells from the distance 2.5 cm in aerobic conditions at the ambient temperature. Their samples were withdrawn at suitable time elapsed and absorbances measured resulting in calculation of the degree of conversion of a substrate. The quantum yields were calculated from Eq. (1) for different degrees of conversion which were extrapolated to the zero degree of conversion which indicates the specific quantum yield of a substrate.

2.7. Calculation of rate constants of photooxidation reactions

Photooxidation reactions of papaverine hydrochloride and papaverinol follow the typical first-order equation:

$$\ln c = \ln c_0 - kt \tag{2}$$

where c and c_0 are concentrations of the substrate at time t and t_0, respectively, and k is an apparent first-order rate constant.