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# Correlation of cyclic voltammetry behaviour and photooxidative properties of indoprofen and its photoproducts

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**Abstract**

The electrochemical behaviour of indoprofen (INP) and its photoproducts was investigated in acetonitrile containing tetrabutylammonium hexafluorophosphate at a Pt or Cv ultramicro-electrodes. These photosensitizers (PS) undergo irreversible oxidation yielding at first a radical cation $PS^{\bullet+}$ and more or less reversible reductions through monoelectronic exchange involving a radical anion $PS^{\bullet-}$. By varying the potential scan speed, the stabilities of the radical anions were evaluated. The determination of the redox potential and Rehm–Weller's equation shows the high exergonicity of the oxidative photodamagings whatever is the compound PS. The difference in DNA photosensitizing properties could rather be related to a kinetic control and then to the relative stabilities of the radical anions $PS^{\bullet-}$. Cyclic voltammetry was found powerful in order to get a new insight in the photosensitizing properties of drugs.


*Keywords:* Indoprofen; Electrochemical behaviour; Photooxidative properties; Photoproducts; Radicals stability

## 1. Introduction

Indoprofen, a non-steroidal anti-infammatory agent (NSAIDs), falls into the class of the 2-arylpropionic acids family, which are among the most commonly used in the treatment of inflammatory diseases, particulary rheumatoid arthritis and osteoarthritis [1]. Nevertheless, a significant number of these drugs has been implicated in photosensitivity reactions [2,3] that generally involved drug-photosensensitized damages to biomolecules [4]. Photosensitization of DNA lesions by NSAIDs has been established in particular for ketoprofen and indoprofen. Previous works have indeed demonstrated that these drugs photoinduced the formation of thymine dimers and guanine oxidative products, respectively by energy and electron transfer mechanisms [5–10]. However, in the case of indoprofen, the formation of these lesions in particular, the formation of cyclobutane thymine dimers was not associated to the drogue itself but to one of its photoproducts [7]. Indeed, indoprofen under UVA irradiation leads to three major stable photoproducts: 2-[4-(1-hydroxy)ethylphenyl]isoindolin-1-one (HOINP), 2-(4-ethylphenyl)isoindolin-1-one (ETINP) and 2-(4-acetylphenyl)isoindolin-1-one (KINP) (Scheme 1) [8]. If only one of them, KINP is involved in the formation of cyclobutane thymine dimers, on the other hand, all photoproducts lead to alkalilabile lesions via an electron transfer mechanism during drug photosensitization [9,10].

The photoinduced electron transfer takes place from the guanine residue, which is the nucleobase having the lowest oxidation potential in DNA [11], to the excited photosensitizer.

It requires the enhancement of the oxidative properties of the photosensitizer according:

$$PS + h\nu \rightarrow PS^*$$

$$G \rightarrow G^{\bullet+}$$

$$PS^* + e \rightarrow PS^{\bullet-}$$

The $\Delta G$, calculated by the Rehm–Weller equation [12] is highly exergonic [10]:

$$PS^* + G \rightarrow PS^{\bullet-} + G^{\bullet+}$$

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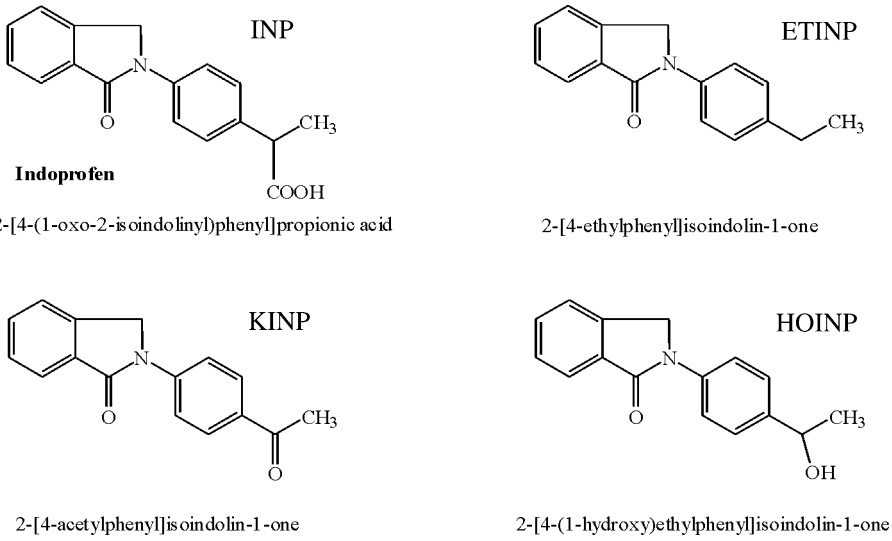


Scheme 1. Indoprofen and its photoproducts.

Since the photobiological properties of a drug are closely linked to its photophysical and photoredox properties, this paper describes the electrochemical behaviour of indoprofen and its photoproducts, which can be correlated to the ability of photosensitizers at inducing alkalilabile sites in DNA by electron transfer from *G* to $PS^*$.

## 2. Experimental

### 2.1. Photolysis of indoprofen and isolation of photoproducts

Indoprofen photoproducts, 2-[4-(1-hydroxy)ethylphenyl] isoindolin-1-one (HOINP), 2-(4-ethylphenyl)isoindolin-1-one (ETINP) and 2-(4-acetylphenyl)isoindolin-1-one (KINP) were obtained by indoprofen (INP) photolysis. Phosphate buffer solutions of indoprofen were irradiated in pyrex photoreactor thermostated at 25 °C using a xenon lamp (Muller 450 W) equipped with a long pass filter $\lambda > 320$ nm (Oriel, WG-320) for 25 h. The power received by the samples was ca. $20 \times 10^{-3}$ W/cm$^2$. The progress of the reaction was monitored by thin-layer chromatography using dichloromethane/ethyl acetate (60/40) as mobile phase. In these conditions, the $R_f$ are 0.89, 0.63 and 0.48, respectively for the ETINP, KINP and HOINP. When irradiation was completed (at the consumption of the drug), the solvent was evaporated at reduced pressure at room temperature and the residue was purified by column chromatography (silica gel: Kieselgel 60, 0.063–0.200 mm) using a mixture of dichloromethane and ethyl acetate (60/40) as eluent. The photoproducts were characterized by $^1$H and $^{13}$C NMR, mass, IR and UV spectra.

### 2.2. Electrochemistry

Electrochemical measurements were carried out at room temperature with an Autolab 20 potentiostat (EcoChemie, Utrecht NL) controlled by a PC computer. The electrochemical cell (10 mL) was a conventional one with three electrodes: working electrodes, platinum Pt (disk diameter: 0.5 mm and 10 μm Tacussel) and glassy carbon (10 μm PAR); counter electrode, Pt wire; and reference electrode, double junction SCE. Cyclic voltammetry and steady state experiments were performed in acetonitrile (HPLC grade, SDS)/$Bu_4NPF_6$ 0.1 M (Fluka, electrochemical grade) under argon atmosphere. The potential of ferricinium ion/ferrocene couple is 0.486 V versus this reference [13] or 0.400 V versus the standard hydrogen electrode SHE [14]. Esr spectra were recorded at ambient temperature on a 9 GHz Bruker (ESP 300 E) instrument. The electrolyses were carried out in the esr tube placed in the Bruker instrument cavity.

## 3. Results and discussion

### 3.1. Electrochemical behaviour

In the electroactivity domain of $CH_3CN/Bu_4NPF_6$, the cyclic voltammograms of photosensitizers show an oxidation process and reduction processes (Fig. 1) at a glassy carbon electrode. At a platinum electrode, the reduction signals around −2.4 V are in the foot of the solvent discharge. On the anodic side, the voltammograms at platinum or glassy carbon are very similar and the paper is then restricted to the electrochemical behaviour at glassy carbon. By calibration with the ferrocene redox couple, according Amatore's procedure [15] which uses steady state and chronoamperometric experiments, the electron transfers appeared to be monoelectronic for oxidation and reduction and should yield radical species at first. This is sustained by the peak currents (oxidation and reduction) which are of the same order of magnitude for a given potential scan speed (Fig. 1). Esr experiments were carried out in an attempt to identify these species. Unfortunately, the esr spectra did not yield conclusive information.

Concerning the oxidative processes (Figs. 1A and 2), the cyclic voltammograms are badly defined and electrode fouling is involved. Although the global electron exchange appears